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Modern Heterocyclic Chemistry

Volume 4

WILEY-VCH Verlag GmbH & Co. KGaA

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Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at http://dnb.d-nb.de.

Typesetting Thomson Digital, Noida, India
Printing and Binding betz-druck GmbH, Darmstadt
Cover Design Schulz Grafik-Design, Fußgönheim

Printed in the Federal Republic of Germany
Printed on acid-free paper

Print ISBN: 978-3-527-33201-4
oBook ISBN: 978-3-527-63406-4

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1
Heterocyclic Compounds: An Introduction

Julio Alvárez-Builla and José Barluenga

1.1
Heterocyclic Compounds: An Introduction

The *IUPAC Gold Book* describes *heterocyclic compounds* as:

"Cyclic compounds having as ring members atoms of at least two different elements, e.g. quinoline, 1,2-thiazole, bicyclo[3.3.1]tetrasiloxane" [1].

Usually they are indicated as counterparts of *carbocyclic compounds*, which have only ring atoms from the same element. Another classical reference book, the *Encyclopaedia Britannica*, describes a heterocyclic compound, also called a *heterocycle*, as:

"Any of a class of organic compounds whose molecules contain one or more rings of atoms with at least one atom (the heteroatom) being an element other than carbon, most frequently oxygen, nitrogen, or sulfur" [2].

Although heterocyclic compounds may be inorganic, most contain within the ring structure at least one atom of carbon, and one or more elements such as sulfur, oxygen, or nitrogen [3]. Since non-carbons are usually considered to have replaced carbon atoms, they are called heteroatoms. The structures may consist of either aromatic or non-aromatic rings.

Heterocyclic chemistry is the branch of chemistry dealing with the synthesis, properties, and applications of heterocycles.

Heterocyclic derivatives, seen as a group, can be divided into two broad areas: aromatic and non-aromatic. In Figure 1.1, five-membered rings are shown in the first row, and the derivative **1** corresponds to the aromatic derivative, furan, while tetrahydrofuran (**2**), dihydrofuran-2-one (**3**), and dihydrofuran-2,5-dione (**4**) are not aromatic, and their reactivity would be not unlike that expected of an ether, an ester, or

Modern Heterocyclic Chemistry, First Edition.
Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.

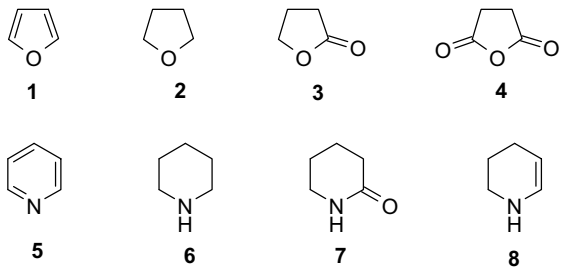


Figure 1.1 Examples of heterocyclic compounds.

a carboxylic anhydride, respectively. The second row shows six-membered rings, initially in an aromatic form as pyridine (**5**), while piperidine (**6**), piperidin-2-one (**7**), and 1,2,3,4-tetrahydropyridine (**8**) are not aromatic; their reactivity would not be very different from that expected of an amine, amide, or enamine, respectively. In general, the reactivity of aromatic heterocycles, which is a combination of that expected from an aromatic system combined with the influence of the heteroatoms involved, is usually more complex, while the reactivity of the non-aromatic systems is not too different from the usual non-cyclic derivatives. Thus, most books on heterocyclic chemistry are mainly devoted to the reactivity of aromatic compounds.

Tables 1.1–1.4 indicate models of the heterocyclic derivatives described in these volumes. Table 1.1 shows simple heterocyclic systems of three or four members. In this case, the literature examples are mainly non-aromatic, as indicated in the table, and the expected reactivity is always related to the ring strain present in all of them, which produces a release of energy when they are opened to give aliphatic products.

Table 1.1 Main three- and four-membered heterocycles.

Ring size	Heteroatom			
	N	**O**	**S**	**Other**
3	 Aziridine	 Oxirane	 Thiirane	
	 Diaziridine	 Dioxirane		 Oxaziridine
4	 Azetidine	 Oxetane	 Thietane	 Seletane Phosphetane

Table 1.2 Main five-membered heterocycles.

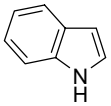
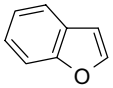
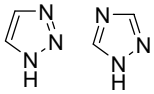
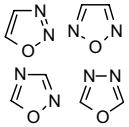
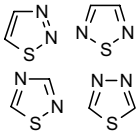
Ring size	Heteroatom				
	N	**Benzo**	**O**	**Benzo**	**S**
5	 Pyrrole	 Indole	 Furan	 Benzofuran	 Thiophene
5	 Pyrazole		 Isoxazole		 Isothiazole
	 Imidazole		 Oxazole		 Thiazole
	 Triazoles		 Oxadiazoles		 Thiadazoles
	 Tetrazole				

Table 1.2 indicates five-membered heterocyclic systems, such as pyrrole, furan, their benzo derivatives, and thiophene, and a set of heterocycles with more than one heteroatom, as 1,2-azoles, 1,3-azoles, triazoles, oxa- and thiadiazoles, and tetrazole.

Table 1.3 shows six-membered rings, namely, pyridine, its benzo derivatives quinoline and isoquinoline, the pyrilium cation, and, as in Table 1.2, other common heterocycles with more than one heteroatom, such as diazines, triazines, and tetrazines.

Finally, Table 1.4 shows the simplest seven-membered ring, that is, azepine and its benzo derivative, as well as examples of the nitrogen bridgehead bicyclic systems, pyrrolizine, indolizines, and quinolizinium cation.

Other additional chapters have been included with special systems relevant from different points of view: 2-azetidinones or β-lactams, benzodiazepines, and two general chapters on new materials based on heterocyclic systems and solid phase and combinatorial chemistry related to heterocyclic derivatives.

Table 1.3 Main six-membered heterocycles.

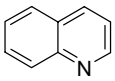
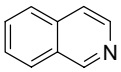
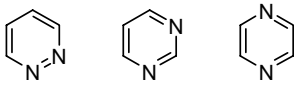
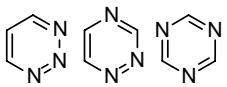
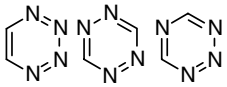
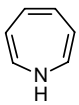
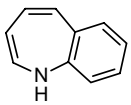
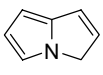
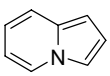
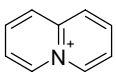
Ring size	N	Benzo	O
6	 Pyridine	 Quinoline  Isoquinoline	 Pyrilium
	 Diazines Pyridazine Pyrimidine Pyrazine		
	 Triazines		
	 Tetrazines		

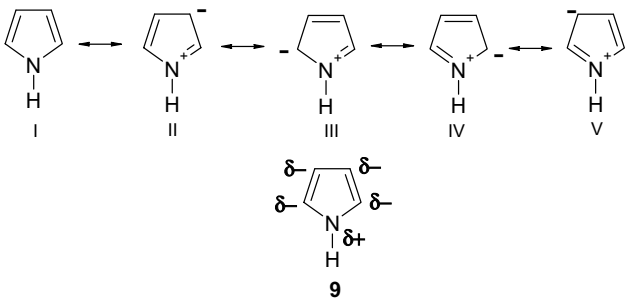
Table 1.4 Other simple heterocycles.

Ring size	Heteroatom	
	N	Benzo
7	 Azepine	 Benzoazepine
5-5, 5-6, 6-6	 Pyrroline  Indolizine  Quinolizinium	

1.2
Structure and Reactivity of Aromatic Five-Membered Systems

As is indicated in most handbooks of heterocyclic chemistry [3, 4], a pictorial valence bond resonance description is used in most chapters, as a simple way to rationalize the reactivity of the most important aromatic heterocycles. Two examples are described in detail as representative of most of the aromatic rings considered: pyrrole as a model of the π-excessive rings, and pyridine as a model of the π-deficient ones.

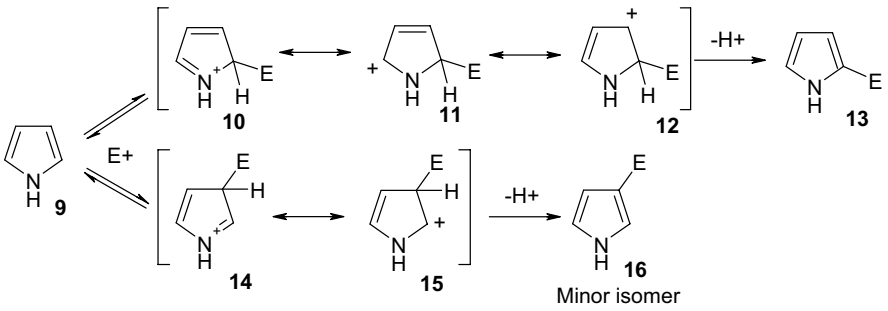
Pyrrole has a structure that is isoelectronic with the cyclopentadienyl anion, but is electrically neutral, having a nitrogen atom with a pair of electrons, which is part of the aromatic sextet, and its resonance hybrid can be represented as a combination of main forms I–V (Scheme 1.1), one without charge, and the others with charge separation. As expected, not all forms contribute equally to the structure of the pyrrole, with the order of importance being I > III, IV > II, V, that is, the major contribution is produced by the non-charged form, and, of the charged ones, those in which the nitrogen is using its lone pair of electrons. As a combination of all forms, structure **9** indicates how the heteroatom bears a partial positive charge, while the carbon positions show an increase in electronic density, compared with the typical aromatic system, benzene. Thus, a π-excessive system such as pyrrole would be easily attacked by electrophiles and not by nucleophiles.



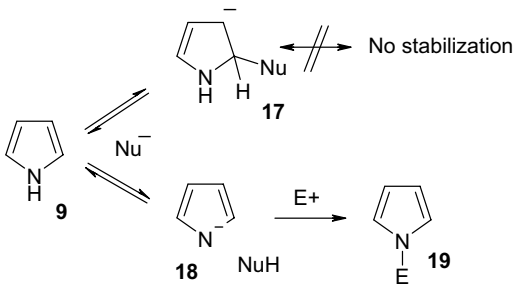
Scheme 1.1 Resonance hybrids of pyrrole.

Scheme 1.2 indicates how the attack of an electrophile usually proceeds. The major isomer **13** is formed through intermediates **10–11–12**, of which the intermediate **10** contributes most to the stabilization of the intermediate. Alternatively, a minor isomer **16** is produced through the less stable intermediates **14** and **15**.

Alternatively, Scheme 1.3 shows the attack of a nucleophile on pyrrole. Intermediate **17** is not stabilized, and the lone pair of electrons on the heteroatom does not contribute to the progress of the process. The only process that usually can be detected is deprotonation of the N–H bond to generate the pyrrolate (**18**), which can be used to make a bond with a suitable electrophile (i.e., an alkyl halide) to produce the N-substituted pyrrole **19**.



Scheme 1.2 Electrophilic attack on pyrrole.



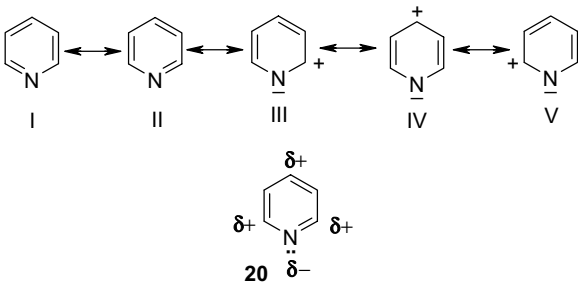
Scheme 1.3 Attack on pyrrole by nucleophiles.

This behavior can be extended with small differences to other π-excessive heterocycles, with the limit due to the existence or not of a N–H bond at position 1. In the case of rings like thiazole or isoxazole, the lack of the acidic bond makes the process **9–18–19** impossible. Attack by radicals or complex organometallic reagents are more complex and are discussed in every chapter.

1.3 Structure and Reactivity of Aromatic Six-Membered Systems

The structure of pyridine is analogous to that of benzene, with one of the carbons replaced by a nitrogen atom. This produces alterations in the geometry, which is no longer perfectly hexagonal, due to the shorter CN bonds; the existence of an unshared pair of electrons, not related with the aromatic sextet, gives the pyridine basic character, along with a permanent dipole in the ring, due to the electronegative character of the heteroatom compared with carbon.

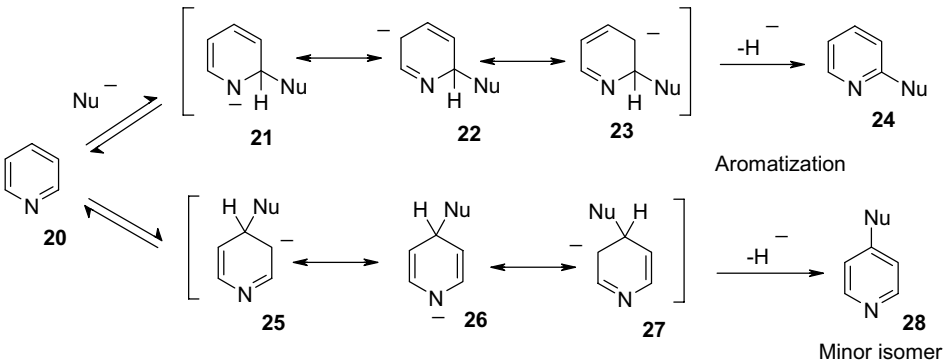
Scheme 1.4 indicates the main canonical forms (I–V) that contribute to the resonance hybrid of the structure of pyridine. Obviously, not all of them contribute equally – the two Kekulé forms I and II, which are not charged, are the more stable



Scheme 1.4 Resonance hybrids of pyridine.

forms, followed by those in which nitrogen is negatively charged. Other forms can be envisaged, but their contributions can be neglected. Thus, the combination of the main forms can be represented as structure **20**, in which the nitrogen bears a partial negative charge, and positions 2, 4, and 6 are electron deficient; usually, positions 2 and 6 are the most deficient due to the inductive effect produced by the heteroatom. Positions 3 and 5 can be considered neutral, comparable to benzene carbons. Thus, the more characteristic reactivity of the pyridine ring would be against nucleophiles, which would attack the more electron-deficient positions.

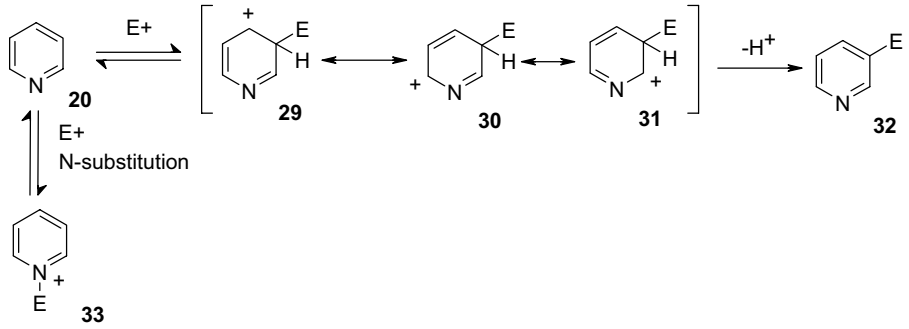
As expected from the structure of pyridine, Scheme 1.5 describes the attack of a nucleophile on the system. The main process goes through intermediates **21–22–23** to produce the major isomer **24**, substituted at position 2. Alternatively, attack can also occur at position 4, through intermediates **25–26–27**, yielding the minor isomer **28**.



Scheme 1.5 Nucleophilic attack on pyridine.

Scheme 1.6 describes an electrophilic attack on pyridine. The initial attack of the electrophile usually takes place on the pyridine nitrogen. When the attacking species can produce a stable bond, the product should be the pyridinium salt **33**, but when this product is not stable enough the process goes through intermediates **29–30–31**,

that is, by attacking the neutral carbons, to produce the 3-substituted derivative **32**. As a general view, the reactivity of pyridine can be taken as a model for other π-deficient systems, and can be easily extended to diazines, triazines, or pyrilium derivatives. Other processes, like radical attack or reaction with complex organometallic reagents are described in every chapter.



Scheme 1.6 Electrophilic attack on pyridine.

1.4
Basic Literature on Heterocyclic Compounds

To introduce the recent literature in heterocyclic chemistry, it is necessary to indicate, among the textbooks available [3–6], two of them: one [3] from Eicher and Hauptmann with a highly structured organization, which is simple and efficient and can be used as the basis of a heterocyclic course. The other [4], from Joule and Mills, combines the condensed format with extensive information about the basic heterocycles considered. As reference books, it is necessary to cite the collection *Comprehensive Heterocyclic Chemistry* from Katritzky and colleagues [7–9]; this is associated with the *Handbook of Heterocyclic Chemistry* [10], which is regularly updated with the *Comprehensive* edition. Heterocyclic series are also of great interest, becoming readable collections that allow an update of the literature in the field. *Progress in Heterocyclic Chemistry* [11] describes mostly the advances in every relevant field of heterocyclic chemistry in a yearly volume. The series of monographs *Advances in Heterocyclic Chemistry* [12], which consists of 101 volumes to date, covers in depth very different topics in the field.

Other recent monographs are of interest in various topics on the field, a good guide called *Name Reactions in Heterocyclic Chemistry* has been given by Li [13] and the monograph *Aromaticity in Heterocyclic Compounds* [14] is also a good basic help for heterocyclic chemists, as is the *Synthesis of Heterocycles via Multicomponent Reactions* [15]. Other recent monographs have centered on synthetic techniques such as palladium chemistry [16], chemistry of heterocyclic carbenes [17–19], or synthesis

with microwaves [20]. In addition, a recent monograph on general heterocyclic chemistry emphasizes the importance of heterocyclic compounds in the field of medicinal chemistry and natural products [21].

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2
Three-Membered Heterocycles. Structure and Reactivity

S. Shaun Murphree

2.1
Aziridines

The field of aziridine chemistry is brimming with activity and, as a consequence, it has been the subject of multiple recent reviews [1–5]. Of particular note are the efficient and engaging article by Sweeney [6], a brief overview of properties and chemistry [7] and a newer monograph with a more encyclopedic sweep [8]. The present work aims not to be comprehensive, but rather to provide a general landscape and to capture the spirit of best practices available to the synthetic chemist, with an emphasis on preparative utility.

2.1.1
Properties of Aziridines

The smallest and most functionally spartan of the nitrogen heterocycles, aziridine (**1**), is an isolable liquid at room temperature, but prone to polymerization and other thermal degradation pathways because of its inherent ring strain [9]. It is weakly basic, with a pK_a of 7.98 [7], and the basicity trends of variously substituted aziridines have been the subject of a recent theoretical study [10]. From the standpoint of molecular geometry, aziridine describes an almost equilateral triangle, with a C–N–C bond angle of 60.58° (Figure 2.1) [11]. The N-inversion energy is relatively high, at almost 17 kcal mol^{-1}; however, conjugating substituents decrease the barrier significantly [12]. The ^{1}H-NMR signals of the methylene protons are centered at 1.4 ppm, while the carbons resonate at about 27 ppm. Coupling constants range from 3.8 Hz for trans vicinal ^{1}H-^{1}H coupling, to 6.3 Hz for cis vicinal ^{1}H-^{1}H coupling, and 168.1 Hz for ^{1}H-^{13}C coupling [13].

Aziridine moieties are imbedded in structurally diverse natural products from various sources (Figure 2.2), and the reader is directed to Lowden's excellent recent treatise on this topic [14]. Isolated from *Streptomyces griseofuscus* [15, 16], azinomycin A (**2**) and azinomycin B (**3**, also known as carzinophilin) are among the most intensely studied members of this class [17–19]. As potent antitumor agents, their

Modern Heterocyclic Chemistry, First Edition.
Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.

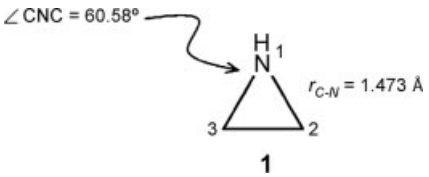

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Figure 2.1 Geometry of aziridine.

biological activity springs from an ability to form interstrand purine base crosslinks in duplex DNA [20–23]. Central to this behavior is the aziridine ring bound up in the 1-aza-bicyclo[3.1.0]hexane system, a structural feature also found in ficellomycin (**4**), an antibacterial isolated from *Streptomyces ficellus* [24]. A similar 3,6-diaza-bicyclo [3.1.0]hexane system is at the functional heart of mitomycin C (**5**), a notable representative of the mitosanes extracted from *Streptomyces verticillatus* [25] and the target of many synthetic studies [26]. For decades, mitomycin C has found place in the arsenal of clinically relevant antibiotic and anti-tumor drugs, and the mitomycins have inspired studies into many promising non-natural analogs [27].

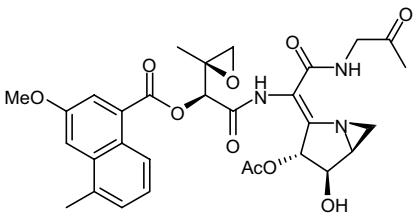
Also equipped with a 2,3-dialkylaziridine residue is the protease inhibitor mirazidine A (**6**), which is isolated from the marine sponge *Theonella* aff. *mirabilis* [28] and which exhibits a linear peptide structure vaguely similar to madurastatin A1 (**7**), a compound demonstrated in a culture of a pathogenic *Actinomadura madurae IFM 0745* strain, which shows activity against *Micrococcus luteus* [29]. An even more exposed aziridine ring is seen in the azicemicins A (**8**) and B (**9**), antibacterials isolated from *Amycolatopsis* sp. *Mj126-NF4* [30, 31]. These naturally occurring aziridine alkaloids have also inspired a genre of semi-synthetic and synthetic analogs of medicinal interest [32].

2.1.2
Synthesis of Aziridines

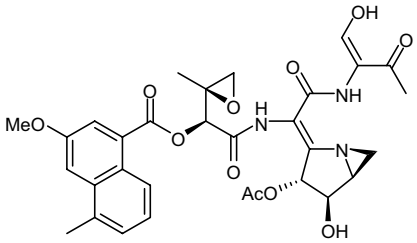
Generally speaking, there are three major synthetic routes to the aziridines (Scheme 2.1): (a) the addition of monovalent nitrogen species to alkenes; (b) the addition of divalent carbon centers to imines; and (c) the N-alkylative ring closure of amines equipped with β-leaving groups . A fourth route (pathway d) is less frequently encountered, but is nevertheless included here because of its potential synthetic utility. Enantioselective protocols in the first two categories have been the subject of a review [33], and aziridine synthesis as a whole has been more generally summarized by Sweeney [34].

2.1.2.1 **Aziridination of Alkenes**

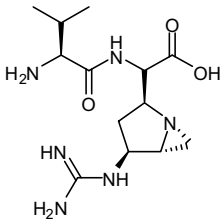
Analogous to epoxidation, in which olefins react with electrophilic oxygen reagents, the aziridination of alkenes involves the addition of nitrenes (or nitrenoids) to a β-bond. Common nitrene precursors include [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane (PhI=NTs), *N*-chloro-*p*-toluenesulfonamide sodium salt (Chloramine-T), and



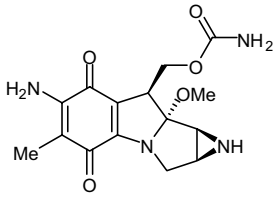
2, Azinomycin A



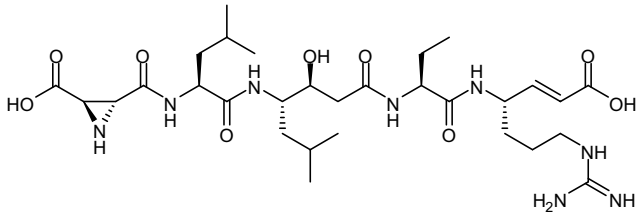
3, Azinomycin B



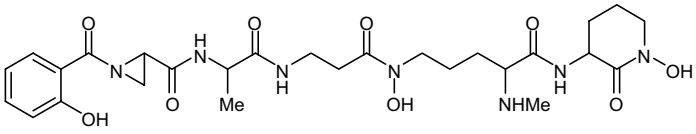
4, Ficellomycin



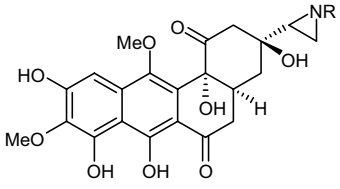
5, Mitomycin C



6, Miraziridine A

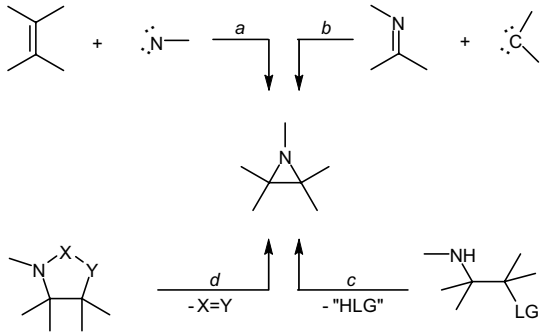


7, Madurastatin A1



8, Aicemicin A, R=H
9, Aicemicin B, R=Me

Figure 2.2 Some naturally occurring aziridines.



Scheme 2.1 General synthetic routes to aziridines.

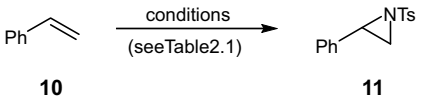
its N-bromo analogue (Bromamine-T), although use of the more esoteric *N*-iodo-*N*-potassio-*p*-toluenesulfonamide (TsN·KI) has also been reported [35]. These precursors can be activated using various transition-metal catalysts (Figure 2.3).

Also mirroring epoxidation methodology, a common model reaction is the aziridination of styrene (Scheme 2.2). Some illustrative examples are summarized in Table 2.1. For example, the copper(I) complex of a fluorinated tris(pyrazolyl)borate (or homoscorpionate) ligand forms an adduct with ethylene (**12a**), which catalyzes the aziridination of styrene with great efficiency using PhI=NTs as a nitrene precursor [36]. The more readily available Chloramine-T can be used effectively in the presence of methyl homoscorpionate complex **12b**, even with equimolar charges of olefin and nitrene precursor [37]. This catalyst motif has been incorporated into a heterogeneous system [38]. Other interesting copper(I) catalysts include those derived from pyridyl-1,5-diazacyclooctanes (e.g., **13**) [39] and bispidones (e.g., **14**) [40]. A particularly intriguing protocol using copper(I)iodide under aqueous phase-transfer conditions (entry 5) has also been reported [41].

Examples of copper(II) catalysts include the 1,4,7-triazacyclononane complex **15**, which requires a rather large excess of olefin [42], copper(II) acetylacetonate immobilized in ionic liquids (entry 7), which can be recycled many times without loss of activity [43], and Cu^{2+} exchanged zeolite Y (CuHY) in acetonitrile (entry 8), which allows for respectable conversion using almost equimolar alkene : nitrene ratios [44]. Other transition metals can be used to advantage, as well. For example, the fluorinated iron(III) porphyrin catalyst **16a** [45], although certainly dearer to synthesize, exhibits marked advantages over its older manganese-based cousin **16b** [46]; and even iron(II) triflate is effective in promoting high-yielding aziridination reactions [47] (Table 2.1, entry 11).

In the realm of precious metals, a novel and structurally interesting disilver(I) complex (**17**) has been shown to function as a competent catalyst in aziridination, a process that may involve high-valent silver intermediates [48]. Some polymer-supported ruthenium porphyrin catalysts have been employed for this transformation; however, conversions tend to be low [51, 52].

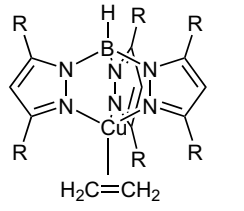
The use of a metal catalyst can be circumvented in some cases. In one particularly convenient example, a nitrene precursor is generated *in situ* from *p*-toluenesulfo-



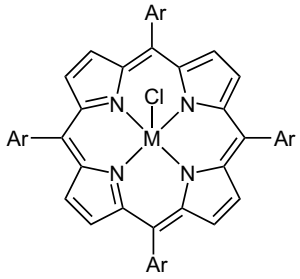
10 **11**

Scheme 2.2 Aziridination of styrene.

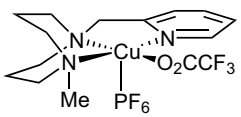
namide using iodobenzene diacetate. The aziridination is facilitated by substoichiometric quantities of iodine [49] (Table 2.1, entry 13). A conceptually related protocol is carried out using t-butylhypoiodite, prepared *in situ* from t-butylhypochlorite and sodium iodide [50] (Table 2.1, entry 14).



12a, R = CF_3
12b, R = Me



16a, Ar = C_6F_5; M = Fe^{III}
16b, Ar = C_6H_5; M = Mn^{III}



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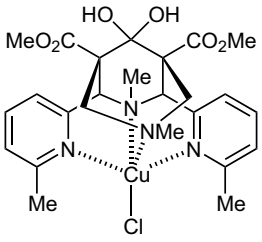

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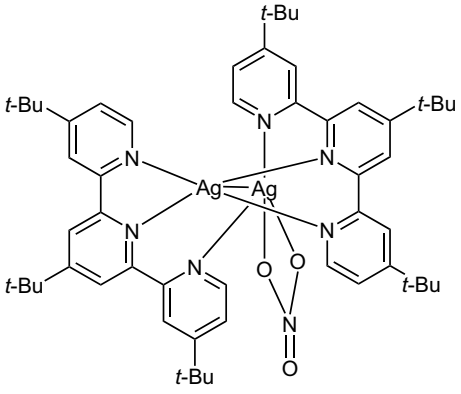

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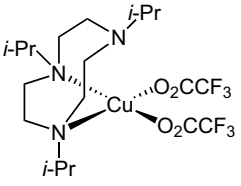

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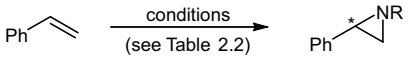
Figure 2.3 Representative catalysts for racemic aziridination.

Table 2.1 Reaction conditions for styrene aziridination.

Entry	Catalyst (mol.%)[a]	Nitrene source	Styrene : nitrene	Solvent	Time (h)	Yield (%)[a]	Reference
Copper(I) catalysts							
1	**12a** (5)	PhI=NTs	1 : 1.5	CH_3CN	16	99	[32]
2	**12b** (5)	Chloramine-T	1 : 1	CH_3CN	n.r.	84	[33]
3	**13** (5)	PhI=NTs	3.8 : 1	CH_3CN	1.5	99	[34]
4	**14** (3.5)	PhI=NTs	2 : 1	CH_3CN	7	80	[35]
5	CuI(10)	Chloramine-T	2 : 1	H_2O[b]	3	91	[36]
Copper(II) catalysts							
6	**15** (5)	PhI=NTs	20 : 1	CH_3CN	16	96	[37]
7	$Cu(acac)_2$ (8)[c]	PhI=NTs	5 : 1	CH_3CN	1	95	[38]
8	CuHY	PhI=NTs	1 : 1.5	CH_3CN	3	86	[39]
Other metal catalysts							
9	**16a** (5)	Bromamine-T	5 : 1	CH_3CN	12	80	[40]
10	**16b** (5)	PhI=NTs	100 : 1	CH_2Cl_2	n.r.	80	[41]
11	$Fe(OTf)_2$ (5)	PhI=NTs	7 : 1	CH_3CN	3	82	[47]
12	**17** (2)	PhI=NTs	5 : 1	CH_3CN	6	91	[42]
No metal catalyst							
13	none	$TsNH_2$/$PhI(OAc)_2$/I_2/*t*-BuOK	1 : 3	DCE	2	88	[49]
14	none	$TsNH_2$/*t*-BuOCl/NaI	2 : 1	CH_3CN	5	95	[50]

a) Based on nitrene source.
b) Bu_4NBr used as PTC.
c) Immobilized in $bmimBF_4$.

Progress continues to be made in the asymmetric aziridination of olefins using the same general approach (Scheme 2.3), but with chiral catalyst systems (Table 2.2). For example, impressive enantioselectivity has been reported for copper-exchanged zeolite Y (CuHY) modified with the chiral bis(oxazoline) **18a** (Figure 2.4) using [*N*-(*p*-nitrosulfonyl)imino]phenyliodinane (PhI=NNs) as the nitrene precursor [53]. Inferior results are obtained when [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane (PhI=NTs) is used [54]. A one-pot homogeneous variant using bis(oxazoline) **18b** and commercially available iodobenzene diacetate has also been reported [55]. Evidence suggests that the ultimate stereochemical outcome may be affected by a secondary reaction between the aziridines formed and other components in the reaction mixture [56].



10 **11**

Scheme 2.3 Asymmetric aziridination of styrene.

Table 2.2 Reaction conditions for asymmetric styrene aziridination.

Entry	Catalyst (mol.%)[a)]	Nitrene source	Styrene : nitrene	Solvent	Time (h)	Yield (%)[a)]	ee (%)	Reference
1	CuHY + **18** (7%)	PhI=NNs	1 : 1.3	CH_3CN	16	82	91	[45]
2	**19** (5)	PhI=NTs	1 : 5	CH_2Cl_2	n.r.	76	94	[49]
3	**20**(0.1)	TsN_3	1 : 1	CH_2Cl_2	24	78	85	[51]

a) based on nitrene source.

Another major avenue for enantioselective aziridination is offered through the use of (salen)manganese(III) complexes, such as the Katsuki catalyst (**19**) [57]. Evidence from the Jacobsen group suggests that the high enantiofacial selectivity observed for aryl alkenes may derive from well-defined bidentate aromatic interactions between substrate and catalyst [58]. Analogous ruthenium-based catalysts (e.g., **20**) allow for the use of tosyl azide as a nitrene precursor and are effective even at extremely low catalyst loadings [59]. Metalloporphyrin catalysts continue to show some promise for asymmetric aziridination, although enantioselectivities remain modest [60].

Some very convenient methodology has developed around bromine-catalyzed aziridination reactions using Chloramine-T as the source of electrophilic nitrogen

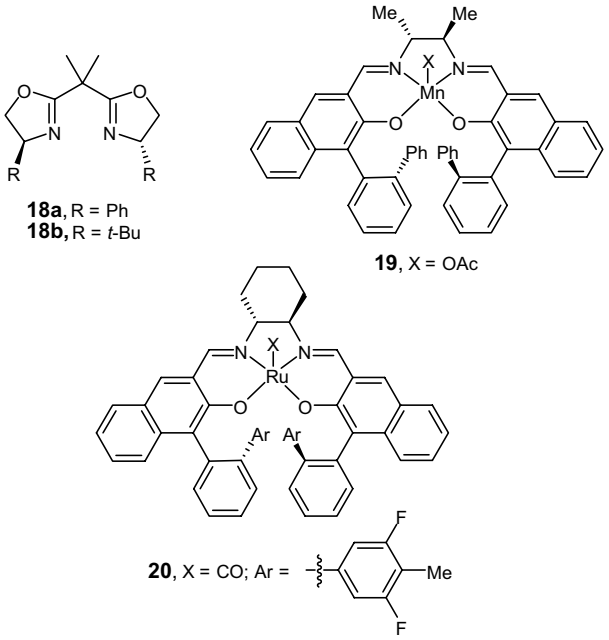
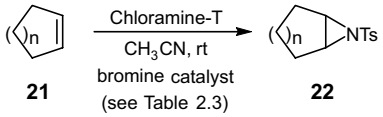


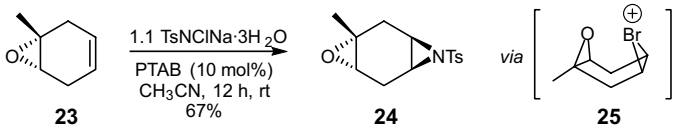
Figure 2.4 Chiral catalysts for asymmetric alkene aziridination.



Scheme 2.4 Bromine-catalyzed aziridination.

(Scheme 2.4). For example, when cyclohexene is treated with Chloramine-T trihydrate in the presence of substoichiometric quantities of hydrogen peroxide and hydrobromic acid, the corresponding bicyclic aziridine is produced in good yield (Table 2.3, entry 1). The process involves the *in situ* generation of hypobromous acid, which in turn gives rise to bromonium intermediates [61]. *N*-Bromosuccinimide is also a competent catalyst in this regard (entry 2) [62]. Both of these protocols might be seen as modifications to an earlier report by Sharpless [63], which describes the use of phenyltrimethylammonium bromide (PTAB) as both bromine source and phase-transfer catalyst (entry 3).

The Sharpless protocol is in some ways complementary to prior art. For example, methylcyclohexadiene oxide (**23**) can be aziridinated in good yield using Chloramine-T trihydrate and catalytic amounts of PTAB (Scheme 2.5), a conversion that failed using PhI=NTs and $Cu(acac)_2$. Interestingly, only the trans aziridino epoxide (i.e., **24**) is observed, presumably due to preferential formation of the *cis*-epoxy bromonium intermediate **25**, which has been calculated to lie about 2.4 kcal mol^{-1} lower in energy than the corresponding *trans* isomer [64].

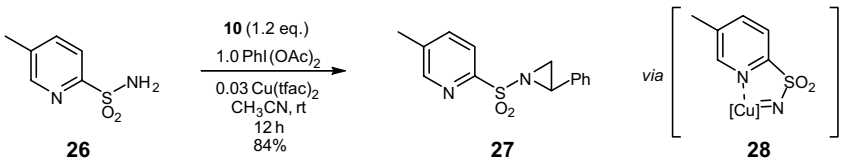


Scheme 2.5 Aziridination of epoxyalkenes.

Some progress has been made in using sulfonamides as starting materials for aziridination. Thus, the pyridinesulfonamide **26** is converted into a nitrene precursor (i.e., **28**) *in situ* using commercially available iodosobenzene diacetate as an oxidant, providing aziridine **27** in very good yield (Scheme 2.6). Another notable aspect of this

Table 2.3 Reaction conditions for bromine-catalyzed aziridination.

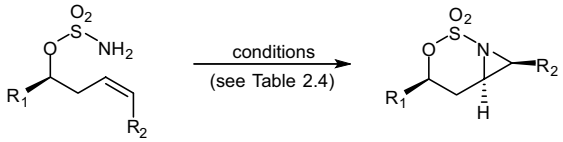
Entry	*n*	Catalyst (loading mol.%)	Chloramine-T type	Olefin : nitrene	Time (h)	Product	Yield (%)	Reference
1	2	H_2O_2/HBr (20)	trihydrate	1 : 1.3	5	**22b**	75	[53]
2	2	NBS (20)	anhydrous	1 : 1.0	3	**22b**	82	[54]
3	1	PTAB (30)	anhydrous	1 : 1.1	12	**22a**	86	[55]



Scheme 2.6 Chelating sulfonamides.

system is that it obviates the need for external ligands and bases, since the pyridyl nitrogen provides intermolecular chelation. The free aziridine can be accessed by deprotection using magnesium in methanol [65]. A copper-catalyzed aziridination of tosylamides using iodine has also been reported [66].

DuBois and Guthikonda [67] have developed a similar rhodium-based strategy for the aziridination of sulfonamides, which they have applied to various unfunctionalized alkenes. With ω-butenyl sulfonamide **29a,** an intramolecular process can ensue to provide the bicyclic aziridine in good yield (Scheme 2.7). These and other investigations have shown the process to be stereospecific (Table 2.4, entry 2), whereby alkene geometry is preserved in the product [68]. Moreover, existing chiral centers can impose diastereoselectivity, as shown by the intramolecular aziridination of alkenyl sulfonamide **29c,** which proceeds with a 10 : 1 syn : anti ratio [69].



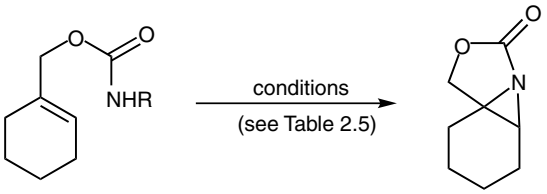
29a, $R_1 = R_2 = H$
29b, $R_1 = H$; $R_2 = Et$
29c, $R_1 = Me$; $R_2 = octyl$

Scheme 2.7 Intramolecular aziridinations.

The Padwa group has reported that the analogous intramolecular aziridination of cycloalkenyl carbamates proceeds without the need of a metal catalyst (Scheme 2.8). Thus, cyclohexenyl carbamate **31a** underwent clean conversion into the tricyclic heterocycle **32a** upon treatment with 2 equivalents of iodosobenzene [70] (Table 2.5,

Table 2.4 Reaction conditions for intramolecular aziridinations.

Entry	Substrate	Catalyst (loading mol.%)	Oxidant	Solvent	Yield (%)	Reference
1	**29a**	$Rh_2(tfacam)_4$ (1)	$PhI(OAc)_2$	Benzene	84	[59]
2	**29b**	$Cu(CH_3CN)_4PF_6$ (10)	PhI=O	CH_3CN	80	[60]
3	**29c**	$Rh_2(Ooct)_4$ (2)	$PhI(OAc)_2$	CH_2Cl_2	84	[61]



31a, R = H
31b, R = Ts

32

Scheme 2.8 Intramolecular aziridination of carbamates.

Table 2.5 Reaction conditions for the intramolecular aziridination of carbamates.

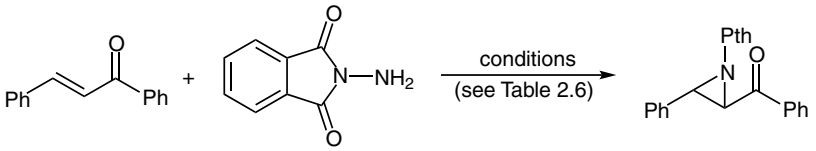
Entry	Substrate	Conditions	Yield (%)	Reference
1	**31a**	PhIO (2.0 eq), CH_2Cl_2, 40°C	75	[71]
2	**31b**	K_2CO_3 (7 eq), $Rh_2(OAc)_4$ (5 mol %), acetone, 25°C	79	[72]

entry 1). A similar rhodium-catalyzed variant has been reported for N-tosyloxycarbamates [71] (Table 2.5, entry 2).

Electron-deficient olefins often require different conditions for efficient aziridination than their unactivated counterparts. Along these lines, while certainly not limited to electron-poor alkenes, N-aminophthalimide (**34**) acts as a versatile nitrogen donor for aziridinations under various oxidizing conditions. The classical protocol involves the mild but environmentally questionable reagent lead tetraacetate [72], under which conditions the active aziridinating agent is believed to be an N-acetoxy species rather than a nitrene [73]. Meanwhile, other innovative methodologies have evolved. For example, using the conventional oxidant of iodosylbenzene diacetate (Table 2.6, entry 1), chalcone (**33**) is aziridinated in excellent yield (Scheme 2.9) [74].

Table 2.6 Reaction conditions for phthalimide aziridinations.

Entry	Eq 34	Oxidant (loading where appropriate)	Additive	Solvent	Time (h)	Yield (%)	Reference
1	1.4	$PhI(OAc)_2$ (1.5 eq)	K_2CO_3	CH_2Cl_2	12	93	[65]
2	1.4	*p*-MeOPhI/mCPBA (1.4 eq)	K_2CO_3	CH_2Cl_2	12	94	[66]
3	1.3	+1.80 V (vs. Ag wire)	Et_3NHOAc	CH_3CN	4	83	[67]



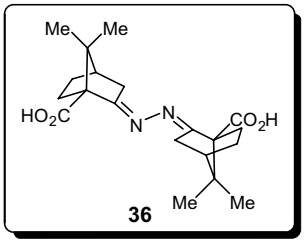
Scheme 2.9 N-Aminophthalimide as nitrogen donor.

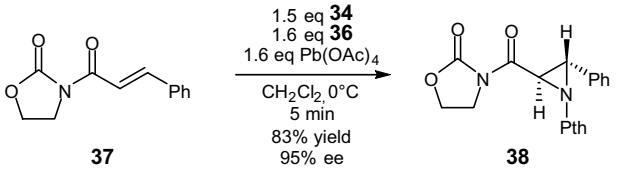
These conditions have also been used to advantage for the aziridination of allylic alcohols [75].

The hypervalent iodine reagent can also be generated *in situ* by combining equimolar amounts of *p*-iodoanisole and *m*-chloroperbenzoic acid (entry 2) with no negative impact on yield [76]. An even more atom-economical approach can be realized using electrochemical conditions (entry 3), a stereospecific process that has been described as a *click* preparation of aziridines [77], and which may proceed via a nitrene intermediate [78–80]. A similarly efficient oxidation has been reported using superoxide ion [81].

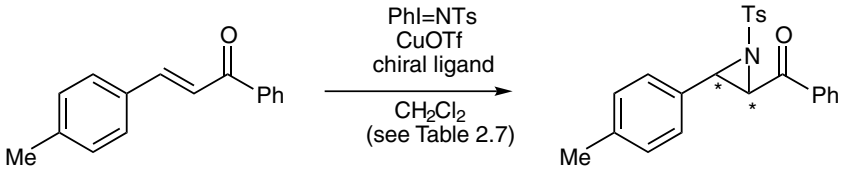
Addition of the chiral camphor-derived ligand **36** (Scheme 2.10) can result in an enantioselective process. Thus, the unsaturated oxazolidinone imide **37** is converted into the corresponding aziridine (**38**) in good yield and impressive enantiomeric excess. By comparison, (+)-tartaric acid gave only 42% ee. The choice of solvent is important, as migration to THF results in no loss of yield but an almost total disappearance of enantioselectivity [82].

Chiral bis(oxazoline) (BOX) ligands allow for a tunable aziridination of chalcones (Scheme 2.11) merely by changing the connecting backbone moiety (Figure 2.5). Thus, use of the cyclohexyl catalyst **41** provides the 2*R*,3*S* product (Table 2.7, entry 1) with very good enantioselectivity [83], while the anthracene derivative **42** yields the

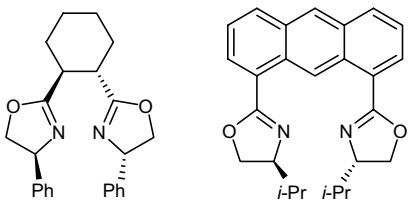




Scheme 2.10 Asymmetric N-aminophthalimide-mediated aziridination.



Scheme 2.11 Tunable BOX-mediated asymmetric aziridination.



41, *S*-cHBOX **42**, AnBOX

Figure 2.5 cHBOX and AnBOX ligands.

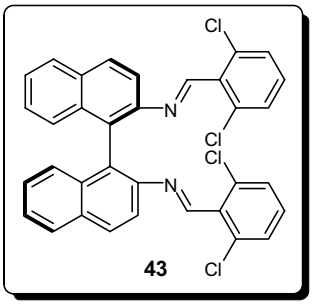
other antipode with even better yield and enantioselectivity (entry 2). The origin of this interesting crossover has been rationalized on the basis of a more crowded steric environment in the latter case [84]. The scope of the organocatalytic asymmetric aziridination of enones has been expanded to substrates other than chalcones by using a hydroquinine-derived catalyst and N-protected hydroxylamine tosylates as nitrogen donors [85].

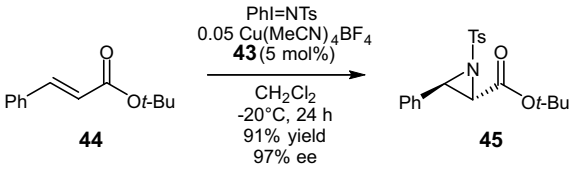
Cinnamate esters can be aziridinated using axially dissymmetric binaphthyldiimine copper(I) catalysts, such as those derived from salen-type ligand **43** (Scheme 2.12). Thus, *trans-t*-butyl cinnamate (**44**) was aziridinated stereospecifically and enantioselectively to provide the product in excellent yield [86]. A later report from another set of investigators using essentially identical conditions gave the same high enantioselectivity but significantly lower yield [87].

Table 2.7 Reaction conditions for tunable BOX-mediated asymmetric aziridination.

Entry	PhI=NTs (eq)[a]	CuOTf (eq)[a]	Ligand (loading mol.%)[a]	Time (h)	Yield (%)[b]	Configuration	ee (%)	Reference
1	0.67	0.03	**41** (4)	5	62	2*R*,3*S*	94	[71]
2	0.67	0.03	**42** (4)	5	86	2*S*,3*R*	98	[72]

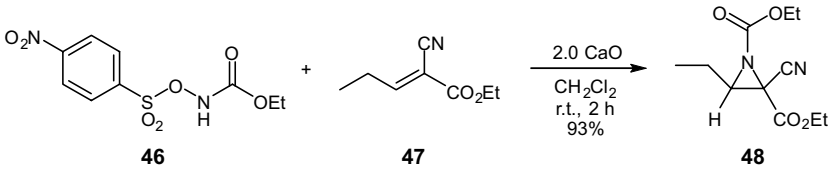
a) Based on olefin.
b) Based on PhI=NTs.





Scheme 2.12 Asymmetric aziridination of cinnamate esters.

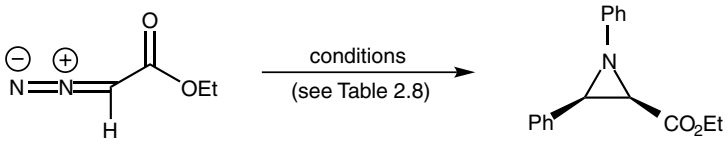
Diactivated alkenes can be converted into aziridines by a somewhat different set of conditions. For example, in the presence of calcium oxide, ethyl nosyloxycarbamate (**46**) functions as a nitrogen source that engages Knoevenagel adducts (e.g., **47**) in aziridination (Scheme 2.13), presumably via nitrene intermediates [88]. Modest diastereoselectivities have been achieved by incorporating a menthol-derived chiral auxiliary into the carbamate reagent. Unfunctionalized alkenes give the products of nitrene C−H insertions under the same conditions [89].



Scheme 2.13 Aziridination of diactivated alkenes.

2.1.2.2 **Aziridination of Imines**

Another powerful approach to the aziridine moiety is through the aziridination of imines using carbene- or ylide-type species [90–92]. One very popular carbene precursor is the commercially available ethyl diazoacetate (**49**). This species can be induced to react with imines to form aziridines (Scheme 2.14) under various conditions, including indium trichloride in methylene chloride [93], lanthanide triflates in protic media [94], boron trifluoride in ether [95], a cyclopentadienyl iron(II) dicarbonyl complex [96], a bis(cyclooctadienyl) iridium(II) chloride complex [97] and



49 **50**

Scheme 2.14 Racemic aziridination using ethyl diazoacetate.

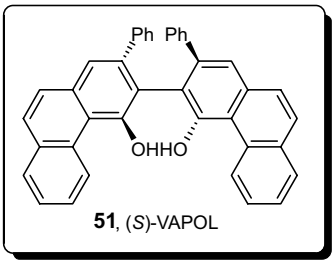
Table 2.8 Reaction conditions for racemic aziridinations with ethyl diazoacetate.

Entry	Aldimine components	Catalyst (loading mol.%)	Solvent	Time (h)	Yield (%)	Reference
1	PhCH=NPh	$SnCl_4$ (1)	CH_2Cl_2	n.r.	>90	[84]
2	PhCH=NPh	None	$bmimPF_6$	5	93	[85]
3	PhCH=O + $PhNH_2$	$LiClO_4$ (10)	CH_3CN	4.5	89	[86]

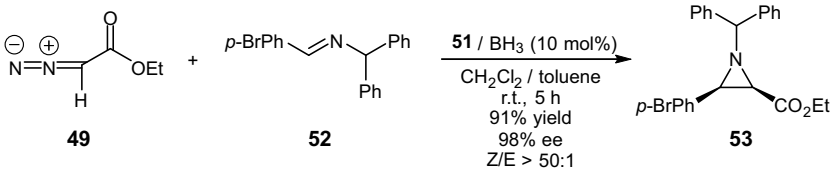
copper(II) triflate in methylene chloride or tetrahydrofuran [98]. These reactions are often very high-yielding, as demonstrated by the tin(IV) chloride mediated reaction of ethyl diazoacetate with *N*-phenylbenzaldimine (Table 2.8, entry 1), which proceeds with a *Z* : *E* selectivity of 15 : 1 [99]. Interestingly, when the same reaction is run using an ionic liquid as solvent (entry 2), the reaction does not require the addition of a catalyst. In this case, the solvent itself is presumed to fulfill the role of Lewis acid [100]. An operationally attractive procedure has been reported in which the aldimine is formed *in situ* using lithium perchlorate as a catalyst (entry 3), providing exclusively the *cis* isomer [101].

Acive methylene compounds serve as useful carbenoid precursors (in the form of phenyliodonium ylides) by treatment with iodobenzene diacetate and a catalytic amount of base under very mild conditions. Thus, tosylaldimines are converted into the corresponding aziridines in a one-pot procedure without the need for a metal catalyst [102].

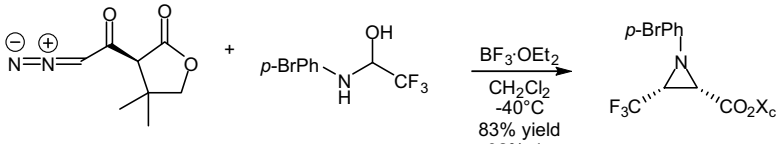
Some noteworthy asymmetric protocols have been developed using diazoesters, particularly those employing vaulted biaryl ligands [103]. For example, a catalyst derived from *(S)*-VAPOL (**51**) and BH_3·THF complex promotes an enantioselective aziridination reaction between ethyl diazoacetate and *N*-diphenylmethyl *p*-bromobenzaldimine (**52**) with very good yields, almost exclusive *cis* selectivity and excellent enantiomeric excess (Scheme 2.15). Curiously, impure commercial samples of BH_3·THF give the best results [104]. Recent crystallographic evidence in an analogous system suggests an unexpected boroxinate species as the active catalyst, the formation of which should be facilitated by adventitious water in the commercial boron reagent [105].



51, (*S*)-VAPOL



49 **52** **53**

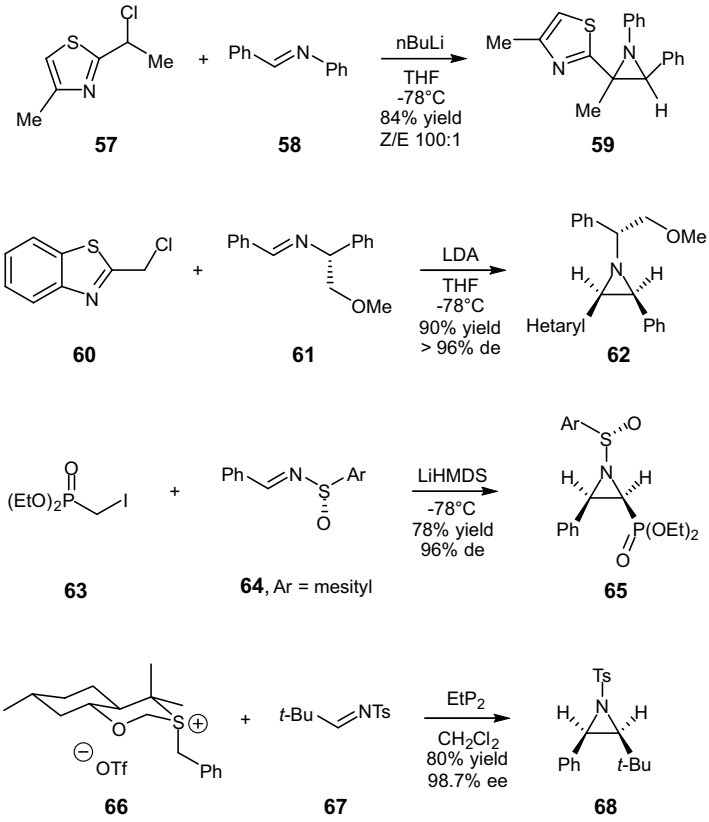


54 **55** **56**

Scheme 2.15 Chiral aziridination using diazoesters.

An alternative approach to asymmetric induction is to attach a chiral auxiliary to the diazoester itself, as exemplified by the *(R)*-pantolactone derived ester **54**. Using boron trifluoride as a Lewis acid catalyst, the trifluoromethyl hemiaminal **55** is converted into the corresponding imine and subsequently aziridinated to give products (i.e., **56**) in high yield and diastereomeric excess [106].

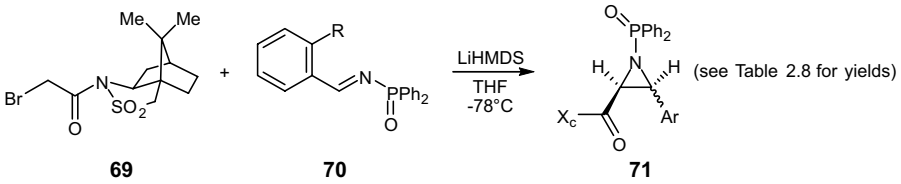
Other carbon donors for the aziridination of aldimines can be drawn from the ranks of ylide haloanions. For example, the chloroethylthiazole derivative **57** (Scheme 2.16) can be deprotonated with *n*-butyllithium to give an anion that reacts with *N*-phenylbenzaldimine (**58**) to provide the corresponding *cis*-aziridinyl thiazole **59** in good yield [107]. In an asymmetric variant of this protocol, the anion derived from chloromethyl benzothiazole **60** adds to the chiral aldimine **61** in a highly diastereoselective fashion [108]. In the same vein, Davis has reported the aza-Darzens reaction between the lithium anion of diethyl iodomethylphosphonate (**63**) and chiral non-racemic arylsulfinyl imines (e.g., **64**), which proceeds in good yield and excellent diastereomeric excess [109, 110]. An analogous reaction occurs between *t*-butylsulfinyl imines and the ylide derived from trimethylsulfonium iodide [111] or ylides derived from substituted allyltetrahydrothiophenium salts, which provide access to chiral non-racemic vinyl aziridines [112].



Scheme 2.16 The ylide/haloanion approach to aziridines.

The chiral sulfur ylide approach has been developed less for aziridine chemistry than for epoxides; nevertheless, some very useful strategies have been pioneered, largely by Dai and Aggarwal [113, 114], and new methodologies continue to appear on the scene. For example, the chiral *S*-benzyl sulfonium triflate **66** can be deprotonated with the commercially available phosphazene base Et_2P to give an ylide that aziridinates *N*-tosyl pivaldimine (**67**) in good yield and excellent enantioselectivity [115]. Aggarwal and Vasse have applied a catalytic version of the sulfur ylide methodology to the synthesis of the taxol side chain [116] which uses a novel camphor-derived ylide scaffold [117]. The *cis* : *trans* ratios in these reactions are very substrate-dependent. A recent computational study of this reaction manifold provides a useful theoretical framework in good agreement with observed experimental results [118]. The catalytic strategy has also been adapted to novel arsonium ylides [119].

The substrate dependent nature of *cis* : *trans* ratios is not limited to sulfur ylide chemistry. A particularly striking example is seen in the reaction of the anion from camphorsultam bromoacetamide **69** with various *o*-substituted benzaldimines **70** (Scheme 2.17). Both the phenyl and the nitrophenyl derivatives give exclusively *cis*-



69 **70** **71**

Scheme 2.17 Camphorsultam as chiral auxiliary in aziridination.

Table 2.9 Yield data for camphorsultam-mediated aziridination.

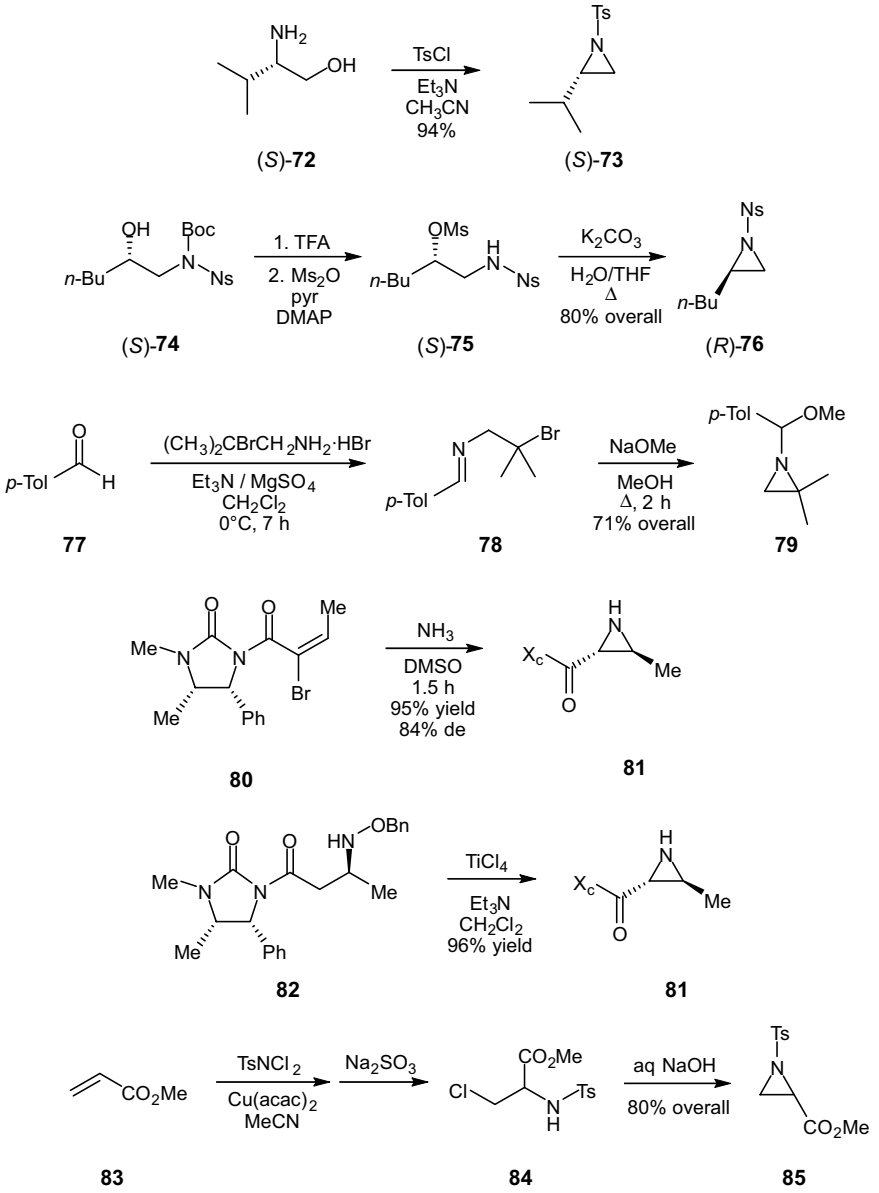
Entry	*R*	Yield (%)	Cis : trans ratio
1	−H	71	100 : 0
2	$-NO_2$	72	100 : 0
3	−Me	87	50 : 50
4	−OMe	65	0 : 100

aziridines (Table 2.9, entries 1 & 2), whereas the *o*-anisole imine provides solely the *trans* isomer (entry 4), and the *o*-tolyl analog yields an equimolar mixture of diastereomers (entry 3). The mechanistic underpinnings for this selectivity are not well understood, but are believed to derive from a complex mixture of polar, steric and chelation effects [120, 121].

2.1.2.3 **Ring Closure of Amines**

The synthesis of aziridines via the ring closure of 2-aminoalcohols has been known for three-quarters of a century [122], and the method has been adapted for such activating agents as triphenylphosphine dibromide [123], diphosphorus tetraiodide [124], the Mitsunobu reagent [125] and molecular sieves [126, 127]. This time-honored approach is, however, still in currency. For example, the chiral nonracemic aminoalcohol **72** (Scheme 2.18) derived from alanine [128] undergoes double tosylation and ring closure in one pot to provide the corresponding *N*-tosylaziridine (**73**) in excellent yield [129]. Similarly, the *N*-(*t*-butoxycarbonyl)-*N*-(2-nitrobenzenesulfonyl) aminoalcohol **74**, derived from the ring-opening of an epoxide, undergoes a sequence of deprotection, *O*-mesylation and carbonate-mediated ring closure to give aziridine **76**, proceeding with inversion of configuration and no loss in optical activity [130].

This concept of ring closure is, of course, open to any good leaving group. For example, an interesting protocol has been reported in which an *N*-2-bromoalkylimine (e.g., **78**), prepared by the addition of the 2-bromoalkylamine hydrobromide to an aldehyde (e.g., **77**), suffers nucleophilic attack by methoxide to give an incipient imide anion that engages in immediate 3-*exo*-*tet* ring closure [131]. Cyclization of a 2-bromoalkylamine is also at the heart of an aziridination of simple amines, such as ammonia, which engages in a tandem series of conjugate addition and ring closure



Scheme 2.18 Aziridines from ring-closing protocols.

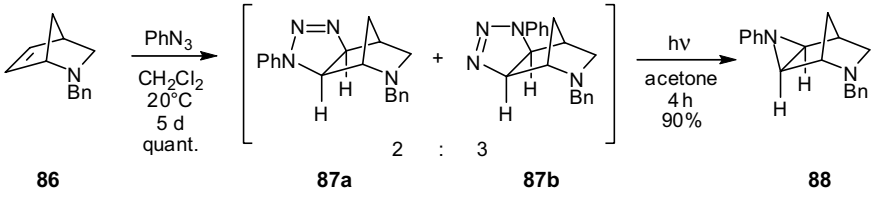
reactions with the chiral α-bromoamide **80** to provide aziridine **81** with good diastereoselectivity [132]. This methodology has also been adapted to a solid-phase protocol using Wang resin derivatives [133].

The same chiral auxiliary can be used to advantage in the synthesis of chiral β-amino acid precursors (e.g., **82**), which can be converted into the corresponding

amino acids by zinc-copper reduction of the N−O bond and lithium peroxide hydrolysis of the amide linkage [134]. However, in the presence of a suitable Lewis acid, **82** is converted into aziridine **81** with remarkable efficiency [135]. Aziridinyl esters (e.g., **85**) are conveniently prepared from methyl acrylate (**83**) or its derivatives by the copper-catalyzed addition of *N,N*-dichlorotosyl sulfonamide and subsequent ring closure [136]. Alternatively, these products can be accessed by treating α,β-dibromoesters with simple primary amines [137].

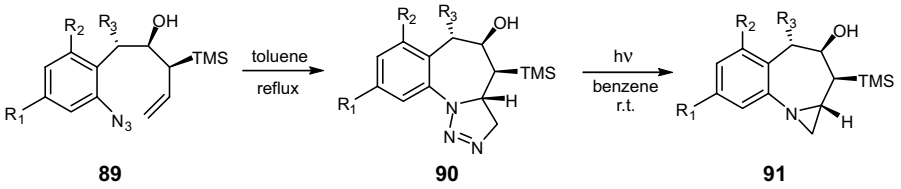
2.1.2.4 Ring Contraction of Other Heterocycles

Aziridines can be accessed through the extrusion of elements from larger nitrogenous heterocycles, most notably triazolines. Thus, for example, azanorbornene **86** undergoes 1,3-dipolar cycloaddition with phenyl azide to yield a 2 : 3 mixture of regioisomeric tricyclic triazolines in quantitative combined yield (Scheme 2.19). Photolysis of these compounds in a quartz reaction vessel using a medium-pressure mercury lamp led to efficient formation of the fused tricyclic aziridine **88** [138].



Scheme 2.19 Azide addition and ring contraction.

The rather sluggish initial cycloaddition is accelerated significantly by tethering the dipole to the dipolarophile, as seen with the ω-alkenylaryl azide **89a** (Scheme 2.20), which undergoes complete cycloaddition within 3 h in refluxing toluene [139]. Even with very highly functionalized substrates (Table 2.10), the cycloaddition step proceeds with excellent yield and complete diastereoselectivity, the latter presumably the result of a preferred chair-like reactive conformer in which the TMS group adopts a pseudo-equatorial attitude [140]. Subsequent irradiation with a Hanovia lamp afforded the corresponding aziridines **91** in fair yield.

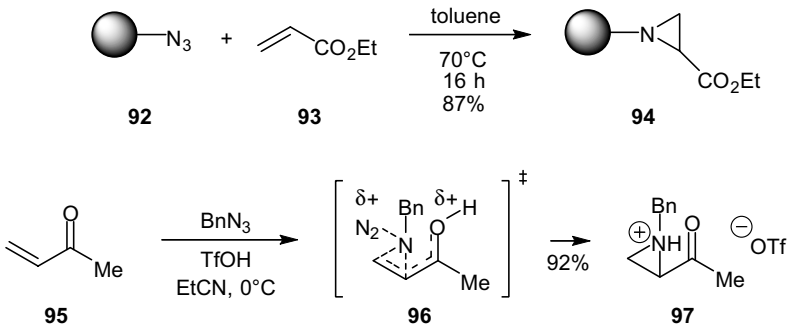


Scheme 2.20 Intramolecular azide addition and ring contraction.

Table 2.10 Yield data for intramolecular azide addition and ring contraction.

Entry	Substrate	R_1	R_2	R_3	Yield **90** (%)	Yield **91** (%)	Reference
1	**89a**	−H	−H	−H	90	77	[118]
2	**89b**	$-CH_2OBn$	−OBn	$-CH_2OBn$	99	68	[119]

Molteni and Del Buttero [141] have reported the direct aziridination of ethyl acrylate (**93**, Scheme 2.21) using an alkyl azide supported on poly(ethylene glycol) monomethyl ether (**92**), which they suggest proceeds through the intermediacy of a triazole. In their studies of triflic acid mediated aziridination of electron-deficient alkenes, however, Johnston and coworkers [142] propose an intriguing concerted mechanism involving a multicentered transition state (i.e., **96**).



Scheme 2.21 Direct aziridination with alkyl azides.

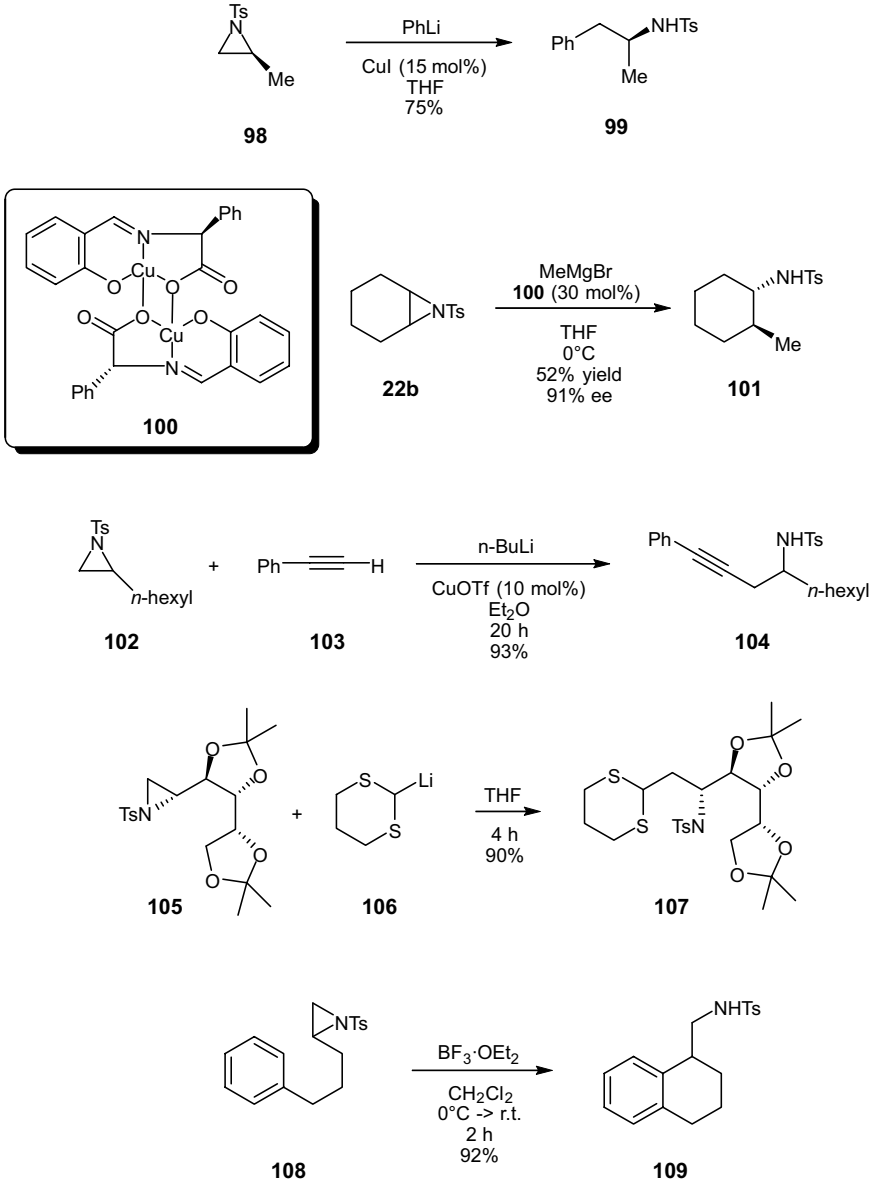
2.1.3
Reactivity of Aziridines

The reactions of aziridines are legion, but most fit into a few broad categories: (i) nucleophilic ring opening, (ii) N-substitution, (iii) aziridinyl anion chemistry and (iv) ring expansion to larger heterocyclic species . Although no longer the most recent, a review of the synthetic applications of chiral aziridines by McCoull and Davis [4] still offers an excellent overview of the diverse field of aziridine chemistry. A more recent (but more specialized) chapter on aziridinecarboxylate esters is equally worthwhile [143].

2.1.3.1 Nucleophilic Ring Opening

Perhaps the most common of aziridine reactions is the ring opening by nucleophiles. This topic has been reviewed recently and fairly comprehensively by Hu [144], and an interesting computational study on CN vs. CC bond cleavage has been published [145]. Some illustrative synthetic examples are given here.

Ring opening can be used as a means of carbon–carbon bond formation when carbon-based nucleophiles are employed [146]. For example, in the presence of catalytic amounts of cuprous iodide, phenyllithium attacks the less substituted site of the *N*-tosyl aziridine **98** (Scheme 2.22) to give the corresponding protected amine [147]. The analogous addition of Grignards onto *meso*-aziridines (e.g., **22b**)



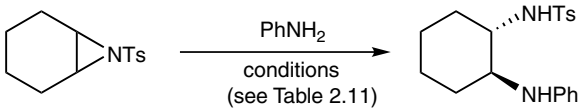
Scheme 2.22 Ring opening of aziridines with carbon nucleophiles.

can exhibit impressive enantioselectivity under the influence of the Schiff base/amino acid copper(II) complex dimer **100**, although relatively high catalyst loadings must be used [148]. Acetylide anions are also competent nucleophiles when a copper(I) catalyst is used, as demonstrated by the high-yielding conversion of the 2-alkylaziridine **102** into the homopropargylamine **104**, resulting from attack at the less hindered carbon [149]. Wu and Zhu have used the diastereoselective addition of an aryl Grignard onto a chiral aziridine as a key step in their total synthesis of (–)-renieramycin M and G and (–)-Jorumycin [150].

This exclusive regioselectivity was used to advantage in an approach to 1-deoxy-mannojirimycin analogs from deoxyglucitol-derived aziridine **105**, which engages in a very well-behaved reaction with 1,3-dithiane anion **106** [151]. Similar regiochemical outcomes are observed for cyanide addition using stoichiometric trimethylsilyl cyanide (TMSCN) and tetrabutylammonium fluoride (TBAF) in catalytic amounts [152], as well as an enantioselective protocol used to alkylate active methine compounds with unsymmetrical aziridines under mild basic conditions using a cinchona derived phase-transfer catalyst [153].

The regioselectivity of ring opening can be reversed under more cationic conditions, however, as illustrated by the Lewis acid-promoted intramolecular ring-opening reaction of phenypropylaziridine **108**, in which the product outcome is doubly supported by the stability of the Friedel-Crafts-like transition state and geometric considerations [154]. The same regiochemistry is observed in the iron(III)-catalyzed attack of electron-rich arenes onto unsymmetrical C-aryl aziridines [155].

Heteroatomic nucleophiles are equally useful in unlocking the synthetic utility of the aziridine ring. For example, **22b** reacts smoothly with aniline to provide the corresponding diamine **110** (Scheme 2.23) under various mild conditions (Table 2.11), including bismuth trichloride in acetonitrile [156], indium tribromide in methylene chloride [157], and lithium perchlorate in acetonitrile [120, 158]. Aqueous conditions have been developed using a cyclodextrin catalyst [159], and silica gel allows for a completely solventless system [160].



22b **110**

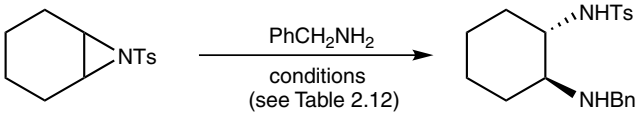
Scheme 2.23 Ring opening of aziridines with aniline.

Table 2.11 Yield data for ring opening of aziridines with aniline.

Entry	Reagent/catalyst	Solvent	Time (h)	Yield (%)	Reference
1	$BiCl_3$	CH_3CN	1.5	96	[130]
2	$InBr_3$	CH_2Cl_2	5.5	90	[131]
3	$LiClO_4$	CH_3CN	5.5	90	[132]
4	β-Cyclodextrin	$H_2O/Me_2C{=}O$	24	89	[133]
5	Silica gel	none	1	91	[134]

The asymmetric ring-opening of meso aziridines such as **22b** is a useful approach for accessing variously substituted chiral amines, and it has been the subject of some very good reviews [144, 146, 161]. One recently reported protocol involves the use of a titanium binolate catalyst, which can achieve ees of 99% [162].

Still other conditions have been worked out for alkylamines, as exemplified by addition of benzylamine (Scheme 2.24). In what may be one of the biggest catalyst sleepers of the century, the commercially available tris(pentafluorophenyl) borane [163] has escaped the niche of specialized polymerization catalysis and now finds application in various other useful synthetic transformations, including the ring opening of aziridines with simple amines (Table 2.12, entry 1). Interestingly, the active catalytic species involves a water-borane complex [164]. Other novel protocols for this reaction include ceric ammonium nitrate (CAN) in acetonitrile [165] and tributyl phosphite in an organic/aqueous medium [166]. Microwave conditions have been developed using resin-bound alkylamines in a protocol suitable for parallel synthesis [167].



22b **111**

Scheme 2.24 Ring opening of aziridines with benzylamine.

Azide is also a popular nitrogen-based nucleophile by virtue of its relatively low basicity, high nucleophilicity and ability to undergo subsequent reduction to the primary amine (i.e., a surrogate for ammonia). To achieve virtually neutral conditions, trimethylsilyl azide can be used as the source of azide (Table 2.13, entry 1), along with catalytic amounts of tributylammonium fluoride (TBAF) to liberate the azide *in situ* [152]. Of course, sodium azide itself can be used as a reactant, with the addition being promoted efficiently by cerium trichloride heptahydrate [168], lithium perchlorate [169] or Oxone [170] (Scheme 2.25). Meso aziridines can be enantioselectively desymmetrized using a dimeric salen yttrium catalyst in near quantitative yield and excellent enantioselectivity [161].

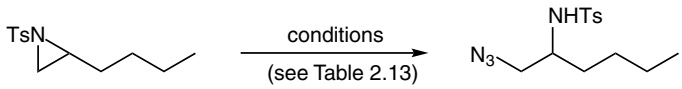
Synthetically useful β-aminoalcohols and aminoethers can be obtained by using oxygen-centered nucleophiles in the ring-opening reaction, and several mild and

Table 2.12 Yield data for ring opening of aziridines with benzylamine.

Entry	Reagent/catalyst	Solvent	Time (h)	Yield (%)	Reference
1	$B(C_6F_5)_3$	CH_3CN	12	99	[136]
2	CAN	CH_3CN	3	93	[137]
3	PBu_3	H_2O/CH_3CN	12	99	[138]

Table 2.13 Yield data for ring opening of aziridines with azide.

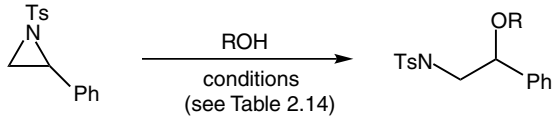
Entry	Azide source	Additive	Solvent	Time (h)	Yield (%)	Reference
1	$TMSN_3$	TBAF (5 mol.%)	THF	6	97	[128]
2	NaN_3	$CeCl_3{\cdot}7H_2O$	CH_3CN	6	90	[139]
3	NaN_3	$LiClO_4$	CH_3CN	6	90	[140]
4	NaN_3	Oxone	H_2O/CH_3CN	3	89	[141]



112 **113**

Scheme 2.25 Ring opening of aziridines with azide.

efficient methods have been reported to effect this transformation. For example, the alcoholysis of phenylaziridine **11** (Scheme 2.26) is promoted by ceric ammonium nitrate (Table 2.14, entry 1), which is effective for both alcohols [171] and water [165]; boron trifluoride etherate (entry 2) or tin(II) triflate [172]; montmorillonite KSF clay (entry 3), which serves as a solid-supported mild acid catalyst [174]; phosphomolybdic acid (PMA) on silica gel (entry 4), which gives excellent yields with various aziridines and alcohols [178]; and copper(II) triflate (entry 5) [175]. The water-tolerant bismuth(III) triflate is particularly well suited to catalyze hydrolysis reactions (entry 6) [176]. Note that in all cases the oxygen is attached to the benzylic position. With branched alkylaziridines (e.g., cyclohexylaziridine) the regioselectivity is reversed. Ring opening can also occur under basic conditions in the absence



11 **114**

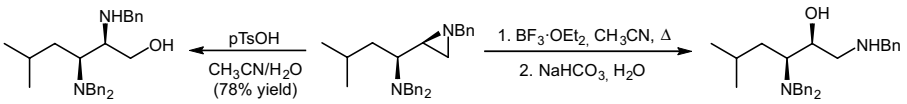
Scheme 2.26 Ring opening of aziridines with alcohols.

Table 2.14 Yield data for ring opening of aziridines with oxygen-centered nucleophiles.

Entry	*R*	Catalyst	Solvent	Yield (%)	Reference
1	Me	CAN	MeOH	90	[142]
2	Me	$BF_3{\cdot}OEt_2$	MeOH	99	[143]
3	Et	KSF	CH_2Cl_2	86	[144]
4	*t*-Bu	PMA/SiO_2	MeCN	94	[145]
5	CH_2CH_2Cl	$Cu(OTf)_2$	$HOCH_2CH_2Cl$	87	[175]
6	H	$Bi(OTf)_3$	$MeCN/H_2O$	88	[176]

of a Lewis acid catalyst, in which case nucleophilic attack occurs at the less hindered position [177].

It was discovered that the regiochemistry of the hydrolysis of α-aminoaziridine **115** (Scheme 2.27) could be controlled by manipulation of the reaction conditions. Thus, use of a protic acid (such as *p*-toluenesulfonic acid) led to attack at the terminal carbon, presumably via the highly reactive aziridinium salt, yielding the hydroxydiamine **116**. In contrast, if a classic Lewis acid was employed (e.g., boron trifluoride etherate) the opposite regiochemistry predominated, providing the secondary alcohol **117**. The stereochemical outcome for the latter product was rationalized on the basis of a double inversion from anchimeric assistance by the dibenzylamino substituent [179].



116 **115** **117**

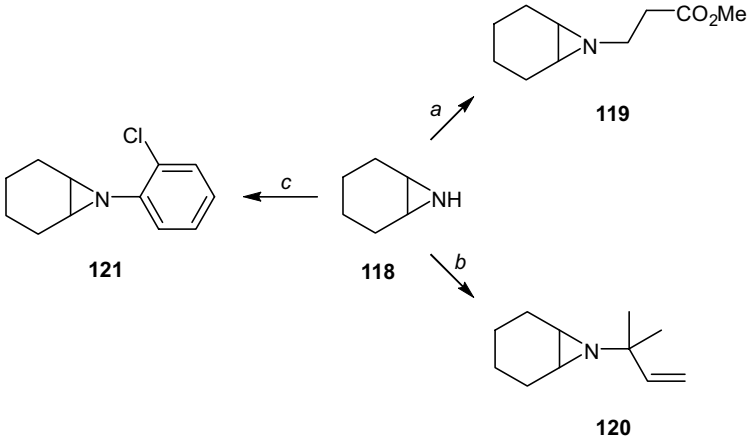
Scheme 2.27 Tunable hydrolysis conditions.

The scope is by no means limited to carbon, nitrogen and oxygen-centered nucleophiles. The nucleophilic palette embraces sulfur-based species, such as thiocyanates and thiols, the addition of which is promoted by a heterogeneous recyclable sulfated zirconia catalyst [180] and poly(ethylene glycol) [181]. The regiochemistry tends to follow the conventional course, with benzylic attack dominating for arylaziridines and terminal attack for alkylaziridines. Thiols can also engage in the enantioselective ring-opening of aziridines under the catalysis of a VAPOL phosphoric acid derivative [182].

The aziridine ring can also be cleaved by phenylselenide [183], reductively cleaved under transfer hydrogenation conditions [184], or opened with halides under fairly straightforward conditions, such as tetrabutylammonium fluoride in DMF [185], aqueous HCl in acetone [186], magnesium bromide in ether [187], and indium triiodide in acetonitrile [188].

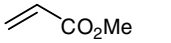
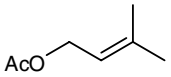
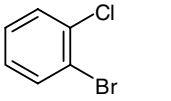
2.1.3.2 *N*-Elaboration Reactions

Aziridines bearing no N-substituent can be elaborated in various ways. For example, cyclohexene imine (**118**) engages in conjugate addition onto methyl acrylate under solvent-free conditions (Scheme 2.28, route a), although two equivalents of the Michael acceptor is needed [164]. The same aziridine undergoes smooth palladium-catalyzed allylation with prenyl acetate, whereby the electrophile is captured at the more substituted terminus (route b), although this regiochemistry is substrate-dependent [189]. N-Arylation is also possible using a palladium/BINAP protocol (route c), in which aryl bromides and arylboronic acids act as suitable reaction partners [190].

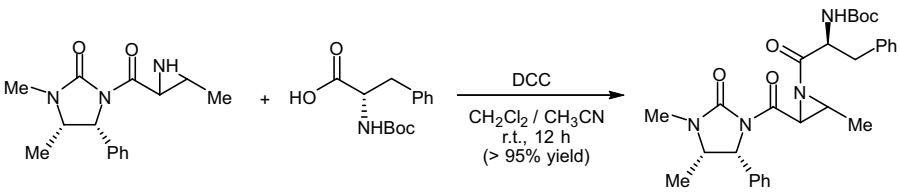


Scheme 2.28 N-Elaboration of cyclohexene imine (Table 2.15).

Table 2.15 Conditions for N-elaboration of cyclohexene imine.

Entry	Route	Electrophile	Catalytic system	Solvent	Yield (%)	Reference
1	a		None	Neat	89	[136]
2	c		$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, BINAP	THF	89	[153]
3	b		$Pd(dba)_3$, BINAP, *t*-BuONa	Toluene	95	[154]

Many other protocols exist in which unprotected aziridines function as nucleophiles, including alkylations using epoxides [191] or alkyl bromides [192] as electrophiles. N-Acylation can be effected with acyl chlorides [193] or a combination of carboxylic acid and dicyclohexylcarbodiimide (DCC) [3, 194] (Scheme 2.29).



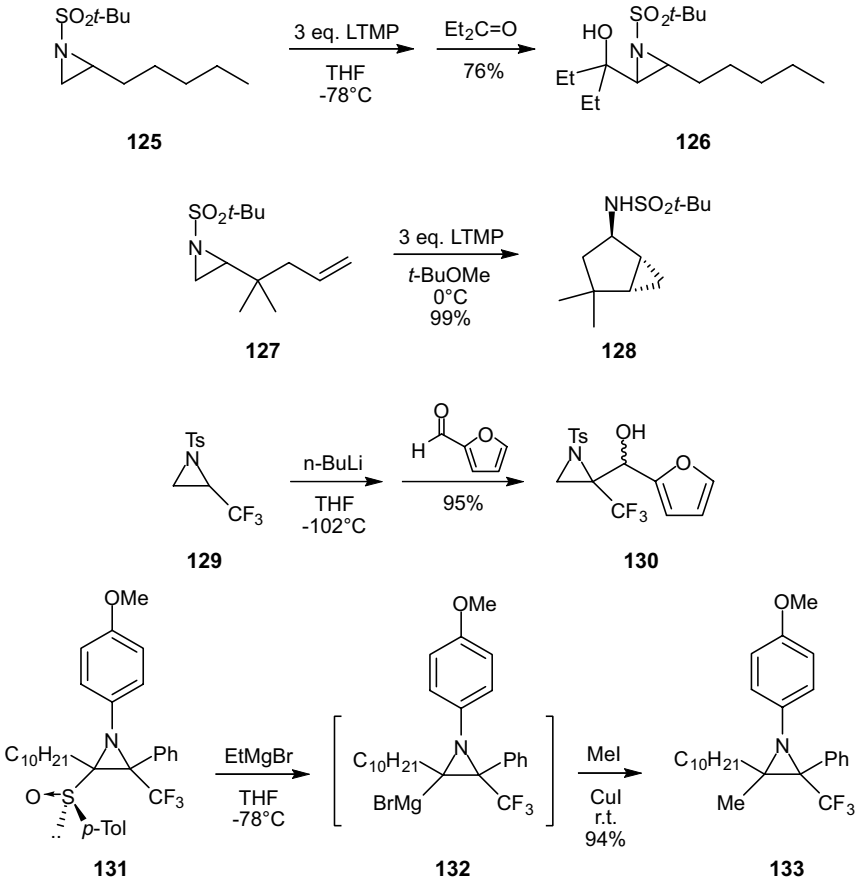
122 123 124

Scheme 2.29 N-Acylation using DCC.

2.1.3.3 **Azirdinyl Anion Chemistry**

Aziridinyl anion chemistry is of growing interest, as evidenced by its inclusion in a symposium-in-print [195]. Hodgson *et al.* have also authored a noteworthy review dedicated to this topic [196], to which the reader is directed, and computational studies on the physical properties of aziridinyl anions are emerging [197].

Protected aziridines can be deprotonated, and the resulting carbanions add to a range of electrophiles. For example, the *t*-butylsulfonyl (Bus) protected pentylaziridine **125** (Scheme 2.30) is deprotonated at the less substituted carbon (i.e., more stable anion) upon treatment with an excess of lithium 2,2,6,6-tetramethylpiperidide (LTMP) at low temperature (−78 °C), and the lithiate adds smoothly to 3-pentanone to give the aziridinyl alcohol **126** in good yield [198]. The aziridinyl anion can also exhibit carbene-like character, so that when alkenes are tethered to the substrate (e.g., **127**)



Scheme 2.30 Reactions of aziridinyl anions.

and the anion is formed at somewhat higher temperatures, a remarkably high-yielding intramolecular cyclopropanation ensues [199].

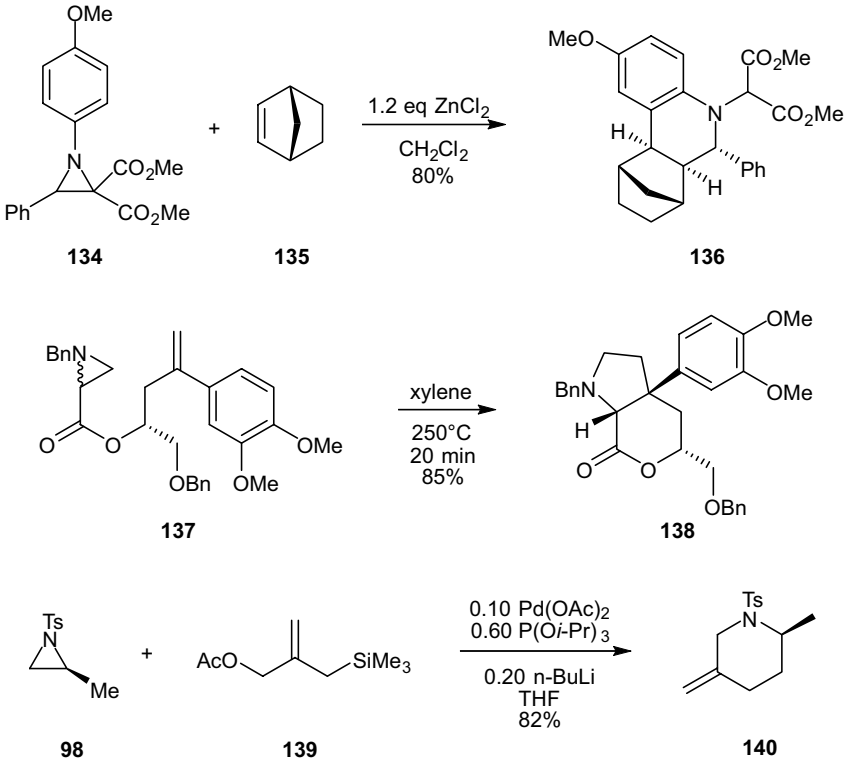
When an electron-withdrawing group is attached to the aziridine ring, it directs deprotonation and stabilizes the resulting anion. Thus, aziridine **129** is lithiated adjacent to the trifluoromethyl group, after which treatment with 2-furaldehyde provides the aziridinyl alcohol **130** in excellent yield [200]. Satoh and coworkers have developed a very useful protocol involving sulfinylaziridines (e.g., **131**), in which the sulfinyl group (having served as a chiral auxiliary in the prior aziridination reaction) is quantitatively removed in the presence of ethyl Grignard to give the corresponding aziridinylmagnesium bromide (i.e., **132**). This anion can then be cross-coupled with alkyl iodides in the presence of cuprous iodide to give alkylated products (i.e., **133**) with net retention of configuration [201, 202].

2.1.3.4 Ring Expansions

Aziridines can serve as handy templates for access to other heterocyclic subunits, and quite a few interesting methodologies have been reported. In the case of vinyl aziridines, near quantitative rearrangement to 3-pyrroline derivatives is promoted by copper(II) hexafluoroacetylacetonate in toluene at elevated temperature [203]. Another general approach to ring expansion is through cycloaddition strategies. For example, in the presence of zinc chloride, *p*-methoxyphenyl protected aziridine **134** (Scheme 2.31) engages in a formal [4 + 2] cycloaddition with norbornene (**135**) to provide the tetracyclic piperidine **136**. The mechanism proceeds through a Mannich reaction with the initially formed ylide and subsequent intramolecular Friedel–Crafts alkylation [204]. Highly substituted pyrroles can be accessed by reacting aziridines with electron-deficient allenes, a process that involves a formal [3 + 2] cycloaddition [205]. Pyrroles are also formed by the platinum(II)-catalyzed electrophilic iodocyclization of propargylic aziridines [206].

The ylide itself can be trapped with olefins under thermal conditions [207], as demonstrated by the intramolecular 1,3-dipolar cycloaddition of the terminal aziridine **137** to give the bicyclic pyrrolidine **138** [208]. Harrity and coworkers [209] have developed a [3 + 3] cycloaddition strategy for access to the piperidine ring system, in which a palladium-trimethylenemethane complex (derived from acetoxy trimethylsilyl methylene compounds such as **139**) adds to an aziridine (e.g., **98**) to form methylenepiperidines such as **140** in generally good yields. The substituent on nitrogen greatly impacts the efficiency of this reaction, with *p*-tosyl and *p*-methoxyphenyl-sulfonyl moieties providing the best results.

The next broad class of transformations could be characterized as carbonyl insertion reactions (Scheme 2.32), although it encompasses the insertion of carbon monoxide and carbon dioxide through various modes. Thus, in the presence of sodium iodide, Boc anhydride serves as a carbon dioxide surrogate in the conversion of the (+)-pseudoephedrine-derived aziridine **141** into oxazolidinone **143**, in which the stereochemistry of the ring substituents is preserved [210, 211]. Hydroxymethylaziridines (e.g., **144**) can be bridged with phosgene into labile fused bicyclic oxazolidinone structures (i.e., **145**), which undergo *in situ* nucleophilic attack by chloride to give chloromethyloxazolidinones (e.g., **146**) in excellent

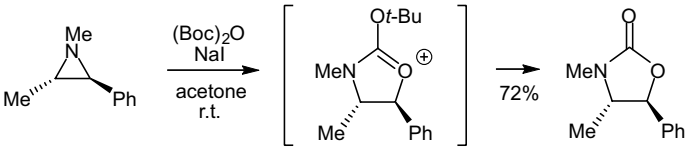


Scheme 2.31 Cycloaddition reactions of aziridines.

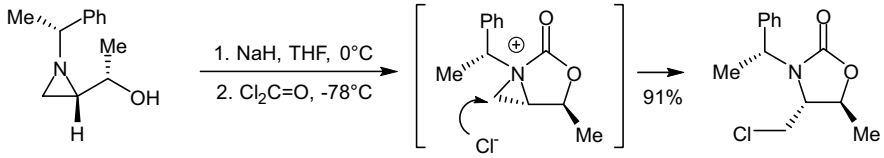
yield [212]. Also, gaseous carbon dioxide itself can be trapped by aziridines at atmospheric pressure using lithium bromide as a catalyst, as shown by the conversion of arylaziridine **147** into the corresponding oxazolidinone **148**. The mechanism proceeds through a series of bromide-induced ring opening, carboxylation of the resulting amide anion, and alkylative ring closure [213]. This transformation has also been shown to proceed under the catalysis of a (salen) chromium(III)/DMAP complex [214].

A novel rhodium-complexed dendrimer (**149**) is effective in promoting the carbonylative ring expansion of aziridines to β-lactams. The near-quantitative yield exhibited by *N*-*t*-butyl-2-phenylaziridine (**150**) is not unusual, although relatively high pressures [approx. 27 atm (400 psi)] and elevated temperatures (90 °C) are required. Nevertheless, the catalyst appears to be easily isolated and recycled without loss of activity [215].

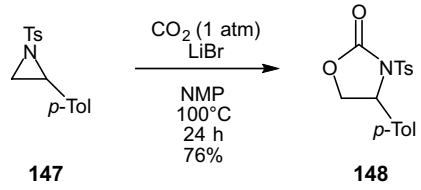
Nitrogen and sulfur can also be introduced via ring expansion strategies. Thus, styrene imine derivative **11** engages in [3 + 2] cycloaddition with acetonitrile in the presence of boron trifluoride etherate at room temperature to give the corresponding imidazoline (**152**) in good yield (Scheme 2.33) [216]. The iminothiazolidine nucle-



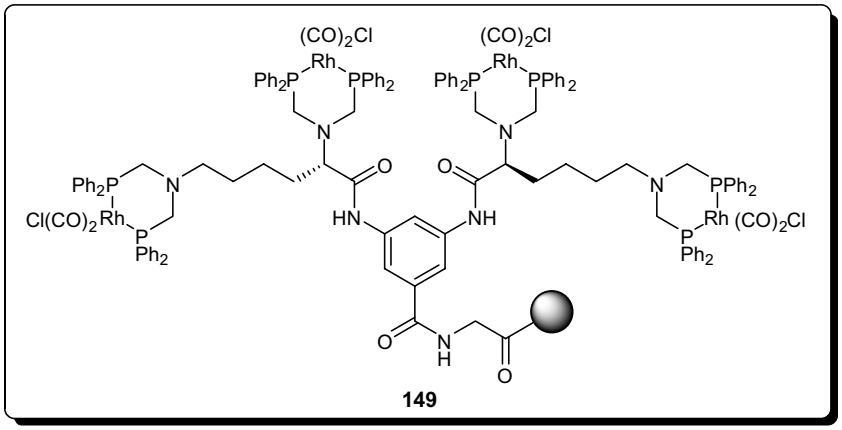
141 142 143



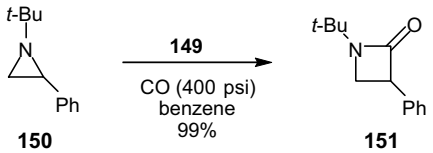
144 145 146



147 148

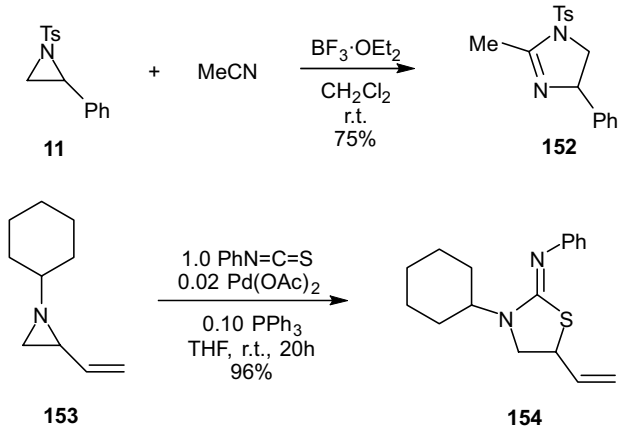


149



150 151

Scheme 2.32 Carbonyl insertions into aziridines.



Scheme 2.33 Insertion of nitrogen and sulfur into aziridines.

us [217] can be derived from aziridines at room temperature using a palladium(II) acetate/triphenylphosphine catalyst system. Thus, phenylisothiocyanate is inserted into the C−N bond of vinylaziridine **153** to give the ring-expanded product **154** in excellent yield [218].

2.2
2*H*-Azirines

Although the level of activity does not match that of the aziridines, research into the chemistry of azirines is healthy and on the increase. Several reviews have appeared in recent years. The reader is directed particularly to two excellent treatises by Palacios and coworkers [219, 220] as well as an earlier work by Rai and Hassner [1].

2.2.1
Properties of Azirines

Also referred to as azacyclopropene (and confoundingly as 1-azirine), 2*H*-azirine is the unsaturated cousin of the aziridine ring, which might well be described metaphorically as a cyclic imine. The alternative 1*H*-tautomer lies some 35 kcal mol^{-1} higher in energy, in part because it constitutes an antiaromatic ring system [221–223]. It is a weaker base than aziridine, which is analogous to the trend in corresponding open-chain amines and imines [221]. Geometrically, according to calculation at the B3LYP/6-311 + G(3df,2p) level of theory, the triangular ring is somewhat scalene, with the C–N single bond being the longest side. Consequently, the sp^2 carbon vertex is the widest at almost 70° (Figure 2.6) [224]. The ^{1}H-NMR signals of the methylene protons resonate at 1.26 ppm, while the olefinic proton is shifted significantly downfield to 14.4 ppm. The C3 carbon appears at 164 ppm [225].

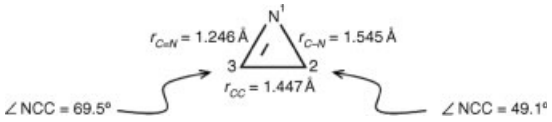
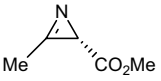
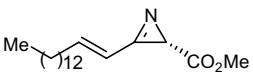


Figure 2.6 Geometry of 2*H*-azirine.

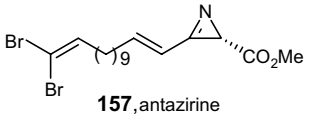
Remarkably, the azirine moiety is found in some naturally occurring compounds. For example, azirinomycin (**155**, Figure 2.7), isolated from *Streptomyces aureus* [226], exhibits antibiotic properties [227]. Two more biologically active azirines, dysidazirine (**156**) and antazirine (**157**), were identified in extracts of the marine sponge *Dysidea fragilis* [228]. While both enantiomers are found in nature, only the *(R)*-isomers of each are associated with desirable cytotoxic activity, the other antipodes being inactive [229].



155, azirinomycin



156, dysidazirine



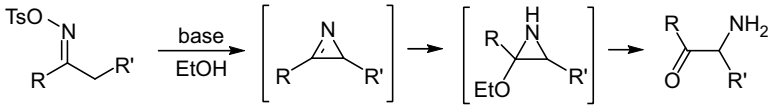
157, antazirine

Figure 2.7 Some naturally occurring 2*H*-azirines.

2.2.2 Synthesis of Azirines

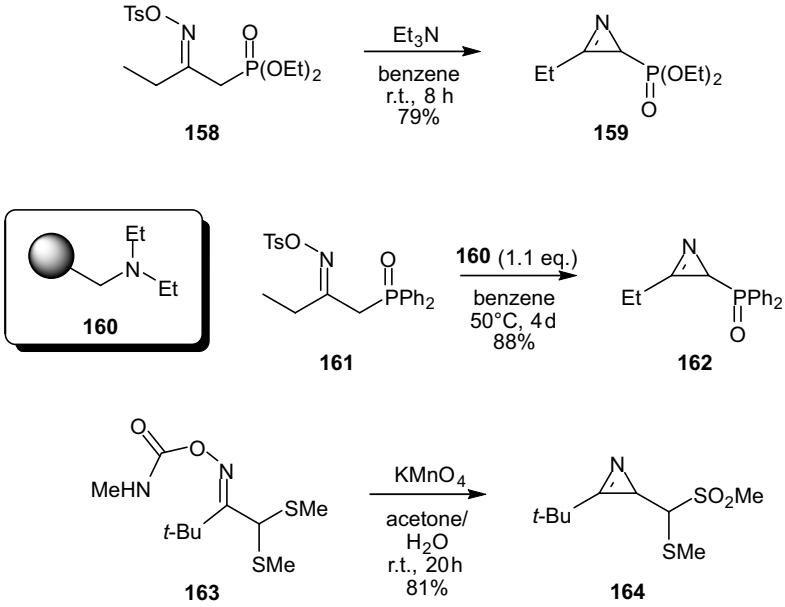
2.2.2.1 Neber Route

This synthetic methodology has a very interesting history. The Neber rearrangement, first reported in 1926 [230], is the base-mediated conversion of oxime derivatives (originally sulfonates) into α-aminoketones (Scheme 2.34). Ultimately, it represents a useful protocol for the α-amination of ketones, which has recently been used to advantage in the total synthesis of dragmacidin F [231, 232]. While most applications still involve this complete transformation, it became clear early on that the mechanism involved an azirine intermediate that could be isolated under the right conditions [233].



Scheme 2.34 Neber rearrangement.

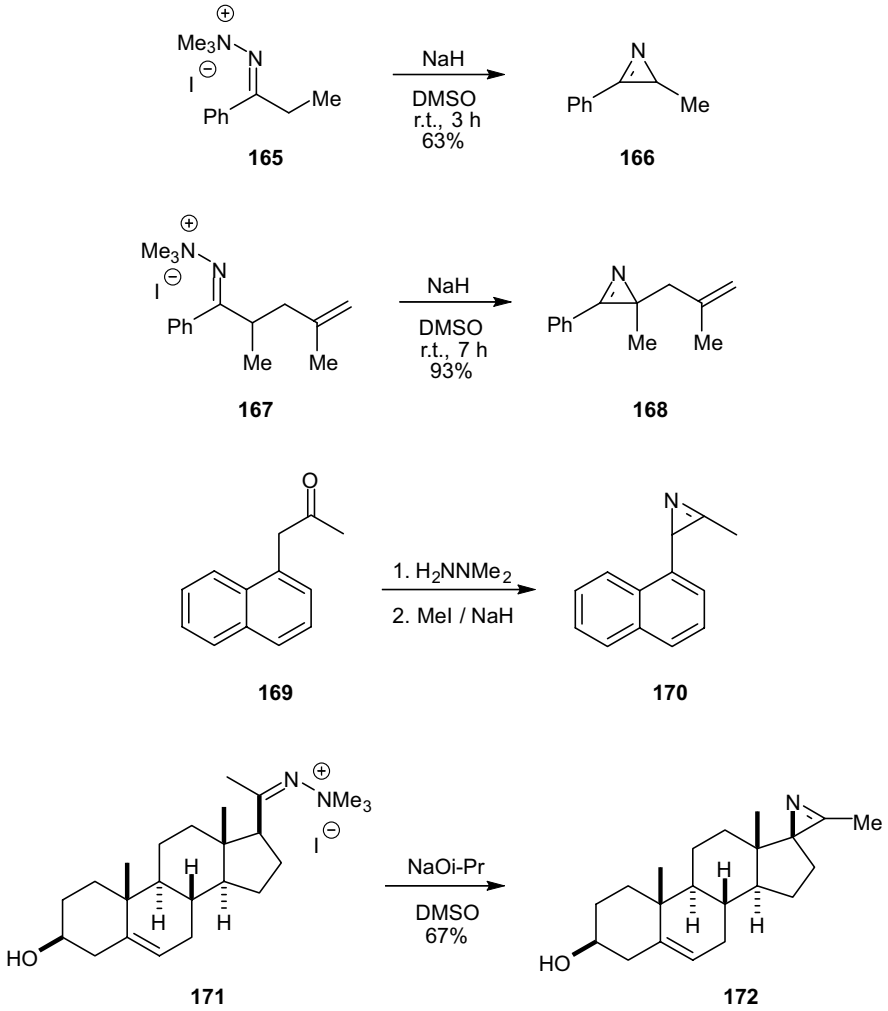
Generally speaking, there are two regiochemical possibilities for α-amination proceeding, in turn, through two regioisomeric azirines. House and Berkowitz [234] demonstrated that the regiochemistry of the Neber rearrangement is driven not by oxime geometry (as with the Beckmann rearrangement), but rather by the relative acidities of the α-protons. In other words, the initial tosylate displacement is effected by the more readily formed carbanion. Thus, in Neber precursors with electron-withdrawing groups, the active methylene almost always ends up as the saturated carbon of the azirine. For example, treatment of phosphonatoketoxime **158** (Scheme 2.35) with triethylamine at room temperature afforded in smooth fashion azirine **159** as the exclusive regioisomer [235]. Equally satisfactory results could be obtained using a solid-supported triethylamine analog (i.e., **160**) [236].



Scheme 2.35 Azirines from oximes with activating groups.

An unusual set of oxidative conditions has been reported for the thioacetal oxime carbamate **163**, which suffers oxidation of only one sulfide linkage in the presence of potassium permanganate and then cyclizes to azirine **164**, presumably under the influence of hydroxide liberated during the oxidation [237].

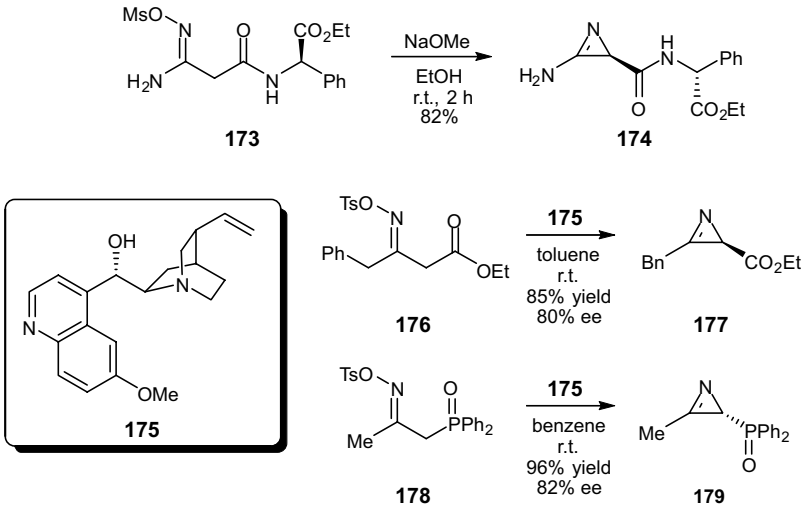
The method is tolerant to other leaving groups on the imino nitrogen. One frequently encountered class of compounds in this regard incorporates the quaternary hydrazonium moiety [238]. For example, the hydrazonium salt **165** (Scheme 2.36) derived from propiophenone is converted into the corresponding azirine **166** in fair yield upon treatment with sodium hydride in DMSO [239], and the similar unsaturated system **167** gives an excellent yield of azirine **168** under identical



Scheme 2.36 Azirines from quaternary hydrazonium salts.

conditions [240]. In these cases, the regiochemistry is unambiguous, as there is only one set of α-protons. However, the process can be selective even when two regioisomers are possible. Thus, the naphthylacetone derivative **169** provides azirine **170** through sequential hydrazone formation, exhaustive methylation and deprotonation, whereby the product formation proceeds via the benzylic anion [241]. Even more subtle is the reaction course of the pregnenolone hydrazonium salt **171**, which gives a reasonably good yield of azirine **172**, corresponding to ring closure via the more substituted aza-enolate species. The latter case provides a striking example of the stability of azirines, as the authors report storage in ethanol for two weeks at room temperature without decomposition [242, 243].

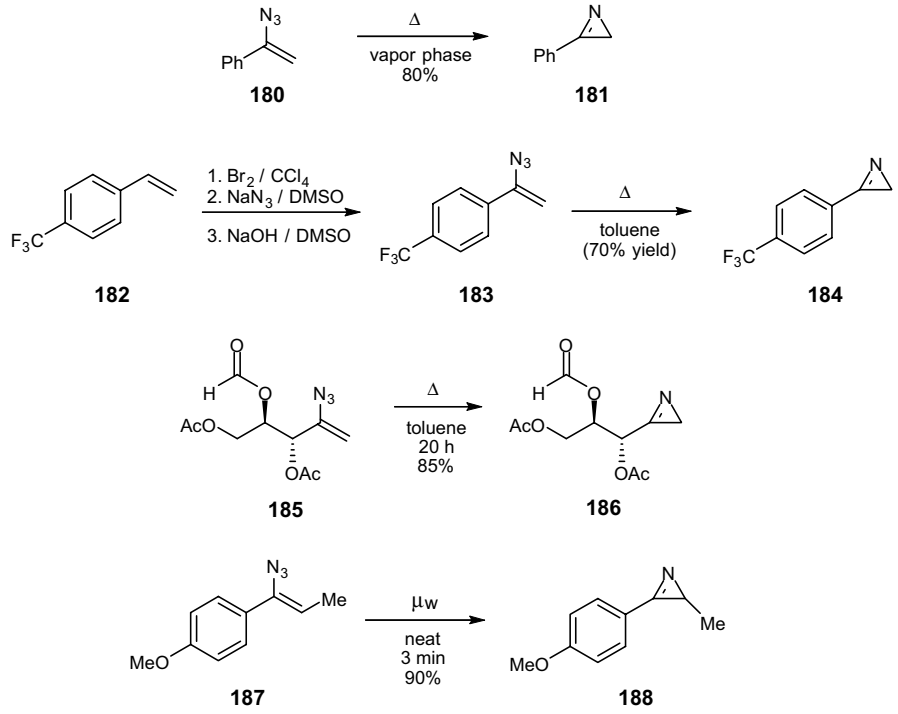
There appears to be no universally applicable approach to chiral nonracemic azirines; however, strides are being made. In one example, the chiral amido oxime derivative **173** (Scheme 2.37) is reported to undergo conversion into azirine **174** with exclusive diastereoselectivity [244]. It is also interesting to note here the ability to isolate the azirine from the type of protic media usually encountered in the Neber rearrangement, which appears promising for adapting such protocols to azirine synthesis. The use of chiral bases has met with marginal success. In one case, modest enantioselectivities (up to 70% ee) were achieved using a chiral phase-transfer agent, which is assumed to form a tight ion pair with hydroxide and thus impose an asymmetric environment around the proton-transfer transition state [245]. A chiral base can also be used with good results, as demonstrated by the preparation of azirine **177** mediated by quinidine (**175**). Best results are obtained using stoichiometric quantities of organic base. However, a 20 mol.% loading could be used in the presence of potassium carbonate with only a slight decrease in selectivity [246]. This strategy has also been applied to the synthesis of azirines derived from phosphine oxides (e.g., **179**) [247].



Scheme 2.37 Asymmetric induction in azirine formation.

2.2.2.2 From Vinyl Azides

Smolinsky reported in 1962 that the vapor-phase thermolysis of α-aziridinylstyrene (**180**, Scheme 2.38) produced substantial quantities of phenylazirine **181** [248, 249]. Subsequently, the method was adapted to be more amenable to the preparative scale, as exemplified by the synthesis of the trifluoromethylphenylazirine **184**, which was carried out on a 10-gram scale [250]. The vinyl azide in this case was synthesized from the corresponding alkene (i.e., **182**) through sequential bromination, azide displace-



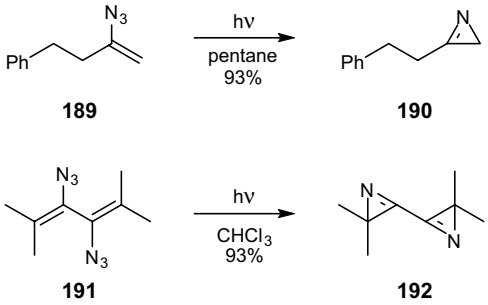
Scheme 2.38 Thermal decomposition of vinyl azides to azirines.

ment and dehydrobromination, a protocol used by Gilchrist and coworkers to access azirinyl esters [251, 252].

More recently, Somfai and coworkers [253] reported a much improved yield of azirine **184** (>95%) by carrying out the thermolysis in methylene chloride at 150 °C for 20 min in a sealed tube. Even at atmospheric pressure the process can be quite high yielding and remarkably tolerant to other functionality. Thus, heating the hexopyranose-derived vinyl azide **185** in toluene for 20 h resulted in the smooth formation of azirine **186** [254]. Perhaps the most convenient route is the neat thermolysis of aryl vinyl azides (e.g., **187**) in an open container under microwave irradiation, which proceeds in very good to excellent yields within a matter of minutes [255].

The course of the thermolytic reaction is substrate-dependent, and Hassner has generalized that azirines are usually formed when the substituent geminal to the azide is an aryl, alkyl, heteroatomic or ester group, whereas unsubstituted or keto-substituted substrates tend to form nitriles and other heterocycles upon thermolysis [256].

The same transformation can also be mediated by photolysis. Thus, irradiation of β-phenylethyl vinyl azide **189** (Scheme 2.39) induces loss of nitrogen and concomitant formation of azirine **190** in excellent yield [257]. The obvious advantage of this approach is that the decomposition can be carried out at low temperature, thus



Scheme 2.39 Photolytic decomposition of vinyl azides to azirines.

affording access to more strained products, including fused bicyclic azirines and bis-azirines such as **192**. In the latter case, the loss of nitrogen occurs stepwise, and the intermediate vinyl azirine can be isolated [258]. One bottleneck for both the thermolytic and photolytic methodology is access to the requisite vinyl azide substrates [259]. One promising recent contribution to solving this problem is the copper (I)/L-proline mediated coupling of sodium azide with (*Z*)-1-iodo-1-alkenes [260] which, in turn, can be accessed stereoselectively via the Wittig reaction of aldehydes with iodomethylenetriphenylphosphorane [261].

The mechanism of this reaction has been the matter of some debate. Careful kinetic studies in solution phase point towards a concerted mechanism involving a multi-centered transition state in which the nascent sp^2 azirinyl carbon exhibits partial positive character (Figure 2.8). This is supported by Hammett studies in which electron-donating substituents on the aryl ring accelerate the decomposition. Thus, in a solvent of 1-butanol at 80 °C, the conversion of the *p*-methoxy derivative (R=4-OMe) is about 50% faster than that of the phenyl substrate (R=H) and almost three times faster than the *m*-nitro analog (R=3-NO_2) [262].

For α-aminoalkenyl azides, then, decomposition to the corresponding aminoazirine is usually spontaneous and rapid even at room temperature. In fact, many protocols simply form the vinyl azide *in situ* from other precursors. For example, keteneiminium salts (**194**, Scheme 2.40), available from the treatment of amides

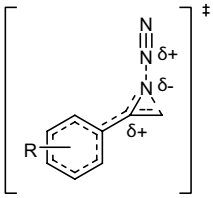
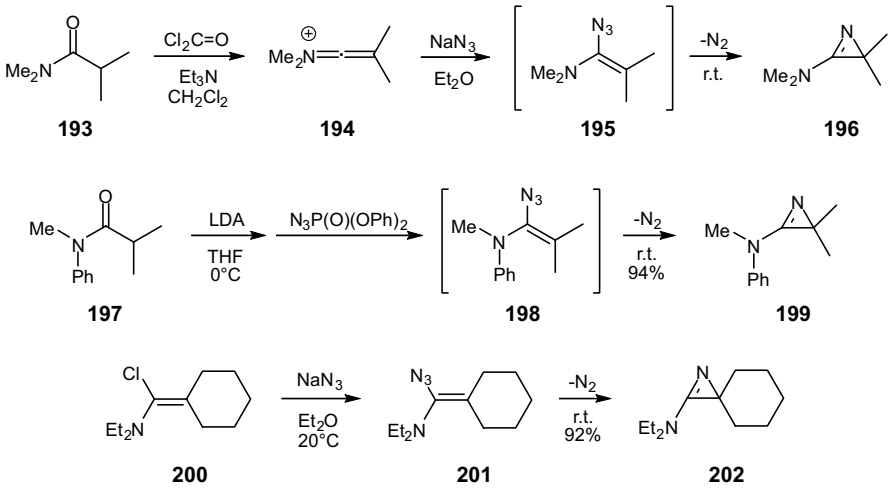


Figure 2.8 Proposed transition state for thermolysis of aryl vinyl azides.

(e.g., **193**) with phosgene, add sodium azide to form transient α-aminovinyl azides (e.g., **195**) that subsequently lose nitrogen at room temperature to provide azirine products (e.g., **196**) [263]. The use of phosgene can be avoided with diphenyl phosphorazidate (DPPA), an aziridinating agent that reacts with amidate anions to give the corresponding azirines directly, as shown by the conversion of *N*-methyl-*N*-phenyl amide **197** into the aminoazirine **199** in 94% yield [264]. This methodology is tolerant of various functionalities [265], but some substrates must first be converted into the thioamide using Lawesson's reagent [266, 267]. Other suitable precursors include α-chloroenamines (e.g., **200**), which undergo sequential azide displacement and rapid thermal conversion into the azirine (e.g., **202**) under very mild conditions [268].

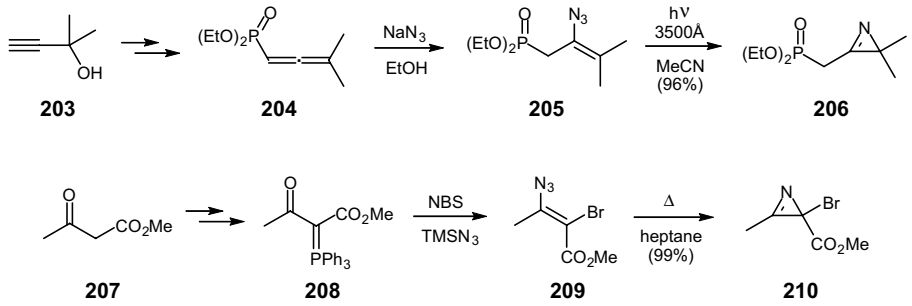


Scheme 2.40 Synthesis of azirines with electron-donating groups.

There are also high-yielding methods for preparing azirines appended with electron-withdrawing substituents. Thus, allenic phosphonates (**204**, Scheme 2.41), which can be accessed from propargyl alcohol derivatives (**203**), are themselves efficient precursors for phosphonylmethyl vinyl azides (**205**). Irradiation of the latter results in extremely high-yielding photolysis to the azirine (**206**) [269]. As an additional entry under the rubric of electron-withdrawing substituents, bromoazirinyl ester **210** is formed in almost quantitative yield from the azidoacrylate derivative **209** under thermal conditions in refluxing hexane [270]. Analogous iodo azirinyl esters can be prepared through similar methodology [271].

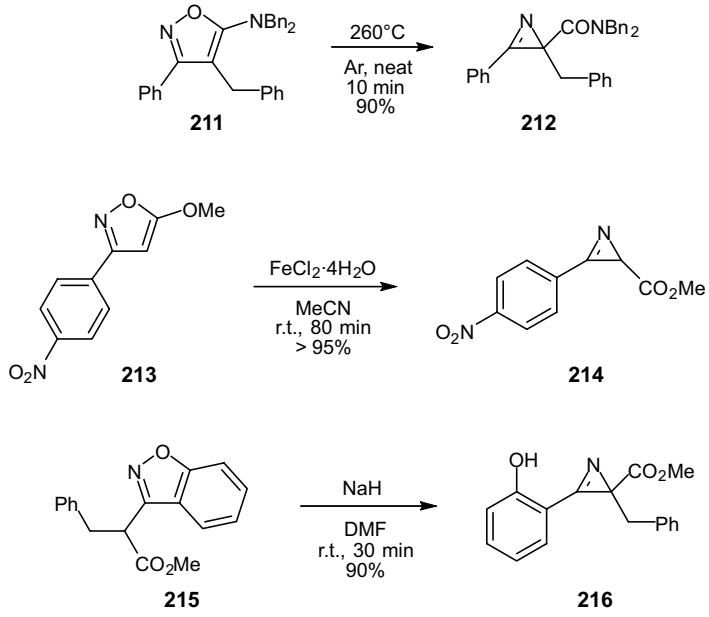
2.2.2.3 From Other Heterocycles

Synthetically useful yields of azirines can be obtained from the thermolysis of isoxazoles (Scheme 2.42), as demonstrated by the thermal rearrangement of ami-



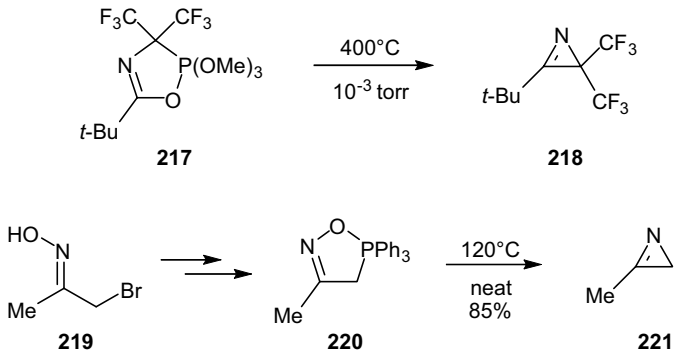
Scheme 2.41 Synthesis of azirines with electron-withdrawing groups.

noisoxazole **211** to azirinyl carboxamide **212** at high temperature under argon. Neat thermolysis is the preferred mode, as the use of solvent was found to give lower yields [272]. Alternatively, iron dichloride promotes the analogous rearrangement of alkoxyisoxazole **213** at room temperature. The 5-alkoxy substituent is crucial, as 5-alkyl or 5-aryl substituents lead to enaminoketones under the same conditions [273]. Benzisoxazole derivatives (e.g., **215**) exhibit a regiochemically distinct mode of thermal rearrangement. Instead of bonding to the internal α-carbon, the nitrogen instead forms the azirine ring with the adjacent carbon of the substituent, so that aromaticity is preserved [274].



Scheme 2.42 Synthesis of azirines from isoxazoles.

In a similar vein, oxazaphosphole **217** (Scheme 2.43) underwent pyrolysis at 400 °C under high vacuum to produce azirine **218**, which was trapped at low temperature and characterized by IR spectroscopy. Pyrolysis at higher temperatures (700 °C) gave nitrile ylides instead [275]. A somewhat more synthetically friendly procedure was reported for oxazaphospholine **220** (available in four steps from α-bromoketoxime **219**), which decomposed at 120 °C and atmospheric pressure to provide methylazirine **221** as a distillate in good yield [276].



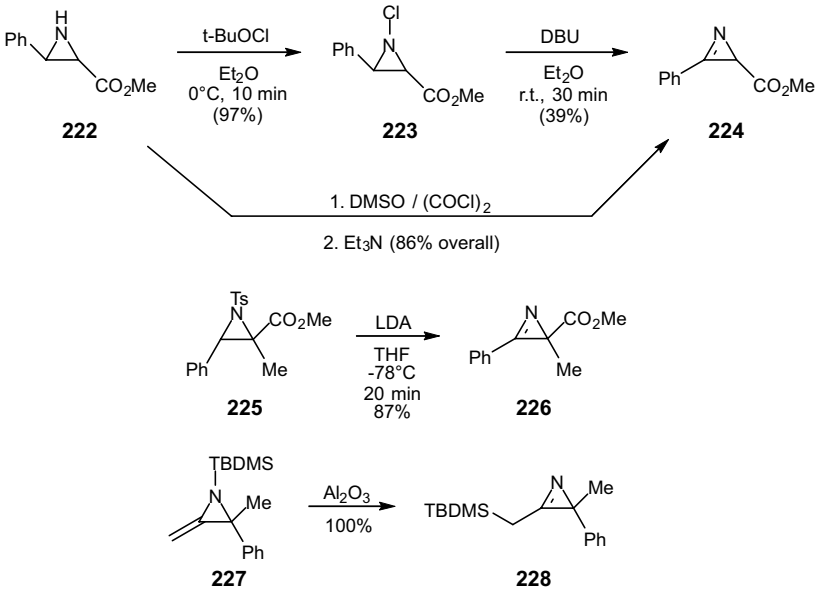
Scheme 2.43 Synthesis of azirines from dihydrooxazaphosphole derivatives.

Finally, azirines can be synthesized from suitably equipped aziridine precursors. For example, aziridinyl ester **222** (Scheme 2.44) was smoothly oxidized using *t*-butyl hypochlorite to give the N-chloro derivative **223** in excellent yield. Subsequent DBU-mediated elimination to the azirine **224**, however, was considerably less efficient [277]. A convenient workaround to this problem was found by using Swern conditions, which effects the same transformation in 86% overall yield [278]. Davis and coworkers have reported an interesting eliminative pathway by treating *N*-sulfinyl or *N*-sulfonylaziridines (e.g., **225**) with lithium diisopropylamide (LDA) at low temperature [279, 280]. Methyleneaziridines can easily be isomerized to azirines, since the latter lie about 9 kcal mol^{-1} lower in energy [281]. Thus, *N*-silyl-methyleneaziridine **227** quantitatively isomerizes to azirine **228** via an alumina-mediated Brooks rearrangement at room temperature [282].

2.2.3 Reactivity of Azirines

2.2.3.1 Addition of Nucleophiles

Inasmuch as azirines incorporate an unsaturated nitrogen center within a three-membered ring, it would be reasonable to think of their expected chemical behavior as that of an activated imine. Consequently, nucleophilic addition to the sp^2 carbon can be a synthetically useful reaction for azirines. For example, azirinyl phosphonate

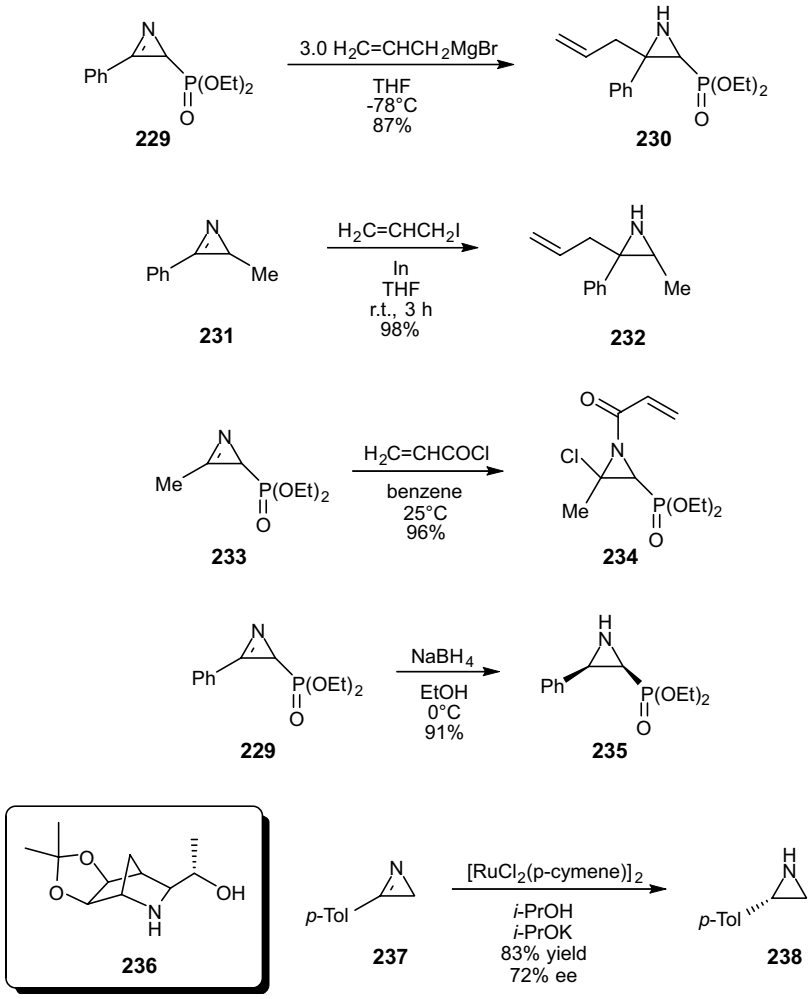


Scheme 2.44 Synthesis of azirines from aziridines.

229 (Scheme 2.45) suffers high-yielding nucleophilic allylation in the presence of excess allyl Grignard [283]. Analogous results can be obtained in excellent yield using allylindium reagents generated *in situ* from the corresponding iodide and indium metal, as shown in the conversion of azirine **231** into allylaziridine **232**. The stereochemistry of the latter reaction depends upon the substituent at the saturated carbon: chelating groups (i.e., keto or hydroxy moieties) led to *cis*-delivery of the nucleophile, whereas alkyl and aryl groups resulted in *trans*-addition [284]. When the azirine is sufficiently activated, even weak nucleophiles can engage in addition to the ring. Thus, exposure of azirinyl phosphonate **233** to acryloyl chloride results in initial N-acylation followed by subsequent rapid addition of chloride to form chloroaziridine **234** [285].

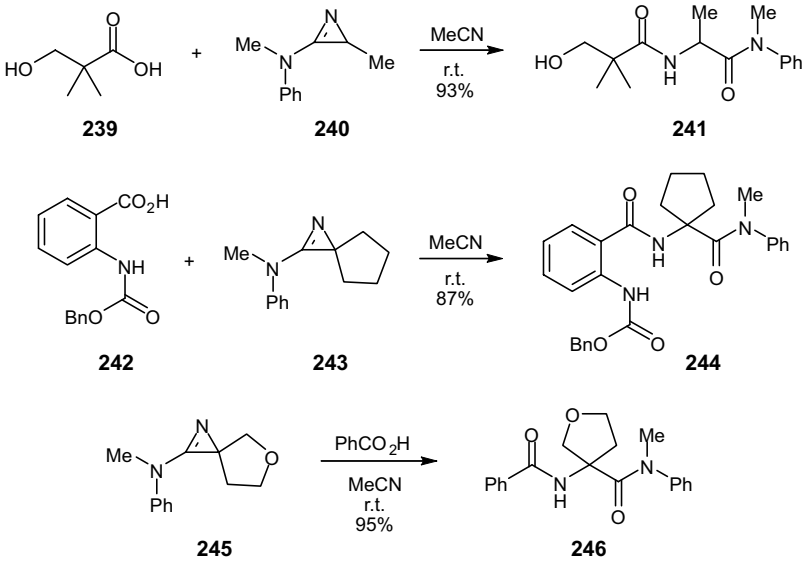
Aziridines can also be accessed by the stereoselective reduction of azirines with hydride reagents. For example, sodium borohydride reacts smoothly in ethanolic medium with azirine **229** to yield the *cis*-aziridine **235**, resulting from the trans-addition of hydride [286]. Alternatively, an asymmetric transfer hydrogenation protocol using the chiral aminoalcohol **236** and a ruthenium catalyst can be used to generate enantiomerically enriched aziridines from achiral azirine precursors. Thus, tolylazirine **237** was converted into *(S)*-tolylaziridine **238** in good yield and promising enantiomeric excess. The mechanism follows the route elucidated in analogous reactions of ketones, in which hydride addition and proton transfer occur simultaneously [287].

A very clever protocol has been developed by Heimgartner and coworkers, which takes advantage not only of the propensity of the azirine to add nucleophiles but also



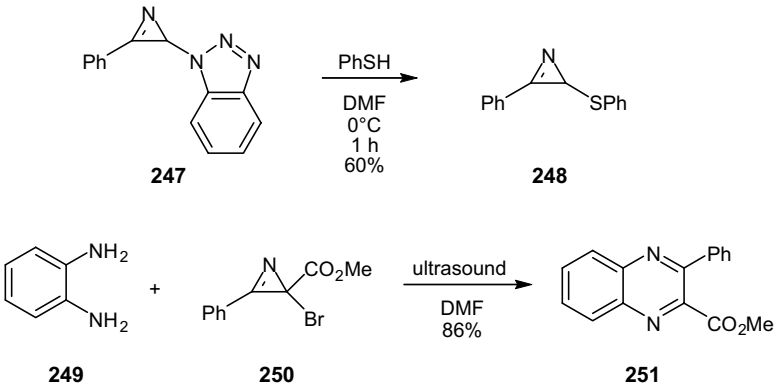
Scheme 2.45 Reaction of azirines with nucleophiles.

of the residual ring strain in the resulting aziridine ring. Thus, aminoazirines such as **240** (Scheme 2.46) engage carboxylates in nucleophilic addition to form transient aziridine intermediates that spontaneously rearrange to give amino acid derivatives (e.g., **241**) [288, 289]. This strategy, dubbed the "azirine/oxazolone method," allows quite a bit of flexibility in introducing structural variation into peptide backbones, as exemplified by the spiroazirines **243** [290] and **245** [266]. Quite a few synthons have been developed within this manifold, including those for 2-methylaspartate [291], α-methylglutamate [267], as well as for dipeptides [292] such as 2-aminoisobutyric acid/4-hydroxyproline [293] and other 2,2-disubstituted glycines [294, 295]. The methodology has been showcased in the synthesis of Trichovirin I derivatives [296] and has been further expanded into the realm of solid-phase synthesis [297, 298].



Scheme 2.46 Addition of carboxylic acids to aminoazirines.

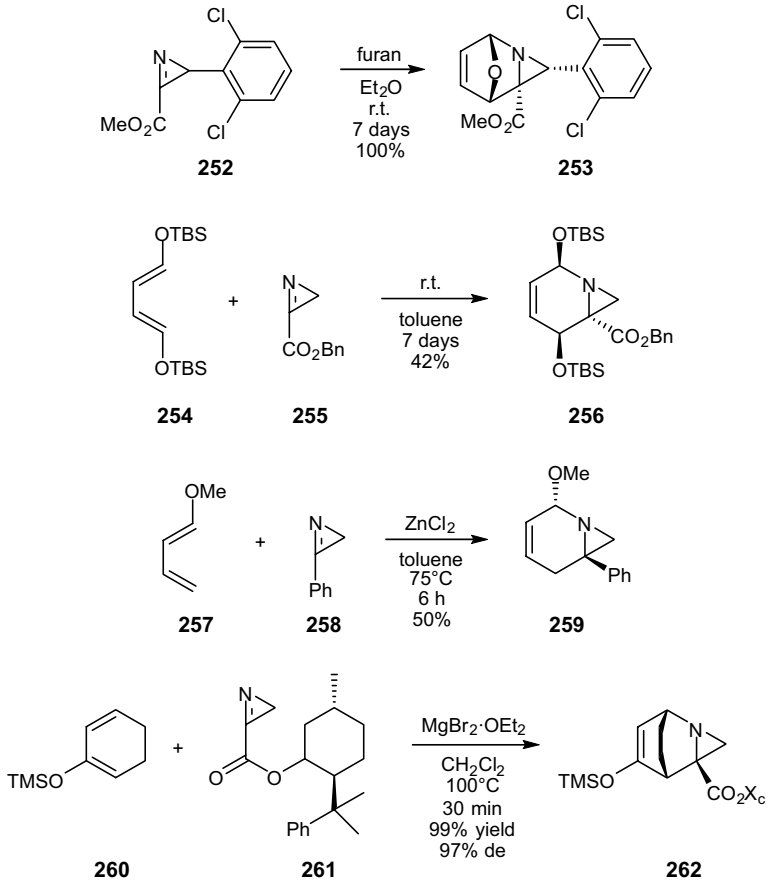
Nucleophilic substitution can actually be carried out at the saturated carbon of certain uniquely functionalized azirines. For example, the benzotriazolyl azirine **247** (Scheme 2.47) takes part in an intermolecular S_N2 reaction with thiophenolate to give the aziridinyl sulfide **248** in fair yield. Carbon-centered nucleophiles, such as Grignard reagents, can also be used [299]. Bromoazirine derivative **250** reacts with *o*-phenylenediamine (**249**) in both modes (nucleophilic addition and S_N2 displacement) to give the disubstituted quinoxaline **251** in very good yield [300].



Scheme 2.47 S_N2-Type additions to azirines.

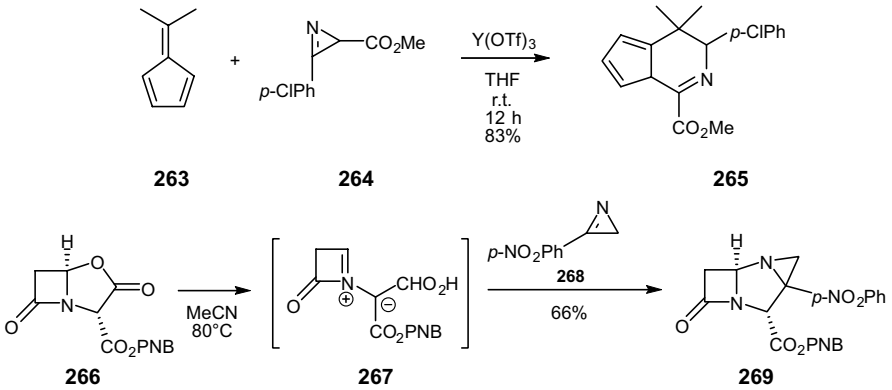
2.2.3.2 Cycloadditions

Perhaps some of the most fascinating chemistry associated with the azirines springs from their propensity to act as 2π donors in cycloaddition reactions. For example, Diels–Alder reactions using azirines as dienophiles [301] can provide synthetically valuable fused azabicyclo[4.1.0]heptane ring systems. In some cases, the reaction proceeds under simple thermal conditions and in very high yield, as illustrated by the quantitative reaction of azirinyl ester **252** (Scheme 2.48) with furan to give the Diels–Alder adduct **253** [302]. The method is amenable to other electron-rich dienes, such as bis(siloxy)diene **254** [303], as well as other dienophiles, such as aziridinyl carboxamides [304]. The reaction rate can be dramatically accelerated and the scope extended to alkyl and aryl aziridines (e.g., **258**) by the use of Lewis acids [305]. A particularly high-yielding result was obtained in the magnesium bromide-mediated Diels–Alder reaction between trimethylsiloxycyclohexadiene (**260**) and chiral non-racemic azirinyl ester **261**, which proceeded with almost exclusive endo- and regioselectivity (but apparently low facial selectivity) [306, 307].



Scheme 2.48 Diels–Alder reactions with azirines.

The field is not limited to [4 + 2] methodology. For example, arylazirine **264** and fulvene **263** engage in a formal [6 + 3] cycloaddition catalyzed by yttrium triflate and mediated by adventitious water, providing a novel entry into the [2]pyridine system (Scheme 2.49) [308]. The *p*-nitrophenylazirine **268** was also shown to be an effective 1,3-dipolarophile in the presence of azomethine ylide **267** (generated by the thermolysis of bicyclic oxazolidinone **266**), forming a fused tricyclic adduct (**269**) that was parlayed into an approach to 1-azacephams [309].



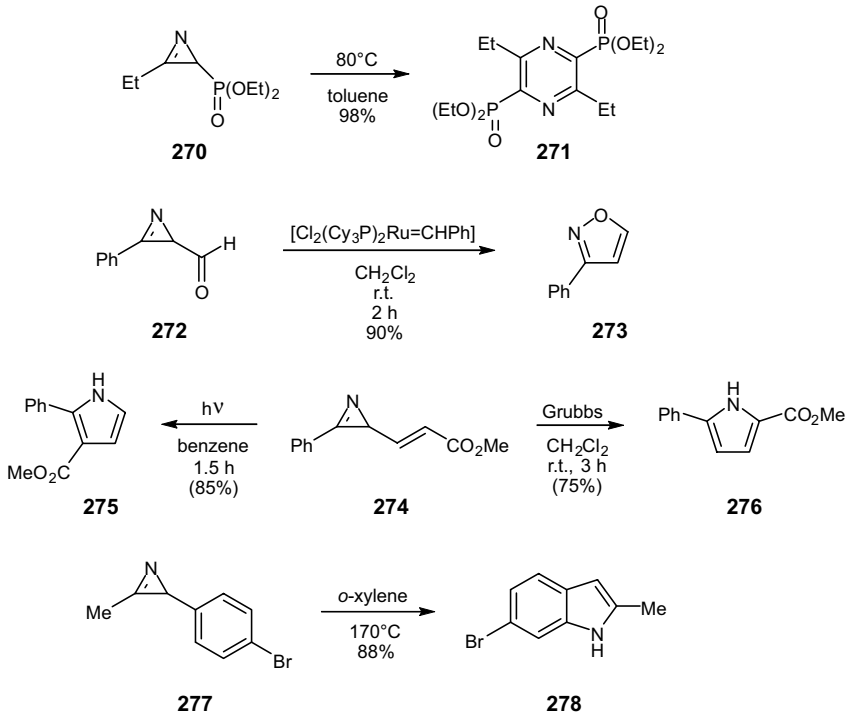
Scheme 2.49 Other cycloadditions with azirines.

2.2.3.3 **Rearrangements into other Heterocycles**

Owing to their strain and functionality, azirines are prone to molecular rearrangement. For example, under neutral thermolytic conditions the alkyl aziridinylphosphonate **270** (Scheme 2.50) is converted almost quantitatively into the pyrazine **271**. The mechanism is believed to involve the dimerization of unstable nitrile ylides generated from the initial thermal ring-opening of the azirine [310]. Furthermore, Padwa and Stengel have reported some fascinating azirine rearrangements promoted by Grubb's catalyst. Thus, the azirinyl aldehyde **272** is transformed cleanly into the isoxazole **273** at room temperature. Similarly, vinyl azirine **274** undergoes thermal rearrangement to form exclusively the 2,5-disubstituted pyrrole **276**, which is complementary to photolytic rearrangement, a process providing only the 2,3-product **275** [311, 312]. Finally, Taber has reported on the high-yielding synthesis of indoles (e.g., **278**) from arylazirines **277**, which are themselves synthesized from the oximes of aryl ketones [313].

2.3 Oxiranes

It may well be said that the field of oxirane chemistry has escaped the confines of a brief comprehensive overview. Indeed, an encyclopedic summary of just the last



Scheme 2.50 Some rearrangements of azirines.

year's activity would occupy volumes. Several significant reviews have appeared recently [8], many of which pertain to specific areas within epoxide chemistry and will therefore be cited in the appropriate context. The present chapter seeks to assemble a sampling of the diverse applications for organic synthesis.

2.3.1
Properties of Oxiranes

Oxiranes (also known as epoxides and oxacyclopropanes) owe much of their utility, whether as synthetic intermediates or biologically active compounds, to ring strain. For example, oxirane itself (bp 10.5 °C) is associated with some 27 kcal mol^{-1} of strain enthalpy. Like most of its congeners, this molecule exhibits the very useful balance of being stable enough for isolation, transportation and so on, while still harboring a remarkable propensity for reaction. Geometrically, oxirane describes an almost equilateral triangle, with a slightly relaxed bond angle at the oxygen center (Figure 2.9). The ^{1}H-NMR signals of the methylene protons resonate at 2.54 ppm and the carbon atoms appear at 39.7 ppm. The increased s-character of the C—H bond leads to an unusually high ^{13}C-H coupling of 176 Hz [7].

The oxirane ring is found in a host of naturally occurring compounds of biological relevance. Occasionally, the structures can be quite simple, with the oxirane being the

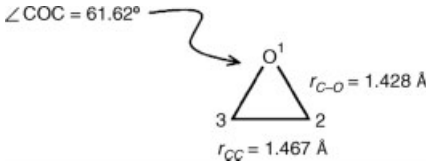


Figure 2.9 Geometry of oxirane.

dominant functional group. Such is the case for the newly discovered stilbene oxide derivative **279** (Figure 2.10), which was isolated from the larval *G. mellonella* infected by the nematode-bacterium complex *H. megidis* 90/*P. luminescens* C9. This compound displays broad antimicrobial activity against many troublesome pathogens, including the drug-resistant strain *Staphylococcus aureus* RN4220 [314].

More commonly, however, the epoxide ring is imbedded within a molecule carrying elaborate functional embellishments. A good example is altromycin B (**280**), a secondary metabolite of soil *Streptomyces* which exhibits both antibiotic and anticancer activity [315]. The mode of action has been traced to the inhibition of DNA synthesis caused by the alkylation of guanine through epoxide ring-opening [316]. Another natural product sporting the oxirane and anthraquinone moieties is dynemicin A (**281**), isolated from *Micromonospora chersina*, which is cytotoxic at concentrations approaching the parts per trillion range. Here the epoxide ring functions as the trigger for a mouse trap: nucleophilic ring opening of the epoxide results in a conformational relaxation that allows for cyclization of the enediyne array, forming the very reactive arene diradical [317].

Ambuic acid (**282**), isolated from the rain forest fungi *Pestalotiopsis* spp. and *Monochaetia* spp., has shown activity against several plant pathogenic fungi [318]. This polyketide-derived natural product is one representative from a broad range of cyclohexane epoxides found in nature, a class that has been the subject of a quite recent and fairly comprehensive review [319]. The structural and biological diversity even within this classification is impressive. Fumagillin (**283**), a cyclohexane spiroepoxide produced by *Aspergillus fumigatus*, is an angiogenic inhibitor that binds to methionine aminopeptidase. Consequently, it is a promising antineoplastic agent and may even inhibit atherosclerosis [320, 321].

Polyketide-derived oxiranyl natural products also extend into macrocyclic species. Amphidinolide B1 (**284**) is one such cytotoxic 26-membered macrolide, isolated from the marine dinoflagellate *Amphidinium* sp. Y-5 [322–324]. Similar cytotoxic activity exhibited by the 16-membered macrolide epothilone A (**285**), a metabolite of the cellulose-degrading myxobacterium *Sorangium cellulosum* (Myxococcales), has made it an interesting anti-cancer candidate and subsequently the subject of active investigation from both a synthetic organic and chemical biology standpoint [325, 326]. Also of marine origin is the bromotyrosine-derived dimeric spiroisoxazoline (+)-calafianin (**286**), which is found in methylene chloride extracts of the Mexican sponge *Aplysina gerardogreeni* n. sp (Aplysinidae). Members in this class of compounds have demonstrated activity against *Mycobacterium tuberculosis* [327, 328].

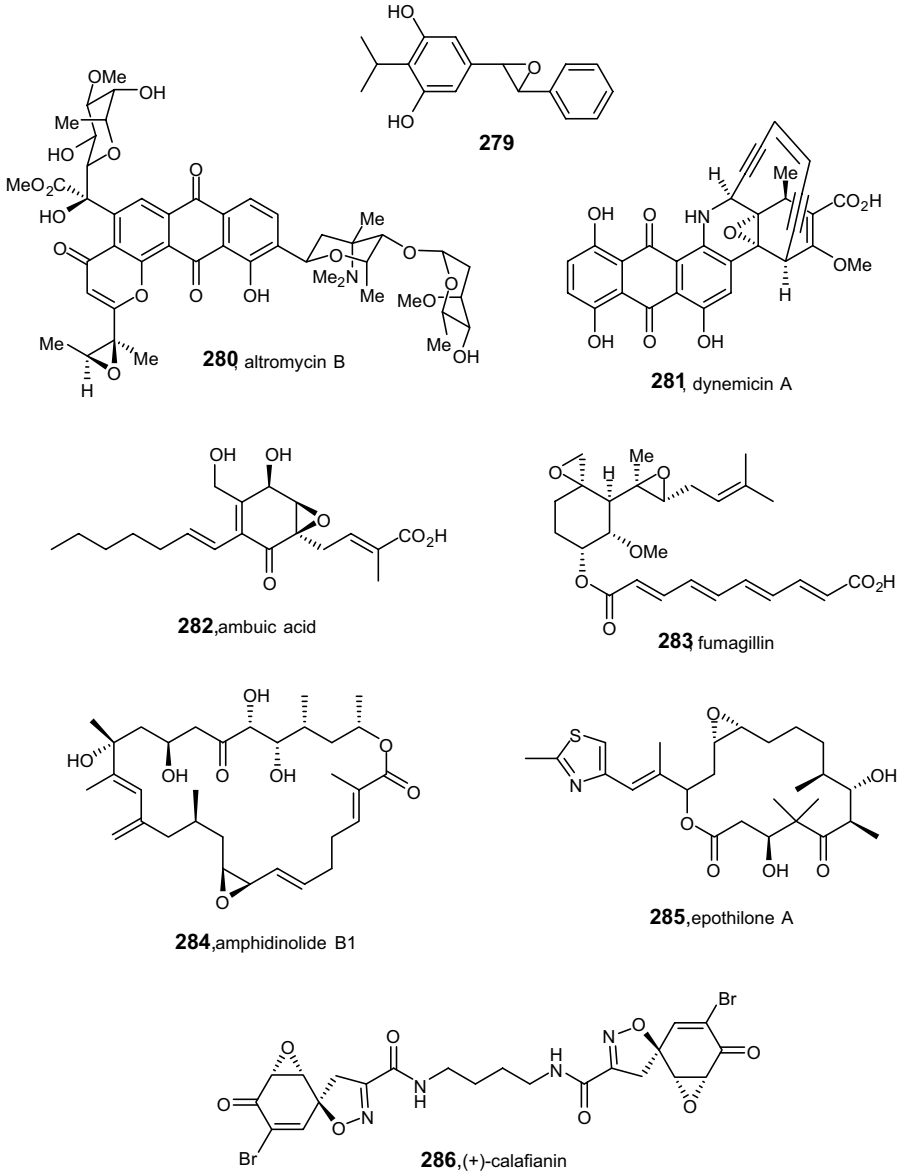


Figure 2.10 Some naturally occurring oxiranes.

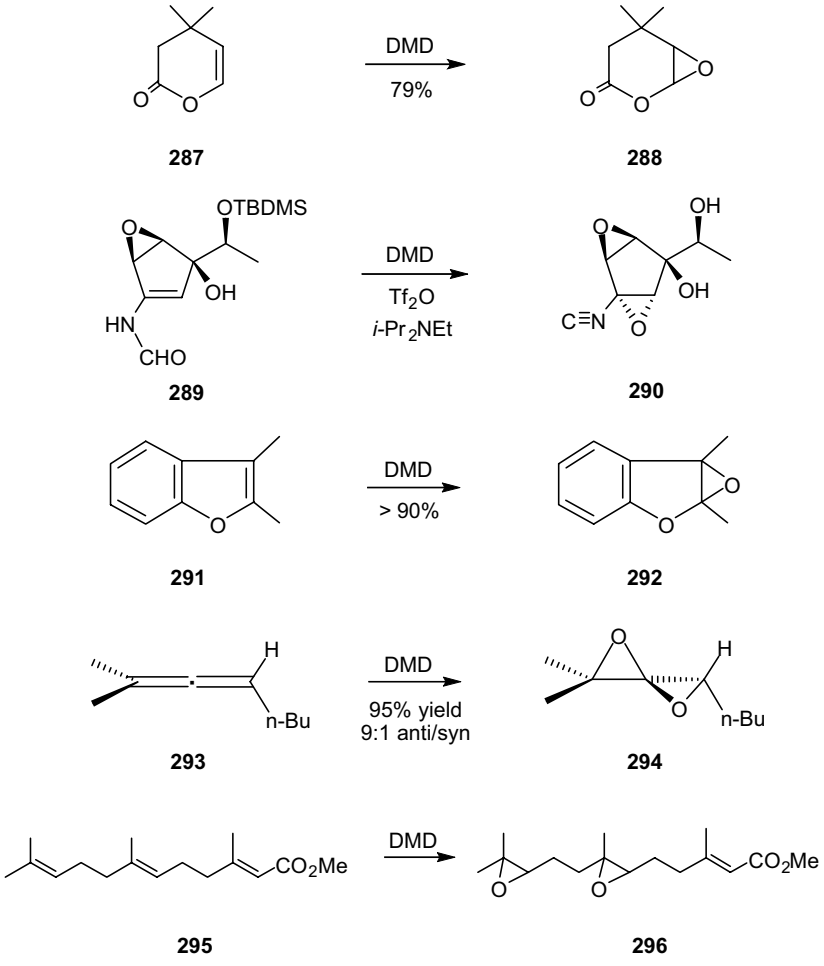
2.3.2
Synthesis of Oxiranes

The synthesis of oxiranes has been the subject of several recent reviews, encompassing biosynthetic routes [329] and asymmetric methodologies [330], including

those proceeding through homo- and heterogeneous catalysis [331] and epoxidations under the influence of chiral auxiliaries [332]. The preparation of vinyl epoxides has also been reviewed recently [333], as have as other topical works mentioned in the appropriate context below.

2.3.2.1 **Using Dioxiranes**

Epoxides can be prepared by the action of dioxiranes on alkenes under mild conditions and low temperature [334]. For unstable epoxides, such as those derived from enol ethers, dioxirane epoxidation is the method of choice. Several reports have exploited this reaction to obtain the previously unisolable acyloxo, alkoxo and silyloxooxiranes. An example of this approach involves the preparation of epoxide **288** from enol lactone **287** (Scheme 2.51) using one of the simplest dioxirane



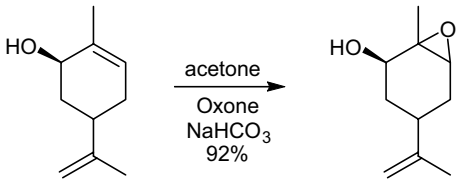
Scheme 2.51 Dimethyldioxirane (DMD) epoxidation of sensitive substrates.

derivatives, dimethyldioxirane (DMD). Similarly, DMD epoxidation of silyl enol ethers afforded the corresponding epoxides in excellent yields. These substrates readily undergo an acid-catalyzed rearrangement to α-trimethylsiloxy carbonyl derivatives [335, 336]. Danishefsky has described the use of DMD for the direct epoxidation of glycals. The 1,2-anhydrosugars produced were employed in the stereospecific construction of β-linked oligosaccharides [337].

Epoxy isonitriles cannot be prepared by the direct epoxidation of vinyl isonitriles. However, the DMD oxidation of a series of vinyl formamides was found to produce epoxy formamides in good yield. These compounds were readily converted into the epoxy isonitriles using triflic anhydride and Hünig's base. A total synthesis of isonitrin B (**290**) was carried out using this methodology [338]. Adam and coworkers reported the first benzofuran epoxide synthesis (i.e., **292**) using DMD in their study on the mutagenesis of benzofuran dioxetanes [339]. The same oxidant has been used to advantage in accessing other labile products, including 1,2-dialkoxyoxiranes [340] and flavone epoxides [341].

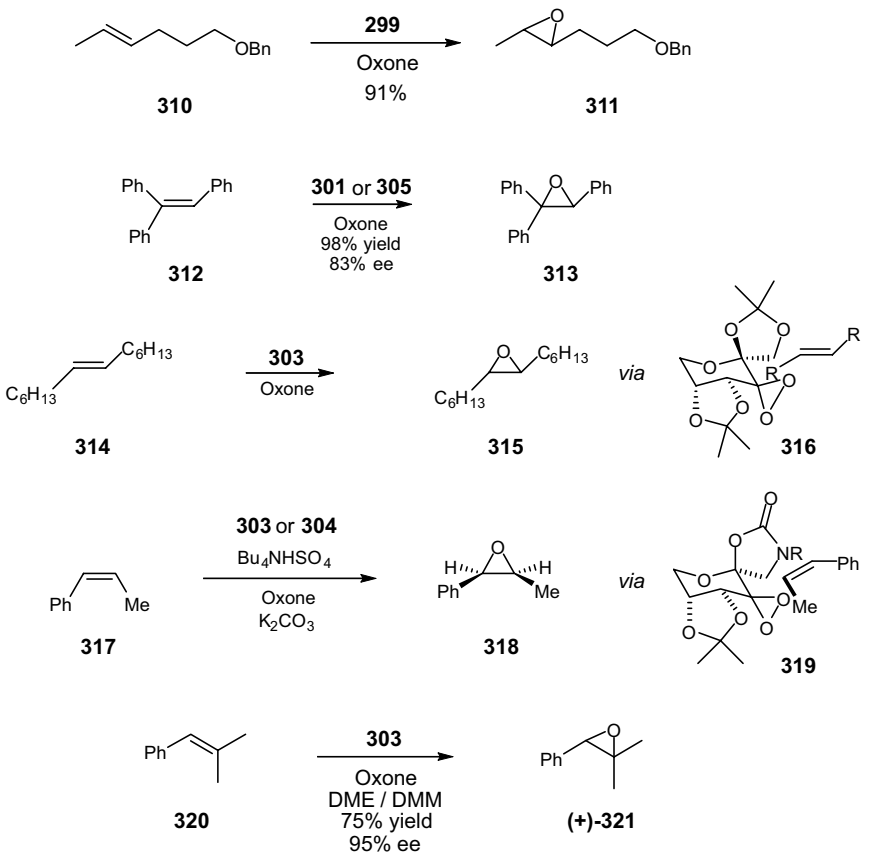
Crandall and coworkers have studied the DMD-mediated epoxidation of various allenes **293**. The corresponding 1,4-dioxiaspiro[2.2]pentanes **294** were produced in good yields, the mono- and di-substituted allenes giving anti diastereomers with good stereoselectivity. These spirodiepoxides then underwent nucleophilic cleavage under buffered conditions (Bu_4NOAc/HOAc) to give highly functionalized α,α′-dihydroxyketone derivatives [342]. Messeguer and coworkers have employed dimethyldioxirane to prepare the diepoxide **296**, a proposed metabolic intermediate of juvenile hormone III [343].

Dioxiranes can also be employed in a catalytic fashion. Practically unrivaled in efficiency and ease of use, DMD itself can be generated *in situ* from acetone in an appropriate buffer. Thus, the dropwise addition of an aqueous solution of Oxone to a stirred mixture of *cis*-carveol (**297**, Scheme 2.52), sodium bicarbonate, and acetone at 0 °C led to the selective formation of epoxide **298** in 92% yield [344]. This general methodology has been expanded to include a wide variety of oxygen carriers. For example, in the area of natural products, Marples and coworkers have used dioxiranes generated *in situ* from a range of ketones to effect 5,6-epoxidation of cholesterol or its acetate in high yield [345]. Bortonlini *et al.* have used sodium dehydrocholate as an organomediator for the sodium perborate (SPB) mediated preparation of acid-sensitive epoxides, in which the intermediacy of a steroidal dioxirane has been suggested [346].



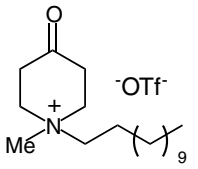
297 **298**

Scheme 2.52 Catalytic epoxidation using DMD.



Scheme 2.53 Epoxidation of alkenes using catalytic dioxiranes.

Denmark has developed a practical phase-transfer protocol for the catalytic epoxidation of alkenes, which uses Oxone as a terminal oxidant. The olefins studied (e.g., **310**, Scheme 2.53) were epoxidized in 83–96% yield. Of the many reaction parameters examined in this biphasic system, the most influential were found to be the reaction pH, the lipophilicity of the phase-transfer catalyst and the counterion present. In general, optimal conditions feature 10 mol.% of the catalyst 1-dodecyl-1-methyl-4-oxopiperidinium triflate (**299**, Figure 2.11) and a pH 7.5–8.0 aqueous methylene chloride biphasic solvent system [347], although these systems are tolerant to neutral and basic pH ranges [348]. The dioxirane derived from the bis(ammonium) ketone **300** also exhibits remarkable reactivity, stability, and water solubility, and has been used to advantage on various substrates [349]. The activation barrier for these reactions is drastically reduced by hydrogen bonding in the transition state, whether by solvent or intramolecularity [350].



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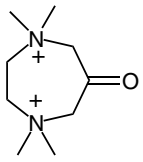

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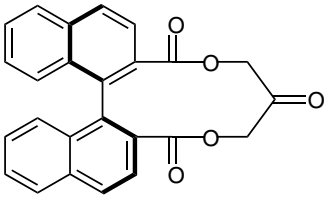

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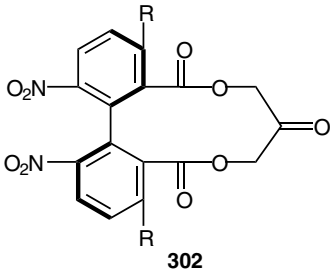

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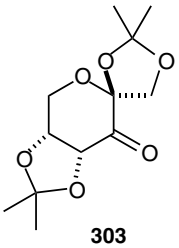

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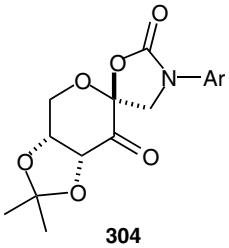

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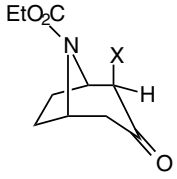

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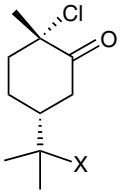

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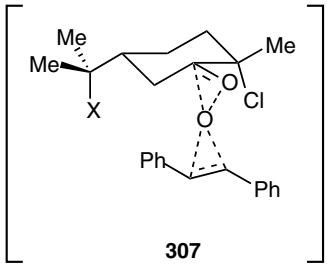

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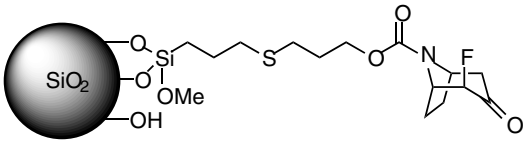

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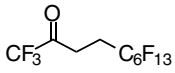


309

Figure 2.11 Ketone precursors for dioxirane oxidations.

The latest twist to this development is the use of chiral ketones in catalytic amounts for the induction of asymmetry during the epoxidation [351]. However, the resultant dioxiranes have two reacting sites, a fact that makes the prediction and execution of asymmetric induction problematic. Yang and coworkers addressed this problem by designing the C2 symmetric, eleven-membered ring ketone **301** as a chiral dioxirane precursor [352]. In this case, both active sites are characterized by the same chiral environment. In fact, a catalytic amount of ketone **301**, in the presence of Oxone as a terminal oxidant, was capable of epoxidizing *trans*-disubstituted and trisubstituted alkenes in excellent yield and modest enantiomeric excess (e.g., **312** → **313**, Scheme 2.53). Electronic and steric embellishments on the ketones (e.g., **302**) can lead to mild enhancements [353]. The main conduit of asymmetric induction is assumed to occur via the "steric sensors" on the aromatic ring. Curiously, enantioselectivity increases with the size of the substituent only to a certain point, then begins to decrease again.

Shi and coworkers have successfully developed ketalized D-fructose derivatives (e.g., **303**) as chiral dioxirane precursors [354]. Excellent ees were obtained, even for the recalcitrant *trans*-disubstituted alkenes (e.g., **314** → **315**, 81% yield, 90% ee) [355] and trisubstituted alkenes (e.g., **320** → **321**, 75% yield, 95% ee) [356]. However, this system appears to be highly substrate dependent, owing to a complex interaction of steric and electronic factors [357–359]. There are several important features of the key dioxirane intermediate. First, the stereogenic centers are in close proximity to the ultimate reactive site of the dioxirane; second, the carbonyl group is flanked by a fused ring on one side and a quaternary center on the other, preventing epimerization; and, finally, only one face of approach is available, since the other is sterically blocked. As for the actual transitions state, the results are consistent with a spiro configuration (**316**) that is directed by steric interactions. The protocol has been optimized so that the chiral ketone **303** can be used in catalytic quantities with Oxone as the stoichiometric oxidant. The key to preserving the lifetime of the chiral auxiliary is pH control during the reaction; the optimum range was found to be 10.5 or above, which is conveniently maintained with potassium carbonate [360, 361].

The related oxazolidinone ketone catalyst **304**, prepared in six steps from D-glucose [362], has the advantage of exhibiting high ees for both *cis*- and terminal olefins [363]. Interestingly, for olefins with aromatic substituents, it appears that the transition state shows a preference for positioning the π-system proximal to the oxazolidinone moiety (as in **319**), so that aromatic groups can be efficiently differentiated during the epoxidation. In studies involving the epoxidation of *cis*-methylstyrene (**317**), the electronic character of the oxazolidino *N*-aryl group was found to influence the outcome of the reaction, presumably by modulating the interaction between the catalyst and the aromatic substituent of the substrate [364]. Similarly, increasing the steric demand adjacent to the amide carbonyl can improve selectivity [365].

Other catalysts also exhibit a combination of these factors. For example, the tropinone-derived chiral ketone **305** owes its enantioselectivity to the structurally rigid and compact asymmetric ring structure. Incorporation of an electron-withdrawing fluoro substituent at the α-position enhanced the catalytic reactivity. Enan-

tiomeric excesses tend to be modest, but occasionally are quite good, as seen in the epoxidation of phenylstilbene (**312**), which takes place in quantitative yield and with 83% ee [366]. The impact of these electronic effects is intriguing, and can be quite dramatic. A particularly noteworthy example is the non-conjugated electronic interactions that result from a remote substituent in the carvone-derived catalyst **306**. In the epoxidation of *trans*-stilbene, the series of small substituents (F, Cl, OH, OEt and H) give ees of 42–87%, exhibiting a very high correlation with the respective Hammett ϱ values. These results have been rationalized on the basis of stabilization of the favored transition state (**307**) by field effects [367]. Some interesting immobilized dioxirane precursors have also been reported, such as the novel heterogeneous ketone **308** [368] and the fluoroketone **309**, designed for use in fluorous media [369].

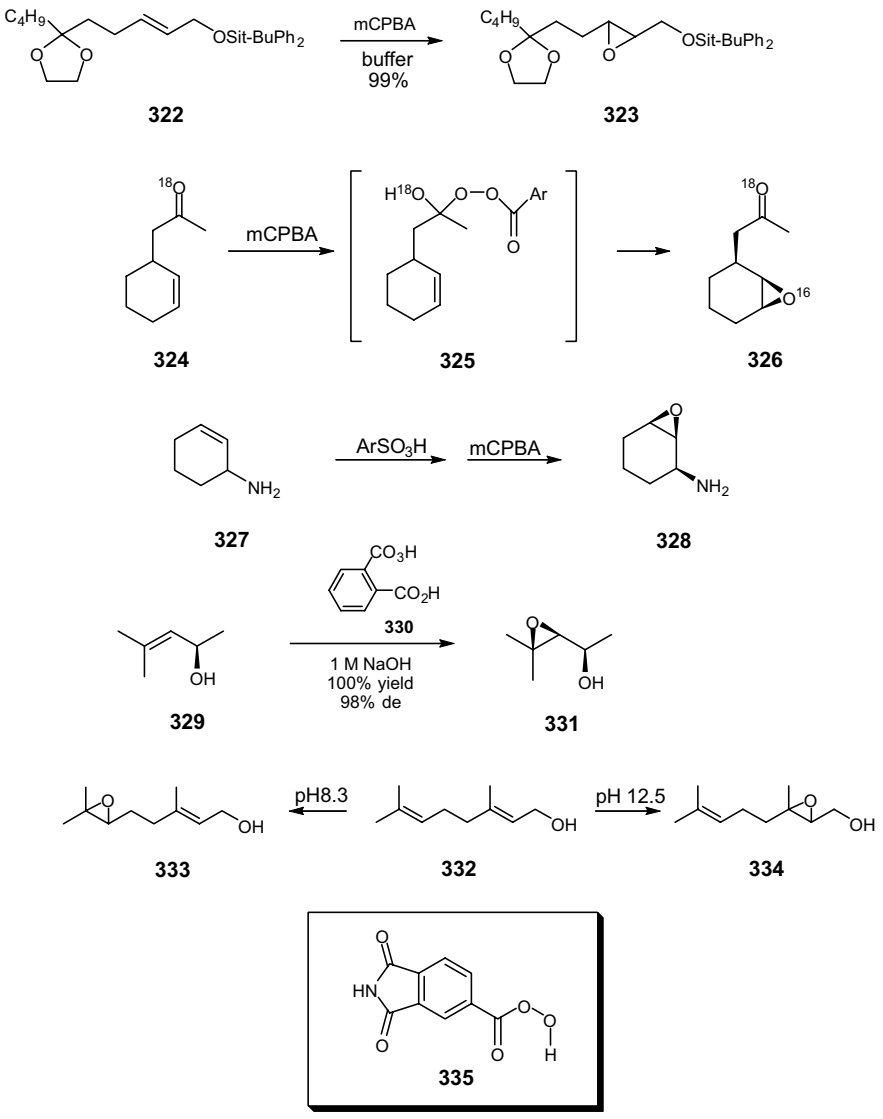
2.3.2.2 Using other Oxidants without Metal Catalysts

The epoxidation of alkenes without metal catalysis represents a large and diverse group of preparative methods for oxiranes, and here the various systems can be characterized largely by two key components: the oxygen carrier (or catalyst) and the terminal (stoichiometric) oxidant. In this regard, *m*-chloroperbenzoic acid (mCPBA) is a tried and true reagent [370], and has been adapted to the large-scale practical synthesis of epoxides [371]. Buffered mCPBA systems are useful for epoxidations in which the alkenes and/or resultant epoxides are acid-sensitive. For example, 2,6-di-*tert*-butylpyridine was shown to give superior results in the case of certain allyl acetals (e.g., **322**, Scheme 2.54) [372]. Bicarbonate [373] and phosphate [374] buffers are also frequently encountered in this context.

Multifunctional alkenes offer some interesting possibilities. For example, enone **324** undergoes ketone-directed epoxidation when treated with mCPBA to give exclusively the syn epoxyketone **326**. As for the mechanism, hydrogen bonding effects were discounted on the basis of solvent insensitivity. Intramolecular attack by some oxidized form of the ketone moiety could be operative, although ^{18}O labeling studies have ruled out a dioxirane intermediate as the active epoxidizing species. Thus, the observed stereoselectivity was rationalized on the basis of intramolecular epoxidation by an α-hydroxy peroxide (i.e., **325**) or possibly by a carbonyl oxide intermediate [375].

Whereas aminoalkenes cannot be converted into epoxides by usual methods (competing N-oxidation), protonation by an arenesulfonic acid and subsequent treatment with mCPBA allows for chemoselective epoxidation. Furthermore, when properly disposed, the pendant ammonium functionality can serve as a potent directing group for the oxidant. Thus, under these conditions cyclohexenylamine **327** affords exclusively the syn epoxide **328** [376].

In the case of dual functionality, the two sites may interact in either a constructive or destructive fashion. This was illustrated by a set of stereoselective epoxidations on a series of allylic carbamates that were appended with a carbomethoxy group, a hydroxymethyl group, or an acetoxymethyl group. In all cases, *threo* epoxides were favored (syn to the carbamate) upon treatment with mCPBA, which reflects the strong directing power of the carbamate group. However, the magnitude of the syn : anti ratio was dependent upon the type and configuration of the other



Scheme 2.54 Epoxidation of alkenes using peracids.

functionality. A relatively low ratio was observed when the two groups compete for face selectivity, whereas "cooperative coordination" leads to higher selectivity. From the magnitude of the perturbation, the following order of directing ability was proposed: carbamate > methyl ester > homoallylic alcohol = acetate [377].

The reaction of allyl alcohol with peroxyformic acid has been examined extensively using molecular modeling calculations [378]. Prompted by the observation that peracid epoxidations can be far more selective in basic aqueous medium than in

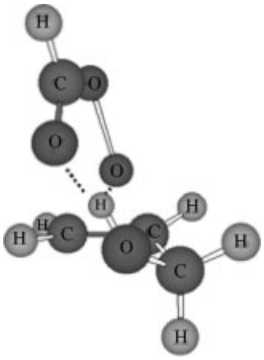


Figure 2.12 TS for epoxidation of allylic alcohol with performate.

organic solvent [379], Washington and Houk studied transition structures from the epoxidation of allylic alcohol with performate ion at the B3LYP/6-31 + G(d,p) level of theory in a CPCM continuum model for water [380]. Their findings indicate a preferential hydrogen bonding of performate with the substrate hydroxyl group rather than with water, leading to a directed epoxidation via the transition state depicted in Figure 2.12. This reaction is similar to the corresponding cyclopropanation of allylic alcohols in the presence of aqueous sodium hydroxide. To test this model experimentally, the chiral allylic alcohol **329** was treated with monoperoxyphthalic acid (MPPA, **330**) in 1 M NaOH to give the syn epoxy alcohol **332** in quantitative yield with 98% syn/anti selectivity.

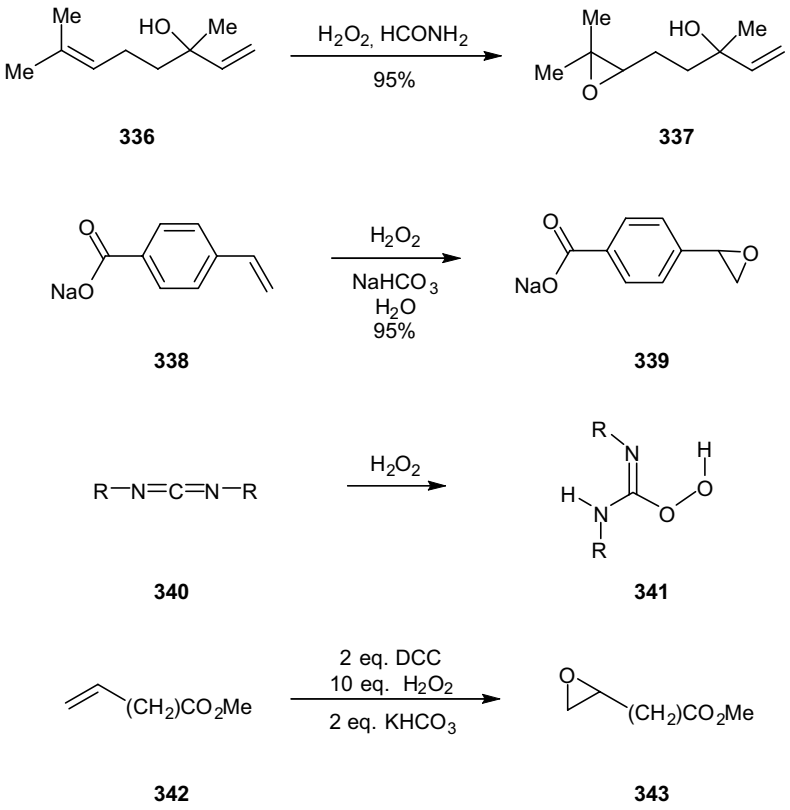
An interesting regiochemical anomaly has been reported by Fringuelli and coworkers [381]. In the epoxidation of geraniol (**332**) by MPPA, the reaction could be directed to either double bond by simple modification to the experimental conditions. In the presence of cetyl(trimethyl)ammonium hydroxide (CTAOH) at pH 12.5, 2,3-epoxygeraniol (**334**) is formed exclusively; however, at pH 8.3 in the absence of CTAOH, the formation of 6,7-epoxygeraniol (**333**) is favored. The magnesium salt of this reagent, magnesium bis(monoperoxyphthalate) hexahydrate (MMPP), is touted as a less expensive and more stable surrogate for mCPBA [382].

With an eye towards industrial applications, Johnstone and coworkers have developed 5-hydroperoxycarbonylphthalimide (**335**) as a new reagent for epoxidation. An easily prepared, shock-stable, crystalline solid, this peroxy acid was designed to exhibit all the desirable properties of more hazardous or expensive reagents (i.e., ease of work-up, low acidity in reaction medium, etc.). Yields, using various substrates, are excellent [383].

Hydrogen peroxide is another frequently used terminal oxidant for epoxidations, and its use with manganese [384] and palladium [385] catalysts has been the subject of recent reviews. Garcia-Bosch and coworkers have demonstrated that metal-catalyzed disproportionation of hydrogen peroxide in some catalytic systems can be suppressed by using a large excess of acetic acid as an additive, presumably facilitating the formation of peracetic acid [386]. Alternatively, Ti(salan) compounds have been

applied effectively to hydrogen peroxide epoxidation systems [387, 388], as well as boron trifluoride in the absence of metal co-catalysts [389].

Another relatively simple metal-free system for the epoxidation of tri- and *cis*-disubstituted olefins (e.g., **336** → **337**, Scheme 2.55) is formamide-hydrogen peroxide in an aqueous medium. This reagent has the advantage of being pH-independent, which makes it attractive for biochemically mediated transformations. No reaction was observed in the case of *trans*-disubstituted and terminal olefins. With bifunctional alkenes, the more reactive double bond is selectively epoxidized [390].



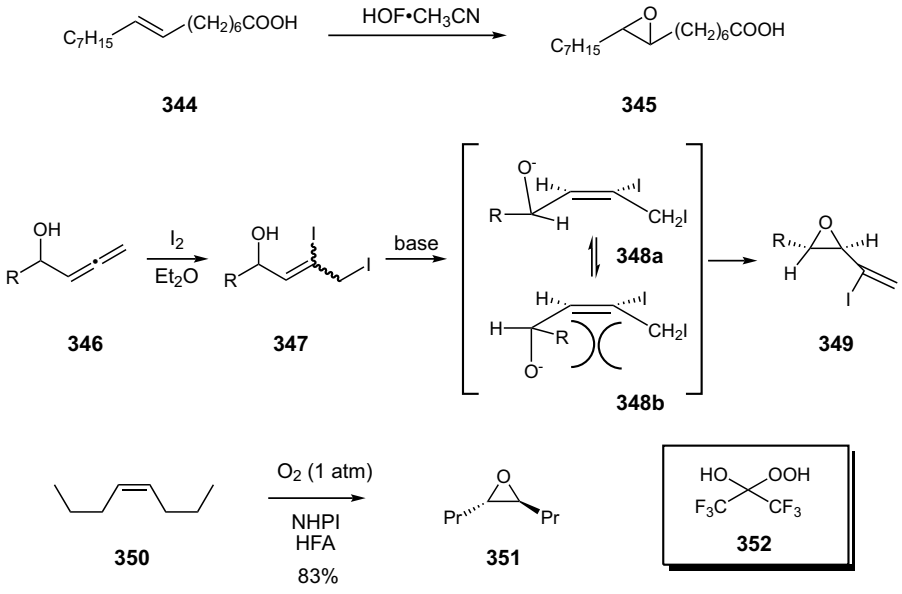
Scheme 2.55 Epoxidation of alkenes using hydrogen peroxide.

Water-soluble alkenes can be epoxidized in remarkably high yields using bicarbonate-activated hydrogen peroxide (BAP). Thus, epoxide **339** was obtained in >95% yield from sodium *p*-vinylbenzoate (**338**). Diol formation is a competing side reaction with some substrates [391].

The epoxidation of olefins with hydrogen peroxide can also be promoted by the addition of carbodiimides, presumably by the initial formation of a peroxyisourea

species (**341**) [392]. Majetich and Hicks have reported on the epoxidation of isolated olefins (e.g., **342**) using a combination of 30% aqueous hydrogen peroxide, a carbodiimide (e.g., DCC) and a mildly acidic or basic catalyst. This method works best in hydroxylic solvents and not at all in polar aprotic media. The type and ratios of reagents are substrate dependent, and steric demand about the alkene generally results in decreased yields [393]. The methodology can be adapted to asymmetric epoxidation by using an aspartate-containing tripeptide [394].

Olefins containing free hydroxyl groups or carboxylic acid moieties can be oxidized rapidly and efficiently at room temperature using an easily prepared acetonitrile complex of hypofluorous acid ($HOF{\cdot}CH_3CN$). The reagent does not induce formation of peroxides with free hydroxy groups, and aromatic rings do not interfere with the reaction. Thus, oleic acid (**344**, Scheme 2.56) was epoxidized in 10 min and in 90% yield [395].



Scheme 2.56 Epoxidation of alkenes using other non-metal oxidizing agents.

Allenic alcohols **346** are converted in the presence of iodine into a mixture of *(Z)*- and *(E)*-diiodides (**347**), which, upon subsequent treatment with base, form the *trans*-iodovinyl epoxides **349** with a diastereomeric excess of >99%. This high degree of selectivity is rationalized on the basis of steric interactions between the R group and the iodine atom in the transition state leading to epoxide formation (i.e., **348a** vs. **348b**) [396].

One of the most attractive oxidants for this chemistry is dioxygen, both from an environmental and cost standpoint. In this vein, a metal-free epoxidation protocol

was reported that proceeded via the *in situ* generation of hydrogen peroxide from O_2 through a complex series of steps involving *N*-hydroxyphthalimide (NHPI). Once formed, the H_2O_2 is activated by addition onto the somewhat esoteric solvent, trifluoroacetone, to give 2-hydroperoxy-hexafluoropropan-2-ol (**352**) as the oxygen transfer reagent. The reaction appears to be general and yields are very good. Regardless of the starting configuration of the alkene, a strong preference for the formation of *trans*-epoxides was observed (e.g., **350** → **351**) [397].

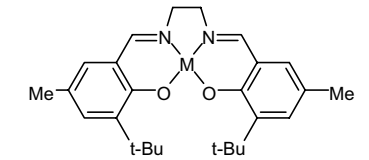
2.3.2.3 Metal-Catalyzed Epoxidation of Alkenes

The topic of metal-based catalysis for alkene epoxidation is expansive, and the reader is directed to two excellent reviews of this chemistry by Adolfsson [398] and Adolfsson and Balan [399], as well as an outstanding treatise on mechanism and kinetics by Oyama [400] and an overview of asymmetric methods by Matsumoto and Katsuki [401]. The development of (salen)metal complexes (Figure 2.13) for the epoxidation of alkenes has been nothing less than revolutionary, providing access to epoxides from simple olefins in much the same way Sharpless chemistry paved the way for the epoxidation of functionalized alkenes. An extensive review specifically on the chromium- and magnesium-salen catalyzed epoxidation of alkenes has recently appeared [402].

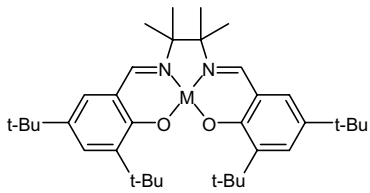
In the absence of other functionality, typical peroxyacid epoxidation of dienes favors reaction on the more substituted double bond. However, the (salen)manganese complex **353** promotes epoxidation of the less substituted double bond (e.g., **362** → **363**, Scheme 2.57), thus providing a complement to conventional methods. This protocol is also useful for substrates that polymerize under peracid conditions [403]. Allylic alcohols are equally suitable substrates, as demonstrated by the epoxidation of **364** using the vanadyl salen oxo-transfer catalyst **354** in supercritical carbon dioxide with *tert*-butyl hydroperoxide as a terminal oxidant [404].

The lion's share of research activity in this area has centered around asymmetric epoxidation using chiral salen catalysts. Thus, the chiral (salen)Mn(III) complex **356**, which is readily available on a large scale in high yield from commercially available starting materials [405, 406], is the centerpiece of Jacobsen's enantioselective synthesis of the taxol side chain **369** [407], in which the epoxy ester **367** is prepared from *cis*-ethyl cinnamate with very high enantiomeric excess (Scheme 2.58). Typically under these conditions, *cis*-double bonds are converted stereospecifically into *cis*-epoxides. However, in the case of conjugated dienes, *trans*-epoxides are the major products. The crossover has been ascribed to a step-wise oxygen transfer mechanism involving an intermediate radical that undergoes bond rotation to give the observed products. This anomalous behavior has been leveraged in a method for the regioselective epoxidation of *cis,trans*-dienes to give *trans,trans*-diene monoepoxides (e.g., **370** → **371**) [408].

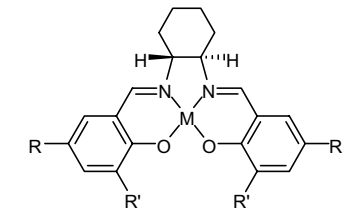
Cyclic and acyclic trisubstituted alkenes are also epoxidized with high enantioselectivity under the catalysis of **356**, as exemplified by the conversion of phenylstilbene **312** into the *(S)*-epoxide **313** with 92% enantiomeric excess. The sense of enantioselection is opposite that of disubstituted alkenes, and a global mechanistic model has been developed to rationalize the stereochemical outcomes of this class of



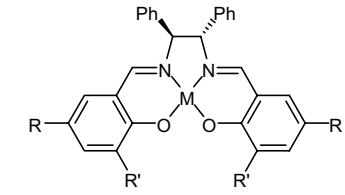
353, M = Mn-Cl
354, R = M = V(O)



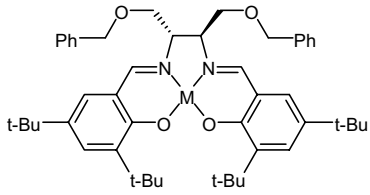
355, M = Mn-Cl



356, R = R' = t-Bu; M = Mn-Cl
357, R = $(i\text{-}Pr)_3SiO$-;R' = t-Bu; M = Mn-Cl
358, R = R' = t-Bu; M = Cr(O)-Cl
359, R = R' = Cl; M = Cr(O)-PF_6



360, R = $(i\text{-}Pr)_3SiO$-;R' = t-Bu; M = Mn-Cl

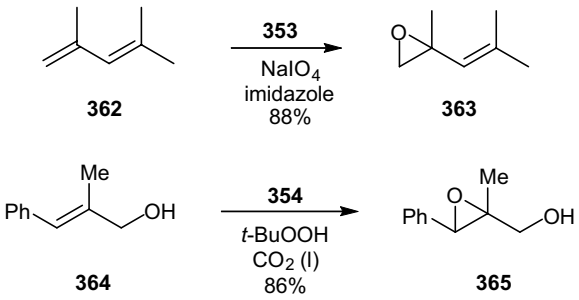


361, M = Cr-OTf

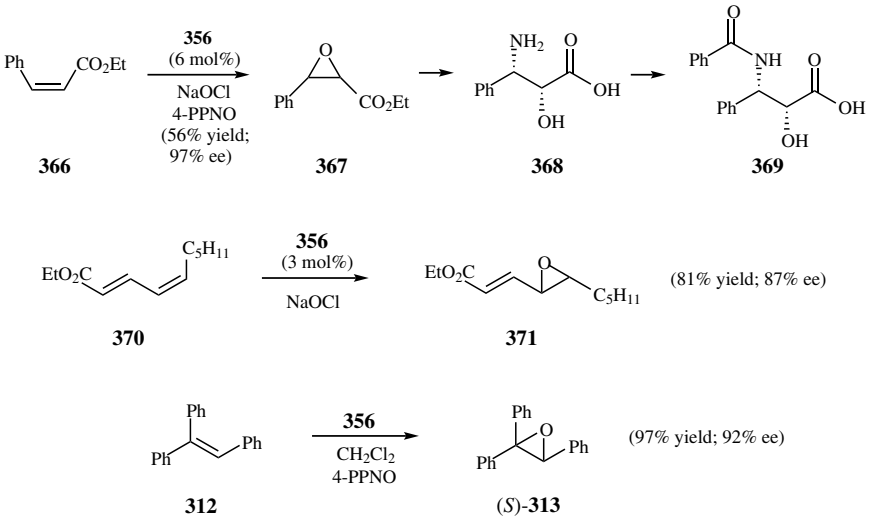
Figure 2.13 Salen metal catalysts for alkene epoxidation.

epoxidations [409]. Furthermore, a wide range of terminal oxidants have been employed with this catalyst, including hydrogen peroxide [410], dimethyldioxirane [411], periodates [403] and the organic-soluble oxidant tetrabutylammonium monopersulfate [412].

Terminal olefins typically give relatively low enantiomeric purities, which might be due to poor enantiofacial selectivity during the oxygen addition or facile rotation of a

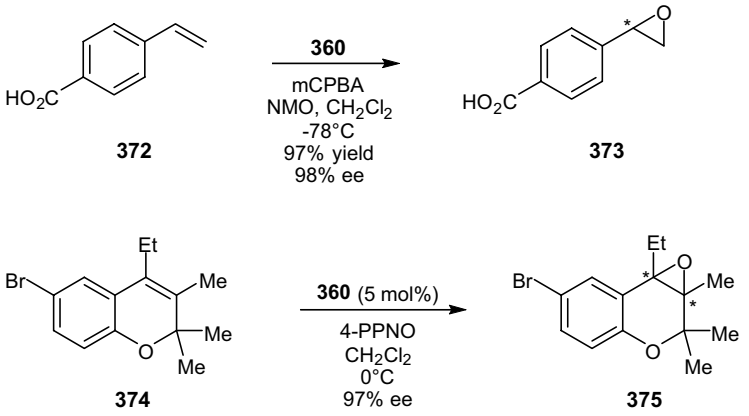


Scheme 2.57 Alkene epoxidations using achiral salen metal catalysts.



Scheme 2.58 Alkene epoxidations using chiral salen metal catalysts.

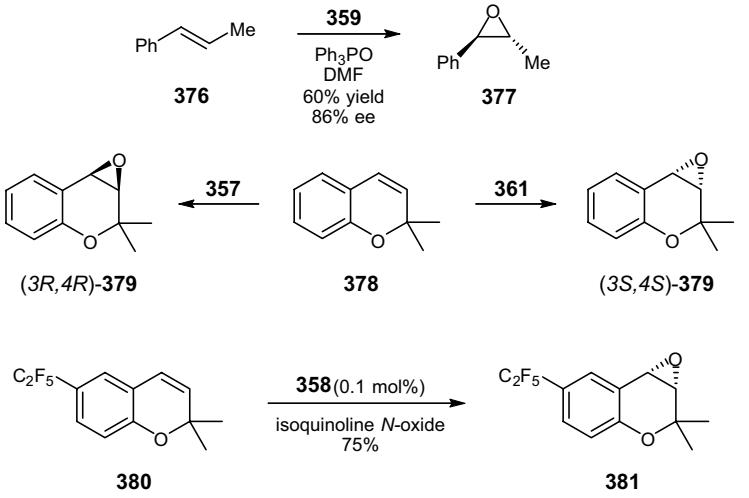
radical intermediate unencumbered by α-substitution. Either of these impediments should be positively impacted by decreasing thermal energy, and this has been borne out by experimental evidence [413]. Katsuki has reported increased ees by adding NaCl to the aqueous hypochlorite system, thus allowing for sub-zero (−18 °C) reaction temperatures [414]. The asymmetric induction may be further enhanced by modification of the catalyst. Replacement of the *tert*-butyl group with the triisopropylsiloxy substituent affords a catalyst (i.e., **357**) that is not only sterically more defined but also electronically attenuated, and thus is milder and more selective [415]. The diphenyl variant **360** was equally effective in epoxidizing a series of recalcitrant olefins, such as vinylbenzoic acid **372** (Scheme 2.59) in the presence of *N*-methylmorpholine *N*-oxide (NMO) as an additive and mCPBA as a terminal oxidant in methylene chloride at −78 °C [416]. These conditions were also advantageous for the epoxidation



Scheme 2.59 More alkene epoxidations using chiral salen metal catalysts.

of tetrasubstituted alkenes, as demonstrated by the conversion of chromene derivative **374** into the corresponding epoxide with 97% ee [417].

Changing the metal center from manganese to chromium can have surprising results. For example, one aggravating phenomenon associated with the (salen)Mn complexes is that the epoxidation of *trans*-olefins proceeds typically with low ees. However, the analogous chromium complexes (e.g., **359**) catalyze such epoxidations with greater selectivity than for the corresponding *cis*-olefins under the same conditions. Here the mechanism is presumed to involve an electrophilic process, which is supported by the fact that only electron-rich alkenes are effectively epoxidized. In the case of *trans*-β-methylstyrene (**376**, Scheme 2.60), enantioselectivities



Scheme 2.60 Salen(Cr)-catalyzed alkene epoxidation.

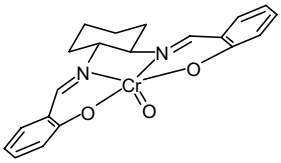


Figure 2.14 Stepped conformation of a salen(Cr) catalyst.

of up to 86% are achieved [418]. Gilheany and coworkers [419] have observed high (>90%) enantioselectivities for *trans*-alkenes using stoichiometric chromium complexes, albeit with modest chemical yields, presumably resulting from the formation of a μ-oxo Cr(IV) dimer *in situ*. A systematic study of the effect of aromatic substituents on enantioselectivities [420] is consistent with an oblique approach of the substrate to a nonplanar (stepped) oxidized catalyst (Figure 2.14).

An interesting reversal of chiral induction in chromium(III)-salen complexes using a tartaric derived alicyclic diamine moiety (i.e., **361**) has been observed by Mosset, Saalfrank and coworkers [421]. Thus, epoxidation of the chromene **378** using catalyst **361** and an oxidant consisting of mCPBA/NMO afforded epoxide **379** in the (3*S*,4*S*) configuration, whereas a classical Jacobsen catalyst (**357**) provided the corresponding (3*R*,4*R*) enantiomer. This approach has been applied to the chiral epoxidation of chromene **380** using the readily available chromium salen catalyst **358** in a synthesis of the novel potassium channel activator BRL55834 [422].

The Katsuki group have focused their attention on (salen)Mn(III) catalysts of a slightly different configuration (e.g., **382–386**, Figure 2.15), which are characterized as having chiral residues at the aromatic 3,3′-positions. These catalysts have been used to advantage in the epoxidation of conjugated *cis*-olefins [423], including chromenes [424, 425], benzocycloheptenes [426], dihydronaphthalenes [427] and enynes [428]. The proposed mechanism involves a flanking attack by the substrate, which is steered by both steric interactions (e.g., the cyclohexyl residue) as well as π–π repulsive forces. Generally speaking, the enantiofacial selection of *cis*-olefins in these catalyst systems appears to be influenced mainly by the chirality on the ethylenediamine bridge, whereas *trans*-olefin epoxidation seems to be directed more by the C3 and C3′ substituents [429].

More subtle arguments have been invoked to rationalize the dichotomous behavior of the so-called "second-generation" Mn-salen catalysts **384** and **385** towards unfunctionalized and nucleophilic olefins. For example, higher yields and ees are obtained with the (*R*,*S*)-complex (**384**) for the epoxidation of indene (**387**, Scheme 2.61). However, *N*-toluenesulfonyl-1,2,3,4-tetrahydropyridine (**389**) gave better results using the (*R*,*R*)-diastereomer (**385**). An analysis of the transition-state enthalpy and entropy terms indicates that the selectivity in the former reaction is enthalpy driven, while the latter result reflects a combination of enthalpy and entropy factors [430].

Other structural modifications to salen catalysts can confer operational advantages. For example, hydrogen peroxide is attractive as a terminal oxidant due to its low cost and ready availability, but epoxidations using this reagent tend to be less enantioselective and more prone to radical-induced side reactions. In some cases, these

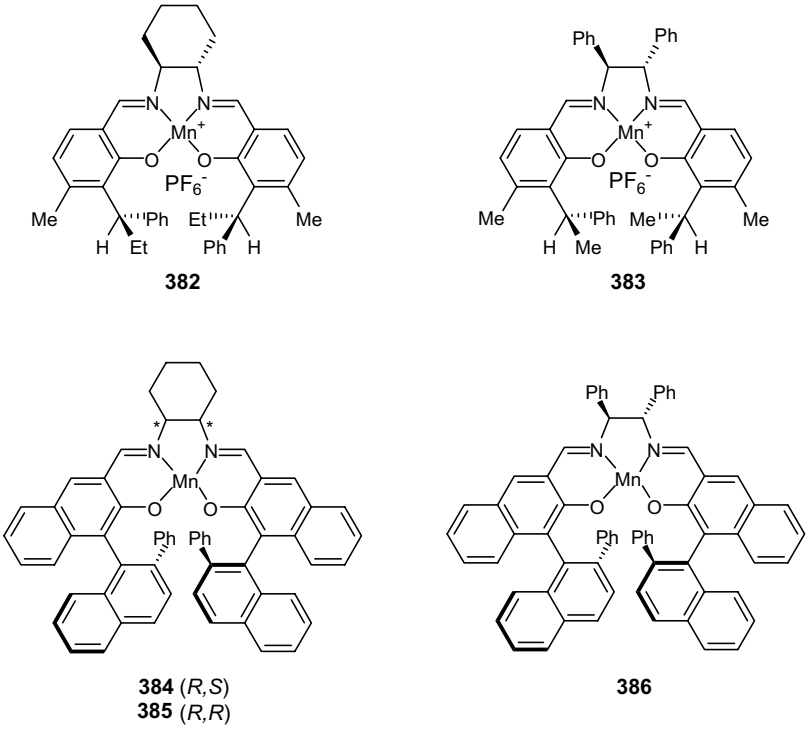
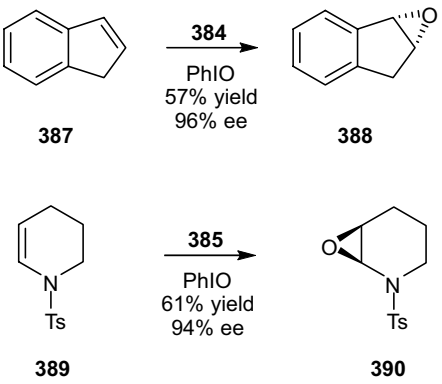


Figure 2.15 Salen catalysts with chirality at the 3-position.



Scheme 2.61 Salen(Mn) catalyzed alkene epoxidation.

disadvantages have been circumvented by using bioinspired models [431]. For example, by tethering an imidazole moiety to a chiral salen-type Mn(III) catalyst, an axial ligand is provided that imitates a peroxidase coordination sphere while still taking advantage of the asymmetric active site of the chiral (salen)Mn(III) species.

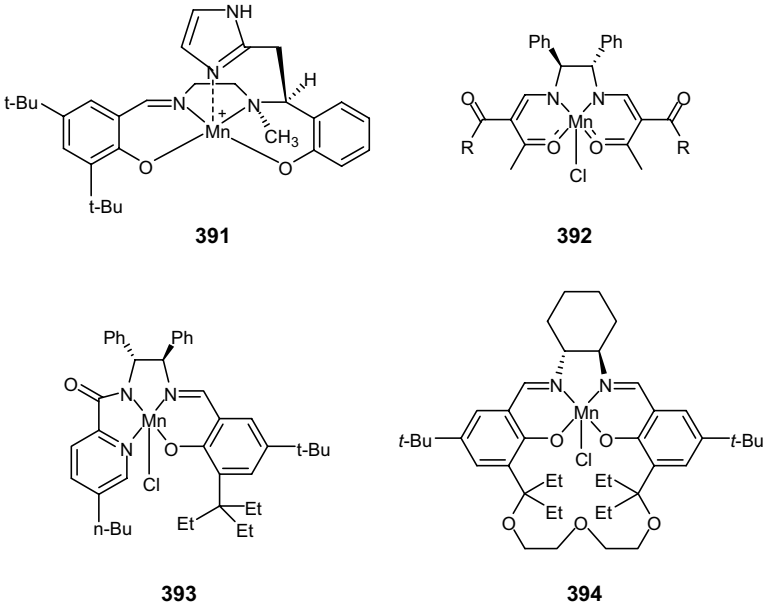


Figure 2.16 Modified salens and salen analogs.

The resulting catalyst (**391**, Figure 2.16) can be used at 10 mol.% loadings with dilute hydrogen peroxide as an oxidant [432]. In a similar vein, the chiral dicarbonyliminato manganese(III) complex **392** is effective using molecular oxygen as the terminal oxidant [433], and the manganese-picolinamide-salicylidene complex **393** exhibits excellent turnover using sodium hypochlorite [434]. The recently disclosed macrocyclic analogue **394** gives very promising results indeed. At a 5 mol.% loading with two equivalents of sodium hypochlorite as a terminal oxidant, chromene **378** is epoxidized in quantitative yield and 93% ee [435].

No small amount of effort has been directed towards the development of immobilized catalysts, both for ease of catalyst recovery and for application to solid-phase combinatorial synthesis. Toward this end, the catalytic moiety has been tethered to a solid support via either the ethylenediamine portion [436] or the salicylaldehyde subunit [437] to give immobilized catalysts of type **395** and **396**, respectively (Figure 2.17). These are the first gel-type resins to give results rivaling solution-phase counterparts. The backbone of Jacobsen's catalyst has also been immobilized on silica gel by radical grafting (e.g., **397**) [438] and it has even been prepared in polymeric form (i.e., **398**) [439]. Other approaches include the use of perfluoroalkyl-substituted catalysts (e.g., **399**) in a fluorous biphasic system [440] and the conventional Jacobsen's catalyst **356** in a medium of the air- and moisture-stable ionic liquid [bmim][PF_6] [441].

A somewhat different approach to catalyst separation has been devised by engineering the chiral salen catalyst to have built-in phase-transfer capability, as exemplified by the Mn(III) complex **400** [442]. Thus, enantioselective epoxidation of

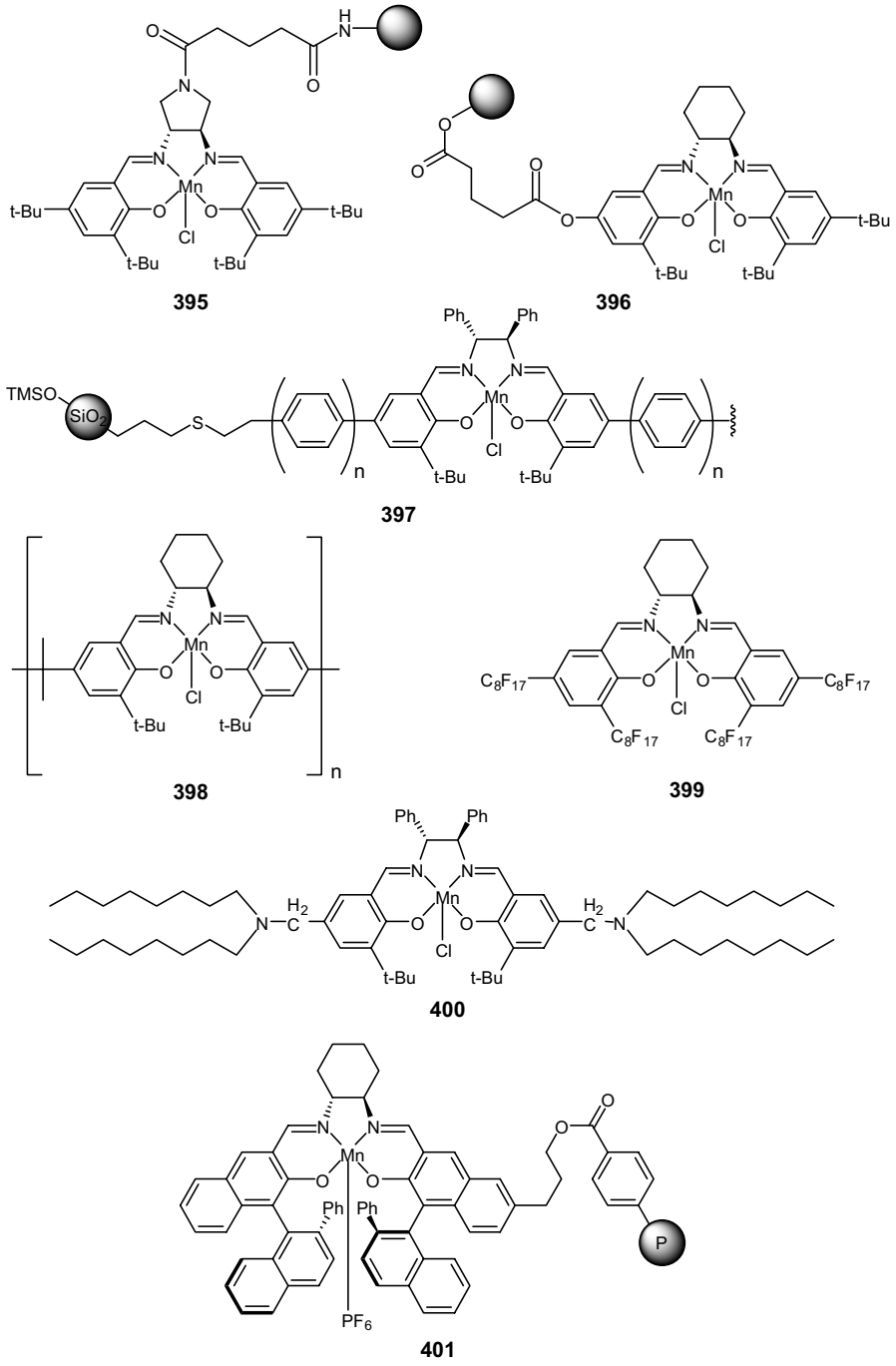
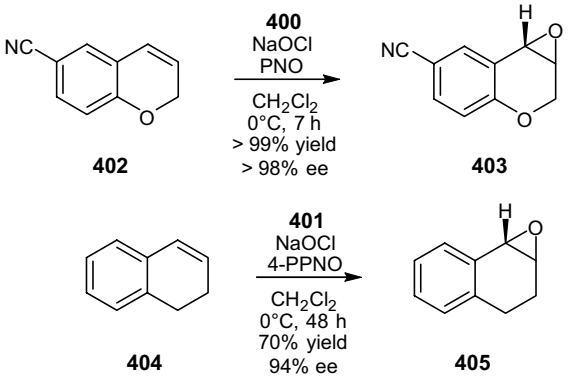


Figure 2.17 Salens designed for biphasic systems.

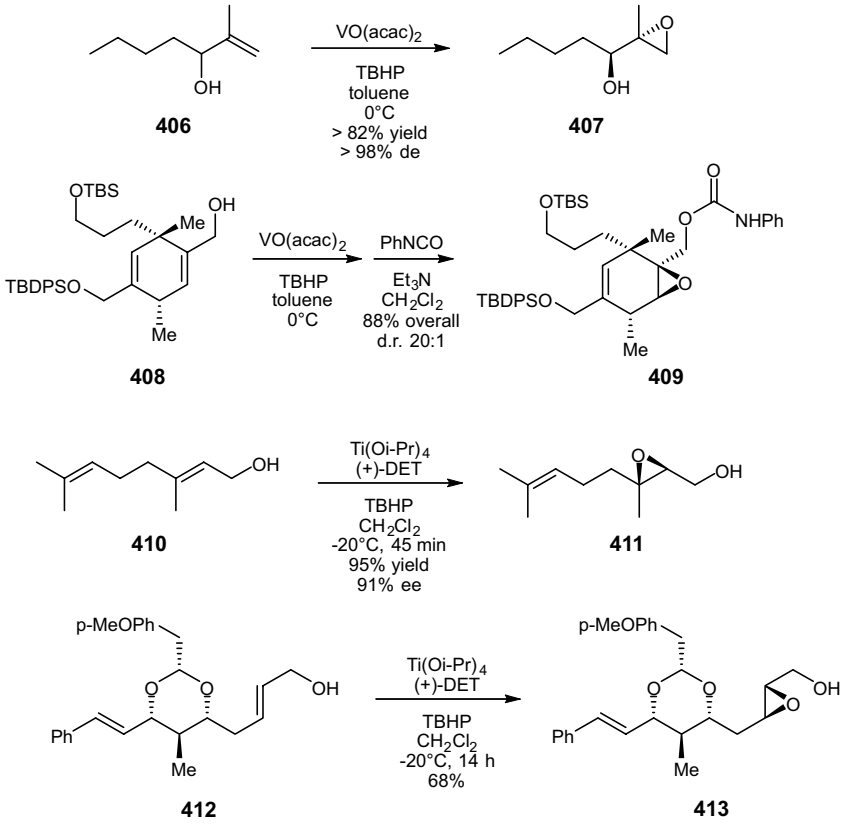
chromene derivatives (e.g., **402**) in the presence of 2 mol.% catalyst **400** and pyridine *N*-oxide (PNO) under phase-transfer conditions (methylene chloride and aqueous sodium hypochlorite) proceeded in excellent yield and very good ees (Scheme 2.62). The catalyst loading could be reduced to about 0.4% with only marginal loss of efficiency. Finally, Smith and Liu [443] immobilized a Katsuki-type salen ligand by an ester linkage to Merrifield's resin to produce catalyst **401**. In a test epoxidation of 1,2-dihydronaphthalene (**404**) using sodium hypochlorite as an oxidant and 4-phenylpyridine *N*-oxide (4-PPNO) as an activator, the immobilized (salen)Mn complex sustained high enantioselectivity (>90%), even after being recycled six times.



Scheme 2.62 Epoxidation with immobilized metal salen catalysts.

No discussion of metal-catalyzed epoxidation could be complete without addressing Sharpless chemistry. Now an imbedded part of the synthetic organic canon, this topic has been very nicely summarized in a recent review article [444]. Two common catalysts in this regard are $VO(acac)_2$ and $Ti(O\textit{i}\text{-}Pr)_4$, and although their first applications were reported decades ago, the methodology is still very much in currency. Thus, the vanadium-mediated diastereoselective epoxidation of allylic alcohols, a key step in the synthesis of *Cecropia* juvenile hormone (i.e., **406** → **407**, Scheme 2.63) described in 1974 [445], was employed in much the same form in 2006 in the epoxidation of the highly functionalized allylic alcohol **408**, providing a key intermediate for an approach to the quartromicins [446]. Likewise, the classic tartrate/titanium-mediated asymmetric epoxidation of allylic alcohols (i.e., **410** → **411**), the scope of which was described in detail by Sharpless in 1987 [447], is an almost indispensable tool for the synthetic chemist, as evidenced by its application in the construction of the bicyclic ether core of (+)-sorangicin A (i.e., **412** → **413**) reported by Crimmins and Haley [448].

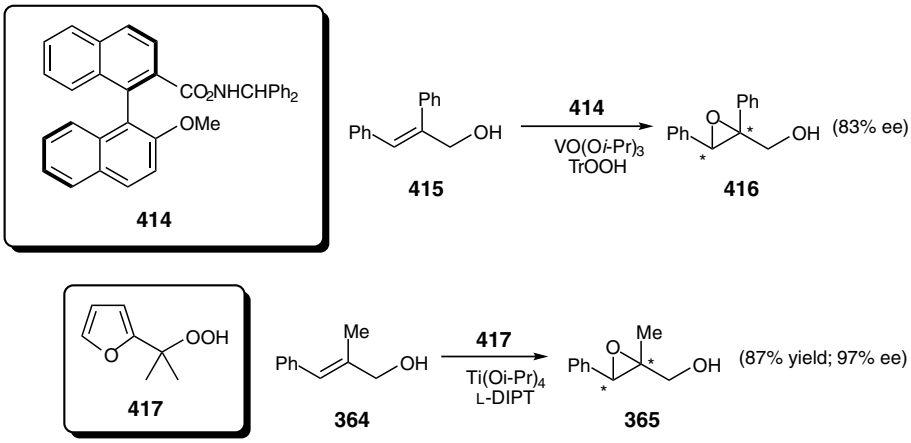
These protocols continue to provide springboards for further development and innovation. For example, Hussain and Walsh [449] have developed a Sharpless-inspired tandem alkylation/epoxidation of prochiral enones to provide chiral non-racemic hydroxyepoxides. Yamamoto and coworkers [450] have developed a chiral



Scheme 2.63 Epoxidation under Sharpless conditions.

hydroxamic acid (**414**) derived from binaphthol, which serves as a coordinative chiral auxiliary when combined with $VO(acac)_2$ or $VO(i\text{-}PrO)_3$ in the epoxidation of allylic alcohols. In this protocol, triphenylmethyl hydroperoxide (TrOOH) provides markedly increased enantiomeric excess, compared to the more traditional *t*-butyl hydroperoxide. Thus, the epoxidation of *(E)*-2,3-diphenyl-2-propenol with 7.5 mol.% $VO(i\text{-}PrO)_3$ and 15 mol.% of **414** in toluene (−20 °C; 24 h) provided the (*2S,3S*) epoxide **416** in 83% ee. Malkov and coworkers were able to carry out the same transformation in 92% yield and 94% ee using a cyclohexylamine-derived sulfonamide hydroxamic acid catalyst [451].

An alternative organic peroxide source is also at the heart of another modified catalytic Sharpless epoxidation of allylic alcohols, in which the tertiary furyl peroxide **417** serves as the terminal oxidant in the presence of L-diisopropyl tartrate (L-DIPT). Thus, *trans*-2-methyl-3-phenylprop-2-en-1-ol (**364**) was converted into epoxide **365** in 87% yield and with 97% ee using a catalyst loading of 20 mol.% [452] (Scheme 2.64).

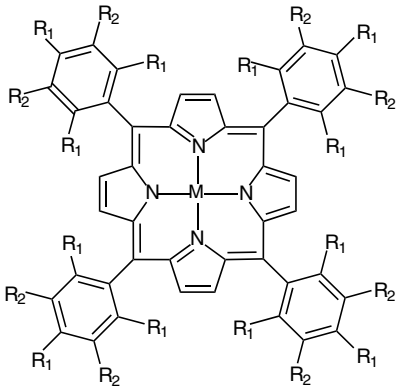


Scheme 2.64 Modified Sharpless conditions.

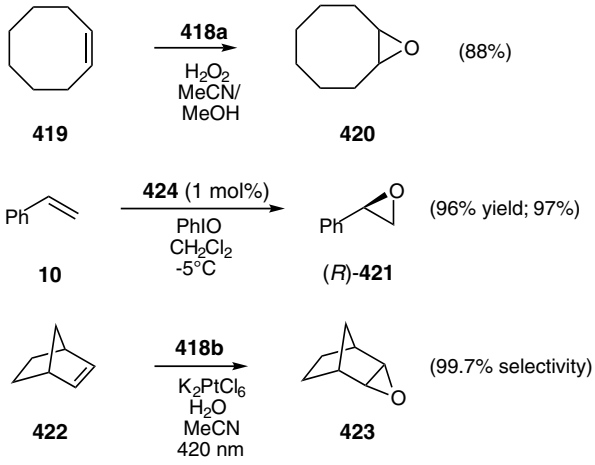
Biological models have inspired the adaptation of metalloporphyrin complexes for synthetic processes. For example, chloroperoxidase (CPO) catalyzes the epoxidation of many simple *cis*-alkenes with high enantioselectivity, although bulkier substrates tend to lead to low conversion and terminal alkenes alkylate the catalyst [453]. A more generally applicable analog can be found in the iron(III) tetrakis(pentafluorophenyl) porphyrin **418a** (Scheme 2.65), for which considerable mechanistic studies have been carried out [454, 455]. Cyclooctene (**419**) is smoothly epoxidized by **418a** using hydrogen peroxide as the terminal oxidant. Many interesting modifications have been made to the porphyrin template, most notably for the purposes of asymmetric induction, which has been the subject of a recent review [456]. Thus, the binaphthyl strapped iron-porphyrin catalyst **424** promotes the enantioselective epoxidation of styrene (**10**) with iodosylbenzene to give *(R)*-styrene oxide (**421**) in excellent yield and enantiomeric excess [457]. Effective non-heme iron catalysts using pentadentate bispidine ligands have also been studied [458].

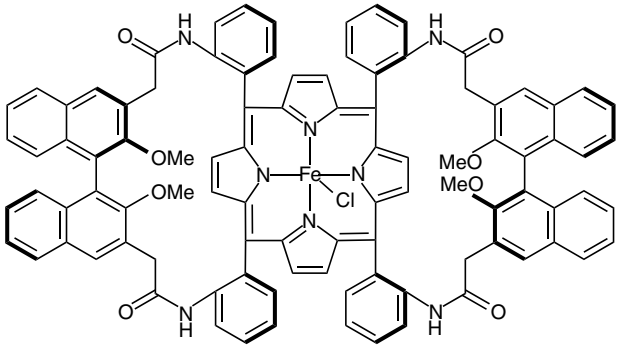
Some interesting ruthenium porphyrins have also been reported, including a dioxoruthenium(VI) species [459] and the ruthenium(II) catalyst **418b**, which functions as a photosensitizer capable of effecting the selective epoxidation of alkenes (e.g., **422**) using water as an oxygen source, although the method suffers from the limitation of requiring hexachloroplatinate as an electron acceptor [460]. Metalloporphyrins of all stripes have been appended to solid supports, and the reader is directed to a recent and effective review on the topic for further information [461].

Polyoxometallates (POMs) have been in the research crosshairs lately, as evidenced by a recent review [462]; this interest stems in some portion from their ruggedness and environmental acceptability. As an example, the sandwich-type POM $[WZnMn^{II}{}_2(ZnW_9O_{34})_2]^{12-}$ catalyzes the selective epoxidation of chiral allylic alcohols with aqueous hydrogen peroxide under mild conditions. Thus, 4-methylpent-3-en-2-ol **425** is converted into the *threo* epoxide **426** in 88% yield and 84% de (Scheme 2.66). The diastereoselectivity is highly sensitive to the substitution about



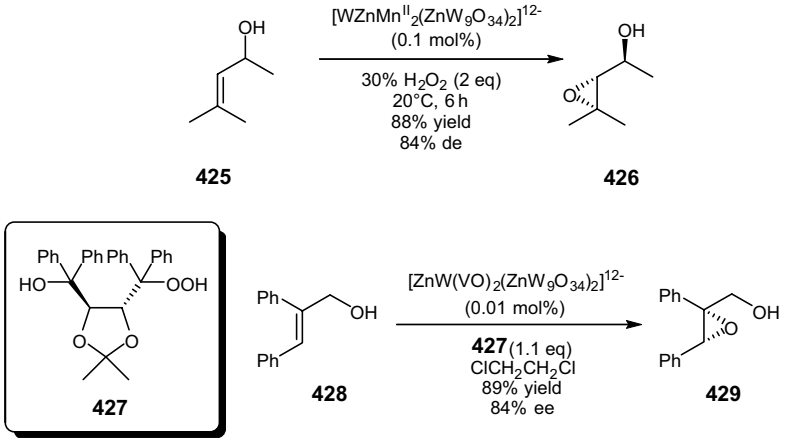
418a, R_1= R_2= F; M = Fe(Cl)
418b, R_1= Me; R_2= H; M = Ru(CO)





424

Scheme 2.65 Epoxidations using metalloporphyrins.

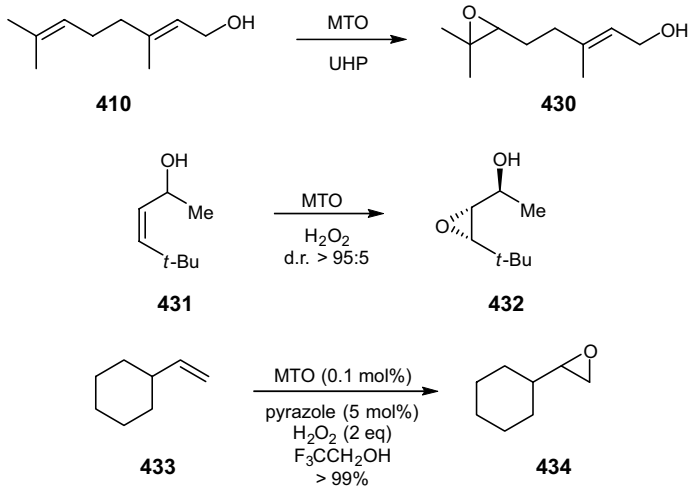


Scheme 2.66 Epoxidations using polyoxometallates (POMs).

the double bond, with *trans*-pent-3-en-2-ol giving a 1 : 1 mixture of *threo* and *erythro* epoxides under the same conditions. The key intermediate is believed to be a tungsten peroxo complex rather than an oxo-Mn species [463]. Self-assembled POM catalysts can also be immobilized within layered double hydroxides (LDH) using ion-exchange techniques [464].

A polyoxometallate is also at the heart of an enantioselective epoxidation of allylic alcohols using C-2 symmetric chiral hydroperoxide **427** derived from 1,1,4,4-tetraphenyl-2,3-*O*-isopropylidene-D-threitol (TADDOL). Thus, in the presence of the oxovanadium(IV) sandwich-type POM $[ZnW(VO)_2(ZnW_9O_{34})_2]^{12-}$ and stoichiometric amounts of hydroperoxide **427**, the stilbenemethanol derivative **428** is converted into the (2*R*) epoxide **429** in 89% yield and 83% ee. The proposed catalytic cycle invokes a vanadium(V) template derived from the POM, substrate and hydroperoxide – a hypothesis supported by the lack of enantioselectivity with unfunctionalized alkenes. The catalytic turnover is remarkably high at about 40 000 TON [465].

Under the rubric of other metal catalysts, methyltrioxorhenium (MTO) represents a fascinating entry. Unlike titanium catalysts (see above), MTO appears not to engage allylic alcohols in tight metal-alcoholate binding, although hydrogen bonding with the substrate can play a role in nonpolar solvents [466]. However, in polar protic media alkenes proximal to a hydroxy group no longer command preferential epoxidation. Thus, treatment of geraniol (**410**) with MTO affords epoxide **430** as the major product (Scheme 2.67), providing a complementary alternative to conventional methods [467]. For simple allylic alcohols (e.g., **431**) formation of the *threo* epoxide (e.g., **432**) predominates – presumably the result of 1,3-allylic strain in the hydrogen bonded catalyst–substrate complex. Unfunctionalized alkenes are also efficiently epoxidized, as illustrated by the practically quantitative conversion of vinylcyclohexane (**433**) into epoxide **434** [468]. Compatible oxygen donors include hydrogen peroxide and its urea adduct (UHP) [469]; perfluoroalkanol solvents tend to



Scheme 2.67 Epoxidations using methyltrioxorhenium (MTO).

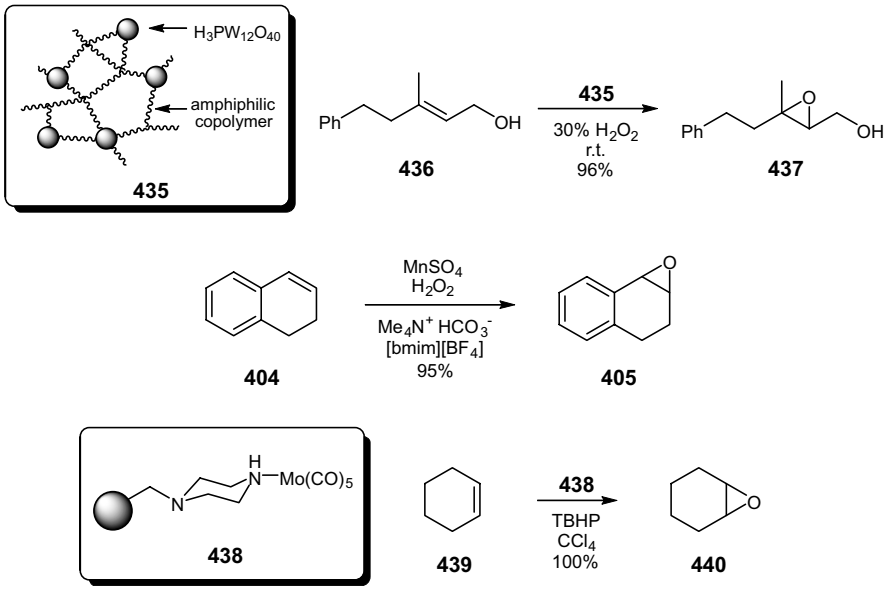
give superior results [470]. A polymer-supported version of MTO has also been disclosed [471].

Other noteworthy biphasic and supported metal catalyst systems [472] include hydrotalcite with hydrogen peroxide [473], cobalt-modified hydrotalcite with molecular oxygen [474], manganese dicarboxylate coordination polymers with hydrogen peroxide [475], a binuclear manganese carboxamide array with dioxygen [476], and aqueous sodium tungstate under phase-transfer conditions [477].

A fascinating "triphase" catalyst for epoxidation of allylic alcohols has been prepared from the combination of phosphotungstic acid and an amphiphilic poly(*N*-isopropylacrylamide)-derived polymer, which yields a macroporous complex (**435**, Scheme 2.68). Thus, treatment of allylic alcohol **436** with 0.003 mol.% catalyst **435** and 2 equivalents of hydrogen peroxide in aqueous medium furnished the corresponding epoxide **437** in 96% yield. The catalyst exhibits a very high turnover rate (35 000), is easily recoverable by filtration and is reusable without loss in efficacy [478]. Also in the category of organic–inorganic hybrids, titanium-silsesquioxane catalysts have been prepared by the complexation of titanium to incompletely condensed silsesquioxanes [479].

Lipophilic alkenes such as **404** can be epoxidized in a triphasic system using ionic liquids, with epoxidation components being provided via an aqueous phase and the reaction products (e.g., **405**) extracted into a pentane layer [480]. Simple alkenes are also converted into epoxides in high efficiency using a recyclable immobilized molybdenum catalyst (**438**) prepared by the reaction of aminated polystyrene and molybdenum hexacarbonyl. For example, cyclohexene (**439**) is quantitatively epoxidized within 5 h using 1 mol.% of catalyst **438** with *t*-butyl hydroperoxide (TBHP) as an oxygen donor [481].

Finally, a combination of wet copper(II) sulfate and potassium permanganate in *t*-butanol (Parish conditions) represents a simple and inexpensive reagent for the



Scheme 2.68 Other immobilized metal epoxidation catalysts.

epoxidation of cyclic alkenes. Thus, stigmasteryl acetate was selectively converted into the 5,6-epoxide in near quantitative yield. The mechanism is believed to involve a series of electron transfers mediated by copper(II) permanganate [482].

2.3.2.4 **Epoxidation of Electron-Deficient Alkenes**

Different conditions usually apply for the epoxidation of electron-poor olefins [483], most of which capitalize on the susceptibility of the substrate toward nucleophilic attack. More recent innovations in this regard include the use of basic hydrogen peroxide in an ionic liquid/aqueous biphasic system [484] or aqueous hydrogen peroxide in the presence of natural phosphate [485] or hydrotalcite with ultrasound [486]. Non-aqueous systems commonly employ TBHP, and this oxidant can be effectively catalyzed by a non-nucleophilic base, such as the guanidine derivative 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) [487], or even by potassium fluoride adsorbed onto alumina [488]. The methodology is not limited to conventional nucleophilic chemistry: electron-deficient alkenes can also be epoxidized under electrochemical conditions using a silver(III)oxo bis(2,2′-bipyridine) catalyst [489] as well as with more electrophilic oxidizing agents, such as iodosylbenzene [490].

As with epoxidation protocols in general, vigorous activity has surrounded the asymmetric synthesis of epoxides from electron-deficient alkenes, and many chiral catalysts and auxiliaries have been developed for this purpose (Figure 2.18). A common test reaction for comparing yields and enantioselectivities is the epoxidation of chalcone (**453**, Scheme 2.69); Table 2.16 summarizes some illustrative contribu-

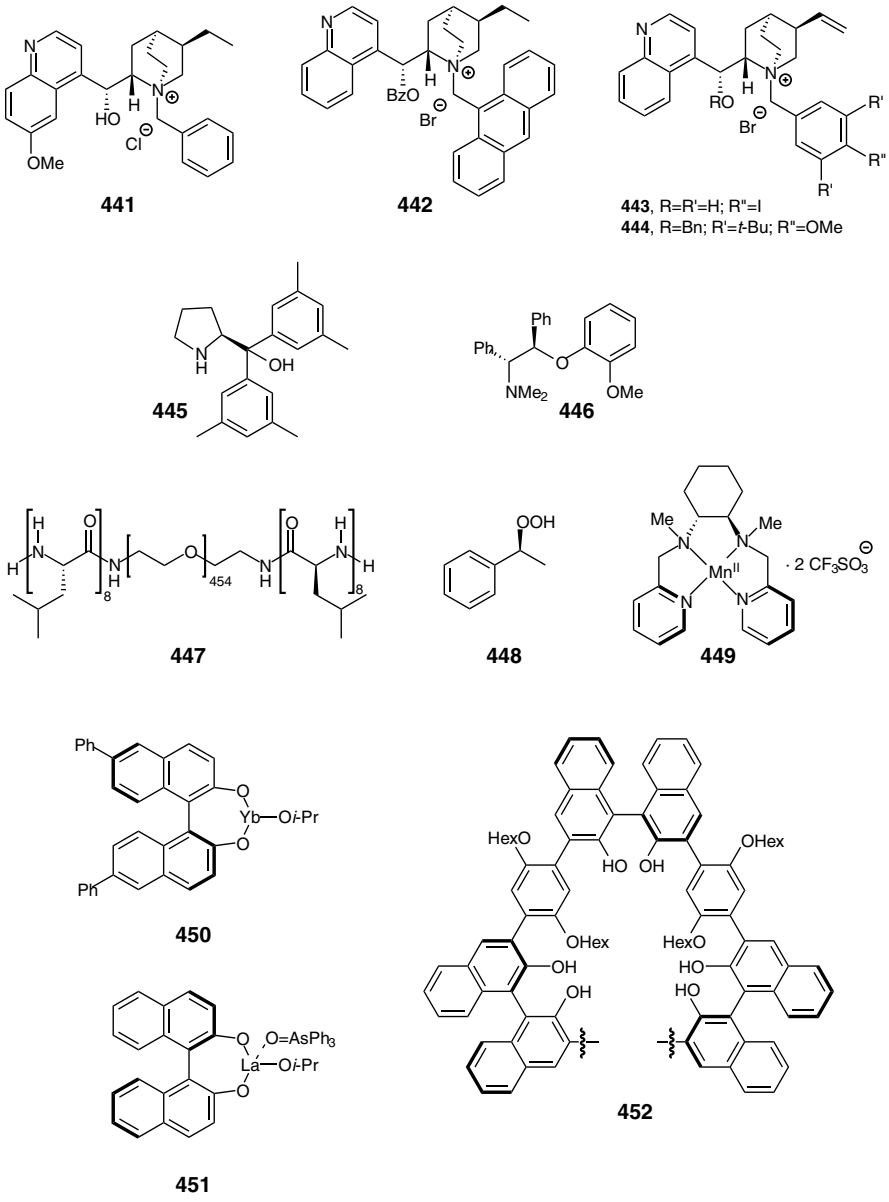
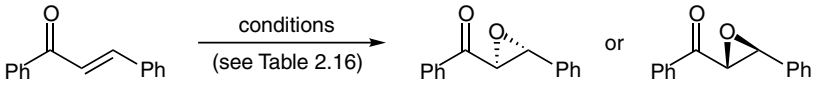


Figure 2.18 Chiral catalysts and auxiliaries for electron-deficient alkenes.

tions to this methodology. For example, *Cinchona*-derived phase-transfer catalysts (e.g., **441**–**444**) are effective in aqueous organic systems (entries 1–3) [491–493]. As a further demonstration of chiral pool inspired catalysts, proline-derived aminoalcohols (e.g., **445**) promote asymmetric epoxidation of enones through non-covalent catalysis [494, 495]. Oligopeptides also show promise as chiral auxiliaries [496], as



453 (+)-**454** (-)-**454**

Scheme 2.69 Asymmetric epoxidation of chalcone.

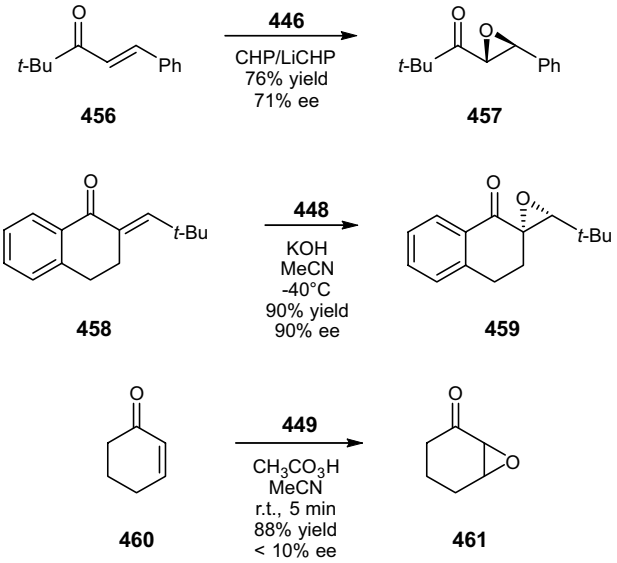
Table 2.16 Yield data for the asymmetric epoxidation of chalcone.

Entry	Catalyst	Oxidant	Solvent	Yield (%)	ee (%)	Conf.	Ref
1	**442**	NaOCl	Toluene	98	86	(+)	[424]
2	**443**	H_2O_2/LiOH	Bu_2O	97	84	(+)	[425]
3	**444**	NaOCl	Toluene	91	60	(+)	[426]
4	**445**	TBHP	Hexane	90	91	(−)	[494]
5	**447**	Urea-H_2O_2		>99	94	(−)	[428]
6	**450**	CHP	THF	91	97	(−)	[429]
7	**451**	TBHP	THF	95	97	(+)	[430]
8	**452**/Et_2Zn	TBHP	Et_2O	95	74	(−)	[432]

illustrated by the novel poly(ethylene glycol)-supported oligo(L-leucine) catalyst **447** used to carry out the Juliá–Colonna epoxidation of chalcone through a continuously operated "chemzyme" membrane reactor with urea-hydrogen peroxide as the terminal oxidant [497].

The chiral ytterbium complex formed from Yb(*i*-PrO)$_3$ and 6,6′-diphenyl-BINOL (**450**) catalyzed the epoxidation in 91% yield and 97% ee using cumene hydroperoxide as the oxygen source [498]. A similar outcome, but a much more rapid conversion, is achieved using the lanthanoid-BINOL-triphenylarsine complex **451**, which provides complete epoxidation in three minutes [499]. This protocol was used as a key step in the synthesis of (+)-decursin from commercially available esculetin [500]. Solid-supported catalysts have also been reported, including the complex formed by treating binaphthyl polymers (e.g., **452**) with diethyl zinc [501].

The tridentate aminodiether ligand **446** has been used with lithium cumene hydroperoxide to give fair to good enantioselectivities in the epoxidation of certain enones (e.g., **456**, Scheme 2.70), presumably through a tetracoordinate lithium complex [502]. The chiral peroxide **448** was effective in the epoxidation of 2-methylene-1-tetralone derivatives, such as **458** [503], as was the immobilized synthetic peptide poly-L-leucine (*i*-PLL) in the presence of urea-peroxide and DBU in a solvent of isopropyl acetate [504]. As is the case with unfunctionalized alkenes, electron-deficient olefins are also subject to asymmetric epoxidation using chiral dioxirane reagents [505]. Interestingly, the chiral cationic manganese bis(pyridyl) catalyst **449** provided for very little asymmetric induction, although it was nevertheless quite efficient in promoting the epoxidation of enones such as cyclohexenone



Scheme 2.70 Other epoxidations with chiral catalysts and reagents.

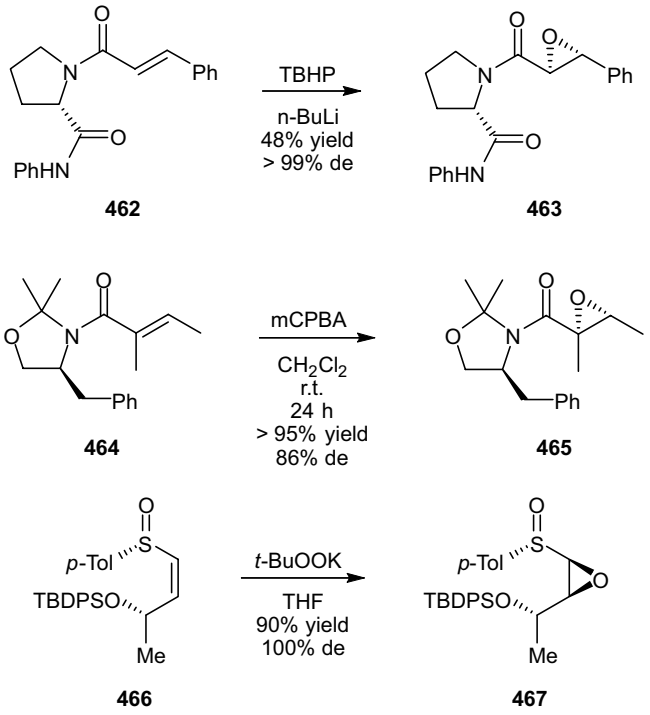
(**460**). When both electron-rich and electron-poor olefins are affixed to the same substrate, the former are preferentially oxidized [506].

In the realm of on-board chiral auxiliaries, proline-derived cinnamides (e.g., **462**, Scheme 2.71) were epoxidized with lithium *t*-butyl hydroperoxide with excellent diastereoselectivity, although in moderate yield [507]. Use of a 2,2-dimethyloxazolidine chiral auxiliary (e.g., **464**) led to superior yields but somewhat attenuated diastereomeric excess [508]. The nucleophilic epoxidation of γ-hydroxy-vinyl sulfoxide derivatives (e.g., **466**) proceeds both in high yield and exclusive diastereoselectivity. The latter outcome has been rationalized by invoking a geometrically constrained chair-like transition state [509].

2.3.2.5 Epoxidation of Carbonyl Compounds

Just as aziridines can be prepared by the addition of carbenes (or carbene equivalents) across imines, so too can epoxides be synthesized from carbonyl compounds, particularly aldehydes. A recent review has brilliantly captured the synthetic utility of this approach [90]. One prototypical example is the conversion of 4-chlorobenzaldehyde (**468**) into the corresponding styrene oxide (**469**) by treatment with diiodomethane and methyllithium at 0 °C. The mechanism is believed to proceed through a sequence of lithium–halogen exchange, carbonyl addition and rapid ring closure of the intermediate iodoalkoxide [510].

The Corey–Chaykovsky synthesis [511], by now a standard method, is nevertheless still the subject of current innovation [512]. This reaction, like most other methylenations, relies upon an intermediate sulfur ylide to serve as a methylene transfer reagent. Recent reports have shown that dry mixtures of trimethylsulfonium iodide

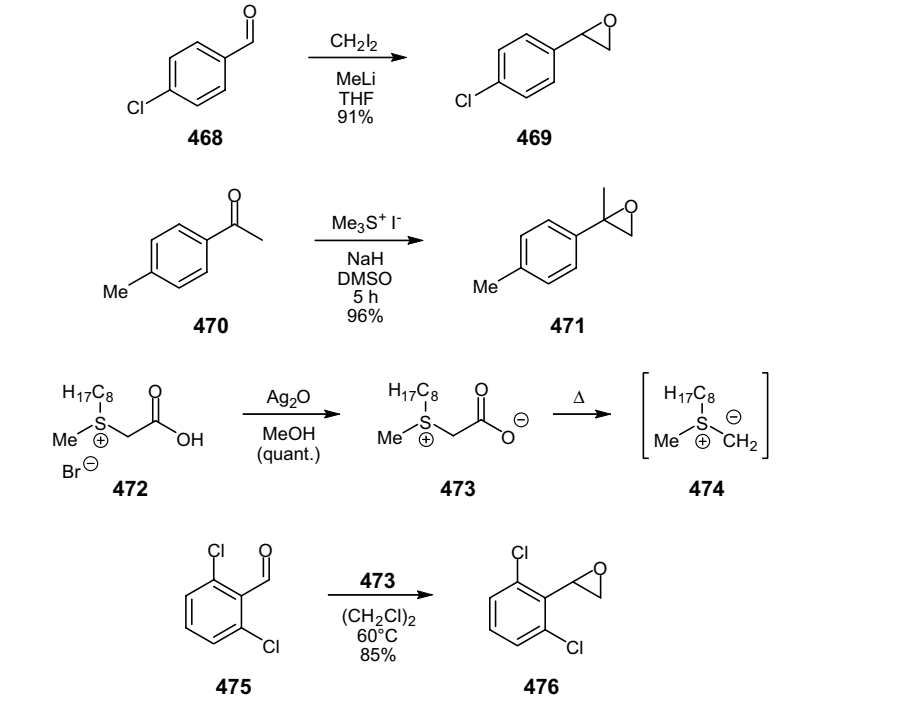


Scheme 2.71 Diastereoselective epoxidations with chiral auxiliaries.

and sodium hydride form a shelf-stable source of "instant methylide" upon treatment with carbonyl compounds in a polar aprotic solvent. Thus, combination of 4-methylacetophenone (**470**, Scheme 2.72) with the "instant methylide" reagent in dimethyl sulfoxide (DMSO) resulted in the high-yielding formation of the corresponding epoxide **471** [513]. The Corey–Chaykovsky epoxidation has also been adapted for use in an ionic liquid medium, such as (bmim)PF_6 [514].

Some methylides are conveniently available through a novel thermal decarboxylation of carboxymethylsulfonium betaines. Thus, treatment of the sulfonium bromide **472** with silver oxide affords the corresponding betaine **473**, which exhibits a half-life of 5 h in chloroform at room temperature, but can be stored for months neat at $<0\,^{\circ}C$. At elevated temperatures, however, a rapid decarboxylation provides the methylide **474**, which reacts with 2,6-dichlorobenzaldehyde (**475**) to give the epoxide **476**. Unsurprisingly, electron-deficient aldehydes give higher yields, with benzaldehyde itself failing to provide any epoxide at all, presumably due to competing thermal decomposition of the ylide **474** [515].

Synthetically useful alkynyl epoxides can be accessed through the treatment of aldehydes with propargyl ylides in the presence of trialkylgallium bases, which lead to (Z)-stereoselectivity [516]. These products are also available through a non-ylide route by treating carbonyls with 1-bromoalkynes and t-butoxide. In this interesting cascade



Scheme 2.72 Epoxidation of carbonyls with methylene equivalents.

reaction, the 1-bromoalkyne is believed to function as both electrophilic halogen source and acetylide equivalent [517].

Asymmetric variants of this protocol have been reported using chiral organic sulfides (Figure 2.19) that are converted into the corresponding ylides, usually either stoichiometrically in a separate step or catalytically *in situ*. The conversion of

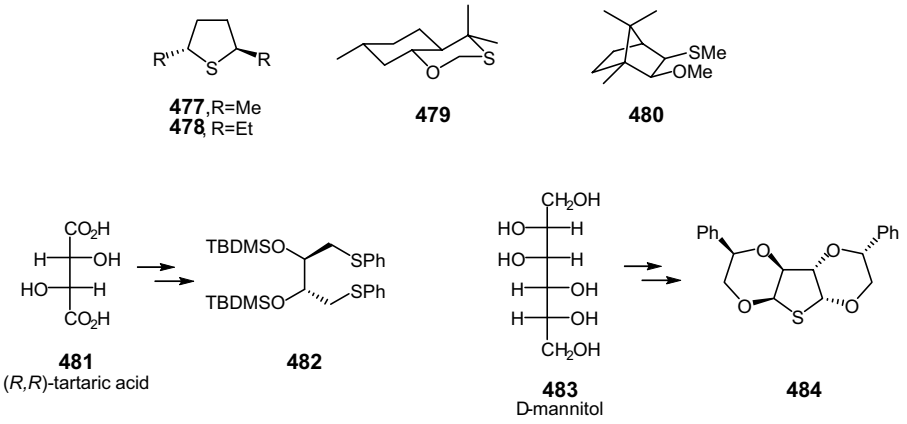
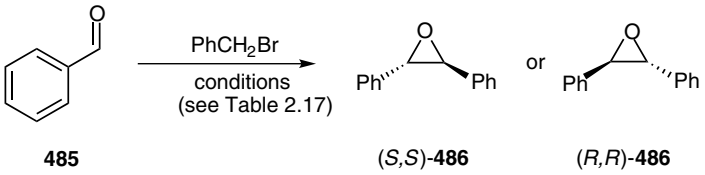


Figure 2.19 Some chiral sulfur ylide precursors.



485 (*S,S*)-**486** (*R,R*)-**486**

Scheme 2.73 Sulfur-mediated asymmetric epoxidation of benzaldehyde.

benzaldehyde (**485**) into *trans*-stilbene oxide (**486**) is a convenient test system for such procedures (Scheme 2.73). The 2,5-dimethylthiolane (**477**) was used in a one-pot stoichiometric variant of this reaction (Table 2.17, entry 1), providing the (*S,S*)-epoxide in excellent yield and good enantioselectivity [518]; even higher optical purity was obtained simply by using the diethyl analog **478** [519].

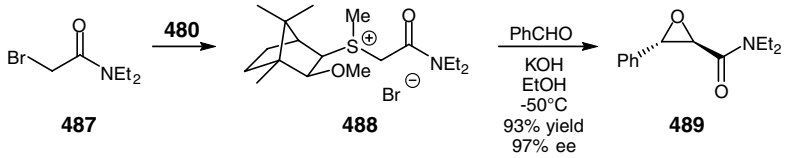
One challenge for this general approach is ready access to chiral auxiliaries in optically pure form. The ideal precursors, therefore, should be available in relatively few steps and on large scale from the chiral pool. The bis-sulfide **482**, obtained from (*R,R*)-tartaric acid (**481**), arguably satisfies these criteria. However, the level of asymmetric induction (Table 2.17, entry 3) falls somewhat short of synthetic utility, most likely because of its conformational flexibility [520]. However, the more rigid tricyclic sulfide **484**, derived from D-mannitol (**483**), provides excellent enantioselectivity (albeit with moderate yields) while operating in a catalytic one-pot environment [521].

A highly enantioselective synthesis of glycidic amides has been reported using stoichiometric amounts of the chiral sulfide **480**, which is available in three steps and in high yield from camphor. Thus, optically pure sulfonium bromide **488** was prepared by treatment of sulfide **480** with bromoamide **487** (Scheme 2.74). Further exposure to benzaldehyde under basic conditions affords glycidic amide **489** in excellent yield and optical purity [522].

One other major route from carbonyls to epoxides involves the addition of metal-stabilized carbenoids to carbonyls. For example, the donor–acceptor rhodium carbenoids derived from aryldiazoacetates **490** add across the carbonyl moiety of α,β-unsaturated aldehydes, such as *trans*-crotonaldehyde (**491**), to give vinyl epoxides

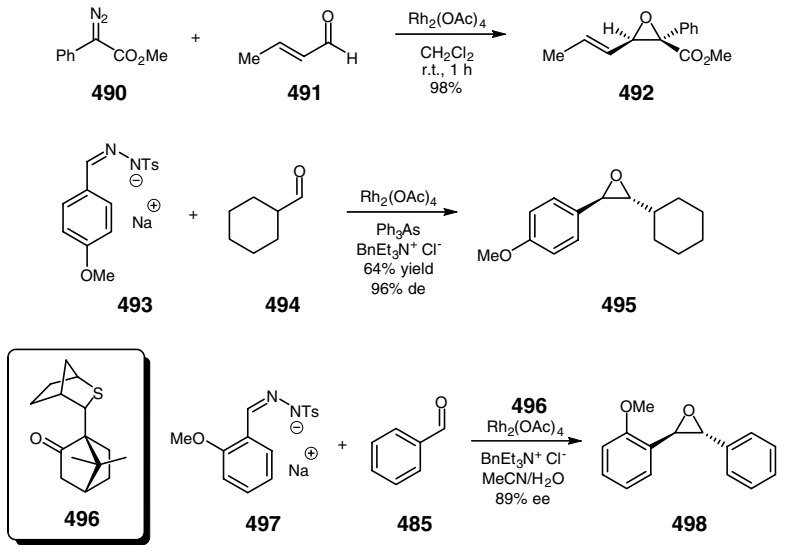
Table 2.17 Yield data for the sulfur-mediated epoxidation of benzaldehyde.

Entry	Precursor	Base	Solvent	Yield (%)	de (%)	ee (%)	Conf.	Reference
1	**477**	KOH	*t*-BuOH/H_2O	92	88	84	(*S,S*)	[446]
2	**478**	KOH	*t*-BuOH/H_2O	97	88	93	(*S,S*)	[447]
3	**482**	NaOH	*t*-BuOH/H_2O	22	48	68	(*R,R*)	[448]
4	**484**	NaOH	MeCN/H_2O	42	82	94	(*R,R*)	[449]



Scheme 2.74 Enantioselective synthesis of glycidic amides.

(e.g., **492**) in good to excellent yield (Scheme 2.75) [523]. Modification of these conditions to include triphenylarsine leads to the formation of intermediate arsonium ylides that function as the active carbon-transfer reagents, resulting in excellent *trans*-selectivities [524]. Asymmetric protocols are also available. Thus, treatment of benzaldehyde (**485**) with a slight excess of the tosyl hydrazone sodium salt **497** in the presence of catalytic amounts of rhodium acetate and 20 mol.% of the camphor-derived sulfide **496** furnishes 1,2-diarylepoxide **498** with 89% ee [525]. However, when the substrate is a heteroaromatic, *n*-alkyl aliphatic, α,β-unsaturated or acetylenic aldehyde, stoichiometric quantities of the preformed chiral sulfur ylide must be used [526].

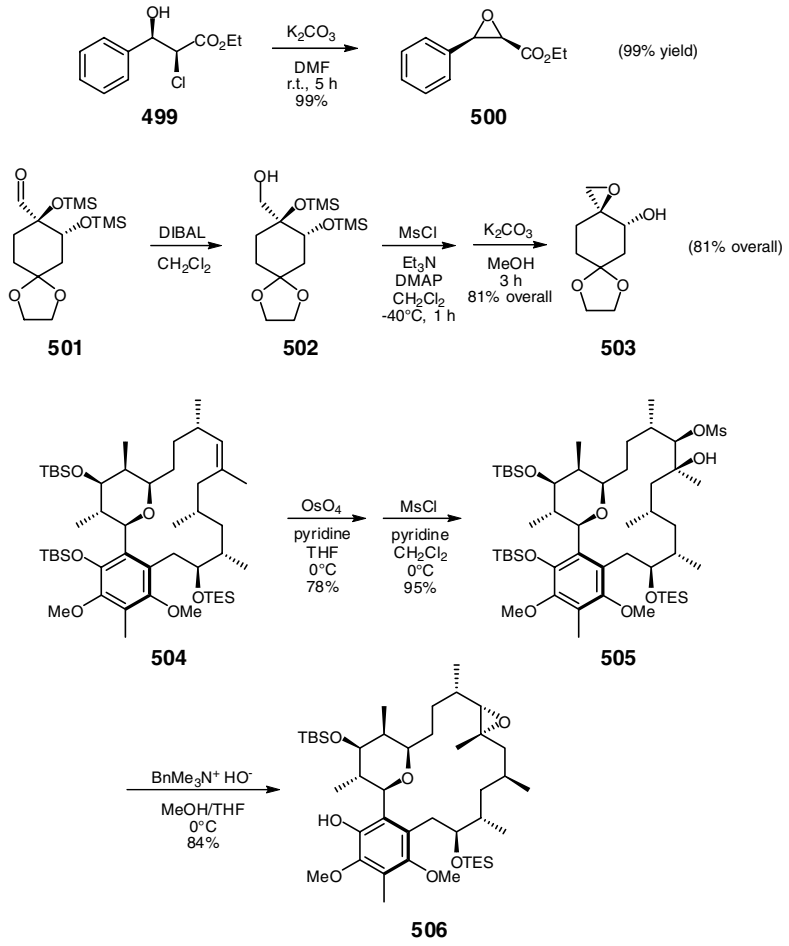


Scheme 2.75 Rhodium-catalyzed epoxidations of carbonyls.

2.3.2.6 **Ring-Closing Reactions**

One of the oldest techniques for preparing epoxides is the base-promoted ring closure of halohydrins, used by Wurtz to synthesize ethylene oxide from β-chloroethanol as early as 1859 [527]. The same procedure is still routinely used

with various modifications. For example, in their approach to the taxol side chain antipodes, Stewart and coworkers treated the optically pure chlorohydrin **499** (Scheme 2.76) with potassium carbonate in DMF to obtain the *cis*-epoxide **500** in almost quantitative yield [528]. A sequential process was used as an early-stage key step in the total synthesis of ovalicin, in which the doubly protected cyclic triol **502** undergoes mesylation, deprotection and ring closure to give the spirocyclic epoxide **503** [529]. A similar procedure assembled the epoxide ring late in the total synthesis of the neocarzinostatin chromophore aglycone [530]. The development of biocatalytic methods for preparing chiral non-racemic chlorohydrins from α-chloroketones has opened a potentially useful pathway towards chiral epoxides by this route [531].



Scheme 2.76 Epoxides from ring-closing reactions.

Ring closure methodology can be employed as a nice complement to other concerted oxygenations. For example, in their total synthesis of (−)-kendomycin, Smith and coworkers carried out a *cis*-dihydroxylation on the macrocyclic alkene **504** to give the corresponding diol. Mesylation of the secondary alcohol afforded the hydroxy mesylate **505**, which suffered ring-closure with inversion under phase-transfer conditions. In this way, a *cis*-alkene was efficiently and controllably converted into the *trans*-epoxide [338].

2.3.3 Reactivity of Oxiranes

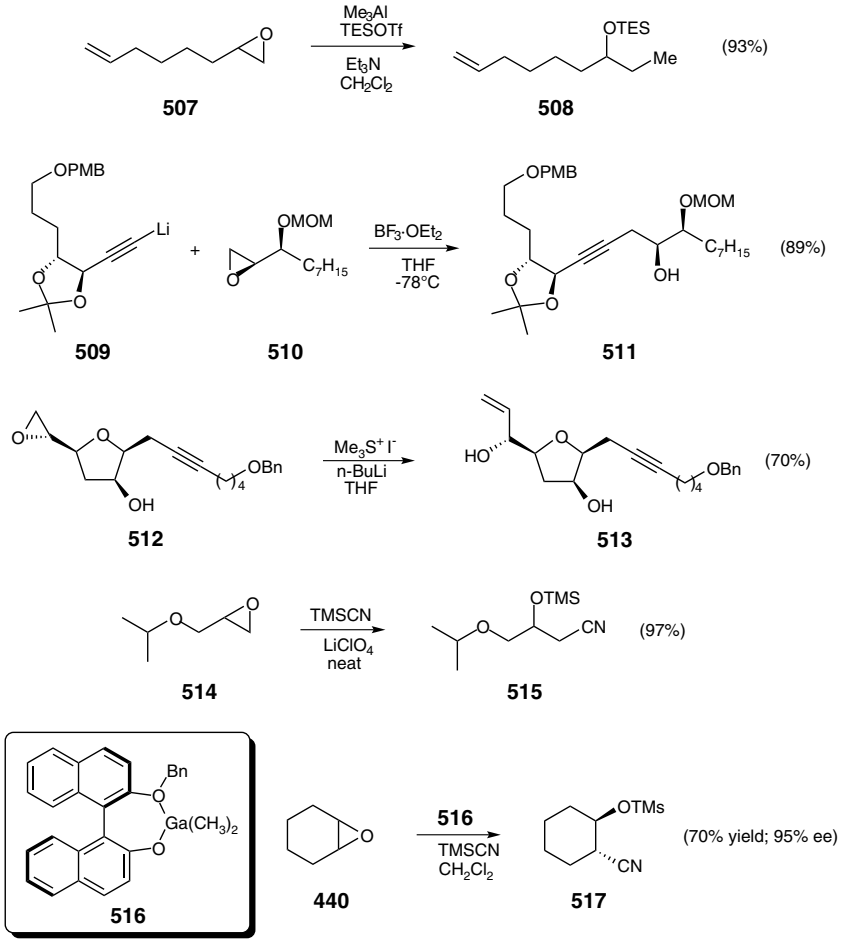
2.3.3.1 Nucleophilic Ring Opening

Cleavage of the epoxide ring by various nucleophiles is one of the most frequently encountered behaviors of this system, both biologically and synthetically. In the latter realm, the extreme versatility of this simple reaction lends it considerable preparative power. The nucleophilic palette runs the gamut, and protocols are being developed continually to direct the nucleophilic ring opening in an enantioselective fashion [532].

Unadorned carbon nucleophiles may be used, as exemplified by the one-pot conversion of alkenyl epoxide **507** (Scheme 2.77) to the homologous silyl ether **508** using a system of trimethylaluminium and silyl triflate. The methyl group is delivered via backside attack on the less substituted terminus of the epoxide, and the alkoxide so formed is silylated *in situ* [533]. An ethyl group can be appended in like fashion using triethylaluminium catalyzed by triphenylphosphine [534]. Similar ring openings also can be carried out using indoles with lithium perchlorate [535] or ruthenium trichloride [536], lithium enolates [537], vinyl magnesium bromide [538], aluminum ester enolates [539], and silyl enol ethers catalyzed by titanium tetrachloride [540]. Vinyl epoxides undergo ring opening at the allylic position using diethylzinc catalyzed by trifluoroacetic acid [541] and alkyllithium reagents catalyzed by boron trifluoride [542].

Alkynyl anions react smoothly with epoxides, as well. For example, Kumar and Naida used this strategy to stitch together the functionalized lithium acetylide derivative **509** and epoxide **510** in their total synthesis of microcarpalide [543]. Other conditions for this reaction include the use of alkynyllithiums with catalytic trimethylaluminium [544] and lithium TMS-acetylide in dimethyl sulfoxide [545]. The addition of vinyl anions per se is not a general reaction; however, there are some interesting vinyl anion equivalents such as trimethylsulfonium iodide, which converts the tetrahydrofuranyl epoxide **512** into the corresponding allyl alcohol (**513**) [546]. Confoundingly, the counterion can play an enormous role in the overall reaction yields; in many cases, the trifluoromethylsulfonyl anion can give superior results [547].

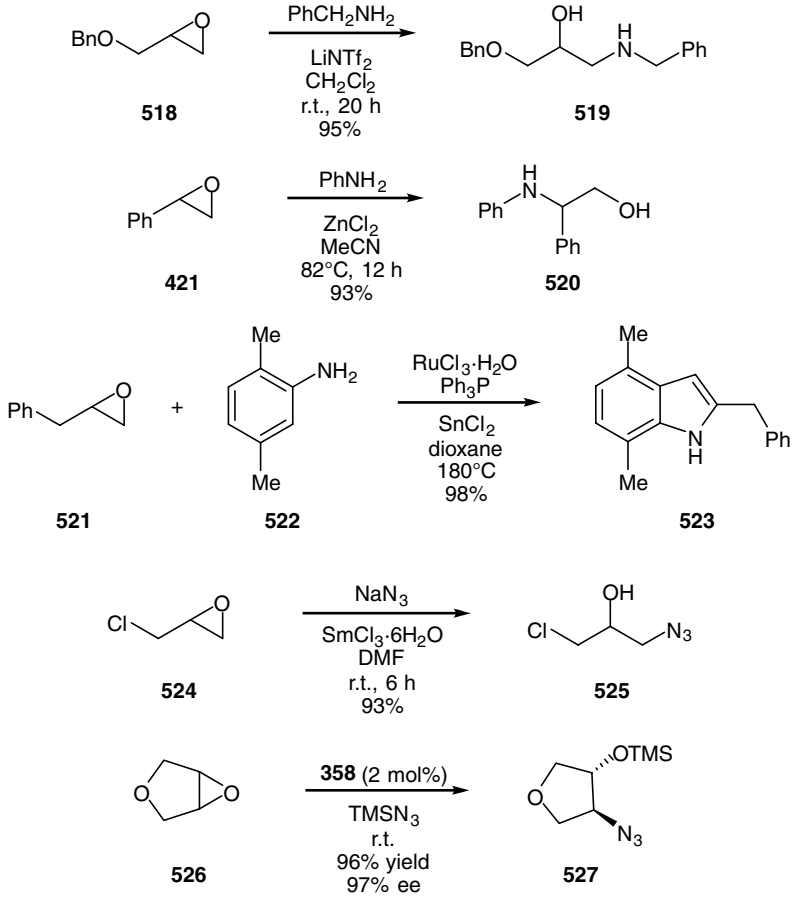
The cyanide anion is a common carbon nucleophile that is also capable of epoxide ring opening. For example, treatment of the terminal epoxide **514** with trimethylsilyl cyanide (TMSCN) in the presence of lithium perchlorate resulted in the delivery of cyanide to the less substituted position in excellent yield [548]. The binaphthyl derived



Scheme 2.77 Epoxide ring opening with carbon nucleophiles.

gallium catalyst **516** represents an asymmetric variant of this process, promoting the addition of cyanide to *meso* epoxides (e.g., **440**) in good yield and excellent enantioselectivity [549].

In the category of nitrogen-based nucleophiles, simple amines add smoothly to epoxides in predictable ways. For example, benzylamine attacks the less hindered carbon of the epoxyether **518** (Scheme 2.78) under the influence of lithium bis-trifluoromethanesulfonimide to give the aminoalcohol **519** in 95% yield [550]. When the epoxide ring bears an aromatic substituent, the regiochemistry is often reversed, as shown by the ring-opening of styrene oxide (**421**) with aniline in the presence of zinc chloride [551]. Amines can also be added using calcium triflate in acetonitrile [552], and in water with erbium(III) triflate as a catalyst [553], with no catalyst under conventional conditions [554], or with the assistance of ultrasound [555].



Scheme 2.78 Epoxide ring opening with nitrogen nucleophiles.

The addition of aromatic amines can be catalyzed by stannic or cupric triflate [556, 557]; β-cyclodextrin [558]; zirconium(IV) chloride [559] or bismuth trichloride [560, 561] in acetonitrile; and zinc oxide [562], ytterbium(III) nitrate [563], or a mesoporous silica immobilized cobalt complex [564] under solvent-free conditions. A ruthenium catalyst in the presence of tin chloride also results in an S_N1-type substitution behavior with aniline derivatives (e.g., **522**), but further provides for subsequent cyclization of the intermediate amino alcohol, thus representing an interesting synthesis of 2-substituted indoles (e.g., **523**) [565]. Certain meso-epoxides can be desymmetrized with aromatic amines under catalytic conditions, for example, using a proline-based N,N'-dioxide-indium tris(triflate) complex [566].

Azide represents a simple, versatile and selective nitrogen nucleophile. In the presence of catalytic quantities of samarium(III) chloride in a medium of *N*,*N*-dimethylformamide (DMF), sodium azide attacks the terminal epoxide carbon of

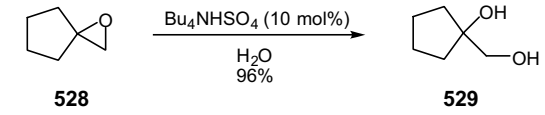
epichlorohydrin (**524**) to give the highly functionalized three-carbon fragment **525** [567]. Azide addition can also be promoted by the use of lithium tetrafluoroborate in *t*-butanol [568] and lithium perchlorate in propionitrile [569]. Attack at the more substituted position is favored by some conditions, including diethylaluminium azide [570] and sodium azide in the presence of ceric ammonium nitrate [571]. Like cyanide, azide can be used to desymmetrize meso-epoxides, as shown by the asymmetric azidolysis of the bicyclic epoxide **526** using TMS-azide and catalytic amounts (2 mol.%) of the salen-chromium complex **358** [572, 573].

Oxygen-centered nucleophiles are also of synthetic importance in this regard, and the reactions of alicyclic epoxy compounds with these nucleophilic species are the subject of a review [574]. Arguably the most readily available oxygen-centered nucleophile for epoxide ring opening is water, but the course of the hydrolysis reaction is dependent upon the reaction environment and structural features of the substrate [575]. Conditions can be exceedingly mild, as shown by the high-yielding hydrolysis of spiroepoxide **528** (Scheme 2.79) using tetrabutylammonium bisulfate [576]; catalytic bismuth triflate in wet acetonitrile can also be used to advantage [176]. In fact, many epoxides can be hydrolyzed simply by heating in water without any catalyst at all [577]. The conversion of epoxides into diols in this manner is the basis for an enormously important method for preparing optically pure epoxides from racemic mixtures through hydrolytic kinetic resolution (HKR) [578]. Chiral nonracemic diols are also available from the hydrolytic desymmetrization of meso-epoxides (e.g., **440**) using an oligomeric Jacobsen-type catalyst (**530**) [579].

Alcohols can be added with equal efficiency. Thus, phenoxymethyl epoxide **532** suffers nucleophilic attack by methanol in the presence of catalytic amounts of potassium dodecatungstocobaltate to provide hydroxyether **533** in quantitative yield [580]. As with other nucleophiles, when an aromatic group is attached to the epoxide ring, attack often predominates at the benzylic position. For example, treatment of stilbene oxide (**421**) with methanol under the catalysis of $TiO(TFA)_2$ yields the primary alcohol **534**. The electrophilic center is cleanly inverted in the process [581]. This addition can also be carried out using ferric perchlorate [579], molybdenum(VI) dichloride dioxide [582], hydrazine sulfate [583], amberlyst-15 resin [584], copper(II) tetrafluoroborate [585], and aminopropylsilica gel (APSG) supported iodine [586]. The hydroperoxide anion functions as a competent nucleophile under the catalysis of silica-supported antimony trichloride [587].

The scope of oxygen nucleophiles extends to carboxylic acids, as illustrated by the titanium-catalyzed addition of pivalic acid to the terminal epoxide **535** [588]. Chromium(III) acetate is a useful catalyst for such additions of carboxylic acids in industrial processes [589]. Finally, nitrates can also be coaxed into serving as oxygen-centered nucleophiles by reagents such as bismuth(III) nitrate [590] and tetranitromethane [591].

Other oxygen-containing heterocycles with varying degrees of structural complexity are conveniently prepared by the intramolecular ring-opening of epoxides [592]. An illustrative example is found with the titanium-promoted cyclization of the highly oxygenated bicyclic epoxide **537** to give the spiroketal **538** with retention of configuration [593]. Similar intramolecular processes have been catalyzed by caesium



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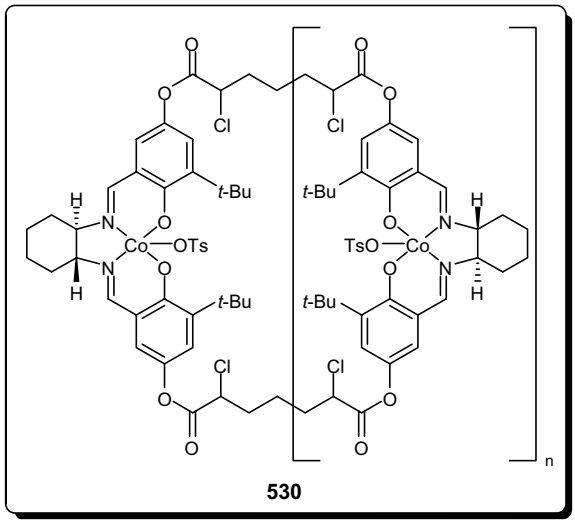

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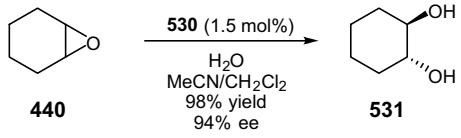

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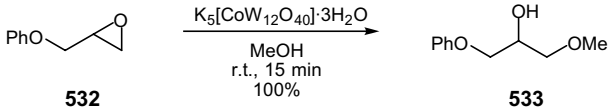

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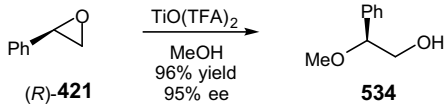
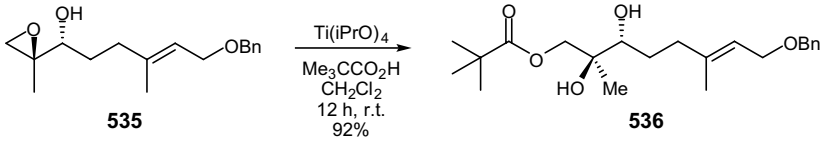


(*R*)-421 534



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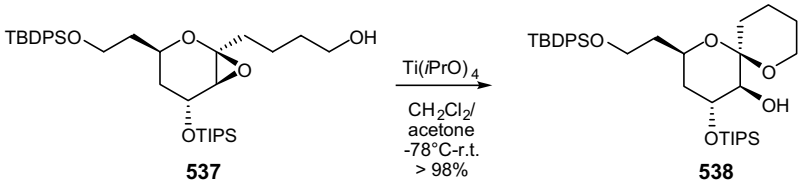
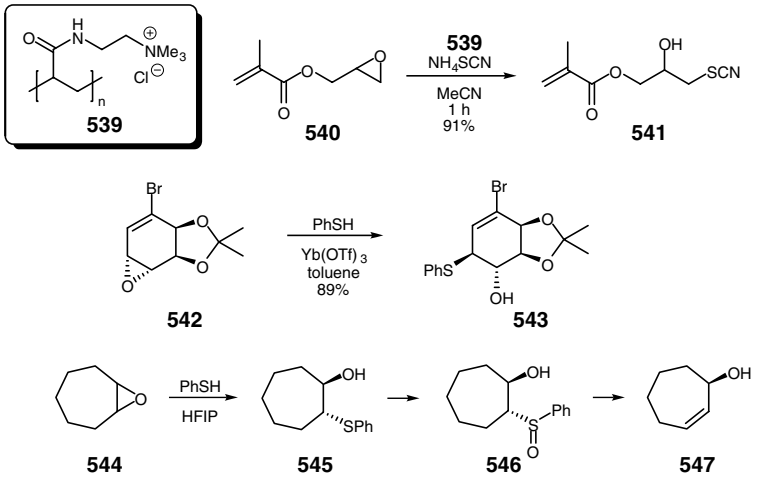


537 538

Scheme 2.79 Epoxide ring opening with oxygen nucleophiles.

carbonate [594] and *p*-toluenesulfonic acid [595]. In one such intramolecular epoxide ring opening – a key step in the diastereoselective synthesis of α-tocopherol – anhydrous hydrochloric acid in ether/acetonitrile was chosen to promote the disfavored 6-*endo-tet* ring closure mode [596].

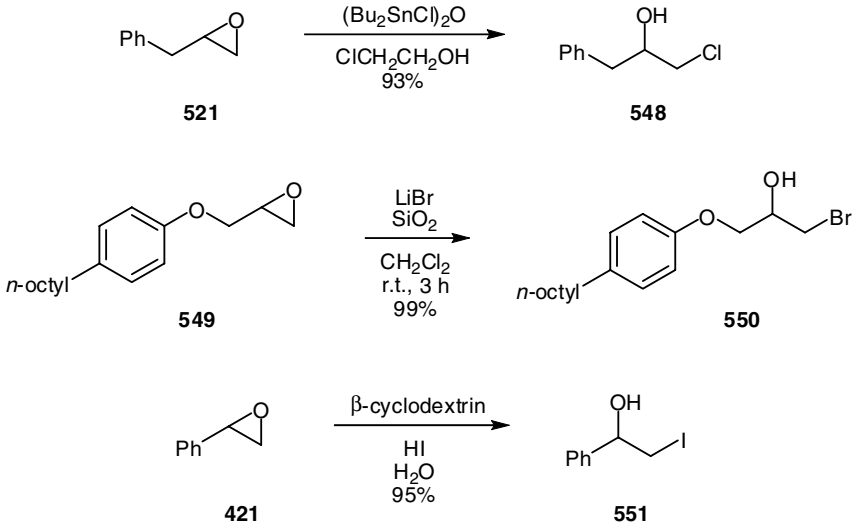
Among sulfur-centered nucleophiles, thiocyanate is frequently encountered. For example, the epoxy ester **540** (Scheme 2.80) is smoothly converted into the thiocyanato adduct **541** using stoichiometric ammonium thiocyanate and a quaternized amino functionalized cross-linked polyacrylamide (**539**) as a solid–liquid phase-transfer catalyst in acetonitrile [597]. Hydroxysulfones can be prepared "on water" by the action of sodium benzenesulfinate on epoxides with no added catalyst [598]. Thiophenol is another useful species that adds under very mild conditions, as shown by the ring-opening of the cyclohexadiene oxide derivative **542** catalyzed by ytterbium triflate in toluene, whereby the thiophenol moiety attacks the allylic site of the epoxide ring [599]. In another example, unfunctionalized epoxides (e.g., **544**) can be transformed into allylic alcohols **547** through an initial epoxide ring-opening with thiophenol in hexafluoroisopropanol (HFIP) and *in situ* oxidation to the sulfoxide (**546**), followed by pyrolysis in the presence of potassium carbonate [600]. Thiols can also be added using tributylphosphite [166], lithium perchlorate [601, 602], montmorillonite K-10 clay under solvent-free microwave conditions [603], in water [604], and in ionic liquids without additional catalysts [605]. The addition of Rongalite® allows for the use of disulfide thiol precursors [606], and the entantioselective cleavage of meso-epoxides with thiophenol can be achieved using a heterobimetallic Ti-Ga-salen catalyst [607].



Scheme 2.80 Epoxide ring opening with sulfur nucleophiles.

Finally, halides are interesting nucleophiles inasmuch as they preserve the electrophilic character of the center they substitute. As a representative example of these additions, chloride can be introduced using bis-chlorodibutyltin oxide in

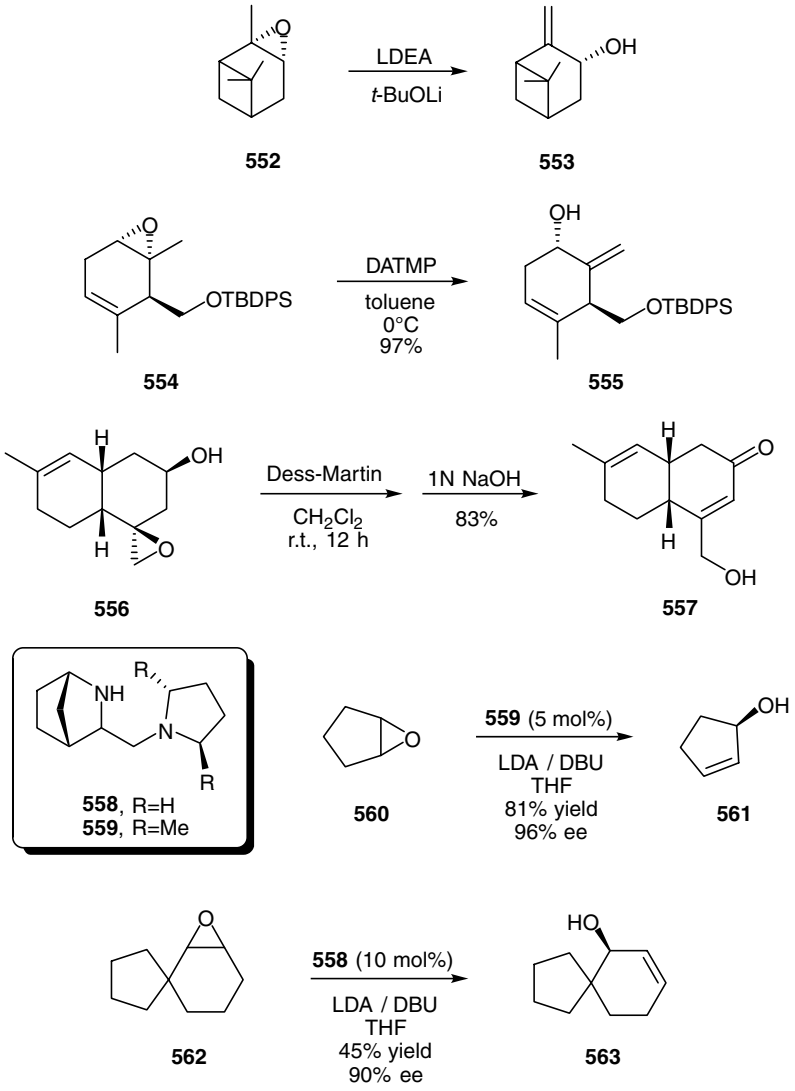
chloroethanol, as shown in the conversion of phenylmethyl epoxide **521** (Scheme 2.81) into chlorohydrin **548** [608]. Similarly, the terminal epoxide **549** is converted almost quantitatively into the bromohydrin **550** with lithium bromide in the presence of silica gel in methylene chloride [609]. Bromide-mediated ring-opening can also be executed using a combination of *N*-bromosuccinimide, triphenylphosphine and dimethylformamide [610]. Most nucleophilic of all, iodide readily attacks styrene oxide (**421**) to give the iodohydrin **551**, and the use of β-cyclodextrin directs the addition to the less-substituted carbon, presumably due to steric hindrance caused by guest–host complexation [611]. In the realm of asymmetric synthesis cyclic meso-epoxides can be desymmetrized by chloride attack using silicon tetrachloride catalyzed by PINDOX [612].



Scheme 2.81 Epoxide ring opening with halide nucleophiles.

2.3.3.2 **Rearrangements**

Epoxides can be isomerized to allylic alcohols using hindered bases. For example, α-pinene oxide **552** (Scheme 2.82) undergoes eliminative ring opening upon treatment with lithium diethylamide. The transformation proceeds in higher yields in the presence of lithium *t*-butoxide, which is believed to disrupt aggregation of the anion [613]. Similarly, the optically pure bicyclic epoxide **554** is converted into the methylenecyclohexenol derivative **555** in excellent yield using diethylaluminium 2,2,6,6-tetramethylpiperidide (DATMP) in toluene [614]. Milder bases can be used when activating groups are nearby. Thus, the hydroxyepoxide **556** is smoothly oxidized to the corresponding ketone under Dess-Martin conditions, making the α-protons acidic enough to remove with sodium hydroxide, leading to the enone



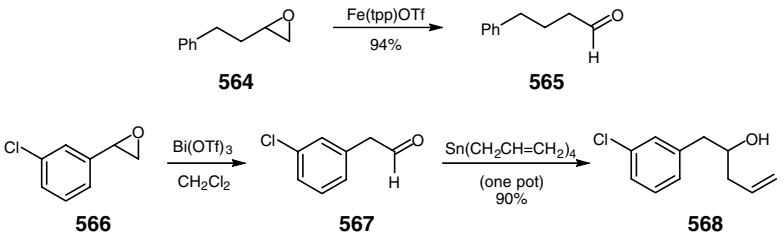
Scheme 2.82 Base-catalyzed rearrangement of epoxides to allylic alcohols.

product **557** [615]. Finally, the isomerization can occur under essentially neutral conditions using titania-supported gold nanoparticles [616].

The enantioselective isomerization of meso epoxides to allylic alcohols continues to be a promising route for the preparation of these materials in high optical purity. In an extension of their ongoing work in this area with lithium amide bases [617], Andersson and coworkers have designed the optically active (1*S*,3*R*,4*R*)-[*N*-(*trans*-2,5-dimethyl)pyrrolidinyl]-methyl-2-azabicyclo[2.2.1]heptane (**559**), which exhibits superior chiral induction in catalytic quantities using lithium diisopropylamide

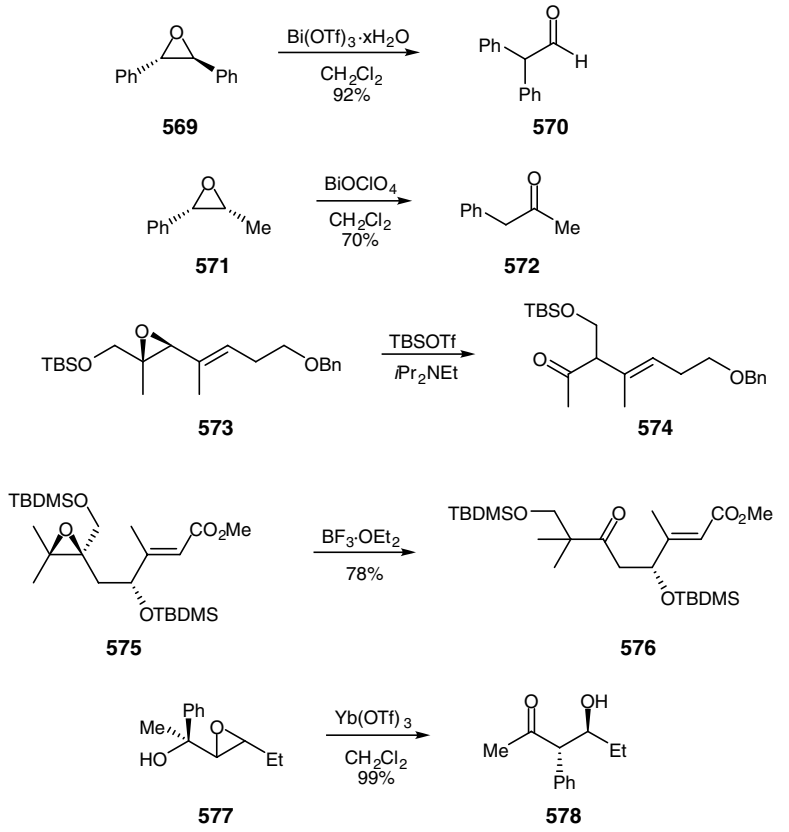
(LDA) as the stoichiometric base. Thus, the challenging substrate cyclopentene oxide (**560**) was cleanly isomerized to the chiral cyclopentenol **561** in 81% yield and with 96% ee – a significant improvement over the 49% ee obtained with higher loadings of the earlier generation catalyst **558** [618]. Diamines derived from *(R)*-phenylglycine have also given promising results [619]. The chiral amide approach has also been applied to the catalytic kinetic resolution of racemic epoxides. For example, exposure of the tricyclic epoxide **562** to 10 mol.% **558** and stoichiometric LDA at 0 °C led to the recovery of the chiral spiro[4.5]decenol **563** with 90% ee and in 45% isolated yield, compared to the theoretical 50% maximum [620]. Chiral nonracemic aminoepoxides are isomerized stereoselectively to aminoalcohols using the superbasic mixture of *n*-butyllithium, diisopropylamide and potassium *t*-butoxide (LIDAKOR) [621].

In addition to β-elimination, the epoxide moiety also undergoes rearrangement to a carbonyl group, and this reactivity can be quite synthetically useful. The course of the rearrangement is highly dependent upon the nature of the substrate. Generally, the regiochemistry is driven by two factors: (i) the stability of the nascent carbocation generated from ring opening and (ii) the migratory aptitude of the adjacent substituents. For example, the simple monoalkyl-substituted epoxide **564** (Scheme 2.83) undergoes regioselective rearrangement in the presence of iron(III)tetraphenylporphyrin to give the corresponding aldehyde (**565**) via a 1,2-hydride shift onto an incipient secondary cationic center [622], a process also promoted by sodium periodate under ambient conditions [623]. Terminal epoxides react with tetraallyltin in the presence of bismuth(III) triflate to give homoallylic alcohols **568**. The reaction involves an initial 1,2-shift to form aldehyde **567**, which is then attacked by the allyl tin species [624]. A similar but operationally more straightforward protocol is available by combining allyl bromide with indium metal, followed by the addition of epoxide [625].



Scheme 2.83 Rearrangement of terminal epoxides to aldehydes.

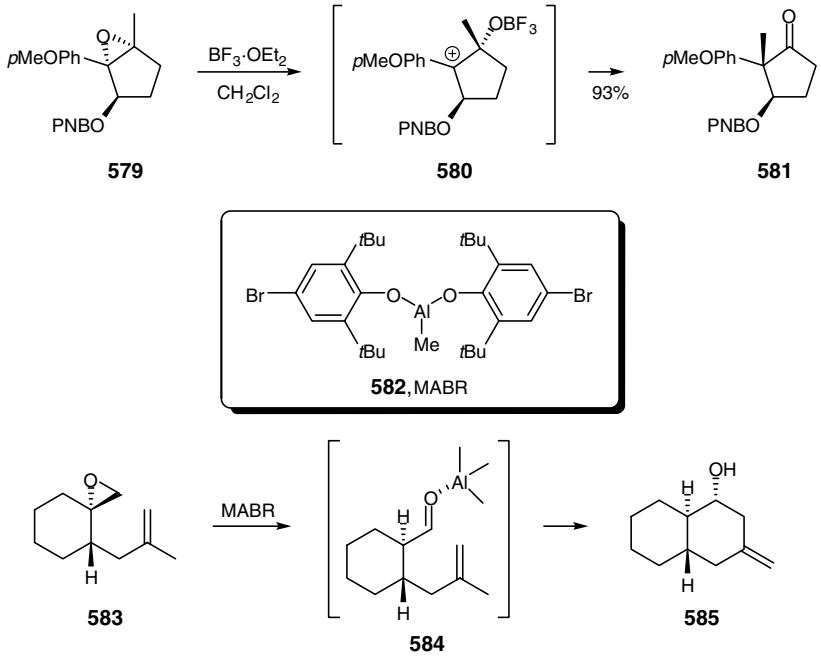
When *trans*-stilbene oxide (**569**, Scheme 2.84) is treated with bismuth triflate, aldehyde **570** is formed through a process of benzylic cation formation and subsequent phenyl migration [626]. However, the structurally very similar epoxide **571** provides a ketone upon treatment with Lewis acid, which reflects a more facile hydride shift to the cationic center [627]. Certain alkoxymethyl groups can also easily migrate, as seen in the rearrangements of epoxides **573** [628] and **575** [629]. In the latter example, the siloxy migration was an unwanted (albeit efficient) side reaction of



Scheme 2.84 Rearrangement of internal epoxides to aldehydes ketones.

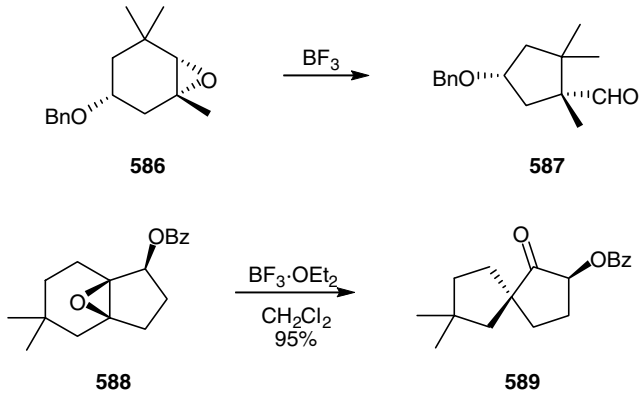
a desired cationic ring closure; changing to a trimethylsilylethoxymethyl (SEM) protecting group resolved this problem. An analogous rearrangement can occur in epoxyalcohols of type **577**, which cleanly produced the hydroxyketone **578** in almost quantitative yield after 3 h upon exposure to 20 mol.% ytterbium triflate in methylene chloride [630].

This process can be used to advantage to access cyclic ketones, as well. For example, the cyclopentene oxide derivative **579** (Scheme 2.85) opens up to the more stable benzylic carbocation (i.e., **580**), which then provides the cyclopentanone derivative **581** via 1,2-methyl migration in 93% yield [631]. An analogous mechanistic step begins the organoaluminium-promoted cyclization of olefinic epoxides (e.g., **583**), whereby the initially formed aldehyde (**584**) undergoes a highly stereoselective Lewis acid-catalyzed intramolecular ene reaction to give the methylenedecalone **585** in the presence of methylaluminium bis(4-bromo-2,6-di-*t*-butylphenoxide) (MABR). This strategy is proposed as a route for the stereoselective synthesis of various terpenes [632].



Scheme 2.85 Rearrangement involving cyclic structures.

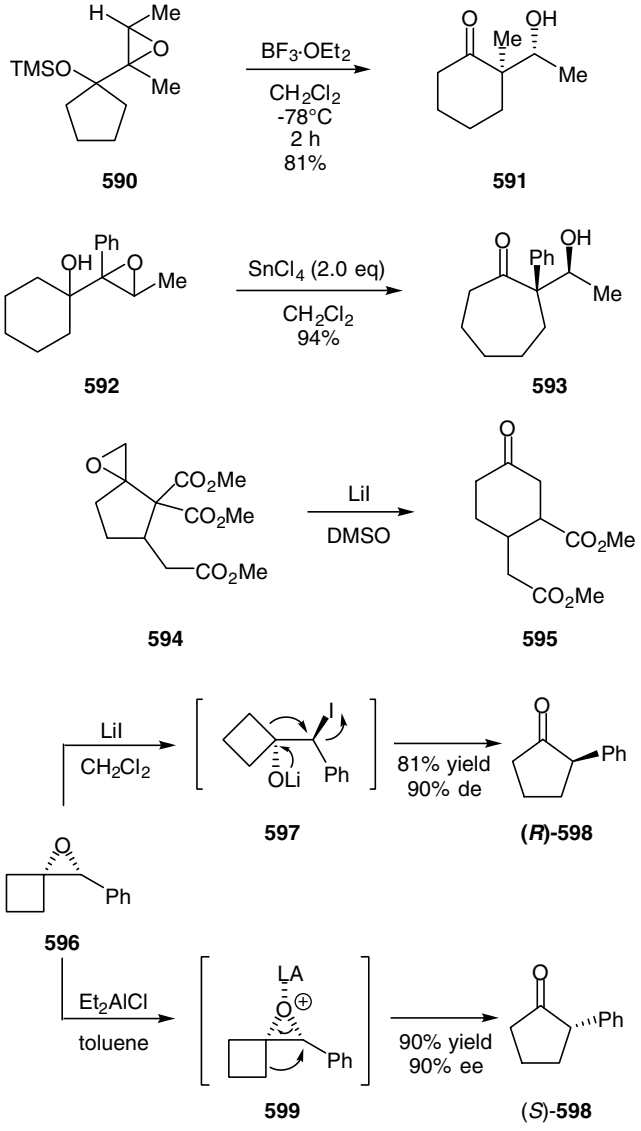
The rearrangement sometimes occurs with concomitant ring contraction, as seen in the conversion of cyclohexene oxide derivative **586** (Scheme 2.86) into the cyclopentanealdehyde product **587** [633]. In a similar vein, Kita and coworkers [634] have used a novel acid-promoted rearrangement of cyclic α,β-epoxy acylates (e.g., **588**) for the stereoselective synthesis of spirocyclanes (e.g., **589**), a technique which is also found in the total synthesis of (–)-pseudolaric acid B by Trost *et al.* [635], and



Scheme 2.86 Rearrangement with ring contraction.

which promises broad application to the preparation of optically active compounds of this type.

Ring expansions are also possible. For example, treatment of the cyclopentylepoxide **590** (Scheme 2.87) with boron trifluoride etherate induces a cascade reaction involving desilylation of the alcohol and rearrangement to the cyclohexanone derivative **591** [636]. Similarly, cyclohexyl epoxides (e.g., **592**) expand to form tropinones (**593**) [637]. Finally, although the process proceeds through a mechanis-



Scheme 2.87 Rearrangement with ring expansion.

tically distinct pathway, the iodide-mediated rearrangement of the spiroepoxide **594** produces the ring-expanded cyclohexanone **595** [638]. This was used in a very clever way to access both antipodes of phenylcyclopentanone (**598**) from spiroepoxide **596**. The anionic iodide pathway led to smooth conversion into the *(R)*-isomer, while Lewis acid catalysis provided equally high optical purity of the *(S)*-enantiomer [639].

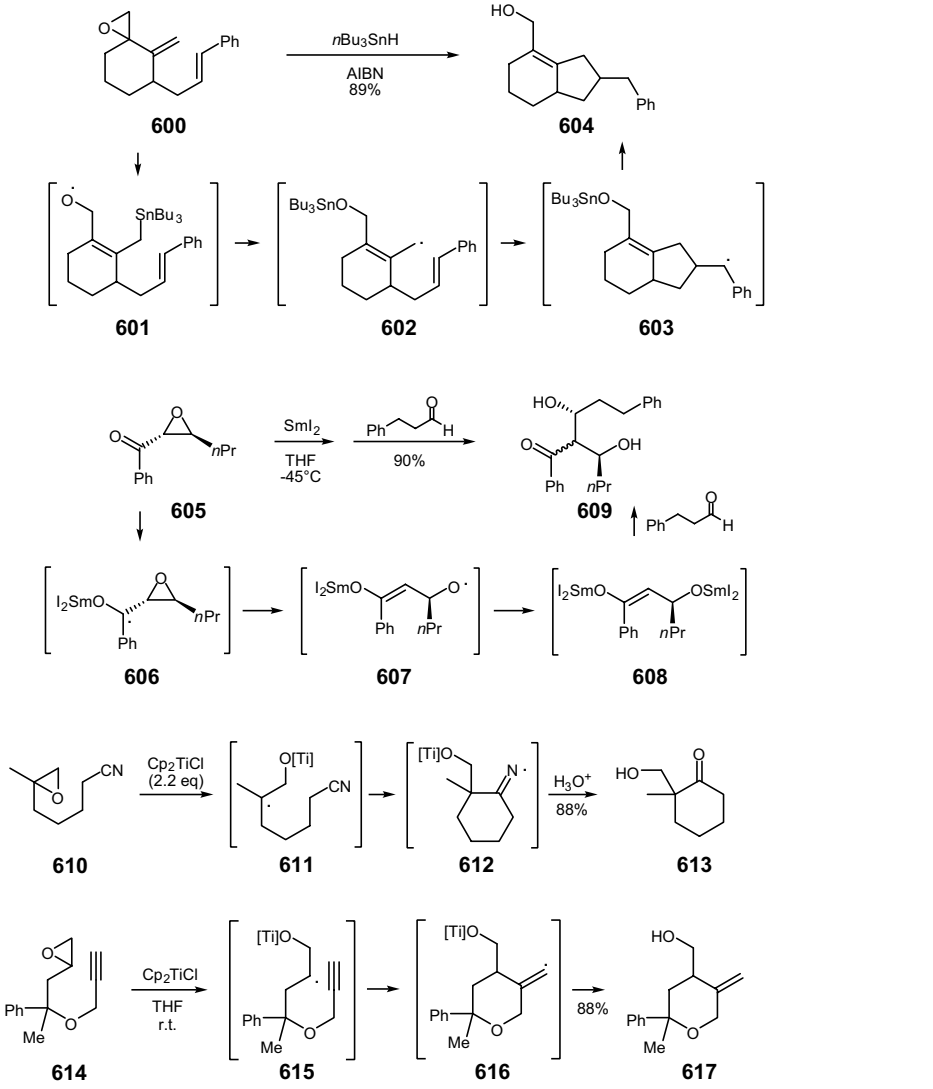
2.3.3.3 Radical Chemistry

Li has authored an excellent overview of the radical reactions of epoxides, to which the reader is directed [640]. While this field encompasses some fascinating chemistry, yields and selectivities tend to be rather widely distributed. Exceptions to this generalization are found in specifically functionalized epoxides. For example, the vinyl epoxide **600** (Scheme 2.88) suffers radical addition of tributyltin radical to give an α-epoxy radical, which immediately opens to the allylic alkoxy radical **601**. This species engages in radical ring closure onto the pendant alkene to give, after hydrolysis, the bicyclic alcohol **604** in 89% yield [641, 642]. Samarium iodide promotes similar reactivity in ketoepoxides such as **605**. Thus, single electron transfer from SmI_2 to the carbonyl moiety gives the typical radical anion, which then isomerizes to the allylic alkoxy radical **607**. Trapping of the samarium stabilized enolate **608** with phenylpropionaldehyde gives the dihydroxyketone **609** in excellent yield [643].

Titanocene-mediated radical cyclization of epoxides has been reviewed very recently [644], and this area is rapidly expanding in synthetic utility. Here a titanocene reagent such as Cp_2TiCl engages the epoxide ring itself in single electron transfer, typically cleaving the weakest C−O bond and forming the more substituted carbon-centered radical, which can take part in further reactivity. For example, the epoxynitrile **610** is smoothly converted into the hydroxymethylcyclohexanone derivative **613** through a cascade of radical ring opening and subsequent cyclization onto the nitrile [645] (the intermolecular version of this methodology is promoted by titanocene [646]). Similarly, the propargylic epoxide **614** undergoes ring cleavage to give the secondary radical (**615**), which proceeds through 6-*exo-dig* radical cyclization to provide the methylenetetrahydropyran derivative **617** in high yield [647].

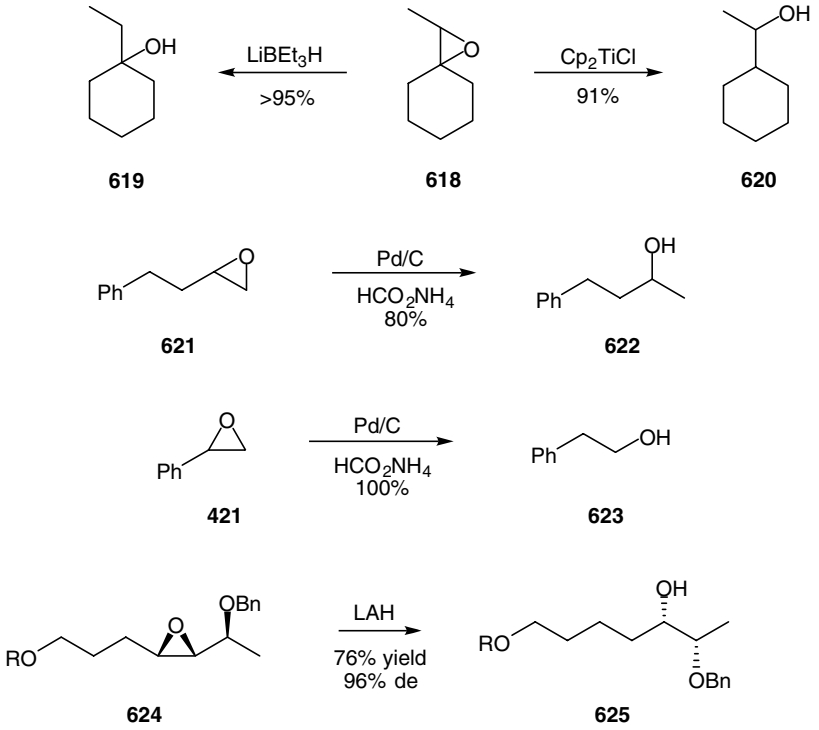
2.3.3.4 Reduction and Deoxygenation

Epoxides can undergo reductive ring opening using various reagents [648, 649]. One extremely mild protocol involves the use of bis(cyclopentadienyl)titanium(III) chloride. Significantly, the regioselectivity of the epoxide cleavage is often quite high, being determined by the stability of a radical intermediate, and sometimes opposite to what is expected for a classical S_N2 epoxide ring opening. For example, treatment of spiroepoxide **618** (Scheme 2.89) with Cp_2TiCl leads to an intermediate carbon radical that can be trapped by a H-atom donor (in this case cyclohexadiene) to give the secondary alcohol **620**. By comparison, a "classical" reductive ring opening with lithium triethylborohydride gives only the tertiary alcohol **619** [650]. Iyer [651] and Dragovich [652] have independently reported the regiospecific ring opening of epoxides by way of a palladium-catalyzed transfer hydrogenolysis using ammonium formate as the hydrogen source. Under these conditions, hydride attacks at the less



Scheme 2.88 Some radical reactions of functionalized epoxides.

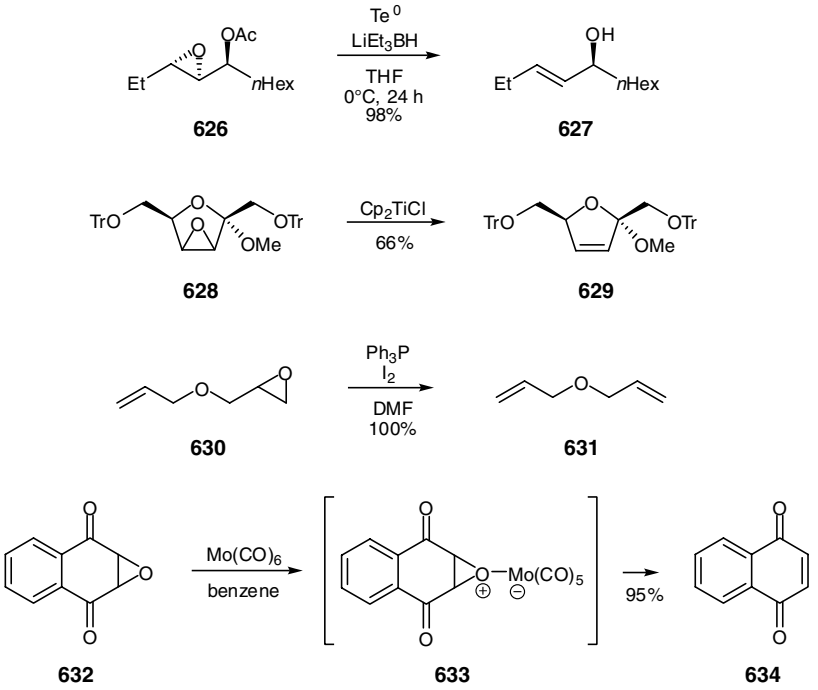
hindered carbon atom (e.g., **621** → **622**), except in the case of aryl-substituted epoxides, where ring opening occurs exclusively at the benzylic position (e.g., **421** → **623**). Lithium aluminium hydride has been used for the regio- and diastereoselective reductive ring opening of chiral nonracemic epoxides, such as **624** [653] (a key step featured in the enantiospecific synthesis of (+)-hernandulcin [654]), and racemic epoxides can be reduced to an enantiomerically enriched mixture of alcohols by treatment with zirconium tetrachloride–sodium borohydride in the presence of L-proline as a chiral auxiliary [655].



Scheme 2.89 Reductive ring opening of epoxides.

The net reversal of the epoxidation reaction, namely the eliminative deoxygenation of epoxides, has been carried out in various ways. For example, tungsten reagents react with epoxides to form tungsten(IV)-oxo complexes that ultimately lead to the corresponding olefins with predominant retention of configuration [656]. Glycidyl acetates **626** (Scheme 2.90) undergo deoxygenation and concomitant deacetylation upon treatment with lithium telluride, which is conveniently prepared *in situ* from tellurium metal and lithium triethylborohydride [657]. Another extremely mild epoxide deoxygenation protocol involves the use of bis(cyclopentadienyl)titanium (III) chloride, which promotes homolytic cleavage of the epoxide C−O bond. The mildness of this reagent is showcased in the deoxygenation of epoxide **628**, which gives the highly sensitive methoxydihydrofuran derivative **629** in 66% yield [650].

Electrophilic halogen reagents are also useful in this regard. Thus, the system of iodine and triphenylphosphine in dimethylformamide effected the quantitative deoxygenation of the allyloxymethyl epoxide **630** [658a]. In addition, a novel deoxygenation protocol has been reported for the conversion of epoxyketones into the corresponding enones using thiourea dioxide as a reducing agent under phase transfer conditions [658b]. Essentially neutral conditions are obtained using molybdenum hexacarbonyl in refluxing benzene. The mechanism proceeds through initial loss of carbon monoxide followed by a complexation of the molybdenum center with



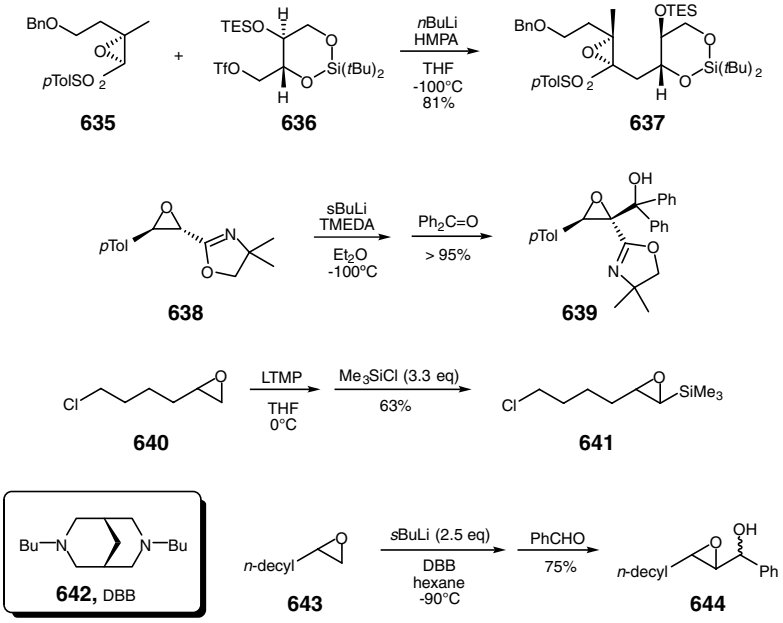
Scheme 2.90 Reductive deoxygenation of epoxides.

the epoxide oxygen to provide an activated species (i.e., **633**) that collapses to form the alkene (i.e., **634**) [659]. The low-valent titanium catalyst Cp_2TiCl, readily available by the *in situ* reduction of Cp_2TiCl_2 with activated zinc, has also been used for this type of deoxygenation [660, 661].

2.3.3.5 Oxiranyl Anions

Epoxides can be deprotonated on the ring, and the anions thus formed undergo interesting and synthetically useful chemistry, much of which has been summarized in recent review articles [196, 662, 663]. When electron-withdrawing groups are present, these stabilized oxiranyl anions engage in smooth S_N2 reaction with various electrophiles. Thus, the sulfonyl epoxide **635** (Scheme 2.91) is deprotonated using *n*-butyllithium in HMPA/THF at low temperature and treated with triflate **636** to give the highly functionalized adduct **637** in 81% yield. This protocol was used for the construction of the ABCDEF-ring systems of yessotoxin and adriatoxin [664]. Similar sulfonyl oxirane strategies have been used in other synthetic applications [665–668]. The oxazolinyl group also provides a useful stabilizing moiety for such alkylations (e.g., **638** → **639**) [669].

In certain cases, even non-stabilized oxiranyl anions can be coaxed into well-behaved conversions. Hodgson and coworkers [670] have reported on a convenient method of deprotonating terminal oxiranes with lithium 2,2,6,6-tetramethylpiperidide (LTMP), followed by trapping of the anion with silyl-based electrophiles, to

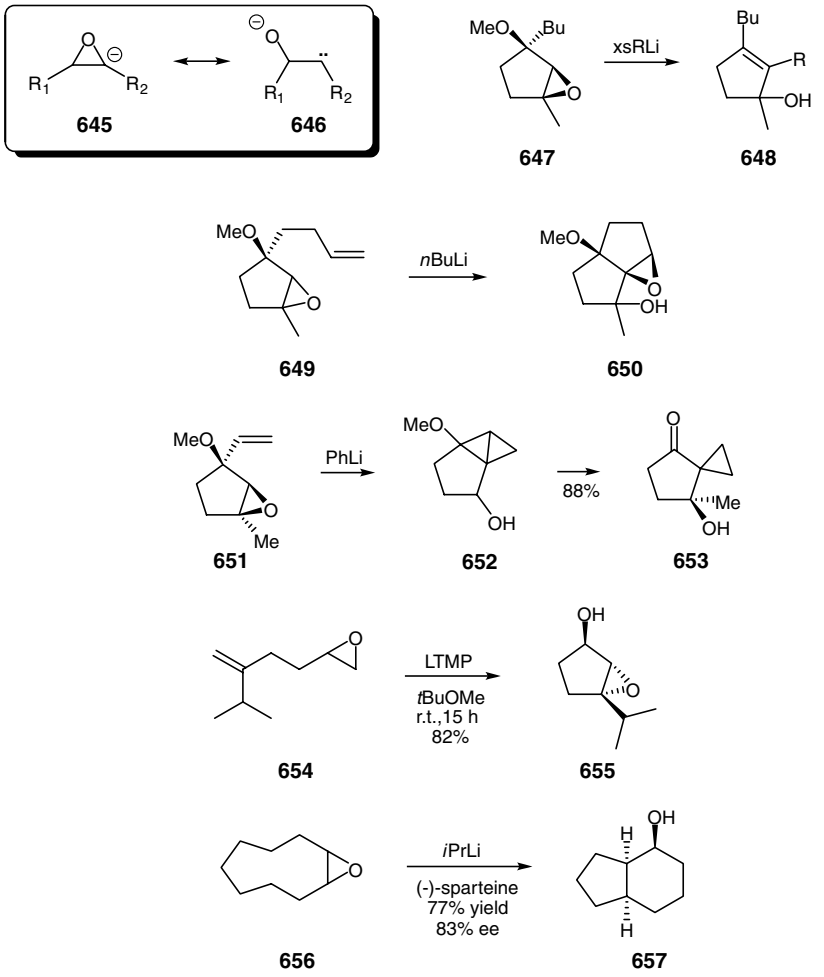


Scheme 2.91 Reaction of oxiranyl anions with electrophiles.

provide α,β-epoxysilanes in good yield. For example, chloro-epoxide **640** underwent clean conversion into epoxysilane **641** at 0 °C. This approach improves upon an earlier method, which employed sparteine derivatives at very low temperature (−90 °C) [671]. The initial proton–lithium exchange can be facilitated by diamines, such as dibutylbispidine (DBB, **642**). Thus, dodecene oxide **643** was deprotonated with *sec*-butyllithium and then treated with benzaldehyde to give the epoxyalcohol **644** in 75% yield [672, 673].

Often, though, when no stabilizing group is present, oxiranyl anions tend to exhibit significant carbenoid behavior, as indicated by resonance structure **646** (Scheme 2.92). Indeed, α-alkyloxyepoxide **647** can be regioselectively deprotonated (presumably under chelation control) to form an oxiranyl anion that undergoes α-eliminative ring opening and alkyl insertion to give cyclic allylic alcohols **648** in good to excellent yield. The carbenoid nature of the intermediates was supported by the isolation of the tricyclic alcohol **650**, the product of intramolecular trapping by an olefin [674]. Other examples of such cyclopropanation reactions include the allylic epoxide **651**, which is deprotonated by phenyllithium to give a highly strained tricyclic intermediate (**652**) that hydrolyzes to provide spirocyclic ketone **653** [675]. Lithium tetramethylpiperidide (LMTP) is also effective in the deprotonation, as shown in the conversion of alkenyl epoxide **654** into the fused bicyclic epoxide **655** [676].

As is the case with other carbene species, the carbene-like oxiranyl anions can engage in C−H insertion reactions. Hodgson and Lee [677] have devised a clever method for accessing enantiopure bicyclic alcohols from meso-epoxides by such a reaction. For example, treatment of cyclononene oxide (**656**) with isopropyllithium in the presence of an excess of (−)-sparteine leads to an enantioselective α-deprotona-



Scheme 2.92 Carbenoid behavior of oxiranyl anions.

tion, followed by intramolecular C–H insertion, to give bicyclononanol **657** in 77% yield and 83% enantiomeric excess.

2.4 Thiiranes

2.4.1 Properties of Thiiranes

Thiiranes [678] (also known as episulfides and thiacyclopropanes) can be thought of as row 3 epoxide analogs. For example, thiirane itself (bp 55 °C) exhibits a ring strain enthalpy of about 20 kcal mol^{-1}, which is about 7 kcal mol^{-1} less than oxirane. This

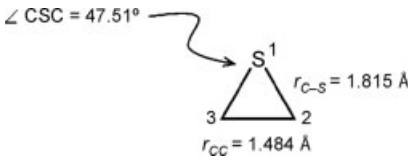
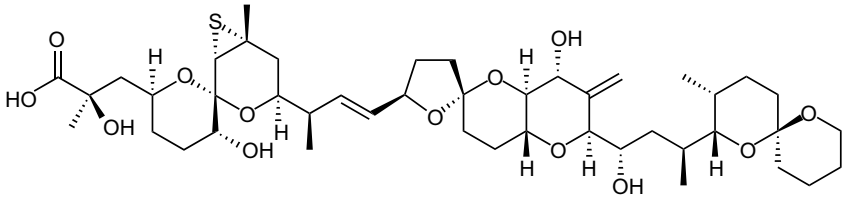


Figure 2.20 Geometry of thiirane.



660, acanthifolicin

Figure 2.21 Natural occurrence of thiiranes.

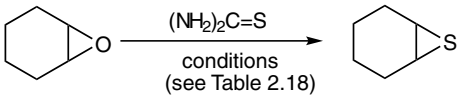
increased stability can be attributed to more flexible geometry about the sulfur center, which is manifested in the extremely acute C–S–C bond angle of less than 48° (Figure 2.20). The ^{1}H-NMR signals of the methylene protons resonate at 2.27 ppm and the carbon atoms appear at 18.1 ppm. The proton NMR shows vicinal coupling of about 6 Hz and geminal coupling of less than 1 Hz [6].

Thiiranes are produced in nature. For example, 3,4-epithiobutanenitrile, also known as 4ETN, is found in many cruciferous vegetables and may function as a weak biological alkylating agent [679], and humulene-4,5-episulfide is one of the components in the essential oil of hops [680]. Acanthifolicin (**660**, Figure 2.21) is an antibiotic polyether carboxylic acid isolated from the extracts of the marine sponge *Pandaros acanthifolium* [681], the activity of which is linked to protein phosphatase inhibition [682]. Synthetic episulfides have also been designed as mechanism-based matrix metalloproteinase inhibitors [683].

2.4.2 Synthesis of Thiiranes

2.4.2.1 From Epoxides

Preparatively, the broadest and most useful technique for obtaining episulfides is to launch from an existing epoxide, essentially exchanging an oxygen atom for a sulfur. One common reagent used to effect this transformation is thiourea, which is preferred for its relative stability and ease of handling, and quite a few experimental conditions have been developed for its use. For example, cyclohexene oxide (**440**, Scheme 2.93) is cleanly converted into the corresponding episulfide using thiourea at elevated temperatures in the absence of solvent (Table 2.18, entry 1) [684]. The reaction also proceeds in methylene chloride under the catalysis of silica gel [685], in



440 **658**

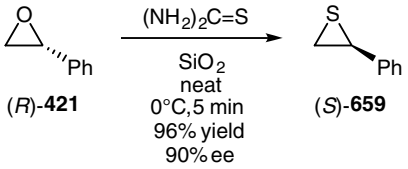
Scheme 2.93 Conversion of epoxides into episulfides using thiourea.

Table 2.18 Yield data for the conversion of epoxides into episulfides using thiourea.

Entry	Activator	Solvent	Temp (°C)	Time	Yield (%)	Ref
1	None	Neat	120	25 min	92	[577]
2	SiO_2	CH_2Cl_2	r.t.	30 min	92	[578]
3	SiO_2-$AlCl_3$	MeCN	45	1.3 h	89	[579]
4	β-Cyclodextrin	H_2O	r.t.	6 h	82	[580]

acetonitrile with silica-supported aluminium chloride [686] and in water using β-cyclodextrin as a catalyst [687].

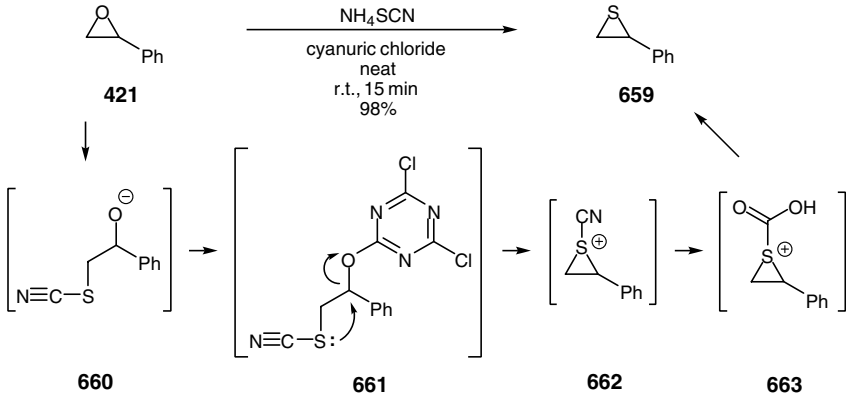
Notably, this sulfurization proceeds with inversion of configuration, and the degree of stereospecificity depends upon the reaction conditions. Thus, when *(R)*-styrene oxide (**421**, Scheme 2.94) is treated with thiourea without solvent, very little optical purity is lost during the reaction. However, in methylene chloride at 0 °C the enantiomeric excess drops to 70% [685].



(*R*)-**421** (*S*)-**659**

Scheme 2.94 Enantiospecific preparation of episulfides from epoxides.

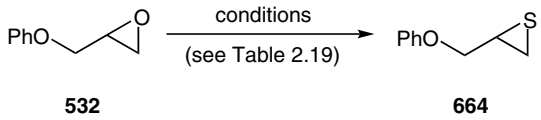
Ammonium thiocyanate is another convenient sulfur donor for these processes, and a very practical method has been described using cyanuric chloride as a co-reagent. Thus, when styrene oxide (**421**, Scheme 2.95) is treated with stoichiometric ammonium thiocyanate and cyanuric chloride in the absence of solvent, the episulfide **659** is produced in almost quantitative yield within 15 min. The mechanism involves nucleophilic ring opening of the epoxide to give an alkoxide intermediate (**660**); reaction with cyanuric chloride activates the oxygen towards displacement by sulfur, yielding a cyanatoepisulfenium species (**662**), which undergoes hydrolysis and subsequent loss of carbon dioxide to provide the observed



Scheme 2.95 Activation of epoxides using cyanuric chloride.

product [688]. Magnesium hydrogen sulfate has also proven to be an effective activating agent [689].

The addition of thiocyanate is also catalyzed by poly(allylamine) (PAA) under slightly basic aqueous conditions. For example, phenyloxymethyl epoxide **532** (Scheme 2.96) is converted into the corresponding episulfide in excellent yield under these conditions (Table 2.19) [690]. Very good yields have been reported using potassium thiocyanate in a biphasic medium of ionic liquid and water with no additional catalyst [579]. Finally, elemental sulfur can be employed as the donor using diethylphosphite, ammonium acetate and alumina in the absence of solvent under microwave irradiation. The mechanism involves a thiophosphate species [691].



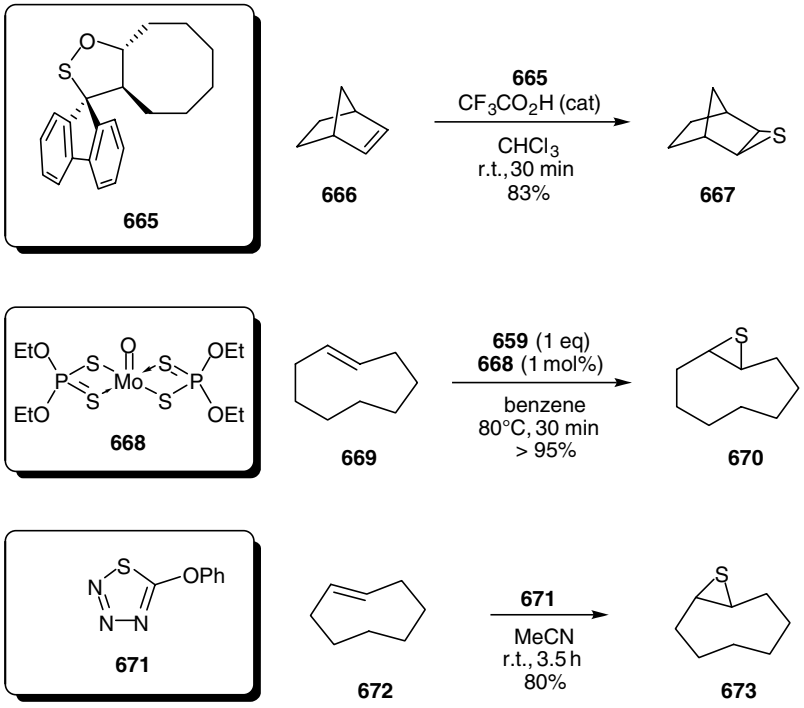
Scheme 2.96 Epoxide–episulfide conversion using other sulfur sources.

Table 2.19 Yield data for epoxide–episulfide conversions.

Entry	S source	Additives	Solvent	Temp (°C)	Time	Yield (%)	Reference
1	NH_4SCN	PAA/NaOH	H_2O	45	70 min	93	[583]
2	KSCN	None	[bmim] PF_6-H_2O	45	1.3 h	89	[579]
3	S/HP(O)$(OEt)_2$	NH_4OAc/Al_2O_3	neat	μw	2 min	68	[584]

2.4.2.2 From Alkenes

If episulfides were strictly analogous to their cousin epoxides, their preparation would spring predominantly from the direct sulfurization of alkenes. This is, however, not the case. The few direct methods have been nicely summarized in a recent review [692]. Nevertheless, there are some protocols that merit special attention. For example, the sultene **665** (Scheme 2.97), an isolable cycloadduct from fluorinethione-*S*-oxide and *trans*-cyclooctene, has been shown to exhibit promising sulfur-transfer capabilities. Thus, treatment of norbornene (**666**) with sultene **665** in the presence of catalytic quantities of trifluoroacetic acid furnishes *exo*-episulfide **667** in 83% yield [693]. The dithiophosphate molybdenum complex **668** actually catalyzes the transfer of sulfur from one episulfide to another alkene. This allows the use of a more readily available substrate (e.g., **659**) as a sulfur donor, as shown in the episulfidation of *trans*-cyclononene **669** [694]. Thiatriazole **671** also functions as a stoichiometric sulfur transfer reagent for a wide range of alkene substrates (e.g., **672** → **673**) [695]. Dinitrogen sulfide has been implicated as the active sulfur-transfer species [696].

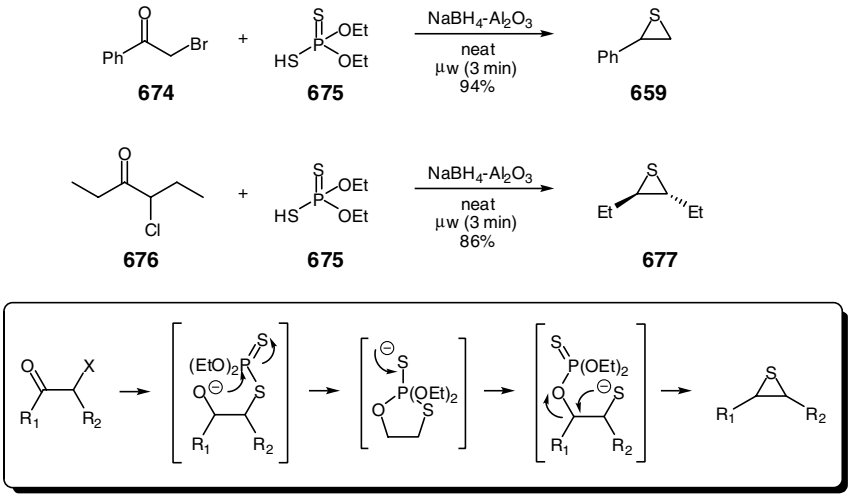


Scheme 2.97 Thiiranes from alkenes.

2.4.2.3 From Haloketones

One very intriguing method that has received surprisingly little attention is the conversion of α-haloketones into episulfides using the commercially available

O,O-diethyl hydrogen phosphodithioate as a sulfur donor under microwave conditions. The procedure appears to be fairly general and high yielding. Thus, bromoacetophenone **674** (Scheme 2.98) provides excellent yield of the corresponding episulfide (**659**) within 3 min. The mechanism is thought to involve a sequence of nucleophilic displacement, phosphorus transfer and cyclization (inset Scheme 2.98). For substrates that yield 1,2-disubstituted episulfides, diastereoselectivity is very high, with trans : cis ratios generally being greater than 10 : 1, as shown in the preparation of diethylepisulfide **677** [697].



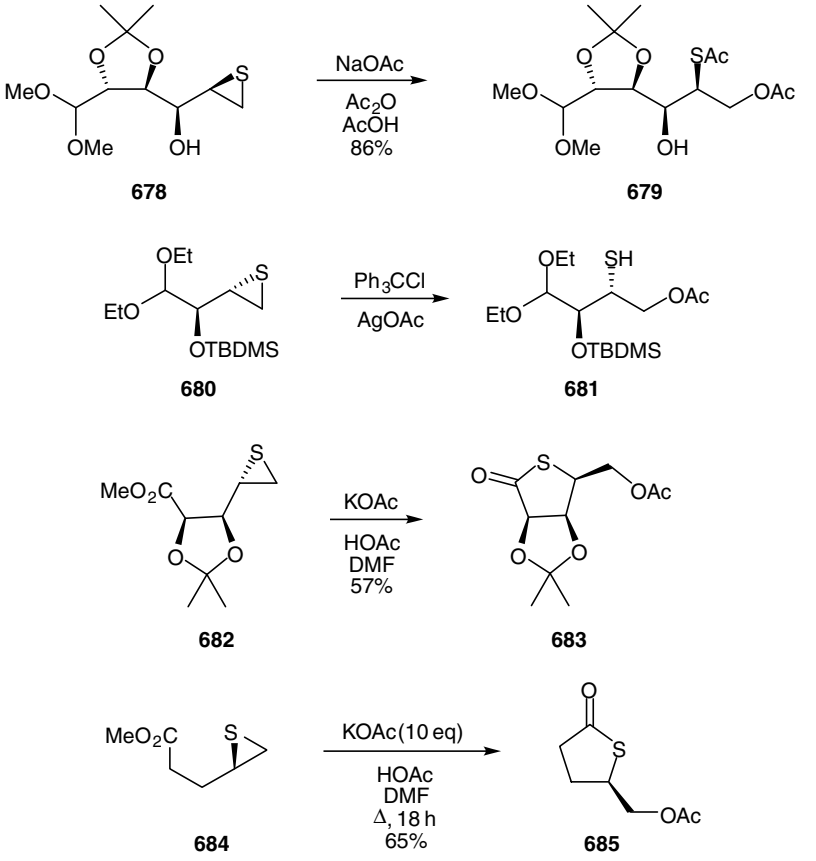
Scheme 2.98 Thiiranes from haloketones.

2.4.3
Reactivity of Thiiranes

2.4.3.1 Nucleophilic Ring Opening

Like the epoxides, episulfides are prone to ring-opening reactions induced by nucleophiles, whereby the C−S bond is cleaved. However, sulfur stabilizes a negative charge better than oxygen and therefore functions as a more active leaving group. The sulfide so-formed is also more nucleophilic than the analogous alkoxide. Furthermore, sulfur supports radical centers more readily than oxygen. Taken together, these behaviors contribute to the fact that the ring opening of episulfides is usually attended by some degree of uncontrolled polymerization and other yield-reducing processes. However, many well-behaved conversions are known, and those outlined below are meant to provide a general impression of synthetic possibilities.

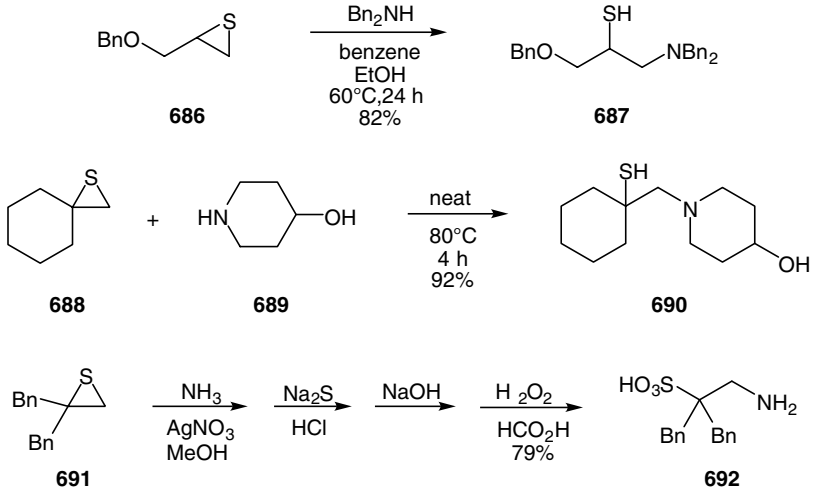
Acetate is a frequently employed nucleophile. For example, in their protocol for preparing sulfur-containing disaccharides, Santoyo-González and coworkers [698] heated a mixture of episulfide **678** (Scheme 2.99), sodium acetate and acetic anhydride in acetic acid to obtain diacetate **679** in very good yield. Similarly, the thiiranyl acetal **680** undergoes ring opening in the presence of silver(I) acetate and



Scheme 2.99 Ring opening of thiiranes with acetate.

triphenylmethyl chloride to provide the acetoxythiol **681**, a key intermediate in the asymmetric total synthesis of thietanose [699]. These ring openings can also trigger subsequent cyclizations from the sulfur center. Thus, the thiiranyl acetonide ester **682** suffers attack by acetate to give an intermediate sulfide, which engages in intramolecular attack of the ester carbonyl to yield the thiolactone **683** [700]. A similar strategy was used to access the acetoxymethyl thiobutyrolactone derivative **685** [701].

Amines are also competent nucleophiles in these reactions. For example, the benzyloxymethylthiirane (**686**, Scheme 2.100) is attacked by dibenzylamine at the less substituted position, providing aminothiol **687** in good yield [702]. In like fashion, spiroepisulfide **688** undergoes aminolysis by 4-hydroxypiperidine (**689**) in solventless thermal conditions to give excellent yield of the β-aminoethanethiol **690** [703]. A twist on this protocol has been reported for the synthesis of taurine derivatives from episulfides. Thus, dibenzylthiirane **691** was treated with ammonia in the presence of silver nitrate to give a silver-chelated adduct that was sequentially treated with hydrogen sulfide (generated *in situ* from sodium sulfide and hydrochloric acid), sodium hydroxide and performic acid (generated *in situ* from formic



Scheme 2.100 Ring opening of thiiranes with amines.

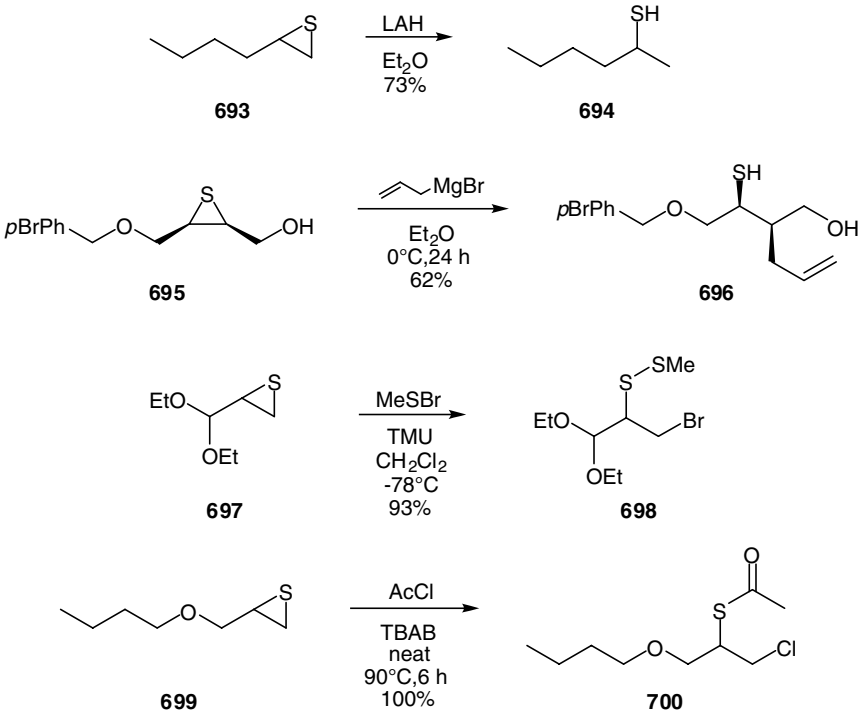
acid and hydrogen peroxide), ultimately generating the 1,1-disubstituted taurine **692** in good overall yield [704].

High-yielding processes using other nucleophiles have also been reported. For example, treatment of the terminal episulfide **693** (Scheme 2.101) with lithium aluminium hydride in ether resulted in hydride-mediated reductive ring opening to give 2-hexanethiol (**694**) in good yield. The internal thiirane **695** underwent nucleophilic ring opening with allyl Grignard, forming the hydroxythiol **696**. The regiochemistry of the attack can be rationalized by chelation control in this case [705]. Even halides can engage in this process when appropriate activating agents are employed. Thus, thiiranyl acetal **697** was converted into the disulfide **698** using methanesulfenyl bromide in a medium of tetramethylurea (TMU) and methylene chloride through a process of electrophilic S-activation followed by nucleophilic ring-opening by bromide [706]. A similar process is promoted by acyl chlorides, as shown in the quantitative conversion of terminal episulfide **699** into the chlorothioester **700** upon treatment with acetyl chloride and catalytic tetrabutylammonium bromide (TBAB) [707].

2.4.3.2 **Desulfurization**

Thiiranes can be converted into alkenes through a process of desulfurization, often in very high yields. For example, methyltrioxorhenium (MTO) catalyzes the stereospecific removal of sulfur by triphenylphosphine, as shown in the quantitative conversion of alkenyl sulfide **701** (Scheme 2.102) to 1,5-hexadiene (**702**). Performance is enhanced when the catalyst is pretreated with hydrogen sulfide; a Re^{V} species has been implicated as the catalytically relevant species [708]. An extremely efficient copper-mediated desulfurization was used as the key step in the synthesis of C_2-symmetric dibenzosuberane (DBS) helicene **704**, which is of interest as a potential chiroptical switch [709].

Alkyllithium reagents, such as *n*-butyllithium and phenyllithium, have been known for some time to function as desulfurization agents, as exemplified by the



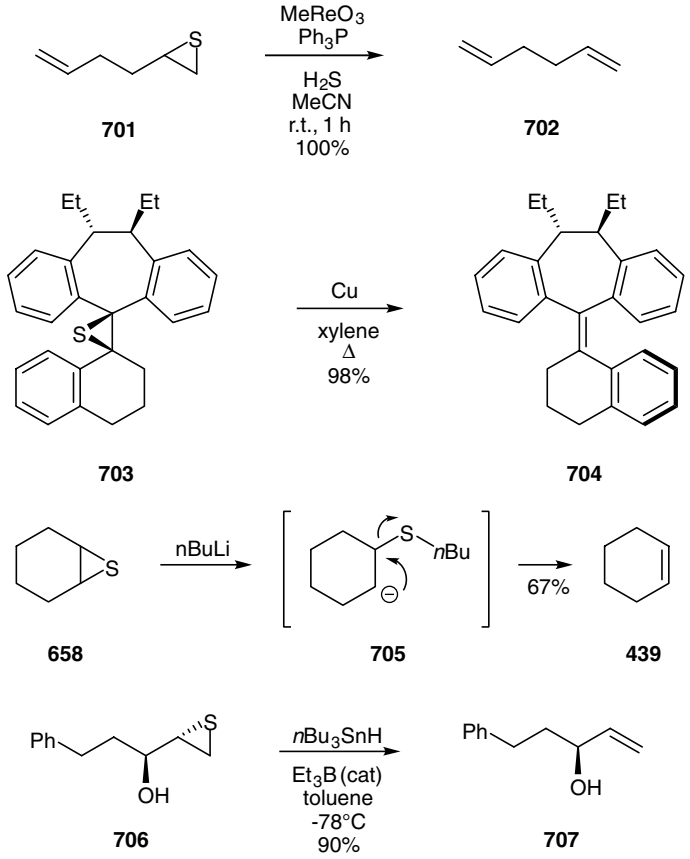
Scheme 2.101 Ring opening of thiiranes with other nucleophiles.

butyllithium-mediated conversion of cyclohexene oxide **658** into the parent alkene **439**. The mechanism involves initial ring-opening by attack on sulfur to give an α-thio anion (i.e., **705**) that rapidly undergoes elimination of butyl sulfide to form the observed product [710]. Tributyltin hydride also effects a reductive desulfurization in the presence of a radical initiator, such as triethylborane at low temperature or AIBN at elevated temperatures. Under these conditions, the thiiranyl alcohol **706** is converted into the corresponding allylic alcohol (**707**) in excellent yield and without the need for protecting group chemistry [711]. Calculations have shown that triethylphosphite should function as a desulfurizing agent through a concerted process, thus promising high stereospecificity [712].

2.5 Diaziridines

2.5.1 Properties of Diaziridines

Diaziridines can be thought of as the smallest cyclic hydrazine derivatives. At 25.5 kcal mol^{-1}, the calculated ring strain for diaziridine itself is slightly less than that of oxirane; and just as the open-chain analog, hydrazine, is more stable toward



Scheme 2.102 Desulfurization of thiiranes.

interheteroatom cleavage than hydrogen peroxide so too is diaziridine less prone to undergo N−N ring opening than dioxiranes are to suffer O−O scission. Calculations have also indicated a proton affinity for diaziridine similar to that of ammonia. Geometrically, the diaziridine ring describes an almost equilateral triangle (Figure 2.22), with the N–C–N bond angle opening about 2° wider than the other two; consequently, the N−N bond is slightly longer than the C−N bond [713]. The ^{1}HNMR signals of the methylene protons resonate at about 2.2 ppm [714].

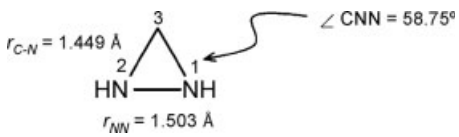


Figure 2.22 Geometry of diaziridine.

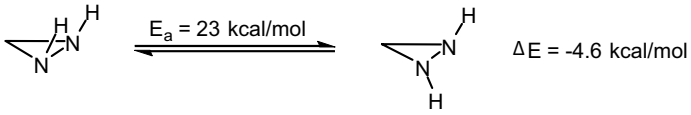


Figure 2.23 Cis–trans isomerism in diaziridine.

From a physical organic perspective, diaziridine is a fascinating species. As there is about a 23 kcal mol^{-1} barrier to inversion about the nitrogen center (Figure 2.23), diaziridines exist as isolable *cis*- and *trans*-isomers, the latter lying about 5 kcal mol^{-1} lower in energy. For *N,N*-dialkyl derivatives, this barrier is even higher. For the di-*t*-butyl variant, it has been calculated at 30 kcal mol^{-1} [715]. As a result, *trans*-*N,N*-disubstituted diaziridines have been recognized as novel C_2-symmetric compounds, and efforts have been made to elaborate methods for their resolution [716, 717]. Diaziridines have also been investigated as possible high-energy materials (although not particularly promising in this regard) [713], and there is at least one report of diaziridine derivatives exhibiting psychotropic activity, particularly with respect to monoamine oxidase inhibition and antidepressant behavior [718].

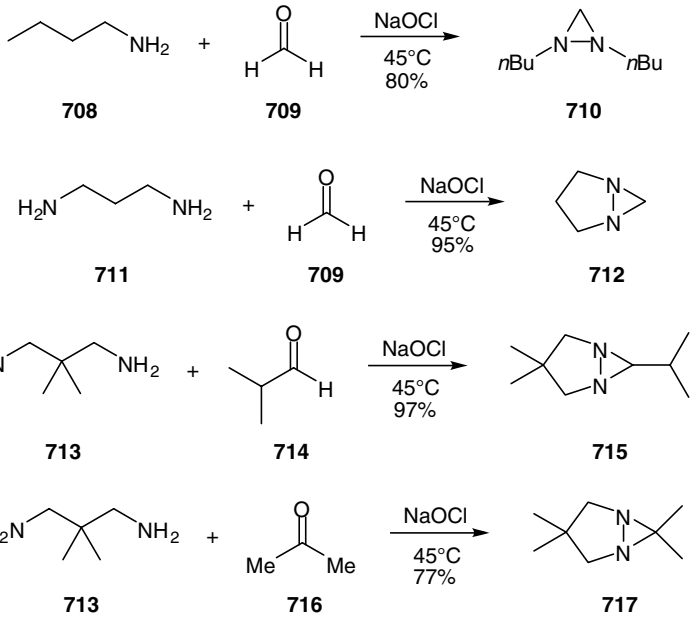
2.5.2 Synthesis of Diaziridines

The synthesis of monocyclic diaziridines and their fused derivatives is the subject of a recent review [719]. Some of the more common synthetic routes are outlined below.

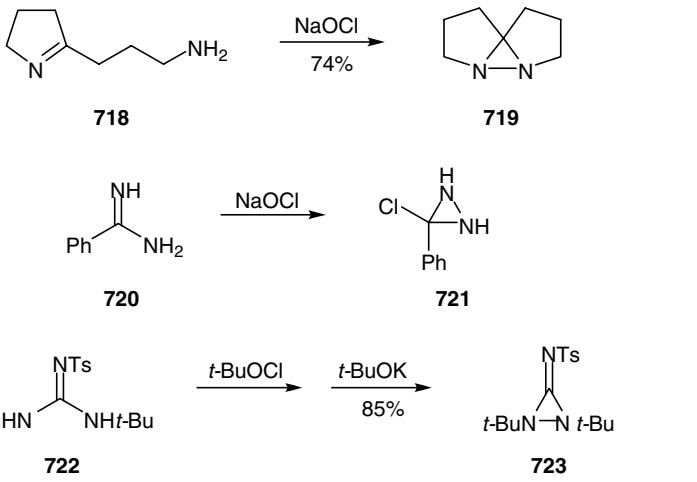
2.5.2.1 Oxidative Methods using Hypohalites

One of the more common routes for accessing diaziridines is the oxidative ring closure of aminals, which are usually formed *in situ* from the respective amines and carbonyl compounds. Thus, *N,N*-dibutyldiaziridine (**710**, Scheme 2.103) is prepared in good yield by combining *n*-butylamine and formaldehyde in the presence of aqueous sodium hypochlorite [720]. The method can be applied to diamine substrates, such as propylenediamine (**711**) to construct fused bicyclic derivatives (e.g., **712**) in excellent yield. Furthermore, the diamines can be condensed onto substituted aldehydes (e.g., **714**) and ketones (e.g., **716**) with equal efficiency. The pH of the reaction medium can have an impact on yields and product distributions [721].

The aminals can be formed from other precursors, as demonstrated by the aminoalkylimine **718** (Scheme 2.104), which produces the fused tricyclic diaziridine **719** in the presence of aqueous sodium hypochlorite [722]. The benzimidamide **720** serves as a precursor for diazirines in similar oxidizing environments; however, an intermediate chlorodiaziridine (**721**) has been identified in the reaction mixture, and it is stable enough to isolate [723]. Similarly, diaziridinimines such as **723** can be prepared in good yield by subjecting tosyl guanidine **722** to sequential treatment by *t*-butyl hypochlorite and *t*-butoxide [724].



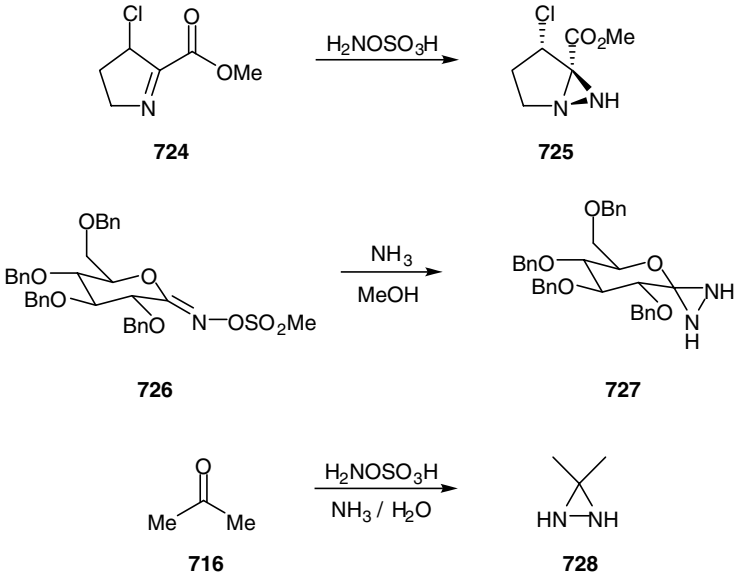
Scheme 2.103 Synthesis of diaziridines from carbonyls and amines.



Scheme 2.104 Synthesis of diaziridines from imines, imidamides, and guanidines.

2.5.2.2 **Via Hydroxylamine Derivatives**

Another alternative for diaziridine synthesis is presented in the use of O-sulfonated hydroxylamine derivatives, which offers the advantage of a much less oxidizing environment. As an example, the cyclic imino ester **724** (Scheme 2.105) is converted into diaziridine **725** upon treatment with hydroxylamine *O*-sulfonic acid [725], and

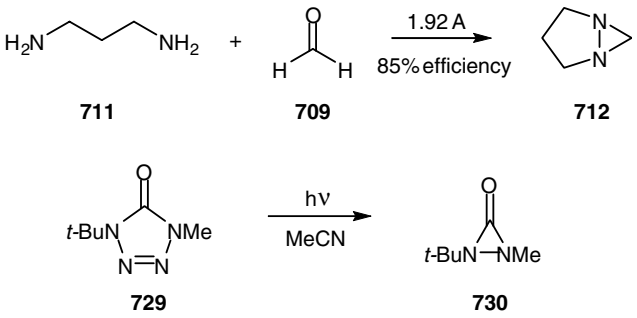


Scheme 2.105 Synthesis of diaziridines from hydroxylamine derivatives.

the same method is effective in preparing the glycosylidene-derived diaziridine **727**, which serves as a precursor for the corresponding diazirine and thus a glycosylidene carbene [726]. An operationally more straightforward variant of the methodology can be used for preparing various 2,2-disubstituted derivatives. Thus, a ketone such as acetone (**716**) is treated with hydroxylamine *O*-sulfonic acid in the presence of aqueous ammonia to give the desired diaziridine (**728**) in one pot [727].

2.5.2.3 **Other Methods**

Although the generality of the methods has not been firmly established, two protocols merit special attention. The first is the direct electrochemical synthesis of diaziridines from amines and aldehydes in a bicarbonate buffered solution, which is directly analogous to methods described in Section 2.5.2.1 but obviating the need for chemical oxidants. Thus, propylenediamine (**711**, Scheme 2.106) and formaldehyde



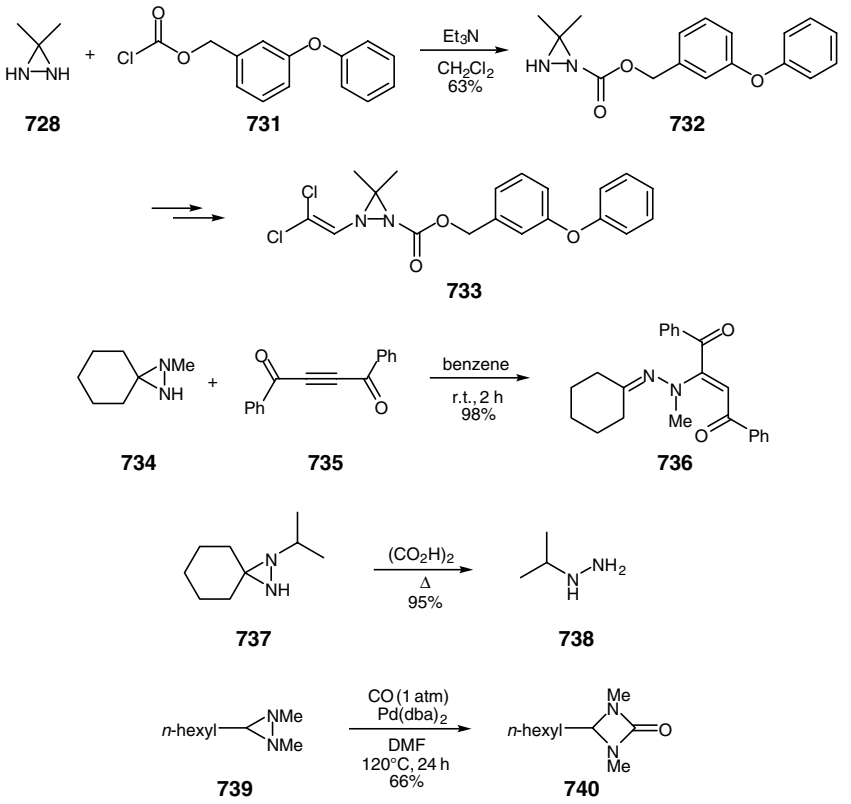
Scheme 2.106 Synthesis of diaziridines via electrical and photochemical means.

cleanly provided bicyclic diaziridine **712** under these electrochemical conditions. The current efficiency reached 85% under optimum conditions [728]. The second method is the photolysis of tetrazolone derivatives (e.g., **729**) to give diaziridinones (e.g., **730**), which could be obtained in high purity [729].

2.5.3 Reactivity of Diaziridines

2.5.3.1 Diaziridines

Like their open-chain analogs, diaziridines are nucleophilic species that engage in well-behaved reaction with various electrophiles. For example, 3,3-dimethyldiaziridine (**728**, Scheme 2.107) is smoothly N-acylated with 3-phenyoxybenzyl chloroformate (**731**) in the presence of triethylamine in a medium of methylene chloride to give the carbamate **732** in 63% yield. The remaining nitrogen was further functionalized to produce the diazapyrethroid analog **733**, and the diaziridine moiety proved to be remarkably stable to the experimental conditions (particularly zinc in acetic acid) [727]. Diaziridines also engage in conjugate addition onto traditional Michael

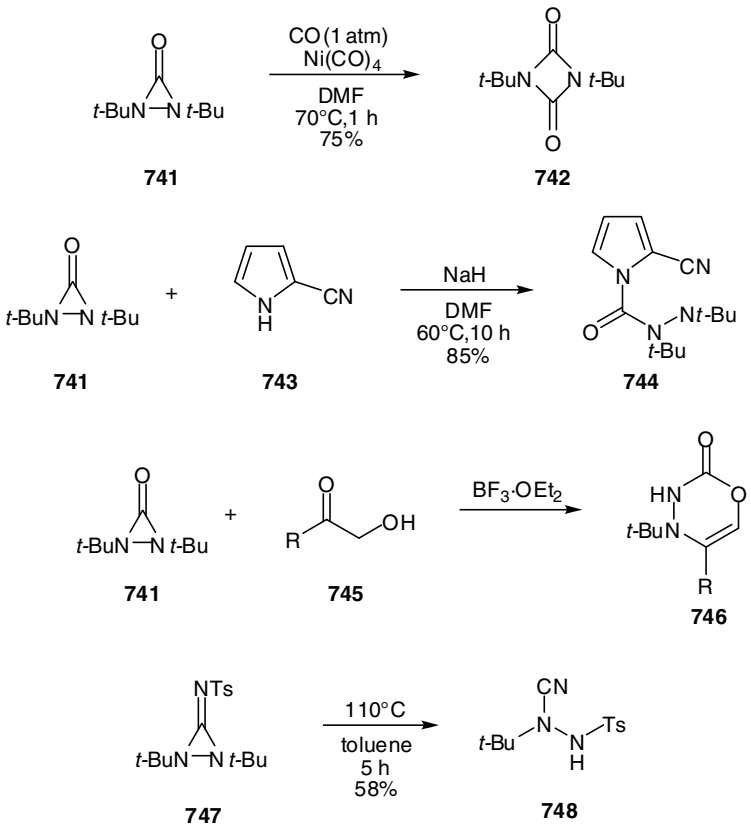


Scheme 2.107 Some reactions of diaziridines.

acceptors, such as DMAD [730] and dibenzoylacetylene [731]. The intermediate diaziridinium species formed by the initial addition suffers ring-opening through scission of the C−N bond to give a hydrazone derivative (e.g., **736**). In fact, under acidic conditions diaziridines spontaneously decompose to form the component hydrazines and carbonyl compounds, as shown by the recovery of *N*-isopropylhydrazine (**738**) in 95% yield upon exposure of the precursor diaziridine **737** to oxalic acid [732, 733]. The cyclic N−N bond is not totally inert, however. For example, palladium catalyzes the insertion of carbon monoxide into the N–N bond, converting diaziridines (e.g., **739**) into the corresponding azalactam derivatives (e.g., **740**) [734].

2.5.3.2 **Diaziridinones and Diaziridinimines**

Diaziridinones also exhibit some interesting chemistry. For example, they too have been reported to engage in carbonyl insertion reactions in the presence of a nickel catalyst to give diazetidine-2,4-diones (e.g., **742**, Scheme 2.108) in reasonable yields [735]. Usually, however, their reactivity involves the nucleophilic attack of the carbonyl carbon, as illustrated by the reaction of *N,N*-di-*t*-butyldiaziridinone (**741**)



Scheme 2.108 Some reactions of diaziridinones and diaziridinimines.

with the sodium salt of cyanopyrrole **743**, which engages in nucleophilic addition to the carbonyl, followed by ring-opening to provide the acylhydrazine **744** in 85% yield [736]. A similar addition event is the first step of many in the Lewis acid-catalyzed conversions of diaziridines into oxadiazinones (e.g., **746**) by α-hydroxy ketones (e.g., **745**) [737]. Finally, the analogous diaziridinimes (e.g., **747**) are thermally unstable, rearranging to *N*-cyanohydrazine derivatives (e.g., **748**) at elevated temperatures [724].

2.6
3*H*-Diazirines

2.6.1
Properties of Diazirines

With a literature age of less than 50 years old [738, 739], diazirines are relative youngsters among their companion three-membered heterocycles, and an interesting lot they are. Although this ring system might intuitively appear quite unstable, the strain energy has been calculated at a remarkably low 21 kcal mol^{-1} [740]. This, combined with very low basicity, is largely responsible for the observed stability (even *in vivo*) of the diazirine ring at room temperature. The double bond character between the two nitrogens results in a short N=N bond distance (1.23 Å), which, in turn, significantly compresses the N–C–N bond angle (Figure 2.24) [741]. Likewise, the diaziridine moiety is planar and symmetrical. Since molecular nitrogen can be rapidly extruded under thermal or photochemical conditions, neat diazirines should be afforded the respect in handling that all potentially explosive compounds deserve.

2.6.2
Synthesis of Diazirines

The lion's share of protocols for the preparation of diazirines proceed through a diaziridine intermediate. For example, 4-aziadamant-1-amine (**750**, Scheme 2.109) was synthesized by the chromium(VI) mediated oxidation of the corresponding diaziridine (**749**) [742]. However, diaziridine precursors can serve as suitable substrates for various one-pot procedures. Thus, the camphor-derived iminium salt **751** was converted into the sterically hindered chiral diaziridine 2-azicamphane **752** by

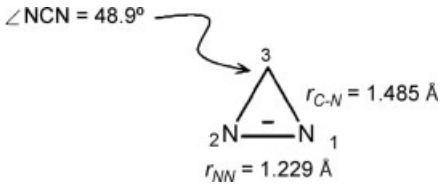
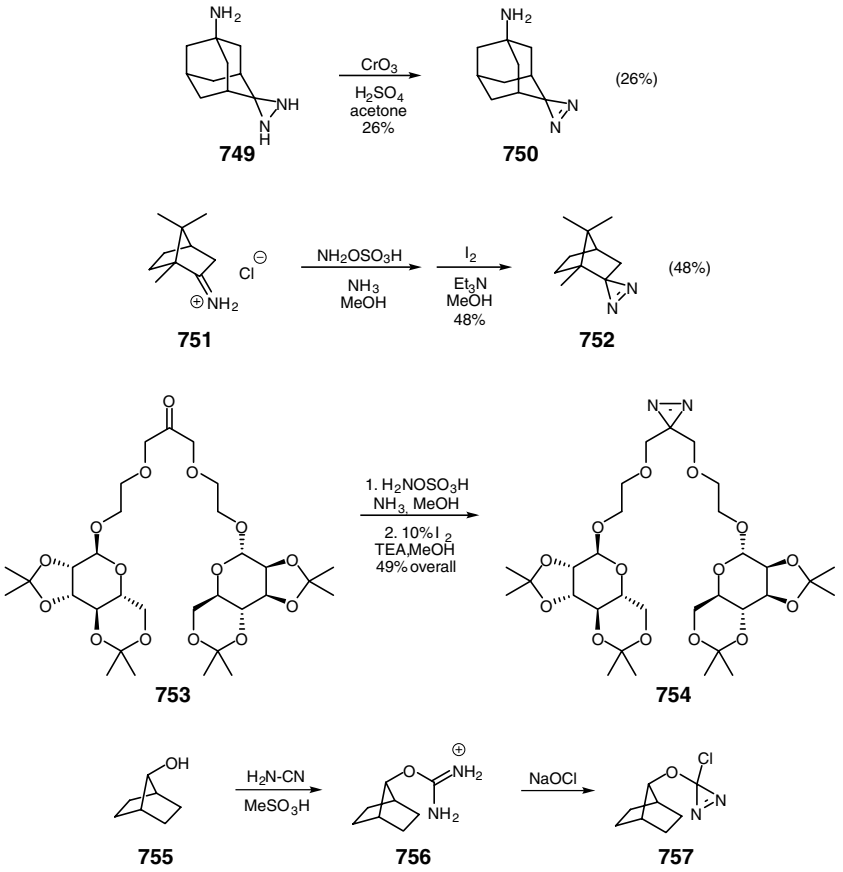


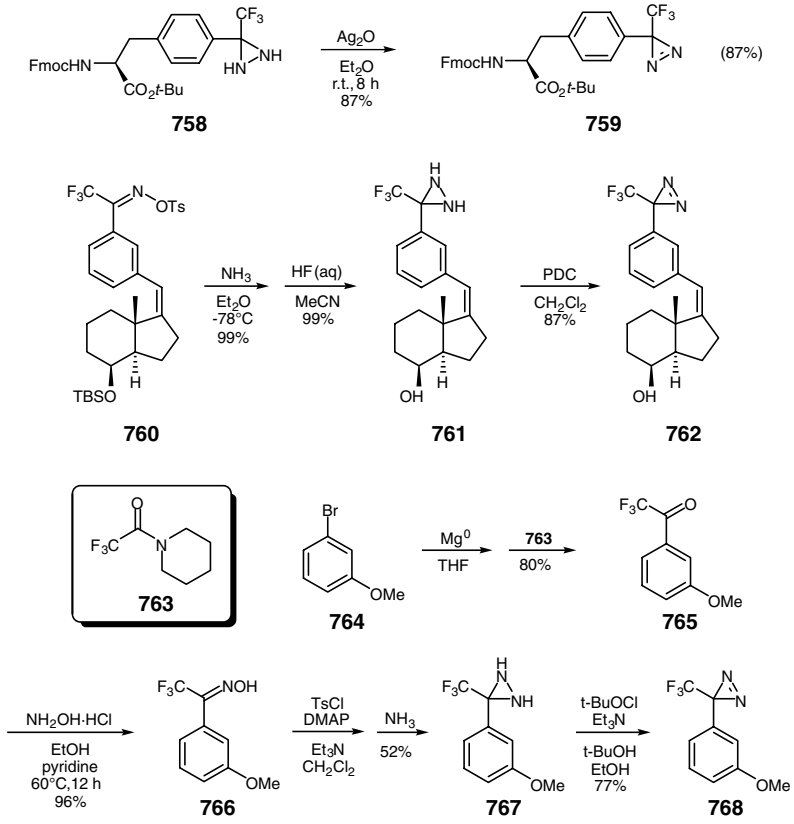
Figure 2.24 Geometry of 3*H*-diazirine.



Scheme 2.109 Synthesis of diazirines.

treatment with hydroxylamine *O*-sulfonic acid in methanolic ammonia, followed by oxidation with iodine in the presence of triethylamine [743]. Ketones can also be used to advantage in this regard, as illustrated by the construction of the diaziridinyl cluster mannoside **754** from ketone **753** [744]. Alkoxy substituted diazirines can be prepared from alcohols. Thus, norboranol **755** was treated with cyanamide and methanesulfonic acid to afford an intermediate isouronium salt (**756**) that was oxidized with hypochlorite to give the diazirine **757** [745]. Diazirines have also been prepared by the partial hydrolysis of nitriles, followed by hypochlorite oxidation [746].

Since they have desirable end-application properties, 3-trifluoromethyldiazirines are of particular interest, and these are prepared in similar fashion. For example, the diazirinyl antiotensin II analogue **759** (Scheme 2.110) was produced in very good yield from the silver(I) oxide mediated oxidation of diaziridine **758** [747]. An equally efficient diazirine synthesis was achieved launching from the *O*-tosyl oxime **760**, which was converted into the diaziridine by treatment with liquid ammonia. After the fluoride-mediated desilylation of the alcohol functionality, PDC oxidation afforded



Scheme 2.110 Synthesis of trifluoromethyldiazirines.

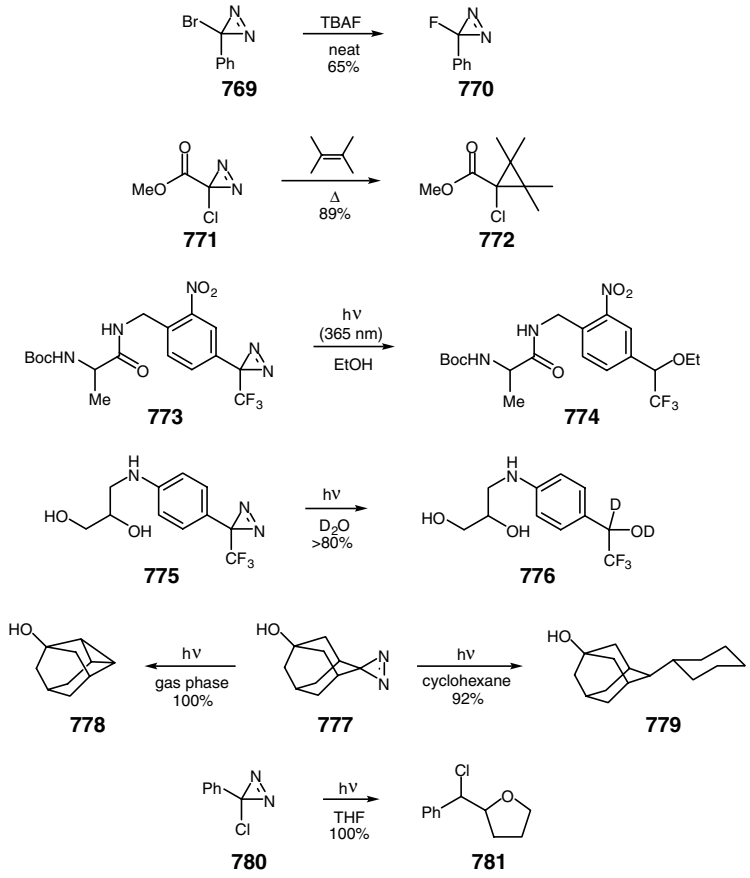
the desired diazirine **762** in remarkably good overall yield. The target was used as the centerpiece for the construction of a vitamin D analog, a testament to the robustness of the diazirinyl moiety toward various experimental conditions [748].

Ultimately, the trifluoromethyl group is usually introduced by way of an activated trifluoroacetic acid derivative. For example, the aryl Grignard derived from *m*-bromoanisole (**764**) smoothly added to *N*-trifluoroacetylpiperidide (**763**) to give the trifluoroacetophenone derivative **765**, which was converted into the corresponding oxime (**764**) in excellent yield using conventional methods. Subsequent *O*-tosylation and treatment with ammonia afforded the diaziridine **767**, which was oxidized to the diazirine **768** using *t*-butyl hypochlorite [749].

2.6.3
Reactivity of Diazirines

Diazirines with leaving groups at the 3-position can undergo substitution reactions without affecting the azo moiety [750]. As one example, the bromodiazirine **769**

(Scheme 2.111) is converted into the fluoro analog **770** upon treatment with anhydrous tetrabutylammonium fluoride (TBAF) under solvent-free conditions [751]. It would be fair to state, however, that the spotlight shines on diazirines for their propensity to extrude molecular nitrogen to form reactive carbene intermediates [752, 753]. Thus, the 3-acyldiazirine **771** suffers loss of nitrogen under thermal conditions in the presence of alkenes to yield products of carbene–olefin cycloaddition [754].



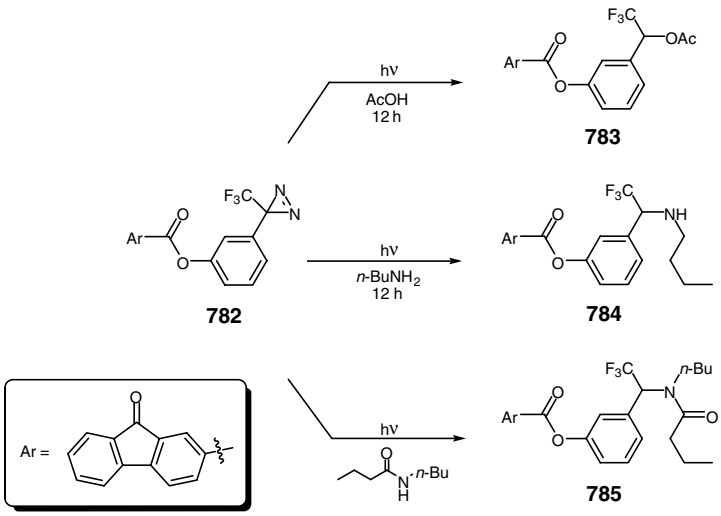
Scheme 2.111 Some reactions of diazirines.

Photolysis of diazirines also generates carbenes, and this procedure is more significant in terms of application [755]. Once the carbene intermediates are formed, the reactivity is much the same as for carbenes generated by any other method. For example, when the aryl diazirine **773** is photolyzed in ethanol, the major product (**774**) results from the insertion of carbene in the O−H bond of the solvent [756]. Similar behavior is observed in aqueous media (i.e., **775** → **776**) [757]. Photolysis of

2-azi-5-hydroxyadamantane (**777**) in the gas phase results in the quantitative formation of the intramolecular 1,3 C−H insertion product **778**. When the same substrate is photolyzed in an organic solvent, then the intermolecular process dominates, as illustrated by the cyclohexane adduct **779** [758]. This behavior is fairly general – the carbene derived from arylchlorodiazirine **780** also quantitatively traps THF when generated in that solvent [759].

To summarize, diazirines can be synthesized with a high degree of regioselectivity, launching from various readily available functional groups. The diazirines themselves have a very long half-life at room temperature and under a broad range of conditions. Reaction can be triggered by photolysis in a manner that engages few, if any, other functionalities. It can be assumed that carbene generation is practically quantitative, and these carbenes react quickly with a wide variety of substrates. This particular confluence of behaviors has earned these substrates an important niche, namely within the realm of photoaffinity labels (PAL), an application that has been nicely summarized in a recent review [760].

Interestingly, for the same reasons, diazirines have been investigated as materials surface modifiers. In their study of the underlying chemistry of these processes, Hayes and coworkers photolyzed the fluorenone-modified diazirine **782** in the presence of acetic acid, *n*-butylamine, and *N*-butylbutanamide as models of the functional group environment encountered in a medium of nylon 6,6 (and, incidentally, proteins *in vivo*). In all cases, they observed extremely efficient (>95%) insertion reactions, leading to the products **783**, **784**, and **785**, deriving from O−H insertion, amine N−H insertion, and amide N−H insertion, respectively [761] (Scheme 2.112).



Scheme 2.112 Insertion reactions of a photoaffinity label (PAL).

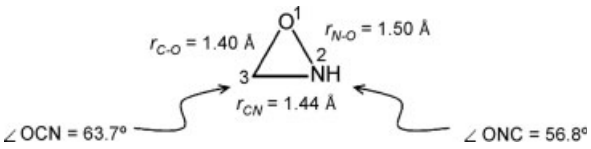


Figure 2.25 Geometry of oxaziridine.

2.7 Oxaziridines

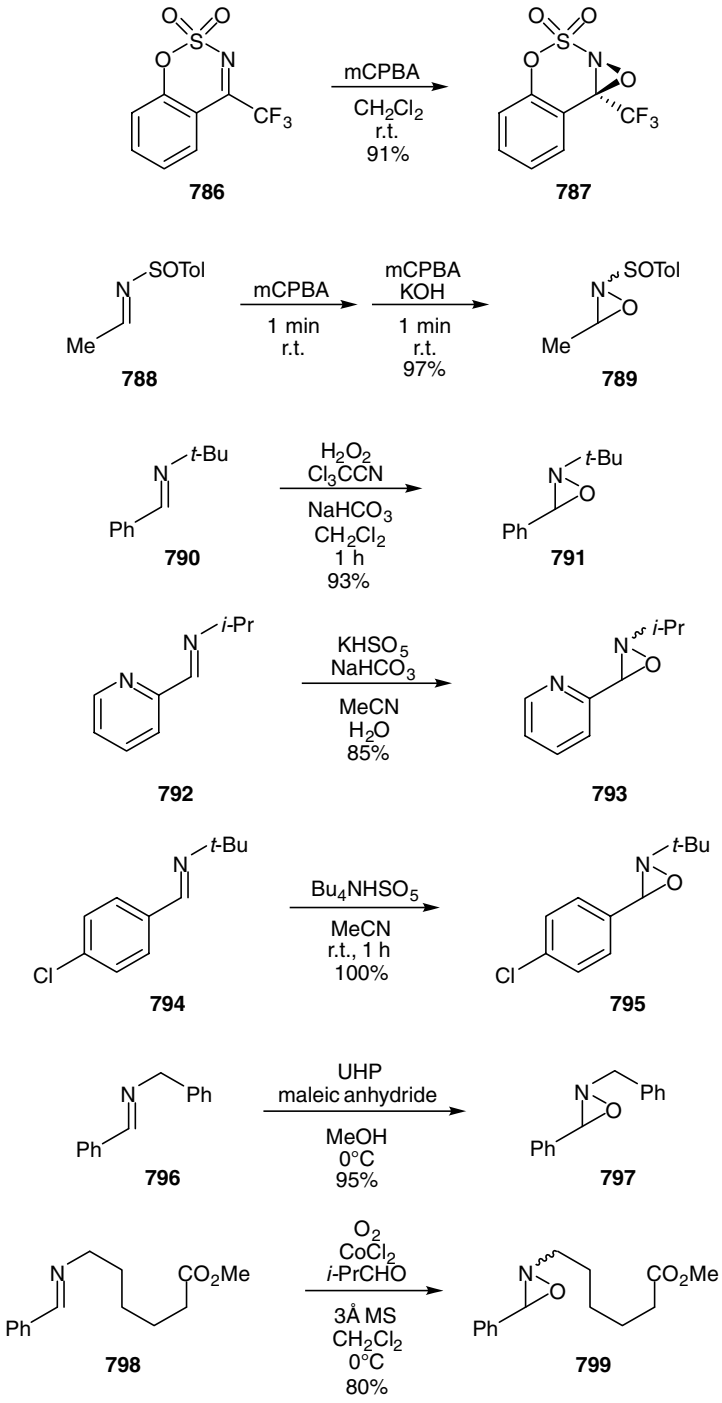
2.7.1 Properties of Oxaziridines

The oxaziridine moiety incorporates an oxygen, nitrogen and carbon within a cyclic three-atom array (Figure 2.25). The conventional strain energy (CSE) for the parent compound has been calculated at 27.6 kcal mol^{-1}, lying between those of cyclopropane and cyclobutane [762]. Each bond in the ring is unique, with lengths ranging from 1.40 Å (C−O) to 1.50 Å (N−O). It follows that the bond angles are also non-identical, with the N–C–O angle being the widest [763]. These physical characteristics are responsible in part for the fascinating reaction diversity exhibited by this class of compounds. Aside from their synthetic utility, oxaziridines have excited interest due to their potential as antifungal [764], antibiotic [765] and antitumor agents [766, 767].

2.7.2 Synthesis of Oxaziridines

There are reports of oxaziridine preparation from nitrones [768], and a calculational study has been carried out regarding this isomerization [763]. Oxaziridines are also the products of oxidative amination of ketones [769]. However, these methods have not found wide application in synthetic methodology. Instead, almost all preparative protocols launch from the oxidation of imines. Nevertheless, there is considerable diversity even within this one general category.

The *N*-alkoxysulfonyl oxaziridine **787** (Scheme 2.113) was efficiently prepared from the precursor imine **786** using the fairly traditional oxidant *m*-chloroperbenzoic acid (mCPBA) [770]. The sulfinylimine **788** was converted into sulfonyloxaziridine **789** in short order and in excellent yield using mCPBA in first acidic and then basic medium [771]. A trichloroacetonitrile–hydrogen peroxide system was found to convert imines such as **790** into oxaziridines in very high yield and exclusive *(E)*-stereochemistry under essentially neutral conditions [772]. Several other near-neutral systems are also available. For example, pyridylimine **792** was oxidized using a buffered monophasic Oxone system [773], and phase-transfer conditions were applied to the mild and quantitative conversion of arylaldimine **794** into the corresponding oxaziridine (**795**) using tetrabutylammonium Oxone in acetonitrile [774]. The combination of storage-stable urea-hydrogen peroxide adduct (UHP) and maleic anhydride in methanolic solution was also effective in the high-yielding



Scheme 2.113 Synthesis of oxaziridines from imines.

oxaziridination of *N*-benzylimine **796** [775]. Even molecular oxygen can be used as the terminal oxidant, using a cobalt catalyst (e.g., **798** → **799**), although the catalyst must be preformed for optimum yields [776].

2.7.3 Reactivity of Oxaziridines

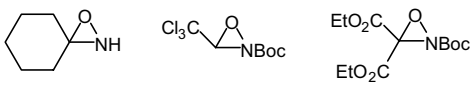
Oxaziridines have quickly become very important synthetic reagents [777–780]. Furthermore, the related oxaziridium ions, which bear a quaternary nitrogen center, are significant in their own right, both as stoichiometric reagents [781] and putative intermediates in catalytic cycles [782–784]. However, the present chapter is limited to neutral oxaziridines.

2.7.3.1 Nitrogen Transfer Reactions

An interesting aspect of oxaziridine chemistry is that either heteroatom can be transferred to other compounds, depending upon the nature of the substrate and the substituents on the oxaziridine [785]. Common oxaziridines used in nitrogen transfer reactions include the spirocyclic derivative of cyclohexanone (**800**, Figure 2.26), as well as those prepared from electron-deficient carbonyls, such as trichloroacetaldehyde (i.e., **801**) and diethyl oxomalonate (i.e., **802**). An overview of the oxaziridine-mediated electrophilic amination of organic compounds can be found in a review from the not-too-distant past [786].

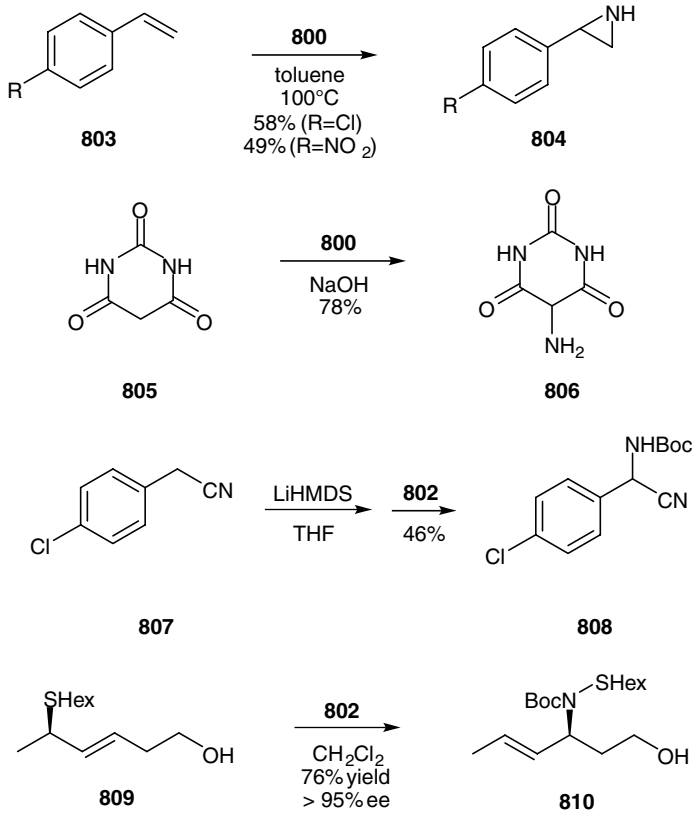
Aziridination has been reported using oxaziridines as nitrogen donors, although this reaction is not general. For example, certain styrene derivatives (**803**, Scheme 2.114) are aziridinated in moderate yield under thermal conditions in the presence of oxaziridine **800** [787], but many other substrates give complex mixtures. The structural influence of this variable behavior has been studied computationally [788]. A more common outcome is the amination of active methylene groups. Thus, treatment of barbituric acid (**805**) with oxaziridine **800** in a medium of dilute sodium hydroxide led to the production of the 5-aminobarbituric acid (**806**) in 78% yield [787]. Similarly, deprotonation of phenylacetonitrile **807** with lithium hexamethyldisylazide (LiHMDS), followed by treatment with oxaziridine **802**, provided the Boc-protected benzylamine **808** in 46% yield [785]. Oxaziridine **802** also mediates the stereospecific conversion of allylic sulfide **809** into the allylic *N*-Boc-sulfimide **810**, a process that involves a [2,3]-sigmatropic rearrangement [789].

Nitrogen can also be transferred to amines. For example, phenethylamine (**811**, Scheme 2.115) is aminated by oxaziridine **802** under very mild conditions, providing the Boc-protected hydrazine derivative **812** in good yield. These compounds were



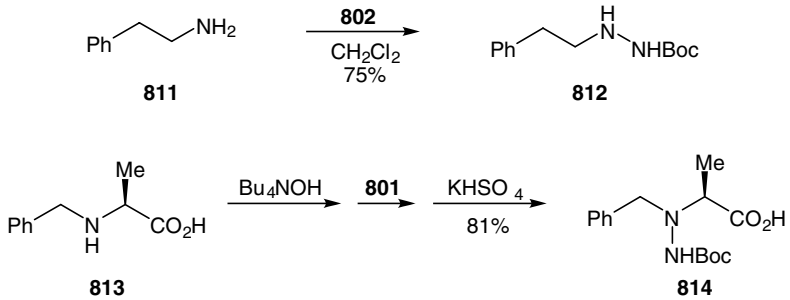
800 **801** **802**

Figure 2.26 Some common oxaziridines used for nitrogen transfer.



Scheme 2.114 Nitrogen transfer to carbon.

then converted into pyrazoles in a one-pot reaction [790]. Hannachi and co-workers [791] have applied this methodology to synthesize orthogonally diprotected L-hydrazino acids (e.g., **814**), which are useful in the biological and structural studies of pseudopeptides containing the N−N−C−C=O fragment.



Scheme 2.115 Nitrogen transfer to amines.

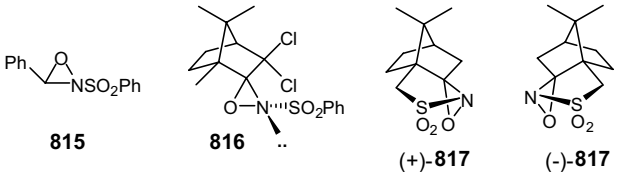


Figure 2.27 Some common oxaziridines used for oxygen transfers.

2.7.3.2 **Oxygen Transfer Reactions**

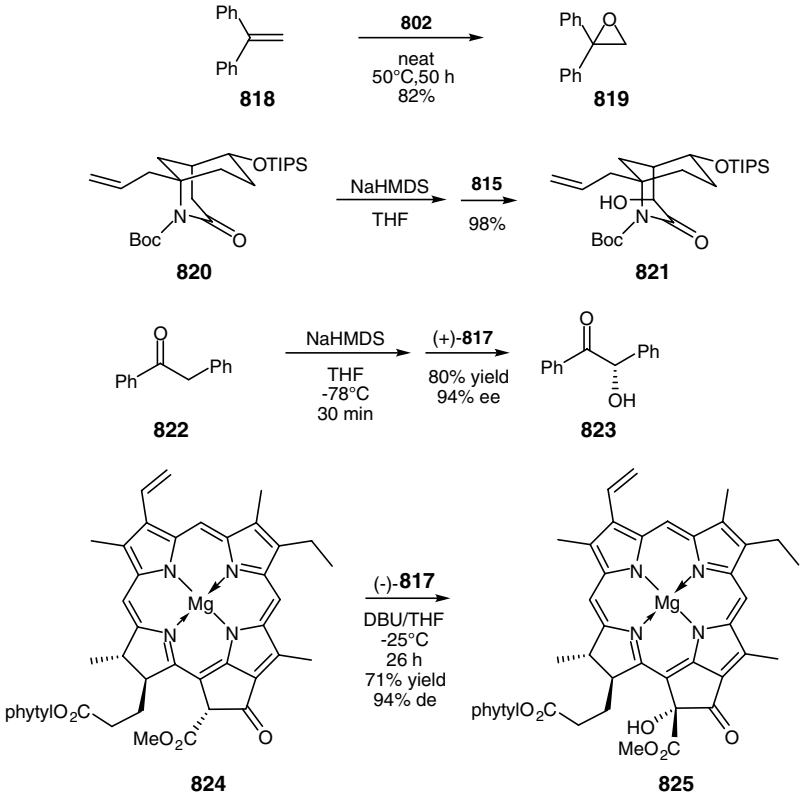
Some very exciting and synthetically useful methodology is available from the oxaziridine-mediated oxygen transfer onto organic compounds, and in many regards this technology is complementary to other methods. Oxygen-donating oxaziridines are generally of the 3-alkyl or 3-aryl variety (Figure 2.27), although there are examples of a given oxaziridine exhibiting both O-donating and N-donating behavior under different experimental conditions.

In isolated cases, oxaziridines can engage in epoxidation reactions, both in an intramolecular sense [792] and as a bimolecular event, as illustrated by the high-yielding conversion of 1,1-diphenylethene (**818**, Scheme 2.116) into the corresponding epoxide (**819**) [793]. However, this reaction is not general, and it is usually carried out more conveniently using conventional epoxidation conditions. In contrast, oxaziridines are superb reagents for selective α-hydroxylation reactions. For example, in their synthetic approach towards the microbial immunosuppressive agent FR901483, Weinreb and coworkers [794] employed the readily accessible oxaziridine **815** for the diastereoselective α-hydroxylation of the bicyclic lactam **820**. Asymmetric hydroxylations are also possible using chiral oxaziridines, such as the camphor derived reagents **816** and **817**. As an illustrative example, the sodium enolate of phenylacetophenone (**822**) was treated with (+)-(10-camphorsulfonyl) oxaziradine (**817**) to provide the α-hydroxyketone **823** in 80% yield and 94% ee. This reagent was also useful in the diastereoselective preparation of 13^2-hydroxylated chlorophylls (e.g., **825**) [795].

Oxaziridines occupy another synthetic niche in the realm of sulfur chemistry, as they engage in some very specific and selective sulfur oxidation reactions. For example, oxaziridine **815** oxidized the lithium salt of 4-fluorothiophenol (**826**) selectively to the sulfinate salt, which could be trapped with active electrophiles such as methyl iodide (Scheme 2.117). This particular strategy was used to access ^{11}C-labeled methyl sulfones [796]. Of particular synthetic utility is the oxaziridine-mediated asymmetric oxidation of prochiral sulfides to chiral nonracemic sulfoxides, which are receiving increasing attention in their own right. Thus, 4-methylthiotoluene (**829**) is converted into *(S)*-methyl tolyl sulfoxide (**830**) in excellent yield and enantiomeric excess under essentially neutral conditions [797].

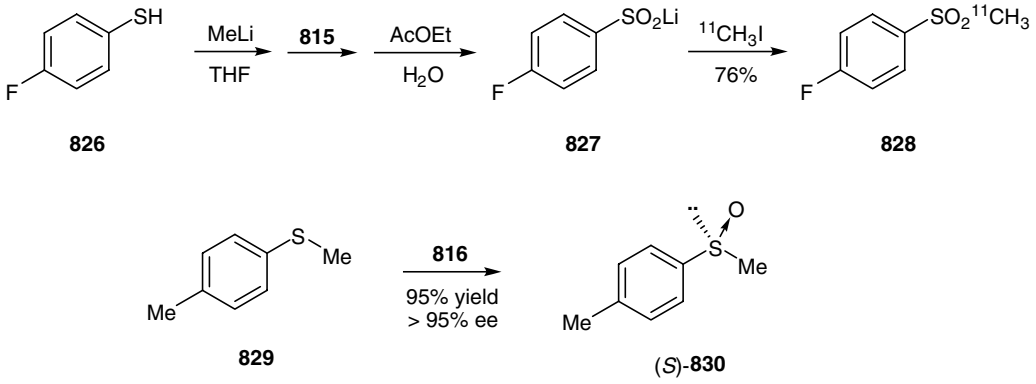
2.7.3.3 **Rearrangements**

Some interesting metal-mediated rearrangements of oxaziridines have been reported, although none appear to be widely general in their scope. For example, the copper(I) catalyst $[Cu(CH_3CN)_4]PF_6$ induces the conversion of oxaziridine **831**



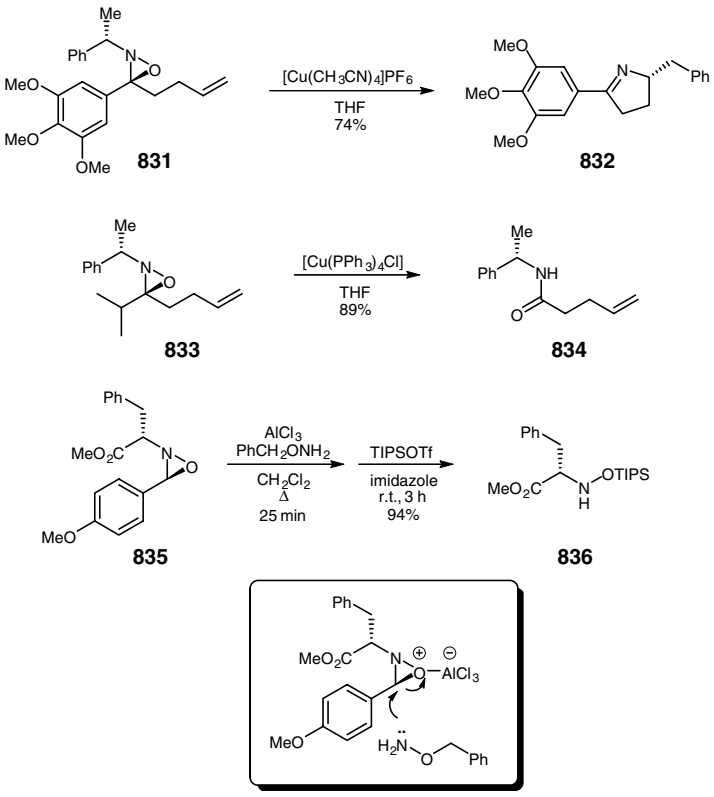
Scheme 2.116 Oxygen transfer to carbon.

into the dihydro-*2H*-pyrrole **832** through a fascinating mechanistic sequence involving initial N–O bond cleavage by single electron transfer, followed by radical cyclization, phenyl migration and loss of acetaldehyde [798]. When the 3-substituent is secondary (or presumably tertiary), the intermediate radical can collapse with



Scheme 2.117 Oxygen transfer to sulfur.

concomitant C−C bond cleavage to give amide derivatives. Thus, the 3-isopropyl oxaziridine **833** yields amide **834** under the same conditions [799]. Under the influence of Lewis acids, the oxaziridine ring can be opened by nucleophiles. For example, the 3-methoxyphenyl-oxaziridine **835** suffers nucleophilic attack at the ring carbon by *O*-benzylhydroxylamine (Scheme 2.118, inset) in the presence of aluminium trichloride, ultimately leading to the liberation of the oxaziridinyl N−O fragment, which is subsequently *O*-protected by the tri(isopropyl)silyl group *in situ* [800].



Scheme 2.118 Metal-mediated rearrangements of oxaziridines.

2.8
Dioxiranes

2.8.1
Properties of Dioxiranes

Dioxiranes are cyclic peroxides, and in many respects their chemical behavior can be described as activated peroxy species, or what Greer has dubbed "unusual peroxides" [801]. The strain energy of the parent compound (Figure 2.28) has been

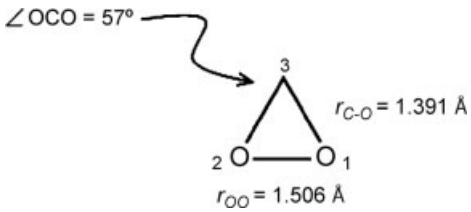
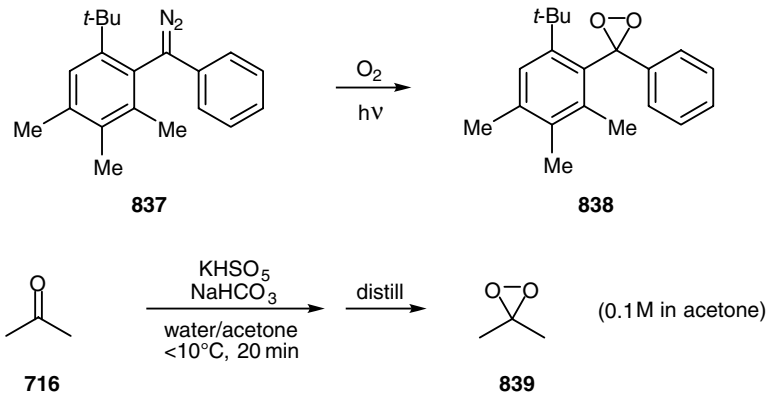


Figure 2.28 Geometry of dioxirane.

calculated at 19.6 kcal mol^{-1}. However, this figure drops by almost half to 10.6 kcal mol^{-1} in the case of 3,3-dimethyldioxirane (DMD) [802, 803]. Geometrically, the unsubstituted dioxirane ring describes a mildly distorted triangle [804].

2.8.2 Synthesis of Dioxiranes

A survey of the preparative synthetic methods for dioxiranes is a little peculiar, because the field is dominated by virtually a single technique. There are certainly isolated alternative conditions that lead to the formation of the dioxirane system, such as the photolytic oxidation of diaryl diazoalkanes (e.g., **837** → **838**, Scheme 2.119) [805]; however, to date they have not been widely adopted by the synthetic laboratory.



Scheme 2.119 Preparation of dioxiranes.

In fact, most procedures involving dioxiranes as reactive intermediates are designed to generate these species *in situ*, usually as part of a catalytic cycle, and usually by oxidizing a ketone precursor. This not only brings the obvious benefit of requiring less than stoichiometric amounts of the ketone precursor (some of which are quite dear), but it also obviates the need to isolate, store and continually titrate mixtures of unstable dioxiranes. Nevertheless, it is sometimes convenient, or even

necessary, to work with "isolated" dioxirane reagents. Toward this end, dilute solutions of dimethyldioxirane (DMD) are available by treating acetone with Oxone in an aqueous bicarbonate buffer at low temperature, after which the dioxirane is distilled at reduced pressure (Scheme 2.119). The distillate so-obtained contains about a 0.1 M solution of DMD in acetone (towards which the dioxirane is stable [806]), and this is usually titrated before use [807, 808]. The dilution factor can be inconvenient [809], although some practical modifications have been disclosed [810, 811], including phase-transfer conditions, which can be applied even to large-scale preparations [812].

Generally, almost all synthetically relevant dioxiranes are prepared by this method; however, the reader is directed to Murray's excellent review of dioxiranes for more detailed information and an historical perspective on the development of dioxirane preparations [813].

2.8.3 Reactivity of Dioxiranes

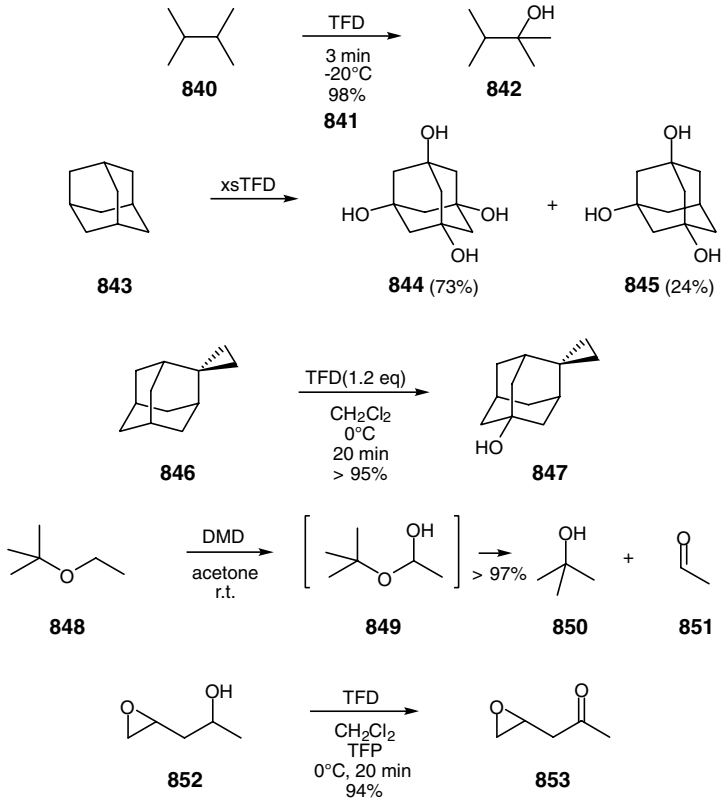
2.8.3.1 Epoxidation of Alkenes

Arguably the most high-profile member of the dioxiranes reactive portfolio, the epoxidation of alkenes is treated in Section 2.3.2.1. The reader is also directed to an outstanding comprehensive review by Adam, Saha-Möller and Zhao [814], as well as a more recent overview by Srivastava [815].

2.8.3.2 Hydroxylation of Alkanes

Another fascinating (and remarkably underutilized) reaction mediated by dioxiranes is the hydroxylation of alkanes, a process that can be quite clean and high-yielding. For example, treatment of 2,3-dimethylbutane (**840**, Scheme 2.120) with 3-methyl-3-trifluoromethyldioxirane (**841**) (TFD) at low temperature results in rapid and almost quantitative conversion to tertiary alcohol **842** [816]. In general, tertiary sites are preferred to secondary, a phenomenon underscored by the oxidation of adamantane (**843**) with excess TFD, in which only tertiary sites are affected [817]. In a selectivity study, Curci and coworkers [818] found that these bridgehead sites were also preferred to cyclopropane methylene positions, as demonstrated by the smooth conversion of the spiro cyclopropyladamantane **846** into the monohydroxy derivative **847**.

Secondary sites are not immune to oxidation. In fact, careful kinetic studies have shown that the reactivity exhibits an almost perfect Hammett correlation to the electron density of the C−H sigma bond [819], which strongly suggests a concerted insertion mechanism. Computational studies also support this idea, although a diradical mechanism cannot be ruled out [804]. In any event, lability towards oxidation is enhanced by adjacent heteroatoms. For example, ethyl *t*-butyl ether (**848**) suffers practically quantitative oxidative degradation to *t*-butanol (**850**) and acetaldehyde (**851**) via an initially formed hemiacetal intermediate (**849**) [820], which explains the previously reported observation that DMD solutions lose titer in the presence of adventitious ether contaminants [821]. Through a similar mechanism, dioxiranes convert alcohols into ketones, as illustrated by the oxidation of epoxyal-



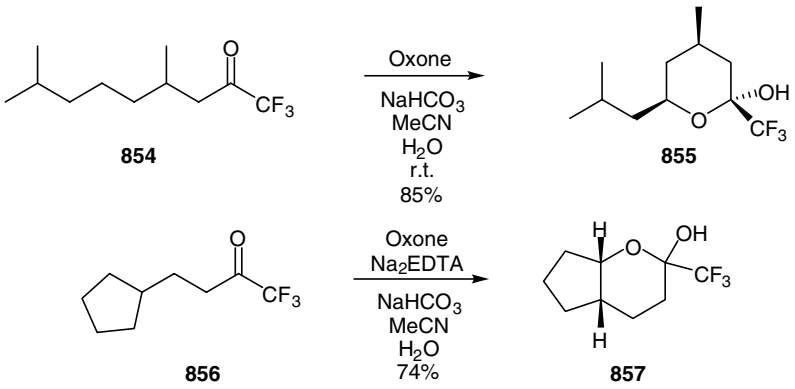
Scheme 2.120 Dioxirane-mediated hydroxylation.

cohol **852** to the corresponding ketone (**853**) in excellent yield upon treatment with TFD in methylene chloride and trifluoropropanone (TFP) [120].

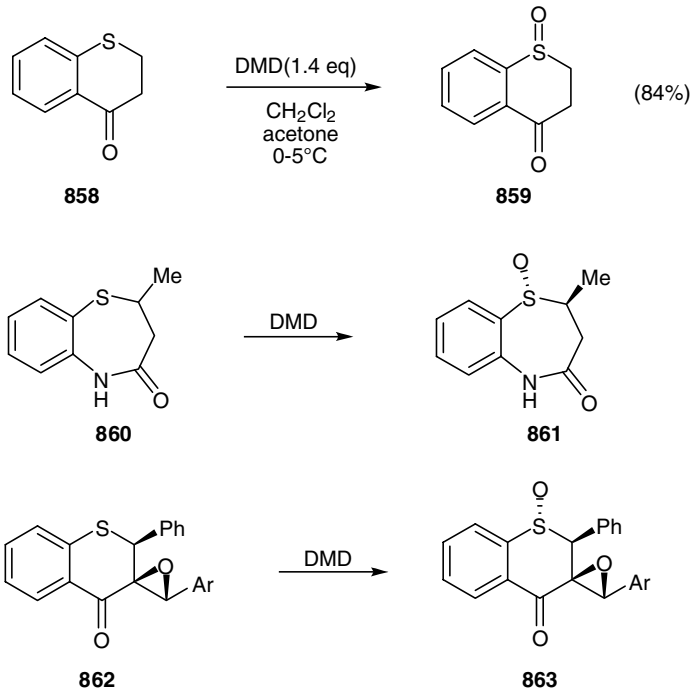
Interestingly, this oxidation can be carried out in an intramolecular fashion – a sort of remote functionalization. For example, when the trifluoromethyl ketone **854** (Scheme 2.121) is treated with Oxone in buffered medium, it forms a dioxirane that oxidizes the δ-methylene position. The hydroxyketone so formed subsequently cyclizes to the stable hemiacetal **855** [822]. In this intramolecular manifestation, geometric factors override electronic preferences. Thus, the dioxirane generated from ketone **856** also engages the secondary δ-position over the adjacent tertiary position, ultimately forming the bicyclic hemiacetal **857** [823].

2.8.3.3 Oxidation of Sulfur

Dioxiranes have been applied to the selective oxidation of sulfides to sulfoxides [824]. For example, the thiochromanone **858** (Scheme 2.122) is converted into the corresponding sulfoxide (**859**) upon treatment with a slight excess of DMD at near-0 °C temperatures. For best selectivity, the reaction was halted at partial conversion (about 75%); longer reaction times and higher loadings of DMD led to excellent yields of



Scheme 2.121 Intramolecular dioxirane-mediated hydroxylation.



Scheme 2.122 Dioxirane-mediated sulfoxidation.

sulfone derivatives [825]. These oxidations can be quite diastereoselective. Thus, the DMD oxidation of 2,3-dihydro-1,5-benzothiazepinone **860** provided an overwhelming majority of the *trans*-sulfoxide **861** [826], and the epoxy thiochromanone **862** provided the *trans*/*cis*-sulfoxide **863** exclusively [827]. The same diastereomeric bias was observed even with the opposite epoxide stereochemistry, which seems to point

toward a pivotal role of the α-substituent. Enantioselective sulfoxidation using chiral ketone precursors appears promising [828], although results are highly variable and substrate-dependent.

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3
Four-Membered Heterocycles: Structure and Reactivity

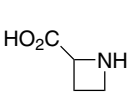
Gérard Rousseau and Sylvie Robin

3.1
Azetidines

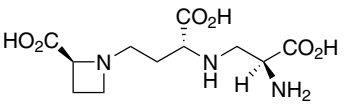
3.1.1
Introduction

This chapter deals with azetidines, which are four-membered rings containing one nitrogen atom. The particular case of azetidin-2-ones (β-lactams) is examined in Chapter 24. Different important reviews have already been reported on their preparation and reactivity [1–3].

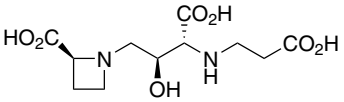
Different natural products of terrestrial or marine origins having an azetidine ring have been isolated. We indicate in this chapter only some representative examples. The simple (*R*) and (*S*)-azetidine-2-carboxylic acids **1** were found in numerous plants [4, 5]. N-Alkyl derivatives such as nicotianamine (**2**) [6] (isolated from a culture of *Streptomyces*) and mugineic acid (**3**) (isolated from a plant) [7] have also been reported.



1

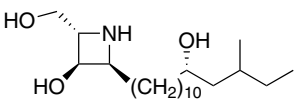


2



3

Some C-alkyl derivatives are known, such as penaresidine-B (**4**) isolated from various sponges [8] and *cis*-polyoximic acid (**5**) isolated from a culture of *Streptomyces* [9, 10].



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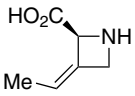

5

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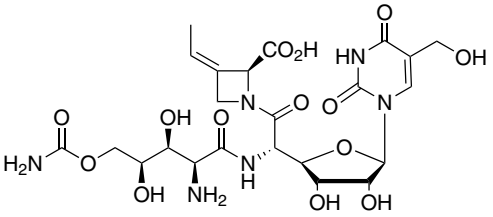
The nucleus azetidine is also present in more complex products, such as polyoxin A (**6**, isolated from culture broth of *Streptomyces cacaoi* var. *asoensis*) [11], gelsemoxonine (**7**) isolated from the creeper *Gelsemium elegans* and vioprolides A ($n = 1$) and B ($n = 2$) **8** [12], obtained by fermentation of a strain of the myxo bacterium *Cystobacter violaceus* [13].



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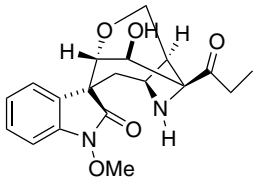

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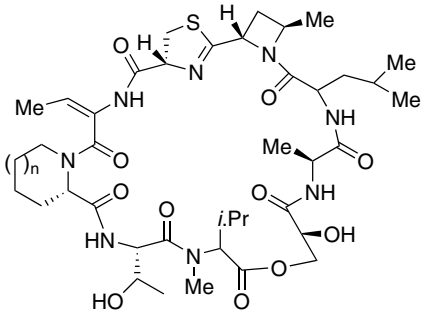
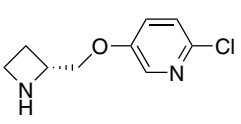


8

Agrochemical applications of azetidine derivatives have been reported [3]. Actions on the central nervous system with various activities (antiepileptic, anticonvulsant, antihypertensive, antidepressant, analgesic, etc.) have been also described [3]. A promising compound appears to be ABT-594 (**9**), synthesized from (+)-epibatidine (**10**), present in frogs [14]. Compound **9** proved to be more powerful than morphine as a painkiller [15].



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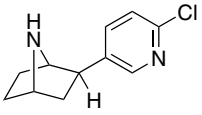

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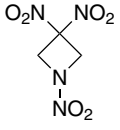


11

The preparation of 1,3,3-trinitroazetidine (**11**) has been reported [16]. This compound was evaluated as a substitute for TNT, due to its high thermal stability. However, its cost of preparation and its high volatility limit its utilization as explosive or propellant.

3.1.2 Physicochemical Data

Azetidines appear to be thermally stable. They are unreactive towards numerous reagents and can be prepared without special precautions. They can be analyzed using gas chromatography or liquid chromatography over silica gel, for example. Their reactivities appear closer to these of higher cyclic amines than aziridines. The strain in azetidines explains their difficult formation by cyclization, which is comparable to these of azepines [17]. Electron diffraction and X-ray crystallographic studies have shown the non-planarity of the ring. For azetidine, the angle between the planes formed by the CCC and CNC bonds is 37°, which is similar to that found for cyclobutane. Inversion of the pyramidal nitrogen is very easy for these heterocycles ($\Delta G^{\#} \approx 10\,\text{kcal mol}^{-1}$).

Azetidines have been studied by NMR spectroscopy. In the absence of substituents the chemical shift of the hydrogens fixed on the carbon at the 2-position are in the range 2.5–3.5 ppm and the hydrogens fixed on the carbon at the 3-position 1 ppm higher. In general the magnitude of the coupling constants for vicinal hydrogens is in the range 6–8 Hz for the cis stereoisomers and 2–4 Hz for the trans stereoisomers. With 3-hydroxyazetidine derivatives, the determination of the stereochemistries could be come very difficult. Structural identification was reported to be possible when the ^{1}H NMR spectra were recorded out in the presence of known amounts of Eu(Fod)$_3$ [18]. In ^{13}C NMR, the carbon shifts in 2,4 positions are close to those of carbons in five- and six-membered cyclic amines. Figure 3.1 shows some representative examples of these chemical shifts. The ^{15}N chemical shift of azetidine (from NH_3) was reported to 25.3 ppm. N-Substituted azetidines showed chemical shifts comparable to other nitrogen heterocycles [19].

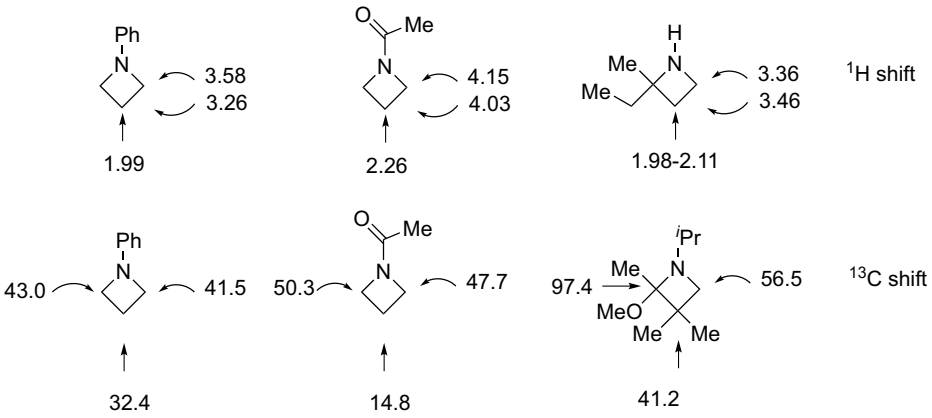


Figure 3.1 Representative examples of chemical shifts.

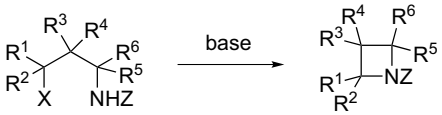
3.1.3 Synthesis

This chapter reports the main methods that lead to azetidines with acceptable yields. Some less synthetically useful methods can be found in previous reviews. These preparations can be divided into three groups: formation (i) by cyclization, (ii) from other heterocycles and (iii) by [2 + 2] cycloadditions.

3.1.3.1 Cyclization Reactions

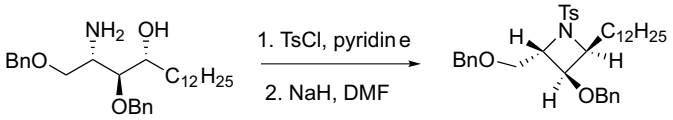
3.1.3.1.1 Formation of a C–N Bond

Ring Closure of γ-Amino Derivatives A powerful and simple preparation of azetidines is the intramolecular displacement of a leaving group fixed on a carbon by a γ-amino group. Bromo, iodo, tosyloxy, mesyloxy and triflyloxy were mainly used as leaving groups, and alkyl, aryl and tosyl were used as protecting groups on the nitrogen atom (Scheme 3.1) [3].

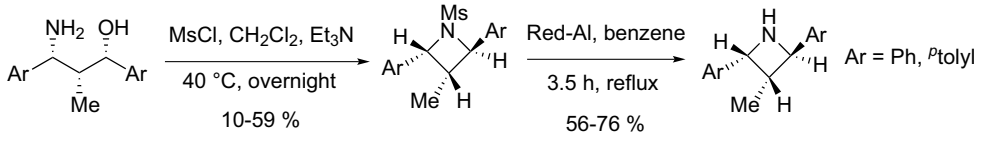


Scheme 3.1

This approach was reported as the key step in a synthesis of penaresidine B (**4**) (Scheme 3.2) [20]. It was subsequently reported that diastereoselective cyclizations of the mesylates lead to similar results (Scheme 3.3) [21].

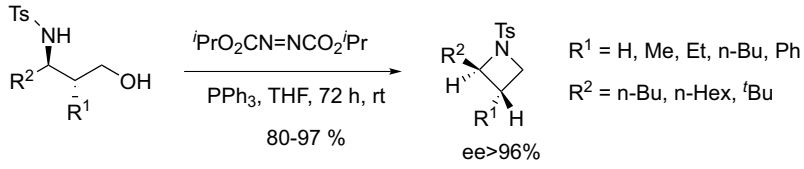


Scheme 3.2



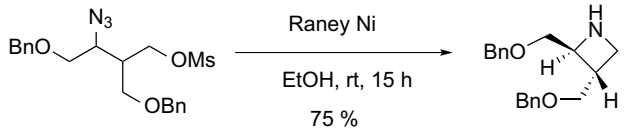
Scheme 3.3

A modification of this method has been investigated. It was shown that utilization of Mitsunobu conditions (X = OH in Scheme 3.1) could be very efficient [22]. This cyclization was applied to the preparation of substituted azetidines, without any epimerization of the chiral centers (Scheme 3.4) [23].



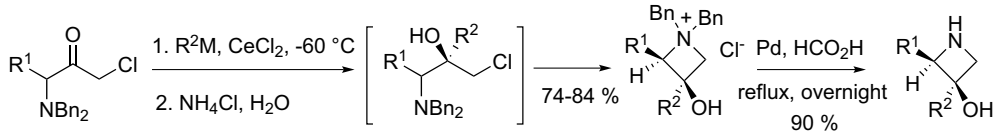
Scheme 3.4

Cyclization of protected 1-azidopropan-1-ols was also reported to lead to the formation of azetidines. This cyclization occurred when the azido group was reduced using Raney-nickel (Scheme 3.5) [24]. This method appears more efficient than when using PPh_3 as reducing agent [25].



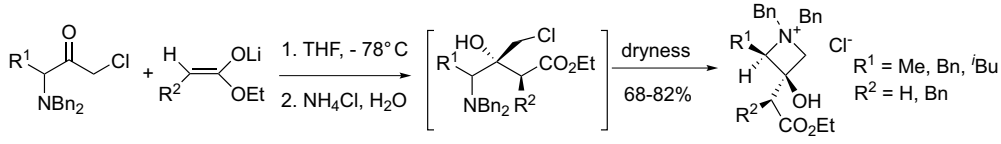
Scheme 3.5

This cyclization was found to be easy with 3-chloroalkylamines obtained by reaction of 1-aminoalkyl chloromethyl ketones with organocerium reagents. The cyclizations occurred during evaporation of the reaction solvents (Scheme 3.6) [26]. These isolable azetidinium salts were subsequently transformed into azetidines by catalytic hydrogenation. Chloromethyl ketones react with ester enolates in similar fashion (Scheme 3.7) [27].



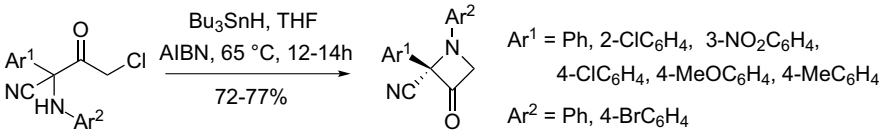
R^1 = Me, ^{i}Bu, Bn, R^2 = Me, Bu, allyl, Bu

Scheme 3.6



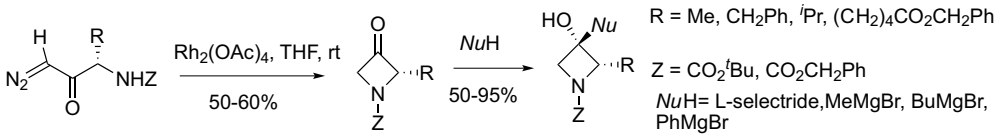
Scheme 3.7

Formation of 3-azetidinones from 1-aminoalkyl chloromethyl ketones was also reported to occur by reaction with tributyltin hydride (Scheme 3.8) [28].



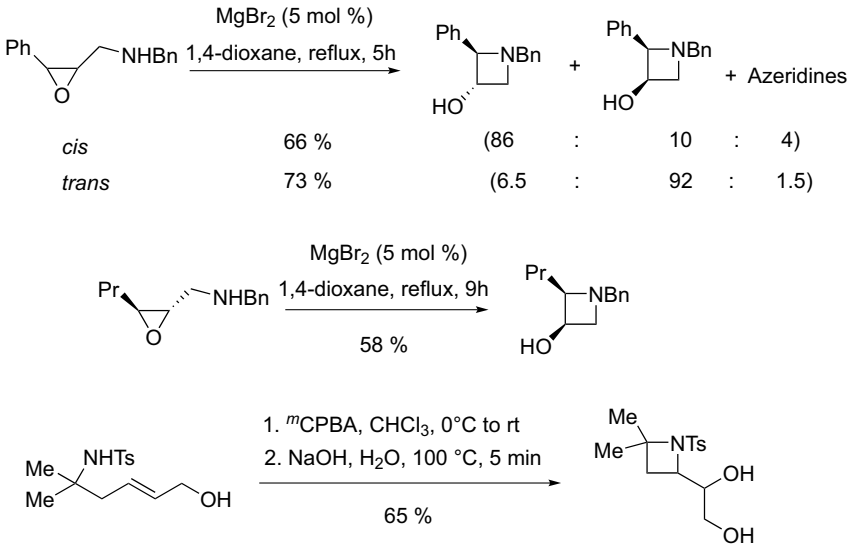
Scheme 3.8

Another interesting preparation of 3-azetidinones involves carbenoid insertion into a N−H bond. 1-Aminoalkyl α-diazomethyl ketones reacts with rhodium acetate to give optically active 2-substituted 3-azetidinones (Scheme 3.9) [29]. These ketones allowed highly diastereoselective additions of nucleophilic reagents or Wittig reactions ($Ph_3P{=}CHCO_2Me$). Utilization of copper acetylacetonate as catalyst has been subsequently reported [30].



Scheme 3.9

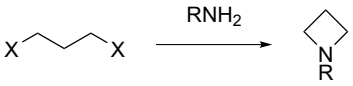
Azetidines can be obtained by $MgBr_2$ catalyzed isomerization of aminomethyloxiranes. A mixture of diastereomers was generally obtained (Scheme 3.10). With the trans epoxide substituted by an alkyl group, only one azetidine was detected [31].



Scheme 3.10

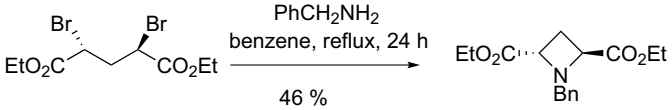
Utilization of sodium hydroxide to carry out ring opening of oxiranes was reported to be possible, if the epoxide function was β of the amino group (4-*exo* mode cyclization) (Scheme 3.10) [32].

Ring Closure of 1,3-Functionnalized Propane Derivatives with Amines 1,3-Dielectrophiles react with primary amines to afford azetidines (Scheme 3.11).



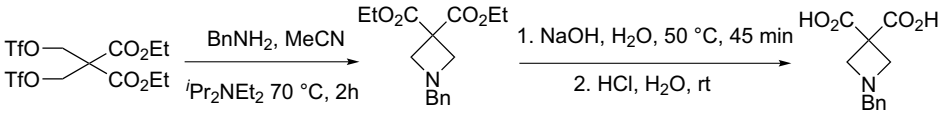
Scheme 3.11

1,3-Dihalopropane derivatives have been used with more or less success, due to the possible formation of side products [3]. However, satisfactory yields were obtained when the halogen atoms were in activated positions (Scheme 3.12) [33].

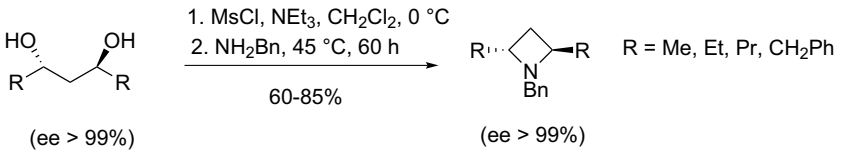


Scheme 3.12

Better yields were observed with 1,3-triflates (Scheme 3.13, reactions carried out a 1 kg scale) [34], 1,3-ditosylates [35] or 1,3-dimesylates (Scheme 3.14) [36].

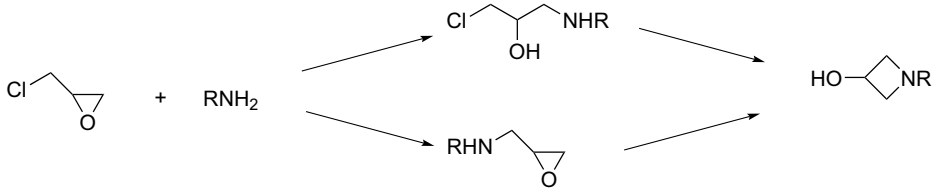


Scheme 3.13



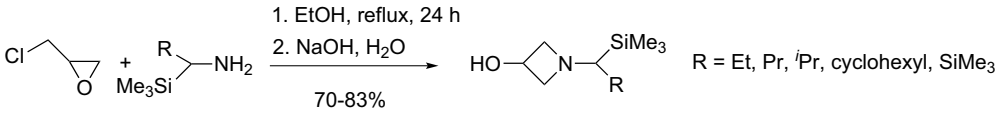
Scheme 3.14

3-Hydroxyazetidines have also been prepared by the reaction of epichlorohydrin with primary amines. The intermediate formation of γ-chloro-β-hydroxyamines or amino methyl oxiranes is a function of the reaction conditions and the nature of the amines. In some cases these two-step reactions were conducted as one-pot reactions (Scheme 3.15).

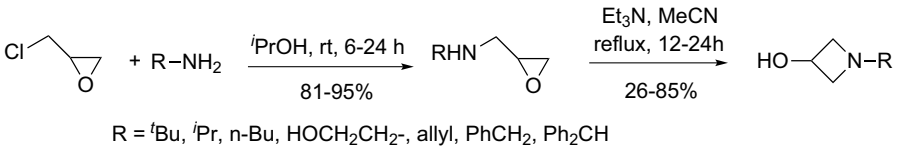


Scheme 3.15

For example, the reaction of epichlorohydrin with 1-silylalkylamine leads to the formation of 3-hydroxyazetidines in excellent yields. This method was used in a new preparation of 1-methyl-3-hydroxyazetidine (Scheme 3.16) [37]. N-Substituted azetidinols were also obtained by heating aminomethyloxiranes in the presence of triethylamine (Scheme 3.17) [38].

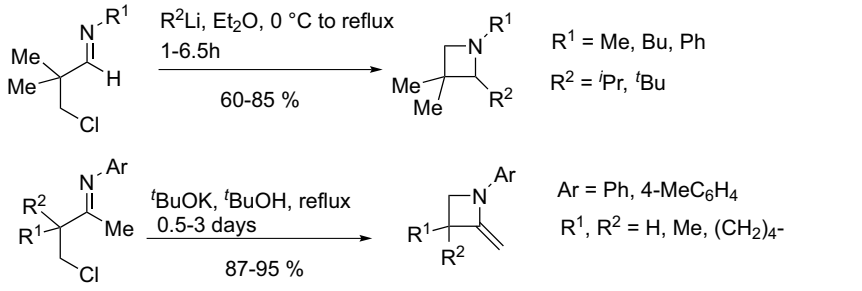


Scheme 3.16



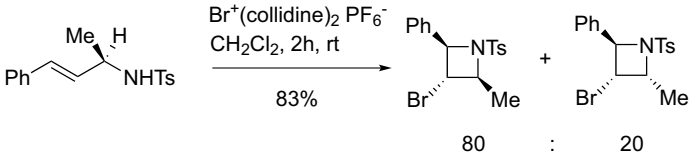
Scheme 3.17

Another approach to azetidines implies the addition of nucleophiles such as cyanide, hydride or organolithium reagents (Scheme 3.18) to β-chloroimines [39]. When the nucleophile is KO^{t}Bu, 2-methyleneazetidines are obtained if the work-ups are carried out in the absence of water (Scheme 3.18) [40].



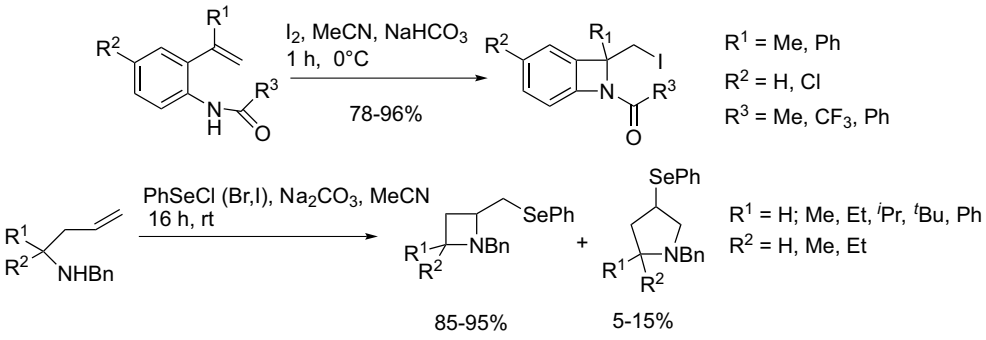
Scheme 3.18

Electrophilic cyclization of N-cinnamyl tosylamides affords azetidines in good yields. These 4-*endo* mode cyclizations are diastereoselective (Scheme 3.19) [41].



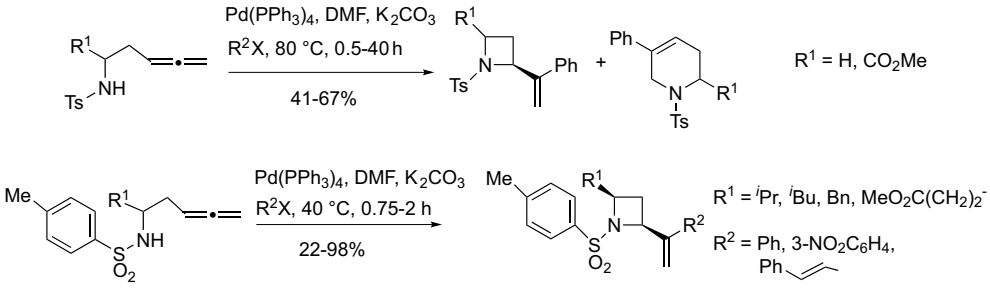
Scheme 3.19

4-*Exo* mode cyclizations of unsaturated amines have also been reported using iodine [42], NBS [43] and selenium reagents (Scheme 3.20) [44].



Scheme 3.20

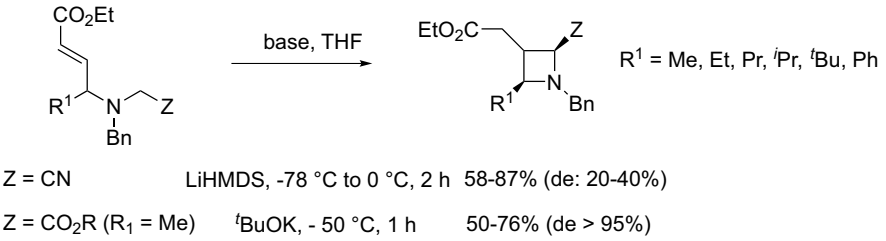
An interesting method for the preparation of enantiopure azetidines is the intramolecular amination of β-aminoallenes catalyzed by $Pd(PPh_3)_4$ (Scheme 3.21). When the protecting group on the nitrogen atom was a tosyl, a mixture of alkenyl azetidine and tetrahydropyridine was obtained (R^2X = aryl iodide, e.g. PhI). However, with enol triflate as alkylating agent, the exclusive formation of azetidines was



Scheme 3.21

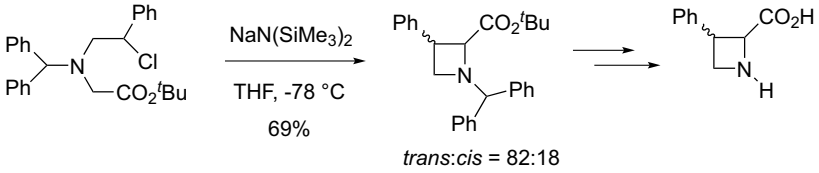
observed (35–40%) [45]. This is also the case when the protecting group was a mesitylenesulfonyl (Scheme 3.21) [46].

3.1.3.1.2 **Formation of a C–C Bond** Intramolecular reaction of α-aminocarbanions with activated carbon–carbon double bonds is an excellent method by which to prepare functionalized azetidines. Mixtures of diastereomers have been obtained from α-aminonitriles. Better diastereoselectivities were observed from α-aminoesters (Scheme 3.22) [47, 48].

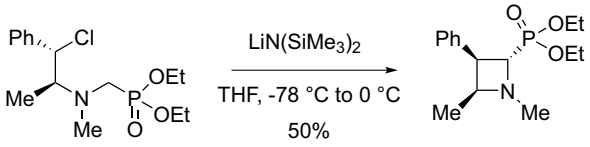


Scheme 3.22

Intramolecular cyclization can also be observed if the carbon β of the amino group bears a leaving group (Scheme 3.23) [49]. This method has been applied to the preparation of *cis* and *trans* 3-phenyl-azetidine-2-carboxylic acids [49], azetidine-2-carbonitriles, [50] and diethyl azetidine-2-phosphonates (Scheme 3.24) [51].

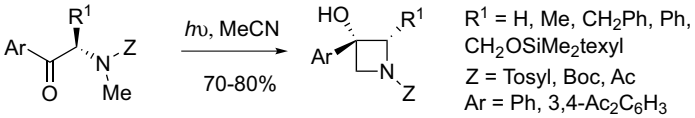


Scheme 3.23



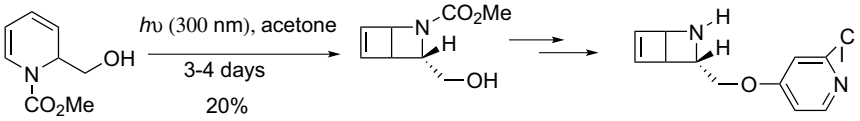
Scheme 3.24

Another diastereoselective preparation of substituted azetidines has been reported by a photochemically induced cyclization of chiral α-amino ketones (Scheme 3.25) [52, 53].



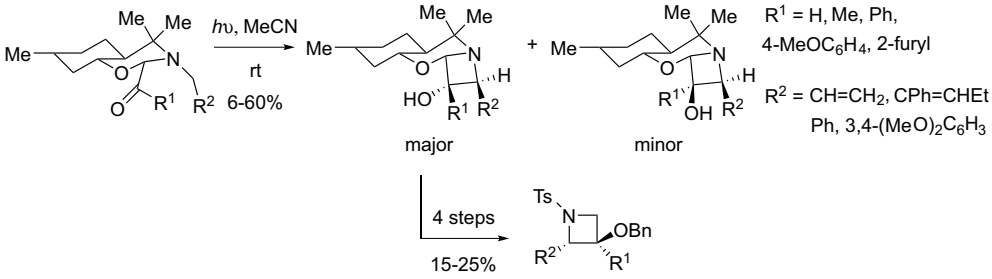
Scheme 3.25

Fused azetidine derivatives have been obtained by irradiation of dihydropyridines (Scheme 3.26) [54a]. This methodology has been applied to the formation of an analog of ABT-594 [54b]. However, this compound appeared less efficient than epibatidine as nicotine agonist.



Scheme 3.26

Irradiation of 3-allyl or 3-benzyl-2-acyl perhydrobenzoxazine furnishes azetidin-3-ol derivatives in moderate chemical yields (50–60%). However, the diastereoselectivity of these cyclizations are good (up to 96%). The menthol part was then removed in low overall yields to give enantiopure azetidin-3-ol derivatives (Scheme 3.27) [55].

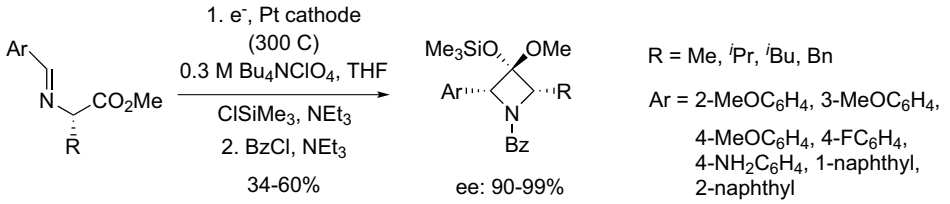


Scheme 3.27

Electroreduction by intramolecular coupling of chiral α–iminoesters in the presence of chlorotrimethylsilane affords *cis*-2,4-disubstituted azetidin-3-ones in good yields (Scheme 3.28) [56].

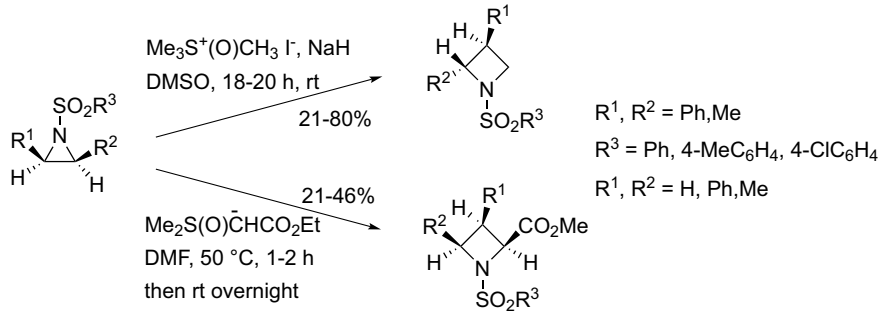
3.1.3.2 **Ring Transformations**

3.1.3.2.1 **Ring Expansions of Aziridines** Reactions of N-arenesulfonylaziridines with dimethyloxosulfonium methylide afford azetidines. These ring expansions are stereoselective. The *cis*-aziridines yield trans-azetidines, and reciprocally, via a



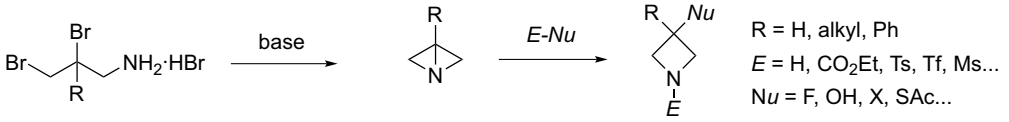
Scheme 3.28

S_N2-type reaction, followed by an intramolecular nucleophilic substitution [57]. This reaction has also been reported using dimethylsulfonium methoxycarbonyl methylide (Scheme 3.29) [58].



Scheme 3.29

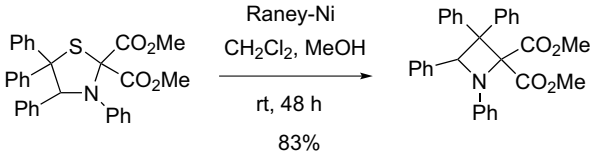
1-Substituted 3-azabicyclo[1.1.0]butanes are easily prepared using the method first developed by Funke [59]. These compounds react with numerous electrophiles to afford azetidines (Scheme 3.30). More recent reports give improved conditions for the preparation of the bicycloaziridines, and their reactions with electrophilic reagents [60–62].



Scheme 3.30

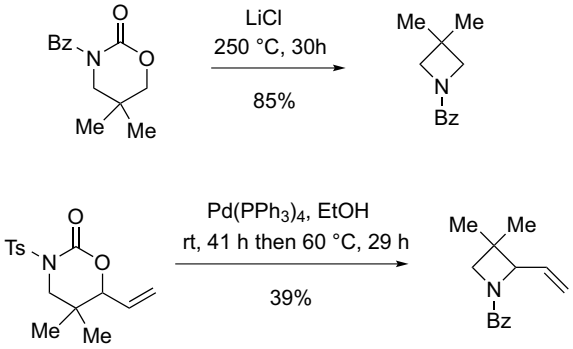
3.1.3.2.2 **Ring Contractions** 5 → 4 Ring contractions appear rather rare. The reaction of a thiazolidine with Raney-nickel has been reported to lead to yield an azetidine (Scheme 3.31) [63].

Two interesting examples of 6 → 4 ring contractions have been also reported. They used the transformation of cyclic carbamates. Heating tetrahydro-3-benzyl-5,5-



Scheme 3.31

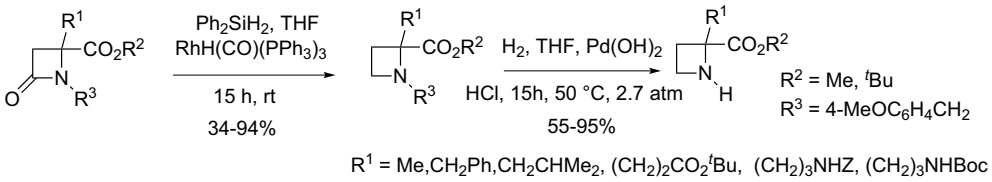
dimethyl-1,3-oxazin-2-one at 250 °C in the presence of LiCl affords the corresponding azetidine [64]. 1,2,2,4-Tetrasubstituted azetidines have been prepared using this method. Reaction of a carbamate with a palladium(0) salt led to a comparable decarboxylation. This reaction has not been studied further (Scheme 3.32) [65].



Scheme 3.32

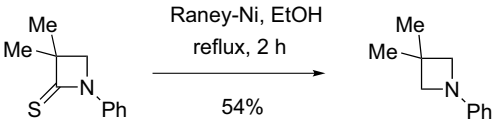
3.1.3.2.3 From β-Lactams

Reductions Reductions of β-lactams into azetidines have been reported with common reducing agents such as $LiAlH_4$, $LiAlH_4$-$AlCl_3$, $ClAlH_2$, Cl_2AlH, AlH_3, BH_3 and DIBAL-H [66–69]. With optically active lactams, these reactions occur in general without loss of enantiomeric purity. However, these reagents were not compatible with the presence of ester groups. In this case, diphenylsilane in the presence of a rhodium salt (Scheme 3.33) could be efficient [70].



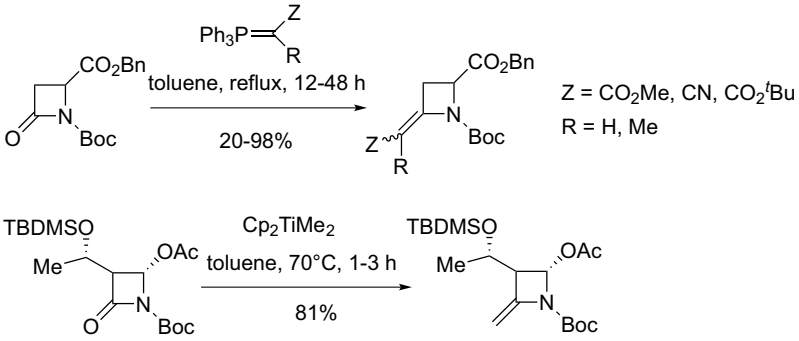
Scheme 3.33

Reduction of azetidine-2,4-dione by AlH_3 into azetidine has also been reported [71], while the reduction of 2-azetidinethiones is possible using Raney-nickel (Scheme 3.34) [72].



Scheme 3.34

Olefinations Stabilized ylides react with 2-azetidinones to afford 2-methyleneazetidines. This olefination does not take place with unstabilized ylides or when a substituent is present at the 3-position [73]. In such a case, methylenation is possible using dimethyltitanocene (Scheme 3.35) [74, 75].



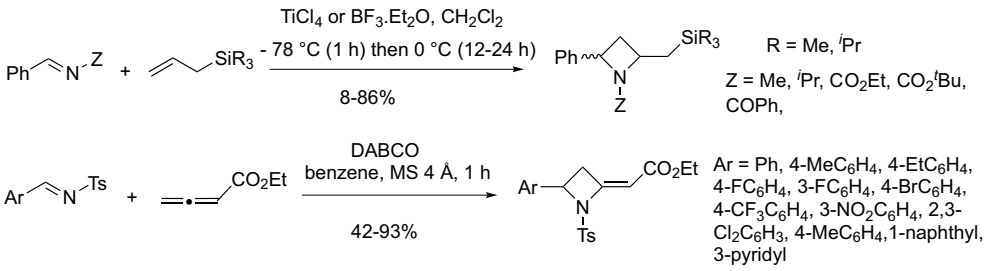
Scheme 3.35

3.1.3.3 **Cycloadditions**

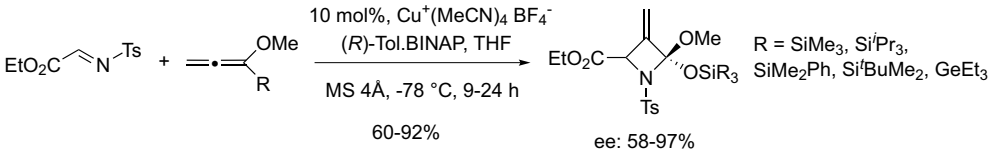
[2 + 2] Cycloadditions of imines or imino compounds with ethylenic derivatives can afford azetidines. However, the yields were generally low [3] until, relatively recently, improved conditions were found. Imines react with allylsilanes catalyzed by Lewis acids to give azetidines in good yields (Scheme 3.36) [76]. Mixtures of diastereomers were obtained. N-Tosylimines have also been reported to react with α-allenic esters and α-allenic ketones in the presence of DABCO (Scheme 3.36) [77].

The reaction of α-imino esters with 1-methoxyallenylsilanes has been achieved by means of copper tetrafluoroborate. In the presence of (*R*)-Tol.BINAP, optically active azetidines with high enantiomeric excesses were obtained (Scheme 3.37) [78].

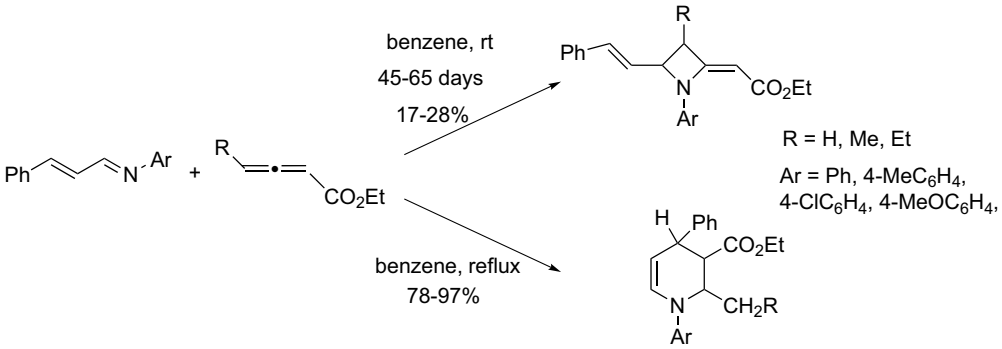
1-Aryl-4-phenyl-1-azadienes undergo [2 + 2] cycloadditions, after more than 40 days, with allenic esters at room temperature. Attempts to decrease the reaction time by heating gave rise to the exclusive formation of [4 + 2] adducts (Scheme 3.38) [79].



Scheme 3.36



Scheme 3.37



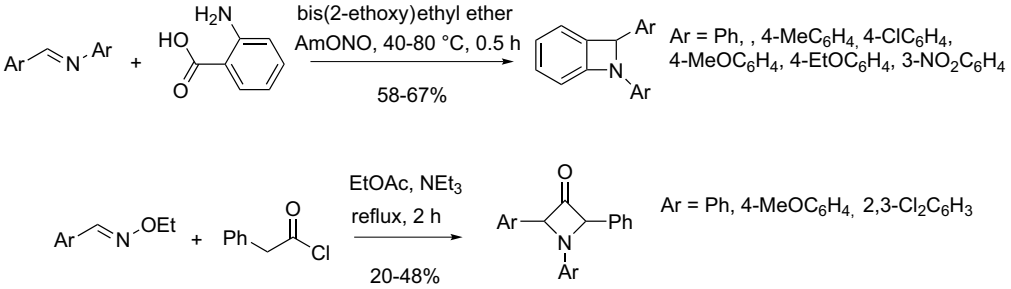
Scheme 3.38

The cycloaddition of benzyne with N-aryl imines occurs in good yields (Scheme 3.39) [80]. This is also the case for the [2 + 2] cycloadditions of alkoxy imines with phenyl ketene [81].

3.1.4 Reactivity and Useful Reactions

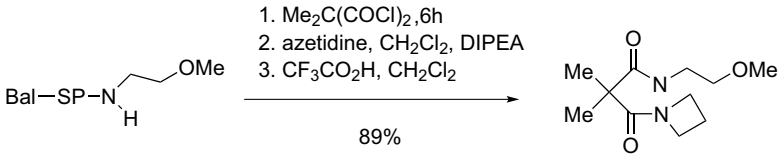
3.1.4.1 Reactions at the Nitrogen Atom

3.1.4.1.1 Reaction with Carboxylic Acid Derivatives Reactions of carboxylic acid chlorides with azetidine derivatives lead to N-acyl derivatives in high yields. These reactions were carried out in the presence of bases such as K_2CO_3 [82], NEt_3 or pyridine [3]. Recently, a solid-phase approach has been described for the preparation



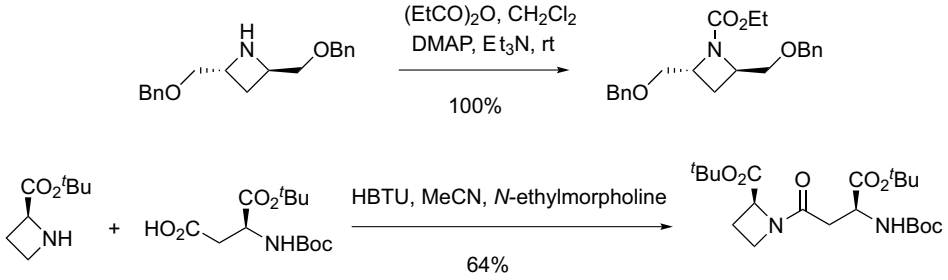
Scheme 3.39

of malondiamides. 2-Methoxyethylamine was fixed on a Bal-resin, and successive reactions with 2,2-dimethylmalonyl dichloride and azetidine lead to the malonamide. Cleavage with trifluoroacetic acid gives rise to the mixed malonamide in high yield (Scheme 3.40) [83].



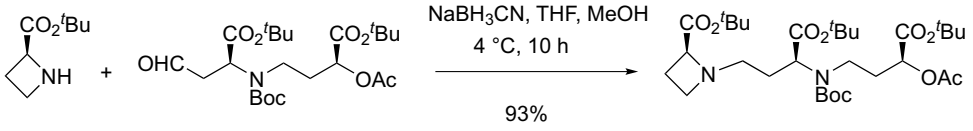
Scheme 3.40

N-Acetylazetidines can also be obtained by reaction with carboxylic anhydrides in the presence of DMAP (Scheme 3.41) [84], by reaction with ester in the presence of Horse Liver esterase [85], or by reaction with acid activated by reagents such as 1-[(3-dimethylamino)propyl]-3-ethylcarbodiimide (DMAP) [86] or 1*H*-1,2,3-benzotriazol-1-ol (HBTU) derivatives (Scheme 3.41) [87–89].



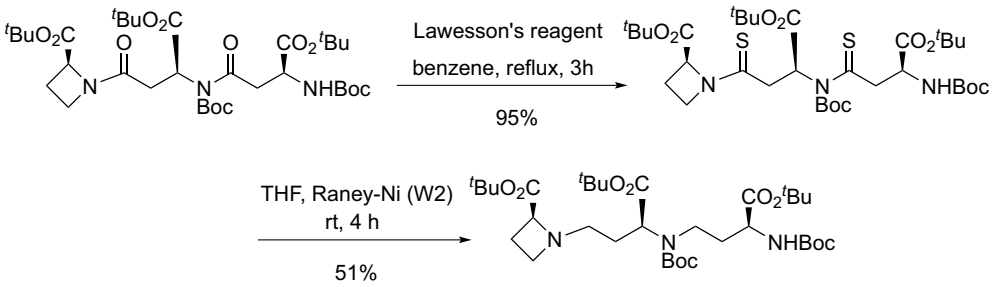
Scheme 3.41

3.1.4.1.2 **Reaction with Aldehydes and Ketones** Aldehydes react in the presence of $NaBH_3CN$ in acetic acid to furnish N-alkylazetidines (Scheme 3.42) [90]. Formic acid was sometimes preferred as the reducing agent [91].



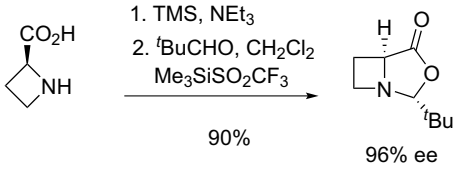
Scheme 3.42

These N-alkyl azetidines have been also obtained from the corresponding N-acyl compounds by carbonyl reduction after transformation into thioamides (Scheme 3.43) [88].



Scheme 3.43

The reaction of *(S)*-azetidine 2-carboxylic acid with pivaldehyde gives a bicyclic compound. When this reaction is catalyzed by CF_3COOH, a racemic product is obtained [92]. With trimethylsilyl-trifluoromethanesulfonate as catalyst, though, racemization was not observed and enantiomerically pure product was obtained (Scheme 3.44) [93].

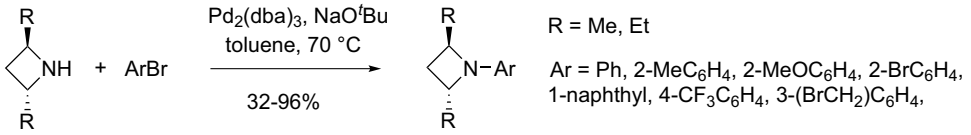


Scheme 3.44

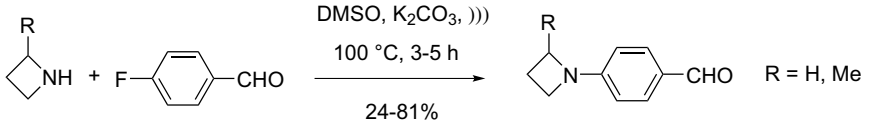
The reaction of azetidines with ketones affords the corresponding enamines. Kinetic studies have shown that these amines are more reactive than pyrrolidine [94].

3.1.4.1.3 **N-Alkylations** N-Aryl azetidines can be obtained by the arylation of N-unsubstituted azetidines with aryl bromide, catalyzed by palladium salts (Scheme 3.45) [36a].

Another interesting method used the S_NAr substitution of the fluorine on fluoroaryl. These reactions were carried out under sonication of the reaction mixture (Scheme 3.46) [95].

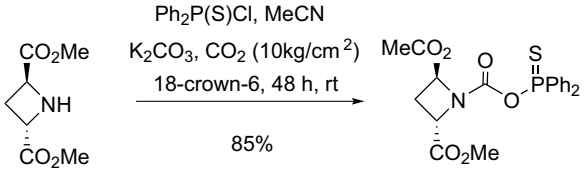


Scheme 3.45



Scheme 3.46

An original preparation of (phosphorothioyl)oxycarbonyl azetidine has been reported by reaction of azetidines with diphenylphosphinothioic chloride [$Ph_2P(S)Cl$] in the presence of K_2CO_3. This reaction was greatly improved when carried out under carbon dioxide in the presence of crown ether (Scheme 3.47) [96].

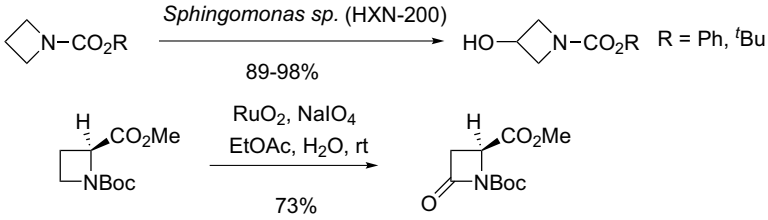


Scheme 3.47

3.1.4.2 **Oxidizing Reactions**

Oxidations of azetidin-3-ols into azetidin-3-ones with common CrO_3, Swern or Dess-Martin reagents have been reported to occur in high yields. No cleavage or degradation of the four-membered ring was noticed [3, 97].

Microbial oxidations of azetidines lead to the formation of azetidin-3-ols (Scheme 3.48) [98, 99]. Oxidations α of the nitrogen-atom (formation of β-lactams) have been performed with a RuO_2-$NaIO_4$ mixture (Scheme 3.48) [100] and

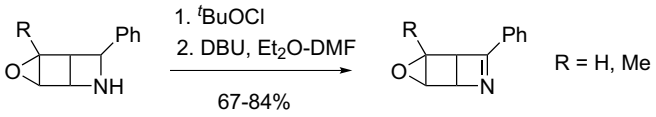


Scheme 3.48

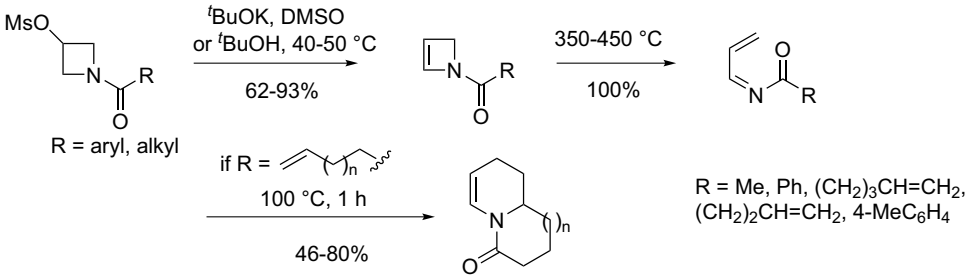
$KMnO_4$ [101]. Transformations of azetidin-2-carboxylic acids and esters into of β-lactams using oxygen have been also reported [102].

3.1.4.3 Reactions with Nucleophiles and Bases

N-Chloroazetidines can react with DBU to furnish stable azetines (Scheme 3.49) [103]. Azetines were also obtained when the leaving group was in the 3-position. The reaction of 3-mesylazetidines with potassium ^{t}butylate leads to the formation of azetines that can be transformed by flash-thermolysis into 1-aza-1,3-dienes. By smooth heating, these later give rise to bicyclic compounds (Scheme 3.50) [104].

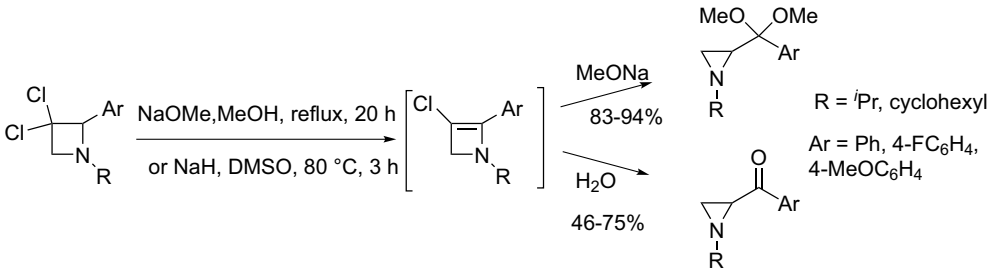


Scheme 3.49



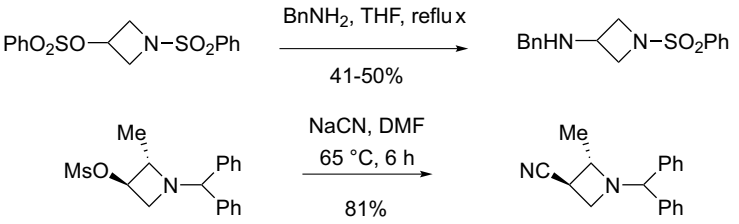
Scheme 3.50

The reaction of 3,3-dichloroazetidines with NaOMe or NaH also leads to azetines. The presence of an aryl substituent at the 2-position seems to increase their reactivities; subsequent reactions lead, finally, to aziridines (Scheme 3.51) [105].



Scheme 3.51

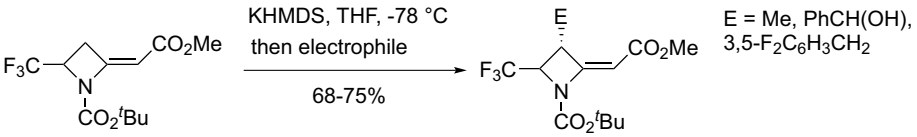
Instead of elimination, substitution occurs when 3-arylsulfonate-azetidines are reacted with benzylamine (Scheme 3.52) [106]. These substitutions, which occur with *retention* of configurations (due to the participation of the ring nitrogen) were also reported with sodium cyanide [107].



Scheme 3.52

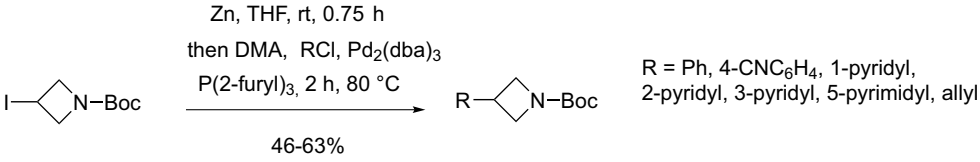
3.1.4.4 Reactions of C-Metallated Azetidines

Lithiation of methyl azetidine-2-carboxylate in α of the ester function has been carried out with LiHMDS as base [108]. Metallation of the azetidine ring of a methyl azetidin-2-ylidenecarboxylate with KHMDS is also effective. Subsequent addition of electrophiles yields 3-substituted azetidines (Scheme 3.53) [109].



Scheme 3.53

Organozinc compounds, formed by the reaction of 3-iodoazetidine with zinc, couple with aryl chlorides in the presence of palladium salts or with allyl bromide in the presence of CuCN to give 3-substituted azetidines in satisfactory yields (Scheme 3.54) [110].

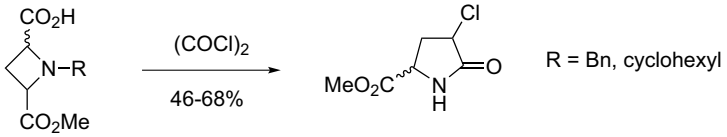


Scheme 3.54

3.1.4.5 Ring Expansions

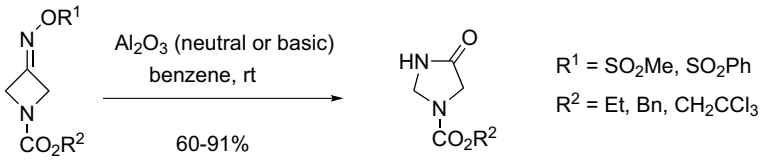
Ring expansions of azetidines into five-, six- and eight-membered heterocycles have been reported. Pyrrolidin-2-ones have been isolated during the preparation

of azetidin-2-carbonyl chlorides (Scheme 3.55) [111] or 2-(azetidin-3-yl)acetyl chloride [112].



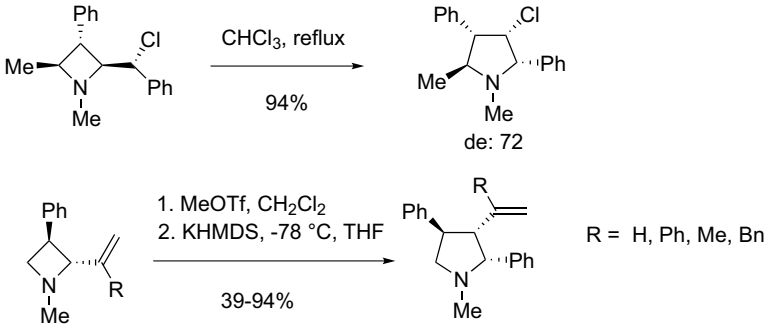
Scheme 3.55

Imidazolidines can also be obtained by Beckmann rearrangement of 3-(mesyloxyimino)- or 3-(tosyloxyimino)azetidines (Scheme 3.56) [113].



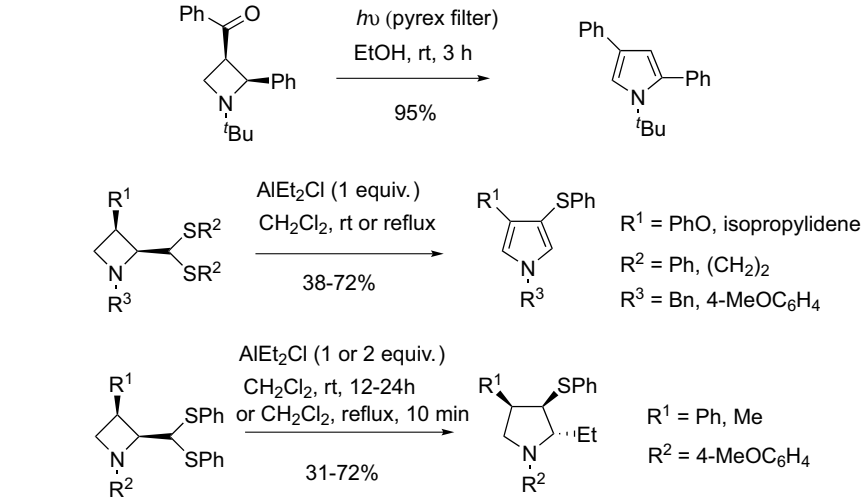
Scheme 3.56

Heating of 2-(phenylselenyl)methyl azetidines [114], 2-(methanesulfonyl)methylazetidines [115] or 2-(chloromethyl)azetidines (Scheme 3.57) [115] affords pyrrolidines in excellent yields. These rearrangements appeared highly diastereoselective. Ring expansions are also possible by treatment of azetidinium salts with bases [116], or by reaction of azetidines with cyclic olefins in the presence of Lewis acids [117].



Scheme 3.57

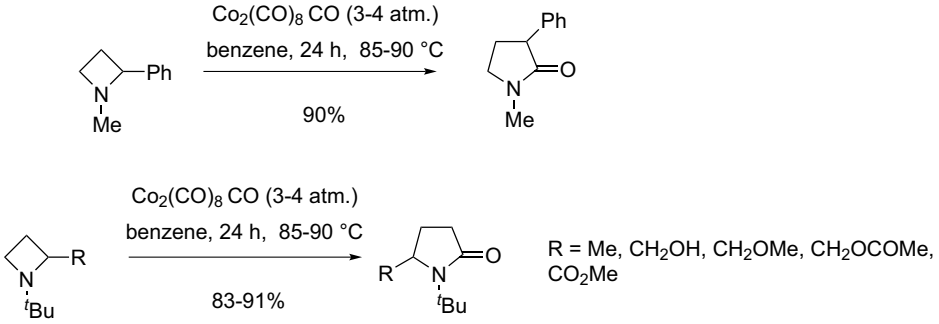
Photochemical rearrangement of 3-benzoylazetidines leads to pyrroles (Scheme 3.58) [118]. Preparation of pyrroles is also possible by the reaction of 3-phenoxy (or 3-isopropylidene) 2-thioacetal-azetidines of cis-stereochemistry with $AlEt_2Cl$ (Scheme 3.58) [119]. When the substituents at the 3-position were phenyl or



Scheme 3.58

methyl groups, the reactions yield pyrrolidines. With cyclic acetals or thioacetals, bicyclic pyrrolidines are obtained [119].

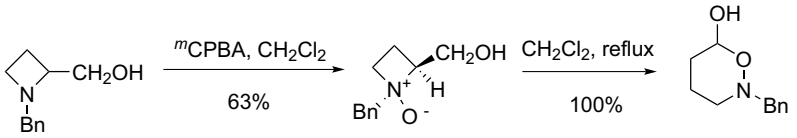
Another interesting preparation of pyrrolidinones is by the cobalt carbonyl catalyzed carbonylation of azetidines. The regioselectivity of the CO insertion depends on the substituent fixed to the nitrogen atom (Scheme 3.59) [120].



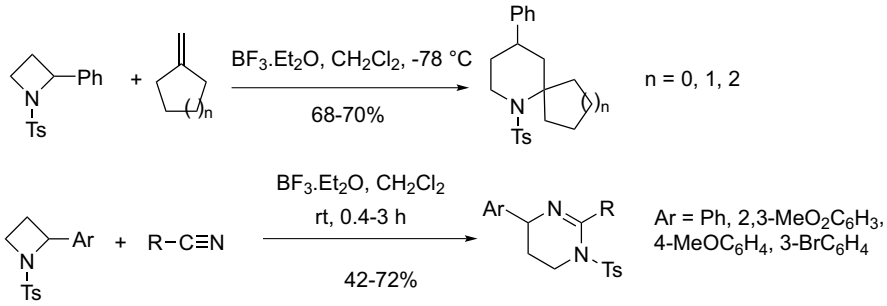
Scheme 3.59

2-Hydroxymethylazetidines react with *m*-chloroperbenzoic acid (*m*CPBA) to furnish the corresponding N-oxides with high diastereoselectivity. Upon heating, these N-oxides rearrange quantitatively into the 1,2-oxazinan-6-ol (Scheme 3.60) [121].

Piperidines, formed by [4 + 2] cycloadditions, have been isolated by reaction of azetidines with methylene-cycloalkanes (Scheme 3.61) [117]. [4 + 2] Cycloadditions have also been reported in the reaction of azetidines with nitriles (Scheme 3.61) [122].

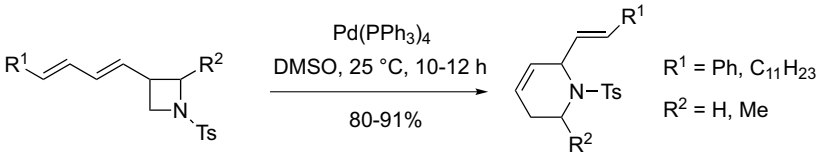


Scheme 3.60



Scheme 3.61

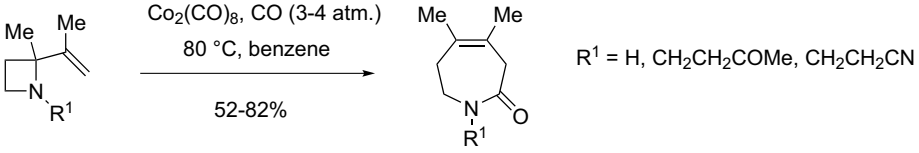
Piperidines are also obtained by the reaction of 1,3-butadienyl-azetidines with a palladium(0) salt. The 1,3-butadienyl entity appears necessary for the rearrangement (Scheme 3.62) [123].



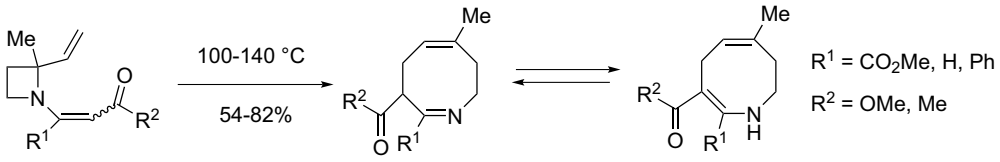
Scheme 3.62

The reaction of 2-alkenyl-azetidines with cobalt carbonyl leads to azepinones instead of piperidinones, as in the case of 2-unsaturated substituents (Scheme 3.63, cf. Scheme 3.59) [120].

Azocanes can be obtained by thermal rearrangement of 1,2-divinylazetidines (Scheme 3.64) [69].



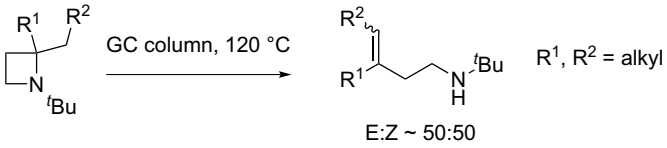
Scheme 3.63



Scheme 3.64

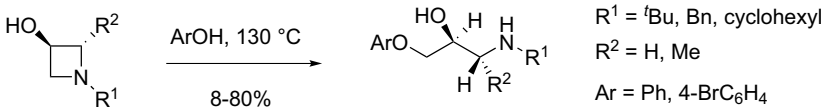
3.1.4.6 Cleavage of the Azetidine Ring

3.1.4.6.1 **Fragmentation Reactions** Flash thermolysis at 900 °C of azetidine gives ethylene and *N*-methylenemethanamine [124]. However, heating under less drastic conditions leads to cleavage of only one of the N–C bonds (Scheme 3.65) [125] to afford unsaturated amines.



Scheme 3.65

3.1.4.6.2 **Reaction with Nucleophilic Reagents** Azetidin-2-carboxylic acid derivatives react with thiophenol (pH 8) to afford a mixture of 3-amino-2-phenyl- and 2-amino-3-phenylthiopropanoic acids [126]. Similarly, 3-hydroxyazetidines can be cleaved with phenols. These reactions are highly stereospecific if a substituent was present in the 2-position (Scheme 3.66) [127].



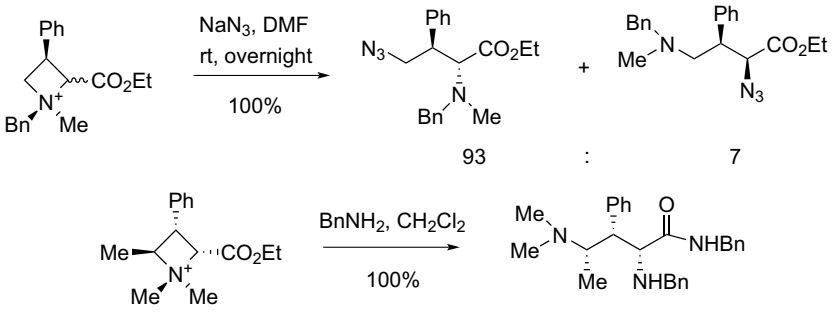
Scheme 3.66

The opening of azetidinium salts with nucleophiles such as NaN_3, butylamine or AcONa has also been examined. The regiochemistry of the cleavage appears to be a function of the substituents fixed on the azetidine ring (Scheme 3.67) [128].

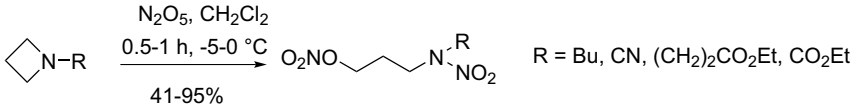
3.1.4.6.3 **Reaction with Electrophilic Reagents** The reaction of N-alkylazetidines with N_2O_5 gives 1,3-nitroamine-nitrates (Scheme 3.68) [129].

3.1.4.7 Enzymatic Resolutions of Azetidines

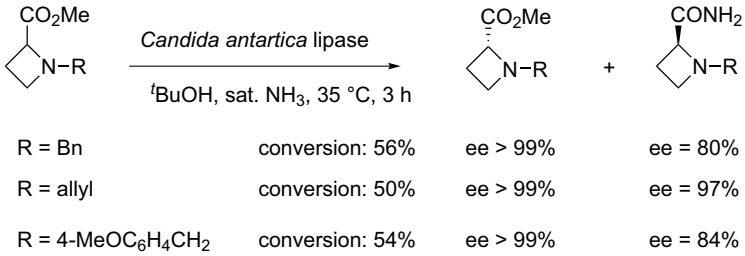
Racemic methyl azetidin-2-carboxylate has been resolved using *Candida antartica* as lipase in ^{t}butanol saturated with ammonia. Excellent enantiomeric excesses were obtained for the remaining ester and the amide formed (Scheme 3.69) [130].



Scheme 3.67

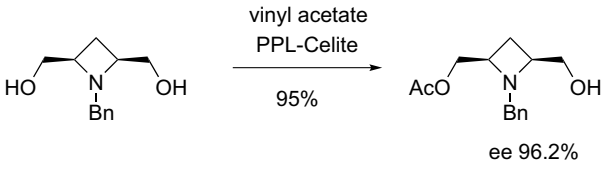


Scheme 3.68



Scheme 3.69

An azetidine with high enantiomeric excess has also been obtained by resolution of a meso-2,4-diol derivative. For a conversion of around 55%, a compound of high enantiomeric purity could be obtained (Scheme 3.70) [131] using porcine pancreas lipase (PPL) immobilized on Celite. Under these conditions, resolution of the racemic *trans*-2,4-diol gave a mixture of mono- and diacetate of lower enantiomeric excesses.



Scheme 3.70

oxetane 2-oxetanone

Figure 3.2 Four-membered oxygenated heterocycles.

3.2 Oxetanes

3.2.1 Introduction

Oxetanes are four-membered oxygenated cycles. Their carbonyl-substituted analogues are named oxetanones and, in particular, the 2-oxetanone family is commonly referred as β-lactones (Figure 3.2).

The search for effective enantioselective methods of preparation is now the most common challenge. Nonetheless, new syntheses are still a topical question due to the frequent presence of these four-membered cyclic ethers in biologically active substances. These compounds have aroused much interest by their large range of reactivities. The ring strain common in both the oxetane and the oxetanone cycles causes significant susceptibility to thermal cleavage. The basicity of the ring oxygen makes the oxetanes sensitive to electrophile reagents and/or consequently to nucleophilic attacks at carbon. Oxetanes can be subject to polymerization. The 2-oxetanones mainly undergo nucleophilic addition at the carbonyl carbon, with or without electrophilic catalysis.

3.2.2 Physicochemical Data

Microwave, electron diffraction and X-ray diffraction methods have permitted a precise determination of bond lengths and angles in several oxetanes [132]. Table 3.1 reports the bond lengths and angles of oxetane and 2-oxetanone.

Notably, the C−O bond is longer than in other types of compounds: (C_{sp3}−O = 1.41 Å). The oxetane ring may be either coplanar or puckered, depending on the substituents present. A rocking motion allows the substituents to attain a less

Table 3.1 Bond lengths and angles of oxetane and 2-oxetanone.

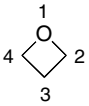
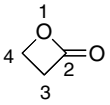
	Bond	Oxetane (Å)	2-Oxetanone (Å)	
	C4−O1	1.449	1.45	
	C3−C4	1.549	1.53	
	C2−O1−C4	91.8°	89°	
	C2−C3−C4	84.55°	83°	

Table 3.2 Chemical shifts of various compounds in deuteriochloroform.

		H^A	H^B	H^C	H^D	H^E	H^F (ppm)
	Oxetane	4.73	4.73	2.72	2.72	4.73	4.73
	2-Me-oxetane	1.35(Me)	4.85	2.24	2.63	4.37	4.49
	4-Me-oxetanone	1.53(Me)	4.57	2.98	3.50	—	—

hindered conformation but is opposed by the resulting increase in bond angle deformation. The 2-oxetanone having a carbonyl group in place of a methylene group is strictly planar.

3.2.2.1 NMR Data

The proton NMR spectroscopy of oxetanes is largely understood [132]. Table 3.2 gives the chemical shifts of various compounds in deuterochloroform. A substituent can have special effects on the proton chemical shifts due to their proximity in the small ring. This could be also induced by changes in the puckering of the ring.

Table 3.3 gives some representative ^{13}C chemical shifts relative to TMS in deuterochloroform [133].

^{17}O NMR spectra of oxetanes and 2-oxetanones referenced to water show values of -13 ppm for the oxetane ether O and 347 ppm (C=O) and 241 ppm (ether O) for the two oxygens in 2-oxetanone [133].

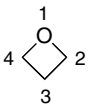
3.2.2.2 Infrared Spectroscopy

A strong absorption band at about 980 cm^{-1} is characteristic of oxetane [132]. The far-IR spectrum of oxetane has been obtained at 205 K. The band of ring puckering transition was assigned at 52.92 cm^{-1}. 2-Oxetanones present an intense absorption at 1840–1820 cm^{-1} due to carbonyl stretching.

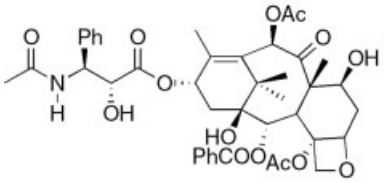
3.2.3 Natural or Bioactive Compounds

The oxetane ring appears in some biologically active compounds. We report in this chapter some representative examples. Taxol **12**, isolated from *Taxus brevifolia* and its derivative the taxotere, is an important drug in cancer chemotherapy [134].

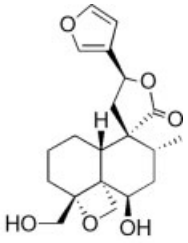
Table 3.3 Representative ^{13}C chemical shifts relative to TMS in deuterochloroform.

		C^2	C^3	C^4	Me
	Oxetane	72.8	23.1	72.8	—
	2-Me-oxetane	78.3	29.0	66.6	24.1

Montanin D (**13**) has antifeedant activity. This substance has been extracted from the plant *Teucrium tomentosum* [135].

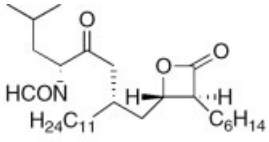


Taxol **12**

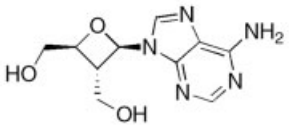


Montanin D **13**

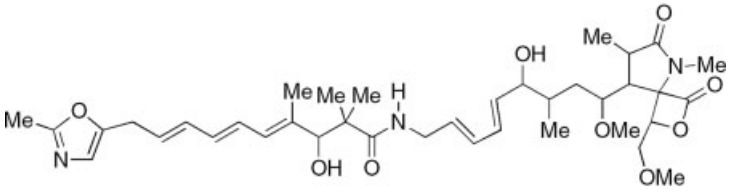
(−)-Tetrahydrolipstatin (**14**) is a triglyceride mimic, an analogue of lisptatin isolated from *Streptomyces toxytricimi*. It is a potent and irreversible inhibitor of pancreatic lipase, used as an antiobesity agent under the name Xenical [136]. The antibiotic oxetanocin A (**15**) is a fermentation product of *Bacillus megaterium*. It is also known as an anti-HIV compound [137]. Curromycin A (**16**) is an antibiotic produced by a genetically modified strain of *Streptomyces hygroscopicus* [138].



(-) tetrahydrolipstatin **14**

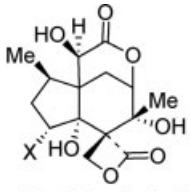


Oxetanocin A **15**



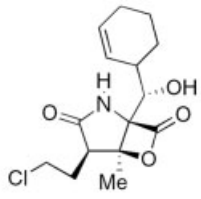
16

Anisatin **17** and neoanisatin **18** are convulsant principles isolated from the fruits of the toxic plant *Illicium anisatum L* [139]. Salinosporamide A (**19**) is a bioactive product of a marine microorganism [140].



X = OH anisatin **17**

X = H neoanisatin **18**

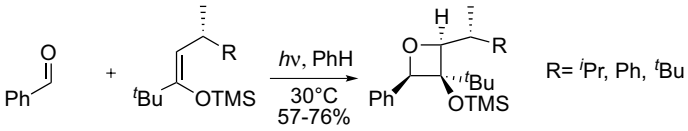


Salinosperomide A **19**

3.2.4
Synthesis of Oxetanes and Oxetan-2-ones

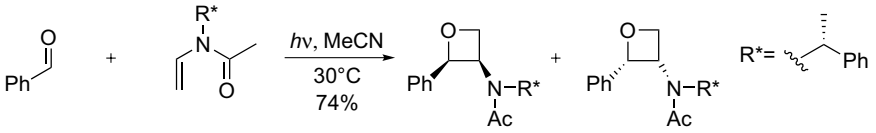
3.2.4.1 [2 + 2] Paterno–Büchi Cyclizations

The [2 + 2] photocycloaddition of carbonyl compounds with alkenes, the Paterno–Büchi reaction, is a useful method in organic synthesis. The challenge in this area is the regio and stereocontrol of the reaction. Bach *et al.* have reported significant facial diastereoselectivities in the reaction with silyl enol ethers carrying a chiral substituent. The carbonyl compound is directed to the less shielded face. With large and polar substituents at the stereogenic center, the facial selectivity leads to diastereomerically pure oxetanes (Scheme 3.71) [141].



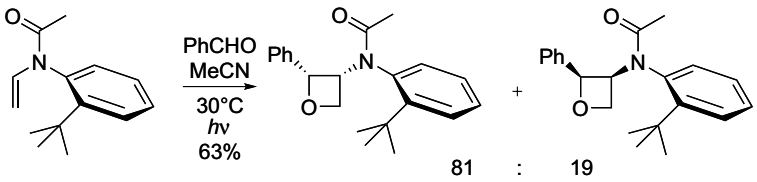
Scheme 3.71

Photocycloaddition of chiral N-acyl enamines with benzaldehyde produces the cis-diastereomers predominantly, with facial diastereomeric excess from 30 to 62% (Scheme 3.72) [142].



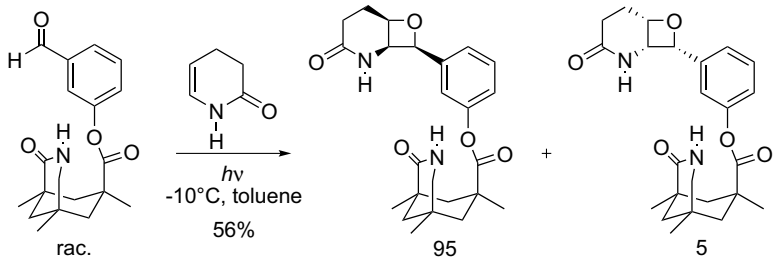
Scheme 3.72

A N-benzylenecarbamate has been irradiated in the presence of various aldehydes. The cis-diastereoselectivity is always predominant [143]. This method has been applied to the synthesis of diastereomerically pure 1,2-amino alcohols. A diastereoselectivity of 62% has been observed in the reaction of benzaldehyde with an atropisomeric enamide (axial chirality) (Scheme 3.73) [144].



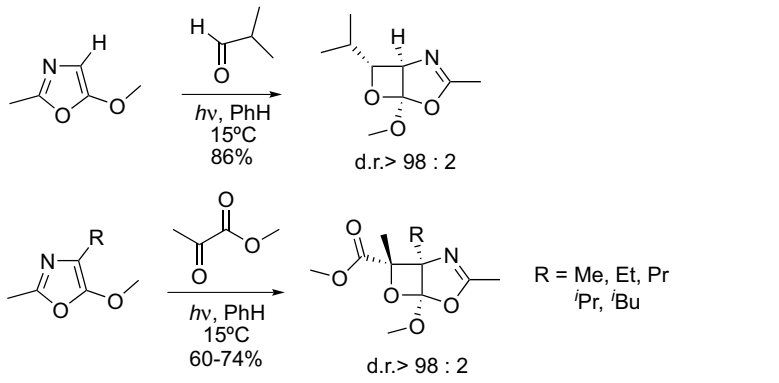
Scheme 3.73

A high facial diastereoselectivity in the photocyclization of a chiral aromatic aldehyde and an enamide has been induced by intermolecular hydrogen bonding. The simple diastereoselectivity led solely to cis-isomers and the facial diastereoselectivity was 95 : 5, when the reaction was carried out at low temperature in toluene (Scheme 3.74) [145]. The same reaction with enantiomerically pure aldehyde produced the oxetane with 95% of enantiomeric excess [146]. Bach *et al*. have studied the Paterno–Büchi reaction with 2,3-dihydropyrrole and α-alkylated enecarbamate as well [147, 148].



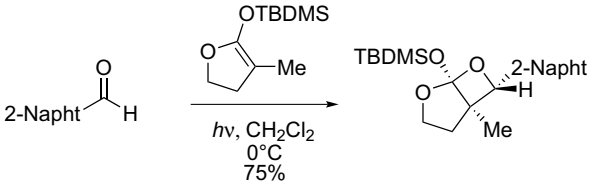
Scheme 3.74

Griesbeck *et al*. have worked on the photocycloadditions of oxazole with carbonyl compounds [149]. The 4-unsubstituted 5-methyloxazole gave the cycloadducts with aromatic or aliphatic aldehydes, in high yield and excellent *exo*-diastereoselectivities (98 : 2) (Scheme 3.75). The cycloadducts are precursor of α-amino β-hydroxycarboxylic acid esters [150]. The [2 + 2] cycloaddition of methyl pyruvate with 4-alkylated 5-methoxyoxazoles led to the *exo*-adducts with high diastereoselectivity. When the reaction was run with phenylglyoxylate, oxetanes were formed with moderate diastereoselectivity (79 : 21) [151]. The same authors also studied the Paterno–Büchi reaction of enols with carbonyl compounds [152]. Hydrogen bonding effect has been explored in the reaction of allylic alcohols [153–155].



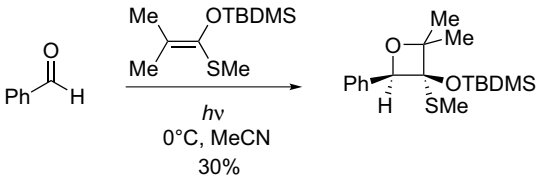
Scheme 3.75

Abe *et al.* have described the formation of 2-siloxy-2-alkoxyoxetanes, which can easily lead to aldol-type adducts, by photoreaction of cyclic ketene silyl acetals with 2-naphthaldehyde (Scheme 3.76) [156].



Scheme 3.76

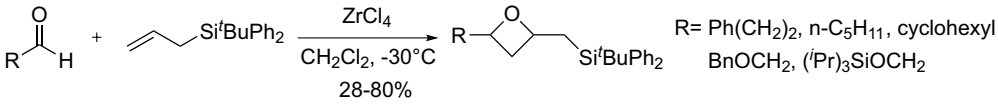
Reaction of aromatic aldehydes with silyl O,S-ketene acetals produced 3-siloxyoxetanes with high regioselectivity due to a S-directed approach (Scheme 3.77) [157]. The same group has also studied the reactivity of furan derivatives in the Paterno–Büchi reaction [158, 159].



Scheme 3.77

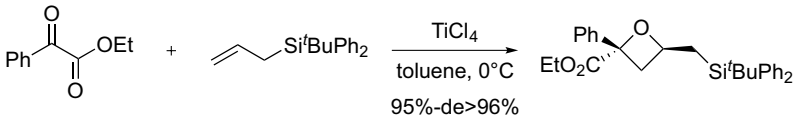
3.2.4.2 **Catalyzed [2 + 2] Cyclizations**

[2 + 2] Cycloaddition can also be performed in a catalytic manner. Oxetanes have been prepared by zirconium(IV) chloride promoted cycloaddition of allylsilane to aldehydes (Scheme 3.78). Previous work was limited to activated carbonyl compounds such as α-ketoesters or α-diketones [160].



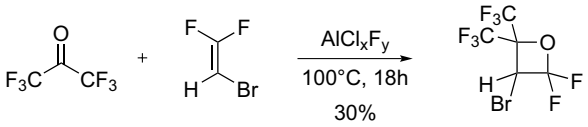
Scheme 3.78

Akiyama and Kirino have developed a stereoselective construction of oxetanes by titanium(IV) chloride promoted [2 + 2] cycloaddition of allylsilane to α-ketoesters. Best results were obtained with bulky substituents on the silicon and toluene as solvent. The diastereoselectivity was up to 96% (Scheme 3.79) [161].



Scheme 3.79

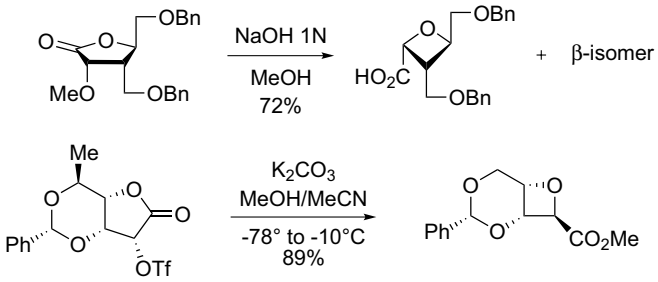
Polyfluorinated oxetanes have been prepared by the reaction between hexafluoroacetone and fluorinated ethylenic compounds. The reaction is catalyzed by aluminium chlorofluoride as Lewis acid. Hydrofluoroethylenes HXC=CF$_2$ (X = H, F, Cl, Br) led to only one regioisomer (Scheme 3.80) [162].



Scheme 3.80

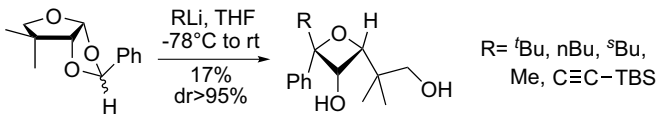
3.2.4.3 Ring Contraction of Butanolides

Ring contractions of γ-lactones into oxetanes have been studied and are used in the synthesis of oxetin or oxetanocin analogues (Scheme 3.81) [163, 164].



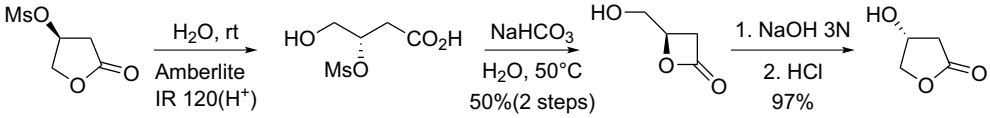
Scheme 3.81

Suzuki and Tomooka have found a new anionic ring contraction reaction. They obtained oxetanes by treating cyclic acetal systems with an excess of alkyl lithium (Scheme 3.82) [165]. The four-membered rings are obtained with high diastereoisomeric excesses.



Scheme 3.82

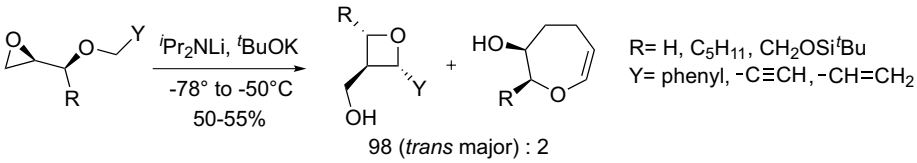
β-Lactones have been obtained by contraction of butanolides via an intramolecular nucleophilic displacement of an activated group by the carboxylate anion. De Angelis *et al.* have produced the total inversion of configuration of the *(S)*-β-hydroxy-γ-butyrolactone via a β-lactone intermediate. This last product was also presented as a versatile chiral synthon (Scheme 3.83) [166].



Scheme 3.83

3.2.4.4 Oxirane Ring Opening by Carbanionic Attacks

Mordini *et al.* have synthesized oxetanes by the isomerization of oxiranes using an equimolar mixture of butyllithium/diisopropylamine/potassium *tert*-butoxide (LIDAKOR) [167]. The reaction occurred when Y is a phenyl or a propargyl group, and the substituted oxetanes were produced in *anti*-(2,3)-configurations (Scheme 3.84) [168].



Scheme 3.84

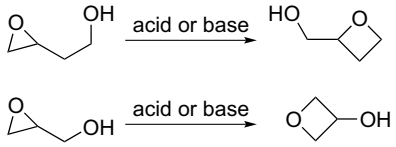
3.2.4.5 Williamson Reactions

The intramolecular Williamson reaction has often been used for the preparation of cyclic ethers like oxetanes (Scheme 3.85). This S_N2 displacement of a leaving group (halogen, mesylate, tosylate, etc.) by the alkoxides moiety can be performed with considerable variation in the choice of base (DBU, KOH, ^{t}BuOK, NaHMDS, etc.) [132, 133]. No recent work has been published about this reaction in particular.

Scheme 3.85

3.2.4.6 Isomerization of Oxiranyl Hydroxyls

Since an epoxy oxygen atom can serve as a good leaving group, the isomerization of oxiranyl hydroxyls has been used for oxetane preparation in total syntheses (Scheme 3.86). This reaction can be performed under acidic ($BF_3{\cdot}Et_2O$) or basic

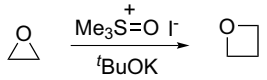


Scheme 3.86

(KOH) conditions [132, 133]. No new studies of this ring opening reaction have been published recently.

3.2.4.7 Oxirane Ring Expansions

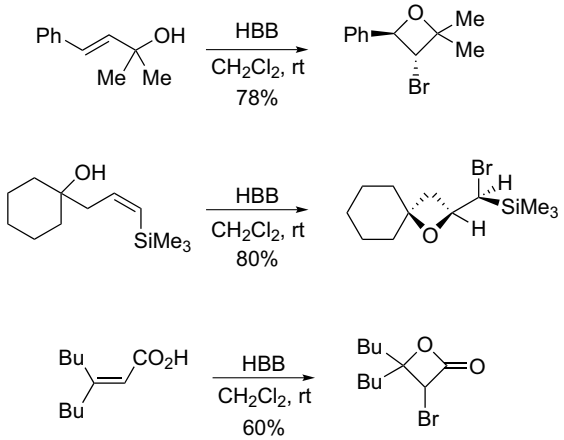
Oxetanes can be obtained by treating oxiranes with dimethyloxosulfonium methylide (Scheme 3.87) [132, 133]. This well-known reaction has not receive renewed interest in recent years.



Scheme 3.87

3.2.4.8 Electrophilic Cyclizations

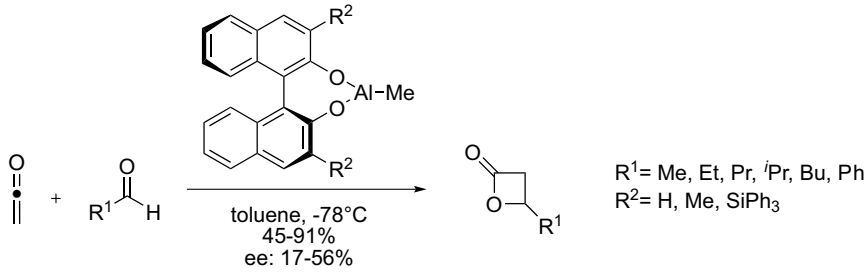
This reaction, which can be performed with mild experimental conditions, is often used in total synthesis. Few methodological studies have been done. Rousseau *et al.* have published the preparation of oxetanes via a 4-*endo* cyclization process on allylic alcohols [169, 170] and via a 4-*exo* cyclization process on homoallylic alcohols [171], using the electrophilic reagent bis(*sym*-collidine)bromine(I) hexafluorophosphate (HBB) or hexafluoroantimonate. This reaction was also used to prepare β-lactones starting from α,β-unsaturated acids (Scheme 3.88) [169].



Scheme 3.88

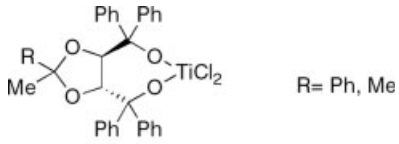
3.2.4.9 [2 + 2] Cycloaddition of Ketene and Carbonyl Compounds

The [2 + 2] cycloaddition of ketenes with carbonyl compounds is an expedient way to substituted β-lactones. Silylketenes are reactant of choice due to their better stability. The most common reagent as Lewis acid is $BF_3{\cdot}Et_2O$, but the goal in this area is now the use of chiral Lewis acid catalysts. Asymmetric [2 + 2] cycloadditions of ketene with aliphatic aldehydes have been catalyzed by chiral aluminium Lewis acids to afford optically active 4-substituted oxetan-2-ones in moderate enantiomeric excesses (Scheme 3.89) [172].



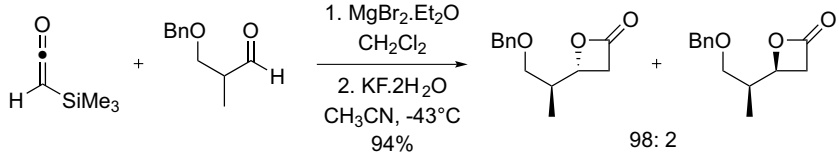
Scheme 3.89

Romo and Yang have developed Ti-TADDOL catalysts such as **20**, which provide good reactivity and moderate enantioselectivity (9–80% ee) in the asymmetric [2 + 2] cycloadditions of silylketenes and aldehydes [173].



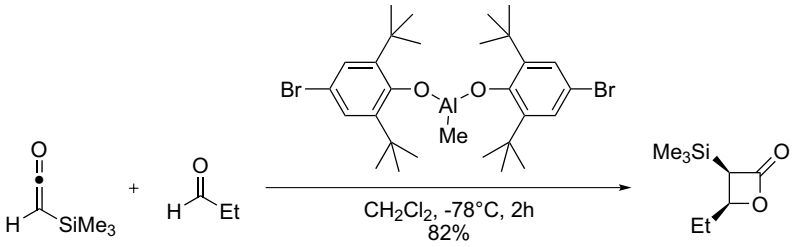
20

The same group has also employed chelation controlled [2 + 2] cycloadditions of trimethylsilyl ketene to chiral α and β-benzyloxyaldehydes to provide a highly diastereoselective route to functionalized β-lactones. The Lewis acid $MgBr_2.Et_2O$ gave the highest selectivities and yields (Scheme 3.90) [174].



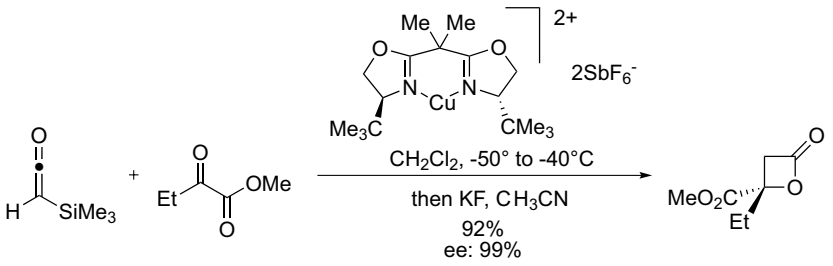
Scheme 3.90

Yamamoto *et al*. have disclosed a highly diastereoselective cyclization under the influence of bulky methyl aluminium bis(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR) as Lewis acid (Scheme 3.91) [175]. No trace of the trans isomer could be detected.



Scheme 3.91

Bis(oxazoline)-Cu(II) complexes have been used by Evans *et al*. to catalyze the enantioselective cycloaddition between silylketenes and chelating carbonyl substrates. β-Lactones have been produced in excellent yields and selectivities (Scheme 3.92) [176].

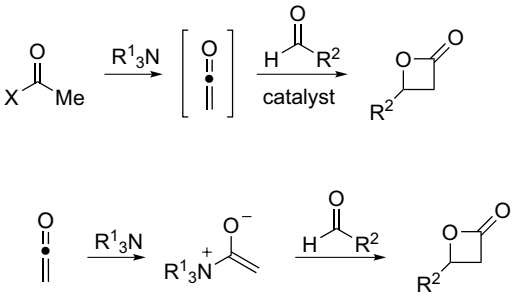


Scheme 3.92

3.2.4.10 **Acyl Halide–Aldehyde Cyclocondensations**

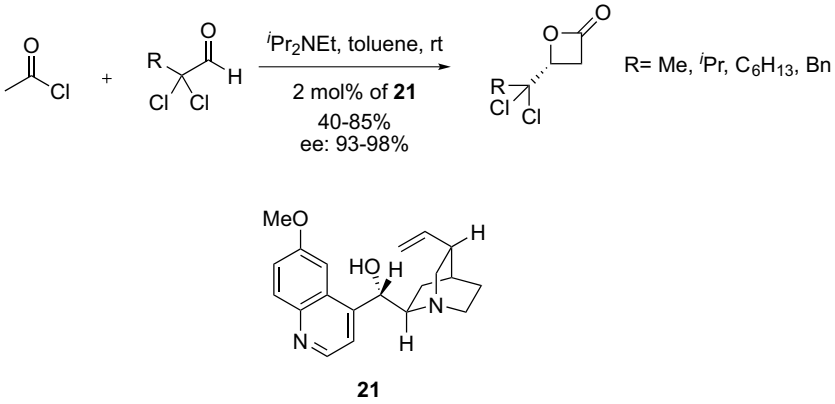
The acyl halide–aldehyde cyclocondensation can be classified between the [2 + 2] cycloaddition of ketenes to carbonyl compounds and the catalyzed aldol-lactonization reaction. Actually, the reaction can progress via *in situ* ketene formation or via an ammonium enolate (Scheme 3.93). This aldol-addition reaction equivalent has induced much interest, especially in its catalyzed asymmetric version. The use of tertiary amines as both base to effect dehydrochlorination and nucleophile to promote the reaction of ketenes and aldehydes has been demonstrated.

Romo and Tennyson have taken their inspiration from the Wynberg procedure [177] for the synthesis of optically active dichlorinated β-lactones via an *in situ* generated ketene. Di-chlorinated aldehydes were reacted with acetyl chloride in the



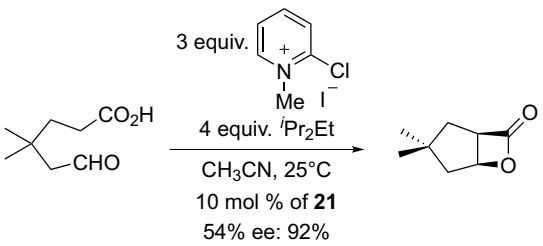
Scheme 3.93

presence of Hunig's base and 2 mol% of quinidine A (**21**). Dichlorinated β-lactones were obtained with 93–98% enantiomeric excesses (Scheme 3.94) [178].



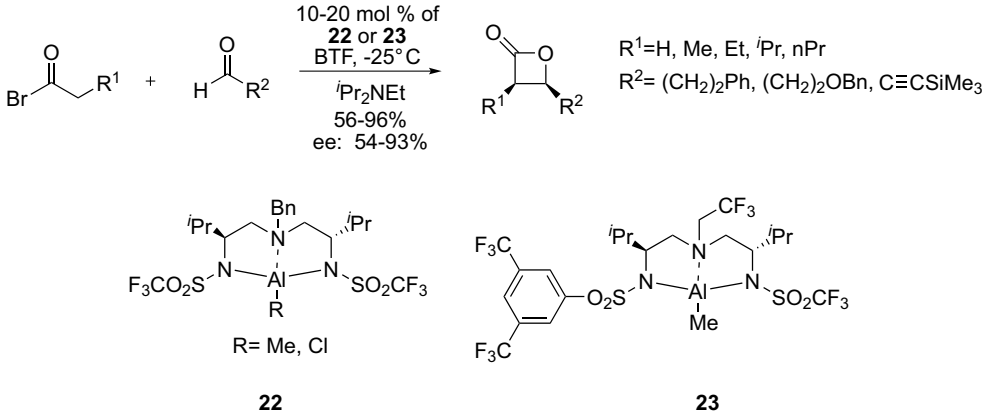
Scheme 3.94

Romo *et al.* have also investigated an intramolecular aldol-lactonization reaction. Chiral bicyclic β-lactones have been obtained with high enantiomeric excess from non-activated aldehydes in the presence of 10 mol% of catalyst **21** (Scheme 3.95) [179].



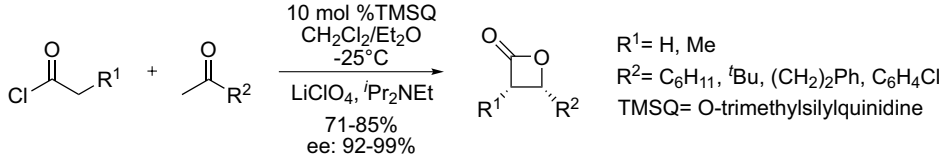
Scheme 3.95

In a first stage, Nelson *et al.* have presented an Al(III)-catalyzed acyl halide–aldehyde cyclocondensation reaction. A catalytic quantity of $Al(SbF_6)_3$ in concert with di(isopropyl)ethylamine constituted the most successful reaction promoter [180].They continued with asymmetric cyclocondensations catalyzed by chiral Al(III) triamine derivatives **22** or **23** [181, 182]. This methodology can be applied to a large range of aldehydes and to substituted ketenes. 3,4-Disubstituted β-lactones are accessible with excellent optical purity (Scheme 3.96).



Scheme 3.96

In attempting to expand the scope of Wynberg's original ketene–aldehyde cycloadditions, Nelson *et al.* have developed a cinchona alkaloid–Lewis acid catalyzed acid chloride–aldehyde cyclocondensation. The TMSQ/$LiClO_4$ catalyst system allows the reaction with α-branched aldehydes or with methyl ketene. The 3,4-disubstituted β-lactones are obtained in excellent enantiomeric excess (Scheme 3.97) [183].

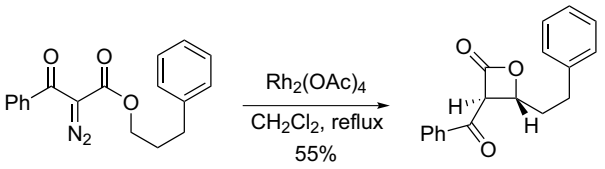


Scheme 3.97

3.2.4.11 **C–H Insertions**

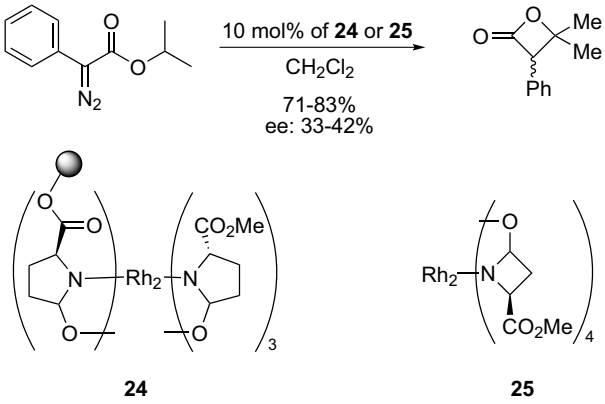
Intramolecular C−H insertion in the catalytic decomposition of diazomalonic esters has often been used in the preparation of β- and γ-lactones. However, this reaction depends on the substitution pattern of insertion centers and the conformational bias

of metallocarbenes, leading to a mixture of both β- and γ-lactones [184, 185]. Balaji and Chanda have shown that steric effects may play a major role in the C–H insertion of inactivated α-diazo-α-aroyl esters, catalyzed by rhodium(II) carboxylates. The reaction of α-diazo-α-benzoyl esters catalyzed by various rhodium carboxylates yielded β-lactones as the only products (Scheme 3.98) [186].



Scheme 3.98

C−H insertion reactions catalyzed with immobilized dirhodium(II) salt having mixed chiral ligands have been reported by Doyle *et al.* They observed that the enantioselectivity was slightly increased with the most selective azetidinone-ligated homogeneous catalyst **25** (Scheme 3.99) [187].

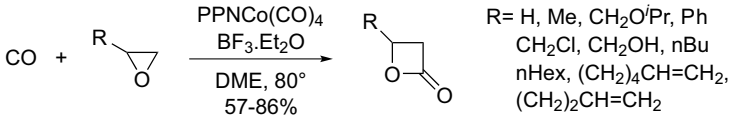


24 **25**

Scheme 3.99

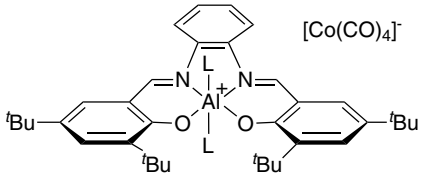
3.2.4.12 **Carbonylative Ring Expansion Reactions**

Alper *et al.* have described the carbonylation of epoxides with a new catalyst, $PPNCo(CO)_4$ [PPN=bis(triphenylphosphine)iminium], used in conjunction with $BF_3{\cdot}Et_2O$. Carbonylations occurred selectively at the unsubstituted C−O bond of the epoxide rings. These reactions tolerate various functional groups such as alkenyls, halides, hydroxyls and alkyl ethers. The β-lactones are obtained in good yields without polymeric by-products (Scheme 3.100) [188].

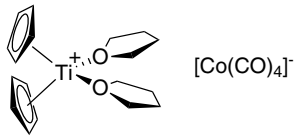


Scheme 3.100

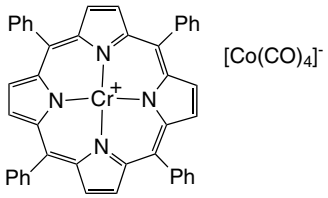
Coates *et al*. have developed three catalyst for the carbonylation of substituted epoxides: [(salph)Al(THF)$_2$][Co(CO)$_4$] (**26**) [189], [Cp$_2$Ti(THF)$_2$][Co(CO)$_4$] (**27**) [190] and [(TPP)Cr(THF)$_2$][Co(CO)$_4$] [**28**, with THF in the axial positions (not shown)] [191]. Catalyst **28** is the most active and selective with a wide range of epoxides.



26 L= THF



27



28

3.2.4.13 β-Hydroxy Acid Cyclizations

The cyclization of β-hydroxy acids is largely used in the synthesis of molecules possessing a β-lactone moiety. This reaction can be executed following an addition–elimination process or a nucleophilic substitution process [132, 133]. In the addition–elimination way, Adam's method (pyridine/ArSO$_2$Cl; Ar = Ph, 4-MePh, 4-NO$_2$Ph) [192] is the most commonly used, but different reactants can also activate the carboxylic acid, such as Et$_3$N/BOPCl [bis-(2-oxo-3-oxazolidinyl)phosphonic chloride], DCC/HOBt, EDC/HOBt, etc. The intramolecular nucleophilic substitution can be pursued by the Mitsunobu reaction (PPh$_3$/DEAD or DMAD) [193].

3.2.5 Reactivity

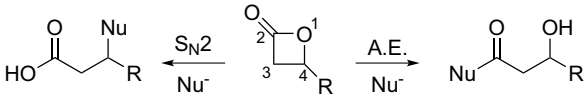
3.2.5.1 β-Lactones

The reactivity of β-lactones has been already [194]. It can be broken down into four areas:

- nucleophilic attack with ring opening;
- Lewis acid promoted rearrangement;

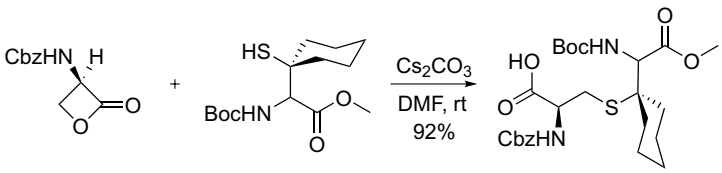
- decarboxylation;
- enolate formation and reaction toward electrophiles.

3.2.5.1.1 **Nucleophilic Attacks** It has already been demonstrated that the ring opening of β-lactones can occur through two different pathways. Attack via an addition–elimination process at the carbonyl residue affords access to β-hydroxy adducts. A nucleophilic substitution reaction at the C4 atom can produce β-substituted carboxylic acid derivatives (Scheme 3.101).



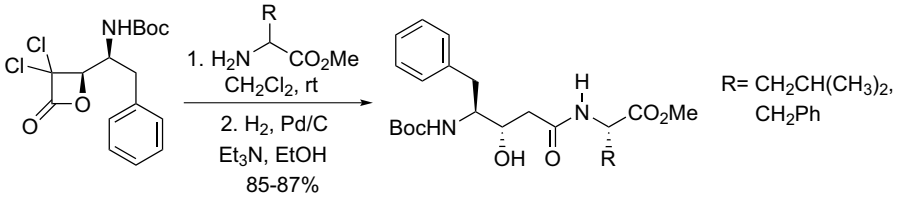
Scheme 3.101

Organomagnesium and organolithium reagents attack β-lactones at the carbonyl, leading to oxygen–acyl cleavage. Organocuprates induce the oxygen alkenyl cleavage. Ring opening of β-lactone by hetero-nucleophiles has been much studied. Goodman *et al.* [195], inspired by Vederas' results [196], have synthesized lanthiomine derivatives by ring opening of a protected serine β-lactone by the thiolate anion of methyl Boc-*(S)*-cysteinate derivatives (Scheme 3.102).



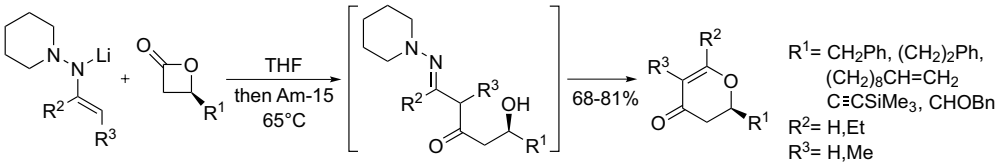
Scheme 3.102

Palomo *et al.* [197] have obtained dipeptides by coupling an α-dichloro β-lactone with *(S)*-leucine or *(S)*-phenylalanine and subsequent dechlorination (Scheme 3.103).



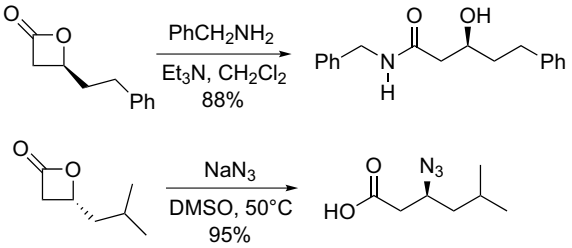
Scheme 3.103

Ring opening of β-lactones by hydrazone anions, followed by dehydroamination cyclizations of the β-ketohydrazone intermediates in the presence of amberlyst-15 acid resin, yields dihydropyrones (Scheme 3.104) [198].



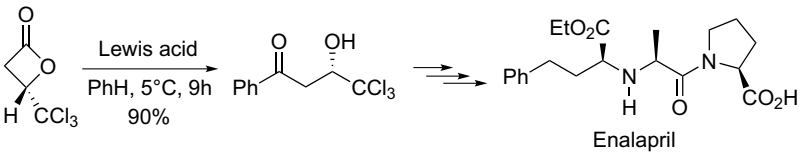
Scheme 3.104

Nelson *et al*. [199] have demonstrated that primary and secondary amines promote a ring opening by addition–elimination to deliver β-hydroxyamides (Scheme 3.105). Sodium azide reacts in an S_N2 manner to produce β-azido acids, and sulfonamide anions give rise to β-amino acids.



Scheme 3.105

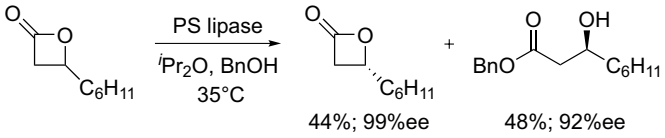
Acylation of aromatic compounds with chiral β-trichloromethyl β-propiolactone in the presence of Lewis acid has been investigated by Fujisawa *et al*. [200]. The Friedel–Crafts products retain completely the stereochemical integrity of the starting β-lactone. This method has been applied to the synthesis of a precursor of enalapril, an angiotensin converting enzyme (ACE) inhibitor (Scheme 3.106).



Lewis acids= $AlCl_3$, $AlBr_3$, $FeCl_3$, $TiCl_4$, $EtAlCl_2$, Et_2AlCl

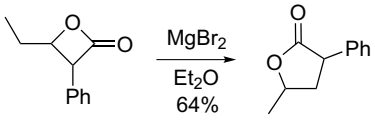
Scheme 3.106

The utility of β-lactones as intermediates for asymmetric synthesis has been limited by the difficulty for their preparation in enantiomerically pure form. Nelson and Spencer [201] have examined enzymatic resolution for the preparation of enantiomerically enriched β-lactones (Scheme 3.107). This method allows the preparation of 4-substituted β-propiolactones with high enantiomeric excesses simultaneously with enantiomerically enriched β-hydroxy esters.



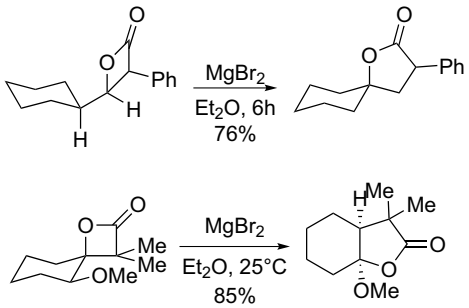
Scheme 3.107

3.2.5.1.2 **Lewis Acid Promoted Rearrangements** Ring expansion of β-lactones to afford γ-lactones can be performed with various Lewis acids, *p*.TsOH, $ZnCl_2$, BF_3.OEt or $Ti(O\text{-}^{i}Pr)_4$. The best catalyst appears to be $MgBr_2$ (Scheme 3.108) [202].



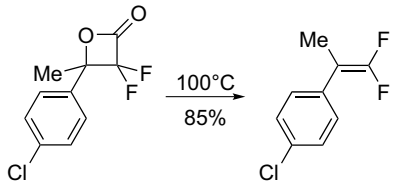
Scheme 3.108

This dyotropic rearrangement involves simultaneous positional interchange of two adjacent atoms having an anti-coplanar stereochemistry relationship. Inversion of stereochemistry at C4 atom is always observed [203]. Black *et al*. have prepared spiro [204] and cis-fused γ-lactones (Scheme 3.109) [205] via such β-lactones rearrangements. β-Elimination can occur in place of rearrangement when the C4 atom is tertiary [206].



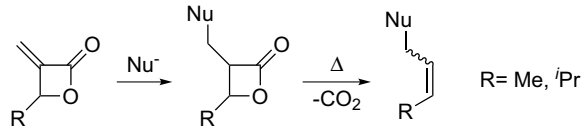
Scheme 3.109

3.2.5.1.3 **Decarboxylations** The thermal decomposition of β-lactones into alkenes takes place between 80 and 160 °C. The reaction is a stereospecific cis-elimination: cis-disubstituted β-lactones lead to a *(Z)*-olefins whereas trans-disubstituted β-lactones lead to *(E)*-olefins. These reactions can be regarded as alternative to Wittig reactions. Dolbier *et al*. have used this method to synthesize 1,1-difluoroalkenes via α,α-difluoro-β-lactones (Scheme 3.110) [207, 208].



Scheme 3.110

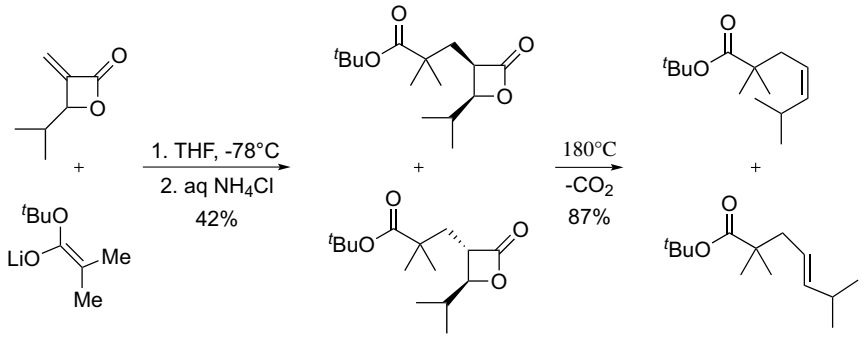
Adam *et al.* [209] have obtained allyl amines and sulfides by conjugate addition of amine and thiol nucleophiles to α-methylene β-lactones and subsequent decarboxylation (Scheme 3.111).



Nu= pyrrolidine	92%	51%
PhSH	97%	86%

Scheme 3.111

With the same strategy the conjugate addition of ester and ketone enolates to α-methylene β-lactones followed by decarboxylation leads to γ,δ–unsaturated esters with complete stereoselectivity (Scheme 3.112) [210].

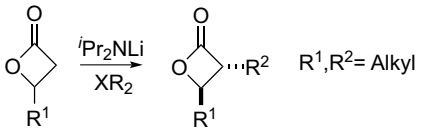


cis/trans : 16/84

Scheme 3.112

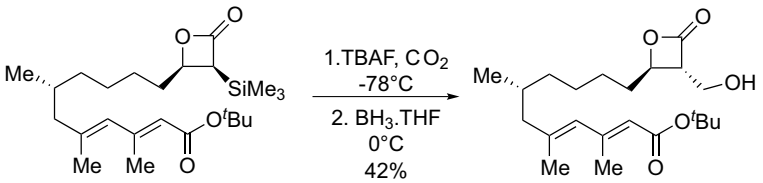
3.2.5.1.4 **Enolate Formation and Reaction Towards Electrophiles** The enolate of β-lactones can be generated by treatment with lithium diisopropylamide and trapped with various electrophiles such as alkyl-, allyl- or propargyl halides, aldehydes,

dimethyl maleate, etc. Diastereoselective reactions take place when oxetan-2-ones are β-substituted, leading to the trans-disubstituted products (Scheme 3.113) [194].



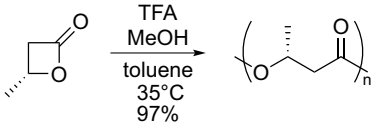
Scheme 3.113

As the alkylation of β-lactones unsubstituted at the α-position leads to low yields, a desilylation–alkylation method has been introduced by Mead *et al.* [211]. Kocienski *et al.* have used this modified procedure, in the synthesis of the hypocholesterolemic agent 1233A, to introduce a hydroxymethyl group α to the carbonyl, via the tetrabutylammonium enolate of a β-lactone (Scheme 3.114) [212].



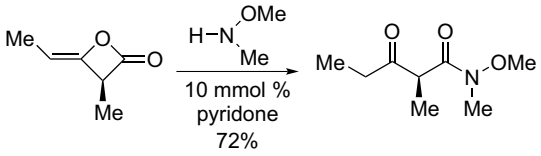
Scheme 3.114

3.2.5.1.5 **Polymerization of β-Lactones** Polymerization of β-lactones has aroused interest as biodegradable polymer products can be applied in biomedical applications [213–215]. Pohl *et al.* [216] have synthesized chiral polyesters by protic acid-catalyzed polymerization of β-lactones. A stereogenic site repeated in each molecular unit can change the polymer properties, in comparison with the racemic polymers (Scheme 3.115).



Scheme 3.115

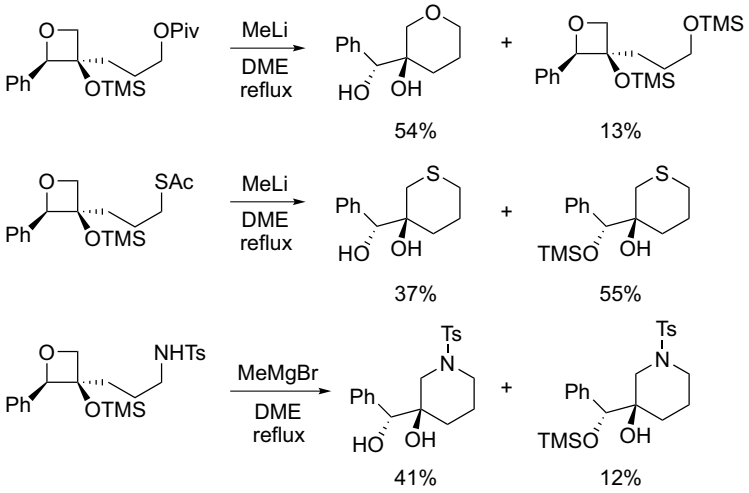
3.2.5.1.6 **Miscellaneous** Methyl ketene dimer has been used to prepare β-ketoesters or β-ketoamides by nucleophilic attack on the carbonyl function by lithium amides or amines (Scheme 3.116) [217].



Scheme 3.116

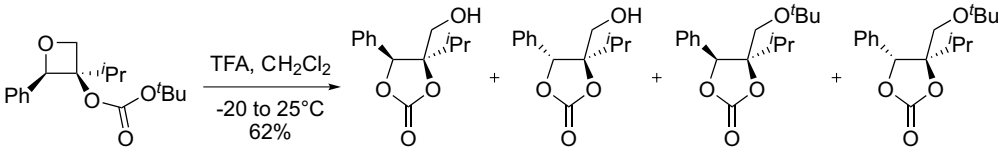
3.2.5.2 Oxetanes

3.2.5.2.1 **Nucleophilic Attacks** Two positions (C2 and C4) in the oxetane are amenable to nucleophilic attack. Bach *et al.* [218] have studied intramolecular ring opening reactions of 2-phenyl-3-oxetanols. They have obtained tetrahydropyrans, thiotetrahydropyrans or piperidines by anionic attack at the C4 carbon atom of a heteroatom attached at the C3 position via an alkyl or aryl chain (Scheme 3.117).



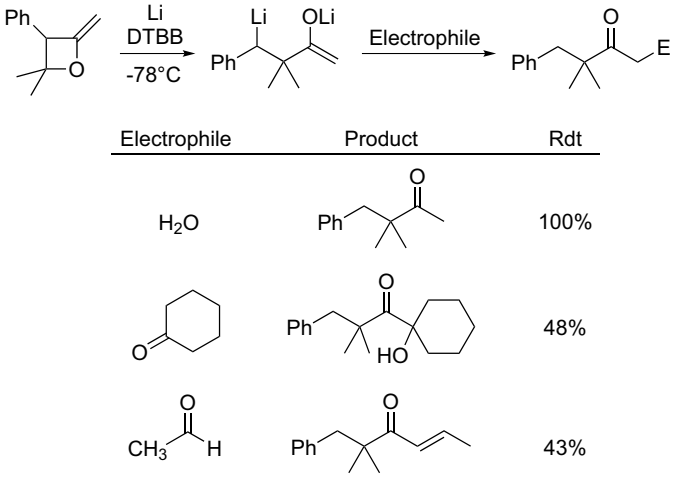
Scheme 3.117

A second ring-opening reaction proceeds by attack at the C2 position upon activation by acid reagents. Boc-protected 3-oxetanols have been transformed into cyclic carbonates as a mixture of diastereomers (Scheme 3.118) [218].



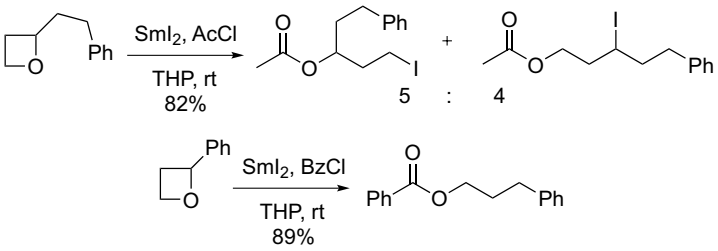
Scheme 3.118

Howell and Hashemzadeh [219] have carried out reductive cleavage of 3,3-dimethyl-2-methylene-4-phenyl oxetane with lithium and 4,4′-di-*tert*-butylbiphenyl (DTBB). The resulting dianion reacts with aldehydes and ketones to give aldol adducts (Scheme 3.119).



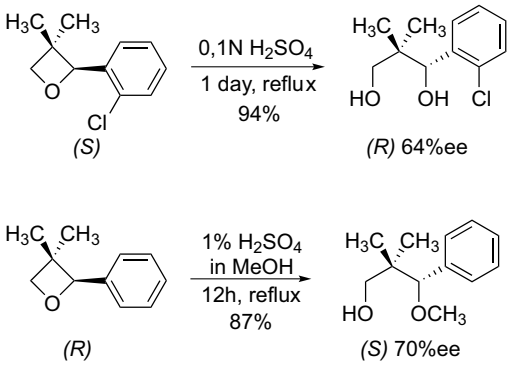
Scheme 3.119

The ring opening of oxetanes by samarium diiodide and acyl chloride has been investigated, but the regioselectivity was not always satisfactory. In general, a mixture of iodo products was obtained. In the particular case of 2-phenyloxetane, only the deiodinated product was isolated (Scheme 3.120) [220].



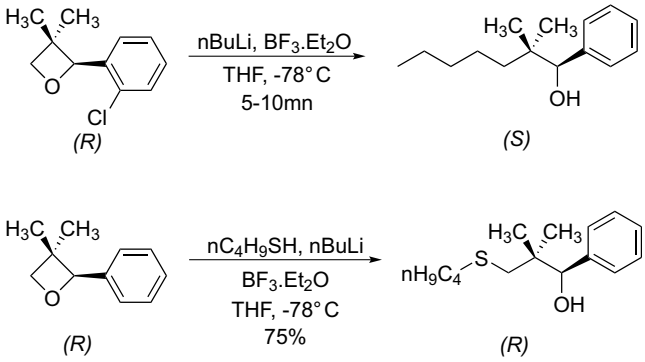
Scheme 3.120

Kellogg *et al.* [221] have studied the acid catalyzed ring opening reactions of optically pure 2-aryl-3,3-dimethyloxetanes. The aqueous or alcoholic sulfuric acid catalyzed ring opening reaction occurs at the benzylic position with partial inversion of configuration (Scheme 3.121).



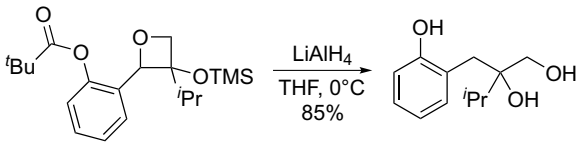
Scheme 3.121

Lewis acid catalyzed nucleophilic ring opening with alkyl lithiums or lithium thiolates occurs at the less hindered carbon with preservation of the stereochemical integrity. Benzyl alcohols are obtained in enantiomerically pure form, with good yields (Scheme 3.122) [221]. Grignard reagents or amines with or without acid catalyst were not successful in the ring opening.



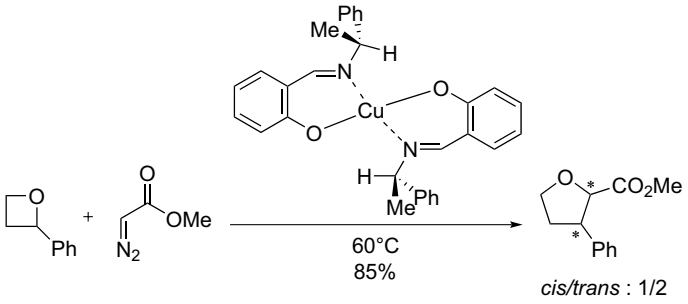
Scheme 3.122

Bach *et al.* [222] have shown that substituted oxetane rings could be opened at the more hindered carbon with $LiAlH_4$. To induce this regioselectivity they attached a hydroxyl group at the arene C2 substituent (Scheme 3.123).



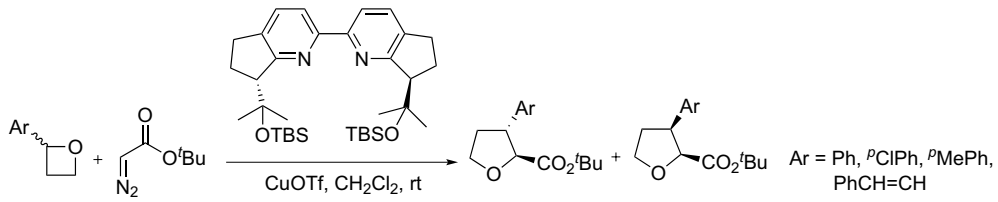
Scheme 3.123

3.2.5.2.2 **Ring Expansions** Nozaki and Noyori first reported in 1966 the asymmetric ring expansion of oxetanes to tetrahydrofurans using chiral copper catalyst (Scheme 3.124) [223].



Scheme 3.124

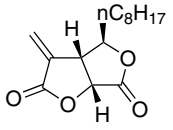
Katzuki has established that this copper-catalyzed reaction proceeds with good stereoselectivity in the presence of bipyridine ligands [224]. Reaction of 2-aryl substituted oxetanes with *tert*-butyl diazoacetate in the presence of a chiral Cu complex furnishes 2,3-disubstituted furan derivatives with high enantiomeric excesses (Scheme 3.125).



(R)-2-Phenyloxetane (89%ee)	Rdt= 35%	89 (92%ee)	11 (16%ee)
(S)-2-Phenyloxetane (85%ee)	Rdt= 30%	25 (11%ee)	75 (93%ee)

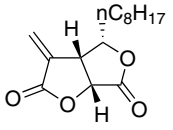
Scheme 3.125

This enantiospecific ring expansion method has been applied to formal syntheses of the natural products (−)-avenaciolide (**29**) and (−)-isoavenaciolide (**30**).



(-)-Avenaciolide

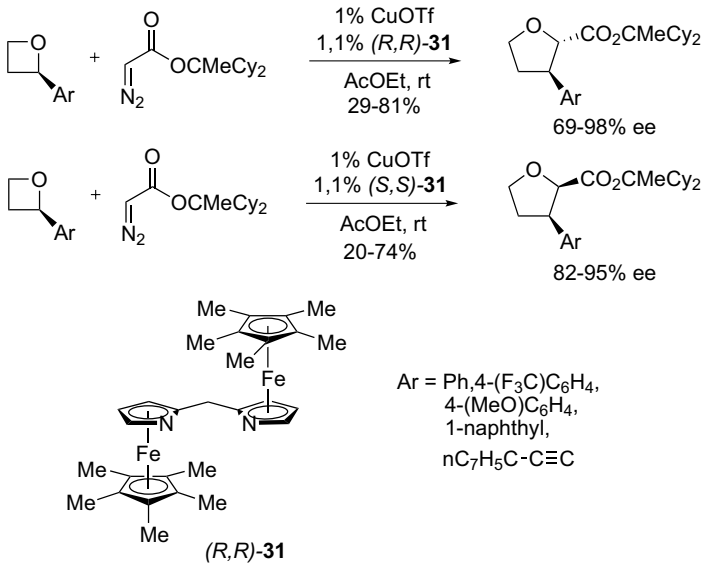
29



(-)-Isoavenaciolide

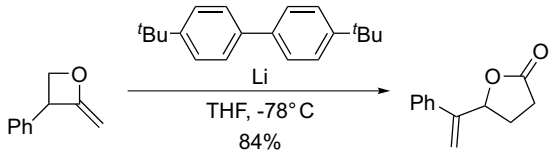
30

Fu *et al.* [225] have explored this reaction with a Cu(I) bisazaferrocene catalyst. Both trans- and cis-disubstituted tetrahydrofurans with good enantiomeric excesses are obtained when (*R,R*) or (*S,S*) catalysts **31** are used respectively (Scheme 3.126).



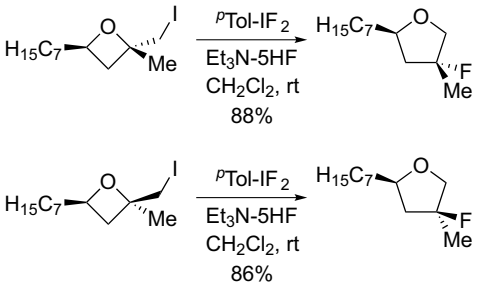
Scheme 3.126

An unusual ring expansion of 2-methyleneoxetane has been observed by Howell *et al.* [226] in the presence of lithium and 4,4′-di-*tert*-butylbiphenyl (Scheme 3.127). The resulting lactone was postulated to arise from a coupling between a radical enolate derived from 2-methyleneoxetane and the acetaldehyde enolate, a decomposition product of THF.



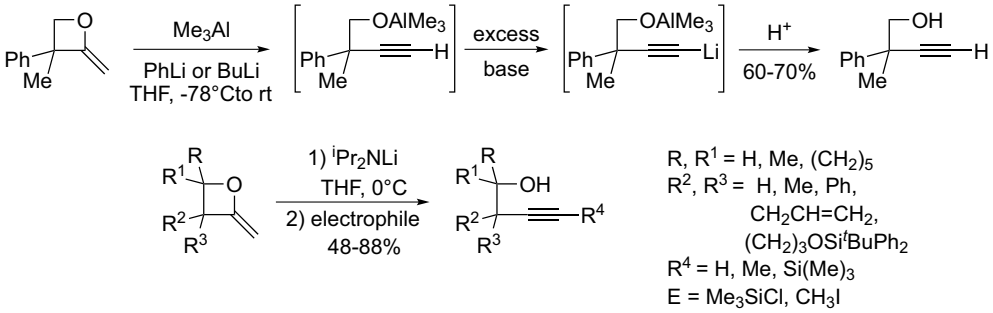
Scheme 3.127

Hara *et al.* [227] have focused on the stereoselective synthesis of fluorinated cyclic ethers, since their derivatives seemed to be involved in biochemical mechanisms. They have reported the ring expansion of oxetanes using 4-iodotoluene difluoride. Fluorinated furans were obtained in good yield and as a single stereoisomer from 2,4-substituted oxetanes (Scheme 3.128).



Scheme 3.128

3.2.5.2.3 **2-Methylene Oxetanes Ring Openings** Howell *et al.* [228] have worked on 2-methyleneoxetane derivatives. This ring system contains several potential reactive features: the ring strain, an exocyclic double bond, electron-rich enol ether and a latent enolate leaving group. They demonstrated that 2-methyleneoxetanes underwent regioselective ring opening at the C2 position when treated with trimethylaluminium and either phenyl- or butyllithium. The homopropargylic alcohol was then isolated as a single product in good yield. The reaction in the presence of LDA, the additive was not necessary (Scheme 3.129).

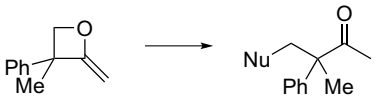


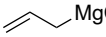
Scheme 3.129

The same group then achieved nucleophilic ring opening of 2-methyleneoxetanes at C4 [229]. Stabilized carbanionic nucleophiles and heteroatom nucleophiles provided C4 ring opening, leading to β-functionalized ketones (Scheme 3.130).

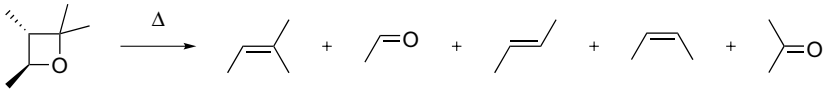
3.2.5.2.4 **Thermolysis and Photolysis** Thermolysis of oxetane derivatives can lead to multiple products from unsymmetrically substituted rings. The lack of regioselectivity has been attributed to similar bond dissociation energies for the carbon–carbon and carbon–oxygen bonds (Scheme 3.131) [132, 133].

Photolytic fragmentation of oxetane is the formal reverse of the Paterno–Büchi reaction. This reaction has attracted some interest as it appears to be involved in the



Conditions	Rdt	Nu
$PhCH_2Li$, BuLi, $PhCH_3$, TMEDA, 0°C	81%	$PhCH_2$
 , THF, reflux	86%	
PhOH, NaH, DMF, 100° C	70%	PhO
NaI, DMF/H_2O, 100°C	40%	I

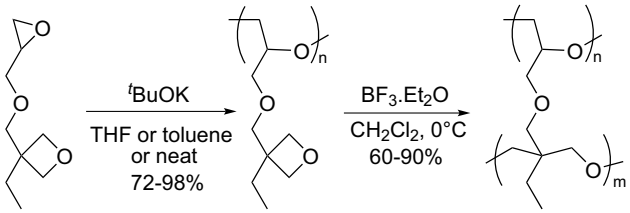
Scheme 3.130



Scheme 3.131

photoenzymatic repair of the (6–4) photoproducts of DNA dipyrimidine sites by the enzyme photolyase [230].

3.2.5.2.5 **Polymerizations** Kakuchi *et al.* [231] have prepared a fused 15-crown-4 polymer, a novel ladder polymer, by a two-step polymerization of an oxetanyl oxirane. This polymer showed metal cation binding properties (Scheme 3.132).



Scheme 3.132

3.3 Thietanes

3.3.1 Introduction

Thietanes have received much less attention than azetidines and oxetanes. Some reviews have, though, been published on their chemistry [232–234]. The ring strain of thietane (80 kJ mol^{-1}) is comparable to that of thiirane (three-membered ring). This

explains their difficult formation by ring closure and, conversely, their easy cleavage by electrophilic and nucleophilic reagents.

3.3.2
Physicochemical Data

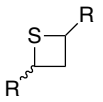
Conformations of 3-substituted thietanes 1-oxide have been studied [235]. *Ab initio* SCF calculations (G-31G* level) of thietanes examined the change of C–C bond lengths and angular deformations [236] compared to sulfur heterocycles of higher ring sizes. Calculations on the reaction of thietane with NH_3 explained the greater reactivity of this compound compared to oxetane [237]. Calculations concerning the ring closure of $HS(CH_2)_3S$- to thietane were also reported [238].

Details concerning the NMR spectroscopy of thietane derivatives have been reported in previous reviews [232, 233]. The α-protons of thietane appear at δ 3.21 ppm (4.09 for thietane 1,1-dioxide). The ^{13}C NMR chemical shifts have been reported to be at 25 ppm for the α-carbons and 27 ppm for the β-carbon. The α-carbon shifts in thietanes appear in general at higher field than those of the β-carbon [233]. The ^{33}S NMR spectra of thietane, thietane 1-oxide and thietane 1,1-dioxide have been recorded [239]. In mass spectra, the main fragmentation includes retro [2 + 2] cycloaddition for thietanes, thiolactones and iminothietanes, and loss of, respectively, SO and SO_2 for thietane 1-oxides and thietane 1,1-dioxides [232].

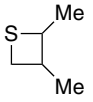
3.3.3
Natural and Bioactive Compounds

Mono and dialkyl thietanes **32–35** have been detected in anal gland secretions of small mammals (ferrets, polecats, stoats, minks, weasels, kiores, voles, etc.).

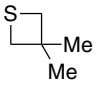
32 R = Me, Et, Pr, ^{i}Pr



33 R = Me, Et

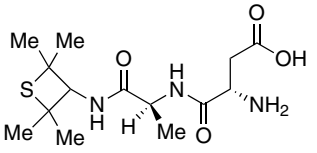


34



35

L-α-Aspartyl-*N*-(2,2,4,4-tetramethyl-3-thietanyl)-D-alaninamide (**36**), a sweetener that is 2000× more efficient than sugar, has been developed by Pfizer under the name Alitame [240] and commercialized in different countries.

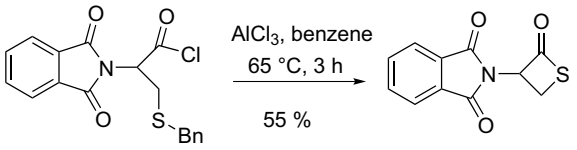


36

3.3.4 Synthesis of Thietanes

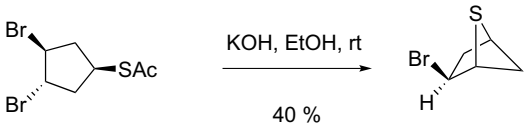
3.3.4.1 Synthesis by Formation of a S–C Bond

3.3.4.1.1 Formation from 3-Halo Thiol Derivatives The reaction of *S*-benzyl-*N*-phthaloylcysteinyl chloride with two equivalents of $AlCl_3$ affords the corresponding thiolactone (Scheme 3.133) [241]. Similar result was obtained for the free thiol function.



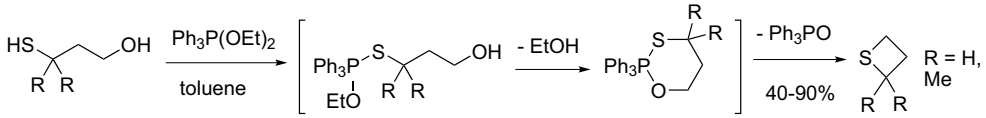
Scheme 3.133

Intramolecular reaction of thiolate, generated by base cleavage of thioacetate, on a secondary bromide leads to a bridged thietane [242] (Scheme 3.134). This approach to thietanes has been little studied.



Scheme 3.134

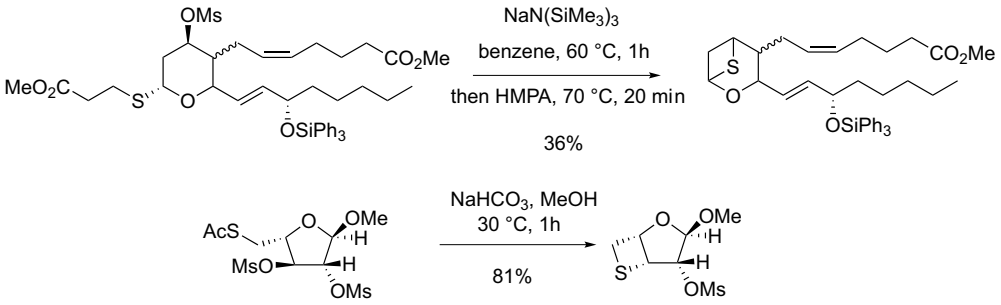
3.3.4.1.2 Formation from 3-Hydroxy Thiol Derivatives Cyclization of 4-thio-4-methylbutanol into 2,2-dimethylthietane occurs in high yield when diethoxytriphenylphosphorane is used as reagent (Scheme 3.135) [243].



Scheme 3.135

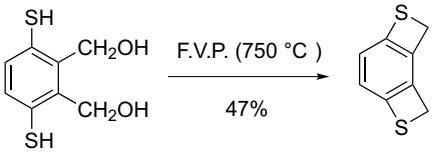
Sulfur analogues of thromboxane A_2 are obtained when the alcohol function is activated as mesylate [244] (Scheme 3.136). Nucleoside derivatives have also been obtained by a similar procedure [245].

Flash vacuum pyrolysis (500–750 °C) of (2-mercaptophenyl)methanol derivatives leads to the formation of thietanes, generally in good yields. For example, heating at



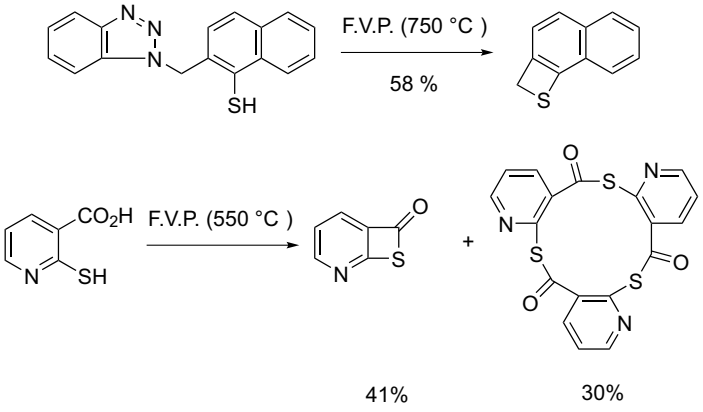
Scheme 3.136

750 °C of (3,6-dimercapto-1,2-phenylene)dimethanol furnishes 4,9-dithiatricyclo [6.2.0.0^{2,5}]deca-1,5,7-triene, which appears to be stable under 90 °C (Scheme 3.137) [246].



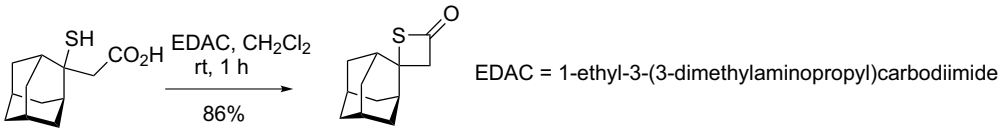
Scheme 3.137

Such thermal formation of thietanes was shown to be possible when benzotriazoles [247] or acids [248] were present as reaction groups instead of alcohol functions (Scheme 3.138).



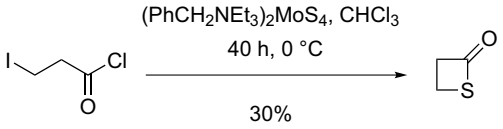
Scheme 3.138

Thietan-2-ones are formed by the reaction of 3-mercaptocarboxylic acids with DCC [249], ^{t}butyl chloroformate [250], methyl chloroformate [251], Ac_2O [252], diethyl cyanophosphonate [253] or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDAC) (Scheme 3.139) [254].



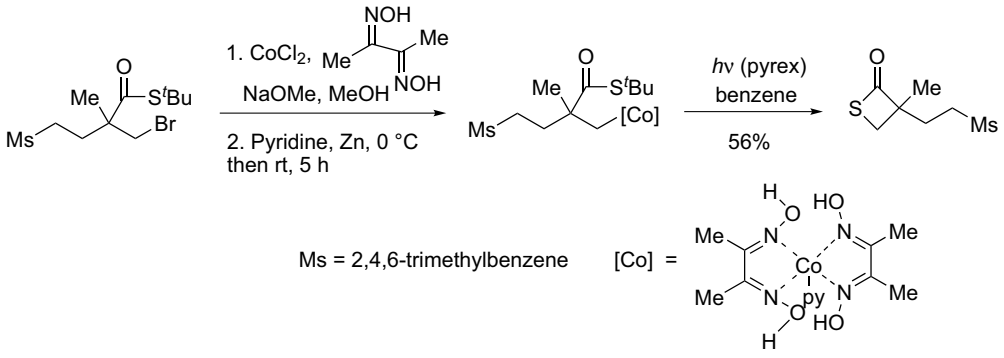
Scheme 3.139

An original preparation of thietan-2-one has also been reported: the reaction of 3-iodopropanoyl chloride with an ammonium tetrathiomolybdate salt (Scheme 3.140) [255].



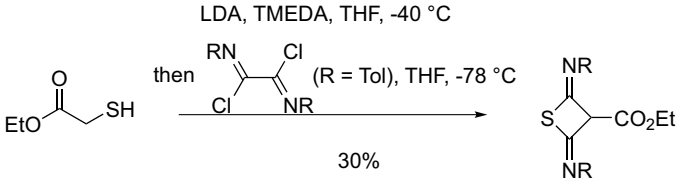
Scheme 3.140

3.3.4.1.3 **Formation from Other 3-Functionalized Thiol Derivatives** α-Bromomethyl thioesters react with cobalt oximes to give the corresponding organocobalt compounds that, under photolysis, afford thietanes. This method appears synthetically useful only for the structure reported in Scheme 3.141 [256].



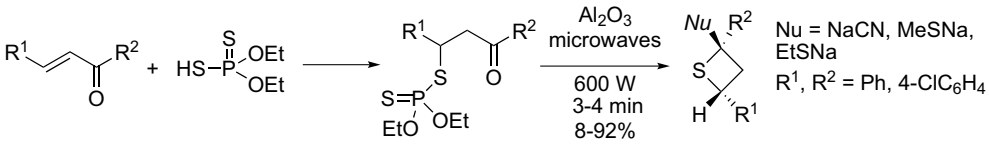
Scheme 3.141

Reaction of ethyl 2-mercaptoacetate with LDA followed by addition of a dichlorodiimine gives a 2,3-diiminothietane derivative (Scheme 3.142) [257]. When the R groups fixed at the nitrogen atoms were phenyl or 4-methoxyphenyl, the 2,3-diiminothietanes were not isolated, due to their ring opening in the reaction mixture.



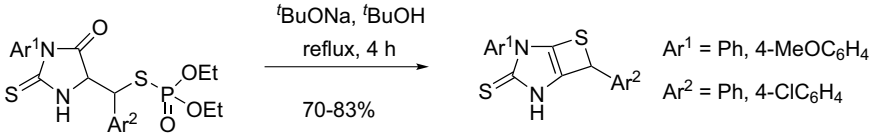
Scheme 3.142

1,4-Addition of *O,O*-diethyl hydrogen dithiophosphate on the carbon–carbon double bond of chalcones affords a compound that then, under microwave irradiation in the presence of nucleophiles, gives thietanes (Scheme 3.143) [258]. This reaction was previously reported to occur by heating in the presence of a NaH–$NaBH_4$ mixture [259].



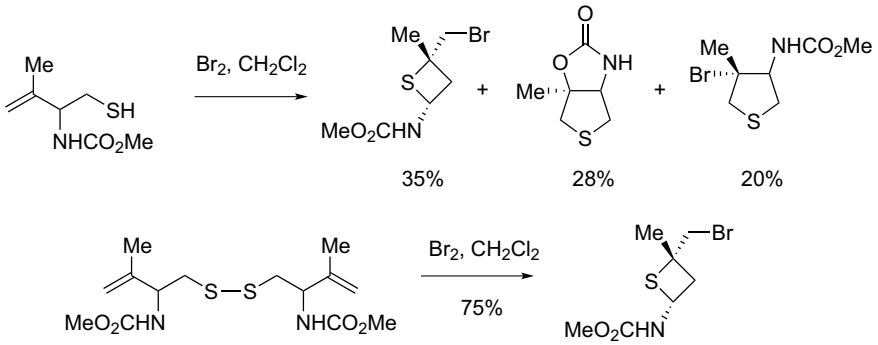
Scheme 3.143

5-Substituted 2-thiooxoimidazolidin-4-ones react with sodium *tert*-butylate to yield bicyclothietenes (Scheme 3.144) [260].



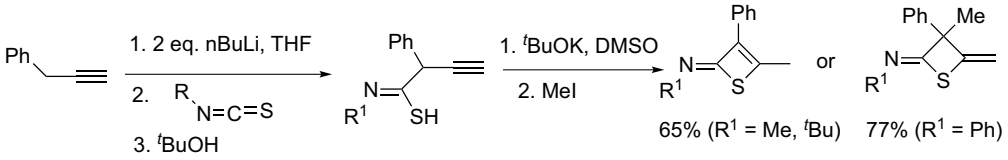
Scheme 3.144

Thietanes are rarely formed by electrophile-induced cyclizations of unsaturated sulfides [261]. A thietane is obtained in mixture with other products by reaction of a γ-unsaturated thiol with bromine (Scheme 3.145). Utilization of the corresponding disulfide allowed exclusive formation of the expected thietane [262].



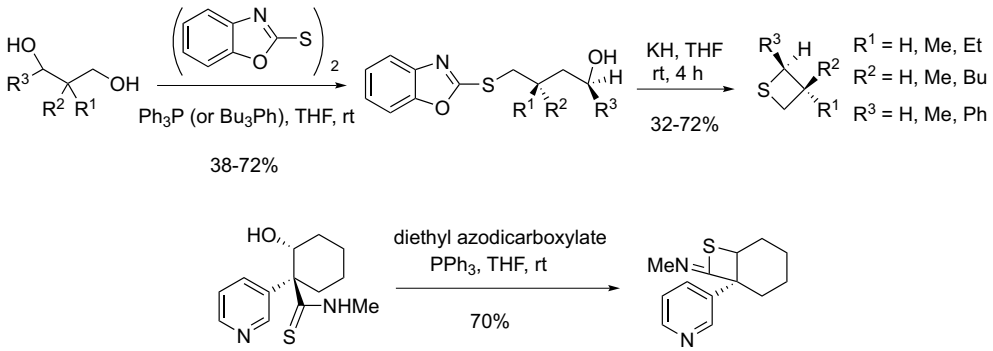
Scheme 3.145

The dianion of 1-(prop-2-ynyl)benzene reacts with phenyl thioisocyanate to give a thioimidate that, by reaction with potassium ^{t}butylate, leads to the formation of a thietane (Scheme 3.146) [263].



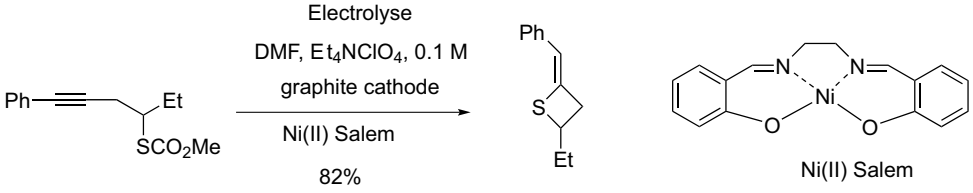
Scheme 3.146

An efficient preparation of thietanes in two steps occurs by reaction of 1,3-diols with dibenzoxazol-2-yl disulfide and tributylphosphine, followed by treatment of the resulting 2-(3-hydroxyalkylthio)benzoxazoles with KH (Scheme 3.147) [264]. The thio-Mitsunobu reaction applied to thioamides gives rise to the formation of α-iminothietanes (Scheme 3.147) [265].



Scheme 3.147

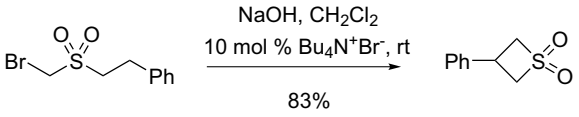
The formation of thietanes is also possible by electroreduction in the presence of Ni(II) salem as catalyst (Scheme 3.148) [266].



Scheme 3.148

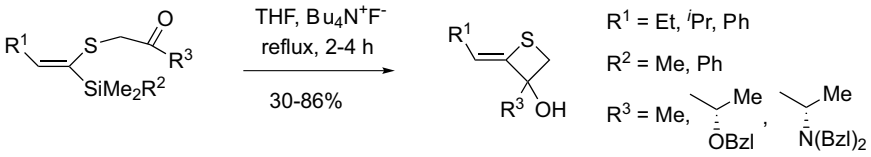
3.3.4.2 Synthesis by Formation of a C–C Bond

Under phase transfer catalysis conditions, 1-bromomethylsulfonyl-2-phenylethane affords, in the presence of sodium hydroxide, 2-phenylthietane-1,1-dioxide, via intramolecular cyclization of the benzyl anion. The Ramberg–Bäcklund product is not observed (Scheme 3.149) [267].



Scheme 3.149

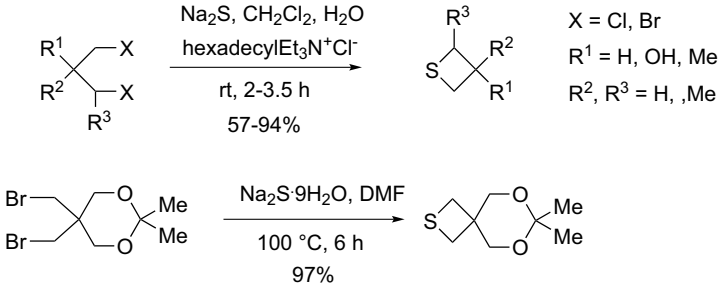
Thietanols can be formed by fluoride-mediated cyclization of (*Z*)-α-silyl vinylsulfides (Scheme 3.150) [268].



Scheme 3.150

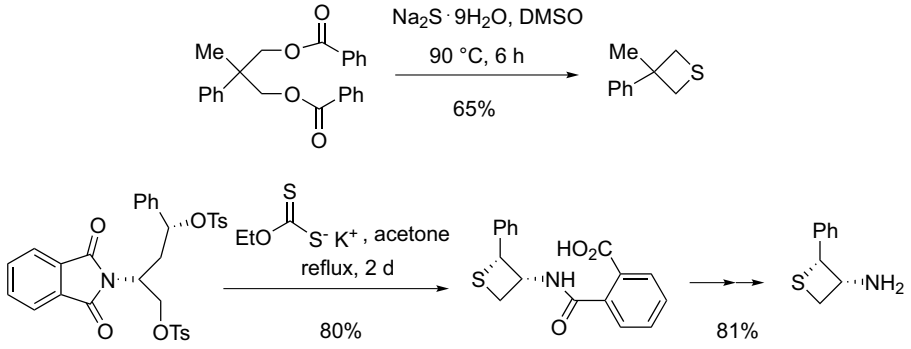
3.3.4.3 Synthesis by Formation of Two S–C Bonds

The oldest method for the preparation of thietanes involves the reaction of 1,3-dihalides with sodium sulfide. Numerous conditions have been studied [232, 233]. Excellent results have been reported for phase transfer conditions (Scheme 3.151) [269]. A spiro thietane is formed upon reaction of a 1,3-dibromo derivative with Na_2S in DMF [270].



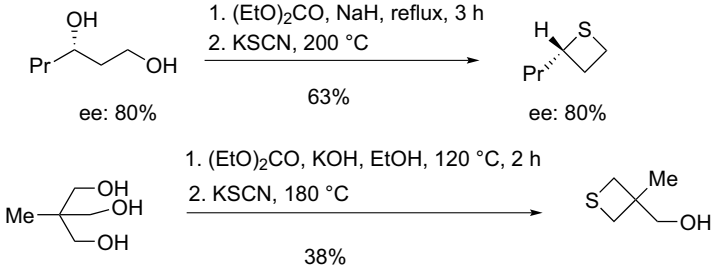
Scheme 3.151

Derivatives of 1,3-diol benzoates (Scheme 3.152) [271], mesylates [272] and tosylates (Scheme 3.152) [273] were also efficient in these preparations.



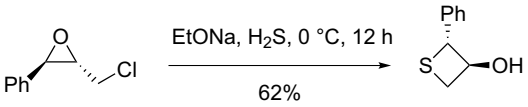
Scheme 3.152

1,3-Diols protected as carbonates can also lead to thietanes by reaction with KSCN at high temperature. This method has been reported for the preparation of *(S)*-2-propylthietane, which is a natural product (Section 3.3.3) (Scheme 3.153) [274]. This procedure was used more recently in the case of a 1,2,3-propane triol derivative [275].



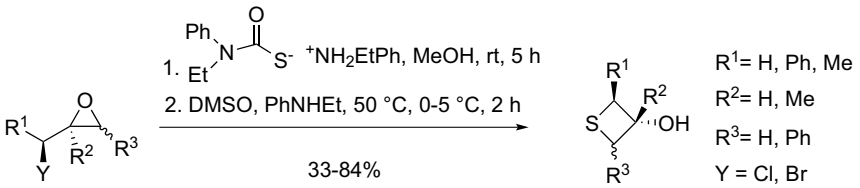
Scheme 3.153

Reactions of β-halo epoxides with different sulfur reagents give rise to 3-thietanols in good yields. The first sulfur reagent used was H_2S in the presence of sodium ethoxide (Scheme 3.154) [276], or $Ba(OH)_2$ [277].



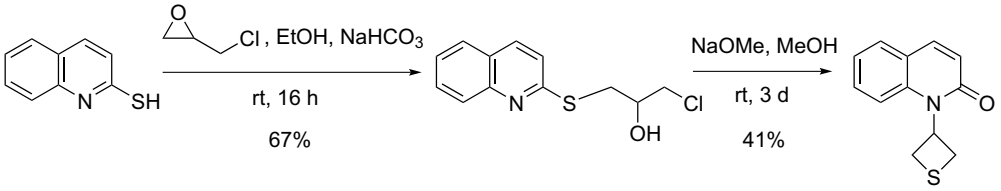
Scheme 3.154

Reactions of Li_2S [278] and benzyltriethylammonium tetrathiomolybdate [279], ammonium thiocarbamates (Scheme 3.155) [280] and thioacetate [281] with β-halooxiranes are very efficient.



Scheme 3.155

Thiols react with epichlorohydrin to give the corresponding addition products, which are then transformed into thietanes when reacted with sodium methoxide (Scheme 3.156) [282].

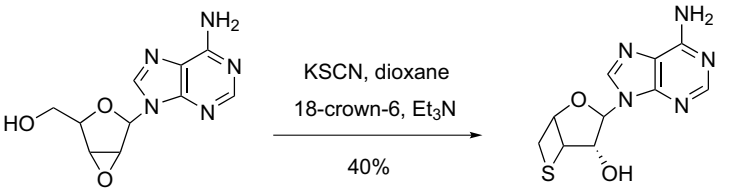


Scheme 3.156

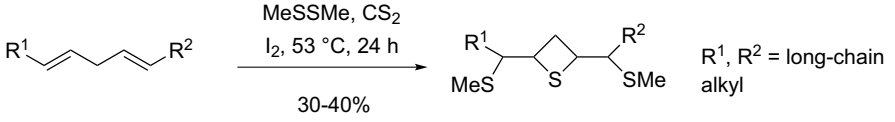
The formation of thietanes by reaction of γ-hydroxyoxiranes with potassium thiocyanate has been also reported (Scheme 3.157) [283].

Thietanes can also be formed by radical addition of dimethyl disulfide on 1,3-dienes, by heating in the presence of iodine (Scheme 3.158) [284].

Electrophilic addition of SCl_2 [285], a mixture of $POCl_3$ (or $POBr_3$)/thiobismorpholine [286] or SO_2 (Scheme 3.159) [287] with norbornadiene produces thietane

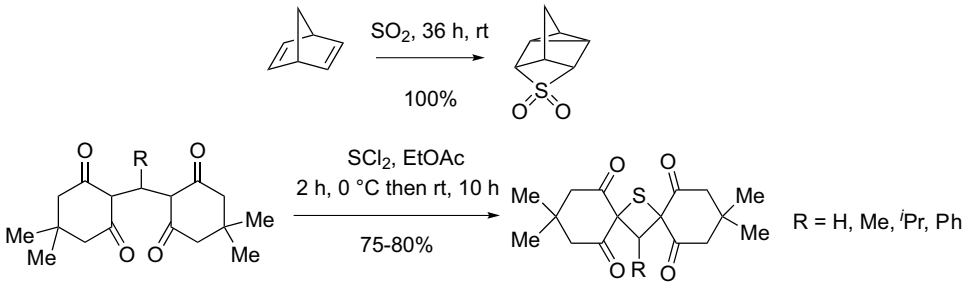


Scheme 3.157



Scheme 3.158

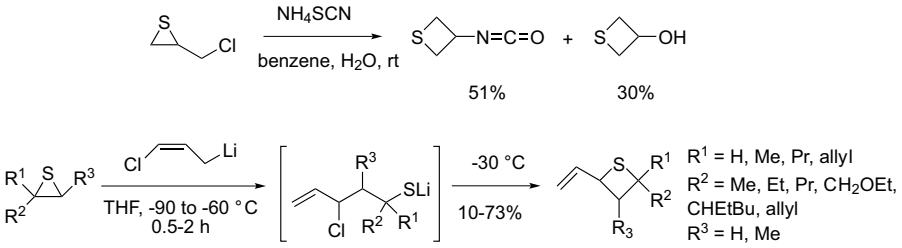
derivatives. The reaction of SCl_2 with δ-diketones leads to thietanes in good yields (Scheme 3.159) [288].



Scheme 3.159

3.3.4.4 Synthesis from Other Sulfur Heterocycles

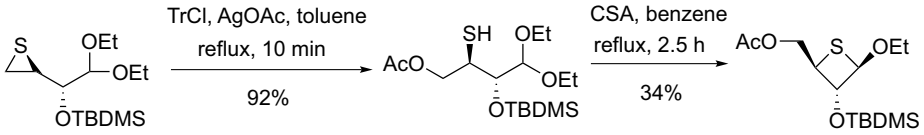
3.3.4.4.1 **Formation from Thiirane Derivatives** The reaction of 2-(chloromethyl) thiirane with sodium acetate gives the corresponding thietane in 82% yield [289]. Similar ring expansions were reported using ammonium thiocyanate (Scheme 3.160)



Scheme 3.160

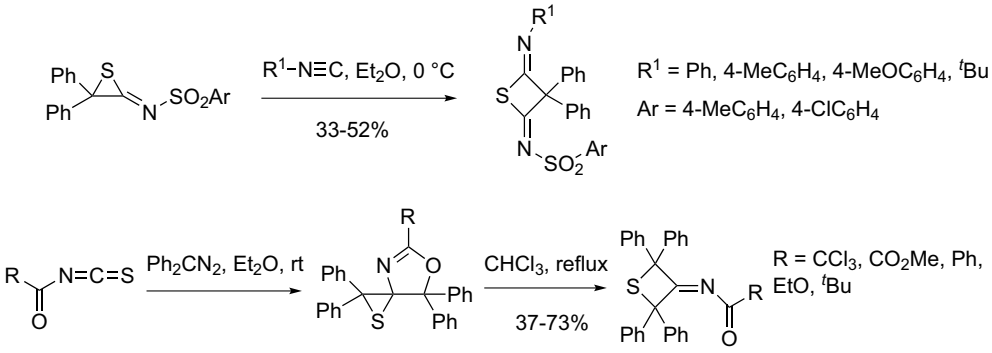
[290], sulfonamides [291] and phenates [291], or from (thiiran-2-yl)methanol under the conditions of the Mitsunobu reaction [292]. Addition of allyl lithium compounds with thiiranes gives rise to thietanes in good yields (Scheme 3.160) [293].

An optically active thiirane has been transformed into a thietane, without epimerization of the chiral centers, in two steps by reaction with silver acetate followed by cyclization of the resultant 3-mercaptoacetal by camphor sulfonic acid (CSA) (Scheme 3.161) [294].



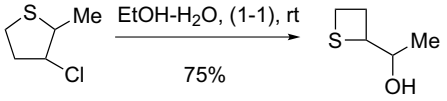
Scheme 3.161

Iminothiiranes react with isocyanates to afford 2,4-diiminothietanes (Scheme 3.162) [295]. This rearrangement of thiiranes into thietanes has also been reported during the reaction of diphenyl diazomethane with acyl isothiocyanate [296].



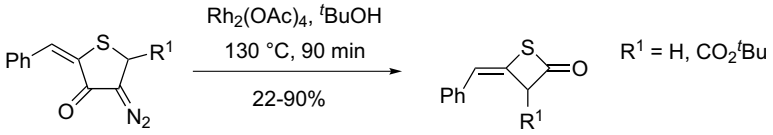
Scheme 3.162

3.3.4.4.2 **Formation from Thiolanes and Derivatives** 3-Chlorotetrahydro-2-methylthiophene reacts with water to give the 2-substituted thietane (Scheme 3.163) [297]. This reaction is reversible, since under acidic conditions (HCl) the tetrahydrothiophene was reformed.



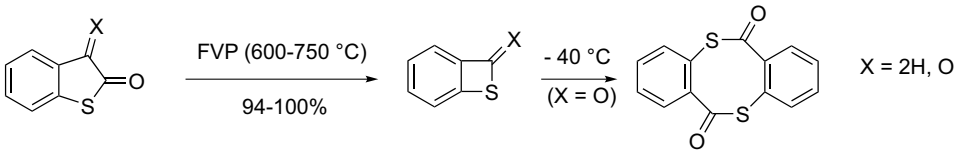
Scheme 3.163

4-Diazodihydrothiophen-3(2*H*)-one derivatives undergo ring contraction to thietan-2-ones upon heating in isooctane [298], irradiation in an alcohol [299] or in the presence of rhodium diacetate (Scheme 3.164) [300].



Scheme 3.164

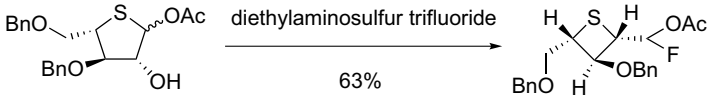
Flash-thermolysis of benzothiophen-2(3*H*)-one (Scheme 3.165; X = 2H) [299] or benzothiophen-2,3-dione (Scheme 3.165: X = O) [301] gives rise to the corresponding thietanes in excellent yields.



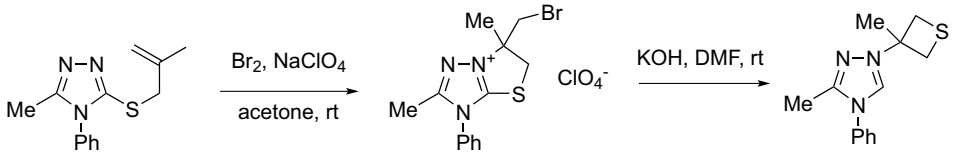
Scheme 3.165

Treatment of a 4-thiofuranose derivatives with diethylaminosulfur trifluoride (DAST) leads to the formation of the ring contraction product (Scheme 3.166) [302].

Rearrangement of thiazolotriazoliums, formed by electrophilic addition of bromine on 3-methallylthiotriazoles in basic conditions, affords thietanes (Scheme 3.167) [303]. The same rearrangement was observed with benzimidazole, benzothiazole and imidazole derivatives.

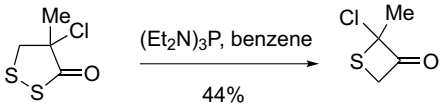


Scheme 3.166



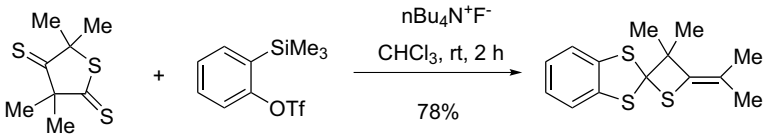
Scheme 3.167

Monodesulfurization of 1,2-dithiolanone with triphenylphosphine or tris(diethylamino)phosphine gives the thietanone in medium yields (Scheme 3.168) [304]. An attempt to use this method for the preparation of optically active thietanes was unsuccessful [305].



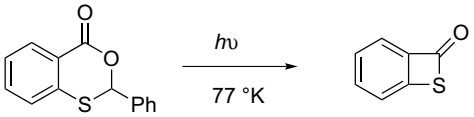
Scheme 3.168

Reaction of benzyne with a thiophen-2,4-dithione gives a 2-thioacetal thietane in good yield (Scheme 3.169) [306].



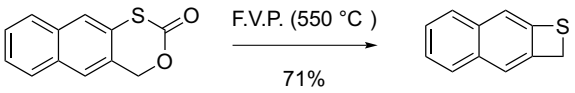
Scheme 3.169

3.3.4.4.3 **Formation for Thiopyranes and Higher Ring Size Thio Heterocycles** Irradiation at low temperature of a 1,3-oxathian-6-one has been reported to lead to an unstable thianone, which leads to the formation of a dimer at room temperature (Scheme 3.170) [301].



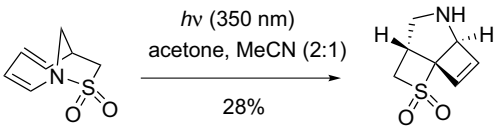
Scheme 3.170

CO_2 is extruded during the flash-thermolysis of 1,3-oxathian-2-ones, affording thietanes that have been isolated in good yields (Scheme 3.171) [307].



Scheme 3.171

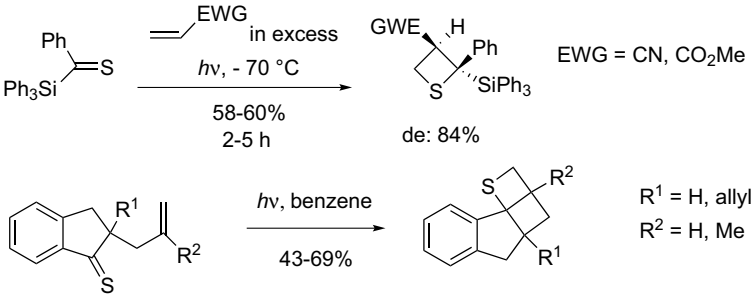
Ultraviolet irradiation of 1-aza-8-thiacylo[4.2.1]non-2,4-diene-8,8-dioxide yields an unusual tricyclic compound (Scheme 3.172) [308].



Scheme 3.172

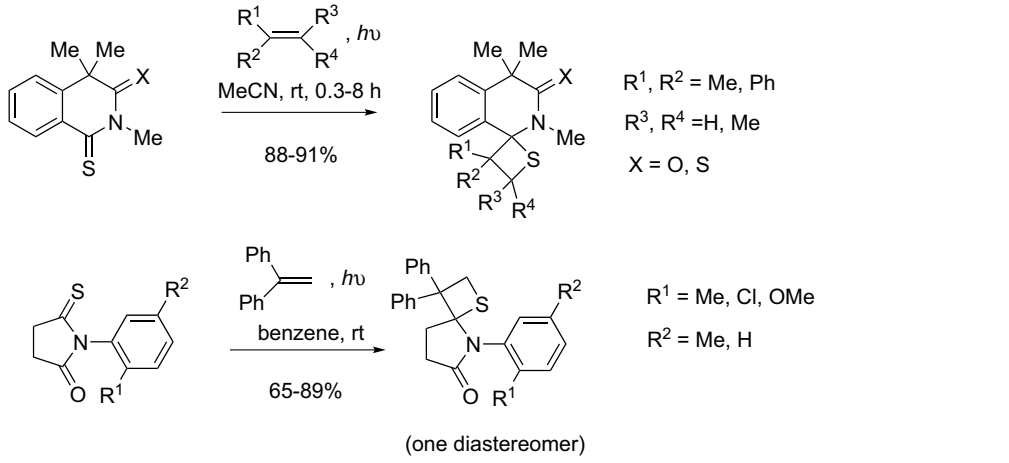
3.3.4.5 Synthesis by [2 + 2] Cycloaddition

Photochemical cycloadditions of thiones with unsaturated compounds have received considerable attention. Aromatic, aliphatic and α,β-unsaturated thioketones react as well with electron-poor rather than electron-rich olefins [232–234]. The more recent result concerns the reaction of silyl thioketones, which can be seen as an equivalent of thioaldehydes, with olefins. Irradiation of phenyl triphenylsilyl thioketone in acrylonitrile, methyl acrylate and *cis*- or *trans*-1,2-dichloroethene give the silylthietanes with high regio- and stereoselectivity (Scheme 3.173) [309]. Lower yields and selectivities are observed during the reaction with vinyl ether. Subsequent protiodesilylation reactions take place with predominant inversion of configuration at the carbon bearing the silicon group. The intramolecular cyclization of thiones was reported to be very efficient (Scheme 3.173) [310].

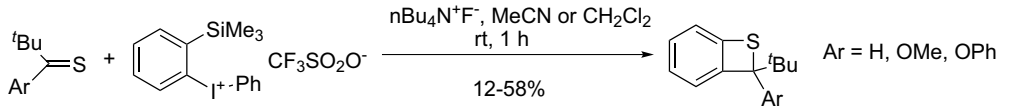


Scheme 3.173

Photochemical additions of olefins on the thiocarbonyl function of thioxo-3,4-dihydroisoquinolinones (Scheme 3.174) [311], benzooxazole-2-thione [312] and 5-thioxopyrrolidinones (Scheme 3.174) [313] have been reported. [2 + 2] Cycloadditions of thiopivalophenones were also reported by reaction with benzyne (Scheme 3.175) [314].

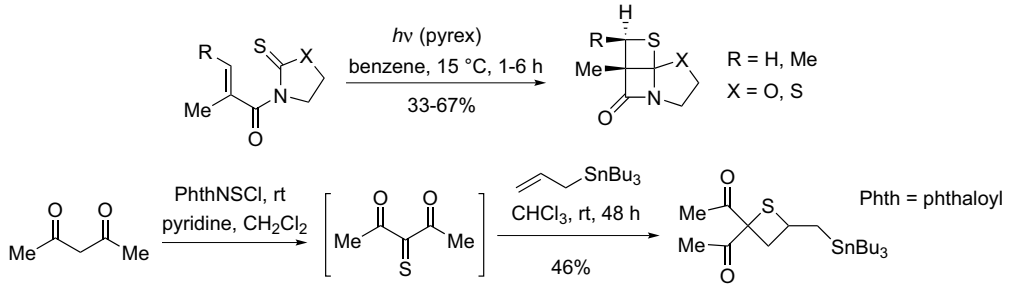


Scheme 3.174



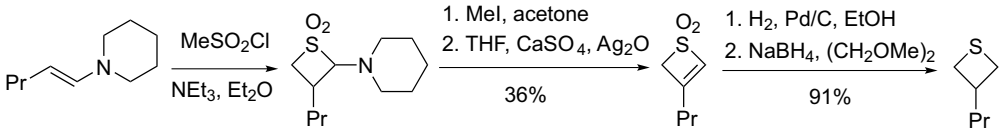
Scheme 3.175

Intramolecular cyclizations of unsaturated N-ethanethioylacetamide derivatives have also furnish tricyclic thietanes (Scheme 3.176) [315]. Cycloaddition of 2,4-dioxopenta-3-thione with allyltributyltin occurs at room temperature [316].



Scheme 3.176

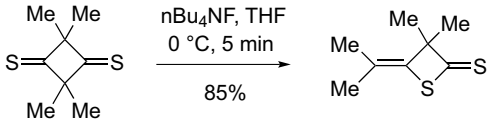
Thietene-1,1-dioxides, which are precursors of thietanes, can be obtained by reaction of enamines with methanesulfonyl chloride in the presence of triethylamine (Scheme 3.177) [317]. Cycloadditions of acrylates with alkyl(chlorosulfonyl)acetate was reported to lead to 2-carboxylate thietanes [318].



Scheme 3.177

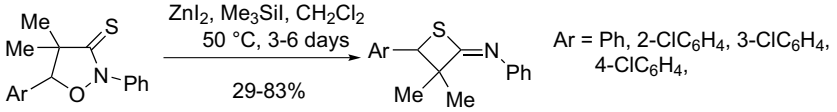
3.3.4.6 Synthesis by Miscellaneous Methods

Isomerization of cyclobutane-1,3-dithiones into thietanones occurs in the presence of strong bases [319]. Utilization of tetrabutylammonium fluoride, allows a transformation under milder conditions (Scheme 3.178) [320]. The same product is obtained by reaction of the cyclobutane-1,3-dione with P_4S_{10} at reflux in pyridine [321].



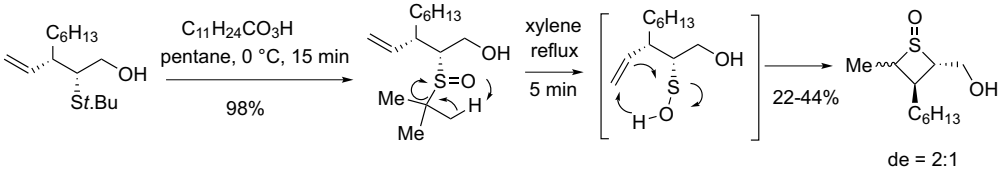
Scheme 3.178

Isoxazolidine-3-thiones react with ZnI_2 in chloroform to give 2-iminothietanes (Scheme 3.179) [322].



Scheme 3.179

An interesting preparation of thietan-1-oxides involves the reaction of ^{t}butyl sulfide with peroxydodecanoic acid (Scheme 3.180). Mixtures of diastereomers were obtained [323].

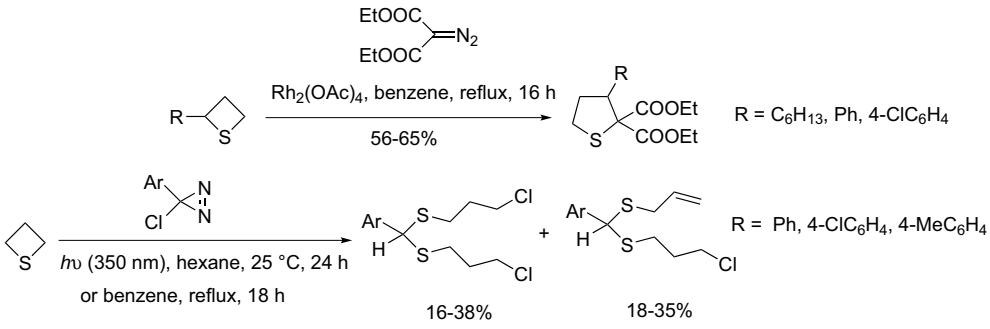


Scheme 3.180

3.3.5 Reactivity and Useful Reactions

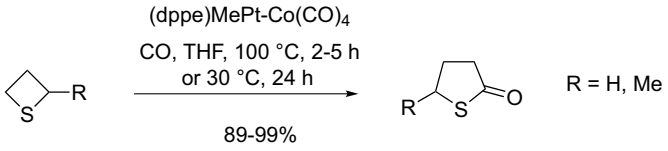
3.3.5.1 Reactions with Electrophilic Reagents

Thietanes react with ethyl diazoacetate [324] or diethyl diazomalonate [325] in the presence of rhodium acetate to give ring expansion products. When the carbenes are generated from diaziridines, ring-opening compounds are obtained (Scheme 3.181) [326].



Scheme 3.181

The reaction of 2- or 3-substituted thietanes with cobalt or ruthenium carbonyl [$Co_2(CO)_8$ or $Ru_3(CO)_{12}$] produces dihydrothiophenones in good yields [327]. More recently, it has been shown that platinum salts can catalyze this CO insertion (Scheme 3.182) [328]. However, these reactions were not observed with 2,4-disubstituted thietanes.

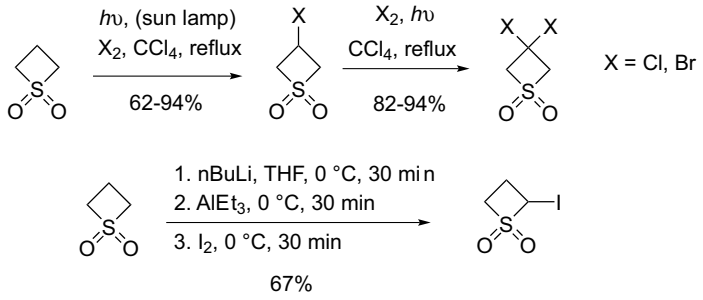


Scheme 3.182

Thietanes undergo ring opening by reaction with chloro reagents [232]. However, mono- or di-chlorinations and brominations of thietane-1,1-dioxides occur easily on C3 by irradiation [329]. 2-Iodination has also been reported by reaction with butyllithium, followed by addition of triethylaluminium and iodine (Scheme 3.183) [330].

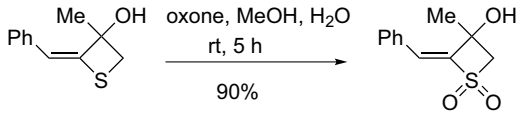
3.3.5.2 Reactions with Oxidizing Agents

Oxidations of thietanes to thietanes-1-oxides and thietane-1,1-dioxides have been reported with the reagents generally used in the case of dialkyl sulfides: $KMnO_4$,



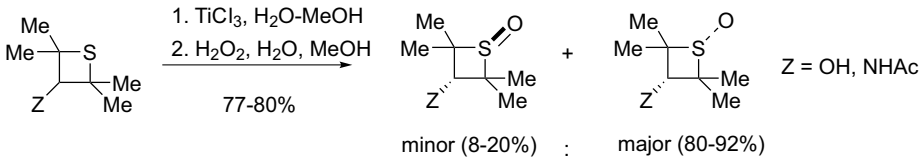
Scheme 3.183

*m*CPBA, $NaIO_4$, H_2O_2 in CH_3COOH or in presence of WO_3-H_2O, CrO_3 [232, 233]. Other reagents have been tested with success, such as cat. OsO_4-4-methylmorpholine *N*-oxide [331], 2-(phenylsulfonyl)-3-phenyl-oxaziridine [332], monoperphthalic acid [333], ^{t}pentyl hydroperoxide in the presence of $MoCl_5$ [334], oxone (Scheme 3.184) [309b] or 1-butyl-4-aza-1-azoniabicyclo[2.2.2]octane dichromate [335].



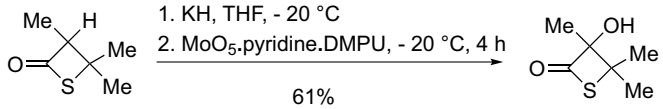
Scheme 3.184

The diastereoselectivity of the formation of thietane-1-oxides from thietanes has been examined using *m*CPBA [336]. Better selectivities have been reported using H_2O_2 in the presence of $TiCl_3$ (Scheme 3.185) [337].



Scheme 3.185

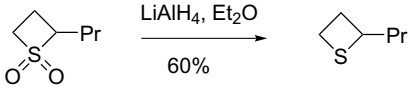
The potassium enolate of a thietan-2-one reacts with MoO_5 to give the corresponding α-hydroxythietanone (Scheme 3.186) [253].



Scheme 3.186

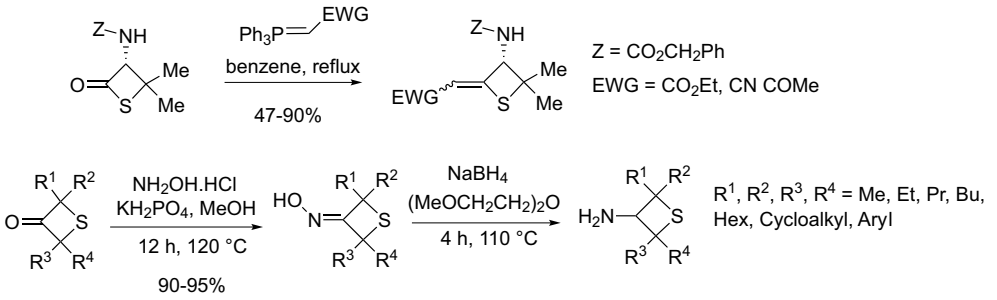
3.3.5.3 Reactions with Nucleophilic Reagents

Thietane-1,1-dioxides have been reduced to thietanes by reaction with $LiAlH_4$ (Scheme 3.187) [317]. Reduction of thietane-1-oxides and sulfimides have been reported with a mixture $MeSiCl_2$-Zn [338].



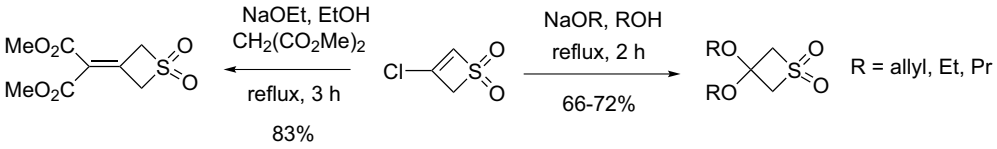
Scheme 3.187

2-Thietanones react with stabilized phosphoranes to give the corresponding *(E)*- and *(Z)*-2-alkylidenethietanes (Scheme 3.188) [339]. 3-Thietanones are easily transformed into the corresponding N-hydroxyimines; subsequent reaction with $NaBH_4$ led to 3-aminothietanes (Scheme 3.188) [340].



Scheme 3.188

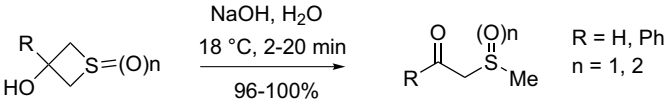
Additions of nucleophiles or 3-chlorothieten-1,1-dioxide affords products without cleavage of the thietane ring. By reaction of sodium ethanoate the corresponding 3-acetal was obtained, while with sodium dimethyl malonate, the 3-alkylidenethietane was formed (Scheme 3.189) [329b].



Scheme 3.189

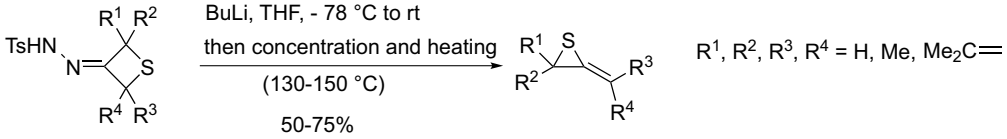
3.3.5.4 Reactions with Bases

Thietanes are readily opened by reaction with sodium hydroxide to give linear sulfurs or polymerization products, depending on their structure [341]. With 3-hydroxythietane-1-oxides, ketones were obtained (Scheme 3.190).



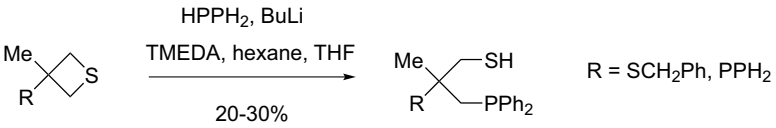
Scheme 3.190

Thiiranes have been formed by pyrolysis of lithium salts of hydrazones formed from thietan-3-ones (Scheme 3.191) [342].



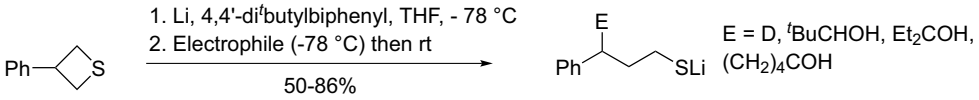
Scheme 3.191

Thietanes react with lithium diphenylphosphine to give the opened products in modest yields (Scheme 3.192) [275].



Scheme 3.192

Reaction of 2-phenylthietane with 4,4′-di-*t*-butylbiphenyllithium (DTBB-Li) has been reported to produce a dianion, which can react with electrophiles (Scheme 3.193) [343]. This reaction was not observed when starting with 2-methylthietane. With CO_2 as electrophile, dihydro-3-phenylthiophen-2(3*H*)-one was formed.

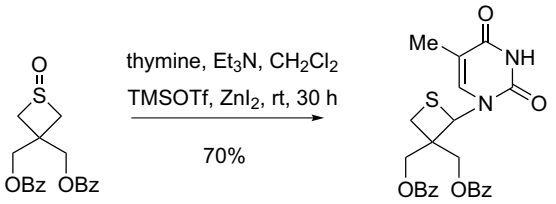


Scheme 3.193

Thietane-1-oxides undergo Pummerer rearrangements, when treated with Lewis acids in the presence of amino bases. This method has been used for the preparation of thietane nucleosides (Scheme 3.194) [264, 267, 344].

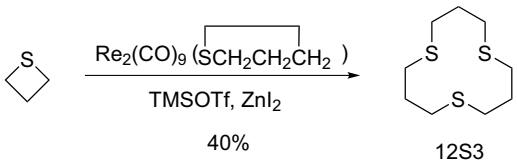
3.3.5.5 Reactions with Metal Complexes and Salts

Thietane is transformed into crown thio ethers (12S3, 16S4, 18S6, etc.) by the reaction of $Re_2(CO)_9$(thietane), $Os_4(CO)_{11}$(thietane) and $W(CO)_5$(thietane). Yields of 40%



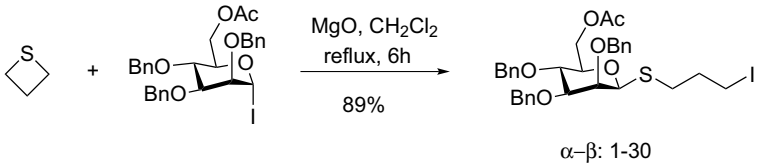
Scheme 3.194

were reported for the formation of the 12S3 crown ether (Scheme 3.195) [345]. This transformation is possible with 2- and 3-methylthietanes and 3,3-dimethylthietanes. Starting from *(R)*-2-methylthietane, the corresponding optically active crown ether has been obtained [346].



Scheme 3.195

Mannosyl iodide reacts with thietane in the presence of MgO to give mainly the thio β-anomer (Scheme 3.196) [347].

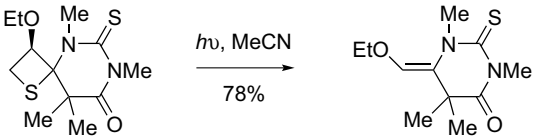


Scheme 3.196

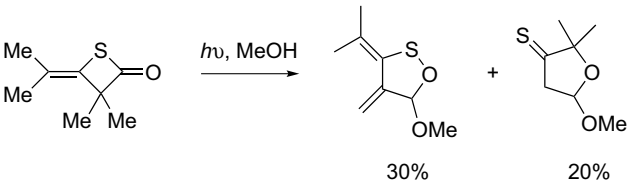
3.3.5.6 **Electrocyclic Reactions**

Retro [2 + 2] cycloadditions of thietanes occur at high temperature to generate ethylenic compounds and thioaldehydes. This fragmentation is also possible by irradiation at low temperature. With thietan-3-one, the formation of ketene has been detected [2]. These retrocycloadditions were observed for substituted thietanes. For example, enol ethers are formed during irradiation of 3-alkoxythietanes (Scheme 3.197) [348]. These reactions also lead to the formation of thioketones or thioaldehydes.

Irradiations of thietan-2-ones in methanol lead, by Norrish I rearrangements, to five-membered heterocycles (Scheme 3.198) [349]. Dithiolactones give rise to the same kind of rearrangements [350].

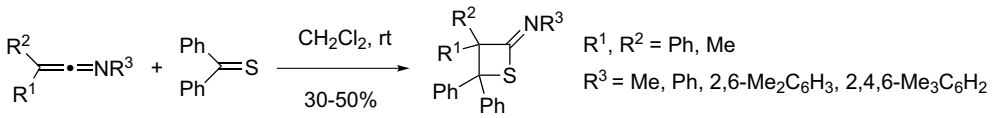


Scheme 3.197



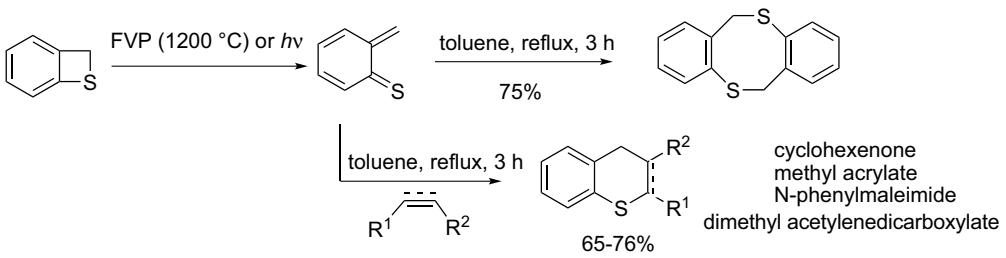
Scheme 3.198

2-Iminothietanes can be formed by cycloadditions of keteneimines with diphenyl thioketone in methylene chloride. Upon smooth heating, these compounds ($R^2 = H$) are transformed into unsaturated thioamides (Scheme 3.199) [351].



Scheme 3.199

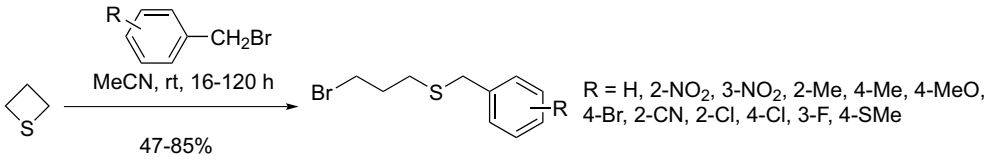
Benzothiete undergoes, by heating or irradiation, an isomerization into methylenecyclohexadienethione. This compound can be trapped by various dienophiles (Scheme 3.200) [299]. In the absence of dienophile, a dimer of methylenecyclohexadienethione is formed. Reaction of this compound with C_{60} [352], imines and diazenes [353] has also been reported.



Scheme 3.200

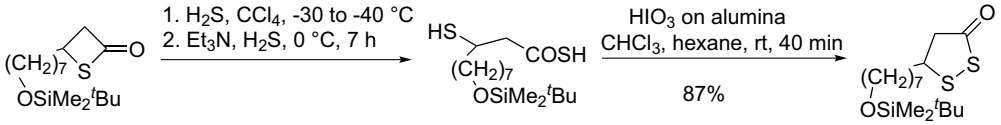
3.3.5.7 Cleavage and Other Reactions

Thietane reacts with benzyl bromide in acetonitrile to give the ring cleavage product (Scheme 3.201) [354].



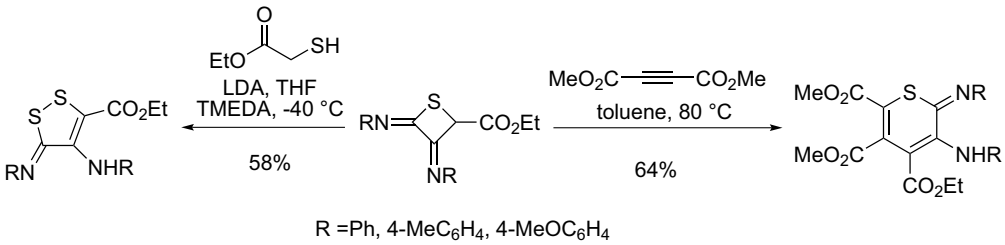
Scheme 3.201

Mercaptothiolic acids have been formed by the reaction of thietan-2-ones with H_2S [355]. These acids can be transformed into 1,2-dithiolan-3-ones by reaction with $FeCl_3$ [253, 356] or HIO_3 (Scheme 3.202) [357].



Scheme 3.202

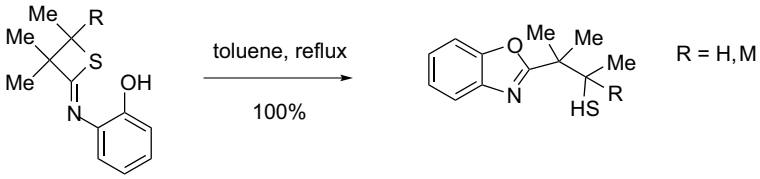
2,3-Diiminothietanes react with the dianion of ethyl mercaptoacetate to give bisthioles, while reaction with dimethyl acetylenedicarboxylate leads to thiopyran derivatives (Scheme 3.203) [358].



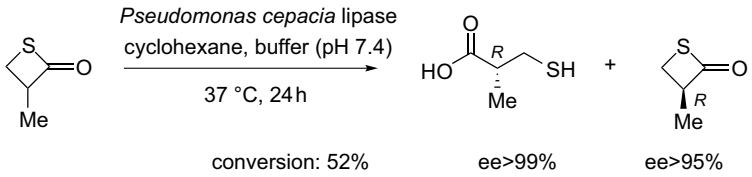
Scheme 3.203

Intramolecular induced ring opening of 2-iminothietanes, in which the imino group bears a phenol function, occurs by simple heating (Scheme 3.204) [359].

Enzymatic resolution of 3-methylthietan-2-one has been studied in the presence of lipases. Best results were reported using *Pseudomonas cepacia* lipase ($E > 100$) (Scheme 3.205) [360].



Scheme 3.204



Scheme 3.205

3.4 Other Four-Membered Heterocycles

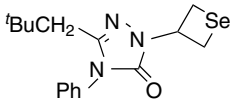
3.4.1 Selenetanes

3.4.1.1 Introduction

The chemistry of four-membered heterocyclic compounds containing one selenium atom has been until recently very little studied. These compounds appear to be stable enough to be synthesized and their reactivity examined, even if they have a relatively low thermal stability.

CNDO/2 calculations have been performed to determine the conformation of the parent compound [361]. Experiment values were measured by ^{1}H NMR in the case of 3,3-dimethylselenetane complexed by palladium(II) halides [362] IR and Raman spectra of this compound have been studied and the different vibrations assigned [363]. ^{1}H and ^{13}C NMR spectra of some selenetanes have been reported. Chemical shifts of protons and carbons appear comparable to those reported for thietanes. The ^{13}C-^{77}Se coupling has been used recently as a criterion of formation of selenetanes, even if the natural abundance of ^{77}Se is only 7% [364]. The X-ray structure of a selenetane has been reported [365]. In mass spectra, the parent ion corresponds to the retro [2 + 2] cycloaddition. All ions containing a Se atom are characteristic due to the particular isotopic abundance of selenium [366].

No natural product containing a selenetane ring has yet been reported. Derivative **37** has been tested as an antiviral compound [367].



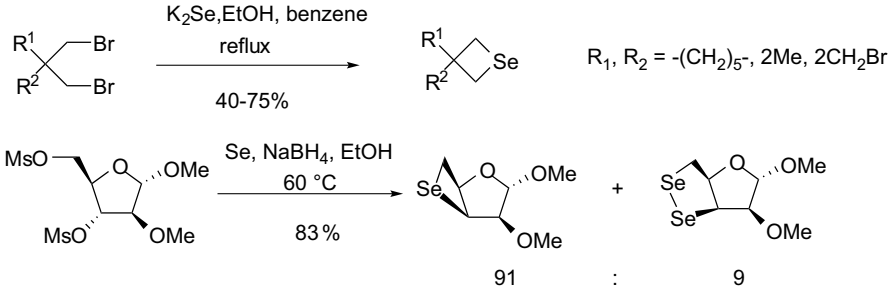
37

3.4.1.2 Synthesis of Selenetanes

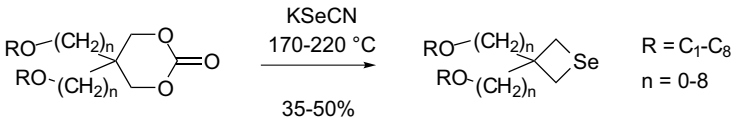
Although much less studied than thietanes, preparations of these compounds have often been made by similar methods.

3.4.1.2.1 **Synthesis by Formation of Two Se–C Bonds** The first attempt to prepare selenetanes was by the reaction of 1,3-dibromopropane with Na_2Se [368]. The selenetane was not characterized due its easy polymerization. This method was reinvestigated and applied to the preparation of various selenetanes (Scheme 3.206) [369]. The parent compound was obtained in low yield (5%). This approach was recently used in the preparation of nucleosides (Scheme 3.206) [364].

Heating cyclic carbonates at high temperature (170–220 °C) in the presence of KSeCN gives selenetanes in satisfactory yields (Scheme 3.207) [370].

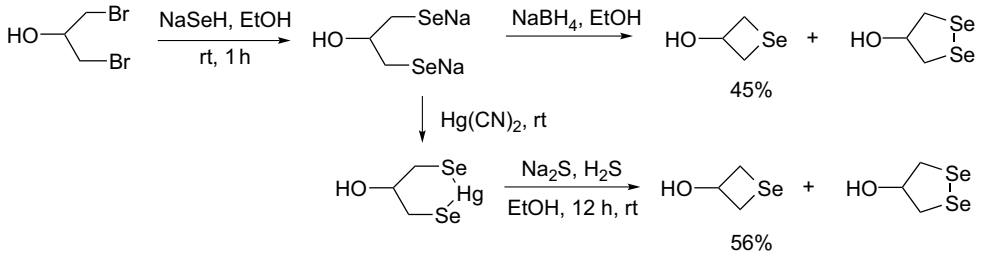


Scheme 3.206



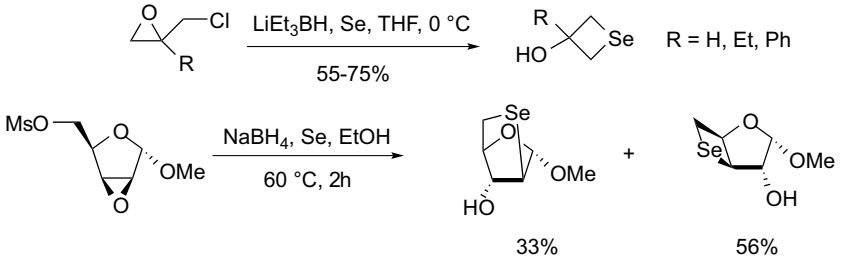
Scheme 3.207

Reaction of an excess of NaSeH with 2-hydroxy-1,3-dibromopropane gives the corresponding di-selenoate. This then leads to the formation of 3-hydroxyselenetane by reaction with $NaBH_4$ or a mixture $Hg(CN)_2$–Na_2S (Scheme 3.208) [371]. The reaction of 2-hydroxy-1,3-dibromopropane with NaSeH under phase transfer conditions has been reported to give 3-hydroxyselenetane in 56% yield [372].



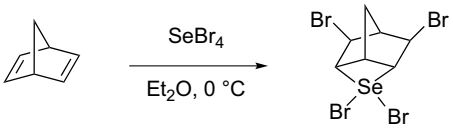
Scheme 3.208

3-Hydroxyseletanes have also been prepared by the reaction of 2-chlorooxiranes with Li_2Se, prepared *in situ* (Scheme 3.209) [372]. Utilization of H_2Se in the presence of $SnCl_4$ gives similar results [373]. The oxirane ring opening has been applied to the preparation of a taxol derivative [374] and nucleosides [375]. Opening of oxiranes with the formation of selenetanes is also possible if the leaving group is in the γ position (Scheme 3.209) [376]. 3-Hydroxyselenetane was also obtained by electrochemical opening of epichlorohydrin in the presence of selenium. The best results were obtained when the graphite electrode was doped with selenium [377].



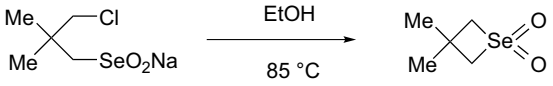
Scheme 3.209

Electrophilic addition of $SeBr_4$ to norbornadiene leads to the formation of a 1,1-dibromoselenetane (Scheme 3.210) [378].



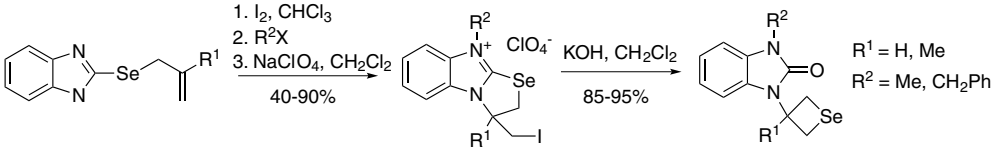
Scheme 3.210

3.4.1.2.2 **Synthesis by Formation of One Se–C Bond** 3,3-Dimethylselenetane-1,1-dioxide can be obtained by heating sodium 3-chloro-2,2-dimethylseleninoate (Scheme 3.211) [369].



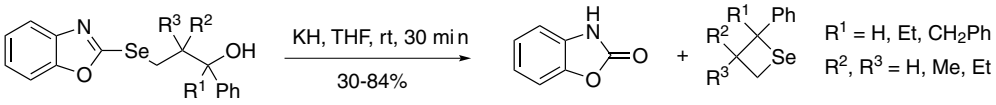
Scheme 3.211

2-Selenoalkenylbenzoimidazole derivatives lead to the formation of selenetanes by the sequence indicated in Scheme 3.212 [302].



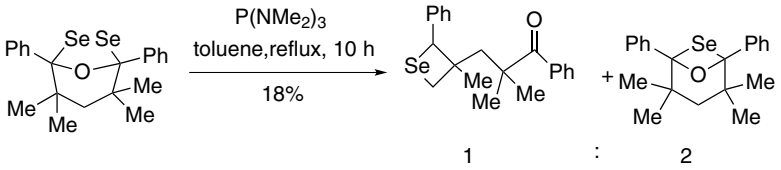
Scheme 3.212

Another interesting preparation of selenetanes uses the reaction of γ-seleno alcohols with KH; good yields were generally obtained (Scheme 3.213) [379].



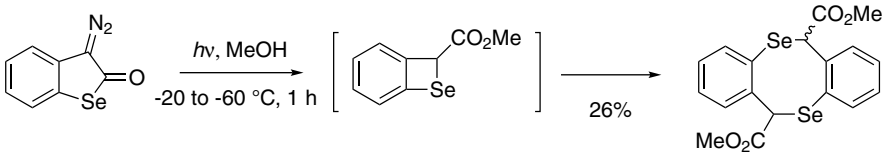
Scheme 3.213

3.4.1.2.3 **Formation by Ring Regression** A selenetane has been prepared in low yield by reaction of a diseleno compound with hexamethylphosphotriamine (Scheme 3.214) [380]. The 1,3-oxaselenetane derivative was obtained in 72% yield when the reaction was carried out in the presence of triphenylphosphine.



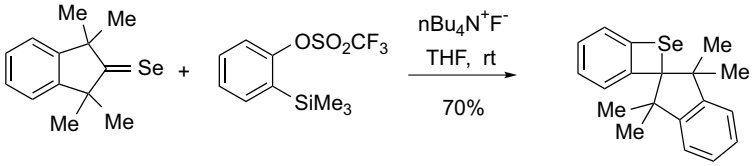
Scheme 3.214

An attempt to prepare benzoselenete by photolysis of 3-diazobenzoselenophenone has been reported. A dimer was isolated, the formation of which was postulated to occur by dimerization of the unstable benzoselenete. Calculations show that benzoselenete is 49.5 kcal mol^{-1} less stable than benzothiete (Scheme 3.215) [381].

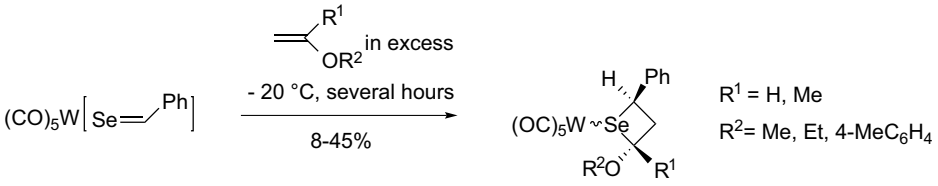


Scheme 3.215

3.4.1.2.4 **Formation by Cycloaddition** Stable benzoselenetes, characterized by X-ray crystallography, have been obtained by cycloaddition of sterically hindered seleno ketones with benzyne (Scheme 3.216) [365].



Scheme 3.216



Scheme 3.217

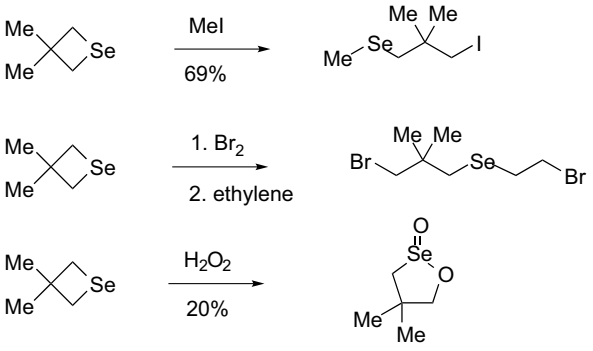
Benzoselenoaldehyde stabilized as a tungsten complex reacts with enol ethers at low temperature to give stable selenetanes (Scheme 3.217) [382].

3.4.1.3 **Reactivity**

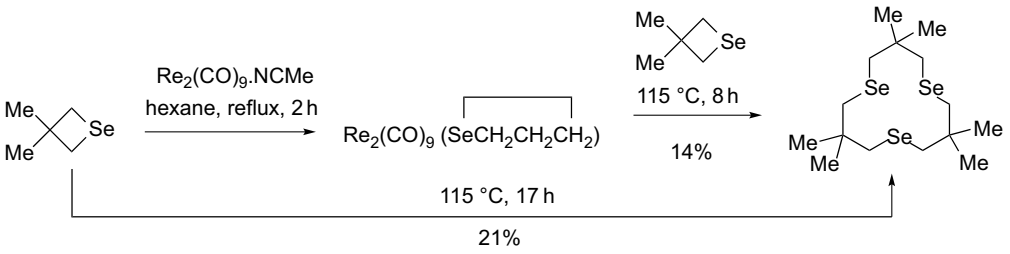
The reaction of 3,3-dimethylselenetane with electrophiles such as MeI, Br_2, I_2, SO_2Cl_2 gives ring cleavage products [383]. Additions of nucleophiles to the reaction mixture allow subsequent reactions. With ozone or hydrogen peroxide, insertions of an oxygen atom in the four-membered cycle are observed (Scheme 3.218).

Seleno crown ethers have been formed by the reaction of 3,3-dimethylselenetane with a rhenium carbonyl complex (Scheme 3.219) [384].

Oxidation of 3-hydroxyselenetane with the Dess-Martin reagent gives selenetan-3-one in quantitative yield [372]. However, this ketone was reported to be highly instable. In the presence of sodium hydroxymethanesulfonate (Rongalite), 3-phenyl-

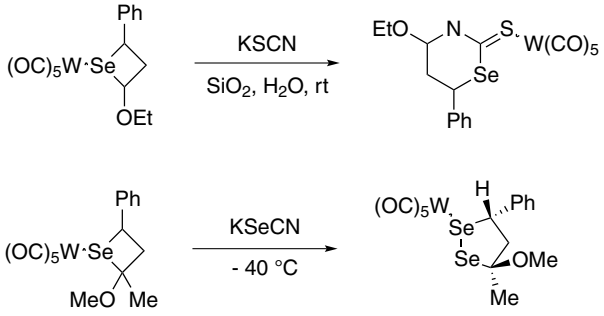


Scheme 3.218



Scheme 3.219

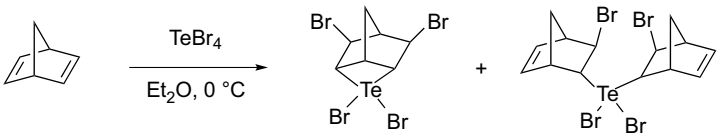
3-hydroxyselenetane leads to the formation 2-phenylallylic alcohol [372]. The reactivity of tungsten-stabilized selenetanes with KSCN and KSeCN has been examined. In the first case a 1,3-selenazinone-2-thione is obtained (Scheme 3.220) [385], while in the second case a 1,2-diselenolane is formed [382b].



Scheme 3.220

3.4.2
Telluretanes

The chemistry of telluretanes is almost unknown, even though the first attempt to obtain the parent compound was reported in 1945 [386]. Reaction of 1,3-dibromopropane with Na_2Te gave, apparently, the unstable tellurane and only a polymer was isolated during work-up of the reaction. A similar report was made on the reaction of a tellurate [387]. The reaction of epichlorohydrin derivatives with Na_2Te was also fruitless [372]. However, a telluretane derivative has been reported by reaction of norbornadiene with $TeBr_4$ (Scheme 3.221) [378].



Scheme 3.221

3.4.3
Phosphetanes

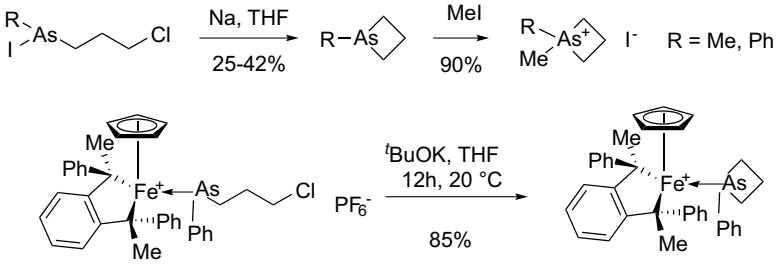
Four-membered phosphorus compounds have been known since 1957. Phosphorus (III) heterocycles have in general a low stability and are stabilized as P(V) derivatives (oxides, sulfurs, boranes, etc.). Chiral phosphetane derivatives have been studied as ligands in catalytic reactions (hydrosilylation, hydrogenation). Their synthesis and chemistry have been reviewed [388–390]. Chapter 23 of this book is devoted to phosphorous heterocycles.

3.4.4
Arsetanes

Arsetanes, also called arsacyclobutanes, have been known since 1977 [391]. Structural data on arsetene have been explored by PM3 semi-empirical studies [392]. These few compounds studied appear moderately stable at room temperature under inert atmosphere.

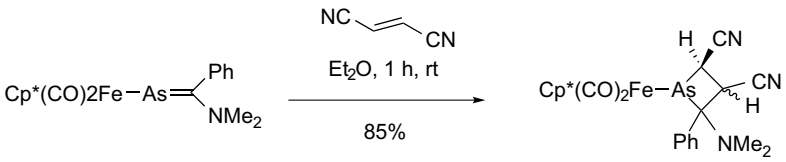
The first reported preparation of arsetanes involves reaction of (3-chloropropyl) iodo-arsines with sodium (Scheme 3.222) [391]. This method was subsequently modified, and it was reported that the ring closure of (3-chloropropyl)arsines could be carried out using potassium *tert*-butylate starting from iron(II) complexes of arsines [393]. 1-Phenylarsetane has been also prepared, by the reaction of dilithium phenyl arsenide with 1,3-dichloropropane [393].

An arsetene has been obtained by reaction of a methylenearsorane derivative complexed by iron with dimethyl fumarate. This arsetene has been characterized by



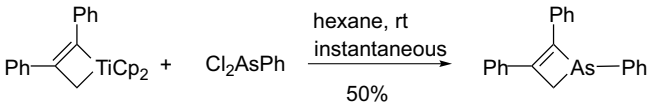
Scheme 3.222

spectroscopic analysis and by X-ray diffraction [394]. Similar cycloaddition, leading to an arsetane, has been reported from fumaronitrile (Scheme 3.223) [395].



Scheme 3.223

An original preparation of an arsetene involves metal exchange between titanium and arsenium, starting from a titanium cyclobutane derivative (Scheme 3.224) [396].



Scheme 3.224

3.4.5 Siletanes

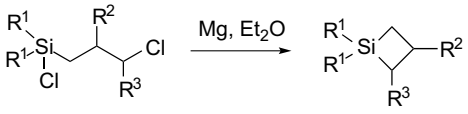
3.4.5.1 Introduction

Siletanes, also called silacyclobutanes, have been known since 1954 [397]. As this family of compounds has been reviewed [398], the present chapter focuses on new aspects of their preparation and reactivity. Siletanes have been studied by numerous theoretical methods. The geometry of 1,1-dimethylsiletane has been reported using gas electron diffraction [399]. *Ab initio* calculations shows that the barrier to inversion of 1-methylsiletane is comparable to that of methylcyclobutane [400]. NMR (^{1}H, ^{13}C and ^{32}Si), IR and UV spectra of substituted siletanes have been

reported [398]. In mass spectra, the main fragmentation corresponds to [2 + 2] retrocycloadditions [398].

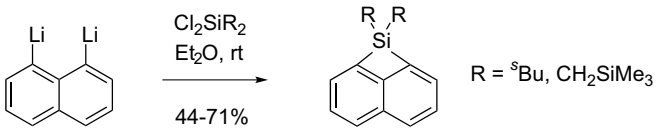
3.4.5.2 Preparation of Siletanes

3.4.5.2.1 **Preparation from Chlorosilanes** Cyclization of 1-chloro-(3-chloropropyl) silanes by the Wurtz reaction using magnesium is an efficient method to obtain siletanes (Scheme 3.225) [398]. Utilization of other metals (Li, Na, Na-K alloy) and electrochemical conditions extend this method [401].



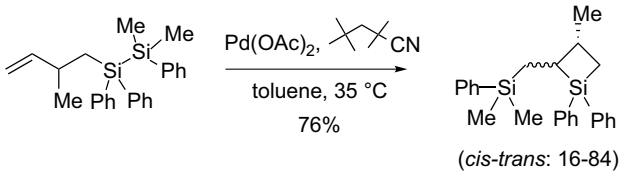
Scheme 3.225

Dichlorosilanes react similarly with 1,3-dimetallic species to form polycyclic silacyclobutanes (Scheme 3.226) [402].



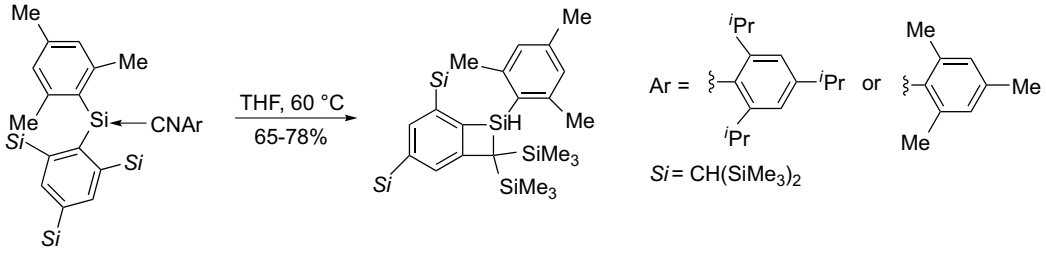
Scheme 3.226

3.4.5.2.2 **Other Intramolecular Cyclizations** 1,2-Bissilylalkanes lead, with alkenes, in the presence of palladium(II) catalyst to the formation of 1,2-bis(organosilyl)alkanes by the addition of a Si–Si bond across C–C double bonds. With 1,2-bissilylalkenes, intramolecular additions have been observed that give rise to silacycloalkanes. When the substituent fixed on one of the silicon atoms is a 3-butenyl chain, siletanes of low stability were formed by 4-*exo* cyclizations (Scheme 3.227) [403].



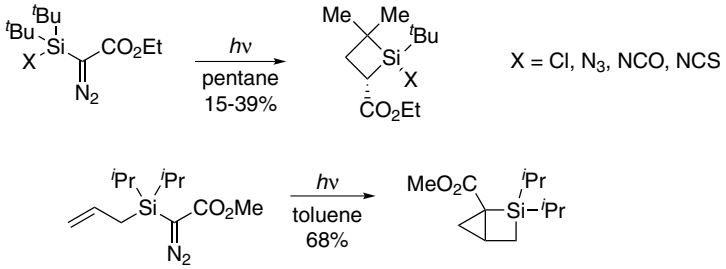
Scheme 3.227

Substitutions of silicon by sterically overcrowded substituents allow the preparation of stable silylenes. When one of the substituents is a silicon aryl substituted group, simple heating leads to rearrangement of these compounds into siletanes (Scheme 3.228) [404].



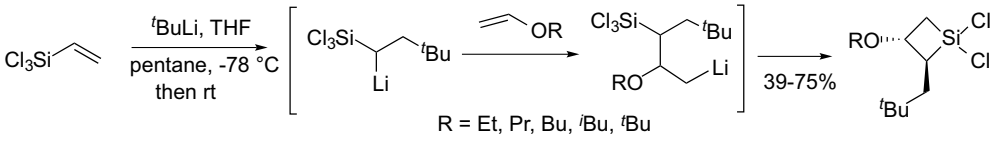
Scheme 3.228

Intramolecular insertion of carbenes into C–H bonds is also possible by irradiation of α-silyl-α-diazoacetates (Scheme 3.229) [405]. If one of the substituents of the silyl group is an allyl group, a bicyclic silacyclobutane is observed [406].



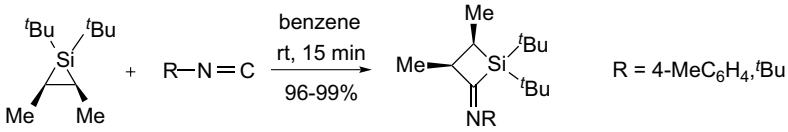
Scheme 3.229

3.4.5.2.3 **[2 + 2] Cycloadditions** Reaction of trichlorovinylsilane with *t*-butyl lithium produces, by 1,2 elimination of LiCl, reactive silenes (Si=C bond). In the presence of enol ethers, elimination does not take place, and the lithio intermediate undergoes an addition on the C=C double bond, leading by 1,4 cyclization to siletanes (Scheme 3.230) [407].



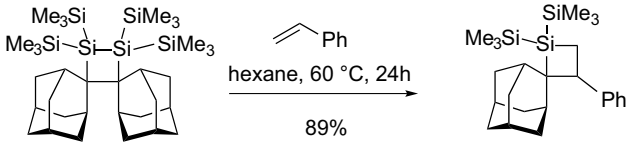
Scheme 3.230

3.4.5.2.4 **Preparation from Other Heterocyclic Compounds** Siliranes (silacyclopropanes) react with diazomethane to give siletanes in good yields [408]. These compounds give rise to similar ring expansions by reaction with isocyanate (Scheme 3.231) [409]. For monosubstituted silacyclopropanes a good regioselectivity in the formation of siletane is observed [409b].



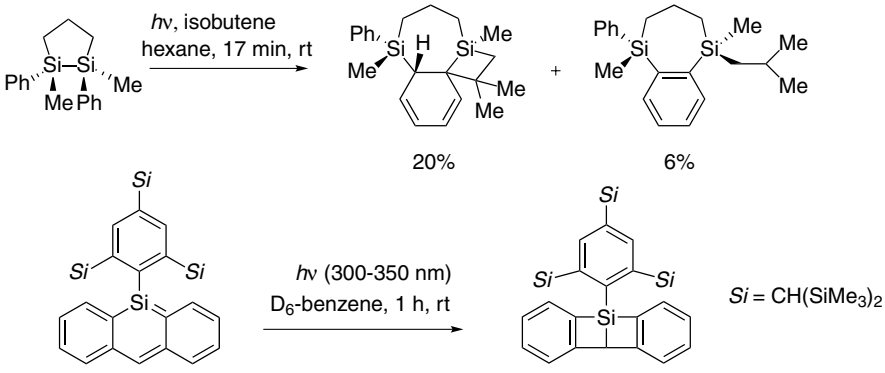
Scheme 3.231

Sterically hindered 1,2-disiletanes lead to the formation of silenes by heating at 60–100 °C. When the reaction is carried out in the presence of styrene, a siletane is formed in excellent yield (Scheme 3.232) [410].



Scheme 3.232

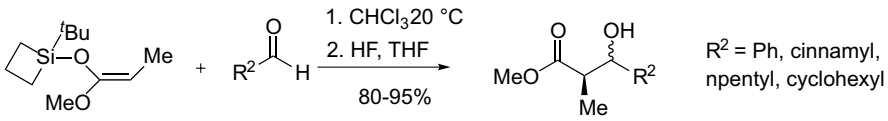
Irradiation of 1,2-disilolane in the presence of isobutene furnishes a stable tricyclic siletane if one of the substituents fixed on the silicon atoms is a phenyl (Scheme 3.233) [411]. Irradiation of a sterically hindered 9-silaanthracene in benzene leads to the formation of a bicyclo[2.2.0] compound of low stability (Scheme 3.233) [412]. On standing at room temperature, the starting anthracene derivative is reformed.



Scheme 3.233

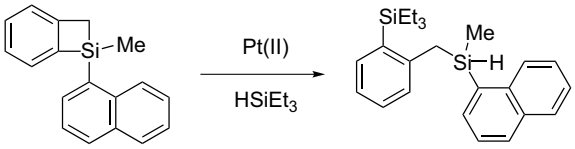
3.4.5.3 Reactivity

Pyrolysis or photolysis of siletanes leads to the formation of silenes [413]. Polymerization of silacyclobutanes has also been studied intensively, and compounds with alternating silicon and trimethylene groups have been obtained [414]. Polymers in which the siletane unit was introduced have also been reported [415]. The presence of siletane cycles instead of trialkylsilanes in functionalized compounds increases their reactivity, allowing much easier reactions. For example, reaction of silyl ketene acetals with carbonyl compounds occurs without any catalyst if a siletane is present (Scheme 3.234) [416]. This increase in reactivity has also been reported for cross-coupling reactions of vinyl- and arylsilanes [417].



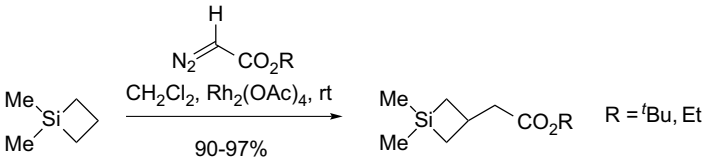
Scheme 3.234

Silacyclobutanes are opened by the action of nucleophilic and electrophilic reagents, sometimes with polymerization [398, 414]. This cleavage can be controlled [418, 419]. For example, in the presence of platinum salts and 1 equivalent of triethylsilane, opening of a benzosiletane occurs cleanly (Scheme 3.235). In the presence of a catalytic amount of triethylsilane, cyclic oligomers or polymers are obtained [418].



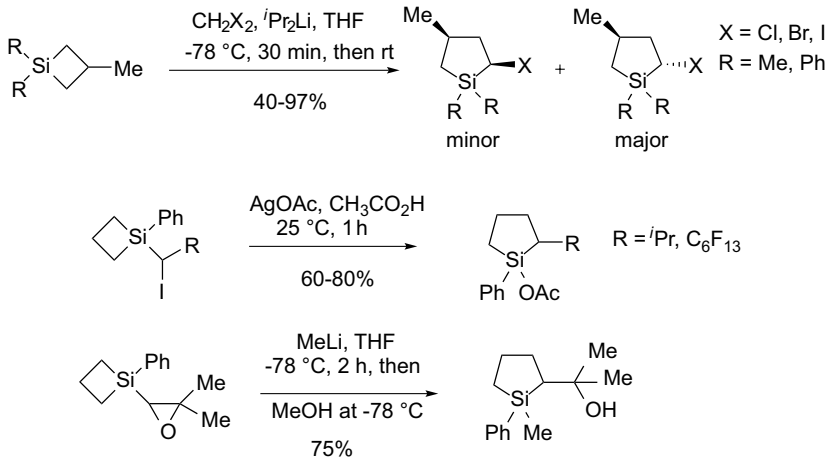
Scheme 3.235

Insertion of a functionalized chain in one of the C–H bonds in the 3-position of 1,1-dimethylsiletane is realized by reaction with diazoacetates in the presence of rhodium diacetate (Scheme 3.236) [420].



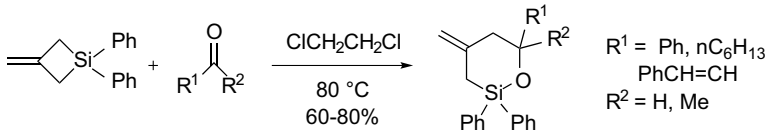
Scheme 3.236

Reactions of siletanes with carbenoids of type CHX_2Li lead to the formation of silacyclopentane derivatives (Scheme 3.237) [421]. Ring expansions are also observed by reaction of 1-(1-iodoalkyl)siletanes with MeLi, ^{t}BuOK or AgOAc and by reaction of 1-oxiranylsiletanes with MeLi (Scheme 3.237) [422]. The insertion of sulfur in 1,1-dimethysiletane is very efficient in the presence of KF and crown ethers, giving rise to 1,2-thiasilolanes [423].



Scheme 3.237

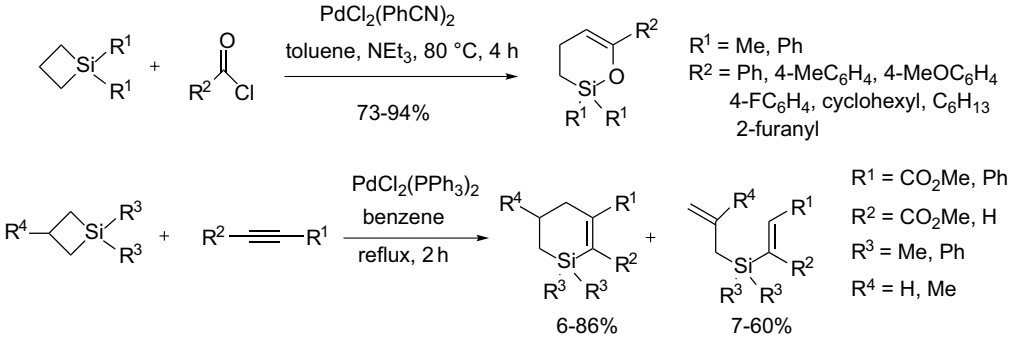
Insertion of the carbonyl function of aldehydes in the cycle of siletanes is possible in the presence of ^{t}BuOK [424]. With 1,1-diphenyl-3-methylenesiletane, ^{t}BuOK is not necessary and the reaction occurs by simple heating. It was subsequently reported that this reaction is also possible with aryl ketones (Scheme 3.238) [425].



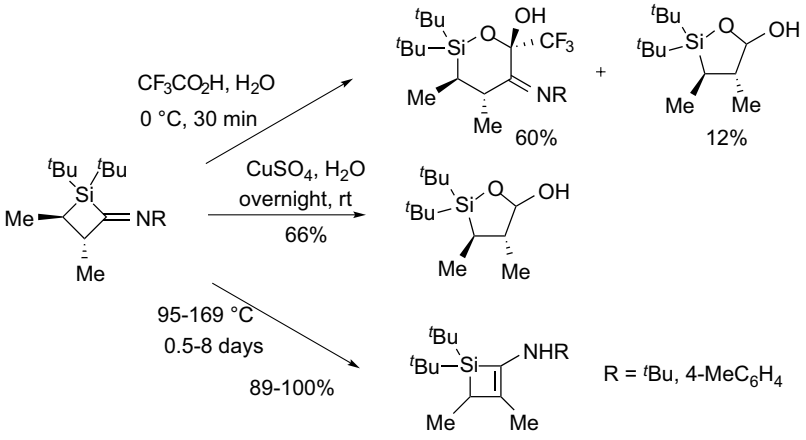
Scheme 3.238

Insertions of SO_2, SO_3 and phosphorus ylides similarly lead to six-membered heterocycles [398]. With acid chlorides and acetylenic compounds, these insertions occur only in the presence of palladium(II) catalysts (Scheme 3.239) [426, 427].

Insertion of the carbonyl function of CF_3COOH into the C–Si bond of 2-iminosiletanes, instead of the expected hydrolysis, has been reported (Scheme 3.240) [409b]. In the presence of an aqueous solution of $CuSO_4$, ring opening of these



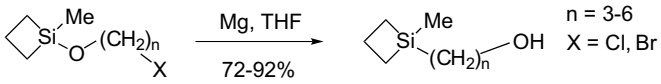
Scheme 3.239



Scheme 3.240

substrates is observed. Heating of these 2-iminosiletanes leads to isomerization of the C−N double bond, to give the corresponding enamines [409b].

The silicon atom of silacyclobutanes has reactivity comparable to that of other silanes, and is not reported in this chapter. An interesting example concerning the reactivity of such compounds has been reported. Reactions of 1(γ-haloalkoxy)-1-methylsilacyclobutanes with magnesium leads to the formation of 1-(ω-hydroxyalkoxy)-1-methylsilacyclobutanes in good yields, by intramolecular Grignard reagent attack on the silicon atom, followed by alcoholate elimination (Scheme 3.241) [428].



Scheme 3.241

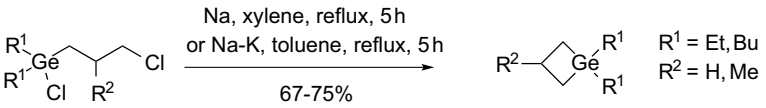
3.4.6 Germetanes

3.4.6.1 Introduction

The chemistry of germetanes has been less examined than that of siletanes, since the first report in 1966 [429]. Only limited spectra data are available concerning these compounds. In the IR spectrum, a vibration at 1120 cm^{-1} seems characteristic of this heterocycle [429]. These compounds appear to be stable at room temperature, and the mechanism of thermal decomposition of 1,1-dimethylgermetane has been examined. The formation of cyclopropane, propene and 1,2-digermacyclobutane was observed [430]. The structure of 1,1,3,3-tetramethylgermetane has been studied by gas electron diffraction and *ab initio* molecular orbital calculations (HF/6–31G* and MP2/6–31G*) [431]. An *ab initio* study has been made on the mechanism of formation of germetane by cycloaddition of alkylidenegermylene and ethylene [432].

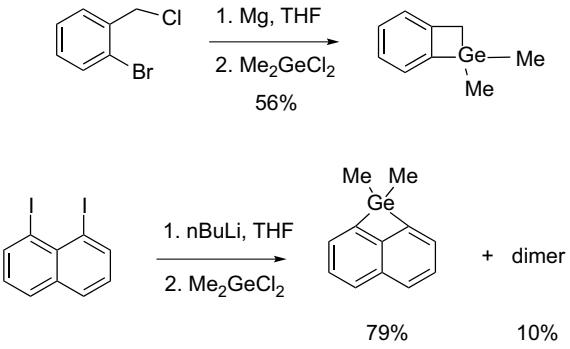
3.4.6.2 Preparations

The first method reported for the preparation of germetanes consists in the cyclization of chloro-(3-chloropropyl)germanes with sodium or sodium/potassium alloy (Scheme 3.242) [429].



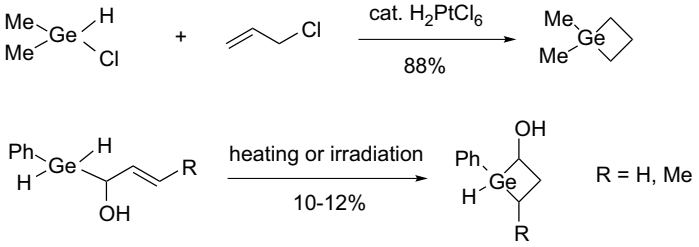
Scheme 3.242

In more recent studies, the reaction of 1,1-dichlorogermanes with 1,3-dimetallo compounds has been preferred [433]. This method has been applied to the preparation of benzo- [434] and tricyclic germetane derivatives (Scheme 3.243) [435].



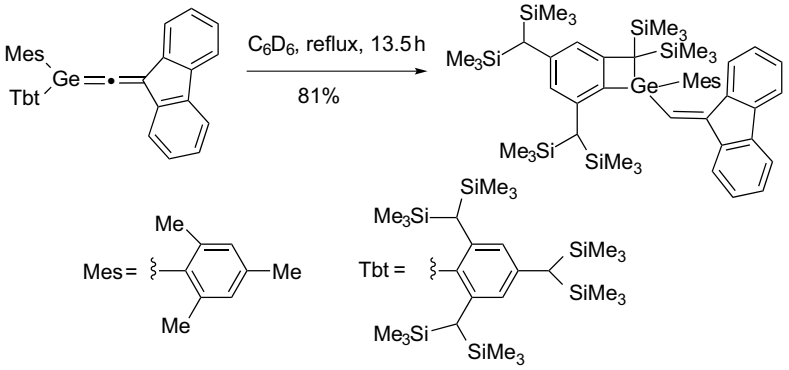
Scheme 3.243

Intermolecular hydrogermanylation has been reported to afford 1,1-dimethylgermetane [436]. Heating of dihydrogermylprop-2-en-1-ols was reported to give 2-hydroxygermetanes in low yields, by intramolecular cyclization (Scheme 3.244) [437].



Scheme 3.244

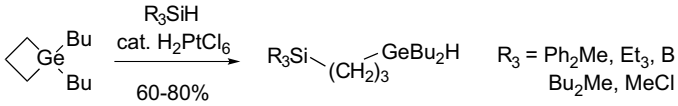
Highly strained germetanes have been obtained by rearrangement of germanylenes [438] and ethylenidene germanes (Scheme 3.245) [439].



Scheme 3.245

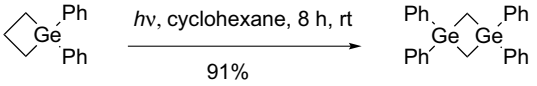
3.4.6.3 **Reactivity**

Germatanes react with electrophilic or nucleophilic reagents to give ring cleavage products. Ring cleavages were reported with halogens, $LiAlH_4$, acids, bases [429], hydrosilanes (Scheme 3.246) [440], phenylphosphinidene [441] and alcohols [442].



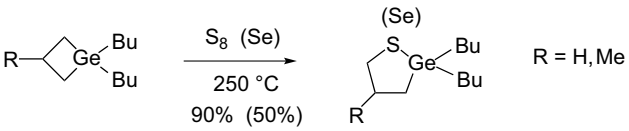
Scheme 3.246

Heating at 160 °C of 1,1-dimethylgermetane leads to formation of a polymer [436], while irradiation of 1,1-diphenylgermane in cyclohexane gives rise to the 1,3-digermanocyclobutane derivative (Scheme 3.247) [442].



Scheme 3.247

When heated (250 °C) in the presence of sulfur, an insertion in one Ge–C bond of a sulfur atom occurs (Scheme 3.248). The same insertion is observed on heating at 260 °C in the presence of selenium [443]. Comparable insertion was reported with dichlorocarbene, generated from the Seyferth reagent [444]. Reactions with SO_2 and SO_3 led, as with siletanes, to the formation of six-membered heterocycles [445].



Scheme 3.248

3.4.7
Bismetanes and Stibetanes

These four-membered ring compounds are still unknown.

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4
Five-Membered Heterocycles: Pyrrole and Related Systems

Jan Bergman and Tomasz Janosik

4.1
Introduction

The history of pyrrole **1** dates back to 1834, when Runge observed the presence of a compound that caused red coloration of a wood splinter moistened with mineral acid, in a fraction obtained through distillation of coal tar. He named the substance pyrrole [1] – a name maintained by Anderson, who later isolated a pure sample by distillation of bone oil [2]. Several years later, the correct structure was established by Baeyer and Emmerling [3]. The biological relevance and intriguing reactivity patterns of pyrrole derivatives have triggered intense interest in their chemistry, which has been exhaustively treated in several excellent monographs covering the advances of most essential aspects of the topic [4–6].

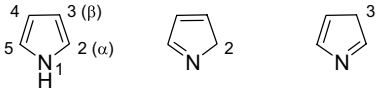
A general review with a practical perspective is included in *Science of Synthesis* [7]. Annual coverage detailing more recent achievements in synthetic pyrrole chemistry is provided in *Progress in Heterocyclic Chemistry* [8], whereas more comprehensive accounts on structure [9], ring synthesis [10], reactivity [11] and applications [12] are available in the second edition of *Comprehensive Heterocyclic Chemistry*. Since the scope of this chapter does not permit in-depth coverage of all aspects of pyrrole chemistry, and will be mainly restricted to 1*H*-pyrroles, which will hereinafter simply be referred to as pyrroles, readers may also want to consult the above mentioned reference works. Additional useful accounts highlighting special topics in pyrrole chemistry are cited in appropriate sections of this chapter.

4.1.1
Nomenclature

The IUPAC numbering convention for pyrrole (1*H*-pyrrole) is shown in structure **1**, including the commonly used designation of the 2(5)-positions as α, and the 3(4)-positions as β. The two remaining conceivable tautomeric forms **1a** and **1b** are known as 2*H*-pyrroles and 3*H*-pyrroles, respectively. Trivial names are relatively rare in the

Modern Heterocyclic Chemistry, First Edition.
Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.

pyrrole series, but are still used for some derivatives of natural origin. The general IUPAC rules are now generally applied to most pyrrole derivatives. Carbon containing substituents, such as carboxylic acid, nitrile, aldehyde, but also sulfonic acid, as well as derivatives thereof, should be incorporated into names as suffixes, although prefixes, for instance cyano-, may sometimes be encountered. Nomenclature that applies to special classes of pyrrole derivatives, such as partially saturated systems, will be evident from appropriate sections of the text.



1 **1a** **1b**

4.2 General Reactivity

4.2.1 Relevant Physicochemical Data, Computational Chemistry, and NMR Data

Pyrrole is a colorless liquid [mp −23 °C, bp 130 °C (760 Torr)] that darkens in contact with air. It has limited water solubility, but is miscible with many common organic solvents. Although some simple pyrroles are oils, many derivatives with higher molecular weights are solids. Pyrrole displays weakly acidic properties ($pK_a = 17.25$ in aqueous medium [13], 17.51 in aqueous hydroxide solution [14] and 23.05 in DMSO [15]). The dipole moment (μ) of pyrrole is 1.74 ± 0.02 D, with the negative pole directed towards the ring carbon atoms [16].

The planar C_{2v} symmetric molecular structure of pyrrole has been determined based on microwave spectra [16]; Table 4.1 provides selected bond lengths and angles. Although it has for some time been possible to calculate quite accurate structural parameters for the structure of pyrrole [9], the increasing level of refinement of modern theoretical methods has enabled even better estimations. Some represen-

Table 4.1 Selected experimental and calculated bond lengths (Å) and angles (°) of pyrrole **(1)**.

	N–C2 (Å)	C2–C3 (Å)	C3–C4 (Å)	C2–N–C5 (°)	N–C2–C3 (°)	C2–C3–C4 (°)	Reference
Experimental	1.370	1.382	1.417	109.8	107.7	107.4	[16]
MM3	1.380	1.382	1.417	110.1	107.1	107.8	[18]
B3P86	1.368	1.374	1.419	109.9	107.6	107.4	[19]
B3LYP/ 6-311G(2df,p)	1.370	1.373	1.421	109.8	107.7	107.4	[20]

tative values are included in Table 4.1. Computational methods involving complex pyrrole containing molecules are now commonplace, facilitating for instance studies of ligand–receptor interactions. The fundamental physicochemical properties of pyrroles, including the advances in spectroscopic and theoretical methods, have been compiled in several reviews [6, 9, 17].

As a "π-excessive" five-membered aromatic heterocycle with six π-electrons, pyrrole displays many features that are usually associated with such systems, such as high resonance energy, and a tendency to participate in substitution reactions. Both experimental and theoretical aspects of the aromaticity of pyrroles have been studied over the years, sometimes arousing controversy; this topic has been reviewed and discussed in considerable detail. The generally accepted relative aromaticity scale for the common five-membered heterocycles featuring one heteroatom versus benzene is: benzene > thiophene > selenophene > pyrrole > tellurophene > furan [21, 22].

Since detailed spectroscopic data, occasionally including complete assignments, are now included in virtually every research paper devoted to pyrroles, there is an immense wealth of information available on the subject [6, 9]. The chemical shifts of the protons attached to the carbon atoms of 1*H*-pyrroles reflect the aromatic character of this ring system, typically appearing in the range 5.5–7.8 ppm. Concentration and solvent dependence accounts for the considerable range of measured values for the proton attached to the nitrogen atom, which is often observed as a broad, sometimes even barely discernible peak.

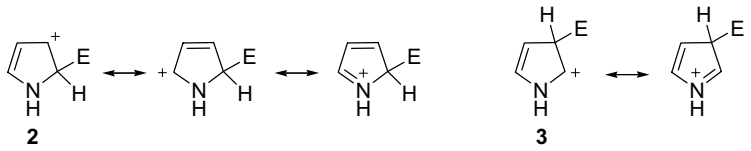
Likewise, much information on ^{13}C NMR spectroscopy on pyrroles has been collected and evaluated in detail. The ^{13}C resonances of 1*H*-pyrroles lie in the aromatic region, and the shifts depend on the electronic effects transferred from the substituents. Alkyl- [9] or aryl [23] substituents at the nitrogen atom usually have only limited influence on the ring carbon chemical shifts regardless of their properties, whereas the presence of electron-withdrawing groups can cause relatively large downfield shifts of the resonances; the magnitude of this effect increases with the electron-withdrawing power of the N-substituent [24]. The tetrahedral carbon of 2*H*-pyrroles usually resonates at 78–98 ppm, in contrast to its counterpart in 3*H*-pyrroles, which appears in the range 49–70 ppm. The resonances originating from the C=N carbon in 2*H*- and 3*H*-pyrroles appear at 161–185 and 173–191 ppm, respectively [9].

The continuous development of two dimensional NMR experiments, such as gradient enhanced ^{15}N-HMBC, allows practical measurement of ^{15}N chemical shifts and $^{1}H-^{15}N$ couplings in pyrrole derivatives. The ^{15}N chemical shifts of pyrroles fall in the approximate δ range between −186 and −236 ppm, and may vary considerably due to influence from the solvent; this should be kept in mind when data recorded in different media are compared [25].

4.2.2
Fundamental Reactivity Patterns

The propensity of pyrrole to react by electrophilic substitution imparts a dominant effect on its general reactivity patterns. Pyrrole itself, as well as simple non-deactivated derivatives thereof, is susceptible to undergo reactions with electrophiles

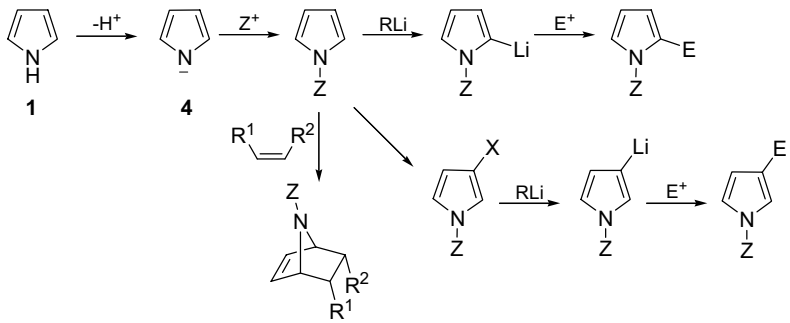
predominantly at C2 (α-position). Certain substituted pyrroles will, however, react with electrophiles selectively at C3, provided that an electron-withdrawing group is present at the nitrogen or at C2, or when both α-positions are blocked. Consequently, electrophilic substitution is a very useful tool for elaboration of pyrrole derivatives. An inspection of the Wheland intermediates resulting from attack on a suitable electrophile (E^+) at C2 (**2**) or C3 (**3**) gives an explanation to the preferred C2 substitution pathway observed for simple pyrroles, as the intermediate **2** is stabilized to a higher degree by more extensive delocalization of the positive charge (Scheme 4.1). Computational data on the differences in the total energy of pyrrole and the possible cationic σ-complexes formed upon its protonation, performed using for example the *ab initio* RHF/6-31G(d) and the DFT B3LYP/6-31G(d) methods [26], are in coherence with the experimental observations.



Scheme 4.1

The electron rich nature of most pyrroles is further manifested by their reluctance to participate in nucleophilic substitution reactions. The intrinsically low reactivity of pyrroles towards nucleophilic regents may, however, be enhanced upon protonation, or introduction of strongly electron-withdrawing substituents. Synthetically useful reactions of pyrroles may also be performed with radical reagents, leading to selective substitution at C2 under special conditions (Section 4.5.7).

Pyrrole reacts readily with strong bases giving the pyrrolyl anion **4** (Scheme 4.2). This ambident nucleophile is also of considerable synthetic importance, as it allows introduction of substituents in particular at the nitrogen atom, but also at the carbon atoms. In contrast, pyrroles possessing appropriate N-blocking substituents are usually metallated at C2, providing access to a wide variety of 2-substituted



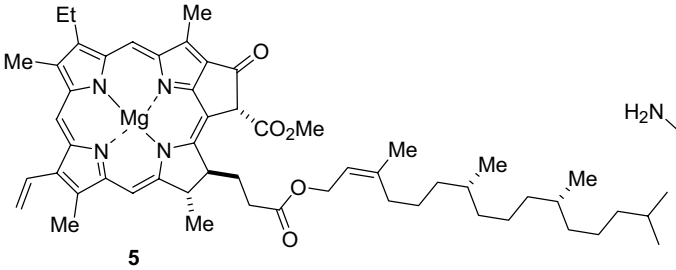
Scheme 4.2

derivatives upon quenching with suitable electrophiles. Metallation of pyrroles at C3 is conveniently accomplished by halogen–metal exchange using 3-halopyrroles incorporating a bulky N-protecting group, which effectively blocks access to C2. Owing to its aromatic character, pyrrole itself does not participate in Diels–Alder reactions, instead giving α-substitution products. However, this reactivity path may be precluded by introduction of an electron-withdrawing group on the nitrogen atom, thereby transforming the pyrrole nucleus into a useful diene component in Diels–Alder reactions. Examples of reactions where pyrroles act as dienophiles are quite rare, but have nevertheless found some applications.

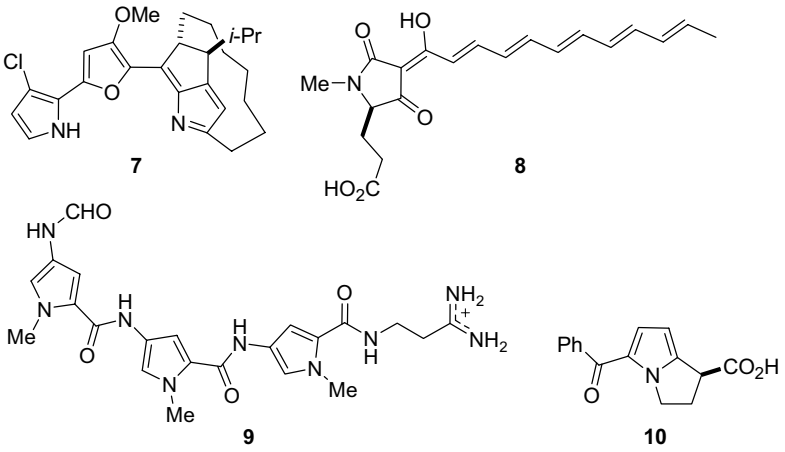
Taken together, these fundamental reactions, combined with reductions, oxidations, classical functional group interconversions, pyrrole ring syntheses, as well as modern developments, such as transition metal catalyzed couplings, constitute a powerful arsenal of tools for the preparation and elaboration of a wide array of pyrrole derivatives. Additional aspects on the reactivity of the pyrrole nucleus are discussed in appropriate sections of this chapter.

4.3
Relevant Natural and/or Useful Compounds

The pyrrole nucleus is an essential component of several naturally occurring macrocyclic complexes of various metals of utmost importance for living systems by virtue of its ability to participate in coordination of metals. One molecule belonging to this class, chlorophyll-*a* (**5**), is a crucial prerequisite for sustaining life on our planet by its ability to participate in the conversion of carbon dioxide into carbohydrates with concomitant liberation of molecular oxygen by photosynthesis. The total synthesis of chlorophyll-*a* (**5**) conducted by Woodward constitutes one of the most prominent achievements in organic chemistry [27]. This, and several related pigments, is biosynthesized from the common building block porphobilinogen (**6**) [28–30]. Likewise, the amino acid L-proline is ubiquitous in biologically important peptides and proteins, as well as other natural products. In addition, numerous naturally occurring compounds incorporating derivatives of proline have been identified [31]. Detailed mechanisms for some of the intricate biosynthetic pathways responsible for pyrrole ring formation and incorporation of pyrrole units in natural products have been formulated [32].



There are many other pyrrole based molecules of natural and of synthetic origin that exhibit various biological activities. The cytotoxic pyrrole alkaloid roseophilin (**7**) [33] is an excellent example of such a compound, and has also attracted considerable attention as a challenging target for total synthesis [34]. An increasing group of naturally occurring pyrrole derivatives feature the tetramic acid motif as the main structural element [35, 36], as illustrated by the plasmodial pigment fuligorubin A (**8**) isolated from the slime mold *Fuligo septica* [37]. The field of monopyrrolic natural products, including tetramic acid derivatives, has been comprehensively reviewed [38]; an account detailing recent synthetic strategies towards antitumor pyrroles bearing oxygenated aryl groups is also available [39]. Distamycin (**9**), an antiviral and antimitotic natural product isolated from a *Streptomyces* sp. [40], has served as a model compound for fruitful studies towards synthetic pyrrole containing polyamides for recognition [41–44] and sequence specific alkylation [45] of DNA. The development of ketorololac (**10**), a drug with potent anti-inflammatory and analgesic properties [46, 47], demonstrates the importance of synthetic pyrroles in medicinal chemistry.



7 **8** **9** **10**

Pyrrole polymers constitute yet an additional group of derivatives that have captured considerable interest, for instance as new materials for electrocatalysis [48], or conducting polymer nanocomposites [49]. Accounts concerning syntheses (e.g., by electropolymerization [50]), properties and applications of polypyrroles are also available [51, 52].

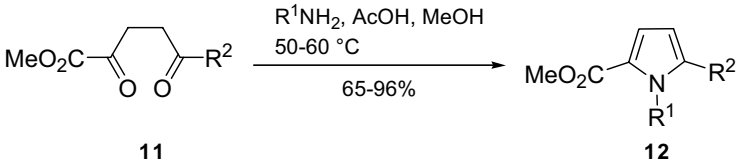
4.4
Pyrrole Ring Synthesis

Numerous different approaches for the construction of pyrrole derivatives from acyclic materials have arisen from over one century of intense research activity in this particular field. Nevertheless, new developments, as well as further extensions of known methods still continue to attract the attention of synthetic chemists, providing

additional effective routes to previously known pyrroles, as well as novel, and more exotic, derivatives. This section focuses particularly on general processes of practical importance. Selected syntheses of more specialized derivatives, such as oxypyrroles, aminopyrroles, pyrrolines and pyrrolidines, are incorporated in the sections devoted to these systems. A review detailing many recent advances in pyrrole ring synthesis since 1995 is available [52], whereas a more specialized account provides a survey of routes to pyrroles bearing two aryl or heteroaryl groups on adjacent positions [53].

4.4.1
Paal–Knorr Synthesis and Related Methods (4 + 1 Strategy)

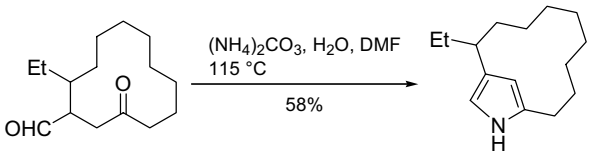
The Paal–Knorr pyrrole synthesis [54, 55] deserves particular recognition as one the most valuable of all pyrrole ring forming reactions, as it relies on the condensation of 1,4-dicarbonyl compounds with primary amines or their equivalents, both of which are quite common and readily available materials. In an illustrative example, the 2,5-dioxohexanoate derivatives **11** are efficiently converted into the corresponding pyrroles **12** upon treatment with appropriate amines in the presence of acetic acid (Scheme 4.3) [56].



11 **12**

Scheme 4.3

The versatility of the Paal–Knorr reaction is neatly demonstrated by the conversion of cyclododecane-1,4-dione into a pyrrole containing cyclophane [57], or transformation of the γ-ketoaldehyde **13** into the bicyclic system **14** in a key step of a synthesis of the bacterial tripyrrole pigment metacycloprodigiosin (Scheme 4.4) [58]. Modern applications emerge continuously, and allow for instance synthesis of 1-aminopyrrole derivatives by using monoprotected hydrazines [59] or *N*-aminophthalimide [60] as the amine components. A variant employing amine hydrobromides in refluxing pyridine is available [61], and an efficient synthesis of cyclopenta[*b*]pyrroles from suitable diketones with hexamethyldisilazane (HMDS) as the ammonia equivalent in

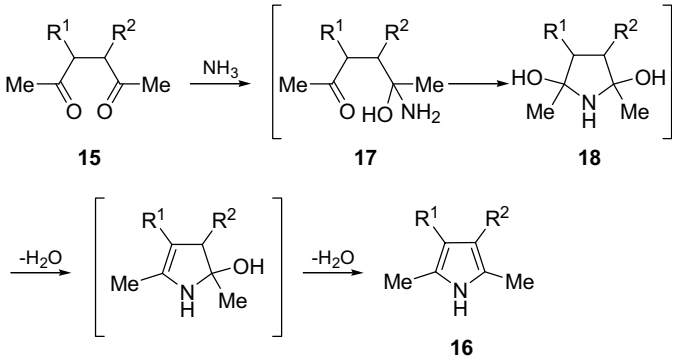


13 **14**

Scheme 4.4

the presence of Al_2O_3 has also been described [62]. Other useful extensions involve montmorillonite KSF clay [63], titanium isopropoxide [64] or iodine [65] as the catalysts. The Paal–Knorr synthesis has recently been performed under microwave irradiation [66–68], and has also been adapted to the solid phase employing immobilized 1,4-diketones [69]. A solution phase combinatorial approach has also been presented, involving construction of the 1,4-diketones from methyl esters by reaction with an excess of vinylmagnesium bromide in the presence of CuCN, followed by oxidation of the alkene unit in the resulting homoallylic ketones using $O_2/PdCl_2/CuCl$ in aqueous DMF [70].

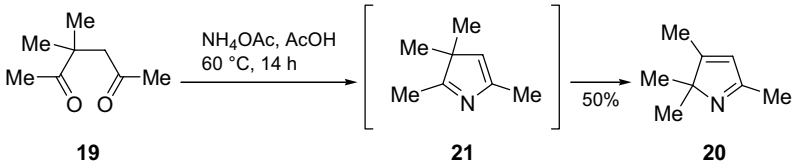
The mechanism of the Paal–Knorr condensation has been scrutinized in detail, here exemplified by the conversion of the substituted 2,5-hexanediones **15** into the 2,5-dimethylpyrrole derivatives **16**, which appears to involve the intermediacy of the aminals **17**, which undergo cyclization to the diols **18**, followed by elimination of two equivalents of water (Scheme 4.5). These conclusions were supported by meticulous kinetic studies [71], as well as probing of the influence of the stereochemistry of the starting 1,4-dicarbonyl compounds [71, 72]. The reversibility of this series of events has recently been demonstrated by conversion of various pyrroles into the corresponding 1,4-dicarbonyl compounds by heating at pH 3, which allows exchange of the N-substituent [73].



15 **17** **18** **16**

Scheme 4.5

This versatile method may also be utilized for the synthesis of 2*H*-pyrroles, as demonstrated by conversion of the 1,4-diketone **19** into the product **20** (Scheme 4.6). The series of events leading to this outcome involves the intermediacy of the

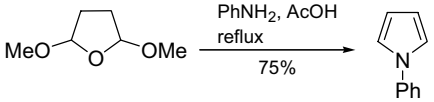


19 **21** **20**

Scheme 4.6

3*H*-pyrrole **21**, which undergoes rearrangement to the 2*H*-pyrrole **20** due to the acidic reaction conditions in combination with heating. Nonetheless, this approach can in certain cases enable isolation of the 3*H*-tautomers [74]. A review detailing the early advances in the chemistry of 2*H*- and 3*H*-pyrroles is available [75].

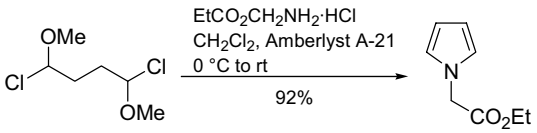
A useful extension of the Paal–Knorr reaction is based on the cyclization of 2,5-dimethoxytetrahydrofuran (**22**) with primary amines, providing facile access to N-substituted pyrroles (e.g., **23**) (Scheme 4.7) [76, 77]. This process is further facilitated by using phosphorus pentoxide as the catalyst [78], or by heating in acetic acid under microwave conditions [79]. It has also been demonstrated that cyclizations involving **22** and amine components incorporating sensitive substituents proceeds in acceptable yields when carried out in a medium containing acetic acid and pyridine via a path featuring acid–base catalysis [80]. Application of arylsulfonamides as the amine synthons constitutes a useful route to 1-(arylsulfonyl)pyrroles [81]. Likewise, heating of 2,5-dimethoxytetrahydrofuran-3-carbaldehyde with ethyl carbamate [82] or *p*-toluenesulfonamide [83] under acidic conditions gives the corresponding N-substituted pyrrole-3-carboxaldehydes. Treatment of the related four-carbon precursor 2,5-dimethoxy-2,5-dihydrofuran with amines in 10% aqueous HCl gives the corresponding N-substituted 3-pyrroline-2-ones in good yield [84]. Initial hydrolysis of **22** in water to 2,5-dihydroxytetrahydrofuran, followed by reaction with primary amines in an acetate buffer, constitutes an additional modification that permits a broader range of N-substituents because of the less acidic conditions [85].



22 **23**

Scheme 4.7

Relatively mild conditions have also been employed in some related syntheses, wherein exposure of 1,4-dichloro-1,4-dimethoxybutane (**24**) to amino acids [86], or primary amides [87], led for example to the pyrrole **25**, or 1-acylpyrroles, respectively (Scheme 4.8).

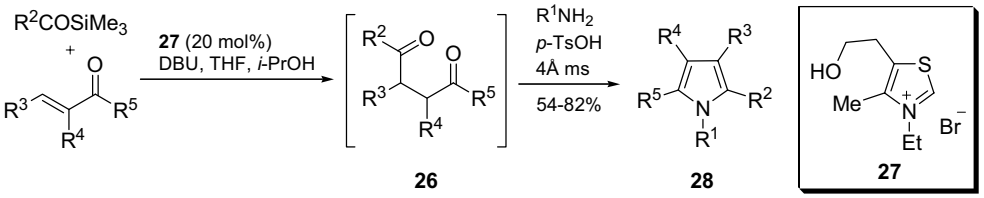


24 **25**

Scheme 4.8

The Paal–Knorr condensation has also been incorporated as the key step in multicomponent approaches to pyrroles. A one-pot procedure, involving initial formation of the highly substituted 1,4-dicarbonyl compounds **26** from acylsilanes and a series

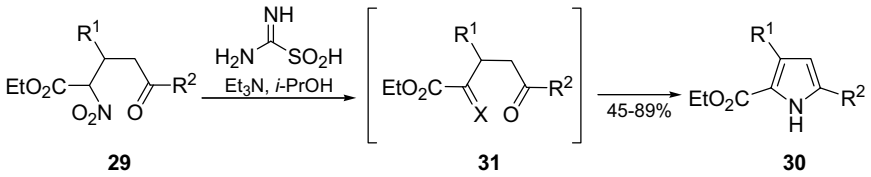
of α,β-unsaturated ketones in the presence of the thiazolium salt **27** as the catalyst, is completed by ring closure using primary amines to the target pyrroles **28** (Scheme 4.9), featuring for example multiple aryl substituents [88]. A similar approach includes palladium-catalyzed coupling of aryl halides with propargylic alcohols, giving α,β-unsaturated ketones, which thereafter undergo thiazolium salt catalyzed Stetter reactions with aldehydes to provide the requisite 1,4-diketone precursors [89].



Scheme 4.9

4.4.2
Other Cyclizations of Four-Carbon Precursors (5 + 0 and 4 + 1 Strategies)

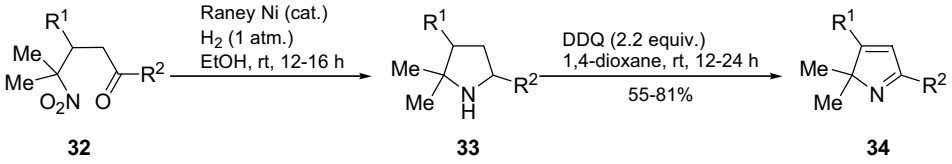
Apart from the classical and modern variants of the Paal–Knorr reaction outlined above, several related approaches involving cyclization of four-carbon precursors are available. Generation of the γ-nitroketones **29** bearing an additional ester functionality geminal to the nitro group by Michael addition of ethyl nitroacetate to suitable enones, and subsequent cyclization thereof with formamidinesulfinic acid and triethylamine, gives the pyrrole-2-carboxylates **30** (Scheme 4.10), via the intermediacy of the oximes or imines **31** (X=NOH or NH) [90].



Scheme 4.10

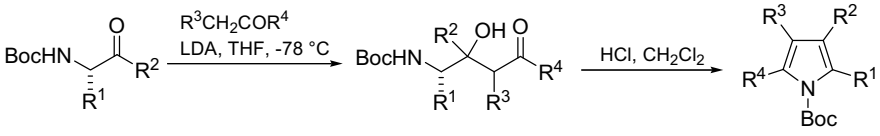
In contrast, reductive cyclization of the precursors **32**, available by conjugate addition of 2-nitropropane to α,β-unsaturated ketones, gives the pyrrolidines **33**, which may thereafter be converted into the corresponding 2*H*-pyrroles **34** upon dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Scheme 4.11) [91].

Suitable four-carbon precursors may also be prepared from the α-aminoaldehydes or -ketones **35**, which are readily available from *N*-Boc-α-amino acids by conversion



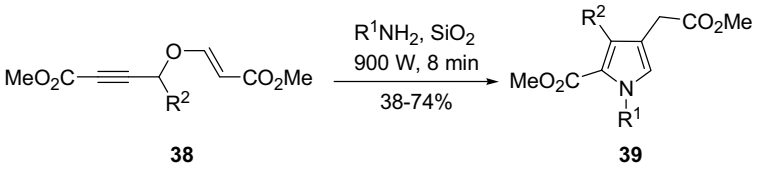
Scheme 4.11

into Weinreb amides, followed by reduction with $LiAlH_4$ or treatment with Grignard reagents, respectively. Thus exposure of **35** to lithium enolates of ketones, followed by cyclization of the resulting aldol adducts **36**, produced the set of pyrroles **37** (Scheme 4.12), including several fused derivatives, in low to moderate yields [92]. Reductive cyclization of similar aldol intermediates available from α-(*N*,*N*-dibenzyl) amino aldehydes or ketones has been utilized in a related, more high-yielding approach to *N*-benzylpyrroles [93]. Acid-induced cyclodehydration of Boc-protected γ-amino-α,β-enals or -enones derived from *N*-Boc-α-aminoaldehydes via Wittig reactions provides a route to various 1-(*tert*-butoxycarbonyl)pyrrole derivatives [94].



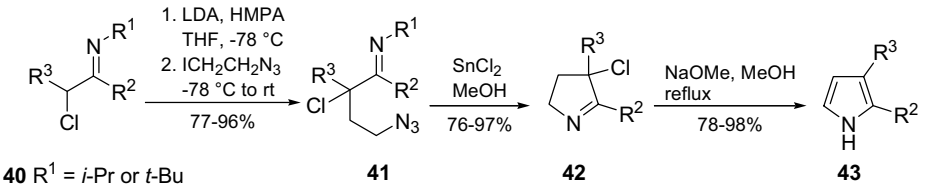
Scheme 4.12

An approach based on a microwave assisted domino process involving primary amines and the alkynoates **38**, which are derived from two equivalents of methyl propiolate and suitable aldehydes (R^1CHO), results in the pyrroles **39** (Scheme 4.13). The series of events leading to this outcome were suggested to involve rearrangement of 1,3-oxazolidine intermediates as the key feature [95]. A set of structurally related substrates has also been converted into pyrroles bearing multiple substituents by initial silver-catalyzed isomerization of the propargyl moiety to an allene, followed by condensation of the resulting intermediates with primary amines, and final gold-catalyzed 5-*exo-dig* cyclizations [96].



Scheme 4.13

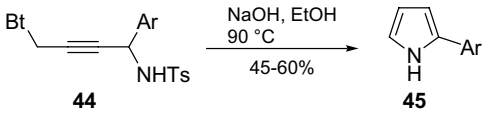
It has been known for some time that pyrroles may be obtained from the reactions of azaallylic anions with suitable α-haloketones [97]. A new application of azaallylic anions in pyrrole synthesis has been realized by conversion of the α-haloimines **40** into the intermediates **41**, which in turn are cyclized to the 1-pyrrolines **42**, eventually giving the pyrroles **43** (Scheme 4.14), including the 3-chloro derivative (R^2=Ph, R^3=Cl) [98].



40 R^1 = *i*-Pr or *t*-Bu **41** **42** **43**

Scheme 4.14

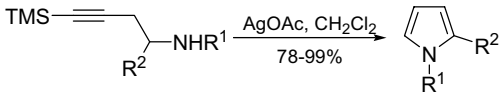
Several approaches based on cyclization of propargylamines and homologues thereof have emerged in recent years. Base induced cyclization of the benzotriazol-1-yl (Bt) substituted precursors **44**, which are readily available from 1-propargylbenzotriazole, gives the corresponding pyrroles **45**, presumably via allene intermediates (Scheme 4.15) [99]. Rhodium-catalyzed hydroformylation of 1,3-disubstituted propargylamines affording 2,4-disubstituted pyrroles has also been accomplished [100].



44 **45**

Scheme 4.15

Homopropargylamines, which are available, for instance, by addition of propargylic Grignard reagents to Schiff bases, are also useful precursors, as exemplified by the silver(I) mediated conversion of **46** into the pyrroles **47** (Scheme 4.16) [101]. A synthetic route to pyrroles involving cyclization of homopropargylamines generated *in situ* by ring opening of ethynylepoxides with amines has also been described [102].

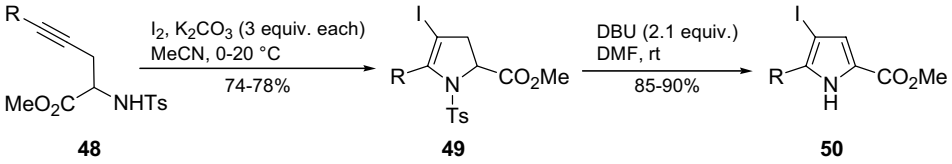


46 **47**

Scheme 4.16

Annulation of the homopropargylic sulfonamides **48** (R=Ph, 2-furyl, 2-thienyl), which are prepared by alkylation of the benzophenone imine of methyl glycinate with propargyl bromide, followed by sequential hydrolysis, tosylation and Sonogashira

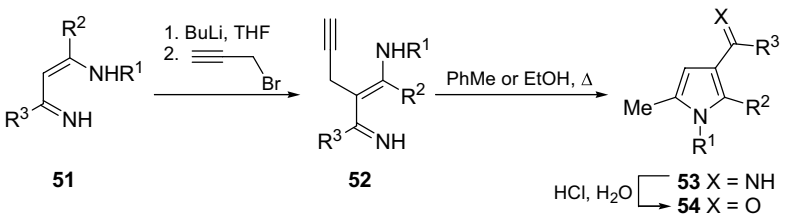
coupling at the terminal acetylene unit, has been reported to give the substituted 4-iodo-2,3-dihydropyrrole derivatives **49** via a 5-*endo-dig* process, eventually leading to the β-iodopyrroles **50** (Scheme 4.17) [103, 104], whereas cyclization of related alkenyl derivatives provides access to β-iodopyrrolidine derivatives [105].



48 **49** **50**

Scheme 4.17

Azadienes **51** may also serve as starting materials for construction of pyrroles, as C-alkylation thereof provides the intermediates **52**, which undergo annulation to the pyrroles **53** upon heating in toluene or ethanol. A subsequent hydrolysis step completes this synthesis, resulting in the 3-acetylpyrrole derivatives **54** in excellent overall yields (Scheme 4.18) [106, 107]. An approach to, for instance, 1,2,3,5-tetra-substituted pyrroles, utilizing thermally induced cyclization of iminoalkyne intermediates derived from various substituted 4-pentynones and suitable amines, has also been reported [108, 109].

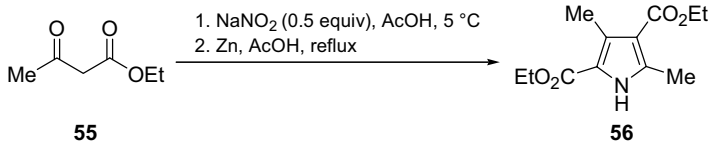


51 **52**

Scheme 4.18

4.4.3
Knorr Synthesis and Related Routes (3 + 2 Strategy)

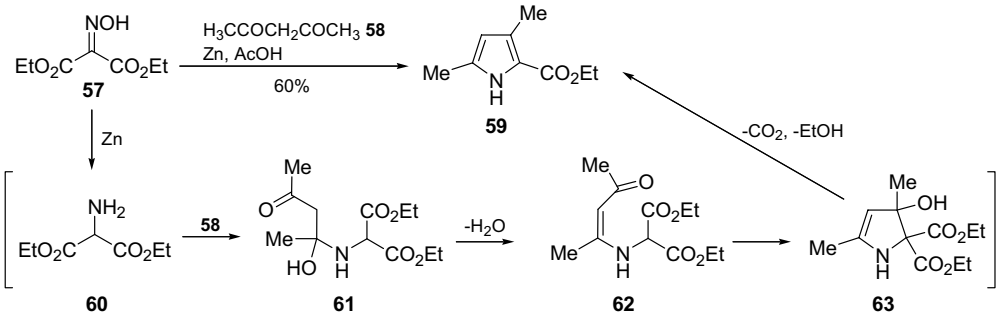
The Knorr pyrrole synthesis [110], which relies on the condensation of an α-aminoketone with a carbonyl compound possessing acidic α-hydrogens (each contributing with a two-carbon fragment to the pyrrole ring) is also of considerable synthetic importance. Since α-aminoketones are rather reactive and difficult to handle, the practical procedures often involve generation thereof *in situ* from a suitable synthetic equivalent, as illustrated by the classical example below (Scheme 4.19), in which addition of one equivalent of sodium nitrite to two equivalents of ethyl acetoacetate (**55**) generates an oxime, which, upon reduction with zinc dust [110, 111] or



Scheme 4.19

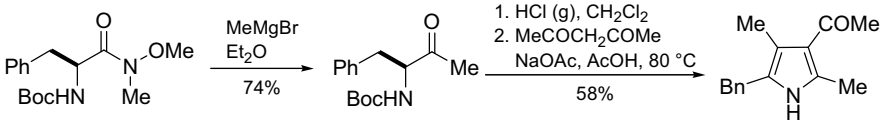
dithionite [112], undergoes condensation with the remaining equivalent of **55** to furnish the pyrrole **56** in excellent yield (Scheme 4.19).

It has also been demonstrated that this reaction may follow a different path if a β-diketone is used as one of the reactants, as treatment of diethyl oximinomalonate (**57**) with 2,4-pentanedione (**58**) under reductive conditions will afford ethyl 3,5-dimethylpyrrole-2-carboxylate (**59**) [113]. Since this process involves the intermediacy of diethyl aminomalonate (**60**), the reductive conditions can be avoided by using this very reagent. The mechanism is considered to feature an initial formation of the aminal **61**, followed by elimination of water to form the enamine **62**, which will cyclize on the ketone carbonyl carbon to provide **63**, eventually leading to the final product **59** (Scheme 4.20) [114, 115]. The use of unsymmetrical 1,3-diketones instead of 2,4-pentanedione usually gives mixtures of regioisomeric pyrroles, unless relatively bulky groups (*i*-Pr, *t*-Bu, Ph) are present at the terminal carbon [116]. Many substituted pyrrole-2-carboxylate derivatives obtained using these procedures may be readily converted into further derivatives by decarboxylation (Section 4.6.2).



Scheme 4.20

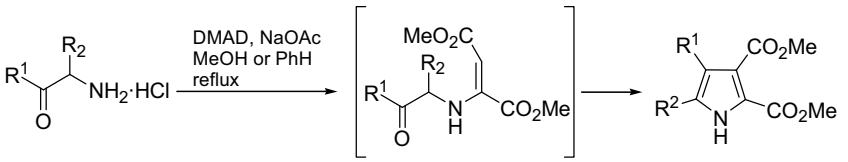
A modern modification of the Knorr pyrrole synthesis involves elaboration of Weinreb amides, for instance **64**, derived from phenylalanine, giving the protected α-aminoketone **65**, which can subsequently be deprotected and condensed with 2,4-pentanedione to provide the pyrrole **66** (Scheme 4.21) [117]. Reaction of similar Weinreb amides lacking the Boc group with enamines gives *N*-methoxy-*N*-methyl-α-enaminocarboxamides, which take part in related conversions into α-enaminoketones, and ensuing annulations to pyrroles [118].



64 65 66

Scheme 4.21

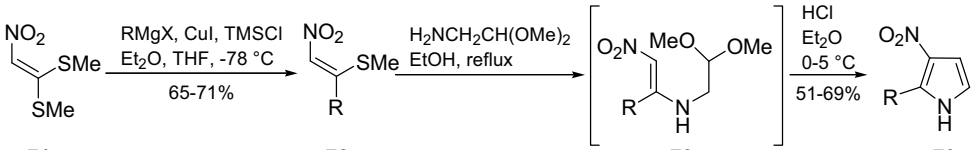
In a related approach involving an initial C−N bond formation between two C_2-fragments, addition of the α-aminoketones **67** to dimethyl acetylenedicarboxylate (DMAD) yields the intermediates **68**, which finally undergo cyclization to give pyrroles **69** (Scheme 4.22) [119]. A related procedure involving initial reactions of α-amino acid esters with DMAD, and cyclization of the intermediate enamines with sodium methoxide in methanol rendering 3-hydroxypyrroles **69** (R^1=OH), has also been reported [120].



67 68 69

Scheme 4.22

A series of 2-substituted 3-nitropyrroles (**70**) has been prepared by displacement of a methylthio group of the nitroalkene **71**, followed by treatment of the resulting products **72** with aminoacetaldehyde dimethylacetal to furnish the intermediate enamines **73**, which underwent a final ring closure in acidic medium (Scheme 4.23) [121]. Intermediates similar to **73** featuring a trifluoroacetyl group instead of the nitro functionality have previously been prepared from β-(trifluoroacetylvinyl) ethers and aminoacetaldehyde dimethylacetal, and were cyclized to the corresponding 3-trifluoroacetylpyrroles in aqueous TFA [122].

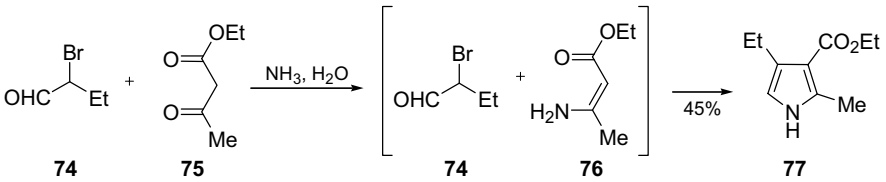


71 72 73 70

Scheme 4.23

4.4.4
Hantzsch Synthesis and Related Approaches (2 + 2 + 1 or 3 + 2 Strategy)

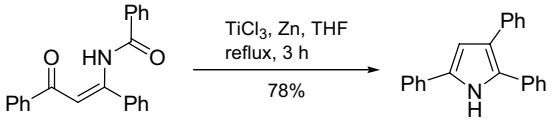
A conceptually related process involving two C_2-fragments and an amine component is the Hantzsch pyrrole synthesis (Scheme 4.24) [123]. In a typical procedure, a mixture consisting of an α-halo carbonyl compound (**74**) and ethyl acetoacetate (**75**) is treated with ammonia. This initially gives the enamine **76** derived from the β-ketoester, which will subsequently undergo cyclization with **74** to provide pyrrole **77** [124]. Application of β-aminoacrylonitriles as the enamine counterparts has been used to prepare 5-(trifluoromethyl)pyrrole-3-carbonitrile derivatives [125]. A solid phase variant utilizing an immobilized enamino component has also been developed [126].



74 **75** **74** **76** **77**

Scheme 4.24

It has also been demonstrated that titanium mediated annulation of substrate **78**, which is available in two steps from the appropriate 1,3-dicarbonyl compound, gives a good yield of 2,3,5-triphenylpyrrole (**79**) (Scheme 4.25). Similar precursors have also been cyclized in the presence of a preformed titanium–graphite reagent [127].

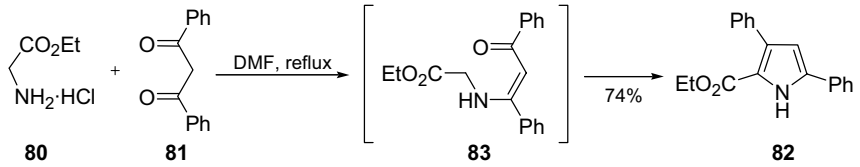


78 **79**

Scheme 4.25

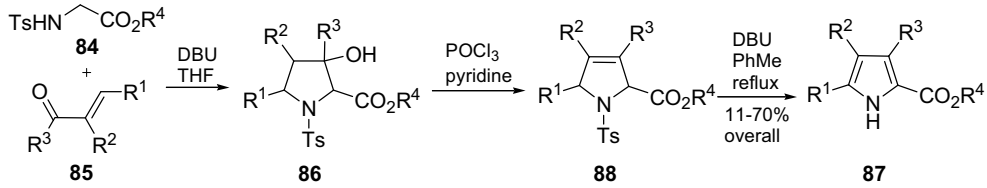
4.4.5
Syntheses Involving Glycine Esters (3 + 2 Strategy)

Several useful routes to pyrroles are based on the reactions of glycine esters or related compounds with suitable C_3-synthons. For example, condensation of ethyl glycinate hydrochloride (**80**) with the 1,3-diketone **81** provides access to the pyrrole **82** [128] via the enaminoketone intermediate **83** (Scheme 4.26). Such intermediates may also be isolated in a stepwise approach involving milder conditions [129], whereas cyclization of related condensation products generated from 3-ethoxyacrolein derivatives and N-substituted glycine esters gives 2,4-disubstituted pyrroles [130].



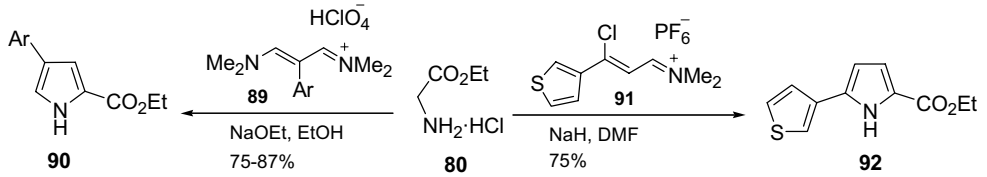
Scheme 4.26

Likewise, it has been demonstrated that *p*-toluenesulfonylglycine esters **84** undergo addition to α,β-unsaturated ketones **85** to render pyrrolidines **86**, which will eventually furnish pyrroles **87** by sequential elimination of water and *p*-toluenesulfinate, via the suggested 3-pyrroline intermediates **88** (Scheme 4.27) [131, 132].



Scheme 4.27

Glycine derivatives may also give pyrroles upon treatment with various iminium salts. For example, the reaction of ethyl glycinate hydrochloride (**80**) with the vinamidinium perchlorates **89** provides 3-arylpyrrole-2-carboxylates (**90**) in good yields [133]. A related reaction involving the salt **91**, which is readily available from 3-acetylthiophene, leads to the thienylpyrrole **92** (Scheme 4.28) [134]. Similar chemistry has also been employed for the preparation of 5-arylpyrrole-2-carboxylates [135] and of various 3,4-disubstituted pyrrole-2-carboxylates [136].

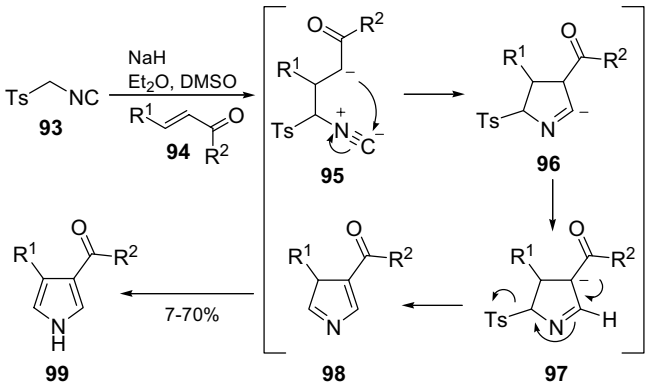


Scheme 4.28

4.4.6
Van Leusen Method (3 + 2 Strategy)

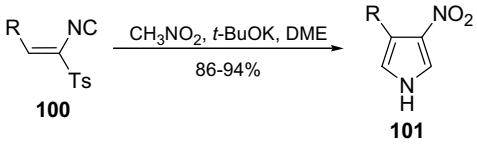
Since its introduction, the van Leusen pyrrole synthesis has enjoyed considerable popularity, as it provides convenient access to 3,4-disubstituted pyrroles from the

readily available building blocks *p*-toluenesulfonylmethyl isocyanide (TosMIC) (**93**) and electron deficient alkenes. Treatment of the anion of TosMIC with the α,β-unsaturated ketones **94** initially gives the intermediate Michael adducts **95**. After cyclization to **96**, followed by tautomerization to **97**, *p*-toluenesulfinate is eliminated giving the 3*H*-pyrroles **98**, which eventually tautomerize to the final products **99** (Scheme 4.29) [137]. Application of methyl 3-arylacrylates in this approach gives methyl 4-arylpyrrole-3-carboxylates, which may be further converted into the corresponding 3-arylpyrroles by saponification and decarboxylation [138]. A variant involving aryl- or heteroarylalkenes, TosMIC and sodium *tert*-butoxide in DMSO allows direct access to 3-aryl- or heteroarylpyrroles, respectively, in moderate yields [139]. When acrylonitriles are used as the alkene reactants, pyrrole-3-carbonitriles are produced [137], whereas application of nitroalkenes [140, 141] or *tert*-butyl (*E*)-4,4,4-trifluorobutenoate [142] gives the corresponding β-nitropyrrole- or β-(trifluoromethyl)pyrrole derivatives, respectively. Extensions involving substituted TosMIC derivatives offer direct routes to 2,3,4-trisubstituted pyrrole derivatives [143], including 2-stannylpyrroles [144]. The closely related reagent benzotriazol-1-ylmethyl isocyanide (BetMIC) has also been evaluated in similar reactions, and may in some cases give better yields [145].



Scheme 4.29

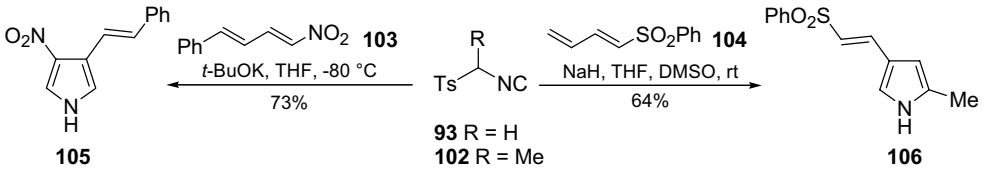
In a further extension of this valuable method, reaction of the 1-isocyano-1-tosyl alkenes **100** with nitromethane in the presence of potassium *tert*-butoxide enables efficient preparation of the 3-nitropyrroles **101** (Scheme 4.30) [146]. Similar transformations involving suitable substituted ketones instead of nitromethane yield



Scheme 4.30

various 3,4-disubstituted pyrroles, even such lacking electron-withdrawing substituents [147]. It is also noteworthy that alkenes generated from aldehydes and alkyl isocyanoacetates in the presence of DBU may react with an additional equivalent of the isocyanoacetate component, affording 2-substituted alkyl pyrrole-2,4-dicarboxylates in a convenient one-pot operation [148].

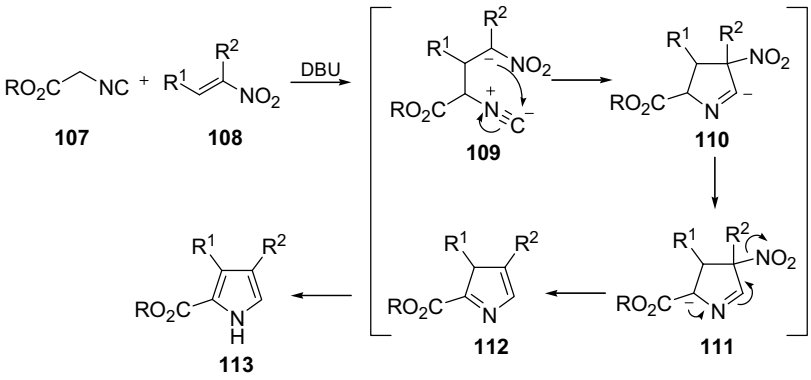
The reactions of TosMIC (**93**) or the methyl derivative **102** with dienes, for instance **103** [141] or **104** [149], furnish the corresponding substituted 3-vinylpyrroles, **105** and **106**, respectively (Scheme 4.31). Treatment of 1,4-disubstituted 2,3-dinitrobutadienes with TosMIC under similar conditions gives 3-alkynylpyrrole derivatives [150].



Scheme 4.31

4.4.7
Barton–Zard Synthesis (3 + 2 Strategy)

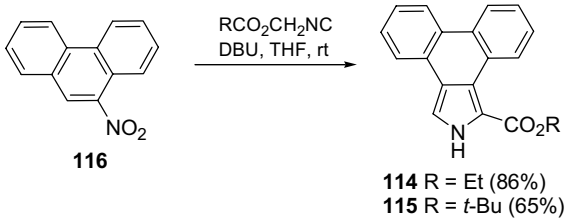
The equally versatile Barton–Zard synthesis features an initial conjugate addition of isocyanoacetate esters **107** to nitroolefins **108** in the presence of a base (e.g., DBU), generating the adducts **109**, which thereafter undergo cyclization to afford **110**. An ensuing isomerization of **110** to **111**, followed by elimination of nitrite, provides the 3*H*-pyrroles **112**, which finally tautomerize to the target pyrrole-2-carboxylate derivatives **113** (Scheme 4.32). Sensitive nitroolefins are preferably formed *in situ* from the corresponding β-nitroacetoxyalkanes [151, 152]. Application of benzyl



Scheme 4.32

isocyanoacetate in this approach allows efficient preparation of benzyl pyrrole-2-carboxylates [153, 154]. Alternatively, the nitroolefin components may be replaced by α,β-unsaturated sulfone derivatives [155–157] or by acetate precursors bearing a vicinal nitro group [158]. A variant of this reaction involving polymer supported reagents has also been developed [159].

Synthesis of the fused pyrrole derivatives **114** and **115** from 9-nitrophenanthrene (**116**) constitutes an interesting application of the Barton–Zard approach (Scheme 4.33) [160, 161]. Other condensed nitroaromatics, such as 3-nitrobenzothiophene, also give fused pyrrole derivatives under these conditions [162]. In cases where relatively unreactive nitroaromatics are involved, the use of a strong phosphazene base may give improved yields [163].



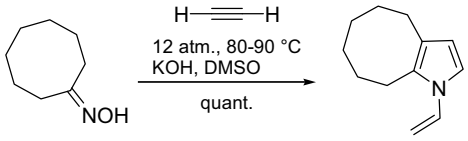
116

114 R = Et (86%)
115 R = *t*-Bu (65%)

Scheme 4.33

4.4.8
Trofimov Synthesis (3 + 2 Strategy)

Various pyrroles have been prepared over the years using the Trofimov synthesis, which relies on cyclization of ketoximes with acetylenes in a strong basic medium [164, 165]. For example, exposure of oxime **117** to acetylene in the presence of KOH in DMSO at elevated pressure and temperature gives the fused pyrrole **118** in excellent yield (Scheme 4.34) [166]. However, the formation of mixtures of N-vinylated products and the corresponding parent pyrroles is a common outcome of this reaction. The N-vinylation may be suppressed by addition of water (about 5%) to the reaction mixture, whereas optimal conditions for synthesis of *N*-vinylpyrroles require the use of a large excess of KOH [165]. A recent application of this method provided access to 2,6-bis(pyrrol-2-yl)pyridines [167]. Several pyrroles incorporating sulfur containing moieties have been prepared using the Trofimov reaction [168].

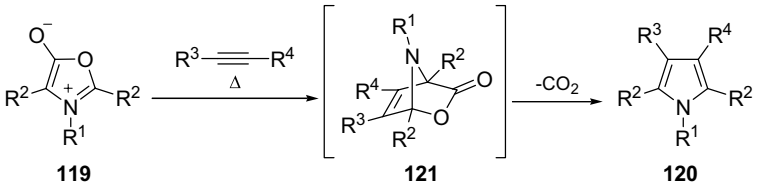


117 **118**

Scheme 4.34

4.4.9
Cycloaddition Reactions and Related Approaches (3 + 2 Strategy)

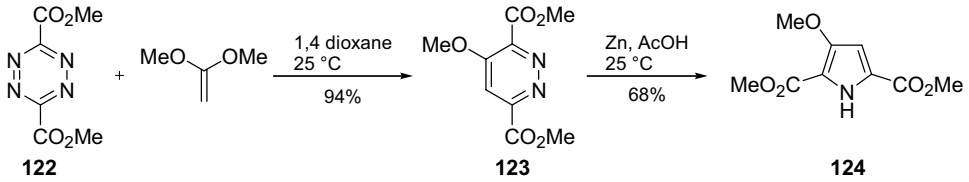
1,3-Dipolar cycloadditions between mesoionic compounds and suitable dipolarophiles, for example alkynes, constitute another useful approach to pyrroles [169, 170]. Thus the alkyl- or aryl-substituted münchnones **119**, which are readily available from α-amino acids, participate in cycloadditions with acetylene derivatives (e.g., diesters) to provide pyrroles **120**, often in excellent yields, through expulsion of carbon dioxide from the intermediate adducts **121** (Scheme 4.35). Münchnones may also be generated *in situ* from *N*-acyl-α-amino acids and acetic anhydride. Preferably, one of the reactants should be symmetrically substituted, thus avoiding formation of mixtures containing isomeric pyrroles [171, 172]. Nevertheless, regiospecific reactions involving polyfluoro-2-alkynoic acid esters have been reported [173]. The use of *N*-acylmünchnones provides access to *N*-acylpyrroles as mixtures of isomers [174], whereas 2-arylthio- or alkylthio-substituted 5-amino-1,3-thiazolium salts give 2-arylthio- or 2-alkylthiopyrrole derivatives, respectively, upon reaction with dimethyl acetylenedicarboxylate (DMAD) via extrusion of isothiocyanates [175]. Modern, multi-component variants that presumably involve münchnones feature generation of the dipoles from imines, acid chlorides, and carbon monoxide via palladium catalysis [176], or by annulation of products derived from Ugi four-component reactions involving carboxylic acids, primary amines, aldehydes and 1-isocyanocyclohexene [177]. A solid phase version using polymer bound münchnones has also been described. [178] Various aspects concerning the regioselectivity of 1,3-dipolar cycloadditions involving münchnones have been discussed in detail; the outcome appears to be influenced by the electronic nature and location of the substituents on the dipole [179], as well as steric factors [180]. In connection with investigations of regioselective cycloadditions of a certain münchnone with a carbohydrate derived nitroolefin, it was concluded that predictions using frontier molecular orbital theory in combination with semi-empirical studies are not applicable for such processes, and that this particular example proceeded through a concerted, although somewhat asynchronous, transition state, as implied by results from *ab initio* MO calculations [181].



Scheme 4.35

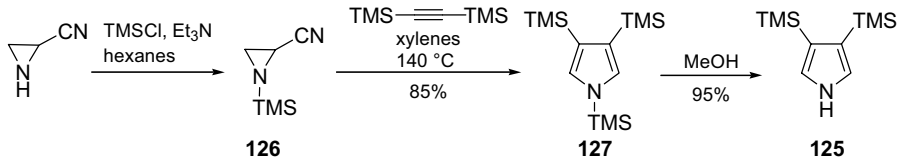
Pyrroles may also be made by cycloaddition of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**122**) with electron rich alkenes, followed by ring contraction of the resulting 1,2-diazines [182, 183]. In a representative procedure, **122** reacts with

1,1-dimethoxyethylene to give intermediate **123**, which is subsequently reduced to the pyrrole **124** (Scheme 4.36) [184]. The alkene components may also be replaced with acetylene derivatives [185]. Advances in ring contraction methodology for the construction of pyrroles have been discussed in detail in a specialized review [186].



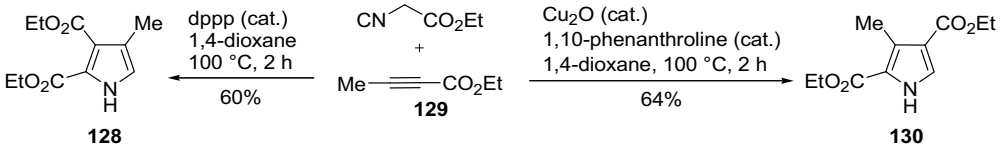
Scheme 4.36

Generation of dipoles from aziridines, and reaction thereof with suitable acetylenes, offers a route to pyrroles [187] that might be otherwise difficult to access. This method has been employed for the synthesis of the 3,4-disilylpyrrole **125** by dipolar cycloaddition of 2-cyano-1-trimethylsilylaziridine (**126**) with bis(trimethylsilyl)acetylene, followed by N-desilylation of the intermediate product **127** in methanol (Scheme 4.37) [188]. Azomethine ylides generated by desilylation of suitable immonium salts have been demonstrated to add to alkynes, giving pyrroles, or to alkenes to render 2-pyrrolines, which could in turn be further converted into the corresponding pyrroles by treatment with DDQ [189]. Based on a previously reported procedure [190], an approach to pyrroles has been devised that relies on reactions involving alkynes and imines in the presence of Ti(*i*-OPr)$_4$, *i*-PrMgCl and carbon monoxide at atmospheric pressure, via azatitanacyclopentene derivatives as intermediates [191].



Scheme 4.37

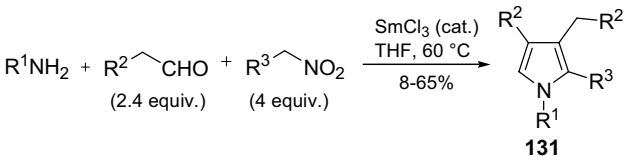
An elegant route to pyrroles from isocyanides and electron deficient acetylenes has also become available. In an illustrative example, pyrrole **128** was obtained upon reaction of ethyl isocyanoacetate with alkyne **129** in the presence of dppp [192]. The regioselectivity may be reversed by changing the catalyst to Cu_2O, giving instead the product **130** (Scheme 4.38) [193]. A related synthesis of pyrroles involving addition of metallated isocyanides to acetylenes, featuring an intramolecular cycloaddition of an alkene unit with the isocyanide moiety in the initially formed intermediates as the key step, has also appeared [194].



Scheme 4.38

4.4.10
Multi-Component Reactions (2 + 2 + 1 Strategy)

Multi-component processes, which are carried out in a one pot operation, have become increasingly popular tools for pyrrole synthesis in recent years. Some of these approaches employ well-known principles for pyrrole ring formation, for example the Paal–Knorr reaction [88], or dipolar cycloaddition of alkynes to münchnones [176, 177] (see above). Samarium-catalyzed three-component coupling of amines, aldehydes and nitroalkanes has been demonstrated to furnish modest to moderate yields of the pyrroles **131** (Scheme 4.39). Two aldehyde units are incorporated in the final products. The aldehydes may also be replaced by α,β-unsaturated aldehydes or ketones in a similar pyrrole ring forming reaction that does, however, not require the use of a catalyst [195]. Likewise, reactions between amines, α,β-unsaturated aldehydes or ketones and nitroethane in the presence of silica [196], or alternatively amines, aldehydes or ketones and nitroalkenes mediated by Al_2O_3 [197] under microwave irradiation, also produce useful yields of various pyrroles. The latter set of components may also be converted into pyrroles by heating in molten tetrabutylammonium bromide [198].

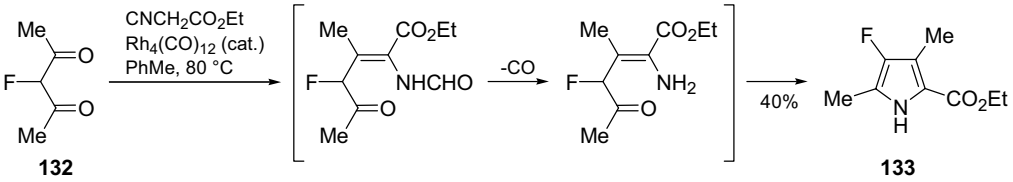


Scheme 4.39

4.4.11
Miscellaneous Transition Metal Catalyzed Methods (3 + 2 and 5 + 0 Strategies)

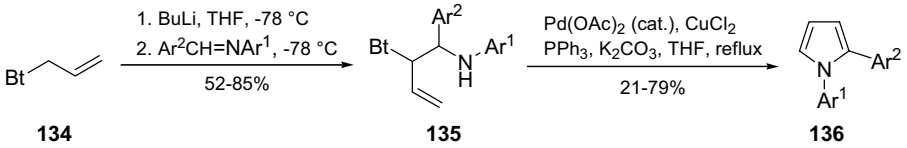
Transition metal catalyzed/mediated transformations of acyclic precursors to pyrroles have also attracted considerable attention. Although conceptually and mechanistically very interesting, some of these developments still appear to suffer from lack of practical synthetic applicability, involving rather complex starting materials and catalysts. Nevertheless, such procedures are now acknowledged as valuable tools for the preparation of exotic pyrroles having unusual substituents, substitution

patterns or oxidation states, which are not easily available via the "classical" procedures. For example, the rhodium-catalyzed reaction of 3-fluoropentane-2,4-dione (**132**) with ethyl isocyanoacetate furnished the fluoropyrrole **133** (Scheme 4.40), whereas the use of unsymmetrical 1,3-diketones gave, in most cases, mixtures of regioisomeric pyrroles [199].



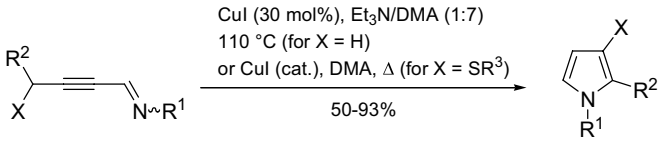
Scheme 4.40

Metallation of *N*-allylbenzotriazole **134**, followed by treatment with imines provided the intermediates **135**, which were thereafter converted into the 1,2-diarylpyrroles (**136**) by palladium-catalyzed annulation (Scheme 4.41) [200]. This approach resembles a previous route featuring lithiation of 1-(3-morpholinoprop-2-enyl)benzotriazole, wherein the final cyclization could be effected under acidic conditions [201].



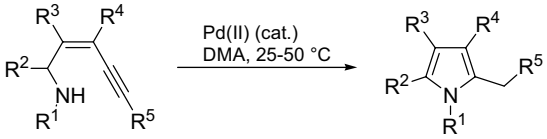
Scheme 4.41

Copper assisted cycloisomerization of the alkynylimines **137** gave useful yields of 1,2-disubstituted pyrroles **138**. This reaction tolerates substituents with rather sensitive moieties, such as TBS-ethers [202]. In a similar process, starting from related alkynylimines **139** possessing an additional arylthio- or alkylthio-substituent geminal to R^2, 2-alkyl-3-thio-substituted pyrroles **140** were produced in good yields via 1,2-migration of the thio group in intermediate thioallenylimines (Scheme 4.42) [203].



Scheme 4.42

The (*Z*)-(2-en-4-ynyl)amines **141** undergo Pd(II) [204, 205] or Cu(II)-catalyzed cycloisomerization to the pyrroles **142** (Scheme 4.43). The copper-catalyzed reactions require higher temperatures. Interestingly, the less stable of the substrates **141** (R^4=H, Ph, CH_2OTHP) underwent spontaneous cycloisomerization to the target heterocycles [205].



141 **142**

Scheme 4.43

4.5 Reactivity

4.5.1 Reactions with Electrophilic Reagents

4.5.1.1 General Aspects of Reactivity and Regioselectivity in Electrophilic Substitution

As indicated in Section 4.2.2, pyrrole is prone to undergo electrophilic substitution predominantly at the α-position (C2). Introduction of substituents alters both regioselectivity and reactivity by changing the electronic properties of the pyrrole nucleus by inductive effects, and sometimes also by steric interactions with the incoming electrophile. The transmission of electronic substituent effects in pyrroles appears to occur through the carbon atoms rather than via the ring nitrogen [206]. For example, it has been demonstrated that 2-methylpyrrole (R^2=Me; Figure 4.1) undergoes trifluoroacetylation at C5 some 23.8 times faster than pyrrole itself [207], whereas the reactivity of 1-methylpyrrole (R^1=Me; Figure 4.1) towards trifluoroacetic anhydride in 1,2-dichloroethane at 75 °C is only 1.9 times higher than that of the

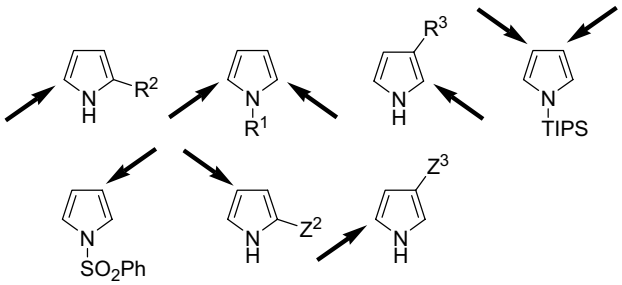


Figure 4.1 Transmission of electronic substituent effects in pyrroles.

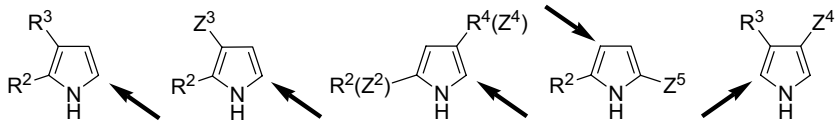


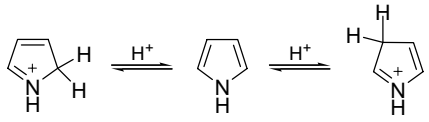
Figure 4.2 General trends of regioselectivity of electrophilic substitution of disubstituted pyrroles.

parent heterocycle [208]. Pyrroles having an electron releasing group at C3 (R^3) display enhanced reactivity both at C2 and C4, but the C2 position is still the most active because of the influence of the ring nitrogen. The introduction of a bulky N-substituent, for instance triisopropylsilyl (TIPS) [209] or trityl [210], gives access to C3 substituted or C3, C4 disubstituted products by blocking the intrinsic α-reactivity by steric interference. Substitution with high selectivity at C3 may also often be obtained with pyrroles having powerful electron-withdrawing substituents at the nitrogen, for example the phenylsulfonyl group [211]. Such electron deficient substrates are also considerably less reactive towards electrophiles than non-deactivated pyrroles. The presence of a strong "meta" directing, electron-withdrawing groups (Z^2) at C2 [212] or at C3 (Z^3) will direct substitution to C4 or C5, respectively. The general effects of various directing groups in monosubstituted pyrroles are summarized in Figure 4.1 (R=alkyl, Z=electron-withdrawing substituent). Additional examples, as well as special cases that deviate from the common pathways are discussed in appropriate sections below.

Prediction of the regioselectivity of electrophilic substitution of disubstituted pyrroles is more complicated, as the outcome is dependent on the combined influence of the substituents. There are also cases when the effects of sterically demanding substituents must be taken into account. Detailed studies of the reactivity of such systems have been conducted [213, 214]; Figure 4.2 depicts the general trends.

4.5.1.2 **Protonation**

In acid solution, pyrrole (**1**) undergoes reversible protonation, predominantly at C2, giving the thermodynamically favored 2*H*-pyrrolium cation **143**, which is stabilized by mesomeric delocalization of the charge (Scheme 4.44). The pK_a of −3.80 has been determined for protonation in dilute sulfuric acid solution [215]. It has also been demonstrated that protonation of pyrrole with the mild acids $C_4H_9^+$ and NH_4^+ in the gas phase occurs at C2, as well as at C3, giving the isomeric 3*H*-pyrrolium cation **144**, and that the affinity for protonation is higher at C2 [216]. The virtually non-existent N-basicity of pyrrole may be rationalized in terms of the absence of

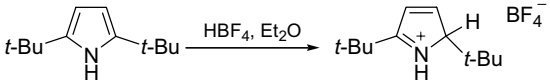


143 **1** **144**

Scheme 4.44

mesomeric charge delocalization in the putative 1*H*-pyrrolyl cation, and the unavailability of the electron pair on the pyrrole ring nitrogen due to its contribution to the aromatic π-electron sextet. This is supported by the fact that the dipole moment of pyrrole is directed into the ring, as opposed to its tetrahydro derivative pyrrolidine, which displays a dipole moment direction towards the nitrogen atom [4].

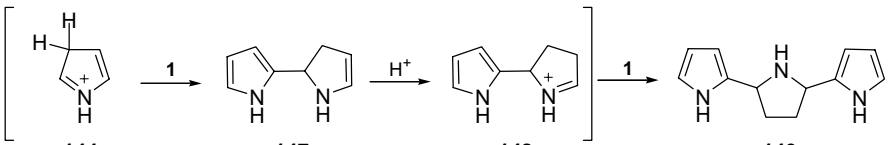
Based on observations during protonation studies involving various substituted pyrrole derivatives [215, 217], it is clear that the basicity is markedly increased by introduction of alkyl groups by stabilizing the corresponding cations. The presence of *tert*-butyl groups even allows isolation of stable 2*H*-pyrrolium salts, for example **145**, which was obtained in quantitative yield as a crystalline solid from pyrrole **146** (Scheme 4.45) [218].



146 **145**

Scheme 4.45

Although the 3*H*-pyrrolium cation **144** is the less stabilized, and thus also the less abundant of the two C-protonated species, it is nevertheless very important, as it plays a major role in the acid-catalyzed oligomerization and polymerization of pyrrole because of its higher reactivity. The electrophilic cation **144** undergoes attack by pyrrole (**1**), thereby forming the unstable dimeric enamine **147** (Scheme 4.46). Protonation thereof generates a new electrophilic intermediate **148**, which reacts with an additional equivalent of pyrrole (**1**), rendering the isolable trimer **149** (ratio trans : cis of 2 : 1) [219], which may subsequently participate in further reactions, eventually giving polymeric products [220], for example fully aromatic polypyrrole [221], unless careful control of the conditions is maintained, and, therefore, the reaction allowing isolation of **149** is performed at 0 °C in 20% aqueous HCl [219]. The propensity of non-deactivated pyrroles to undergo polymerization makes such substrates unsuitable for reactions that involve strongly acidic conditions.



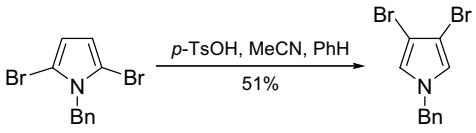
144 **147** **148** **149**

Scheme 4.46

4.5.1.3 **Halogenation**

Many electron rich halogenated pyrroles are rather unstable compounds that decompose readily upon exposure to air. Hence, in the early days, the availability

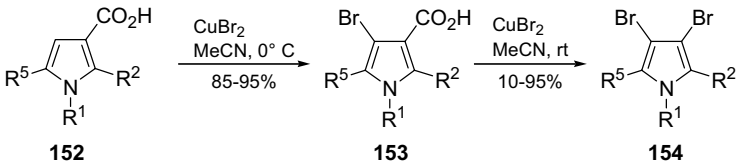
of such pyrrole derivatives was severely limited, although syntheses of several relatively stable iodinated pyrroles, for example 2,3,4,5-tetraiodopyrrole [222], as well as some other bromo- or iodopyrroles featuring additional electron-withdrawing substituents were described [223, 224]. An early study on the bromination of methyl pyrrole-2-carboxylate and pyrrole-2-carboxaldehyde under various conditions clearly demonstrated that formation of mixtures containing several halogenation products is a common course of many of these reactions, thus illustrating yet another complicating factor [225]. The labile 1-chloropyrrole, generated in 65–72% yield by chlorination of pyrrole with NaOCl, was shown to rearrange readily to give mixtures containing several species, such as 2-choro- and 3-chloropyrrole, when subjected to acidic conditions or heated in methanol [226]. Previous findings indicated that both 2-chloro- and 2-bromopyrrole undergo rapid degradation, 2-chloropyrrole being somewhat more stable. Introduction of 1-alkyl substituents increases the stability of these compounds, whereas the presence of C-alkyl groups appears to lead to even faster decomposition. Since hydrogen chloride, which is formed during degradation of 2-chloropyrrole, also catalyzes the decomposition, the process is probably autocatalytic. Stabilization can be effected to some extent by storage in the presence of a suitable base [227]. Consequently, practical halogenations of pyrroles are generally performed under mild conditions that avoid generation of acidic by-products. Bromination of some 1-alkylpyrroles with one or two equivalents of *N*-bromosuccinimide (NBS) in THF provides the corresponding 2-bromo- or 2,5-dibromopyrrole derivatives, respectively. Chlorination with *N*-chlorosuccinimide (NCS) in THF gives similar results, albeit with lower selectivity [228]. Interestingly, treatment of 1-methylpyrrole with NBS at $-78\,^{\circ}C$ to $-10\,^{\circ}C$ in THF employing PBr_3 as the catalyst selectively gives 3-bromo-1-methylpyrrole, whereas the use of one equivalent of triethylamine as the additive allows regiospecific synthesis of 2-bromo-1-methylpyrrole [229]. Notably, however, treatment of 1-alkylpyrroles with NCS in chloroform with or without $NaHCO_3$ leads instead to introduction of the *N*-succinimide moiety at C2 [230]. Application of *N*-halosuccinimides in DMF provides convenient access to a series of 2,5-disubstituted or 2,4,5-trisubstituted 3-chloro-, 3-bromo- and 3-iodopyrrole derivatives [231]. The selective rearrangement of 1-benzyl-2,5-dibromopyrrole (**150**) with *p*-toluenesulfonic acid into the product **151** (Scheme 4.47) is also worth mentioning in this context [232]. In general, 3,4-dihalopyrroles, even such lacking additional electron-withdrawing groups, are stable compounds, which have been studied in detail [233].



150 **151**

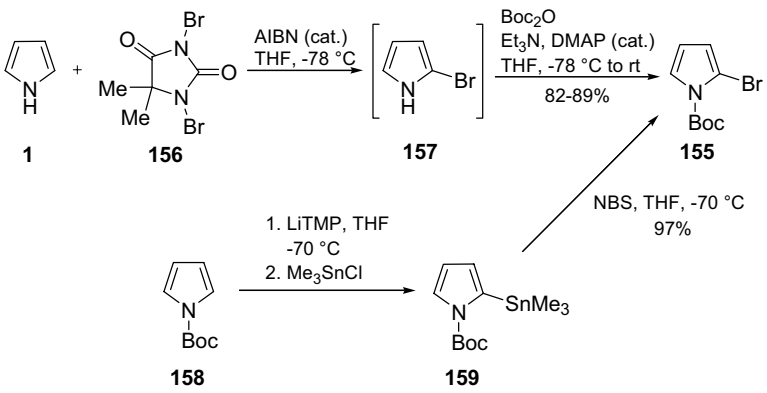
Scheme 4.47

As implied above, the introduction of electron-withdrawing groups increases the stability of halogenated pyrroles. Halogenation of a series of substituted 3-acetylpyrroles with $CuBr_2$ in acetonitrile gave the corresponding 3-acetyl-4-bromopyrrole derivatives in moderate to high yields [234]. Similar bromination of rather densely substituted pyrrole-3-carboxylates **152** furnished the 4-bromo derivatives **153**, which could in turn be converted into the 3,4-dibromopyrroles **154** with concomitant decarboxylation (Scheme 4.48) [235]. 1-Methyl-2-(trichloroacetyl)pyrrole undergoes regioselective bromination upon treatment with NBS in chloroform at −10 °C, rendering 4-bromo-1-methyl-2-(trichloroacetyl)pyrrole in 79% yield [236].



Scheme 4.48

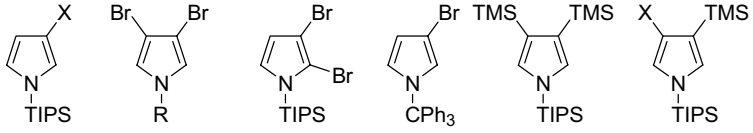
Stable and synthetically useful simple halogenated pyrroles have become readily available by introduction of the Boc protecting group (Scheme 4.49, cf. Section 4.5.1.6). Efficient preparation of 2-bromo-1-(*tert*-butoxycarbonyl)pyrrole **155**, as well as the related 2,5-dibromo derivative, has been accomplished by bromination of pyrrole with 1,3-dibromo-5,5-dimethylhydantoin **156**, followed by installation of the Boc-group on the intermediate 2-bromopyrrole **157** (Scheme 4.49) [237, 238]. On the other hand, 2,5-dibromo-1-(*tert*-butoxycarbonyl)pyrrole has also been obtained in 61% yield by exposure of **158** to NBS [239]. An alternative route to **155** encompasses conversion of 1-(*tert*-butoxycarbonyl)pyrrole (**158**) into the 2-stannyl derivative **159**, which thereafter undergoes a stannyl–bromo exchange reaction. 2-Bromo-1-(phenylsulfonyl)pyrrole may also be prepared in a similar manner [240]. The closely related 2-bromo-1-



Scheme 4.49

(*p*-toluenesulfonyl)pyrrole is readily available in two steps from pyrrole via bromination with 1,3-dibromo-5,5-dimethylhydantoin, followed by N-tosylation [241].

The presence of a bulky, removable N-substituent on the pyrrole nucleus enables introduction of halogen atoms at C3 and C4 even in the absence of stabilizing/blocking groups at C2 and/or C5. Initial studies on the bromination of the sterically hindered 1-(triisopropylsilyl)pyrrole (**160**) with two equivalents of NBS gave 3,4-dibromo-1-(triisopropylsilyl)pyrrole (**161**), along with the 2,3-dibromo derivative **162** in a 1 : 1 ratio. The use of only one equivalent of NBS afforded predominantly the 3-brominated derivative **163**, together with minor amounts of the 2-bromo isomer (ratio 97 : 3) [209, 242]. Improved conditions, featuring a portion-wise addition of NBS at −78 °C, allow selective preparation of **163** in 78% yield [243]. It was also later emphasized that careful temperature control is essential to suppress the formation of side products [244]. Consequently, useful and high-yielding procedures for the synthesis of **163** are available [244, 245]. Investigation of the synthetic potential of **160** also revealed that attempted chlorination with NCS gives complex mixtures of products and unchanged starting material, whereas iodination with elemental iodine in the presence of mercuric acetate provides **164** in 61% yield [244]. Blocking of the normal α-substitution pathway by a bulky N-substituent has also been employed in the monobromination of 1-tritylpyrrole with pyridinium bromide perbromide, which proceeds cleanly to afford 3-bromo-1-tritylpyrrole (**165**) in 75% yield [210]. Treatment of the pyrrole **166** with NBS gives the 3-bromo derivative **167** via *ipso*-bromination. Similarly, *ipso*-iodination of **166** to provide **168** can be achieved employing iodine in the presence of silver trifluoroacetate [246, 247]. In addition, 3,4-dibromo-1-(*p*-toluenesulfonyl)pyrrole (**169**) has been prepared in 43% yield by treatment of 1-(*p*-toluenesulfonyl)pyrrole with bromine in refluxing acetic acid [248].



160 X = H **161** R = TIPS **162** **165** **166** **167** X = Br
163 X = Br **169** R = Ts **168** X = I
164 X = I

Direct fluorination of pyrroles is a process of rather limited applicability, as the strongly oxidizing properties of most common fluorinating agents exert a highly destructive influence on the pyrrole nucleus. Nonetheless, XeF_2 has been employed successfully to convert pyrroles possessing an electron-withdrawing group into the corresponding α-fluoro derivatives in low to moderate yields [249, 250]. Other miscellaneous approaches include fluoro-decarboxylation of pyrrole-2-carboxylates with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) in modest yields [251], or photolysis of a pyrrole-β-diazonium tetrafluoroborate [252].

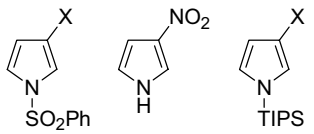
Halogenation on an α-methyl group of certain polysubstituted pyrroles with sulfuryl chloride in ether [253] or bromine in acetic acid [254] gives the corresponding α-(chloromethyl)- or α-(bromomethyl)pyrrole derivatives, respectively. Such halogenation processes have been suggested to occur via an initial electrophilic attack of the

pyrrole ring, followed by a rearrangement rendering the final α-(halomethyl)pyrrole products [255, 256].

4.5.1.4 Nitration

Because of the sensitivity of simple pyrroles towards strongly acidic media, nitration must be conducted under relatively mild conditions, or involve deactivated substrates. Nitration of pyrrole itself with nitric acid in acetic anhydride normally gives mixtures of 2-nitropyrrole and 3-nitropyrrole in a ratio of approximately 4 : 1 over a wide temperature range. The reactivities at C2 and C3 are 1.3×10^5 and 3×10^4 times higher than for benzene, respectively [257]. A similar reactivity pattern was observed in the case of 1-alkyl- and 1-aryl-pyrroles, with C2/C3 nitration ratios ranging between 3.15 : 1 for 1-methylpyrrole and 0.25 : 1 for 1-(*tert*-butyl)pyrrole, depending on the electronic and steric properties of the N-substituent. The high reactivity of pyrrole is further manifested in the easy formation of di-, tri-, and even tetranitropyrrole derivatives [258]. Introduction of a deactivating acyl group either on the nitrogen atom or at C2 also proved to be insufficient for selective nitration [259]. Selective and efficient (80% yield) conversion of pyrrole into 2-nitropyrrole has more recently been accomplished using $(NH_4)_2Ce(NO_3)_5 \cdot 4H_2O$ in acetic anhydride [260].

Other practical procedures are based on pyrroles having strategically located, strongly deactivating or bulky N-substituents. For example, 2-(trichloroacetyl)pyrrole (Section 4.5.1.6) may be nitrated with 90% HNO_3 at −50 °C to provide the corresponding 4-nitro derivative as the major product in 77% yield [212]. In addition, β-acylated pyrroles are cleanly converted into the corresponding 4-acyl-2-nitropyrroles upon treatment with nitric acid in acetic anhydride at −15 °C [259]. Likewise, an extensive series of 1,5-dialkyl-4-nitropyrrole-2-carboxylates has been prepared involving nitration of suitable precursors at C4 [261]. Nitration of 1-(phenylsulfonyl)pyrrole (**170**) with nitric acid in acetic anhydride provides a selective route to 3-nitropyrrole **171** [211, 262]. The parent 3-nitropyrrole (**172**) can thereafter be obtained after removal of the phenylsulfonyl group with base [262]. In addition, the readily available 1-(triisopropylsilyl)pyrrole (**160**) can serve as an excellent precursor to 3-nitropyrrole (**172**), as demonstrated by nitration of **160** with cupric nitrate trihydrate in acetic anhydride to give **173** (77% yield), which may subsequently be efficiently desilylated [244].



170 X = H
171 X = NO_2

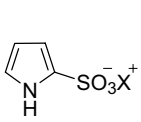
172

160 X = H
173 X = NO_2

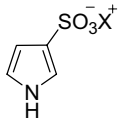
4.5.1.5 Reactions with Sulfur-Containing Electrophiles

Sulfonation of pyrrole with the sulfur trioxide–pyridine complex has long been recognized to give pyridinium pyrrole-2-sulfonate (**174**) [263, 264]. A more recent reinvestigation of this reaction provided, however, strong evidence that substitution

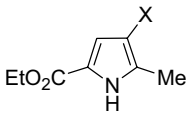
seems instead to occur at C3, leading to the isomeric pyridinium pyrrole-3-sulfonate (**175**), the formation of which was verified by detailed NMR studies of the corresponding sodium salt **176**, and preparation of several pyrrole-3-sulfonamides [265]. This intriguing preference for selective C3 substitution has yet to be rationalized in detail. When the pyrrole nucleus is already deactivated, sulfonation using acidic reagents is feasible, as illustrated by the transformation of the pyrrole **177** into the sulfonyl chloride **178** in 81% yield using chlorosulfonic acid [266]. Likewise, sulfonation of 1-(arylsulfonyl)pyrroles with chlorosulfonic acid in acetonitrile gives practical access to the corresponding pyrrole-3-sulfonyl chlorides in moderate yields [267]. Similar regioselectivity was observed upon treatment of 1-(phenylsulfonyl)pyrrole with dimethylsulfamoyl chloride in the presence of bismuth (III) trifluoromethanesulfonate, providing *N*,*N*-dimethyl-1-(phenylsulfonyl)pyrrole-3-sulfonamide in 49% yield. As noted in connection with studies of the latter reaction, one has to consider the possibility that the 3-substituted products may arise by a rearrangement of the conceivable 2-substituted products (see below), and further studies are required to gain deeper insight into the mechanistic pathways of such transformations [268].



174 $X^+ = C_5H_6N^+$

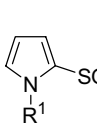


175 $X^+ = C_5H_6N^+$
176 $X^+ = Na^+$

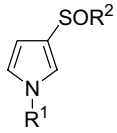


177 X = H
178 X = SO_2Cl

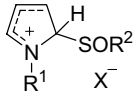
The reaction of pyrrole and 1-methylpyrrole with alkyl- or aryl-sulfinyl chlorides at 0 °C offers a route to the 2-sulfinylpyrroles **179** (R^1=H or Me) in moderate to good yields, provided that the products are protected from the influence of the liberated hydrogen chloride. Without that precaution, rearrangement of the kinetic products **179** affords the corresponding C3 substituted isomers **180** as the major products. This outcome could be ascribed to an initial protonation of **179** to generate the intermediate **181**, which may thereafter undergo a sigmatropic rearrangement, followed by loss of a proton to give **180**. Crossover experiments also indicated the possibility of an intermolecular process involving dissociation of the complex **181**. Clean conversion of **179** into **180** can be effected by treatment with *p*-toluenesulfonic acid [269] or TFA [270]. Introduction of the phenylsulfinyl group at C2 may also be accomplished using *N*-(phenylsulfinyl)succinimide [269].



179

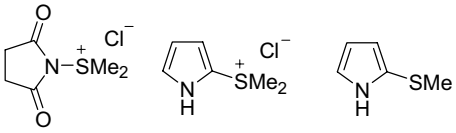


180



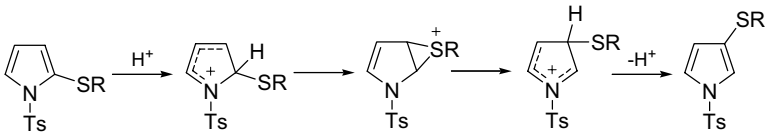
181

Several different approaches are available for the synthesis of (alkylthio)- or (arylthio)pyrroles. Treatment of pyrrole with the *N*-chlorosuccinimide–dimethyl sulfide adduct **182** (formed *in situ*) afforded the salt **183**, which could then subsequently be converted, by thermal decomposition, into 2-(methylthio)pyrrole **184** in 58% overall yield [271]. Reaction of 1-alkylpyrroles with 1-(methylthio) morpholine in the presence of acid, or, even better, excess pyridine, gives access to 2,3,4,5-tetra(methylthio)pyrroles [272]. Exposure of 2-thiocyanatopyrrole (see below) to phenyl- [273] or alkylmagnesium bromides [274] provides useful routes to 2-(phenylthio)pyrrole or the corresponding 2-(alkylthio)pyrroles, respectively. Notably, the alkylthio unit serves as a protecting group for the α-position of pyrrole in a new approach to dipyrromethanes [274]. A synthesis of densely substituted 3,3′-dipyrrolyl sulfides possessing electron-withdrawing groups by treatment of suitable pyrroles having a vacant β-position with sulfur dichloride has also been reported [275].



182 **183** **184**

In analogy to the behavior of the sulfoxides **179** (see above), the 2-(alkylthio) pyrroles **185** undergo rearrangement to furnish the isomeric C3 substituted derivatives **186** exclusively in good yields upon heating in a 1 : 1 mixture of TFA and 1,2-dichloroethane (Scheme 4.50) [276]. This behavior contrasts with the propensity of unprotected or N-methylated 2-(alkylthio)pyrroles and 3-(alkylthio)pyrroles to undergo acid induced equilibration under mild conditions [277]. The events leading to the conversion of **185** into **186** have been suggested to involve an initial protonation to provide the intermediate **187**, subsequent rearrangement via the episulfonium salt **188** to the C3-substituted intermediate **189**, and a final deprotonation. This mechanistic rationale was supported by crossover experiments, as no crossover products could be detected [276].



185 **187** **188** **189** **186**

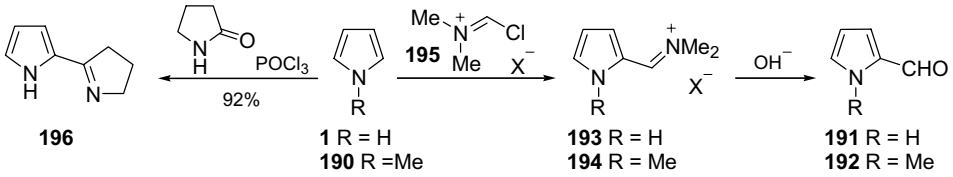
Scheme 4.50

Thiocyanation of pyrroles with cupric thiocyanate [278, 279], thiocyanogen chloride [276] or, more conveniently, ammonium thiocyanate in the presence of iodine in methanol [280] or CAN [281], provides access to 2-thiocyanatopyrroles.

4.5.1.6 **Acylation**

Several useful procedures for N-acylation of pyrroles are available, for example by acyl transfer from 1-acetylimidazole, which offers an efficient route to 1-acetylpyrrole [282]. Alternative attractive methods for N-acylation rely on the use of acetic anhydride [283], or acyl chlorides in the presence of and triethylamine and DMAP as the catalyst [284]. Exposure of pyrroles to di(*tert*-butyl)dicarbonate in the presence of DMAP in acetonitrile solution gives access to many useful 1-(*tert*-butoxycarbonyl) pyrroles in high yields [285].

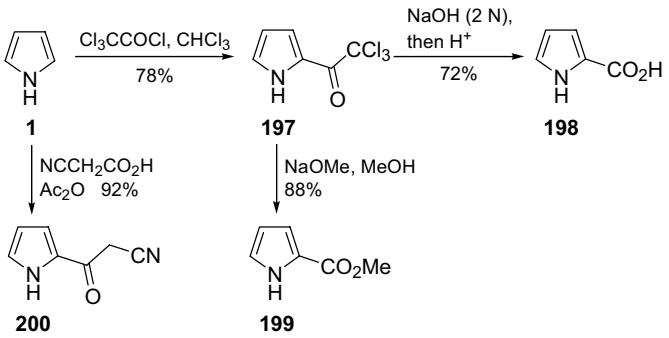
Formylation of pyrrole is most conveniently accomplished using the Vilsmeier–Haack reaction. Both pyrrole (**1**) [286, 287], 1-methylpyrrole (**190**) [287], as well as several C-methyl derivatives thereof [288], provide excellent yields of the corresponding pyrrole-2-carboxaldehydes **191** and **192** via the intermediates **193** and **194**, respectively, upon treatment with the reagent **195** [289], which is readily generated *in situ* from $POCl_3$ and DMF (Scheme 4.51). The presence of N-alkyl groups larger than methyl leads to mixtures of products formylated at C2 and C3, while sterically demanding N-substituents favor substitution at C3 over C2. Thus, for instance, for 1-*tert*-butylpyrrole the ratio of products is 14 : 1 in favor of 1-(*tert*-butyl)pyrrole-3-carboxaldehyde. The reactivity differences in the 1-arylpyrrole series are less pronounced (with prevalence for the C2 products), and are influenced by both steric and electronic effects. Formylation of 1-acetyl-, 1-benzoylpyrrole and ethyl pyrrole-2-carboxylate leads exclusively to substitution at C2 [290]. Interestingly, Friedel–Crafts acylation of intermediates such as **193** and **194**, followed by hydrolysis, provides a one-pot procedure to 4-acylpyrrole-2-carboxaldehydes due to the strong "meta"-directing properties of the iminium substituent [291]. Salts related to **193** have also been exploited in reactions with bromine or SO_2Cl_2, eventually yielding various pyrrole-2-carboxaldehyde derivatives halogenated at C4, or C4 and C5 [292]. Vilsmeier–Haack-type reagents generated from pyrophosphoryl chloride lead to increased preference for substitution at C3 due to more pronounced steric interaction with N-substituents [293]. Likewise, treatment of 1-(triisopropylsilyl)pyrrole with iminium salts gives substitution at C3 [294]. When extended to lactams, the Vilsmeier–Haack reaction allows preparation of imines such as **196** [295], whereas the use of *N*,*N*-dimethylamides, for instance DMA, provides an effective route to 2-acylpyrroles [296]. In addition, exposure of pyrroles to Vilsmeier–Haack reagents generated from aroylamides gives good yields of 2-aroylpyrroles [297]. An approach to 3,4-dialkylpyrrole-2,5-dicarboxaldehydes relying on treatment of 3,4-dialkylpyrrrole-2-carboxylic acids with triethyl orthoformate in TFA has also been described [298].



196 | **1** R = H, **190** R = Me | **193** R = H, **194** R = Me | **191** R = H, **192** R = Me

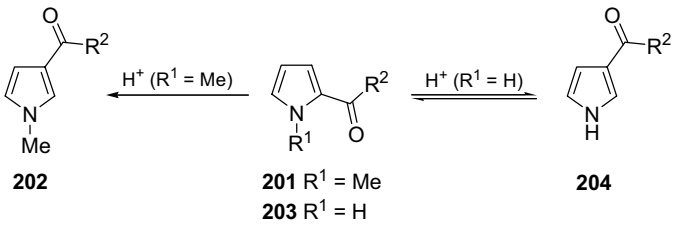
Scheme 4.51

Pyrroles are readily acylated at C2, as exemplified by the selective conversion of pyrrole itself into 2-(trichloroacetyl)pyrrole **197** (Scheme 4.52). This material provides easy access to pyrrole-2-carboxylic acid (**198**) upon alkaline hydrolysis [299]. Likewise, treatment of pyrrole with TFAA in the presence of *N,N*-dimethylaniline gave the corresponding trifluoroacetyl derivative, which could also be efficiently converted into **198** [300]. Alcoholysis of 2-(trichloroacetyl)pyrroles enables preparation of the corresponding esters, for example, methyl pyrrole-2-carboxylate (**199**). This reaction is, however, synthetically useful only with primary alcohols [301]. Acetylation with acetic anhydride is not practical, as it has been reported to give 2-acetylpyrrole in 39% yield, and minor amounts (8%) of the C3 acetylated isomer [302]. In contrast, acylation of pyrrole with cyanoacetic acid in acetic anhydride allows smooth introduction of a cyanoacetyl functionality, giving **200**. Alkylpyrroles are also cyanoacetylated at C2, unless both C2 and C5 are substituted, leading instead to 3-(cyanoacetyl)pyrrole derivatives in good yields [303]. Both pyrrole itself, as well as 1-methylpyrrole, are also effectively acylated at C2 using *N*-acylbenzotriazoles in the presence of $TiCl_4$ [304].



Scheme 4.52

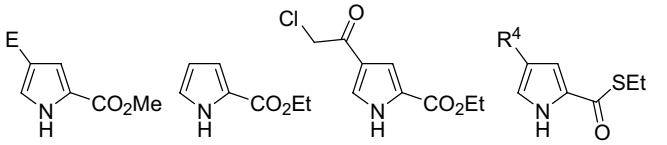
Studies on the acid mediated rearrangements of acylpyrroles under anhydrous conditions revealed that 2-acylpyrroles possessing an N-methyl group (**201**) undergo conversion into the corresponding 3-acylpyrroles (**202**). In contrast, the parent 2-acylpyrroles (**203**) give equilibrium mixtures containing **203** and **204** under similar conditions (Scheme 4.53). Experiments aimed at explaining this discrepancy failed to



Scheme 4.53

give conclusive results, although it seems likely that a 1,2-acyl shift of a C2-protonated intermediate is involved [305].

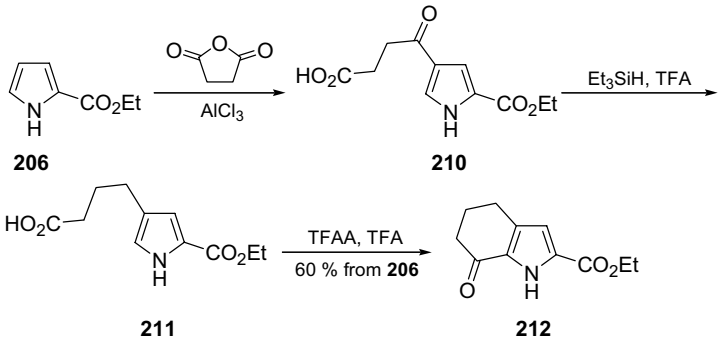
Pyrroles acylated at C2 are valuable precursors for elaboration to more complex derivatives. As a result of the deactivating and "meta" directing properties of the trichloroacetyl group, 2-(trichloroacetyl)pyrrole **197** undergoes electrophilic substitution at C4 with various reagents, producing the substituted methyl pyrrole-2-carboxylates **205** (E=Cl, Br, I, COMe) in good overall yields after subsequent methanolysis [212]. The scope and limitations of Friedel–Crafts acylation reactions of ethyl pyrrole-2-carboxylate (**206**) using acyl chlorides have been evaluated in detail, leading to the conclusion that selective C4 acylation or aroylation is best achieved employing $AlCl_3$ as the catalyst, as the use of weaker Lewis acids, such as zinc chloride or boron trifluoride etherate, affords mixtures of C4 and C5 substituted products. This approach allows efficient syntheses of potentially useful pyrroles, for instance **207** [306]. Chlorination of **199** with two equivalents of SO_2Cl_2 in chloroform gives the corresponding 4,5-dichloro derivative, which may be subsequently iodinated at C3 using iodine in the presence of silver trifluoroacetate to provide methyl 4,5-dichloro-3-iodopyrrole-2-carboxylate, a useful partner for regioselective Suzuki reactions (Section 4.5.11) [307]. Pyrrole-2-carbonitrile, which is readily available by treatment of pyrrole with chlorosulfonyl isocyanate followed by warming in DMF [308], displays similar reactivity, affording 4-substituted pyrrole-2-carbonitriles [308, 309]. Likewise, ethyl pyrrole-2-thiolcarboxylate (**208**) (readily prepared by the action of ethyl chlorothiolformate on pyrrolyl magnesium halides) also takes part in electrophilic substitution reactions, providing good yields of 2,4-disubstituted pyrroles, for example **209**. These products can thereafter be converted into the corresponding 3-substituted pyrroles by treatment with Raney nickel [310] or to 3-alkylpyrroles by Wolff–Kishner reduction with concomitant decarboxylation [311]. A detailed study describing the applicability of β-acylpyrroles as useful substrates for Friedel–Crafts reactions leading to 2,4-diacylpyrroles is also available [312].



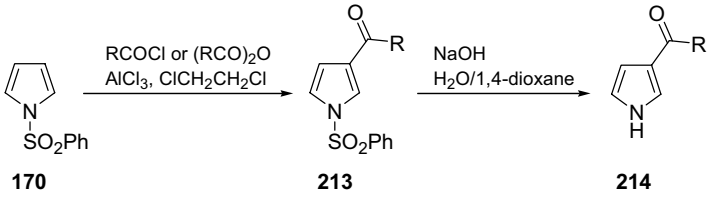
205 **206** **207** **208** R^4 = H **209** R^4 = COMe

In an interesting application of Friedel–Crafts chemistry, treatment of **206** with succinic anhydride in the presence of $AlCl_3$ gave the 2,4-disubstituted pyrrole **210**. Reduction of the ketone functionality of **210** afforded **211**, which was eventually subjected to an acid induced intramolecular acylation, leading to the fused system **212** in 60% overall yield (Scheme 4.54) [313].

The synthetic potential in acylation reactions of pyrrole derivatives possessing removable, strongly electron withdrawing, or bulky N-substituents, is nicely demonstrated by the selective and efficient conversion of 1-(phenylsulfonyl)pyrrole **170** (Section 4.5.1.4) into the corresponding C3 acylated products **213** (Scheme 4.55)



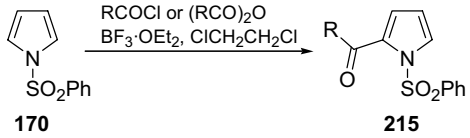
Scheme 4.54



Scheme 4.55

upon treatment with acyl chlorides or carboxylic acid anhydrides in the presence of $AlCl_3$. An ensuing base-induced cleavage of the N-phenylsulfonyl group provides excellent overall yields of pyrroles **214** (R=alkyl or aryl) [211, 262, 314, 315]. However, there are cases when mixtures of C2 and C3 acylated products have been encountered in connection with related reactions involving relatively electron rich aroyl chlorides [316, 317]. Even though similar selectivity problems were noted during the reaction of **170** with 1-naphthoyl chloride in the presence of $AlCl_3$, selective C3 substitution was achieved by using nitromethane as the co-solvent [318]. Acylation at C3 may also be conveniently performed employing 1-(triisopropylsilyl) pyrrole as the substrate [244]. 1-(Triisopropylsilyl)pyrrole may be selectively acylated at C3 upon reaction with 1-acylbenzotriazoles assisted by $TiCl_4$ in refluxing CH_2Cl_2 [304].

In contrast, when $BF_3{\cdot}OEt_2$ instead of $AlCl_3$ is used as the catalyst during acylation of **170**, a dramatic change in regioselectivity is induced, as exclusive formation of the 2-substituted products **215** takes place (Scheme 4.56), providing an alternative route to the parent 2-acylpyrroles after removal of the protecting group under basic conditions. Although attempts to rationalize these differences in regioselectivity in terms of kinetic, steric or electronic factors have been made, no clear conclusions could be drawn [315]. A new contribution to this field allows selective α-acylation of 1-(*p*-toluenesulfonyl)pyrroles with carboxylic acids and TFAA, presumably involving mixed anhydrides as the acylating agents [319]. Friedel–Crafts acylation of 3-alkyl-1-(phenylsulfonyl)pyrroles with acetic anhydride also proceeds with pronounced

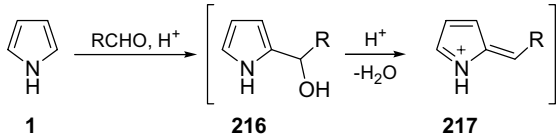


Scheme 4.56

selectivity, provided that the alkyl group at C3 is not too bulky, giving 2-substitution with $AlCl_3$, and 5-substitution with $BF_3{\cdot}OEt_2$ [320].

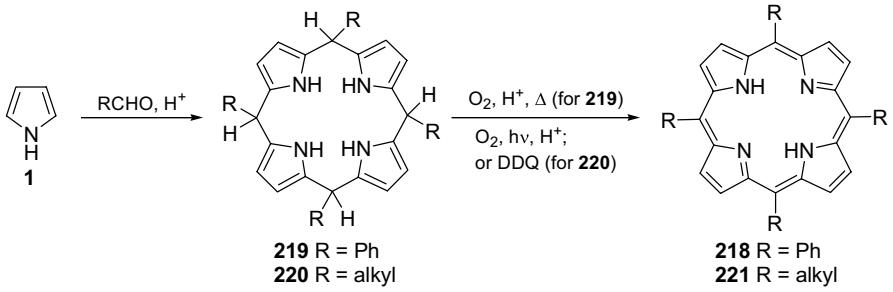
4.5.1.7 Reactions with Aldehydes, Ketones, Nitriles and Iminium Ions

The reactions of pyrroles with aldehydes and ketones have been studied extensively, as some of these transformations constitute powerful tools for the construction of the important porphyrin skeleton. Treatment of pyrrole with aldehydes in the presence of acid initially generates the intermediate carbinols **216** (Scheme 4.57), which readily lose water to provide the highly electrophilic 2-alkylidenepyrrolium (azafulvenium) ions **217** (Section 4.5.10).



Scheme 4.57

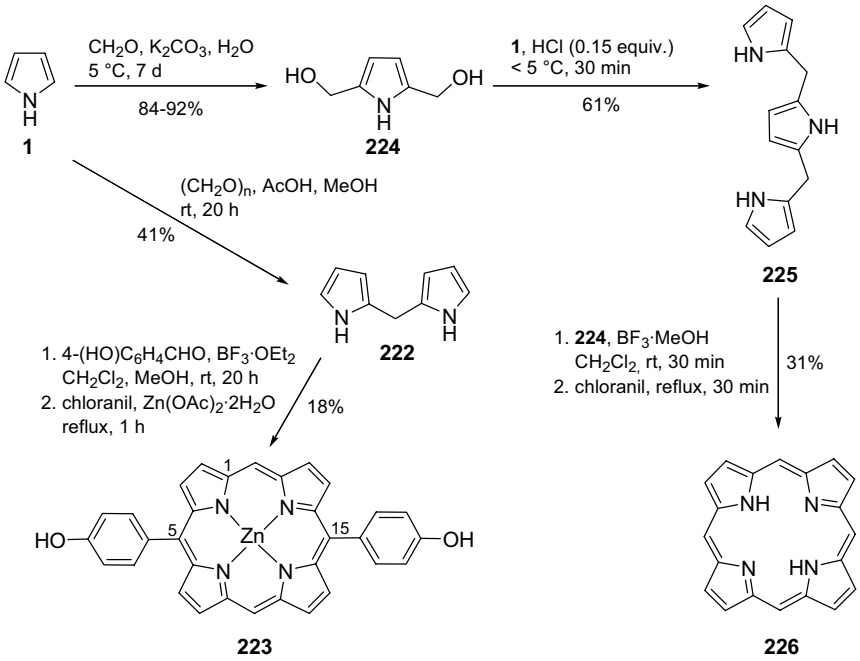
Such condensation reactions eventually lead to the formation of porphyrins (Scheme 4.58) [321, 322], along with other oligomeric or polymeric products [323], for instance so-called "N-confused porphyrins," which are porphyrin isomers featuring a pyrrole unit linked through its α and β′ positions [324–327]. A widely used older procedure for the preparation of *meso*-tetraarylporphyrins **218** involves heating of pyrrole with an appropriate benzaldehyde in propionic acid (Scheme 4.58) [328]. This process involves the intermediacy of the porphyrinogens



Scheme 4.58

219, which subsequently spontaneously undergo a rate limiting air oxidation step leading to **218** [329]. More recently it has been demonstrated that pyrrole and benzaldehydes react reversibly at ambient temperature in the presence of an acid catalyst to provide porphyrinogens, which may subsequently be irreversibly converted into the corresponding porphyrins by addition of an oxidant. Consequently, the method of choice relies on initial reaction of pyrrole with an appropriate benzaldehyde in anhydrous CH_2Cl_2 in the presence of $BF_3{\cdot}OEt_2$ or TFA at room temperature, followed by treatment of the resulting mixture with *p*-chloranil at reflux [330]. Reactions involving aliphatic aldehydes generate relatively stable *meso*-tetraalkylporphyrinogens (**220**), the conversion of which into the corresponding *meso*-tetraalkylporphyrins (**221**) requires an additional forced oxidation step [331, 332]. Likewise, condensation of pyrrole and acetone in the presence of acid gives a good yield of a cyclic tetramer [333, 334]. In contrast, the reactions between pyrrole and ortho esters under acidic conditions give rise to tris(pyrrol-2-yl)alkanes [335, 336]. Moreover, condensation reactions between suitable pyrrole fragments and pyrrole-2-carboxaldehyde derivatives constitute a common strategy to numerous dipyrrins and dipyrrinones [337].

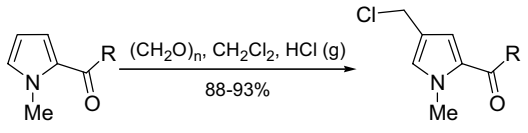
Under carefully controlled conditions, the reaction of pyrrole with formaldehyde may give bis(pyrrol-2-yl)methane (dipyrromethane) (**222**), which is a useful precursor for the synthesis of 5,15-disubstituted porphyrins, for example **223** (Scheme 4.59) [335]. Exposure of aldehydes to excess pyrrole, in the presence of



Scheme 4.59

TFA or $BF_3{\cdot}OEt_2$ as catalysts, constitutes an effective protocol (yields up to 86%) for the preparation of *meso*-substituted dipyrromethanes [338]. Alternatively, such systems are also effectively generated in 5 min from pyrrole and aldehydes (ratio 25 : 1) in the presence of TFA (0.1 equiv.) [339], or in water solution with catalytic amounts of HCl [340]. Treatment of pyrrole with formalin under basic conditions permits isolation of the dialcohol **224**, which can subsequently react with two equivalents of pyrrole to provide trimer **225**, which is an excellent precursor to the parent macrocycle **226** [341].

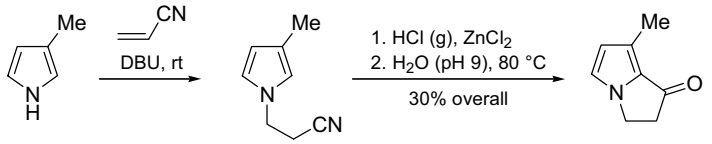
In a related process, the 2-acylpyrroles **227** (R=CF_3, CO_2Et) have been exposed to paraformaldehyde in the presence of HCl under anhydrous conditions, leading to efficient and selective chloromethylation to render the disubstituted pyrroles **228** (Scheme 4.60) [342].



227 **228**

Scheme 4.60

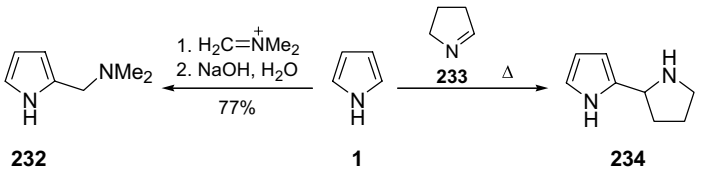
Application of a nitrile as the electrophilic reagent has been utilized in a concise one-pot synthesis of the monarch butterfly pheromone danaidone (**229**), wherein N-alkylation of 3-methylpyrrole (**230**) with acrylonitrile in the presence of DBU gave the intermediate **231**, which subsequently underwent intramolecular cyclization, followed by hydrolysis of the intermediate imine (Scheme 4.61) [343].



230 **231** **229**

Scheme 4.61

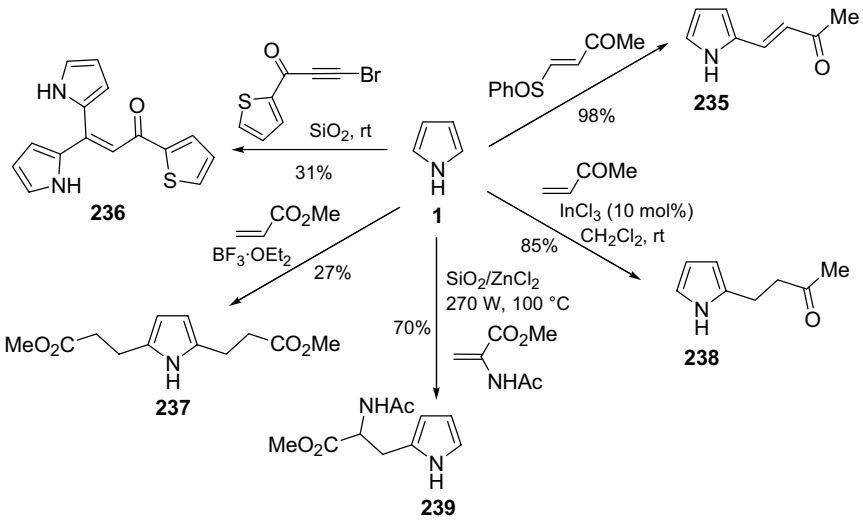
Pyrroles also react readily with iminium ions, generated *in situ* from formaldehyde and dialkylamines in acetic acid, to provide 2-(dialkylaminomethyl)pyrroles, which are useful synthetic intermediates (Section 4.5.10), or with the Vilsmeier–Haack reagent, affording pyrrole-2-carboxaldehydes (Section 4.5.1.6). Likewise, pyrrole (**1**) may be converted in high yield into 2-(dimethylaminomethyl)pyrrole **232** via the Mannich reaction (Scheme 4.62) [344]. It has also been found that pyrrole adds upon heating (neat) to 1-pyrroline **233**, leading to 2-(pyrrolidin-2-yl)pyrrole (**234**) [345].



Scheme 4.62

4.5.1.8 Conjugate Addition to α,β-Unsaturated Carbonyl Compounds

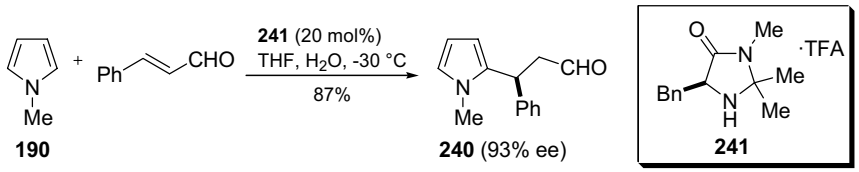
Pyrroles are useful nucleophiles in conjugate addition reactions (Scheme 4.63). For instance, pyrrole has been alkenylated efficiently by treatment with (*E*)-4-(phenylsulfinyl)-3-buten-2-one to furnish the alkenyl derivative **235**. This reaction probably proceeds via a sequence featuring a Michael addition, followed by elimination of phenylsulfenic acid [346]. Addition of pyrrole to 1-acyl-2-bromoacetylenes in the presence of silica gives rise to modest yields of di(pyrrol-2-yl)ethenes, for example **236**, as the major products [347]. When the silica is replaced by alumina under solvent free conditions, pyrroles ethynylated at C2 are produced in useful yields [348]. Addition of pyrrole to methyl acrylate occurs in the presence of $BF_3{\cdot}OEt_2$, providing the diester **237** [349]. Other Lewis acids, such as $InCl_3$, can also catalyze such processes efficiently, as illustrated by the synthesis of **238** [350]. Silica supported zinc chloride has been demonstrated to promote conjugate addition of pyrrole to methyl α-acetamidoacrylate under microwave irradiation to give the amino acid derivative **239** in considerably better yield than under conventional thermal conditions [351]. Michael addition of pyrroles to a series of electron deficient alkenes under microwave irradiation has also been performed without solvent in the presence of silica gel only,



Scheme 4.63

whereas reactions involving some more sluggish substrates required the use of catalytic amounts of $BiCl_3$ [352]. A further development includes the efficient addition of pyrroles to electron deficient alkenes in water catalyzed by aluminium dodecyl sulfate trihydrate [353].

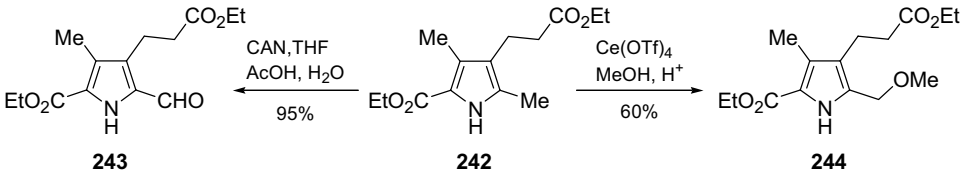
An interesting modern contribution to this field is the asymmetric Friedel–Crafts-type alkylation of pyrroles with α,β-unsaturated carbonyl compounds, which has, for example, been achieved employing organocatalysis by chiral imidazolinones, as illustrated by the conversion of 1-methylpyrrole (**190**) into the product **240** (Scheme 4.64) [354]. A study of additions of pyrroles to a set of α,β-unsaturated 2-acylimidazoles demonstrated that such reactions can also proceed with high yields and enantioselectivity using a bis(oxazolinyl)pyridine scandium(III) triflate complex as the catalyst [355].



Scheme 4.64

4.5.2 Reactions with Oxidants

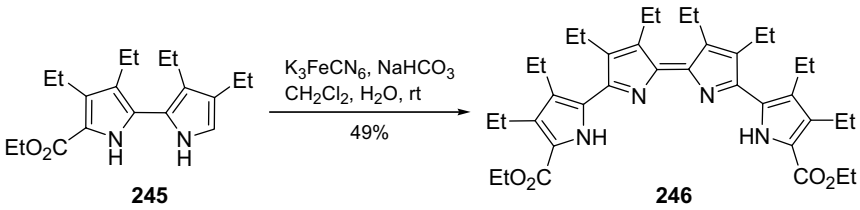
Powerful oxidants usually have a severely destructive effect on pyrroles, often leading to extensive decomposition or rather complex product mixtures [356]. Consequently, most useful transformations involving pyrroles and oxidizing agents require careful matching of substrates and reagents. A reaction belonging to this category is the oxidation of α-methylpyrroles to the corresponding carboxaldehydes, which can be effected by using $Pb(OAc)_4/PbO_2$ as the oxidant system [357]. Certain 2-methylpyrroles have also been successfully oxidized employing $Pb(OAc)_4$ [358]. The oxidation of pyrrole α-methyl groups with ceric ammonium nitrate (CAN) provides a reliable and selective route to the corresponding carboxaldehydes, as exemplified by the conversion **242** into the aldehyde **243** (Scheme 4.65) [359]. An extension of this approach allows, for example, preparation of the 2-(methoxymethyl)pyrrole derivative



Scheme 4.65

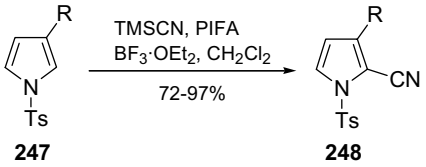
244 using ceric triflate in methanol [360]. Substituted pyrrolecarboxaldehyde derivatives have also been accessed by oxidation of the corresponding α-methylpyrroles with IBX in DMSO [96]. An alternative route to pyrrole-2-carboxaldehydes involves oxidative cleavage of 2-(polyhydroxyalkyl)pyrroles with CAN [361]. In cases where the pyrrole nucleus is strongly deactivated, oxidation of an aldehyde functionality at C2 to the corresponding carboxylic acid may be achieved using the strong oxidant $KMnO_4$ [362].

A useful oxidative coupling reaction has been elaborated, providing access to quarter-, penta- and sexipyrrole derivatives. For instance, coupling of the 2,2′-bipyrrole **245** with K_3FeCN_6 afforded the system **246** (Scheme 4.66), which could thereafter be converted into its reduced form by treatment with $NaBH(OAc)_3$ [363].



Scheme 4.66

Treatment of the 1-(*p*-toluenesulfonyl)pyrroles **247** with phenyliodine bis(trifluoroacetate) (PIFA) and $BF_3{\cdot}OEt_2$ in the presence of TMSCN gives the pyrrole-2-carbonitrile derivatives **248** (Scheme 4.67). This cyanation reaction was suggested to involve initial formation of a pyrrole radical cations, which thereafter react with cyanide ions by a one-electron oxidation, giving the final products after deprotonation [364]. Similar radical cation intermediates are presumably involved in the PIFA/TMSBr (bromotrimethylsilane) mediated oxidative coupling of electron rich pyrroles to bipyrroles [365].



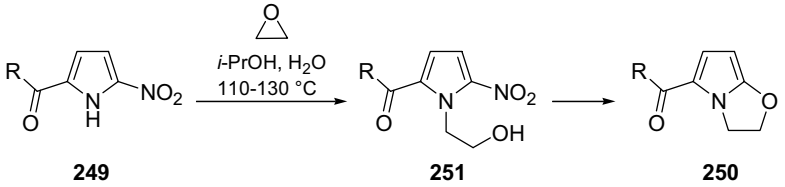
Scheme 4.67

The action of benzoyl peroxide on 1-alkyl- or 1-arylpyrroles leads to mixtures of the corresponding 2-hydroxy- and 2,5-dihydroxypyrrole-*O*-benzoates, whereas pyrrole itself gives only intractable mixtures under the same conditions [366]. Careful oxidation of pyrrole with hydrogen peroxide gives a modest yield of 3-pyrrolin-2-one (Section 4.6.3).

4.5.3
Reactions with Nucleophiles

Owing to their electron rich properties, most pyrroles are relatively unreactive towards nucleophilic reagents, with the exception of some derivatives or intermediates having strongly electron-withdrawing substituents, or carrying a positive charge resulting from, for instance, protonation (Section 4.5.1.2).

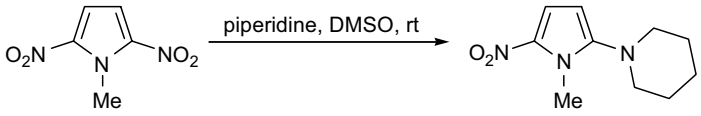
Treatment of the nitropyrroles **249** with ethylene oxide provides a route to the pyrrolo[2,1-*b*]oxazoles **250** via intramolecular displacement of the nitro group in the intermediates **251** (Scheme 4.68) [367]. Intramolecular displacement of methanesulfinate- or bromide ions at C2 in electron deficient pyrroles by sodium enolates constitutes an alternative approach to [1,2-*a*]-fused pyrrole derivatives [271].



249 **251** **250**

Scheme 4.68

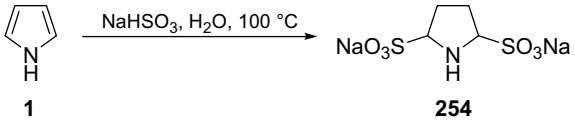
The rather electron deficient molecule 1-methyl-2,5-dinitropyrrole (**252**) reacts with piperidine in DMSO to produce the substitution product **253** (Scheme 4.69). A similar reaction occurs more readily with methoxide [368], and the rate is further enhanced by the presence of an additional electron-withdrawing substituent (NO_2, CN) at the adjacent C3 position [369]. Likewise, exposure of 1-methyl-2,3-dinitropyrrole to sodium methoxide in methanol furnishes 2-methoxy-1-methyl-3-nitropyrrole in 93% yield [370]. The treatment of 1-alkyl-2-nitropyrroles with Grignard reagents gives mixtures of C3- and C5 alkylated products [371], whereas treatment of the anion of chloromethyl phenyl sulfone affords the corresponding 5-substituted 1-alkyl-2-nitropyrrole derivatives via vicarious nucleophilic substitution [372]. It has also been established that the bromine atom in 2-acetyl-5-bromo-1-methyl-4-nitropyrrole may be displaced with various nucleophiles, such as azide, cyanide, alkoxides, thiophenols or amines [373].



252 **253**

Scheme 4.69

An unusual example of nucleophilic attack has been observed upon heating pyrrole with sodium hydrogen sulfite, affording the pyrrolidine derivative **254** (Scheme 4.70). This transformation presumably involves the intermediacy of a C3 protonated pyrrole [374].

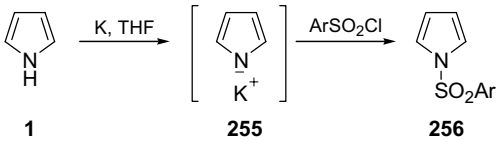


Scheme 4.70

4.5.4 Reactions with Bases

4.5.4.1 N-Metallated Pyrroles

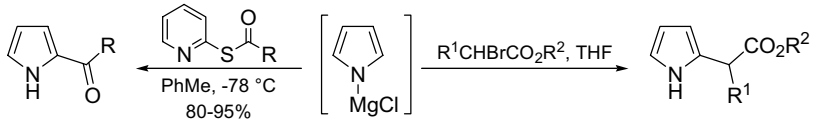
As a consequence of its weakly acidic properties [13–15], pyrrole will react readily with virtually any strong base to generate a reactive ambident pyrrolyl anion, which can either undergo reaction with electrophiles at the nitrogen atom or at C2/C3. The reaction site is dependent on the properties of the metal–nitrogen bond, and on the solvating power of the solvent used. In general, N-substitution is favored by increasing ionic character of the metal–nitrogen bond, and by stronger solvating power (polarity) of the solvent [375, 376]. Treatment of pyrrole (**1**) with potassium metal gives the salt **255** [377], which can thereafter be converted into a wide variety of N-substituted derivatives, for instance the useful 1-(arylsulfonyl)pyrroles **256** (Scheme 4.71) [378]. Such procedures have now in most cases been supplanted by modern methods, and the pyrrole anion is now usually generated by treatment of pyrrole with commercially available alkyl lithiums [377, 379]. N-Alkylation of **255** formed by deprotonation of pyrrole by KOH in DMSO offers a high-yielding route to 1-alkylpyrroles [380], although several more convenient and effective procedures rely on phase transfer conditions using 18-crown-6 as the catalyst, in combination with KOH in anhydrous benzene [381], or with potassium *tert*-butoxide in diethyl ether [382]. Phase transfer alkylation of pyrrole by alkyl halides with aqueous NaOH in CH_2Cl_2 in the presence of tetrabutylammonium bromide constitutes a useful alternative [383]. Interestingly, 2,5-dialkylpyrrolyl anions generated in the superbase system KOH–DMSO will instead react at C3 with carbon disulfide, providing a route



Scheme 4.71

to pyrrole-3-carbodithioates [384]. The pyrrolyl anion is also easily converted into the corresponding 1-silylated pyrroles by treatment with triisopropylsilyl chloride (TIPSCl) [244] or *tert*-butyldimethylsilyl chloride (TBSCl) [385], as well as with other trialkylsilyl chlorides [386]. The high reactivity of the pyrrolyl anion is neatly demonstrated by the reaction of pyrrolylsodium with hexafluorobenzene, which gives hexa(pyrrol-1-yl)benzene via a S_NAr mechanism [387]. Pyrrolylthallium(I), prepared from pyrrole and thallium(I) ethoxide, can also be utilized for N-alkylation of pyrroles [388], but should perhaps be avoided because of its toxicity.

Pyrrolylmagnesium halides, which are easily prepared by the action of alkylmagnesium halides on pyrrole, display more complex reactivity patterns towards most alkylating agents, rendering mixtures of C2 and C3 substituted products, as well as di- and tri-alkylpyrroles [383, 389]. In contrast, acylation of pyrrolylmagnesium halides is more selective, giving 2-acylpyrroles as the prevailing products [390]. Excellent selectivity for C2 acylation of pyrrolylmagnesium chloride **257** under mild conditions can be achieved by treatment with readily available 2-pyridylthiol esters, which gives high yields of the corresponding 2-acylpyrroles **258** (Scheme 4.72), probably as a result of coordination of the pyridine nitrogen atom to the magnesium [391]. The reaction of **257** with alkyl bromoacetates is an efficient way for selective synthesis of the alkyl (pyrrol-2-yl)acetates **259**, which is in this case mediated by coordination between the metal and the carbonyl oxygen of the alkylating agent [392]. A series of (pyrrole-2-yl)acetone derivatives have been prepared by employing a new heteroarylation reaction involving the pyrrolyl anion and suitable enolates in the presence of a Cu(II) oxidant [393]. Transmetallation of pyrrolylsodium with $ZnCl_2$ gives pyrrolylzinc chloride, which undergoes perfluoroalkylation at C2 upon exposure to perfluoroalkyl iodides in the presence of $PdCl_2(PPh_3)_2$ (10 mol.%) and PPh_3 [394].

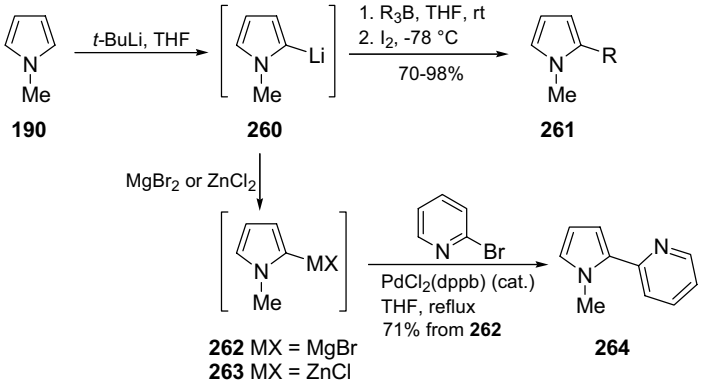


258 **257** **259**

Scheme 4.72

4.5.4.2 C-Metallated Pyrroles

Pyrroles possessing suitable N-blocking substituents undergo C-metallation upon treatment with sufficiently strong bases. Initial studies early established that 1-methylpyrrole (**190**) is slowly metallated at C2 using BuLi in ether to give 2-lithio-1-methylpyrrole (**260**) (Scheme 4.73) [379], but the yield of the lithiopyrrole is improved significantly if *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) is used as the additive [395]. It was later demonstrated that quantitative and selective generation of **260** is easily achieved using 2.5 equivalents of BuLi in hexane at ambient temperature in the presence of TMEDA [396], while a larger excess (4.5 equivalents) of BuLi and elevated temperatures promotes increasing formation of 2,5- and 2,4-dilithio- derivatives [396, 397]. Generation of **260** may also be carried out using BuLi at

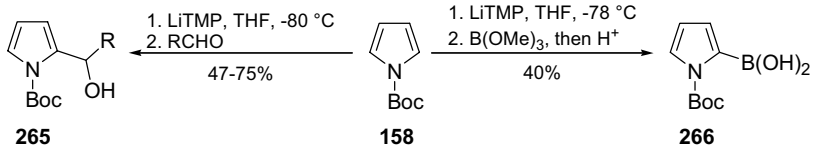


Scheme 4.73

ambient temperature in THF–hexane (2 : 1). This lithiopyrrole will subsequently react readily with a wide variety of electrophiles [398], and may for example also be converted into the 2-alkyl-1-methylpyrroles **261** by treatment with trialkylboranes, followed by addition of iodine or NCS [399, 400]. Quenching of 2-lithio-1-methyl-5-*n*-octylpyrrole with *N*-fluorodibenzenesulfonamide has been used to prepare the labile 2-fluoro-1-methyl-5-*n*-octylpyrrole [401]. Transmetallation of **260** formed from 1-methylpyrrole and *t*-BuLi with $MgBr_2$ or $ZnCl_2$ gives the corresponding metallated pyrroles **262** and **263**, which can subsequently participate in palladium-catalyzed cross-coupling reactions leading to 2-arylpyrroles, or to the 2-pyridylpyrrole **264** [402]. A procedure for selective C2 metallation and functionalization of 1-vinylpyrrole employing the base system BuLi/*t*-BuOK catalyzed by *i*-Pr_2NH, followed by addition of LiBr and suitable electrophiles, has also been described [403].

Selective C2 mercuration of pyrroles is effected by exposure of 1-acetyl- or 1-(phenylsulfonyl)pyrrole to mercuric chloride. The corresponding diorganomercury compounds, which are useful for the synthesis of pyrrole containing transition metal complexes, can thereafter be obtained after treatment with sodium iodide [404]. For N-H pyrroles, mercuration with mercury(II) acetate leads to N-mercuration, while various N-substituted pyrroles are mercurated at C2 or C3. Such C-mercurated pyrroles undergo Heck-type reactions with alkenes [405].

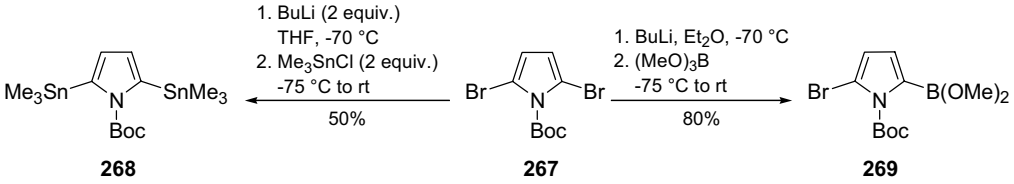
The development of directed metallation techniques has allowed facile access to a multitude of 2-substututed pyrroles that were previously difficult to prepare. The ideal N-protecting and directing group should be easily installed and cleaved, and induce high regioselectivity during metallation. The *tert*-butoxycarbonyl (Boc) group fulfils all these requirements, and has consequently proven to be extremely useful. For example, 1-(*tert*-butoxycarbonyl)pyrrole (**158**) [285] is efficiently lithiated at C2 by LiTMP, and subsequent quenching with aldehydes or acid chlorides gives the corresponding pyrrol-2-yl methanols **265** (Scheme 4.74) and 2-acylpyrroles, respectively. The Boc group may be removed by treatment with sodium methoxide in methanol [406], under thermal conditions [407] or using acid, which may, however, not always be compatible with electron rich substrates. Similar metallation of **158**



Scheme 4.74

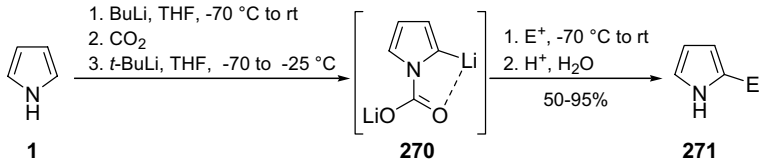
followed by quenching with trimethyl borate and subsequent hydrolysis provides a route to the useful boronic acid **266** [239]. An excellent recent review covers the advances in pyrrole protection strategies [408].

An alternative route permits introduction of two α-substituents by halogen–metal exchange on 2,5-dibromo-1-(*tert*-butoxycarbonyl)pyrrole (**267**) (Section 4.5.1.3), eventually producing the corresponding 2,5-disubstituted pyrroles, for instance **268** (Scheme 4.75) [237, 239]. Moreover, mono-lithiation of **267** offers access to 2-bromopyrroles having an additional substituent at C5 (e.g., **269**) [239].



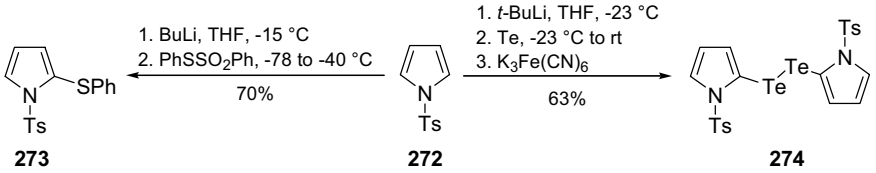
Scheme 4.75

Pyrroles that are N-protected with the *N-tert*-butylcarbamoyl group are also very useful substrates for C2 lithiation; the directing group can subsequently be removed by LiOH in MeOH–THF [409]. Generation of the dilithio species **270**, followed by quenching with suitable electrophiles, and final acidic work up which cleaves the carbamate, constitutes a one-pot protocol for preparation of C2 functionalized pyrroles **271** (Scheme 4.76) [410].



Scheme 4.76

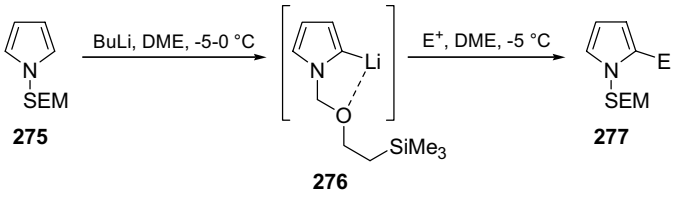
Lithiation of 1-(*p*-toluenesulfonyl)pyrrole (**272**) also occurs at C2 with high selectivity, and subsequent quenching with $PhSSO_2Ph$ gives the sulfide **273** (Scheme 4.77) [276]. Similar techniques can also be utilized in synthesis of other chalcogen containing systems, as illustrated by the conversion of **272** into the



Scheme 4.77

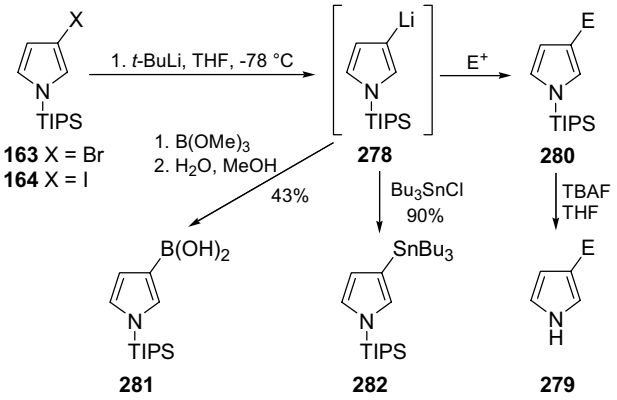
ditelluride **274** [411]. Magnesium can be introduced at C2 in 1-(phenylsulfonyl) pyrrole by the action of 3 equivalents of *i*-PrMgBr in the presence of 5 mol.% *i*-PrNH; ensuing treatment with electrophiles gives the corresponding 2-substituted pyrroles in moderate yields [412].

The N-protected pyrroles discussed above are neatly complemented by 1-[2-(trimethylsilyl)ethoxymethyl]pyrrole (1-SEM-pyrrole) (**275**), which is available by deprotonation of pyrrole with NaH in DMF, followed by treatment with SEMCl [413]. Lithiation is also in this case directed to C2, rendering the lithiopyrrole **276**, treatment of which with appropriate electrophiles affords the 2-substituted N-protected pyrroles **277** in moderate to good yields (Scheme 4.78). The electron releasing SEM group may thereafter be conveniently cleaved using tetrabutylammonium fluoride (TBAF) under conditions that tolerate sensitive functionalities [414]. Even structurally rather complex and sterically congested electrophiles may be used in this approach, providing useful yields of unusual 2-substituted pyrroles [415]. Notably, lithiation of 1-(*N*,*N*-dimethylamino)pyrrole also occurs at C2, and this electron releasing directing group can subsequently be removed by treatment with $Cr_2(OAc)_4 \cdot 2H_2O$ [416].



Scheme 4.78

Metallation of pyrroles at C3 has enabled convenient preparation of derivatives that were prepared previously by cumbersome means [417]. Selective C3 metallation is achieved conveniently by halogen–metal exchange on 3-bromo-1-(triisopropylsilyl) pyrrole (**163**) by virtue of the steric bulk of the TIPS group (Scheme 4.79) [245]. Subsequent treatment of the so-obtained 3-lithiopyrrole **278** with suitable electrophiles, followed by desilylation with TBAF gives the corresponding 3-substitued pyrroles **279** via the 1-TIPS derivatives **280** [242]. Intermediate **278** may also be generated by lithiation of 3-iodo-1-(triisopropylsilyl)pyrrole (**164**), and converted into, for example, the boronic acid **281** or the stannyl derivative **282**, which are useful substrates in palladium-catalyzed coupling reactions (Section 4.5.11) [418]. Similar

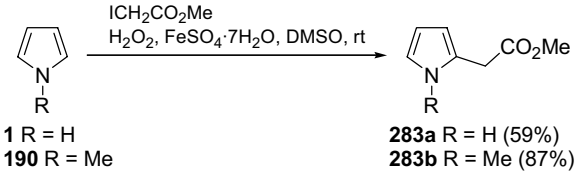


Scheme 4.79

techniques have been employed for the synthesis of 3-fluoro-1-TIPS-pyrrole in 50% yield by quenching of 3-lithio-1-TIPS-pyrrole by *N*-fluorobenzenesulfonimide [419]. Conversely, lithiations involving pyrroles having a trimethyl or triethylsilyl groups at the nitrogen are more difficult to control in terms of regioselectivity, and are under certain conditions further complicated by migration of the silyl groups [420]. Treatment of dimethoxyethyl protected 4-iodopyrrole-2-carbonitrile with *i*-PrMgCl and subsequent quenching with electrophiles provides a route to 4-substituted pyrrole-2-carbonitriles in good yields [421].

4.5.5
Reactions with Radical Reagents

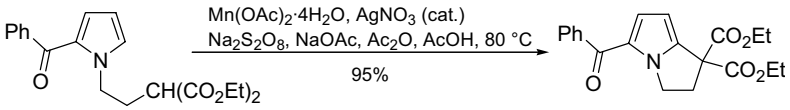
Synthetically useful reactions of pyrroles with radical reagents were not been studied in much detail until it was demonstrated that effective and regioselective synthesis of 2-alkylpyrrole derivatives can be accomplished by radical substitution. The pyrrole-2-acetic acid derivatives **283** are readily available by treatment of the pyrroles **1** or **190** (Scheme 4.80) with radicals generated from α-carbonyl-, α,α′-dicarbonyl- and α-cyano-alkyl iodides [422]. Alternative procedures for the synthesis of pyrrole-2-acetic acid derivatives involve generation of radicals from various iodoacetates induced by stannanes [423] or under conditions avoiding stannanes, by irradiation



Scheme 4.80

in the presence of $Na_2S_2O_3$ as the I_2 reductant, Bu_4NI to aid in solubility, and propylene oxide [423, 424] or epoxydecane as the HI trap [425]. Pyrroles possessing electron-withdrawing groups at C2 undergo related alkylation reactions at C5 with α-acetyl or α-acetonyl radicals generated by exposure of suitable xanthate based precursors to dilauroyl peroxide [426].

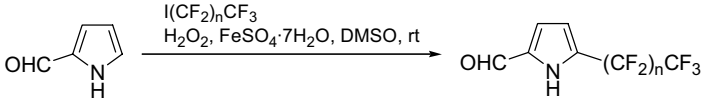
Similar intramolecular processes provide routes to fused pyrroles, as illustrated by the manganese(III) acetate generated *in situ* induced conversion of the 2-aroylpyrrole **284** into the fused system **285** (Scheme 4.81), a useful precursor to the analgesic molecule ketorolac (**10**) [427]. In addition, [1,2-*a*]-fused pyrroles are also available via intramolecular radical cyclization of 1-(bromoalkyl)pyrroles induced by Bu_3SnH in the presence of AIBN [428, 429], annulation of 1-(iodoalkyl)pyrroles with the H_2O_2/Fe(II) system (*vide supra*) [430], or employing electroreduction with a Ni(II) complex as the electron-transfer catalyst [431]. Intramolecular cyclization of acyl radicals onto pyrroles leading to [1,2-*a*]-fused pyrrole derivatives in modest yields has also been reported [432].



284 **285**

Scheme 4.81

It has been known for some time that 2-(perfluoroalkyl)pyrroles are formed in low yields upon heating of pyrroles in the presence of perfluoroalkyl iodides under forcing conditions [433]. Application of the H_2O_2/Fe(II) protocol offers a practical procedure for the preparation of, for example, the perfluoroalkylpyrroles **286** from pyrrole-2-carboxaldehyde (**191**) and perfluoroalkyl iodides via a homolytic substitution process (Scheme 4.82) [434]. In contrast, perfluoroalkylation of pyrroles at C2 using bis(perfluoroalkanoyl) peroxides follows a different mechanistic path, which appears to proceed via coupling of perfluoroalkyl radicals with pyrrole cation radicals [435].



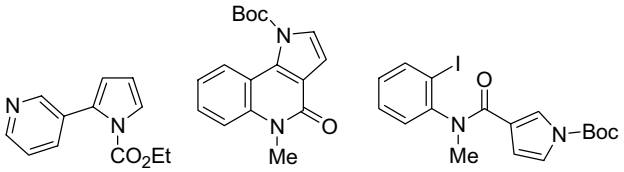
191

286a n = 2 (64%)
286b n = 3 (55%)

Scheme 4.82

Addition of the 3-pyridyl radical generated from *N*-nitroso-*N*-(3-pyridyl)-isobutyramide to ethyl pyrrole-1-carboxylate gives **287** in 23% yield [436]. More efficient radical C2 arylations of pyrroles having an electron-withdrawing substituent at the nitrogen atom have been afforded using anilines in the presence of amyl nitrite in

warm acetic acid [437]. Intramolecular radical arylations involving pyrroles are useful tools for the construction of more complex systems, such as the tricyclic derivative **288**, which was derived from the precursor **289** by exposure thereof to tributyltin hydride in the presence of AIBN in refluxing toluene [438, 439]. Related cyclization reactions may also produce spiropyrrolidinyloxindoles, depending on the properties of the pyrrole protecting group [440].

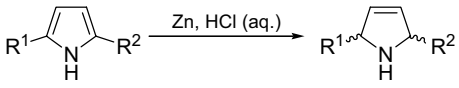


287 **288** **289**

A radical displacement reaction at C2 of 1-phenylsulfonyl-2-(*p*-toluenesulfonyl) pyrrole with stannyl radicals generated by the reagent combination Bu_3SnH/AIBN in refluxing benzene, resulting in the corresponding 2-stannylpyrrole derivative, has also been described [441].

4.5.6
Reactions with Reducing Agents

It has long been established that reduction of pyrroles **290** with zinc in hydrochloric acid gives 2,5-dihydropyrroles (3-pyrrolines) **291** (Scheme 4.83) [442, 443], although it was later found that the material obtained from the reduction of pyrrole itself is frequently contaminated with pyrrolidine, which is difficult to separate from the desired product [444]. The synthetic utility is further compromised by the fact that the formation of both *cis* and *trans* products occurs upon reduction of 2,5-dimethylpyrrole [445]. Nevertheless, this procedure seems to be useful in certain applications, and a modified version thereof has been applied successfully for the reduction of some 1,2-disubstituted pyrroles to give the corresponding 3-pyrroline derivatives *en route* to the antibiotic (±)-anisomycin [446]. Treatment of pyrrole-2-carboxamide with phosphonium iodide in fuming hydroiodic acid affords 3,4-dehydroprolinamide as the major product, provided that careful control of the reaction conditions is maintained [447]. A similar reduction using the combination H_3PO_2/HI in acetic acid has been used for the conversion of pyrrole-2-carboxylic acid into 3,4-dehydroproline in 74% yield on a large scale [448]. Reduction of C2 or C3 substituted

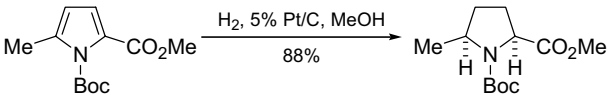


290 **291**

Scheme 4.83

1-phenylsulfonylpyrroles with $NaCNBH_3$ in TFA leads to the corresponding 3-pyrrolines in good yields, offering a convenient complement to the procedures discussed above [449].

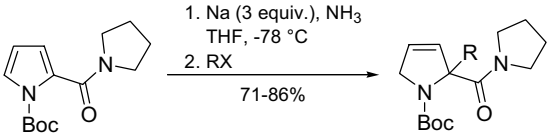
Catalytic hydrogenation of pyrroles leads to pyrrolidines, and can be performed under various conditions, often proceeding exclusively with cis-stereoselectivity. Useful catalysts for this application are 5% Rh on Al_2O_3 [450–452], PtO_2 or 10% Pd/C in 6 N aqueous HCl [453] or alternatively Pd/C in the presence of catalytic amounts of H_2SO_4 [454]. Moreover, catalytic hydrogenation of pyrroles at atmospheric pressure offers a convenient procedure for the synthesis of *cis*-2,5-disubstituted pyrrolidines, as illustrated by the conversion of pyrrole **292** into pyrrolidine **293** (Scheme 4.84) [455].



292 **293**

Scheme 4.84

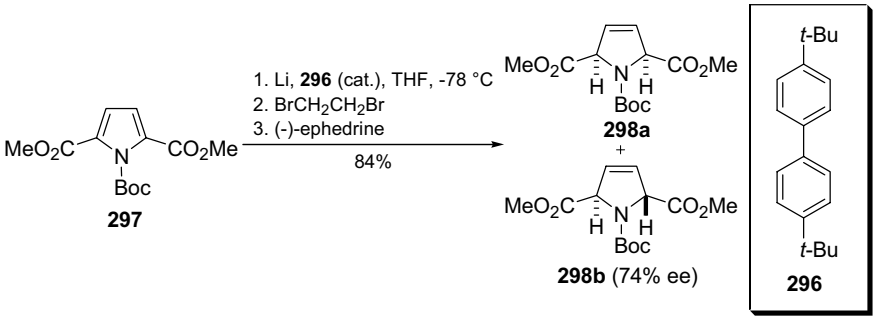
Birch reduction of pyrroles has not been explored until recently, but has already attracted considerable attention as a tool for preparation of interesting 3-pyrrolines and 2,3-dihydropyrroles (2-pyrrolines). Initial studies demonstrated that pyrroles possessing electron-withdrawing groups, for instance **294**, undergo efficient conversion into 3-pyrrolines **295** upon Birch reduction and subsequent alkylation (Scheme 4.85) [456, 457]. Diastereoselectivity at C2 may be induced in alkylation [458] or protonation [459], by using for example pyrrole-2-carboxylates or pyrrole-2-carboxamides, respectively, containing chiral moieties as substrates. A variant featuring a reductive aldol reaction has also been developed [460]. It was later established that such reductions may also be conveniently performed by employing lithium in THF in the presence of bis(methoxyethylamine) and naphthalene [461, 462], or 4,4′-di-*tert*-butylbiphenyl (**296**, see below) [463], thus supplanting the classical Birch conditions. Further extensions of this methodology allow reductive acylation [462], and aldol reactions with excellent *anti*-selectivity [464, 465].



294 **295**

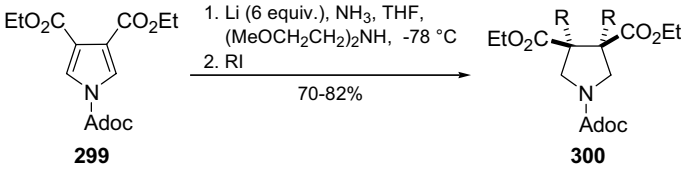
Scheme 4.85

A recent contribution to this field concerns the enantioselective partial reduction of pyrroles involving chiral protonation using (−)-ephedrine. Thus, diester **297** underwent conversion into a 1 : 1 mixture of the cis- and trans-diastereomers **298a** and **298b**, the latter of which was found to be formed with an enantiomeric excess of 74%. A simple recrystallization of **298b** provided material with >94% ee (Scheme 4.86) [466].



Scheme 4.86

Pyrroles bearing amide or ester functionalities at the β-position also undergo Birch reduction, and ensuing alkylation provides the corresponding 4,4-disubstituted 2-pyrrolines [467]. The 3,4-disubstituted pyrrole **299** (Adoc=adamantyloxycarbonyl) is converted into *cis*-pyrrolidines **300** under similar conditions (Scheme 4.87). Sequential alkylation with two different electrophiles gives access to unsymmetrically substituted derivatives [468].



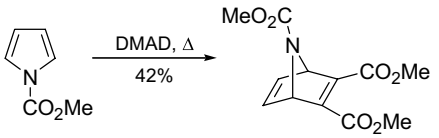
Scheme 4.87

4.5.7
Cycloaddition Reactions

Cycloaddition reactions involving pyrroles constitute a powerful tool for crafting rather complex heterocyclic structures from simple precursors. It was early recognized that some pyrroles, for example 1-methylpyrrole, give mainly C2 substituted products resulting from Michael-type addition to maleic anhydride [469]. Interestingly, the reaction of 1-methylpyrrole with dimethyl acetylenedicarboxylate (DMAD)

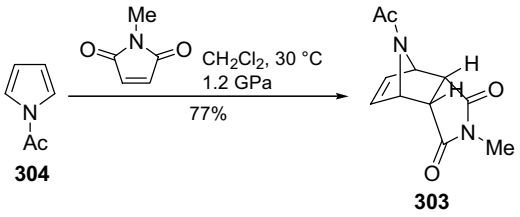
gives a product for which an indolic structure was proposed [470] – the true identity was later elucidated by Acheson [471]. Further studies of these reactions suggested that Michael additions are favored in the presence of a proton source, whereas under neutral conditions and at elevated temperatures Diels–Alder additions will take place. The adducts, however, being rather unstable, undergo retro Diels–Alder reactions to the starting materials, yield further pyrrole derivatives via extrusion of acetylene derivatives, or react further with DMAD to give more complex indolic products [472]. Based on the results of *ab initio* calculations on the reaction of 1-methylpyrrole with DMAD, which support the preferential formation of Diels–Alder products instead of Michael adducts, a step-wise mechanism involving a zwitterionic intermediate was suggested, rather than a concerted pericyclic process [473].

Even though elimination of acetylene from intermediate Diels–Alder adducts of the deactivated methyl pyrrole-1-carboxylate with DMAD has also been observed [474, 475], stable addition products could nevertheless be isolated in very low yields from the reactions of 1-benzylpyrrole [476] or methyl pyrrole-1-carboxylate [477] with acetylenedicarboxylic acid. A different decomposition path is in operation during reactions of 1-aminopyrroles with DMAD, which give substituted benzene derivatives as the final products [478]. Conditions for practical Diels–Alder reactions involving deactivated pyrroles soon became available, permitting the synthesis of adduct **301** in a moderate yield upon heating of the pyrrole **302** in neat DMAD (Scheme 4.88) [479], whereas the same reaction performed in CH_2Cl_2 in the presence of five equivalents of $AlCl_3$ at 40 °C is much faster and gives the adduct in 93% yield [480]. The use of high pressure (15 kbar) also leads to high yields of **301**, but, even under these conditions, pyrrole itself undergoes mainly C2-substitution [481].



Scheme 4.88

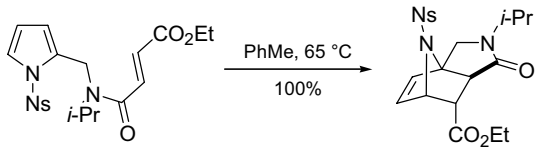
Deactivated pyrroles also give good yields of Diels–Alder adducts with alkenes at elevated pressure, as demonstrated by the synthesis of the *endo*-adduct **303** from 1-acetylpyrrole (**304**) and *N*-methylmaleimide (Scheme 4.89). In some cases,



Scheme 4.89

mixtures of *exo*- and *endo*-adducts are produced, and it has been proposed that the *endo*-isomers are in some cases formed under kinetic control and isomerize to the *exo*-products [482]. Mixtures of *exo*- and *endo*-adducts have also been encountered during high pressure reactions of methyl 3-methylthio- or 3-phenylthiopyrrole-1-carboxylate with *N*-phenylmaleimide or methyl acrylate [483]. However, it appears that 1-acylpyrroles do not participate in Diels–Alder reactions with alkenes at atmospheric pressure [484].

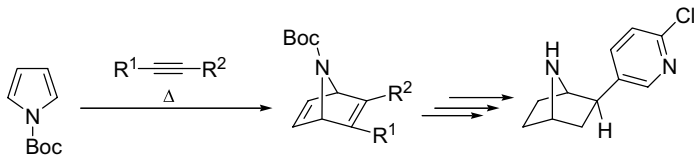
An intramolecular cycloaddition reaction involving the precursor **305** (Ns=2-nitrophenylsulfonyl), incorporating a deactivated pyrrole as the diene component has been used in an elegant synthesis of the tricyclic system **306** (Scheme 4.90). This study was extended to the efficient construction of several conformationally strained analogues, featuring stereoselective generation of multiple stereogenic centers [485].



305 **306**

Scheme 4.90

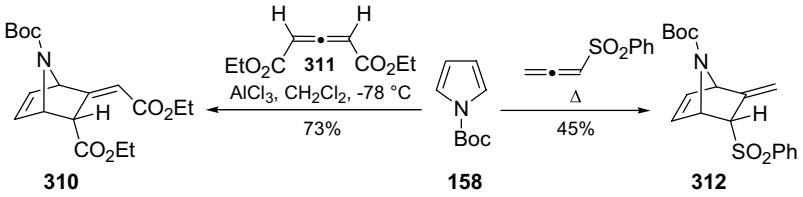
Diels–Alder reactions involving pyrroles and acetylenes are the key feature of several total syntheses of the powerful analgesic natural product epibatidine (**307**) (Scheme 4.91). The common 4π-component 1-(*tert*-butoxycarbonyl)pyrrole (**158**) undergoes efficient conversion into the bicyclic system **308** upon heating with the electron deficient dienophile (*p*-toluenesulfonyl)acetylene [486]. A similar reaction involving **158** and methyl pyrrole-1-carboxylate has previously been demonstrated to give excellent results [487, 488]. The intermediate **308** proved to be a useful precursor for the synthesis of epibatidine (**307**) [489, 490]. Other related approaches to **307** employ Diels–Alder reactions of methyl pyrrole-1-carboxylate with (*p*-toluenesulfonyl)acetylene [491], or a (6-chloro-3-pyridyl)acetylene derivative [492]. Likewise, heating of the pyrrole **158** with the dienophile methyl 3-bromopropiolate gives the adduct **309**, which is also a useful vehicle for further manipulations that eventually lead to **307** [493, 494].



158 **308** R^1 = Ts, R^2 = H (86%) **307**
309 R^1 = CO_2Me, R^2 = Br (60%)

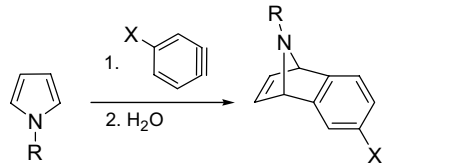
Scheme 4.91

Allenes may also participate in Diels–Alder reactions with electron deficient pyrroles, and high selectivity can be attained, depending on the choice of starting materials and conditions. For example, 1-(*tert*-butoxycarbonyl)pyrrole (**158**) gives exclusively the *endo*-isomer **310** with diethyl allene-1,3-dicarboxylate **311** (Scheme 4.92). Under similar conditions, 1-methyl- or 1-benzylpyrrole give only C2 substitution products [495]. Variants involving *endo*-selective Diels–Alder addition of **158** to an optically active allene-1,3-dicarboxylate [496], or 1-(benzenesulfonyl)-1,2-propadiene to provide **312** [497], have also been disclosed.



Scheme 4.92

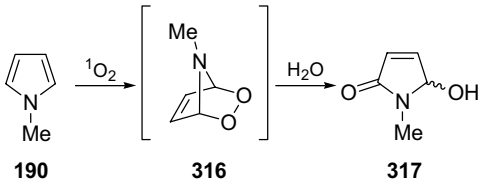
The reactions of 1-methylpyrrole or 1-benzylpyrrole with benzyne give rather unstable adducts that could only be isolated in low yields as the methiodide or the picrate, respectively, as they readily react further with benzyne, finally rendering carbazole derivatives [498, 499], or rearrange to 2-naphthylamines [500]. In contrast, 1-(*tert*-butoxycarbonyl)pyrrole (**158**) reacts with benzyne, to afford a stable adduct (**313**) in moderate yield (Scheme 4.93) [501], as do 1-alkyl-2,3,4,5-tetramethylpyrroles [502, 503]. Tetrafluorobenzyne also adds readily to for, example, 1-methylpyrrole to form a stable adduct [504], whereas the reaction of the benzyne generated from 1-bromo-2,5-difluorobenzene with 1-(trimethylsilyl)pyrrole (**314**) gives **315** with concomitant desilylation [505]. Related addition products have also been obtained upon addition of tetrachlorobenzyne to 1-alkylpyrroles [506].



Scheme 4.93

Although the photooxygenation of pyrroles was discussed already in 1912 [507], evidence for the mechanism was not available until almost 70 years later, when it was demonstrated that addition of singlet oxygen to 1-methylpyrrole (**190**) provides the unstable endoperoxide **316**, which undergoes a subsequent rearrangement or reacts

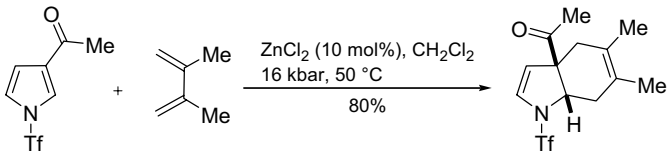
with water to furnish, among other products, the oxypyrrole **317** (Scheme 4.94). The intermediacy of **316** was suggested on the basis of low-temperature NMR measurements [508].



190 **316** **317**

Scheme 4.94

Owing to their aromatic character, the applicability of pyrroles as the 2π reactants in normal electron demand Diels–Alder reactions has been quite limited, requiring harsh conditions and giving only moderate yields of products as mixtures of regioisomers [509]. Recently, however, it was demonstrated that pyrroles possessing the strong electron-withdrawing trifluoromethylsulfonyl (Tf) group plus an acetyl group can indeed act as dienophiles at elevated pressure, as illustrated by the conversion of **318** into **319** (Scheme 4.95) [510, 511].

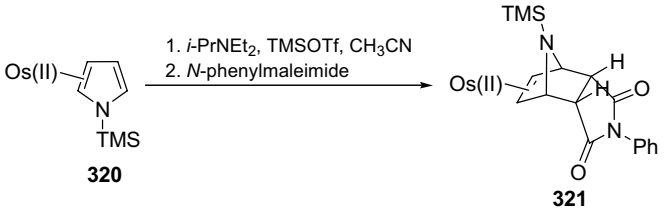


318 **319**

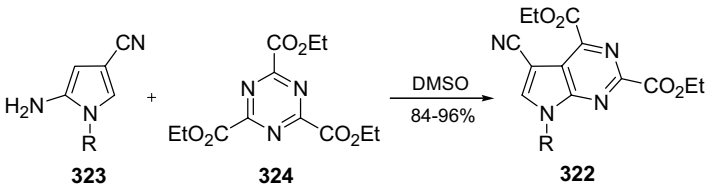
Scheme 4.95

Pyrroles may also play the role of dipolarophiles in cycloaddition reactions. Thus for instance, the reactions of certain 1-alkylpyrroles with nitrileimines have been demonstrated to give pyrrolo-fused pyrazoles [512, 513], whereas intramolecular cyclization of nitrile oxide functionalities onto pyrroles involved unstable pyrrolo-fused isoxazole adducts that underwent ring opening of the isoxazole ring [514]. It has also been established that a series of osmium pyrrole complexes, for example **320** [Os(II)=$[Os(NH_3)_5](OTf)_2$], participate as dipoles in cycloadditions with alkenes, for instance providing the *endo*-adduct **321** in good yield along with minor amounts of the *exo*-isomer (Scheme 4.96) [515, 516].

Inverse electron demand Diels–Alder reactions have been used successfully for the synthesis of the pyrrolo[2,3-*d*]pyrimidines **322** from the 2-amino-4-cyanopyrroles **323** and the 1,3,5-triazine **324** (Scheme 4.97). This process is remarkable, as it proceeds readily even at ambient temperature [517]. Based on a theoretical study of the reaction between 2-aminopyrrole and 1,3,5-triazine, it appears that these transformations involve an initial nucleophilic attack of the aminopyrrole on the triazine to form a zwitterionic intermediate, which is in equilibrium with a neutral species, eventually



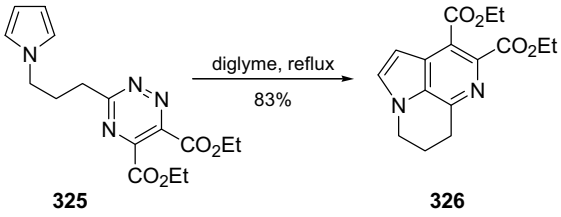
Scheme 4.96



Scheme 4.97

undergoing a rate determining cyclization step [518]. The related reaction between 1-methylpyrrole and 4,5-dicyanopyridazine gave only a low yield of 5,6-dicyano-1-methylindole [519].

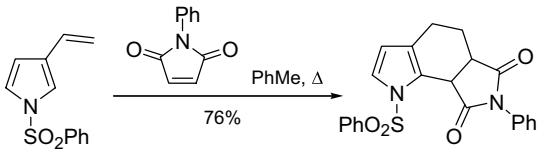
An intramolecular inverse electron demand Diels–Alder reaction involving pyrrole as the dienophile component has been employed for conversion of the pyrrole-tethered 1,2,4-triazine **325** into the tricyclic system **326** in good yield (Scheme 4.98) [520]. Likewise, 1-acyl- or 1-benzoylpyrroles have been used as 2π-components in cycloadditions to masked *o*-benzoquinones [521].



Scheme 4.98

Since the initial reports that 1-alkyl- and 1-aryl-2(3)-vinylpyrroles may serve as diene components in Diels–Alder reactions leading to indoles with interesting substitution patterns [522, 523], several studies exploiting this strategy have emerged. Heating of 1-triisopropylsilyl-(*E*)-2-(2-phenylsulfinylvinyl)pyrrole with suitable acetylenecarboxylic acid derivatives furnished TIPS protected 4-acylindoles in good yields [524]. A more practical approach involves the readily available 3-vinylpyrrole **327**, which gives the adduct **328** upon reaction with *N*-phenylmaleimide and

subsequent isomerization (Scheme 4.99). Similar reactions yielding isomeric adducts were performed using 1-(phenylsulfonyl)-2-vinylpyrrole [525]. Other related indole syntheses encompass the use of silyl enol ethers of 2-acylpyrroles [526, 527], or a diene generated by S-alkylation of 1-methyl-3-thioacetylpyrrole [528] as the 4π-components. It is also noteworthy that some sterically hindered N-substituted 2-vinylpyrroles give mainly Michael-type addition at C5, as the required *cisoid* conformation is disrupted by steric interaction between the group at the pyrrole nitrogen and the substituted vinyl moiety [529].

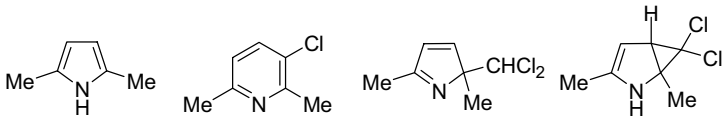


327 **328**

Scheme 4.99

4.5.8
Reactions with Carbenes and Carbenoids

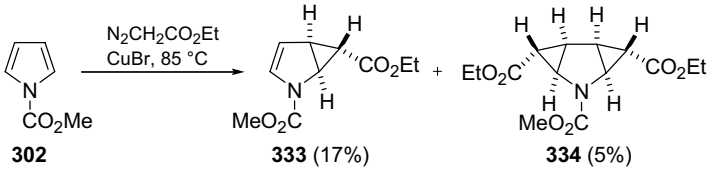
Although it was established early on that pyrroles readily undergo substitution reactions with carbenes [530] the synthetic utility of this reaction appears to be severely limited, as simple pyrroles, for example 1-methylpyrrole, give mixtures of C2 and C3 substituted products [531–533]. Interestingly, in this context, the reactivity rate of pyrrole versus naphthalene towards thermally generated (ethoxycarbonyl) carbene at 150 °C is 23 times higher [534]. A useful ring expansion reaction occurs when 2,5-dimethylpyrrole (**329**) is exposed to dichlorocarbene under neutral aprotic conditions, rendering the pyridine **330**. Under basic protic conditions, very little of **330** is formed, along with even lower amounts the 2*H*-pyrrole **331** [535]. A similar mixture of products, although in considerably higher total yield, is obtained under basic conditions in the presence of a phase transfer catalyst [536]. The pyridine product may result from a rearrangement of the dichlorocyclopropane intermediate **332**, in analogy with observations during studies on similar reactions of 2-*tert*-butyl-5-methylpyrrole [537].



329 **330** **331** **332**

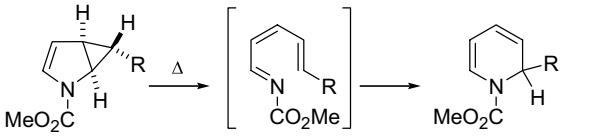
Addition of carbenes to pyrroles possessing electron-withdrawing groups at the nitrogen atom is recognized to lead to cyclopropanation, as illustrated by the transformation of pyrrole **302** into the bicyclic system **333**, with co-formation of the

product **334** (Scheme 4.100) [538, 539]. An analogous outcome giving cyclopropanated products can be observed upon CuCl-catalyzed decomposition of diazomethane in the presence of **302** [539, 540]. Similar conditions involving CuOTf $^1/_2C_6H_6$ as the catalyst allow cyclopropanation of 1-acylpyrroles with methyl diazoacetate in up to 44% yield [541].



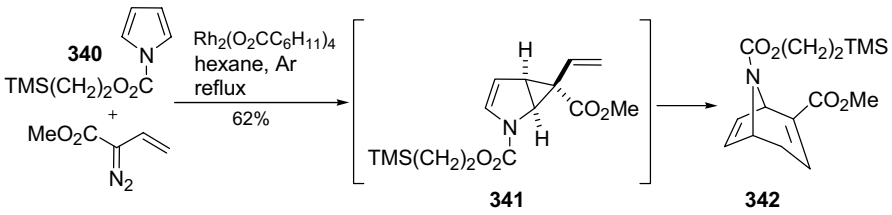
Scheme 4.100

Further studies also indicated that **333** undergoes rearrangement to the dihydropyridine derivative **335** by heating at 285 °C. This is also true for the diazomethane adduct **336**, which is completely converted into **337** within 30 min under the same conditions (Scheme 4.101) [539]. Based on detailed mechanistic studies, these transformations were suggested to proceed through the intermediate acyclic azatrienes **338**/**339**, which give the dihydropyridines **335**/**337** after final 6π-electrocyclization [539, 542].



Scheme 4.101

Stabilized vinyl carbenes also add readily to deactivated pyrroles, for example **340**, providing the expected cyclopropanated intermediates **341**, which, however, can not be isolated, as an ensuing Cope rearrangement leads directly to the tropane skeleton **342** (Scheme 4.102) [543, 544]. In analogy with previous findings (see above), pyrrole

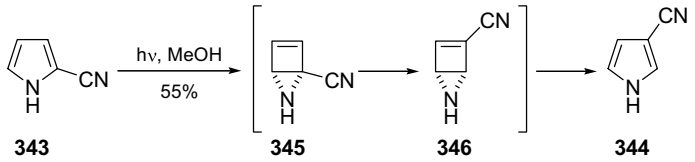


Scheme 4.102

itself gives instead a mixture of C2 and C3 substitution products under similar conditions [543].

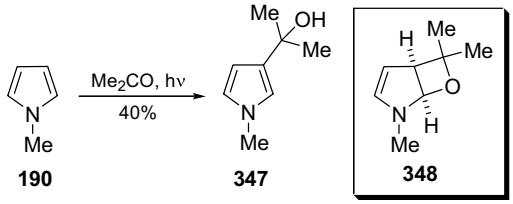
4.5.9
Photochemical Reactions

The photochemistry of pyrroles has been studied relatively scantily, and only few synthetically useful procedures have appeared over the years. Interestingly, during the irradiation of pyrrole-2-carbonitrile (**343**) in methanol solution the isomeric pyrrole-3-carbonitrile **344** was isolated in 55% yield as the major product (Scheme 4.103) [545]. This intriguing isomerization has been suggested to encompass initial generation of the unstable Dewar pyrrole **345**, and a subsequent rearrangement involving the aziridine nitrogen to form intermediate **346** [546]. The *N*-ethoxycarbonyl derivative of the parent ring system of **345** has, interestingly, been generated and trapped as an adduct with 1,3-diphenylisobenzofuran [547], although the formation and reactions of tetrakis(trifluoromethyl) derivatives thereof had been reported previously [548, 549].



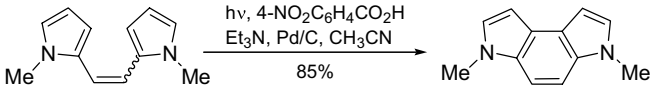
Scheme 4.103

The photo-induced reaction of pyrroles with aldehydes or ketones provides a route to C3 substituted pyrroles, as illustrated by the conversion of **190** into **347** (Scheme 4.104). Based on NMR studies of the reaction mixture, the oxetane **348** was proposed as a conceivable intermediate [550]. Similar reactions of 1-benzoylpyrrole with 3- or 4-benzoylpyridine led to the isolation of low yields of related bis-adducts [551].



Scheme 4.104

Light-induced cyclizations of suitable pyrrole containing precursors offer useful routes to more complex fused pyrroles. Thus the heterocyclic stilbene analog **349** undergoes conversion into the system **350** upon irradiation in the presence of Pd/C



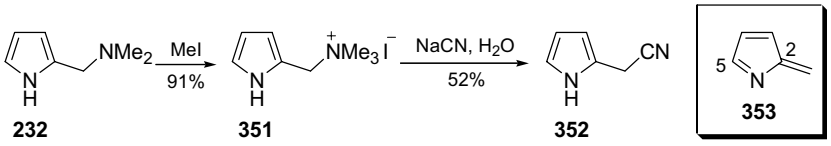
349 **350**

Scheme 4.105

as the dehydrogenating catalyst (Scheme 4.105) [552]. Photochemical annulation reactions of related precursors may also be performed in the presence of iodine with access to air, or alternatively by employing iodine and excess propylene oxide under an argon atmosphere [553].

4.5.10
Pyrryl-C-X Compounds: Synthesis and Reactions

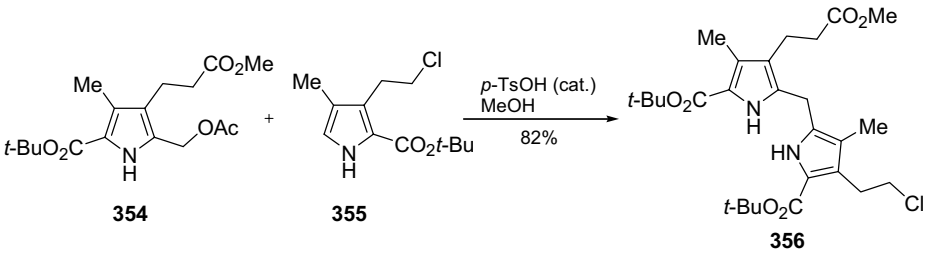
Pyrrolyl-C-X compounds constitute an important class of derivatives, as pyrroles possessing aminomethyl- or hydroxymethyl substituents are excellent substrates in reactions with nucleophilic reagents. Conversion of the readily available 2-(dimethylamino)pyrrole **232** into the methoiodide **351**, followed by treatment with NaCN provides convenient access to (pyrrol-2-yl)acetonitrile (**352**, Scheme 4.106) [554], whereas a similar displacement with the anion of diethyl phosphite gives the useful diethyl (pyrrol-2-yl)methylphosphonate in 91% yield [555]. This type of elimination–addition processes with N-substituted pyrroles has been implied to involve the intermediacy of azafulvenium ions [287] (Section 4.5.1.7), or in the case of pyrrole itself the azafulvene **353** [556, 557], both of which are prone to attack by nucleophiles at the *exo*-cyclic carbon. Likewise, 2,5-bis(dimethylaminomethyl)pyrrole may, for example, be converted into the corresponding 2,5-bis(phenylthiomethylene)pyrrole via an intermediate quaternization with iodomethane in good overall yield [558]. However, products that presumably resulted from nucleophilic attack at C5 of 1-methylazafulvenium ions have also been observed [555, 559].



232 **351** **352** **353**

Scheme 4.106

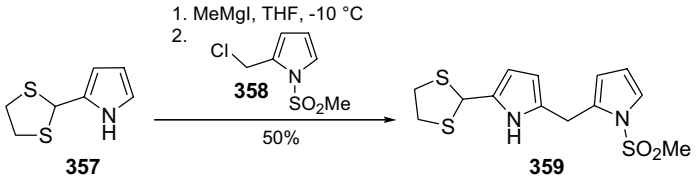
Pyrroles containing acetoxymethyl groups at C2 are particularly useful for the construction of di(pyrrol-2-yl)methanes [560–562]. The reaction of the 2-(acetoxymethyl)pyrrole derivative **354** with **355** leading to the molecule **356** (Scheme 4.107) serves as an excellent illustration of the applicability of such approaches [561]. Related transformations may also be carried out using 2-(hydroxymethyl)pyrroles [341, 563], as well as 3-(hydroxymethyl)pyrroles, which display similar behavior, and may for instance be converted into the corresponding 3-(cyanomethyl)pyrroles upon



Scheme 4.107

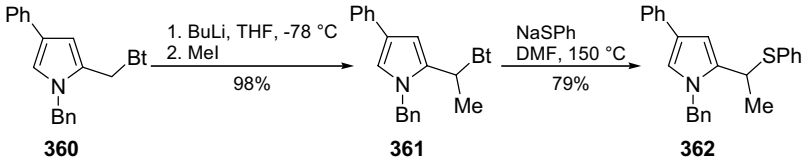
treatment with NaCN [564]. Introduction of the strong electron-withdrawing (trifluoromethyl)sulfonyl group at the nitrogen of 2-(hydroxymethyl)pyrroles blocks the pathway involving azafulvenium ions, thus enabling Mitsunobu-type reactions at the hydroxymethyl moiety [565].

Di(pyrrol-2-yl)methanes have also been prepared under non-acidic conditions, as demonstrated by the reaction of a magnesium derivative of **357** with the 2-(chloromethyl)pyrrole **358** to afford the product **359** (Scheme 4.108). The compound **358** is readily available from pyrrole-2-carboxaldehyde by N-protection, followed by reduction, yielding a 2-(hydroxymethyl)pyrrole, and treatment thereof with methanesulfonyl chloride in the presence of Hünig's base [566]. 2-(Haloalkyl)pyrroles may also be used in displacement reactions with, for example, azide ions [567], pyridine or alkoxide ions [568], giving additional useful synthetic intermediates.



Scheme 4.108

Pyrroles bearing an (benzotriazol-1-yl)methyl (Bt) substituent at C2, for example **360**, may also serve as versatile substrates for conversion into more exotic derivatives, employing a route featuring initial metallation and alkylation to give **361**, followed by nucleophilic displacement of the benzotriazol-1-yl moiety to furnish the final product **362** (Scheme 4.109) [102]. Similar reactions involving α,β-unsaturated aldehydes or



Scheme 4.109

ketones instead of alkyl halides as the electrophiles, eventually leading to indole derivatives, have also been reported [569].

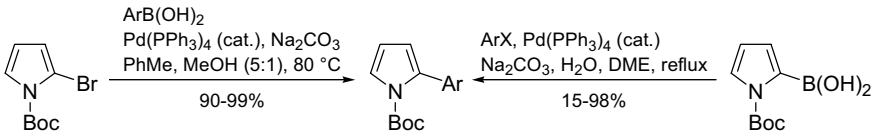
Reduction of 3-acyl-1-(*p*-toluenesulfonyl)pyrroles with 0.5 equivalents of $NaBH_4$ in refluxing dioxane containing 1 equivalent of *i*-PrOH gives the corresponding intermediate 1-(pyrrol-3-yl)methanol derivatives, which undergo dehydration in hot DMSO, rendering 3-vinylpyrroles [570]. C-Vinylpyrroles are useful in various applications, for example cycloaddition reactions (Section 4.5.7), and comprehensive reviews highlighting the preparation [571] and synthetic uses of these compounds have appeared quite recently [572].

4.5.11
Transition Metal Catalyzed Coupling Reactions

The availability of stable halopyrroles, stannylpyrroles and pyrroleboronic acids has opened new possibilities for functionalization of the pyrrole nucleus by transition metal catalyzed reactions, enabling the synthesis of derivatives otherwise difficult to access [573]. A few reactions involving transition metal catalyzed C−H activation in pyrroles have also emerged.

There are only a few examples of N-arylation of pyrrole itself using aryl bromides, performed in the presence of *t*-BuONa and catalytic amounts of $Pd(OAc)_2$ and diphenylphosphinoferrocene (DPPF) and a suitable base [574], or employing the combination $Pd(dba)_2/P(t\text{-}Bu)_3/Cs_2CO_3$ [575]. Pyrrole has also been N-arylated with an aryl iodide using CuI/*trans*-1,2-cyclohexanediamine in the presence of K_3PO_4 as the catalytic system [576]. 2-Acetylpyrrole, as well as pyrrole-2-carboxaldehydes possessing an additional electron-withdrawing substituent at C4, undergoes efficient N-arylation with arylboronic acids at ambient temperature using stoichiometric amounts of $Cu(OAc)_2$ [577]. Treatment of pyrroles with vinyl triflates in the presence of the system $Pd_2(dba)_3/Xphos/K_3PO_4$ constitutes a new route to 1-vinylpyrroles [578]. It has also been reported that N-alkynylation of electron deficient pyrroles can be achieved using alkynyl bromides in the presence of catalytic amounts of $CuSO_4{\cdot}5H_2O$ and 1,10-phenanthroline [579].

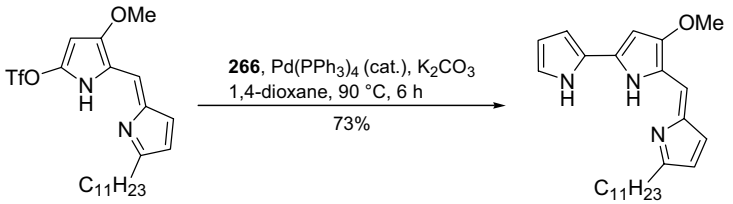
The readily available N-protected 2-bromopyrrole **155** is an excellent partner for Suzuki couplings, offering a convenient route to the 2-arylpyrroles **363** (Scheme 4.110) [580, 581]. An alternative approach is based on coupling of the pyrrole-2-boronic acid **266** with aryl bromides or iodides [582]. Suzuki reactions have also been performed using 1-(phenylsulfonyl)pyrrole-2-boronic acid [583], 2-bromo-1-(*p*-toluenesulfonyl)pyrrole [241] and 2-iodo-1-(phenylsulfonyl)pyrrole [412]. In



Scheme 4.110

addition, it has been demonstrated that electron deficient di- or tribrominated pyrroles undergo selective Suzuki reactions at the α-position with phenylboronic acid derivatives [584]. Heck reactions at the α-position of iodinated pyrroles involving vinylbenzene derivatives [585, 586], as well as Pd(0)-catalyzed couplings with alkynes [587], have also been reported.

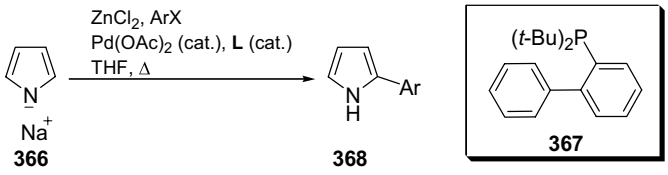
Suzuki coupling of the triflate **364** with the boronic acid **266** has been employed as the final step in an elegant synthesis of undecylprodigiosin (**365**) (Scheme 4.111) [588], as well as during preparation of a series of analogues thereof [589].



364 **365**

Scheme 4.111

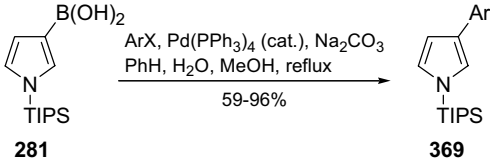
A new arylation reaction of pyrrolylsodium (**366**) (Section 4.5.4.1) has been developed. In a representative set of conditions, exposure of **366** to various aryl chlorides or bromides and $ZnCl_2$ in the presence of $Pd(OAc)_2$ and 2-(di-*tert*-butylphosphino)biphenyl (**367**), afforded 2-arylpyrroles **368** in high yields (Scheme 4.112). The products **368** may also be subjected to further arylation under similar conditions at the remaining free α-position, providing access to various 2,5-diarylpyrroles [590]. It has also been known for some time that palladium mediated arylation of 1-acylpyrroles with arenes occurs at the α-position. However, this requires stoichiometric amounts of the palladium source [591]. A recent interesting contribution involving C−H activation features regioselective palladium-catalyzed oxidative alkenylation of N-protected pyrroles at C2 or C3 using alkenes under aerobic conditions. The regioselectivity is highly dependent on the steric and electronic properties of the N-substituent of the substrate. For instance, the use of 1-(*tert*-butoxycarbonyl)pyrrole gives C2 alkenylated products, whereas implementation of 1-TIPS-pyrrole leads to functionalization at C3 [592].



366 **368** **367**

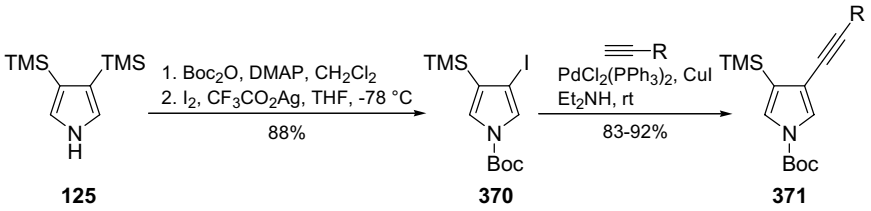
Scheme 4.112

Cross-coupling techniques may also be applied to the preparation of various 3-substituted pyrroles. The pyrrole-3-boronic acid **281**, which is derived from 1-triisopropylsilyl-3-iodopyrrole, takes part in Suzuki couplings with both electron rich and electron deficient aryl halides (X=Br or I) to provide useful yields of the 3-arylpyrroles **369** (Scheme 4.113). Stille reactions of 1-triisopropylsilyl-3-(tributylstannyl)pyrrole with suitable aryl halides constitute an alternative route to pyrroles of type **369**, whereas palladium-catalyzed coupling of 1-triisopropylsilyl-3-iodopyrrole with terminal acetylenes gives high yields of the corresponding 3-ethynylpyrroles. The TIPS group in all products may be removed efficiently by treatment with Bu_4NF [418]. In connection with studies on Suzuki couplings involving ethyl 4-bromopyrrole-2-carboxylate, a competing dehalogenation of the halopyrrole was observed. This side reaction was, however, suppressed by using the corresponding N-Boc-protected derivative, leading to good yields of ethyl 4-arylpyrrole-2-carboxylates with a concomitant removal of the Boc-group during the process [593]. Other useful developments in this area encompass palladium-catalyzed coupling of 1-(*p*-toluenesulfonyl)-4-(tributylstannyl)pyrrole-2-carboxaldehyde with aryl- and heteroaryl halides giving the corresponding 4-arylpyrrole-2-carboxaldehydes [594], and synthesis of 3-vinylpyrroles by Stille reactions between various 3-iodopyrroles and vinyltributyltin [595]. In addition, Suzuki couplings involving the triflate derived from 1-benzylpyrrolidine-3-one are accompanied by concomitant dehydrogenation, giving access to 3-aryl-1-benzyl-pyrroles [596]. Finally, both 2-iodo-1-(phenylsulfonyl) pyrrole and its 3-iodo isomer are efficiently cyanated using CuCN in the presence of catalytic amounts of $Pd_2(dba)_3$ and dppf [597].



Scheme 4.113

In an interesting approach towards unsymmetrically 3,4-disubstituted pyrroles, the 3,4-disilylated pyrrole derivative **125** was N-protected, followed by an *ipso*-iodination to provide the key intermediate **370**, which was in turn subjected to various cross-couplings, providing, for example, the products **371** via the Sonogashira reaction (Scheme 4.114) [246, 247], or the corresponding aryl derivatives



Scheme 4.114

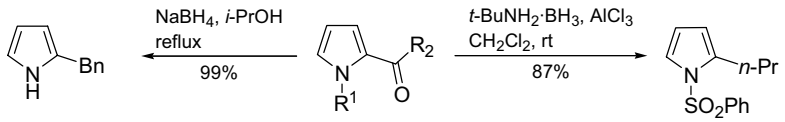
employing Suzuki conditions. A second *ipso*-iodination and subsequent palladium-catalyzed coupling reactions give access to further derivatives [247]. Moreover, phosphine-free Suzuki reactions involving methyl 4,5-dichloro-3-iodopyrrole-2-carboxylate occur selectively at C3, giving access to 3-arylpyrrole-2-carboxylates after final removal of the chlorine atoms by catalytic hydrogenation [307].

4.6 Pyrrole Derivatives

4.6.1 Alkyl Derivatives

N-Alkylation of pyrroles is a well documented process that is conveniently accomplished by treatment of pyrrolyl anions with suitable alkylating agents under various conditions (Section 4.5.4.1).

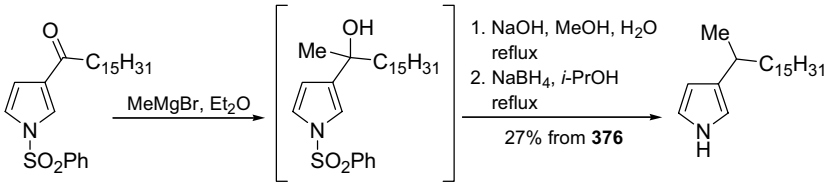
Direct C-alkylation is often not particularly practical, as it has been demonstrated that treatment of pyrrolyl anions with allyl-, crotyl- and benzyl-halides gives mixtures of N- and C- monoalkylated products, along with disubstituted derivatives [375]. The methods of choice for the synthesis of alkylpyrroles rely on pyrrole ring formation from acyclic precursors (Section 4.4), or reduction of readily available 2- or 3-acylpyrroles (Section 4.5.1.6). Reduction of 2-benzoylpyrrole (**372**) with $NaBH_4$ in boiling 2-propanol gives a high yield of 2-benzylpyrrole (**373**) (Scheme 4.115) [598]. An alternative procedure employs a *tert*-butylamine–borane complex in the presence of $AlCl_3$ as the reducing system, enabling for example effective transformation of the N-protected 2-acylpyrrole **374** into the corresponding 2-alkylpyrrole **375**. This approach is also useful for the reduction of 1-phenylsulfonylpyrrole-2-carboxaldehyde to the corresponding 2-methylpyrrole derivative [599].



373 **372** R^1 = H, R^2 = Ph; **374** R^1 = SO_2Ph, R^2 = Et; **375**

Scheme 4.115

These reductions are neatly complemented by the possibility of crafting a secondary alkyl substituent, as illustrated by the conversion of the 3-acylpyrrole **376** into the 3-alkylpyrrole **377**, which proceeds via the unstable tertiary alcohol **378** (Scheme 4.116) [598]. A somewhat related approach involving addition of organometallic reagents to 2-acylpyrroles, followed by reduction with lithium in liquid ammonia, has also been described [600].



376 **378** **377**

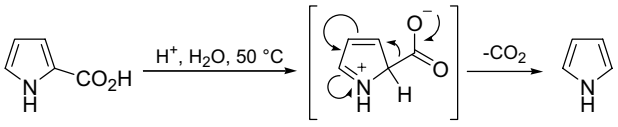
Scheme 4.116

4.6.2

Pyrrole Carboxylic Acids and Carboxylates

Many pyrrole carboxylic acids are readily available compounds, which are quite prone to decarboxylation. This particular characteristic is very attractive from a synthetic point of view, extending the scope of those pyrrole ring syntheses that give pyrrole carboxylates (Section 4.4). Pyrrole-2-carboxylates are useful substrates for further functionalization by means of electrophilic substitution, as the substituent is strongly "meta" directing, thereby allowing selective synthesis of 2,4-disubstituted pyrroles (Section 4.5.1.6). It is also worth mentioning that amides derived, for instance, from pyrrole-2,5-dicarboxylic acids have recently attracted interest as anion receptors and membrane transport agents for HCl [601].

Decarboxylation of pyrrole-3-carboxylic acids may, for example, be effected by heating [602], whereas ethyl pyrrole-3-carboxylates can be hydrolyzed and decarboxylated in one pot by heating with aqueous NaOH at 175 °C in a sealed vessel [124]. Based on kinetic studies, the mechanism of the decarboxylation of pyrrole-2-carboxylic acid **198** in acidic media has been suggested to proceed through the intermediate **379**, which eventually releases carbon dioxide (Scheme 4.117) [603]. A striking feature during saponification of pyrrolecarboxylates is the relatively high rate constant for pyrrole-2-carboxylates compared to that of the C3 substituted isomers. This behavior has been ascribed to the possibility of intramolecular hydrogen bonding in the intermediate resulting from the attack of a hydroxide ion on the carbonyl carbon in the C2 isomers [604, 605].

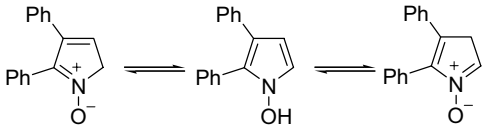


198 **379** **1**

Scheme 4.117

4.6.3
Oxy Derivatives

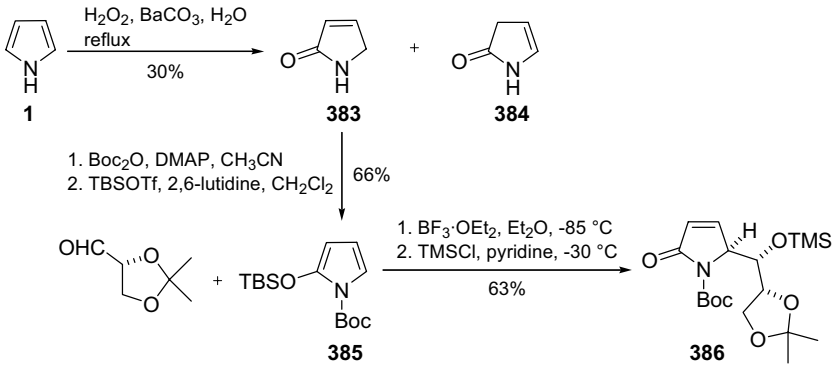
1-Hydroxypyrrole derivatives are available by several routes, for example employing hydroxylamine in the Paal–Knorr pyrrole synthesis [606], by thermolysis of 1-(*tert*-butyl)-3-pyrrolin-1-oxide to 1-hydroxy-3-pyrroline [607] or via treatment of suitable monooximes derived from 1,2-dicarbonyl compounds with sodium hydride, followed by vinyltriphenylphosphonium bromide, which gives 2,3-disubstituted 1-hydroxypyrroles [608]. Deuterium exchange studies with D_2O in $CDCl_3$ performed on 1-hydroxy-2,3-diphenylpyrrole (**380**) indicated incorporation of deuterium at C4 and C5 along with the expected deuterium exchange at the oxygen, suggesting contributions from the tautomeric forms **381** and **382** (Scheme 4.118) [608].



381 **380** **382**

Scheme 4.118

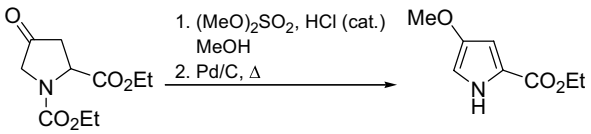
Oxidation of pyrrole employing hydrogen peroxide gives a modest yield of the tautomeric 2-oxypyrroles **383** and **384**, the former being the prevalent component as judged from NMR data (ratio **383** : **384** = 9 : 1 in acetone-d_6) (Scheme 4.119) [609]. Purified samples of **383** remain rather stable for several weeks upon storage at −10 °C, whereas the isomer **384** undergoes much faster isomerization [610]. After initial N-protection of **383**, access to a useful synthetic intermediate is gained by trapping of the corresponding 2-hydroxypyrrole tautomer as the silyl ether **385**, which reacts with aldehydes, rendering for example the 5-substituted pyrroline-2-one **386** [611, 612]. The oxypyrrole **385** has also been efficiently prepared on multi-kilogram scale via cyclization of racemic 4-amino-3-hydroxybutyric acid with HMDS



Scheme 4.119

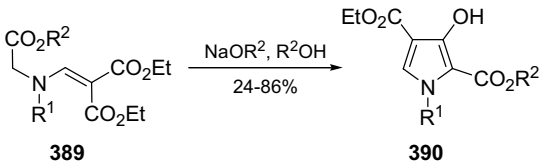
in the presence of pyridine to 4-(trimethylsiloxy)pyrrolidine-2-one, which underwent subsequent Boc-protection, desilylation and elimination to yield 1-(*tert*-butoxycarbonyl)-3-pyrroline-2-one. This material could then be efficiently converted into **385** using TBSOTf in the presence of triethylamine [613]. It is also noteworthy that electrolytic fluorination of 2-cyano-1-methylpyrrole with $Et_3N{\cdot}3HF$ in acetonitrile, followed by treatment with water, gives 5,5-difluoro-1-methyl-3-pyrrolin-2-one, a useful starting material for the construction of some *gem*-difluorinated heterocycles [614].

The reaction of ethyl *N*-ethoxycarbonyl glycinate with ethyl fumarate in the presence of sodium in benzene solution, followed by decarboxylation, provides convenient access to the 3-oxypyrrole derivative **387** [615]. This material may for instance be further converted into the substituted 3-methoxypyrrole **388** by ketalization and dehydrogenation over Pd/C with concomitant cleavage of the carbamate functionality (Scheme 4.120) [616]. 3-Alkoxypyrroles have also been prepared by cyclization of alkyl 4-bromo-3-alkoxy-2-butenoates with suitable amines to 4-alkoxy-3-pyrrolin-2-ones, and subsequent treatment thereof with diisobutylaluminium hydride [617].



Scheme 4.120

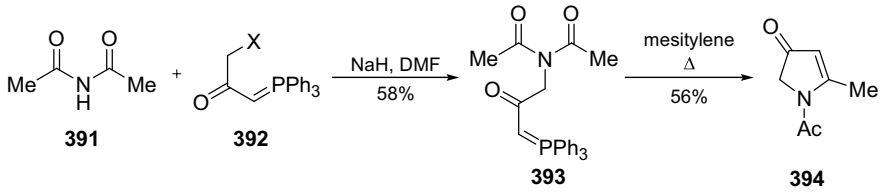
Cyclization of the precursors **389**, which are readily available from glycine esters and diethyl ethoxymethylenemalonate, provides a route to the stable 3-hydroxypyrrole derivatives **390** (Scheme 4.121). The C4 substituent may be selectively removed by alkaline hydrolysis, followed by decarboxylation [618].



Scheme 4.121

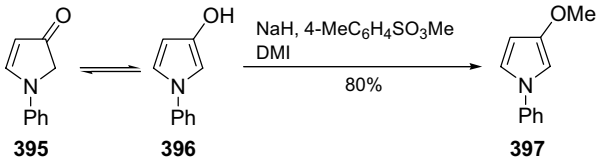
In an approach based on intramolecular Wittig olefination, alkylation of, for example, *N*-acetylacetamide (**391**) with the reagents **392** (X = Br or Cl) afforded the precursor **393**, which was in turn cyclized to the 3-oxypyrrole derivative **394** under thermal conditions (Scheme 4.122) [619].

Apart from the examples mentioned above, 3-oxypyrroles are also available by for instance flash vacuum pyrolysis of N,N-disubstituted aminomethylene derivatives of



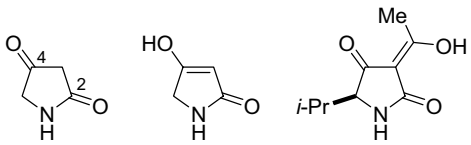
Scheme 4.122

Meldrum's acid [620]. A representative member of this class, 1-phenyl-1*H*-pyrrol-3(2*H*)-one, exists as mixtures of the tautomeric forms **395** or **396** depending on the medium. In general, polar solvents favor the enol form **396**, whereas in the solid state the keto tautomer **395** alone was detected (Scheme 4.123) [621]. The enol form was also detected as the prevalent species in DMSO solution in the case of the parent 3-hydroxypyrrole [622]. In addition, preference for the enol tautomers has been observed in connection with studies of derivatives containing an ester functionality at the adjacent C4 position [623]. Regiospecific O-alkylation of 3-hydroxypyrroles can be accomplished in polar aprotic solvents such as dimethylimidazolidinone (DMI), using the hard alkylating agent methyl *p*-toluenesulfonate to give, for example, pyrrole **397**. In contrast, the use of soft alkylating agents, such as iodomethane in relatively nonpolar solvents, leads to increased amounts of C-alkylated products [624].

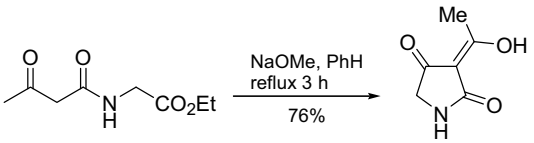


Scheme 4.123

Derivatives of tetramic acid (**398**) constitute a relatively large class of oxygenated pyrroles, which has been studied in considerable detail [35, 625]. The parent compound **398** is a relatively weak acid, (pK_a=6.4 in water), which exists in the keto from in the solid state, whereas in aqueous solution a minor contribution from the enol **399** may be discerned [626]. The enolization behavior of 3-acetyltetramic acids is more complex; studies involving for instance the 3-acetyl-5-isopropyl derivative revealed a considerable contribution from the *exo*-enol tautomer **400** [627].



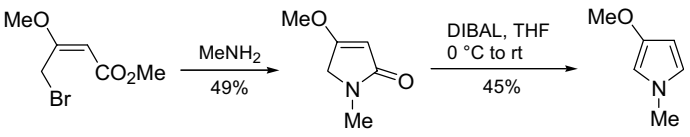
The most practical and widely used approach to tetramic acid derivatives has been developed by Lacey, and involves Dieckmann cyclization of *N*-acyl-α-amino esters. For example, the precursor **401**, which is available by treatment of ethyl glycinate with diketene, gives 3-acetyltetramic acid **402** upon treatment with sodium methoxide (Scheme 4.124) [628]. Application of these conditions to substrates derived from optically active amino acids may cause racemization, which can, however, be avoided by conducting the cyclization in the presence of TBAF in THF, or potassium *tert*-butoxide in *tert*-butanol during short periods of time. These modified routes also involve generation of the acyclic precursors from β-ketothioesters and amino acids [629]. Suitable precursors to tetramic acids may also be prepared by treatment of hippuric acid [630] or aceturic acid [631] derivatives with anions of active methylene compounds. The Dieckmann cyclization strategy has also been utilized in a solid phase approach starting from amino acid derivatives attached to the resin by an ester linkage [632]. A recent contribution to this field encompasses preparation of 5-substituted teramic acid derivatives by cyclocondensation of amidines with DMAD, followed by alkaline hydrolysis of the intermediate 5-amino-4-pyrrolin-3-ones [633].



401 **402**

Scheme 4.124

The methyl tetramate **403**, as well as several similar compounds, is available by treatment of methyl 4-bromo-3-methoxy-2-butenoate **404** with methylamine [634], and may be converted into the corresponding 3-alkoxypyrroles, for instance **405**, by treatment with diisobutylaluminium hydride (Scheme 4.125) [617]. Furthermore, the representative tetramate **403** undergoes metallation at C5 upon exposure to butyllithium, and the resulting lithio derivative gives access to various C5 substituted products after subsequent treatment with suitable electrophiles [635]. It has also been established that methyl tetramates of type **403** having an isopropyl moiety [636] or two substituents [637] at C5 may be acylated at C3 via lithiation, followed by introduction of aldehydes, and oxidation of the intermediate alcohols. The active methylene unit of tetramates may also participate in condensation reactions with aldehydes in the presence of sodium hydroxide in aqueous DMSO [588].

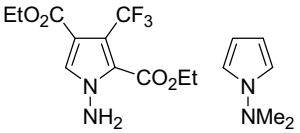


404 **403** **405**

Scheme 4.125

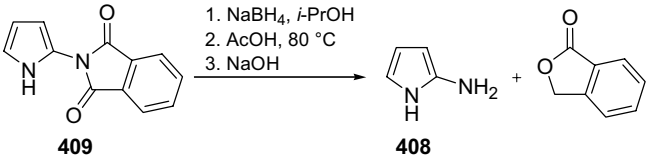
4.6.4
Aminopyrroles

Simple aminopyrroles are highly electron rich and thus often labile species, but the stability may be improved considerably by the presence of electron-withdrawing substituents. A series of 1-aminopyrroles, including **406**, has been prepared by N-amination of the corresponding NH-pyrroles with anhydrous ethereal NH_2Cl in the presence of NaH [638]. Recently, a more convenient N-amination protocol for pyrroles has been realized under phase transfer conditions using *in situ* generated chloramine as the electrophilic aminating agent [639]. Interestingly, 1-(*N*,*N*-dimethylamino)pyrrole (**407**) can be easily prepared by heating 2,5-dimethoxytetrahydrofuran and *N*,*N*-dimethylhydrazine in acetic acid, and is cleanly lithiated at C2 [416].



406 **407**

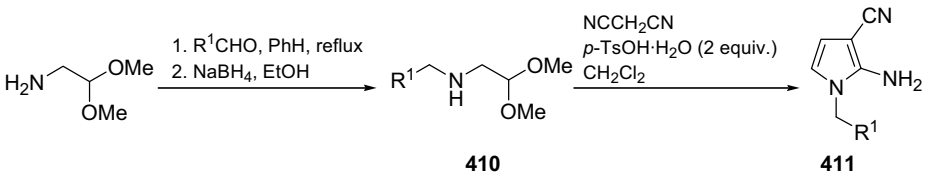
The parent 2-aminopyrrole (**408**) was generated from the (pyrrole-2-yl)phthalimide **409** [640], which is in turn available by treatment of 1-trimethylsilylpyrrole with chlorophthalimide followed by aqueous workup (Scheme 4.126) [230, 641]. The aminopyrrole **408**, as well as 1-alkyl- and 1-aryl derivatives thereof, have to be kept in acid solution. A fast proton exchange at C5 in this series was observed in glacial acetic acid [640], and further NMR studies indicated that the conjugate acids of the 2-aminopyrroles exist as protonated imines under these conditions [641]. It has also been demonstrated that 2-aminopyrroles incorporating an electron-withdrawing substituent at the adjacent β-carbon can undergo protonation at either the exocyclic nitrogen atom or C5, depending on the conditions, but react at the exocyclic nitrogen only with acylating agents, thus behaving like typical aromatic amines rather than enamines [642].



409 **408**

Scheme 4.126

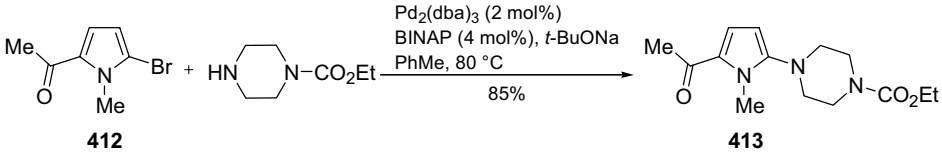
A useful approach featuring a pyrrole ring synthesis involves treatment of the readily available aminoacetaldehyde dimethyl acetals **410** with malononitrile under acidic conditions to provide facile access to the 2-aminopyrrole-3-carbonitriles **411** in moderate yields (Scheme 4.127). Similar products may also be prepared from ethyl 3-cyanopyrrole-2-carboxylates using a route based on the Curtius rearrangement [643]. 2-Aminopyrroles have also been obtained by base induced condensation reactions



Scheme 4.127

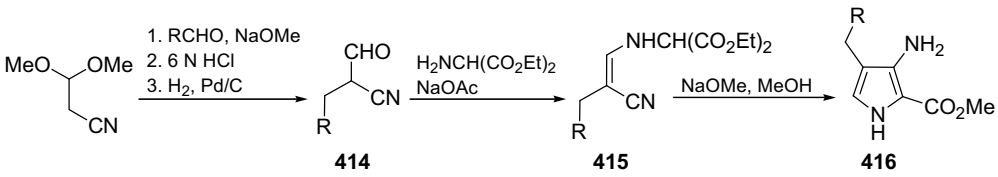
between acetylaminoacetone and substituted acetonitriles [644], or from *N*-acetyl-α-aminoketones and malononitrile [645].

Yet another contribution to aminopyrrole chemistry is represented by a procedure for palladium-catalyzed amination of 2-acetyl-5-bromo-1-methylpyrrole (**412**), which can be performed using various primary and secondary amines, giving for example the 2-aminopyrrole derivative **413** (Scheme 4.128) [646]. An effective amidation of methyl 4-bromo-1-methylpyrrole-2-carboxylate with *tert*-butyl carbamate in the presence of the combination CuI/K_3PO_4/*N,N*′-dimethylethylenediamine has also been reported [236].



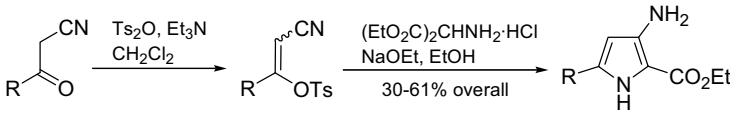
Scheme 4.128

3-Aminopyrroles featuring electron-withdrawing moieties have attracted some interest as building blocks for pyrrolo[2,3-*d*]pyrimidines [647, 648]. Consequently, several synthetic approaches to such derivatives have been described. The α-cyanoaldehydes **414**, which are derived from suitable aldehydes by base induced condensation with 3,3-dimethoxypropionitrile, followed by hydrolysis of the acetal and catalytic hydrogenation, serve as excellent substrates for the generation of enamine intermediates **415** by treatment with diethyl aminomalonate (Scheme 4.129). A final cyclization step afforded the 3-aminopyrrole derivatives **416** in moderate to good overall yields [648]. A route based on cyclization of similar enamine intermediates has been used for the synthesis of methyl 3-amino-4-arylpyrrole-2-carboxylates [649].



Scheme 4.129

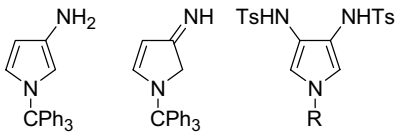
A different substitution pattern is displayed in the pyrroles **417**, which were prepared by tosylation of the cyanoacetyl compounds **418** rendering the precursors **419** (Scheme 4.130). These intermediates were in turn converted into the target heterocycles by reaction with diethyl aminomalonate hydrochloride in the presence of ethoxide [650]. Treatment of benzyl 4-oxoproline-2-carboxylate derivatives protected at the nitrogen by the 9-(9-phenylfluorenyl) group with primary or secondary amines in the presence of catalytic amounts of *p*-TsOH provides an efficient route to 4-aminopyrrole-2-carboxylates [651].



418 **419** **417**

Scheme 4.130

3-Amino-1-tritylpyrrole (**420**) has been prepared from the corresponding pyrrole-3-carboxylic acid in several steps using a route involving the Curtius rearrangement, and was demonstrated to exist exclusively as the 3-imino tautomer **421** in $CDCl_3$ solution [210]. A series of 1-arylpyrroles, as well as 1-methylpyrrole, has recently been shown to undergo amination, providing the interesting derivatives **422** in good yields using *N*-(*p*-toluenesulfonyl)imino-phenyliodinane (PhI=NTs) in the presence of a ruthenium(II) porphyrin catalyst [652].



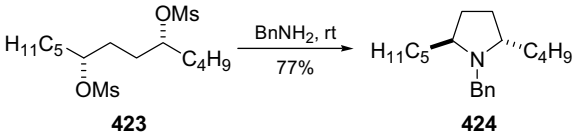
420 **421** **422**

4.6.5
Dihydro- and Tetrahydro-Derivatives

The scope of this chapter only allows inclusion of selected examples of procedures involving dihydro- and tetrahydro derivatives, but it is important to emphasize that many significant compounds belong to these thoroughly studied systems, for instance the amino acid L-proline. Both 2- and 3-pyrrolines (2,3-dihydro- and 2,5-dihydropyrroles), as well as pyrrolidines (tetrahydropyrroles), are available by reduction of pyrrole derivatives (Section 4.5.6). The reverse transformation, that is, conversion of pyrrolidines into pyrroles, may be accomplished for instance by dehydrogenation with MnO_2 in refluxing THF [653].

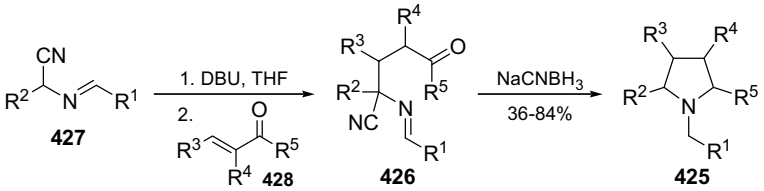
In more recent years, several useful ring syntheses of partially, or completely saturated pyrrole derivatives have emerged, for example 2,5-disubstituted pyrrolidines [654]. Several practical approaches rely on the cyclization of suitable diol

derivatives, for instance **423**, which gives the *trans*-pyrrolidine **424** upon treatment with benzylamine (Scheme 4.131) [655]. Base induced annulation of mesylates derived from suitable chiral γ-aminoalcohols constitutes an alternative procedure for the stereoselective preparation of *cis*- or *trans*-2,5-disubstituted pyrrolidines [656].



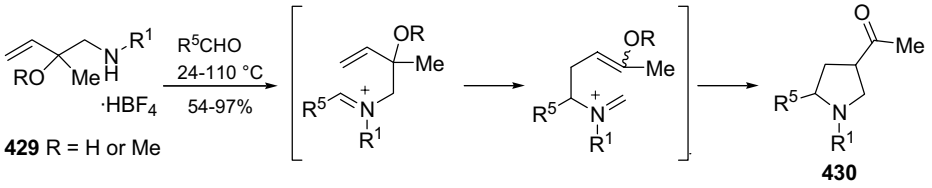
Scheme 4.131

Reductive amination of 1,4-diketones with ammonium acetate [657] or amines in the presence of $NaCNBH_3$ provides routes to pyrrolidines as mixtures of cis- and trans-isomers, the former being favored by increasing size of the amine reactant [658]. A related one-pot approach giving the 1-(2-naphthyl)methylene- or 1-(3,4-dimethoxybenzyl)pyrrolidines **425** involves reductive cyclization of the four-carbon precursors **426**, which are in turn available by conjugate addition of the α-(alkylideneamino)nitriles **427** to the α,β-unsaturated ketones **428** (Scheme 4.132) [659].



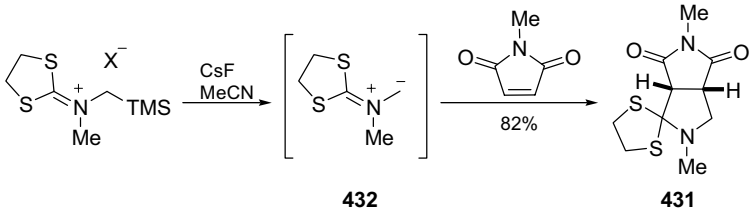
Scheme 4.132

Pyrrolidines containing sensitive substituents have been prepared under mild conditions using a tandem cationic aza-Cope rearrangement–Mannich process. Thus, treatment of the substituted 3-butenamines **429** with appropriate aldehydes in benzene or toluene affords moderate to excellent yields of the substituted 3-acetylpyrrolidines **430** (Scheme 4.133) [660].



Scheme 4.133

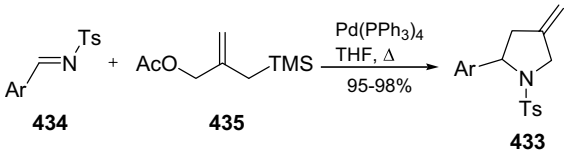
A general approach to pyrrolidines involves 1,3-dipolar cycloadditions of alkenes and azomethine ylides, which are for instance available by desilylation of α-silyl iminium salts [661]. This strategy has been exploited in construction of the system **431**, which resulted from a reaction of the ylide **432** with *N*-methylmaleimide (Scheme 4.134) [662]. The various routes to enantiopure pyrrolidine derivatives based on cycloaddition reactions involving azomethine ylides have been recently summarized in a review [663].



432 **431**

Scheme 4.134

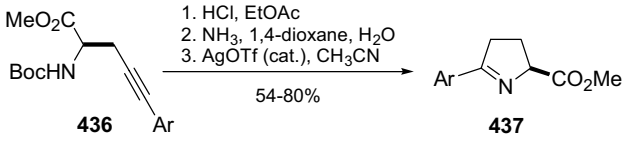
The pyrrolidines **433** incorporating an exocyclic double bond have been synthesized by cycloaddition of the *N*-tosylimines **434** with a palladium complex derived from the precursor **435** (Scheme 4.135). Similar syntheses of various pyrrolidine derivatives may also be performed starting from aliphatic *N*-tosylimines (readily generated from the corresponding aldehydes by treatment with chloramine-T and elemental selenium), nitrimines or other electron deficient imines [664].



434 **435** **433**

Scheme 4.135

Based on a previous approach for palladium-catalyzed cyclization of 3-alkynylamines yielding 1-pyrrolines [665], the precursors **436**, derived from a propargylglycine derivative via Sonogashira coupling, were deprotected under acidic conditions, followed by silver-catalyzed cyclization, providing a route to the 1-pyrrolines **437** (Scheme 4.136) [666]. Palladium-catalyzed ring closure of related precursors may instead give 2-pyrrolines, whereas the application of 4-alkynylamines in similar

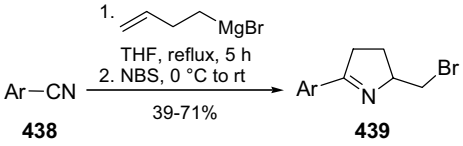


436 **437**

Scheme 4.136

processes gives pyrrolidines incorporating an exocyclic double bond [667]. Densely substituted 1-pyrrolines may also be accessed by 1,3-dipolar cycloaddition reactions between acrylamide derivatives and nitrile ylides generated from imidoyl chlorides [668]. Preparative routes and transformations involving 1-pyrrolines have been reviewed [669].

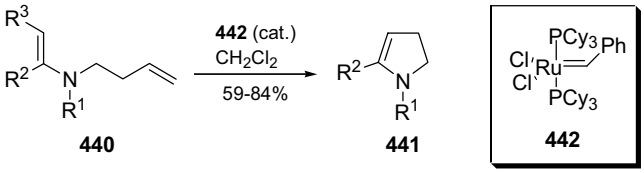
A traditional approach to 1-pyrrolines relies on addition of Grignard reagents to γ-halonitriles, which gives rise to the 2-substituted systems [670, 671]. It was later demonstrated that application of hydrocarbon/ether solvent mixtures for such reactions constitutes a practical modification [672]. Addition of but-3-enylmagnesium bromide to benzonitriles **438**, followed by treatment with NBS, leads to formation of 1-pyrrolines **439** (Scheme 4.137) [673], whereas chlorination using NCS gives the related 5-(chloromethyl)-1-pyrroline derivatives [674].



438 **439**

Scheme 4.137

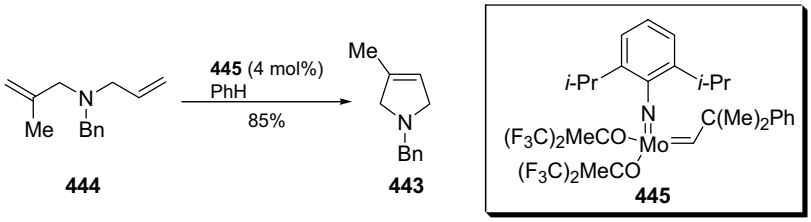
Ring closing metathesis (RCM) of the enamides **440** (R^1=Ts, Bz, CO_2Et) has been employed for the preparation of the 2-pyrrolines **441** using the catalyst **442** (Scheme 4.138). In some cases, better yields were obtained using a related, Ru–imidazoline RCM catalyst [675].



440 **441** **442**

Scheme 4.138

Likewise, RCM methodology is also applicable for the construction of 3-pyrrolines, as illustrated by the synthesis of **443** from the diene **444** (Scheme 4.139) [676]. In a



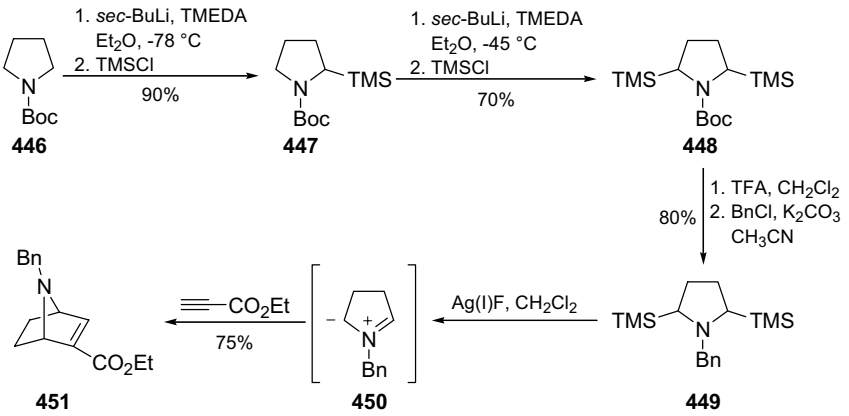
444 **443** **445**

Scheme 4.139

related RCM approach to 3-pyrrolines, a suitable set of N-SES protected dienes were constructed from 2-(trimethylsilylethane)sulfonamide, aldehydes and methyl acrylate in an aza-Baylis–Hillman reaction [677]. On the other hand, the cyclization of diallylamines using the second generation Grubbs' catalyst (10 mol.%) in combination with $RuCl_3 \cdot H_2O$ (2 mol.%) gives rise to pyrroles in moderate yields [678]. An alternative route to 3-pyrrolines relies on triphenylphosphine-catalyzed [3 + 2] cycloaddition reactions of methyl 2,3-butadienoate with *N*-tosyl aldimines [679].

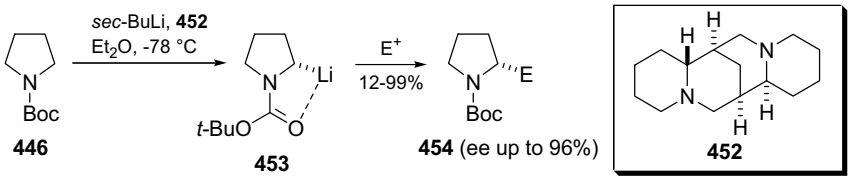
As a typical secondary amine, pyrrolidine displays pronounced basic character, and reacts readily as an N-nucleophile, affording, for example, amides. A well known application of pyrrolidines is its condensation with carbonyl groups to give enamines, which may subsequently be alkylated or acylated, providing an excellent and versatile route to α-substituted carbonyl compounds after a final hydrolysis step [680].

Reactions at the carbon atoms of simple pyrrolidines have been less studied. Nevertheless, several synthetically useful transformations have been described. It has for example been established that deprotonation and subsequent silylation of *N*-Boc-pyrrolidine (**446**) gives the intermediate **447** (Scheme 4.140) [681]. This material was subjected to a second lithiation/silylation cycle to provide the pyrrolidine derivative **448**. After removal of the Boc-group, followed by N-benzylation, the resulting pyrrolidine **449** was converted into the azamethine ylide **450**, which was trapped with ethyl propiolate to furnish adduct **451** [682]. An enantioselective cycloaddition between **450** and a chiral alkene has also been described [683]. Deprotonation of methyl 3-pyrroline-1-carboxylate with LDA at C2, and subsequent quenching with suitable electrophiles, provides an example of the functionalization of 3-pyrrolines [684].



Scheme 4.140

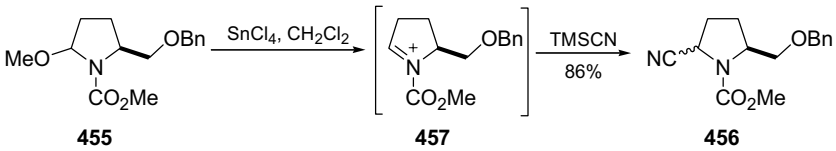
In an interesting example of enantioselective functionalization at C2, *N*-Boc-pyrrolidine **446** was treated with *sec*-BuLi in the presence of (−)-sparteine (**452**) to produce the chiral lithio derivative **453**, which upon quenching with suitable electrophiles gave the 2-substituted derivatives **454** (Scheme 4.141) [685, 686]. Two



Scheme 4.141

sequential lithiations of **446**, each followed by quenching with dimethyl sulfate, furnished the corresponding *trans*-2,5-dimethylpyrrolidine derivative [686]. The species **453** may also be used for enantioselective ring opening of epoxides, provided that one equivalent of $BF_3{\cdot}OEt_2$ is added directly after the electrophile [687]. Transmetallation of **453** with CuCN·2LiCl generates a corresponding cuprate with retention of configuration, and subsequent reactions thereof with, for example, vinyl iodides or triflates give vinylated products with excellent enantioselectivity [688].

Pyrrolidine derivatives may also be functionalized via conversion into *N*-acyliminium ions, as illustrated by the conversion of the pyrrolidine **455** into the product **456** (cis : trans ratio 7 : 3) employing $SnCl_4$ and TMSCN, via the intermediate **457** (Scheme 4.142) [689].



Scheme 4.142

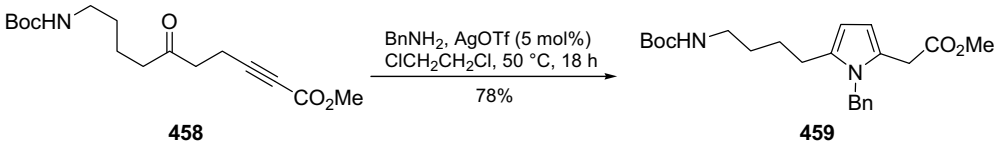
4.7 Addendum

Even a rather superficial glance at the most recent literature of organic chemistry clearly reflects the tremendous amount of effort currently invested in research activities focusing on pyrrole based molecules. This addendum highlights some selected new developments reported during the production process of this book, as well as some related relevant studies. As usual, an annual summary of the most important recent advances in *Progress in Heterocyclic Chemistry* provides an excellent source of information [690]. In addition, the new edition of *Comprehensive Heterocyclic Chemistry* has appeared, covering various aspects of pyrrole chemistry explored during the last decade [691–694]. Several specialized reviews have also emerged, discussing for example some synthetic aspects of pyrroles bearing multiple substituents [695], or asymmetric synthesis of pyrrolidines by [3 + 2] cycloadditions of azomethine ylides [696]. Because much novel pyrrole chemistry is directed towards synthesis and applications of macrocycles, topics such as carbaporphyrins and related porphyrinoids [697], acyclic oligopyrroles [698], expanded porphyrins [699],

and their transition metal complexes [700], and nonlinear optical properties of porphyrins [701], as well as synthetic work towards porphyrins involving the Barton–Zard reaction [702], have received treatment. In addition, the pyrrole alkaloids lamellarins and their relatives have been discussed in detail [703].

Mechanistic aspects of the Paal–Knorr synthesis have been addressed in a density functional theory study [704], supporting the previously suggested pathway [71] that involves a cyclization of a hemiaminal intermediate in the rate-limiting step (Section 4.4.1). Although the extensive arsenal of well-established routes for pyrrole ring synthesis gives access to a wide variety of products, there is a continuous stream of new approaches that attempt to target pyrroles with rare substitution patterns, or serve as complementary methods for construction of known groups of useful derivatives.

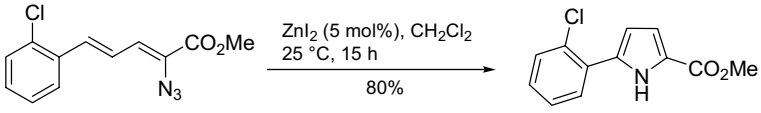
Numerous routes rely on reactions of substrates containing all the necessary carbon atoms. It has been shown that $PtCl_4$ catalyzes cyclization of homopropargyl azides in the presence of a bulky pyridine as the base, affording for instance 2,5-substituted pyrroles, or tetrahydroindole derivatives [705]. The recent surge in gold- or silver-catalyzed organic transformations has also exerted some impact on heterocyclic chemistry, as illustrated by the conversion precursor **458** into the pyrrole **459** by exposure to benzyl amine in the presence of silver trifluoromethanesulfonate (Scheme 4.143). Such transformations can also be performed using the catalytic system AuCl/AgOTf/PPh_3 [706]. Moreover, palladium-catalyzed reactions between N-protected γ-aminoalkenes and functionalized aryl bromides in the presence of a phosphine ligand and a base have furnished a set of multiply substituted pyrrolidines [707]. A series of potentially useful pyrroles has also been prepared by CuI-catalyzed cyclization of 1,4-dihalo-1,3-dienes with *tert*-butyl carbamate [708].



458 459

Scheme 4.143

Azidodienes are readily available by condensation of azidoacetic acid esters with α,β-unsaturated aldehydes, and contain all the atoms necessary for a construction of a pyrrole ring. This fact was exploited in the conversion of precursor **460** into the pyrrole-2-carboxylate **461** in good yield upon treatment with catalytic amounts of zinc iodide, providing a representative illustration of this route (Scheme 4.144). The

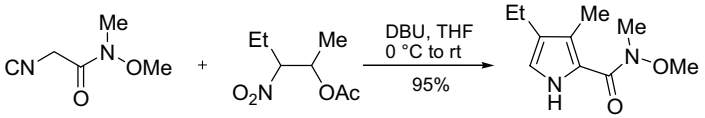


460 461

Scheme 4.144

procedure could be applied for the preparation of various pyrrole-2-carboxylates bearing aryl, heteroaryl, and alkyl groups [709]. Likewise, pyrrole derivatives have also been constructed by initial reactions of 1,3-dicarbonyl anions with α-azidoketones, and ensuing annulation of the resulting intermediates employing the Staudinger–aza-Wittig reaction [710]. Precursors for similar reductive cyclizations may also be assembled from 1,3-bis-silyl enol ethers and 1-azido-2,2-dimethoxyethane in the presence of TMSOTf [711].

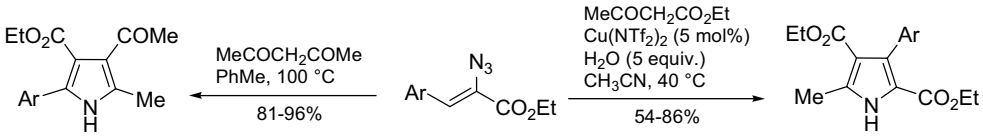
The elaboration of new [3 + 2] strategies, as well as the development of new aspects of the classical methods, continues, as illustrated by a new variation of the Barton–-Zard pyrrole synthesis (Section 4.4.7), which has been applied for construction of pyrrolic Weinreb amides *en route* to pyrrole-2-carboxaldehydes and pyrroline-3-ones. For example, the isocyanide **462**, which is available in four steps from Boc-glycine, was converted upon reaction with the β-nitroacetate **463** into the Weinreb amide **464** (Scheme 4.145) [712]. The use of ketene *S,S*- or *S,N*-acetals in Barton–Zard reactions provides a route to substituted pyrroles bearing methylthio- or amino groups at C3. Such systems could also be prepared employing the related van Leusen method (Section 4.4.6) for the pyrrole ring formation [713]. A practical one-pot route to 4-substituted pyrrole-3-carboxylates on a multi-kilogram scale has been presented, featuring a Horner–Wadsworth–Emmons reaction of aliphatic or aromatic aldehydes with trimethyl phosphonoacetate, followed by a van Leusen pyrrole synthesis involving TosMIC [714].



462 **463** **464**

Scheme 4.145

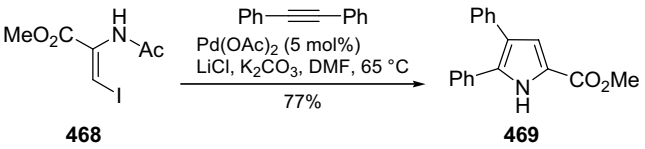
It has been demonstrated that the vinyl azides **465** may serve as an excellent starting point for pyrrole synthesis, as heating of such substrates with acetylacetone in toluene produced pyrroles **466** (Scheme 4.146). Interestingly, a related copper-catalyzed reaction involving instead ethyl acetoacetate proceeded with different regioselectivity, to provide the ethyl pyrrole-3-carboxylates **467**, thereby widening the scope of this strategy [715].



466 **465** **467**

Scheme 4.146

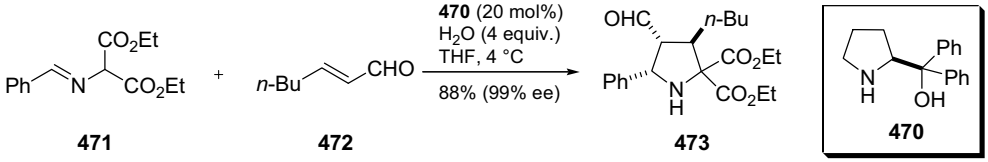
Palladium-catalyzed pyrrole ring synthesis from the halogenated aminoester **468** with various acetylenes has been examined. For instance, reaction between **468** and diphenylacetylene in the presence of $Pd(OAc)_2$ affords pyrrole **469** with concomitant loss of the acyl group (Scheme 4.147). However, some similar cyclizations gave products where the acyl group was untouched. The use of certain unsymmetrical alkynes (e.g., 1-phenyl-2-trimethylsilylacetylene) can give rise to regioselective formation of pyrroles [716].



468 **469**

Scheme 4.147

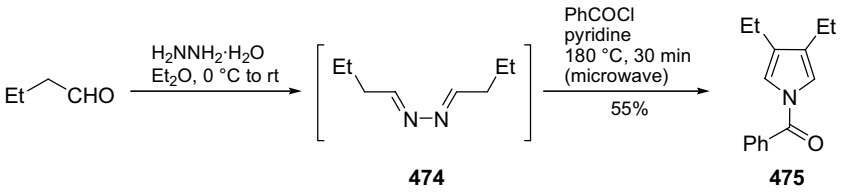
Pyrrolidines (Section 4.6.5) may be produced efficiently by cycloaddition reactions involving azomethine ylides [696]. An organocatalytic application of this approach has now became available, utilizing the catalyst **470**, which could for instance mediate the efficient and enantioselective [3 + 2] cycloaddition of components **471** and **472**, affording the pyrrolidine **473** (Scheme 4.148) [717]. It should also be mentioned that application of α-(alkylideneamino)nitriles in reactions with nitroalkenes provides a useful pyrrole synthesis, which relies on elimination of HCN and HNO_2 as the driving force for aromatization. This pathway involves a stepwise annulation mechanism rather than a cycloaddition [718]. In addition, a series of 4-hydroxypyrrole-2,3-dicarboxylates have been prepared by reactions of α-amino acids with acetylenedicarboxylates in the presence of cyclohexyl isocyanide or *N,N′*-dicyclohexylcarbodiimide as the coupling reagents [719].



471 **472** **473** **470**

Scheme 4.148

The largely neglected Piloty–Robinson [720–722] pyrrole synthesis has been adapted to microwave conditions [723], providing a route to 3,4-dialkylpyrroles, in particular 3,4-diethylpyrrole, a building block for construction of octaethylporpyrins [724, 725]. Thus, the intermediate azine **474** was generated by exposure of butyraldehyde to hydrazine hydrate in diethyl ether. Subsequent heating of **474** in the presence of benzoyl chloride in pyridine in a microwave apparatus gave the N-substituted product **475** (Scheme 4.149), which could subsequently be hydrolyzed to the desired 3,4-diethylpyrrole [723].



474 **475**

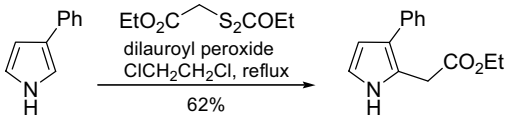
Scheme 4.149

Several new direct pyrrole syntheses based on multicomponent reactions (Section 4.4.10) have emerged recently, featuring for instance imines, diazoacetonitrile, and alkynes as the reactants in the presence of a rhodium(II) catalyst. The sequence of events leading to pyrroles presumably involves initial decomposition of the diazo compound, formation of an intermediate azomethine ylide upon reaction with the imine, and finally cycloaddition with the alkyne [726]. Similar sets of starting compounds, namely, imines, acid chlorides, and alkynes, may also be converted into pyrroles in the presence of either isocyanides [727] or phosphines [728]. The latter approaches have been suggested to proceed via cycloaddition reactions between mesoionic intermediates with the alkyne components [727, 728]. Intermediate münchnones can also be generated by a palladium-catalyzed reaction between certain α-amidoethers with carbon monoxide, eventually affording pyrroles via cycloadditions with suitable alkynes [729]. Additional efforts resulted in conversion of 1,3-dicarbonyl compounds, arylglyoxals, and ammonium acetate into 2-alkyl-5-aryl-4-hydroxypyrroles in water as the reaction medium [730], and preparation of 4,5-dimethylpyrrole-2,3-dicarboxylates by cyclizations of butane-2,3-dione with ylides derived from acetylenedicarboxylates and ammonium acetate in the presence of triphenylphosphine [731].

Some useful developments for modification of existing pyrrole rings have also appeared, such as an efficient procedure for CuI-catalyzed arylation of pyrroles with aromatic or heteroaromatic halides in the presence of simple *N*-hydroxyimides [732]. Moreover, a protocol for assembly of various 2,2′-bipyrrole-5,5′-dicarboxaldehydes by homocoupling of 5-iodopyrrole-2-carboxaldehyde precursors employed palladium on carbon and activated zinc dust as the catalyst [733]. Classical cross-coupling techniques have also found new applications, further demonstrating their extraordinary synthetic potential in pyrrole chemistry. For example, tetramic acid triflates have been demonstrated to participate in Suzuki couplings at C4, giving access to 3,4-diarylpyrrolin-2-ones [734], whereas Suzuki reactions have been employed in regioselective conversion of 1-methyltetrabromopyrrole into its 5-aryl-2,3,4-tribromo- or 2,5-diaryl-3,4-dibromo- derivatives [735], or transformations involving 1-phenylsulfonyl-3,4-dibromopyrrole [736]. A reaction sequence featuring an initial iridium-catalyzed borylation of 1-*tert*-butoxycarbonyl-2-trimethylsilylpyrrole at C4, followed by Suzuki coupling, as well as an intramolecular palladium-catalyzed C−H bond functionalization at C5, has been implemented in an elegant synthesis of the alkaloid rhazinicine [737]. Efficient conditions for generation of pyrrole-3-boronate esters by

palladium-catalyzed reactions of pinacol borane with 3-bromopyrroles, and their subsequent Suzuki reactions in the presence of a monophosphine based catalyst, have also been established [738].

A series of 2,2′-bipyrroles has been obtained by regioselective oxidative coupling of pyrroles in the presence of phenyliodine(III) bis(trifluoroacetate) (PIFA) and bromotrimethylsilane (TMSBr), whereas for instance *N*-benzylpyrrole gave a 2,3′-coupled product in good yield under different conditions where $BF_3{\cdot}OEt_2$ was used instead of TMSBr [739]. Intermolecular radical alkylation of some 3-substituted pyrroles with xanthates mediated by dilauroyl peroxide occurs at C2 in moderate to good yields with high regioselectivity, as shown by preparation of the product **476** from 3-phenylpyrrole **477** (Scheme 4.150) [740].



477 **476**

Scheme 4.150

Catalytic hydrogenation of 2- or 3-nitropyrroles in the presence of carboxylic acid anhydrides has resulted in a new useful route to the corresponding series of pyrrolylamides or pyrrolylimides [741]. Alternatively, similar chemistry may also be accomplished using tin or indium as the reducing agents [742], while application of 1,4-diketones instead of anhydrides has provided efficient access to 1,2′- and 1,3′-bipyrroles [743].

Finally, it should also be mentioned that determination of the second-order rate constants of the reactions of a series of pyrroles with benzhydrylium ions in acetonitrile provided the basis for a nucleophilicity scale, where 1-triisopropylsilylpyrrole was the least nucleophilic member and 3-ethyl-2,4-dimethylpyrrole was the strongest nucleophile, comparable to enamines in its reactivity [744]. A systematic reinvestigation of an acylation, where a solution of 1-(*p*-toluenesulfonyl)pyrrole and $AlCl_3$ as the Lewis acid in 1,2-dichloroethane as the solvent was quenched with an acyl halide, led to the conclusion that this process may involve the initial formation of pyrrolic organoaluminium species, which thereafter react with the highly reactive electrophile at C3 via a reactant-like transition state [745]. This is in contrast with earlier findings, which gave no evidence of complex formation of the closely related 1-(phenylsulfonyl)pyrrole with $AlCl_3$ in CH_2Cl_2 [315]. On the other hand, reactions featuring weaker Lewis acids such as $EtAlCl_2$ or Et_2AlCl, or less than equimolar amounts of $AlCl_3$, gave considerable amounts of products substituted at C2, proceeding via a normal Friedel–Crafts mechanism, where the pyrrole undergoes acylation by a complex generated from the Lewis acid and an acyl chloride [745]. Clearly, these very useful, but mechanistically complex, reactions are not yet completely understood, and further studies are necessary to provide a complete picture accounting for the observed outcomes.

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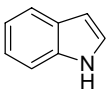
5
Five-Membered Heterocycles: Indole and Related Systems

José Barluenga and Carlos Valdés

5.1
Introduction

5.1.1
General Introduction

Indole (1*H*-indole) (**1**) is the benzopyrrole with the ring fusion through the 2 and 3 positions of pyrrole. It is one of the most abundant heterocycles found in natural products and biologically active molecules. In fact, it can be regarded as the most important of all the privileged structures in medicinal chemistry [1]. For this reason, research in the different areas of indole chemistry has been, and continuous to be, extraordinarily intense. Many excellent reviews, covering advances in specific topics in the chemistry of indoles, are available and will be referred to throughout this chapter. The present chapter covers the developments in indole chemistry that appeared in the literature until mid-2006 (some subsequent developments are given in the Addendum). For further information the monographs cited in References [2, 3] are recommended.



Indole
1*H*-Indole

1

The discovery and structure elucidation of indole dates from 1866, when Adolf von Baeyer synthesized indole by zinc-dust pyrolysis of oxindole (**2**), which had been obtained by reduction of isatin (**3**), a product of the oxidation of the natural blue pigment Indigo (**4**) [4]. Consequently, the name Indole derives from that of *Ind*igo.

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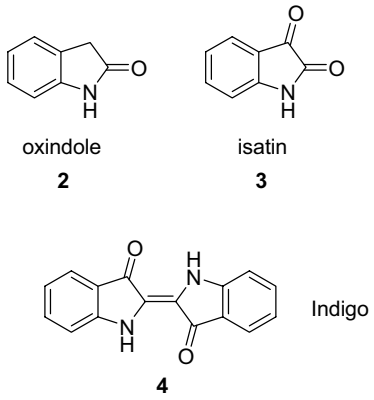


5.1.2
System Isomers and Nomenclature

The tautomers of 1*H*-indole are 2*H*-indole and 3*H*-indole (Figure 5.1). Both systems are highly unstable, although 3*H*-indole has been characterized spectroscopically, and its derivatives have been isolated [5]. High level quantum chemical DFT calculations predict an energy difference of 5.20 and 24.1 kcal mol^{-1} between 1*H*-indole and 3*H*-indole, and 1*H*-indole and 2*H*-indole respectively [6].

The other isomeric benzopyrroles are isoindole and indolizine. Indoline is the name for 2,3-dihydro-1*H*-indole.

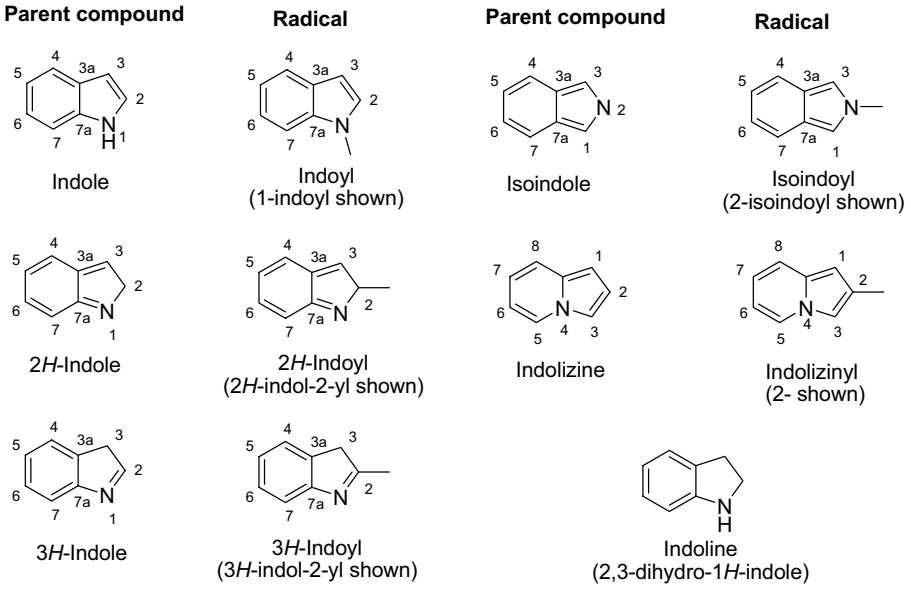


Figure 5.1 Indole, tautomers and isomers with conventional numbering.

5.2
General Properties

5.2.1
Physicochemical Data

Indole is a crystalline solid (mp = 54–54 °C, bp = 253–254 °C) with a fecal smell. The main commercial source of indole comes from the 220–260 °C fraction of coal-tar distillation. It is soluble in organic solvents such as diethyl ether, ethanol and benzene, and also in hot water.

The crystal structure of indole [7] and of several simple derivatives is available [8]. In addition, state of the art quantum chemical DFT calculations provide very accurate results regarding structural [9], electronic [10] and chemical properties of indole and indole derivatives (Figure 5.2) [11]. DFT calculations of the magnetic properties, to estimate the aromaticity of the indole ring, reveal a stabilization due to the π-molecular orbital delocalization of 10 electrons between the two aromatic rings [12].

The ^{1}H NMR spectra of indole feature all the resonances for the hydrogens in the aromatic region, and corroborate the aromaticity of the ring (Figure 5.3). The upfield shifts observed for H3 and C3 in the ^{1}H and ^{13}C NMR spectra indicate the higher electron density around C3. Substitution on the indole ring may cause important variations in the chemical shifts of H2 and H3, which can be rationalized in terms of resonance and inductive effects (Table 5.1).

5.2.2
General Reactivity

Indole is a π-excessive aromatic heterocycle with ten π-electrons. The lone pair of the nitrogen atom (which features sp^2 hybridization) completes the ten π-electrons delocalized across the ring. As in pyrrole, the π-excessive nature of the aromatic ring governs its reactivity and chemical properties.

Indole is a weak base ($pK_a = -2{,}4$ for the conjugated acid), as protonation of the nitrogen atom would disrupt the aromaticity of the five-membered ring. In contrast, as a π-excessive aromatic heterocycle, electrophilic aromatic substitution is one of the most characteristic reactions. Unlike pyrrole, addition of electrophiles takes place preferentially at C3. A simple explanation for this can be deduced by analysis of the Wheland intermediates resulting from the attack of a nucleophile at C2 and C3 (Scheme 5.1).

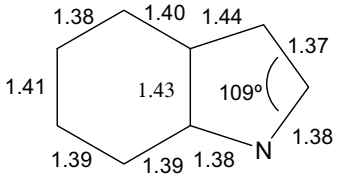


Figure 5.2 Indole structural parameters at the B3LYP/6-311 + G(2p,d) level of theory.

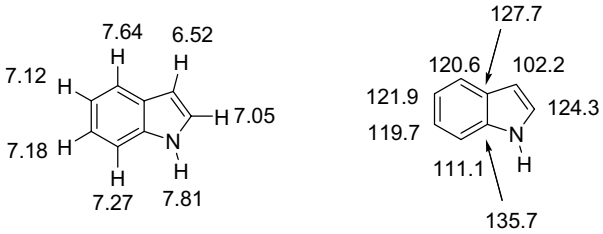


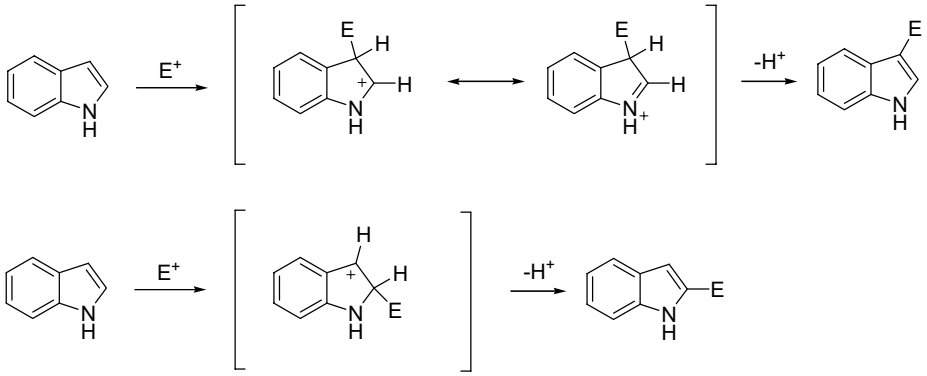
Figure 5.3 ^{1}H and ^{13}C NMR chemical shifts in $CDCl_3$ (δ, ppm) for indole.

The intermediate of the attack at C3 is stabilized by delocalization of the positive charge. However, no delocalization is possible in the intermediate derived from attack at C2 without disrupting the aromaticity of the six-membered ring.

Frontier Molecular Orbital theory considerations provide an alternative theoretical explanation for this reactivity trend. Indole features a relative high-energy HOMO, with the highest value at C3 (Figure 5.4). Moreover, the condensed Fukui function for electrophilic attack f_q^- [17], takes values of 0.08, 0.05 and 0.15 for N, C2 and C3, respectively, pointing to the higher reactivity of C3 towards soft electrophiles [12].

Table 5.1 Chemical shifts for H-1 and H-2 in substituted indoles ($CDCl_3$).

Substituent	δ H2 (ppm)	δ H3 (ppm)
None	7.05	6.52
1-Me	6.90	6.43
2-Me	—	6.20
3-Me	6.85	—
1-CO_2Me [13]	7.55	6.57
2-CO_2Me [14]	—	7.15
3-CO_2Me [15]	7.93	—
2-Cl [16]	—	6.41
3-Cl	7.44	—



Scheme 5.1 Possible regioisomers in the electrophilic attack on the indole ring.

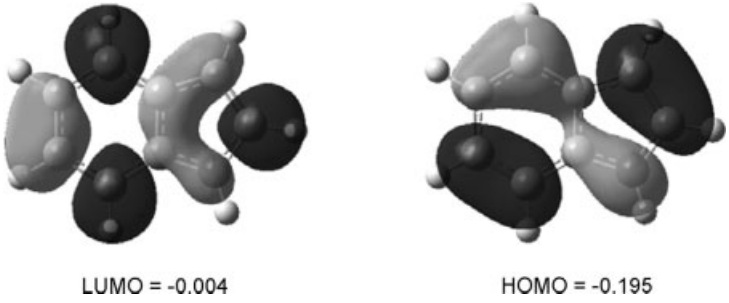
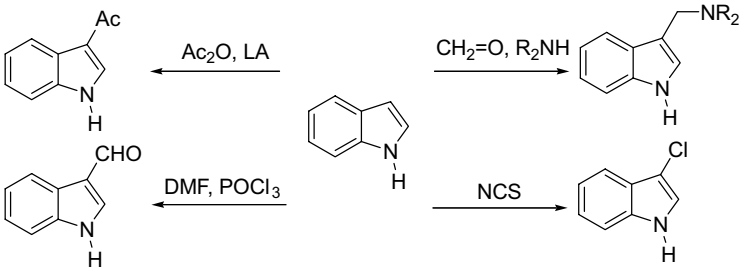


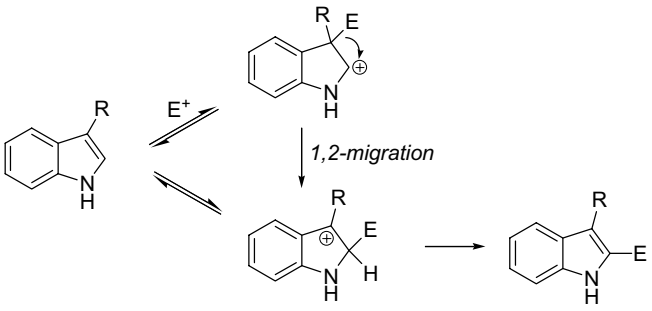
Figure 5.4 Graphical representation of indole frontier orbitals.

Typical electrophilic aromatic substitution reactions that allow for the introduction of functionalized side-chains at C3 are Friedel–Crafts acylations, Vilsmeier–Haack reaction, Mannich type alkylations and halogenations (Scheme 5.2).



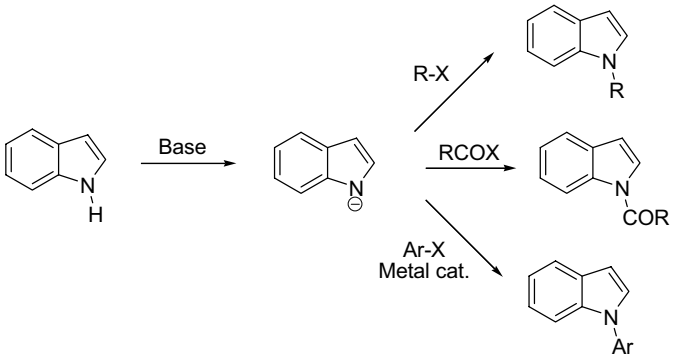
Scheme 5.2 Some typical electrophilic substitution reactions of indole.

Electrophilic substitution at C2 can be achieved in 3-substituted indoles, although the reaction usually starts with electrophilic attack at C3, followed by rearrangement or reversal of the reaction to produce the substitution at C2 (Scheme 5.3).



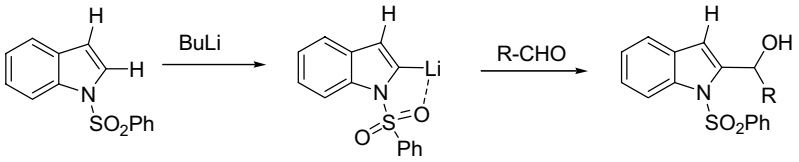
Scheme 5.3

The indole N–H is weakly acidic and, thus, can be deprotonated by strong bases (pK_a 16.7 in water) to provide the indolyl anion. Therefore, substitution at the nitrogen can be achieved through base-promoted processes, such as alkylations, acylations and, more recently, transition metal catalyzed arylations (Scheme 5.4).



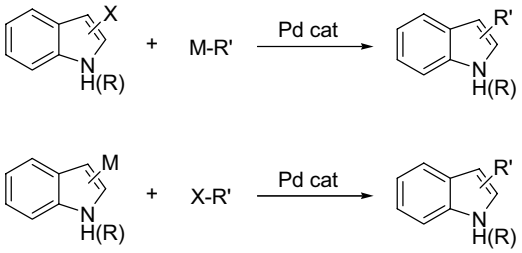
Scheme 5.4

The most reliable method to carry out the substitution at C2 is the heteroatom assisted metallation at C2 of *N*-acyl or *N*-sulfonylindoles, followed by reaction with an electrophile (Scheme 5.5).



Scheme 5.5

Metal catalyzed cross-coupling reactions represent nowadays one of the main ways to modify the substituents in both rings of indole. All kinds of Pd catalyzed processes (Stille, Suzuki and Buchwald–Hartwig) can be achieved successfully from properly substituted indole species (Scheme 5.6).



Scheme 5.6

5.3
Relevant Natural and/or Useful Compounds

The indole nucleus is present in the essential amino acid tryptophan (**5**), in many metabolites derived from tryptophan and also in natural molecules with high structural complexity.

Among the naturally occurring molecules that feature the indole ring in their structure, two worth noting: (i) the family of *tryptamines* [18], such as serotonin **6**, a very important neurotransmitter with numerous functions in the human body, and melatonin **7**, a hormone that participates in the regulation of the circadian rhythms (sleep–wake); (ii) the *auxins*, a group of plant growth substances, such as the natural auxin indole 3-acetic acid (**8**) and the synthetic auxin indole-3-butyric acid (**9**) (Figure 5.5) .

The indole structure is also present in structurally complex indole alkaloids with biological activity. To name a few: the hallucinogen D-lysergic acid diethyl amide (LSD) (**10**); the strichnous family of alkaloids (e.g., strychnine, **11**); the family of marine indole alkaloids isolated from blue-algae such as Fischer-indole I (**12**) [19], the bisindole alkaloids vinblastine (**13**) and vincristine (**14**), which are extremely potent cytotoxic agents, used in the therapy of leukemia and lymphoma tumor types [20, 21]; and reserpine **15**, a pentacyclic alkaloid that is a central nervous system depressant employed in the treatment of hypertension and psychiatric disorders (Figure 5.6) [22].

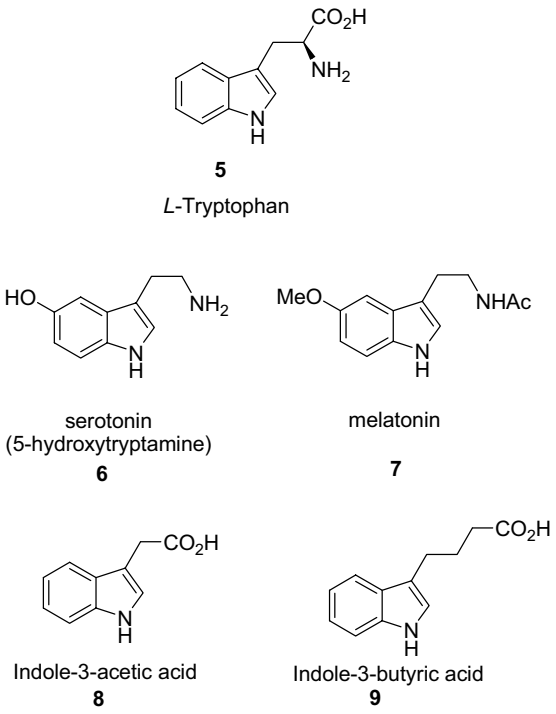
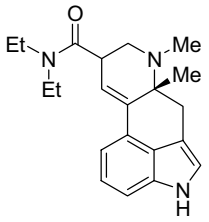
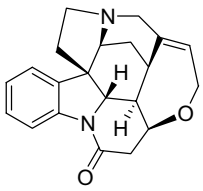


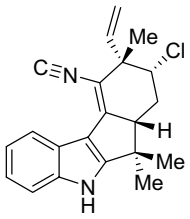
Figure 5.5 Some important simple indole natural products.



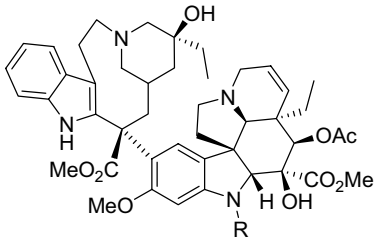
D-Lysergic acid diethyl amide (LSD)
10



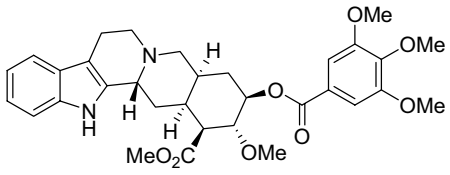
Strychnine
11



12 Fischer-indole I



13 R = CH_3, vinblastine
14 R = CHO, vincristine



15 (-)-Reserpine

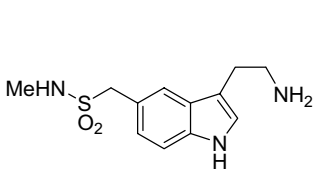
Figure 5.6 Some important indole alkaloids.

In contrast, several synthetic drugs currently in use contain the indole nucleus, for instance Sumatriptan, a synthetic tryptamine used in the treatment of migraine [23], and the non-steroidal anti-inflammatory drugs Indomethacin and Etodolac (Figure 5.7).

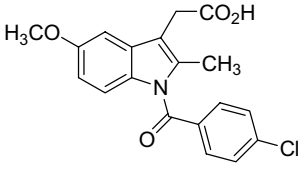
5.4
Indole Synthesis

5.4.1
Introduction

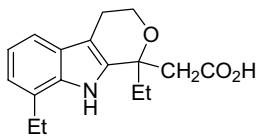
Indole is one of the most important heterocycles, as a result of its abundance in natural products and pharmaceuticals. For this reason, the synthesis of the indole



Sumatryptan



Indomethacin

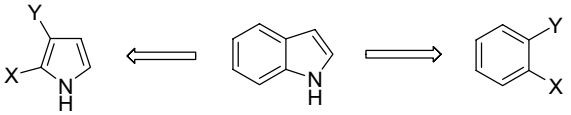


Etodolac

Figure 5.7 Indole-containing drugs currently in use.

ring has attracted great attention in synthetic organic chemistry, and, in turn, an extraordinary large number of different approaches to the synthesis of the indole ring have been devised over the years [24]. Despite the ample repertoire of methods available to build the indole ring, it continues to be an area of active research due to the enormous interest in the indole structure. Moreover, while most classic approaches to the indole ring usually rely on a final cyclization through a condensation reaction, the development of new methodologies for transition catalyzed C–C and C–N bond-forming reactions has led to a new family of methods in which the cyclization step is a metal-catalyzed process. In this area, the Pd-catalyzed reactions have a prominent position. This subject has been reviewed and monographs dealing with this particular subject are available [25, 26]. In addition, the rise of combinatorial approaches to drug discovery has motivated the development of new methodologies, and the adaptation of solution phase chemistries into solid phase synthesis. Specific reviews on this topic are also available [27]. The variety of different approaches to the indole ring is enormous, and an exhaustive coverage would largely exceed the aim of this book. For this reason, this chapter is restricted to the classical methods that still find application in the preparation of indoles and the more recent advances in the area, with particular attention to transition metal catalyzed processes.

From a retrosynthetical point of view, the indole ring can be constructed by two main strategies: formation of the pyrrole ring onto a properly substituted benzene precursor and formation of the benzene ring by annelation of a substituted pyrrole. By far, the strategies that start from a substituted benzene have been more extensively used (Scheme 5.7).



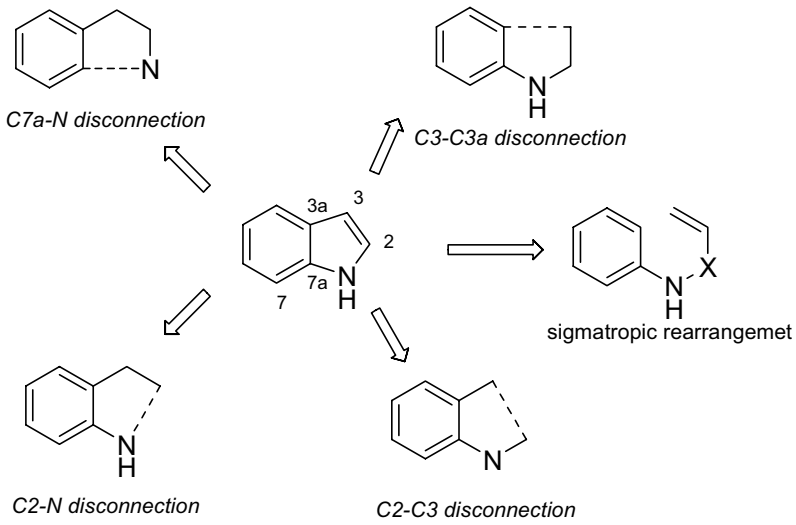
Scheme 5.7

5.4.2
Synthesis of the Indole Ring from a Benzene Ring

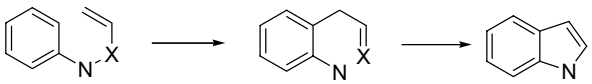
In an attempt to organize the many methods, they have been classified according to the formation of the last bond in the cyclization process (Scheme 5.8). Of particular importance in the construction of the indole ring are methods involving a sigmatropic rearrangement: the Fischer indole synthesis and related process, which will be covered in a specific section.

5.4.2.1 Indole Synthesis Involving a Sigmatropic Rearrangement

Indole ring syntheses that include a sigmatropic rearrangement are particularly appealing strategies since no *o*-substitution is required in the starting aniline (Scheme 5.9). The C–C bond is formed during the rearrangement. The most prominent member of this family of methods is the Fischer indole synthesis.

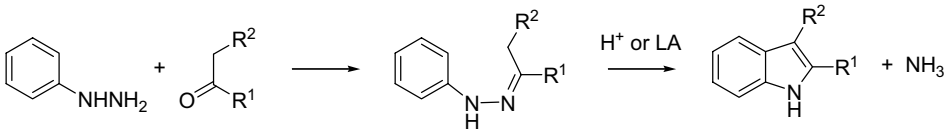


Scheme 5.8 General strategies for the construction of the five-membered ring of indole.



Scheme 5.9

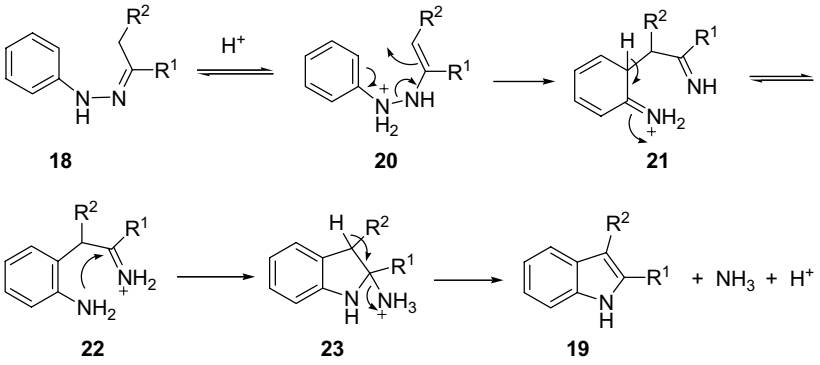
5.4.2.1.1 **Fischer Synthesis** The Fischer indole synthesis [28], which was first discovered in 1883, is still considered as the most popular, and one of the most general and efficient approaches to the indole ring. It consists of the acid-catalyzed cyclization of aryl hydrazones **18** with loss of ammonia. The aryl hydrazones are easily obtained by condensation of a ketone (**17**) with an aryl hydrazine (**16**) (Scheme 5.10).



Scheme 5.10 Fischer indole synthesis.

The mechanism accepted for the overall reaction was already formulated by Robinson and Robinson back in 1924. It involves a [3,3] sigmatropic rearrangement of the ene-hydrazine tautomer **20** of the arylhydrazone **18**, with cleavage of the N−N bond and formation of a C−C bond. Aromatization of **21** to give the intermediate **22**, followed by cyclization and NH_3 elimination provides the indole **19** (Scheme 5.11).

The Claisen-like sigmatropic rearrangement is strongly accelerated by an acid catalyst. Both protic and Lewis acids are effective catalyst for the Fischer indolizidation.

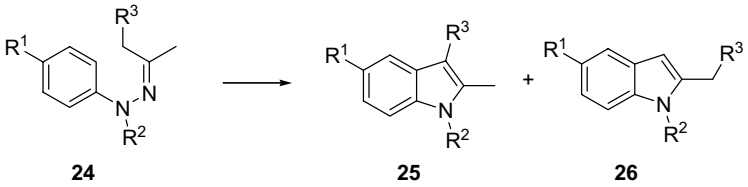


Scheme 5.11 Accepted mechanism for the Fischer indole synthesis.

Sulfuric and hydrochloric aqueous, alcoholic or acetic acid solutions have been used to promote the Fischer cyclization, as well as *p*-toluenesulfonic acid and phosphorous trichloride. Among the Lewis acids, $ZnCl_2$ is the most frequently used catalyst. Very recently, solid supports such as montmorillonite AK10/$ZnCl_2$ have been used to promote the indolizidation, in combination with microwave heating. This technique allows for the preparation of indoles unavailable through the standard conditions [29].

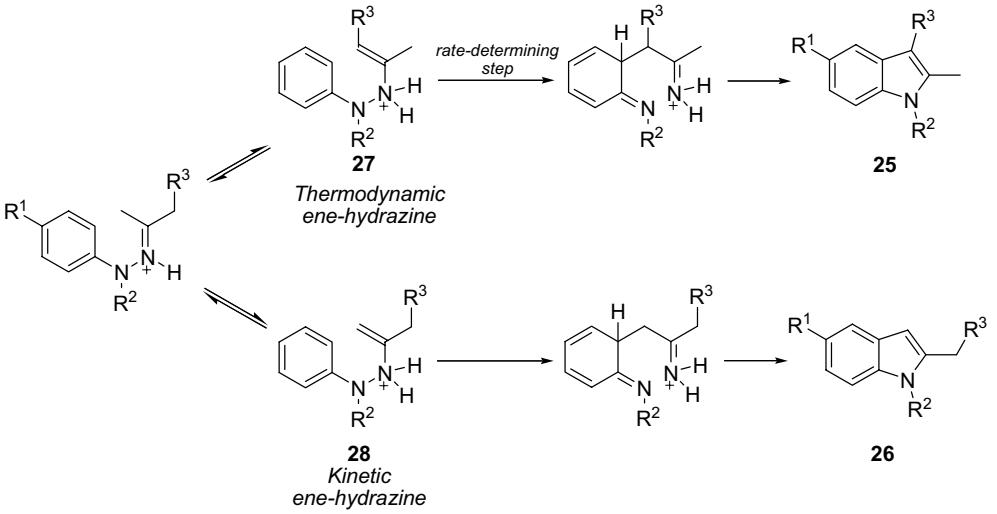
The nature of the substituents on the aromatic ring exerts a remarkable influence on the rate of the overall reaction: electron-donating substituents accelerate the reaction, while electron-releasing substituents slow the cyclization. For further information, detailed reviews covering all these topics are available [3].

The regioselectivity in the indole synthesis is an issue of major importance when unsymmetrical ketones or *m*-substituted aromatic rings are involved in the cyclization. For instance, the cyclization of hydrazones of type **24**, derived from methyl alkyl ketones, can deliver regioisomeric indoles **25** and **26** (Scheme 5.12).



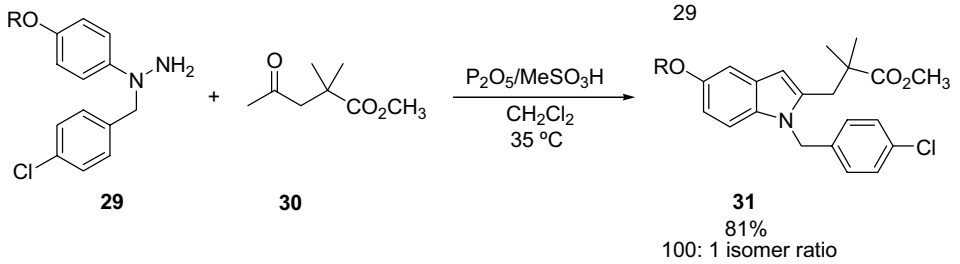
Scheme 5.12

Usually, under standard conditions, the major (or unique) product obtained is indole **25**, the one derived from the more highly substituted ene-hydrazine **27**, which is considered the thermodynamically controlled product. Therefore, for indole **25** to be the major isomer, the [3,3] rearrangement must be the rate-determining step of the whole sequence (Scheme 5.13).



Scheme 5.13 The problem of the regioselectivity in the Fischer indole synthesis.

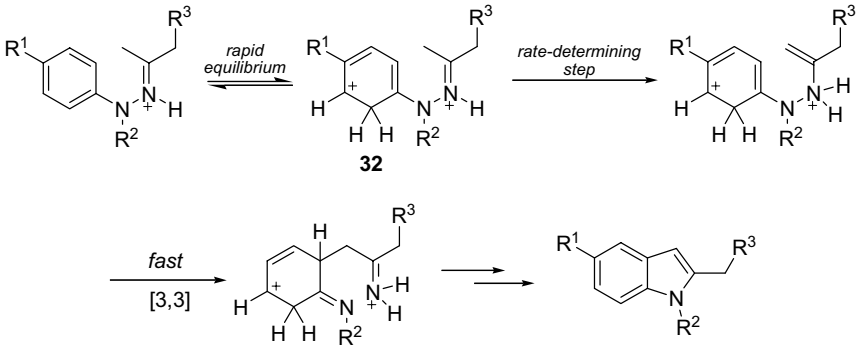
Nevertheless, it has been possible to obtain selectively 3-unsubstituted indoles such as **31** by reacting hydrazine **29** with the unsymmetrical methylketone **30** under kinetic conditions by employing very strong acids such as Eaton's acid ($P_2O_5/MeSO_3$) (Scheme 5.14) [30].



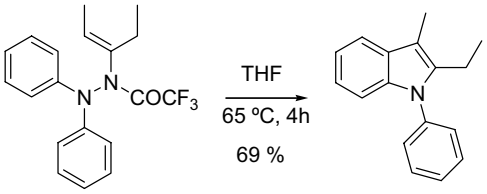
Scheme 5.14 Fischer indole synthesis under kinetically controlled conditions.

Mechanistic studies have suggested that under kinetic conditions the reaction proceeds through the doubly protonated intermediate **32**. The activation barrier for the [3,3] rearrangement in this case must be lower (since no aromaticity is lost during the rearrangement) and therefore, the formation of the ene-hydrazine intermediate (and not the rearrangement) becomes rate determining (Scheme 5.15) [31].

In some instances the cyclization can be carried out thermally, in the absence of acid catalyst, although it requires much harsher conditions and a protic solvent as a proton source. In contrast, preformed *N*-trifluoroacetyl enehydrazines **33** undergo cyclization without the need acid catalyst or very high temperatures to provide 2,3-disubstituted indole **34** [32] (Scheme 5.16).

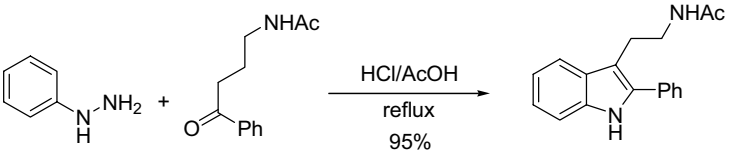


Scheme 5.15



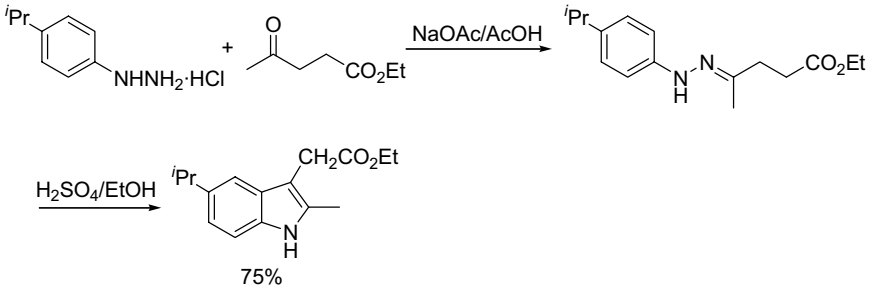
Scheme 5.16

The Fischer indolizidation is a very general process that proceeds with yields ranging from moderate to quantitative, depending on the substrate. Moreover, a large array of functional groups are tolerated by the reaction conditions, including the relatively sensitive, amide, ester or hydroxy. Schemes 5.17–5.20 depict some representative recent examples of the application of the Fischer indole synthesis.

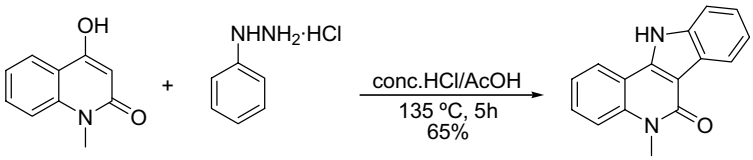


Scheme 5.17 [33].

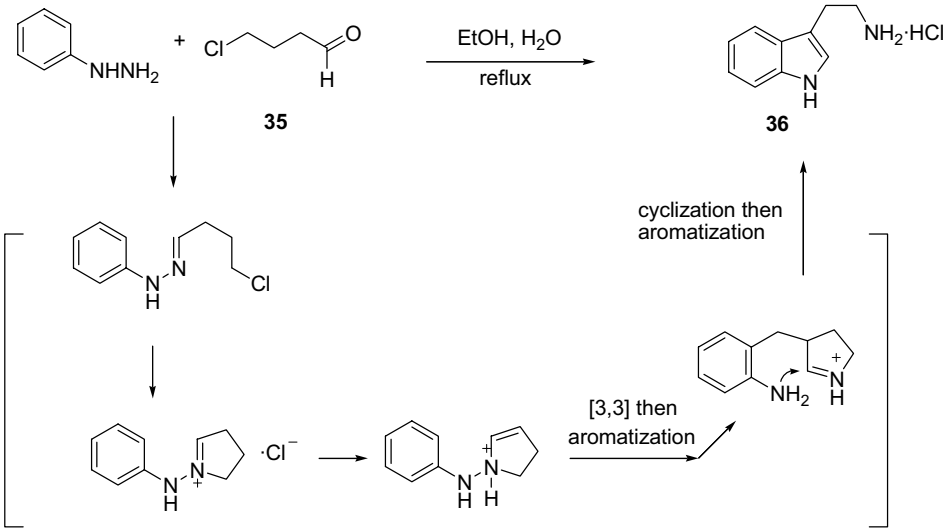
An interesting variation of the Fischer indolizidation gives rise directly to tryptamines **36**, a particularly important type of indole, due to their biological activity. This so-called Grandberg indole synthesis employs 4-halobutenals **35** as carbonyl components. The nitrogen atom, which is usually liberated as ammonia in the Fischer indolizidation, is incorporated to the molecule, likely through the pathway represented in Scheme 5.20 [36].



Scheme 5.18 [34].

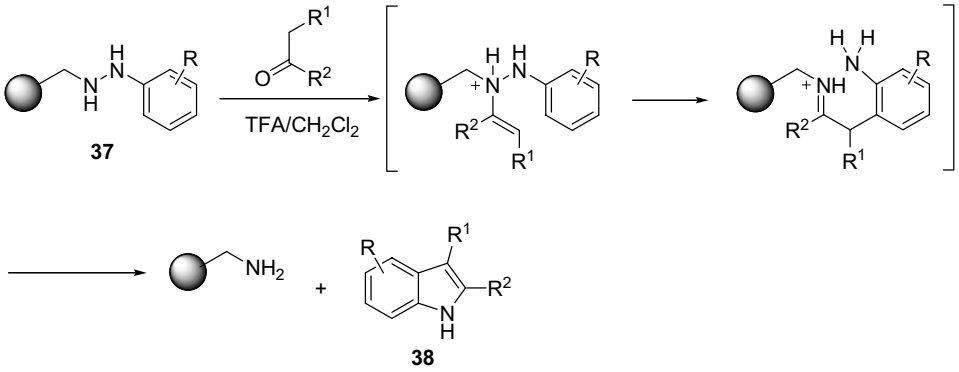


Scheme 5.19 [35].



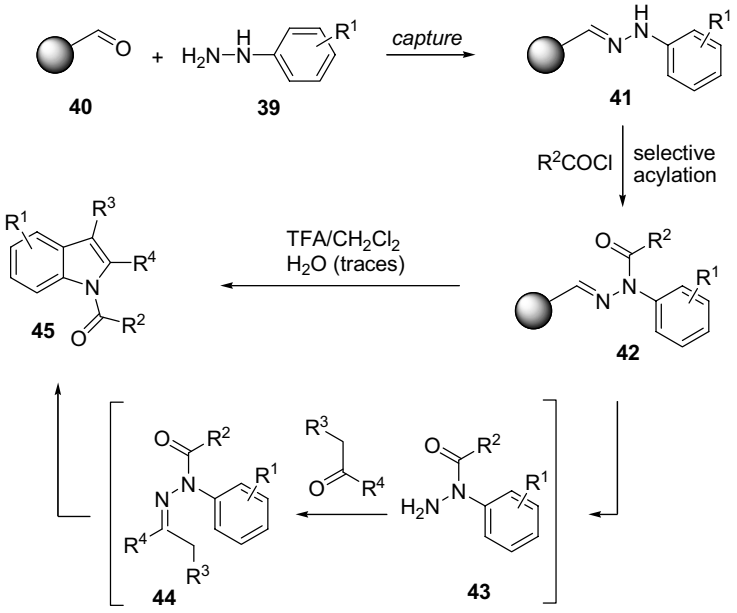
Scheme 5.20 Grandberg indole synthesis.

Several examples of the Fischer indole synthesis in the solid phase have been described [37]. A very elegant traceless synthesis has been reported that employs a solid supported hydrazine (**37**) [38], which participates in the Fischer indolizidation upon treatment with a ketone in the presence of TFA. Interestingly, during the cyclization step, indole **38** is released from the resin in a traceless manner (Scheme 5.21).



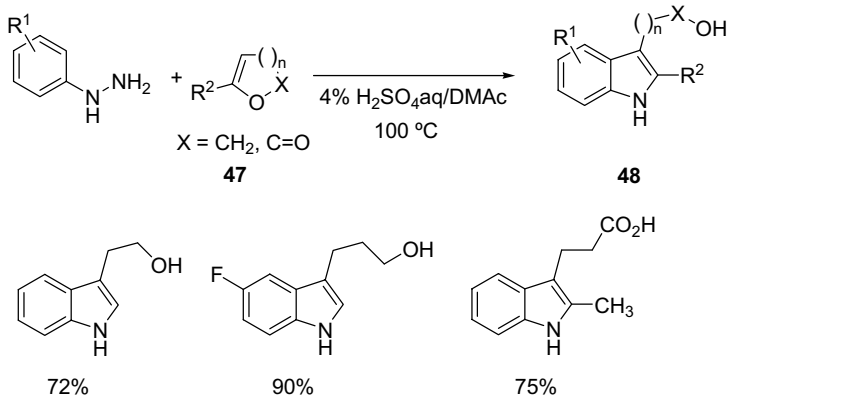
Scheme 5.21 A traceless solid-phase Fischer indole synthesis.

A library of structurally diverse indomethacine analogs (**45**) have been prepared by a "resin-capture-release" strategy, a technique that combines solid-supported and solution chemistry. Aryl hydrazine **39** is "captured" by an aldehyde functionalized resin (**40**), and the unprotected N−H is acylated, to build an array of solid supported protected acylhydrazines (**42**). Treatment with trifluoroacetic acid (**46**) releases the hydrazine **43**, which then reacts with a ketone, to provide hydrazone **44**, which suffers the indolizidation to deliver the corresponding indole **45** (Scheme 5.22) [39].



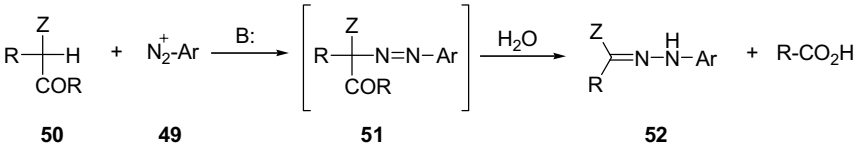
Scheme 5.22 Solid-supported synthesis of indomethacine analogs.

Cyclic enol-ethers and enol-lactones **47** have been used as synthetic equivalents of aldehydes and ketones, giving rise directly to functionalized indoles **48** (Scheme 5.23) [40].



Scheme 5.23 Fischer indole synthesis with enol ethers and enol lactones.

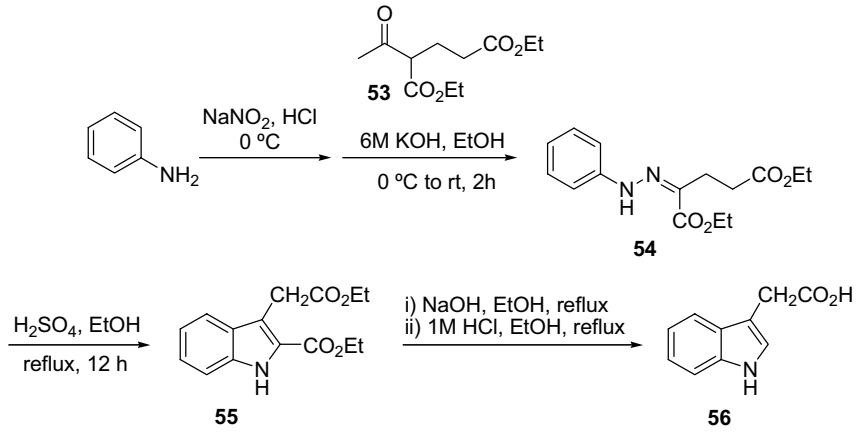
5.4.2.1.2 **Japp–Klingemann Reaction** The condensation of carbonyls (or synthetic equivalents) with aryl hydrazines is not the only route to the aryl hydrazones required for the Fischer indolizidation. The coupling of aryldiazonium salts (**49**) with the enolates of ketones **50** – the Japp–Klingemann reaction [41] – represents an alternative that has been employed extensively. Hydrazone **52** is formed after a deacylation step of the intermediate diazo compound **51** (Scheme 5.24).



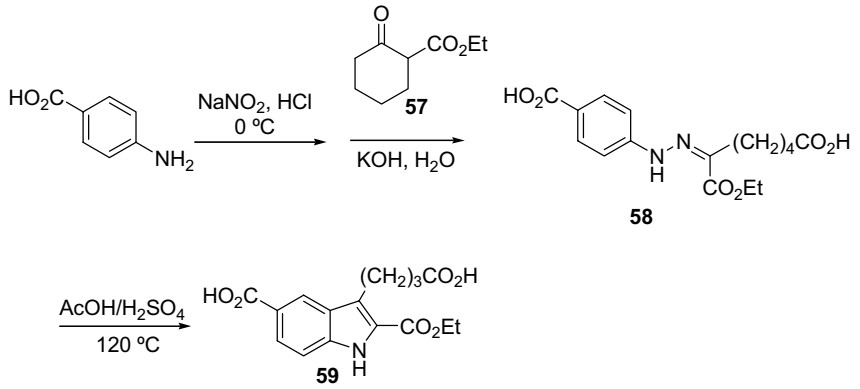
Scheme 5.24 General scheme of the Japp–Klingemann reaction.

β-Ketoesters are the usual substrates for the Japp–Klingemann reaction. For instance, ketoester **53** reacts with benzenediazonium chloride in an alkaline solution to form hydrazone **54**. Indolizidation of hydrazone **54** under standard Fischer conditions affords 2,3-disubstituted indole **55**, which can be decarboxylated to give 3-substituted indole **56** (Scheme 5.25) [42].

When cyclic β-ketoesters (e.g., **57**) are used, deacylation by ring opening occurs under the basic conditions of the reaction, to provide the carboxylic acid **58**. Fischer indolization of **58** gives rise to 2,3-disubstituted indoles **59** [43] (Scheme 5.26).



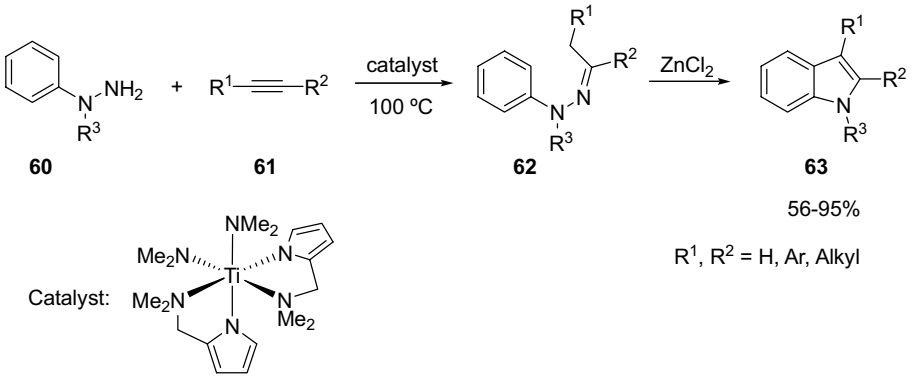
Scheme 5.25



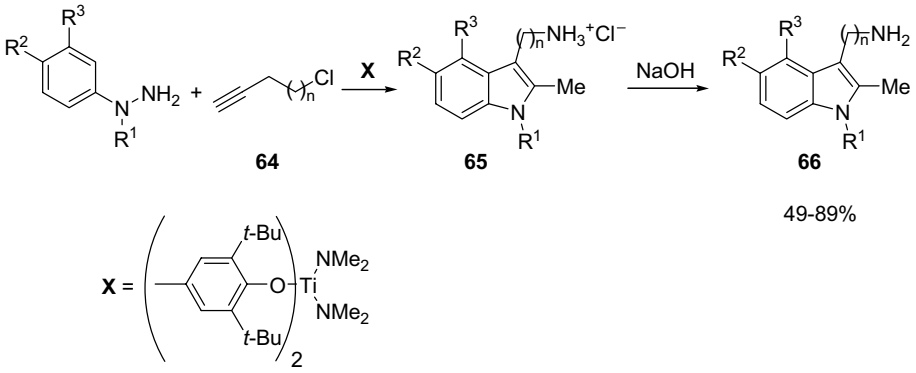
Scheme 5.26

5.4.2.1.3 **Hydroamination-Based Fischer Indole Synthesis** Recently, an interesting variation to the traditional Fischer approach has been introduced that uses alkyne hydroamination as an alternative way to access the intermediate arylhydrazone. Scheme 5.27 presents a *one pot* approach to the indole framework based on intermolecular titanium amide-catalyzed hydroamination reactions of alkynes **61** with 1,1-disubstituted hydrazines **60**. Subsequent addition of 3–5 equiv $ZnCl_2$ is necessary to convert the generated hydrazone **62** into the corresponding indole **63** [44].

The Grandberg strategy has been combined with the hydroamination to prepare tryptamine analogs **66** (Scheme 5.28) [45]. The Ti-catalyzed hydroamination of terminal chloroalkynes **64** gives rise directly the hydrochloric salt of aminoindoles **65**.



Scheme 5.27 Hydroamination-based Fischer indole synthesis.



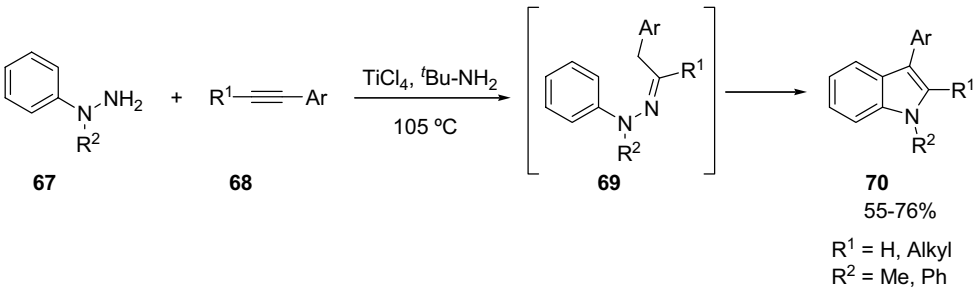
Scheme 5.28 Hydroamination-based Grandberg indole synthesis.

This one pot process involves a titanium-catalyzed Markovnikov hydroamination to furnish the corresponding hydrazone, which can follow the same reaction pathway as that proposed in the original Grandberg route.

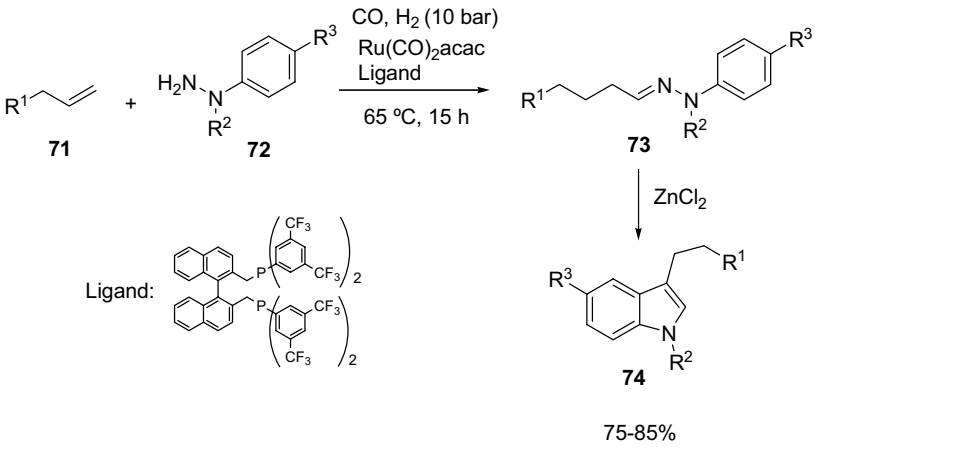
Another interesting modification of the hydroamination makes use of inexpensive $TiCl_4$ as precatalyst for the hydroamination reaction, and it also serves as Lewis acid for the cyclization process. This methodology allows for the preparation of 1,2,3-trisubstituted indoles **70** from unsymmetrical alkynes **68** (Scheme 5.29) [46].

The aryl hydrazones required for the Fischer cyclization have also been prepared through a novel rhodium-catalyzed hydroaminomethylation of olefins [47]. Thus, reaction of aliphatic olefins **71** with synthesis gas ($CO : H_2$, 1 : 1) and aryl hydrazines **72** in the presence of rhodium phosphine catalysts leads to the corresponding hydrazones **73**, which can be subsequently transformed into indole **74** by treatment with $ZnCl_2$ in a *one pot* process (Scheme 5.30) [48].

As an alternative method, the Buchwald–Hartwig amination has been applied for the synthesis of the arylhydrazines required for the Fischer synthesis [49]. Thus,



Scheme 5.29



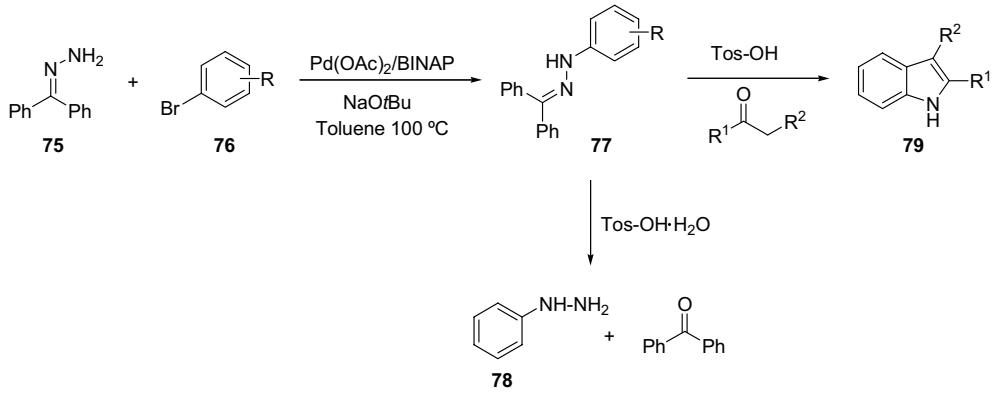
Scheme 5.30

Pd-catalyzed cross-coupling of aryl bromides **76** with benzophenone hydrazone (**75**) furnishes *N*-arylbenzophenone hydrazone **77**, which is hydrolyzed to the arylhydrazine **78** by treatment with acid. If the hydrolysis is carried out in the presence of a carbonyl compound, indole **79** is formed in a one pot process, without isolation of any of the intermediates (Scheme 5.31).

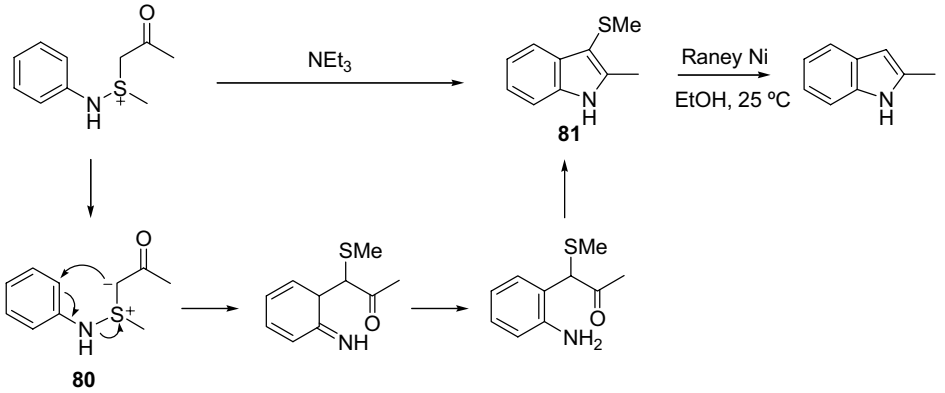
5.4.2.1.4 **Gassman Synthesis** A [2,3] sigmatropic shift of anilinosulfonium ylide **80** is the key step in the Gassman synthesis [50]. The sulfur substituted indoles **81** so-obtained can be easily reduced with Raney Ni (Scheme 5.32).

In the original Gassman procedure the indole is formed directly from the corresponding aniline **82** in a *one pot–three step* procedure that involves the formation of chloramine **83**, which then reacts with a α-thioketone to form the anilinosulfonium salt **84**. Low temperature rearrangement of **84** yields the 3-thioindole **85** (Scheme 5.33).

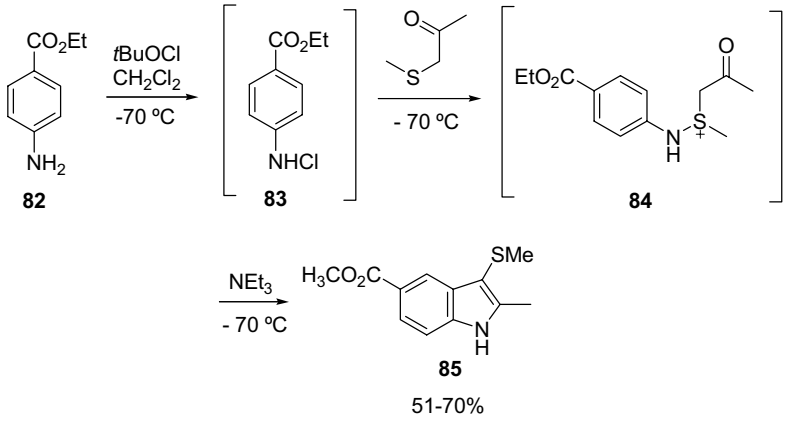
The anilinosulfonium salt **86** can be accessed also by a modified procedure that avoids the use of *t*BuOCl and provides slightly better yields. This strategy has been employed in the synthesis of oxyindoles **87** (Scheme 5.34) [51].



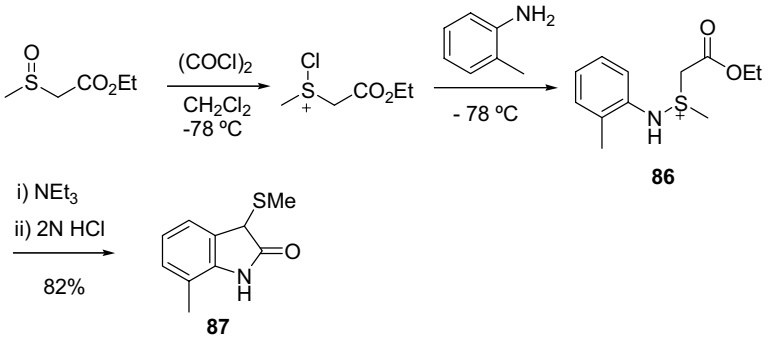
Scheme 5.31



Scheme 5.32

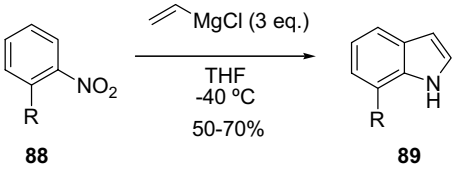


Scheme 5.33



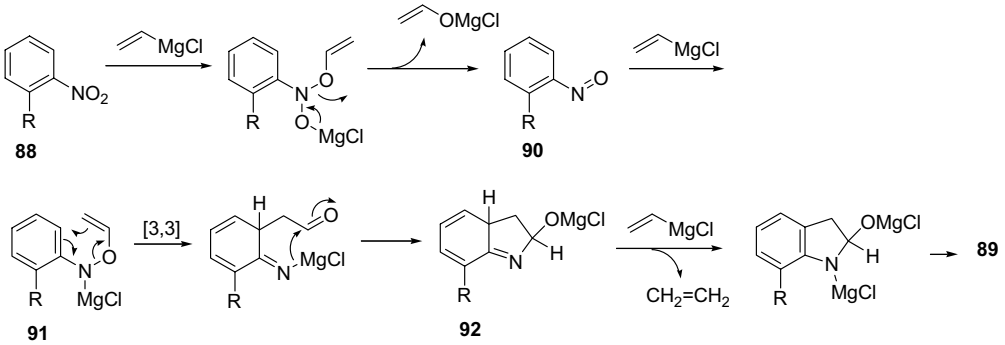
Scheme 5.34

5.4.2.1.5 **Bartoli Synthesis** In the Bartoli synthesis, 7-substituted indoles **89** are obtained from 2-substituted nitrobenzene **88** upon treatment with 3 equivalents of vinylmagnesium chloride (Scheme 5.35) [52]. The availability of the starting materials and its simplicity make this reaction one of the most efficient methods for the preparation of 7-substituted indoles. The necessity of an ortho-substituent on the aromatic ring is the main limitation. Nevertheless, Br is a very suitable substituent that can enforce the sigmatropic rearrangement as requested by the mechanism (see below), and can be easily removed or transformed thereafter.



Scheme 5.35

Scheme 5.36 depicts the mechanism proposed for the Bartoli reaction. The reaction starts with the addition of the first equivalent of vinyl Grignard to an oxygen



Scheme 5.36

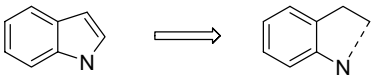
atom of the nitro group of **88**, with subsequent elimination of acetaldehyde enolate, to generate nitrosobenzene derivative **90**. Then, the second equivalent attacks the oxygen atom of the nitroso functionality. The intermediate **91** generated suffers a Claisen-like [3,3]-sigmatropic rearrangement, with cleavage of the N–O bond, followed by heterocyclization to form the five-membered ring. A third equivalent of the Grignard is required to abstract a proton on **92** before the final elimination takes place.

Slightly modified Bartoli protocols [53], including a solid phase version [54], have been implemented more recently.

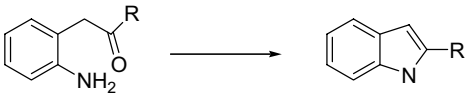
Other examples of [3,3] sigmatropic rearrangement-based indoles synthesis have been described [55, 56].

5.4.2.2 Cyclization by Formation of the N–C2 Bond

The construction of the indole ring with formation of the N–C2 bond includes the most popular approaches other than the Fischer synthesis.



An important class of methods for indole ring synthesis involves a cyclization of an aminoketone (**93**) with formation of the C2–N bond (Scheme 5.37). Usually, the precursor that suffers the intramolecular condensation has to be preformed in a preliminary step, and must contain a carbonyl or masked carbonyl (imine, enamine, enolether) functionality.

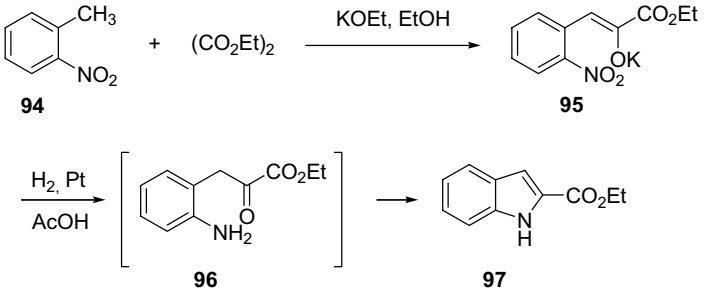


93

Scheme 5.37

Many different approaches have been investigated to generate the cyclization precursor. Among them, those that rely on the reductive cyclization of *o*-substituted nitroaryls are noteworthy.

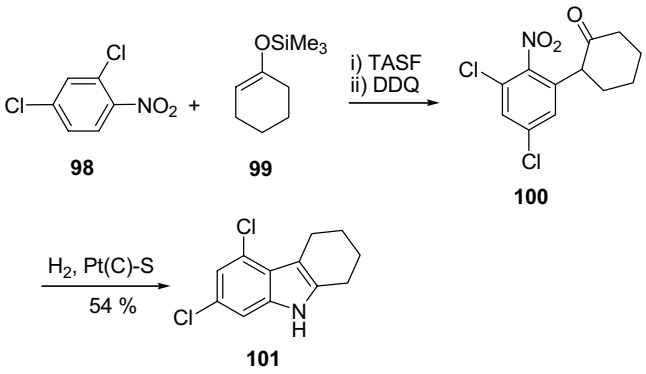
5.4.2.2.1 **Reissert Indole Synthesis** The Reissert indole synthesis is a very reliable method for the preparation of benzene-substituted indole-2-carboxylates [57]. In the first step, condensation of *o*-nitrotoluene (**94**) with ethyl oxalate under basic media affords the potassium salt of *o*-nitrophenylpyruvate **95** (Scheme 5.38). The key step in the Reissert synthesis is the reductive cyclization of this intermediate, which generates the aminoketone **96** that undergoes cyclization to provide the indole-2-carboxylate (**97**). The reductive cyclization has been effected under different catalytic hydrogenation conditions (Pt/AcOH, Pd-C/EtOH [58]) and also with various low oxidation state metal salts ($SnCl_2$-$TiCl_3$) [59].



Scheme 5.38 Classic Reissert indole synthesis.

Many variations on the classic Reissert synthesis are known, which differ in the way the intermediate *o*-aminobenzyl ketones or aldehydes, ready for the cyclization, are obtained [60].

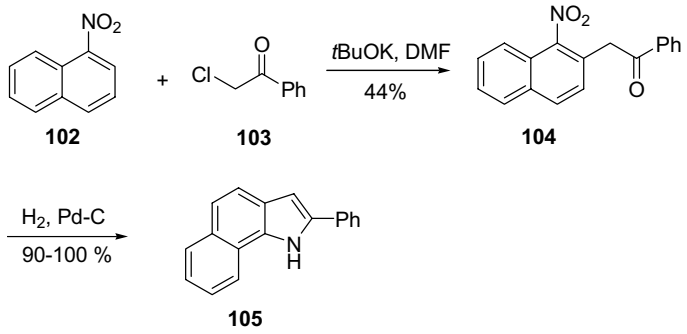
Nucleophilic substitution on nitroarenes has been applied extensively in several approaches, a theme that has been reviewed [61]. Silylenol ethers **99** activated with fluoride anion [tris(dimethylamino)sulfonium difluorotrimethylsiliconate (TASF)] behave as strong C-nucleophiles and add to nitroarenes **98** in the ortho position to the nitro group. Subsequent aromatization of the intermediate generated with DDQ leads to *o*-(2-nitroaryl)alkyl ketones **100**. Finally, reductive cyclization under standard conditions provides the indole **101** (Scheme 5.39) [62].



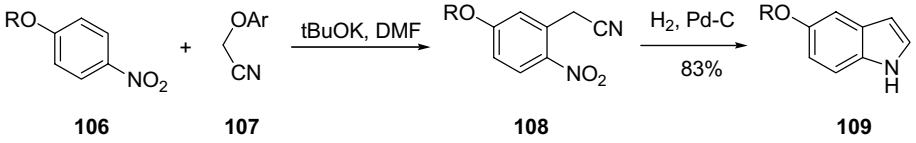
Scheme 5.39

The vicarious nucleophilic substitution (VNS) of hydrogen [63] in nitroarenes **102** with α-chloroalkyl ketones **103** gives rise to nitroaryl ketones **104**, which are converted into indoles **105** under classical Reissert conditions (Scheme 5.40).

A similar valuable approach to indoles consists of the reductive cyclization of (*o*-nitroaryl)acetonitriles **108** (Scheme 5.41). The cyanomethyl group is efficiently introduced in nitroarenes **106** by VNS of hydrogen with chloroacetonitrile **107** or aryloxyacetonitrile. Catalytic hydrogenation transforms the cyano group into an



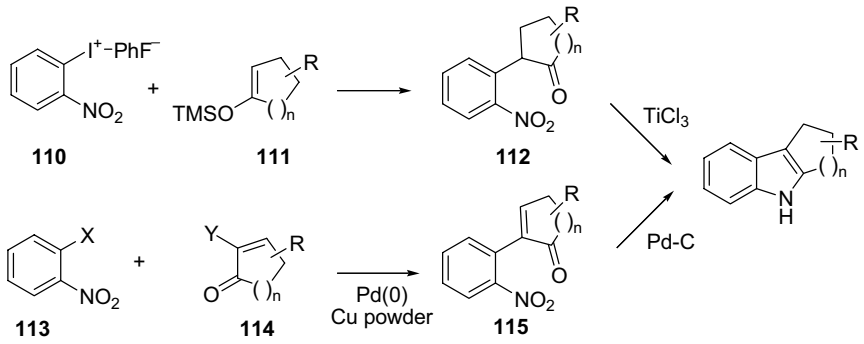
Scheme 5.40



Scheme 5.41

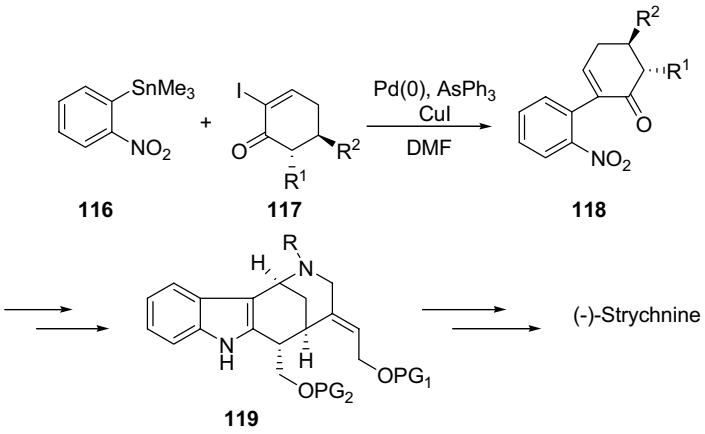
imine and the nitro group to an amine, giving rise to **108**, which cyclizes spontaneously to the indole **109** [64].

Carbocyclic-fused indoles have been prepared by several other alternative routes that involve the cyclization of a α-(*o*-nitrophenyl) ketone (Scheme 5.42). For instance, the intermediate nitroketones **112** can be obtained by arylation of cyclic silylenolether **111** with (*o*-nitrophenyl)phenyliodonium fluoride **110** [65]. This methodology was employed in the total synthesis of (−)-tabersonine [66]. In a different approach, an Ullman-type cross-coupling of *o*-halonitroarenes **113** with α-haloenones **114** has been also employed to obtain the *o*-nitroarylketones **115** [67]. In both cases, reductive cyclization affords the expected indole ring.



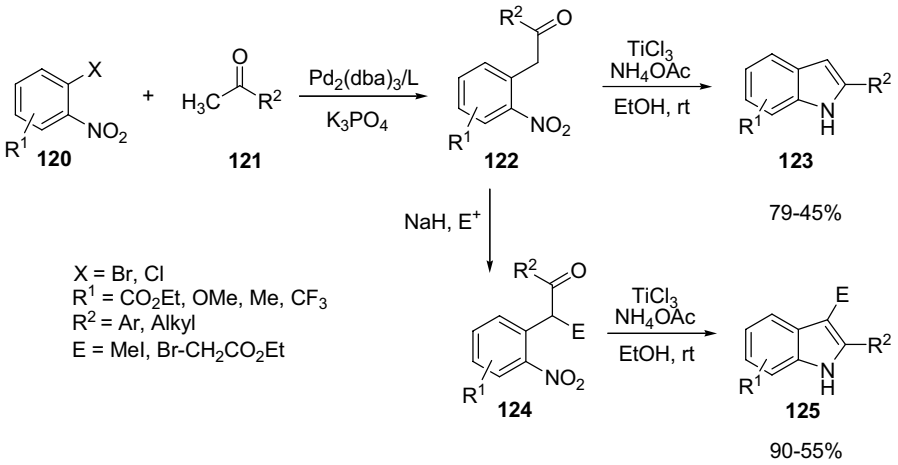
Scheme 5.42

In Shibasaki's total synthesis of strychnine [68] an advanced intermediate is also an α-(*o*-nitrophenyl)ketone (**118**), which is prepared by Stille cross-coupling of *o*-nitrostannylbenzene (**116**) with a vinyl iodide (**117**) (Scheme 5.43).



Scheme 5.43

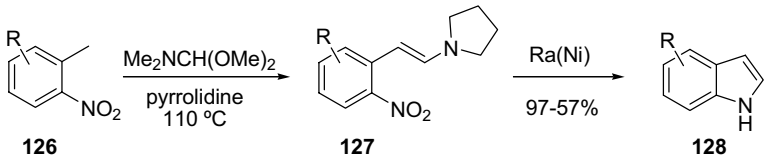
A remarkable innovation has been uncovered by Buchwald – applying the Pd-catalyzed arylation of ketone enolates [69] to transform *o*-bromonitrobenzene derivatives **120** into *o*-nitroketones **122** (Scheme 5.44). Subsequent reductive cyclization provides the corresponding indoles **123** [70]. The reaction is very general and has been utilized successfully in the synthesis of indoles bearing both electron-withdrawing and electron-donating substituents on the benzene ring and a wide variety of ketones **121**. Moreover, additional substitution can be introduced if the intermediate



Scheme 5.44

nitroketone **122** is deprotonated and alkylated before the reductive cyclization step to furnish substituted nitroketones **124**. Therefore, this important development allows for the preparation of very highly substituted indoles **125**.

5.4.2.2.2 **Leimgruber–Batcho Synthesis** The Leimgruber–Batcho synthesis is a very convenient method to prepare indoles with substitution only in the benzene ring [71]. The two-step procedure starts with the three-components reaction of an *o*-methylnitroaryl (**126**) with dimethylformamide dimethylacetal in the presence of pyrrolidine, to provide *o*-nitro-β-pyrrolidinostyrene **127** (Scheme 5.45). Reductive cyclization on **127** furnishes indoles **128**, usually in very high yields.

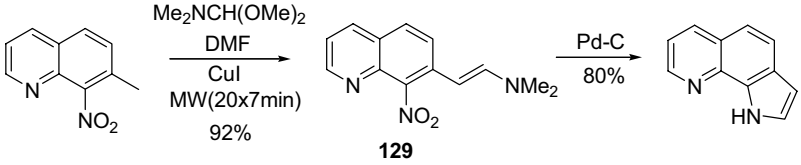


126 **127** **128**

R = -CH_3, -OCH_3, OBn, F, Cl, -$CH(OCH_3)$, -CO_2R, CN

Scheme 5.45

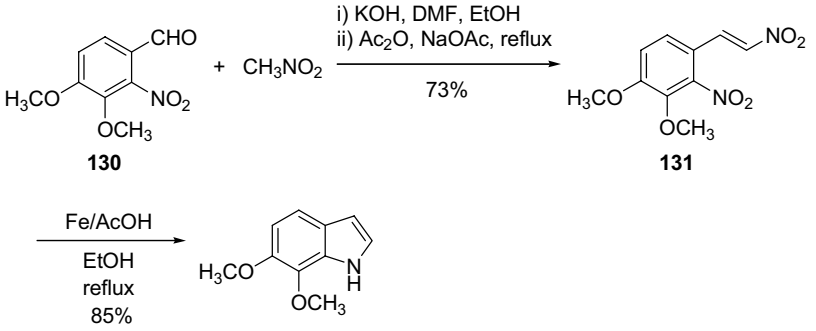
Strong points of this approach are the compatibility with many functional groups, and the ready availability of the starting materials, which make this method a very interesting entry to polysubstituted indoles [72–74]. Enhanced conditions for a Lewis acid catalyzed version of the reaction using microwave acceleration have been described recently [75]. This modification has been applied to the synthesis of a wide variety of substituted nitroenamines, including several examples of heteroaromatics such as **129**, which expand the scope of the Leimbruger–Batcho synthesis (Scheme 5.46).



129

Scheme 5.46

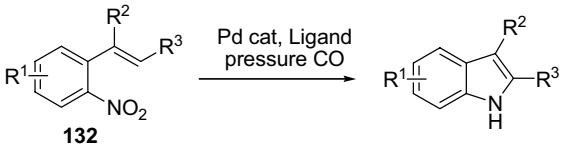
5.4.2.2.3 **Reductive cyclizations *o*-Nitrostyrenes** The reductive cyclization *o*,β-dinitrostyrenes is another two step synthesis of indoles closely related with the Leimbruger–Batcho approach. The formation of the *o*,β-dinitrostyrenes **131** is usually achieved by Henry condensation [76, 77] of nitromethane with *o*-nitrobenzaldehydes **130**, or by nitration of benzaldehydes [78]. The reduction step has been carried out with several classes of reducing agents, including different metal/acid combinations [79] and catalytic hydrogenation conditions (Scheme 5.47) [80]. This



Scheme 5.47

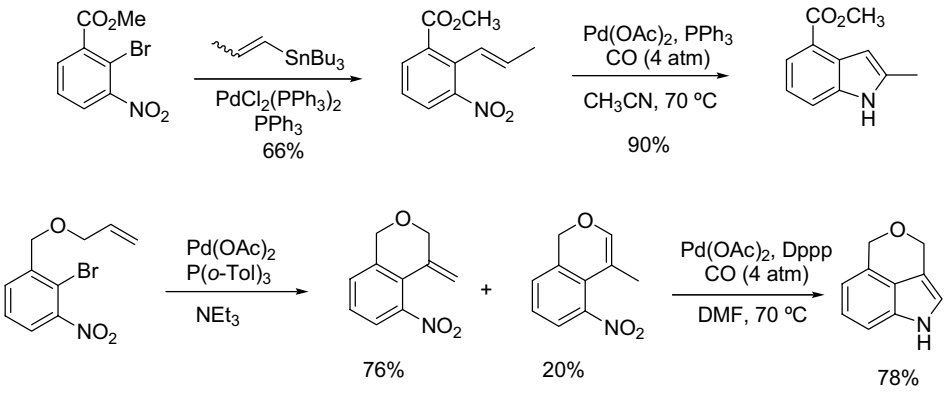
methodology has been applied as starting point in the synthesis of several natural products containing the indole skeleton [81–84].

A versatile methodology, related with the methods described above, is the palladium-catalyzed reductive N-heteroannulation of *o*-nitrostyrenes **132** [85, 86]. The reaction is carried out under CO pressure and in the presence of a Pd/ligand catalytic system (Scheme 5.48) [87].



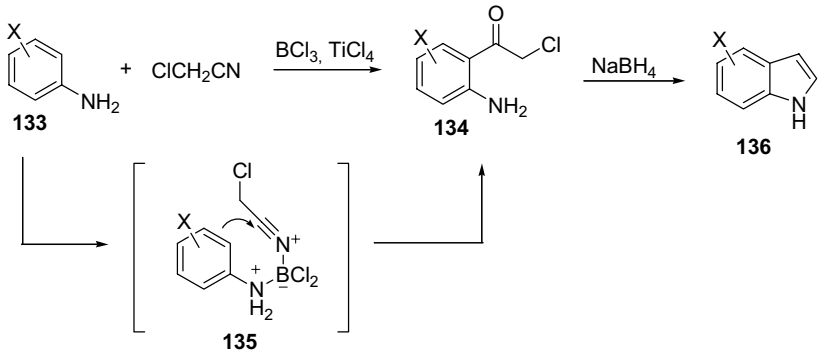
Scheme 5.48

The required precursors, the *o*-nitrostyrenes, are readily available from *o*-bromonitrobenzenes, through metal-catalyzed reactions, such as Stille couplings [88] or Heck reactions [89]. Examples of both approaches are represented in Scheme 5.49.



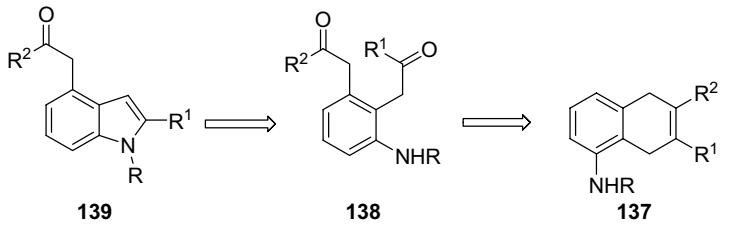
Scheme 5.49

5.4.2.2.4 **Sugasawa Synthesis** Another synthesis of the indole ring from anilines is based on the *o*-chloroacetylation of aniline, the so-called Sugasawa reaction (Scheme 5.50) [90, 91]. Treatment of an aniline (**133**) with chloroacetonitrile in the presence of BCl_3 and another Lewis acid furnishes *o*-chloroacetylaniline **134**, through the intermediate **135**. Chloroacetylaniline **134** can be cyclized to the indole **136** by reduction with $NaBH_4$. The Sugasawa synthesis has been used very efficiently for the preparation of N−H unprotected indoles with substitution in the benzene ring [92, 93].



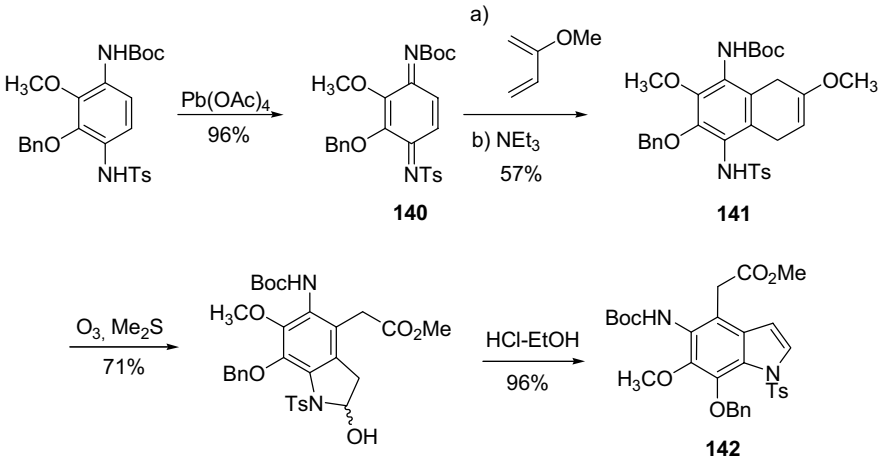
Scheme 5.50

5.4.2.2.5 **Indoles from 5-Aminodihydronaphthalenes: Plieninger Indole Synthesis** The oxidative cleavage of 5-aminodihydronapthalenes **137** provides the amino carbonyl **138** required for the N−C2 condensation reaction to form 7-substituted indoles **139** (Scheme 5.51) [94].



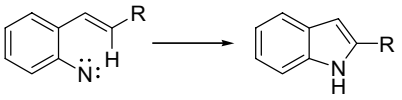
Scheme 5.51

The key intermediate in this synthesis, the 2-aminodihydronaphthalene **141**, is best obtained by [4 + 2] cycloaddition reaction of a *p*-benzoquinone mono- or di-imine, such as **140** with electron-rich dienes [95]. The great potential of this approach is exemplified by the synthesis of the polysubstituted indole **142**, *en route* to the total synthesis of the antitumor agent (+)-yatakemycin (Scheme 5.52) [96].



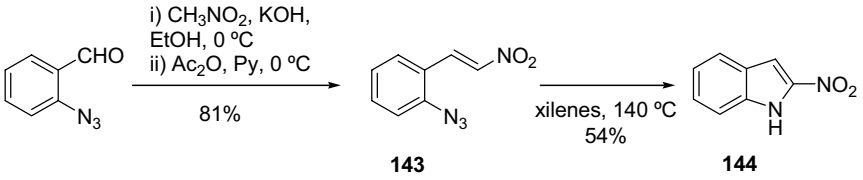
Scheme 5.52

5.4.2.2.6 **Cyclizations of Nitrenes** Another type of cyclization with formation of the N−C2 bond involves the insertion of nitrenes in a vinylic C−H bond to form indoles (Scheme 5.53). Obviously, the key in this type of methodology is the generation of the unstable nitrene species.



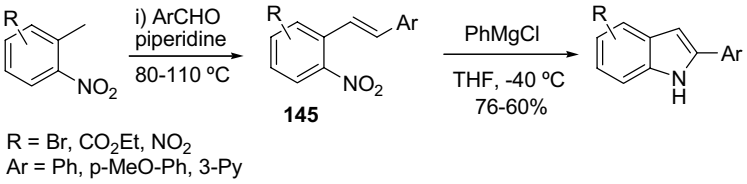
Scheme 5.53

The intermediate nitrenes can be formed by thermolysis of β-substituted-*o*-azidostyrenes **143**, which undergo insertion to form the indole [97, 98]. Scheme 5.54 shows, as an example, the synthesis of 2-nitroindole **144**, which is not easily available through other procedures [99].



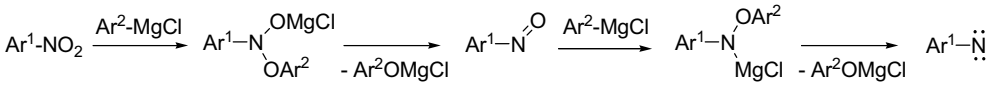
Scheme 5.54

Nitrenes have also been generated from *o*-nitrostyrenes or *o*-nitrostilbenes by deoxygenation of the nitro group with triethyl phosphite [100, 101]. In a more recent modification of this approach, the nitrene is generated by treatment of the nitroarene **145** with phenylmagnesium chloride under very mild conditions (Scheme 5.55) [102].



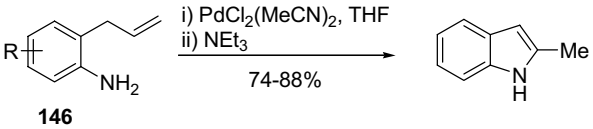
Scheme 5.55

Scheme 5.56 shows the mechanism proposed for this novel nitrene generation reaction.



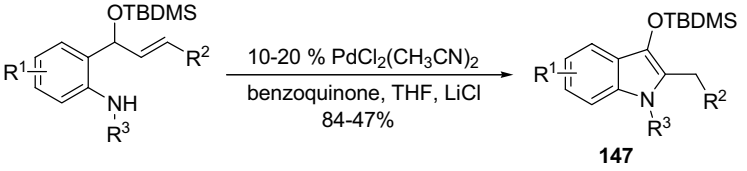
Scheme 5.56

5.4.2.2.7 **Synthesis from *o*-Allylanilines or *o*-Vinylanilines** Palladium-catalyzed intramolecular C−N bond formation is one of the most powerful methods for the synthesis of the indole ring. The first contributions in this area were due to Hegedus, who described the cyclization of *o*-allylanilines **146** using stoichiometric amounts of Pd(II) in a Wacker-type process (Scheme 5.57) [103]. The reaction tolerates functional groups as well as substitution in the allyl moiety.



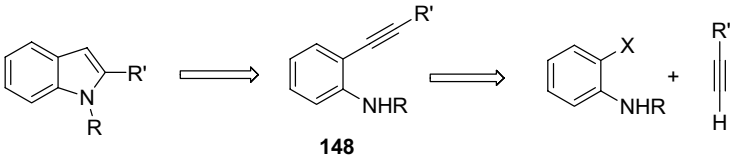
Scheme 5.57

During the reaction the Pd(II) species is reduced to Pd(0). To avoid the use of stoichiometric Pd, benzoquinone is used in the catalytic process as reoxidant. This methodology has been applied in the synthesis of 3-hydroxyindoles **147** (Scheme 5.58) [104].

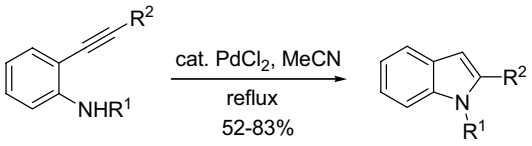


Scheme 5.58

5.4.2.2.8 **Synthesis from *o*-Alkynylanilines or *o*-Alkynylanilides** Intramolecular hydroamination of *o*-alkynylanilines **148**, through a 5-*endo*-dig cyclization, is one of the most popular modern methods for the construction of the indole ring (Scheme 5.59). The required alkynylanilines are usually synthesized by a Pd-catalyzed Sonogashira cross-coupling of an *o*-iodoaniline with a terminal acetylene [105]. The cyclization reaction has been studied extensively and applied in numerous synthetic efforts. Several metal-based catalytic systems are able to promote the cyclization. Among them, Pd and Cu have been the most studied. Detailed accounts of this methodology have been published [106]. Typically, the cyclization is carried out in the presence of a Pd(II) catalyst, such as $PdCl_2$ (Scheme 5.60) [107].



Scheme 5.59



R^1 = H, -COR; R^2 = Alkyl, Ar

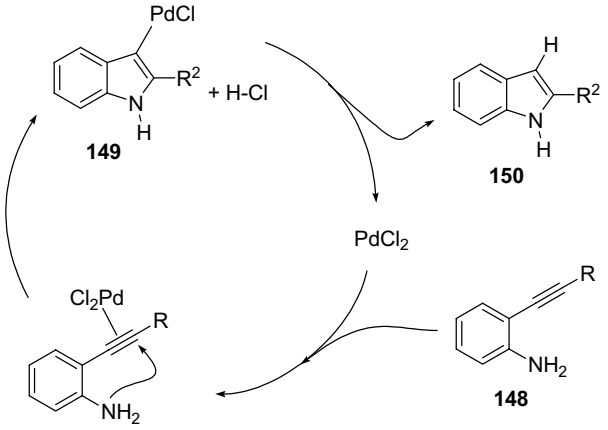
Scheme 5.60

The mechanism of the reaction is postulated to proceed via an intramolecular aminopalladation of the alkynylaniline **148**, which produces the a σ-indolylpalladium species **149**, followed by protonolysis of the C−Pd bond, which releases the indole **150** and recovers the Pd(II) catalyst (Scheme 5.61).

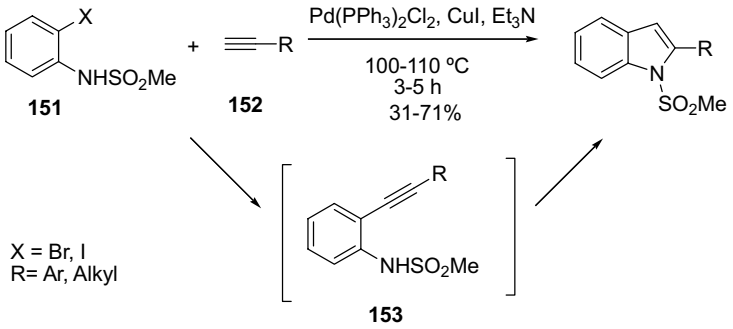
The *one pot* synthesis of 2-substituted indoles from *o*-haloaniline derivatives **151** and terminal acetylenes **152** can be achieved by employing a combination of Pd(II) and Cu(I) catalyst (Scheme 5.62). In this process, the Sonogashira coupling to form alkynylaniline **153** and the intramolecular hydroamination occur consecutively and are promoted by the same catalytic system [108, 109].

Indoles are also prepared in *one pot* fashion from *o*-chloroalkynylbenzene **154** derivatives and primary amines **155** (Scheme 5.63) [110]. In a first step, a Pd-catalyzed aryl amination takes place to furnish the *o*-alkynylaniline **156**, which then cyclizes to give the indole **157**, in a process promoted by the same Pd catalyst.

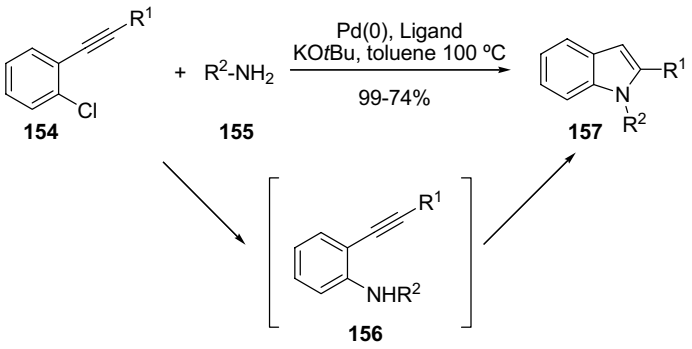
An interesting variation of this methodology is the "aminopalladation/reductive elimination" domino reaction that provides 2,3-disubstituted indoles **160** from *o*-alkynyl trifluoroacetanilides **158** and organic halides **159** (Scheme 5.64) [111].



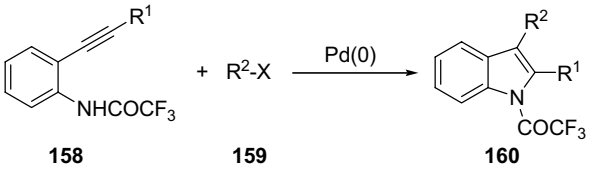
Scheme 5.61



Scheme 5.62

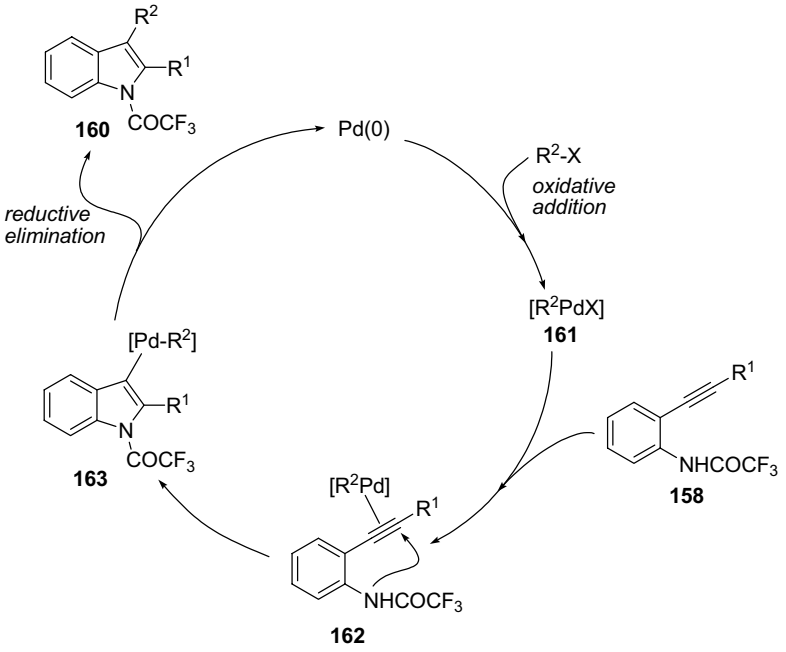


Scheme 5.63



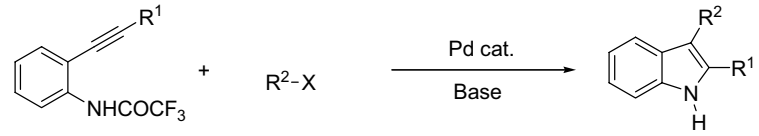
Scheme 5.64

A plausible mechanism for this Pd(0)-catalyzed domino reaction involves: (i) oxidative addition of the halide to the Pd(0) species to form Pd complex **161**; (ii) coordination of the Pd(II) species **161** to the triple bond of **158** to form the (η^2-alkyne) organopalladium complex **162**; (iii) intramolecular nucleophilic attack of the nitrogen across the triple bond to form the σ-indolylpalladium intermediate **163**; and (iv) reductive elimination that regenerates the Pd(0) catalyst and releases the 2,3-disubstituted indole **160** (Scheme 5.65).

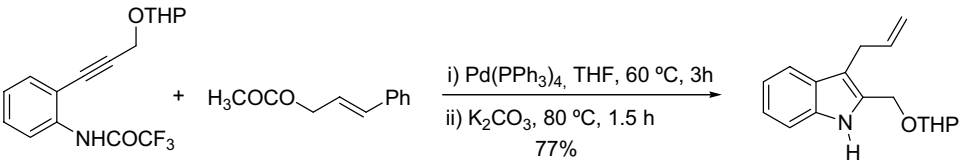


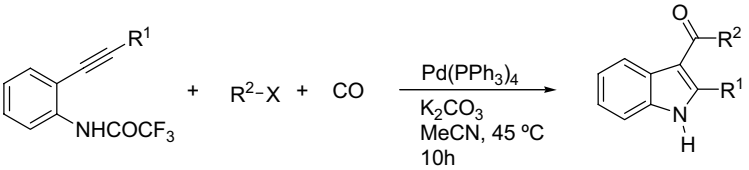
Scheme 5.65

The reaction has been carried out employing aryl halides [112], alkenyl triflates, alkynyl bromides [113], and allylic carbonates [114] to provide the corresponding 2,3-disubstituted indoles. Moreover, if the process is carried out under CO atmosphere, a three-component reaction takes place with incorporation of the carbon monoxide molecule, to yield 3-acyl-substituted indoles (Scheme 5.66) [115].



R^2 = Aryl, alkenyl, alkynyl; X = I, Br, OTf





R^2 = Aryl, alkenyl, X = I, Br, OTf

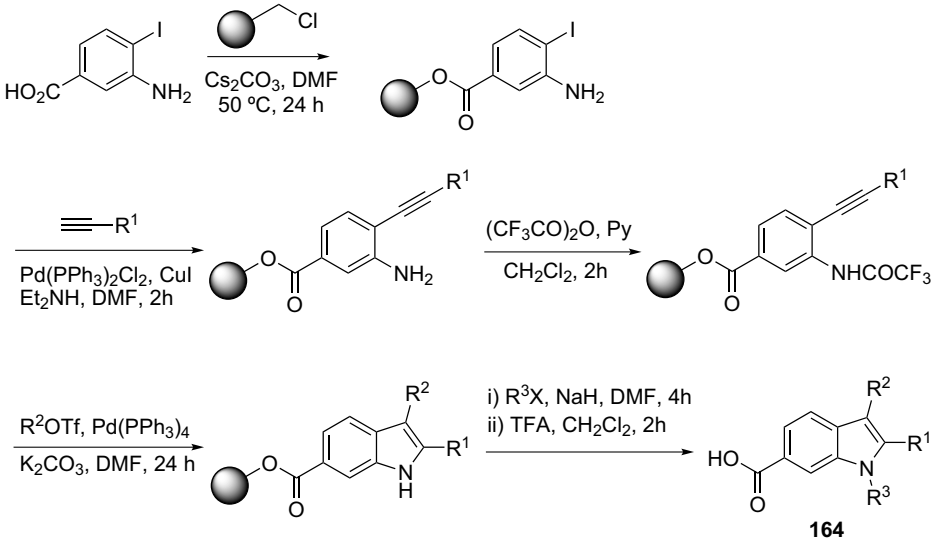
Scheme 5.66

This domino chemistry has been also carried out with a solid support and applied to the preparation of a combinatorial library of indoles **164** with three points of diversity (Scheme 5.67) [116].

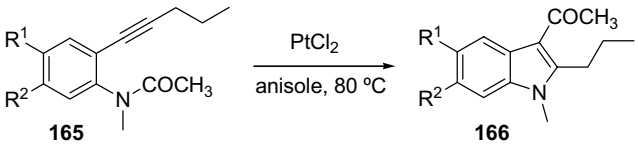
A very impressive extension of this approach is the recently described Pt-catalyzed carboamination of *o*-alkynylanilides **165** [117]. A representative example is presented in Scheme 5.68. During the reaction, the acyl group migrates from the N-atom to C3 to form acylated indole **166**. Therefore, this methodology constitutes a very attractive method for the preparation of 2,3-disubstituted indoles.

The indolization of *o*-alkynylanilines has been performed with alternative promoters other than the classic transition metal catalysts. For instance, K and Cs bases promote successfully the cyclization (Scheme 5.69) [118]. This simple procedure appears to be very general regarding the substituents in the alkyne and the aromatic system, and has been adapted to solid-supported synthesis. Moreover, a similar strategy has been applied to the preparation of oxindoles.

Iodinating reagents, such as bis(pyridine)iodonium(I) tetrafluoroborate (IPy_2BF_4) [119], can also promote the cyclization of *o*-alkynylanilines **167** (Scheme 5.70). Interestingly, the reaction affords 3-iodoindoles **168**, offering the opportunity of further transformation by substitution of the iodine substituent by well known cross-coupling protocols. Moreover, the reaction has also been carried out on a solid support.

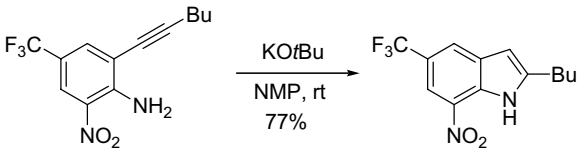


Scheme 5.67

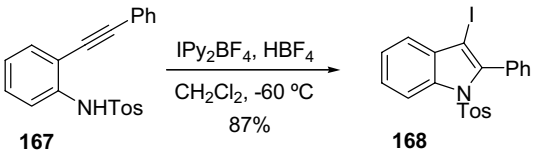


R^1 = OMe, R^2 = H: 89%
R^1 = H, R^2 = OMe: 99%

Scheme 5.68

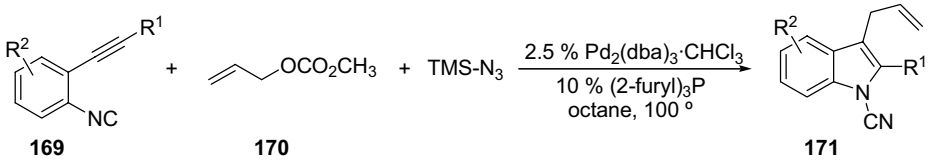


Scheme 5.69



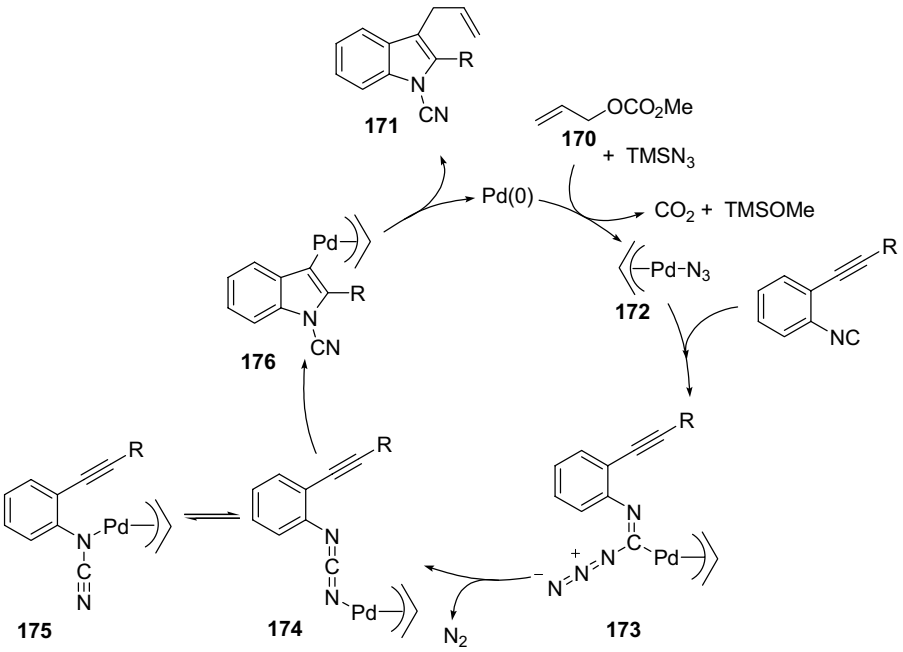
Scheme 5.70

5.4.2.2.9 **Synthesis from *o*-Alkynyl isocyanides or *o*-Alkynyl Isocyanates** *N*-Cyanoindoles **171** are prepared by a very elegant Pd-catalyzed three-component coupling reaction of *o*-alkynylphenylisocyanide **169**, allyl carbonate **170** and trimethylsilyl azide (Scheme 5.71) [120].



Scheme 5.71

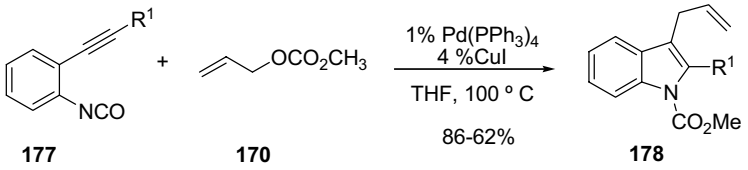
The catalytic cycle proposed for this remarkable cascade process (Scheme 5.72) starts with the reaction of the Pd(0) species with allyl carbonate **170** and $TMSN_3$ to give the π-allylpalladium azide complex **172**. Insertion of the isocyanide in the Pd−N_3 bond would give a new π-allylpalladium complex (**173**). Elimination of N_2, with 1,2-migration of the π-allylpalladium moiety from C to N, would provide π-allylpalladium carbodiimide complex **174**. This rearrangement can be envisioned as a π-allylpalladium



Scheme 5.72

mimic of the Curtius rearrangement. Complex **174** can be in equilibrium with the π-allylpalladium cyanamide complex **175**. Insertion of the alkyne in the Pd−N bond of π-allylpalladium **175** would provide the 2-indolyl-π-allylpalladium complex **176**, which upon reductive elimination yields the cyanoindole **171** and the Pd(0) catalyst.

A related reaction can be applied to prepare *N*-methoxycarbonylindoles **178** from *o*-alkynylisocyanates **177** and allyl carbonate **170**. In this case a Pd^0-Cu^I bimetallic catalyst is required (Scheme 5.73) [121].



177 **170** **178**

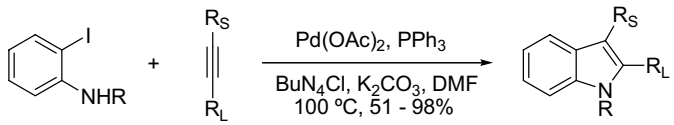
R^1 = Aryl, Cyclopentyl

Scheme 5.73

5.4.2.2.10 **Synthesis from *o*-Haloanilines and Acetylenes: The Larock Indole Synthesis**

The Pd-catalyzed synthesis of indoles from *o*-iodoanilines **179** and internal alkynes **180** is known as the Larock indole synthesis, and stands as one of the more powerful methods for the preparation of 2,3-disubstituted indoles **181** (Scheme 5.74) [122].

When unsymmetrical alkynes are used, the annulation reaction is regioselective, with the bulkiest substituent being placed at C2 in the indole. In particular, silylated alkynes afford exclusively the C2 silylated indole.

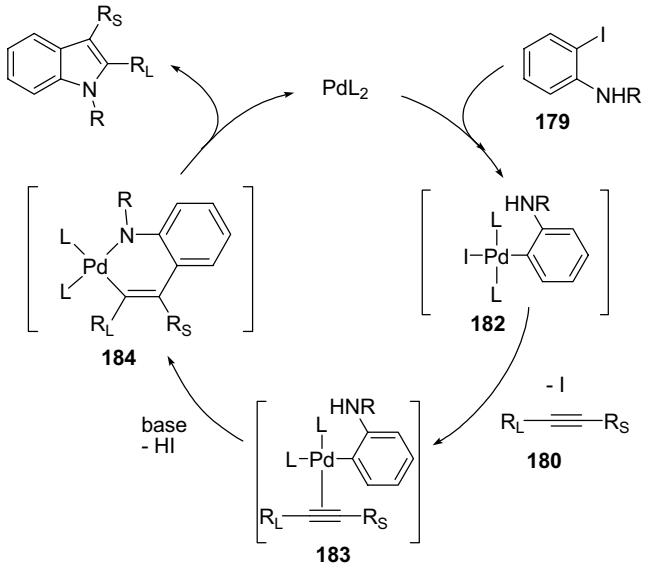


179 **180** **181**

R = H, Me, Ts
R_S, R_L = Alkyl, Ar, Alkenyl, CH_2OH, TMS

Scheme 5.74

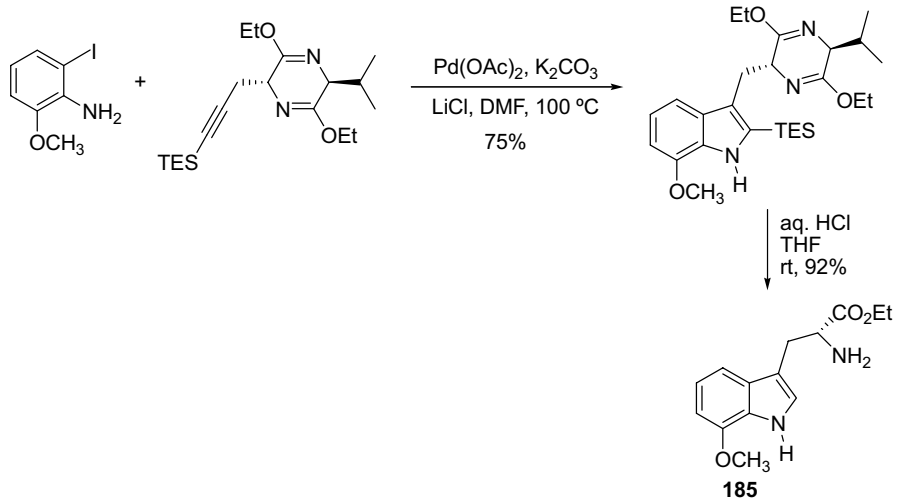
It is postulated that the mechanism of the annulation involves (Scheme 5.75): (i) oxidative addition of the aryl iodide **179** to the Pd(0) species to form arylpalladium complex **182**; (ii) coordination of the alkyne **180** to the arylpalladium complex to form complex **183**; (iii) insertion of the alkyne in the Pd−C_{Ar} bond, and coordination of the nitrogen with ligand displacement to generate palladacycle intermediate **184**; and (iv) reductive elimination to form the indole and regenerate the Pd(0). The regioselectivity of the reaction is determined by the insertion of the alkyne in the Pd−C bond.



Scheme 5.75

The bulkier substituent is situated next to the Pd, to avoid steic interactions with the aromatic ring.

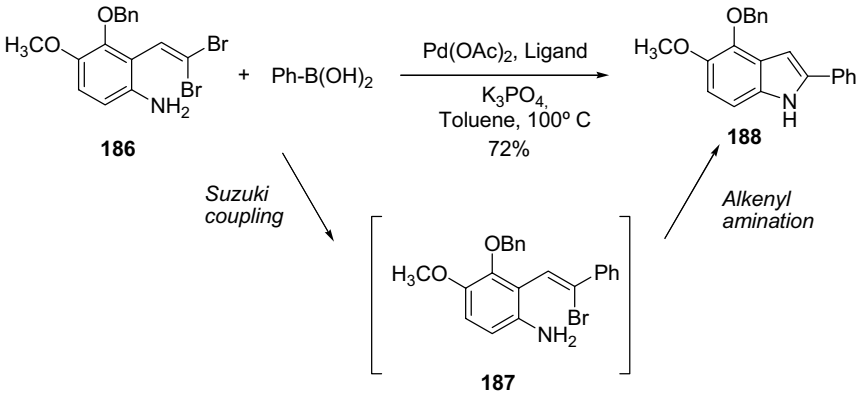
Larock's heteroannulation has been applied as the key step in the preparation of several indole alkaloids and heterocycles. For instance, 7-methoxytryptophan **185**, an early intermediate in the preparation of some indole alkaloids, has been efficiently synthesized with this methodology (Scheme 5.76) [123]. Moreover, recently, the scope



Scheme 5.76

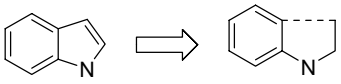
of the reaction has been extended to *o*-bromo- and *o*-chloroanilines, by using an appropriate supporting ligand for the Pd, which enhances its reactivity towards oxidative addition [124].

A different Pd-catalyzed tandem process, which shares some mechanistic features with Larock's indolization, has led to indoles from *o*-(2,2-dibromovinyl)anilines **186** [125]. In this case, the tandem process takes advantage of the different reactivity of the two C−Br bonds towards oxidative addition. Thus, in a first step, Suzuki coupling with substitution of the more reactive trans-bromine atom gives the bromovinyl aniline **187**, which undergoes Pd-catalyzed intramolecular C−N bond formation to provide the indole **188** with high yields (Scheme 5.77).

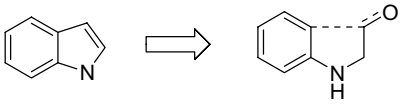


Scheme 5.77

5.4.2.3 Ring Synthesis by Formation of the C3−C3a Bond



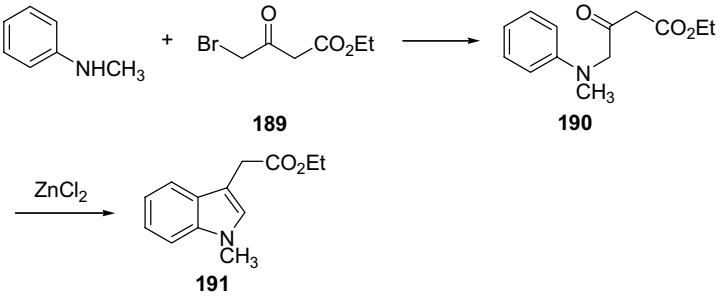
5.4.2.3.1 **Electrophilic Cyclizations of the Aromatic Ring: The Bischler Synthesis** This section includes those indole syntheses in which the key step is a cyclization by electrophilic attack of the aromatic ring to a nucleophilic center in a 5-exo-trig type of cyclization (Scheme 5.78).



Scheme 5.78

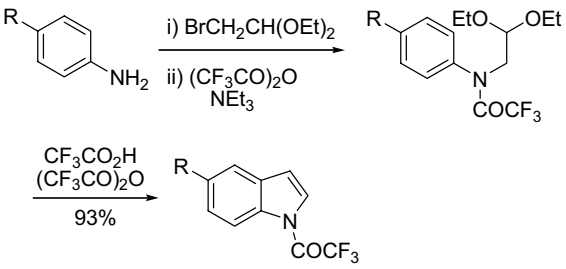
Cyclization of α-(*N*-arylaminoketones), known as the Bischler synthesis, and discovered over 100 years ago [126], is the most characteristic representative of this

approach. In the original protocol, arylaminoketone **190** is obtained from *N*-methylaniline and α-haloketones **189**. Acid-catalyzed 5-exo-trig cyclization then leads to indole **191** (Scheme 5.79).



Scheme 5.79

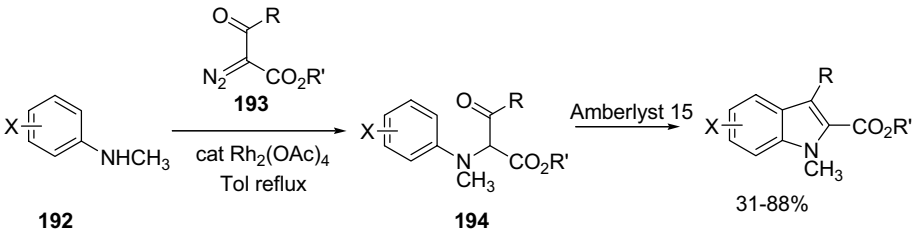
Notable among the most relevant modifications of this procedure are the use of an acetal as a masked aldehyde functionality and the acylation or sulfonation [127] of the nitrogen, which allows a much more controlled cyclization. The Nordlander synthesis [128] exemplifies such variations (Scheme 5.80).



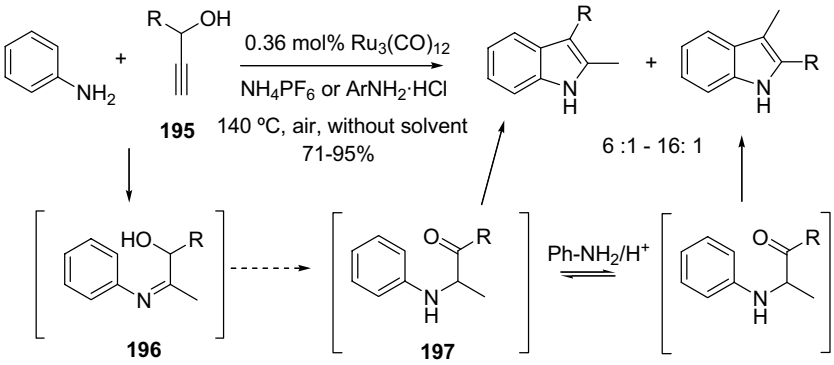
Scheme 5.80

In another modification of the Bischler synthesis, the intermediate α-(*N*-arylaminoketones) **194** are prepared by the N−H insertion reaction of anilines **192** with rhodium carbenoids [129], generated from diazocarbonyl compounds **193** [130]. The final cyclization is carried out using the acidic ion-exchange resin Amberlyst 15, which provides better results than the usual Lewis acid catalysts (Scheme 5.81). A further refinement of the reaction by the same authors allows for the preparation of N−H indoles [131].

Hydroamination of propargylic alcohols with anilines represents another transition metal catalyzed alternative to the classic Bischler synthesis [132]. In a *one pot* process, the hydroxyimine **196**, which comes from the ruthenium-catalyzed hydroamination of the propargylic alcohol **195**, undergoes hydrogen migration to the Bischler intermediate **197**, followed by cyclization to provide a mixture of regioisomeric 2,3-substituted indoles (Scheme 5.82).



Scheme 5.81

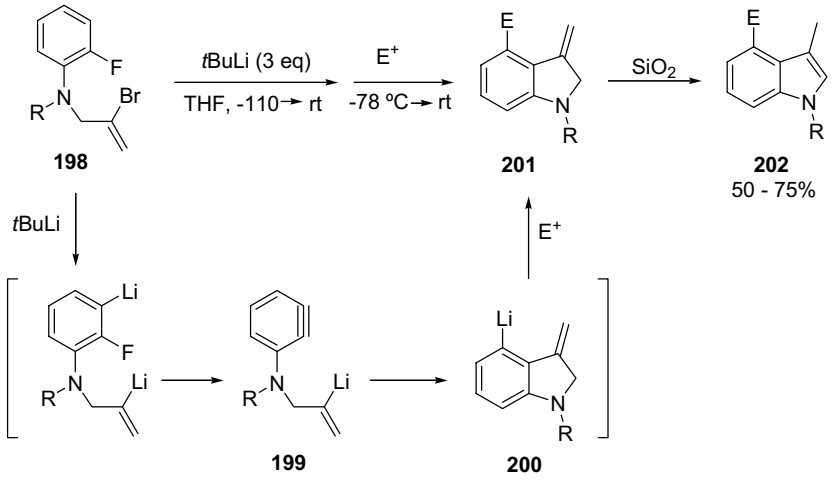


Scheme 5.82

5.4.2.3.2 **Carbometallation of *N*-(2-Lithioallyl)anilines** The intramolecular carbometallation of lithiated double bonds has been used to prepare several types of functionalized indoles [133]. For instance, *N*-bromoallyl-*o*-fluoroanilines **198** are converted into indoles by treatment with 3 equivalents of *t*BuLi. Cyclization of the benzyne intermediate **199** generated gives rise to C(4)-lithiated 3-methyleneindoline derivative **200**. Quenching of the lithiated species **200** with selected electrophiles allows functionalization at this position to provide methyleneindoline **201**, which isomerizes on workup or on silica gel chromatography to the corresponding indole derivatives **202** (Scheme 5.83) [134].

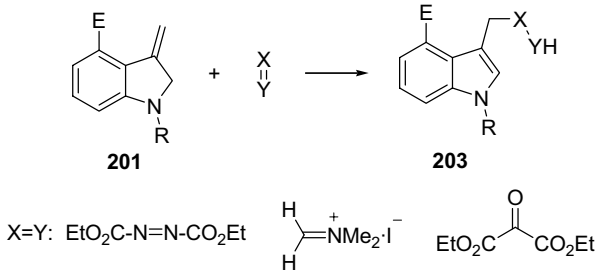
Interestingly, 3-methyleneindolines such as **201** are known to participate in Alder-ene reactions with activated enophiles to furnish 3,4-disubstituted indoles **203** (Scheme 5.84) [135].

Taking advantage of this reaction, addition of an enophile to the reaction mixture provides 3,4-disubstituted indoles in a *one-pot* sequence. Schemes 5.85 and 5.86 show, as representative examples, the one-pot synthesis of a tryptamine analog **204** and a substituted carbazole **205**, respectively.



E: Bu_3SnCl, PhCHO, Me_2CO, $ClCO_2Et$, Me_3SiCl, PhCH=NPh

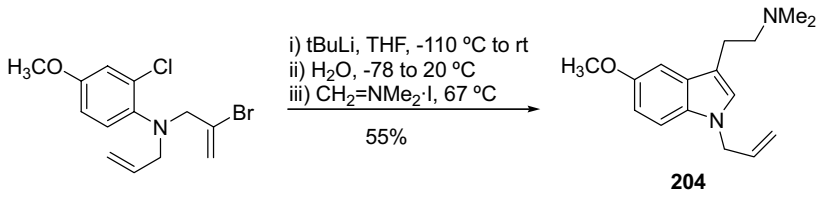
Scheme 5.83



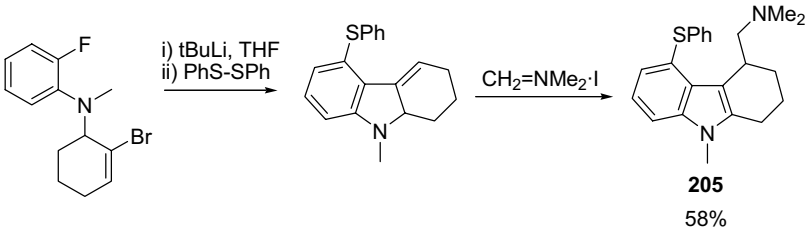
Scheme 5.84

5.4.2.3.3 **Palladium-Catalyzed Heck Reactions** The intramolecular Heck reactions of *o*-halo-*N*-allylanilines **206** and *o*-halo-*N*-vinylanilines **207** are very effective methods for the construction of the indole ring (Scheme 5.87).

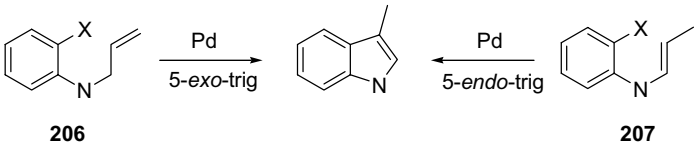
The Pd-catalyzed cyclization of *N*-allyl-*o*-haloanilines, such as **208** [136–138], is a very reliable method for the preparation of indoles. The intramolecular Heck reaction



Scheme 5.85

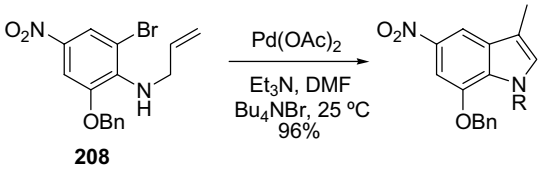


Scheme 5.86



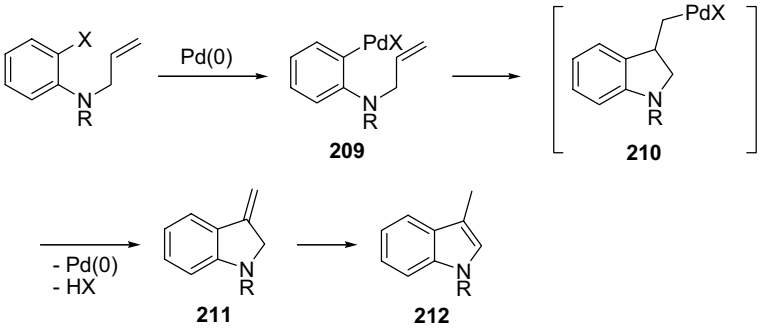
Scheme 5.87

is usually achieved under Pd ligandless conditions and in the presence of a base (Scheme 5.88) [139, 140].



Scheme 5.88

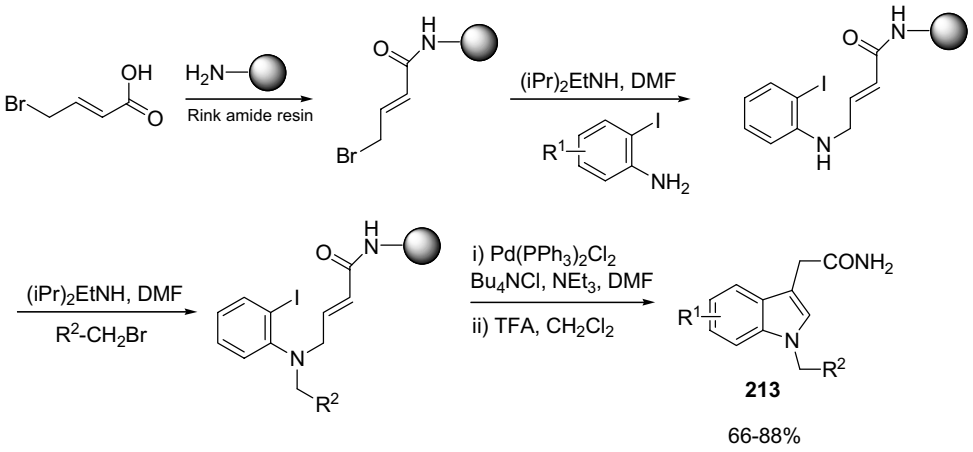
The formation of the indole can be explained by the accepted mechanism of the Heck reaction. Oxidative addition of the aryl halide to form arylpalladium complex **209**, followed by cyclization by olefin insertion, gives rise to the Pd(II) substituted indoline **210**. β-Elimination regenerates the Pd(0) species and produces a 3-methylenindoline **211**, which isomerizes spontaneously to indole **212** (Scheme 5.89).



Scheme 5.89

Nevertheless, it is possible to isolate the intermediate indoline under certain reaction conditions, which include the use of silver carbonate as base [141].

Many examples have appeared in the literature of the application of this methodology in the synthesis of complex molecules [142], including adaptation to solid-phase synthesis [143]. Scheme 5.90 shows a solid-phase synthesis of trisubstituted indoles **213** that allows for the introduction of several points of diversity in the indole scaffold [144].



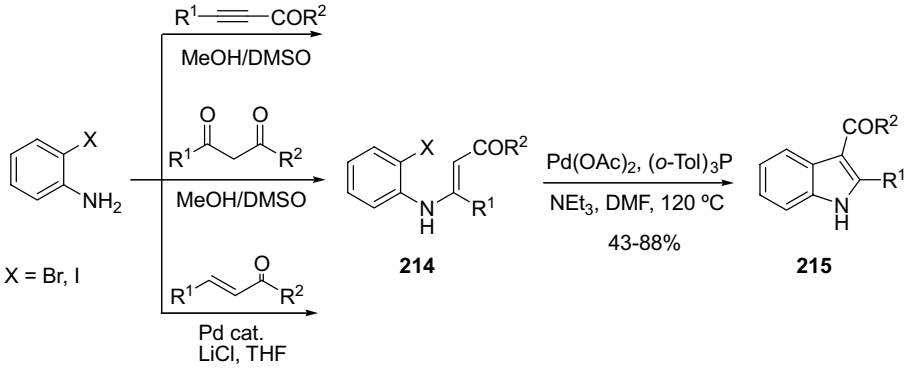
Scheme 5.90

The Heck reaction of *o*-haloenamines has attracted comparatively less attention than the previously discussed reaction with *N*-allylanilines. The instability of the enamines when compared with the allylamines, as well as the more difficult 5-endo-trig cyclization when compared with the 5-exo-trig, may account for this difference. The first examples of this approach were carried out with acylenamines **214**, easily prepared through different procedures, which undergo Pd-catalyzed cyclization to provide 2,3-disubstituted indoles **215** (Scheme 5.91) [145].

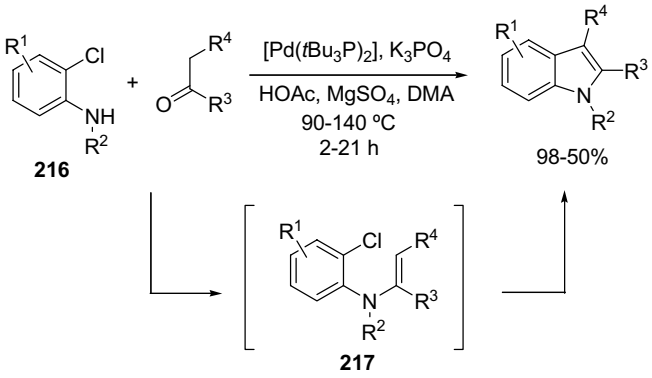
Direct annulation of *o*-iodoanilines with ketones is a very convenient variation of this route [146]. The reaction has been extended recently to the more easily available chloroanilines **216** [147]. In a first step, condensation of the amine with the ketone forms the enamine **217**, which then undergoes Pd-catalyzed cyclization (Scheme 5.92). The use of a very active catalytic system is crucial.

Enamine **217** required for the cyclization has also been prepared by acetylene hydroamination. Thus, the indole ring has been formed from acetylenes **219** and *o*-chloroaniline (**218**), in a *one pot* process that requires two different metal catalysts: a Ti catalyst for the hydroamination, and a Pd catalyst for the Heck reaction (Scheme 5.93) [148].

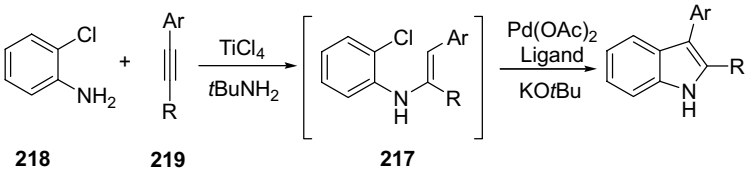
In a related process, indoles have been synthesized from *o*-haloanilines **220** and alkenyl bromides **221**. Notably, in this process the same Pd catalyst promotes two



Scheme 5.91



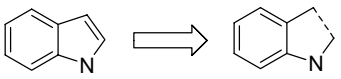
Scheme 5.92

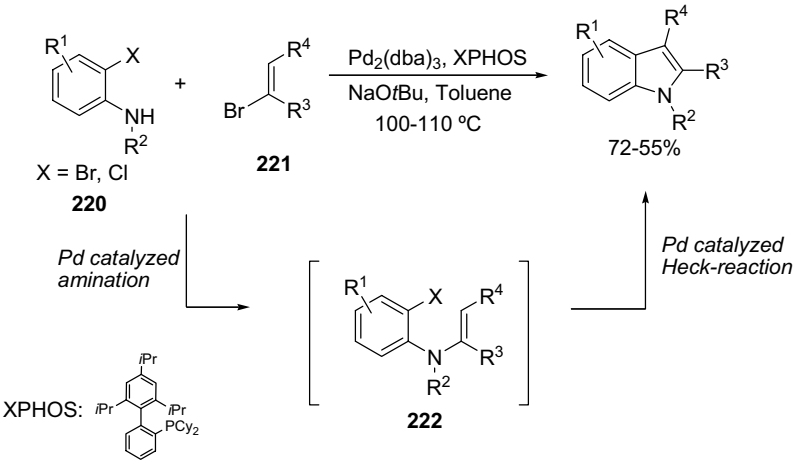


Scheme 5.93

different reactions: the alkenyl amination, which forms the intermediate enamine **222**, and the subsequent Heck reaction to form the indole (Scheme 5.94) [149].

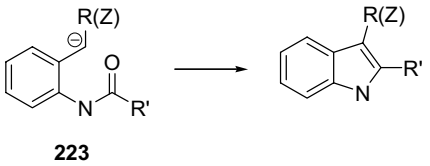
5.4.2.4 Ring Synthesis by Formation of the C2–C3 Bond





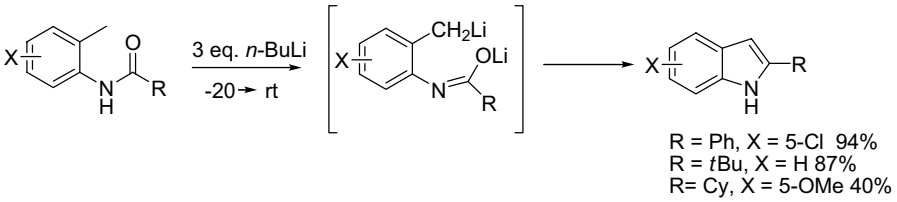
Scheme 5.94

5.4.2.4.1 **Madelung Synthesis** The construction of the indole ring by cyclocondensation of 2-methylanilides (**223**) is known as the Madelung indole synthesis (Scheme 5.95). In its original formulation the reaction used bases such as $NaNH_2$ and KO*t*Bu, and required extremely harsh reaction conditions with temperatures over 250 °C (check out the procedure published in *Organic Synthesis Collective*) [150]. The replacement of these bases by alkyllithiums or LDA allows the reaction to take place under much milder reaction conditions (Scheme 5.96) [151, 152].



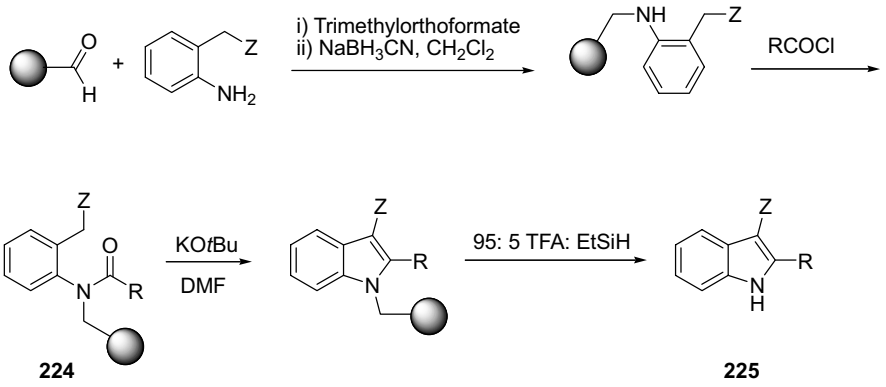
223

Scheme 5.95



Scheme 5.96

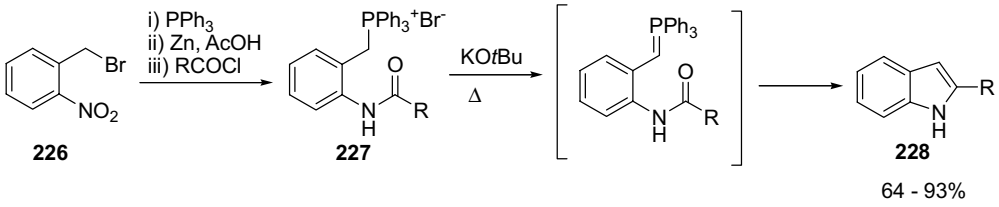
Introduction of electron-withdrawing substituents at the ortho-methyl group makes the benzylic proton of derivatives **224** more acidic and thus facilitates the overall process [153]. This approach is illustrated by the solid-phase synthesis of a library of 2,3-disubstutited-indoles **225** (Scheme 5.97) [154].



Z = CN, CO_2tBu, $CONH_2$

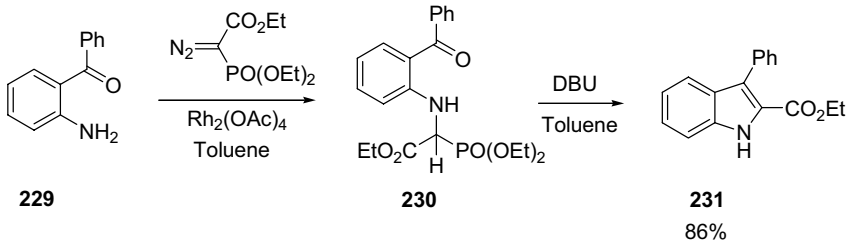
Scheme 5.97

In another variation of the Madelung synthesis, phosphonium salts **227** led to the corresponding indoles through a Wittig-like intramolecular reaction in the presence of base [155] or under thermal conditions [156]. The required phosphonium salts can be easily obtained from *o*-nitrobenzyl bromide (**226**) in a sequence that includes substitution with triphenylphosphine, reduction of the nitro group and acylation [157]. This procedure has been applied to the preparation of 2-alkyl, 2-alkenyl and 2-arylindoles **228** (Scheme 5.98). A solid-phase version of this procedure using a polymer-bound triphenylphosphine has also been developed [158].



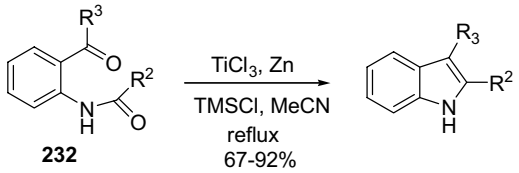
Scheme 5.98

2,3-Disubstituted indoles **231** have been prepared by a very original strategy from *o*-aminoketones **229** through an intramolecular Horner–Wadsworth–Emmons reaction. The key step in this synthesis is the generation of the intermediate phosphonate **230**, required for the olefination reaction, which was prepared by insertion in a N−H bond of an *in situ* generated Rh carbenoid (Scheme 5.99). The whole sequence can be conducted in a one-pot process [159].



Scheme 5.99

5.4.2.4.2 **Fürstner Synthesis** The intramolecular reductive cyclization of oxo-amides **232** promoted by low-valent titanium (an intramolecular McMurry coupling) [160] is known as the Fürstner indole synthesis [161] (Scheme 5.100).



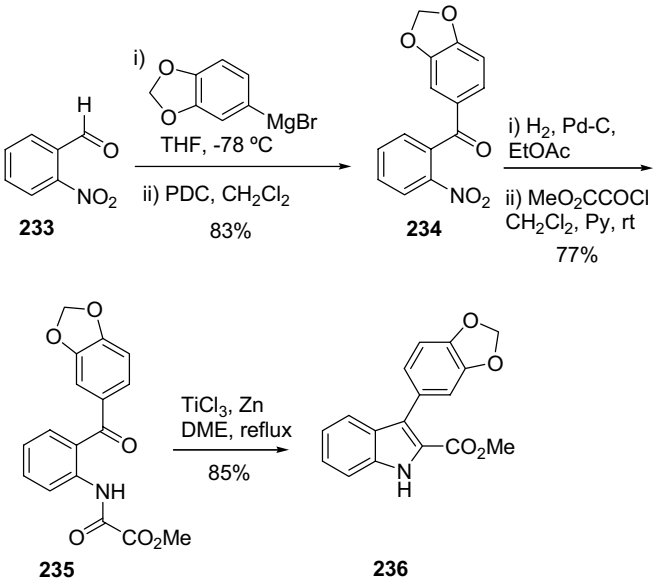
Scheme 5.100

This coupling reaction is a very powerful method for the preparation of 2,3-disubstituted indoles – in particular of 2-arylindoles – and has been applied in the total synthesis of several indole alkaloids and biologically active molecules [162]. Scheme 5.101 shows a particular example of this methodology, applied to the preparation of an endothelin receptor antagonist [163]. The oxo-amide **235** required for the cyclization reaction is easily prepared from *o*-nitrobenzaldehyde (**233**). Addition of an aryl Grignard followed by oxidation of the resulting alcohol installs the ketone functionality to obtain **234**. Then, catalytic hydrogenation of the nitro group followed by acylation provides the amido functionality of **235**, which is transformed into indole **236** under the standard low-valent-titanium reduction.

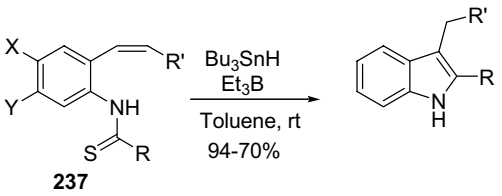
5.4.2.4.3 **Radical Cyclizations** A wide range of 2,3-disubstituted indoles can be prepared by the tin-promoted radical cyclizations of 2-alkenylphenylisonitriles [164] and 2-alkenylthioanilides **237** devised by Fukuyama [165] (Scheme 5.102).

The cyclizations are carried out in the presence of tributyltin hydride and a radical initiator. In a first step, the tin radical adds to the thioamide **237** to form a sp^3 radical **238** or an imidoyl radical **239**, which cyclizes to yield the indole after a tautomeric equilibrium (Scheme 5.103).

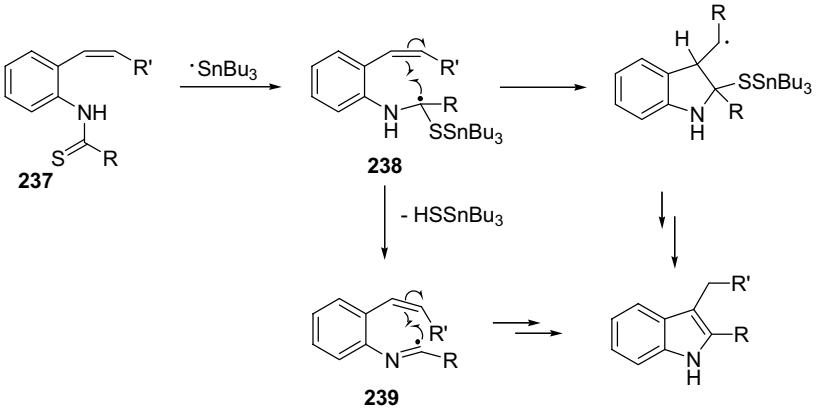
The tin-promoted cyclizations are compatible with a wide range of functional groups. Moreover, the required 2-alkenylthioamides are easily available through various procedures. All this factors make this approach a very useful method for the preparation of 2,3-disubstituted indoles. For instance, this reaction has been applied by Fukuyama to build both indole rings present in the alkaloid (+)-vinblastine, a



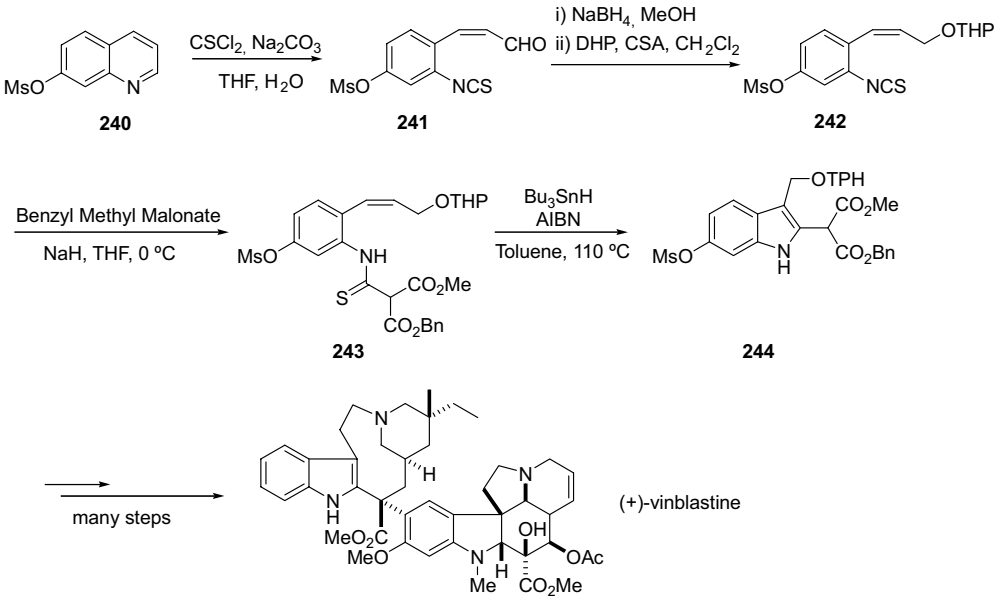
Scheme 5.101



Scheme 5.102



Scheme 5.103

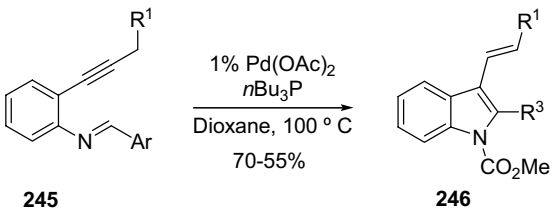


Scheme 5.104

potent agent for cancer therapy (Scheme 5.104) [166]. In this example, the 2-alkenylthioamide is prepared in several steps from quinoline **240**. Ring opening of quinoline **240** promoted by thiophosgene produces **241**. Reduction the of the aldehyde functionality, followed by protection of the hydroxyl group with dihydropyran, leads to the isothiocyanide **242**, which is transformed into the thioamide **243** by addition of a nucleophile. Finally, radical cyclization under standard conditions gives rise to the highly functionalized indole **244**.

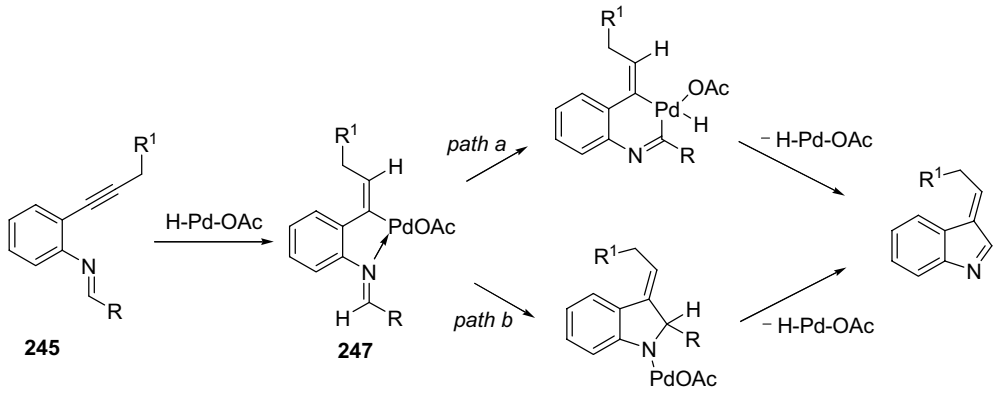
5.4.2.4.4 **Palladium-Catalyzed Cyclizations** The Pd-catalyzed cyclization of 2-(1-alkynyl)-*N*-alkylideneanilines **245** gives rise to 3-alkenylindoles **246** [167] (Scheme 5.105).

According to the authors' proposal, the reaction most probably proceeds through the regioselective insertion of a Pd hydride in the triple bond of **245**, to form vinylpalladium intermediate **247**. From this intermediate, both an "oxidative



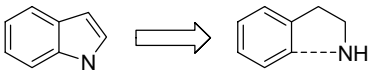
Scheme 5.105

addition/reductive elimination" sequence (path a) and carbopalladation of the imine followed by β-elimination (path b) can explain the formation of the indole (Scheme 5.106).

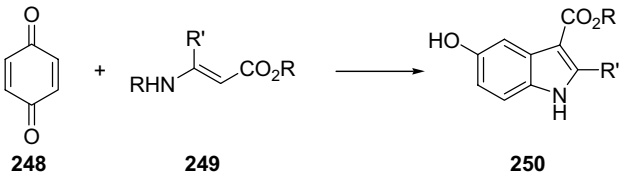


Scheme 5.106

5.4.2.5 Cyclizations with Formation of the N–C7a Bond

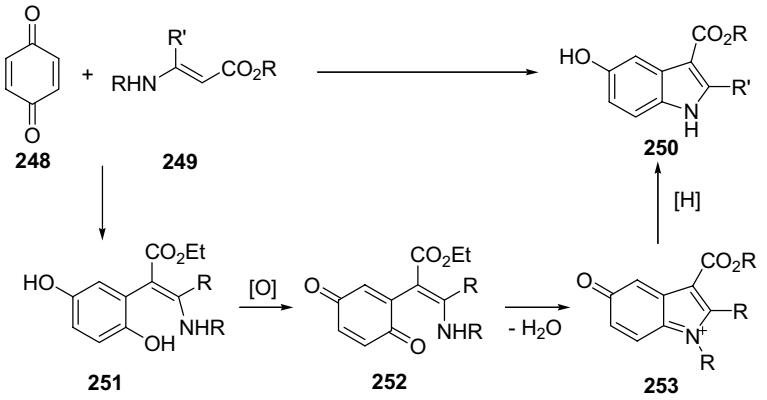


5.4.2.5.1 **Nenitzescu Indole Synthesis** The preparation of 5-hydroxyindole **250** derivatives from 1,4-benzoquinone (**248**) and a β-enaminoester **249** is known as the Nenitzescu reaction and was first reported in 1929 (Scheme 5.107) [168].



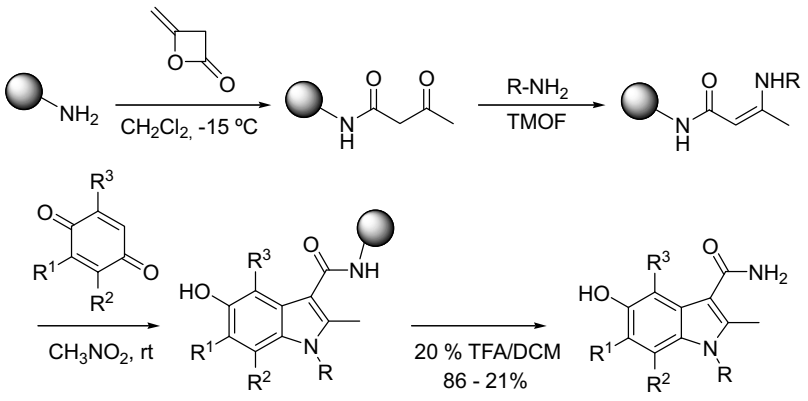
Scheme 5.107

Although the mechanism of the reaction remains somewhat obscure, it is presumed that it involves an internal oxidation–reduction process within the following steps: Michael-type addition of the enamine **249** to the quinone **248**, oxidation of the hydroquinone **251** into a substituted benzoquinone **252**, condensation to form the quinoimmonium cation **253** and reduction to form 5-hydroxyindole **250** (Scheme 5.108).



Scheme 5.108

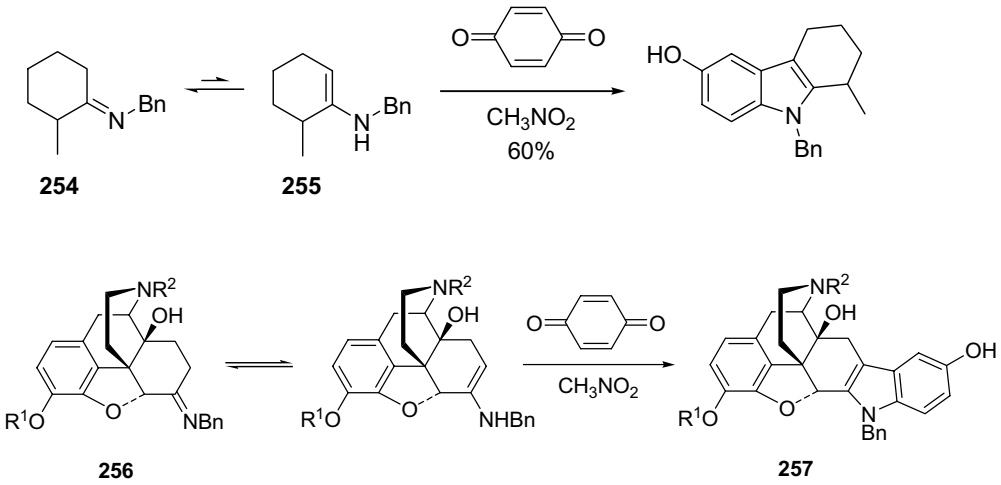
The Nenitzescu synthesis has been widely used for the preparation of 5-hydroxyindole derivatives with additional substituents in both rings [169]. An example of its implementation to solid-phase synthesis is given in Scheme 5.109 [170].



Scheme 5.109

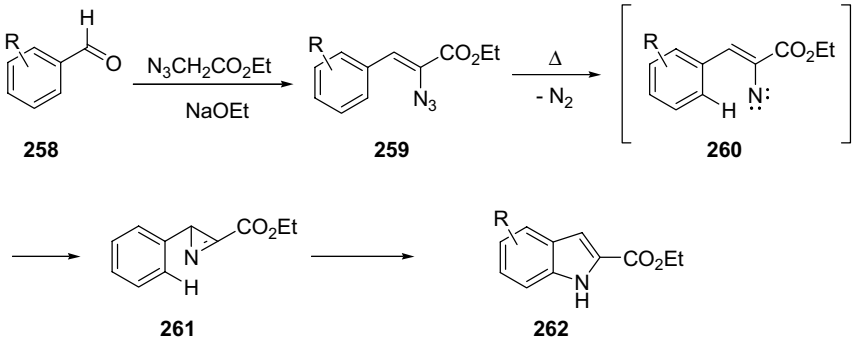
The scope of the Nenitzescu reaction has been recently extended to substrates different than the classical β-enaminocarbonyls. Pyrimidine-2,4,6-triamines react with *p*-benzoquinones to provide hydroxypyrimido[4,5-*b*]indoles with moderate yields [171].

Benzylimines of simple ketones (**254**), which are in tautomeric equilibrium with the corresponding enamines **255**, are also good substrates for the indolization. This new reaction has been applied to simple cyclic imines, and also to more complex systems such as **256** to prepare new hydroxyindolomorphinans **257** with potent biological activity (Scheme 5.110) [172].



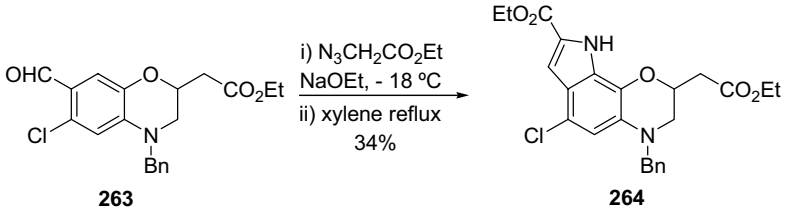
Scheme 5.110

5.4.2.5.2 **Synthesis by Nitrene Insertion: The Hemetsberger Synthesis** The indole ring can be built by insertion of a nitrene placed on the side-chain (**260**). In this approach, commonly known as the Hemetsberger indole synthesis, cyclization is achieved by thermolysis of the corresponding azides **259** [173]. Although the reaction may be understood as a nitrene insertion into a C−H bond, an azirine intermediate **261** has been isolated at lower temperatures [174], which provides the indole **262** after a subsequent rearrangement (Scheme 5.111).



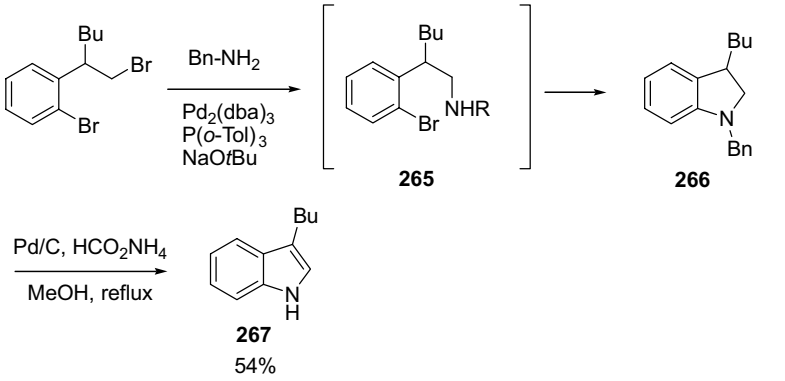
Scheme 5.111

The vinylazides are best obtained by condensation of azidoacetate with aryl aldehydes **258**. Thus, this methodology is particularly useful for the preparation of 2-carboxyindoles **262** from aromatic aldehydes [175]. This protocol has been employed successfully in the preparation of polycyclic indole derivatives. For instance, application of the Hemetsberger sequence to the formylbenzoxazine **263** gives oxazinindole **264** in moderate overall yield (Scheme 5.112) [176].



Scheme 5.112

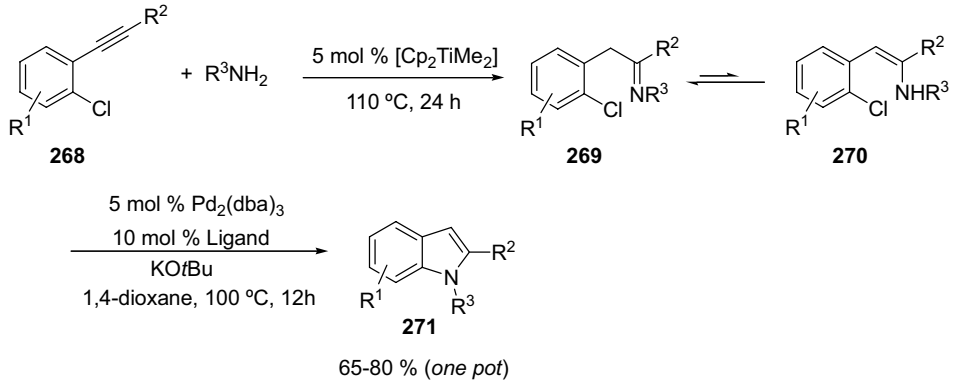
5.4.2.5.3 **Intramolecular Buchwald–Hartwig Amination** The Pd-catalyzed cross-coupling of aryl halides with amines is nowadays one of the most powerful methods for the formation of $C_{aryl}-N$ bonds [177]. The intramolecular version of the reaction leads to indolines, which can be converted into indoles by treatment with Pd/C. Scheme 5.113 shows the cyclization of the *in situ* generated 1-(*o*-bromophenyl)-2-ethylamine **265** to furnish the corresponding indole **267** after the oxidation step of the intermediate indoline **266** [178]. Further optimization of the reaction showed that modification of the ligand and the base provides better yields under milder conditions [179]. Moreover, a similar copper-catalyzed cyclization has also been reported [180, 181].



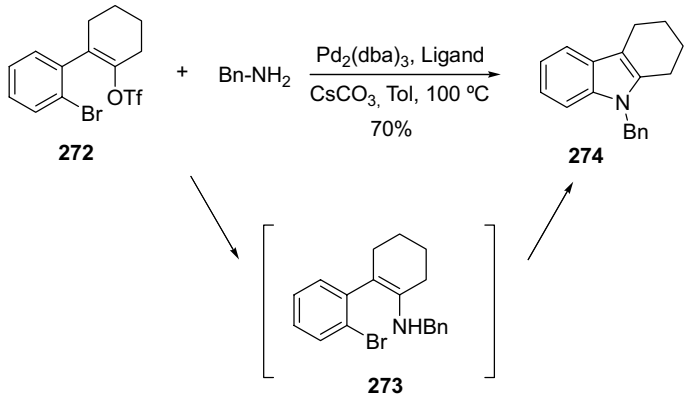
Scheme 5.113

Intramolecular N-arylation of enamines has also been applied in the synthesis of indoles. Enamine **270** (in tautomeric equilibrium with the imine **269**), which is ready for cyclization, is obtained by Ti-catalyzed hydroamination of the *o*-chloro-substituted alkynylbenzene **268**. Then, the Pd-catalyzed C–N bond-forming reaction furnishes *N*,2-disubstituted indoles **271** with good yields in a one-pot process (Scheme 5.114) [182].

Indoles have been prepared by two consecutive Pd-catalyzed amination reactions on the enoltriflate **272** in a closely related strategy that features two reactive positions towards Pd-catalyzed amination (Scheme 5.115) [183]. First, amination of the more reactive enoltriflate occurs, to produce the enamine **273**, which then undergoes intramolecular aryl amination to give indole **274**.



Scheme 5.114



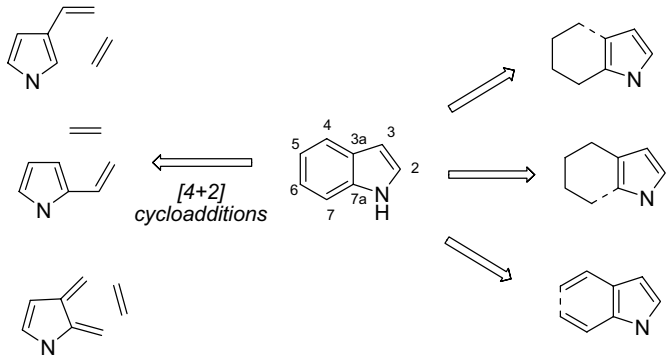
Scheme 5.115

5.4.3
Synthesis of the Indole Ring by Annelation of Pyrroles

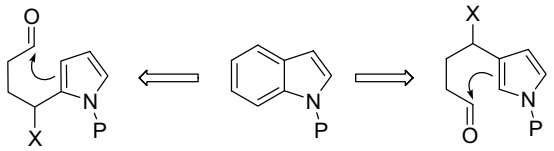
Construction of the indole ring by annelation of pyrroles has been much less exploited. Nevertheless, several efficient methods have been disclosed during the last two decades. Most of the existing methods lie in one of the retrosynthetic schemes represented in Scheme 5.116.

5.4.3.1 Synthesis by Electrophilic Cyclization

The most popular type of methods for synthesis of the indole ring from pyrroles involves an electrophilic cyclization, with formation of either the C7–C7a or C3a–C4 bond (Scheme 5.117). In both cases, annelation takes place by an intramolecular electrophilic attack of the pyrrole to a carbonyl function. To facilitate aromatization, a leaving group is usually present in the carbon chain. The different methods described in the literature differ in the way to synthesize the intermediate carbonyl pyrrole ready for the cyclization.

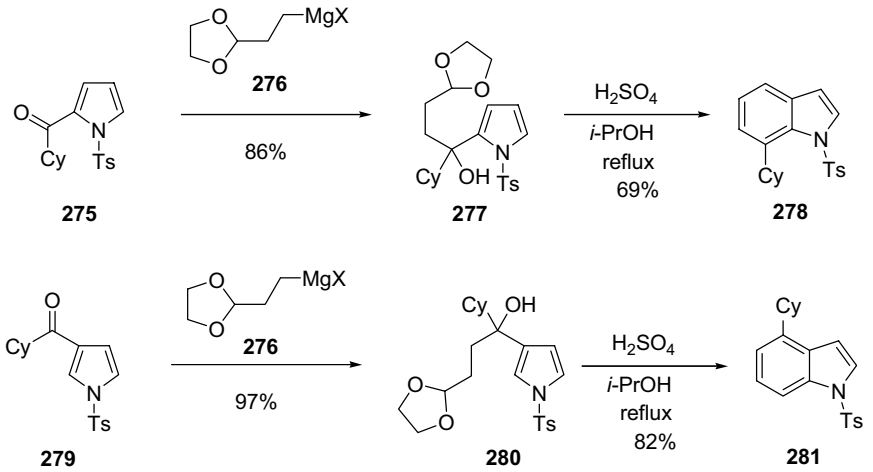


Scheme 5.116



Scheme 5.117

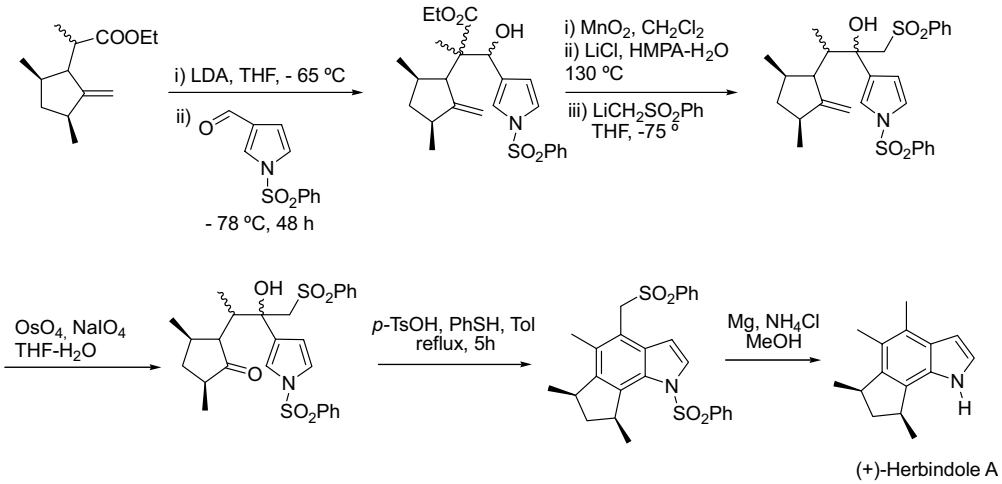
5.4.3.1.1 **Natsume Synthesis** In the Natsume approach, the intermediate for cyclization is prepared by addition of a organometallic bearing a masked carbonyl functionality (**276**) to a pyrrolyl ketone (**275**). Acid-catalyzed cyclization on the resulting functionalized pyrrole **277**, with concomitant aromatization, provides indole **278**. This method is a very powerful strategy for the preparation of alkyl-substituted indoles in the benzene portion. Scheme 5.118 shows the preparation of



Scheme 5.118

both a 7-substituted (**278**) and a 4-substituted indole (**281**) by application of the same methodology but starting from 2-acyl (**275**) and 3-acyl (**279**) substituted pyrrole, respectively [184].

Modifications of this strategy have been applied to the preparation of several natural indole alkaloids, characterized by complex alkyl-substitution in the benzene ring, such as herbindoles and trikentrins (Scheme 5.119) [185].



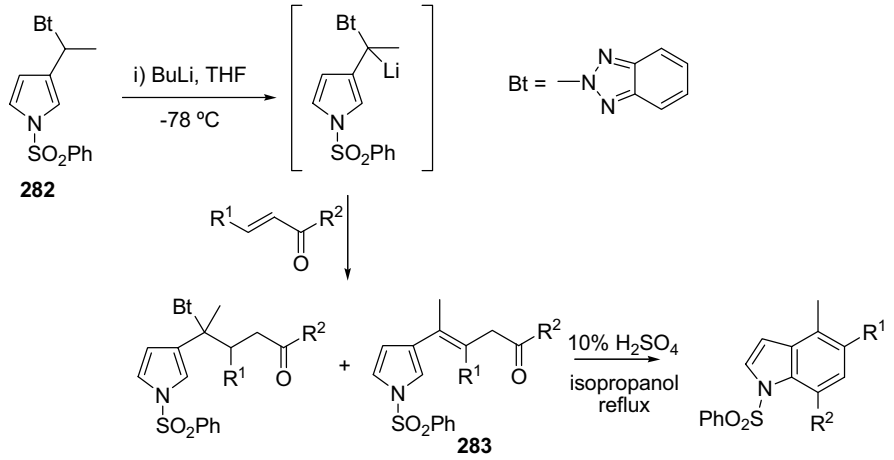
Scheme 5.119

5.4.3.1.2 **Katritzky Synthesis** In the method by Katritzky, the carbonyl substituted pyrrole **283** ready for the cyclization, is generated by a Michael-type addition of the carbanion generated from a benzotriazole (Bt)-substituted pyrrole (**282**) with a α,β-unsaturated ketone (Scheme 5.120) [186]. The benzotriazolyl functionality acts as both an anion-stabilizing group and leaving group in the overall transformation. Both approaches, cyclization by formation of the C3a−C4 bond (Scheme 5.120) or the C7−C7a bond (Scheme 5.121), have been conducted [187].

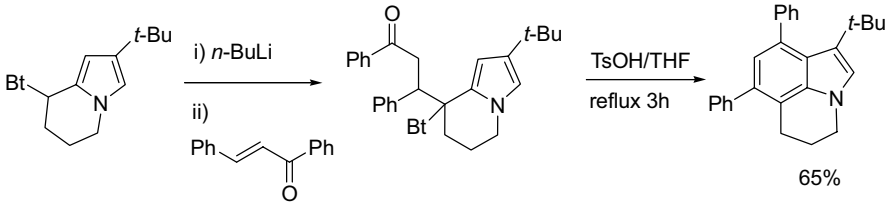
5.4.3.2 Palladium-Catalyzed Cyclizations

The six-membered ring of the indole skeleton has also been constructed by Pd-catalyzed intramolecular Heck reactions. In the example shown in Scheme 5.122, a 6-exo-trig cyclization of a bromo-substituted pyrrole (**284**), bearing a double bond in an appropriate position, provides an advanced intermediate for the synthesis of the antitumor antibiotic duocarmycin SA [188].

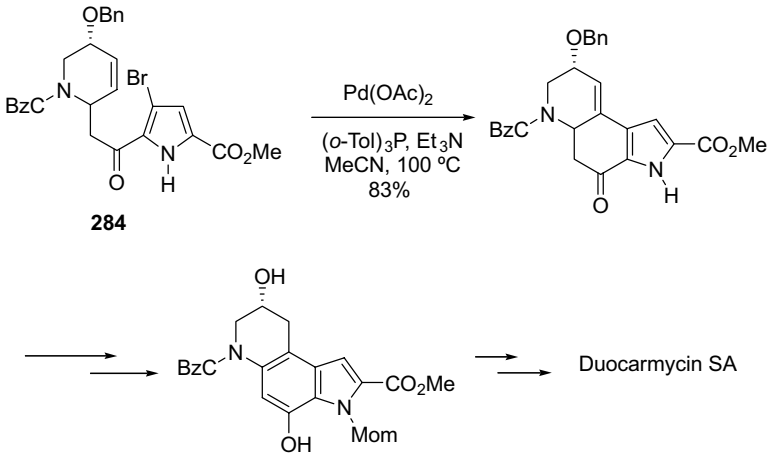
The intramolecular Heck reaction has also been employed to build the benzene ring of the indole system with formation of the C5−C6 bond [189].



Scheme 5.120



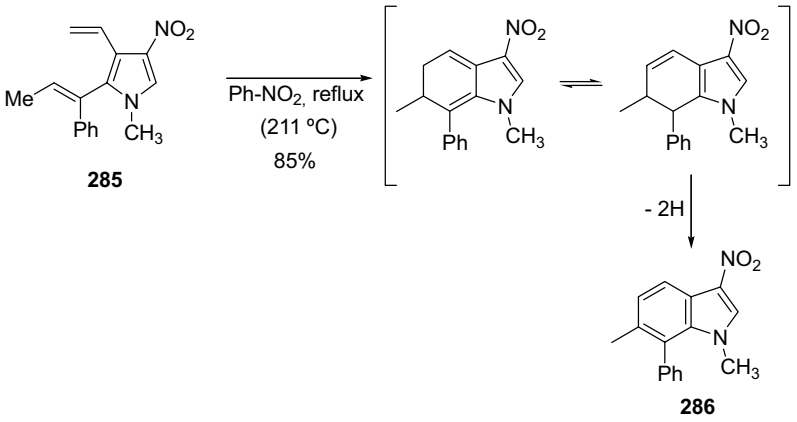
Scheme 5.121



Scheme 5.122

5.4.3.3 Electrocyclizations

Electrocyclization of 2,3-dialkenyl-4-nitropyrroles **285** gives rise to 3-nitroindoles **286** – compounds that are difficult to prepare selectively through other routes. After the thermal 6π-electrocyclization, aromatization of the intermediate dihydroindoles occurs to provide the indole directly (Scheme 5.123) [190].



Scheme 5.123

5.4.3.4 [4 + 2] Cycloadditions

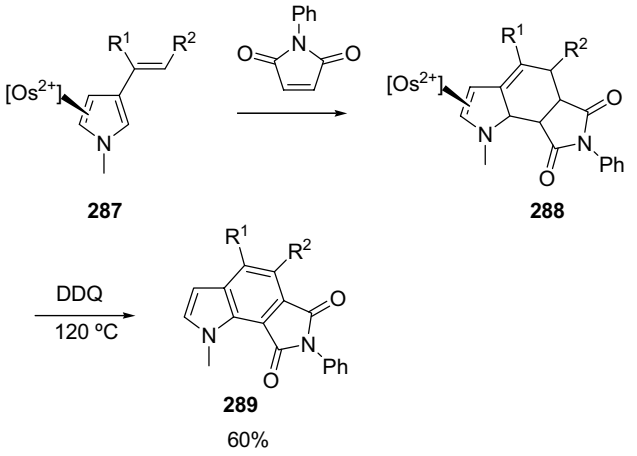
The cycloaddition of 2- and 3-vinyl pyrroles should allow for the preparation highly functionalized indoles in the benzene ring [191]. In a particularly interesting approach, 4,5-η^2-Os(II)pentaammine-3-vinylpyrrole complexes **287** readily undergo Diels–Alder reactions with activated dienophiles such as *N*-phenylmaleimide to generate the 5,6,7,7a-tetrahydroindole nucleus. The tetrahydroindole complexes **288** can be decomplexed and oxidized with DDQ to generate highly functionalized indoles **289** (Scheme 5.124) [192].

In contrast, the cyclic pyrrolo-2,3-quinodimethanes **290** undergo Diels–Alder cycloaddition with alkynes. After CO_2 loss, indoles with high substitution in the benzene ring (**291**) are obtained (Scheme 5.125) [193].

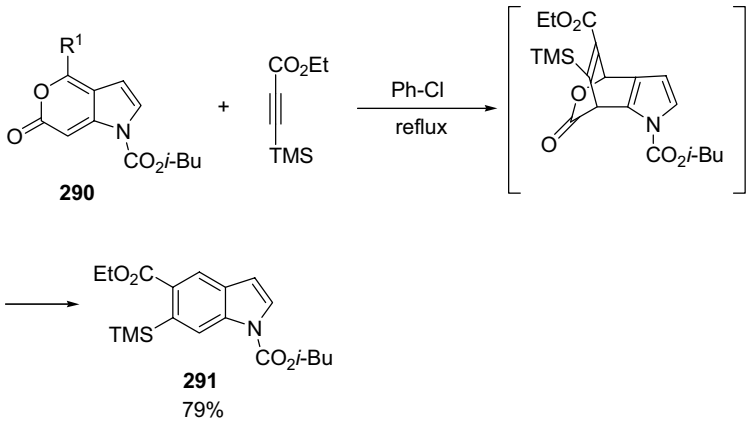
5.4.3.5 Indoles from 3-Alkynylpyrrole-2-Carboxaldehydes

Benzannulation of readily available 3-alkynylpyrrole-2-carboxaldehydes **292** with alkenes, promoted by iodonium ions, yields indoles **293** with a high level of substitution and functionalization in the benzene ring (Scheme 5.126) [194].

The mechanism proposed for this unusual transformation is represented in Scheme 5.127. Interaction of the iodonium ion with the triple bond of **292** would promote the formation of intermediate **294**. Nucleophilic attack of the alkene to the electrophilic carbon of **294**; subsequent intramolecular cyclization would then provide **296**. The simple loss of a proton to give a conjugated double bond then yields **297**. Finally, aromatization by elimination of HI gives the indoles **293**. This



Scheme 5.124



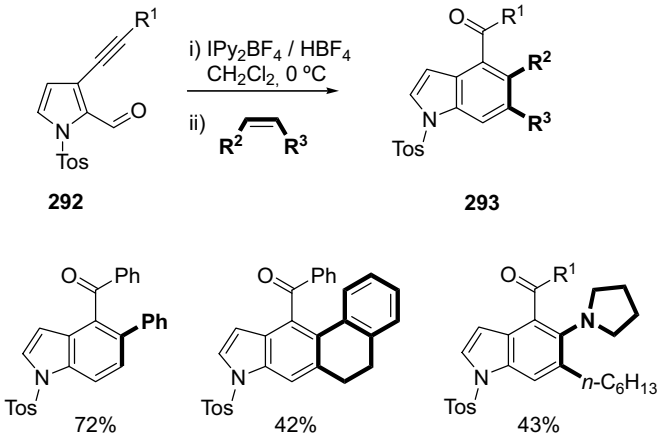
Scheme 5.125

proposal is supported by detailed mechanistic and spectroscopic studies, which allowed the isolation of analogues of the cationic intermediates **294** and **296** [195].

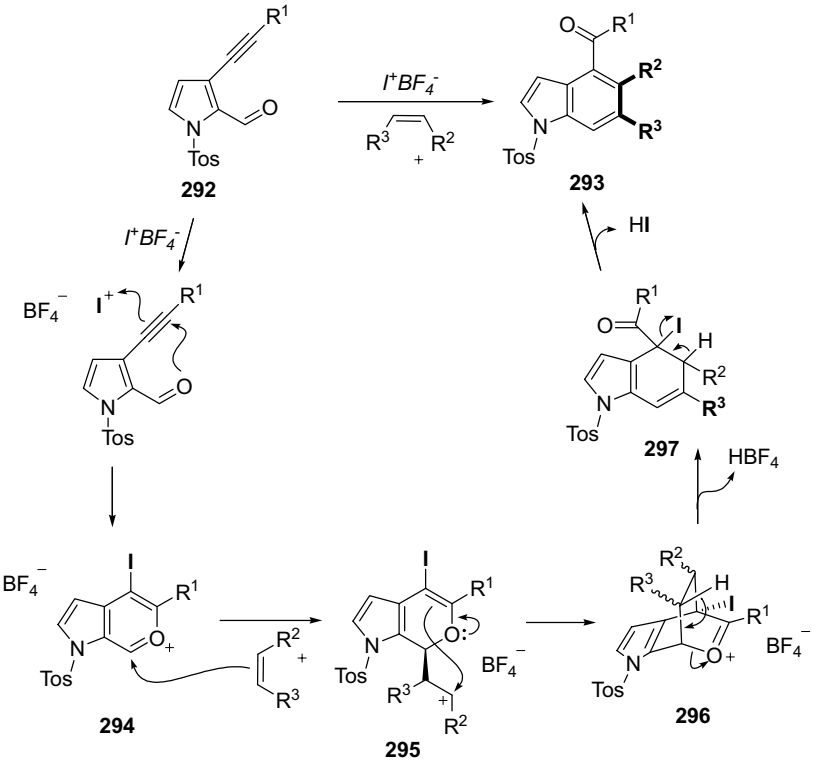
5.5
Reactivity of Indole

5.5.1
Reactions with Electrophiles

The chemistry of indole is dominated by the strong electrophilic character of the π-electron excessive heterocycle. Electrophilic aromatic substitution takes place at C3, and is one of the most efficient methods for the introduction of substituents on



Scheme 5.126



Scheme 5.127

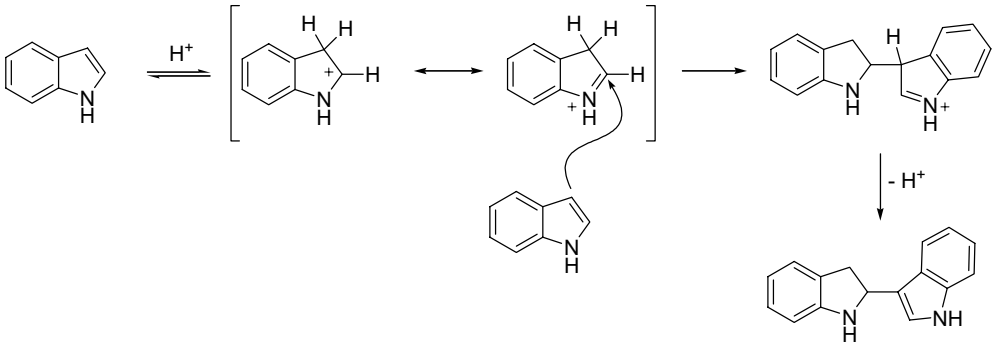
the indole ring at that position. The regioselectivity of the electrophilic aromatic substitution is easily explained by the different stability of the intermediate indolium cations generated. The positive charge at C2, generated by electrophilic attack at C3, can be delocalized between C2 and the N atom without compromising the aromaticity of the benzene ring. In contrast, electrophilic attack at C2 generates an indolium cation with the positive charge at C3, which cannot be delocalized without breaking the aromaticity of the benzene ring. Electrophilic aromatic substitution on the benzene ring occurs only on indoles strongly deactivated on the five-membered ring.

The method of choice to introduce electrophiles at the C2 position of indoles consists in a stepwise procedure, involving N-protection, lithiation at C2, reaction with the electrophile and N deprotection.

5.5.1.1 **Protonation**

Indole and substituted indoles are weak bases, with pK_a values ranging from -2.4 for protonated indole to −0.3 for the protonated electron-richer 2-methylindole [196]. As expected, C3 is the main site for protonation of indole, to produce the 3-*H*-indolium cation. Although the N-protonated indole (1-*H*-indolium cation) is not detected, even spectroscopically, it is believed that N-protonation occurs rapidly and equilibrates into the more stable C3 protonated species.

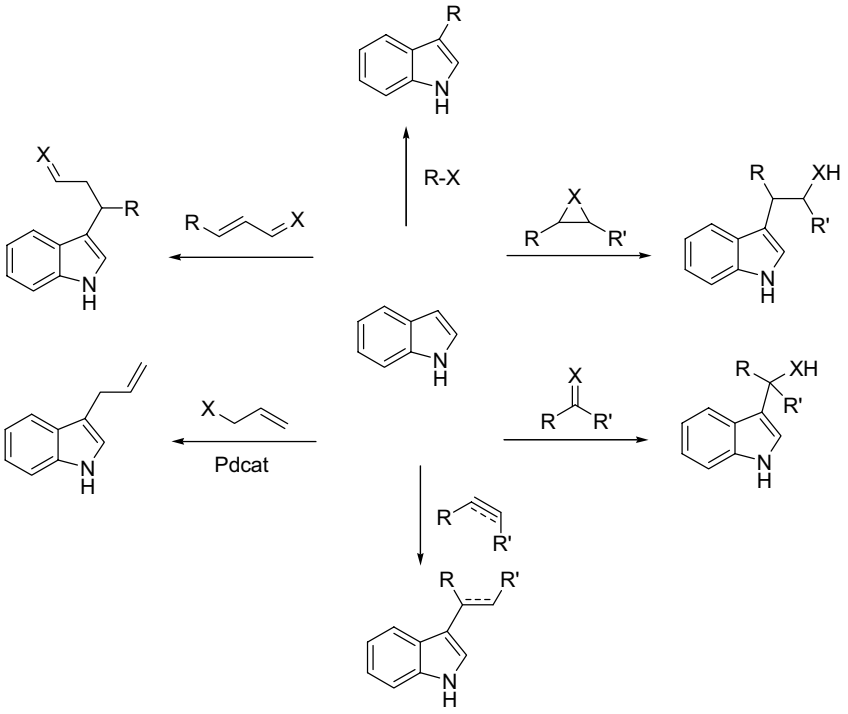
Under weak acidic media indole undergoes dimerization and oligomerization by attack of a molecule of non-protonated indole to the strong electrophilic C2 position of the 3-*H*-indolium cation (Scheme 5.128).



Scheme 5.128

5.5.1.2 **Friedel–Crafts Alkylations of Indole**

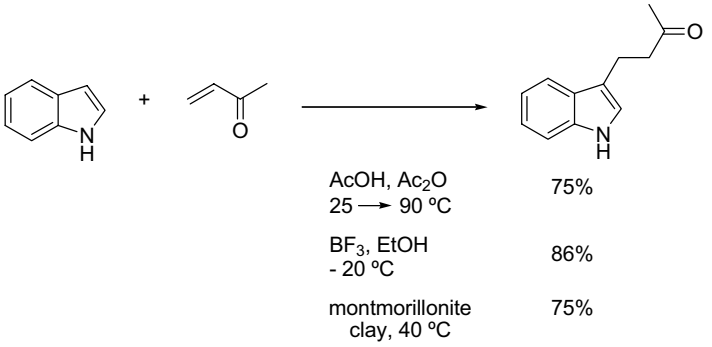
Indolyl compounds can be regioselectively alkylated at C3 through different Friedel–Crafts (FC) type of reactions (Scheme 5.129). Alkyl halides, epoxides and aziridines, carbonyl compounds and imines, α,β-unsaturated compounds, alkenes and alkynes, and allylic acetates or carbonates have all been employed as electrophiles. The amount of literature regarding this topic is enormous. These types of reaction usually proceed smoothly in the presence of a Lewis or protic acid as catalyst. Thus, the most recent advances have focused mainly on developing catalytic systems



Scheme 5.129

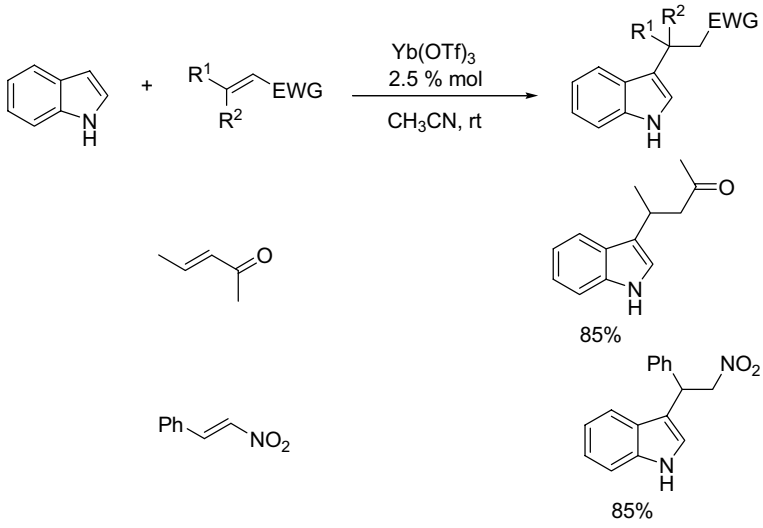
to perform the electrophilic aromatic substitution reaction in a milder, regio- and stereoselective manner [197].

5.5.1.2.1 **Michael Additions** The reactions of indoles with α,β-unsaturated compounds, such as α,β-unsaturated ketones, nitriles and nitroolefins, usually require activation of the electrophile by an acid, and proceed with either protic [198] or Lewis acids [199] and clays [200] to provide the corresponding 3-substituted indoles (Scheme 5.130).



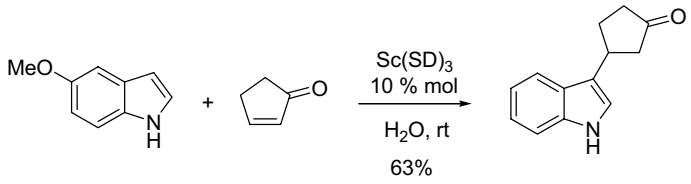
Scheme 5.130

These transformations have attracted much attention in recent years, and several different new Lewis acids have been developed, including bismuth(III) salts [201], cerium salts [202], Pd salts [203] and iodine [204]. For instance, the use of lanthanide-based Lewis acids allows for the alkylation of indoles at the 3-position with various Michael acceptors and under mild conditions (Scheme 5.131) [205].



Scheme 5.131

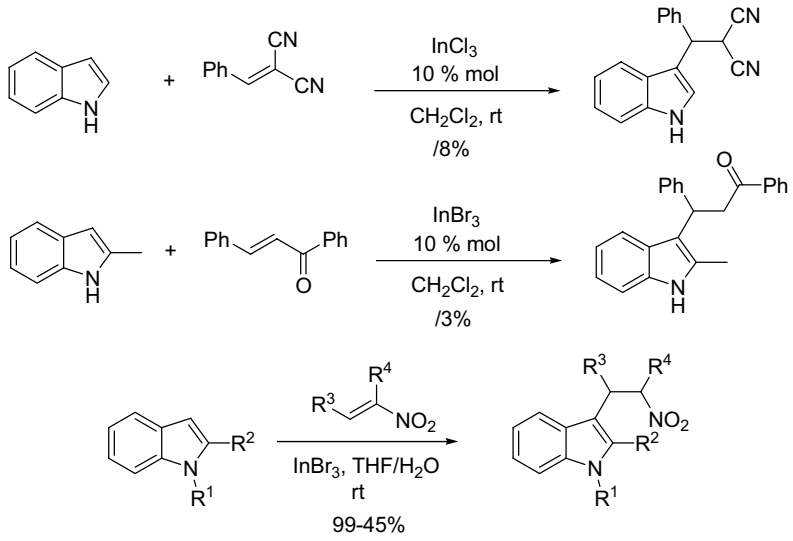
Michael additions have been carried out in water at room temperature using a scandium salt of an anionic surfactant – $Sc(DS)_3$ (scandium dodecyl sulfate) (Scheme 5.132) [206].



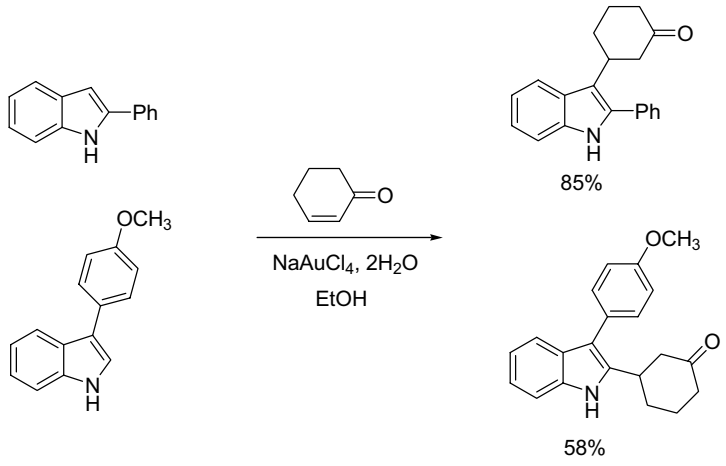
Scheme 5.132

Indium salts are amongst the most general and effective Lewis acids to promote the Michael addition, which can be performed with relatively hindered enones and 2-substituted indoles [207, 208]. The same catalyst promotes the reaction with nitroalkenes, under aqueous conditions, with excellent yields in most instances (Scheme 5.133) [209].

Gold(III) salts are also excellent catalysts for this reaction [210]. Interestingly, when the Michael addition is carried out with 3-substituted indoles, substitution occurs at C2 although with relatively lower yields (Scheme 5.134).



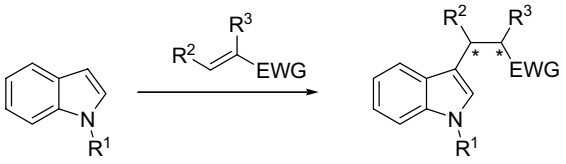
Scheme 5.133



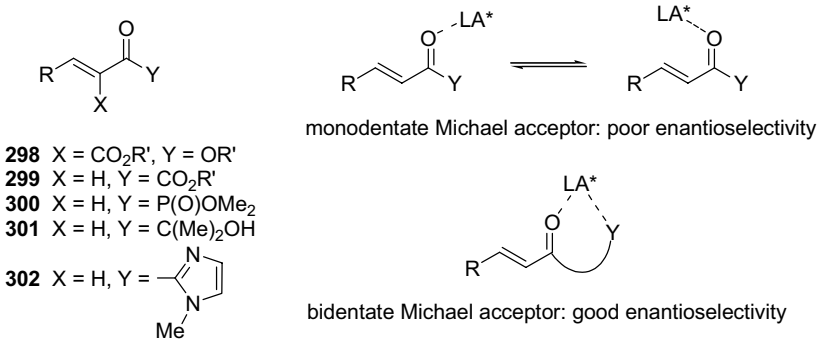
Scheme 5.134

In the reaction of indoles with β-substituted-α,β-unsaturated compounds one or two new stereogenic centers can be created. Control of the enantioselectivity of such processes has aroused much interest in recent years (Scheme 5.135).

Few examples have appeared of the catalytic asymmetric Michael reaction of indoles. To achieve good enantioselectivities the use of bidentate chelating Michael acceptors is required, to keep fixed the chiral environment provided by the ligand (Scheme 5.136). Good to excellent enantioselectivities have been achieved in reactions of alkylidene malonates **298** [211], β,γ-unsaturated α-ketoesters **299** [212], acyl



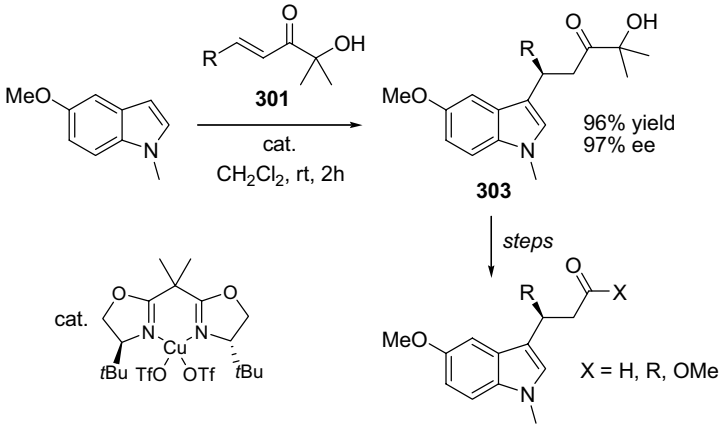
Scheme 5.135



Scheme 5.136

phosphonates **300** [213], α′-hydroxyenones **301** [214] and α,β-unsaturated-2-acylimidazoles **302** [215, 216], using appropriate chelating C_2 symmetric chiral ligands combined with Cu or lanthanide Lewis acids.

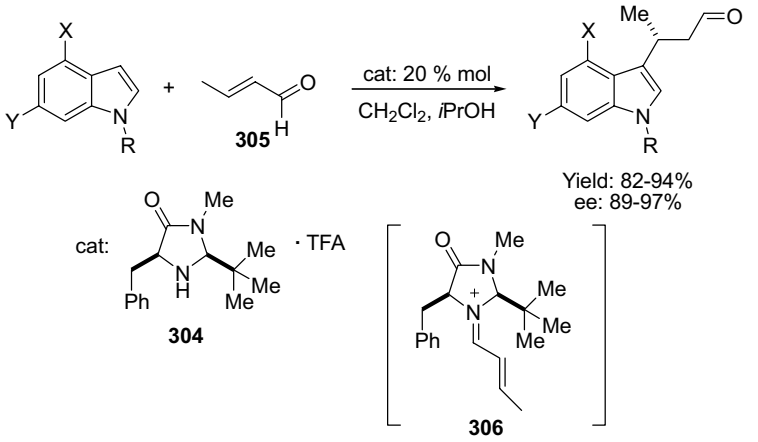
Scheme 5.137 shows the asymmetric Friedel–Crafts alkylation of indoles with α′-hydroxyenone **301**, yielding 3-substituted indole **303** with very high ee.



Scheme 5.137

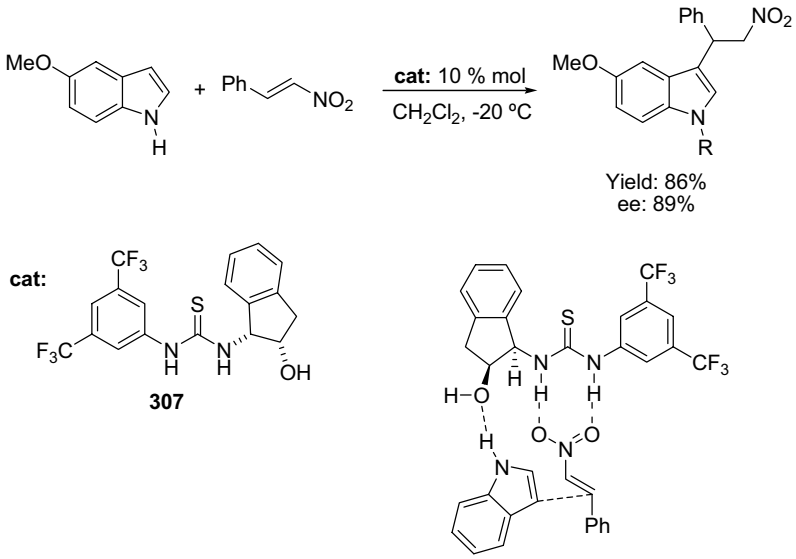
In a totally different and extremely elegant approach, the asymmetric Michael addition of indoles to α,β-unsaturated aldehydes has been achieved using a chiral imidazolidinone (**304**) as an asymmetric organocatalyst [217]. The imidazolidinone

plays a double catalytic role: to activate the aldehyde **305** by the formation of the highly reactive iminium species **306**, and to create a chiral environment that differentiates both enantiotopic faces of the Michael acceptor (Scheme 5.138).



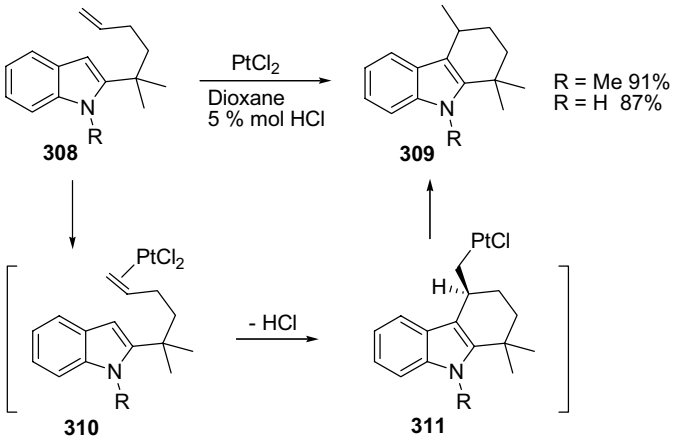
Scheme 5.138

Thiourea-based organocatalyst **307** promotes the asymmetric Friedel–Crafts alkylation of indoles with nitroalkenes with high yields and enantiomeric excesses. The stereochemical course of the reaction is controlled by the asymmetric platform provided by the chiral thiourea organocatalyst, which forms hydrogen bonds simultaneously with both reactants (Scheme 5.139) [218].



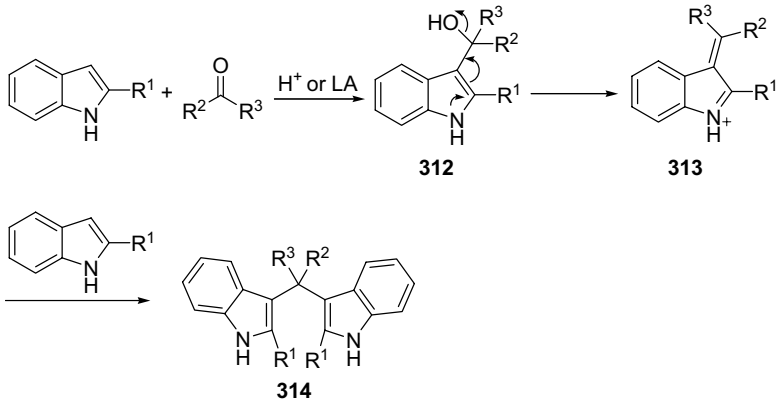
Scheme 5.139

5.5.1.2.2 **Reactions with Unactivated Olefins** The intramolecular cyclization of alkenylindoles **308** can be promoted by $PtCl_2$ to give tetrahydrocarbazole derivatives **309** [219]. The cyclization proceeds through nucleophilic attack of the indole on the Pt(II) complexed olefin in intermediate **310**, followed by protonolysis of the C–Pt bond in **311** (Scheme 5.140). The same authors have recently reported an extension of this methodology to the use of Pd(II) and Cu(II) catalysts [220].



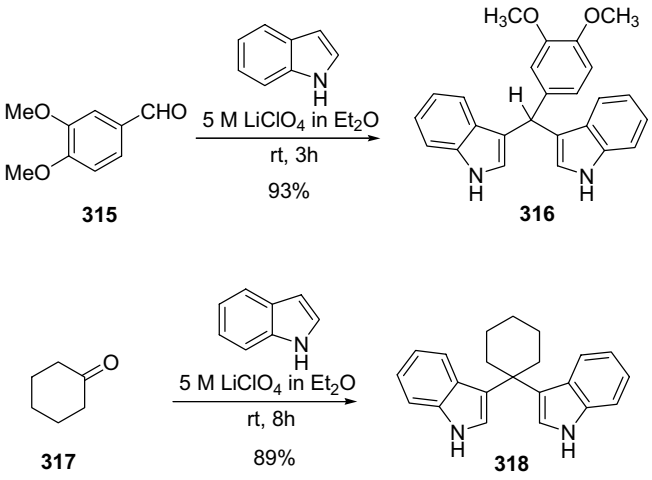
Scheme 5.140

5.5.1.2.3 **Reactions with Carbonyl Compounds** Friedel–Crafts alkylation of indoles with aldehydes and ketones takes place under Brønsted [221] or Lewis acid catalysis. The initially formed indole-3-yl-carbinols **312** are usually not isolated and evolve to produce the azafulvenium salts **313**. Finally, addition of a second molecule of indole to the azafulvenium salt gives rise to bis(indoylmethanes) **314** (Scheme 5.141).



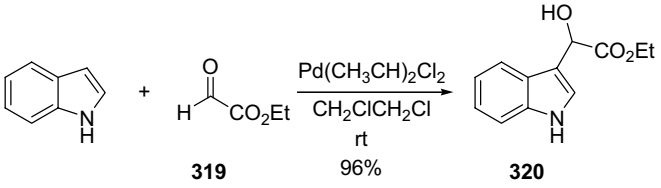
Scheme 5.141

Several different types of protic and Lewis acid catalysts have been employed for this transformation. For instance, reaction of indole with aldehydes or ketones such as **315** and **317**, in the presence of $LiClO_4$, affords the bis(indoylmethanes) **316** and **318**, respectively, in excellent yields (Scheme 5.142) [222].



Scheme 5.142

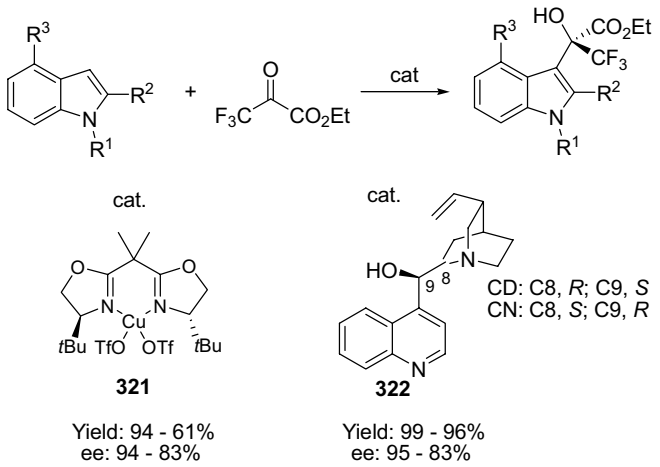
When the reaction is carried out with 2-oxoesters such as glyoxalate **319**, the indoylcarbinol **320** does not undergo elimination and can be isolated (Scheme 5.143) [223].



Scheme 5.143

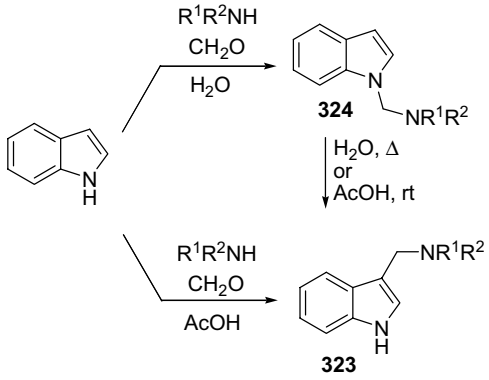
The enantioselective version of this reaction has been successfully carried out both with copper-based chiral Lewis acids **321** [224] and with *Cinchona* alkaloid organic catalysts **322** (Scheme 5.144) [225]. The organocatalyzed reaction, although not well understood yet, is remarkable, as the appropriate choice of alkaloid (chinchonidine, CD or Chinchonine, CN) provides either enantiomer in quantitative yield and with very high ee.

5.5.1.2.4 **Reactions with Imines and Imminium Ions: Mannich Reaction** Under typical Mannich conditions indole undergoes alkylation at C3. This reaction leads to the synthesis of gramines **323**, which are important intermediates for the



Scheme 5.144

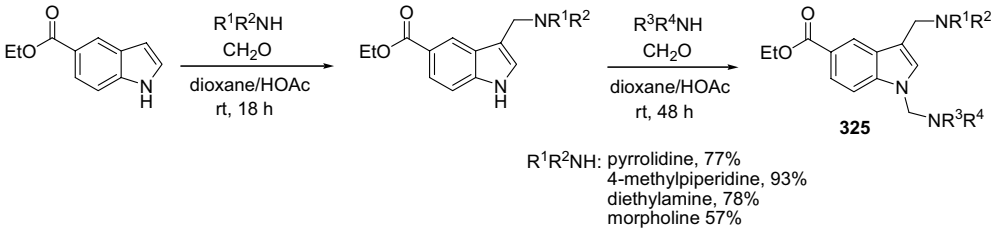
preparation of substituted indoles (Section 5.6.1). When the reactions are conducted in water at low temperatures, the kinetically controlled N-alkylation product **324** is obtained [226]. The resulting N-aminal indoles are relatively stable but convert into the thermodynamically more stable C3-substituted aminomethyl indoles upon heating at neutral pH or acid treatment at room temperature (Scheme 5.145).



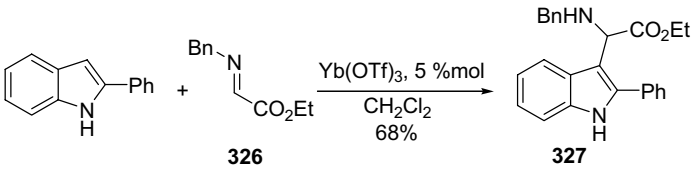
Scheme 5.145

Gramines can undergo a second Mannich reaction, yielding 1,3-disubstituted indoles **325**. This reaction has been applied to the parallel synthesis of an indole-based library (Scheme 5.146) [227].

Indole reacts with imines under acidic conditions to give substituted gramines. For instance the reaction of glyoxylimine **326** with indoles employing $Yb(OTf)_3$ as Lewis acid leads to gramine derivatives **327** (Scheme 5.147) [228, 229].

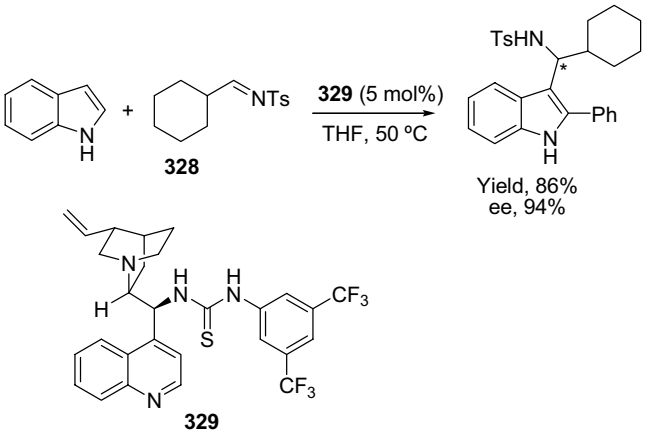


Scheme 5.146



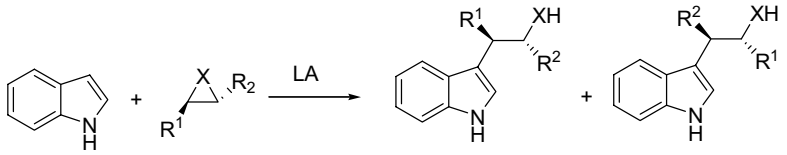
Scheme 5.147

Asymmetric versions of this reaction have been carried out employing Cu-based chiral catalysts [230] and also organic catalysts. Scheme 5.148 presents the Friedel–Crafts alkylation of indoles with *N*-tosylimines, such as **328**, promoted by the quinine-based organic catalyst **329** [231].



Scheme 5.148

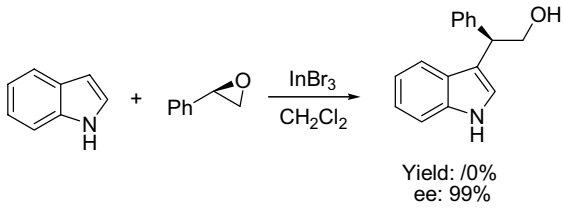
5.5.1.2.5 **Epoxide and Aziridine Ring Opening** Epoxides and aziridines are versatile alkylating agents for indole. The ring opening of these strained heterocycles by indole proceeds with Lewis acid, bases and solid acids, giving rise to triptophols and tryptamine derivatives respectively (Scheme 5.149). Moreover, the ready availability of enantioenriched cis and trans epoxides makes this approach a very valuable entry



Scheme 5.149

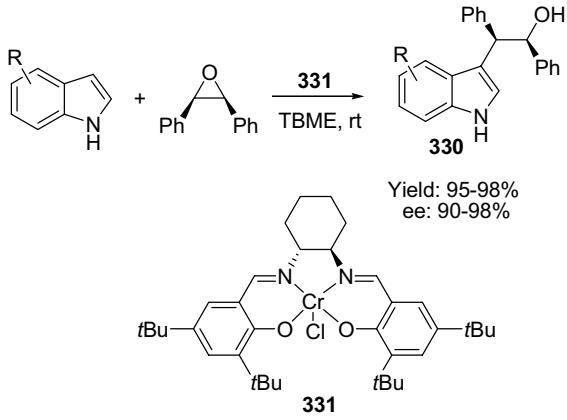
into enantiomerically pure indoles. The regiochemistry and stereochemistry of the ring opening are the main issues that have to be addressed during the reaction.

The alkylation of indole with enantiomerically pure styrene oxide is catalyzed by most of the common Lewis acids, with $InBr_3$ being the most efficient in terms of regioselectivity, enantioselectivity and yield (Scheme 5.150) [232, 233]. Other catalysts such as $Sc(OTf)_3$ and $SnCl_4$ [234] also promote the ring opening without racemization.



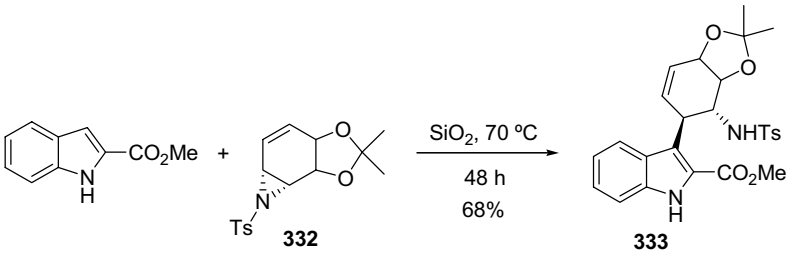
Scheme 5.150

Enantioenriched chiral triptophols **330** can also be prepared by kinetic resolution of racemic epoxides, or by desymmetrization of *meso* epoxides, employing Cr(Salen) Cl complex **331** as chiral catalyst (Scheme 5.151) [235].



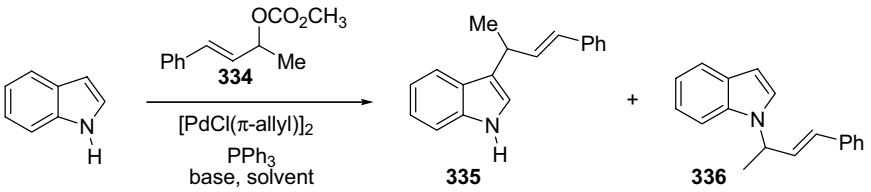
Scheme 5.151

The ring opening of aziridines with indoles provides tryptamine derivatives. Lewis acids based on Zn [236], Sc, Yb, and indium [237], and SiO_2 promote efficiently the FC reaction. Scheme 5.152 shows the alkylation of methyl indole-2-carboxylate with chiral aziridine **332** to produce the enantiomerically pure substituted indole **333**. The alkylation occurs cleanly simply by adsorbing both reagents in SiO_2 and heating the mixture at 70 °C [238].



Scheme 5.152

5.5.1.2.6 **Indole as Nucleophile in Palladium-Catalyzed Allylic Alkylations** Indoles are also competent nucleophiles for Pd-catalyzed allylic substitutions (Tsuji–Trost reaction) [239]. The reaction between allyl carbonate **334** and indole leads regioselectively to the C3-allylated indole **335** or the *N*-allylated indole **336**, depending on the reaction conditions applied (Scheme 5.153) [240].

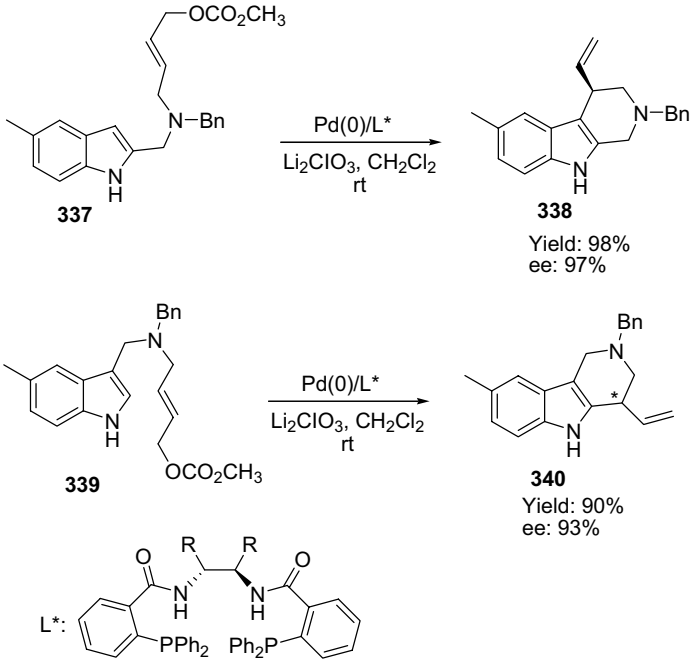


Scheme 5.153

The intramolecular variant of this reaction provides a new entry into polycyclic fused indoles. Remarkably, use of the appropriate chiral ligand allows for the asymmetric allylic alkylation (AAA) reaction [241] to take place with very high ee, giving rise to tetrahydro-β-carbolines **338** (Scheme 5.154) [242]. Moreover, when the pedant group is attached at C3, such as in **339**, the allylic alkylation takes place at C2, also with very high regio- and enantioselectivity, to produce tetrahydro-γ-carbolines **340**.

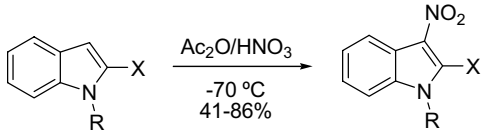
5.5.1.3 **Nitration**

Indoles are highly sensitive to acids, and for this reason the nitration of the indole ring requires carefully designed experimental conditions. Although C3 is the



Scheme 5.154

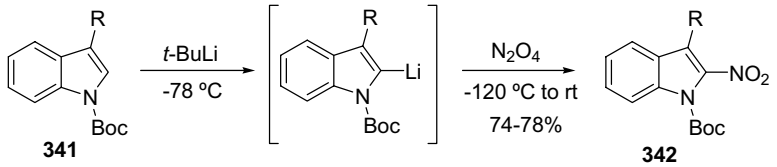
preferred position for electrophilic attack on indole, nitration under strong acid conditions proceeds through the 3-*H*-indolium cation, and nitration occurs mainly at C5, owing to the directing influence of the iminium substituent. Indole itself can be nitrated at C3 with moderate yield with benzoyl nitrate [243], and 2-arylindoles can be successfully nitrated at C3 by treatment with 2-cyano-2-propyl nitrate under phase transfer catalysis conditions [244]. More interestingly, N-protected indoles can be successfully nitrated at C3 by treatment with *in situ* generated acetyl nitrate at very low temperature (Scheme 5.155) [245].



R = Me, Bn, CO_2R, SO_2Ph
X = H, Me

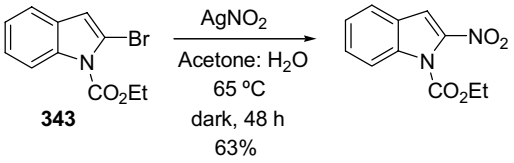
Scheme 5.155

In contrast, 2-nitroindoles **342** can be synthesized by a lithiation-nitration protocol on *N*-protected indoles **341** at very low temperature (Scheme 5.156) [246], and by treatment of N-protected-2-bromoindoles **343** with silver nitrite (Scheme 5.157) [247].



R = H, Me

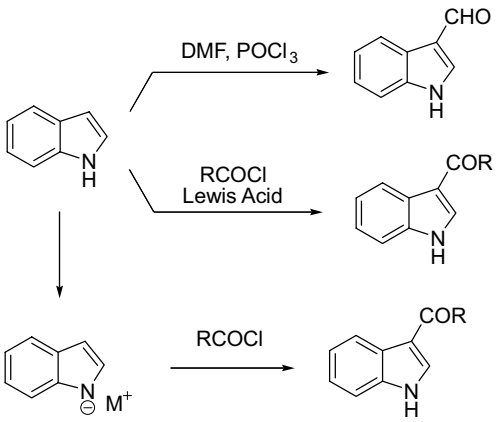
Scheme 5.156



Scheme 5.157

5.5.1.4 **Acylation**

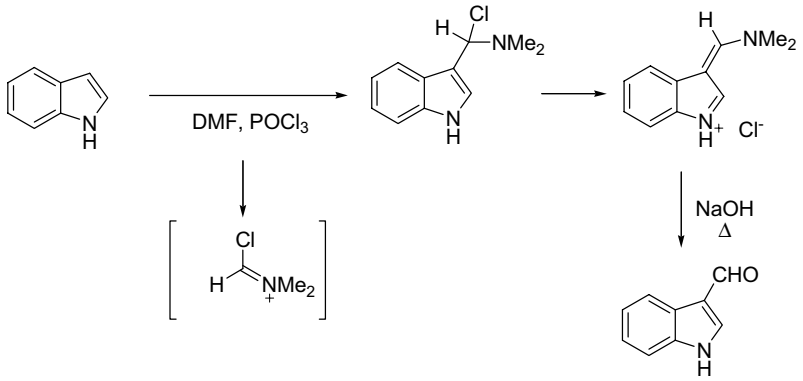
Indoles can be acylated at C3 by the Vilsmeier–Haack reaction [248], by Friedel–Crafts acylations [249] and also by reactions of indole Grignard reagents [250] or indole zinc chloride salts with acid chlorides (Scheme 5.158) [251].



Scheme 5.158

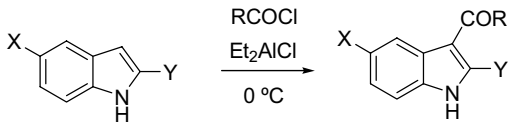
The Vilsmeier–Haack reaction is the classical method for the preparation of 3-formylindole and other 3-acylindoles, starting from tertiary amides. This reaction provides good yields for the acylation of indoles but is limited to formamide and alkylcarboxamides (Scheme 5.159).

Friedel–Crafts acylation is a very convenient process for electron-withdrawing-substituted indoles and for N-protected indoles. However, the reaction of N−H indoles requires a fine tuning of the catalyst and the reaction conditions to avoid



Scheme 5.159

N-acylation and polymerization reactions [252]. The use of an excess of dialkylaluminium chlorides as Lewis acids represents a very general method for the Friedel–Crafts acylation of indoles [253]. The excess dialkylaluminum reagent is required to quench the HCl liberated in the acylation process, thereby avoiding side reactions, such as dimerization and polymerization, that might be originated by the presence of the acid (Scheme 5.160).



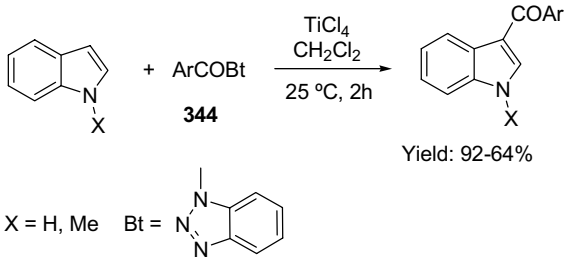
X = H; Y = Me; R = Me	89%
X = H; Y = Me; R = CH=CH-CH_3	80%
X = MeO; Y = H; R = Me	89%
X = MeO; Y = H; R = CH=CH-CH_3	71%
X = MeO_2C-; Y = H; R = Me	91%

Scheme 5.160

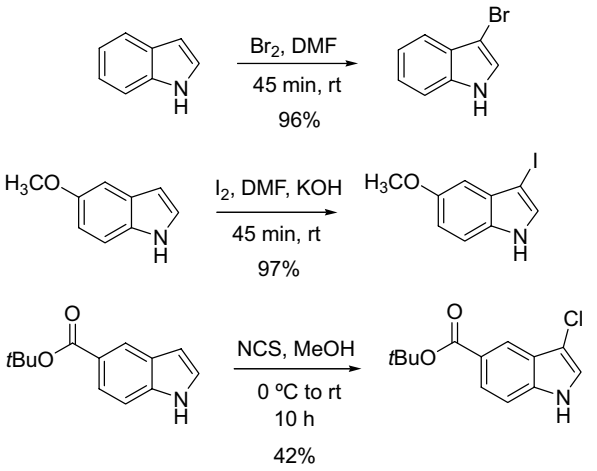
The use of *N*-acylbenzotriazoles **344** represents an alternative to acid chlorides, eliminating the complications associated with the release of HCl [254]. This procedure permits the acylation of both *N*-H and *N*-alkylindoles (Scheme 5.161).

5.5.1.5 **Halogenation**

The indole ring can be easily halogenated at C3 by employing bromine and iodine in DMF (the presence of potassium hydroxide is required for the iodination reaction), providing nearly quantitative yields of the corresponding 3-haloindoles [255], while 3-chloroindoles are best prepared with *N*-chlorosuccinimide (NCS) (Scheme 5.162) [256, 257]. Many other reagents have been described to promote these transformations [258, 259].



Scheme 5.161



Scheme 5.162

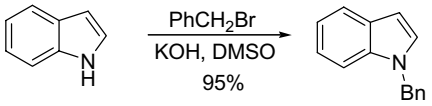
Halogens are best introduced at C2 by the metallation–halogenation sequence discussed in Section 5.5.2.2.

5.5.2 Reactions with Bases

5.5.2.1 *N*-Metallation of Indoles

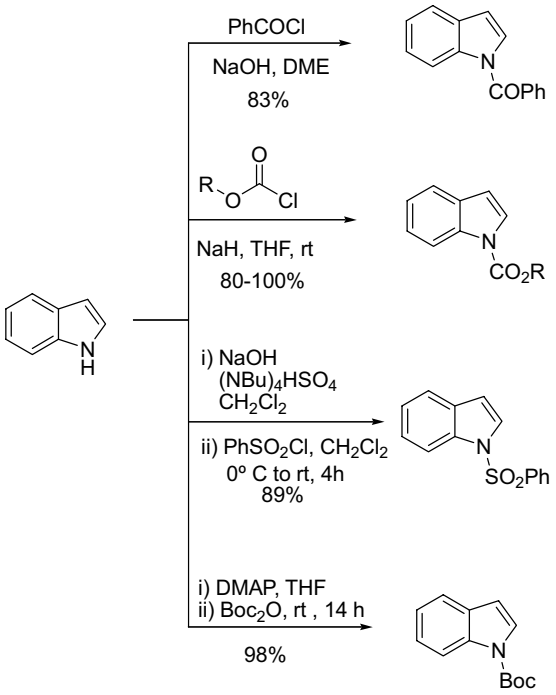
Indole is a weak acid ($pK_a = 16.7$ and 20.9 in water [260] and DMSO [261], respectively) and therefore undergoes deprotonation by strong bases to provide a reactive anion. Most of the reactions involving substitution at nitrogen – alkylation, acylation, and sulfonation – are carried out through the indolyl anion.

The usual methods for the N-alkylation of indole involve the use of alkali metal hydroxides [262], alkali metal hydrides [263] or $NaNH_2$ in polar aprotic solvents (Scheme 5.163). Alternatives include the use of potassium hydroxide in acetone under phase transfer catalysis conditions [264], caesium carbonate in either DMPU [265] or in the presence of a crown ether [266].



Scheme 5.163

Both N-acylation and N-sulfonation of indoles are synthetically relevant transformations, not only for the interest in *N*-acyl and *N*-sulfonyl indoles themselves, but also because the protection of the indole N−H in a synthetic sequence almost always involves an acylation or sulfonation step [267]. The use of acid chlorides and anhydrides in the presence bases make up the most common reaction conditions. In particular, the Boc group has been introduced using di-*tert*-butyl dicarbonate, phenyl-*tert*-butyl carbonate and $BocN_3$ [268]. Scheme 5.164 depicts some representative reactions for the N−H acylation of indole with different acylating agents [269–271].

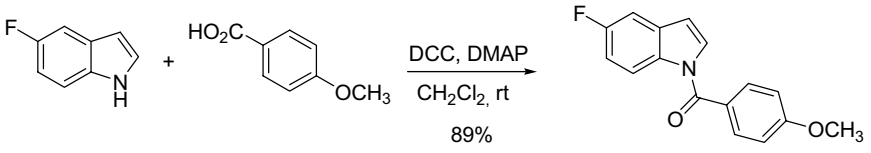


Scheme 5.164

Direct acylation of indoles with aromatic carboxylic acids can be achieved using DCC as coupling agent (Scheme 5.165) [272].

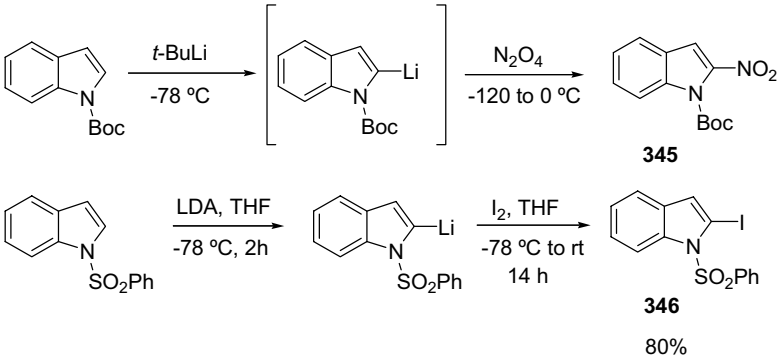
5.5.2.2 C-Metallation of Indoles

N-Substituted indoles undergo direct lithiation at C2, and in certain cases at C3 upon treatment with organolithium reagents [273]. In fact, lithiation followed by reaction with an electrophile is the most common strategy to introduce substituents at C2.

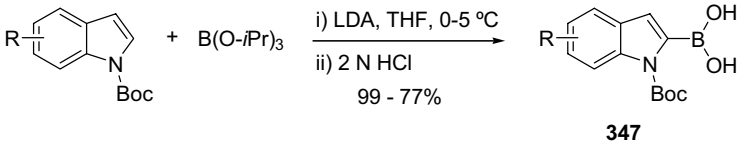


Scheme 5.165

Both *N*-acyl and *N*-sulfonyl indoles can be selectively lithiated at C2 by treatment with organolithium reagents. The presence of the coordinating group at N1 assists the lithiation at C2 and governs the regioselectivity of the process. Recent applications of this strategy are found in Gribble's syntheses of 2-nitroindole **345** [274] and 2-iodoindole **346** [275] from, respectively, *N*-Boc-indole and *N*-phenylsulfonylindole (Scheme 5.166) and in the preparation of the important synthetic intermediates 2-indolylborates **347** (Scheme 5.167) [276].



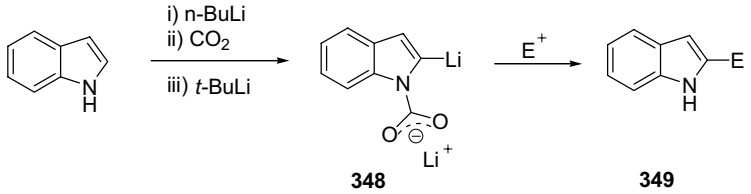
Scheme 5.166



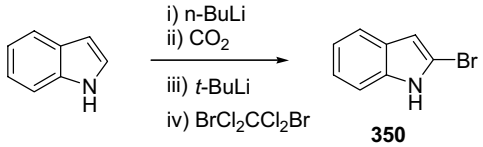
Scheme 5.167

Substitution at C2 on NH indoles can be achieved by employing Katritzkýs elegant indole C2 lithiation protocol [277]. In this sequential process the dilithiated intermediate **348** is formed, which provides the C2 substituted indole **349** after reaction with an electrophile and aqueous workup (Scheme 5.168). A typical example of the application of this methodology is Bergman's synthesis of 2-bromoindole **350** (Scheme 5.169) [278].

The nature of the N-substituent can direct the position of the lithiation in *N*-alkyl indoles. While indoles substituted with non-bulky alkyl groups are lithiated at C2, the

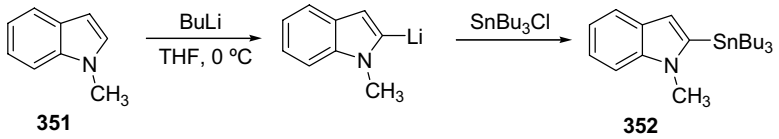


Scheme 5.168



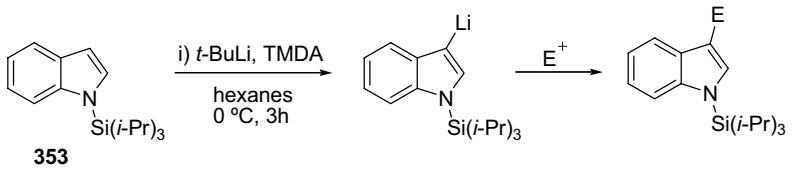
Scheme 5.169

presence of a bulky non-coordinating group drives the lithiation at C3. For instance, *N*-methyl-2-stannylindole **352** is selectively synthesized from *N*-methylindole (**351**) by deprotonation at C2 with BuLi, followed by reaction with tributylstannyl chloride (Scheme 5.170).



Scheme 5.170

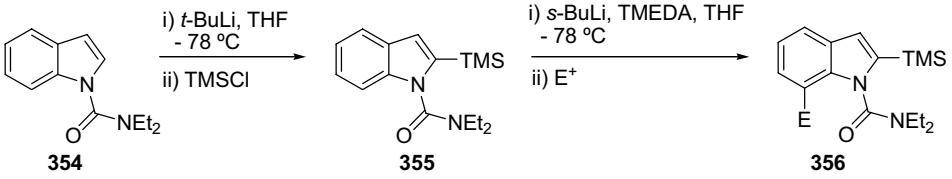
In contrast, indole **353**, bearing the very bulky triisopropylsilyl N-substituent, is lithiated selectively at C3 upon treatment with *t*-BuLi (Scheme 5.171) [279].



Scheme 5.171

The directing effect of the N-protecting group has been also applied to effect regioselective ortho-metallation at the C7 position [280]. For this purpose, it is necessary to protect the C2 position with a removable group, such as TMS. Then, treatment of *N*-CONEt$_2$ protected indole **354** with *t*-BuLi/THF at −78 °C followed by quench with TMSCl gives rise to the indole silylated at C2 **355**. Treatment of **355** with *s*-BuLi/TMEDA/THF at −78 °C produces the regioselective metallation at C7, which

provides the corresponding C7 functionalized indole **356** upon reaction with an electrophile (Scheme 5.172). Interestingly, the whole process can be conducted in a *one pot* fashion.



Scheme 5.172

5.5.3
Transition Metal Catalyzed Reactions

The most reliable synthetic methods to create C−C and C−X bonds from C-sp^2 are currently transition metal catalyzed reactions. The well-developed Pd-catalyzed Heck and cross-coupling reactions are doubtless the most prominent methods, and have been applied successfully to the incorporation of new substituents in the indole ring. Moreover, alternative methodologies that make use of different transition metals are also noteworthy, and are discussed in this section.

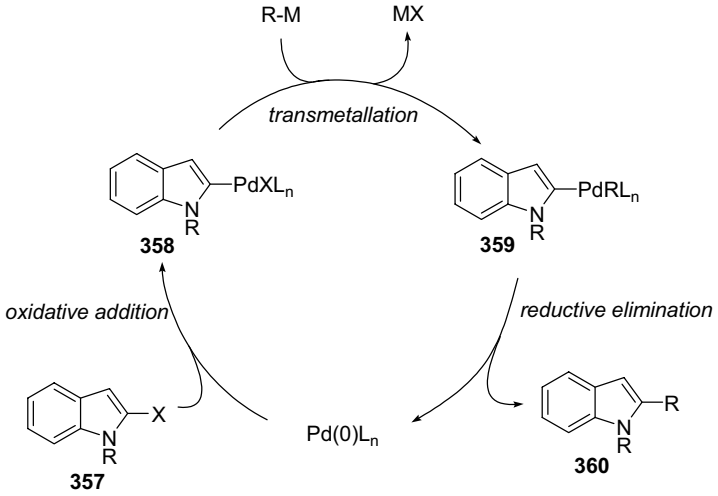
5.5.3.1 General Considerations on Palladium-Catalyzed Cross-Coupling Reactions

Indolyl halides or triflates behave as regular aryl halides in Pd-catalyzed cross-coupling reactions. Thus, 2- and 3-halo or triflate substituted indoles have been employed to synthesize numerous indole derivatives. The process starts with the oxidative addition of indolyl halide **357** to the Pd(0) catalyst to form indolyl-Pd(II) complex **358**. The nature of the coupling partner, alkene, alkyne, stannane, boronate, organozinc, amine, determines the subsequent steps of the cross-coupling process. In a prototypical cross-coupling reaction, transmetallation of the organometallic partner followed by reductive elimination produces the cross-coupling product **360** and releases the Pd(0) catalyst (Scheme 5.173).

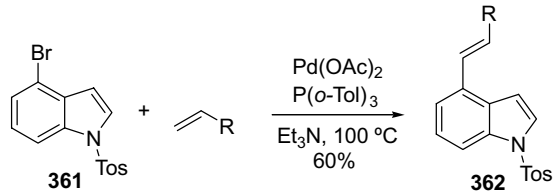
5.5.3.2 Reactions with Alkenes and Alkynes: Heck Reactions

The reaction of indolyl halides or pseudohalides with alkenes under standard Heck conditions gives rise to vinylindoles [281]. For instance, *N*-protected-4-bromoindole **361** can be transformed into 4-alkenylsubstituted indoles **362** under standard Heck conditions (Scheme 5.174) [282].

The higher reactivity of iodide than bromide towards oxidative addition to Pd, allows for the sequential substitution of 3-iodo-4-bromoindole **363** through two consecutive Heck reactions. In the first step substitution of the more reactive iodine occurs to yield **364**. A second Heck reaction with substitution of the bromine leads to **365** (Scheme 5.175). This strategy was employed by Hegedus in the synthesis of ergot alkaloids [283].



Scheme 5.173



R = CO_2Me (86%), $C(Me)_2OH$ (97%), Ph (74%)

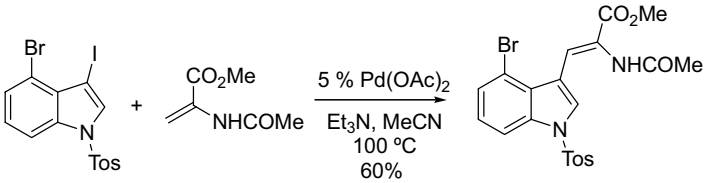
Scheme 5.174

In a similar manner to other Pd-catalyzed cross-couplings, the reaction is general regarding the position of the leaving halogen. For instance, 3-substituted 2-iodoindole **366** reacts with methyl acrylate to furnish 2-alkenylindole **367** (Scheme 5.176) [284].

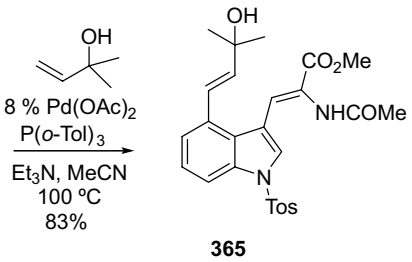
The intramolecular Heck reaction is particularly appealing, as it leads to polycyclic indole derivatives that might be difficult to synthesize through other strategies [285]. For instance, *N*-allylindoles **368** undergo cyclization to give 3*H*-pyrroloquinoline **369** under typical Heck reaction conditions (Scheme 5.177) [286], and carbolines **371** are easily prepared from 3-iodoindoles **370** (Scheme 5.178) [287].

5.5.3.3 **Sonogashira Reaction**

Indolyl halides or triflates react under typical Sonogashira [288] conditions with terminal alkynes to give rise to the corresponding alkynes (Scheme 5.179) [289]. The alkynylation can be employed to prepare 2-alkynylindoles **372**, 3-alkynylindoles **373**, and also to introduce the alkyne in the benzene ring [290] from the corresponding indolyl halides or triflates.

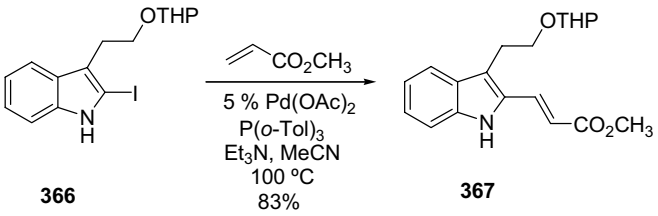


363 **364**



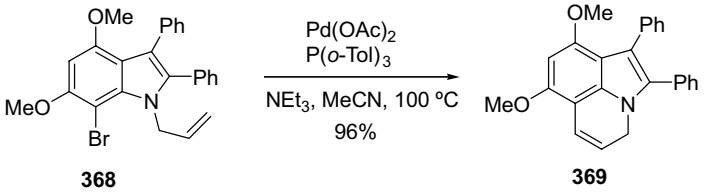
365

Scheme 5.175



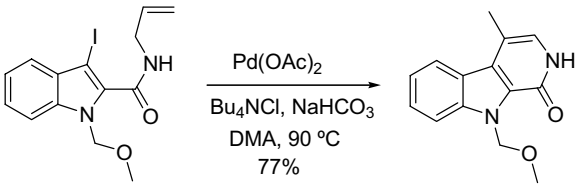
366 **367**

Scheme 5.176



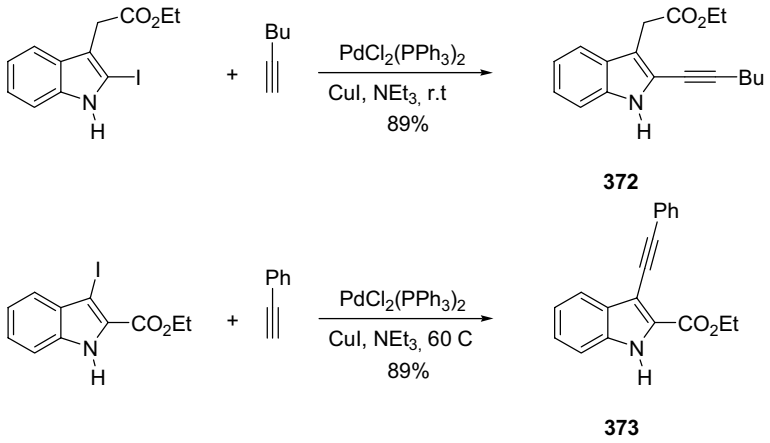
368 **369**

Scheme 5.177



370 **371**

Scheme 5.178

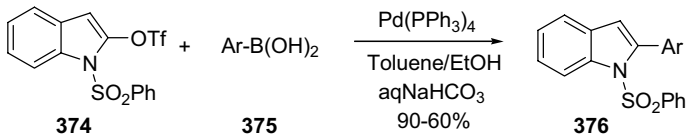


Scheme 5.179

5.5.3.4 **Cross-Coupling Reactions with Organometallic Reagents**

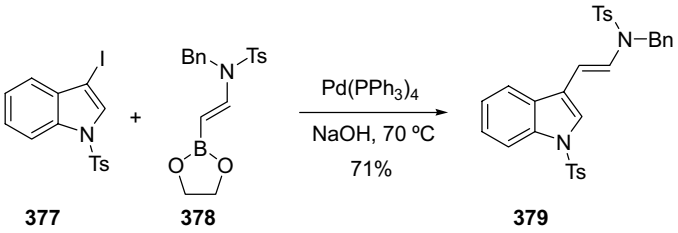
Typical Pd-catalyzed cross-couplings consist of the reaction of an organic halide with an organometallic reagent. The most popular methods involve the use of organotin (Stille reaction), organoboron (Suzuki–Miyaura reaction) [291] and organozinc (Negishi reaction) [292] compounds. Two different strategies are possible to conduct a cross-coupling reaction involving an indole derivative: (i) couple an indolyl halide or triflate with an organometallic reagent and (ii) react an indolylmetal derivative with an organic halide. Regardless of the strategy chosen, in most of the cases, cross-coupling reactions involving indolyl species can be performed efficiently under the typical conditions developed for cross-couplings with benzenoid systems.

5.5.3.4.1 **Suzuki–Miyaura Cross-Coupling** The Pd-catalyzed reaction of a boronic acid and an aryl or alkenyl halide or sulfonate is one of the most popular C−C bond-forming reactions involving aromatic species, and has been extensively applied to the functionalization of indoles on every position of the ring. Indolyl halides and triflates have been employed in the coupling reaction. For instance, the reactions of 2-indolyl triflates with aryl boronic acids afford the corresponding aryl substituted indoles in high yields (Scheme 5.180) [293].



Scheme 5.180

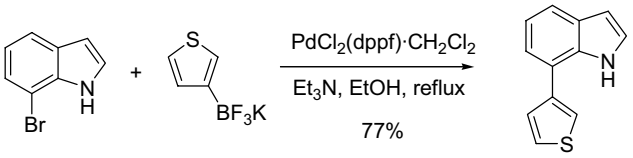
The Suzuki coupling has been also applied to the preparation of vinylindoles. One example is the reaction of vinylboronate **378** with 3-iodoindole **377**, which leads to 3-vinylindole **379** (Scheme 5.181) [294].



377 378 379

Scheme 5.181

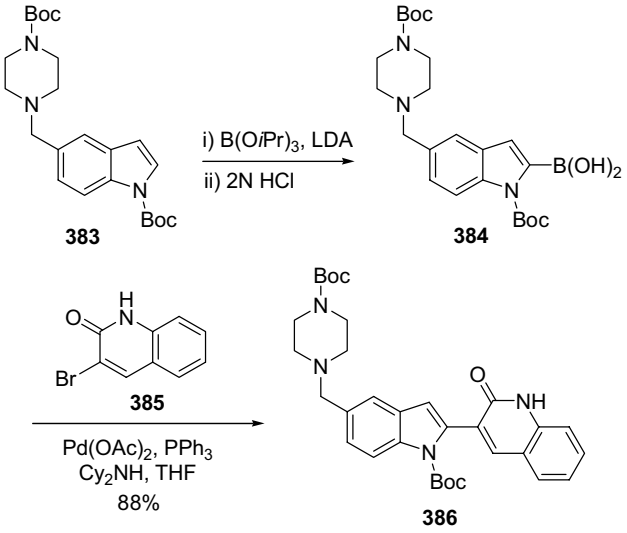
Thiophen-3-trifluoroborates **381** have been employed in a coupling reaction with 7-bromoindole **380**, giving rise to the corresponding thiophene-substituted indole **382** (Scheme 5.182) [295].



380 381 382

Scheme 5.182

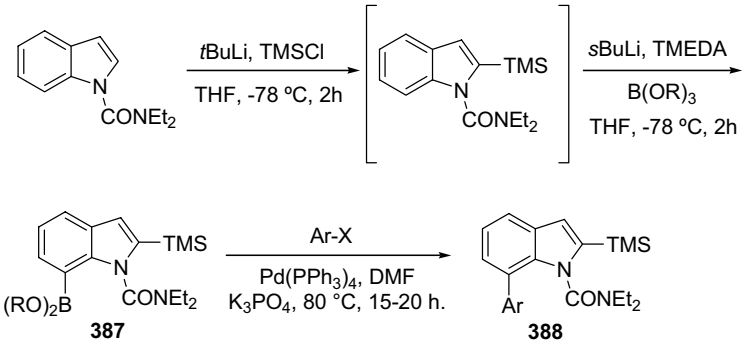
Indoylboronic acids are also appropriate coupling partners in cross-coupling reactions [296]. The sometimes difficult purification of indolylboronic acids recommends its utilization as crude products. An example of this methodology is represented in the synthesis of **386** (Scheme 5.183), a precursor of a tyrosine kinase



Scheme 5.183

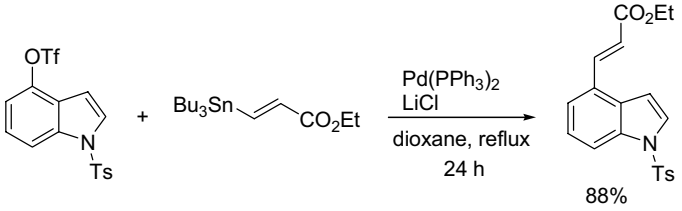
inhibitor. The indolylboronic acid **384** required is prepared by metallation of indole **383**, followed by reaction with triisopropylborate. The coupling reaction with the corresponding bromide **385** then affords **386** [297]. Remarkably, the sequence can be conducted on a multi-kilogram scale.

7-Arylsubstituted indoles can be synthesized from the corresponding boronates **387**, which can be prepared by the synthetic sequence discussed in Scheme 5.167. Subsequent Suzuki reaction leads to the 7-aryl substituted indoles **388** (Scheme 5.184) [298].



Scheme 5.184

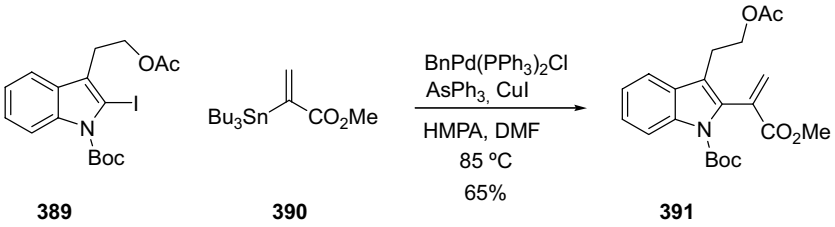
5.5.3.4.2 **Stille Cross-Coupling** The Pd-catalyzed coupling of organostannanes with halides or pseudohalides is generally known as the Stille reaction. This coupling reaction has been widely employed in the modification of indoles. Both indolyl triflates (Scheme 5.185) [299, 300] and halides have been employed in the coupling reaction.



Scheme 5.185

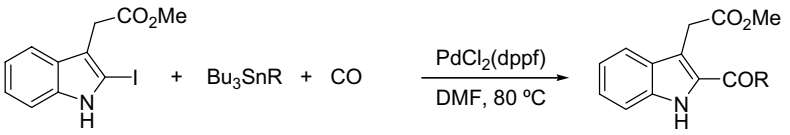
The Stille coupling has been employed in many syntheses of biologically active indole alkaloids [301]. In the example represented in Scheme 5.186, 2-vinylindole **391** (an intermediate in the synthesis of the natural alkaloid tabersonine) was prepared from 2-iodoindole **389** and vinylstannane **390** [302].

Interestingly, when the Stille cross coupling conditions are applied under a CO atmosphere, the corresponding α,β-unsaturated ketones are isolated (Scheme 5.187) [303].

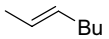


389 **390** **391**

Scheme 5.186



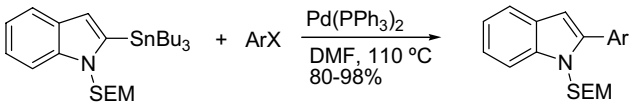
392

R =  78%

R = H 85%

Scheme 5.187

Indolylstannanes [304] have also been widely utilized for the functionalization of indoles, mostly at C2 [305] and C3 [306]. Scheme 5.188 presents the synthesis of 2-arylindoles by coupling of *N*-protected-2-indolylstannane **393** with aryl halides under typical Stille conditions. A variation of this reaction has also been adapted to a solid-phase synthesis [307].



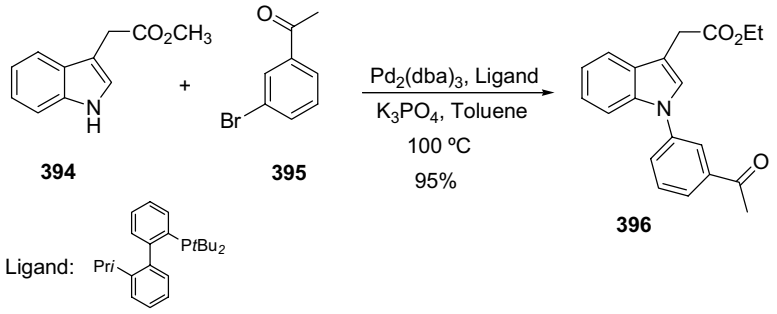
393

SEM: -$CH_2OCH_2CH_2TMS$

Scheme 5.188

5.5.3.5 C−N Bond-Forming Reactions

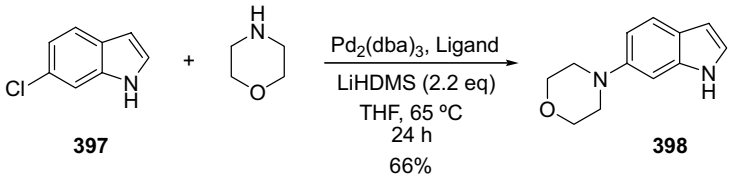
Application of the Buchwald–Hartwig arylation to N−H indoles allows for the preparation of *N*-arylindoles from N−H indoles and aryl halides [308–310]. The reaction is very general regarding the structure of both coupling partners, the indole and the aryl halide. Aryl bromides, chlorides, and triflates can be employed successfully upon selection of the proper combination of ligand and base. Scheme 5.189 gives an example of a coupling reaction between indole **394** and *m*-bromoacetophenone (**395**). The reaction proceeds in the presence of potentially sensitive functional groups to give arylated indole **396** in quantitative yield. In a similar procedure,



Scheme 5.189

treatment with vinyl halides allows for the preparation of the corresponding *N*-vinylindoles [311].

On the other hand, Buchwald–Hartwig amination can be applied to incorporate an amino group into the indole structure. Thus, coupling of haloindoles with amines provides the corresponding aminoindoles. The coupling reaction can even be conducted with NH-containing indoles such as **397** to give amino substituted indole **398**, provided that an excess of base is employed (Scheme 5.190) [312].



Scheme 5.190

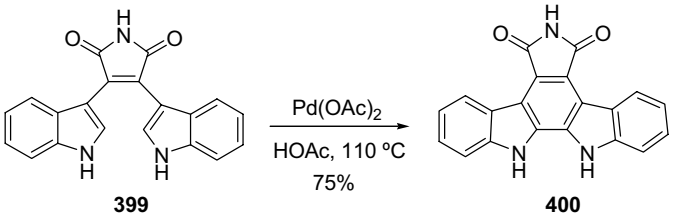
5.5.3.6 **Transition Metal Catalyzed C−H Activation**

Modification of the indole ring via substitution of a C−H bond by a C−C bond is a very desirable reaction, as it does not require the previous presence of a reactive functionalization such as C–halogen, C–triflate, or C–metal bond in the indole ring. Nevertheless, this challenging transformation has been comparatively much less studied than the cross-coupling reactions, and at the present suffers from some limitations, such as lack of selectivity and generality.

Many examples exist of intramolecular Pd(II)-catalyzed oxidative cyclizations of indoles with a proper pedant aryl or alkenyl group [313]. For instance, the oxidative cyclization of bisindolylmaleimides **399** gives rise to indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazoles **400** [314], a substructure that is present in a large number of natural products (Scheme 5.191).

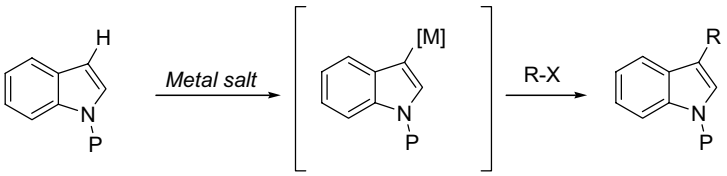
One approach for the direct substitution of the C−H bond is the reaction with metal salts that usually starts with the electrophilic metallation of the indole (Scheme 5.192).

An interesting recent example is the Pd-catalyzed oxidative annulation of alkenyl indoles **401** (Scheme 5.193), which gives rise to tricyclic derivatives **402** [315].

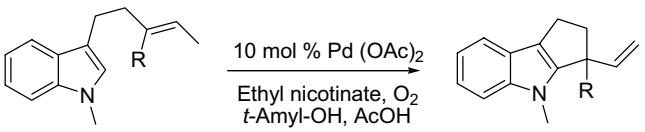


399 **400**

Scheme 5.191



Scheme 5.192

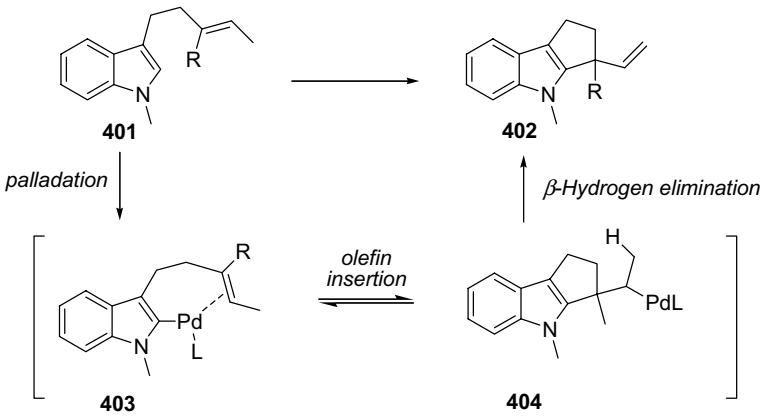


401 **402**

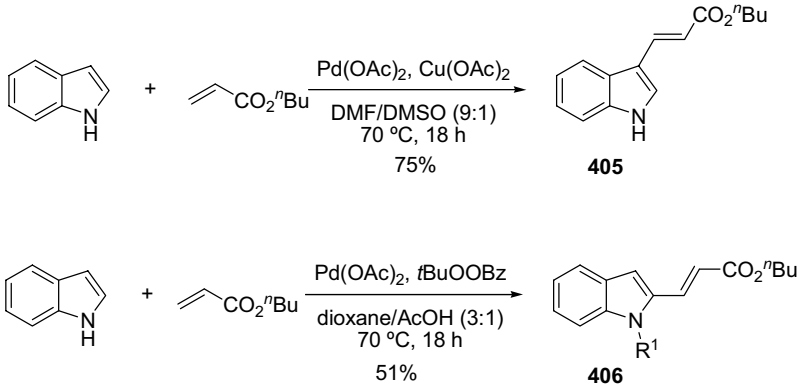
Scheme 5.193

The mechanism proposed for this annulation includes (i) electrophilic palladation of the indole to form indolyl palladium complex **403**; (ii) intramolecular olefin insertion to give palladated complex **404**; and (iii) β-hydrogen elimination, which gives rise to the annulated indole **402** and releases a Pd(0) species. To obtain a catalytic reaction, reoxidation of the Pd(0) to Pd(II) is necessary. In this example, a pyridine derivative (ethyl nicotinate) in an oxygen atmosphere is responsible for reoxidation of the Pd catalyst (Scheme 5.194).

Some examples of the intermolecular oxidative coupling of indoles with olefins and alkynes have been also described [316, 317]. The intermolecular oxidative Heck reaction of indoles with alkenes allows for the selective alkenylation at C2 or C3, depending on the solvent and reaction conditions chosen [318]. Thus, when the reaction is carried out using a mixture of DMF and DMSO as solvent, and $Cu(OAc)_2$ as oxidant, the expected C3 oxidative alkenylation is produced, giving rise to the C3-alkenylindole **405** (Scheme 5.195). However, if the reaction is performed under acidic conditions (dioxane : AcOH), employing *tert*-butyl benzoyl peroxide as oxidant, the



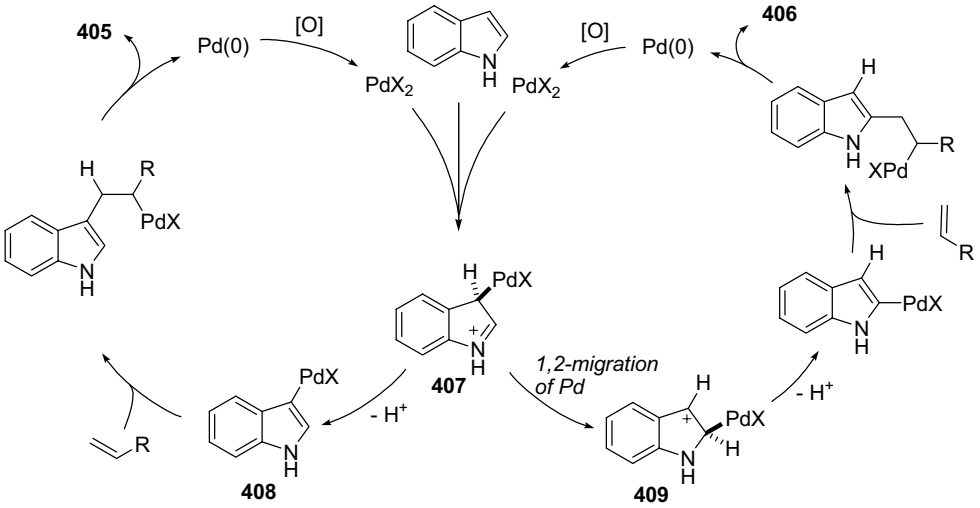
Scheme 5.194



Scheme 5.195

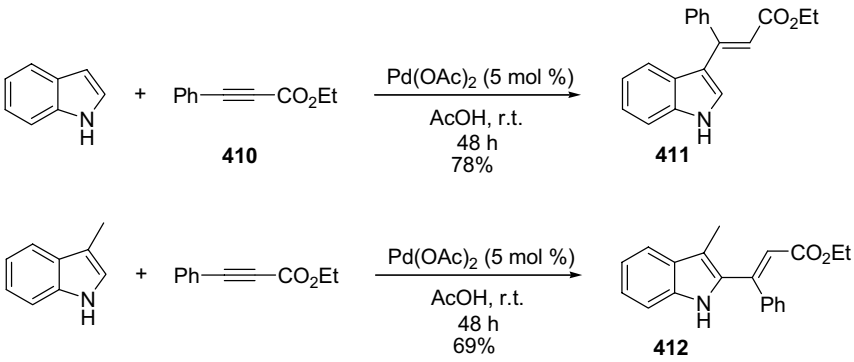
regioselectivity of the alkenylation is switched to the 2 position to give alkenylindole **406** as the major product.

An explanation of this switch in the regioselectivity can be found in the mechanisms proposed for each process as represented in Scheme 5.196. The reaction starts with the electrophilic palladation at the electron-richer C3 position, to provide cationic indole complex **407**. At this point, aromatization by loss of a proton leads to indolyl palladium complex **408** (left-hand cycle), which then follows the path of a typical Heck reaction. The catalytic cycle is completed by oxidation of the Pd(0) species liberated. When the reaction is carried out under acidic media, the deprotonation of complex **407** is disfavored (right-hand cycle). Instead, 1,2-Pd migration takes place to give the new cationic complex **409**, which then follows the reaction path of a Heck reaction to produce alkenylation at C2.



Scheme 5.196

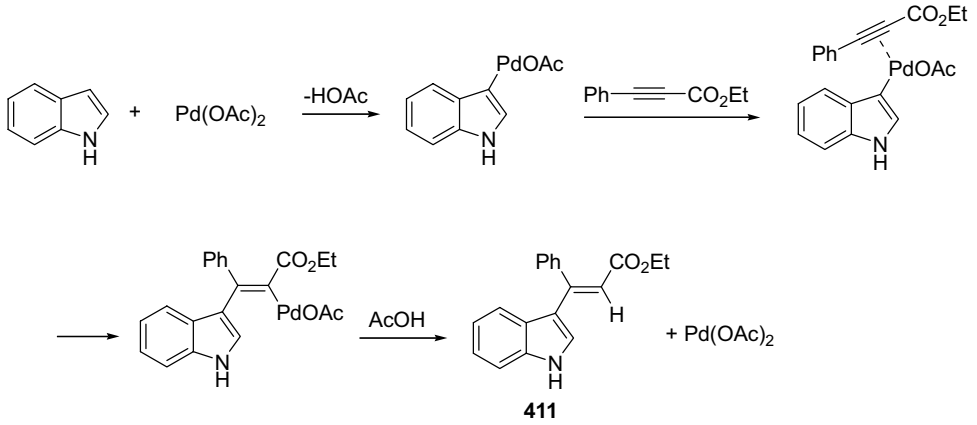
In a similar way, indoles add regioselectively to alkynoates **410** in the presence of $Pd(OAc)_2$ and acetic acid [319]. Indole itself gives rise to 3-alkenylindoles **411**, while 3-methylindole provides 2-alkenylindoles **412**, also with good yields (Scheme 5.197).



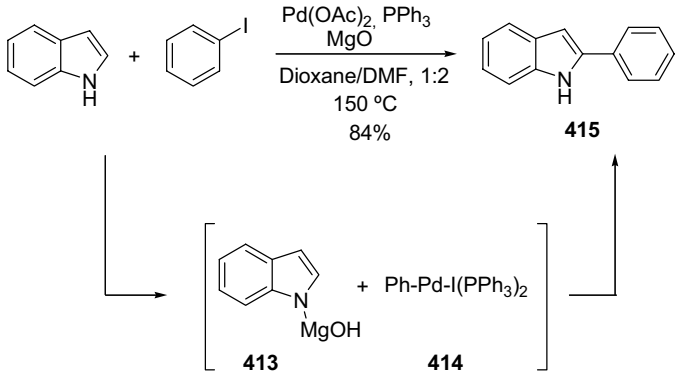
Scheme 5.197

The mechanism proposed for the reaction involves (i) electrophilic palladation of the indole to form indolyl palladium complex; (ii) complexation of the alkyne followed by regioselective carbopalladation of the triple bond to provide vinyl palladium complex; and (iii) protonolysis of the C−Pd bond by action of the AcOH, affording alkenylated indole **411** and liberating the Pd(II) species (Scheme 5.198) .

Direct Pd-catalyzed C−H substitution has also been accomplished by reaction of indolyl anions **413** with organopalladium complexes **414**, generated *in situ* from Pd(0) complexes and aryl halides (Scheme 5.199). Arylation of NH-indoles can be carried out selectively either at C2 [320, 321] or C3 [322], depending on the reaction



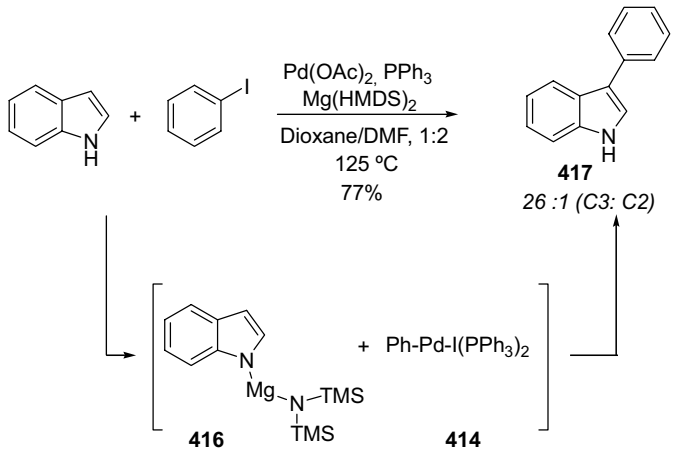
Scheme 5.198



Scheme 5.199

conditions (Scheme 5.200). Thus, reaction with MgO as base gives rise exclusively the C2 arylated product **415**, while the use of larger bases such as $Mg(HMDS)_2$ provides the C3 arylated indole **417** with very high regioselectivity.

A rationale for this reactivity trend has been found after detailed mechanistic investigations (Scheme 5.201). Electrophilic palladation of the indolylmagnesium salt with the arylpalladium complex **414** gives rise to the cationic indolinylarylpalladium complex **418**. Aromatization by deprotonation gives indolylaryl palladium complex **419**, and reductive elimination produces the C3 arylated indole **417**. In contrast, palladium migration on complex **418** leads to the C2 palladated indole **420**, which will evolve through 2-indolylaryl palladium complex to furnish the C2 arylated indole **415**. The driving force for the migration step has been related to stabilization of the carbon–palladium bond by the adjacent nitrogen atom on **420**. However, bulky ligands on the magnesium destabilize the C2 palladated indole **420** and, therefore, the migration does not occur and so the arylation takes place at C3 (Scheme 5.201).

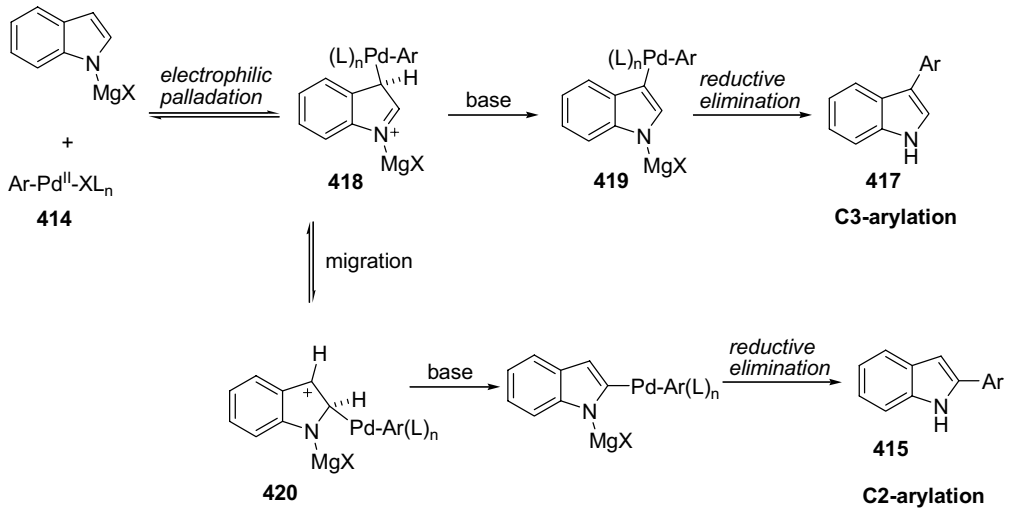


Scheme 5.200

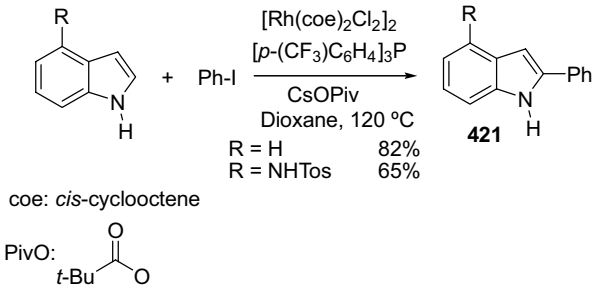
In contrast, when the steric interactions are minimized with small bases, such as MgO, the migration step is favored and the arylation occurs at C2. In agreement with this hypothesis, bulkier ligands on the Pd also drive the reaction to the C3 arylation product.

Regioselective indole C2 arylation has also been conducted employing Rh(III) complexes as catalysts. The coupling process is achieved in the presence of a catalyst that is assembled *in situ* from a rhodium species, a phosphine ligand and CsOPiv as base (Scheme 5.202) [323].

The proposed catalytic cycle involves (i) oxidative addition of the aryl halide, to form Rh(III) complex **422**, (ii) complexation of the indole to form complex **423**, followed by

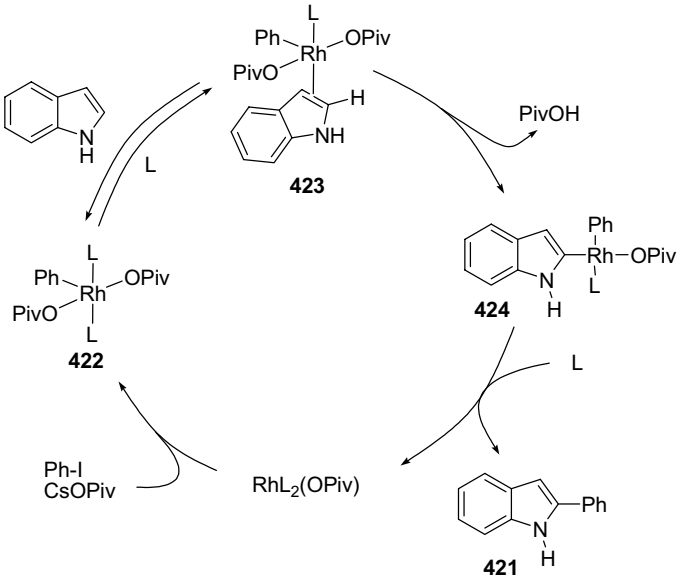


Scheme 5.201



Scheme 5.202

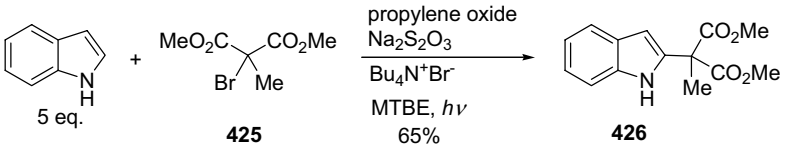
pivalate promoted C−H bond metallation to give indolyl rhodium complex **424** and (iii) reductive elimination to release the C2 arylated indole **421** (Scheme 5.203).



Scheme 5.203

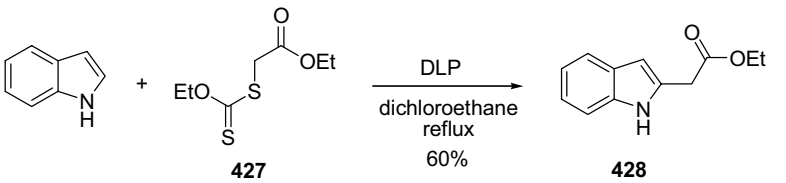
5.5.4
Radical Reactions

Intermolecular radical aromatic substitution on indole can be effected at C2 with electrophilic carbon-centered radicals. For instance, indole reacts with radicals generated from iodoacetates or bromomalonates **425** to give the alkylated indole **426** (Scheme 5.204) [324, 325]. The reactions proceed with high regioselectivity, although a large excess of indole is required to avoid polysubstitution reactions.



Scheme 5.204

A more efficient procedure for the oxidative radical alkylation of indoles employs α-acetyl or α-acetonyl radicals generated from the corresponding xantenes **427**. In this way, radical alkylation can be accomplished to prepare 2-indolyl acetate **428** in preparatively useful yields without the need of excess indole (Scheme 5.205) [326, 327].



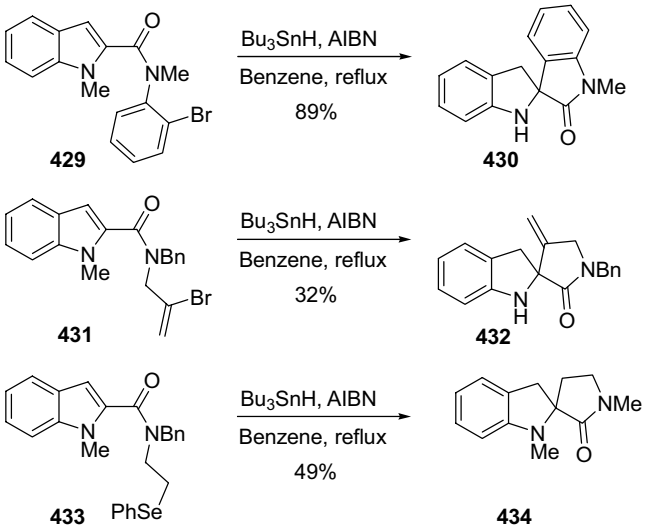
DLP: dilauryol peroxide

Scheme 5.205

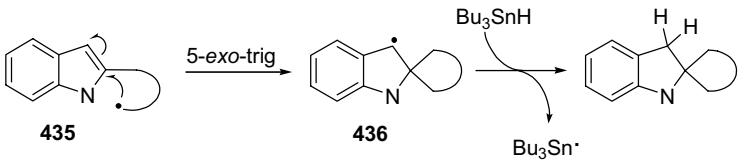
While the intermolecular reactions of indoles with radicals have found limited application, there are many examples of intramolecular radical additions to the indole ring that have been employed as an entry into more complex heterocyclic structures [328–331]. For instance, spirocyclic dearomatized indole derivatives **430**, **432**, and **434** are formed via 5-exo-trig cyclizations from aryl, vinyl and alkyl radical precursors **429**, **431**, and **433**, respectively (Scheme 5.206) [332].

In these examples the reaction proceeds by attack of the intermediate radical **435** to the C2 position of the indole ring (Scheme 5.207). The additional stability of the benzylic radical **436** might account for the preference of the C2 attack instead of C3 attack.

Nevertheless, it has been observed that the nature of the pedant group may influence the course of the cyclization, and, in some cases, the addition of the radical at C3 is the main or unique reaction pathway [333, 334]. This is the case of the tandem radical sequence that has been applied to the preparation of functionalized indolenine **441** from amidoindole **437** (Scheme 5.208) [335]. Reaction of indole amide **437** with the tributylstannyl radical produces the aryl radical **438** by bromine atom abstraction. The aryl radical undergoes [1,5]-hydrogen atom abstraction, which generates the amido radical **439**. Intramolecular addition of the radical to the C3 position of the indole produces indolyl radical **440**, which leads to the indolenine **441** after hydrogen atom abstraction of the tributylstannyl hydride. The same authors have further extended the radical sequence to the preparation of tetracyclic structures [336].



Scheme 5.206

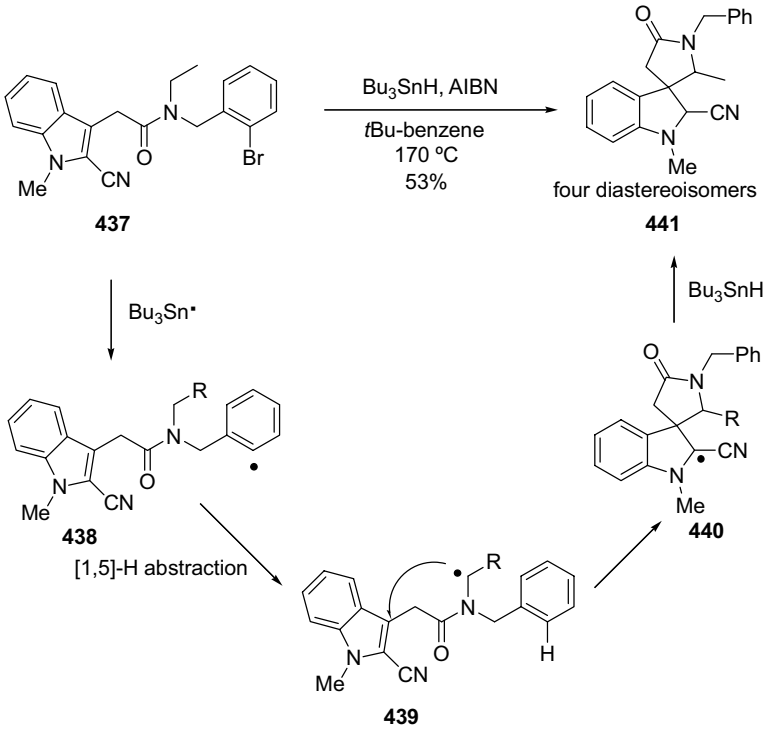


Scheme 5.207

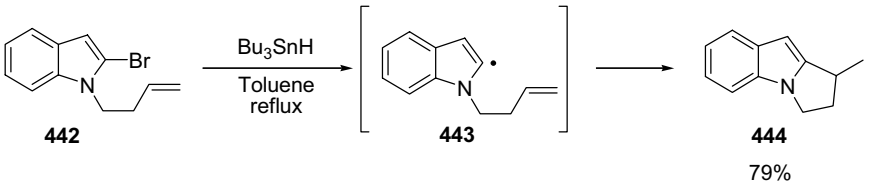
On the other hand, indolyl radicals can be generated from the corresponding haloindoles by treatment with tributyltin hydride in the presence of a radical initiator. The indolyl radical can be trapped in an intermolecular [337] or in an intramolecular sense by reaction with a suitable radical acceptor. Scheme 5.209 shows the generation of 2-indolyl radical **443** from a 2-bromoindole (**442**) and the subsequent intramolecular cyclization to provide the tricyclic indole **444** [338].

Indolyl radicals such as **446**, generated from bromoindole **445**, which cannot undergo a direct intramolecular annulation, evolve through a [1,5]-hydrogen atom abstraction reaction to generate transient radical **447**. Then, intramolecular radical addition to the indole ring leads to the tetracyclic radical **448**, and finally to indoline **449** as a single diastereoisomer (Scheme 5.210) [339]. The reaction proceeds with moderate yield, as a 42% yield of dehalogenated indole **450** is also recovered.

A 3-indolyl radical can be also generated by oxidation of the corresponding anion. This strategy has been applied to devise an extremely potent coupling between unprotected indoles and ketone enolates [340]. Thus, simultaneous deprotonation of



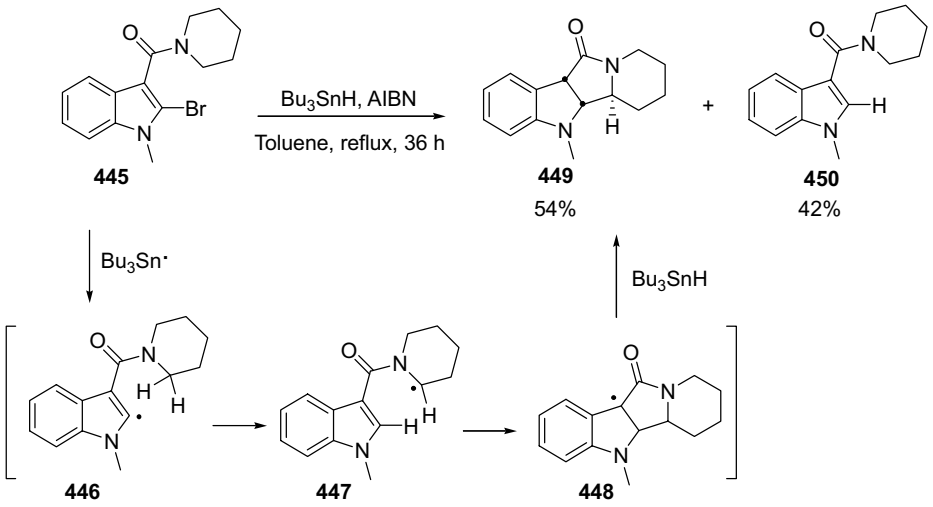
Scheme 5.208



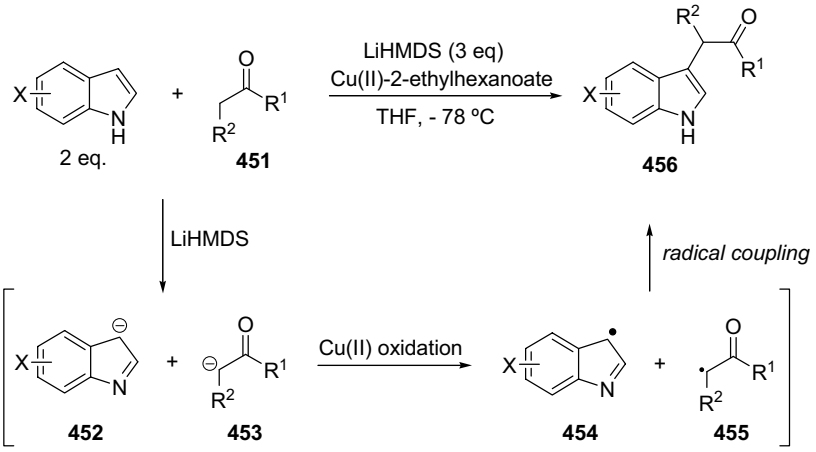
Scheme 5.209

indole and the ketone **451** gives indole anion **452** and ketone enolate **453**. Oxidation with a Cu(II) salt provides 3-indolyl radical **454** and ketone radical **455**, which upon radical coupling lead to substituted indole **456** (Scheme 5.211).

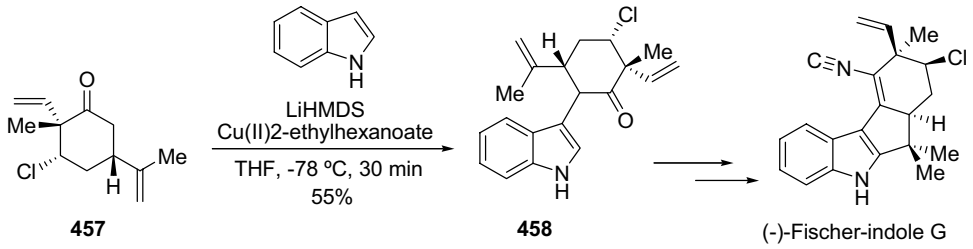
Importantly, the application of this methodology to ketones bearing stereogenic centers leads to the corresponding coupling products as single diastereoisomers. This strategy has been applied in the crucial step of a highly convergent total synthesis of various indole alkaloids such as Fischer-indoles I and G and welwitindolinone A [341]. Scheme 5.212 shows the coupling of ketone **457** with indole to give enantiomerically pure substituted indole **458**.



Scheme 5.210



Scheme 5.211

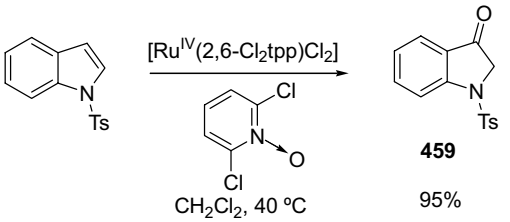


Scheme 5.212

5.5.5
Oxidation Reactions

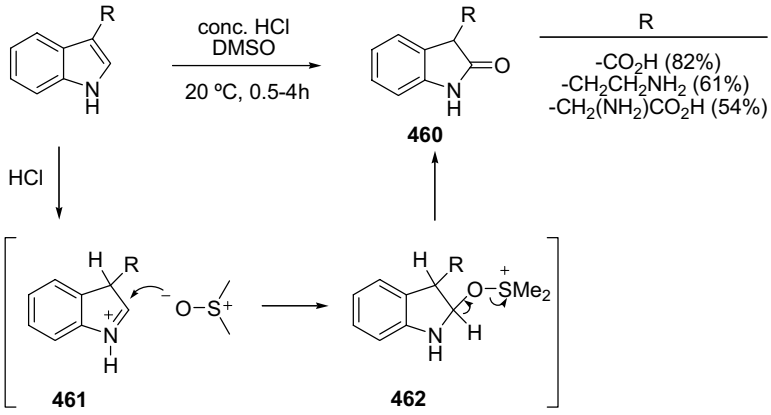
Indoles are highly sensitive to oxidation and, thus, undergo aerial autooxidation to produce 3-hydroperoxo-3*H*-indoles, which are rarely isolated but decompose to produce complex mixtures of degradation and polymerization derivatives.

The transformation of *N*-tosylindole into indoxyl **459** has been described with oxodiperoxomolybdenum(IV) [342, 343], and by catalytic oxidation with dichlororuthenium(IV)*meso*-tetrakis(2,6-dichlorophenyl)porphyrin complex [Ru^{IV}(2,6-Cl_2tpp)Cl_2]. The latter process requires the presence of 2,6-dichloropyridine *N*-oxide as stoichiometric oxidant (Scheme 5.213) [344].



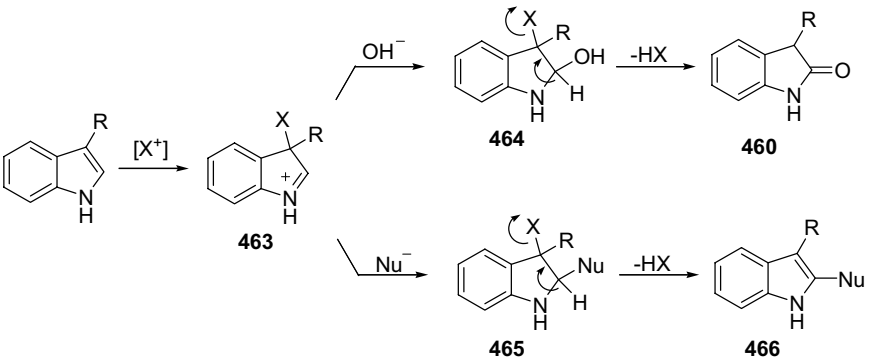
Scheme 5.213

Indoles can be converted into oxindoles through several different oxidative strategies. A general reaction is the treatment of indoles with conc. HCl in dimethyl sulfoxide, which provides cleanly the corresponding oxindoles **460** [345]. The reaction is likely to proceed through C3 protonation of indole to give indolenium intermediate **461**, followed by electrophilic addition of the DMSO to give intermediate **462** followed by elimination of dimethylsulfane (Scheme 5.214).



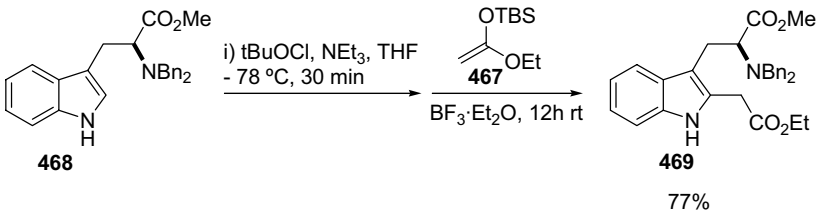
Scheme 5.214

Oxidation of indoles to oxindoles **460** can also be produced by treatment of the indole with a halogenating agent, followed by hydrolysis. Thus, the intermediate indolenium cation **463** formed gives 2-hydroxy-3-halodihydroindole **464**, which suffers dehydrohalogenation to give oxindole **460** (Scheme 5.215) [346]. A closely related procedure allows for the substitution of indoles at C2. This oxidative-coupling procedure involves reaction of the indole with a suitable electrophile [X^+]. Addition of a nucleophile [Nu^-] to the transient indolenium cation **463** formed gives **465**, and aromatization by elimination of HX furnishes the functionalized indole **466**.



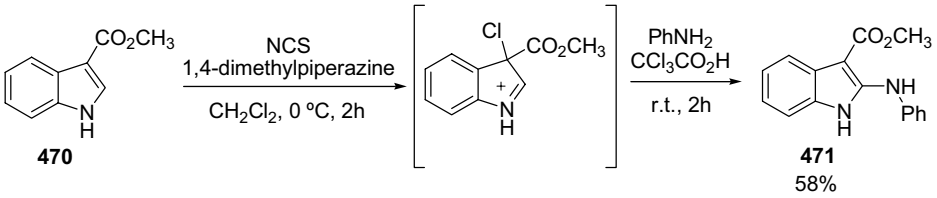
Scheme 5.215

Halogenating agents, such as *t*BuOCl, NCS or NBS are the electrophiles of choice. The oxidative-coupling strategy has been performed with various carbon nucleophiles, such as allyl boranes and stannanes, enol ethers, enamines, acetylide and even indole. Scheme 5.216 presents the synthesis of C2 substituted tryptophan **469** by nucleophilic addition of a silylenol ether (**467**) to the indolenium cation generated from protected tryptophan **468** [347].



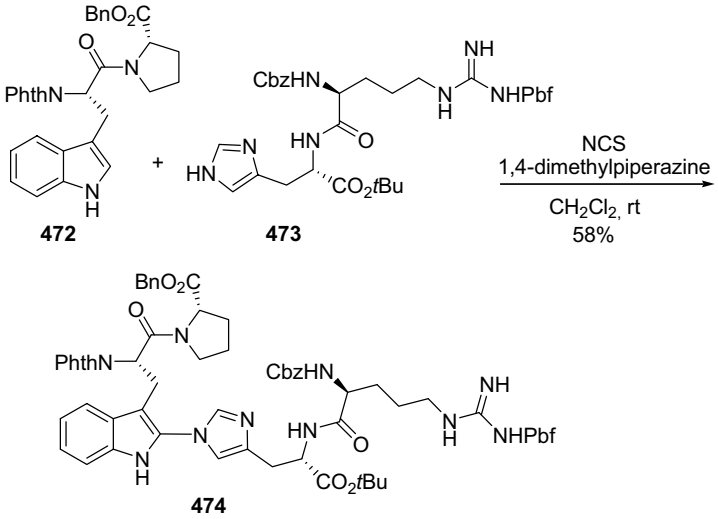
Scheme 5.216

Heteronucleophiles such as alcohols [348], anilines, phenols and thiophenols [349] are also appropriate reagents for the oxidative coupling, providing the corresponding C2 functionalized indoles. For instance, 2-aminoindole **471** can be prepared from indole **470** by employing this sequence (Scheme 5.217).



Scheme 5.217

Moreover, the versatility and functional group compatibility of this oxidative-coupling procedure has been shown in the coupling of a tryptophan derived peptide **472** with the imidazole ring of the histidine-containing peptide **473**, which represents the key step in the synthesis of the right-hand ring of the natural octapeptide celogentin (**474**) (Scheme 5.218) [350].

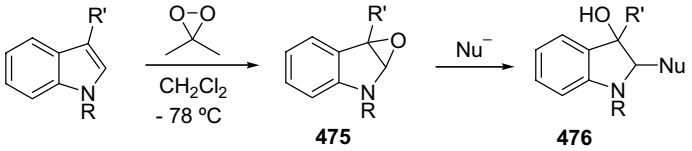


Scheme 5.218

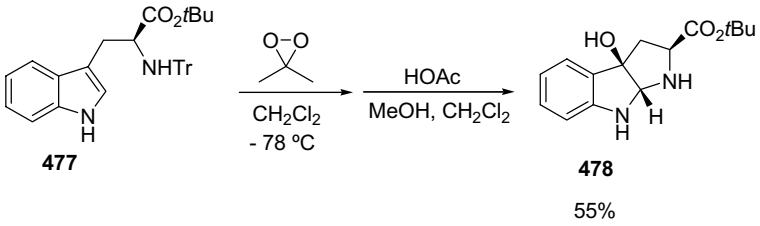
A very valuable synthetic transformation is the oxidation of indoles with dimethyldioxirane, which produces the corresponding epoxides **475** [351]. Although the epoxides are unstable in most cases, their generation in the presence of a nucleophile gives rise to 3-hydroxyindoline derivatives **476** (Scheme 5.219).

The application of this strategy to protected tryptophan **477** led to pyrrolo[2,3-*b*] indole **478**, an early key intermediate in Danishefsky's total synthesis of himastatin (Scheme 5.220) [352].

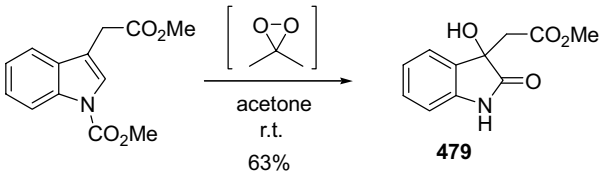
In contrast, aqueous workup of the preformed epoxide leads to 3-hydroxyoxindoles **479** (Scheme 5.221) [353].



Scheme 5.219



Scheme 5.220



Scheme 5.221

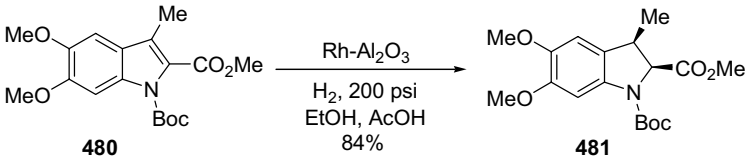
5.5.6
Reduction of the Heterocyclic Ring

Indoles are reduced to indolines by several methods, including catalytic hydrogenation, dissolving metals and metal hydrides. Some detailed reviews on this subject are available [354].

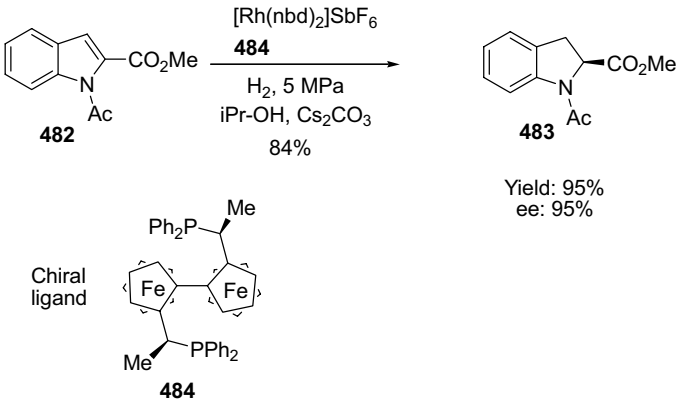
5.5.6.1 Catalytic Hydrogenation

Catalytic hydrogenation of the heterocyclic ring has been achieved employing various heterogeneous catalysts, but usually requires harsh conditions and sometimes is not very selective. In the presence of strong acids, relatively milder conditions can be used, as the reaction proceeds through the C3 protonated indole [355]. For instance, *N*-Boc-2,3-disubstituted indoles **480** are hydrogenated to the corresponding *cis*-2,3-disubstituted indolines **481** over a rhodium-alumina catalyst in a EtOH/AcOH mixture (Scheme 5.222) [356].

The catalytic asymmetric hydrogenation of *N*-acylindoles **482** has been performed employing as catalyst a rhodium complex bearing the chiral diphosphine ligand **484**. In this way, optically active substituted indolines **483** can be obtained in high yield and enantiomeric excesses (Scheme 5.223) [357].



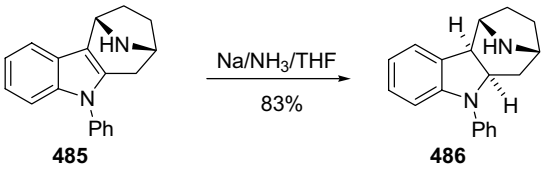
Scheme 5.222



Scheme 5.223

5.5.6.2 **Metal-Promoted Reductions**

The reduction of indoles with dissolving metals may give partial reduction of both the benzene and the heterocyclic ring, depending on the particular substrate and reaction conditions applied. In certain examples, high chemo- and stereoselectivity can be achieved. For instance, *N*-phenylindoles **485** are converted into the corresponding indolines **486** upon treatment with Na/NH_3 in THF (Scheme 5.224) [358].

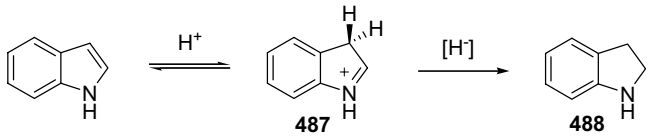


Scheme 5.224

On the other hand, 2-acylindoles can be reduced to the indolines through several protocols involving metal–acid combinations, such as Mg/MeOH [359] and Sn/HCl [360].

5.5.6.3 **Metal Hydride Complexes**

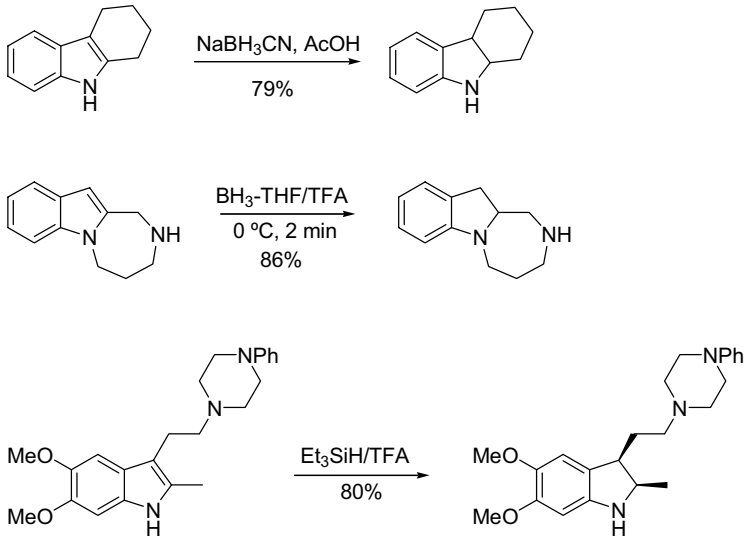
A very general method for the reduction of indoles to indolines **488** consists of treatment with a hydride reagent under acidic conditions (Scheme 5.225). The



Scheme 5.225

reaction proceeds via initial protonation at C3 to generate indolenium ion **487** which is subsequently reduced by the hydride donor [361].

Hence, the best results have been obtained with hydride sources that are stable to acid, such as $NaBH_3CN$ in AcOH [362], BH_3/THF in TFA [363] and triethylsilane in TFA [364]. Representative examples are given in Scheme 5.226.

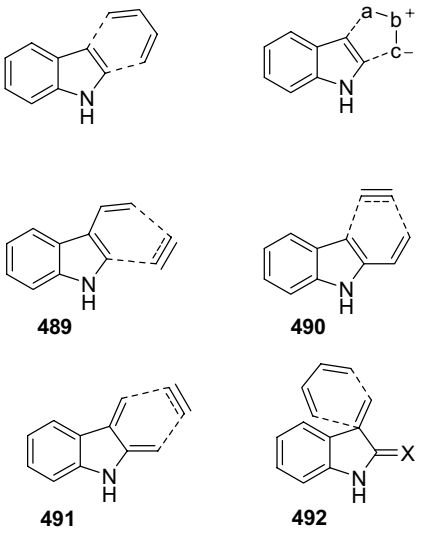


Scheme 5.226

5.5.7
Pericyclic Reactions Involving the Heterocyclic Ring

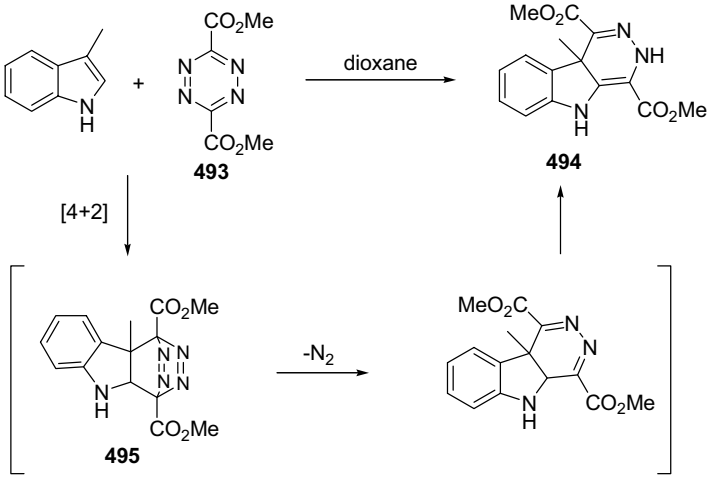
5.5.7.1 Cycloaddition Reactions

The C2–C3 double bond of indole can participate in different types of cycloaddition processes as a 2π or 4π component. As a 2π component it can behave as a dienophile in [4 + 2] cycloadditions, and as dipolarophile in dipolar [3 + 2] cycloadditions. On the other hand, 3-vinylindoles **489** and 2-vinylindoles **490** take part as dienes in [4 + 2] cycloadditions. Moreover, orthoquinodimethane indole derivatives **491** are highly reactive dienes in Diels–Alder reactions, and methylene indolines **492** and oxindoles can react as 2π components in [4 + 2] and dipolar cycloadditions (Scheme 5.227).



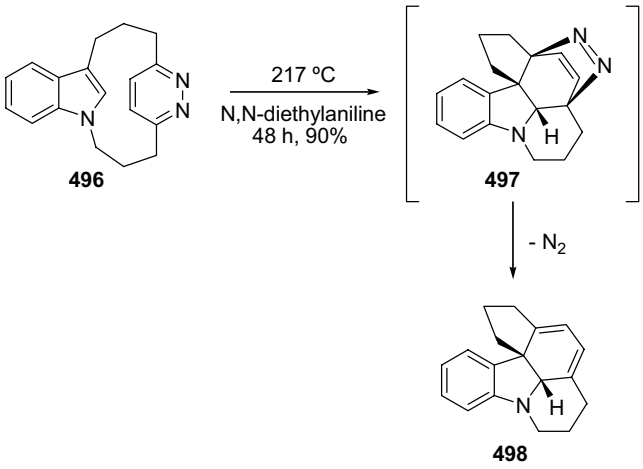
Scheme 5.227

Owing to the high electron density of the C2–C3 double bond, indole derivatives have been mostly employed as electron-rich dienophiles in inverse-electron-demand Diels–Alder reactions [365]. In particular, the use of aromatic heterodienes such as 1,2,4,5-tetrazines, 1,2,4-triazines and pyridazines represents a versatile route into more complex polycyclic structures [366]. Scheme 5.228 shows the synthesis of a 3,9b-dihydro-5*H*-pyridazino[4,5-*b*]indole **494** by cycloaddition of 3-methylindole with the 1,2,4,5-tetrazine **493**. The final compound **494** is obtained after loss of N_2 and hydrogen transposition of the initially formed cycloadduct **495** [367].



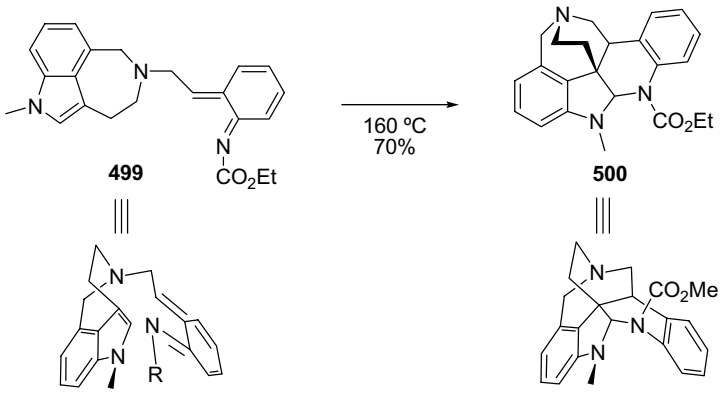
Scheme 5.228

The application of [4 + 2] cycloaddition methodology in an intramolecular version leads to polycyclic skeletons in very short synthetic sequences [368], and has been employed in several approaches to complex indole alkaloids. For instance, transannular cycloaddition of the pyridazinoindolophane **496** gives polycyclic adduct **497**, which provides the final dihydrocarbazole **498** after loss of N_2 via a retro-Diels–Alder reaction [369]. This particular sequence is the key step in a total synthesis of strychnine (Scheme 5.229) [370].



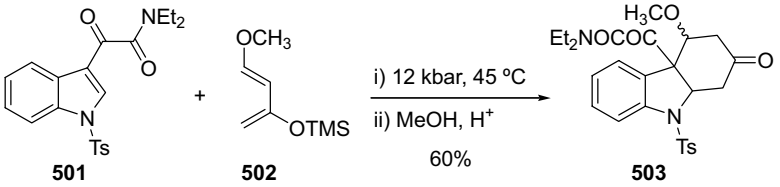
Scheme 5.229

Another example of an intramolecular inverse-electron-demand Diels–Alder reaction is the cycloaddition of **499**, a molecule that features a substituted indole and an aza-*o*-xylylene, a very reactive heterodiene moiety [371]. Cycloaddition gives rise to **500**, which features the heptacyclic ring system present in the natural alkaloid communesin B (Scheme 5.230).



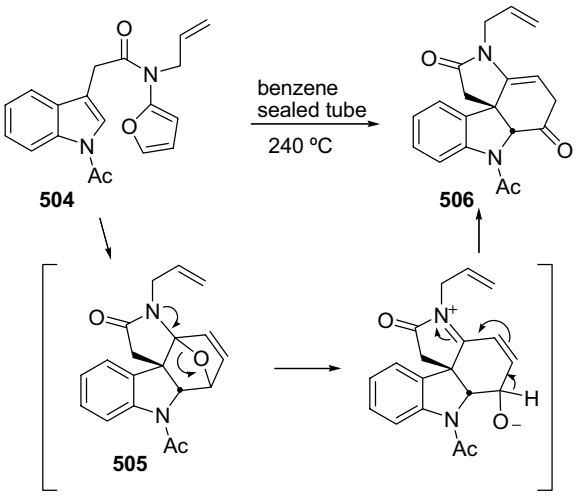
Scheme 5.230

Indoles substituted with electron-withdrawing groups in positions 1 and 3, such as **501**, can react with electron-rich dienes like Danishefsky's diene **502**, in normal electron-demand cycloadditions [372]. Very high temperatures are required unless activation by Lewis acids or high pressure are employed (Scheme 5.231) [373, 374].



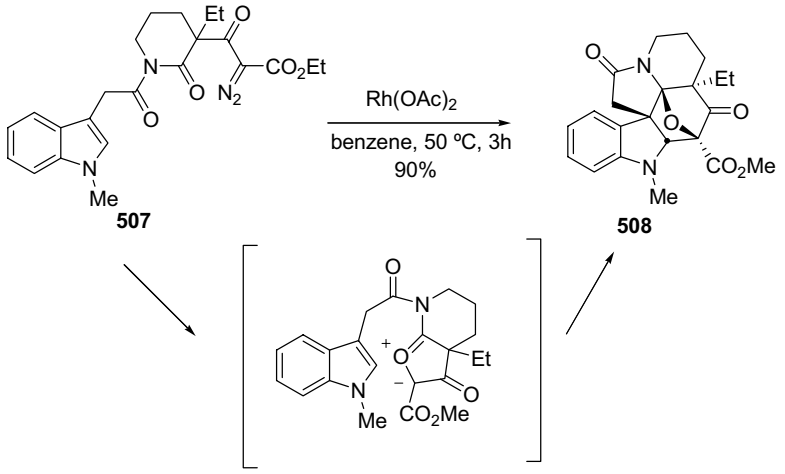
Scheme 5.231

The intramolecular [4 + 2] cycloaddition of **504**, which features an amidofuran moiety tethered onto an indole, can be regarded also as an example of a normal electron-demand cycloaddition [375]. In this process, the cycloadduct **505** undergoes spontaneous rearrangement onto tetracycle **506** [376]. The reactions proceed at very high temperatures and only substrates substituted with an electron-withdrawing group at the indole nitrogen undergo the cycloaddition (Scheme 5.232).



Scheme 5.232

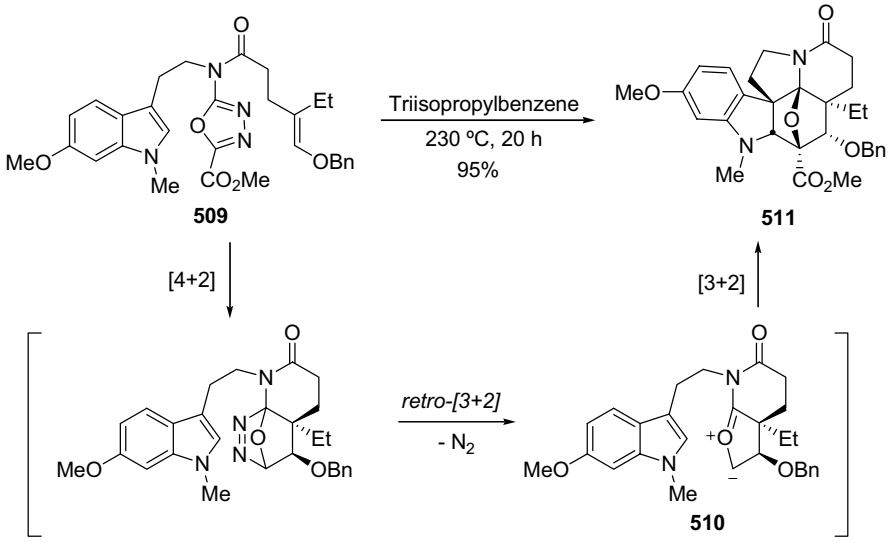
The electron-rich C2–C3 bond of indole can also participate as dipolarophile in 1,3-dipolar cycloaddition reactions. Nitrones [377], azomethine ylides [378], azides [379] and carbonyl ylides are among the dipoles successfully employed, in most cases in an intramolecular fashion. In the example presented below, the carbonyl ylide, generated by cyclization of a rhodium carbenoid generated from diazoimide **507**, reacts with the tethered indole giving rise to **508**, which presents the



Scheme 5.233

pentacyclic skeleton of Aspidosperma alkaloids (Scheme 5.233) [380]. The carbonyl ylide–indole cycloaddition can be also conducted in an intermolecular fashion [381].

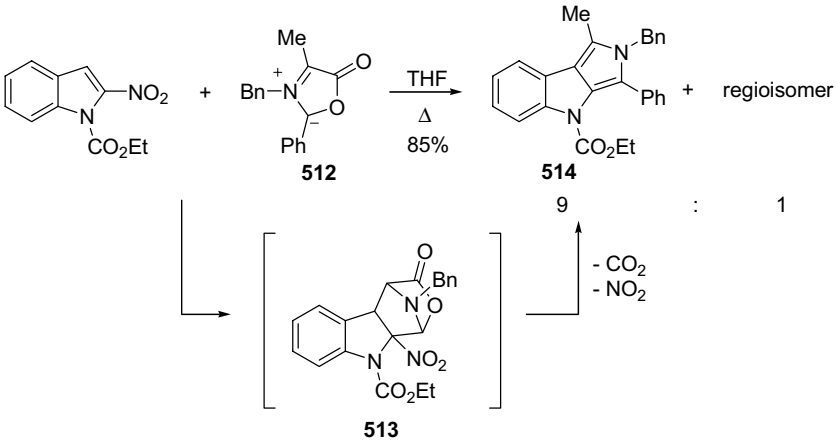
The power of intramolecular cycloadditions across the C2−C3 double bond has been shown in a remarkable application of cycloaddition cascades employed by Boger *et al*. in the total synthesis of (–)-vindoline (Scheme 5.234) [382]. The reaction is initiated by the [4 + 2] cycloaddition of the tethered enol ether with the 1,3,4-oxadiazole on **509**, to give a cycloadduct. Loss of N_2 by a retro-dipolar cycloaddition then generates the intermediate carbonyl ylide **510**. Intramolecular [1,3] dipolar



Scheme 5.234

cycloaddition across the indole C2–C3 double bond provides the polycycle **511** with total control of the stereochemistry on the six new stereogenic centers generated along the cascade process.

Among the very few intermolecular 1,3-dipolar cycloadditions of indoles known, noteworthy is the reaction of 2- and 3-nitroindoles with the mesoionic münchnones **512** [383]. The reaction gives rise to pyrrolo[3,4-*b*]indoles **514** in a highly regioselective manner, and is thought to proceed through a 1,3-dipolar cycloaddition to form the unstable cycloadduct **513**, which gives the final compounds after loss of CO_2 and NO_2 (Scheme 5.235).

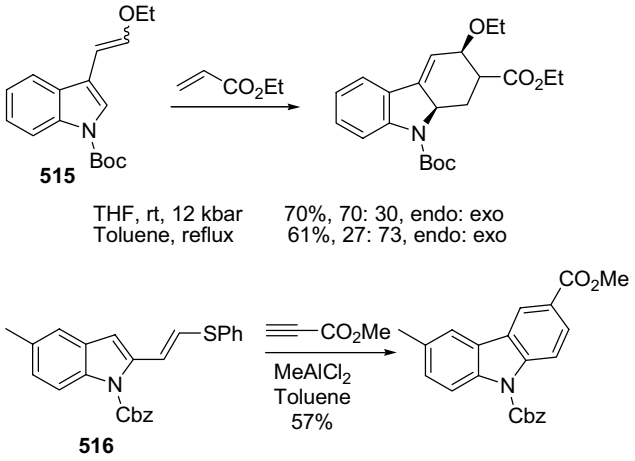


Scheme 5.235

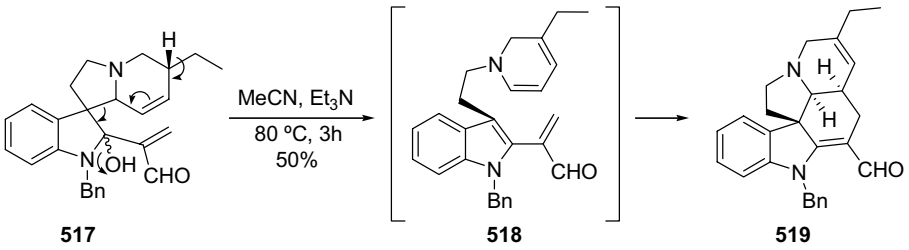
Many examples have been described of [4 + 2] cycloadditions of 2- and 3-vinylindoles as 4π-electron components. Vinylindoles can be seen as electron-rich dienes, and therefore will react preferentially with electron-poor dienophiles in normal electron-demand cycloadditions. Thus, intermolecular reactions involve typical dienophiles such as methyl acetylenedicarboxylate [384], *N*-phenylmaleimide [385], and benzoquinones [386]. When asymmetric dienophiles are employed, the regiochemistry can be predicted by employing frontier molecular orbital theory principles. For instance, the regiochemistry of the reactions of 3-vinylindole **515** with ethyl acrylate [387], and the cycloaddition of 2-vinylindole **516** with methyl propiolate can be both explained assuming the directing interaction of the HOMO of the vinylindole with the LUMO of the dienophile (Scheme 5.236) [388, 389].

The intramolecular version of the [4 + 2] cycloaddition leads to complex structures in a convergent manner. In a classical example, the 2-vinylindole **518** generated *in situ* from indoline **517** undergoes cycloaddition with the enaminic double bond to give **519**, a very advanced intermediate in the total synthesis of pseudotabersonine (Scheme 5.237) [390, 391].

Intramolecular Diels–Alder reactions of 3-vinylindoles usually involve a dienophile tethered through the nitrogen atom. For instance, the intramolecular

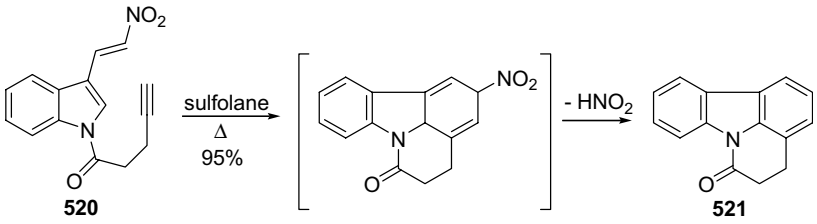


Scheme 5.236



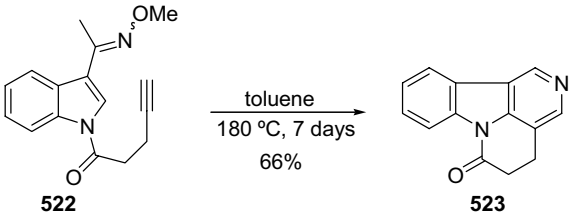
Scheme 5.237

cycloaddition of the nitrovinylindole with a terminal alkyne **520** provides the tetracyclic structure **521** after loss of HNO_2 (Scheme 5.238) [392].



Scheme 5.238

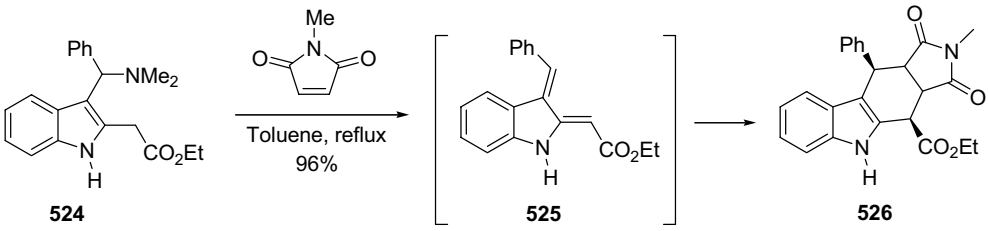
The oxime-substituted indole **522** behaves as an 1-aza-1,3-butadiene in an intramolecular hetero-Diels–Alder reaction with a tethered alkyne, to give tetracycle **523**, which features the skeleton of Canthine alkaloids (Scheme 5.239) [393].



Scheme 5.239

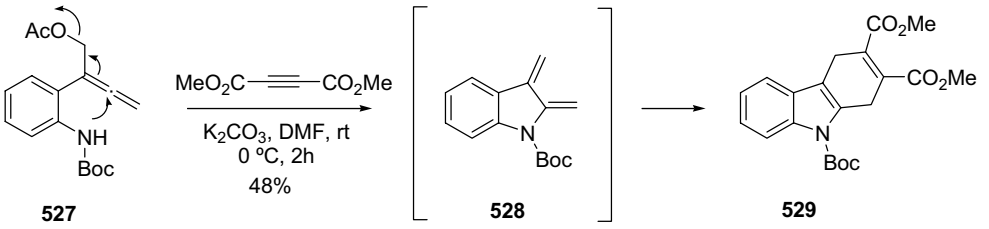
Indole-2,3-quinodimethanes are highly reactive dienes in [4 + 2] cycloadditions and represent a very valuable entry into the carbazole ring structure [394]. They can be generated *in situ* by fluoride or iodide ion induced 1,4-elimination of silylated indolyl ammonium salts [395], by double elimination on *N*-protected-2,3-bis(dibromomethyl)indoles [396], by thermal fragmentation of 2-substituted 3-aminomethylindoles [397] and by [1,5]-H shift on 3-cyanomethyl-2-vinylindoles [398]. Moreover, the anionic indole-2,3-dienolate can be formed by deprotonation of 1,2-dimethylindole-3-carboxaldehyde [399].

For instance, disubstituted indole-*o*-quinodimethane **525** is generated by thermal decomposition of gramine **524** in the presence of the dienophile; it then reacts to give the tetracyclic adduct **526** in very high yield (Scheme 5.240).



Scheme 5.240

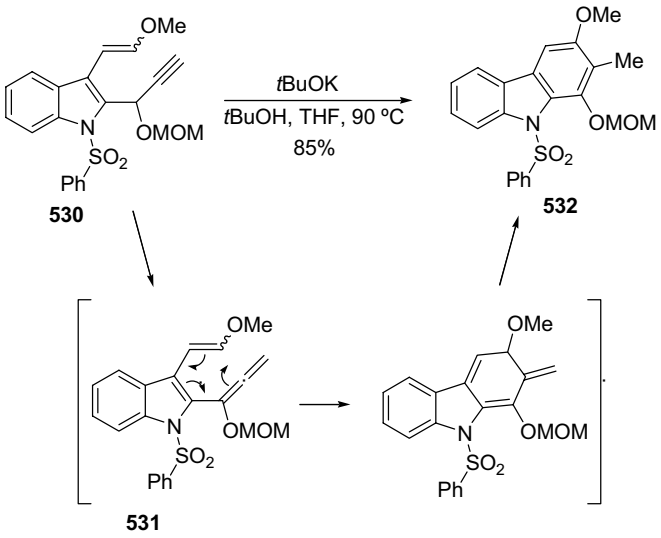
Alternatively, reactive indole-2,3-quinodimethane intermediates **528** can be generated from *o*-allenylanilines **527**, and trapped with dienophiles to obtain directly the corresponding carbazole derivatives **529** in moderate yields (Scheme 5.241) [400].



Scheme 5.241

5.5.7.2 Electrocyclizations

The C2–C3 double bond of indole can participate in electrocyclic reactions. Although the 6π-electron electrocyclization of 2,3-divinylindoles is known, the participation of allene intermediates is more efficient. Thus, a versatile route to carbazoles is based on an allene-mediated electrocyclic reaction of a 6π-electron system involving the indole 2,3-bond [401]. This strategy has been applied in the preparation of numerous alkaloids containing the carbazole moiety. Scheme 5.242 depicts the preparation of oxygenated carbazole **532** from propargyl ether containing indole **530**. Treatment with KO*t*Bu produces the acetylene–allene isomerization to give intermediate **531**, which suffers electrocyclization leading to the carbazole.



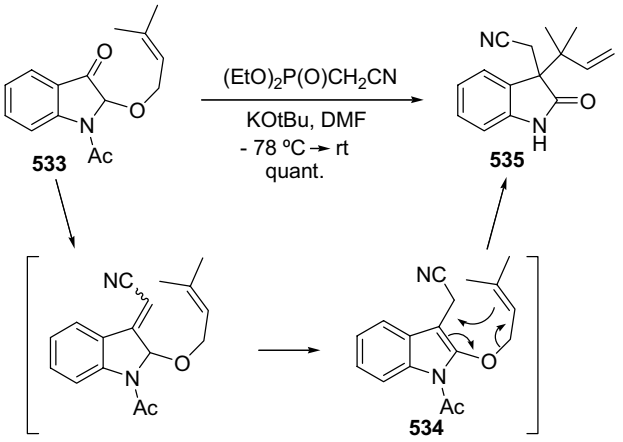
Scheme 5.242

5.5.7.3 Sigmatropic Rearrangements

The indole C2–C3 bond can participate in [3,3] sigmatropic rearrangements, and this strategy has been employed in many synthetic efforts to introduce additional substitution at C2 or C3 [402–404].

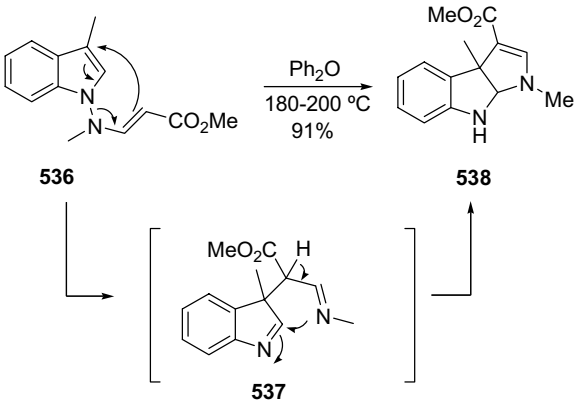
The Claisen rearrangement of 2-allyloxiindoles leads to oxindoles with creation of a quaternary center. For example, allyloxyindole **534**, generated *in situ* by olefination of 2-allyloxiindoxyl **533**, suffers the [3,3]-rearrangement to provide oxindole **535** (Scheme 5.243) [405]. The required 2-allyloxiindoles can be also generated by oxidative coupling of indoles with allyl alcohols (Section 5.5.5) [406].

Another type of [3,3]-rearrangement with functionalization at C3 is found in the conversion of 1-vinylaminoindole **536** into tricyclic compound **538** under thermolysis conditions [407]. The formation of **538** can be explained by [3,3]-rearrangement to form imine **537**, which generates the pyrrolo[2,3-*b*]indole by intramolecular



Scheme 5.243

cyclization (Scheme 5.244). On the other hand, the incorporation of a substituent at C2 by a Claisen rearrangement has been also described [408].

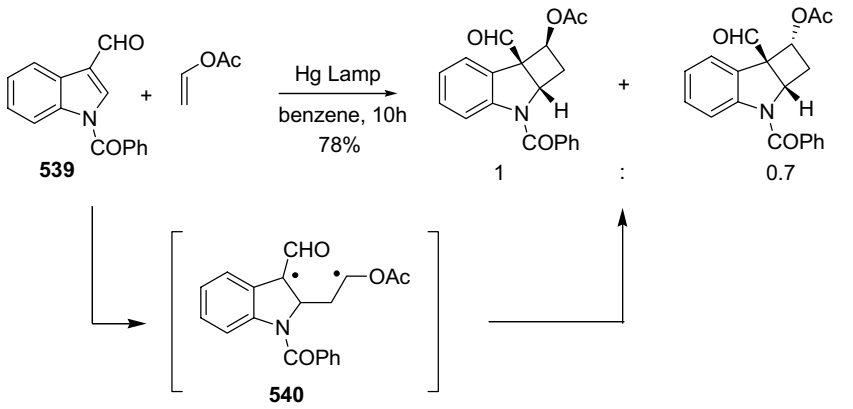


Scheme 5.244

5.5.8
Photochemical Reactions

Synthetic applications of indole photochemical reactions are very limited, and therefore this technique has been scarcely employed. Ultraviolet light irradiation promotes the [2 + 2] cycloaddition of N-protected indoles with alkenes and alkynes [409, 410]. For instance, *N*-acylindoles **539** undergo [2 + 2] photocycloaddition with monosubstituted alkenes to form the cyclobutane ring regioselectively regardless of the nature of the substituent on the alkene [411]. The reaction is

postulated to proceed through the biradical intermediate **540**, which is formed by bonding the 2-position of the indole with the less substituted position of the alkene (Scheme 5.245).

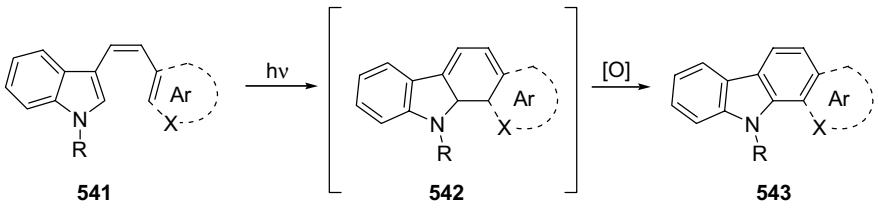


Scheme 5.245

Several examples have been reported of the intramolecular version of the [2 + 2] photocycloaddition [412]. Interestingly, the intramolecular reaction with the double bond tethered through the N atom leads to the opposite regiochemistry in the [2 + 2] cycloadduct [413].

The [4 + 2] cycloaddition reaction of indoles with electron-rich dienes, which does not proceed thermally, can be promoted photochemically by electron-transfer catalysis. Nevertheless, at present, these procedures are far from being synthetically practical [414].

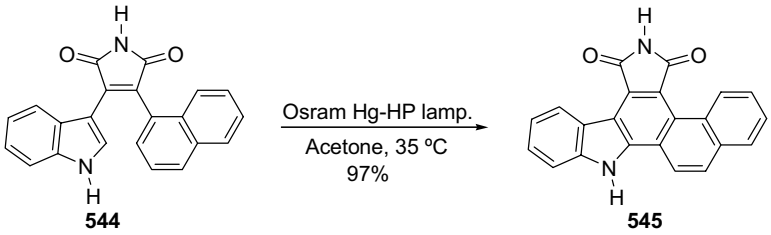
Another synthetically useful photochemical transformation is the photocyclization of indole-containing stilbenes **541** and related systems to give polycycles **543** featuring the carbazole moiety. The reaction occurs through a 6π-electron conrotatory electrocyclization to give **542**, followed by oxidation to furnish directly the aromatic system. Thus, the photocyclization is usually carried out in the presence of an oxidant, such as iodine or Pd/C (Scheme 5.246) [415].



Scheme 5.246

The main application of this methodology is in the preparation of [2,3-*a*]pyrrolo [3,4-*c*]carbazoles, a substructure that is present in several naturally occurring

alkaloids with potent biological activities [416], such as rebeccamycin [417] and staurosporin [418]. In a recent example, naphtho[2,3-*a*]carbazole **545** is obtained by photooxidation of 2-naphthylindolyl maleimide **544** in nearly quantitative yield (Scheme 5.247) [419, 420].

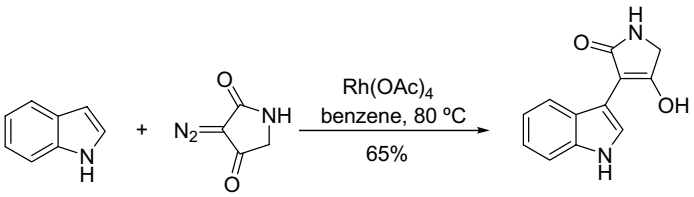


544 **545**

Scheme 5.247

5.5.9
Reactions with Carbenes and Carbenoids

The reaction of indole with carbenes or carbenoids does not lead to cyclopropanation but, instead, insertion in the C3–H double bond occurs, to give the corresponding substitution product [421]. In the example shown in Scheme 5.248, the rhodium carbenoid generated from the cyclic diazo compound **546** reacts with indole to give the C3-substituted indole **547** [422]. This chemistry has been applied in the preparation of natural indolocarbazole alkaloids.



546 **547**

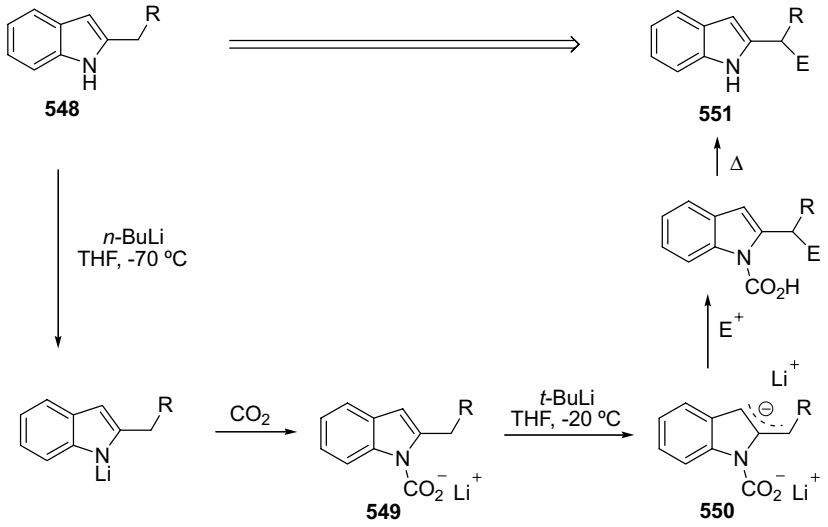
Scheme 5.248

5.6
Chemistry of Indole Derivatives

5.6.1
Alkylindoles

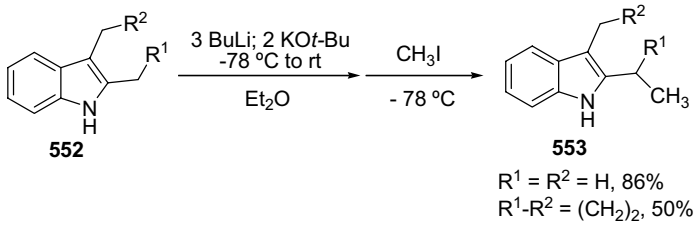
Deprotonation of the alkyl chain of indoles is usually difficult. Nevertheless, NH-2-alkylindoles **548** can be lithiated at the α-position through a one pot sequence that

involves formation of the lithium carbonate **549**, by NH deprotonation with BuLi and quench with CO_2, followed by treatment with *t*-BuLi to obtain dianion **550**. Subsequent reaction with an electrophile yields the 2-(substituted a1kyl)indole **551** after thermally induced loss of CO_2 (Scheme 5.249) [423].



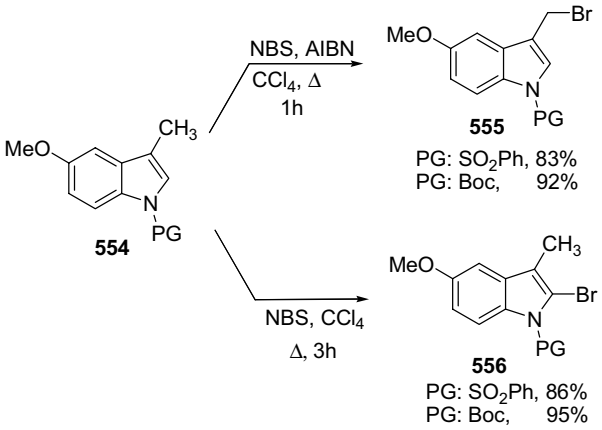
Scheme 5.249

Alternatively, NH-2,3-dialkylindoles **552** can be directly deprotonated by treatment with an excess of base that consists of a combination of BuLi and KO*t*-Bu. Treatment with an electrophile provides the 2-substituted indole **553**, indicating that the lithiation is produced exclusively at the C2 side-chain (Scheme 5.250).



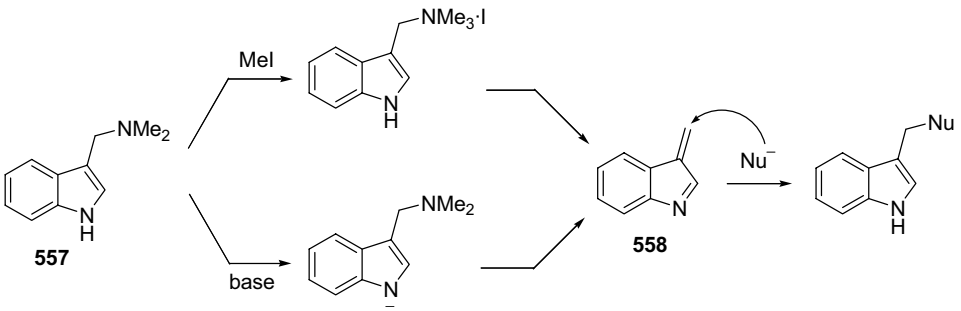
Scheme 5.250

Bromination of the side-chain of N-protected indoles such as **554** can be carried out by treatment with NBS in the presence of a radical initiator. Interestingly, while the reaction under radical conditions provides the indole brominated on the side-chain **555**, the same reaction in the absence of the radical initiator gives rise to the C2-brominated indole **556** (Scheme 5.251) [424].



Scheme 5.251

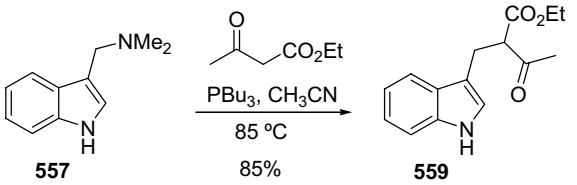
Among functionalized alkylindoles, the chemistry of gramines **557** is noteworthy. The elimination of the dimethylamino group can be promoted either by quaternization or by treatment with bases, generating the highly reactive electrophile **558**, which undergoes the addition of a nucleophile. The overall reaction is the substitution of the dimethylamino group by the nucleophile (Scheme 5.252). This strategy has been employed for the introduction of different types of carbon [425], nitrogen [426] and sulfur nucleophiles [427].



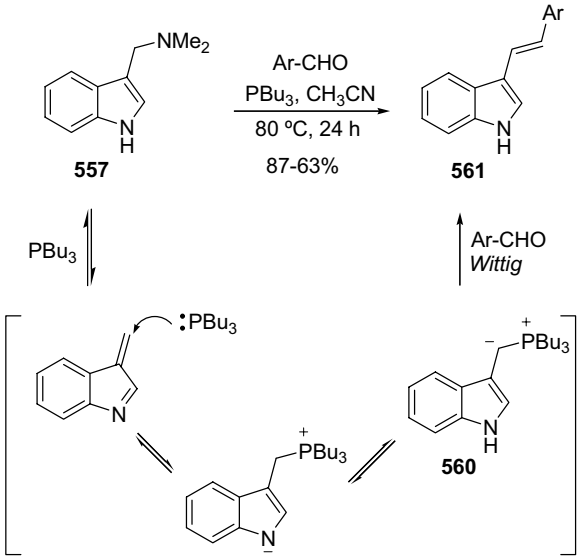
Scheme 5.252

Scheme 5.253 presents the use of gramine **557** as electrophile in a typical acetylacetate alkylation, leading to substituted indole **559** [428].

This chemistry has been applied in an original method for the preparation of vinylindoles, in a substitution/Wittig olefination tandem sequence. Thus, treatment of gramine with an aromatic aldehyde in the presence of an excess of PBu_3, affords directly the vinylindole **561**, through the *in situ* generated ylide **560** (Scheme 5.254) [429].



Scheme 5.253



Scheme 5.254

5.6.2 Oxiderivatives

Oxindole and indoxyl are the stable tautomeric forms of 2-hydroxy- and 3-hydroxyindole respectively (Figure 5.8). The aromatic 2-hydroxyindole is unstable and undetectable. In contrast, 3-hydroxyindole contributes in the tautomeric equilibrium, and in some 2-substituted-indoxyls is the thermodynamically controlled product.

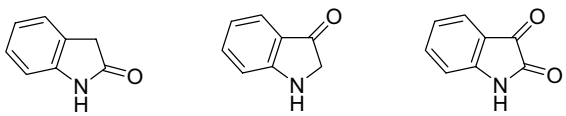


Figure 5.8 Structures of oxi-derivatives of indole.

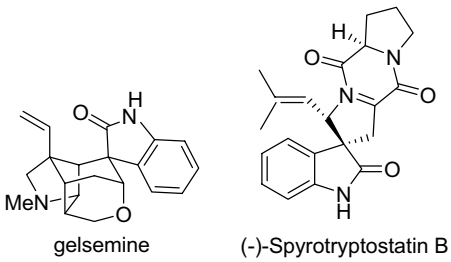


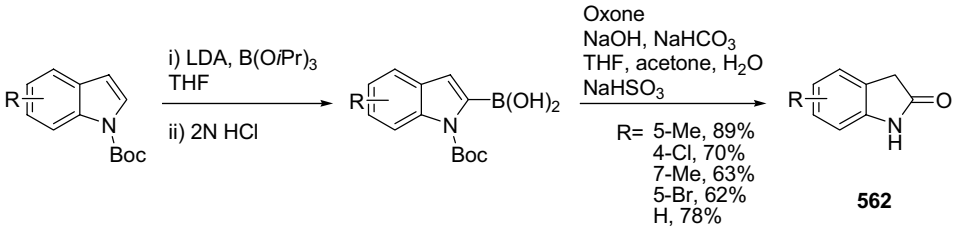
Figure 5.9 Some important oxindole alkaloids.

5.6.2.1 **Oxindole**

The substructure of oxindole is present in numerous naturally occurring alkaloids and pharmaceutically active compounds. Substituted oxindoles and, in particular, spirocyclic oxindoles featuring a quaternary center at C3 are attractive targets in organic synthesis due to their usefulness as drug candidates and as intermediates in alkaloid synthesis. Figure 5.9 shows some natural oxindole-containing alkaloids such as the well-known hexacyclic cage-like alkaloid gelsemine [430] and the highly potent cytotoxic agent spyrotryprostatin B [431].

Numerous methodologies for the preparation of oxindoles are available, and detailed coverage would largely exceed the aim of this chapter. Oxindoles can be prepared from indole or indole derivatives, by derivatization of isatin (Figure 5.8), and by cyclization processes.

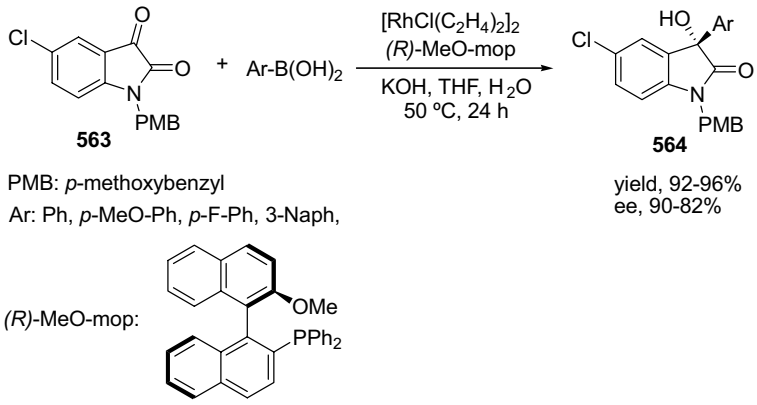
5.6.2.1.1 **Synthesis of Oxindoles from Indoles** Indoles can be transformed into oxindoles under the oxidation protocols discussed in Section 5.5.5. Additionally, *N*-Boc-indoles can be cleanly converted into *N*-Boc-oxindoles **562** by a two-step sequence that involves formation of a 2-indolylborate [432] and oxidation with oxone (Scheme 5.255) [433]. Moreover, as discussed in Section 5.5.7.3, oxindoles can be prepared by Claisen rearrangement of 2-allyloxiindoles.



Scheme 5.255

5.6.2.1.2 **Synthesis of Oxindoles from Isatins** Isatin (Figure 5.8) features two carbonyl groups, a ketone and an amide carbonyl. The higher reactivity of the C3 ketone carbonyl can be exploited to introduce functionalization and prepare 3-substituted oxindoles. Thus, reductions [434], aldol reactions [435], additions of

nucleophiles [436] and Wittig olefinations [437] lead to the corresponding substituted oxindoles. Notably, the rhodium-catalyzed asymmetric addition of arylboronic acids to isatin **563** gives rise to enantiomerically enriched 3-substituted-3-hydroxyoxindoles **564** (Scheme 5.256) [438].



Scheme 5.256

5.6.2.1.3 **Synthesis of Oxindoles by Cyclization Reactions** Cyclization strategies are usually reminiscent of the methods employed for the synthesis of indoles, such as the Fischer synthesis [439], cyclization of *o*-aminophenylacetic acid derivatives [440], intramolecular Friedel–Crafts alkylations [441], radical cyclizations [442], intramolecular Heck reactions [443], intramolecular Buchwald–Hartwig amidations [444] and intramolecular α-arylation of amide enolates [445]. Extensive coverage of the methods of synthesis of oxindoles is beyond the scope of this chapter, and the reader is referred to the original papers. Nevertheless, some relevant modern alternatives to the general approaches depicted in Figure 5.10 is briefly presented.

Cyclization of *o*-aminophenylacetic acid derivatives is one common approach to the synthesis of oxindoles. Several different strategies can be applied to prepare the intermediate amino acid [446]. The [3,3]-sigmatropic rearrangement of the enolate **568**, generated from *N,O*-diacylated phenyl hydroxylamine **567**, is the key step in a three-step synthesis of oxindoles from *N*-acylhydroxylamines **565** and carboxylic acids **566** [447]. The *N*-protected amino acid **569** generated in the rearrangement is condensed to give the spirocyclic oxindole **570** (Scheme 5.257).

Samarium iodide reductive coupling of isocyanates with a tethered α,β-unsaturated ketone (**571**) gives rise to oxindoles **572** (Scheme 5.258) [448]. In this original approach, the oxindole is built by formation of the C2−C3 bond, and has been employed in the preparation of advanced intermediates towards the synthesis of welwitindolinone alkaloids.

Intramolecular Friedel–Crafts alkylation of α-chloroacetanilides is one of the most classical methods for the synthesis of oxindoles. A variant of this reaction has been recently disclosed by Buchwald, avoiding the harsh reaction conditions required in

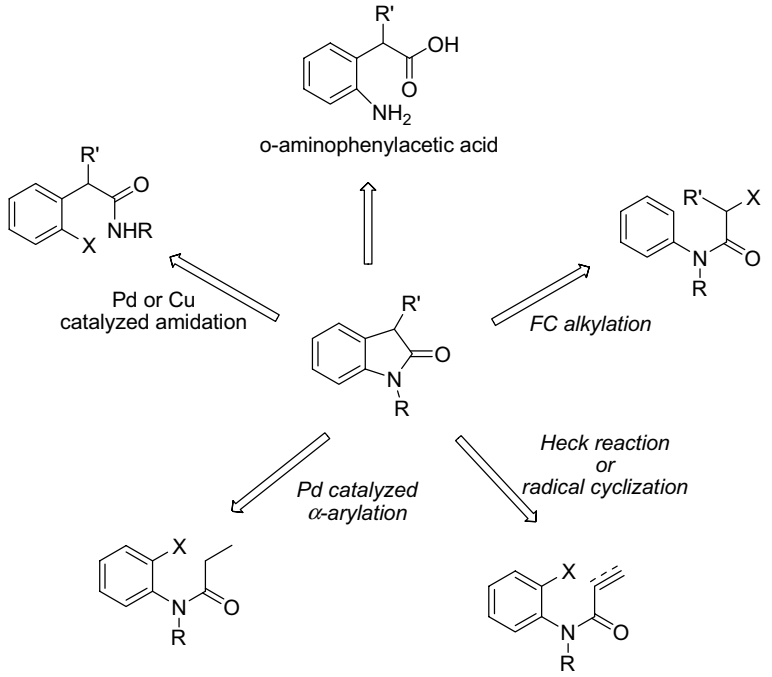
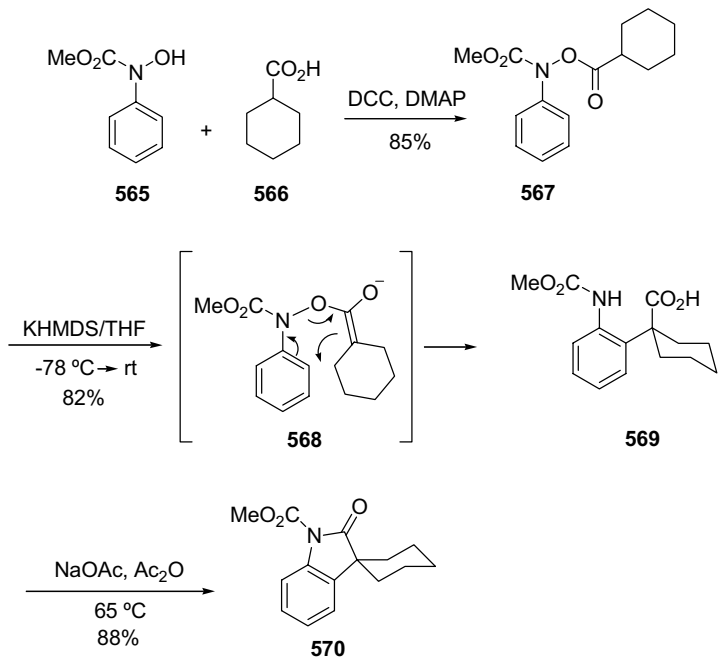
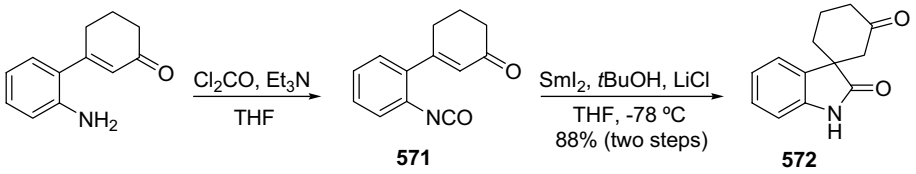


Figure 5.10 General approaches to the synthesis of oxindoles through cyclization reactions.

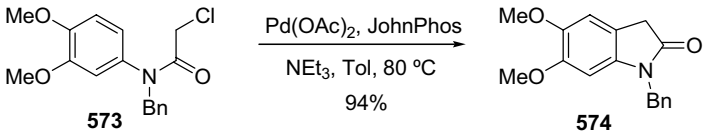


Scheme 5.257



Scheme 5.258

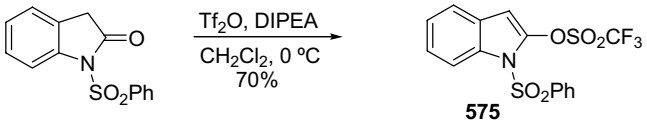
the FC alkylation. Thus, treatment of α-chloroacetanilides **573** with a Pd(0)-based catalytic system leads to the oxindoles **574** in excellent yields, under milder conditions and with high functional group tolerance (Scheme 5.259) [449]. Interestingly, the overall process results in a Pd-catalyzed aromatic C−H activation. Nevertheless, at present there is no unambiguous mechanistic proposal.



Scheme 5.259

5.6.2.1.4 **Oxindole Reactivity** The chemistry of oxindole resembles a typical five-membered ring lactam. Deprotonation at the β-carbon occurs readily, as the resulting anion is stabilized by the aromatic character of the oxindole enolate. Thus, the oxindole anion can react with electrophiles in alkylation, acylation and condensation reactions.

On the other hand, oxindoles can be transformed into the corresponding indolyl-triflates **575** (Scheme 5.260) [450], which can be further employed in metal-catalyzed cross-coupling reactions (Section 5.5.3.6).



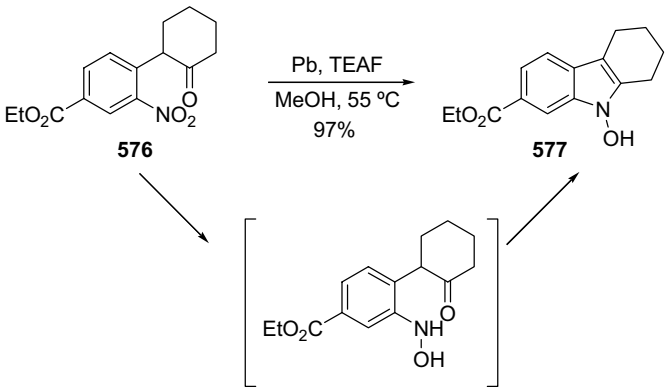
Scheme 5.260

5.6.2.2 *N*-Hydroxyindoles

The structure of *N*-hydroxyindole is also present in a considerable number of biologically molecules. Moreover, several *N*-hydroxylated analogues of biologically inactive indoles have shown biological activity [451].

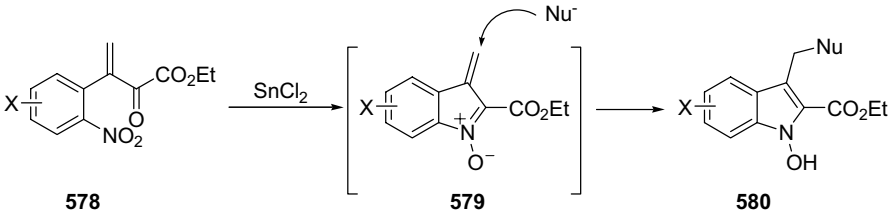
The most common approach to the preparation of *N*-hydroxyindoles is the reductive cyclization of *o*-nitrobenzylketones **576** or aldehydes in the presence of a metal reducing agent [452]. A fairly general and chemoselective protocol is the

reaction with the Pb/TEAF system (TEAF: triethylammonium formate), which provides *N*-hydroxyindoles **577** in very high yields (Scheme 5.261) [453].



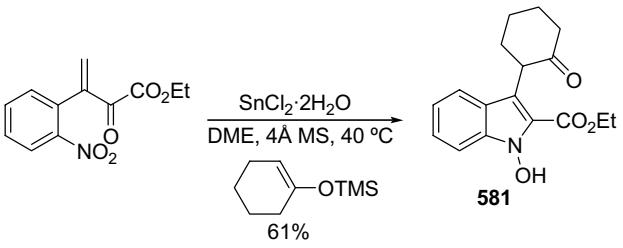
Scheme 5.261

In a closely related reaction, structurally diverse substituted *N*-hydroxyindoles **580** can be prepared in a tandem process from nitroaromatic α,β-unsaturated keto-esters **578** [454]. The initially formed nitrone **579** is trapped by a hetero- or carbonucleophile to provide substituted *N*-hydroxyindoles **580** (Scheme 5.262).



Scheme 5.262

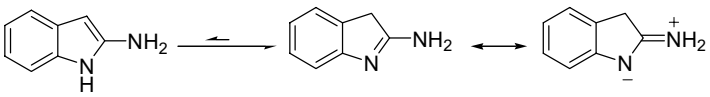
For instance, the reaction in the presence of silylenol ethers gives rise to the corresponding C-alkylated derivatives **581** (Scheme 5.263).



Scheme 5.263

5.6.3
Aminoindoles

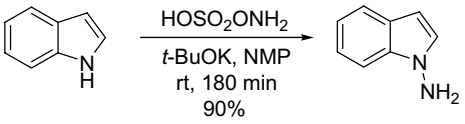
Although most amino-substituted heterocycles exist mainly in the amino tautomer, 2-aminoindole exists predominantly as the 3*H*-tautomer, which is stabilized by the amidine resonance form (Scheme 5.264).



Scheme 5.264

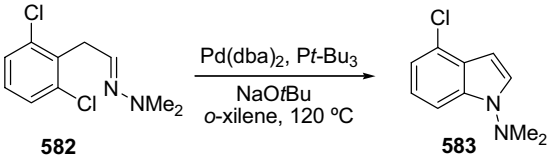
Regarding the synthesis, the most reliable modern method to introduce an amino group in the heterocyclic indole ring is Pd- or Cu-catalyzed amination (Section 5.5.3.5).

N-Amination of indole can be accomplished with different "NH_2^+" type of reagents such as monochloramine (NH_2Cl) [455] or hydroxylamine *o*-sulfonic acid [456] under basic media (Scheme 5.265).



Scheme 5.265

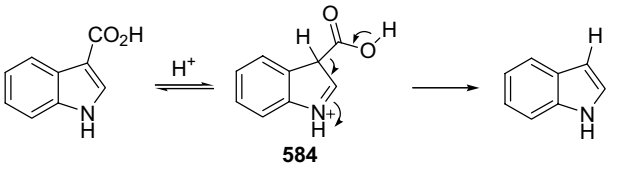
On the other hand, *N*-aminoindoles **583** can be prepared by the Pd-catalyzed intramolecular cyclization of *o*-chloroarylacetaldehyde hydrazones **582** (Scheme 5.266) [457].



Scheme 5.266

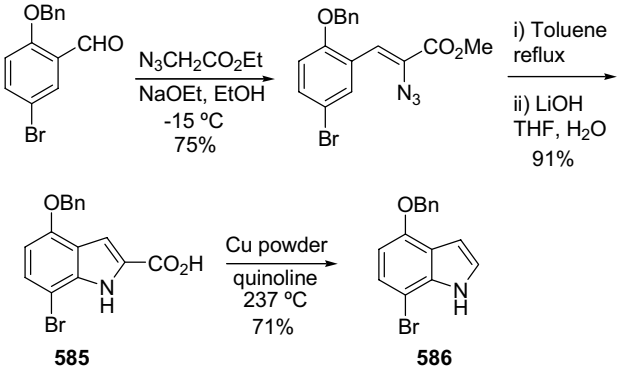
5.6.4
Indole Carboxylic Acids

Decarboxylation of indole-3-carboxylic acid, and also indoyl-2-acetic acid, takes place under reflux of water (Scheme 5.267). The reaction proceeds through the protonated 3*H*-indolium cation **584** [458].



Scheme 5.267

Decarboxylation of indole-2-carboxylic acid requires much harsher conditions, such as heating in the presence of either mineral acids or copper powder [459]. The latter is a valuable synthetic transformation that has been employed to prepare 2-unsubstituted indoles **586** from the more readily available 2-indole carboxylates **585**. Scheme 5.268 gives an example of the application of this sequence [460, 461].



Scheme 5.268

5.7 Addendum

During the production of this book, and since the initial elaboration of this chapter, remarkable advances have occurred in the field of indole chemistry, which indicate the high interest in this particular type of heterocyclic structure. This addendum is not intended to be a comprehensive revision of the most recent literature, and collects only some important advances that have not been mentioned above. First of all, several reviews covering synthesis and different aspects of indole reactivity have appeared recently [462].

5.7.1 Ring Synthesis

5.7.1.1 Fischer Indole Synthesis

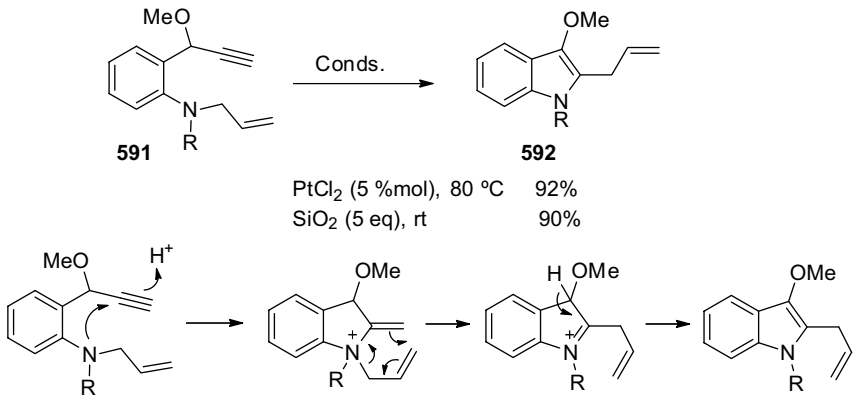
The direct synthesis of N-Cbz indoles from the corresponding N-Aryl-N-Cbz hydrazide has been disclosed [463].

An improved methodology for the sequence hydrohydrazination of alkynes/Fischer indolization has been described employing inexpensive and environmentally friendly Zn salts as catalysts [464].

5.7.1.1.1 **Cyclizations by Formation of the N–C2 Bond** The synthesis of indoles by cyclization of nitrenes, generated from aryl azides, has been carried out employing rhodium catalysts [465].

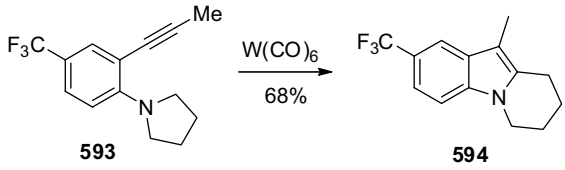
The aryl amination/hydroamination sequence on *o*-chloroalkynyl benzenes has been implemented for the preparation of indoles with sterically demanding N-substituents [466]. Similar routes have been employed for the synthesis of 2-aminoindoles [467] and 4-alkoxyindoles [468]. A multicomponent domino process for the preparation of 2-aminomethyl indoles, involving the cyclization of an *o*-alkynylaniline, has been reported [469].

A new approach for the synthesis of indoles is the cycloisomerization of 2-propargylanilines (**591**). This reaction has been effected employing Pt-based and Brønsted acid catalysts, and leads to functionalized indole skeletons **592** (Scheme 5.269). The mechanism proposed for the acid-catalyzed reaction involves a 5-*exo*-dig cyclization followed by an aza-Cope rearrangement [470].



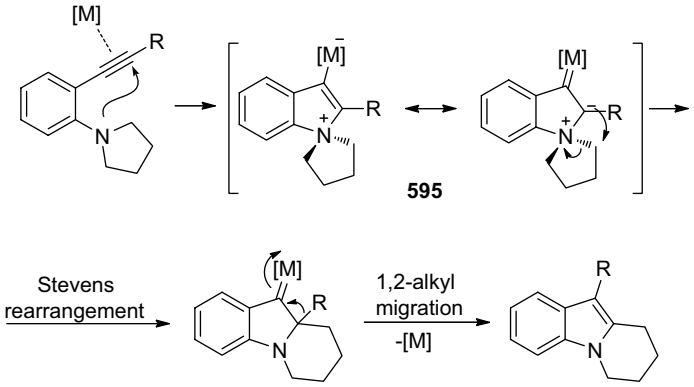
Scheme 5.269 Synthesis of índoles by cycloisomerization of propargylanilines.

A 5-*exo*-dig cyclization is also the first step for the cycloisomerization of *o*-alkynyl-*N*,*N*-dialkylanilines **593** that leads to annulated indoles **594** (Scheme 5.270) [471].



Scheme 5.270 Cycloisomerization of *o*-alkynyl-*N*,*N*-dialkylanilines.

The reaction involves activation of the alkyne by the action of the metal catalyst, followed by 5-*exo*-dig cyclization to produce a metal-containing ammonium ylide (**595**). Then, a [1,2]-Stevens rearrangement, followed by a [1,2]-alkyl migration, renders the fused indole structure (Scheme 5.271).

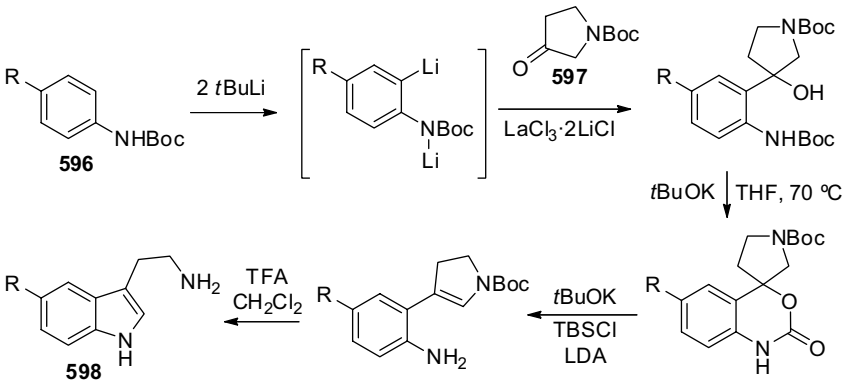


Scheme 5.271 Mechanism proposed for the cycloisomerization of *o*-alkynyl-*N*,*N*-dialkylanilines.

Indoles have been synthesized from *o*-iodobenzoic acids and alkynes in a sequential process that involves a Curtius rearrangement followed by a Pd-catalyzed Larock-type indolization [472]. Quite similarly, *o*-alkynylamides have been employed to synthesize indoles through a Hoffmann-rearrangement/alkyne hydroamination sequence [473].

The Pd-catalyzed synthesis of indoles from *o*-amino-*gem*-dihalostyrenes has been studied in detail, and represents a very powerful methodology for the synthesis of substituted indoles [474].

A new approach to tryptamines from readily available *N*-Boc anilines **596** and *N*-Boc-3-pyrrolidinone **597** has been developed (Scheme 5.272). The process, which

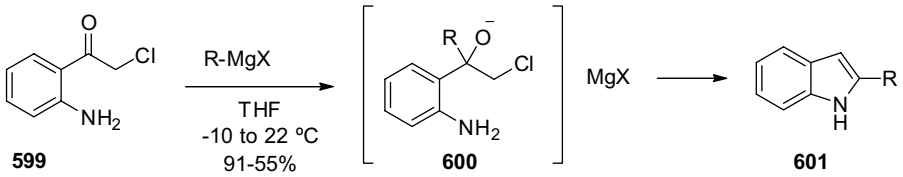


Scheme 5.272 Stepwise synthesis of triptamines.

consists of various steps, as represented in the scheme, allows for the synthesis of a large variety of tryptamines **598** substituted in the benzene ring [475].

5.7.1.1.2 **Cyclizations by Formation of the C2—C3 Bond** The synthesis of cyclic-ketone fused indoles has been achieved by a Pt-catalyzed cycloisomerization of *N*-(2-alkynylphenyl)lactams [476].

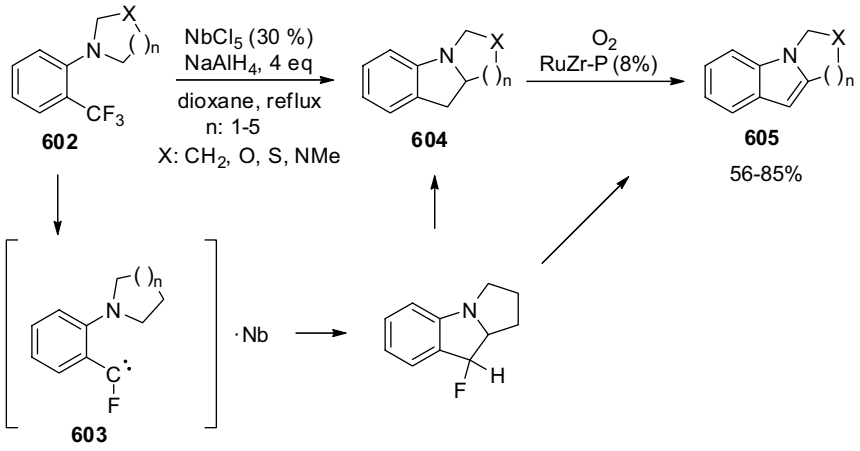
A structural variety of 2-substituted indoles **601** can be prepared from *o*-amino-2-chloroacetophenones **599** and Grignard reagents [477]. The reaction involves a [1,2]-migration of the R group from the intermediate magnesium alcoholate **600** (Scheme 5.273).



R: Alkyl, aryl, alkynyl

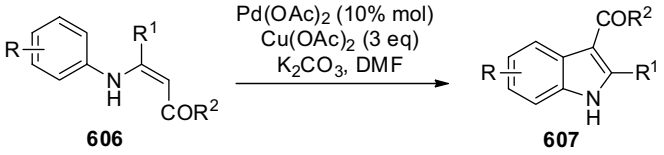
Scheme 5.273

N-fused indoles have been synthesized through a catalytic carbenoid C–H insertion approach. In this novel reaction, a niobium carbenoid (**603**) is generated from a CF_3 group of the *o*-trifluoromethylaniline derivative **602** (Scheme 5.274). Then, an intramolecular C–H insertion leads to a mixture of indole **605** and indoline **604**. Subsequent oxidation leads to the N-fused indoles **605** with good yields.



Scheme 5.274

5.7.1.1.3 **Cyclizations by Formation of the C3—C4 Bond** A very versatile new methodology for indole ring synthesis is the Pd-catalyzed oxidative cyclization of

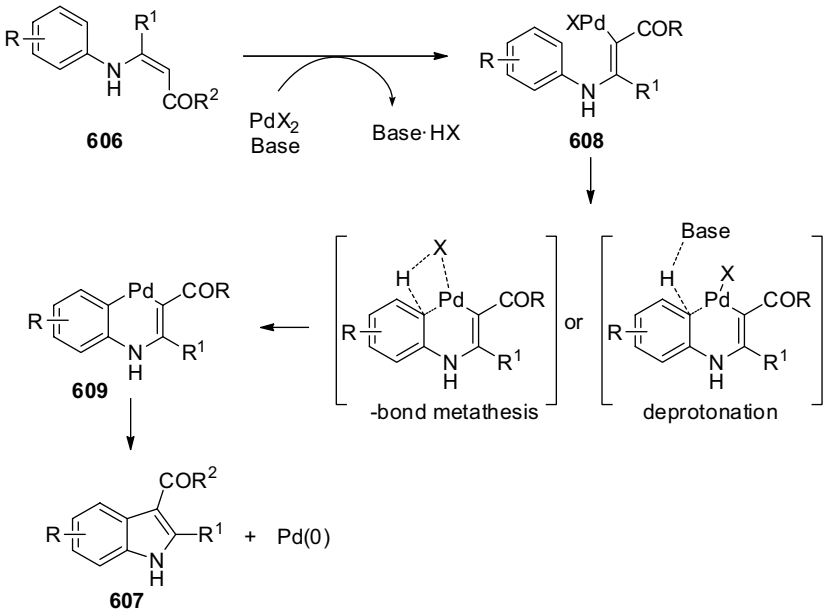


Scheme 5.275

N-arylenaminones **606** (Scheme 5.275) [478]. This methodology, which leads to 3-acyl substituted indoles **607**, is clearly advantageous when compared with strategies based on intramolecular Heck reactions, which require *o*-haloanilines as starting materials.

The mechanism proposed for this reaction (Scheme 5.276) starts with the electrophilic palladation of the enaminone **606**, to give acylpalladium intermediate **608**, followed by formation of palladacycle **609** by a σ-bond metathesis or a base-assisted deprotonation. Reductive elimination furnishes the indole **607** and releases a Pd(0) species that is reoxidized to the active Pd(II) by the stoichiometric Cu(II) salt.

More recently, a similar reaction, but employing CuI as a catalyst [479], and a metal-free version of this transformation, mediated by phenyl-iodide diacetate, have been reported [480].



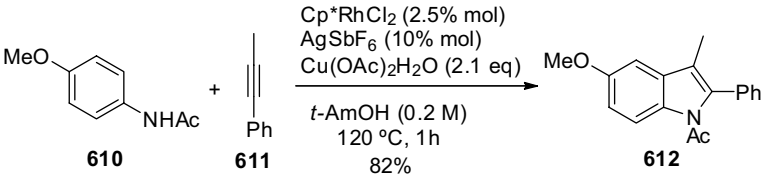
Scheme 5.276

Moreover, this type of cyclization has been adapted to a domino process in which indoles are prepared directly from electrophilic alkynes and anilines in a Pd(II)-catalyzed process [481].

The same type of products obtained from the cyclization of enaminones has been obtained by a metal-free cascade reaction between N-arylamides and ethyl diazoacetate [482].

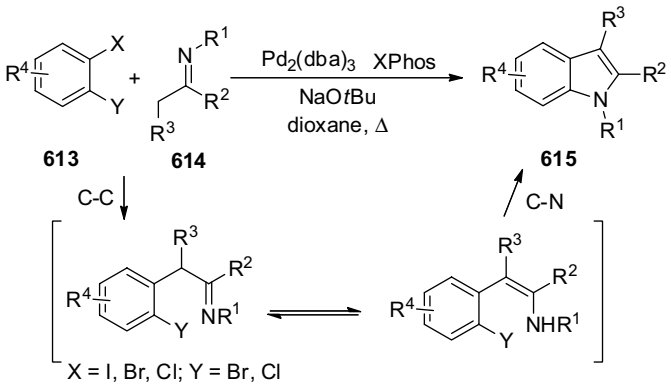
Some other Heck based cyclizations have been reported recently: a Pd-catalyzed Suzuki–Heck sequence [483], a Pd-catalyzed aryl amination-Heck sequence [484], and a Cu-catalyzed cyclization of 2-iodoenaminones [485].

Acetanilides have been employed in a rhodium-catalyzed oxidative indole synthesis (Scheme 5.277). In this impressive reaction, 2,3-disubstituted indoles **612** are built from acetanilides **610** and internal alkynes **611** [486]. As in the oxidative cyclization of enaminones described above, the reaction does not need an ortho substituent to enable the cyclization.



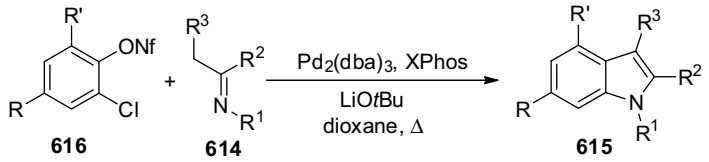
Scheme 5.277

5.7.1.1.4 **Cyclizations with Formation of the N−C7a Bond** A Pd-catalyzed N−C7a bond-forming reaction is the last step in the Pd-catalyzed cascade synthesis of indoles from 1,2-dihalobenzene **613** derivatives and imines **614** (Scheme 5.278). This synthesis consists of two independent reactions catalyzed by the same Pd catalyst: the imine α-arylation and the intramolecular C−N bond-forming reaction. It is worth noting the high modularity of this synthesis of indoles, which are prepared from three fragments: the aromatic system and the carbonyl compound and the amine employed in the preparation of the imine [487].

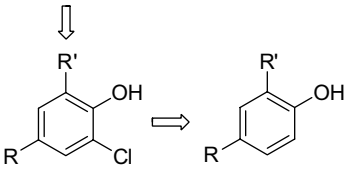


Scheme 5.278

This methodology has been extended to employ *o*-chlorononafluorosulfonates (*o*-chlorononaflates) **616** (Scheme 5.279). The reaction is totally regioselective, with the C−C bond being formed between imine α-carbon and the C-atom that supports the nonaflate. This is an important improvement, because *o*-chlorononaflates are readily prepared from phenols, and moreover is particularly adequate for the preparation of 6-substituted and 4,6-disubstituted indoles, which are not easily prepared by other conventional methods [488].

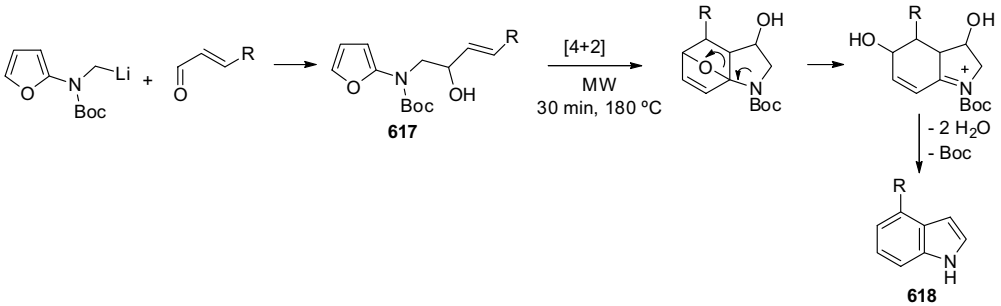


Nf: $O_2SCF_2CF_2CF_2CF_3$



Scheme 5.279

5.7.1.1.5 **Synthesis of Indoles by a [4 + 2] Cycloaddition** A very elegant construction of the functionalized indole skeleton has been carried out by the sequence presented in Scheme 5.280 [489]. The key step is the MW-promoted intramolecular [4 + 2] cycloaddition of the aminofuran intermediate **617**, which forms both rings at the same time. The method is particularly useful for the synthesis of 4-substituted indoles (**618**).



Scheme 5.280

5.7.2 Reactivity

5.7.2.1 Reactions with Electrophiles

5.7.2.1.1 **Michael Additions and Reactions with Nitroolefins** The recent explosion of the field of asymmetric organocatalysis has had an important impact in the chemistry of indoles, in particular in the reactions of indoles with electrophiles such as α,β-unsaturated compounds, nitroolefins, carbonyl compounds, and imines. A review on this field is available [490].

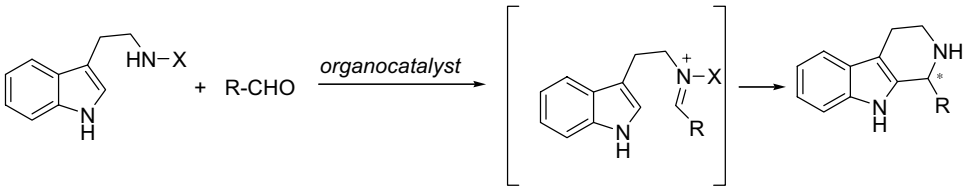
The Friedel–Crafts alkylation of indoles with α,β-unsaturated carbonyl compounds has been carried out employing chiral primary amines as organocatalyst [491].

A chiral binol *N*-triflylphosphoramide derivative has been employed as a Brønsted acid catalyst in the Friedel–Crafts alkylation of indoles with β,γ-unsaturated-α-ketoesters [492]. An intramolecular version has also been reported [493].

Regarding Lewis acid based asymmetric catalysis, highly enantioselective Friedel–Crafts alkylations with α,β-unsaturated phosphonates have been uncovered employing bis(oxazolinyl)pyridine-scandium(III) triflate complexes [494].

Several organocatalytic approaches for the asymmetric addition of indoles to nitroolefins have been reported, employing thiourea based organocatalysts [495], and promoted by a chiral phosphoric acid derivative [496]. Also noteworthy is a recent catalytic asymmetric version employing a Cu(I) chiral catalyst [497].

5.7.2.1.2 **Asymmetric Organocatalyzed Pictet–Spengler Reactions** Several asymmetric variants of the Pictet–Spengler (Scheme 5.281) reaction of have been reported [498].

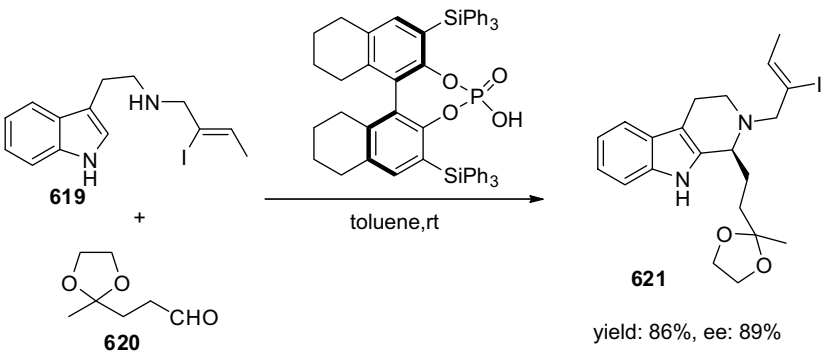


Scheme 5.281

For instance, carboline **621** was obtained in the chiral Brønsted acid catalyzed reaction between a properly functionalized tryptamine (**619**) and aliphatic aldehyde (**620**) (Scheme 5.282) [499].

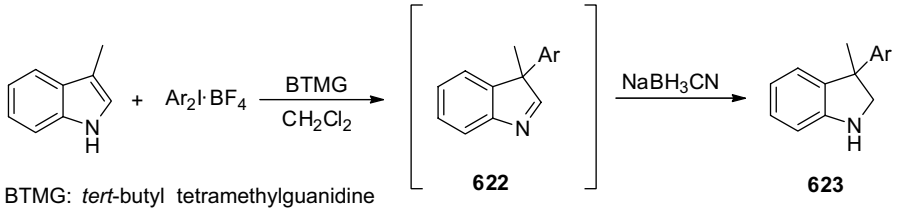
5.7.2.1.3 **Indole as Nucleophile in Pd-Catalyzed Allylic Alkylations** The Pd-catalyzed allylic alkylation reaction has been applied in the allylation of 3-substituted indoles, leading to indolenines featuring a C3-quaternary center [500].

The electrophilic arylation of 3-substituted indoles employing diaryl λ^3-iodanes as electrophilic aryl transfer reagents leads to indolenines **622**, which also feature a C3-



Scheme 5.282

quaternary center (Scheme 5.283) [501]. The relative unstable indolenines **622** are isolated upon reduction to the corresponding indolines **623**.



Scheme 5.283

5.7.2.2 Transition Metal Catalyzed Reactions

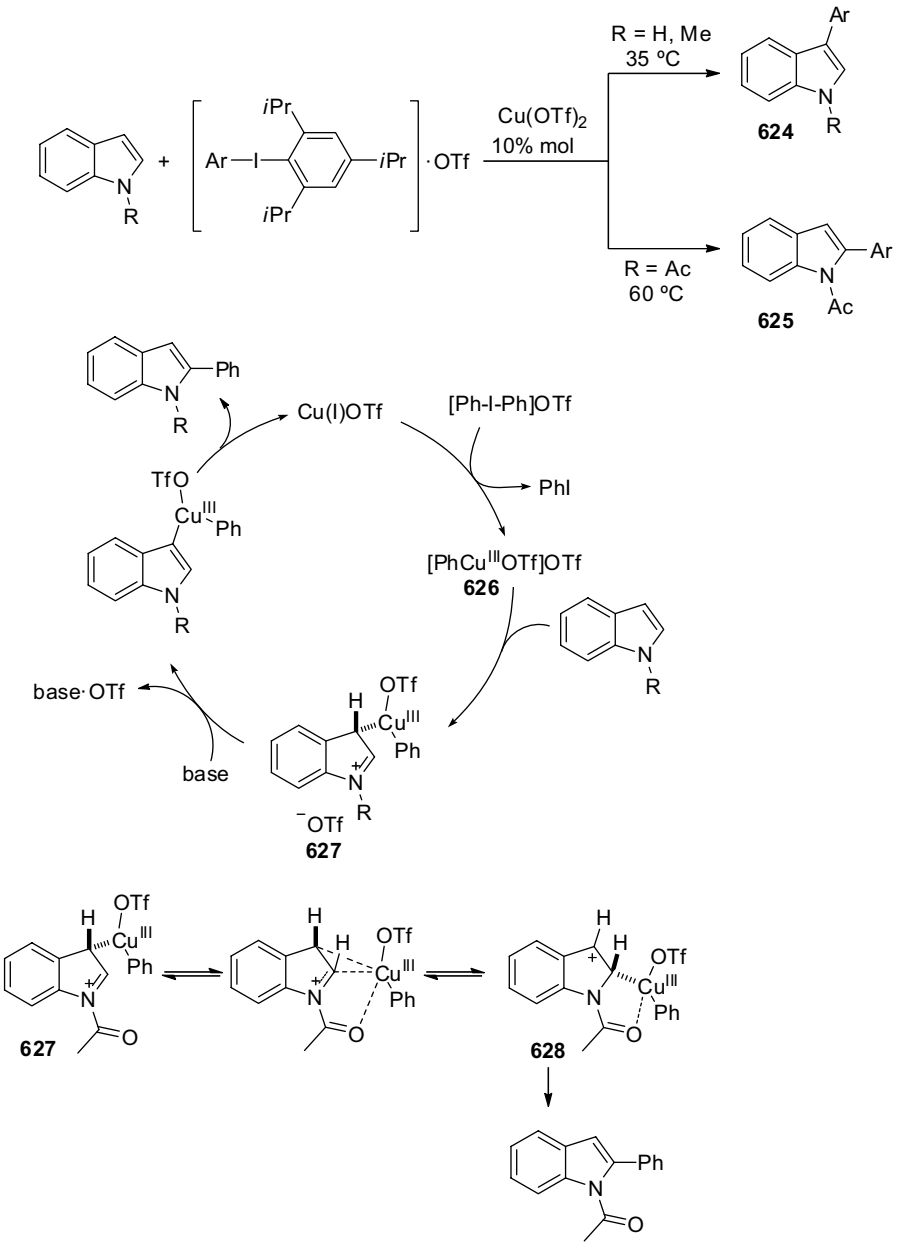
5.7.2.2.1 **Direct Alkenylation, Alkynylation, and Arylation reactions** The indole ring has served as a platform to develop new C−C bond-forming cross-coupling from C−H bonds. Indeed, much effort has been made in very recent years in the study of the direct arylation of indoles, which has led to very exciting achievements in transition metal catalysis. A review in this field is available [502].

Palladium(II)-catalyzed C2-alkenylation has been reported that employs *N*-(2-pyridyl)sulfonyl indoles [503].

Very recently, an intermolecular Au(I)-catalyzed alkynylation of indoles has been disclosed [504].

Palladium-catalyzed selective arylation of indoles at C2 under mild conditions has been accomplished employing a $Pd^{II/IV}$ catalytic cycle [505]. A different strategy for the C–H arylation, employing boronic acids, has also been reported [506].

Site-selective arylation at either C2 or C3 has been described that employs a Cu(II) catalyst and diaryl-iodine(III) reagents as electrophiles (Scheme 5.284) [507]. Aryla-



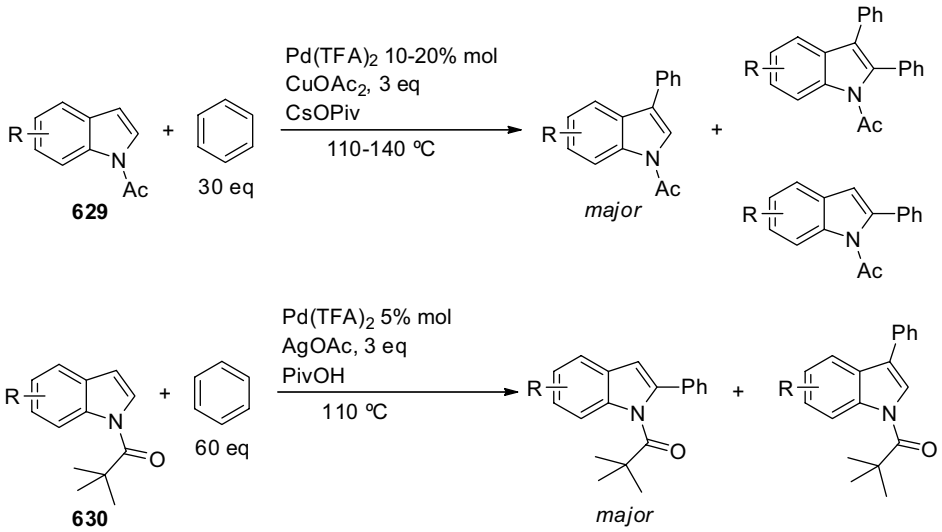
Scheme 5.284

tion at C3 to give **624** occurs on N-H and N-Me indoles, while N-acetylated indoles undergo arylation at C2 leading to **625**. The catalytic cycle proposed for this reaction involves a Cu^{I}/Cu^{III} system (Scheme 5.284), and involves oxidative addition to give a highly electrophilic Cu(III) species (**626**) that undergoes attack at the 3 position of the

indole to form intermediate **627**. Rearomatization and reductive elimination releases the arylated product and regenerates the Cu(I) catalyst.

For the N-acetylated indole, the intermediate **627** suffers a C3–C2 migration directed by complexation with the oxygen atom of the carbonyl, giving rise to the C2-metallated system **628**. Reductive elimination and rearomatization provide the C2-arylates indole.

A truly remarkable achievement, carried out by the group of the late Keith Fagnou, is the arylation of indoles with unactivated arenes (Scheme 5.285) [508]. The reactions take place in the presence of a Pd(II) catalyst and a stoichiometric oxidant. C3 or C2 selectivity can be controlled by modification of several parameters: the stoichiometric metal oxidant, the substitution at the N atom of the indole, and the additives present in the reaction. Typically, N-acetyl indoles **629** give C3 arylation, while N-pivaloyl indoles **630** suffer arylation at C2.

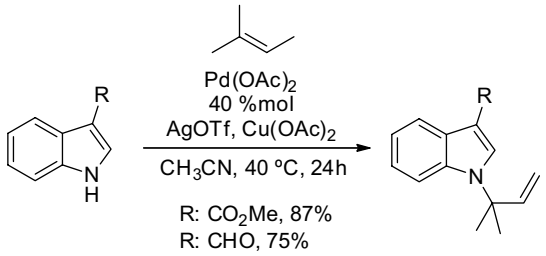


Scheme 5.285

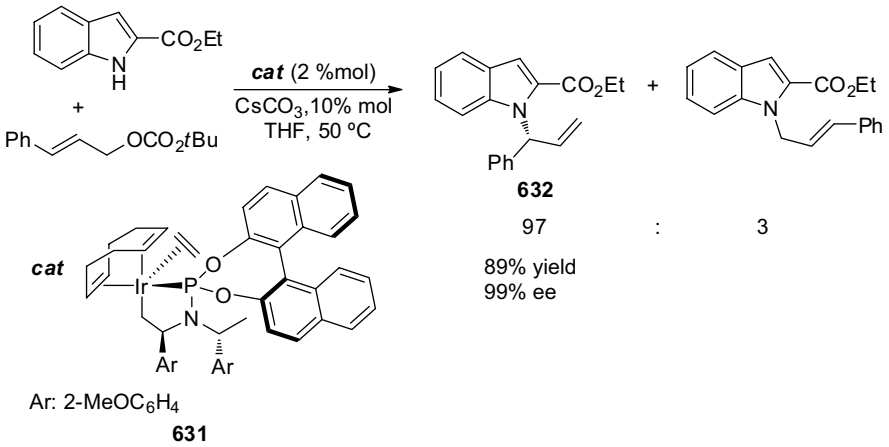
5.7.2.2.2 **C—N Bond-Forming Reactions** The introduction of secondary and tertiary substituents at the N position of the indole is a challenging transformation. Important advances in this sense have been achieved recently.

A one-step *tert*-prenylation of indoles has been devised employing a Pd(II) catalyst (Scheme 5.286) [509]. This is an important transformation as the prenyl group is present in a large number of indole natural products and intermediates.

Various contributions have appeared regarding the asymmetric N-allylation of indoles [510]. For instance, a method has been described employing a chiral metallacyclic iridium phosphoramidite complex (**631**, Scheme 5.287) [511]. This important reaction provides the corresponding N-allylated indoles **632** with total regioselectivity (no C3-allylation occurs) for a wide range of 2,3-disubstituted, 3-



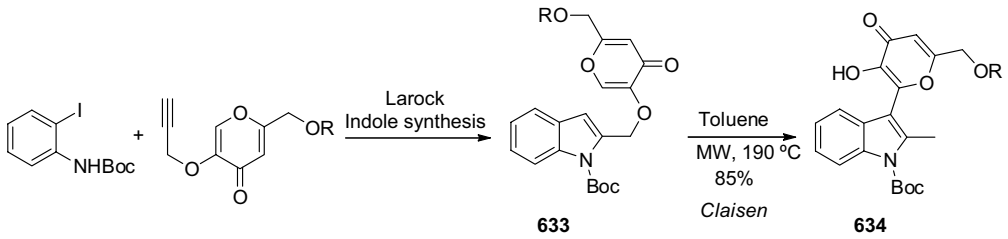
Scheme 5.286



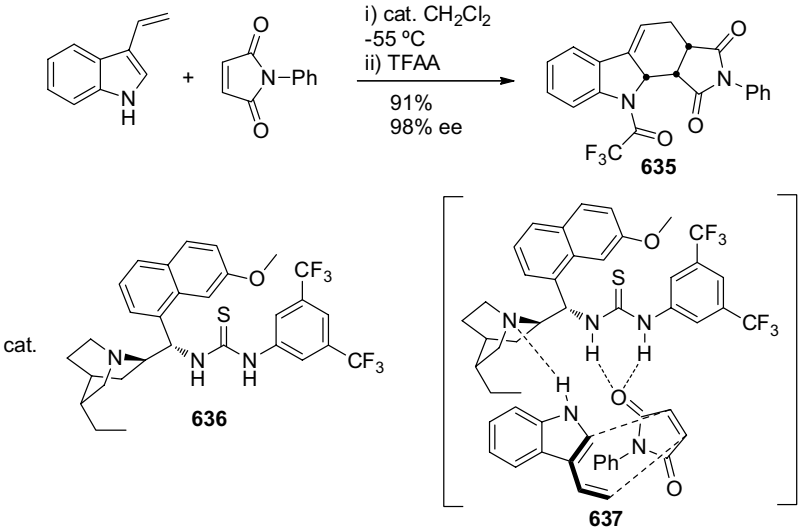
Scheme 5.287

substituted, and also 2-substituted indoles. In the last case, the presence of an electron-withdrawing group at C2 is necessary to reduce the reactivity of the C3 position and direct the reaction to the N-position. The branched regioisomer **632** is always obtained as major or exclusively with very high enantiomeric excesses.

5.7.2.2.3 **Pericyclic Reactions** A Claisen rearrangement involving the C2–C3 bond of the indole is the key step in the synthesis of kojic acid derivatives **634** (Scheme 5.288) [512]. The intermediate pyranone substituted indole **633** is prepared employing the Larock indole synthesis.



Scheme 5.288



Scheme 5.289

A highly enantioselective organocatalytic [4 + 2] cycloaddition of 3-vinylindoles with maleimides has been reported recently (Scheme 5.289) [513]. The reaction gives rise to indolenines **634** with very high yields and enantioselectivities. The chiral thiourea **635** is the catalyst for the reaction. The nearly complete enantioselectivity obtained has been justified by the simultaneous interaction of the organocatalyst with diene and dienophile, as presented in the transition state model **636**.

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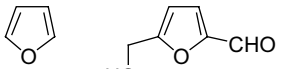
6
Five-Membered Heterocycles: Furan

Henry N.C. Wong, Xue-Long Hou, Kap-Sun Yeung, and Hui Huang

6.1
Introduction

Furan (**1**) is prepared by a gas-phase decarbonylation procedure starting from furfural, which, in turn, is produced in large amounts via an acid treatment of vegetable residues after industrial production of porridge oats and cornflakes [1]. In addition, acid-promoted dehydration of saccharides such as D-fructose also leads to the formation of hydroxymethylfurfural (**2**) [2, 3]. In this connection, furan (**1**) and hydroxymethylfurfural (**2**) are generally regarded as compounds that are readily accessible from renewable resources.



1 **2**

The structure of **1** is closely related to those of pyrrole and thiophene. There are two electron lone pairs on the oxygen atom, one being conjugated with the two double bonds to form a sextet, and the other located in the molecular plane in an sp^2 hybrid orbital.

Furan molecular frameworks are found in many naturally occurring molecules, and play a very significant role in the field of heterocyclic chemistry. Furans have been applied to various commercially important products such as pharmaceuticals, flavors and fragrant products, and functional polymers. They are also versatile precursors and synthetic intermediates in the preparation of cyclic and acyclic molecules. For example, furans are latent 1,4-dicarbonyl units and are also widely employed as 1,3-dienes in Diels–Alder reactions. Efficient synthesis of polysubstituted furans therefore continues to be of great interest to synthetic chemists due to their widespread applications and frequent occurrence in Nature [4].

Modern Heterocyclic Chemistry, First Edition.
Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.

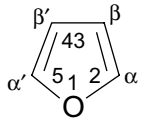


Figure 6.1 Numbering of the furan ring system.

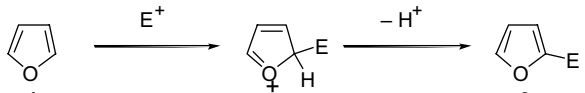
6.1.1 Nomenclature

The positions next to the oxygen atom are indicated as α and α′, while those away from the oxygen are called β and β′. Figure 6.1 shows the numbering of the furan ring system [5]. Reduced furans are called 2,3-dihydrofuran (**3**), 2,5-dihydrofuran (**4**) and 2,3,4,5-tetrahydrofuran (**5**).

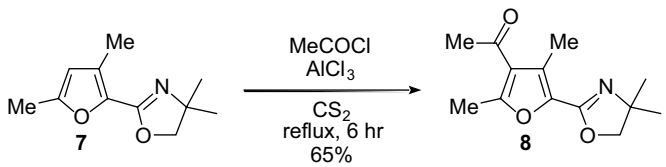
3 **4** **5**

6.1.2 General Reactivity

Sections 6.3 and 6.4 give a much more thorough discussion on the reactions of furan **1** and its derivatives. Here we concentrate on the overall reactivity of **1** [1, 6]. In general, furans are rather stable towards weak aqueous acids. However, in concentrated sulfuric acid or Lewis acids the furan framework will be decomposed. Of the three types of five-membered heterocycles that contain NH, S or O, furans are the least aromatic [7] and would therefore react like dienes. Electrophilic substitution reactions with **1** are regiospecific and lead to mostly α-substituted furans **6** via a general addition–elimination pathway (Scheme 6.1) [1, 6, 8]. β-Substitution reactions only occur when both the α and α′ positions are occupied by substituents. Scheme 6.2 depicts an example of β-acylation, in which **7** is converted into **8** [9].

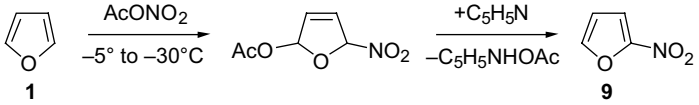


Scheme 6.1



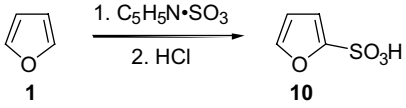
Scheme 6.2

In a nitration reaction, furan **1** reacts with acetyl nitrate to give, initially, an addition product, which undergoes subsequent elimination to offer 2-nitrofuran (**9**) (Scheme 6.3).



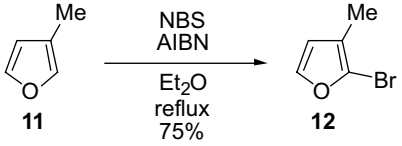
Scheme 6.3

In sulfonation reactions, furan (**1**) is again sulfonated at C2, with a pyridine–sulfur trioxide complex, followed by acidification with hydrochloric acid to afford **10** (Scheme 6.4).



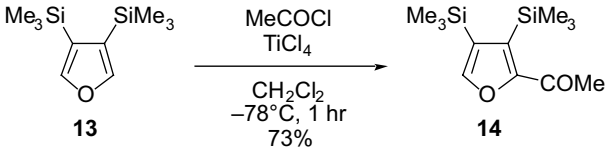
Scheme 6.4

Halogenation reactions are trickier with furans. Thus, polyhalogenated products are obtained from **1** through reactions with chlorine and bromine at room temperature. Pure 2-chlorofuran and 2-bromomfuran can only be obtained when **1** reacts with chlorine in dichloromethane at $-40\,^{\circ}C$, and bromine in dioxane at $0\,^{\circ}C$, respectively. 3-Methylfuran (**11**), in contrast, reacts with *N*-bromosuccinimide (NBS) to furnish 2-bromo-3-methylfuran (**12**) (Scheme 6.5) [10].



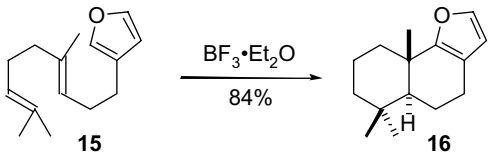
Scheme 6.5

Acylation under Vilsmeier–Haack conditions with a catalyst such as boron trifluoride etherate or phosphoric acid converts **1** into 2-acylfurans. As shown in Scheme 6.6, treatment of 3,4-bis(trimethylsilyl)furan (**13**) with acetyl chloride and titanium(IV) chloride affords the α-acetylfuran **14** [11].



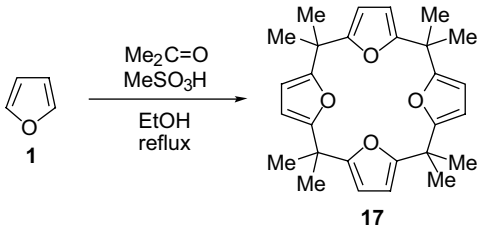
Scheme 6.6

Scheme 6.7 gives an appropriate example of a Lewis acid catalyzed alkylation of a furan moiety (**15**) [12]. This reaction is stereospecific, leading only to the trans-fused diastereomer **16**.



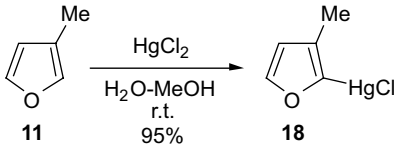
Scheme 6.7

Condensation of **1** with acetone in the presence of an acid, intriguingly, gives 16-membered macrocycle **17** (Scheme 6.8) [13].

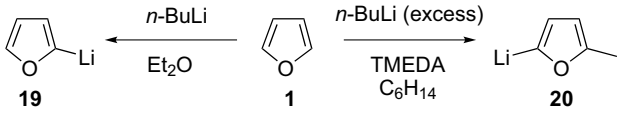


Scheme 6.8

Metallation such as mercuration with mercury (II) chloride and sodium acetate leads to α-mercurated furans. As demonstrated in Scheme 6.9, 3-methylfuran (**11**) undergoes mercuration to give the corresponding furanmercuric chloride **18** [14]. Lithiation with alkyllithium in refluxing diethyl ether proceeded smoothly at C2, providing a 2-lithiofuran (**19**). In the presence of tetramethyl ethylenediamine (TMEDA) in hexane, 2,5-bis(lithio)furan (**20**) is formed instead (Scheme 6.10) [15].

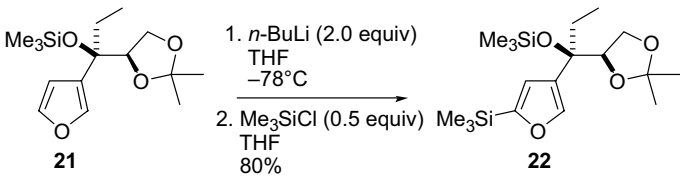


Scheme 6.9



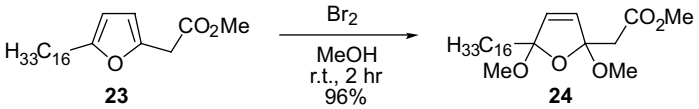
Scheme 6.10

Lithium chemistry opens up an avenue for the realization of some useful α-substituted furans. An example is shown in Scheme 6.11 [16]. As can be seen, an excess of butyllithium presumably generates a 2,5-bis(lithio)furan, which is then silylated at the less hindered side to give furan **22** with a 2,4-disubstituted pattern.



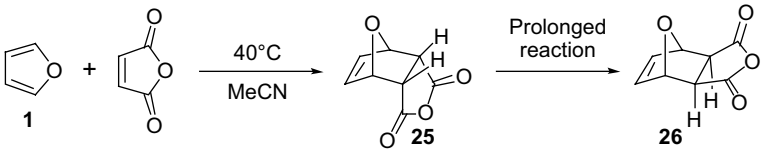
Scheme 6.11

Furan (**1**) undergoes catalytic hydrogenation to afford the very commercially important solvent tetrahydrofuran. As mentioned above, furans behave like a 1,3-diene, so the reaction of 2,5-disubstituted furan **23** with methanolic bromine produces 2,5-dimethoxy-2,5-dihydrofuran **24** (Scheme 6.12) [17].



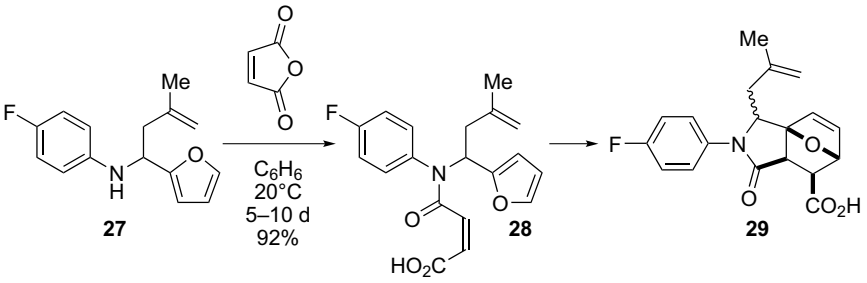
Scheme 6.12

The diene character of furan can be further demonstrated by its Diels–Alder cycloaddition reaction with maleic anhydride, forming the *endo*-adduct **25** at a lower temperature as the kinetic product, and an *exo*-product **26** as the thermodynamic product after much longer reaction times or at a higher temperature (Scheme 6.13). Notably, this cycloaddition reaction was one of the reactions that led Otto Diels and Kurt Alder to report their now famous Diels–Alder reaction [18]. A recent example utilizing an intramolecular Diels–Alder reaction between the furan unit **27** and maleic anhydride, leading to the Diels–Alder adduct **29** via **28**, is shown in Scheme 6.14 [19].



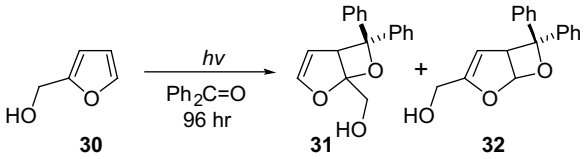
Scheme 6.13

Under the conditions of the Paterno–Büchi reaction, hydroxymethylfuran (**30**) reacts readily with benzophenone to form the [2 + 2] adducts oxetanes **31** (65%) and

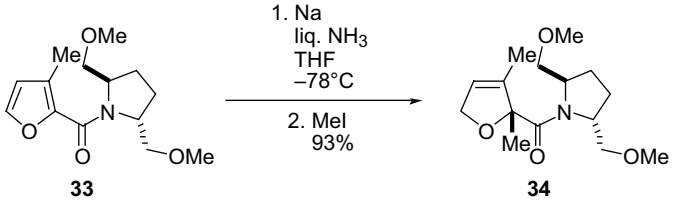


Scheme 6.14

32 (20%) (Scheme 6.15) [20]. Reductive methylation of furan **33** with sodium in liquid ammonia and subsequent addition of methyl iodide, on the other hand, afforded 2,5-dihydrofuran **34** (Scheme 6.16) [21].



Scheme 6.15



Scheme 6.16

6.1.3
Relevant Physicochemical Data [8]

Furan (**1**) shows only limited solubility in water (1 part in 35 at 20 °C) [8]. The hydrogen bonding effect of its oxygen atom with the water protons is the reason why it is more soluble in water than thiophene (1 part in 700 at 20 °C).

Microwave spectroscopy of **1** and its deuterated analogs in the gas phase has been reinvestigated, and highly accurate structure parameters have been obtained [22]. The dimensions are shown in Figure 6.2. In contrast, the solid-state structural dimensions of furan-2-carboxylic acid [23] and furan-3,4-dicarboxylic acid [24] have been determined by an X-ray diffraction study; the values obtained are in good agreement with those found in the gas phase study [22].

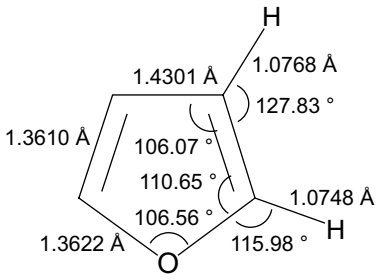


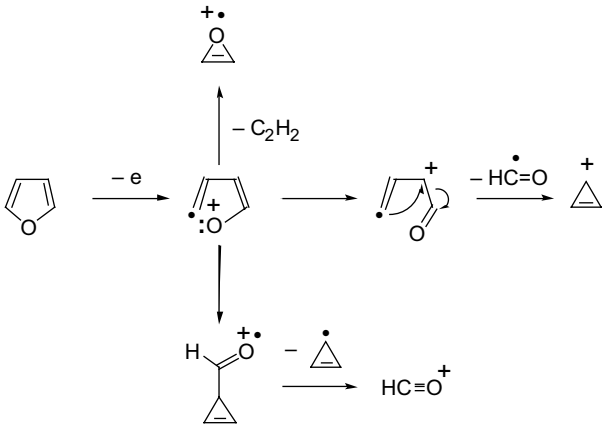
Figure 6.2 Geometry of furan.

The UV/Visible spectroscopic absorption maximum of furan (**1**) in ethanol is λ_{max} 208 nm (log ε 3.9). This value is the smallest amongst pyrrole (210 nm) and thiophene (235 nm), and is therefore a good indication that **1** behaves more like a diene than a conjugated system [25].

Chemical shifts of protons are related to the electron-density of the carbons they are attached to, with lower field shifts corresponding to electron-deficient carbon centers. Thus, the α-proton signals of furan (**1**) at δ 7.29 are at a lower field than those of the β-protons (δ 6.24), which is primarily due to the inductive electron-withdrawing effect of the oxygen atom [26]. Coupling constants between protons on **1** are $J_{2,3} = 1.75$ Hz, $J_{2,4} = 0.85$ Hz, $J_{2,5} = 1.40$ Hz and $J_{3,4} = 3.30$ Hz [27]. ^{13}C NMR chemical shifts also show the electron-withdrawing effect of the oxygen atom, giving signals at δ 142.7 ppm of the α-carbons and δ 109.6 ppm for the β-carbons [28].

In its mass spectrum, the fragmentation pathway of furan **1** is like that of other five-membered heterocycles (Scheme 6.17). For **1**, the strongest peak (70%) is the molecular ion [29].

The He(1α) photoelectron spectrum of furan (**1**) [30] reveals the energy of the third molecular orbital (π_3) as 8.89 eV, which is also the energy of the highest occupied



Scheme 6.17

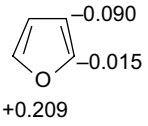


Figure 6.3 π-Electron excess at positions 2 and 3 of furan.

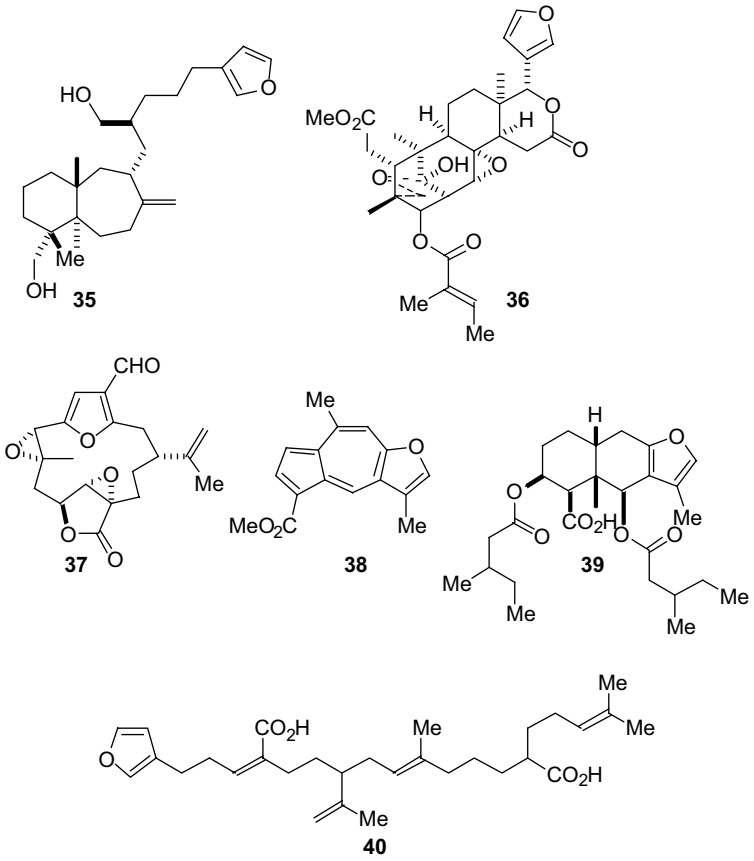
molecular orbital as well as close to the first ionization potential (IP_1) of **1** (8.99 eV) [31]. Other molecular orbital energies π_1 and π_2 are measured at 14.4 and 10.2 eV, respectively. Since a high π-donation character of a compound always leads to substantial π-electron excess, the best measure of π-donation is the value of the first ionization potential (IP_1). In this connection, furan and thiophene ($\pi_3 = 8.92$ eV) [32] show almost equal π-donor properties, while that of pyrrole is significantly larger ($\pi_3 = 8.2$ eV) [32]. HMO calculations lead to the same conclusion, namely that the total π-electron excess of **1** is smaller than that of pyrrole [8]. As can be seen in Figure 6.3, the β-carbon atoms carry significantly larger negative charges than the α-carbons. Such a distribution of π-electron excess is also in good agreement with the larger shielding of H_β- and C_β-nuclei in the proton and ^{13}C NMR spectra, respectively [8].

The Pariser–Parr–Pople (PPP) approximation method reproduces well the electronic spectral features of furan (**1**) [33], while the simple Hückel method has also been employed to compute the resonance energy of **1** in a quantitative manner, providing a value of 18 kcal mol^{-1}, which is less stable than thiophene (resonance energy 29 kcal mol^{-1}) [34]. Satisfactory molecular geometry and heat of formation for **1** have been obtained from MINDO/3 semi-empirical MO calculations [35]. In addition, MINDO/3 calculated vibration frequencies for **1** [36] agree well with values obtained experimentally [37]. In addition, satisfactory dipole moment [38] and ionization energies [39] for **1** have been obtained from an *ab initio* calculation. The electronic spectrum [40] and electronic structure [41] of **1** have also been computed by other *ab initio* methods.

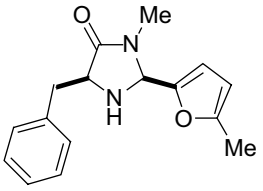
6.1.4
Relevant Natural and Useful Compounds

As mentioned in Section 6.1, the furan molecular skeleton is found widely in many naturally occurring molecules. Shown below are several furan-containing natural products (**35**–**40**) identified in 2004 and 2005. Thus, shinsonefuran (**35**), a sesterterpene exhibiting cytotoxicity against HeLa cells with an IC_{50} of 16 μg mg^{-1}, was obtained from the deep-sea sponge *Stoeba extensa* [42]. A limonoid containing also a 3-substituted furan, namely xyloccensin L (**36**), was isolated from the stem bark of *Xylocarpus granatum* [43]. The new furanocembranolide **37** was isolated from the octocorals *Leptogorgia alba* and *Leptogorgia ridida* collected on the Pacific coast of Panama [44]. The linderazulene **38**, a novel azulenoid showing moderate activity against the PANC-1 pancreatic cell line with an IC_{50} of 18.7 μg ml^{-1}, was obtained from a deep-sea gorgonian *Paramuricea* sp. [45]. In

a chemical and genetic study of *Ligularia tongolensis* in the Hengduan Mountains of China, a strongly Ehrlich-positive furanoeremophilane compound (**39**) was identified [46]. During automated screening for small-molecule agonists to peroxisome proliferator-activated receptor-γ (PPAR-γ), a new biologically active linear triterpene **40** was isolated and characterized from the bark of *Cupaniopsis trigonocarpa* [47].



Furan-containing molecules are also useful as catalysts, pharmaceuticals and electronic devices. For example, in the synthesis of a highly potent and selective serotonin reuptake inhibitor (BMS-594726), MacMillan's furan-containing imidazolidinone catalyst **41** [48] has been employed in the key enantioselective indole alkylation step, leading to a desired product with an enantiomeric excess of 84% [49]. Ranitidine (**42**) (Zantac©), a histamine H_2-receptor antagonist that inhibits gastric acid secretion, possesses a furan framework as the pivotal structural unit [50]. Anther furan-containing oligoarylcyclophanene (**43**) – showing a strong broad luminescence at 499 nm, due presumably to an intramolecular interaction between the chromophores and the presence of a double bond – has potential use in opto-electronic devices [51].



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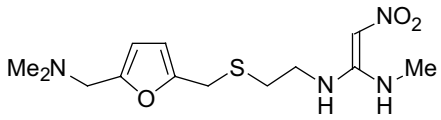

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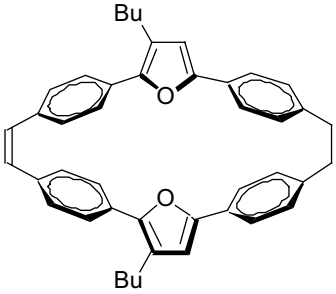


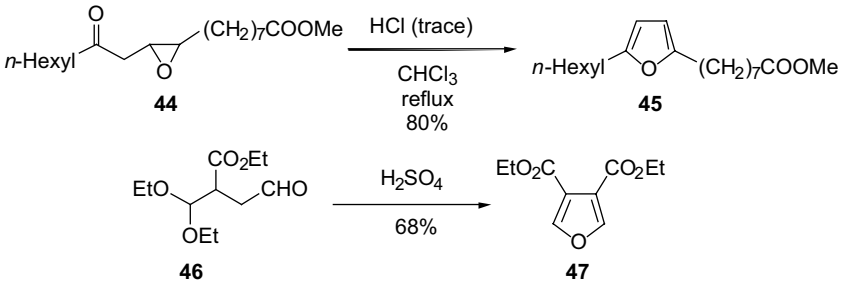
43

6.2 Synthesis of Furans

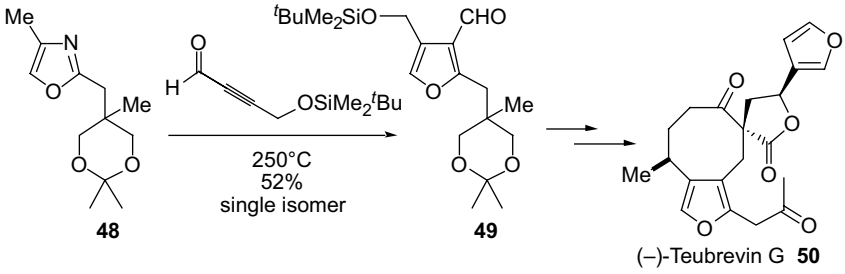
6.2.1 Introduction

The synthesis of furans has continued to attract the attention of synthetic chemists during the past several decades [4]. In this connection, many efficient procedures have been documented. Some of these methods have become standard procedures and have been extremely useful in the synthesis of furans with different substituted patterns. One of these classical methods is the acid-catalyzed dehydration reaction of 1,4-diketones to form furans, known as the Paal–Knorr synthesis [52]. Not only 1,4-ketones but also masked diketones, such as chloroallyl ketones and oxiranes with appropriate substituents, as well as 1,4-dicarboxylic acid derivatives, including esters and nitriles, are suitable substrates. Many variants have also been recorded. Furthermore, cyclization of γ-hydroxy ketones or aldehydes in the presence of an acid catalyst can also provide the corresponding substituted furans. Various acids, such as sulfuric acid, *p*-toluenesulfonic acid, oxalic acid, Amberlyst 15 and zinc bromide, have been used as catalyst. Some examples (**44** → **45** and **46** → **47**) are shown in Scheme 6.18 [53].

Reaction of oxazole derivative **48** and a dienophile via a Diels–Alder cycloaddition–retro-Diels–Alder reaction strategy provides a useful protocol to produce furan **49** with different substitution patterns, provided these starting materials are carefully chosen (Scheme 6.19). The procedure has been employed in the total synthesis of (−)-teubrevin G (**50**) [54]. Furans themselves may also serve as dienes in the reaction with electron-deficient alkynes, leading to 7-oxabicyclic compounds, which undergo a retro-Diels–Alder reaction to provide the corresponding furans. The advantages of this strategy lie in the functional group compatibility as well as the starting material



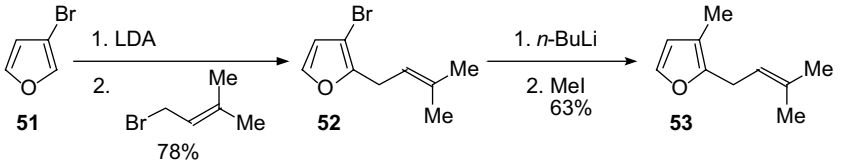
Scheme 6.18



Scheme 6.19

accessibility. If the availability of starting materials is not a problem, this procedure may be regarded as the simplest and the most efficient.

Organometallic compounds have found significant application in furan synthesis in recent years. A lithiation–electrophile trapping strategy has been widely applied to the synthesis of 2,3-disubstituted and 2,3,5-trisubstituted furans. These furyllithium species have been obtained by various means, such as the direct metallation of furans at the α-position using *n*-BuLi or LDA (Scheme 6.10) [15] or using lithium magnesates [55] and metal–halogen exchange methodology. All these furyllithium compounds can be converted into the corresponding substituted furans upon quenching with various electrophiles such as halides or carbonyls. As shown in Scheme 6.20, 3-bromofuran **51** can be lithiated and alkylated at the α-carbon to afford **52**, which undergoes further reactions to give rosefuran (**53**) [56]. Furyllithium species can also be converted into other organometallic species, such as titanium and manganese derivatives through a transmetallation procedure. In addition to titanium and manganese derivatives, organocopper, zinc and tin have all been utilized in the preparation of polysubstituted furans [57].



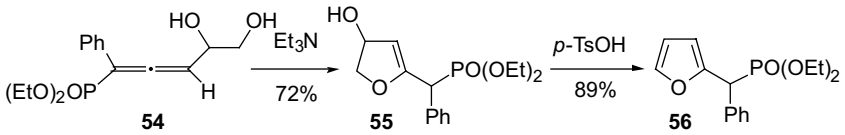
Scheme 6.20

Despite the fact that a lot of strategies and procedures for the synthesis of furans have been recorded, the quest for efficient and reliable synthetic methodologies, especially with acceptable regioselectivity, is still an active research field. Some progress in this area is reviewed in the following section.

6.2.2 Monosubstituted Furans

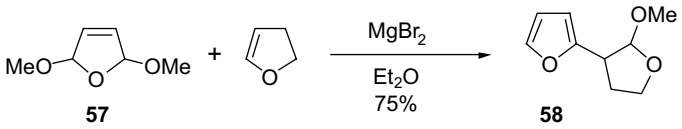
Transition metal catalyzed coupling reactions of arenes and halides and amines have been very popular in the synthesis of arene derivatives. These protocols can also be used in the synthesis of furans with substituents at different positions. C–N cross-coupling reaction of a bromo-substituted furan with various amides, carbamates and lactams catalyzed by CuI furnishes 2- and 3-substituted amidofurans in 45–95% yield [58]. Arylboronic acid has been employed as an aryl source in the synthesis of 2-arylfuran under Mn(II) acetate-promoted radical reaction conditions. Although the yields are not high, they are better than those of the phase-transfer Gomberg–Bachmann synthesis using arenediazonium ions [59]. Arylation of 3-furoate with 3-bromonitrobenzene using $Pd(PPh_3)_4$ as catalyst in toluene affords 2,3-disubstituted furan while 5-aryl products are generated predominantly when Pd/C is used as the catalyst and NMP as solvent [60].

2-Substituted furan **56** has been prepared using the phosphorylated allenic glycol **54** through a cyclization pathway under basic conditions, followed by dehydration of intermediate **55** in the presence of a catalytic amount of *p*-TsOH (Scheme 6.21) [61].



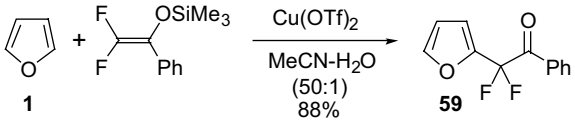
Scheme 6.21

2-Substituted furans can be prepared under mild conditions. Thus, reaction of 2,5-dimethoxy-2,5-dihydrofuran (**57**) and an appropriate vinyl ether in the presence of a catalytic amount of $MgBr_2 \cdot Et_2O$ affords a functionalized 2-alkylfuran **58** in good yields (Scheme 6.22). The reaction might proceed through a concerted mechanism, in which the $MgBr_2$-activated dihydrofuran reacts with the vinyl ether via a cyclic intermediate [62].



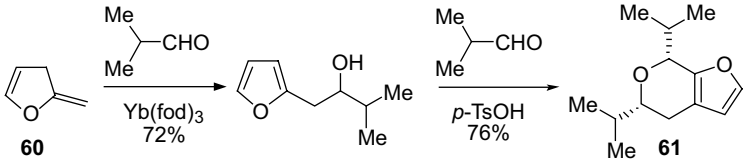
Scheme 6.22

Furyldifluoromethyl aryl ketones **59** are formed when furan (**1**) is allowed to react with difluoroenol silyl ethers in the presence of $Cu(OTf)_2$ as depicted by an example in Scheme 6.23 [63]. If 2-furfurylcarboxylate is used, the corresponding substituted furan is also obtained [63].



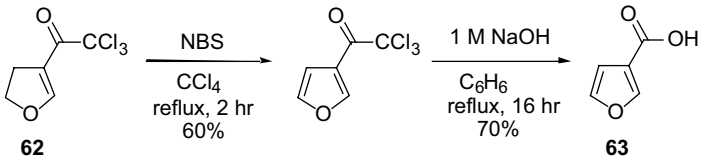
Scheme 6.23

The $Yb(fod)_3$-catalyzed carbonyl-ene reaction of 3-methylene-2,3-dihydrofuran (**60**) and aldehydes is a mild, efficient way to provide 2-substituted furans, which can be transformed into furano[2,3-*c*]pyrans **61** in good yield via the oxa-Pictet–Spengler procedure (Scheme 6.24) [64]. Similarly, **60**, produced from the Wolff–Kishner reduction of 2-furylhydrazone, reacts with aldehydes in the presence of $Yb(fod)_3$ or $Ti(OPr\text{-}i)_4$, to afford the same 2-substituted furans. Notably, an optically active product is realized when $Ti(OPr\text{-}i)_4$/(*S*)-BINOL is the catalyst [65].



Scheme 6.24

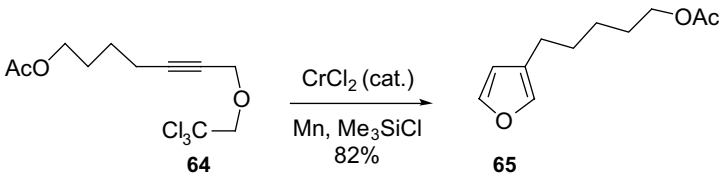
The 2-position of furan is usually derivatized by a simple electrophilic aromatic substitution or metallation. However, the introduction of a substituent to the 3-position of furans requires special strategies. Several such procedures have been developed, one of which is the synthesis of furan-3-carboxylic acid (**63**) via aromatization of 3-trichloroacetyl-4,5-dihydrofuran (**62**) followed by a nucleophilic displacement with hydroxide, alcohols and amines (Scheme 6.25) [66].



Scheme 6.25

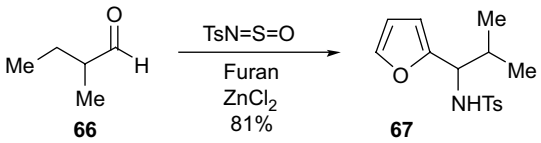
Reductive annulation of 1,1,1-trichloroethyl propargyl ether **64** in the presence of a catalytic amount of Cr(II) regenerated by Mn/Me_3SiCl provides another entry to

a 3-substituted furan (**65**) in high yields (Scheme 6.26). The reaction conditions proved compatible with most other common functional groups. Some natural products, such as perillene and dendrolasin, have been prepared by utilizing this procedure [67].



Scheme 6.26

The reaction of furan with *N*-tosylimine produced *in situ* from TsN=S=O and aldehydes in the presence of $ZnCl_2$ gives no Diels–Alder reaction products. Instead, furyl sulfonamides have been separated in high yields (Scheme 6.27) [68]. This procedure provides an efficient synthesis of 2-substituted furans such as **67** from **66**, and is general with respect to aldehydes. Moreover, it is possible to synthesize 2,3-disubstituted furans by an intramolecular aromatic substitution of *N*-tosylimines at the 3-position of furans.

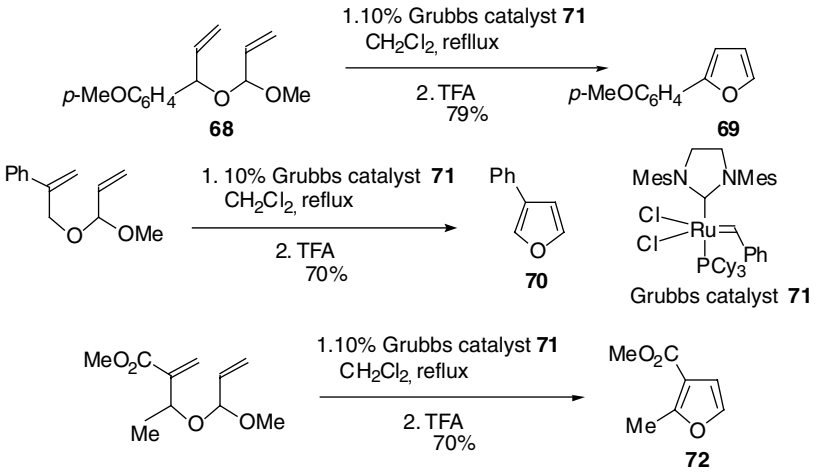


Scheme 6.27

Ring closing metathesis (RCM), one of the most powerful tools for ring-formation, has demonstrated its high efficiency and functional group tolerance. Recently, the RCM reaction has also been employed in the synthesis of substituted furans (e.g., **68** → **69**). A range of different substitution patterns and functional groups are compatible with this sequence, such as the formation of both **70** and **72**, employing also the Grubbs catalyst **71**(Scheme 6.28) [69].

6.2.3
Disubstituted Furans

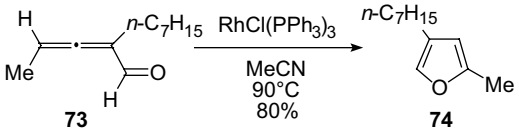
Direct metallation of 2-substituted furan with *t*-BuLi in the presence of TMEDA followed by treatment of the lithiated furan species with electrophiles provides a simple and efficient way to the corresponding 2,3-disubstituted furans [70]. 2-Furancarboxamide reacts with vinylsilanes catalyzed by $Ru_3(CO)_{12}$ or RuHCl $(CO)(PPh_3)_3$ to deliver 3-trialkylsilyl-2-furancarboxamide also in high yield [71]. A general protocol has been developed towards a mild, regioselective arylation of



Scheme 6.28

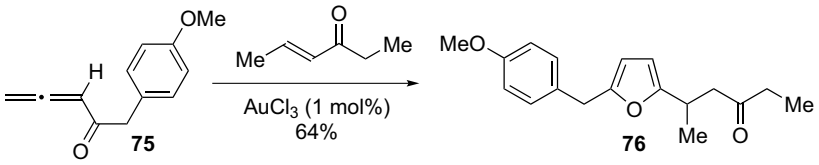
2-furaldehyde using functionalized aryl halides in the presence of a catalytic amount of $PdCl_2$-PCy_3. Slow addition of aryl halides to the reaction mixture avoids the homo-coupling efficiently [72]. A one-pot Suzuki coupling of aryl halides with *in situ* generated 5-(diethoxymethyl)-2-furylboronic acid catalyzed by palladium(0) also gave 5-aryl-2-furaldehydes in high yields [73]. A simple procedure to prepare 5-aryl- and 5-pyridyl-2-furaldehydes from the inexpensive and commercially available 2-furaldehyde diethyl acetal through direct lithiation–transmetallation–electrophile trapping has been reported. The reaction proceeded in a four-step, one-pot manner and the yields of the coupling step were usually 58–91% [74].

Allene derivatives are useful starting materials in the synthesis of furans containing different substitution patterns. In 1990, Marshall found that Rh(I) and Ag(I) can catalyze the isomerization of allene **73** to the corresponding substituted furan **74** in high yield (Scheme 6.29) [75]. Later, this strategy was successfully applied to the synthesis of furanocembranes and other related natural products [76].



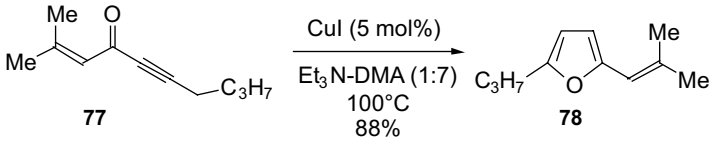
Scheme 6.29

Several reports have discussed the isomerization between allenes and propargyl groups. One example is the intermolecular reaction of allenyl ketone **75** and an α,β-unsaturated ketone catalyzed by $AuCl_3$, which gives rise to 2,5-disubstituted furan **76** in good yield (Scheme 6.30) [77]. Both ethyl propargyl ketone and ethyl allenyl ketone lead to the same 2,5-disubstituted furan.



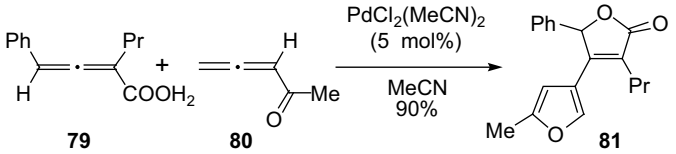
Scheme 6.30

A general, efficient procedure for the preparation of 2,5-disubstituted furans containing acid- and base-labile groups via CuI-catalyzed cycloisomerization of alkynyl ketones such as the conversion of **77** into **78** has appeared (Scheme 6.31), for which a plausible mechanism has been proposed [78]. The allenyl ketone produced from the triethylamine-Cu(I)-catalyzed isomerization of the starting material should be the intermediate. Coordination of copper to the terminal double bond of allene followed by an intramolecular nucleophilic attack of the oxygen lone pair and subsequent isomerization eventually leads to furans as final products. Indeed, 2-phenylfuran was afforded in 33% yield when allenyl phenyl ketone was treated with CuI in DMA.



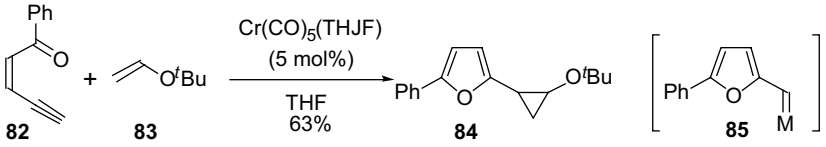
Scheme 6.31

2,4-Disubstituted furan **81** has been obtained in high yield through a novel oxidative cyclization–dimerization reaction between the two different allenes **79** and **80** (Scheme 6.32) [79].



Scheme 6.32

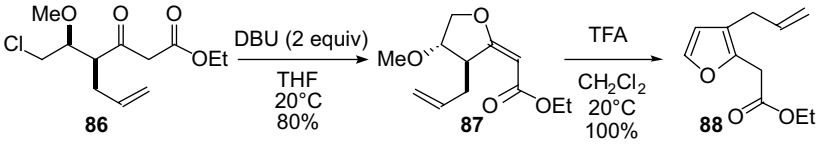
As shown in Scheme 6.33, 2,5-disubstituted furan **84**, with a cyclopropane subunit at the 5-position, has been synthesized in acceptable yield by a metal-catalyzed



Scheme 6.33

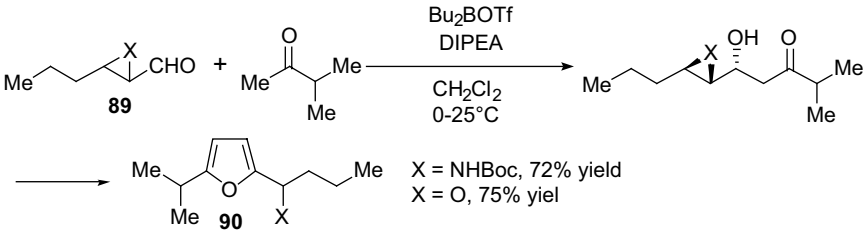
cyclization reaction of 1-benzoyl-*cis*-1-buten-3-yne (**82**) and the enol ether **83** via (2-furyl)carbene complex **85**. Many types of metal complexes, such as Mo, W, Ru, Rh, Pd, and Pt, complexes are suitable catalysts [80].

Reaction of 2-alkynal acetal with a divalent titanium reagent and aldehydes provides, after an acid work up, 2,3-disubstituted furans in good to excellent yields [81]. Michael addition–aldol condensation reactions of α,β-unsaturated enones with an organocopper reagent and (tetrahydropyranyloxy)acetaldehyde have been followed by treatment of the products with *p*-TsOH to afford 2,3-disubstituted furans in moderate to good yields [82]. α,β-Unsaturated carbonyl compounds with an appropriate leaving group undergo 1,5-electrocyclization reactions to yield 2,5-disubstituted furans upon heating in the presence of an acid, presumably through an intermediate formed from 1-oxapentadienyl cations, whose conformational and energy properties were also studied by DFT calculations (B3LYP/6-31 + G*) [83]. A 2,3-disubstituted furan, such as **88**, with different functionalities has been synthesized through an acid-catalyzed elimination reaction of 2-alkylidenetetrahydrofuran **87**, which can be prepared from the cyclization of **86** in high regioselectivity (Scheme 6.34) [84]. 2-Substituted furans and bicyclic furans can be synthesized by this methodology.



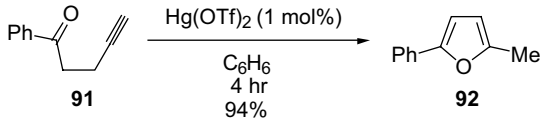
Scheme 6.34

Aldol reaction of aziridine and α,β-epoxyaldehydes (e.g., **89**) followed by an intramolecular enol cyclization in the presence of Bu_2BOTf/DIPEA furnishes 5-substituted-2-furyl amines and carbinols **90** in good yields. The reaction proceeds in a one-pot manner (Scheme 6.35) [85].



Scheme 6.35

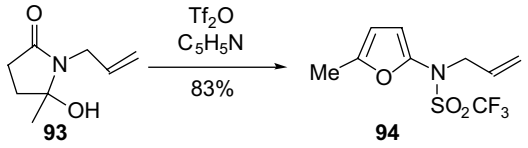
Mercury triflate-catalyzed cyclization of 1-alkyn-5-one **91** produces 2-methyl-5-phenylfuran (**92**) (Scheme 6.36). The reaction may involve a protodemercuration of a vinylmercury intermediate generated *in situ*. When the substituent is at the



Scheme 6.36

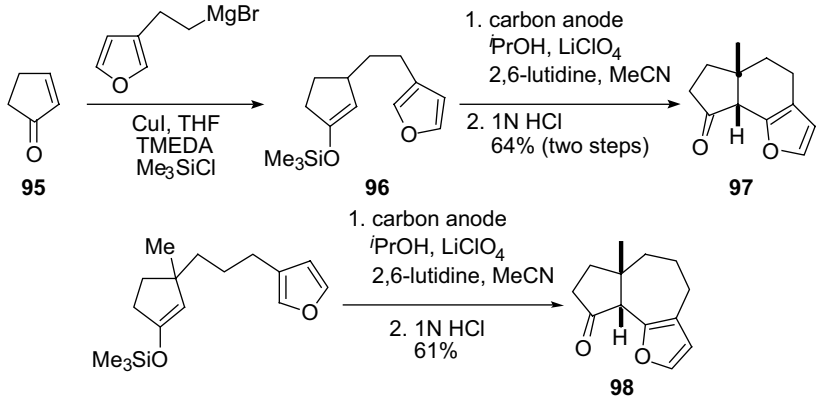
α-position of the carbonyl group, 2-methyl-4,5-disubstituted furans are formed. A plausible reaction mechanism has also been provided [86].

Trifluoromethylsulfonamidofuran **94** has been prepared in high yield through the reaction of a cyclic carbinol amide **93** with triflic anhydride (Scheme 6.37). Many lactams have been tested and the reaction proceeds under mild conditions. Keto-amides are also suitable substrates in these reactions [87].



Scheme 6.37

A two-step electrochemical annulation directed to polycyclic systems containing annulated furans has been developed. This pathway involves an initial conjugate addition of a furylethyl cuprate to cyclopentenone (**95**) and trapping of the enolate as the corresponding silyl enol ether **96**. The second step involves anodic coupling of the furan and the silyl enol ether to form the cis-fused six-membered ring **97** with high stereoselectivity (Scheme 6.38) [88]. The reaction can be extended to the formation of seven-membered ring fused furan **98** [89]. However, the substituent on the 3-position of cyclopentanone is important for the formation of a seven-membered ring fused



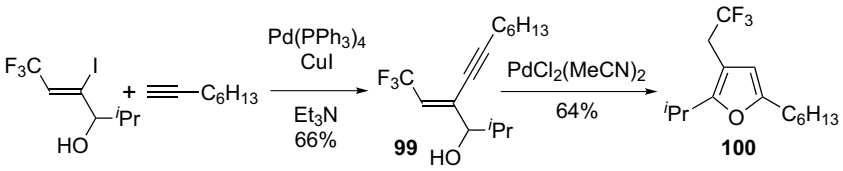
Scheme 6.38

furans. If the substituent is H, no desired cyclization product is provided. The results show that the gem-dialkyl effect plays a crucial role in this electron transfer reaction.

6.2.4
Trisubstituted Furans

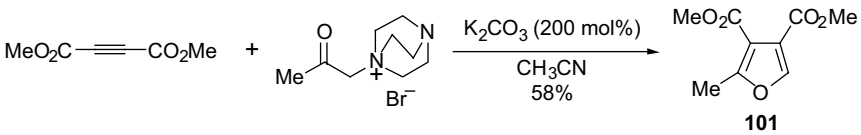
Many procedures mentioned above can also be utilized effectively to the synthesis of 2,3,4- and 2,3,5-trisubstituted furans. In addition, several novel procedures have also been reported.

3-Trifluoromethylfuran **100** has been obtained from (*Z*)-2-alkynyl-3-trifluoromethyl allylic alcohol **99** through a palladium-catalyzed cyclization-isomerization procedure (Scheme 6.39) [90].



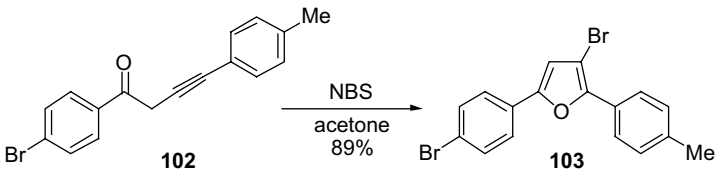
Scheme 6.39

A mild, simple reaction of dimethyl acetylenedicarboxylate with an ammonium ylide supplies trisubstituted furan **101** in good yield (Scheme 6.40) [91].



Scheme 6.40

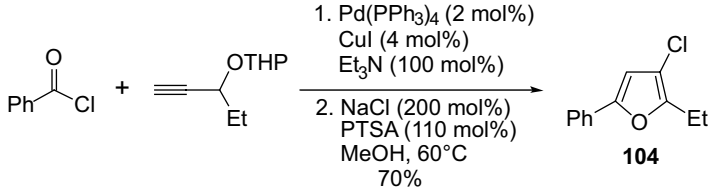
The reaction of 1,4-diarylbut-3-yne-1-one **102** with NBS, NIS or ICl affords, via a 5-endo-dig electrophilic cyclization, 3-halofuran **103** in high regioselectivity and high yield (Scheme 6.41) [92].



Scheme 6.41

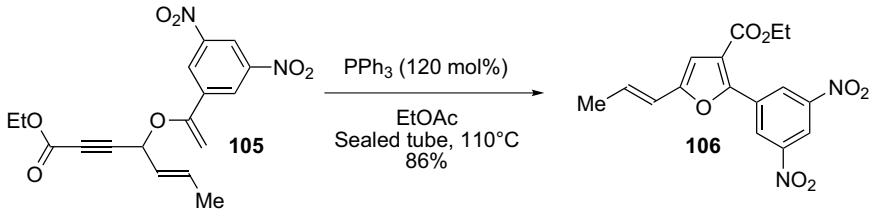
Müller has reported the synthesis of 3-halofurans [93]. Thus, cross-coupling of acid chlorides with THP-protected propargyl alcohols gives rise to the corresponding

alkynones, which undergo an acid-assisted electrophilic addition of hydrogen halide with concomitant deprotection and cyclization to afford 3-chlorofuran **104**. If RB $(OH)_2$ is added to the reaction system before workup, this reaction can provide Suzuki-coupling products in moderate yields (Scheme 6.42).



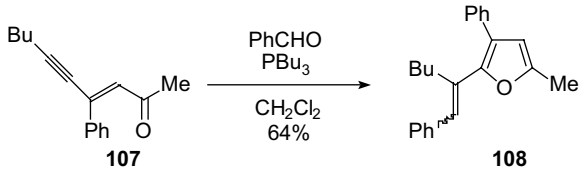
Scheme 6.42

Organic molecules can also be used as catalysts in furan ring formation reactions. Krische has reported an example of organophosphine serving as catalyst in the construction of substituted furans, in which various γ-acyloxybutynoates such as **105** were converted into 2,3-disubstituted, 2,4-disubstituted, and 2,3,5-trisubstituted furans (e.g., **106**) (Scheme 6.43) [94].



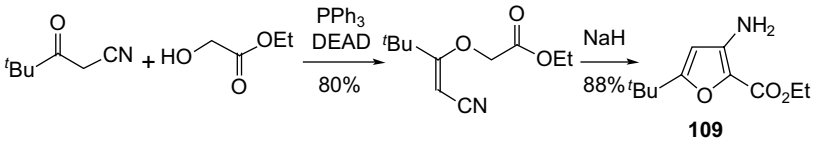
Scheme 6.43

Reaction of 2-penten-4-yn-1-one **107** with benzaldehyde initiated by tributylphosphine delivers 2-vinyl substituted furan **108** in a good yield. The reaction might proceed through a 1,6-addition of phosphine to the enynes, and is followed by ring closure and Wittig reaction between the ylide resulting from cyclization and an aldehyde (Scheme 6.44) [95].



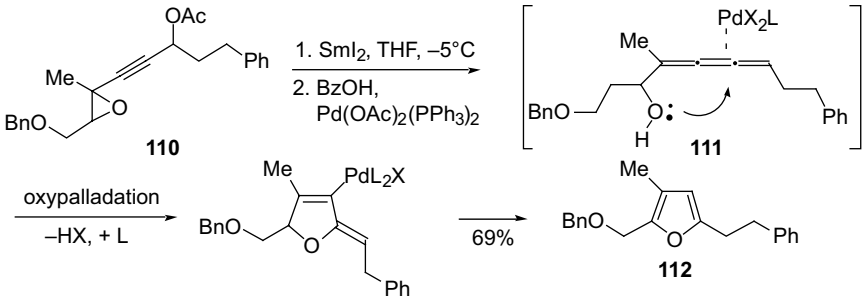
Scheme 6.44

3-Aminofuran-2-carboxylate **109** has been prepared in good yield through the reaction of a cyanoketone with glycolate under Mitsunobu conditions followed by treatment with NaH (Scheme 6.45). 4-Pyridylcarbinol and 4-nitrobenzyl alcohol can also react with cyanoketone to furnish 3-aminofurans [96].



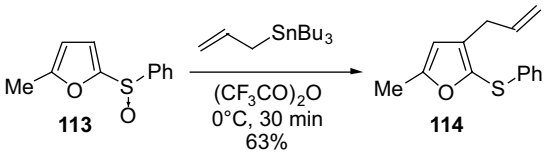
Scheme 6.45

2,3,5-Trisubstituted furan **112** has been synthesized from a two-step one-pot reaction from epoxyalkyne **110**. A facile SmI_2-mediated reduction generates 2,3,4-trien-1-ol **111**, and the reduction is followed by a Pd(II)-catalyzed cycloisomerization (Scheme 6.46) [97]. An attractive variant of this reaction has been extended to the preparation of tetrasubstituted furans. Thus, when electrophilic Pd(II) complexes are generated *in situ* by an oxidative addition of aryl halides or triflates to Pd(0), the oxypalladation process is followed by a reductive elimination and, as a result, tetrasubstituted furans are formed [98].



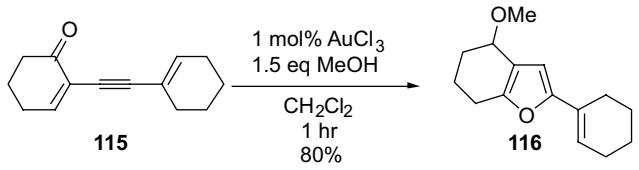
Scheme 6.46

Nucleophilic substitution of sulfinylfuran **113** with acetylacetone and allyl tin reagent via a Pummerer-type reaction has been used in the formation of 2,3,5-trisubstituted furan **114**, as well as with other 2,3-disubstituted furans, in high regioselectivity (Scheme 6.47) [99].



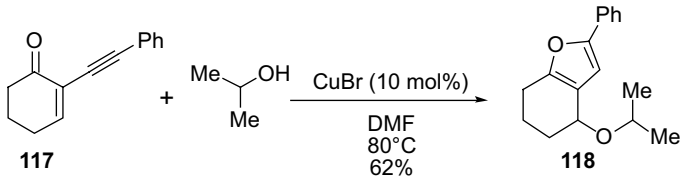
Scheme 6.47

Regioselective gold-catalyzed cyclization of 2-(1-alkynyl)-2-alken-1-one **115** in the presence of a nucleophile affords 2,3,5-trisubstituted furan **116** in an efficient, atom-economical manner. Various alcohols, 1,3-diketones as well as some indoles and amines can serve as nucleophiles. This reaction provides another good example of using gold as catalyst in furan synthesis (Scheme 6.48) [100].



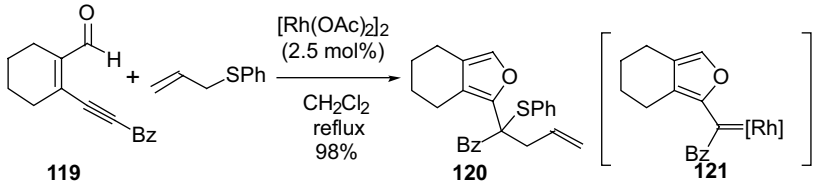
Scheme 6.48

Yamamoto has demonstrated that, in the presence of CuBr as a catalyst, trisubstituted furan **118** is formed from **117** and isopropanol (Scheme 6.49) [101], while Liu has shown that tetrasubstituted 3-iodofurans are afforded on employing similar starting materials and I_2/K_3PO_4 as reagents (see below) [102].



Scheme 6.49

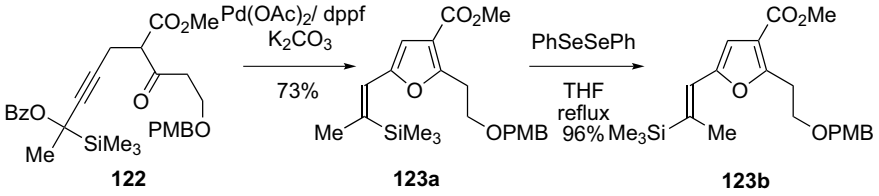
Conjugated ene-yne-carbonyl **119** has been employed as a precursor of 2-furylcarbene **121**. In this way, **121** was allowed to react with an allyl sulfide to form an *S*-ylide followed by [2,3]sigmatropic rearrangement to give the corresponding trisubstituted furan **120** in an excellent yield (Scheme 6.50) [103].



Scheme 6.50

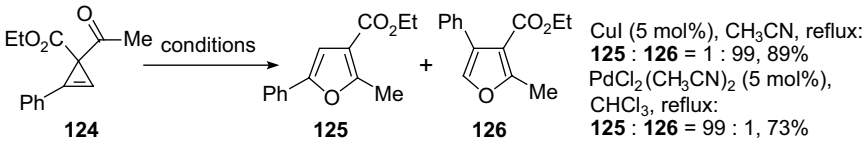
Palladium-catalyzed cyclization of α-propargyl α-keto ester **122** provided 2-alkenyl-4,5-disubstituted furan **123a.** High *E*/*Z*-selectivity is realized when the Me_3Si- group is introduced to the α′-position of the triple bond. The geometry of the double bond

in **123a** is almost completely inverted by reaction with a catalytic amount of diphenyl diselenide, providing **123b**. (Scheme 6.51) [104].



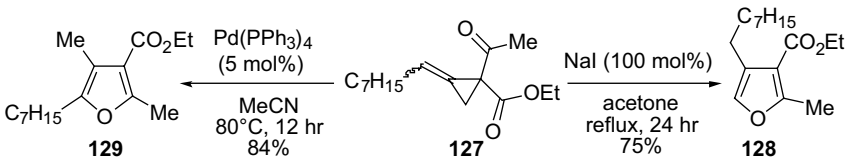
Scheme 6.51

Ma has reported an elegant regioselective synthesis of 2,3,4-trisubstituted furan **126** using a Cu-catalyzed ring-opening cycloisomerization reaction of cyclopropenyl ketone **124** (Scheme 6.52). Notably, the regioselectivity of this reaction can be tuned using different catalysts. 2,3,5-Trisubstituted furan **125** is produced from the same starting materials with excellent regiocontrol using a Pd catalyst [105].



Scheme 6.52

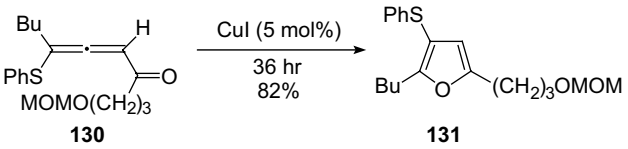
Alkylidenecyclopropyl ketones, analogs of allene ketones, have been used as a starting material in the synthesis of polysubstituted furans. Ma has given another example in which highly regiocontrolled transformation of an alkylidenecyclopropyl ketone (**127**), easily prepared by the regioselective cyclopropanation of an allene or the reaction of alkylidenecyclopropanyllithium with *N*,*N*-dimethyl carboxylic acid amide, into 2,3,4-trisubstituted furan **128** is realized in the presence of NaI. Interestingly, the same starting material **127** gives rise to 2,3,4,5-tetrasubstituted furan **129** if Pd $(PPh_3)_4$ or $PdCl_2(MeCN)_2$ is the catalyst (Scheme 6.53) [106].



Scheme 6.53

Allene derivatives are important precursors in the regioselective synthesis of substituted furans. One example is the reaction of thioallenyl ketone via a 1,2-migration of the thio group from an sp^2 carbon atom in allenyl sulfide **130** catalyzed

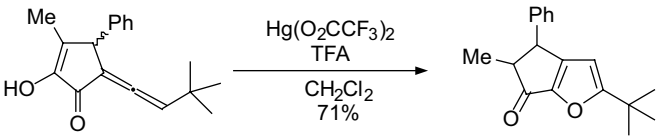
by CuI to afford trisubstituted furan **131** in high yield (Scheme 6.54) [107]. Propargyl sulfides led to similar results. If thiopropargyl aldehydes are used as starting materials, 2,3-disubstituted furans are obtained. This route therefore provides a simple entry for the preparation of disubstituted and trisubstituted furans. Similarly, reaction of propargylic dithioacetals with an organocopper reagent followed by treatment with an aldehyde and then with acid also furnishes 2,3,5-trisubstituted furans, in moderate to good yields [108].



130 **131**

Scheme 6.54

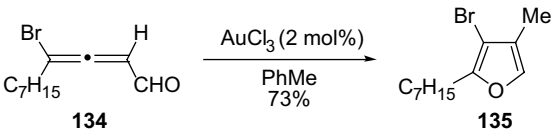
Isomerization of α-allenylcyclopentenone **132**, obtained from propargyl ether and morpholino unsaturated amide, in the presence of Hg-catalyst gives furylcyclopentenone **133**, therefore providing another example of the conversion of allenyl ketones into furans (Scheme 6.55) [109].



132 **133**

Scheme 6.55

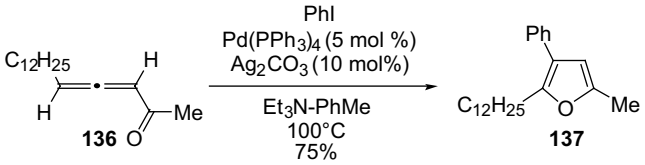
Gevorgyan has reported a regio and divergent synthesis of halofuran **135** via 1,2-halogen migration of haloallenyl aldehyde **134** catalyzed by $AuCl_3$ (Scheme 6.56) [110]. The procedure furnished 3-halofurans, some of which are otherwise difficult to access.



134 **135**

Scheme 6.56

Reaction of aryl or alkyl-1-enyl halides with allenyl ketone **136** in the presence of Pd-catalyst followed by cyclization affords substituted furans with aryl or alk-1-enyl as substituent at the 3-position. This reaction is a new route to 3-substituted furan **137** (Scheme 6.57) [111].

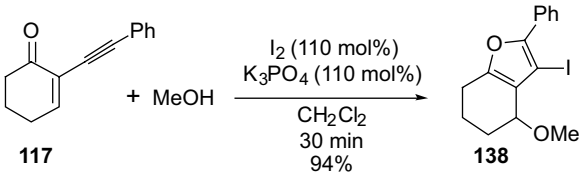


Scheme 6.57

6.2.5 Tetrasubstituted Furans

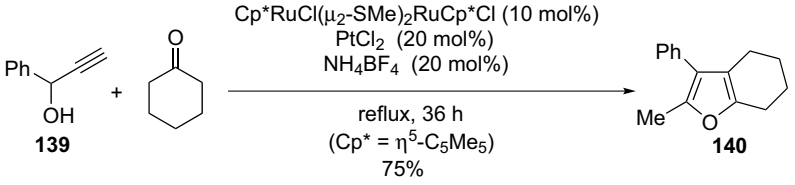
Many procedures discussed above are also suitable for the synthesis of tetrasubstituted furans if there are substituents at appropriate positions in the starting materials. However, some special methodologies have also been developed solely for the synthesis of tetrasubstituted furans.

Liu has shown that cyclization of 2-(1-alkynyl)-2-alken-1-one **117** in the presence of a nucleophile affords fully substituted furan **138** in high regioselectivity and a good yield if I_2 and K_3PO_4 are also used. This reaction provides a mild, efficient route to 3-iodofurans. The reaction might be initiated by the formation of iodonium through coordination of the triple bond to an iodine cation, followed by cyclization and, finally, a nucleophilic attack (Scheme 6.58) [102].



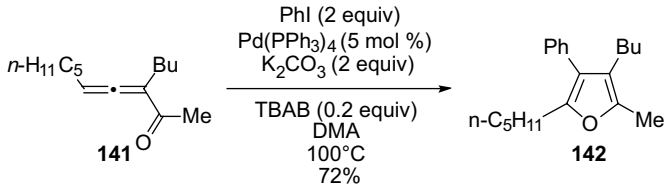
Scheme 6.58

Ruthenium- and platinum-catalyzed sequential reaction of propargylic alcohols (e.g., **139**) and cyclohexanone affords tri- and tetrasubstituted furans such as **140** (Scheme 6.59) [112]. In this reaction, two different kinds of catalysts sequentially promote each catalytic cycle in the same medium and give the products in high regioselectivity and good yields.



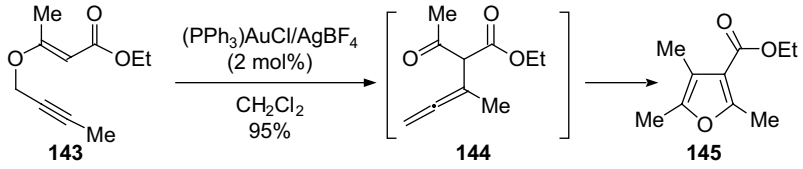
Scheme 6.59

Another example of the regioselective synthesis of substituted furan **142** from the reaction of allenyl ketone **141** with organic halides initiated by Pd-catalyzed nucleophilic attack of the aryl group to allene followed by cyclization reaction has been reported (Scheme 6.60) [113]. This methodology shows a high substituent-loading capacity and functional group tolerance, as well as generality and versatility. If one of the substituents of the allenyl ketones is H, 2,3,4- and 2,3,5-trisubstituted furans can also be generated.



Scheme 6.60

Gold-catalyzed reactions of propargyl vinyl ether **143** furnish tetrasubstituted furan **145** in high yield. The reaction proceeds through cyclization of the 2-allenyl-1,3-dicarbonyl intermediate **144** produced from a propargyl-Claisen rearrangement (Scheme 6.61) [114].



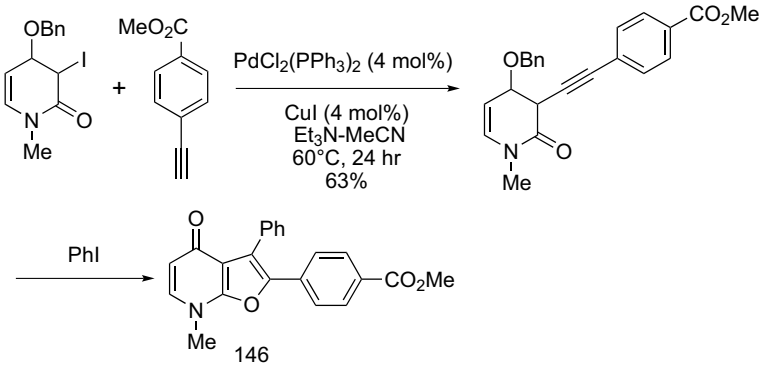
Scheme 6.61

Palladium-mediated sequential cross-coupling Sonogashira reaction–Wacker-type heteroannulation and deprotection reactions of pyridones, alkynes and organic halides furnish substituted furo[2,3-*b*]pyridones (e.g., **146**) in a one-pot operation (Scheme 6.62) [115]. The coupling products of pyridones and alkynes can be separated and a single palladium catalyst intervenes in three different transformations.

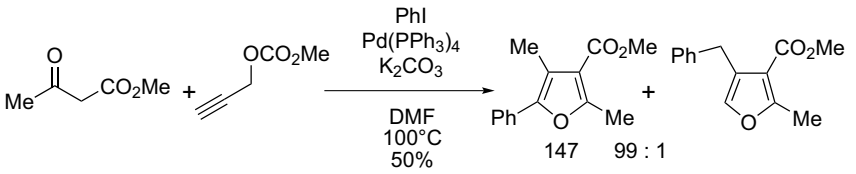
A palladium-catalyzed three-component cyclization–coupling reaction of acetoacetate, propargyl bromide or carbonate and aryl halides gives tetrasubstituted furan **147** in high regioselectivity and a good yield (Scheme 6.63) [116].

Several examples concerning the synthesis of tetrasubstituted furans utilizing acetylenecarboxylate, aldehydes and nitrile or isonitrile have been reported. One such example is a one-pot reaction, affording tetrahydrofuro[2,3-*c*]pyridine **148** in high yield (Scheme 6.64) [117].

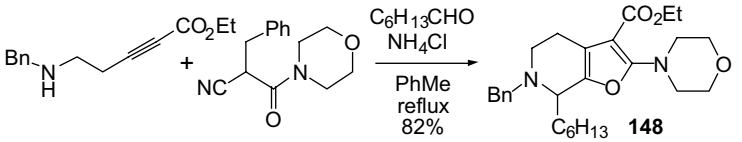
Scheme 6.65 shows a further example, in which the reaction is carried out in an ionic liquid under mild conditions, leading to tetrasubstituted furan **149** in high



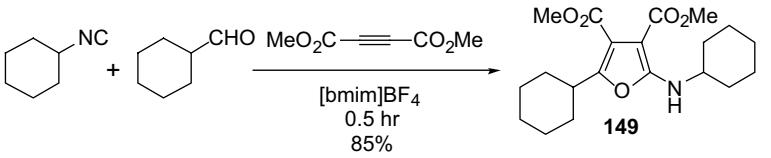
Scheme 6.62



Scheme 6.63



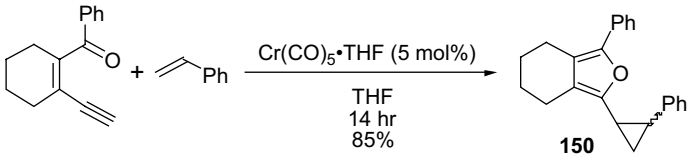
Scheme 6.64



Scheme 6.65

yield [118]. A similar reaction employing 2-furyl-2-oxoacetamides instead of aldehydes in the preparation of substituted furylfurans was also recorded [119].

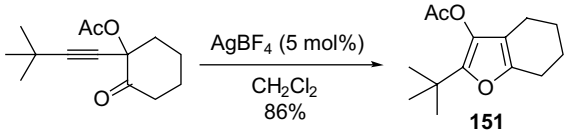
A detailed description of the synthesis of furylcyclopropane **150** from the reaction of an alkene and previously reported 2-furylcarbenoid by a metal-catalyzed cyclization of enyne ketone has been disclosed (Scheme 6.66) [120]. This protocol has been expanded by the same authors to the synthesis of furylcyclopropane-containing



Scheme 6.66

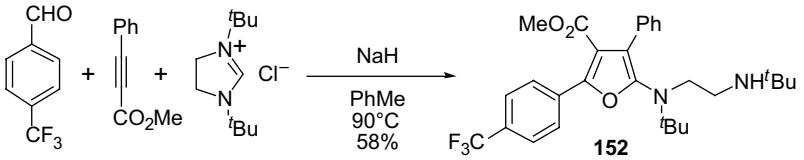
polymers as well as furfurylidene-containing polymers when phenyl enyne ketones with a vinyl and formyl group at the *ortho* position of the benzene ring are employed [120].

Cycloisomerization of acyloxy-, phosphatyloxy- and sulfonyloxy-substituted alkynylketones gives tri- and tetrasubstituted furans (e.g., **151**) with good regioselectivities; the allene intermediates are produced *in situ* via migration of the substituents, catalyzed by CuCl or $AgBF_4$ (Scheme 6.67) [121].



Scheme 6.67

N-Heterocyclic carbenes (NHC) have found use as reagents in the synthesis of polysubstituted aminofurans. Multicomponent reaction of an imidazolinium salt with an aldehyde and an acetylenecarboxylate in the presence of NaH leads to tetrasubstituted furan **152** in a good yield (Scheme 6.68). A plausible reaction mechanism has been proposed [122]. A similar procedure for the synthesis of tetrasubstituted 3-aminofurans, using a thiazolium salt, aldehydes and acetylenedicarboxylate, has also been reported [123].



Scheme 6.68

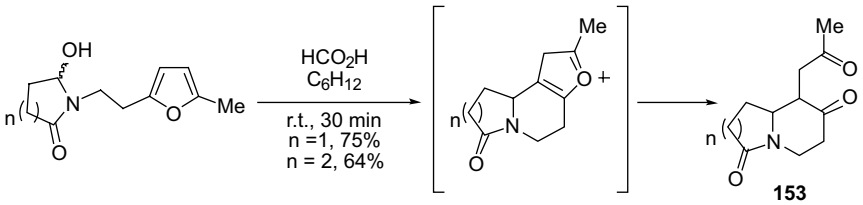
6.3 Reactivity

This section primarily deals with the reactivity of furans that results in an overall transformation of the ring. Reactions of furans, particularly reactions of *C*-metallated

furans, that lead to substituted furan derivatives have been discussed in Section 6.2.1. Most examples in this section are extracted from recent literature so as to document the progress made in each reaction category [4].

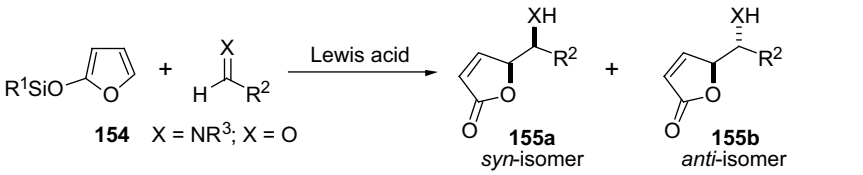
6.3.1
Reactions with Electrophilic Reagents

Furans are reactive π-nucleophiles. Nucleophilic additions of furans to electrophiles, from either the 2-position or 3-position, often involve regeneration of the furan ring from the oxonium ion intermediate by loss of a proton, as shown, for example, in Scheme 6.7, Section 6.1.2. An interesting example of direct hydrolytic cleavage that occurs subsequent to furan addition to an *N*-acyliminium ion is shown in Scheme 6.69. The initially formed oxonium ion likely undergoes a 1,5-proton shift to generate an intermediate that is then hydrolyzed to the dicarbonyl compound **153** [124].



Scheme 6.69

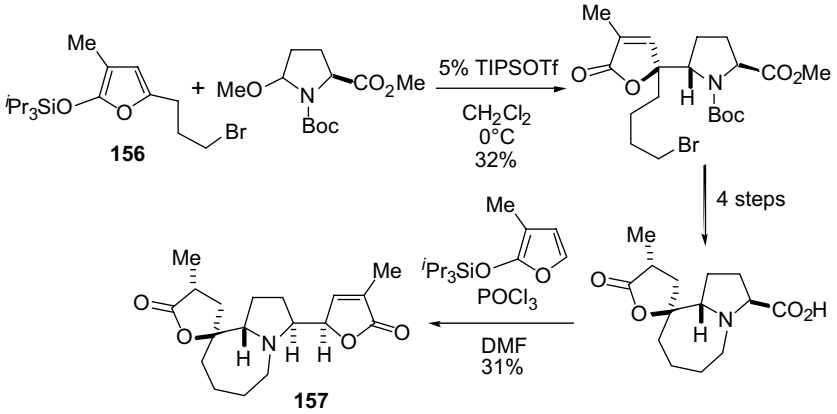
2-Silyloxyfurans **154** are chemically equivalent to "cyclic" vinyl silyl ketene acetals, and have been employed for vinylogous additions to electrophiles under Lewis acid catalyzed conditions to provide γ-butenolides **155**, which are common structures present in natural products. These include vinylogous Mannich [125, 126], aldol [126] and Michael reactions. Consistent with vinylogous reactions of acyclic silyloxy dienolates, additions generally occur at the 5-position of 2-silyloxyfurans **154** (Scheme 6.70). Further synthetic manipulations of these adducts can lead to carbocycles, piperidines, sugars and azasugars. A subsequent intramolecular Michael/hetero Michael addition to the α,β-unsaturated system of butenolide can also be exploited to form polycyclic ring structures [127]. Although the factors and the transition state structures (Diels–Alder like versus open chain) that govern the stereoselectivity have not been well-defined, *anti* (*erythro*) adducts are in general isolated as the major isomers for additions to iminium ions, except cyclic acylimi-



Scheme 6.70

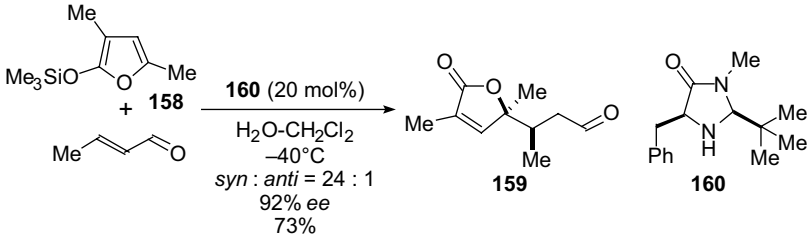
nium ions, from which the *syn*-isomers are obtained preferentially. For reactions with aldehydes, *syn* (*threo*) products generally predominate.

The synthetic utility of vinylogous additions using 2-siyoxyfurans (e.g. **156**) is exemplified by the total synthesis of the plant alkaloid croomine (**157**), in which two vinylogous Mannich reactions of 2-silyloxyfuran to a pyrrolinium ion constitute the key steps for assembling the carbon framework (Scheme 6.71) [128].



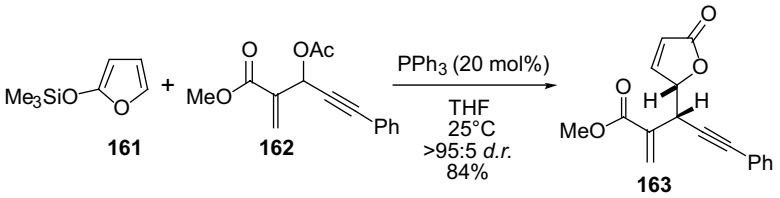
Scheme 6.71

Vinylogous Michael additions of 2-silyloxyfurans to 3-alkenyl-2-oxazolidinones are *anti*-selective, and are highly enantioselective in the presence of a BINAP-Lewis acid catalyst [129]. As illustrated in Scheme 6.72, a complementary, *syn*-selective, organocatalytic, enantioselective vinylogous Michael addition of 2-silyloxyfuran **158** with an α,β-unsaturated aldehyde to produce γ-butenolide **159** has been achieved by using the chiral amine catalyst **160** [130].



Scheme 6.72

As shown in the example in Scheme 6.73, 2-trimethylsilyloxyfuran (**161**) also reacts with Morita–Baylis–Hillman acetate **162** to provide the interesting γ-butenolide **163**. These triphenylphosphine-catalyzed substitutions proceed regio- and diastereoselectively. However, the reaction mechanism (vinylogous Michael versus Diels–Alder) has not been elucidated [131].



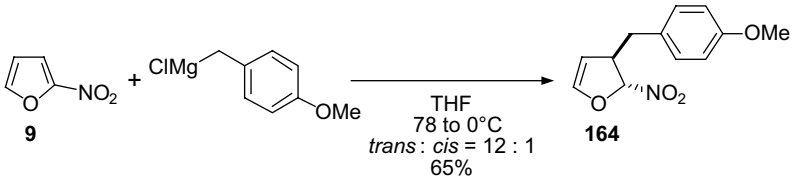
Scheme 6.73

Similar to 2-silyloxyfuran, the relatively unexplored 3-silyloxyfuran also participates in an aldol addition manner with aldehydes under Lewis acidic conditions. High *syn*-diastereoselectivity is obtained with bulky α-branched aldehydes [132]. In addition, 2-methoxy, 2-aryloxy and 2-phenylthiofurans also serve as nucleophiles [133].

The nucleophilicity of furans can be modulated by complexation to transition metals. When furan is dihapto-coordinated to a rhenium π-base, the nucleophilicity of the uncoordinated C3-position is enhanced. In this manner, furan acts as an enol ether [134].

6.3.2
Reactions with Nucleophilic Reagents

Electron-deficient furans, for example 2-nitrofuran (**9**), can undergo nucleophilic substitutions. Various Grignard reagents react with **9** in a Michael addition fashion, providing predominantly *trans*-2,3-disubstituted 2,3-dihydrofurans such as **164** (Scheme 6.74) [135].

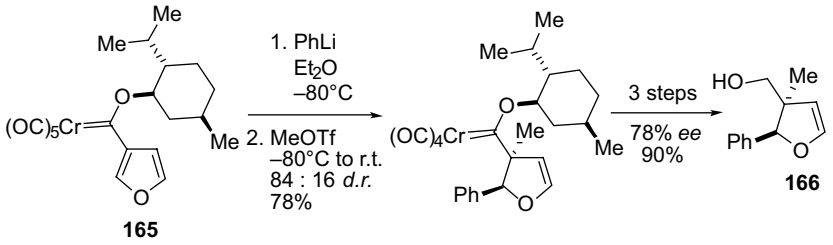


Scheme 6.74

The chiral Fischer-type furan carbene complex **165** (Scheme 6.75) participates in 1,4-addition with organolithium reagents in a regioselective and diastereoselective manner. Consecutive oxidative decomplexation and reductive cleavage of the chiral auxiliary provides 2,3-dihydrofuran **166**, which contains a quaternary C3 center [136].

6.3.3
Reactions with Oxidizing Reagents

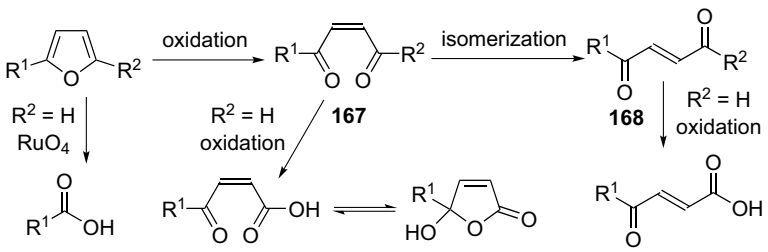
Furans are valuable precursors to 1,4-dicarbonyl compounds, which are not directly accessible from the reactions between electrophiles and nucleophiles, such as those employed for the synthesis of 1,3- and 1,5-dicarbonyl compounds. Furans are



Scheme 6.75

hydrolytically cleaved to saturated 1,4-dicarbonyl compounds under reflux in strongly acidic conditions (Section 6.3.5). The 1,4-dicarbonyl moiety can also be revealed by oxidation of furans using various oxidizing reagents [4, 137].

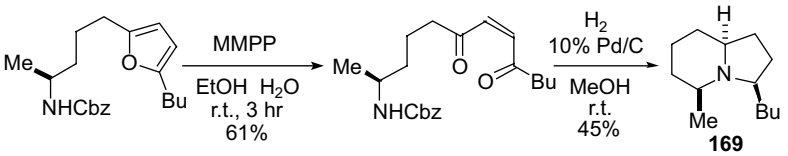
2,5-Dialkoxy-2,5-dihydrofurans formed from the oxidation of furans in a methanolic solution of bromine (e.g., Scheme 6.12, Section 6.1.2) can be hydrolyzed to *cis*-α,β-unsaturated-1,4-dicarbonyls. Oxidation of 2-substituted or 2,5-disubstituted furans to *cis*-α,β-unsaturated-1,4-dicarbonyls **167** can be performed using *m*-CPBA, PCC or NBS [4, 137], magnesium monoperoxyphthalate (MMPP) [138], dimethyldioxirane [139], methyltrioxorhenium/urea hydrogen peroxide [140] and buffered sodium chlorite [141] (Scheme 6.76). The corresponding *trans* isomers **168** are obtained by *in situ* isomerization, especially in the presence of an amine base, or directly by $Mo(CO)_6$-catalyzed oxidation using cumyl hydroperoxide [142]. Furans also serve as surrogates to carboxylic acids, which are obtained by oxidative disassembly of the aromatic ring using ruthenium tetroxide [143].



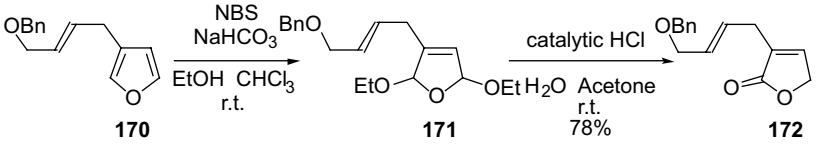
Scheme 6.76

The 1,4-dicarbonyl compounds are useful precursors towards the syntheses of cyclopentenones and cyclopentanones [137]. Interception of the transient oxonium ion during oxidation of furans (e.g., by NBS) by pendant nucleophiles leads to interesting spiro ring systems [144]. Scheme 6.77 depicts an application of furan oxidation in the total synthesis of the indolizidine alkaloid monomorine (**169**) [145].

Regioselective oxidation of unsymmetrical 3-substituted furan **170** to butenolide **172** has been accomplished by using alcoholic bromine or NBS and controlling the acid-catalyzed hydrolysis of the 2,5-dialkoxy intermediate **171** in acetone–water mixture [146] (Scheme 6.78).

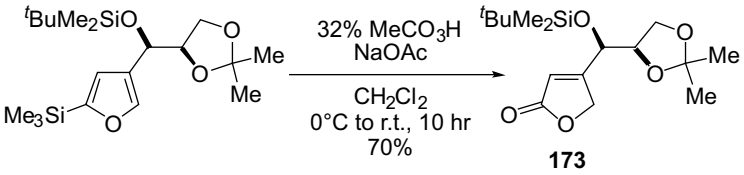


Scheme 6.77



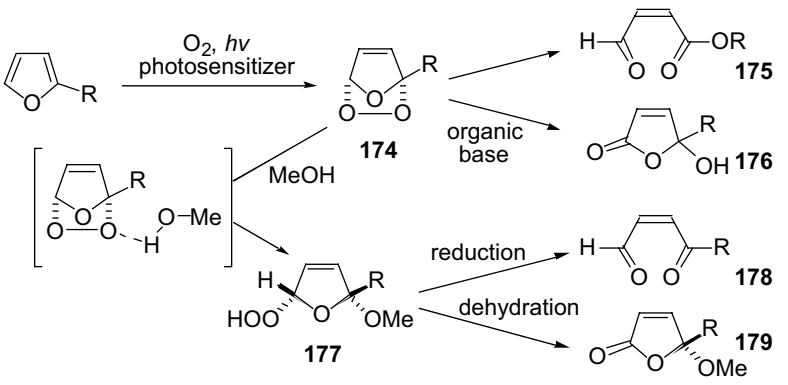
Scheme 6.78

Alternatively, regioselectivity can be controlled by the incorporation of a silyl group in the furan ring (Scheme 6.79), producing **173** in a regiospecific manner [147].



Scheme 6.79

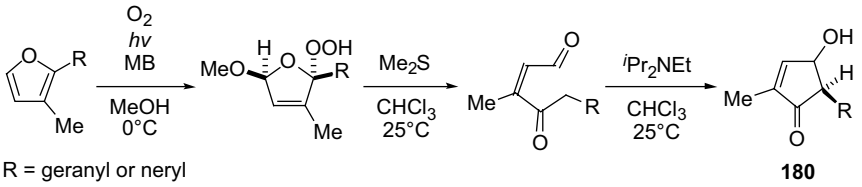
Photooxidations of furans by singlet oxygen, sensitized by, for example, methylene blue, Rose Bengal or tetraphenylporphyrin, generate endoperoxides [148] (e.g., **174**, Scheme 6.80) via a Diels–Alder cycloaddition. Intermediate **174** is prone to Baeyer–Villiger type rearrangement to provide carboxylate **175** (R including silyl).



Scheme 6.80

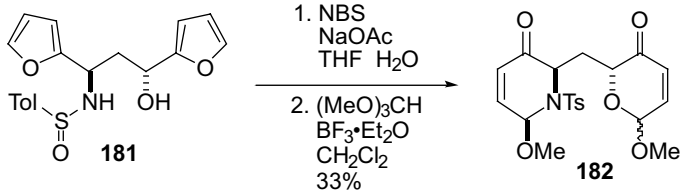
Deprotonation at the bridgehead carbon of **174** by an organic base provides hydroxybutenolide **176**. This provides a useful method for the regioselective oxidation of unsymmetrical 3-substituted furans by using a hindered base (e.g., *i*-Pr_2NEt) [149]. Reaction of **174** with an alcohol (MeOH is often used as a solvent) at higher temperature forms hydroperoxide **177** regio and stereoselectively due to a hydrogen bonding assisted front side attack of the alcohol on the most stabilized carbocation. Reduction of hydroperoxide **177** and subsequent eliminative ring opening provides 1,4-dicarbonyl compound **178**, while dehydration of **177** gives butenolide **179**. Photooxidations of furans have the benefit of being performed selectively in the presence of alkenes.

Scheme 6.81 shows a novel example of taking advantage of the singlet-oxygen photooxidation of furan in the presence of two trisubstituted alkenes in the side chain (R group) during the total synthesis of litseaverticillols **180** [150]. The unusual regio and diastereochemistry obtained from the methylene blue (MB) sensitized oxidation in MeOH is, presumably, the result of a backside attack of MeOH on the intermediate endoperoxide.



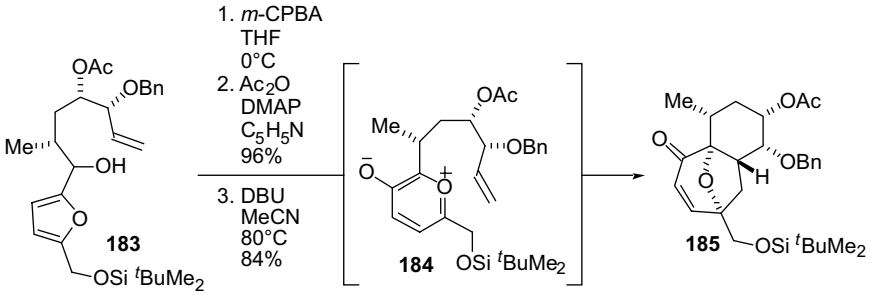
Scheme 6.81

Oxidation of furfuryl alcohols under similar conditions leads to ring expansion to form dihydropyranones. These Achmatowicz oxidations are often accomplished by using buffered NBS, $VO(acac)_2$/*t*-BuOH and singlet oxygen. Dimethyldioxirane [139] and methyltrioxorhenium/urea hydrogen peroxide [140] are also effective oxidants. The corresponding aza-Achmatowicz oxidation of furfurylamines [151], frequently by NBS or *m*-CPBA, provides a novel method for the synthesis of azasugars and piperidine-containing compounds [152]. An interesting example of simultaneously applying both reaction variants in the synthesis of aza-*C*-linked disaccharide, such as **182** from **181**, is shown in Scheme 6.82 [153].



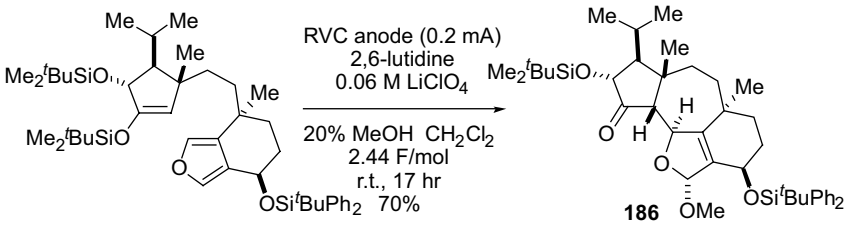
Scheme 6.82

A novel route for the construction of the daphnane BC-ring in the quest for resiniferatoxin (Scheme 6.83) employed furan **183** in an Achmatowicz rearrangement via, presumably, oxidopyrylium ion **184**, which participates in an intramolecular [5 + 2] cycloaddition to provide dihydropyranone **185** [154, 155].



Scheme 6.83

The furan nucleus can be oxidized electrochemically, and the radical cations generated at the anode can be trapped by the reaction medium, for example, methanol, to give 2,5-dioxygenated-2,5-dihydrofurans. Intramolecular electrochemical annulation of furans provides an interesting avenue for the synthesis of polycyclic ring systems. Anodic oxidation of furans that contain pendant vinylsulfide, methyl or silyl enol ethers generates radical cation intermediates that cyclize to form six- and seven-membered rings [156]. Scheme 6.84 shows a recent example of the construction of the complex tetracyclic core **186** of guanacastepenes, obtained as a single diastereoisomer, by such an electron transfer reaction [157]. A *gem*-dialkyl effect has been identified as essential for the efficient formation of a seven-membered ring in this type of reaction [89, 158].

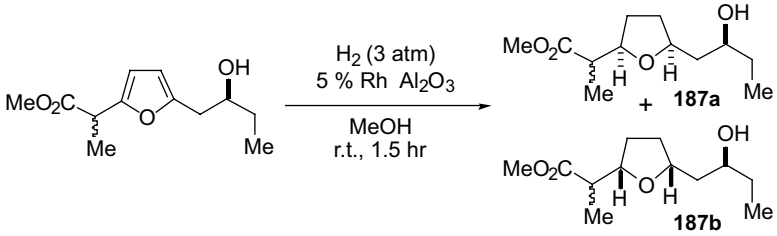


Scheme 6.84

6.3.4
Reactions with Reducing Reagents

Furans are reduced by catalytic hydrogenation (Pd/C, Raney Ni and Rh), dissolving metals (Birch reduction) and alkylsilanes to dihydrofurans and tetrahydrofur-

ans [159]. 2,5-*cis*-Reduction products **187a** and **187b** are obtained from 2,5-disubstituted furans, an example that is essential in the total synthesis of tetranactin (Scheme 6.85) [160].

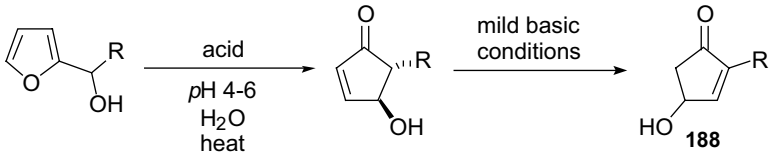


Scheme 6.85

In the stereoselective reduction of electron-deficient chiral furoic amides (Scheme 6.16, Section 6.1.2), under Birch-type reductive alkylation to form dihydrofuran derivatives, methyl and trimethylsilyl substituents at the 3-position of the furan moiety are essential for achieving high diastereoselectivity in the alkylation step, presumably by controlling the enolate geometry [161].

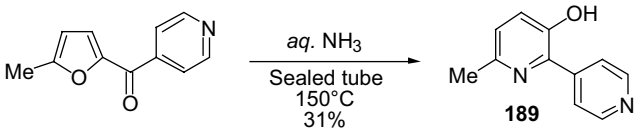
6.3.5
Reactions with Acids or Bases

Rearrangement of furfuryl alcohols in aqueous acidic medium at *p*H 4.0–6.0 is a useful reaction for the preparation of hydroxycyclopentenones on a preparative scale (Scheme 6.86). 5-Unsubstituted and 5-methylfurfuryl alcohols having a range of R groups are generally good substrates for this type of reaction. 5-Nitrofurfuryl alcohol, however, does not undergo the rearrangement [137]. As illustrated in Scheme 6.86, this kind of rearrangement provides *trans*-4-hydroxy-5-substituted 2-cyclopentenones, which can isomerize to 2-substituted 2-cyclopentenones **188** under mild basic conditions, for example, using alumina and phosphate buffer *p*H 7.9 [137], as well as amine bases [162]. When R is phenyl or 2-thienyl, a reaction in refluxing water without the use of any acid leads directly to isomer **188** [163].



Scheme 6.86

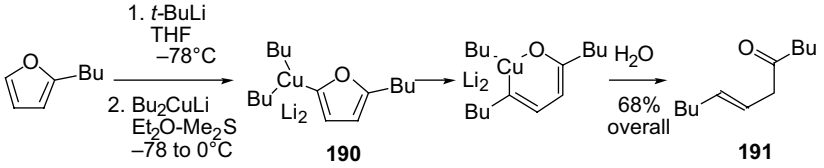
A 2-acylfuran derivative reacts with aqueous ammonia to give 3-hydroxypyridine **189** (Scheme 6.87). An initial attack of ammonia at the C5-position of the furan followed by a subsequent ring opening/ring closing sequence has been proposed as the reaction mechanism [164].



Scheme 6.87

6.3.6
Reactions of *C*-Metallated Furans

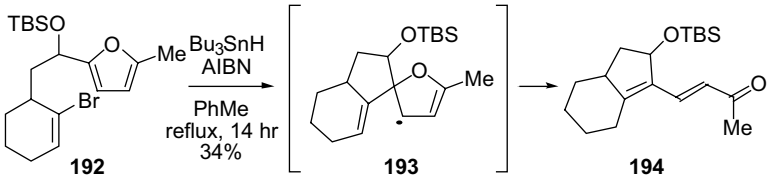
C-Metallated furans are primarily used for the synthesis of substituted furans (Section 6.2.1). 2-Furylcuprate **190**, as shown in Scheme 6.88, was recently discovered to undergo a 1,2-metalate rearrangement to form **191** [165]. A similar dyotropic rearrangement of 2-furylzirconocene complexes has also been reported [166].



Scheme 6.88

6.3.7
Reactions with Radical Reagents

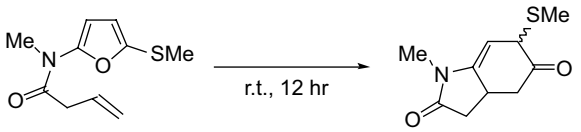
Furans react with radical reagents at the α-positions. For example, an acetyl radical, generated from a xanthate, reacts with 2-acetylfuran to provide the α-substituted product [167]. As illustrated in Scheme 6.89, addition of the alkenyl radical generated from the cyclohexenyl bromide **192** to the pendant furan moiety gives the spiro-dihydrofuran radical intermediate **193**. Radical fragmentation in **193** then provides a cyclohexyl radical, leading to unsaturated ketone **194** [168]. Similar methodology has been examined in the synthesis of polycyclic ring system [169].



Scheme 6.89

6.3.8
Electrocyclic Reactions

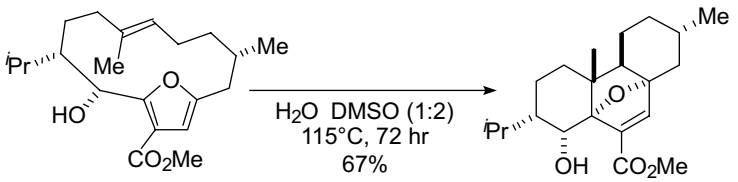
There is a large volume of literature on both inter- and intramolecular Diels–Alder reactions of furans with dienophiles, for example, alkenes, alkynes, allenes and benzynes, under thermal, Lewis acid promoted or high-pressure conditions. These [4 + 2] cycloadditions, which form six-membered rings, have been applied to the total synthesis of natural products, and are well documented and reviewed [4, 170]. Diels–Alder reaction of furans often requires elevated reaction temperature, as furans are generally poor dienes, unless the dienophiles are reactive or Lewis acids are used. However, structural elements can be incorporated into the starting materials such that these cycloadditions proceed at or below ambient temperature. For example, the cycloaddition of **195** which has an unactivated double bond, occurs at room temperature to furnish **196** (Scheme 6.90). This reaction is a consequence of **195** being populated in a reactive conformation imparted by the amide carbonyl of the tether [171].



195 **196**

Scheme 6.90

Examples of transannular Diels–Alder reactions of furanophanes are very rare. In such an approach, macrocyclic conformational control can offer high diastereoselectivity, as demonstrated in the synthesis of the chatancin core **198** from **197** (Scheme 6.91) [172].

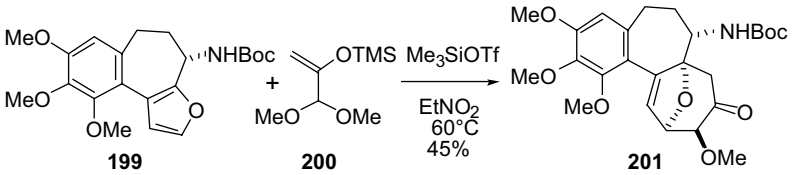


197 **198**

Scheme 6.91

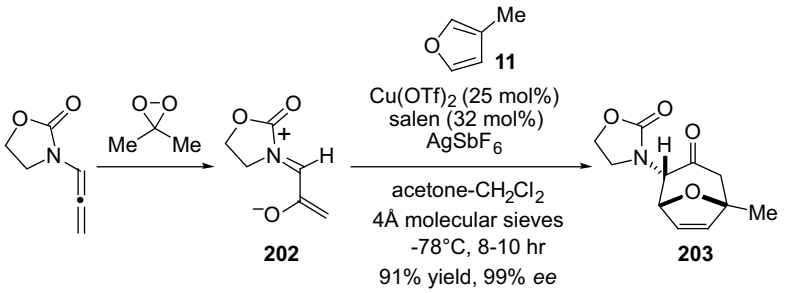
The [4 + 3] cycloadditions of furans have been used to form seven-membered rings, which are widely present in natural products. Reactions with oxyallyl cations are the most explored [4 + 3] cycloadditions of furans [173], although reactions with oxyallyl equivalents, for example, silyloxyacroleins [174] and cyclopropanone hemiacetals [175], and aminoallyl cations [176], have also been reported. These cycloadditions of furans with oxyallyl cations and their equivalents are generally considered as concerted processes. However, theoretical calculations support an alternative

stepwise mechanism for certain examples [174, 177]. An example of employing such a reaction as the key step in the total synthesis of colchicine is shown in Scheme 6.92 [178]. Thus, coupling of the highly substituted furan **199** with the oxyallyl cation generated from silyl enol ether **200** produces the desired *endo*-adduct **201** as a single isomer.



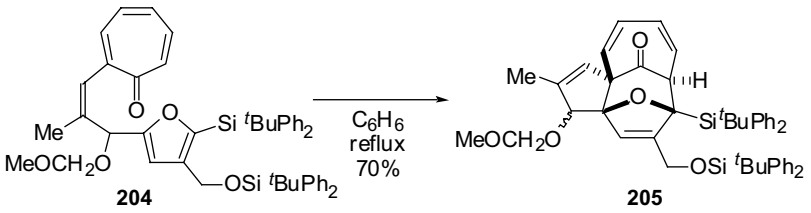
Scheme 6.92

An enantioselective organocatalytic [4 + 3] cycloaddition of furan using the chiral amine catalyst **160** has been realized [179]. As shown in Scheme 6.93, the *endo* selective [4 + 3] cycloaddition between 3-methylfuran (**11**) and the nitrogen stabilized oxyallyl cation **202** derived from an allenamide can also be rendered highly enantioselective by using a 1,2-cyclohexanediamine derived C_2 symmetric salen(Cu) complex as the catalyst, leading to the formation of **203** [180].



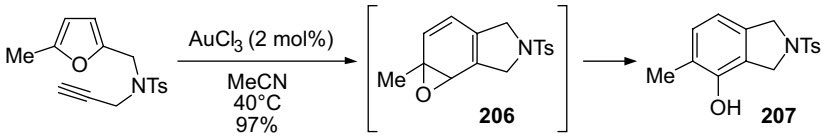
Scheme 6.93

The [6 + 4] cycloaddition between furan and tropone, a previously unsuccessful transformation, has recently been realized in an intramolecular conversion of **204** into **205** during the assembly of the ABC-ring of ingenol (Scheme 6.94) [181].



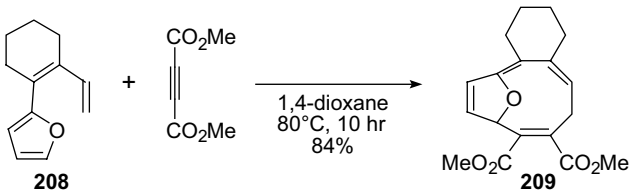
Scheme 6.94

Gold-catalyzed intramolecular cycloisomerization of furans with a pendant terminal alkyne provide phenol product **207** (Scheme 6.95) [182]. Although the reaction may be a result of a [4 + 2] or [2 + 2] process, a viable mechanism has not been identified. The formation of arene oxide intermediate **206**, however, has been characterized experimentally [183].



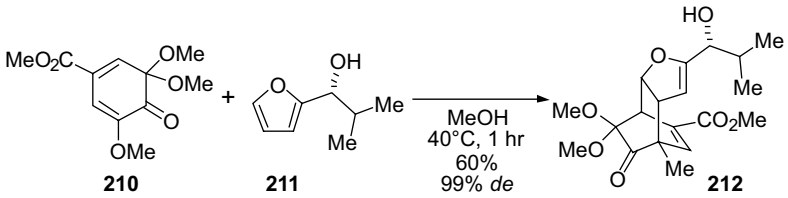
Scheme 6.95

2-Vinylfurans participate in extra annular [4 + 2] cycloadditions in which the vinyl group and the furan 2,3-π bond function as the 4π component to form tetrahydrobenzofurans [184]. 2-Butadienylfuran **208** has recently been shown to behave as an 8π-component in cycloaddition with dimethyl acetylenedicarboxylate, providing an oxygen-bridged ten-membered ring (**209**, Scheme 6.96) [185].



Scheme 6.96

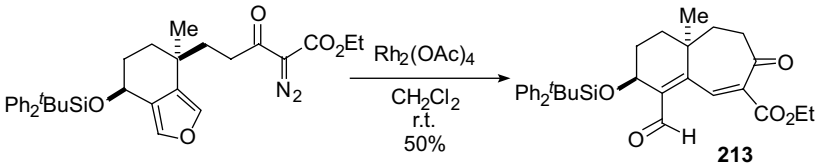
Furans also behave as dienophiles and dipolarophiles. The 2,3-π bonds of furans react with *o*-quinodimethide [186] and *o*-benzoquinones. Scheme 6.97 shows an example of a regio- and diastereoselective cyclization involving (*R*)-furfuryl alcohol **211** and a masked *o*-benzoquinone **210**, producing the *ortho, endo* adduct **212** [187]. The α-hydroxyl group controlled the facial selectivity of the Diels–Alder type reaction. Recent studies, however, suggest a stepwise, double Michael addition as the mechanism for this type of reaction [188].



Scheme 6.97

Furans are less reactive dipolarophiles. However, 1,3-dipolar cycloaddition between nitrile oxides and furans to give furoisoxazolines has been developed as a novel entry to amino sugars and amino acids [189]. Recently, intramolecular cycloaddition of a furan with a carbonyl ylide dipole was also shown to proceed under microwave promoted conditions, providing the cycloadduct in modest yield [190].

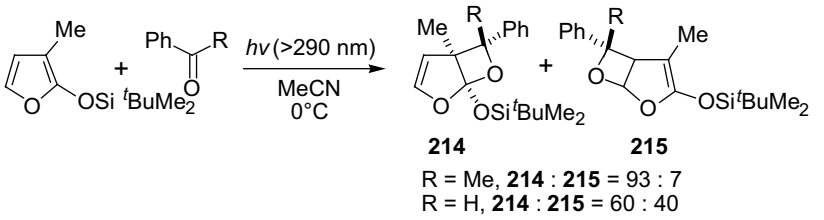
The furan 2,3 π-bond also undergoes cyclopropanation with metal carbenoids. Asymmetric cyclopropanation of furan-2-carboxylate with ethyl diazoacetate to provide the *exo*-diastereoisomer has been achieved under copper(I)-bisoxazoline catalyzed conditions [191]. A retro-Claisen type rearrangement often accompanies cyclopropanation with diazocarbonyl compounds, leading to a 2,4-diene-1,6-dicarbonyl structural motif. Intramolecular versions are attractive methods for synthesizing [6,7]-, [6,6]-, [6,5]- and even [6,4]-fused ring systems [192]. Scheme 6.98 gives an example of a rhodium-catalyzed reaction as applied in the synthesis of guanacastepene core structure **213** [193].



Scheme 6.98

6.3.9
Photochemical Reactions

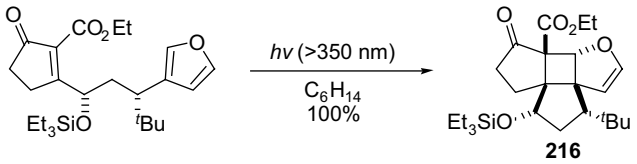
In addition to furan behaving as a 4π-component in photochemical reactions with aromatic compounds, the furan 2,3-π bond also reacts photochemically. The most synthetically interesting photochemical reaction involving furans is the Paterno–Büchi [2 + 2] cycloaddition with carbonyl compounds. The oxetane products obtained are useful intermediates for the synthesis of natural products. Regio- and stereoselectivities of the reaction are determined by the conformational stability of the triplet diradical intermediate [194]. As illustrated in a study with 2-silyloxyfurans (Scheme 6.99) [195], reaction with ketones provided higher substituted products



Scheme 6.99

(e.g. **214**) regioselectively, while those with aldehydes are regio-random. As usual, *exo*-oxetanes were produced predominantly in both examples.

The [2 + 2] photocycloaddition of furans with alkenes is also synthetically useful. A remarkable example is the pivotal intramolecular cyclization to form **216** (Scheme 6.100), as employed in the total synthesis of ginkgolide B [196].



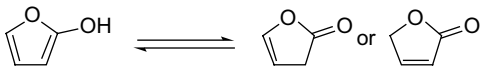
216

Scheme 6.100

6.4 Oxyfurans and Aminofurans

6.4.1 Oxyfurans

Hydroxyfurans exhibit fairly low stability that is quite different from their benzenoid counterparts. This phenomenon can be explained by a careful structure investigation on 2-furanol (**217**), which can be treated as the enol form of 2- or 3-butenolide. Estimations of resonance energy reveal that 2-furanol is of much higher energy than the corresponding furanone structure. Therefore, 2(3*H*)-furanone (**218**) and 2(5*H*)-furanone (**219**) dominate at equilibrium in the absence of additional stabilizing effect for enolization (Scheme 6.101) [197, 198].



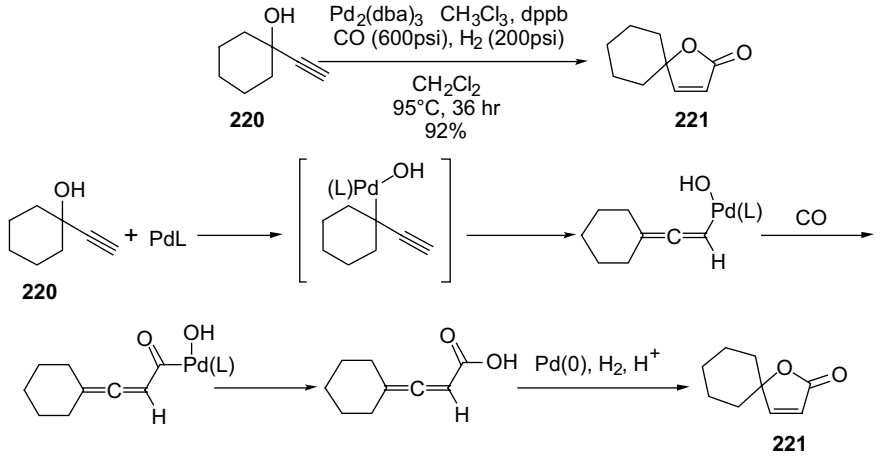
217 **218** **219**

Scheme 6.101

Both the 2(5*H*)-, and 2(3*H*)-furanone structures widely occur in biologically active natural products. They are, in general, also called "butenolides," as derivatives of 4-hydroxybutenoic acids, and not as furan derivatives. Thus, 3-butenolide corresponds to 2(3*H*)-furanone (**218**) and 2-butenolide corresponds to 2(5*H*)-furanone (**219**) [199].

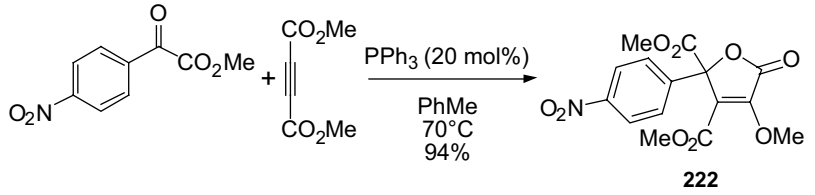
2(5*H*)-Furanones are important synthetic intermediates in the construction of substituted γ-butyrolactones. In addition, they also serve as useful building blocks in the syntheses of various organic compounds [200]. Several excellent reviews dealing with the synthesis of these unsaturated lactones have been published [199, 201–203]. Instead of providing a thorough literature survey, only recent advances are discussed here.

Palladium-catalyzed cyclocarbonylation of propargyl alcohol is an excellent method for the construction of 2(5*H*)-furanones. Thus, a combination of $Pd(dba)_2$ and dppb has been used to catalyze the transformation of **220** into 5,5-disubstituted 2(5*H*)-furanone **221**. The reaction mechanism involves the insertion of a Pd(0) species into the C−O bond of the substrate, followed by rearrangement to the allenylpalladium intermediate. Insertion of CO and subsequent reductive elimination then lead to the 2,3-dienoic acid, which then affords **221** (Scheme 6.102) [204].



Scheme 6.102

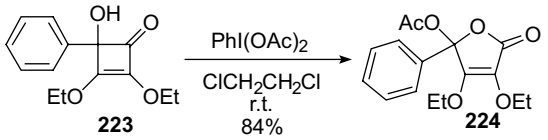
A highly functionalized 2(5*H*)-furanone (**222**) has been prepared from a triphenylphosphine-catalyzed reaction of activated carbonyl compound with dimethyl acetylenedicarboxylate (Scheme 6.103) [205].



Scheme 6.103

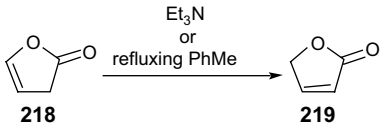
Besides acyclic substrates, 2(5*H*)-furanones can also be synthesized from cyclobutenone precursors. Thus, when hydroxycyclobutenone **223** was subjected to reaction with a hypervalent iodine reagent, an oxidative ring enlargement took place to give 5-acetoxy-2(5*H*)-furanone **224** (Scheme 6.104) [206].

The presence of an α,β-unsaturated carbonyl moiety renders the 2(5*H*)-furanones highly reactive towards different reagents (Section 6.3).



Scheme 6.104

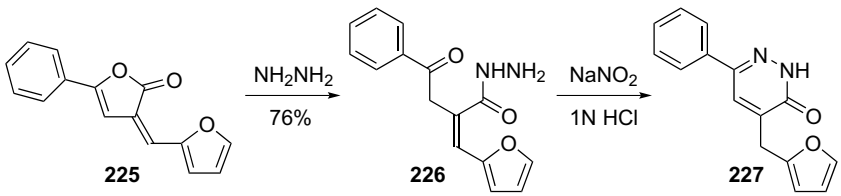
Attempts to synthesize simple 2(3*H*)-furanones usually result in a mixture containing also 2(5*H*)-furanones [207]. Generally, 2(3*H*)-furanone (**218**) is thermodynamically less stable than 2(5*H*)-furanone (**219**). Computational (SCF-MO) results reveal that the energy of 2(3*H*)-furanone (**218**) is of 53 kJ mol^{-1} higher than that of 2(5*H*)-furanone (**219**) [198]. Experimentally, isomerization can be achieved by amine bases or at elevated temperature (Scheme 6.105) [208].



Scheme 6.105

The reactively low stability of 2(3*H*)-furanones makes them susceptible to nucleophilic attack to give ring-opening products, which may be employed to construct other important heterocyclic systems [209].

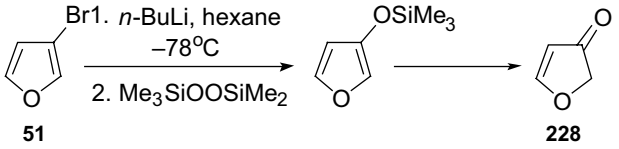
As illustrated in Scheme 6.106, a hydrazide **226** is formed on treatment of furanone **225** with hydrazine hydrate. Further reaction with a mixture of $NaNO_2$ and HCl promotes ring closure to afford **227** with a pyridazinone structure [210].



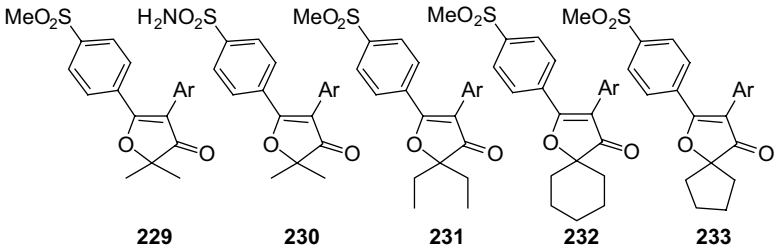
Scheme 6.106

Similar to their 2-hydroxyl isomers, 3-hydroxyfurans tend to exist in the keto form as 3(2*H*)-furanones [198]. As depicted in Scheme 6.107, free 3(2*H*)-furanone **228** can be synthesized from 3-bromofuran (**51**) [211].

Although the 3(2*H*)-furanone motif is less common than 2(5*H*)-furanones and 2(3*H*)-furanones in bioactive naturally occurring molecules, a series of 4,5-diaryl substituted 3(2*H*)-furanones (**229**–**233**) have been studied as cyclooxygenase-2 inhibitors and show excellent anti-inflammatory activities [212].

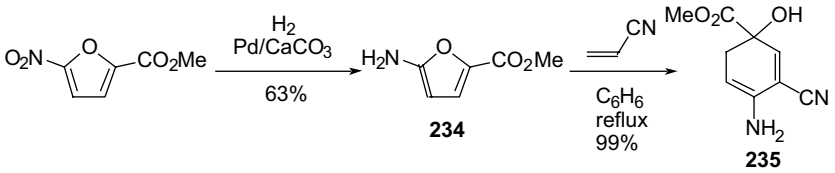


Scheme 6.107



6.4.2
Aminofurans

3-Aminofuran is stable only in an inert atmosphere or *in vacuo*. It polymerizes rapidly upon contact with air. 2-Aminofuran is also a reactive species. However, as illustrated in Scheme 6.108, **234** is one of the exceptions, whose stability may be attributed to the presence of a conjugated electron-withdrawing group on the furan ring. When **234** is treated with a dienophile, the rearranged cycloadduct **235** is obtained in high yield [213].



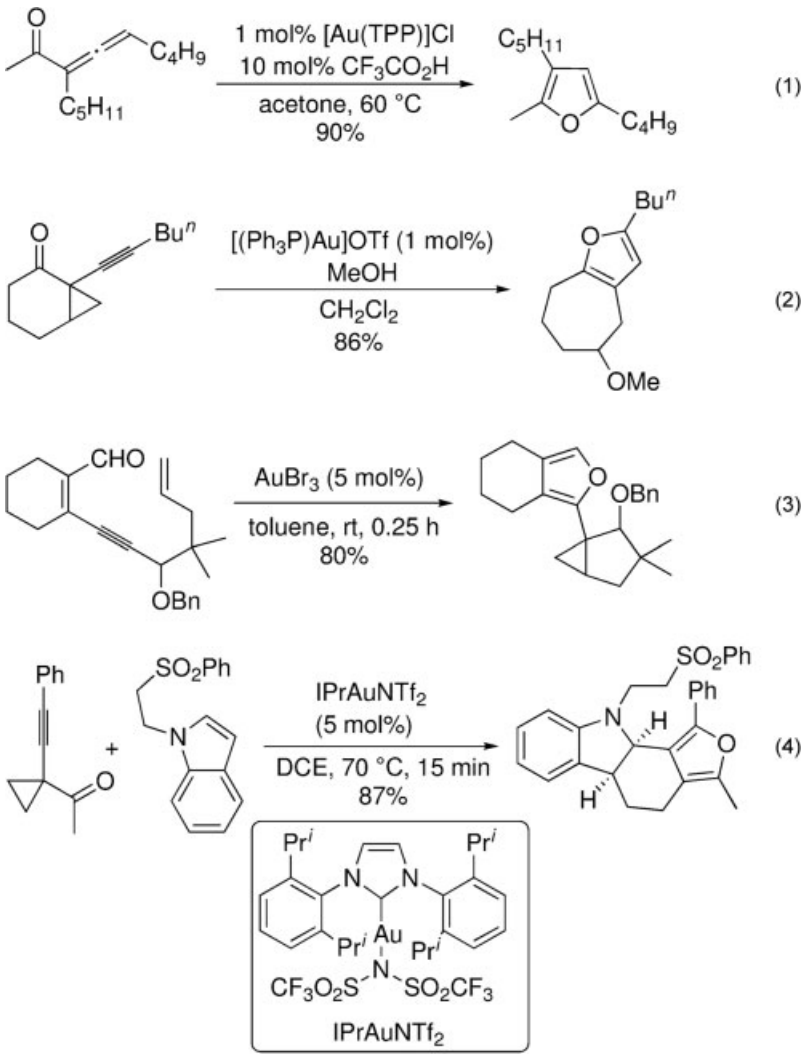
Scheme 6.108

6.5
Addendum

6.5.1
Additional Syntheses of Furans

In the past few years, several procedures for the synthesis of substituted furans in high regioselectivity and efficiency have appeared. Amongst them, reports on the using of Au-catalysts have increased substantially. In all cases the starting materials

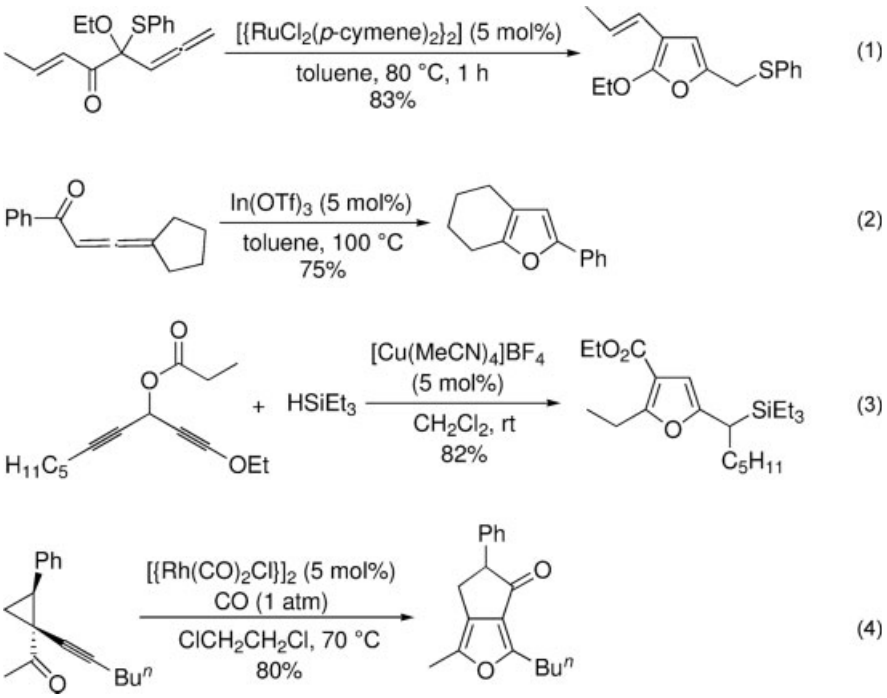
contain an alkynyl or allenyl group. Because of the exceptionally alkynophilic, but not as oxophilic, property of Au-catalysts, the Au-catalyzed reactions are oxygen-, water-, and alcohols-tolerated and thus do not need air- and moisture-free conditions. Also noteworthy is that in Au-catalyzed reactions non-classical carbocation or carbenoid intermediates are very often involved so that the selectivity of these reactions can be controlled. A few examples are shown below. Cyclization of allenones in the presence of Au(III)-porphyrin gave rise to the corresponding substituted furan in good to high yields. The catalyst can be recycled several times and its catalytic activity remained intact [Scheme 6.109, reaction (1)] [214a]. Another example of Au catalysis has been



Scheme 6.109

reported using alkynyl cyclopropyl ketones as a starting material. Trisubstituted furans were afforded in high yields under mild conditions via a domino reaction process [Scheme 6.109, reaction (2)] [214b]. A carbonyl-ene-yne compound is also a suitable starting material in Au-catalyzed furan formation. In the presence of Au-catalyst, 2-alkynyl-1-cycloalkenecarbaldehydes were converted into trisubstituted furans via an Au-carbene intermediate [Scheme 6.109, reaction (3)] [214c]. Alkynyl cyclopropyl ketones have also been employed as starting material, as 1,4-dipoles in an Au-catalyzed [4 + 2] annulation reaction, providing fully substituted furans in high yields [Scheme 6.109, reaction (4)] [214d].

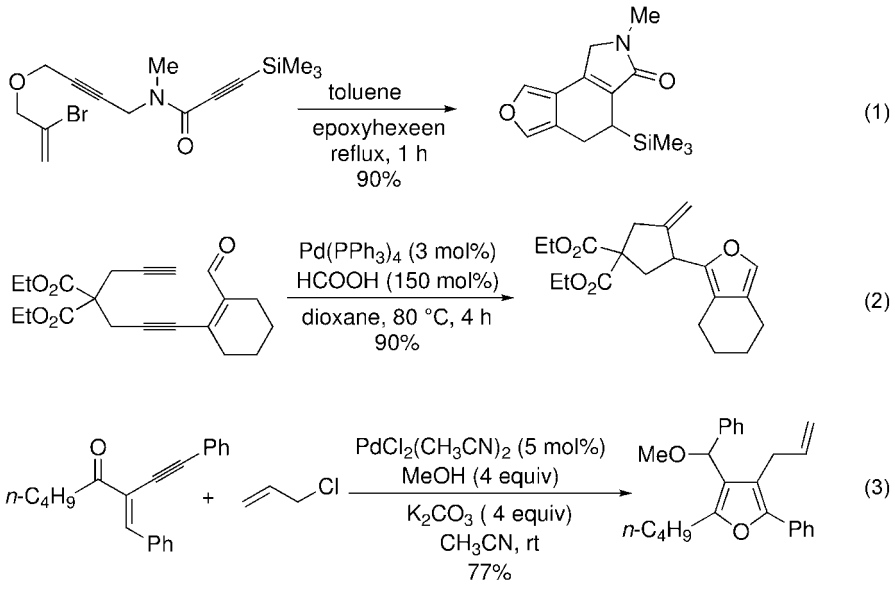
In addition to Au-catalysis, transition metals were still used widely as efficient catalysts in the synthesis of furans with full control of regioselectivity. Employing ruthenium complexes as catalysts, trisubstituted furans have been provided through an unprecedented 1,4-shift of the sulfanyl group of allenyl sulfides in high yields. Furan products have also been afforded in a one-pot reaction from α-diazocarbonyls and propargyl sulfide using both Rh- and Ru-complexes or only Ru-complexes as catalysts [Scheme 6.110, reaction (1)] [215a]. The second reaction in Scheme 6.110 provides another example of furan synthesis using metal catalysts. In the presence of $In(OTf)_3$, terminal disubstituted allenyl ketones were smoothly converted into



Scheme 6.110

tri- and tetra-substituted furans in high yields. The 1,2-shift of the terminal alkyl group was a key step in this reaction [215b]. In addition to In salt, some other Lewis acids, such as $Sn(OTf)_2$, AgOTf, and [Au(PPh3)]OTf, could also be used in similar reactions. Control of regioselectivity in the synthesis of multi-substituted furans has been realized by using Cu-catalyst in the reaction of *bis*-propargylic ester via Cu-carbene intermediate [Scheme 6.110, reaction (3)]. The reaction is suitable for the preparation of tetra-substituted furans, and silane is not necessary when CuBr or CuCl is the catalyst [215c]. 1-(1-Alkynyl)-cyclopropyl ketones have proved useful as a building block in the synthesis of multi-substituted furans by using an Au-catalyst [215b,c]. They are also useful in transition-metal catalyzed furan-formation reactions. In the presence of Rh-catalyst, carbonylation takes place and thus the procedure was developed for the synthesis of tetra-substituted furans in high regioselectivity via a Rh-catalyzed carbonylation/cyclization [Scheme 6.110, reaction (4)] [215d].

A domino-reaction is a powerful strategy that has been adopted by many groups to synthesize furans. Some examples are shown below (Scheme 6.111). Thermally induced cascade cyclizations under metal-free conditions using epoxyhexene as acid scavenger provided polycyclic furans in high yields [Scheme 6.111, reaction (1)] [216a]. Another Pd-catalyzed cascade reaction using conjugated enynals as starting materials has been reported. Here, good to high yields of 2,3,4-trisubstituted furans were realized [Scheme 6.111, reaction (2)] [216b]. Tetrasubstituted furans have been obtained in the three-component Michael addition–cyclization–cross coupling reaction by using a Pd-complex as catalyst. [Scheme 6.111, reaction (3)] [216c].



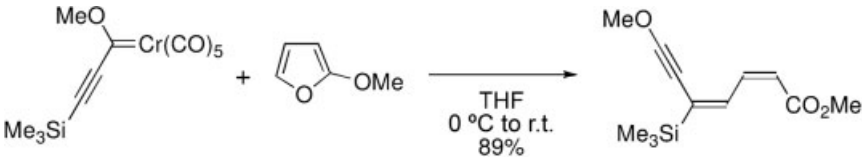
Scheme 6.111

6.5.2
Additional Reactions of Furans

Noteworthy and interesting transformations of furan nucleus that are related to the types of furan reactions as described in Section 6.3 have been reported between 2006 and 2009.

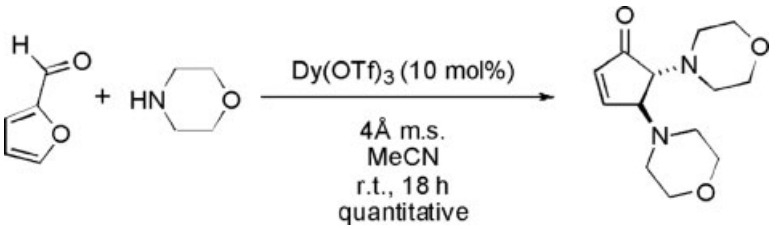
The reaction of a furan tethered at the 2-position to an iminium ion gave a spiro-2,5-dihydrofuran derivative as the sole diastereoisomer. This spirocyclization has been used in forming the ABC tricyclic core of manzamine A [217]. Several new catalytic asymmetric addition reactions of silyloxyfurans to electrophiles using various chiral catalysts have been developed and reviewed in detail [218]. The addition of 2-trimethylsilyloxyfuran to Morita–Baylis–Hillman acetates to form γ-butenolides has been rendered enantioselective by using a chiral phosphine catalyst [219].

As exemplified in Scheme 6.112, regioselective addition of 2-methoxyfuran or 2-trimethylsilyloxyfuran to chromium(0) alkynylcarbene complexes furnished interesting dienyne and dienediyne carboxylates by proceeding through a formal vinylogous Michael intermediate [220]. 2-Methoxyfuran reacted with chiral tungsten (0) alkenylcarbene complexes in a similar fashion [221].



Scheme 6.112

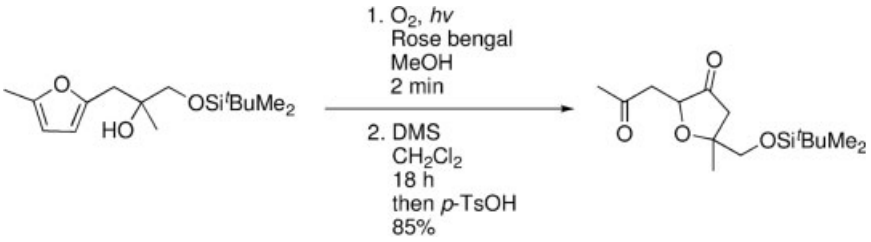
Scheme 6.113 shows a reaction of 2-furaldehyde with a secondary amine nucleophile in a lanthanide-catalyzed condensation/ring-opening/electrocyclization process to provide *trans*-4,5-diaminocyclopenten-2-ones, presumably via a ring-opened, deprotonated Stenhouse salt [222].



Scheme 6.113

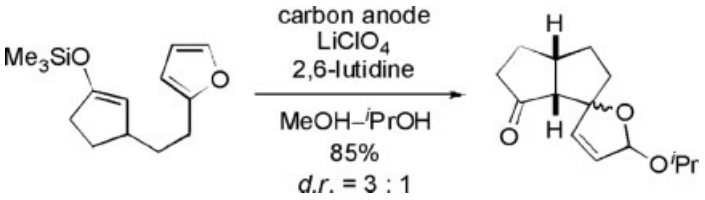
The opposite regioselectivity was obtained in the photooxidation of 3-bromofuran to bromo-γ-hydroxybutenolides by using DBU and phosphaxene [223]. The regioselectivity provided by the commonly used Hünig's base was reversed by using *n*-Bu_4NF in the photooxidation of unprotected furan Baylis–Hillman adducts to α-substituted γ-butenolides [224].

2-Furanyl carbamates undergo iodine-promoted oxidative rearrangement to form 5-methoxypyrrol-2(5*H*)-ones, which have been used as intermediates for the synthesis of 2,4-disubstituted pyrroles [225]. Enantiomeric enriched dihydropyranones can be obtained from Achmatowicz oxidation of furfuryl alcohols under Sharpless kinetic resolution conditions. This approach was adopted in a recent total synthesis of the acetogenin pyranicin [226]. As illustrated in Scheme 6.114, a "homologous" Achmatowicz oxidation of 2,5-disubstituted, 2-(β-hydroxyalkyl)furans by singlet oxygen produced 3-keto-tetrahydrofurans, presumably *via* a Michael addition to an intermediate 1,4-enedione [227].



Scheme 6.114

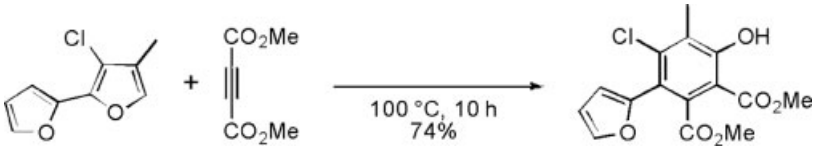
As depicted in Scheme 6.115, electrochemical oxidation of furans tethered to silyl enol ethers at the 2-position leads to a spiroannulation product as a result of the higher nucleophilicity of the furan 2-position [228].



Scheme 6.115

An enantioselective hydrogenation has been developed in which 2-substituted furans using chiral iridium/pyridine-phosphinite complexes as catalysts provide tetrahydrofurans with ee up to 93% [229]. Another interesting example is the Rh/butiphane-catalyzed enantioselective *cis*-hydrogenation of a furylnucleoside to form the reduced product with 72% ee [230].

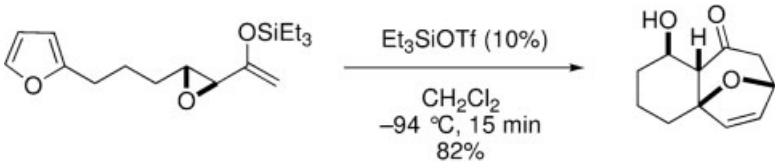
The presence of a halogen or methoxy substituent at the 2-position of furan enhances the rate of intramolecular Diels–Alder reactions and the yield of cycloadduct. This phenomenon is attributed to the decreased activation energy and a greater stabilization of the cycloadduct imparted by the substitution as determined by CBS-QB3 calculations. The same substitution at the 3-position can also provide a similar effect although to a lesser extent than that of the 2-position [231]. In the example shown in Scheme 6.116, the Diels–Alder reaction occurred mainly at the 3-chloro-



Scheme 6.116

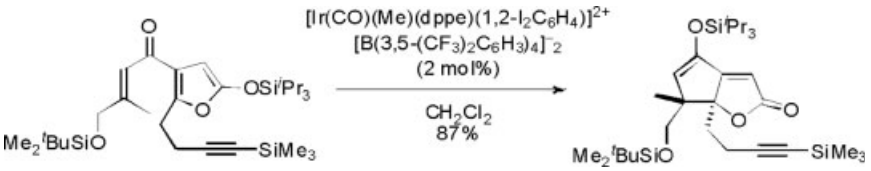
furan ring, which suggests a dominant effect of a 3-halo substituent on intermolecular cycloaddition [232].

The [4 + 3] cycloaddition of furans with epoxy enol silane derived oxyallyl cations (Scheme 6.117) has been rendered a viable process by optimization of the reaction conditions and use of a bulky triethylsilyl group [233]. Dioxines were used as oxyallyl cation equivalents in a Au/Ag-catalyzed [4 + 3] cycloaddition with furan [234].



Scheme 6.117

A novel Nazarov cyclization of silyloxyfuran as catalyzed by a strong Lewis acidic iridium complex (Scheme 6.118) was the pivotal step in a total synthesis of the sesquiterpene merrilactone A [235].



Scheme 6.118

Besides reacting with rhodium carbenoids, furans also react regioselectively with ruthenium and platinum carbenoids derived from tertiary propargyl carboxylates [236] and *sec*-O-propargyl thiocarbamates [237], leading to interesting triene systems.

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7
Five-Membered Heterocycles: Benzofuran and Related Systems

Jie Wu

7.1
Introduction

Benzofuran is a very important heterocycle and broadly found in natural [1] and biologically important [2] molecules and is frequently used as a building block in materials science [3a] and in organic synthesis [3b]. Several recent mini-reviews cover the investigation of benzo[*b*]furans in natural products, bioactivity and synthesis [4]. Two general approaches are commonly used for the preparation of substituted benzofurans: (i) functionalization of existing benzofuran-containing precursors by introduction of new substituents [5] and (ii) the formation of a new benzofuran ring by cyclization of acyclic substrates [6–10]. The methods based on the first approach are not general. Derivatization of benzofuran via an electrophilic substitution is not easy due to poor regioselectivity and the low stability of benzofurans under strongly acidic conditions, whereas protocols involving metallation of benzofuran derivatives followed by trapping of the benzofuryl anion with electrophiles are limited to base-stable benzofuran substrates and, in the case of alkylation, to primary electrophiles only. Among cyclization approaches, the classical oxidative cyclocondensation of phenol or related precursor remains the most powerful method for the construction of some naturally occurring benzofurans. Significant attention has been paid to the development of metal-catalyzed approaches aimed at cascade cyclization with substituted phenols or iodophenols under rather mild or neutral conditions [10]. In this chapter, in consideration of the limited space, we first discuss recent progress in the synthetic methods for metal-catalyzed benzofuran synthesis based on the reaction classification, and then discuss their important uses in terms of drug discovery and material science. For other synthetic methods regarding the synthesis of benzofurans, please see the references provided.

Modern Heterocyclic Chemistry, First Edition.
Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.

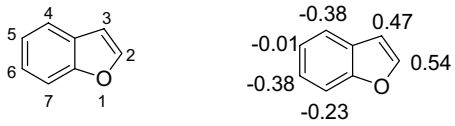


Figure 7.1 Structure numbering and frontier electron populations of benzo[*b*]furan.

7.2
General Structure and Reactivity

7.2.1
Relevant Physicochemical Data, Computational Chemistry and NMR Data

Benzo[*b*]furan is an aromatic compound and is usually recognized as a heterocyclic analog of naphthalene. Each of the ring atoms in the benzo[*b*]furan rings is in the same plane and has a p-orbital perpendicular to the ring plane. Additionally, (4*n*+2)p-electrons are associated with each ring. The oxygen in benzo[*b*]furan acquires considerable positive charge since it provides two p-electrons for the aromatic sextet. Accordingly, the same amount of negative charge is displayed in the all ring carbon atoms.

Figure 7.1 illustrates the frontier electron populations of the parent benzo[*b*]furan according to frontier orbital theory [11], and Table 7.1 shows the UV absorption bands and NMR signals of benzo[*b*]furan.

In benzo[*b*]furan, the π-electron excess of C2 is lower than that of C3. Consequently,. ^{13}C NMR chemical shifts show that C2 (141.5 ppm) is deshielded in comparison with C3 (106.9 ppm). It is noticeable that C7 is in the upfield position compared with the other benzenoid carbons at positions 4, 5, and 6. The benzenoid protons H4 and H7 appear downfield from H5 and H6. Also noteworthy is that the long-range coupling between H3 and H7 is of considerable diagnostic value in establishing the orientation of a substituent on the benzo[*b*] furan ring [12b].

Table 7.1 UV and NMR data of benzo[*b*]furan [12].

UV (ethanol) λ (nm) (ε, $mol^{-1}\,dm^3\,cm^{-1}$)	^{1}H NMR (acetone-d_6) [δ (ppm)]		^{13}C NMR [δ (ppm)]	
244 (4.03)	H2: 7.79	H6: 7.30	C2: 141.5	C6: 124.6
274 (3.39)	H3: 6.77	H7: 7.52	C3: 106.9	C7: 111.8
281 (3.42)	H4: 7.64		C4: 121.6	C3a: 127.9
	H5: 7.23		C5: 123.2	C7a: 155.5

7.3
Isolation of Naturally Occurring Benzofurans

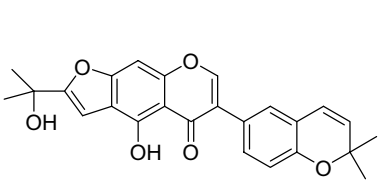
Numerous biologically active benzofurans have been isolated from natural sources [1]. Table 7.2 shows some examples of naturally occurring compounds containing the benzo[*b*]furan skeleton.

For instance, a new benzofuran dimer, 5,6,5′,6′-tetrahydroxy[3,3′]bibenzofuranyl-2,2′-dicarboxylic acid dimethyl ester (kynapcin-24, entry 5) has been isolated from *Polyozellus multiflex* and shown to noncompetitively inhibit prolyl endopeptidase (PEP), with an IC_{50} of 1.14 μM. Kynapcin-24 is less inhibitory to other serine proteases such as chymotrypsin, trypsin and elastase [1c].

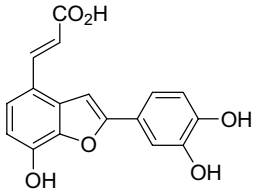
Recently, naturally occurring furocarbazole alkaloids were also identified [13]. These molecules have a broad range of useful pharmacological activities [14]. Their useful bioactivities and their interesting structural features attracted the attention of synthetic chemists and has led, over the last decade, to the development of many different synthetic strategies [13a, 15].

Table 7.2 Naturally occurring compounds containing benzo[*b*]furan skeleton.

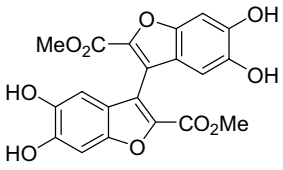
Entry	Compound name	Source	Biological activity	Reference
1	Ulexins C, A and D	*Ulex europaeus* ssp. *europaeus*	No inhibition of the growth of *Cladosporium cucumerinum*	[1a]
2	Paradisin C	Grapefruit juice	Inhibition of cytochrome P450 (CYP) 3A4 ($IC_{50} = 1.0$ μM)	[1b]
3	Skimmianine and dictamnine	*Teclea trichocarpa* Enge. (Rutaceae)	N/A	[1g]
4	Millettocalyxin C and pongol methyl ether	Stem bark of *Millettia erythrocalyx*	N/A	[1d]
5	Kynapcin-24	Fruiting bodies of *Polyozellus multiflex*	Non-competitively inhibited prolyl endopeptidase (PEP) ($IC_{50} = 1.14$ μM)	[1c]
6	Stemofurans A–K	Roots of *Stemona collinsae*	Antifungal activity against *Cladosporium herbarum*	[1f]
7	Tournefolal and tournefolic acid B	Stems of *Tournefortia sarmentosa*	Anti-LDL-peroxidative activity	[1e]



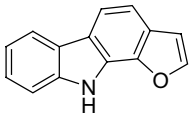
Ulexin A



Tournefolic acid B



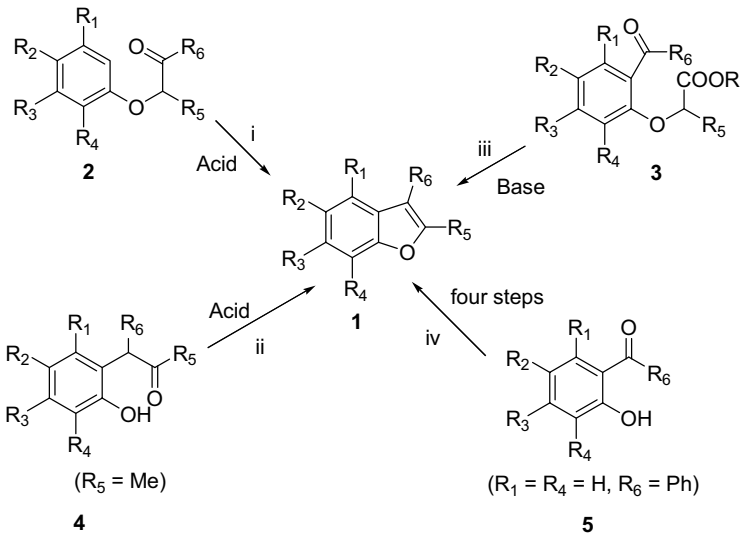
Kynapcin-24



furocarbazole

7.4
Synthesis of Benzofuran

As described above, major synthetic strategies for benzofurans include (Scheme 7.1): (i) dehydrative cyclization of α-(phenoxy)alkyl ketones [6a–6e]; (ii) dehydration of *o*-hydroxybenzyl ketones under acidic conditions [7a, 7b]; (iii) decarboxylation of *o*-acylphenoxyacetic acids or esters on treatment with a base [8a–8d]; (iv) cyclofragmentation of oxiranes, prepared in three or four steps from the corresponding *o*-hydroxybenzophenones [9]; and (v) palladium(II)-catalyzed cyclization of arylacetylenes [10a–10e].

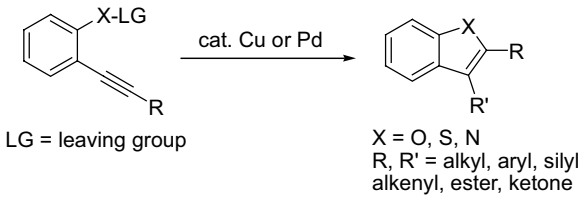


Scheme 7.1

7.4.1
Transition Metal Catalyzed Benzofuran Synthesis

7.4.1.1 Synthesis of 2,3-Disubstituted Benzo[*b*]furans

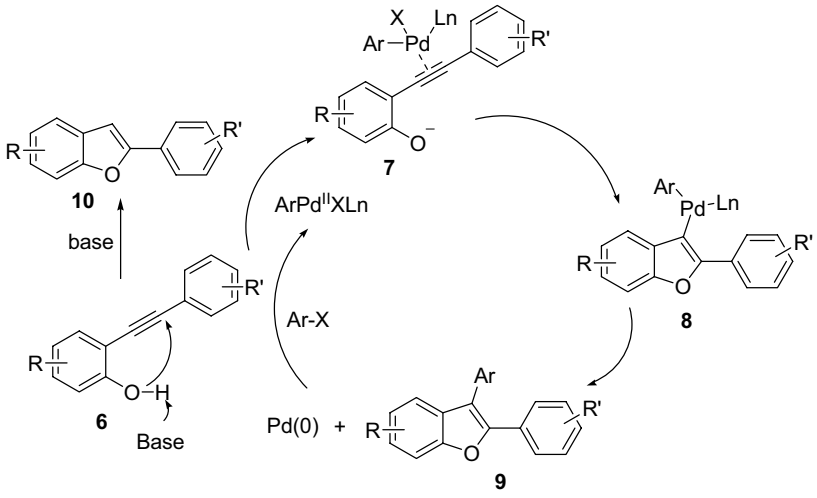
The metal-catalyzed intramolecular cyclization of aryl-substituted alkynes possessing a nucleophile in proximity to the triple bond has proven effective for the synthesis of five-membered heterocycles (Scheme 7.2) [16]; the first report describing synthetic



Scheme 7.2

efforts relevant to 2,3-diarylbenzo[*b*]furan with this approach was given by Arcadi in 1996 [17a].

The reaction of *o*-ethynylphenols with a wide variety of unsaturated halides or triflates RX (R=vinyl, aryl; X=Br, I, OTf) in the presence of a palladium catalyst gives 2-vinyl- and 2-arylbenzo[*b*]furans **10** in good to high yield, through an intramolecular cyclization step (Scheme 7.3). Small amounts of 2,3-disubstituted benzo[*b*]furans **9** are usually isolated as side products. In some cases, however, benzofurans **9** are generated in significant yield or even as the main products. The formation of **10** can be prevented by employing alternative procedures that use *o*-[(trimethylsilyl)ethynyl] phenyl acetates as starting building blocks. One procedure is based on the palladium-catalyzed reaction of *o*-[(trimethylsilyl)ethynyl]phenyl acetates with RX in the presence of $Pd(PPh_3)_4$, Et_3N and n-Bu_4NF, followed by the hydrolysis of the resultant coupling derivative under basic conditions. The other procedure affords **10** through an *in situ* coupling/cyclization of *o*-[(trimethylsilyl)ethynyl]phenyl acetates with RX in the presence of $Pd(PPh_3)_4$ and KOBut. The utilization of *o*-alkynylphenols as the starting alkynes in the palladium-catalyzed reaction with RX leads to the formation of 2,3-disubstituted benzo[*b*]furans through an annulation process promoted by

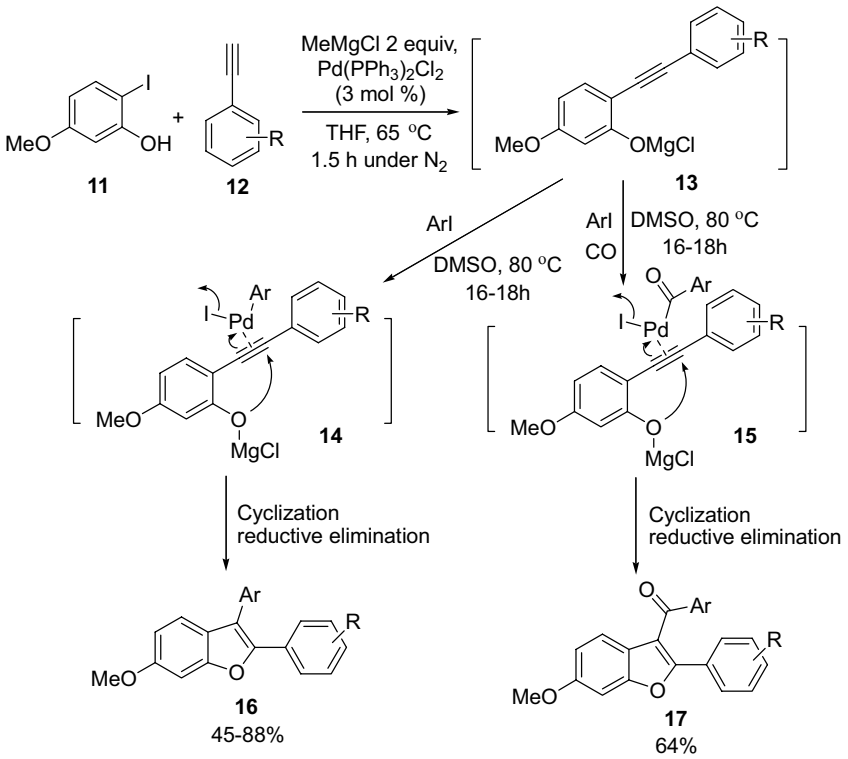


Scheme 7.3

σ-vinyl- and σ-arylpalladium complexes generated *in situ*. The best results in this case are obtained by using KOAc and $Pd(PPh_3)_4$. In the presence of KOAc and $Pd(PPh_3)_4$, and under an atmosphere of carbon monoxide, the reaction of *o*-alkynylphenols with RX provides 2-vinyl- and 2-aryl-3-acylbenzo[b]furans.

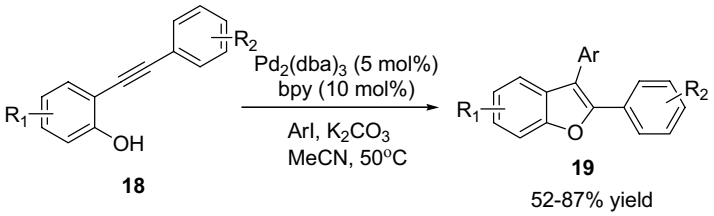
Later, Arcadi reported that the 5-*endo-dig*-iodocyclization of 2-alkynylphenols with I_2 in the presence of $NaHCO_3$ at room temperature produces 2-substituted 3-iodobenzo[b]furans, which are useful synthetic intermediates for the preparation of 2,3-disubstituted benzo[*b*]furans via Pd-catalyzed cross-coupling reactions [17b].

More recently, Flynn and colleagues [18] have disclosed an efficient approach to synthesize 2-substituted-3-arylbenzo[*b*]furan by a palladium-catalyzed multicomponent sequential coupling strategy, starting from iodophenol and terminal phenyl acetylene. In this reaction, MeMgBr was used as an essential base to form the corresponding magnesium salts of phenolate. Although the method was applied successfully to one substituted iodobenzene, utilization of MeMgBr to form the magnesium salts could hamper application of this method to other substrates having functional groups such as ketone, ester or amide, thus limiting the universality required in diversity oriented synthesis (Scheme 7.4).



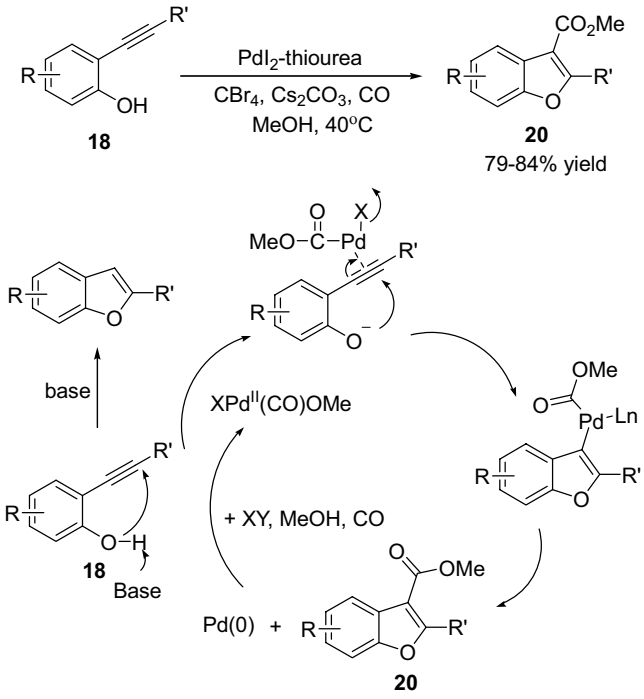
Scheme 7.4

To realize a strategy of diversity oriented synthesis and branching reaction pathways Yang [19] has described the palladium/bpy-catalyzed annulation of *o*-alkynylphenol with various aryl halides to generate diversified 2,3-diarylbenzo[*b*]furans (**19**). In the reaction process, the presence of bpy ligand is essential for the successful transformation. This method provides an efficient synthetic pathway for the combinatorial synthesis of conformationally restricted 2,3-diarylbenzo[*b*]furan (Scheme 7.5).



Scheme 7.5

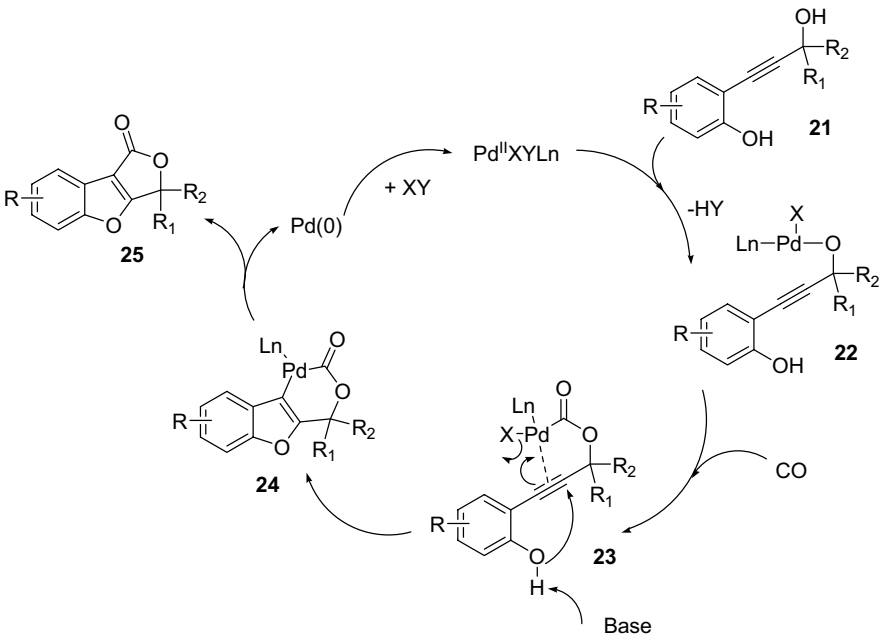
Yang [20a] has also developed a highly effective co-catalysis system (PdI_2-thiourea and CBr_4) for carbonylative cyclization of both electron-rich and electron-deficient *o*-hydroxylarylacetylenes to the corresponding methyl benzo[*b*]furan-3-carboxylates. This was the first time using carbon tetrabromide (CBr_4) as a superior oxidative agent for the turnover of palladium(0) to palladium(II) (Scheme 7.6).



Scheme 7.6

The overall process may involve attack of a carboalkoxypalladium(II) intermediate on the alkyne **18** to generate a complex, followed by nucleophilic addition of the phenolic oxide to the $XPd^{II}(CO)OR$-activated alkyne to give intermediate, which went through reductive elimination to produce ester **20** and palladium(0). The palladium(0) is then oxidized to palladium(II), which re-enter the catalytic cycle. The method has been successfully applied in the solid-phase synthesis of benzo[*b*] furan-3-carboxylates [20e].

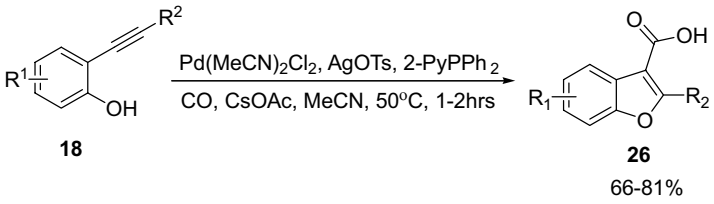
Further studies shows the carbonylative annulation of *o*-alkynylphenols mediated by $PdCl_2(PPh_3)_2$ and dppp in the presence of CsOAc at 55 °C in acetonitrile under a balloon pressure of CO generates functionalized benzo[*b*]furo[3,4-*d*]furan-1-ones **25** in good yields [20b]. This novel synthetic approach provides a highly efficient method for diversification of the benzofuran scaffold for combinatorial synthesis. The authors speculated that the overall process may involve attack of alcohol **21** on the $Pd^{II}XYLn$ to generate complex **22**, followed by insertion of CO to give intermediate **23**. Intramolecular nucleophilic addition of the phenolic oxide to the resulting acyl-palladium complex **23** leads to formation of intermediate **24**, which might undergo reductive elimination to produce the five-membered lactone **25** and palladium(0). The palladium(0) is then oxidized to palladium(II), thereby completing the cycle (Scheme 7.7).



Scheme 7.7

Recently, Yang [20h] further described a novel, mild method for the rapid synthesis of benzo[*b*]furan-3-carboxylic acids **26** directly from the substituted *o*-alkynyl- phenols

18 in good yields by utilizing a Pd^{II}-mediated carboxylative annulation since, from a drug discovery perspective, synthesis of benzofuran-based carboxylic acids could be more interesting because of their increased solubility in aqueous media and the potential enhancement of ionic interactions with basic residues in their association with biological receptors (Scheme 7.8).



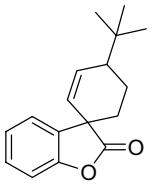
18 **26**

66-81%

Scheme 7.8

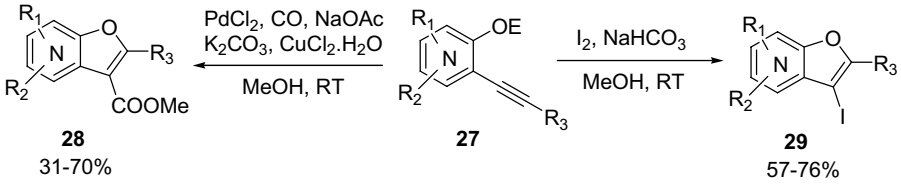
Cacchi has also described palladium catalysis in the construction of the benzo[*b*] furan ring from alkynes and organic halides or triflates [16m,16n].

3-Spiro-fused benzofuran-2(3*H*)-ones can be conveniently synthesized starting from vinyl triflates and o-iodophenols through palladium-catalyzed chemoselective carbonylation and subsequent regioselective intramolecular Heck reaction. For example, 2-iodo-4-methylphenol reacted with trifluoromethanesulfonic acid 4-(1,1-dimethylethyl)-1-cyclohexen-1-yl ester leading to 4-(1,1-dimethylethyl)-1-cyclohexene-1-carboxylic acid 2-iodo-4-methylphenyl ester. Subsequent ring closure of this intermediate furnishes spirobenzofuranone C (85% yield) [17c].



Spirobenzofuranone C

Arcadi [17d] has reported the synthesis of 2,3-disubstituted furo[3,2-*b*]pyridines, 2,3-disubstituted furo[2,3-*b*]pyridines and 2,3-disubstituted furo[2,3-*c*]pyridines under mild conditions via the palladium-catalyzed cross-coupling of 1-alkynes with *o*-iodoacetoxy- or *o*-iodobenzyloxypyridines, followed by electrophilic cyclization by I_2 or by $PdCl_2$ under a balloon of carbon monoxide (Scheme 7.9).

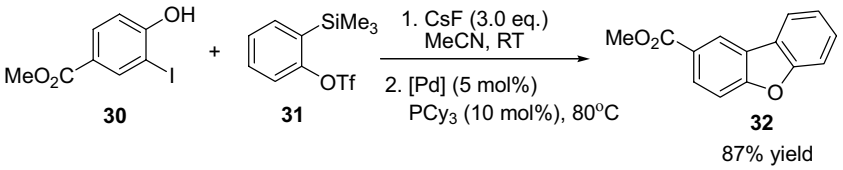


28 **27** **29**

31-70% 57-76%

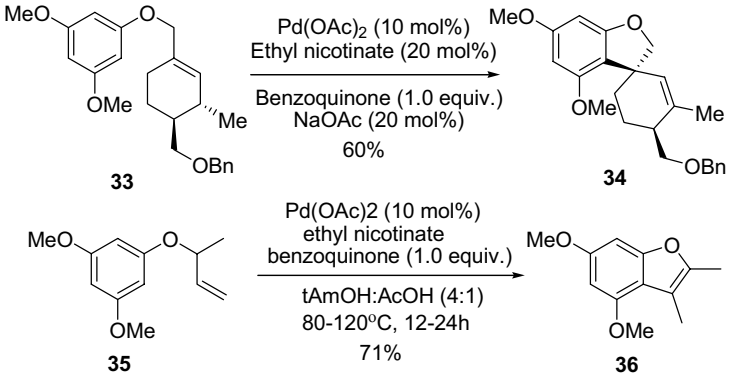
Scheme 7.9

Dibenzofuran-type molecules can be formed from the reaction of *o*-iodophenols with silylaryl triflate in the presence of a palladium catalyst. Nucleophilic addition of *o*-iodophenols to benzyne (generated by treatment of silylaryl triflate with CsF) and subsequent Pd-catalyzed intramolecular arylation are involved in the reaction [21] (Scheme 7.10).



Scheme 7.10

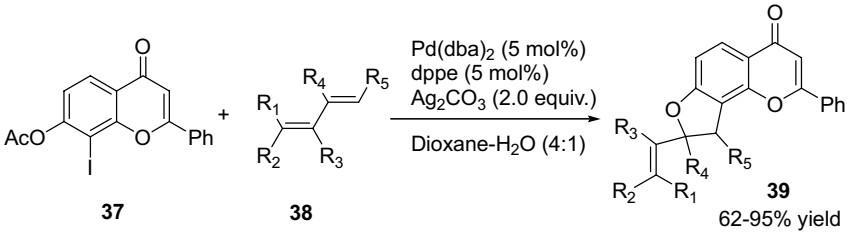
Recently, Stoltz [22] has developed a method for the synthesis of electron-rich, highly substituted benzofuran and dihydrobenzofuran derivatives (50–80% yields) via an intramolecular Fujiwara-Moritani/oxidative Heck reaction (Scheme 7.11); 15 examples are demonstrated in the article. No extra functionalization step was required for palladium(II)-catalyzed oxidative carbocyclizations, which provided highly substituted benzofurans and dihydrobenzofurans by net dehydrogenation. The direct C−H bond functionalization of the aromatic ring and cyclization with unactivated olefins is involved in the oxidation process. Furthermore, the products contain quaternary carbon stereocenters that can be obtained in diastereomerically pure form.



Scheme 7.11

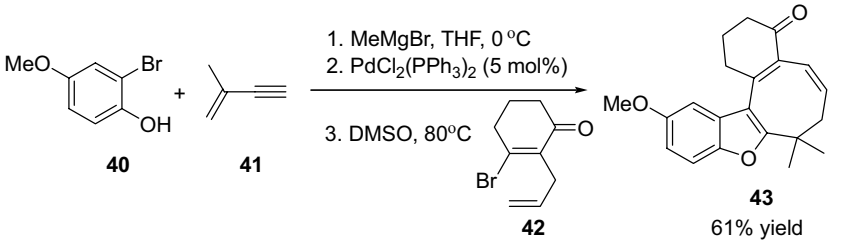
Ionic liquid ([BMIm]BF_4) has been utilized as an effective solvent for the $PdCl_2$-catalyzed benzofuran formation via an intramolecular Heck reaction [23]. This strategy has been applied to construct the seven-membered ring based (−)-frondosin B [24].

The palladium-catalyzed annulation of 1,3-dienes with *o*-iodoacetoxyflavonoids for the generation of biologically interesting dihydrofuroflavonoids was realized (Scheme 7.12). This reaction is quite general and regioselective, and a wide variety of terminal, cyclic and internal 1,3-dienes are applicable [25].



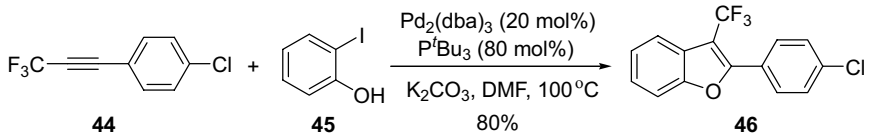
Scheme 7.12

One of the key intermediates (**43**) towards the total synthesis of frondosin B has been synthesized by a sequential reaction from phenol **40**, enyne **41**, and bromide **42** in a one-pot operation (Scheme 7.13) [26]. Palladium-catalyzed intramolecular C−O bond formation between aryl halides and enolates has been employed to form 2,3-disubstituted benzo[*b*]furans [27].



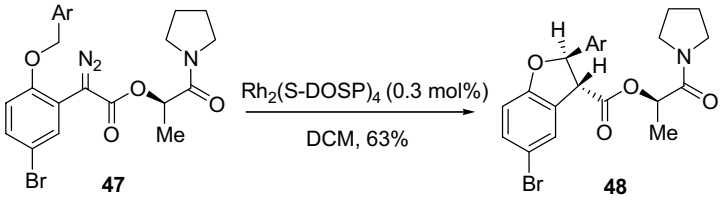
Scheme 7.13

Synthesis of 3-fluoroalkylated benzo[*b*]furans was achieved via a palladium-catalyzed reaction of fluorine-containing internal alkynes with various 2-iodophenols in the presence of $P(^tBu)_3$ as an essential ligand [28] (Scheme 7.14).



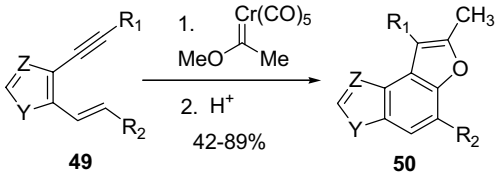
Scheme 7.14

As shown in Scheme 7.15, the optically active dihydrobenzo[*b*]furan-ring **48** has been constructed efficiently via a C−H insertion reaction, leading to the total synthesis of (−)-ephedradine A [29].



Scheme 7.15

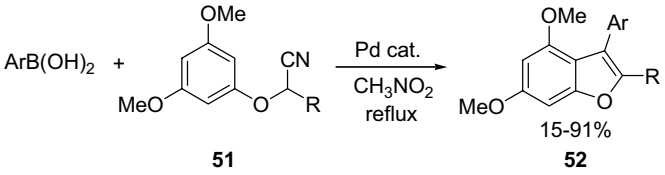
Herndon has reported benzannulation of heterocyclic ring systems through coupling of Fischer carbene complexes and heterocycle-bridged enynes [30]. The benzofuran rings are easily annulated onto furan, thiophene and imidazole ring systems in a reaction process involving the coupling of Fischer carbene complexes with either 2-alkenyl-3-alkynyl- or 3-alkenyl-2-alkynyl-heteroaromatic systems (Scheme 7.16).



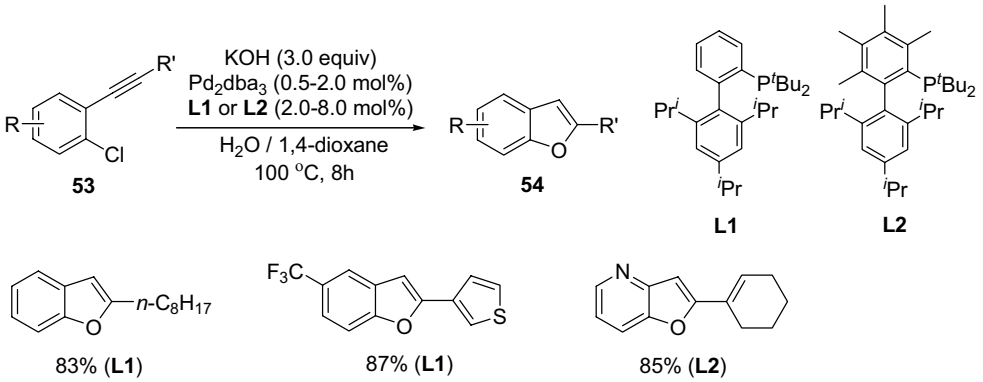
Scheme 7.16

Arylboronic acids reacted with nitriles catalyzed by a cationic palladium complex leading to aryl ketones in moderate to good yields [31]. Based on this result, a one-step synthesis of benzofurans from phenoxyacetonitriles under the catalysis of $[(bpy)Pd^{+}(OH)]_2(^{-}OTf)_2$ or $[(bpy)Pd^{2+}(H_2O)_2](^{-}OTf)_2$ has been developed that shows that the cationic palladium catalyst is highly active for these addition reactions (Scheme 7.17).

2-Chloroaryl alkynes, which are generated from 1,2-dihaloarenes using known methodology, undergo the reaction conditions shown in Scheme 7.18 successfully providing benzofurans **54** in good yields [32]. While the cyclization of 2-hydroxyalk-



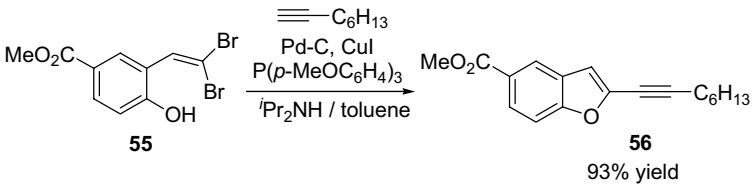
Scheme 7.17



Scheme 7.18

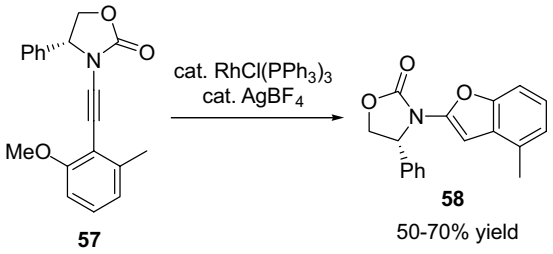
ynyl arenes is known, this is the first time this strategy has been employed starting with a 2-haloaryl alkyne.

The formation of 2-alkynyl benzofurans is described via a new tandem coupling approach [33]. This reaction utilizes easily accessible *gem*-dibromovinyl substrates and terminal alkynes and proceeds via Pd/C- and CuI-catalyzed tandem Ullman/ Sonogashira couplings (Scheme 7.19).



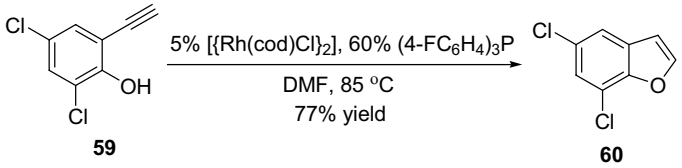
Scheme 7.19

An efficient synthesis of benzofurans from *o*-anisole-substituted ynamides has been reported by Hsung and co-workers via an unexpected Rh(I)-catalyzed demethylation-cyclization sequence (Scheme 7.20) [34]. The silver salt is critical for the successful transformation in the reaction process.



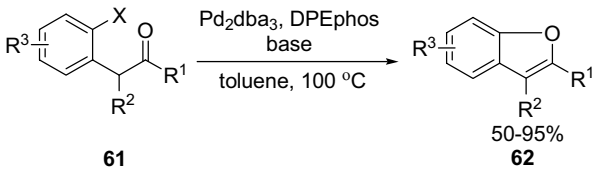
Scheme 7.20

Trost has reported that benzofurans can be formed chemoselectively from the Rh-catalyzed cyclo-isomerization reaction of easily prepared 2-alkynylphenol substrates (e.g., 2,4-dichloro-6-ethynylphenol) [35]. The reaction may proceed by nucleophilic capture of a vinylidene intermediate (Scheme 7.21).



Scheme 7.21

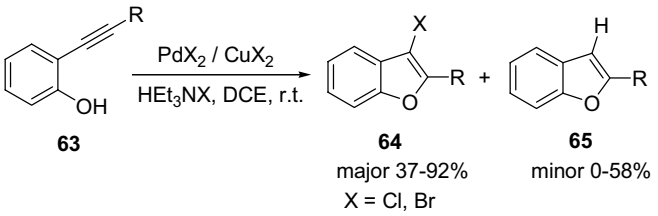
Benzofuran products can be delivered in good yields through palladium-catalyzed intramolecular C−O bond formation of enolates derived from α-(ortho-haloaryl)-substituted ketones (Scheme 7.22) [36]. A catalyst generated from $Pd_2(dba)_3$ and the ligand DPEphos effects the key bond formation to produce various substituted products from both cyclic and acyclic precursors. In the meantime, a cascade sequence that produces the required α-aryl ketones *in situ* has been developed. However, the substrate scope is more restricted.



Scheme 7.22

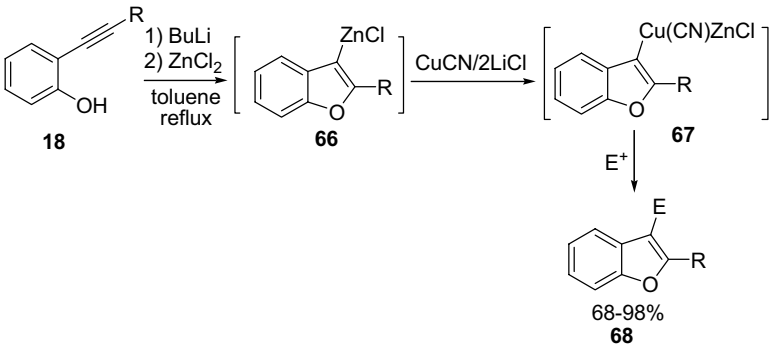
Li has presented a novel and selective palladium-catalyzed annulation of 2-alkynylphenols method for the synthesis of 2-substituted 3-halobenzo[*b*]furans [37]. In the presence of PdX_2, 2-substituted benzo[*b*]furans were afforded in good yields, whereas in the presence of 5–10 mol% of PdX_2, 3.0 equiv of CuX_2 and 0.2 equiv of

HEt_3NI, 2-disubstituted 3-halobenzo[*b*]furans were selectively produced as the major products (Scheme 7.23). A possible mechanism was also proposed.



Scheme 7.23

3-Zinciobenzofurans **66**, generated in excellent yield through a metallative 5-*endo-dig* cyclization reaction of 2-alkynylphenoles in the presence of BuLi and ZnCl2, can be further transmetallated to the corresponding cuprates **67**, which then react with electrophiles to produce various 2,3-disubstituted benzofurans **68** [38] (Scheme 7.24).

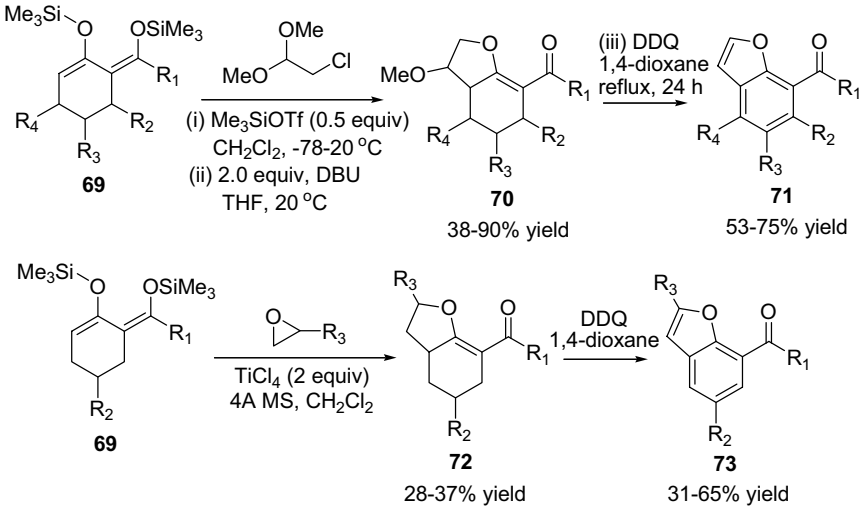


Scheme 7.24

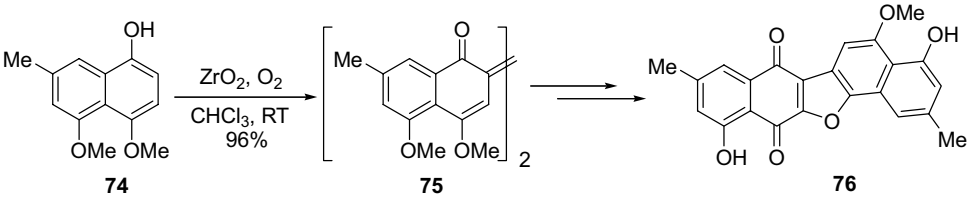
7.4.2
Oxidative Cyclization

Recently, Bellur [39] has reported an efficient synthesis of functionalized benzofurans based on a [3 + 2] cyclization/oxidation strategy. The functionalized benzofurans were prepared by DDQ oxidation of 2-alkylidenetetrahydrofurans, which are readily available by one-pot cyclizations of 1,3-dicarbonyl dianions or 1,3-bis-silyl enol ethers (Scheme 7.25).

The first total and biomimetic synthesis of violet-quinone has been accomplished by utilizing an oxidative dimerization of a substituted 4-methoxy-1-naphthol with a ZrO_2/O_2 system, the so-formed dimer eventually led to the target molecule (Scheme 7.26) [40]. The same research group later published the $SnCl_4$-mediated oxidative biaryl coupling reaction to build up the dinaphthanofuran framework [41]. Silver(I) acetate is an efficient agent with which to obtain the dimer of resveratrol in



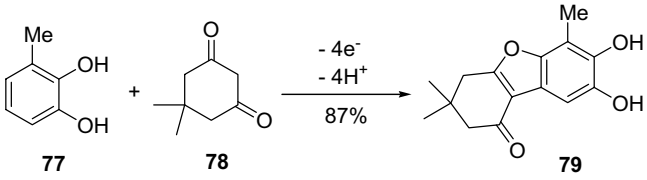
Scheme 7.25



Scheme 7.26

high yield [42]. Oxidation of phenol with PIFA has also been applied to construct the framework of (−)-galanthamine [43].

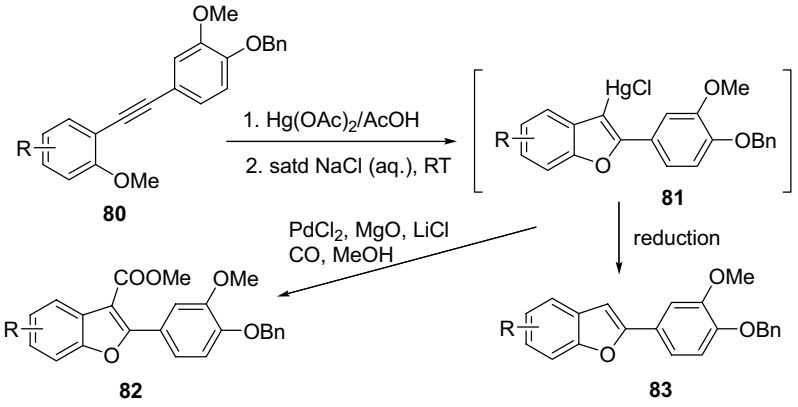
A new family of benzo[*b*]furans has been synthesized by an anodic oxidation of an aqueous solution of 3-substituted catechols followed by coupling with dimedone (**78**) (Scheme 7.27) [44].



Scheme 7.27

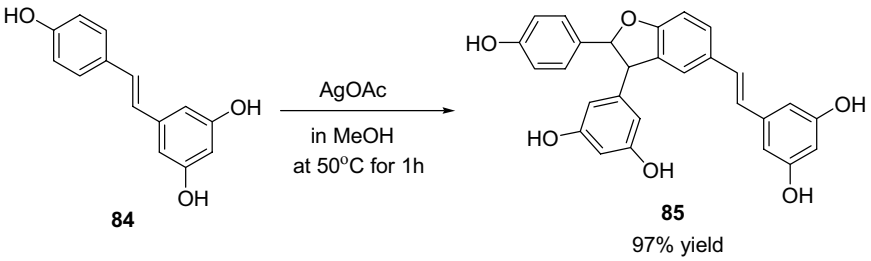
Compound **80** can be cyclized in the presence of either mercury acetate in acetic acid or bromine in chloroform to give 3-chloromercurio- or 3-bromobenzofuran,

respectively. The 3-chloromercurio intermediates could be reduced to proton or derivatized to ester or bromide, leading to the synthesis of ailanthoidol (30% yield), XH-14 (15% yield) and obovaten (11% yield), respectively [45] (Scheme 7.28).



Scheme 7.28

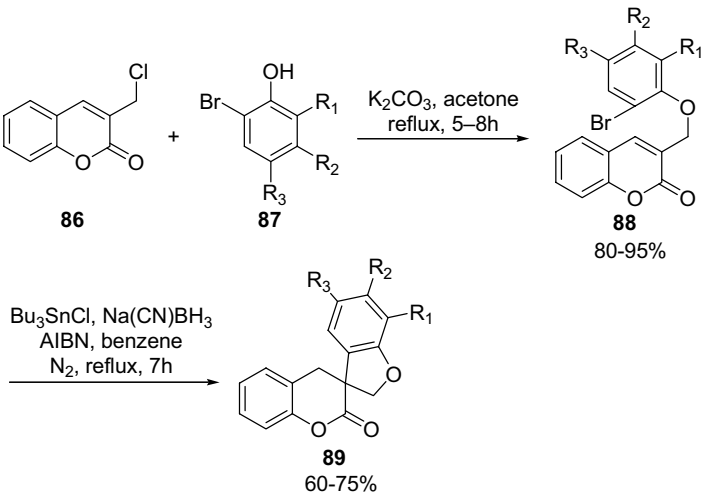
5-[2-(4-Hydroxyphenyl)vinyl]benzene-1,3-diol **84** (resveratrol) was treated with an equimolar amount of silver(I) acetate in dry MeOH to afford its (*E*)-dehydrodimer, 5-{5-[2-(3,5-dihydroxyphenyl)vinyl]-2-(4-hydroxyphenyl)-2,3-dihydrobenzofuran-3-yl} benzene-1,3-diol **85**, as a racemic mixture in high yield [46] (Scheme 7.29). This method is applicable to the oxidative dimerization of 4-hydroxystilbenes such as *trans*-styrylphenol and 5-{6-hydroxy-2-(4-hydroxyphenyl)-4-[2-(4-hydroxyphenyl)vinyl]-2,3-dihydrobenzofuran-3-yl}benzene-1,3-diol (viniferin), giving rise to the corresponding 2-(4-hydroxyphenyl)-2,3-dihydrobenzofurans.



Scheme 7.29

7.4.3
Radical Cyclization

A radical initiated benzo[*b*]furan formation has been applied to the synthesis of spiro [chroman-3,3′-(2′*H*)-benzofurans] in the presence of *n*-Bu_3SnCl and $Na(CN)BH_3$ [47] (Scheme 7.30).



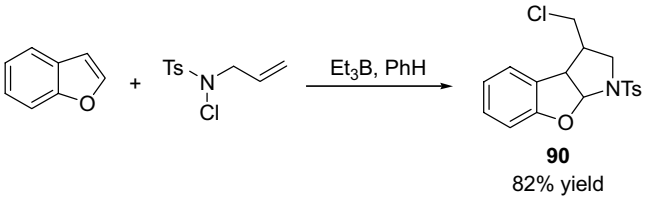
Scheme 7.30

A similar approach has also been demonstrated by the same group to obtain spiro [pyrimidine-6,3′-2′,3′-tetrahydrobenzofuran]-2,4-diones [48]. On the other hand, *n*-Bu_3GeH is reported to be an effective alternative compared with *n*-Bu_3SnH in the synthesis of 3-substituted-2,3-dihydrobenzo[*b*]furans [49]. Moreover, a photo-induced fast tin-free reductive radical dehalogenation has found use for the synthesis of 2,3-dihydrobenzo[*b*]furans [50].

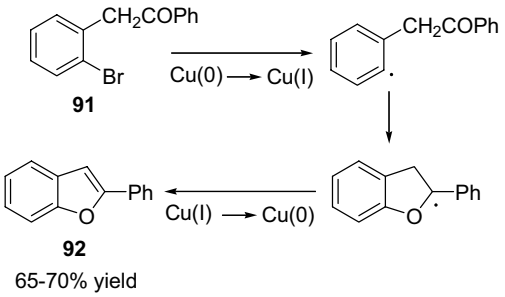
2,3-Disubstituted benzofuran derivatives have been synthesized from *o*-acylphenols in two steps. The β-aryloxyacrylates prepared from the o-acylphenols react with n-Bu_3SnH/AIBN and then with 5% HCl-EtOH leading to 2,3-disubstituted benzofurans [51].

A radical [3 + 2] annulation reaction with an N-centered radical has been developed. The reaction of alkenes with *N*-allyl-*N*-chlorotosylamide yields the corresponding pyrrolidine derivatives **90** in good yields, in the presence of Et_3B as a radical initiator, via an atom-transfer process [52] (Scheme 7.31).

Grimshaw [53] has reported that the cyclization of 2′-bromodeoxybenzoin with Cu powder in refluxing $AcNMe_2$ gives 2-phenylbenzofurans in 65–70% yield (Scheme 7.32).



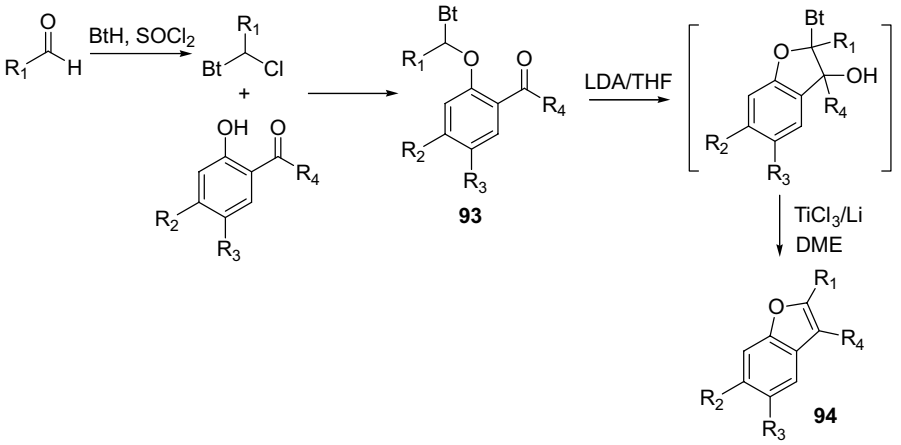
Scheme 7.31



Scheme 7.32

7.4.4
Acid- and Base-Mediated Cyclization

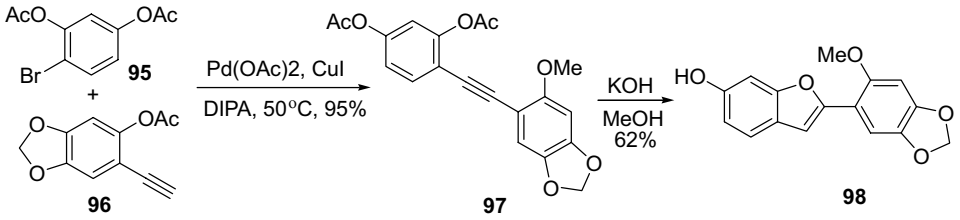
Katritzky [54] has disclosed the preparation of 2,3-disubstituted benzofurans by reactions of *o*-hydroxyphenyl ketones or *o*-(1-hydroxy-2,2-dimethylpropyl)phenol with 1-benzotriazol-1-ylalkyl chlorides in two or three steps (Scheme 7.33). These



Scheme 7.33

approaches provide a facile route to a variety of benzofurans in good overall yields and complements a previous benzotriazole-mediated preparation of benzofurans.

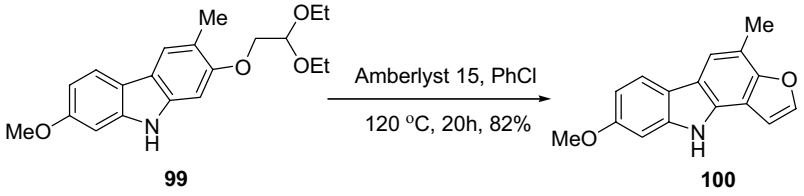
2-Arylbenzo[*b*]furan can be cyclized in a modest yield from a non -symmetrical diarylethyne, which was generated via palladium -catalyzed Sonogashira reaction of an aryl bromide and an aryl acetylene (Scheme 7.34) [55]. Other types of 2-alkyl/aryl substituted benzo[*b*]furans have also been obtained by the palladium-catalyzed coupling reaction of *o*-iodophenols (even *o*-iodophenols with a base-labile nitro group) with various alkynes in the presence of prolinol as base in water. This environmental friendly procedure does not need the phase transfer or water-soluble phosphine ligands and is free from the use of any organic co-solvent [56]. A similar process has also been reported with an amphiphilic polystyrene–polyethylether (PS-PEG) resin-supported palladium-phosphine complex as a catalyst in water to give the corresponding aryl-substituted alkynes in high yield under copper-free conditions [57]. In the total synthesis of pterulinic acid, the core structure of 2-substituted benzofuran was generated by the palladium-catalyzed heteroannulation of an *o*-iodophenol derivative with methyl 3-butynoate [58].



Scheme 7.34

Base-mediated conditions have also been applied to afford 2-arylbenzo[*b*]furan, employing the coupling product generated from the ultra-fine nickel-catalyzed Sonogashira reaction of iodophenols with phenylacetylenes [59]. Four 2,6-linked and 2,5-linked benzo[*b*]furan trimers as organic electroluminescent materials have been prepared by the base-mediated cyclization of 2-alkynylphenols [60].

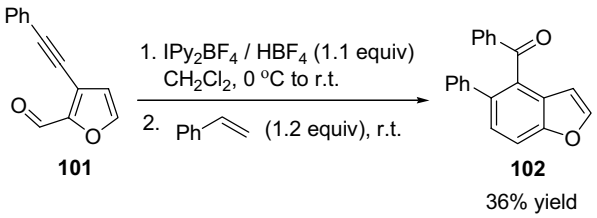
In the synthesis of furoclausine A, acid-catalyzed conditions were used to produce the furo[3,2-*a*]carbazole framework from a ketal as depicted (Scheme 7.35) [61]. An acid-catalyzed intramolecular cyclization to form the scaffold of furoquinoline



Scheme 7.35

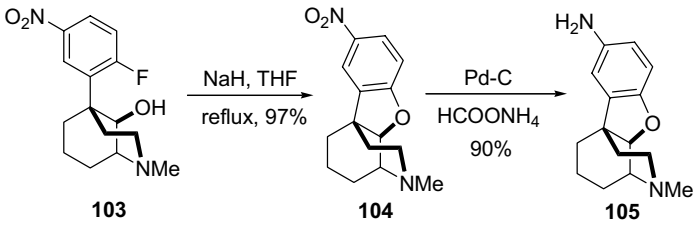
alkaloids has also been achieved from 3-oxiranylquinolines [62]. Furanoeremophilane sesquiterpenes have been synthesized by acid-mediated furan ring formation from their corresponding phenolic-ketone ethers [63]. 3-Aryl-2,2-dialkyl-2,3-dihydrobenzo[*b*]furans have been delivered from phenols and 2-aryl-2,2-dialkylacetaldehydes in the presence of a catalytic amount of CF_3SO_3H [64]. A $ZnCl_2$-mediated benzo[*b*]furan formation has been utilized to produce 2-carboxylate benzo[*b*]furans from 3-dimethylaminopropenoates [65].

Synthesis of different types of substituted benzoheterocycles under metal-free protocols have been developed. The combination of *o*-alkynylbenzaldehyde derivatives, iodonium ions and alkenes was demonstrated to effectively produce the corresponding benzofurans [66]. The rapid access to benzofurans with interesting di- and tri-substitution patterns and featuring the 2,3-unsubstituted ring motif has been established (Scheme 7.36).



Scheme 7.36

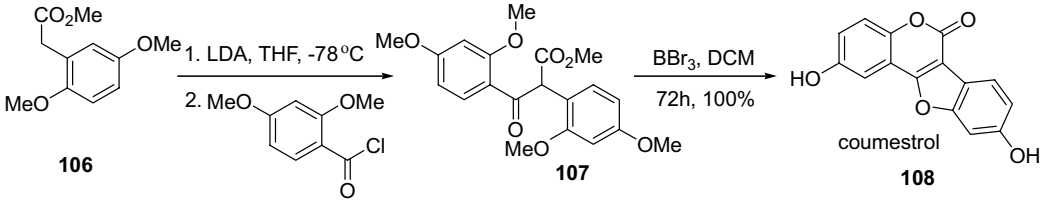
A simple procedure for the construction of the *trans*-5,6-ring system existing in phenylmorphans was developed by the displacement of nitro-activated aromatic fluorine with a hydroxyl group [67] (Scheme 7.37).



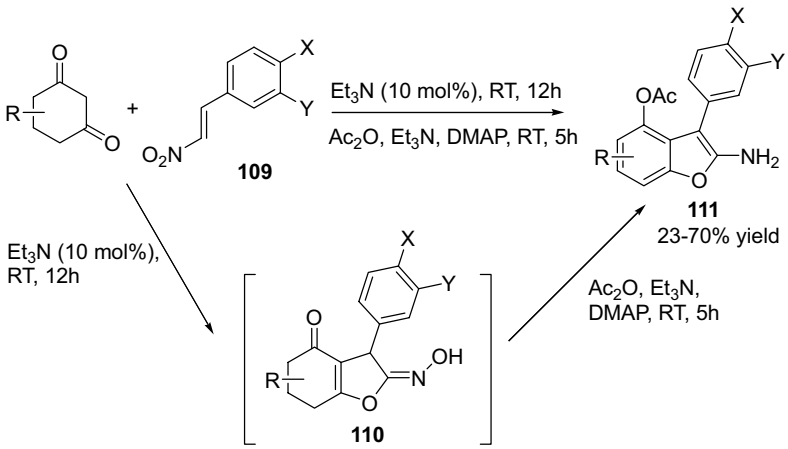
Scheme 7.37

Synthesis of coumestrol (**108**) has been achieved by sequential condensation between phenyl acetate and benzoyl chloride, followed by demethylation and cyclization (Scheme 7.38) [68].

Hellwinkel has reported 2-arylbenzofurans formation using MF/Al_2O_3 base-systems [69]. Saito has described a novel method for the generation of 4-acetoxy-2-amino-3-arylbenzofurans from 1-aryl-2-nitroethylenes and cyclohexane-1,3-diones [70]. This one-pot operation shows high efficiency (Scheme 7.39).

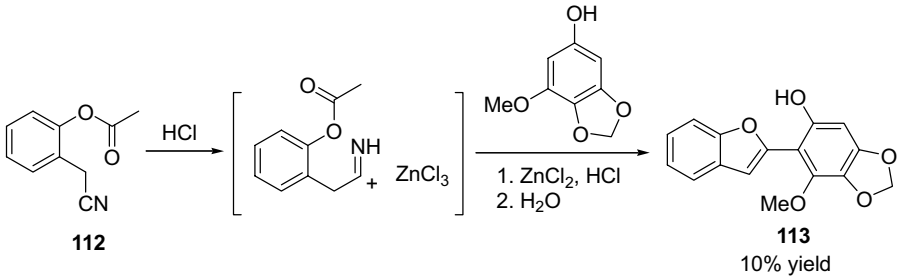


Scheme 7.38



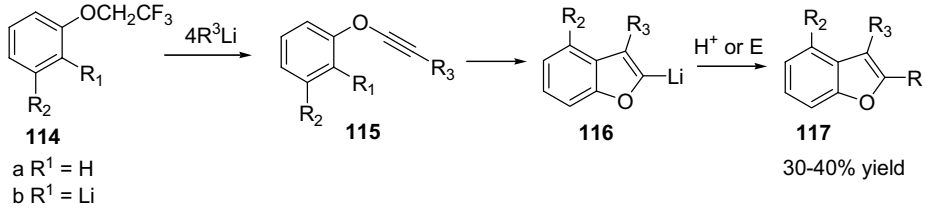
Scheme 7.39

Wagner [71] has described the synthesis of 2-(6-hydroxy-2-methoxy-3,4-methylenedioxyphenyl)benzofuran (**113**, Scheme 7.40) via an acid mediated cyclization.



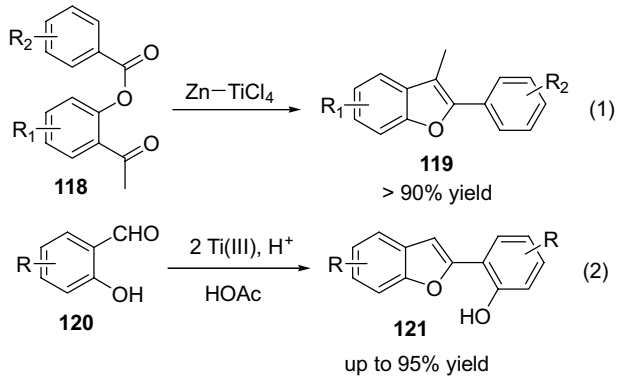
Scheme 7.40

Johnson [72] has reported benzofuran formation via a organolithium-induced cyclization. Treatment of 2,2,2-trifluoroethyl phenyl ethers with 4 equivalents of an aryl or alkyl lithium reagent (R^3Li) causes in almost all cases complete dehalogenation of the trifluoroethyl side chain with the concomitant introduction of an alkyl or aryl group (R^3) at the acetylenic 2-position (Scheme 7.41). This is followed apparently by ortholithiation to give the lithio intermediates; the latter then spontaneously cyclize to the 2-lithioheterocyles. Subsequent electrophilic quenching leads to the corresponding benzofurans depending whether the electrophile is a proton or another electronegative species.



Scheme 7.41

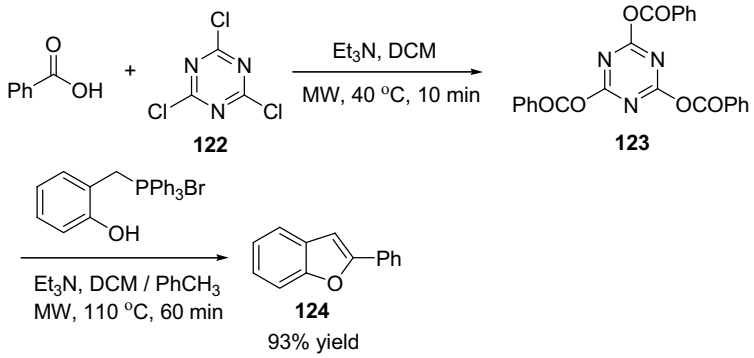
Banerji [73] [Scheme 7.42 (1)] and Clerici [74] [Scheme 7.42 (2)] have reported titanium-mediated benzofuran synthesis, respectively.



Scheme 7.42

Jha has also reported a facile synthesis of 2-arylbenzo[*b*]furans through an unusual acid-catalyzed 1,2-elimination [75]. 2-Phenoxyalkanals react with methanol at room temperature under homo- or heterogeneous acid-catalysis conditions leading to the formation of diacetal as well as some quantities of appropriate 2-alkylbenzofurans. 2-Alkylbenzofurans can be obtained in high yields via cyclization of the 1,1-dimethoxy-2-phenoxyalkanes under mild conditions over Amberlyst 15 [76].

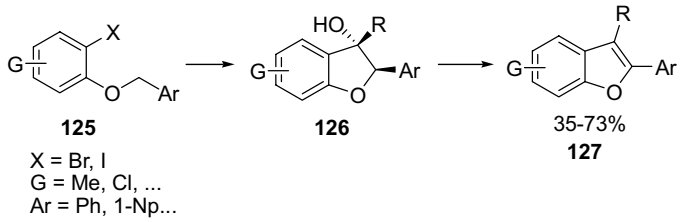
An effective route to chiral optically active 2-substituted benzofurans directly from carboxylic acids has been reported (Scheme 7.43) [77]. This procedure, which allows



Scheme 7.43

the preparation of R-alkyl-2-benzofuranmethanamines from N-protected R-amino acids without sensible racemization phenomena, proceeds in good yields under mild conditions with the help of microwave irradiation.

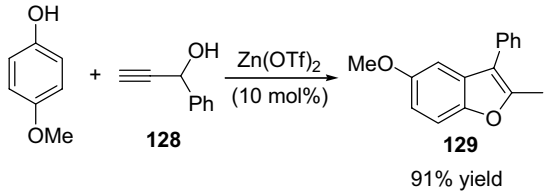
Treatment of benzyl 2-halophenyl ethers with 3 equivalents of t-BuLi results in Li–halogen exchange and lithiation at benzylic methylene simultaneously. These dianions can be trapped with electrophiles. Their reactions with carboxylic esters afford the corresponding 2-aryl-3-hydroxy-2,3-dihydrobenzo[*b*]furans, which subsequently undergo acid-catalyzed or mediated dehydration to give moderate to good overall yield of various 2-aryl-3-substituted benzo[*b*]furans (**127**) (Scheme 7.44) [78].



Scheme 7.44

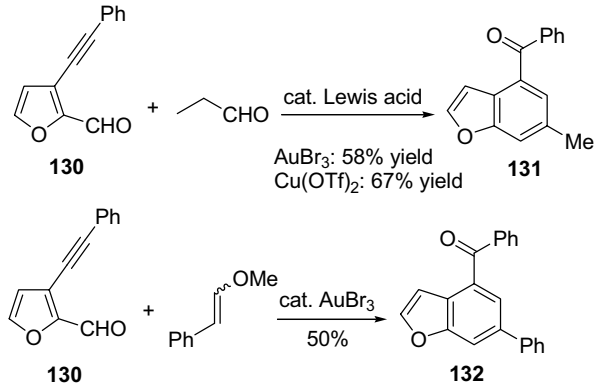
$Zn(OTf)_2$ (10 mol%) catalyzes the cyclization of propargyl alcohols with PhOH in hot toluene (100 °C) without additive to give benzofuran products in good yields. Its mechanism has been elucidated. This catalytic cyclization is also applicable to the synthesis of oxazoles through the cyclization of propargyl alcohols and amides without a 1,2-nitrogen shift (Scheme 7.45) [79].

Asao has described an efficient synthesis of functionalized aromatic compounds from enynals and carbonyl compounds [80]. The reaction most probably proceeds through the reverse electron demand-type Diels–Alder reaction between the pyrylium intermediate and enol 2π-system, derived from carbonyl compounds. The scope of the reaction was extended to the synthesis of benzofused heteroaromatic compounds. For instance, benzofuran synthesis using furan derivatives **130** has been



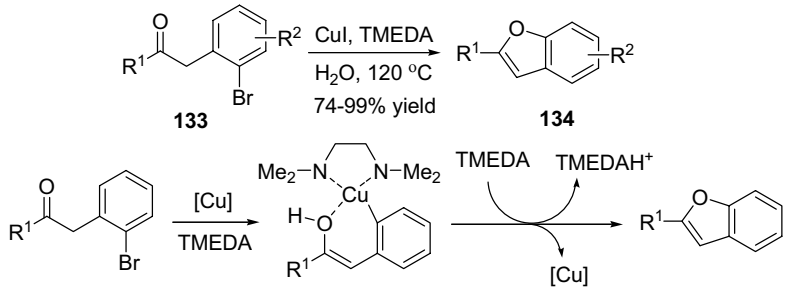
Scheme 7.45

examined. As expected, the reaction of **130** with propionaldehyde proceeded in the presence of $AuBr_3$ or $Cu(OTf)_2$ catalyst to give the corresponding product **131** in 58 or 67% yields, respectively. The $AuBr_3$-catalyzed reaction of **130** with β-methoxystyrene gave **132** in 50% yield (Scheme 7.46).



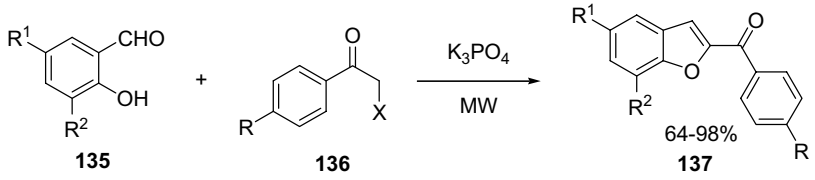
Scheme 7.46

SanMartin has reported copper-catalyzed straightforward synthesis of benzo[*b*] furan derivatives in neat water [81]. This on-water methodology delivers a range of benzo[*b*]furans (**134**) in good to excellent yields starting from readily available substrates **133** (Scheme 7.47).



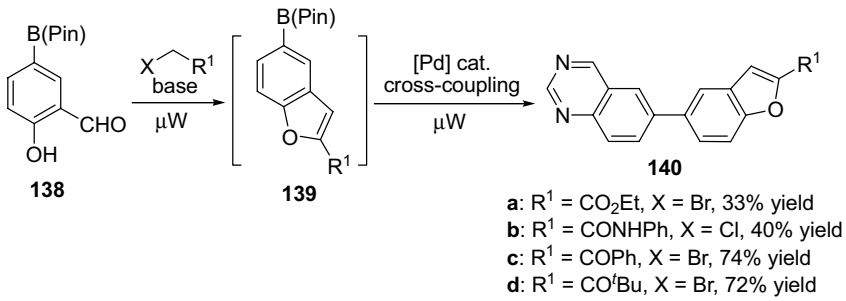
Scheme 7.47

A microwave-mediated solvent-free Rap–Stoermer reaction has been reported for the synthesis of benzofurans from various salicylaldehydes and phenacyl halides (Scheme 7.48) [82]. Some of the advantages and highlights of this microwave protocol include, solvent-free clean reaction conditions and high yields of benzofurans obtained in short reaction times. In addition, the 2-aroyl benzofurans formed using this method are also important as the corresponding carbinols (reduction products) are known to have hypolipidemic activity.



Scheme 7.48

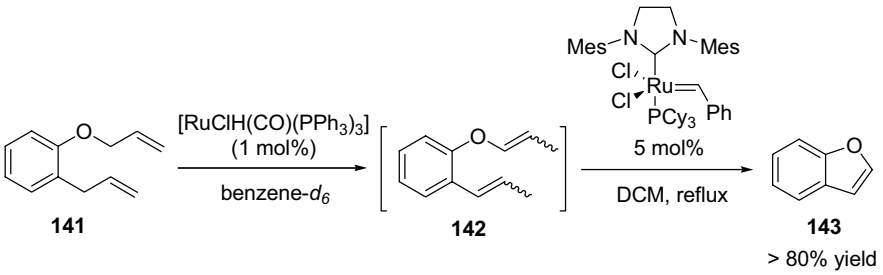
DiMauro has reported a rapid, efficient synthesis of various substituted fused benzofurans using a microwave-assisted one-pot cyclization-Suzuki coupling approach [83]. The benzofuran scaffold was formed under base conditions. Further elaboration via Suzuki cross-coupling reactions afforded the desired products **140** in moderate yields (Scheme 7.49).



Scheme 7.49

7.4.5
Olefin-Metathesis Approach

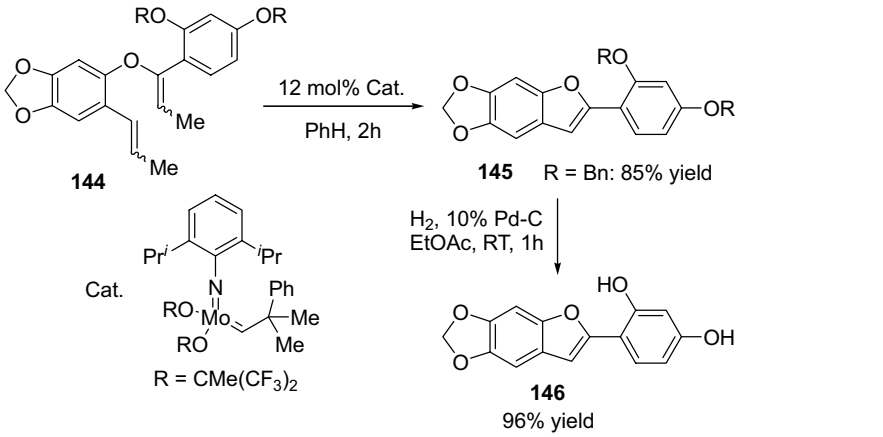
Sequential isomerization and ring-closing metathesis for the synthesis of benzo-fused heterocycles has been reported [84]. 2-Allylphenol is converted into allyl-2-(allyloxy)benzene (**141**) under suitable conditions. [RuClH(CO)(PPh_3)$_3$] is then added to a solution of **141** in benzene-d_6 or toluene-d_8 and the reaction mixture heated at 60–80 °C for 18 h (Scheme 7.50). Analysis by ^{1}H NMR spectroscopy confirmed that the isomerization of both allyl substituents had occurred to afford



Scheme 7.50

the acid-labile compound, which was not isolated. The introduction of catalyst (Grubbs Generation I) then readily affords the benzo[*b*]furan in excellent conversion, as determined by further ^{1}H NMR spectroscopy. This result constitutes a novel approach to the ubiquitous benzo[*b*]furan skeleton.

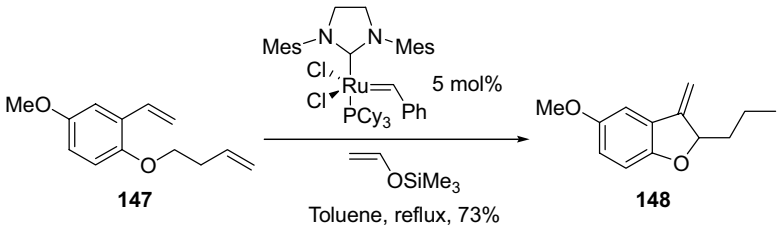
Grubbs *et al*. have described a method for the synthesis of cyclic enol ethers (including benzofuran) via molybdenum alkylidene-catalyzed ring-closing metathesis (Scheme 7.51) [85]. To demonstrate an application of this process, the authors chose the naturally occurring benzofuran 2,4,2′,4′-dihydroxyphenyl-5,6-(methylenedioxy)benzofuran (*Sophora* compound I), the antifungal phytoalexin isolated from aerial part of *Sophora tomentosa* L [86], as a synthetic target.



Scheme 7.51

Several 2,3-dihydrobenzo[*b*]furans can be made by the Ru-catalyzed olefin metathesis approach in the presence of trimethylsilyl vinyl ether (Scheme 7.52) [87]. The isovanillin derived benzo[*b*]furan has also been synthesized by the C-propenylation-O-vinylation and olefin metathesis approach [88].

A strategy employing a second generation Grubbs catalyst to facilitate the production of various cyclic enol phosphates, including benzofuran-2-yl enol phosphate scaffolds, has been described. This work represents the first case of an olefin

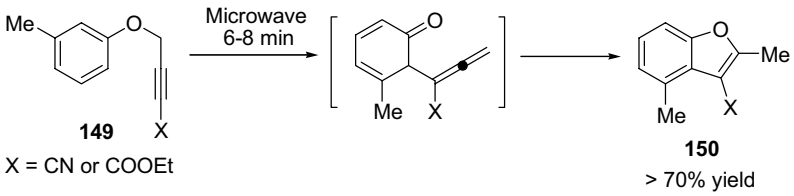


Scheme 7.52

metathesis reaction in which one of the groups participating in the metathesis event is an enol phosphate moiety [89].

7.4.6
Miscellaneous

3-Cyano or ethoxycarbonyl-2-methyl-benzo[*b*]furans have been prepared in a one-step synthesis by the microwave induced Claisen rearrangement under solvent-free conditions (Scheme 7.53) [90]. The Fries rearrangement has been employed in the synthesis of benzo[*b*]naphtha[2,3-*d*]furan-6,11-dione [91]. A [2,3]-Stille–Wittig rearrangement has also been utilized to make 2,3-disubstituted benzo[*b*]furans from 2-stannane substituted benzo[*b*]furans [92].

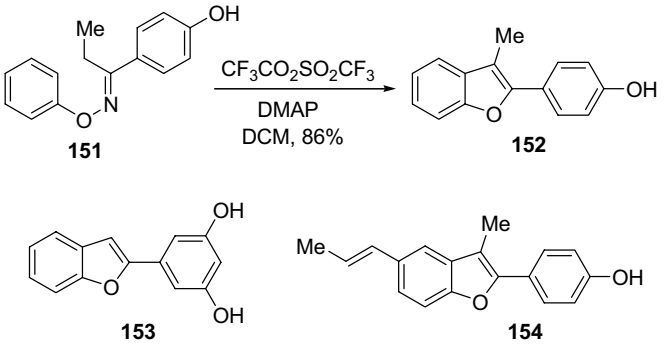


Scheme 7.53

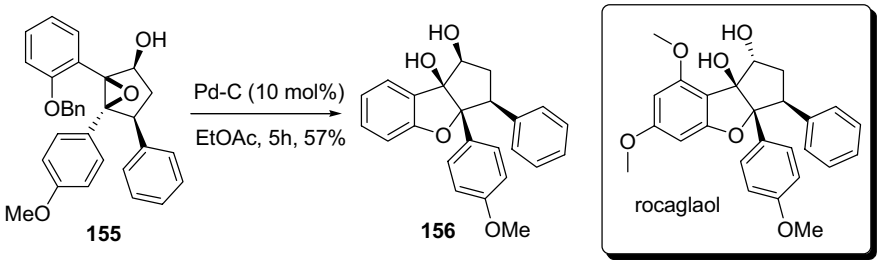
An efficient generation of 2-arylbenzofurans proceeds via a route involving acylation and subsequent [3,3]-sigmatropic rearrangement of oxime ethers [93]. Its synthetic utility is demonstrated by a short synthesis of stemofuran A (**153**) and eupomatenoid (**154**) in which no procedure for protection of the phenolic hydroxyl groups is needed (Scheme 7.54).

The synthetic strategy involving an intramolecular hydroxyl epoxide opening has been applied to build up the cyclopenta[*b*]benzofuran ring for the total synthesis of naturally occurring rocaglaol [94] (Scheme 7.55).

Horaguchi has reported the synthesis of benzofurans using photocyclization reactions of aromatic carbonyl compounds [95]. Benzofurans functionalized with hydroxy and acetyl functionalities are not only the core structures found in numerous biological important natural products but are also the vital precursors for several



Scheme 7.54



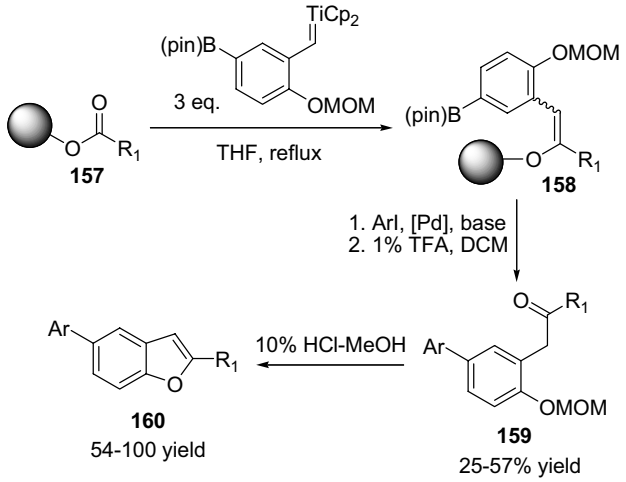
Scheme 7.55

naturally occurring furanoflavonoids. Numerous synthetic methodologies are available in the literature for the synthesis of functionalized benzofurans, but few references appear on the access of benzofurans with adjacent hydroxy and acetyl functionalities. Dixit [96] has reported a highly convenient synthesis of nature-mimicking benzofurans and their dimers from easily accessible precursors. The crystal structure of 5,5′-diacetyl-2′,3′-dihydro-2,3′-bibenzofuran-6,6′-diol is reported.

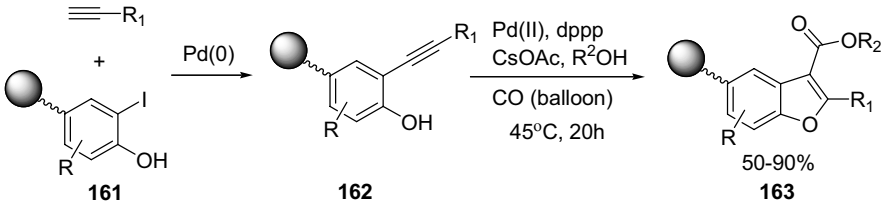
7.4.7
Progress in Solid-Phase Synthesis

Novel titanium benzylidenes (Schrock carbenes) bearing an arylboronate group are generated from thioacetals with low-valent titanium species, $Cp_2Ti[P(OEt)_3]_2$, and alkylidenate Merrifield resin-bound esters to give enol ethers. Treatment with 1% TFA gives 2-substituted (benzo[*b*]furan-5-yl)boronates, and solid-phase Suzuki cross-coupling gives 2,5-disubstituted benzofurans (Scheme 7.56) [97].

Yang *et al*. have reported a combinatorial synthesis of a 2,3-disubstituted benzo[*b*]furan library via palladium(II)-mediated cascade carbonylative annulation of *o*-alkynylphenols on silyl linker-based macrobeads (Scheme 7.57) [98].



Scheme 7.56



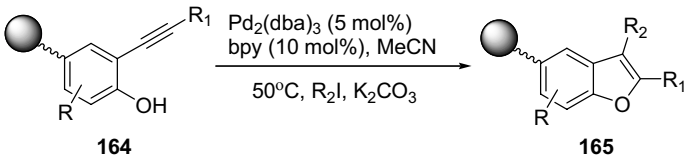
Scheme 7.57

The same authors have developed a novel catalytic system of AgOTs-$CuCl_2$-TMEDA for the homocoupling of aliphatic acetylenes on solid support. It is the first observation that an Ag(I)-activated triple bond can facilitate Cu(II)-mediated oxidative acetylenic homocoupling. This procedure provides an efficient way to synthesize a diversified symmetric 1,3-alkadiynediol bis(benzo[*b*]furan-carboxylate) library on solid support [99].

Furthermore, a split-pool synthesis of dimeric benzo[*b*]furans has been developed employing the Sonogashira reaction, palladium-mediated carbonylative annulation and olefin cross-metathesis as the key steps on high-capacity, lightly cross-linked, silyl-linker-based polystyrene macrobeads. This protocol provides direct access to a range of dimeric molecules that are ideal for high-throughput screening of protein–protein interactions in a cell-based assay system [100].

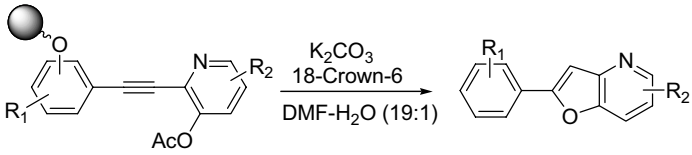
Subsequently, the authors described a conformationally restricted 2,3-diarylbenzo[*b*]furan library built up on a solid-phase by the palladium/bipyridyl-catalyzed annulation of *o*-alkynyl phenols with aryl halides (Scheme 7.58) [101].

A 2-substituted furo[3,2-*b*]quinolines library has been made on solid support by K_2CO_3-mediated sequential deprotection and cyclization [102] (Scheme 7.59).



164 **165**

Scheme 7.58



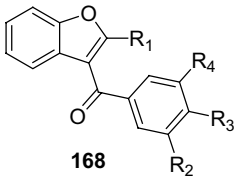
166 **167**

Scheme 7.59

7.5
Uses of Benzofuran

7.5.1
Uses of Benzofuran in Drug Discovery

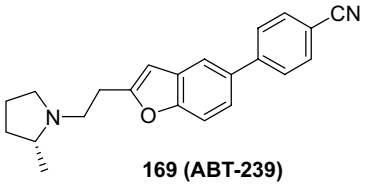
Jones has synthesized benzbromarone analogs (**168**) screened for inhibitory potency against 2C19, or used as substrates or metabolite standards [103]. The findings illustrate the increased utility of benzbromarone analogues since they have now been adapted to act as 2C19 inhibitors. According to this study with benzbromarone and previous works on phenobarbital analogues and proton pump inhibitors, it is demonstrated that for 2C19, ligands with two hydrophobic regions separated by a polar group are the most complementary. Interestingly, high-affinity binding of benzbromarone ligands to 2C19 appears to be achieved without constraining substrate mobility within the enzyme.



168

A series of benzofuran-2-yl-(phenyl)-3-pyridylmethanol derivatives have been prepared in good yields using an efficient one-step procedure. Additionally, to determine the effect of the benzene ring in benzofuran with respect to inhibitory activity, furan-2-yl-(phenyl)-3-pyridylmethanol derivatives have been synthesized in the meantime. The pyridylmethanol derivatives were all evaluated *in vitro* for inhibitory activity against aromatase (P 450AROM, CYP19), using human placental microsomes. The benzofuran-2-yl-(phenyl)-3-pyridylmethanol derivatives displayed good to moderate activity ($IC_{50} = 1.3–25.1\,\mu M$), which was either better than or comparable with aminoglutethimide ($IC_{50} = 18.5\,\mu M$) but lower than arimidex ($IC_{50} = 0.6\,\mu M$), with the 4-methoxyphenyl substituted derivative displaying optimum activity. Moreover, it shows the activity to reside with the (S)-enantiomer based on molecular modeling of the benzofuran-2-yl-(4-fluorophenyl)-3-pyridylmethanol derivatives. The essential role of the benzene ring of the benzofuran component for enzyme binding is demonstrated since the furan-2-yl-(phenyl)-3-pyridylmethanol derivatives were devoid of activity [104].

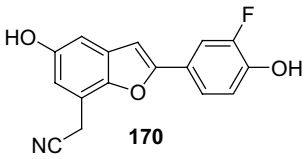
Histamine H_3 receptor antagonists are being developed to treat various neurological and cognitive disorders that may be ameliorated by enhancement of central neurotransmitter release. A nonimidazole, benzofuran ligand ABT-239 [4-(2-{2-[(2*R*)-2-methylpyrrolidinyl] ethyl}-benzofuran-5-yl)benzonitrile] (**169**) has been utilized in the *in vitro* pharmacological and *in vivo* pharmacokinetic profiles and compared with several previously described imidazole and nonimidazole H_3 receptor antagonists. The assay results demonstrate that ABT-239 is a selective, nonimidazole H_3 receptor antagonist/inverse agonist with similar high potency in both human and rat and favorable drug-like properties [105]. The potency and selectivity of this compound and of analogs from this class support the potential of H_3 receptor antagonists for the treatment of cognitive dysfunction [106].



169 (ABT-239)

A series of 2-(4-hydroxyphenyl)benzofuran-5-ols with relatively lipophilic groups in the 7-position of the benzofuran has been synthesized for measurement of the affinity and selectivity for ERβ. Some analogs are active as potent and selective ERβ ligands. The structural modifications at the benzofuran 4-position as well as at the 3′-position of the 2-Ph group (e.g., **170**) further increase selectivity. Such

modifications have lead to compounds with <10 nM potency and >100-fold selectivity for ERβ [107].



170

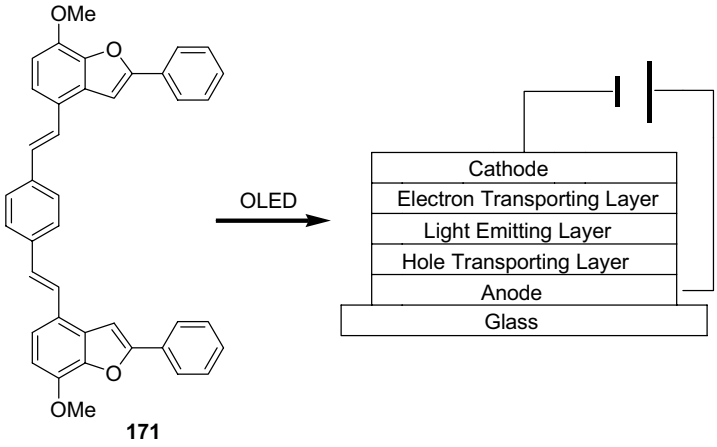
5-Chloro-3-methyl-2-acetylbenzofuran reacts with bromine in acetic acid leading to 5-chloro-3-methyl-2-bromoacetylbenzofuran, which then undergoes condensation with various substituted aromatic amines to afford 2-*N*-arylaminoacetyl-5-chloro-3-methylbenzofurans. These compounds have been screened for their antibacterial, antifungal, analgesic, antiinflammatory and diuretic activities and some hits were discovered [108].

A series of 1-(1-benzofuran-2-yl-ethylidene)-4-substituted thiosemicarbazides along with some derived ring systems, substituted-2,3-dihydro-thiazoles and thiazolidin-4-ones, have been synthesized and evaluated for their *in vitro* anti-HIV, anticancer, antibacterial and antifungal activities. Among the tested compounds, two produced a significant reduction the viral cytopathic effect (93.19% and 59.55%) at concentrations of $>2.0 \times 10^{-4}$ M and 2.5×10^{-5} M, respectively. One compound displayed moderate anti-HIV activity. Several compounds showed mild antifungal activity. However, no significant anticancer activity was discovered for the tested compounds [109].

7.5.2
Uses of Benzofuran in Material Science

New functionalized mono- and bis-benzo[*b*]furan derivatives which possess a CN, CHO, CH=CHPh, $CH=CPh_2$, or CH=CHCOOH group at C4 have been synthesized and developed as blue-light emitting materials [110]. Two benzo[*b*]furan nuclei in bis-benzo[*b*]furan derivatives have been connected by a divinylbenzene bridge. Bis-benzo[*b*]furan **171** was fabricated as a device with good volatility and thermal stability. It emitted blue light with brightness 53 430 cd m^{-2} (at 15.5 V) and a high maximum external quantum efficiency 3.75% (at 11 V) (Scheme 7.60).

The direct anodic oxidation of 2,3-benzofuran on stainless steel sheet in boron trifluoride di-Et etherate (BFEE) contained 10% poly(ethylene glycol) (PEG) with a molar mass of 400 (by vol.) affords a visible-light transparent high-quality substrate-supported poly(2,3-benzofuran) (PBF) film [111]. The oxidation potential of 2,3-benzofuran in this medium was measured to be only 1.0 V vs SCE, which is lower than that determined in acetonitrile + 0.1 M Bu_4NBF_4 (1.2 V vs SCE). Good electrochemical behavior and good thermal stability with a condense of 10^{-2} S cm^{-1}, are displayed for these PBF films, and the doping level of as-prepared PBF films was determined to be only 8.9%. The structure of the polymer has been studied by UV/Vis, IR spectroscopy and SEM.

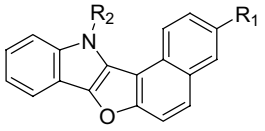


171

Scheme 7.60

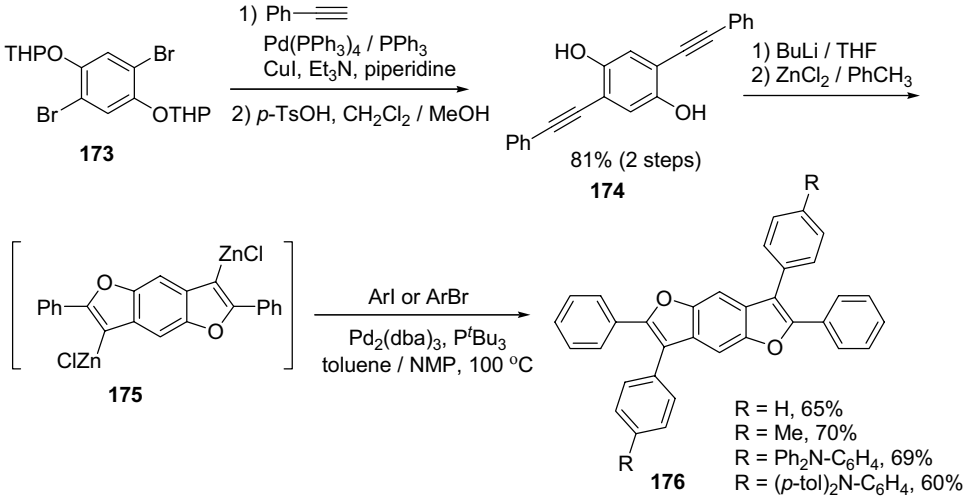
Yang has reported the synthesis and spectral properties of novel 4-benzofuranyl-1,8-naphthalimide derivatives [112]. A series of 4-benzofuranyl-*N*-alkyl-1,8-naphthalimides has been prepared from 4-ethynyl-*N*-alkyl-1,8-naphthalimides and substituted *o*-iodophenols catalyzed by a $Pd(PPh_3)_2Cl_2$/CuI system under mild conditions. The absorption and fluorescence spectra of these benzofuran-1,8-naphthalimides have been recorded and the quantum yields are measured using quinine sulfate as the standard. The UV/Vis absorption spectra were in the range of 380–400 nm and the emission spectra were in the range of 500–520 nm.

A novel fluorescence active 12*H*-benzo[*e*]indolo[3,2-*b*]benzofuran and its derivatives (**172**) has been prepared from 6-R^1-2-naphthols in good yields. The synthesized compounds with planar geometry and extended conjugation exhibit excellent fluorescence properties [113].



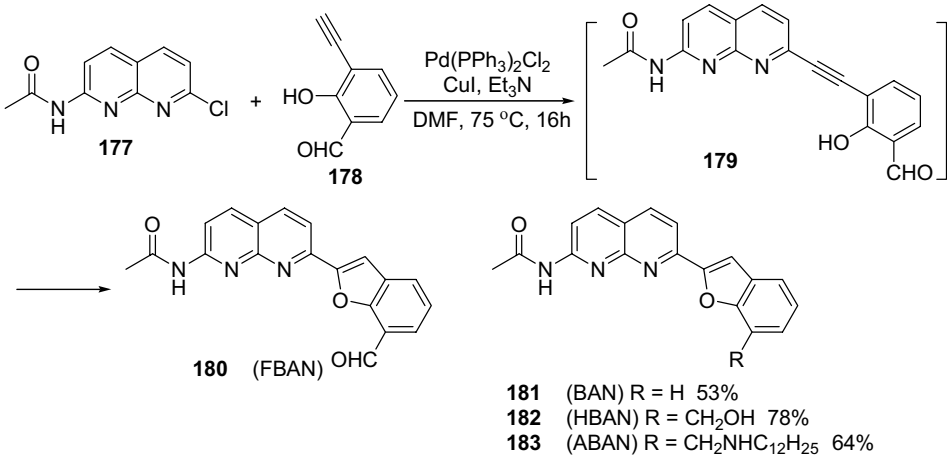
172

Four linear benzofuran trimers have been prepared and tested as materials for organic electroluminescence (OEL). The solubility, aggregation, and film-forming properties were modulated by *tert*-butyl and *n*-hexyl substituents on the benzofurans. Additionally, two *tert*-butyl groups prevented aggregation in the solid state, thus maintaining emission in the blue region of the visible spectrum. The OEL characteristics of the *tert*-butyl-substituted benzofuran trimer have been explored, and blue emission observed. The two-stage synthetic procedure employed for the preparation of these benzofuran trimers may be applied to a wide variety of benzofuran oligomer and polymer targets [114].



Scheme 7.61

Recently, Nakamura has described a facile route to 2,3,6,7-tetraarylbenzo[1,2-*b*:4,5-*b*]difurans (BDFs) (Scheme 7.61), which could be functioned as the hole-transporting material (HTM) in layered organic light-emitting diodes (OLEDs) [115]. The high performance of the compounds is primarily due to the BDF core itself, which is in sharp contrast to the fact that the biphenyl scaffold in R-NPD alone does not function as a HTM. They also found that there is a synergetic effect of the BDF core and the substituents. The physical properties can be improved by suitable functionalization. It can be expected that the BDF molecule will serve as a useful new molecular scaffold on which multiple functional groups can be attached to obtain new properties.



Scheme 7.62

Benzofuran-naphthyridine links show high-yield fluorescence with solvatochromic properties. For instance, after formation of fluorescent organic nanoparticles (FONs1.) of **ABAN** (**183**, Scheme 7.62), the photophysical properties (such as the spectral features and intensity) are remarkably different from those at the molecular level (solution) and in bulk material [116].

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8
Five-Membered Heterocycles: 1,2-Azoles. Part 1. Pyrazoles

José Elguero, Artur M.S. Silva, and Augusto C. Tomé

8.1
Introduction

Pyrazoles belong to the family of azoles, which for some authors include pyrroles and indoles while for others it contains only by imidazoles, benzimidazoles, pyrazoles, indazoles, 1,2,3-triazoles, benzotriazoles, 1,2,4-triazoles, tetrazoles and pentazoles. The dubious position of pyrroles is due to their very different reactivity and less aromatic stability.

We have carried out a search in the *Chemical Abstracts* "on line" (1987–2004) using the following truncated words: pyrazol*, indazol*, imidazol*, benzimidazol*, triazol* (thus treating together 1,2,3 and 1,2,4-triazoles), benzotriazol*, tetrazol* and pentazol*. In this way, fused compounds are included although they will not be discussed in detail in this chapter. Table 8.1 gives the number of references and the percentages in each case.

The evolution of the number of publications between 1999 and 2004 show an increase of all of them, with the most cited, imidazoles and pyrazoles, growing the fastest.

From Figure 8.1 is can be concluded that benzazoles are much less studied than the corresponding azoles and that an increase in the number of nitrogen atoms diminishes the importance of the azoles, with pentazoles being only a curiosity.

In the *Chemical Abstracts* 2004, the word pyrazol* appears 1931 times. Regarding these 1931, it is possible to classify them (at the price of some simplifications) into six different fields (Table 8.2).

As expected, the medicinal chemistry aspects of pyrazoles dominates largely the 2004 production, but note their great importance as ligands in coordination chemistry. As materials, the main applications are as dyes, inks and luminescent devices.

Modern Heterocyclic Chemistry, First Edition.
Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.

Table 8.1 Relative importance of azoles in the literature.

Azol*	Total	%
Pyrazol*	20701	22.12
Indazol*	1451	1.55
Imidazol*	31118	33.25
Benzimidazol*	10158	10.85
Triazol*	15688	16.76
Benzotriazol*	6429	6.87
Tetrazol*	8008	8.56
Pentazol*	42	0.05

Another way to classify pyrazoles is to made a class of 1,2-azoles formed by pyrazoles, isoxazoles and isothiazoles. This is not entirely satisfactory, because there is an important difference between pyrazoles on the one hand and isoxazoles and isothiazoles (Chapter 9) on the other: the presence of an NH (NR) in pyrazoles (**1**–**3**)

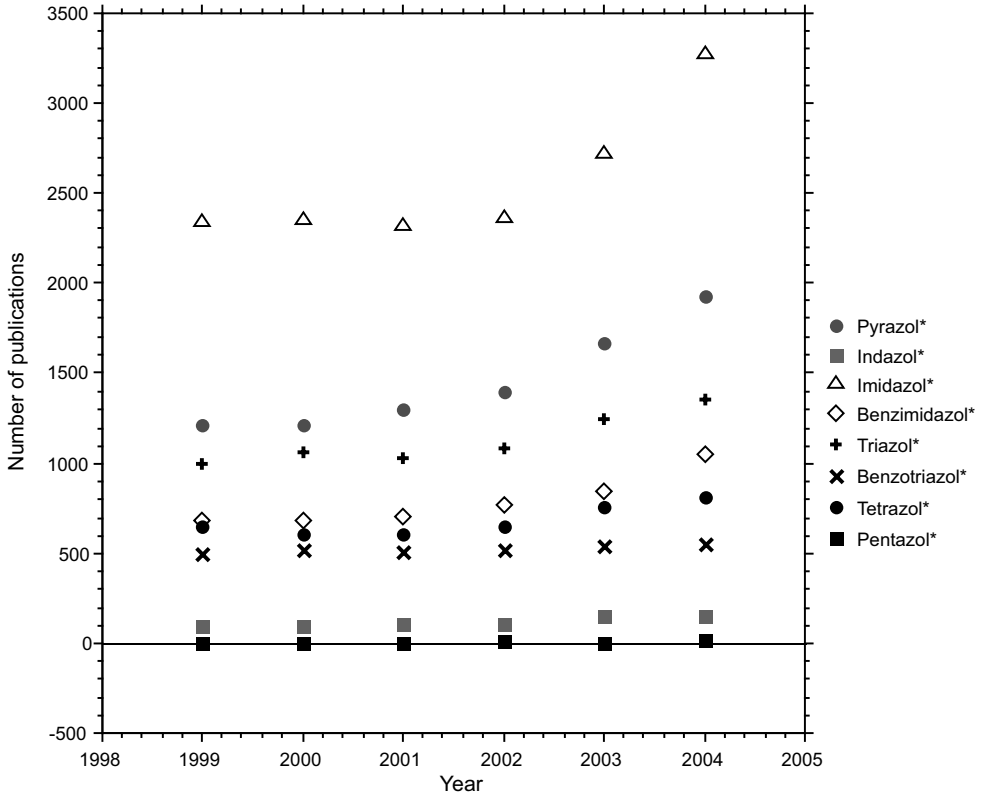
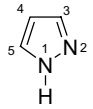


Figure 8.1 Evolution of the number of publications devoted to azoles between 1999 and 2004.

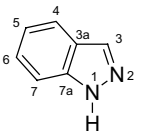
Table 8.2 Use of pyrazoles according to the number of citations.

Pyrazol*	References	%	% Without biol. appl.
Biological applications	785	40.65	—
Coordination chemistry	423	21.91	36.91
Synthesis	375	19.42	32.72
Properties	125	6.47	10.91
Application as materials	118	6.11	10.30
Reactivity	105	5.44	9.16

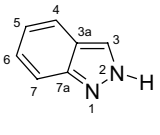
that confers to this heterocycle a specific behavior to the point that we have treated it separately from the two other heterocycles.



1*H*-pyrazole (**1**)



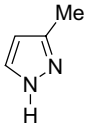
1*H*-indazole (**2**)



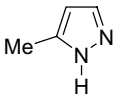
2*H*-indazole (**3**)

8.1.1 Nomenclature

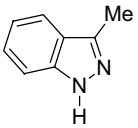
We have represented above the three main heterocycles of this chapter. Notably, the migration of the proton of a pyrazole from N1 to N2 changes the numbering of the ring, that is 3-methyl-1*H*-pyrazole (**4a**) becomes 5-methyl-1*H*-pyrazole (**4b)**, whereas in indazoles the same migration transforms 3-methyl-1*H*-**5a** into 3-methyl-2*H*-indazole (**5b**).



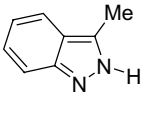
4a



4b



5a



5b

A series of books or chapters in books have been devoted to this heterocycle, including its benzo derivative, indazole, with exclusion of the very large topic of pyrazoles fused with other heterocycles. In 1966, Kost and Grandberg published the first systematic approach to pyrazole chemistry [1]. It is still a valuable source of information because it summarizes in a short and clear way the knowledge

accumulated in Russia after the seminal contribution of Karl Friedrich von Auwers (1863–1939) to the chemistry of these compounds. A year later, a book appeared that contains tables describing many pyrazoles, indazoles and their reduced derivatives, one of the authors, Fusco, was at that time very active in the chemistry of pyrazoles [2]. A book on all azoles is very useful since it represents a more structural and comparative study with much spectroscopic data [3]. In 1984 (updated in 1996) *Comprehensive Heterocyclic Chemistry* provided an extensive treatment of the structure and reactivity of pyrazoles and indazoles but with a concise report on synthetic aspects [4, 5]. The synthesis is well developed in *Houben-Weyl, Methoden der Organischen Chemie* and its continuation, *Science of Synthesis*, which contains synthetic recipes [6–9].

8.2
General Reactivity

Depending on the oxidation degree, pyrazoles can be classified into different families (Scheme 8.1). Indazoles saturated in the benzene ring (4,5,6,7-tetrahydroindazoles) are better considered as 3(5),4-tetramethylenepyrazoles. The 3*H*-indazoles, a third isomer of indazoles, are unstable if one (or both) of the substituents at position 3 is an H atom, that is, there are no 3*H*-indazole tautomers.

8.2.1
Relevant Physicochemical Data, Computational Chemistry and NMR Data

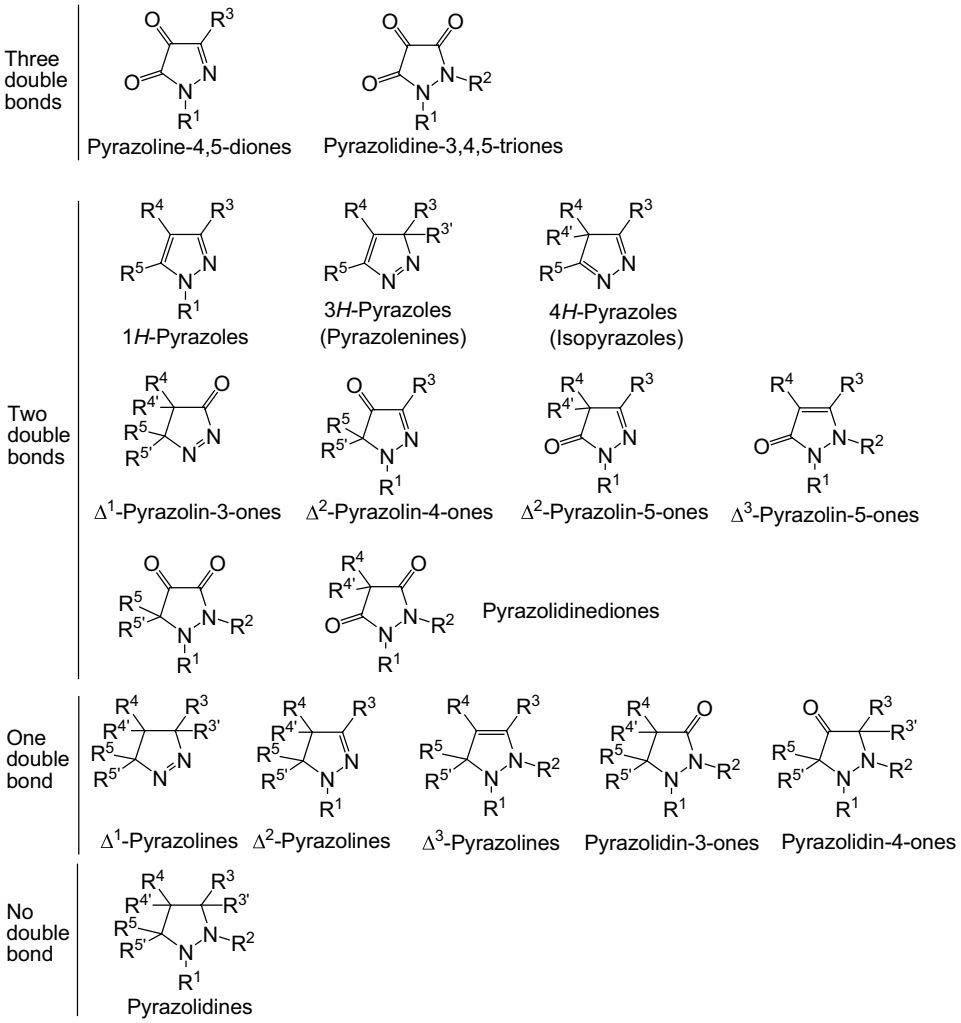
Figure 8.2 shows the structures of the three parent compounds, giving an image of their compact character. Table 8.3 summarizes the properties of pyrazole (**1**) and 1*H*-indazole (**2**) (the other tautomer, **3**, is unstable – see under tautomerism).

In general, pyrazoles unsubstituted at position 1, NH-pyrazoles, and NH-indazoles are solids, the exception being some pyrazoles substituted at position 4, like 4-methylpyrazole [28]. The N-substitution, especially the N-alkylation, is accompanied by a large decrease in the melting point.

Figure 8.3 presents, in a simplified manner, the geometry of **1** in the gas phase (both from MW spectroscopy and from high-level theoretical calculations). Pyrazole is planar and to a first approximation has a regular pentagonal geometry. Closer examination reveals alternating single (C3-C4)/(C5-N1) and double (C4-C5)/(N2-C3) bonds. Particularly relevant to determining the position of the NH, when it is not observed in X-ray crystallography due to disorder, is the fact that the angle on N1 is always larger than that on N2 (the same happens at C3 and C5).

Structural assignment of pyrazoles and indazoles is usually carried out by NMR (Schemes 8.2–8.4), at one time by using tables of reference compounds and/or coupling constants [29] but now more often by 2D spectroscopy, such as NOESY, which detects the proximity of substituents [30].

The identification of pyrazole isomers is easy by NMR when there is only one substituent at positions 3(5). The ^{1}H NMR chemical shifts are dependent on the



Scheme 8.1 Different structures of pyrazole derivatives depending on their oxidation degree

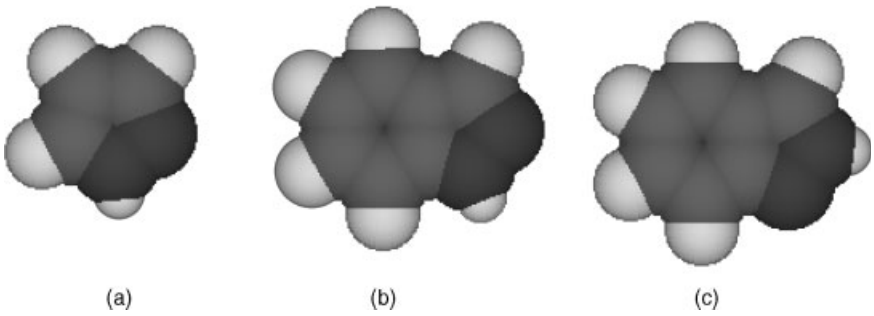


Figure 8.2 Space filling models of (a) pyrazole (**1**), (b) 1*H*-indazole (**2**) and (c) 2*H*-indazole (**3**).

Table 8.3 Properties of the parent compounds.

Property	Pyrazole (**1**)	Indazole (**2**)
Mp (°C)	69–70	145–149
Bp (°C)	186–188 (758 mmHg)	269–270 (743 mmHg)
Log *P*	0.13–0.26	1.82
Dipole moment (μ, D)	1.92 (benzene)	1.60 (benzene)
pK_a (proton addition)	2.52	1.31
pK_a (proton loss)	14.21	13.80
Enthalpies of formation (kJ mol^{-1})	179.4 [10]	243.0 [10]
UV (λ_{max} nm, log ε)	211 (3.49) [4]	250 (3.65), 284, 296 (3.52) [4]
IR (cm^{-1})	3524 (ν_{NH} gas) [4]	Source: [11]
X-ray (CSD) [12]	PYRZOL	INDAZL
^{1}H NMR	Source: [13]	Source: [13, 14]
^{13}C NMR	Source: [15]	Source: [16]
^{15}N NMR	Source: [17]	Source: [17]
MS	Source: [18]	Source: [19]
PES	Source: [20]	Source: [21]
MW	Source: [22]	Source: [23]
Best theoretical calculations	Source: [24]	Source: [25]
Aromaticity (benzene = 0.991)	0.900: [26]	0.808: [26][a)]

a) Naphthalene: 0.811, 2*H*-indazole: 0.792 (using as criteria the HOMA) [27].

solvent, but the $^3J_{34}$ vs. $^3J_{45}$ coupling constants are not, so the fact that $J_{45} > J_{34}$ is always a useful test. The ration J_{45}/J_{34} depends on the substituent on the nitrogen, with EWG (like tosyl) the difference is large and the criteria easy to apply. With EDG (like amino) the difference tends to blur and $J_{34} \approx J_{45}$ [31].

For isomeric pyrazoles bearing different substituents at positions 3 and 5, the ^{13}C chemical shifts of carbons C3 and C5 is a better method of assignment if both isomers are available. If only one is obtained, one must rely on a comparison with the large amount of data available [15]. In contrast, indazoles are easily identified by ^{13}C NMR spectroscopy [16].

^{15}N NMR spectroscopic data can be routinely obtained from unlabelled samples (natural abundance). But their utility as a diagnostic tool is limited. Note that the ^{15}N chemical shifts are very sensitive to hydrogen bonds and, obviously, to protonation.

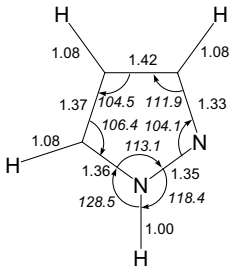
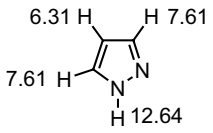
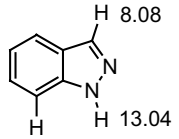


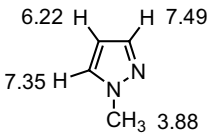
Figure 8.3 Geometry of pyrazole.



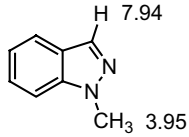
Solution CCl_4
(fast tautomerism)



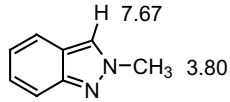
Solution DMSO-d_6
(only this tautomer)
J_{37} = 1.1 Hz



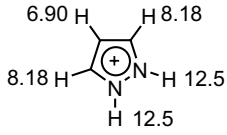
Solution $CDCl_3$
J_{34} = 2.0, J_{45} = 2.3
J_{35} = 0.7 Hz



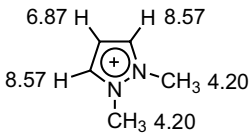
Solution $CDCl_3$



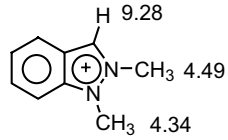
Solution $CDCl_3$
J(Me-H3) = 0.5 Hz



Solution H_2SO_4

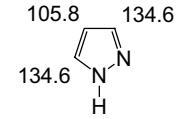


Solution DMSO-d_6

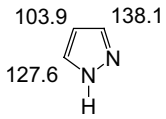


Solution DMSO-d_6

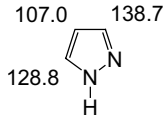
Scheme 8.2 ^{1}H NMR spectra [δ (ppm) and J (Hz)] of some representative compounds



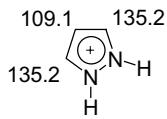
Solution CH_2Cl_2
(fast tautomerism)



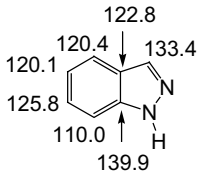
Solution HMPT (–17°C)
(slow tautomerism)



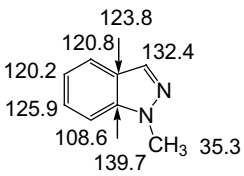
Solid state (CPMAS)



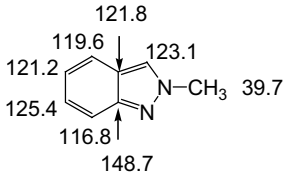
Solution H_2O



Solution DMSO-d_6
(only this tautomer)



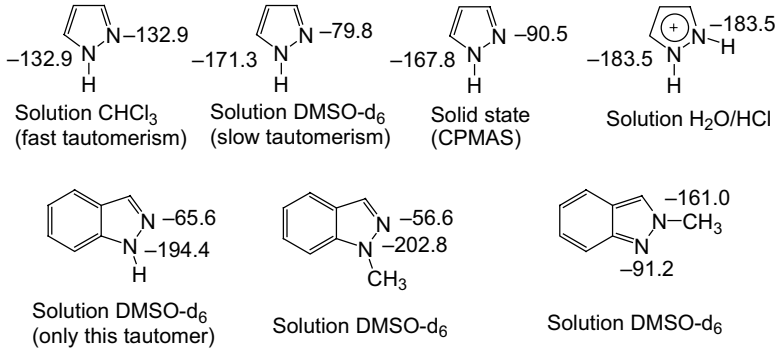
Solution $CDCl_3$



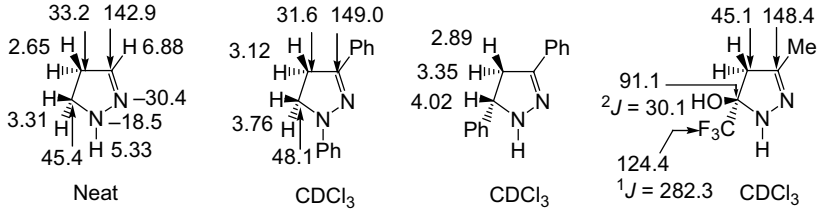
Solution $CDCl_3$

Scheme 8.3 ^{13}C NMR spectra [δ, (ppm)] of some representative compounds

NMR information on the non-aromatic derivatives of pyrazoles is very abundant, particularly on Δ^2-pyrazolines and on pyrazolones [4, 7]. Scheme 8.5 contains some multinuclear NMR data on Δ^2-pyrazolines.



Scheme 8.4 ^{15}N NMR spectra [δ, (ppm)] of some representative compounds

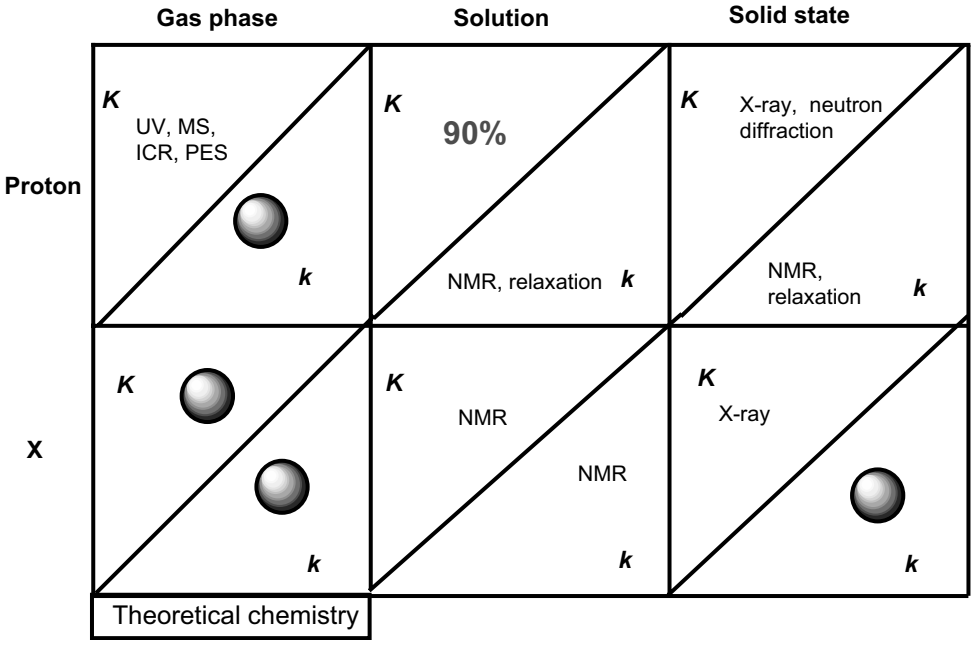


Scheme 8.5 NMR data on some Δ^2-pyrazolines

8.2.2 Tautomerism

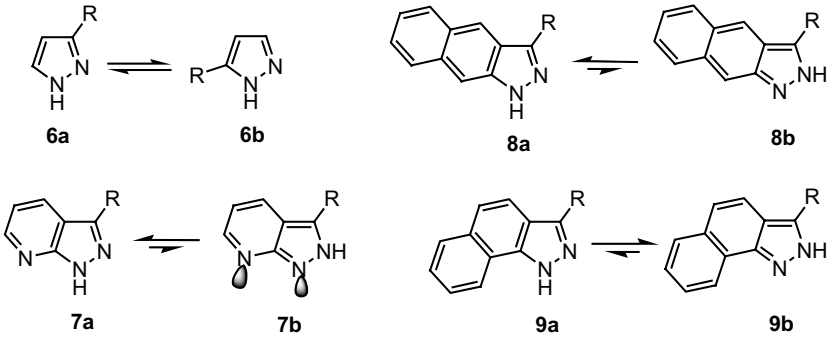
The study of the tautomerism of NH-pyrazoles and indazoles (annular tautomerism) and that of functional compounds (e.g., pyrazolones) has been of considerable importance for the development of structural chemistry [32–34]. Some protonated cations also shown tautomerism. This huge amount of data is difficult to summarize, but the principal conclusions are as follows:

1) Tautomerism occupies a multidimensional space (Scheme 8.6): the three states of the matter, the thermodynamic and kinetic aspects, and the proton (prototropy versus elementotropy). All these aspects have been observed in pyrazoles although those situations marked with a gray circle are very rare. Theoretical studies of the tautomerism of pyrazole and its derivatives mainly concern the gas phase.
2) Concerning thermodynamic aspects, the main conclusion about annular tautomerism of pyrazoles (**6a** ⇌ **6b**) is that the equilibrium tautomeric constant K_T is never far from 1 [35–37]. The preference of **6a** versus **6b** has been analyzed using the Taft–Topson model [35, 36]. BH_2, COF, CO_2H, and CHO substituents stabilize the **6a** tautomer, while the **6b** tautomer is stabilized by OH, F, NH_2, Cl, $CONH_2$, CN, NO_2, and CH_3 groups (this paper contains a wealth of information about the IR of NH-pyrazoles) [37]. A more detailed analysis of the annular tautomerism of 3(5)-aminopyrazoles (R=NH_2) shows that both tautomers are present in solution and even in the solid state [38].



Scheme 8.6 The tautomerism twelve regions

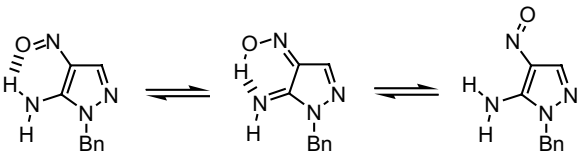
For indazole, the 1*H*-tautomer (**2**) is more stable than the 2*H*-tautomer (**3**) by about 20 kJ mol^{-1}, and this tendency cannot be reversed by phase effects; consequently, in solution and in the solid state the only tautomer present is **2** [39]. To displace the equilibrium towards one of the tautomers it is necessary to use a combination of substituents, aza and annelation effects [39]. For instance, substituents like NO_2 and CO_2Me at position 3 favor the 2*H*-tautomer, the replacement of a CH by an N atom at position 7 favors the 1*H*-tautomer (by lone-pair/lone-pair repulsion in **7b**), and a fused benzo group at positions [*f*] and [*g*] favors, respectively, the 1*H*- (**8a**) and 2*H*-tautomers (**9b**).



3) In terms of kinetic aspects, the transfer of group R between both nitrogen atoms is an intermolecular process in the case of prototropy [40]. This requires other

molecules (another pyrazole, water, a solvent, etc.) or a surface, for instance that of the measuring instrument [41]. Other groups on the nitrogen migrate either intermolecularly (COR, CH_3, etc.) or intramolecularly (SiR_3, GaR_2, GeR_3, SnR_3, HgR) with barriers that can be very low in some cases [34, 41].

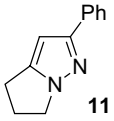
4) The tautomerism of functional derivatives, such as pyrazolones, is well understood and is no longer a research subject [32, 34]. However, there remains always some interesting cases, for instance that of 4-nitroso-5-aminopyrazoles **10** [42]. The compound exists as a mixture of rotamers **10a**/**10c** of the amino-nitroso tautomer, rather than a mixture of amino-nitroso/imino/oxime tautomers **10a**/**10b**.



10a **10b** **10c**

8.3
Relevant Natural and/or Useful Compounds

The common belief is that heterocycles are natural if they can be found in DNA (nucleosides and nucleotides) or in proteins. That is why indole (tryptophan), pyrrole (proline, porphyrins), imidazole (histidine, biotine) and benzimidazole (vitamin B12) are considered "naturals" while pyrazole is not. One of the rare natural products that contains a pyrazole ring is Withasomnine [5,6-dihydro-3-phenyl-4*H*-pyrrolo[1,2-*b*]pyrazole (**11**) an alkaloid isolated from the roots of an Indian medicinal plant, *Withania somnifera*]: its simplicity means that several synthesis are known, with the most recent described in 2002 [43, 44].



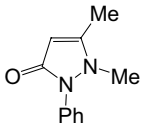
11

Other pyrazoles found in nature are pyrazofurin or pyrazomycin (an antibiotic isolated from the fermentation broth of *Streptomyces candidus*), formycin (a naturally occurring isomer of adenosine) and L-β-pyrazolylalanine (found in the seeds of many species of Cucurbitaceae).

From this it must not be concluded that the pyrazole skeleton is not a good scaffold for making drugs. A recent review examines the topic "Pyrazoles as Drugs: Facts and Fantasies" [45]. This review describes the past and the present of pyrazole derivatives in medicinal chemistry. From an important past, exemplified in the analgesic and anti-inflammatory pyrazolones and pyrazolinediones, not devoid of severe complications, to a glorious present with some of the most important drugs of recent times (sildenafil, celecoxib) being pyrazole derivatives.

Analgesics were, by far, the main area of biological activity of pyrazoles, often associated with antipyretic activity. They belong to three main classes: pyrazolin-5-ones [antipyrine –phenazone – (**12**), pyramidon (**13**), dipyrone (**14**)], pyrazolin-3,5-diones [phenylbutazone (**15**)] and pyrazoles [actually, an acetic acid, lonazolac (**16**)] [46].

Indazole proved to be an interesting nucleus in this field. Structural modifications of the anti-inflammatory agent bendazac (**17**), an indazole derivative, have been realized and, in some cases, the synthesized compounds showed analgesic effects along with anti-inflammatory properties [47].



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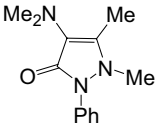

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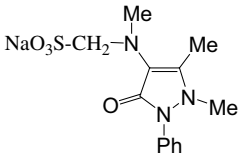

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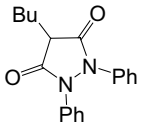

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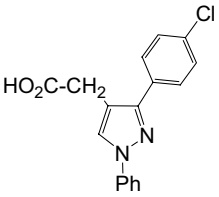

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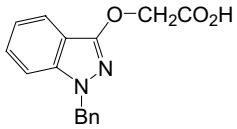
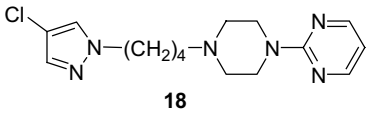


17

Lesopitron (**18**) (E-4424), a pyrimidylpiperazine substituted by 1-butyl-4-chloropyrazole, was introduced as a new non-benzodiazepine anxiolytic acting on 5-HT_{1A} receptors. It differed from other 5-HT_{1A} receptors ligands mainly because of its greater anxiolytic potency, its lack of sedative effects, its sustained activity even on long-term treatments and its lack of withdrawal problems [48]. Lesopitron, currently in advanced clinical trials (phase III), and has been shown to be efficient and safe in patients with generalized anxiety disorder. Of particular interest is zaleplon, *N*-[3-(3-cyanopyrazolo[1,5-*a*]pyrimidin-7-yl)phenyl]-*N*-ethylacetamide (**19**), a BZ_1-receptor selective ligand [49]. Zaleplon (Sonata, Wyeth-Pharma, MI **10165**) is a non-benzodiazepine sedative hypnotic that has been recently introduced for clinical use. It is indicated for short-term treatment of insomnia and presents the advantages of showing weak anxiolytic activity and reduced risk of tolerance.



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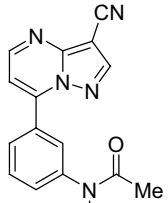
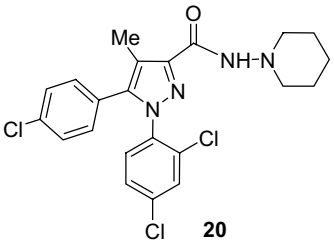


19

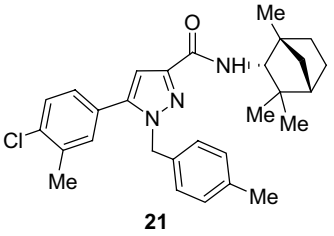
The implication of glutamate receptors in memory processes has initiated great interest in anti-Alzheimer therapy. In an attempt to obtain heterocyclic analogs of glutamic acid, a synthetic strategy has been developed to prepare pyrazoles that show biological activity at central glutamate receptors [50].

The discovery by Sanofi [51] in 1994 of the pyrazole SR141716A (**20**) has been of great interest in the field of cannabinoids because this study reported the first cannabinoid antagonist possessing nanomolar affinity. This selective and orally active CB_1 receptor subtype antagonist has become an experimental tool for insights into CB_1 subtype recognition and activation and for clinical applications such as treatment of psychosis, eating disorders or memory deficits [52]. Recent studies of analogs retaining the central pyrazole structure of **20**, tested for CB_1 binding affinity and in a battery of *in vivo* tests, suggest that the structural properties of 1- and 5-substituents are primarily responsible for the antagonist activity of SR141716A.



20

The availability in 1997 of the highly specific antagonist SR144528 (**21**) [53] for the CB_2 receptor has allowed the investigation of both the architecture of ligand binding sites, an approach that is difficult due to the structural disparity of cannabinoid agonists, and the respective contribution of cannabinoid receptor subtypes in functional cannabinoid effects *in vivo*. Its potential therapeutic applications include immune disorders such as rheumatoid arthritis, multiple sclerosis, psoriasis, infections and asthma.

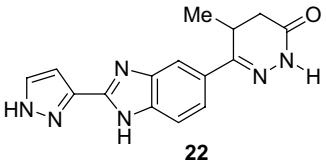


21

Various derivatives of SR141716A have been synthesized [54] and Makriyannis *et al.* [55] have reported a study of structure–activity relationships of pyrazole derivatives as cannabinoid receptor antagonists and have proposed structural requirements for CB_1 antagonistic activity.

6-Aryl-tetrahydropyridazin-3-ones are prototypes of cardiotonic agents, having both inotropic and vasodilator activities. Imazodan and bemoradan are two representatives of this family, which are supposed to exert their actions by selective inhibition of phosphodiesterase type 3 enzymes (PDE3). Many different structural variations have been devised in this series and, related to pyrazoles, the most interesting compound from a series of heterocyclic benzimidazolyl-pyridazinones is meribendan (**22**). It inhibited myocardial PDE3, showed an interesting calcium sensitizing effect and was selected for development as a positive inotrope [56].

The synthesis and inhibitory effects on cyclooxygenase, lipoxygenase and thromboxane synthetase of 3-amino-4,5-dihydro-1*H*-pyrazoles and related compounds have been reported. Among these, the trifluoromethylphenyl derivative **23** is the most interesting [57].



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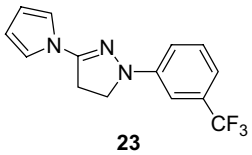
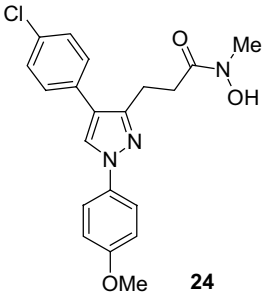


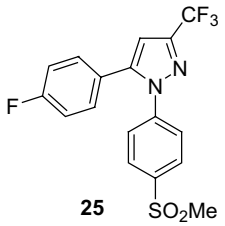
23

Progress in understanding inflammatory processes has led to the search of inhibitors of both the cyclooxygenase (COX) and lipoxygenase (LOX) pathways of the arachidonic acid cascade. In this way tepoxalin (**24**) has been prepared and found to be a potent anti-inflammatory agent [58].



24

The discovery of a second, inducible form of cyclooxygenase (COX-2) that exists along with the constitutive form (COX-1) led to the hypothesis that selective inhibitors of COX-2 would be anti-inflammatory without causing the side effects associated with inhibition of COX-1 in the gastrointestinal tract and kidney. This is the moment most promising approach at present and has ultimately led Searle to SC-58125 (**25**) and then to *celecoxib* SC-58635 (**26**) (**MI** 1968), which is useful for the treatment of rheumatoid arthritis and osteoarthritis [59]. Other pharmaceutical companies have explored this avenue; for instance Fujisawa has developed **27** [60].



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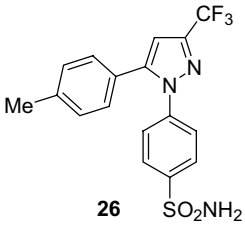

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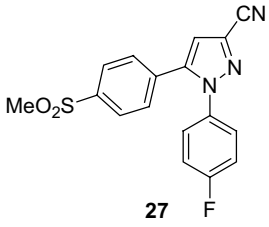
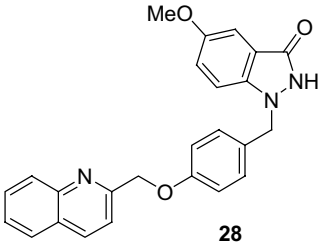


27

Other groups, like ASTA, have approached the problem by inhibiting the enzyme 5-LOX. By analogy with zileuton, one of the first launched 5-LOX inhibitors for the treatment of asthma, they prepared a series of 1,5-disubstituted indazol-3-ones, the most potent being **28** [61]. Mosti *et al*. have also reported indazoles related to angelicin, like compound **29a**, which shows good anti-inflammatory and antipyretic properties, while **29b** shows significant local anesthetic activity [62].

For the treatment of diabetes, a series of hypoglycemic agents derived from pyrazoles have been prepared and tested. The most interesting antidiabetic in this field is WAY-123783 (**30**) – obtained after extensive SAR studies; it acts by blocking SGTL (sodium-glucose co-transporter) in the kidney [63].



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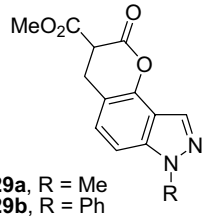
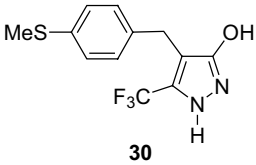
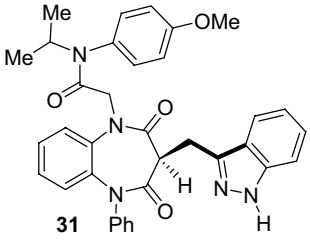


29a, R = Me
29b, R = Ph



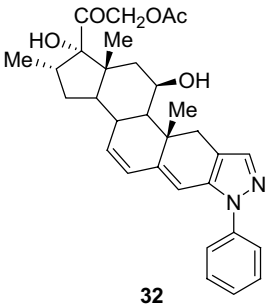
30

For the treatment of obesity, Henke from Glaxo Wellcome has optimized a series of 3-(1*H*-indazol-3-ylmethyl)-1,5-benzodiazepines – potent and orally active CCK-A agonists derived from **31** [64].



31

Steroidal pyrazoles have long been known. Kirschke [6] has reported several of these compounds, like cortivazol (**32**) (X-ray structure) [65] and stanozolol (**33**), both important and commonly used drugs. Cortivazol (**32**) is an anti-inflammatory glucocorticoid while stanozolol (**33**) is an anabolic steroid used as androgen. Nivazol (**34**) also belongs to the glucocorticoid class [66].



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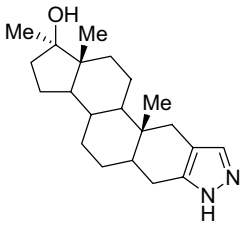

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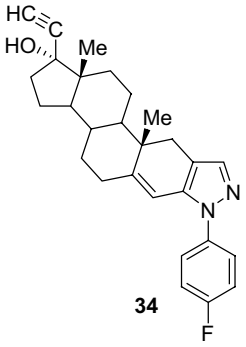


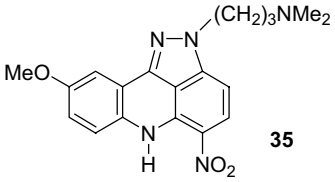
34

Liver alcohol dehydrogenase (EC 1.1.1.1) catalyzes the first step in alcohol metabolism and is a rational target for inhibiting alcohol metabolism. Prevention of poisoning by methanol and damaging effects of ethanol metabolism are potential applications of inhibitors of alcohol dehydrogenase. From the pioneering work of Theorell [67] it is known that pyrazole and some of its 4-substituted derivatives (4-methyl, 4-iodo and 4-bromo) are potent inhibitors of ethanol metabolism *in vivo*. Pyrazoles have been proposed as therapeutic agents for treatment of alcohol intoxication. Unfortunately, pyrazole is itself toxic and may not be useful for long-term treatment of humans.

Although some interesting efforts have been made, including X-ray studies and molecular modeling [68], 4-methylpyrazole (fomepizol) continues to be the most efficient and less toxic of all the liver alcohol dehydrogenase inhibitors and inactivators. Note also that pyrazole itself, an alcohol dehydrogenase inhibitor, has dual effects on *N*-methyl-D-aspartate (NMDA) receptors of hippocampal pyramidal cells, agonist and noncompetitive antagonist [69].

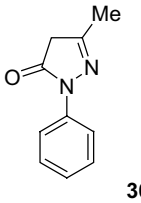
One of the most prominent of the anticancer agents with a pyrazole skeleton is pyrazoloacridine (PZA, **35**), 2-(*N,N*-dimethylaminopropyl)-9-methoxy-5-nitro-(6*H*)-pyrazolo[3,4,5-*kl*]acridine (NSC 366140). PZA is the first of a new class of rationally synthesized acridine derivatives to undergo clinical testing as an anticancer agent. Recent studies suggest that PZA might be a dual inhibitor of DNA topoisomerases I and II and exerts its effects by diminishing the formation of topoisomerase-DNA adducts. Consistent with this unique mechanism of action, PZA exhibits broad-spectrum antitumor activity in pre-clinical models *in vivo*. In addition, this agent displays several remarkable properties, including solid tumor selectivity, activity against hypoxic cells, and cytotoxicity in noncycling cells. PZA has been studied in phase I trials in adults and children, and is currently undergoing broad phase II trials in several tumor types. No significant anti-tumor activity has been seen in

gastrointestinal malignancies and prostate cancer. Owing to its unique properties, combination studies with other antineoplastic agents are in progress [70].



35

We end this section by summarizing the most promising fields of application of pyrazoles and indazoles with four compounds. First, edaravone –norphenazone–, 3-methyl-1-phenyl-2-pyrazolin-5-one (**36**), is a very simple compound, known from old, that it is a free radical scavenger and a very potent antioxidant agent against lipid peroxidation. *In vivo* studies have revealed that edaravone shows brain-protective activity in a transient ischemia model [71]. The second one is tolfenpyrad, 4-chloro-3-ethyl-1-methyl-*N*-[4-(*p*-tolyloxy)benzyl]pyrazole-5-carboxamide (**37**) one of the most promising insecticides recently discovered in Japan [72].



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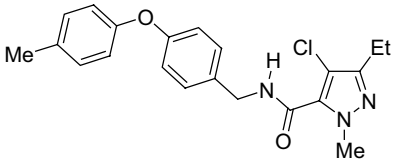
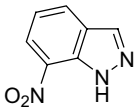


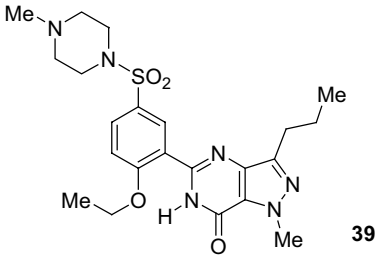
37

The normal biological functions regulated by nitric oxide are attributed to three nitric oxide synthase (NOS) isoforms (neuronal, endothelial or inducible macrophage). A dysfunction of these enzymes is implicated in various diseases such as Alzheimer's disease, septic shock, inflammatory arthritis, schizophrenia, impotence and susceptibility to infection. 1*H*-Pyrazole-1-carboxamidines are competitive inhibitors of all three isoforms: the most selective compound, 1*H*-pyrazole-*N*-(3-aminomethylanilino)-1-carboxamidine, is 100-fold selective for neuronal NOS over endothelial NOS [73]. In the field of neuroprotective activity, studies carried out by Wolff and Gribin [74] on inhibition of nitric oxide synthase by indazole agents confirmed the proposal that 5-nitro-, 6-nitro- and 7-nitroindazoles exert inhibitory actions by interaction of nitric oxide synthase such that oxygen does not bind. 7-Nitroindazole (**38**), a selective inhibitor of neuronal nitric oxide synthase, has been studied for neuroprotective activity and has been used to investigate the role of nitric oxide [75–77].



38

On 27 March 1998 the US Food and Drug Administration approved sildenafil citrate (Viagra) (**39**) for treating male erectile dysfunction (MED). The drug works by inhibiting cyclic guanosine monophosphate (cGMP) phosphodiesterase Type 5 (PDE5). Further structural manipulations have included α-thiagra, the thiophene bioisostere [78], and Monagra, a chiral 5-(2-methyl-2,3-dihydro-7-benzofuryl)-pyrazolopyrimidone analog [79]. At Bristol-Myers Squibb a PDE5 screening of a series of pyrazolopyridines identified a lead compound with modest potency. Based on this template, and using parallel synthesis, from a large and diverse library emerged a new pyrazolopyridine showing comparable *in vitro* functional PDE5 inhibition when compared to sildenafil and improved PDE isozyme selectivity. Thus, due to its pharmacokinetic profile, it is expected to have fewer PDE-related side effects than sildenafil [80].



39

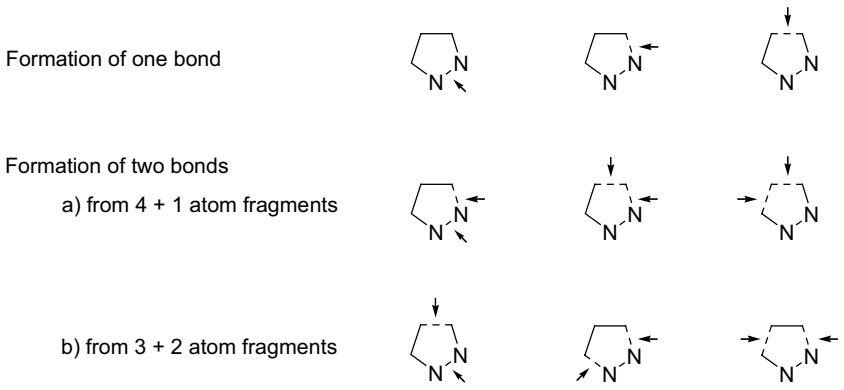
8.4
Synthesis of Pyrazoles and Indazoles

Since the synthesis of pyrazoles and indazoles have very few items in common it is better to treat them separately. Ring transformations, when a heterocycle is transformed into a pyrazole (or indazole), are discussed in the synthesis section. On the other hand, cases where a pyrazole (or indazole) is transformed into another heterocycle are reported under reactivity (Section 8.5). For the same reasons, oxido-reduction reactions, for example, transformation of pyrazolines into pyrazoles or vice versa, will also be covered under reactivity.

8.4.1
Synthesis of Pyrazoles

There are many methods for the synthesis of the pyrazole ring; it can be formed both by cyclization and by cycloaddition reactions. The reaction of hydrazines with 1,3-dicarbonyl compounds (or their equivalents) is probably the most general and versatile method; however, a disadvantage, in some cases, is the formation of mixtures of isomeric pyrazoles from unsymmetrical dicarbonyl compounds. The 1,3-dipolar cycloaddition reaction of diazo compounds, nitrilimines and azomethine imines with alkynes is also a general route to pyrazoles.

Scheme 8.7 shows the different possibilities for the creation of the pyrazole ring according to the bonds formed.

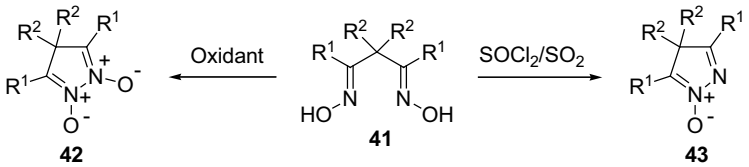


Scheme 8.7

The synthesis and chemistry of pyrazoles has been the subject of recent reviews [6, 8, 81–84].

8.4.1.1 Formation of One N–N Bond

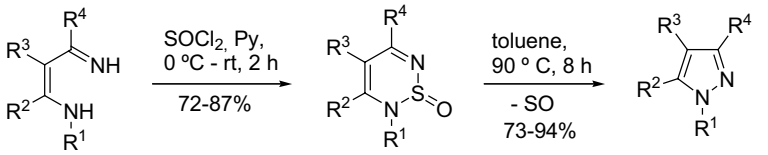
Dioximes of 1,3-dicarbonyl compounds give oxidative cyclization to 4*H*-pyrazole-1,2-dioxides **42** (Scheme 8.8). Various oxidants have been used, namely lead(IV) acetate [85, 86] and *N*-bromoacetamide [87–89]. Dehydration of dioximes **41** with thionyl chloride leads to the monooxides **43** [88, 89]. Base-induced cyclization of 1,3-diketone dioximes affords 1-hydroxypyrazoles, but in low yield (10–30%) [90].



Scheme 8.8

Imines **44** react with thionyl chloride, at room temperature, to furnish 1,2,6-thiadiazine 1-oxides **45**. Thermal extrusion of sulfur monoxide leads to pyrazoles **46** (Scheme 8.9). Alternatively, reaction of imines **44** with thionyl chloride in pyridine at 90 °C leads directly to pyrazoles **46** [91, 92].

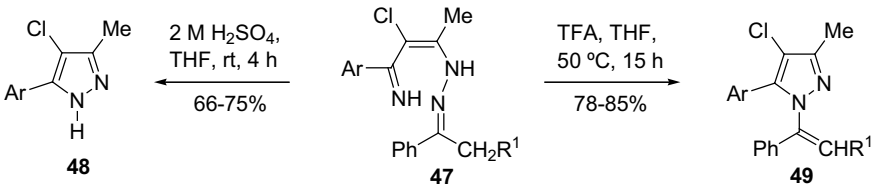
Iminohydrazones **47** give NH-pyrazoles **48** when treated with an aqueous solution of sulfuric acid (Scheme 8.10). In contrast, they are converted into the *N*-alkenyl derivatives **49** when treated with an equimolar amount of anhydrous trifluoroacetic acid in dry THF [93].



44 **45** **46**

R^1 = Ph, *o*-Tolyl, *p*-Tolyl; R^2 = Ph, 4-ClC_6H_4; R^3 = H, Me, Cl, Br; R^4 = Ph, *p*-Tolyl, cyclohexyl

Scheme 8.9



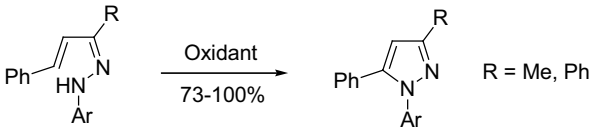
48 **47** **49**

Ar = Ph, 4-ClC_6H_4, 4-MeC_6H_4; R^1 = H, Me

Scheme 8.10

8.4.1.2 Formation of One N–C Bond

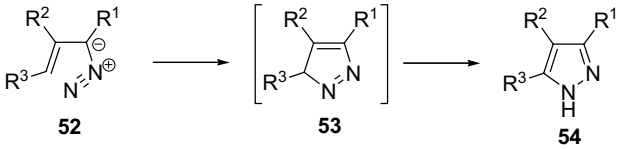
Oxidative cyclization of arylhydrazones **50** leads to 1,3,5-trisubstituted pyrazoles **51** in high yields (Scheme 8.11). Lead tetraacetate [94], manganese dioxide [95] and thianthrene cation radical perchlorate [96] have been used as the oxidants in these transformations.



50 **51**

Scheme 8.11

Diazoalkenes **52** give 1,5-electrocyclizations to 3*H*-pyrazoles **53**, which isomerize spontaneously to 1*H*-pyrazoles **54** (Scheme 8.12). These reactive intermediates can be generated by alkaline decomposition of ethyl alkenylnitrosocarbamates [97], tosylhydrazones of α,β-unsaturated carbonyl compounds [98] or *N*-methoxypyrida-



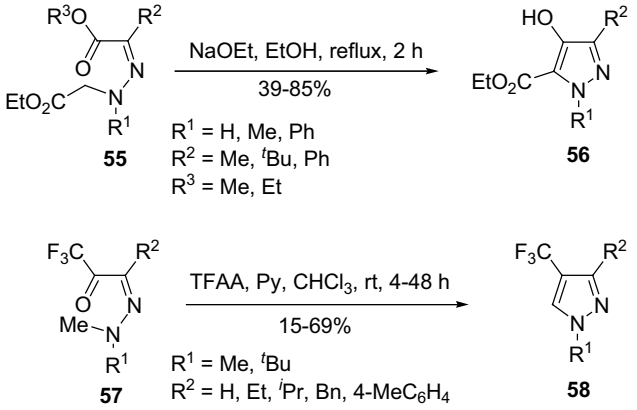
52 **53** **54**

Scheme 8.12

zinium salts [99] or from the reaction of carbonyl compounds with ethyl lithiodiazoacetate [100].

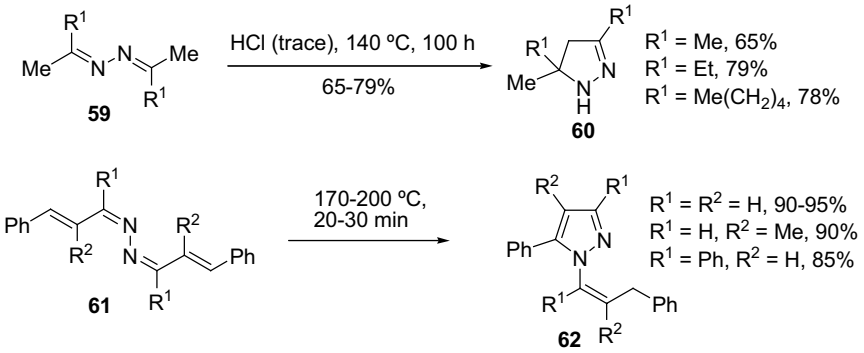
8.4.1.3 Formation of One C–C Bond

Dieckmann cyclization of hydrazones **55** leads to 4-hydroxypyrazole-5-carboxylic acid derivatives **56** in moderate to good yields (Scheme 8.13) [101, 102]. Trifluoroacetic anhydride-pyridine induced cyclization of hydrazones **57** affords 1-alkyl-4-trifluoromethylpyrazoles **58** [103].



Scheme 8.13

When heated with trace amounts of concentrated hydrochloric acid at 140 °C for 100 h, azines of methyl ketones **59** are converted into 3,5-dialkyl-5-methyl-2-pyrazolines **60** in 65–79% yields (Scheme 8.14) [104]. Heating these azines with nickel or cobalt(II) halides at 200 °C also affords pyrazolines **60** in good yields [105]. Under these conditions, other azines give pyrrole derivatives [105]. When acetone azine is heated at 100 °C in the presence of trace amounts of $TiCl_3$, 90% conversion into pyrazoline **60** (R^1=Me) is effected after 20 h [106].



Scheme 8.14

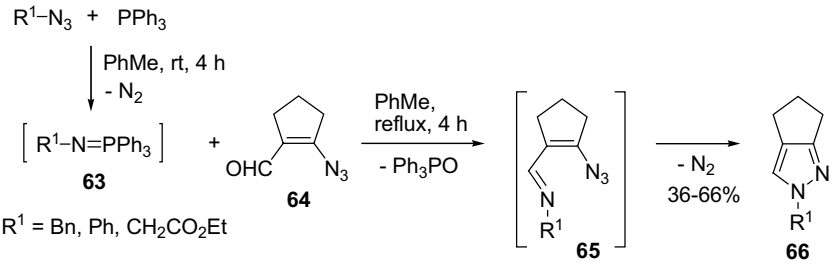
Cinnamaldehyde azine and derivatives **61** are converted into pyrazoles **62** in high yields when heated at about 200 °C (with or without solvent) (Scheme 8.14) [107]. Other α,β-unsaturated azines behave similarly [108, 109]. The thermal decomposition of polyhalogenated propenal azines can be used for the synthesis of mono- and dihalogenated *N*-unsubstituted pyrazoles [110].

Treatment of benzyl phenyl ketazine with two equivalents of LDA generates a dianion that, when heated at 65 °C for 1 h in THF-HMPA, provides 3,4,5-triphenylpyrazole [111].

8.4.1.4 Formation of Two Bonds

8.4.1.4.1 From 4 + 1 Atom Fragments

Formation of One C–N and One N–N Bond [N-C-C-C + N] Iminoposphoranes **63** react with 2-azido-cyclopent-1-enecarbaldehyde **64** to afford azidoimines **65**. When heated in refluxing toluene, these compounds extrude nitrogen and cyclize to pyrazoles **66** (Scheme 8.15) [112].

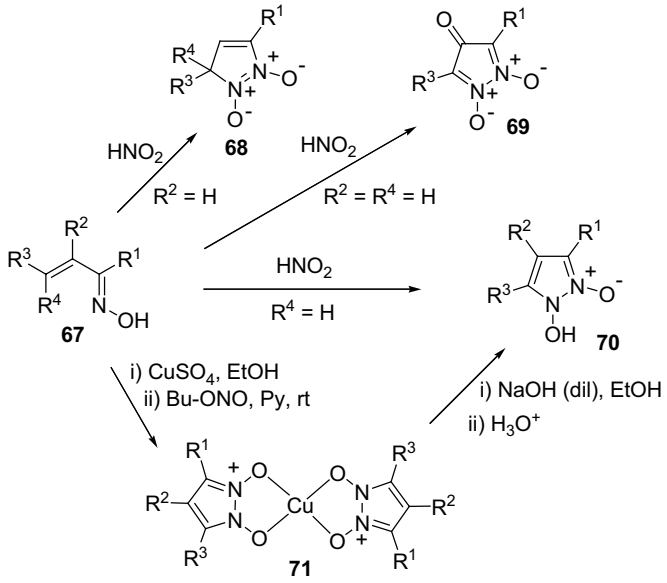


Scheme 8.15

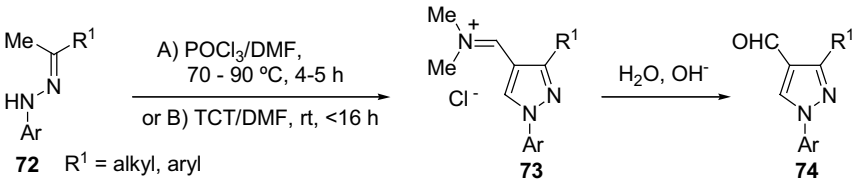
Nitrosation of α,β-unsaturated oximes unsubstituted in the α-position with sodium nitrite and acetic acid leads to pyrazole 1,2-dioxides **68** and **69** while the α-substituted ones afford 1-hydroxypyrazole 2-oxides **70** (Scheme 8.16) [113–115]. Nitrosation of oximes **67** with butyl nitrite in the presence of pyridine and copper sulfate affords copper complexes **71**, which can be conveniently converted into the 1-hydroxypyrazole 2-oxides **70** [116].

Formation of One C–N and One C–C bond [N-N-C-C + C] Hydrazones of methyl ketones react with the Vilsmeier–Haack reagent to afford 1*H*-pyrazole-4-carbaldehydes **74** (method A, Scheme 8.17) [117]. The reaction time can be reduced from 4–5 h to 35–50 s if microwave irradiation is used instead of conventional heating [118]. An interesting variation of method A consists in the substitution of phosphorus oxychloride by cyanuric chloride (2,4,6-trichloro[1,3,5]triazine, TCT) (method B) [119]. This variation requires milder reaction conditions.

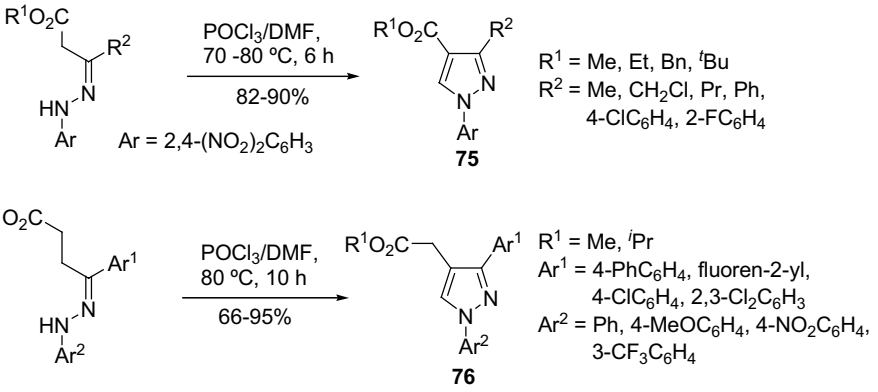
Condensation of the Vilsmeier–Haack reagent with arylhydrazones of β-ketoesters and γ-ketoesters yields, respectively, pyrazole-4-carboxylic acid esters [120] **75** and 4-pyrazoleacetic acid esters [121] **76** (Scheme 8.18).



Scheme 8.16

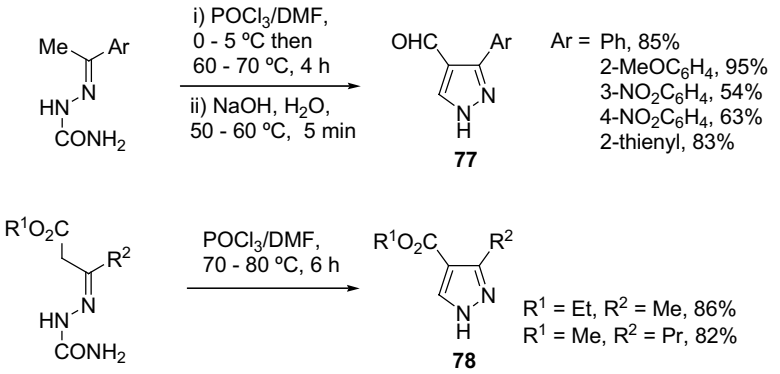


Scheme 8.17



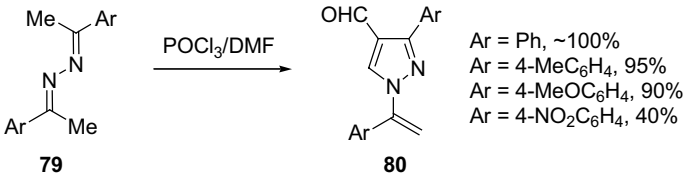
Scheme 8.18

Aminocarbonylhydrazones of methyl ketones [122] or of β-ketoesters [120] react with the Vilsmeier–Haack reagent to afford, respectively, *N*-unsubstituted pyrazole-4-carbaldehydes **77** and *N*-unsubstituted pyrazole-4-carboxylic acid esters **78** (Scheme 8.19).



Scheme 8.19

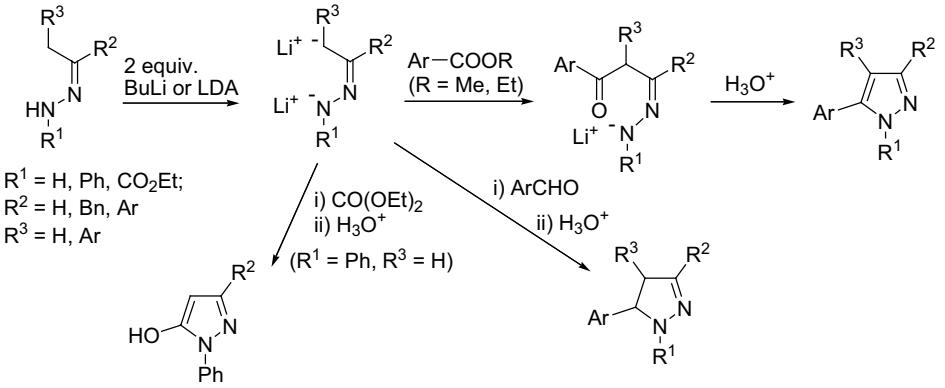
Acetophenone azines **79** also react with the Vilsmeier–Haack reagent to afford 1*H*-pyrazole-4-carbaldehydes **80** in excellent yields (Scheme 8.20) [123].



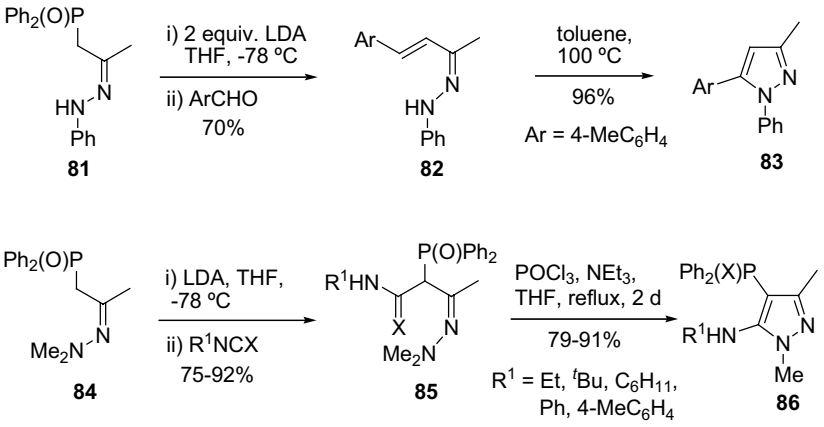
Scheme 8.20

Anions generated from hydrazones with an α-hydrogen undergo a series of reactions affording N-heterocycles, namely pyrazoles [124]. The reaction of dilithiated hydrazone anions with electrophiles (esters [125–129], acyl chlorides [128, 130], nitriles [131], amides [128], α-haloketones [128], aldehydes [132] or diethyl carbonate [133]) followed by acid-catalyzed ring closure furnishes adequately functionalized pyrazoles (Scheme 8.21).

The anion derived from the *N*-phenyl-α-phosphinylhydrazone **81** reacts with aromatic aldehydes to afford hydrazones **82**. Heating at 100 °C in toluene leads to pyrazoles **83** in excellent yields (Scheme 8.22) [134]. In a similar way, deprotonation of the *N,N*-dimethylhydrazone **84**, addition of isocyanates (X=O) or isothiocyanates (X=S) and cyclization leads to pyrazoles **86** [135].

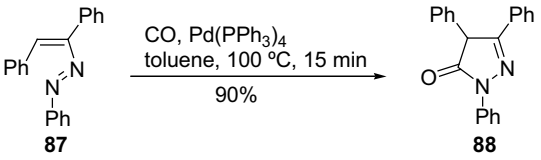


Scheme 8.21



Scheme 8.22

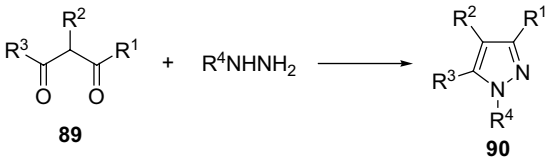
Treatment of a solution of diazabutadiene **87** in toluene with 1–10 mol% of Pd(0) catalyst under an atmosphere of CO (1–2 atm) at 100 °C for 15 min affords 1,3,4-triphenylpyrazol-5-one (**88**) in excellent yield (Scheme 8.23) [136].



Scheme 8.23

8.4.1.4.2 From 3 + 2 Atom Fragments

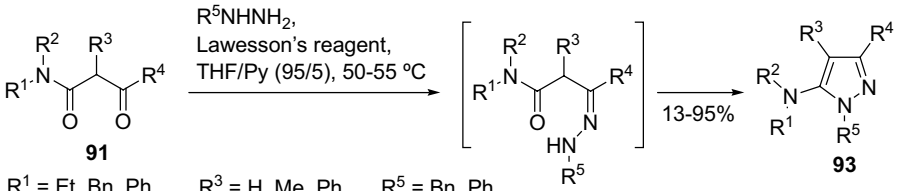
Formation of Two C–N Bonds [C-C-C + N-N] The addition of hydrazines (double nucleophiles) to three-carbon units featuring two electrophilic carbons in a 1,3-relationship is one of the most versatile routes to pyrazoles. The condensation of hydrazines with 1,3-diketones, for instance, is perhaps the most common route to the construction of the pyrazole ring (Scheme 8.24) [137–139]. Several other 1,3-bis (electrophilic) compounds react with hydrazines to yield pyrazoles, namely β-keto-aldehydes, β-ketoesters, β-ketoamides, β-ketonitriles, vinyl ketones, alkynyl ketones, and so on.



89 **90**

Scheme 8.24

Substituted 5-alkylamino and 5-(arylamino)pyrazoles **93** can be prepared in one-pot synthesis from a β-ketoamide **91**, an aryl or alkyl hydrazine and Lawesson's reagent (Scheme 8.25) [140]. Hydrazones **92** are probable intermediates. This method has also been applied for the solid-supported synthesis of 5-(*N*-monosubstituted-amino)pyrazoles [141].



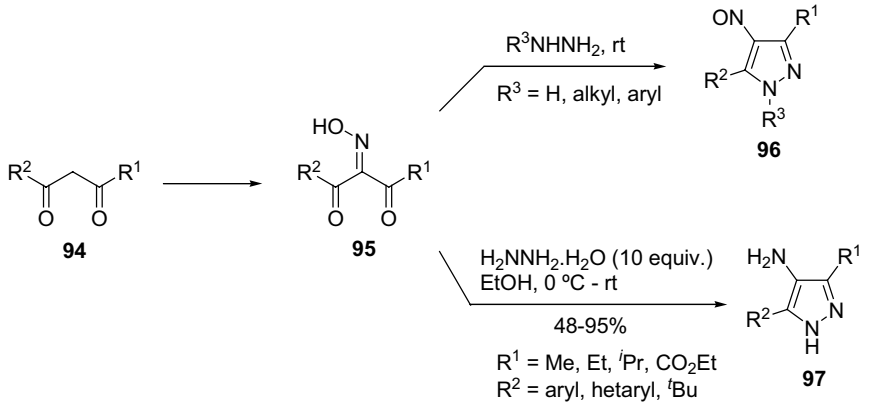
91 **92** **93**

R^1 = Et, Bn, Ph
R^2 = H, Me, Et
R^3 = H, Me, Ph
R^4 = Me, Ph
R^5 = Bn, Ph
Bn = CH_2Ph

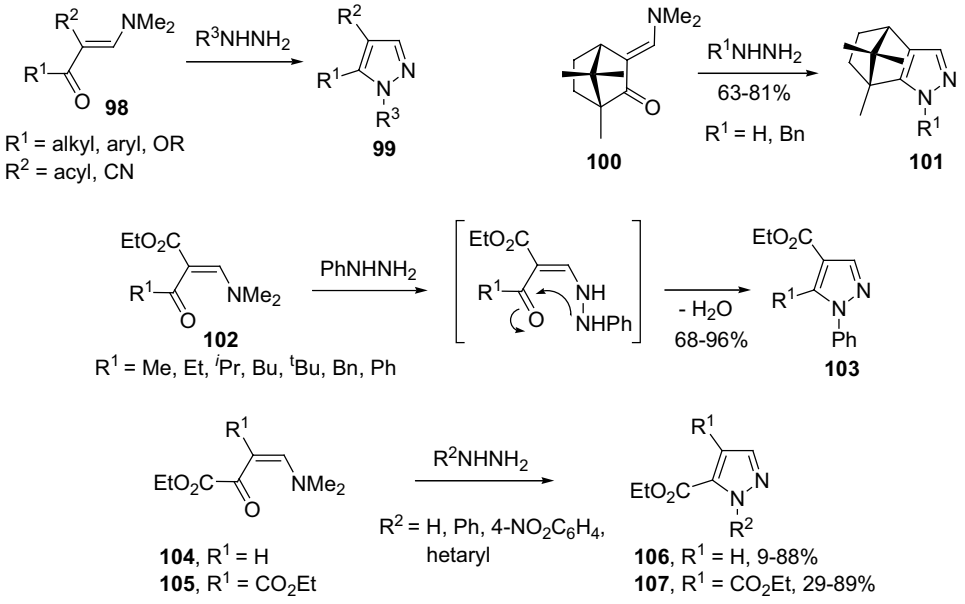
Scheme 8.25

Diketo oximes **95** (prepared from 1,3-diketones **94**) react with hydrazines to yield 4-nitrosopyrazoles **96** (Scheme 8.26) [142, 143]. However, if a large excess of hydrazine is used the isolated products are the corresponding 4-amino-3,5-disubstituted pyrazoles **97** [144].

Enamines of general type **98** react with hydrazine derivatives to afford pyrazoles **99** (Scheme 8.27) [145]. For instance, reaction of (+)-camphor derivative **100** with hydrazine or benzylhydrazine leads to pyrazoles **101** [146]. Also, compounds **102** react with phenylhydrazine to afford 1,4,5-trisubstituted pyrazoles **103** in moderate to excellent yields [147]. Similarly, ethyl 4-dimethylamino-2-oxo-3-butenoate **104** and its diester analogue **105** react with a range of hydrazine derivatives to afford pyrazoles **106** and **107**, respectively [148].



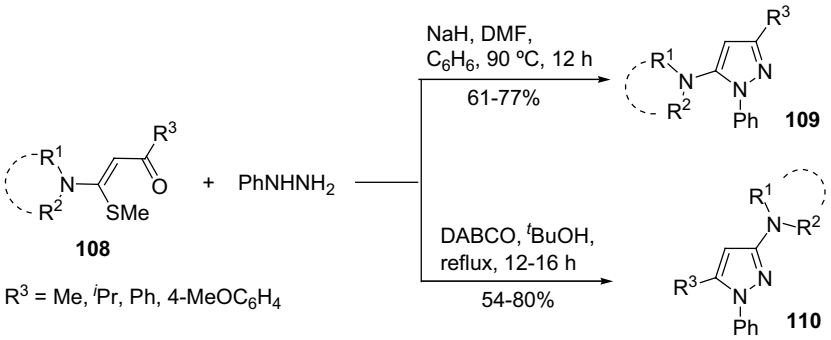
Scheme 8.26



Scheme 8.27

The use of microwave irradiation in this type of chemistry allows the formation of pyrazole derivatives in a few minutes while it requires several hours under conventional heating [149]. The formation of pyrazoles from polymer-bound 2-acyl-3-aminopropenoates has also been described [150, 151].

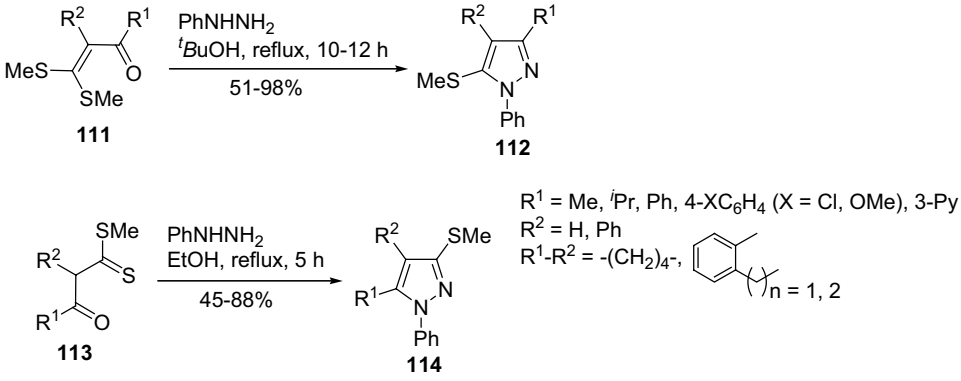
Cyclocondensation of α-oxoketene *N,S*-acetals **108** with phenylhydrazine gives regioselectively 3- or 5-(*N*-cycloamino)pyrazoles just by variation of the reaction conditions (Scheme 8.28) [152]. Reaction of 2-cyanoketene *N,S*-acetals with substi-



Scheme 8.28

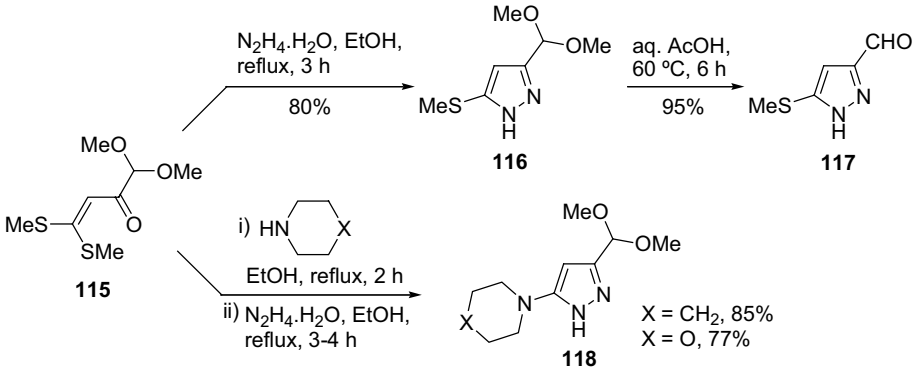
tuted hydrazines in refluxing ethanol containing a catalytic amount of piperidine gives the corresponding 5-amino-3-anilino-1*H*-pyrazole-4-carboxamides [153].

α-Oxoketene dithioacetals **111** react with phenylhydrazine to give selectively 5-methylthio-1-phenyl-3,4-substituted/annulated pyrazoles **112** (Scheme 8.29) [154]. Regioisomeric 3-methylthio-1-phenyl-4,5-substituted/annulated pyrazoles **114** are obtained selectively from the reaction of β-oxodithioesters **113** with phenylhydrazine [154].



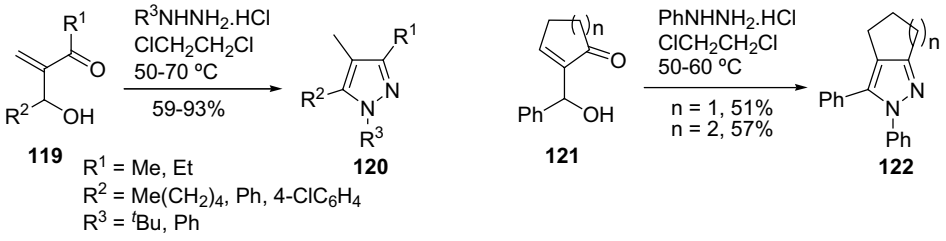
Scheme 8.29

Cyclocondensation of 1-bis(methoxy)-4-bis(methylthio)-3-buten-2-one (**115**) with hydrazine hydrate gives pyrazole **116** with a masked aldehyde functionality (Scheme 8.30) [155]. The corresponding 5(3)-cycloaminopyrazole derivatives **118** can also be synthesized in a one-pot sequence by prior displacement of one of the methylthio groups of **115** by the respective amine. Hydrolysis of the dimethylacetal moiety of **116** with aqueous acetic acid (50%) affords the corresponding pyrazole-3 (5)-carbaldehyde in 95% yield.



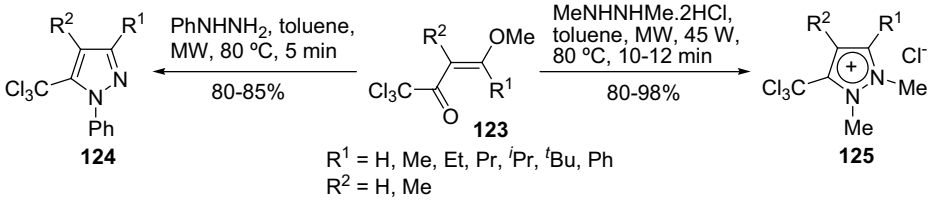
Scheme 8.30

Baylis–Hillman adducts **119** and **121** react with hydrazine hydrochlorides to afford regioselectively 1,3,4,5-tetrasubstituted pyrazoles **120** and **122** respectively (Scheme 8.31) [156].



Scheme 8.31

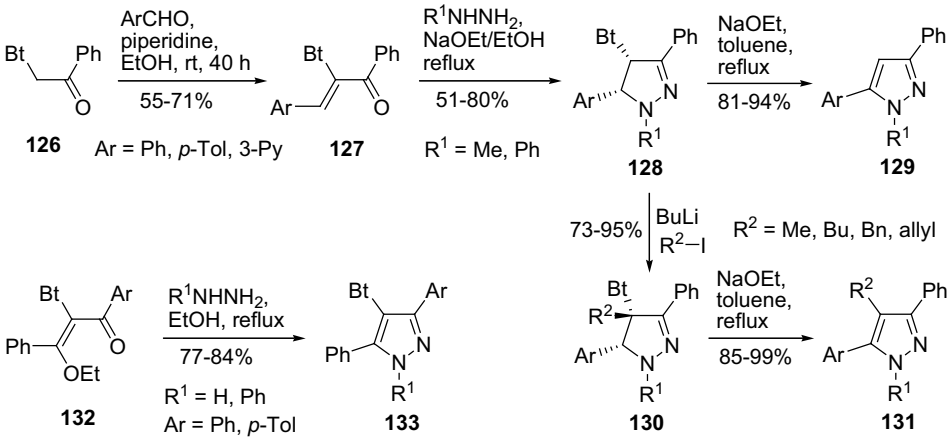
5-Trichloromethyl-1-phenyl-1*H*-pyrazoles **124** and 5-trichloromethyl-1,2-dimethylpyrazolium chlorides **125** can be synthesized in 80–98% yield by the cyclocondensation of β-alkoxyvinyl trichloromethyl ketones **123** with phenylhydrazine and 1,2-dimethylhydrazine dihydrochloride, respectively, under microwave irradiation and using toluene as solvent (Scheme 8.32) [157]. While the use of microwave and classical methods are comparable for making pyrazoles, the pyr-



Scheme 8.32

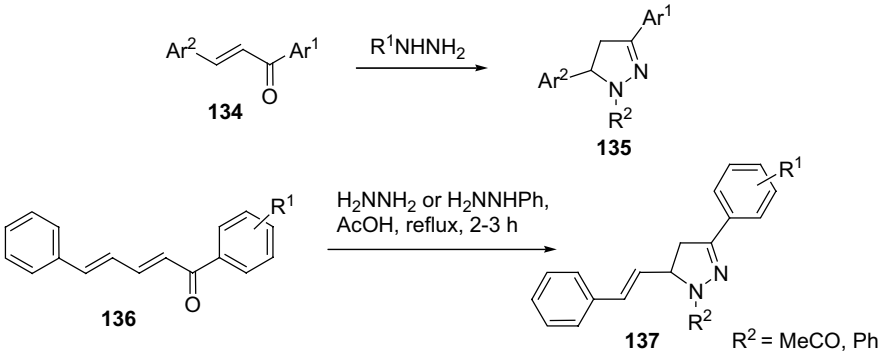
azolium chlorides can be obtained in a significantly shorter time and in some cases better yield. The trifluoromethyl analogues of **123** react with 7-chloro-4-hydrazinoquinoline to afford 1*H*-pyrazol-1-yl quinolines in high yields [158].

Treatment of α-benzotriazolyl-α,β-unsaturated ketones **127** with monosubstituted hydrazines leads to the regioselective synthesis of benzotriazolylpyrazolines **128**, which, by treatment with a base, can be converted into the trisubstituted pyrazoles **129** (Scheme 8.33) [159]. Alkylation of pyrazolines **128** at the 4-position of the pyrazoline ring is a versatile route to unsymmetrical 1,3,4,5-tetrasubstituted pyrazolines **130** and -pyrazoles **131** [159]. The α-benzotriazolyl-β-ethoxy-α,β-unsaturated ketones **132** react with hydrazines to afford directly the corresponding 4-benzotriazolylpyrazoles **133** [160].



Scheme 8.33

Chalcones **134** react with substituted hydrazines to yield 1-substituted-3,5-diaryl-4,5-dihydro-1*H*-pyrazoles **135** (Scheme 8.34) [84]. With hydrazine hydrate, in acetic

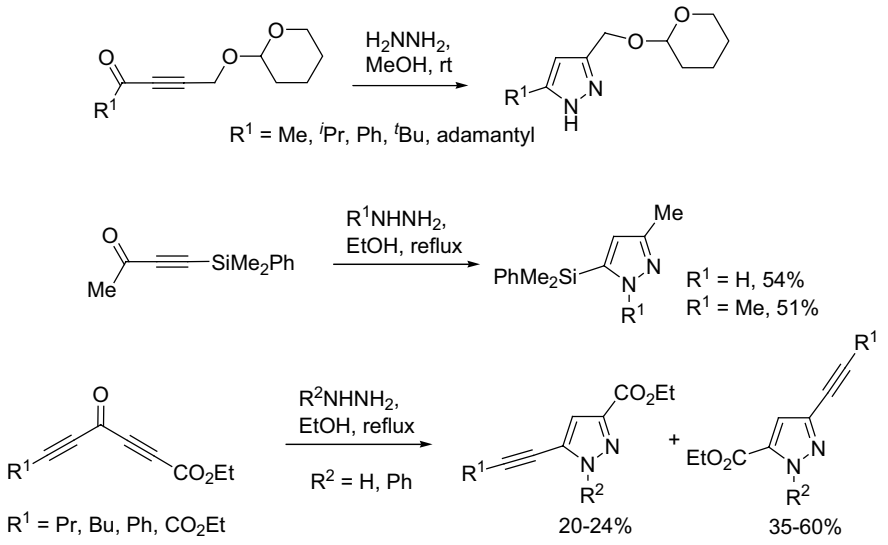


Scheme 8.34

acid, they afford the 1-acetyl derivatives; some of them are potent and selective inhibitors of monoamine oxidase [161]. Chalcones **134** undergo a rapid cyclization with phenylhydrazine under solvent-free and silica-supported conditions using microwave irradiation to afford 4,5-dihydro-1*H*-pyrazoles **135** in good yields in 2–3 min [162]. Chalcone-epoxides react with hydrazine hydrate, in refluxing ethanol, to afford 3,5-diaryl-1*H*-pyrazoles in high yield [163].

Cinnamylideneacetophenones **136** react with hydrazine hydrate or phenylhydrazine to afford the dihydropyrazoles **137** (Scheme 8.34) [164]. In a similar process, chalcones, bis(chalcones) and oligo(chalcones) react with hydrazine hydrate or hydrazine derivatives to yield pyrazolines, bis(pyrazolines) and oligo(pyrazolines), respectively [165, 166].

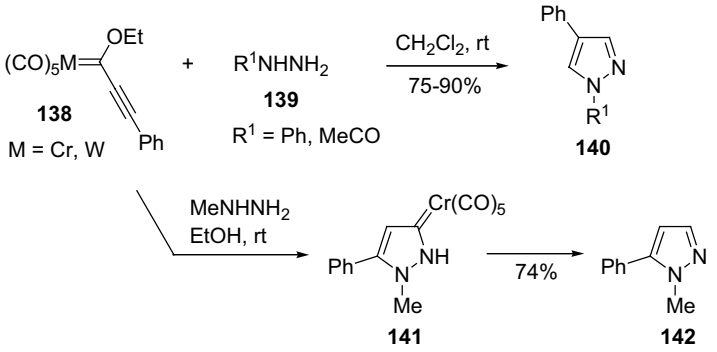
Addition of hydrazine to alkynyl ketones is a simple and regioselective route to pyrazoles. Some examples are shown in Scheme 8.35 [167–170].



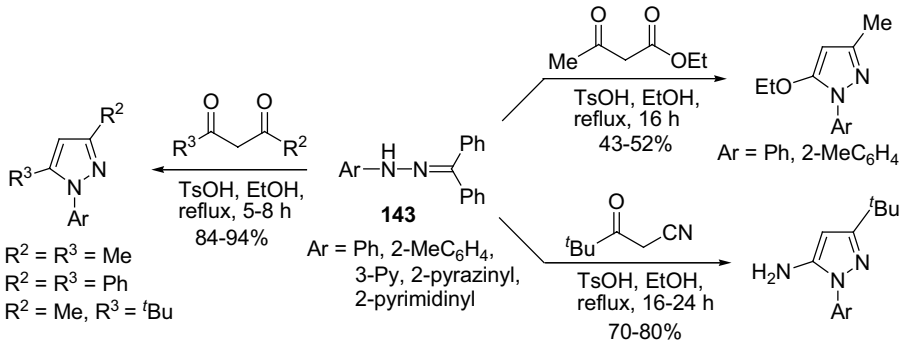
Scheme 8.35

Alkynylcarbene complexes **138** react with hydrazines **139** to form selectively 1,4-disubstituted pyrazoles **140** (Scheme 8.36) [171]. With methylhydrazine it leads to the cyclic aminocarbene complex **141**, which can be demetallated to 1-methyl-5-phenylpyrazole (**142**).

Aryl benzophenone hydrazones **143** are convenient substitutes of arylhydrazines in the synthesis of pyrazoles. These hydrazones react with various 1,3-bifunctional substrates under acidic conditions to afford adequately functionalized pyrazoles in good yields (Scheme 8.37) [172, 173]. The obtained regioselectivity is consistent with transhydrazonation followed by subsequent cyclization. This synthetic route is especially attractive for the synthesis of 1-hetaryl-pyrazoles, since *N*-hetaryl benzo-



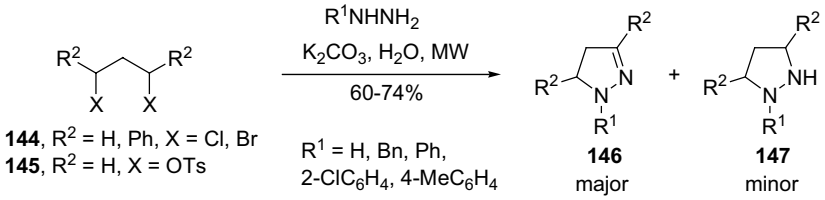
Scheme 8.36



Scheme 8.37

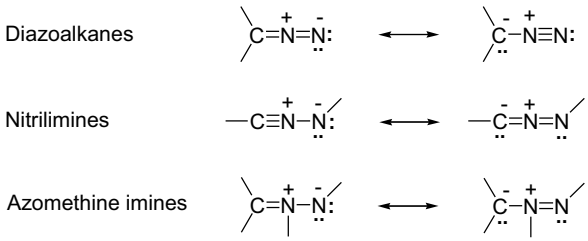
phenone hydrazones can easily be prepared following Buchwald–Hartwig procedures [173].

The cyclocondensation of hydrazines with 1,3-dihalopropanes **144** or propane-1,3-diol ditosylate (**145**) in aqueous alkaline medium and under microwave irradiation affords 4,5-dihydropyrazoles **146** as major products instead of the anticipated pyrazolidines **147** (Scheme 8.38) [174].



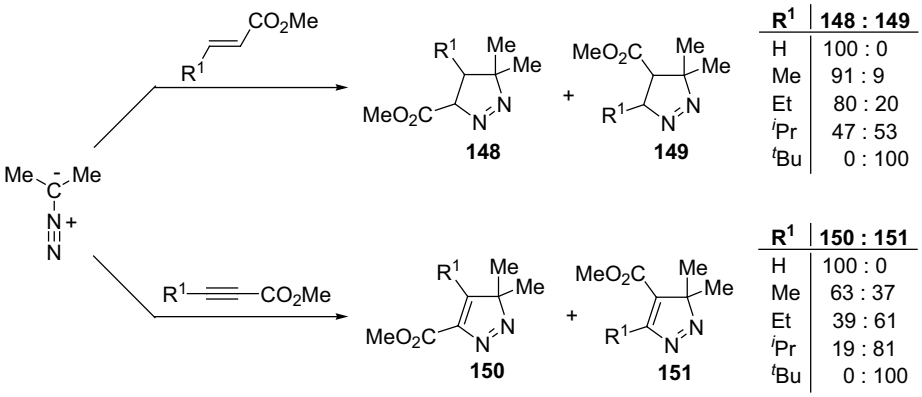
Scheme 8.38

Formation of One C–N Bond and One C–C Bond [N-N-C + C-C] The 1,3-dipolar cycloaddition of diazoalkanes, nitrilimines or azomethine imines to alkynes, alkenes or to functionalized alkenes (enamines or enol ethers, for instance) is a versatile method for the synthesis of pyrazoles. The dipole is the source of the [CNN] fragment while the dipolarophile contributes with the [CC] fragment. This method suffers from the disadvantage that a mixture of two isomeric pyrazoles may be formed when unsymmetrical dipolarophiles are used.



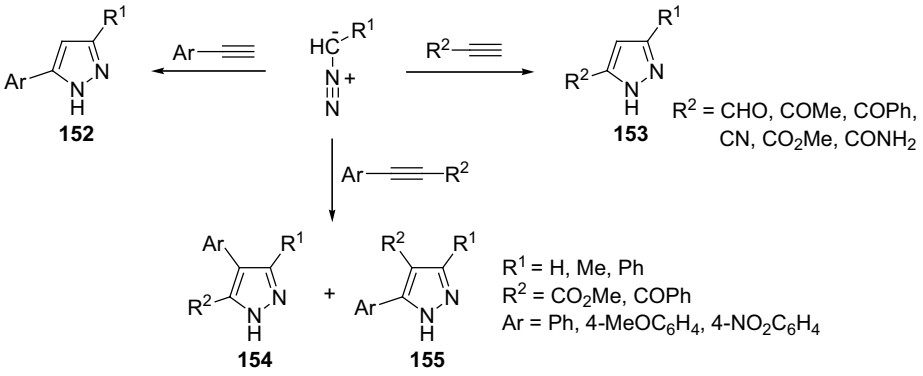
Diazoalkanes react with alkenes and alkynes to give, respectively, Δ^1-pyrazolines and 3*H*-pyrazoles [175–177]. However tautomerization may take place, especially if diazomethane or a monosubstituted diazoalkane is used.

The orientation of the dipole–dipolarophile interaction is mainly governed by electronic effects, as described by the FMO theory. However, as indicated in Scheme 8.39 [178], the regioisomer ratios are also strongly dependent on steric effects, which are more pronounced in the case of alkynes.



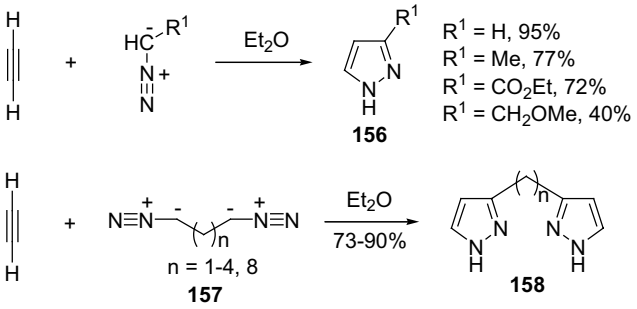
Scheme 8.39

Diazoalkanes react with arylalkynes and acylalkynes to afford, with high regioselectivity, pyrazoles **152** and **153**, respectively (Scheme 8.40). In both cases, the polarization of the triple bond is such that the nucleophilic carbon atom of the dipole attacks the terminal position of the alkyne. With acylarylalkynes, a mixture of the two possible regioisomers **154** and **155** is frequently obtained. For each alkyne, the ratio **154** : **155** is strongly dependent on the diazoalkane used [177, 179].



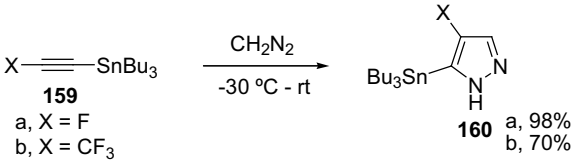
Scheme 8.40

Pyrazole itself can be synthesized from the reaction of diazomethane with acetylene. When this reaction is carried out under pressure, almost quantitative yields are obtained [180]. Under identical conditions, addition of diazoethane, ethyl diazoacetate or α,ω-bis(diazo)alkanes **157** to acetylene gives rise to the corresponding pyrazoles **156** or bispyrazoles **158** (Scheme 8.41) [180].



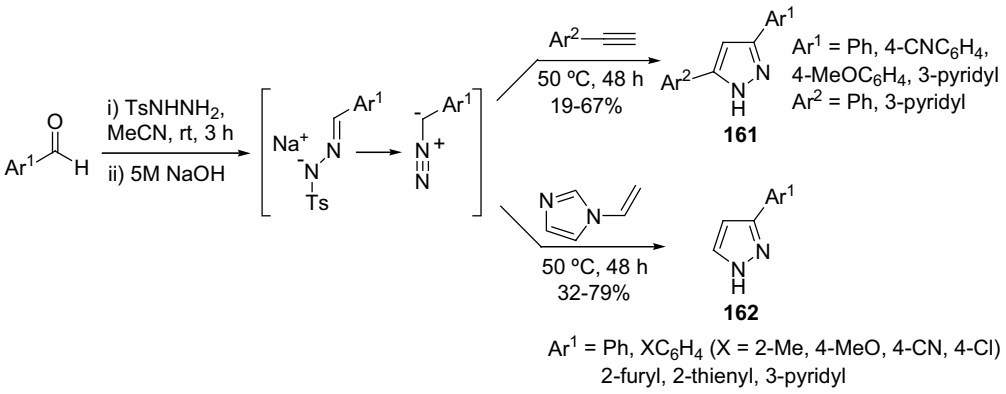
Scheme 8.41

Addition of an ethereal diazomethane solution to fluoro(tributylstannyl)acetylene (**159a**), at −30 °C, gives the corresponding 5-tributylstannyl-4-fluoropyrazole (**160a**) in 98% yield (Scheme 8.42) [181]. The trifluoromethyl analogue **160b** can be obtained in the same way [182].



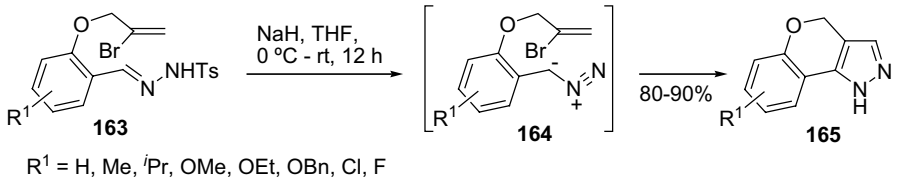
Scheme 8.42

A one-pot procedure for the preparation of 1*H*-pyrazoles involving aryldiazomethanes generated *in situ* has been reported [183]. The 1,3-dipoles are generated *in situ* from aldehydes, via tosylhydrazone sodium salts, and then react with arylacetylenes to furnish regioselectively 3,5-diaryl-1*H*-pyrazoles **161** (Scheme 8.43). When they are generated in the presence of *N*-vinylimidazole, an acetylene equivalent, 3-substituted-1*H*-pyrazoles **162** are obtained.



Scheme 8.43

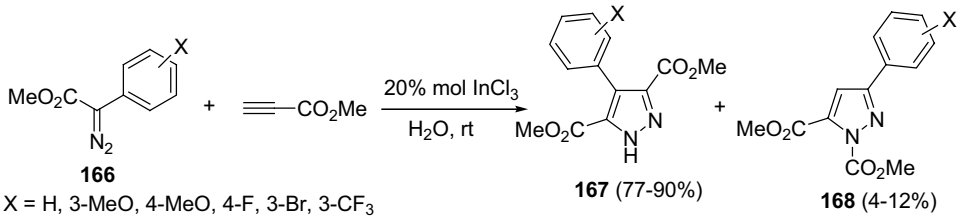
The generation of aryldiazomethanes **164** from bromovinyl tosylhydrazones **163** leads to benzopyrano[1*H*]pyrazoles **165** in high yields (Scheme 8.44) [184].



Scheme 8.44

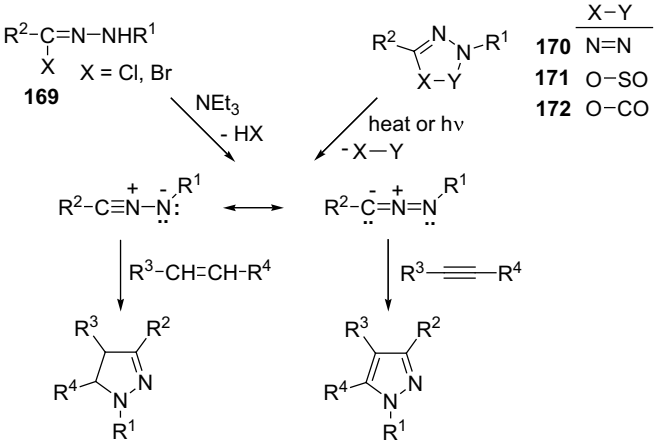
An efficient $InCl_3$-catalyzed 1,3-dipolar cycloaddition of diazocarbonyl compounds and alkynes to synthesize pyrazoles has been reported recently [185]. The reaction is carried out in water, at room temperature, and the catalyst, which stays in the aqueous phase after the work-up, can be reused without loss of catalytic activity. The reaction is applicable to various α-diazocarbonyl compounds and alkynes with a carbonyl group at the neighboring position. As an example, methyl α-diazoarylacetates **166** react with methyl propiolate to afford pyrazoles **167** and **168** in excellent combined yields (Scheme 8.45).

Nitrilimines are also interesting intermediates in the synthesis of pyrazoles and Δ^2-pyrazolines [186, 187]. These 1,3-dipoles are typically generated by dehydroha-



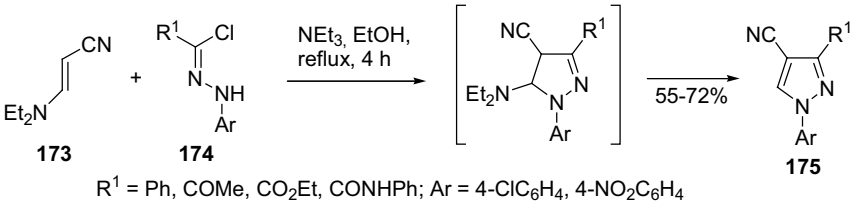
Scheme 8.45

logenation of *N*-arylhydrazonoyl halides **169** with triethylamine in an inert solvent in the presence of the dipolarophile (Scheme 8.46) [188]. Useful alternatives for the generation of nitrilimines are the cycloreversion [189] of tetrazoles **170**, oxathiadiazolinones **171** and 1,3,4-oxadiazolin-2-ones **172** and the oxidation of aldehyde hydrazones with chloramine T, lead tetraacetate [190] or with (diacetoxy)iodobenzene [191, 192].



Scheme 8.46

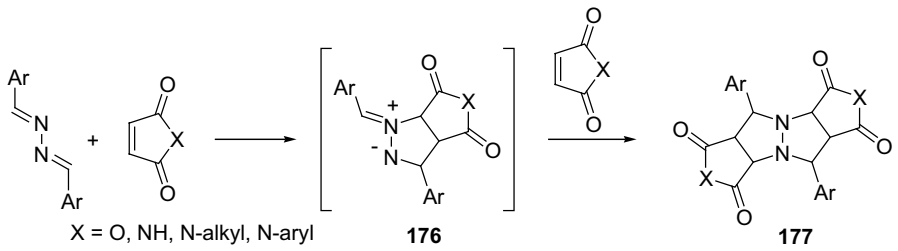
3-Diethylaminoacrylonitrile (**173**) reacts readily with nitrilimines generated from hydrazonoyl chlorides **174** and triethylamine to yield selectively 1,3-disubstituted pyrazole-4-carbonitriles **175** (Scheme 8.47) [193]. Bis-pyrazolophanes have been



Scheme 8.47

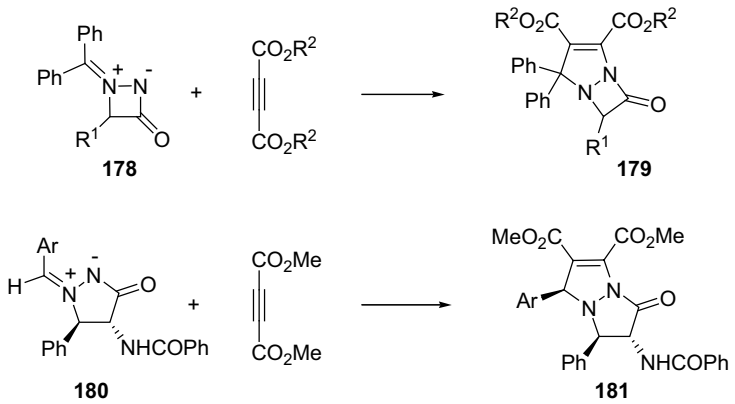
prepared via double cycloadditive macrocyclization of bis-hydrazonoyl chlorides with bis-allyl ethers, a bis-vinyl ether and a bis-propargyl ether [194].

Diaryl azines react with maleic anhydride, maleimide or N-substituted maleimides to give pyrazolo[1,2-*a*]pyrazole derivatives **177** by (1,3 : 2,4)-dipolar cycloadditions (also known as *crisscross* cycloadditions) (Scheme 8.48) [195–197]. Azomethine imines **176** are probable intermediates in these transformations.



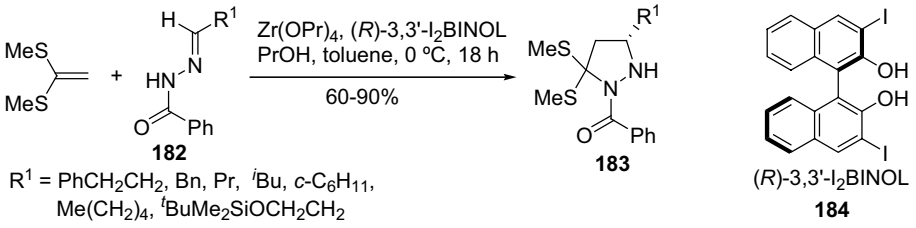
Scheme 8.48

Azomethine imines of types **178** and **180** have been used in the synthesis of aza-β- and aza-γ-lactams (Scheme 8.49) [198, 199].



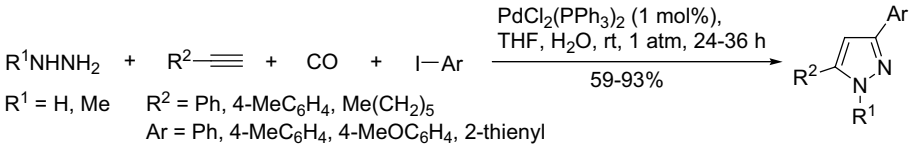
Scheme 8.49

A highly enantioselective catalytic intermolecular [3 + 2] cycloaddition of acylhydrazones **182** to electron-rich alkenes has been reported [200]. Tetrahydropyrazoles **183** are obtained in high yield and with high ee (95–98%) (Scheme 8.50). The reaction proceeds in the presence of a chiral zirconium catalyst prepared from zirconium propoxide ($Zr(OPr)_4$), *(R)*-3,3′-I_2BINOL (**184**) and propanol. A concerted mechanism has been proposed for this reaction.



Scheme 8.50

Formation of Two C–N Bonds and One C–C Bond [N-N + C-C + C] A four-component one-pot construction of pyrazoles via a palladium-catalyzed coupling of terminal alkynes, hydrazine (or methylhydrazine), carbon monoxide and aryl iodides has been described recently (Scheme 8.51) [201]. The reaction proceeds at room temperature and an ambient pressure of carbon monoxide in an aqueous solvent system. The reaction is completely regioselective and the yields are excellent. Under similar conditions, the reaction with phenylhydrazine does not afford the corresponding pyrazole.



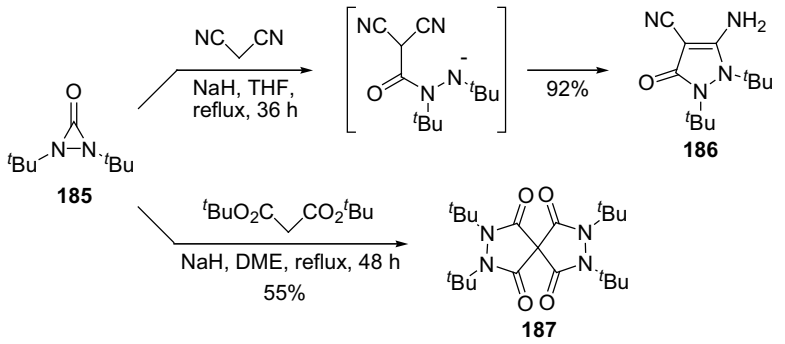
Scheme 8.51

8.4.1.5 From Other Heterocycles

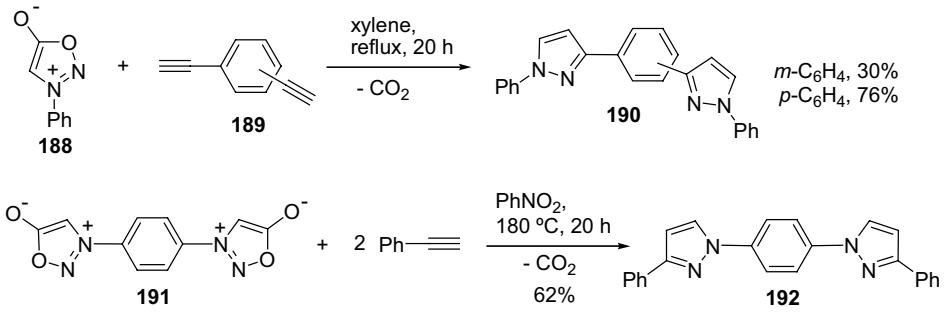
Many heterocyclic compounds can be converted into pyrazoles. However, despite some synthetically interesting exceptions, in most cases the starting heterocycles are not readily available and the routes are unlikely to be general. A few examples of ring enlargement, ring modification and ring contraction reactions leading to pyrazoles are shown in the following schemes.

Ring enlargement of diaziridinone **185** by reaction with bifunctional carbanions leads to pyrazolinone **186** or to spiroheterocycles **187** (Scheme 8.52) [202].

Sydnones give 1,3-dipolar cycloadditions with a range of dienophiles to yield pyrazoles. For instance, the reaction of 3-phenylsydnone (**188**) with *meta*- and *para*-diethynylbenzene in refluxing xylene gives *meta*- and *para*-phenylenedipyrazoles **190**, respectively (Scheme 8.53) [203]. Similarly, the reaction of *para*-phenylene-3,3′-disydnone (**191**) with phenylacetylene provides 3,3′-diphenyl-1,1′-*para*-phenylenedipyrazole (**192**). A range of polysubstituted pyrazoles have been obtained in high yield and with elevated regioselectivity from the reaction of 3,4-disubstituted sydnones with 1-aryl-3,3,3-trifluoromethylpropynes [204]. The 1,3-dipolar cycloaddition reactions of nitrilimines with a great variety of heterocyclic compounds, many of them leading to pyrazoles, have been reviewed [187].

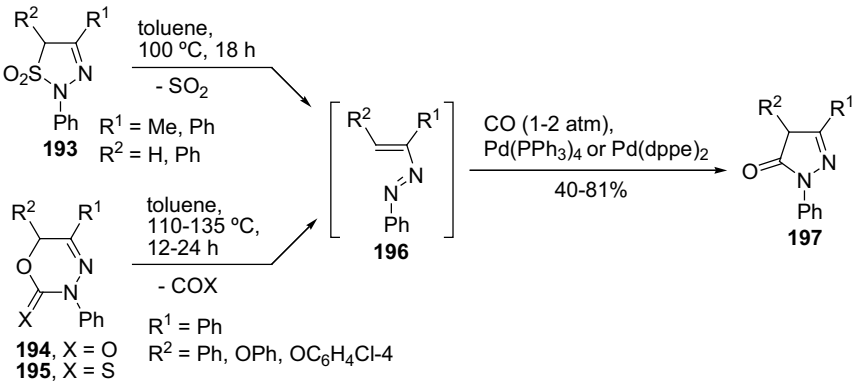


Scheme 8.52



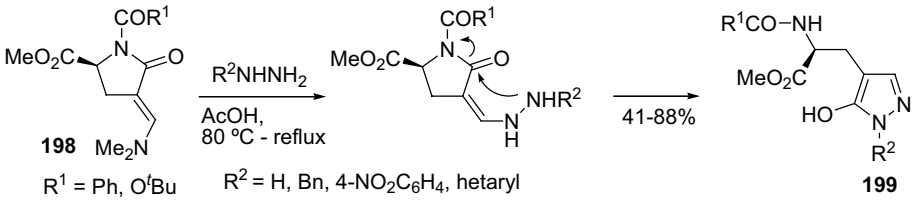
Scheme 8.53

Pd(0)-catalyzed carbonylation of 1,2-diaza-1,3-butadienes **196**, generated *in situ* by thermal extrusion of SO_2, CO_2 or COS from heterocyclic precursors **193–195**, respectively, under 1–2 atm of CO affords pyrazol-5-ones **197** in good yields (Scheme 8.54) [136].



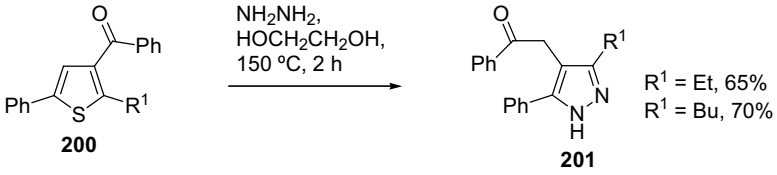
Scheme 8.54

Addition of hydrazine derivatives to *(S)*-1-acylpyrrolidin-2-ones **198** in refluxing acetic acid leads to *(S)*-*N*-acyl-3-(1-substituted-5-hydroxy-1*H*-pyrazol-4-yl)alanine methyl esters **199** (Scheme 8.55) [205].



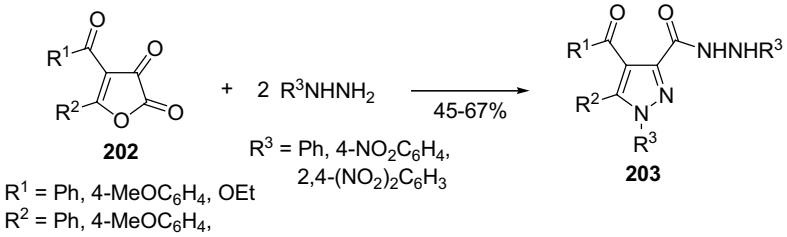
Scheme 8.55

3-Benzoyl-2-substituted-5-phenylfurans **200** react with hydrazine to afford the corresponding 4-benzoylmethyl-3(5)-phenylpyrazoles **201** (Scheme 8.56) [206].



Scheme 8.56

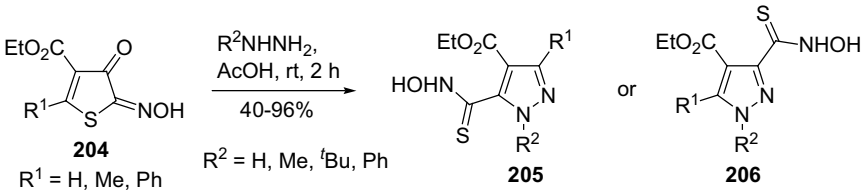
Furan-2,3-diones **202** react with hydrazines under different conditions to yield pyrazole-3-carboxylic acid hydrazides **203** (Scheme 8.57) [207].



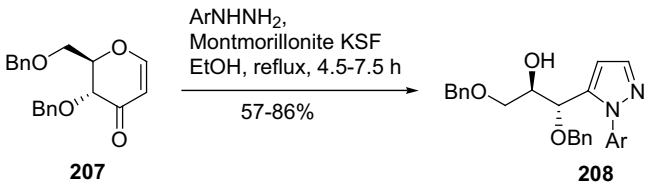
Scheme 8.57

4,5-Dihydro-5-(hydroxyimino)-4-oxothiophene-3-carboxylic esters **204** react with hydrazines to yield pyrazole-3- or -5-thiohydroxamic acids (**205** and **206**, respectively), depending on the substituents R^1 and R^2 (Scheme 8.58) [208].

2,3-Dihydro-4*H*-pyran-4-ones **207** undergo rapid condensation with arylhydrazines in the presence of montmorillonite KSF clay to afford enantiomerically pure 5-substituted pyrazoles **208** in good yields (Scheme 8.59) [209]. In the absence of the clay, no reaction is observed between the pyranones and arylhydrazines. The catalyst



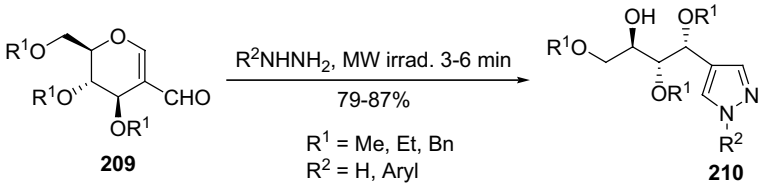
Scheme 8.58



Scheme 8.59

can be recovered by simple filtration and reused three times without any significant decrease in activity after being washed with methanol and activated at 120 °C.

2-Formyl glycals **209** undergo rapid condensation with arylhydrazines under solvent-free conditions to give the corresponding optically pure 4-substituted pyrazoles **210** in good yields with high selectivity (Scheme 8.60) [210]. Like arylhydrazines, hydrazine hydrate itself also affords the respective pyrazoles in good yields.

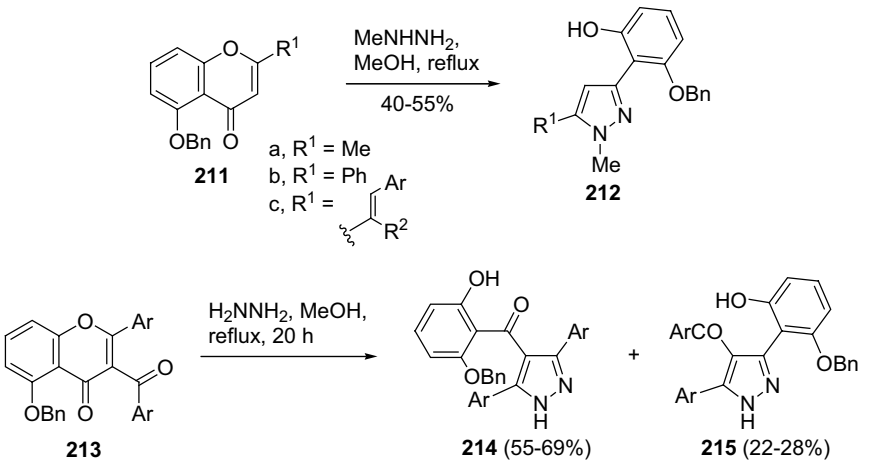


Scheme 8.60

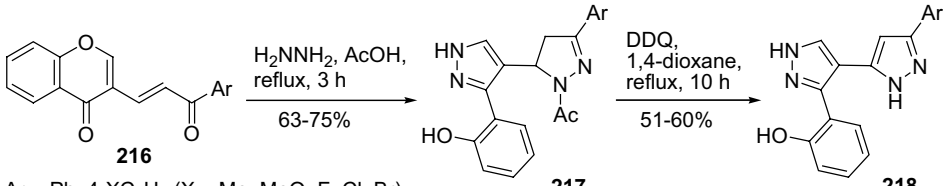
2-(Methyl, phenyl, or styryl)chromones **211** react with methylhydrazine to afford the corresponding 3-(2-benzyloxy-6-hydroxyphenyl)pyrazole derivatives **212** (Scheme 8.61) [211]. Similarly, treatment of 3-aroylflavones **213** with hydrazine gives a mixture of the two aroylpyrazoles **214** and **215** [212].

Treatment of the 3-(3-aryl-3-oxopropenyl)chromen-4-ones **216** with hydrazine hydrate in hot acetic acid afforded the 1-acetyl-3-aryl-5-[3-(2-hydroxyphenyl)pyrazol-4-yl]-2-pyrazolines **217** in good yields (Scheme 8.62) [213]. Oxidation of the 2-pyrazoline ring with DDQ gave the bispyrazoles **218**. *N*-Deacylation occurred during the oxidation.

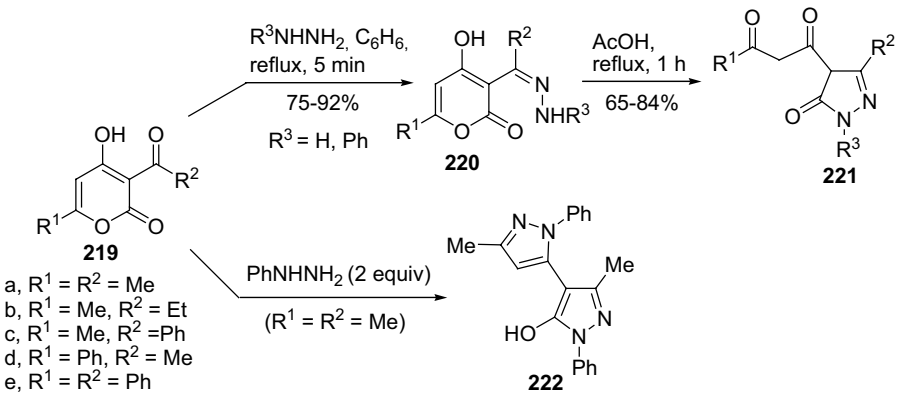
3-Acyl-2*H*-pyran-2,4-diones **219** react with one equivalent of phenylhydrazine to give hydrazones **220a–d** (R^3=Ph) (Scheme 8.63) [214]. Reaction of **219a** with



Scheme 8.61



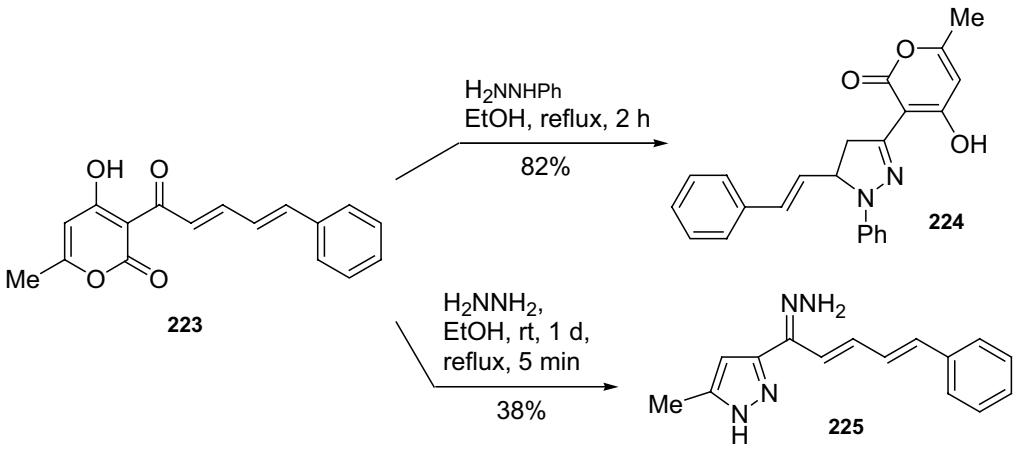
Scheme 8.62



Scheme 8.63

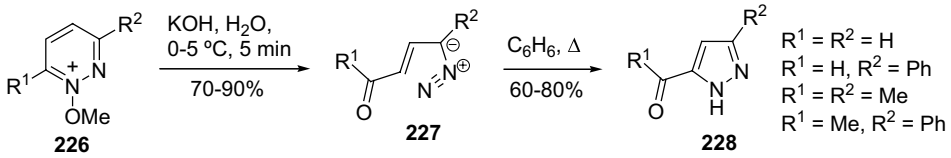
hydrazine hydrate affords **221a** (R^3=H) [215]. Hydrazones **220** can be converted into pyrazolin-5-ones **221** in good yields [214]. 3-Acetyl-2*H*-pyran-2,4-dione **219a** reacts with two equivalents of phenylhydrazine to give the pyrazolylpyrazole **222** [214].

Surprisingly, 2*H*-pyran-2,4-dione **223** reacts with phenylhydrazine to afford dihydropyrazole **224** while with hydrazine it gives pyrazole **225** (Scheme 8.64) [216]. The formation of **225** involves a decarboxylation process, not observed in the reaction of compound **219a** with hydrazine [215]. 3-Aryl-1-(3-coumarinyl)propen-1-ones also react with hydrazines to afford 1-substituted 5-aryl-3-(3-coumarinyl)-2-pyrazolines [217].



Scheme 8.64

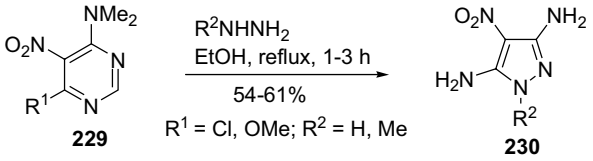
N-Methoxypyridazinium salts **226** react with hydroxide ion to give vinyl diazomethanes **227**, which cyclize to 3(5)-acyl-1*H*-pyrazoles **228** when heated in benzene (Scheme 8.65) [99].



Scheme 8.65

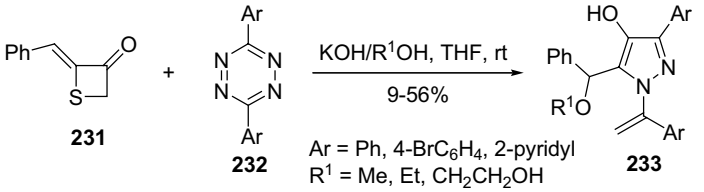
Under the action of hydrazines, pyrimidines give ring contraction transformations to pyrazoles. For instance, 5-nitropyrimidine reacts with hydrazine hydrate at room temperature for 2 days, or at 100 °C for half an hour, to yield 4-nitropyrazole in nearly quantitative yield [218]. More recent work has shown that treatment of 4-(dimethylamino)-6-chloro (or 6-methoxy)-5-nitropyrimidine with hydrazine hydrate or

methylhydrazine (2 equiv.) leads to 3,5-diamino-4-nitropyrazole and 3,5-diamino-1-methyl-4-nitropyrazole, respectively, in moderate yields (Scheme 8.66) [219]. The conversion of 5-acylpyrimidines and 5-acyl-uracils into a range of pyrazole derivatives has been reviewed [220].



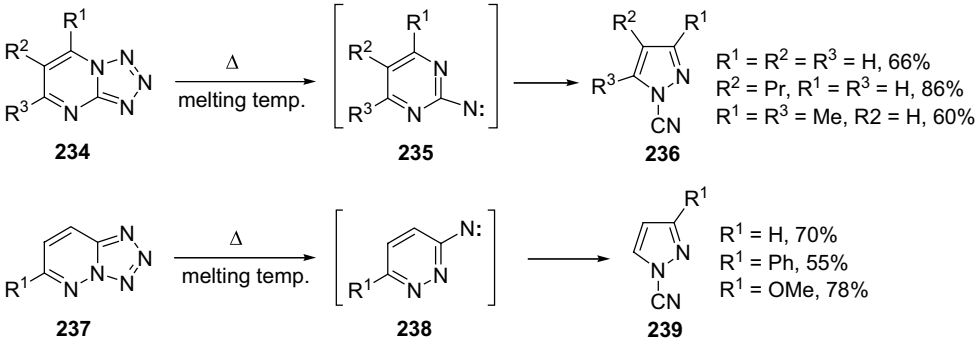
Scheme 8.66

A novel one-step synthesis route to fully substituted pyrazol-4-ols was reported recently. It is based on the reaction of thietanone **231** with 1,2,4,5-tetrazines **232** (Scheme 8.67) [221]. All of the elements of the thietanone, except its sulfur, are incorporated in the products. Quoting the authors of that work, this is a simple yet non-obvious method for the construction of pyrazol-4-ols.



Scheme 8.67

Thermolysis of the tetrazolo[1,5-*a*]pyrimidines **234** and tetrazolo[1,5-*b*]pyridazine **237** gives 1-cyanopyrazoles in good yields (Scheme 8.68) [222]. When these heterocyclic compounds are heated at about 10–20 °C over their melting temperature evolution of nitrogen is observed. The reactions are particularly fast (few minutes)



Scheme 8.68

and the pyrazole derivatives **236** and **239** are the only detectable products. Nitrenes **235** and **238** are probable intermediates in these ring contraction reactions.

8.4.2 Synthesis of Indazoles

There are several methods for the synthesis of indazoles [4, 5, 7, 9, 223, 224]. Most start from benzene derivatives, where the pyrazole ring is formed by ring closure. However, a few examples start from pyrazoles. The different possibilities for the construction of the indazole ring can be regarded according to the bonds formed, as described for the pyrazoles, and their synthesis will be organized in that way.

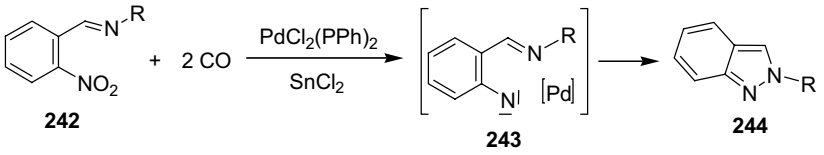
The major part of indazole ring-closure procedures involves creating a bond between the two nitrogen atoms (N−N) as the last step; nevertheless, ring closure by creation of a N−C bond through the formation of N2−C3 or N1−C7a bond is also common. A few examples involving a C3–C3a ring closure are also reported.

8.4.2.1 Formation of One N–N Bond

One of the simplest syntheses of indazoles by an N–N ring closure involves the reduction of *N-ortho*-nitrobenzaldimines **240** with triethyl phosphite, to afford 2-aryl-2*H*-indazoles **241** (Scheme 8.69) [225]. The same type of imines (**242**) can be converted into 2*H*-indazoles **244** by reductive *N*-heterocyclization of *N*-(2-nitrobenzylidene)amines **242** with the catalyst system dichlorobis(triphenylphosphine)palladium(II)–tin(II) chloride at 100 °C for 16 h under 20 kg cm^{-2} of initial carbon monoxide pressure (Scheme 8.70) [226]. Carbon monoxide operates as a reducing agent of the nitro substituent into a nitrene intermediate **243**, which strongly coordinates palladium, along with the generation of carbon dioxide. The electrophilic nitrene can then attack the nitrogen atom of the imino group to give the corresponding 2-substituted 2*H*-indazoles **244**.

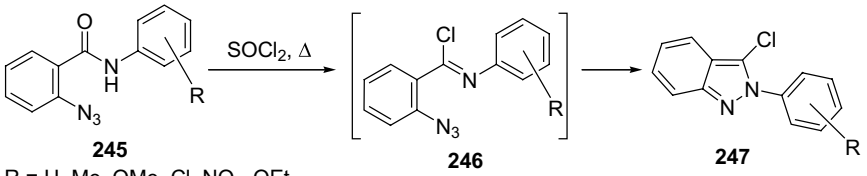
Scheme 8.69

2-Aryl-3-chloro-2*H*-indazoles **247** are obtained by the treatment of *ortho*-azidobenzanilides **245** with thionyl chloride at reflux (Scheme 8.71). The mechanism proposed for this transformation probably involves the initial formation of *ortho*-azidobenzimidoyl chlorides **246**, which cyclize into **247** by a concerted pericyclic process with loss of nitrogen [227]. The required anilides **245** can be prepared in high



R = Pr, *i*-Pr, $(CH_2)_3OMe$, Ph, 2-ClC_6H_4, 2,6-$Me_2C_6H_3$

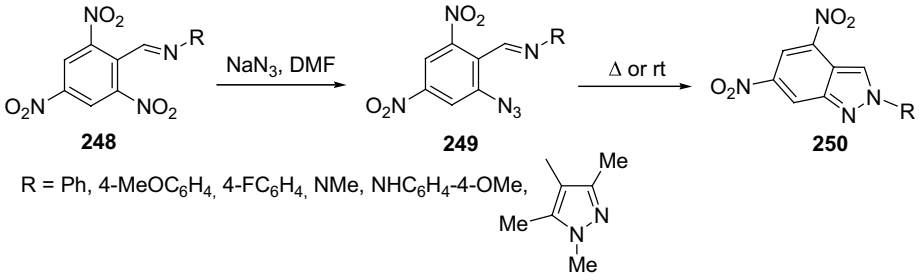
Scheme 8.70



R = H, Me, OMe, Cl, NO_2, OEt

Scheme 8.71

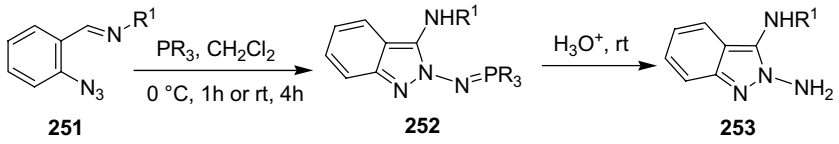
yield from the reaction of the appropriate arylamine with *ortho*-azidobenzoyl chloride in pyridine solutions. 2-Substituted-2*H*-indazoles **250** are obtained from *N*-(2,4,6-trinitrobenzylidene)anilines and hydrazones **248** by a similar synthetic process (Scheme 8.72). Treatment of **248** with sodium azide leads to the regiospecific substitution of the *ortho*-nitro group by the azido group, and the thermolysis of the obtained **249** give 4,6-dinitro-2-substituted-2*H*-indazoles **250**. In some cases, compounds **248** are converted into 2*H*-indazoles **250** even in the process of the azide formation [228]. The thermal decomposition of other 2-azidobenzylideneamine derivatives into 2-substituted-2*H*-indazoles is also described [229].



R = Ph, 4-$MeOC_6H_4$, 4-FC_6H_4, NMe, NHC_6H_4-4-OMe,

Scheme 8.72

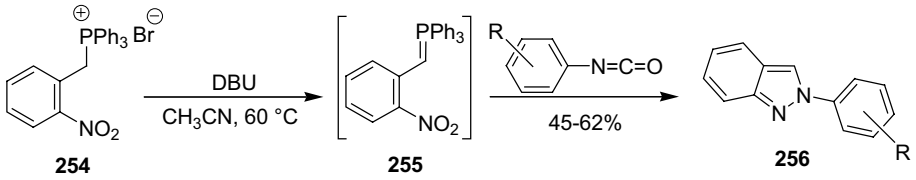
2-Amino-3-(alkyl or aryl)amino-2*H*-indazoles **253** are also prepared from the reaction of *ortho*-azidobenzaldimines **251** with tertiary phosphines followed by acid hydrolysis of the obtained iminophosphoranes **252** (Scheme 8.73) [230].



251 **252** **253**

Scheme 8.73

2-Aryl-2*H*-indazoles are also prepared by a base-catalyzed reaction of *ortho*-nitrobenzyl triphenylphosphonium bromide **254** and aryl isocyanates (Scheme 8.74) [231]. Deprotonation of the triphenylphosphonium bromide **254** with DBU gives a purple ylide **255**. When sodium hydride is used, the expected indazoles are accompanied by small amounts of 2-nitrotoluene as a by-product. Treatment of the ylide with aryl isocyanates, bearing electron-withdrawing or electron-donating substituents, affords 2-aryl-2*H*-indazoles **256** in moderate to good yields; the nitrogen of the nitro group being transformed into the indazole N1 atom.



254 **255** **256**

R = 4-OMe, 2-OMe, 4-OPh, 4-CO_2Et, 4-F, 3-CN, 3,4,5-$(OMe)_3$

Scheme 8.74

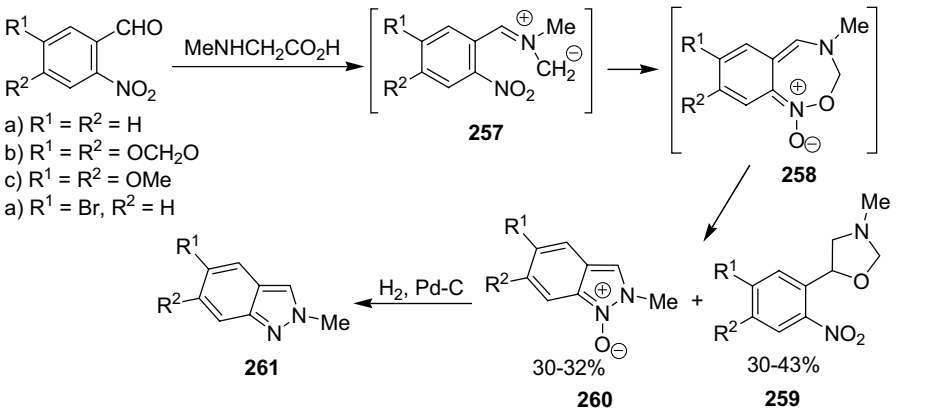
2*H*-Indazole-2-oxides **260** are obtained via the 1,7-electrocyclization of non-stabilized azomethine ylides **257**, formed from *ortho*-nitrobenzaldehydes and sarcosine, onto the nitro group to give the unstable benz-1,2,6-oxadiazepine **258**, which undergoes a ring contraction, resulting in the elimination of formaldehyde and the formation of 2-methyl-2*H*-indazole-1-oxides **260** in moderate yield (32–40%) (Scheme 8.75) [232, 233]. In these reactions, 3-methyl-5-aryl-oxazolidines **259** are also formed, resulting from the reaction of the starting *ortho*-nitrobenzaldehydes with an azomethine ylide obtained from formaldehyde generated *in situ* and the excess of sarcosine.

2*H*-Indazole-1-oxides **260** are deoxygenated in the presence of Pd–C to afford 2-methyl-2*H*-indazoles **261** [232, 233].

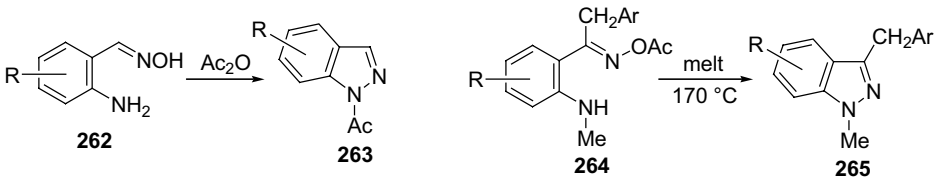
A N−N bond in the synthesis of 1-substituted-1*H*-indazoles **263** and **265** can be created by dehydration of oximes **262** with acetic anhydride [223] or by heating the oxime acetate **263** in the melt at 170 °C, under vacuum [234], respectively (Scheme 8.76).

8.4.2.2 Formation of One N2–C3 Bond

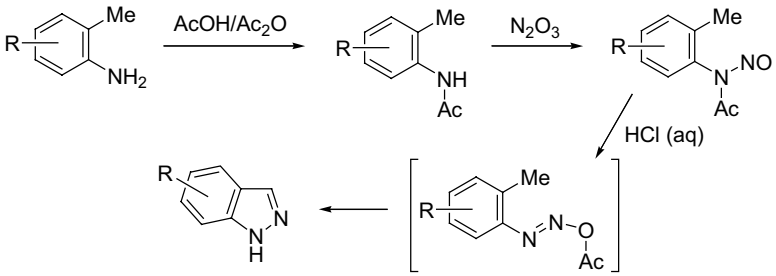
One of the most common methods for the synthesis of indazoles involving a N2−C3 ring closure starts from an *ortho*-toluidine (Scheme 8.77) [235]. Acetylation of the



Scheme 8.75



Scheme 8.76

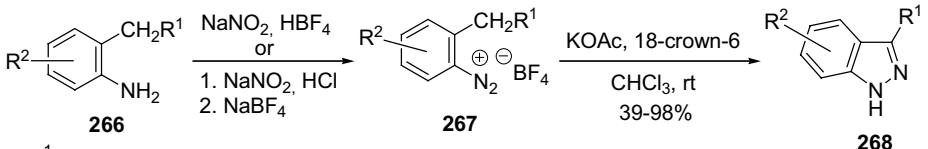


Scheme 8.77

aniline, followed by nitrosation with nitrous gases, formed by the action of nitric acid on sodium nitrite, and subsequent intramolecular azo coupling, with an initial acyl migration, leads to the 1*H*-indazoles. This classic protocol is also employed in the synthesis of several potential biologically active *N*-substituted-1*H*-indazoles, although with small changes in the experimental procedure [236–238].

The diazotization of *ortho*-toluidines in acid or neutral aqueous solution is also a well-know procedure to prepare indazole rings [239, 240]. However, the reactions are successful only for *ortho*-methylbenzenediazonium salts bearing an electron-with-

drawing nitro or halogen group on the aromatic ring and involve the isolation of an explosive *ortho*-methylbenzenediazonium chloride. The improvement of this synthetic procedure allows the preparation of 1*H*-indazoles **268** bearing electron-withdrawing or electron-donating substituents from the reaction of non-explosive *ortho*-alkylbenzenediazonium tetrafluoroborates **267** (Scheme 8.78) [241, 242]. *ortho*-Alkylbenzenediazonium tetrafluoroborates **267** are obtained from the reaction of *ortho*-alkylanilines **266** with sodium nitrite in fluoroboric acid or sodium nitrite in hydrochloric acid followed by the addition of sodium tetrafluoroborate. Treatment of **267** with two equivalents of potassium acetate, 5 mol% of 18-crown-6 in ethanol-free chloroform at room temperature affords 1*H*-indazoles **268** in moderate to good yields. The presence of the phase transfer catalyst 18-crown-6 is essential; in its absence no indazole is formed.



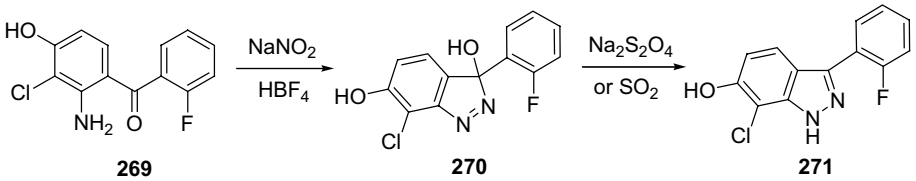
266 **267** **268**

R^1 = H, Me

R^2 = H, 4-NO_2, 5-NO_2, 6-NO_2, 4-Cl, 5-Cl, 3-Me, 4-Me, 5-Me, 6-Me, 7-Me, 4-OMe

Scheme 8.78

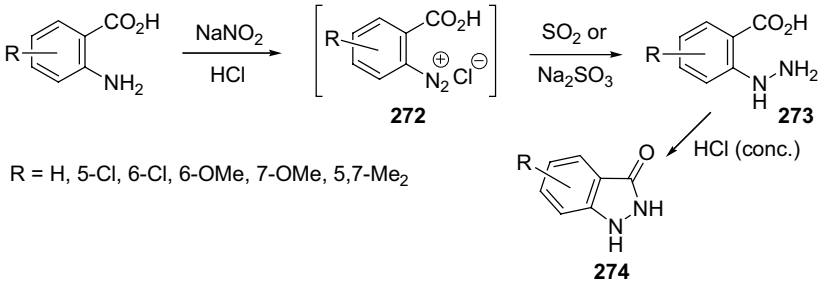
3-(2-Fluorophenyl)-1*H*-indazole **271** is prepared from the diazotization of the corresponding 2-aminobenzophenone **269** under strongly acidic conditions (HBF_4), followed by reduction with sodium dithionite (Scheme 8.79) [243]. Zhang *et al.* describe a similar synthesis, save the reduction of the intermediate **270**, which is made with SO_2 [244].



269 **270** **271**

Scheme 8.79

The most common synthesis of 1,2-dihydro-3*H*-indazol-3-ones **274** (or their enolic forms 3-hydroxy-1*H*-indazoles) starts from diazonium salts of anthranilic acid **272**, which are reduced with sulfites or sulfur dioxide to the corresponding *ortho*-hydrazinobenzoic acid derivatives **273** (Scheme 8.80) [224]. Cyclization to **274** may be carried out with phosphoryl chloride, by boiling in nitrobenzene or refluxing in an

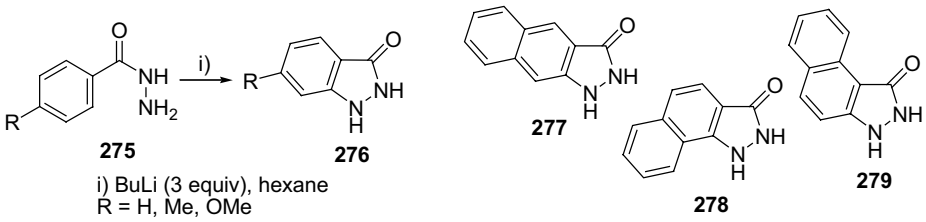


Scheme 8.80

aqueous solution of either acidic or buffered with sodium acetate. A variation of this method consists in the nitrosation of *N*-substituted anthranilic acids or esters, with nitrous acid, followed by reduction of the formed nitroso derivatives. This reduction must be done with sodium hydrosulfide when the *N*-substituent is a hydrogen or halogen atom or an alkyl group; for compounds with an *N*-aryl group as substituent the reduction must be carried out with zinc in acetic acid or lithium aluminium hydride [224].

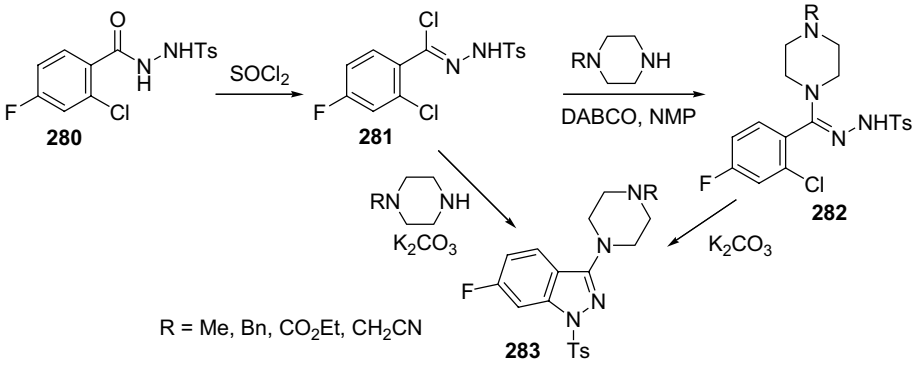
8.4.2.3 **Formation of One N1–C7a Bond**

Aromatic hydrazides are converted into indazol-3-ones when treated with an excess of butyllithium (Scheme 8.81) [245]. Benzoylhydrazines **275** afford 2*H*-indazol-3-ones **276** in 61–80% yield. The same transformation has been carried out replacing butyllithium by sodium or potassium hydride, but the corresponding 2*H*-indazol-3-one was obtained in lower yields (49 and 56%, respectively, when R=H). 2*H*-Indazol-3-ones **277–279** are obtained by the same procedure from appropriate aromatic hydrazides, while aliphatic and heterocyclic hydrazides afford the corresponding aldehydes [245].



Scheme 8.81

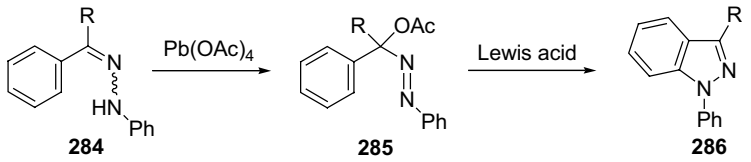
3-Substituted-1-tosyl-6-fluoro-1*H*-indazoles **283** are obtained from 2-chlorobenzoylhydrazides **280** (Scheme 8.82) [246]. Treatment of **280** with thionyl chloride affords the corresponding imidoyl chloride **281**, which reacts with piperazine derivatives, in the presence of DABCO, to yield imidates **282**. This is a trick reaction, the best yields being obtained when 1.1 molar equivalents of piperazine derivatives



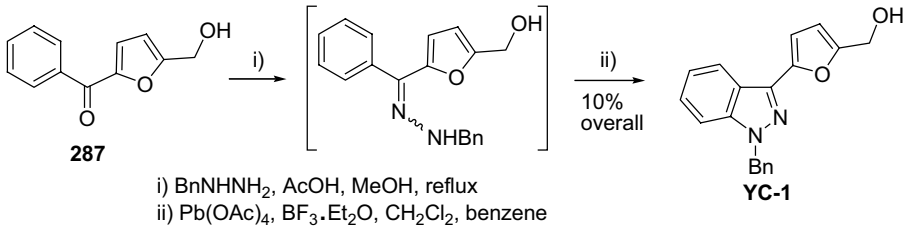
Scheme 8.82

and 0.7 molar equivalents of DABCO are used; the presence of an amine more basic than piperazine is required. However, imidoyl chlorides **281** are also transformed into 1*H*-indazoles **283** in one-pot transformation; after the *in situ* formation of imidate **282**, milled potassium carbonate is added to the mixture and the 3-substituted-1-tosyl-6-fluoro-1*H*-indazoles **283** are obtained.

Another general method involving the formation of the N1−C7a bond consists in the cyclization of phenylhydrazone derivatives. Lead tetraacetate oxidation of phenyl ketone phenylhydrazones **284** leads to the formation of azoacetates **285**, which furnish 1-phenyl-1*H*-indazoles **286** when treated with Lewis acids (e.g., $AlCl_3$, $BF_3.Et_2O$) (Scheme 8.83) [247–252]. 1-Benzyl-3-(5-hydroxymethyl-2-furyl)indazole **YC-1**, an indazole possessing important biological applications, is obtained from the hydrazone of ketone **287**, although in a modest yield (Scheme 8.84) [253]. **YC-1** is obtained in higher yield starting from the unsubstituted-2*H*-indazol-3-one [254].

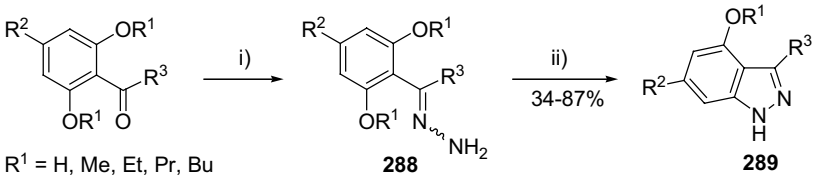


Scheme 8.83



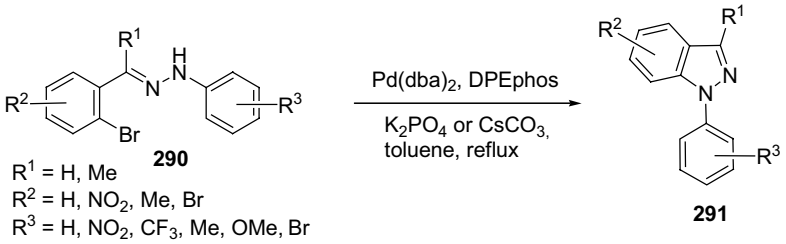
Scheme 8.84

A variation of this method consists in the cyclization of *para*-nitrophenylhydrazones of several acetophenones, benzophenones and benzaldehyde by reaction with polyphosphoric acid at high temperature (150–165 °C), affording 1-(4-nitrophenyl)-1*H*-indazoles [255, 256]. Another variation involves the cyclization of arylhydrazines possessing a leaving group in the *ortho* position (F, NO_2, OH or OR) [243, 257–261]. These methods also require harsh experimental conditions, such as very high temperatures (200–270 °C), although there are references to the synthesis of indazoles by the reaction of *ortho*-fluorobenzophenone or pentafluoroacetophenone with hydrazine in refluxing ethanol or toluene, respectively [243, 262]. Treatment of 2′,6′-(dialkoxy- or dihydroxy)acetophenone or benzophenone hydrazones **288** with polyphosphoric acid gives 4-(alkoxy- or hydroxy)-3-substituted-1*H*-indazoles **289** in moderate to good yields (Scheme 8.85) [263, 264].



Scheme 8.85

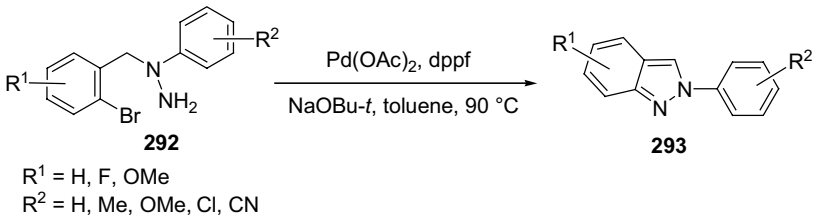
The palladium-catalyzed cyclization of arylhydrazones of 2-bromobenzaldehydes and 2-bromoacetophenones **290** constitutes an easy, efficient method for the synthesis of 1-aryl-1*H*-indazoles **291** (Scheme 8.86) [265–267]. *N*-Arylindazole derivatives are synthesized in a one-pot reaction of 2-bromobenzaldehydes with arylhydrazines in the presence of a catalytic amount of a palladium catalyst, a phosphorous chelating ligand and sodium *tert*-butoxide [265]. The use of preformed hydrazones is the key to obtaining higher yields, milder reaction conditions and to extend the scope of this method to heterocyclic substrates and to 2-chlorobenzaldehyde [267]. In addition, better yields can be obtained using $Pd(dba)_2$ and chelating phosphines



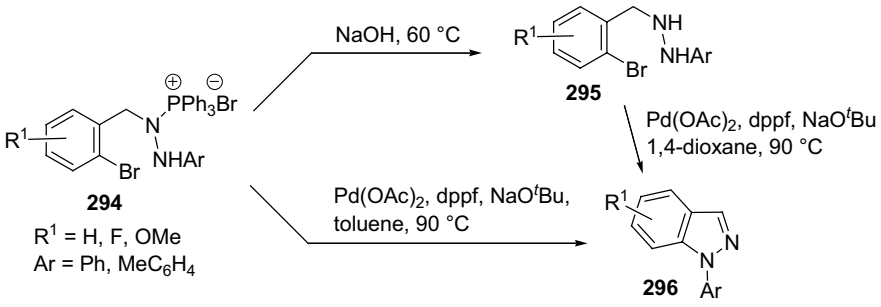
Scheme 8.86

(*rac*-BINAP, DPEphos and dppf) in the presence of a base, such as caesium carbonate or potassium phosphate. This method is applicable for the synthesis of a wide range of 1-aryl-1*H*-indazoles bearing electron-donating and electron-withdrawing substituents.

Various 2-aryl-2*H*-indazoles **293** and 1-aryl-1*H*-indazoles **296** can be prepared by the palladium catalyzed intramolecular amination of the corresponding *N*-aryl-*N*-(2-bromobenzyl)hydrazines **292** and *N*-aryl-*N*′-(2-bromobenzyl)hydrazines **295**, followed by spontaneous aromatization of the formed aryl-substituted-2,3-dihydro-1*H*-indazoles (Schemes 8.87 and 8.88, respectively) [268, 269]. [*N*-Aryl-*N*′-(2-bromobenzyl)hydrazinato]triphenylphosphonium bromides **294**, intermediates in the synthesis of **295**, also underwent cyclization under suitable conditions to afford 1-aryl-1*H*-indazoles **296** (Scheme 8.88). Toluene is used as solvent when starting with *N*-aryl-*N*′-(2-bromobenzyl)hydrazines **295** and 1,4-dioxane with [*N*-aryl-*N*′-(2-bromobenzyl)hydrazinato]triphenylphosphonium bromides **294** due to the insolubility of the latter in toluene.

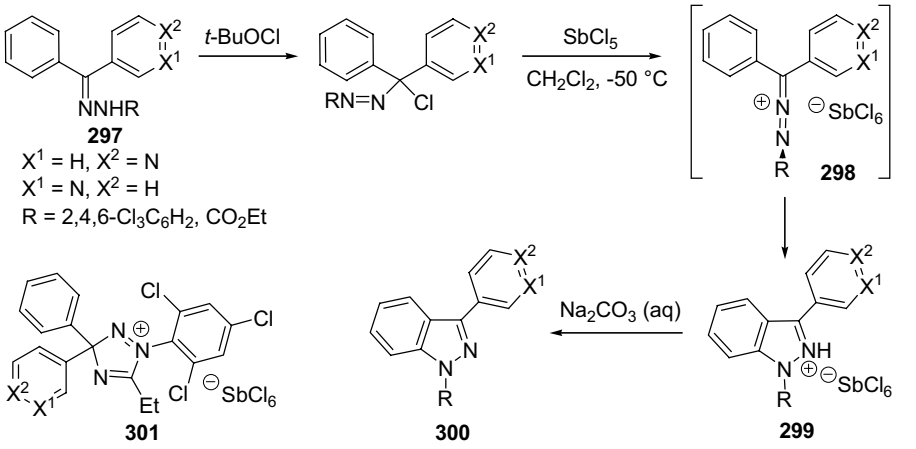


Scheme 8.87



Scheme 8.88

1-Aza-2-azonia allene salts **298**, formed by oxidation of hydrazones **297** with *tert*-butyl hypochloride followed by treatment with $SbCl_5$ in dichloromethane at −50 °C, can be used as starting materials for the preparation of 1-substituted-1*H*-indazoles **300** (Scheme 8.89) [270]. Treatment of **298** with $SbCl_5$ induces an intramolecular cyclization to afford 3-pyridyl-1*H*-indazolium hexachloroantimonates **299**. It is worth



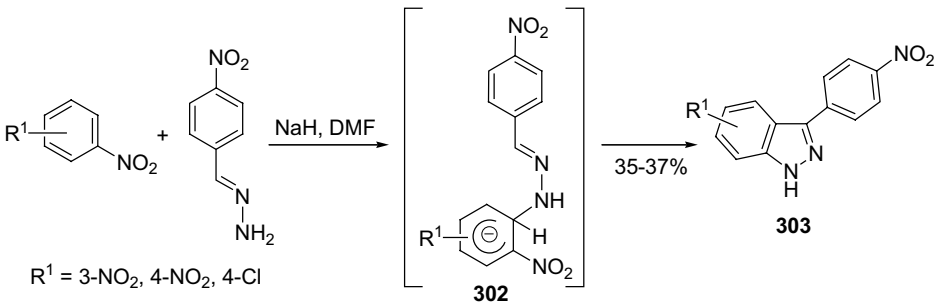
Scheme 8.89

noting the complete regioselectivity of the cycloaddition. The reaction of 1-aza-2-azonia allene salts **298**, bearing a trichloropyridyl substituent, with propionitrile gives 3*H*-1,2,4-triazolium hexachloroantimonates **301** instead of **300**.

8.4.2.4 Formation of One C3—C3a Bond

The cyclization of *para*-nitrophenylhydrazones of ketones and aldehydes with polyphosphoric acid gives 1-arylindazoles through a C3–C3a ring closure [271], while *N*′, *N*′-diphenylhydrazides are converted into 1-phenylindazoles by means of trifluoromethanesulfonic anhydride [yields from 2% (R=H) to 50% (R=Ph)] [272].

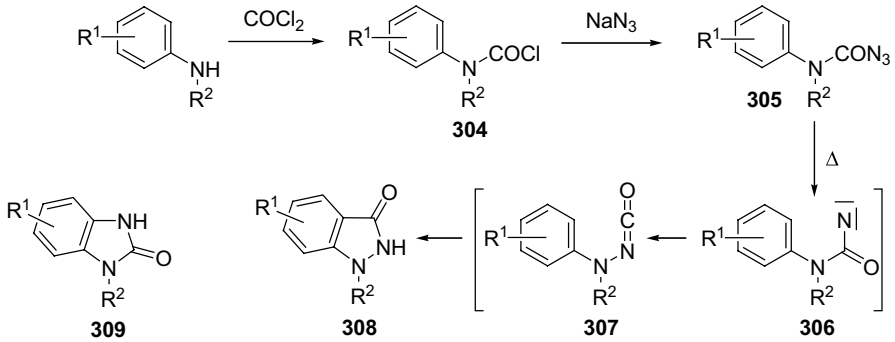
1*H*-Indazoles **303** can also be obtained in moderate yield from the reaction of nitroarenes with aromatic hydrazones in alkaline medium (Scheme 8.90) [273]. The presence of electron-withdrawing groups in both reagents is required for the formation of 1*H*-indazoles **303**. Other substituents originate displacement of the chlorine atom or hydrogen atom in the 4-position of the nitroarene by the hydrazone anion. Although the mechanism of this reaction is not clear, a possible reaction sequence could be described as an initial attack of the hydrazone anion to



Scheme 8.90

the *ortho*-position of the nitroarene, to give a Meisenheimer intermediate (**302**). The presence of an electron-withdrawing substituent on the nitroarene facilitates the attack of the hydrazone anion and stabilizes the anion **302**. Displacement of the nitro group leads to indazoles **303**.

1,2-Dihydro-3*H*-indazol-3-ones **308** are also obtained from anilines (Scheme 8.91). Treatment of substituted anilines with phosgene in toluene affords carbamoyl chlorides **304**, which react with sodium azide in methanol to give carbamoyl azides **305**. Thermal cyclization of **305** gives indazol-3-ones **308** [224, 274, 275]. This cyclization must proceed via intermediates **306**, which are converted into isocyanates **307**, which then cyclize to indazol-3-ones **308**. The existence of intermediate **306** is confirmed by the concomitant formation of benzimidazolinones **309** [224, 274–276].



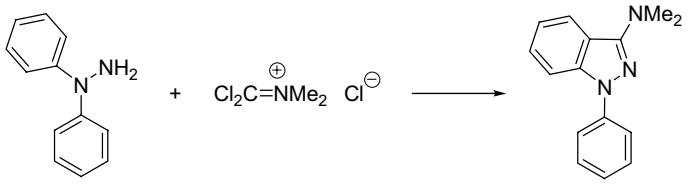
R^1 = H, Cl, NO_2
R^2 = H, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-$OMeC_6H_4$, Bu

Scheme 8.91

8.4.2.5 Formation of Two Bonds

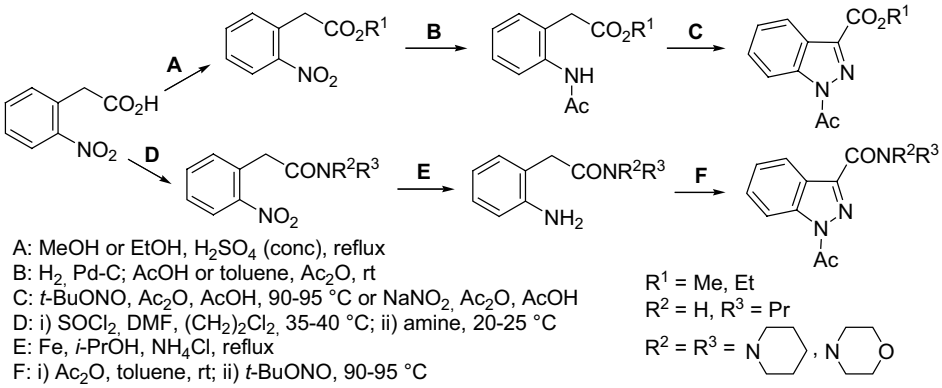
8.4.2.5.1 From 4 + 1 Atom Fragments

Formation of One C–N and One C–C Bond [C-C-N-N + C] 3-Dimethylamino-1-phenyl-1*H*-indazoles are obtained from the reaction of *N,N*-diphenylhydrazine with phosgene iminium chloride (Scheme 8.92) [277].



Scheme 8.92

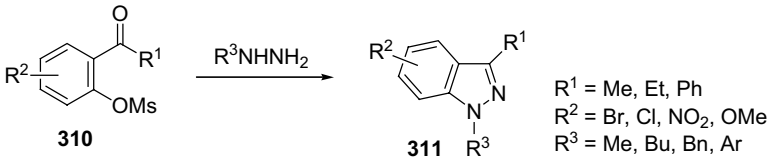
Formation of One C–N and One N–N Bond [C-C-C-N + N] Several 1*H*-indazol-3-carboxamide or carboxylate derivatives are prepared from 2-nitrophenylacetic acid derivatives (Scheme 8.93) [278, 279]. The nitro group is reduced to the amino derivative, then *tert*-butyl nitrite or sodium nitrite in acetic acid promotes the cyclization to the corresponding 1*H*-indazole. The hydrolysis of the ester and amide groups with a great excess of sodium hydroxide in water affords the corresponding 1*H*-indazol-3-carboxylic acids.



Scheme 8.93

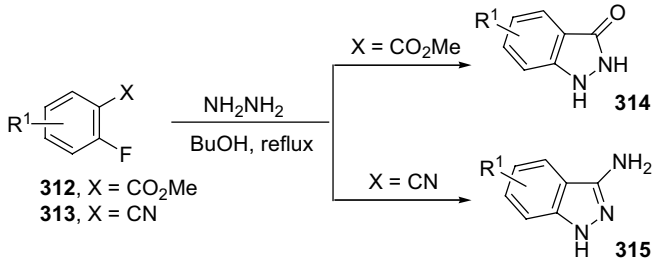
8.4.2.5.2 From 3 + 2 Atom Fragments

Formation of Two C–N Bonds [C-C-C + N-N] Like pyrazoles, indazoles can be prepared by the [C-C-C + N-N] approach. The standard method consists of the condensation of a 1,3-difunctional compound with hydrazine or hydrazine derivatives. 1*H*-indazoles **311** are synthesized by cyclization of hydrazones of 2-mesyloxyphenyl ketones **310** (Scheme 8.94) [280]. Conversion of the appropriate mesylate **310** into the desired 1*H*-indazoles **311**, by the reaction with hydrazine derivatives, proceeds through the hydrazone intermediate, which cyclizes to indazoles by nucleophilic aromatic substitution of the mesylate group. The reaction needs a slightly acidic medium to catalyze the conversion of the ketone into the hydrazone and it is imperative the use of a Dean-Stark apparatus to eliminate the water, to avoid mesylate hydrolysis to the corresponding phenol, which does not cyclize to indazoles under these reaction conditions.



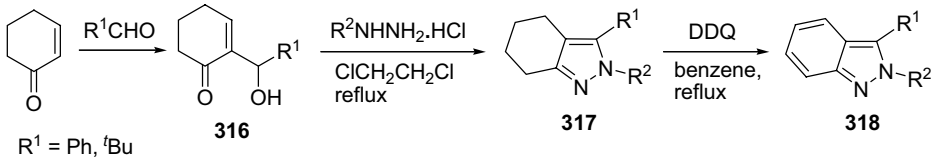
Scheme 8.94

A related method involves the reaction of benzoic acid derivatives bearing a leaving group in the *ortho* position with hydrazine. For instance, treatment of methyl 2-fluorobenzoate **312** with hydrazine in refluxing butanol gives the corresponding 1*H*-indazole-3-ones **314** (Scheme 8.95) [261]. Under identical conditions, *ortho*-fluorobenzonitriles **313** afford 3-amino-1*H*-indazoles **315** (Scheme 8.95) [237, 281, 282].

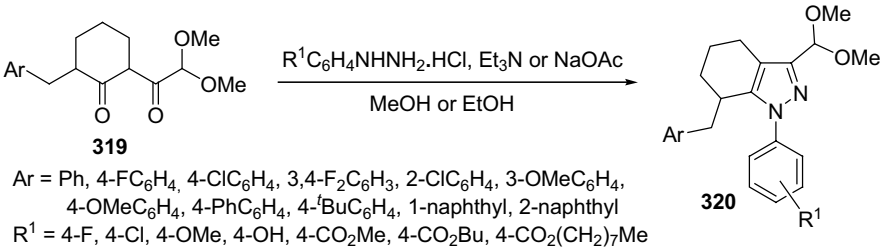


Scheme 8.95

4,5,6,7-Tetrahydro-2*H*-indazoles **317** are obtained from the reaction of the Baylis–Hillman adducts of cyclohexen-1-ones (**316**) with hydrazine derivatives. These tetrahydroindazoles (**317**) are oxidized to 2-substituted-2*H*-indazoles **318** by treatment with DDQ (Scheme 8.96) [283]. 3-Substituted-1-aryl-4,5,6,7-tetrahydro-1*H*-indazoles **320** are obtained by the reaction of diketone **319** with arylhydrazines (Scheme 8.97) [284]. Various 4,5-dihydro-1*H*-benzo[*g*]indazole-based ligands for cannabinoid receptors have been prepared by a similar procedure [285]. Tetrahydro-



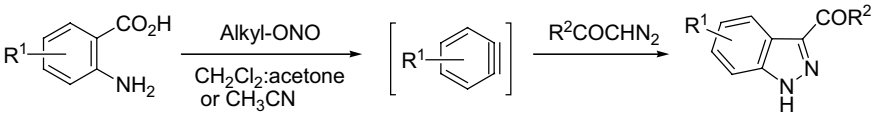
Scheme 8.96



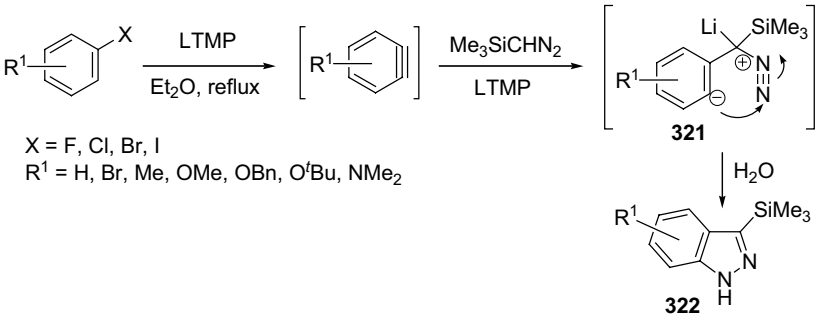
Scheme 8.97

and hexahydro-1*H*- and 2*H*-indazole derivatives are also obtained from the reaction of appropriate chalcone-type compounds or β-diketones with hydrazine derivatives [283, 284, 286–288].

Formation of One C–C and One C–N Bond [C-N-N + C-C] The 1,3-dipolar cycloaddition reactions of diazo compounds with benzyne is a versatile method for the synthesis of indazoles (Scheme 8.98) [289–291]. Benzyne is conveniently generated *in situ* from the reaction of anthranilic acid with alkyl nitrite in an aprotic media (mixtures of dichloromethane : acetone or acetonitrile) [292]. Aoyama *et al.* describe the synthesis of 3-trimethylsilyl-1*H*-indazoles **322** from the [3 + 2] cycloaddition reactions of lithium trimethylsilyldiazomethane with benzyne, generated from halobenzenes and lithium 2,2,6,6-tetramethylpyperidine (LTMP) (Scheme 8.99) [293]. LDA, a less hindered base, can also be used, but a significant decrease in the yield of indazole is observed. The reaction mechanism involves a nucleophilic attack of $(CH_3)_3SiC(Li)N_2$ to the benzyne, subsequent cyclization of the indazole intermediate **321** and reaction with water to afford 3-trimethylsilyl-1*H*-indazoles **322** (Scheme 8.99).



Scheme 8.98

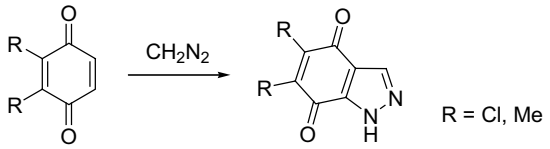


Scheme 8.99

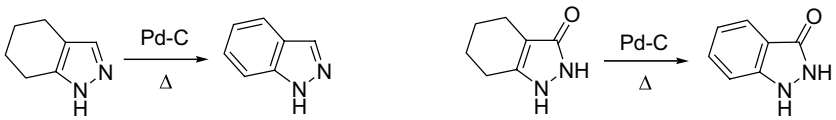
1,3-Dipolar cycloaddition reactions of diazomethane to quinones originate the corresponding 1*H*-indazole-4,7-diones (Scheme 8.100) [294, 295].

8.4.2.6 **Other Synthetic Methods**

Dehydrogenation of tetrahydro-1*H*-indazoles in boiling decalin with 5% palladium on activated carbon gives the corresponding 1*H*-indazoles (Scheme 8.101) [296].

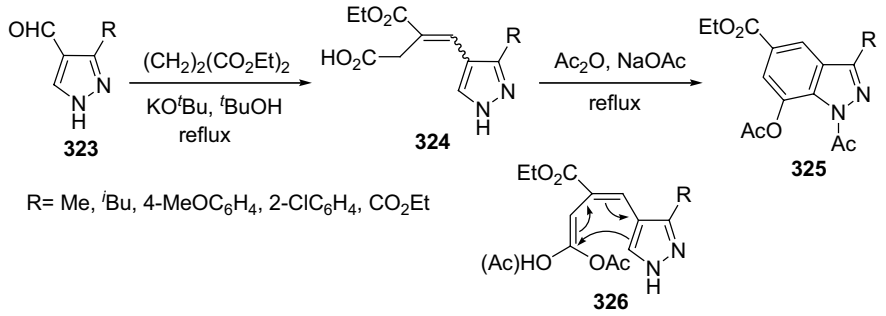


Scheme 8.100



Scheme 8.101

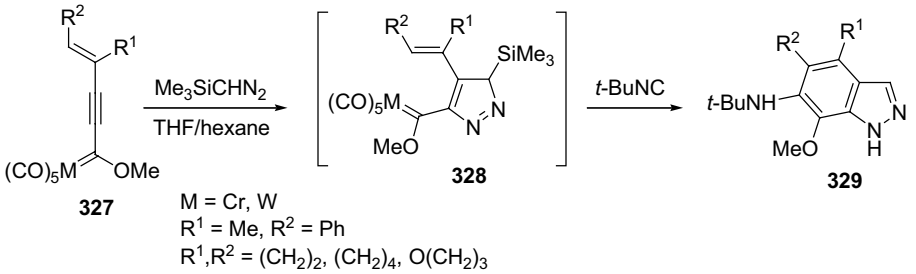
Most syntheses of indazoles proceed from benzene derivatives, where the pyrazole ring is generated by ring closure. However, a few examples of the synthesis of indazoles starting from pyrazoles are known [297–299]. One of them involves the condensation of 3-substituted pyrazole-4-carbaldehydes **323** with diethyl succinate in the presence of potassium *tert*-butoxide, affording esters **324** (mixture of geometric isomers), which undergo cyclization to 1*H*-indazoles **325** by reaction with sodium acetate in acetic anhydride (Scheme 8.102) [297]. The ring closure step probably takes place by an electrocyclization process after the enolization of the mixed anhydride **326**.



Scheme 8.102

Another example of synthesis of indazoles from pyrazoles consists in the reaction of stable chromium and tungsten Fischer dienyl carbenes **328**, formed from a [3 + 2] cycloaddition reaction of alkenylethynyl carbene **327** with trimethylsilyl diazomethane, with isocyanides to give highly functionalized 1*H*-indazoles **329** (Scheme 8.103) [298].

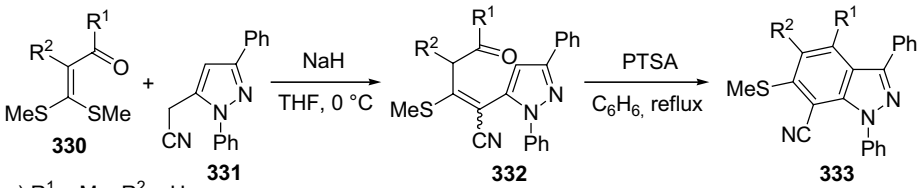
1,3-Diphenyl-1*H*-indazoles **333** are obtained from base induced addition–elimination of 5-cyanomethyl-1,3-diphenylpyrazoles **331** to various α-oxoketene



327 **328** **329**

Scheme 8.103

dimethylthio acetals **330**, followed by acid-assisted cycloaromatization of the resulting adducts **332** (Scheme 8.104) [299]. The cycloaromatization of adducts **332** is more efficient (in terms of yield and work-up) in the presence of *para*-toluenesulfonic acid (PTSA) than with various protic and Lewis acids. By using cyclic of α-oxoketene dimethylthio acetals it is possible to obtain annulated indazoles.



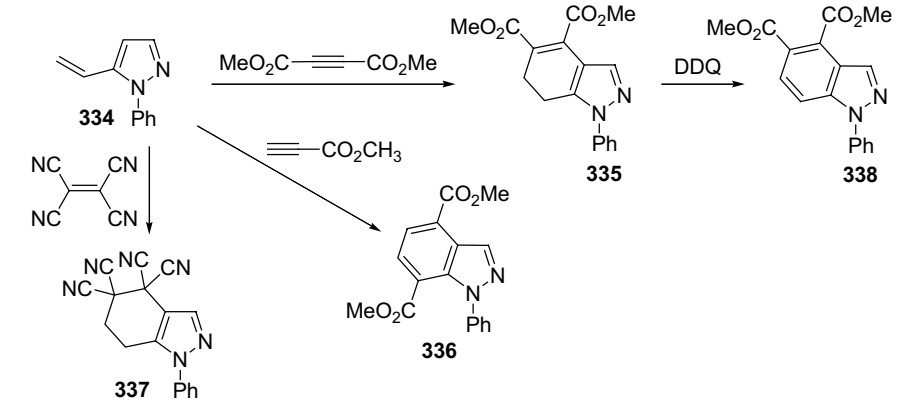
330 **331** **332** **333**

Scheme 8.104

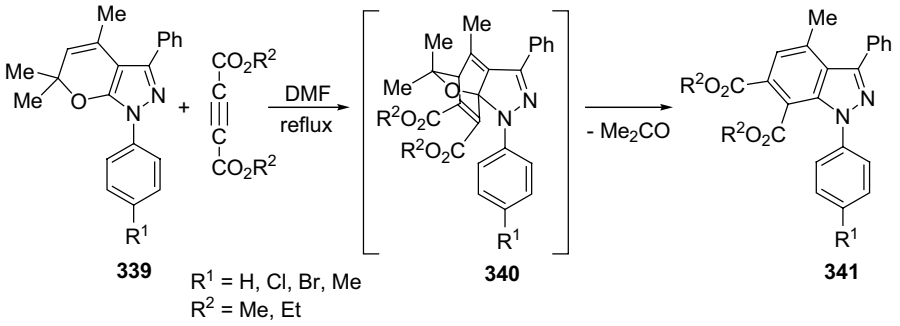
1-Phenyl-5-vinyl-1*H*-pyrazole (**334**) gives cycloaddition reactions with several dienophiles to furnish 1-phenyl-1*H*-indazole derivatives **335–337** (Scheme 8.105) [300]. The reaction of **334** with methyl propiolate affords 1-phenyl-1*H*-indazole **336** as a result of a double Diels–Alder cycloaddition with extrusion of ethylene. 1-Phenyl-1*H*-indazole **338** is obtained by oxidation of its dihydro derivative **335** by treatment with DDQ.

Highly substituted-1*H*-indazoles **341** have been obtained from the cycloaddition reaction of 1-aryl-3-phenyl-1,6-dihydropyrano[2,3-*c*]pyrazoles **339** with dialkyl acetylenedicarboxylates in refluxing DMF (Scheme 8.106) [301]. The resulting cycloadducts **340** spontaneously eliminate acetone to give 1-aryl-6,7-dialkoxycarbonyl-4-methyl-3-phenyl-1*H*-indazoles **341**.

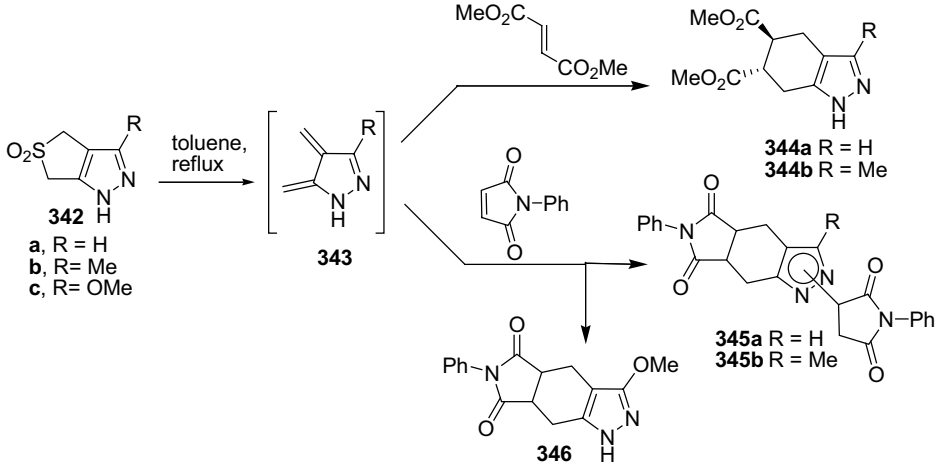
N-Unsubstituted pyrazole *ortho*-quinodimethanes **343**, generated by thermal extrusion of sulfur dioxide from *NH*-pyrazole-fused 3-sulfolenes **342**, react with dienophiles to give 4,5,6,7-tetrahydro-1*H*-indazoles **344–346** (Scheme 8.107) [302]. Thermolysis of sulfones **342a**,**b** in refluxing toluene or chlorobenzene in the presence



Scheme 8.105



Scheme 8.106

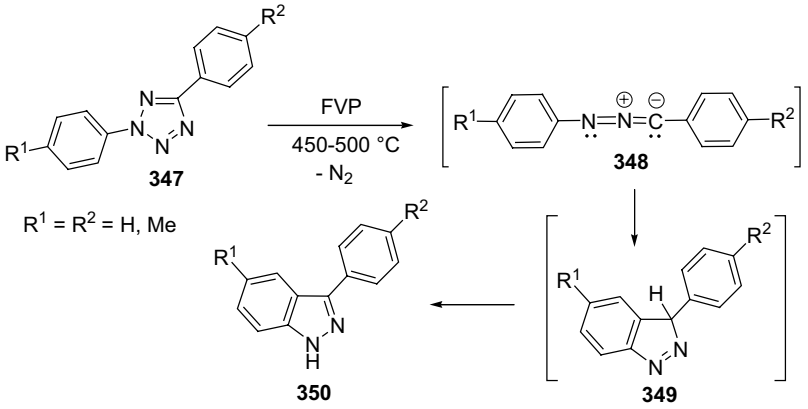


Scheme 8.107

of dimethyl fumarate gives the 1 : 1 Diels–Alder cycloadducts **344a,b** without the competition of the Michael addition. However, thermolysis of the same sulfones in the presence of *N*-phenylmaleimide gives the 2 : 1 cycloadducts **345a,b**. Adducts **345a, b** were obtained as diastereomeric mixtures of the 1- and 2-substituted indazole isomers. Thermolysis of sulfone **342c** in the presence of *N*-phenylmaleimide gives the tetrahydro-1*H*-indazole **346** as the only product.

8.4.2.7 Ring Synthesis from Heterocycles

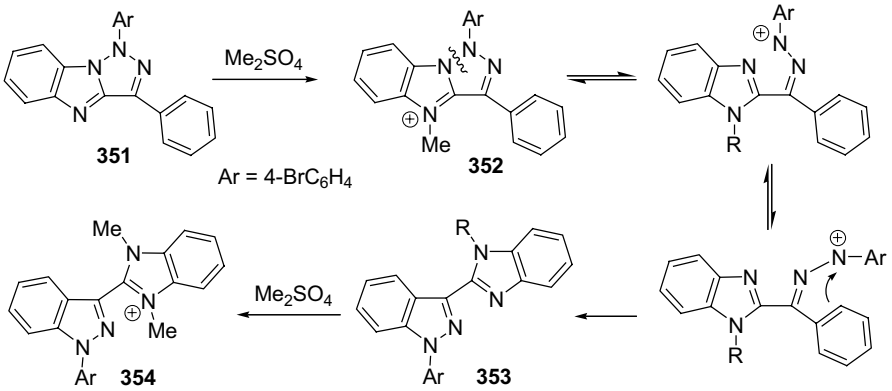
Flash vacuum pyrolysis of 2,5-diaryltetrazoles **347** at 400–500 °C gives almost quantitative yields of 3-aryl-1*H*-indazoles **350** (Scheme 8.108) [303]. Under these conditions, tetrazoles **347** eliminate nitrogen, leading to nitrilimines **348**, which undergo cyclization onto the remote aromatic ring to afford 3-aryl-3*H*-indazoles **349**, which spontaneously isomerize to 3-aryl-1*H*-indazoles **350**. 3-Substituted-1*H*-indazoles are also prepared by flash thermolysis (400–500 °C) of 2-substituted-4-phenyl-1,3,4-oxadiazolin-5-ones [303, 304]. In this case, the same type of nitrilimines is also involved, being generated by elimination of carbon dioxide.



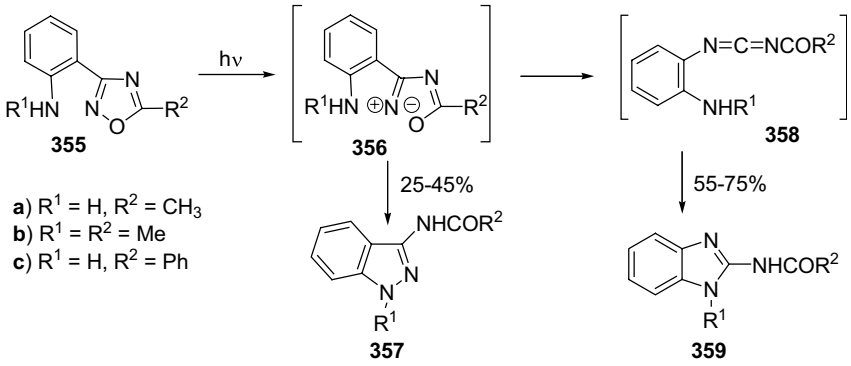
Scheme 8.108

Treatment of 1*H*-[1-3]triazolo[1,5-*a*]benzimidazole **351** with dimethyl sulfate at elevated temperature results in the formation of benzimidazolyl-1*H*-indazole **354** [305]. Instead of the simple methylation to yield **352**, a ring opening reaction take place and, via formation of a nitrenium cation, indazole **353** is formed (Scheme 8.109). This intermediate is then alkylated to the dimethyl salt **354**. Similar transformations occur when **351** is treated with trifluoroacetic acid at reflux, resulting in the formation of 1*H*-indazole **353** (R=H) [306].

The photochemistry of some 3,5-disubstituted-1,2,4-oxadiazoles **355** bearing a nitrogen nucleophilic group, such as an *ortho*-aminophenyl moiety, at C3 of the oxadiazole ring leads to the concomitant formation of indazoles **357** and benzimidazoles **359** (Scheme 8.110) [307]. The photochemistry of **355** is characterized by



Scheme 8.109



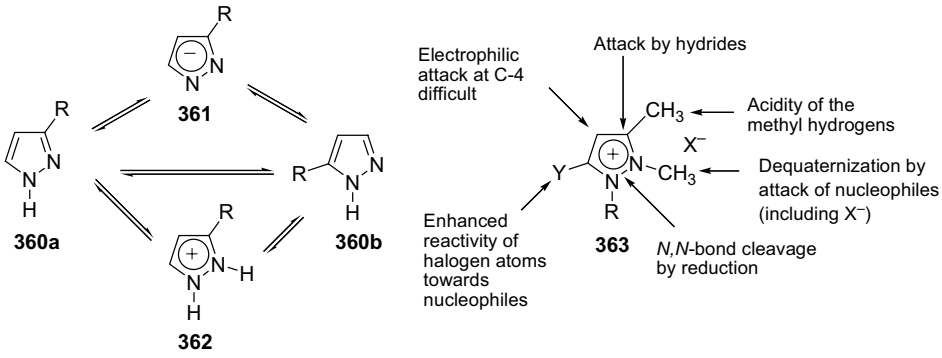
Scheme 8.110

photolysis of the O−N bond to give open compounds **356**, which rearrange to 1*H*-indazoles **357** through the N−N bond closure. The photolytic species **356** can also be converted into carbodiimides **358**, precursors of the benzimidazoles **359**.

1*H*-Indazoles **357** can also be obtained from 3,5-disubstituted 1,2,4-oxadiazoles **355** in almost quantitative yield, by heating these compounds, without solvent, at a temperature much higher than their melting points [308].

8.5 Reactivity

The reactivity of pyrazoles is related to the tautomerism of the neutral forms **360** and to their acid (conjugated anion **361**) and basic properties (conjugated cation **362**) (Scheme 8.111). It is very important when discussing the reactivity of pyrazoles and indazoles to determine the form that reacts. The "pyridinic" N2 atom is susceptible to



Scheme 8.111

electrophilic attack and the "pyrrolic" N1 is unreactive, but the N1 proton can be removed by bases to afford the anion **361**. Electrophilic attack on C4 is generally preferred. Since indazoles have the pyrazolic C4 position substituted, electrophilic attack on indazoles takes place in the 3-position and in the benzene ring (positions 5 and 7).

We have also represented in Scheme 8.111 the effect of a positive charge (pyrazolium salts) on pyrazole reactivity. In contrast, the anions (pyrazolates) show the expected inversion of reactivity when compared with the cations. Note that in general *N*-alkyl pyrazoles and indazoles are prepared from the corresponding anions.

8.5.1 Reactions with Electrophilic Reagents

8.5.1.1 Electrophilic Attack at Nitrogen

This is the most characteristic reaction of pyrazoles. The reactivity of the nitrogen atom in neutral pyrazoles and indazoles corresponds to that of pyridine N atom. Notably, the apparent rate of formation of an *N*-substituted derivative depends more on the rate of reaction of a given tautomer than on the tautomeric equilibrium constant.

8.5.1.1.1 **Basicity of Azoles** Pyrazoles are medium to weak bases, much weaker than for instance imidazole ($pK_a = 6.95$). Some significant values are reported in Table 8.4 from a large collection described in Reference [309]. In general, the effect of the substituents is additive and the acidity and basicity pK_as are linearly related [309].

8.5.1.1.2 **Acidity of Azoles** Pyrazole and indazole are very weak acids, unless they bear a strong EWG such as NO_2 (Table 8.4).

8.5.1.1.3 **Metal Ions (see also Section 8.6.4.3)** Pyrazoles and indazoles form sodium, potassium and silver salts that are hydrolyzed to a large extent by water. The resulting anions react very readily with electrophiles. Pyrazoles, pyrazolate anions

Table 8.4 pK_a for proton addition (basicity) and proton loss (acidity).

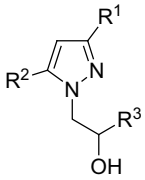
Azole	pK_a (basicity)	pK_a (acidity)
Pyrazole	2.52	14.21
3(5)-Methyl	3.32	—
4-Methyl	3.09	—
3,4,5-Trimethyl	4.63	—
4-Nitro	−1.96	9.05
3,5-Dinitro	—	3.14
1-Methyl	2.09	—
1-Phenyl	0.44	—
Indazole	1.31	13.80
1-Methyl	0.42	—
2-Methyl	2.02	—

and polypyrazolylborates (scorpionates) [310] are much used ligands in coordination chemistry.

8.5.1.1.4 ***N*-Alkylation and *N*-Arylation** *N*-Alkylation is one of the most important and most studied reactions of pyrazoles and indazoles. Alkylations have been carried out using alkyl halides (usually iodides and bromides), dialkyl sulfates, arenesulfonates, diazomethane and dialkyl phosphates. Microwave irradiation has proved very effective for carrying out this reaction [311, 312]. With neutral pyrazoles and alkyl halides, the alkylation yields salts of the corresponding acids.

The orientation of the entering group strongly depends on the substituents on the pyrazole ring, on the nature of the alkylating agent and on the experimental conditions. Phase transfer catalysis has been used with success to prepare *N*-substituted pyrazoles [4]. When polyhalogenoalkanes are used as alkylating agents, poly-*N*-pyrazolylalkanes (useful ligands in coordination chemistry) are obtained.

Only activated halogenated benzenes (*para*-fluoronitrobenzene, 1-fluoro-2,4-dinitrobenzene, picryl chloride) [313] and halogeno substituted heterocycles (such as 3,6-dichloropyridazine, cyanuric chloride and brominated derivatives) [314] react with pyrazoles and indazoles [4]. Pyrazolate anions react with hexafluorobenzene to yield hexapyrazolylbenzenes (propellenes, Section 8.6.4.3) [5, 315]. An efficient synthesis of β-hydroxyethyl-pyrazoles **364** and **365** from propylene and styrene oxide using Cs_2CO_3 has been reported [316].



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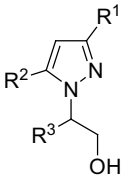
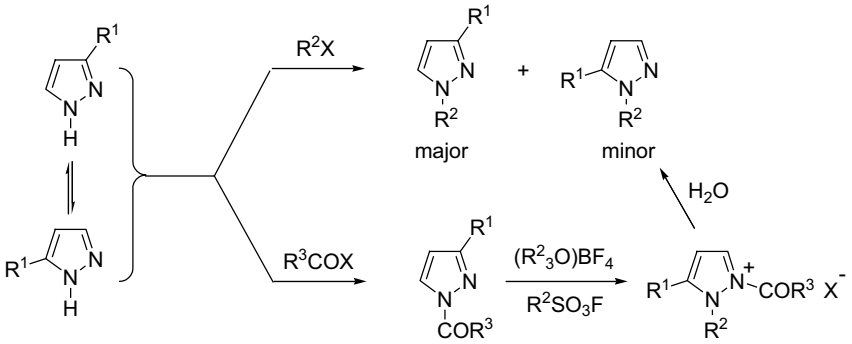


365

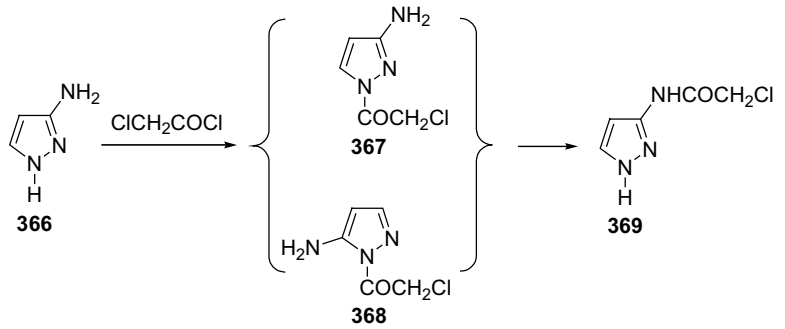
Through the use of Bi, B and Pb derivatives and copper-catalyzed cross-coupling reactions it is possible to make N–C bonds between pyrazoles and unsubstituted phenyl rings [317–320], or between indazoles and aryl rings [321].

8.5.1.1.5 ***N*-Acylation (see also Section 8.6.4.2)** *N*-Acetylated pyrazoles are obtained from *N*-unsubstituted pyrazoles by treatment with acetyl chloride (alone or in the presence of pyridine) or acetic anhydride. The fact that the isomeric structure of azolides is thermodynamically controlled has been used to prepare the less accessible 1-alkylpyrazoles regioselectively (Scheme 8.112) [4].



Scheme 8.112

Acylation of 3(5)-aminopyrazole **366** with chloroacetyl chloride affords a mixture of **367** and **368**, both of which rearrange in the solid state to 3-(chloroacetamido)pyrazole **369** (Scheme 8.113) [322].



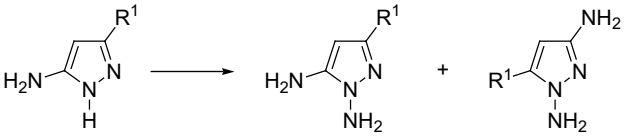
Scheme 8.113

8.5.1.1.6 **Michael Addition** *N*-Unsubstituted pyrazoles and indazoles add to compounds containing activated double and triple bonds [1–5]. Amongst C–C double and triple bonds, maleic anhydride, acrylic acid esters and nitriles, acetylenecar-

boxylic and -dicarboxylic esters, quinones, and some α,β-unsaturated ketones have been used with success. With an activated C−C triple bond two successive additions can occur if the intermediate alkene is reactive enough; this occurs, for instance, with DMAD. For additions on C−O double bonds see Section 8.6.4.2.

8.5.1.1.7 ***N*-Halogenation** *N*-Halogenated pyrazoles are unstable compounds (Cl > Br > I) that are seldom isolated. 1-Bromopyrazole resembles NBS and can act as a source of the electrophilic brominium ion [4].

8.5.1.1.8 ***N*-Amination and *N*-Nitration** The powerful aminating agents hydroxylamino-*O*-sulfonic acid and *O*-mesitylenesulfonylhydroxylamine have been used to aminate pyrazole and indazole (60% of 1-amino and 40% of 2-aminoindazole) [4]. Amination of *C*-aminopyrazole **370** affords both diamino isomers **371** and **372** (Scheme 8.114) [323].



Scheme 8.114

8.5.1.2 Electrophilic Attack at Carbon

Pyrazole is less reactive towards electrophiles than pyrrole. As a neutral molecule it reacts as readily as benzene and, as an anion, as readily as phenol. Pyrazole cations (pyrazolium ions), formed in strong acid media, show a pronounced deactivation (nitration, sulfonation, Friedel–Crafts reactions). Electrophilic attack on pyrazoles takes place at C4.

8.5.1.2.1 **Nitration** Pyrazole is very stable in acid media and even under rather vigorous conditions neither ring opening nor ring oxidation was observed. Nitration occurs at the 4-position; in the case of 4-R substituted pyrazoles, mono- and dinitration at positions 3 and 5 are observed [4].

8.5.1.2.2 **Sulfonation** Direct sulfonation of the pyrazole ring is rather difficult due to cation formation and takes place at position 4 only on prolonged heating with 20% oleum [4, 5].

8.5.1.2.3 **H/D Exchange** Qualitatively it was observed that in D_2SO_4 exchange of 1-methylpyrazole occurs initially at C4 and then simultaneously at C3 and C5, while in 1,2-dimethylpyrazolium it occurs only at C4 [4, 5].

8.5.1.2.4 **Halogenation** Halogenation is one of the most studied electrophilic substitutions in the pyrazole series [4]. Many reagents can chlorinate pyrazoles:

chlorine-water, chlorine in carbon tetrachloride, hypochlorous acid and chlorine in acetic acid (one of the best experimental procedures). Bromine in chloroform and bromine in acetic acid are the reagents used most often to brominate pyrazoles. To effect polybromination of pyrazoles the use of iron as catalyst is necessary. Pyrazole does not react with iodine although pyrazolsilver is converted into 4-iodopyrazole.

Ultrasound irradiation using *N*-halosuccinimides [324], *N*-iodosuccinimide [325] and a mild and efficient method for the regioselective iodination of pyrazoles have been reported [326].

8.5.1.2.5 **Acylation: Vilsmeier–Haack and Friedel–Crafts reactions** 1-Substituted pyrazoles are formylated and acetylated at C4. *C*-Alkylation of pyrazoles is rather uncommon and only groups like benzyl or adamantyl can be introduced directly on the 4-position.

8.5.1.2.6 **Diazo Coupling and Nitrosation** Generally, pyrazoles do not react with diazonium salts. However, when an activating group (hydroxy, alkoxy, amino) is present at position 3 or 5, the reaction proceeds easily at position 4. The reaction is very common in pyrazolone chemistry; pyrazolone diazo coupling is an important industrial reaction since the resulting azo derivatives are important dyestuffs, like tartrazine. The behavior of pyrazoles towards nitrosation is similar to that towards diazo coupling.

8.5.2
Reactions with Oxidizing Agents

Pyrazoles are resistant to oxidation but with agents like potassium permanganate the indazole ring is completely destroyed. Side chains can be oxidized; for instance, methyl groups into carboxylic acids.

8.5.2.1 Oxidation

The most important of all oxidation reactions in the chemistry of pyrazoles is the aromatization of pyrazolines into pyrazoles. Various oxidizing agents transform pyrazolines into pyrazoles: sulfur, bromine, chloranil, potassium permanganate, lead dioxide and mercury(II) acetate are all effective.

The problem is not totally solved, as shown by the numerous papers devoted to this topic. Oxidations using chlorine in CCl_4 [327], chloranil [164, 328], trichloroisocyanuric acid [329], Pd/C in acetic acid [330], DDQ [331] and $Bi(NO_3)_3$ with MW irradiation [332] have been reported.

8.5.3
Reactions with Nucleophilic Reagents

Little is known about nucleophilic attack on an unsubstituted carbon atom of pyrazoles. Some nucleophiles do not attack the heterocyclic ring carbon atoms but

instead the substituent linked to nitrogen with subsequent *N*-deprotection, for instance dequaternization (pyrazolium salts) [4] or debenzylation (pyrazoles and indazoles) [333].

8.5.3.1 Reduction by Complex Hydrides

When an electron (mass spectrometry, electrochemistry) attacks a pyrazolium salt, two different radicals are formed, one leading to a pyrazoline (reduction of a C−C double bond) and the other to an open-ring diamine (N−N bond cleavage) [334]. With lithium aluminium hydride, Δ^3-pyrazolines and pyrazolidines are obtained from quaternary pyrazolium salts [4].

8.5.4
Reactions with Bases

This section corresponds to topics like metallation at ring carbon atoms (mainly lithiation) [335], hydrogen/deuterium exchange in neutral pyrazoles and pyrazolium cations, ring cleavage via *C*-deprotonation (opening to β-amino acrylonitriles or *ortho*-cyano anilines in the case of indazoles) – all of them of secondary importance.

8.5.5
Reactions of *N*-Metallated Pyrazoles

The main use of *N*-metallated pyrazoles and indazoles (sodium or silver salts) is for the preparation of *N*-substituted derivatives.

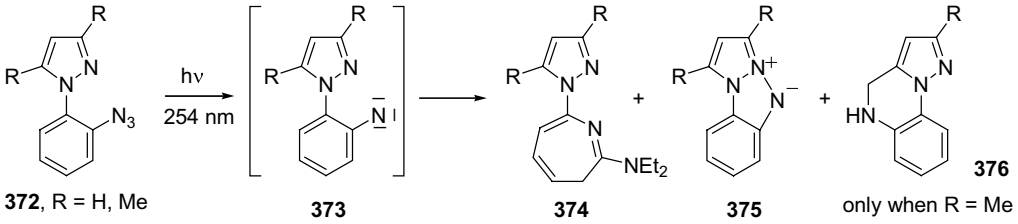
8.5.6
Reactions of *C*-Metallated Pyrazoles

This is a field of growing importance related to Suzuki, Miyaura, Sonogashira [325] and other cross-coupling reactions. Examples of C-arylation [52, 54, 154, 336], C-alkylation [154, 159] and C-alkynylation [325, 337, 338] have been reported.

8.5.7
Reactions with Radicals

Expansion of pyrazoles into pyridazines by the action of dichlorocarbenes has been reported [4]. Similarly, indazole and chloroform at 555 °C yields 2-chloroquinazoline. Little interest has been shown in the radical reactions (methyl and phenyl radicals) of pyrazoles because they afford mixtures of *C*-substituted derivatives.

A complete study of the chemistry of ground and excited state of *ortho*-pyrazolylphenyl nitrenes **373** (Scheme 8.115) has been carried out by Carra, Bally and Albini: different kinds of heterocycles have been isolated, amongst them **374–376** [339].



Scheme 8.115

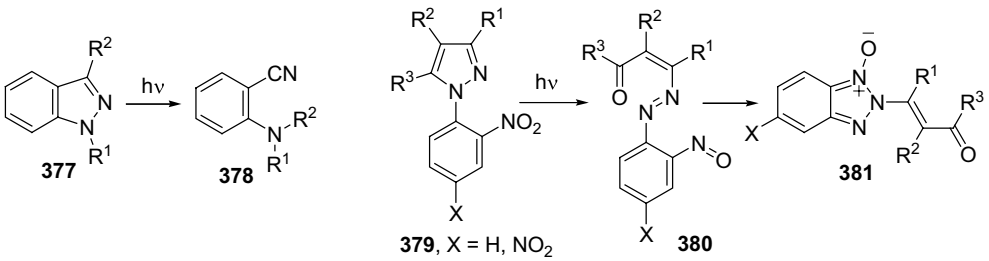
8.5.8
Reactions with Reducing Agents

The reduction of pyrazole and 1-phenylpyrazole with H_2, in the presence of palladium on active charcoal, gives the pyrazolines or, under more drastic conditions, the pyrazolidines [4].

8.5.9
Ring Transformations

8.5.9.1 Ring Opening without Fragmentation

Scheme 8.116 shows two of the most illustrative examples of this kind of reaction: the opening of 1-substituted indazoles **377** into 2-alkylaminobenzonitriles and the rearrangement of 1-(*ortho*-nitrophenyl)pyrazoles **379** into benzotriazole 1-oxides (*cis* and *trans* **381**) through intermediate azo compound **380** [4].



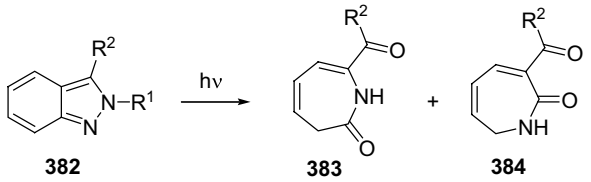
Scheme 8.116

8.5.9.2 Ring Isomerization

The most studied reaction is the transformation of pyrazoles into imidazoles and of 2-substituted indazoles into benzimidazoles.

8.5.9.3 Ring Enlargement

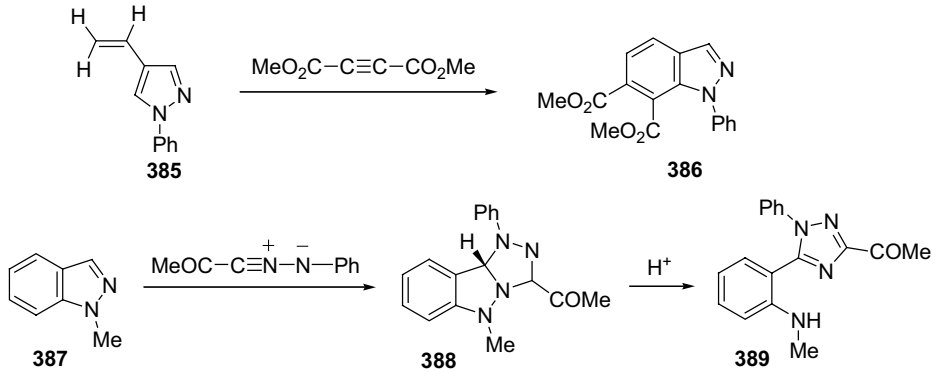
In dilute sulfuric acid (pH 2–4) rearrangement of indazoles **382** (Scheme 8.117) into benzimidazoles is suppressed and dihydroazepinones **383** and **384** are formed [4].



Scheme 8.117

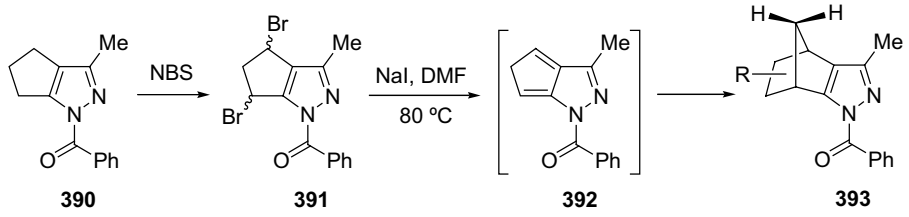
8.5.10 Electrocyclic Reactions

Concerning Diels–Alder and 1,3-dipolar cycloadditions, pyrazole never reacts as an alkene towards a diene or a 1,3-dipole nor as an azadiene towards a dienophile. There are very few examples of reactions related to this topic: some are reported in Schemes 8.105–8.107 and 8.118 [4, 5].



Scheme 8.118

Stephanidou-Stephanatou *et al.* have described the sequence of reactions reported in Scheme 8.119. From the *N*-benzoyl derivative **390**, through bromination and dehydrobromination, pyrazole *ortho*-quinodimethane **392** was generated and trapped with several dienophiles to afford the Diels–Alder adducts **393** [340].



Scheme 8.119

8.6
Derivatives

8.6.1
C-Substituted Pyrazoles and Indazoles

In pyrazoles the simplest way to characterize the carbon atoms is to consider that C3 is similar to the pyridine α-position, C4 to the pyrrole β-position and C5 to both the γ-pyridine and the α-pyrrole positions.

8.6.2
Oxy- and Aminopyrazoles and Indazoles

Probably the most studied pyrazole derivatives are the oxy (pyrazolones and indazolones) and the amino derivatives in the order 5-substituted > 3-substituted ≫ 4-substituted. For a long time, the only comprehensive source on pyrazolones was the book from Wiley and Wiley of 1964 [341]. Fortunately, Varvounis *et al*. have updated it recently (they use 3-ones for the 3- and 5-ones, a logical but uncommon decision) [342].

Pyrazolin-4-ones exist as 4-hydroxypyrazoles and are much less common [4–6, 8], although deserving attention for their biological potentialities. Indazolones exist as such and not as 3-hydroxyindazoles [343]. The chemistry of pyrazolidinones has been reviewed [344].

3-, 4- and 5-Aminopyrazoles are interesting in themselves and also as precursors of many pyrazoles with fused five- [345], and six-membered rings [323, 346–349], as well as larger heterocyclic rings [350].

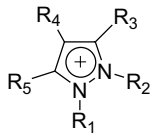
8.6.3
Other Substituents

The synthesis and reactivity of many different *C*-substituted pyrazoles have been described in the literature. Some of the most important (because of much studied or because very rare) are: CHO [351], C≡CR [352], NO_2 [353–355], ^{11}B [356], ^{19}F [357–360], ^{31}P [361, 362], ^{32}S [363], ^{28}Si (for instance TMS) [364] and ^{127}I [326, 337, 365, 367].

8.6.4
N-Substituted Pyrazoles and Indazoles

8.6.4.1 Quaternary Pyrazolium and Indazolium Salts

Pyrazolium **394** and indazolium salts **395** main importance was as precursors of Δ^3-pyrazolines and indazolines [4, 5]. But in recent years the extraordinary development of ionic liquids has promoted the study of pyrazolium salts as an alternative to imidazolium salts [366, 367]. Pyrazolium salts have been used to generate carbenes [368], and several papers dealing with their mass spectrometry have been published [369].



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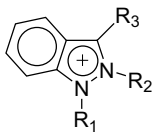
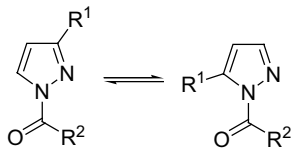


395

8.6.4.2 **Azolides**

N-Acyl azoles (azolides) are much studied compounds both for their use as synthons and for their structural properties [370]. Pyrazolides **396** and related compounds (like the addition products to aldehydes **397** and **398**) are in an equilibrium similar to prototropy and only the most stable isomers are usually isolated [371].



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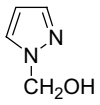

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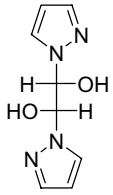


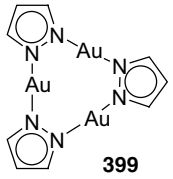
398

8.6.4.3 **Coordination Chemistry of Pyrazoles**

As we recalled in the introduction, the use of pyrazoles as ligands is one of the most prominent in their chemistry. Not considering biological properties, which include most patents, this aspect represent 36% of all 2004 references, according to the *Chemical Abstracts* (Table 8.2).

Since this topic has been covered in several reviews, only a classification of the pyrazoles as ligands is described here (see Refs [4, 5, 372–375]).

- Simple pyrazoles: pyrazolate anions. Both examples of pyrazoles acting as exobidentate ligands (**399**) and, much less common, as endobidentate – chelating – agent (**400**).



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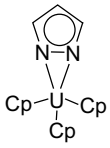
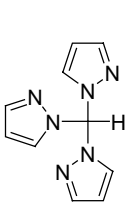


400

- Simple pyrazoles: neutral pyrazoles. These compounds act as 2-monohapto-pyrazoles.
- Bis-, tris- and poly-pyrazolyl derivatives: Ligands such as **401** (polypyrazolylmethanes) [376], **402** [poly(pyrazolylmethyl)benzenes] [377], **403** (polypyrazolylbenzenes, propellenes) [315], and **404** (polypyrazolylazines) [378] often form chelate complexes with different metals.



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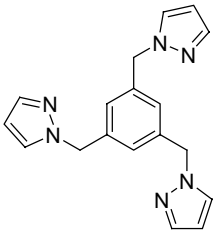

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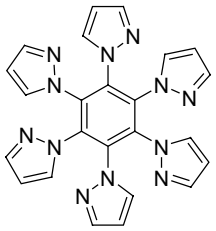

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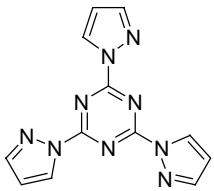
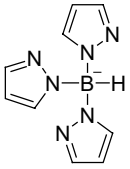


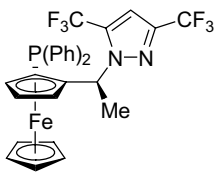
404

- Tris(pyrazolyl)borates (scorpionates) [310, 379]: The synthesis by Trofimenko of the pyrazolylborates (bis, tris and tetrakis, the tris **405** being the most interesting) is one of the major discoveries of pyrazole coordination chemistry. The anionic nature of **405**, which can be isolated with the Cp anion, confers to **405** and related compounds very rich coordination chemistry.

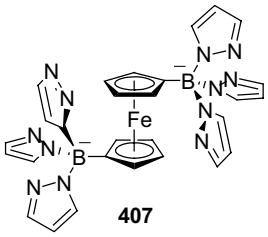


405

- Ferrocenylpyrazoles: The possibility that the pyrazole has a *C*-substituent with interesting properties has enriched the usefulness of pyrazoles in organometallic chemistry. Amongst these substituents, ferrocene is one of the most promising. Two representative structures are **406** [380] and **407** [381]. Other ferrocene-based pyrazolylborates (similar to **407**) have been described by Wagner *et al.* [382] Multidentate ferrocenyl-pyrazoles have been described by Thiel *et al.* [383].



(*S*)-(*R*)-**406**



407

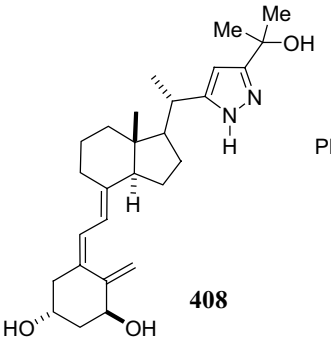
8.6.5
Chiral Derivatives

The increasing interest in chiral compounds comes from the pharmaceutical industry and from the catalytic properties of coordination complexes (e.g., asymmetric hydrogenation). The chiral pyrazoles can be classified into three groups: (i) the

chirality is in the substituent; (ii) the chirality is in a fused ring, tetrahydroindazoles from natural chiral ketones; (iii) the chirality pertains to a ring that is partially – pyrazolines – or totally – pyrazolidines – saturated.

8.6.5.1 Pyrazoles bearing *N*- or *C*-Chiral Substituents

Pyrazoles derived from steroids, carbohydrates and vitamins share the chiral properties of the starting materials. Thus compound **408**, an analogue of vitamin D, has been prepared [384]. Others, like **409**, a CNS agent, have been obtained by resolution [385]. Pyrazoles substituted at position 3 by (2*R*)-bornane-10,2-sultam **410** have been described and their annular tautomerism determined by X-ray and NMR spectroscopy [386]. Compounds related to Tröger's bases, such **411**, retain the inherent chirality of this family of compounds [387]. The synthesis of enantiomerically pure 5-substituted pyrazoles from 2,3-dihydro-4*H*-pyran-4-ones and from 2-formyl glycals has been reported (Schemes 8.59 and 8.60) [209, 210].



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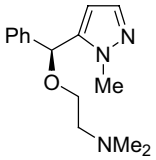

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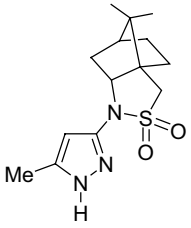

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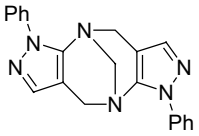
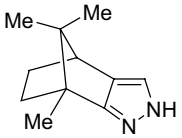


411

8.6.5.2 Tetrahydroindazoles from the Chiral Pool

Here, the most important compound by far is camphopyrazole – (4*S*,7*R*)-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-2*H*-indazole – **412**; this compound and related ones have been the subject of many studies: synthetic [146, 388–390], structural [391], reactivity [392, 393] and coordination chemistry [394, 395]. Other ketones found in natural sources have also been used to prepare compounds such as **413** [396–399].



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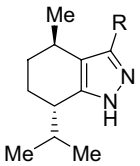
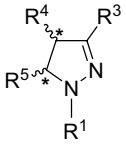


413

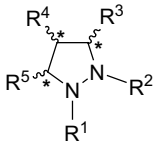
8.6.5.3 Pyrazolines and Pyrazolidines

These compounds have several stereogenic centers: carbons C4 and C5 in Δ^2-pyrazolines **414** and carbons C3, C4 and C5 in pyrazolidines **415**. Even taking into

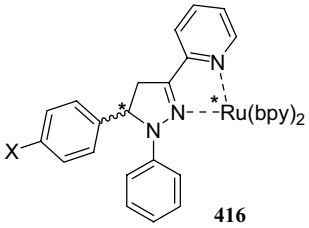
account the nitrogen inversion, stereogenic nitrogen atoms should be considered. Chiral pyrazolines have been prepared by resolution [400], and by inclusion in a chiral host [401]. The formation of a ruthenium complex from a racemic pyrazoline lead to diastereomeric structures **416** that have been separated [402].



414

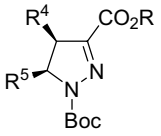


415

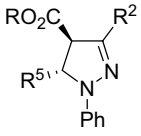


416

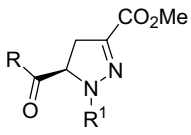
Using cycloaddition methodologies a series of pyrazolines and pyrazolidines enantiomerically pure have been prepared by Barluenga (**417**, and then reduced to pyrazolidines) [403], **418** [404], Molteni (**419**) [405], Ortuño (**420**) [406] and Kobayashi (**421**) (Scheme 8.50) [200]. A highly enantioselective [3 + 2] acylhydrazone-enol ether cycloaddition has been reported for the preparation of mono-benzoyl (similar to **421**) and dibenzoylpyrazolidines [407]. This is a very interesting field that it is expected to become very important in the near future.



417



418



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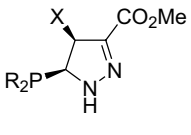

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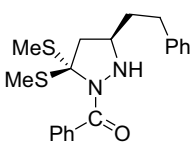
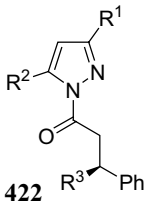
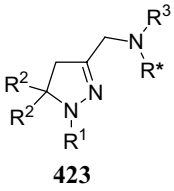


421

A series of compounds by Sibi are worth mentioning in this context: **422** (used for enantioselective intermolecular free radical conjugate additions) [408], **423** (a new ligand system) [409] and **424** (a pyrazolidinone template used with chiral Lewis acids) [410].



422



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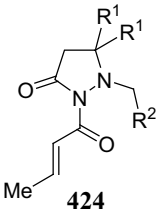
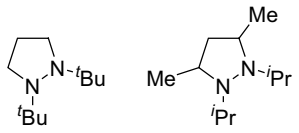


424

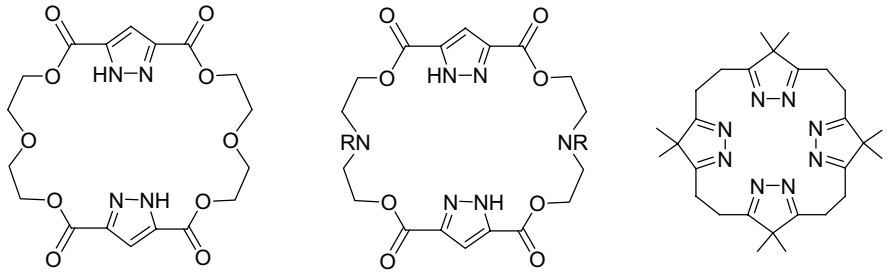
Finally, the resolution of compounds **425** and **426**, whose chirality resides exclusively in the nitrogen atoms, has been reported by Kostyanovsky [411]. For previous studies on chiral nitrogen atoms in pyrazole reduced derivatives due to hindered inversion see Reference [412].



425 **426**

8.6.6
Macrocyclic Pyrazoles

This is an important field that has been treated in detail in other monographs [4, 5]. Particularly relevant are the results of Navarro *et al.* [413–415] (structures **427** and **428**) and of Kohnke *et al.* (**429**) [416].



427 **428** **429**

8.6.7
Labeled Derivatives

For biological purposes or by spectroscopic necessities (microwave, IR, NMR, etc.) many labeled pyrazoles have been prepared, mainly deuterium and ^{15}N derivatives for spectroscopy [4, 5, 417], and radioligands for biological studies: tritium [418, 419], ^{11}C [420], ^{18}F [421], and ^{125}I [422].

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9
Five-Membered Heterocycles: 1,2-Azoles. Part 2. Isoxazoles and Isothiazoles

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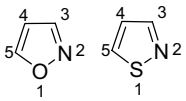
9.1
Introduction

Isoxazole **1** (1,2-oxazole) and isothiazole **2** (1,2-thiazole) are five-membered heterocyclic compounds having a pyridine-like N-atom bonded to an O- or an S-atom, respectively. These N−O and N−S σ-bonds are the weakest bonds in each molecule, being their energy much lower than that of N−C, O−C or S−C bonds, and are cleaved in all ring-opening reactions. Isothiazoles react more slowly with nucleophiles than isoxazoles and in both cases the reactions usually originate ring-opening [1].

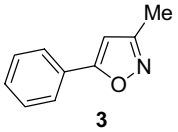


1 **2**

The first reference to the isoxazole structure **1** was made by Claisen in 1888, for the reaction product of benzoylacetone with hydroxylamine [2]. He proposed the corrected structure (3-methyl-5-phenylisoxazole **3**) for a compound isolated several years before and suggested the name monoazole; however, Hantsch modified it to isoxazole, a name derived from the already know isomeric ring oxazole [3]. Claisen reported the fundamental outline of isoxazole chemistry in 1891 [4] and synthesized the parent compound of the series, isoxazole **1**, in 1903, by oximation of propargylaldehyde acetal [5]. After the fundamental work of Claisen and coworkers and some other contemporary authors [6], the next important contribution to the chemistry of isoxazoles was made by Quilico in 1946, when he began to study the formation of isoxazoles from *N*-oxides and acetylenic compounds [7]. The saturated derivatives had long been know (1892) but it was only in the 1960s that these compounds were studied extensively [8]. The extensive studies on isoxazoles since the 1980s are due to their versatility in the synthesis of various compounds, namely heterocycles and natural products, as well as their applications in several fields, such as agriculture, medicine and industry [1, 6, 8, 9]. In terms of the literature on isoxazole derivatives,

Modern Heterocyclic Chemistry, First Edition.
Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.

one can find an enormous number of references on their chemistry, physicochemical and biological properties, as well as some book chapters (in *Comprehensive Heterocyclic Chemistry*, 1984 [10] updated in 1996 [8], and *Science of Synthesis* [11–13]) and monographs (*Isoxazoles and Related Compounds*, published in 1962 by Quilico [14] and *Isoxazoles – Part 1 and Part 2*, published in 1991 [6] and 1999 [9] by Grünanger and Vita-Finzi) which collate all this information. Part 1 of the last monograph is restricted to mononuclear isoxazoles and their hydrogenated derivatives (dihydroisoxazoles and tetrahydroisoxazoles), except for the isoxazolones, while Part 2 is devoted to the chemistry of condensed isoxazoles, namely benzisoxazoles and related compounds.



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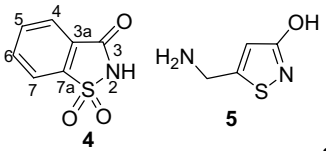
Isothiazole (**2**) was first described in 1956 [15] while the benzisothiazoles have long been known. The most widely known derivative, saccharin (**4**), the first non-carbohydrate sweetening agent discovered in 1879, is 300–500 times as sweet as sucrose [16]. Saccharin (**4**) is manufactured commercially by the cyclization of *ortho*-substituted benzenesulfonamides with strong bases [17]. It still be used in many countries as a non-nutritive sweetener, although it was found that massive doses administered to rats caused bladder cancer, a fact which led to its ban in developing countries [18]. The controversy over its danger when used in small amounts is still unresolved [19]. Although all types of pharmacological activity have been claimed for isothiazoles, some are notable, such as that of thiomuscinol (**5**) on the central nervous system, as a potent agonist of γ-aminobutyrate (GABA) receptors [20], and the significant antifungal activity of isothiazolones (**6**) (marketed under the name Kathon) [21]. Several reviews on isothiazoles and on benzisothiazoles have been published [21–26]; the chapters in *Comprehensive Heterocyclic Chemistry* (1984 [16] and updated in 1996 [27]) and *Science of Synthesis* [28, 29] describe both types of compounds.



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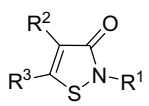

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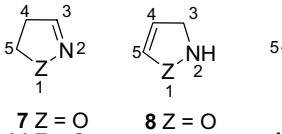
6a R^1 = Me, R^2 = R^3 = H
6b R^1 = Me, R^2 = H, R^3 = Cl
6c R^1 = Me, R^2 = R^3 = Cl
6d R^1 = *n*-octyl, R^2 = R^3 =H

9.1.1 Nomenclature

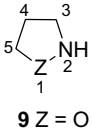
The structure and numbering system of the two mononuclear heterocycles (**1** and **2**) treated in this chapter and some of their best known derivatives is shown above.

However, before discussing their physicochemical properties, synthesis and transformations, it is important to present the structure and nomenclature of all known saturated and benzo-derivatives. For isoxazoles, one can find 4,5-dihydroisoxazoles (**7**) (also known as Δ^2-isoxazoline or 2-isoxazoline), 2,3-dihydroisoxazoles (**8**) (also known as Δ^4-isoxazoline or 4-isoxazoline), isoxazolidines (**9**), 1,2-benzisoxazoles (**10**), 2,1-benzisoxazoles (**11**) and 2,3-dihydro-1,2-benzisoxazoles (**12**). Structure **10** has also been described as indoxazene, 4,5-benzisoxazole, α,β-benzisoxazole and benzo[*d*] isoxazole (IUPAC nomenclature) and benzisoxazole. It is indexed in *Chemical Abstracts* as 1,2-benzisoxazole and numbered as shown below. The first member of the family, 3-phenyl-1,2-benzisoxazole (**13**), was synthesized at the end of the nineteen century (1892) [30] and the 1,2-benzisoxazole itself **10** was obtained in 1908 [31]. Structure **11** has also been described as anthranil, anthroxan, 3,4-benzisoxazole, β,γ-benzisoxazole, benzo[*c*]isoxazole (IUPAC nomenclature) and benzisoxazole. It is indexed in *Chemical Abstracts* as anthranil and numbered as shown below.

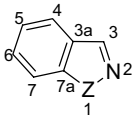


7 Z = O
14 Z = S

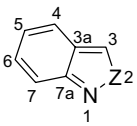
8 Z = O
15 Z = S



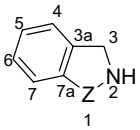
9 Z = O
16 Z = S



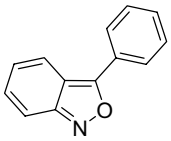
10 Z = O
17 Z = S



11 Z = O
18 Z = S



12 Z = O
19 Z = S



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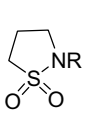
For isothiazoles one can find the same type of dihydroisothiazoles (**14** and **15**), tetrahydroisothiazoles (**16**), and benzisothiazoles (**17** and **18**) and their reduced form (**19**). The saturated isothiazole 1,1-dioxides **20** are known as sultams and 1,2-benzisothiazole 1,1-dioxides **21** are called saccharins.



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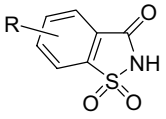

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9.2
General Reactivity

9.2.1
Relevant Physicochemical Data, Computational Chemistry and NMR Data

The calculated π-electron density distributions of isoxazole (**1**) and isothiazole (**2**) are consistent with electrophilic substitution occurring at the 4-position (highest electron

density) rather than at other ring positions [32–34]. The positional selectivity in the electrophilic attack on heterocyclic molecules can be explained according to the magnitude of the HOMO electron density of each atomic center [35], which predicts the reactivity order of electrophilic substitution of isoxazole (**1**) as C4 > C5 > C3, in agreement with the experimental data. Comparison of partial rate factors of isothiazole (**2**) with those of benzene and related compounds shows that its 4-position is $\sim 10^4$ times more reactive towards electrophiles than expected on the basis of the calculated π-electron density at carbon atoms and the electronegativity of the heteroatoms [36]. This indicates that when attempting to correlate the theoretical calculations with chemical reactivity one must be careful and consider whether ground or excited states are involved, or whether it is the electron density of intermediates, rather than the original molecule, that determines the product of a chemical transformation.

The π-electron density distribution also suggests that nucleophiles must attack the 3-position of both isoxazole (**1**) and isothiazole (**2**) since it presents the lowest electron density.

The positional reactivity of isothiazole **2** can also be evaluated by ^{1}H NMR. The relative rate of deuterium exchange of H5 and H3, under basic conditions, has been demonstrated to be 400 : 1, with no exchange of H4, whereas those of the hydrogens of the methyl groups of 5-, 4- and 3-methyl-isothiazoles were $100 : 1 : 10^{-4}$, respectively [37]. The high reactivity of the 5-position can be due not only to the electron distribution in the ground state but also to the stabilization of the formed anion by the σ-3d (sulfur) bonding. A similar study with isoxazoles provided the same conclusions [36, 38].

The very low π-order of the N−O bond of isoxazole (**1**) (Table 9.1) relative to those of the other ring bonds and the largest localized dipole due to the N−O bond suggests that this bond can be a site of attack of hydrolytic reagents, which is in agreement with the experimental reactivity.

Jug classified isoxazole (**1**) in the range of moderate aromatic compounds (1.548–1.332), based on the index of aromaticity, which corresponds to the value of the lowest bond order (Table 9.1, calculated by MO-SINDO1) [39]. These calcula-

Table 9.1 Calculated π-bond orders of isoxazole **(1)** and isothiazole **(2)**.

X(O,S)-N	N-C	C3-C4	C4-C5	C-X(O,S)	Calculation method	Compound, Reference
0.285	0.795	0.546	0.817	0.342	HMO	**1**, [42]
0.412	0.772	0.580	0.776	0.458	MO-LCAO	**1**, [43]
0.404	0.735	0.617	0.738	0.526	PPP-SCF-CI	**1**, [44]
0.296	0.858	0.452	0.833	0.448	CNDO/2	**1**, [45]
1.361	1.957	1.501	1.955	1.498	MO-SINDO1	**1**, [39]
0.502	0.705	0.634	0.707	0.594	HMO	**2**, [21]
0.474	0.707	—	—	—	PPP	**2**, [46]
0.227	0.870	0.410	0.850	0.302	CNDO/2	**2**, [34]

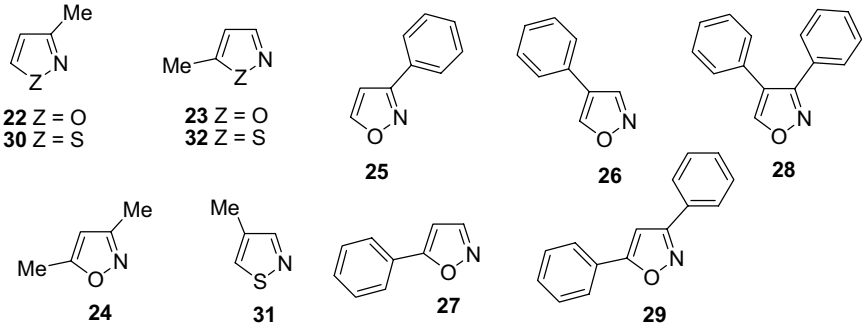
tions indicate that isoxazole (**1**) (1.361) is less aromatic than oxazole (1.392) and imidazole (1.423) but more than pyrazole (1.297). These results have been confirmed by using other quantitative measurements of aromaticity, such as empirical resonance energy values for heteroaromatic systems as well as conjugation energies [40]. The aromaticity of isothiazole (**2**) is greater than that of isoxazole (**1**), just as the aromaticity of thiophene is greater than that of furan.

The tendency of $^{1}J_{CC}$ coupling constants in ^{13}C NMR to converge towards that of benzene (56 Hz) is another possible criterion of degree of aromaticity, increasing with the convergence [41]. Although an interesting model, these coupling constants also depend on the geometry of the molecule. The fact that isothiazole (**2**) is planar and their $^{1}J_{CC}$ ($^{1}J_{C3-C4}$ 52.5 Hz and $^{1}J_{C4-C5}$ 62.2 Hz) are less divergent than those of the less aromatic isoxazole (**1**) ($^{1}J_{C3-C4}$ 48.7 Hz and $^{1}J_{C4-C5}$) 67.7 Hz) seems to support this method.

The proton resonances of isoxazole (**1**) and isothiazole (**2**) are strictly related to electron density distribution on the ring (referred above). The ^{1}H NMR spectrum of isoxazole (**1**), neat or dissolved in various solvents, has been reported in many papers (Table 9.2) [34, 47–49]. The signals of H4 (δ, 6.28–6.41 ppm) appear at lower frequency values than those of H3 (δ, 8.15–8.40 ppm) and H5 (δ, 8.39–8.61 ppm), but all of them are in the aromatic region. For isothiazole (**2**) the same kind of chemical shifts appears, H5 is at a higher frequency than H3, but in some cases it can be reversed. The resonance is deshielded (0.5 ppm) when spectra are acquired in DMSO-d_6 solution, owing to the interaction of this hydrogen with proton acceptors.

Table 9.2 ^{1}H NMR chemical shifts (δ, ppm) of some isoxazole and isothiazole derivatives.

Compound	H3	H4	H5	$^{3}J_{H3-H4}$ (Hz)	$^{3}J_{H4-H5}$ (Hz)	$^{3}J_{H3-H5}$ (Hz)	Solvent
1 [47]	8.34	6.41	8.51	1.5	1.5	—	$CDCl_3$
1 [48]	8.40	6.40	8.61	1.7	1.7	0.5	Neat
1 [49]	8.19	6.32	8.44	1.6	1.6	—	CCl_4
1 [34]	8.15	6.28	8.39	1.78	1.69	0.27	CS_2
22 [49]	(2.28)	6.02	8.13	—	1.6	—	CCl_4
23 [49]	7.90	5.85	(2.42)	1.6	—	—	CCl_4
24 [49]	(2.24)	5.85	(2.41)	—	—	—	CCl_4
25 [49]	—	6.58	8.39	—	1.6	—	CCl_4
26 [49]	8.43	—	8.58	—	—	—	CCl_4
27 [49]	8.15	6.39	—	2.0	—	—	CCl_4
28 [52]	—	—	9.08	—	—	—	$CHCl_3$
29 [49]	—	6.74	—	—	—	—	CCl_4
2 [53]	8.54	7.26	8.72	1.66	4.66	0.15	CCl_4
30 [53]	(2.46)	7.00	8.54	—	4.55	—	CCl_4
31 [53]	8.24	(2.32)	8.21	—	—	0.33	CCl_4
32 [53]	8.24	6.92	(2.56)	1.63	—	—	CCl_4



The interaction between H3 and the ring nitrogen atom, due to the quadrupole relaxation of ^{14}N, is responsible for the broadening of H3 signals of isoxazole and isothiazole derivatives. This broadening is sometimes the diagnostic for the differentiation of H3 and H5 resonances and it is generally reduced in solvents with high viscosity, lower temperatures or nitrogen protonation [$^{2}J(^{14}N3\text{-}H3)$ from ~10 to 3 Hz] [47, 50].

As one can see from Table 9.2, the presence of methyl substituents (electron-donating groups) causes a shielding in the resonances of the isoxazole **22–24** and isothiazole **30–32** protons. The ^{1}H NMR spectra of methylisoxazoles can be used as a tool to calculate the ratio of 3- and 5-methylisoxazoles in some reaction mixtures and to determine the isomeric purity of products, since the chemical shift of the corresponding methyl groups are very different.

The ^{1}H NMR chemical shifts of the isoxazole ring of 3-, 4- and 5-phenylisoxazoles **25–27** seem to indicate a different conformation for these compounds, presenting different angles between the planes of the two ring, the most important being that of 5-phenylisoxazole (**27**). This conclusion is based on the deshielding effect of the phenyl ring on the protons lying in the same plane, which decreases with increasing torsional angle.

The resonance of H4 can also be used to distinguish between isomeric 3,5-disubstituted isoxazoles [51]. In the case of unsymmetrical 3(5)-substituted-5(3)-phenyl-isoxazole derivatives bearing one substituent more electron-donating than the phenyl ring, the H4 resonance is shielded ($\Delta\delta$ 0.03–0.80 ppm) for the isomers where the electron-donating substituent group is at the 5-position. Opposite results were obtained for those compounds containing stronger electron-withdrawing groups. In these cases the H4 resonance is deshielded ($\Delta\delta$ 0.11–0.31 ppm) for compounds bearing an electron-withdrawing substituent at the 5-position of the isoxazole ring compared to those of the 3-isomer.

The ^{1}H NMR spectra of 1,2-benzisoxazole and 1,2-benzisothiazole derivatives have the characteristics of both condensed benzene and isoxazole/isothiazole rings. A typical resonance of these compounds is that of H3, which appears around δ 8.7–8.8 ppm and presents long-range coupling with H-7 (^{5}J 0.9–1.2 Hz) due to the well-known zigzag route [22, 54]. The vicinal coupling constants of the phenyl ring protons are consistent with some degree of *ortho*-quinonoid structure and

Table 9.3 ^{13}C NMR chemical shifts (δ, ppm) of some isoxazole and isothiazole derivatives.

Comp.	C3	C4	C5	Comp.	C3	C4	C5
1 [56]	150.0	140.5	158.9	**2** [58]	157.0	123.4	147.8
22 [57]	159.2	105.7	159.2	**30** [58]	166.7	123.9	148.1
23 [57]	150.9	101.4	169.2	**32** [58]	157.6	123.3	163.0

Table 9.4 Physical properties of isoxazole, isothiazole and their fused benzo-derivatives.

Compound	1	10	11	2	17	18
Mp (°C)	−80	—	—	—	37	
Bp (°C/mmHg)	95/769	84/11	994.5/11	113/760	—	242/760
pK_a	−2.03	—	—	−0.51	—	−0.05
Dipole moment (μ, D)	2.90	—	—	—	2.44	—

correlate with the bond orders of 2,1-benzisoxazoles and 2,1-benzisothiazoles ($^3J_{H4\text{-}H5} \sim 9$ Hz and $^3J_{H5\text{-}H6} \sim 7.5$ Hz) [55].

Table 9.3 presents the ^{13}C resonances of isoxazole (**1**), isothiazole (**2**) and some of their methyl derivatives as examples of the ^{13}C NMR spectra of such compounds. The presence of a methyl group as ring substituent implies a deshielding into the signal of the carbon to which the methyl is bonded.

A comprehensive collection of ^1H and ^{13}C NMR chemical shifts of several isoxazole derivatives is reported in the first monograph of isoxazoles [6].

Unsubstituted isoxazole (**1**) (Table 9.4) and its alkylisoxazole derivatives are usually liquids; the introduction on the ring of more than one substituent with a long chain leads to solid compounds. Phenylisoxazoles are usually solids [6].

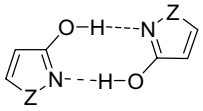
Isothiazole (**2**) and their alkylisothiazole and benzisothiazole derivatives are usually liquids or solids with low melting points (Table 9.4). The presence of polar substituents increases the melting points. Isothiazole (**2**) has a low solubility in water (∼3.5%) and is miscible with most organic solvents. Benzisothiazoles are insoluble in water, but are soluble in strong acids (salt formation) and in organic solvents [6].

Table 9.4 shows the physical properties of unsubstituted compounds, isoxazole (**1**) and isothiazole (**2**), and their fused benzo-derivatives, 1,2- and 2,1-benzisoxazole (**10**) and (**11**) and 1,2- and 2,1-benzisothiazole (**17**) and (**18**), discussed in this chapter.

9.2.2 Tautomerism

Annular tautomerism does not occur in isoxazoles, benzisoxazoles, isothiazoles and benzisothiazoles, but they present some substituent tautomers. Isoxazolin-3(5)-ones

or isothiazolin-3(5)-ones can exist in equilibrium with the corresponding hydroxy-derivatives. Isoxazolin-3-ones or isothiazolin-3-ones have been more studied than the corresponding 5-substituted derivatives. The spectroscopic data indicate that they exist as 3-hydroxy tautomers in solid state or in non-polar solvents, such as cyclohexane or ether, but more polar solvents resulted in a great contribution of the keto tautomers [6, 21, 59, 60]. In the solid state these compounds form hydrogen-bonded dimers **33**. One of the best known 3-hydroxyisoxazoles, due its important neuropharmacological activity, is the natural compound muscinol (**34**), isolated from an *Amanita* species [61, 62].



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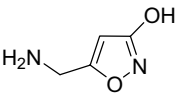

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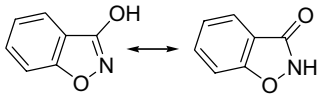
The infrared (IR) spectra have been useful in establishing the position of the tautomeric equilibrium in 1,2-benzisoxazolin-3-one. The enol form of **35** is preferred in the solid state, as shown by the strong band at 3000–2500 cm^{-1} and the lack of carbonyl band and the C=N band at 1620 cm^{-1}. Both tautomeric forms are present in chloroform solution, since the carbonyl (1670 cm^{-1}) and hydroxyl band (as above) are present [63]. However, X-ray and other spectroscopic data show that 1,2-benzisothiazolin-3-one and its derivatives, 2,1-benzisothiazolin-3-one and saccharin, all exist in the keto form [64].

Studies on tautomerism have shown that in general isoxazolin-4-ones exist preferentially as 4-hydroxy-isoxazoles [65]. The structure of the bioactive natural compound triumferol (**36**) has also been established as a 4-hydroxy-derivative by ^1H NMR (δ_{H3} 8.25 ppm, δ_{H5} 8.33 ppm, δ_{OH} 8.18 ppm, acetone-d_6) and *O*-acyl and *O*-methyl derivatives [66].



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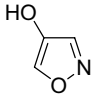
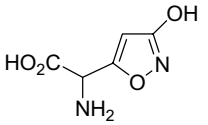


36

9.3
Relevant Natural and/or Useful Compounds

Although isoxazole and isothiazole moieties are rarely found in nature, they present important biological applications. Muscinol (**34**), a potent CNS depressant and agonist of the neurotransmitter 4-aminobutyric acid [67], has been isolated from *Amanita muscaria* [61, 62]. The naturally occurring amino acid ibotenic acid (**37**), a widely used neurotoxin and pharmacological tool for studies of glutamic acid receptors [68], has also been isolated from *Amanita muscaria* and from *Amanita pantherina* [62]. Brassilexin (**38a**) and sinalexin (**38b**) are

phytoalexins, with fungicidal activity, isolated from the leaves of *Brassica juncea* (Cruciferae) [69, 70]. Aulosirazole (**39**) is the major cytotoxin in the blue-green alga (cyanobacterium) *Aulosira fertilissima* Ghose. It shows selective cytotoxicity against solid tumors [71].



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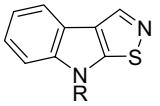
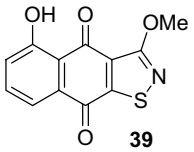
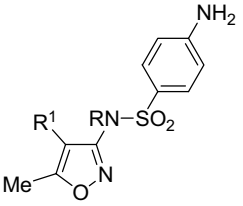


38a, R = H
38b, R = OMe

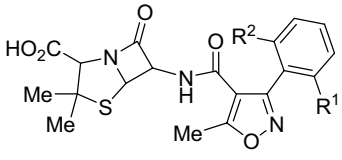


39

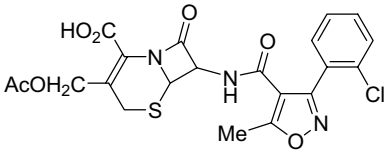
Isoxazoles are a large group of heterocyclic compounds that display interesting medicinal, agricultural and some other industrial utilities. Some of the most important are the pharmacologically active isoxazoles, including antibacterial sulfonamides **40–42**, semi-synthetic penicillins **43–46**, semi-synthetic cephalosporin **47**, anabolic steroid **48** and the monoamine oxidase inhibitor **49** (used in psychotherapy) [72].



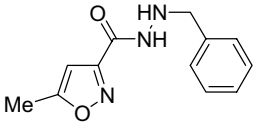
40 R = R^1 = H, Sulfamethoxazole
41 R = H, R^1 = Me, Sulfisoxazole
42 R = Ac, R^1 = Me, Acetylsulfisoxazole



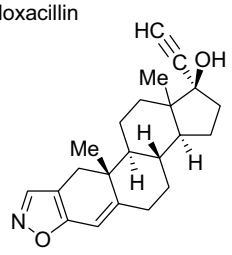
43 R^1 = R^2 = H, Oxacillin
44 R^1 = H, R^2 = Cl, Chloxacillin
45 R^1 = R^2 = Cl, Dichloxacillin
46 R^1 = R^2 = Cl, Floxacillin



47 Cefoxazole

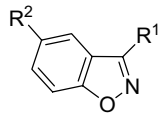


49 Isocarboxazid

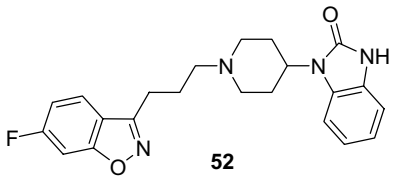


48 Danazol

The isosteric relationship of 1,2-benzisoxazole with that of the indole nucleus has led to its use as a carrier of pharmacophoric moieties in the search for potential drugs. From the many compounds studied, only a few have emerged as candidates for clinical use. 1,2-Benzisoxazole-3-sulfonamide **50** (zonisamide) is a potent antiepileptic drug [73], 6-fluoro-1,2-benzisoxazole **51** (risperidone) is a potent antipsychotic agent with thymosthenic properties [74], its analogue **52** (HRP 913) is a potent dopamine antagonist with antipsychotic properties [75], and 1,2-benzisoxazole-3-acetamidoxime **53** (PF-257) is a psychotropic agent with seemingly new properties [76]. Phosphonate **54** (Bay 52957) is a potent insecticide [77]



50 $R^1 = CH_2SO_2NH_2$, $R^2 = H$
53 $R^1 = CH_2C(NH_2)NOH$, $R^2 = H$
54 $R^1 = OP(S)(OC_2H_5)_2$, $R^2 = Cl$



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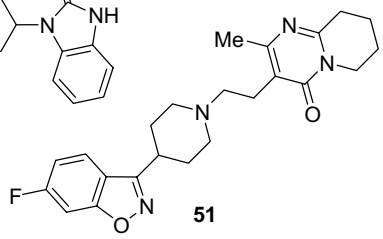
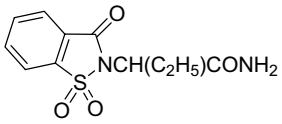


51

As referred to in the introduction, the most widely known isoxazole derivative is the benzisothiazole saccharin (**4**), the first non-carbohydrate sweetening agent discovered [16, 27]. Although many isothiazole compounds exhibited biological activities (all types of pharmacological activity have been claimed!), the most important are (i) saccharin derivative **55**, which presents potent sedative, hypnotic and anticonvulsant activity [78]; (ii) the adrenergic β-blockers **56** [79]; (iii) the cyclizine analogue **57**, which presents appetite suppressant activity [80]; (iv) the amide **58**, which has potent anti-inflammatory activity [81]; (v) thiomuscinol (**5**), which is active on the CNS as a potent agonist of GABA receptors (Section 9.1) [20]; (vi) the acid **59**, the most interesting compound in the agrochemical sphere, having high herbicidal activity [17, 78]; and (vi) the allyloxy-1,2-benzisothiazole 1,1-dioxide **60**, known as Probenazole or Oryzaemate, which is useful in rice crop protection [82].



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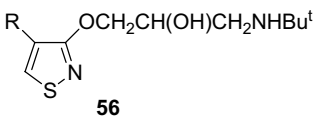

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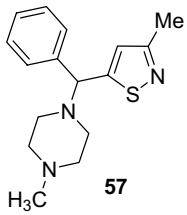

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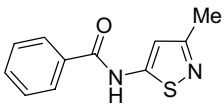

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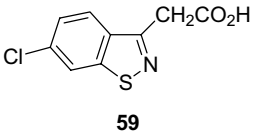

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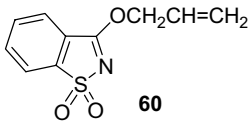


60

Numerous biological, pharmacological and biocidal activities are fully described in reviews and monographs published about the compounds treated in this chapter [6, 8–10, 16, 26, 27, 83].

9.4
Synthesis of Isoxazoles and Isothiazoles

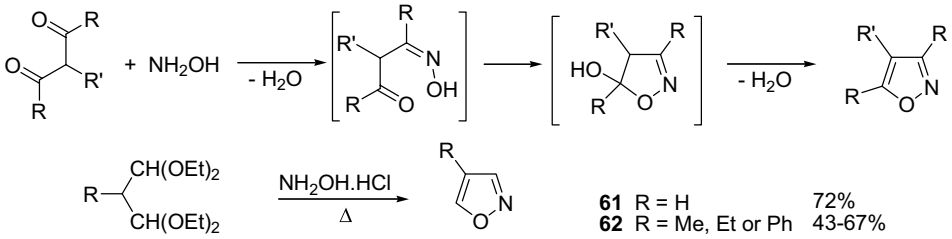
9.4.1
Isoxazoles

Synthetic methodologies for the construction of the isoxazole ring can be classified based on the number of atoms of the component synthons, which are subdivided

according to the type and arrangement of the atoms in each component. The [3 + 2] approach includes the two major routes to isoxazoles: CCC + NO reactions (reaction of hydroxylamine with a three-carbon atom component) and CNO + CC reactions (1,3-dipolar cycloaddition of nitrile oxides). Isoxazoles can also be obtained via [4 + 1], [5 + 0] and [3 + 1 + 1] routes. Ring transformation reactions also lead to isoxazoles.

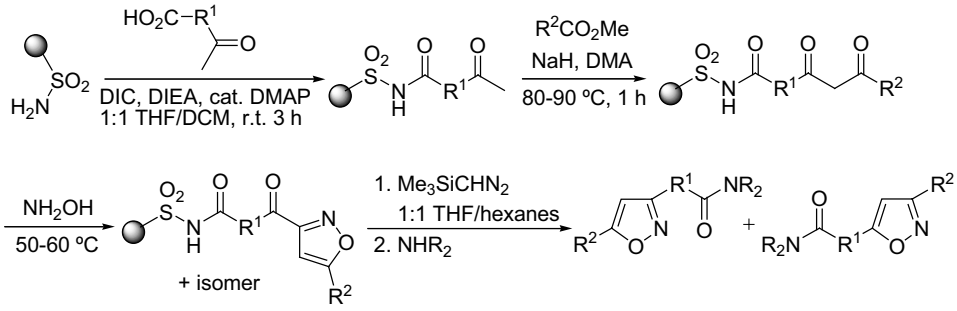
9.4.1.1 [3 + 2] Routes

9.4.1.1.1 [CCC + NO] Reactions: Reactions of Hydroxylamine with a Three-Carbon Atom Component In 1888 Claisen described the first general synthesis of isoxazoles [2]. The process involved the reaction of β-diketones with hydroxylamine followed by cyclization–dehydration of the intermediate oxime (Scheme 9.1). This became an important route to 4-unsubstituted or 4-substituted isoxazoles bearing the same substituent at 3- and 5-positions. 4-Monosubstituted isoxazoles **62** and unsubstituted isoxazole **61** have also been prepared from the reaction of tetraalkoxypropanes (or β-dialdehydes) with hydroxylamine (Scheme 9.1) [6, 10, 84, 85]. This route was applied to the synthesis of 3,5-disubstituted isoxazole-4-carbaldehydes using also diketones as the three-carbon building-block in the reaction with hydroxylamine [86].



Scheme 9.1

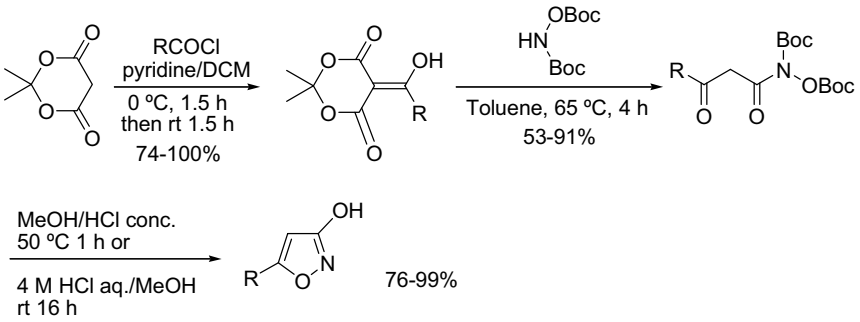
The drawback of this approach is that unsymmetrical 1,3-diketones or their derivatives can lead to mixtures of the two isomeric isoxazoles. This is the case in the solid-phase synthesis of isoxazoles outlined in Scheme 9.2 [87]. However, the



Scheme 9.2

selection of a CCC synthon with dissimilar terminal carbon atoms in terms of electronic and/or steric effects, the protection of one terminal carbon or the control of the pH of the medium can lead to selectivity. Nevertheless, many variants of this reaction have been developed and in fact isoxazoles have been prepared from the reaction of hydroxylamine with several three-carbon atom components, namely β-keto aldehydes, β-keto esters, α-acetylenic ketones or aldehydes, α,β-unsaturated ketones, β-imino nitriles and β-keto nitriles [6, 10, 84, 85].

3-Hydroxy-isoxazole is a synthetic unit present in several biologically active compounds. They have been prepared mainly by cyclization of β-keto esters with hydroxylamine. However, this method usually leads to the formation of isoxazol-5-ones as a by-product. By using Meldrum's acids the problem of the lack of regioselectivity in the addition of hydroxylamine can be overcome (Scheme 9.3) [88].



Scheme 9.3

The regioselective synthesis of 5-substituted 3-alkoxyisoxazoles can be achieved using β-oxo thionoesters (Table 9.5, entry 1) [89]. 3-Aryl-5-alkoxyisoxazoles have been obtained in moderate yields from cyclocondensation of acylketene O,S-acetals with hydroxylamine in the presence of sodium alkoxide/alcohol (Table 9.5, entry 2). 5-Alkoxy-3,4-annulated isoxazoles can also be obtained using the same synthetic approach (Table 9.5, entry 3) [90].

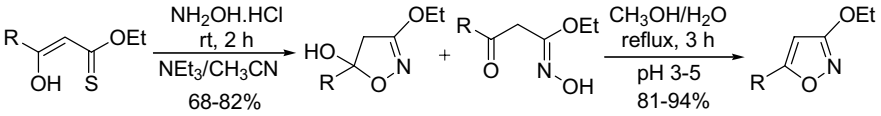
The α-keto methylene group in 3,5-diarylcyclohexen-2-ones has been used to obtain fused isoxazoles via Claisen-like condensation with ethyl formate followed by cyclocondensation with hydroxylamine hydrochloride (Table 9.5, entry 4). The same type of approach can be applied to prepare other types of fused isoxazoles [91], including those derived from triterpenoids, namely methyl oleanonate and lanost-8-en-3-one [92].

The reaction of vinyl ketones bearing a potential leaving group at the β-position (such as halogen, alkoxy or dialkylamino) with hydroxylamine has been extensively explored (Scheme 9.4) [6, 10, 84, 85, 93, 94].

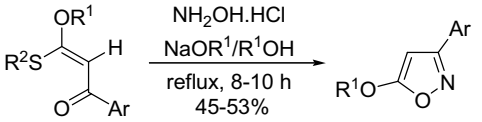
The amine exchange reaction of an enamine ketone has also been used for the regioselective synthesis of 4,5-diarylisoxazoles [95–98]. The one-pot reaction of enamino ketones **63** with hydroxylamine hydrochloride leads to the corresponding

Table 9.5 Reaction of hydroxylamine with three-carbon atom components.

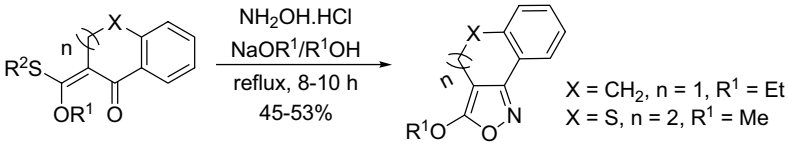
1 [10]



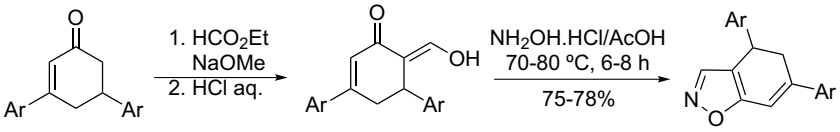
2 [90]



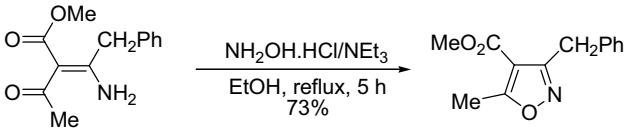
3 [90]



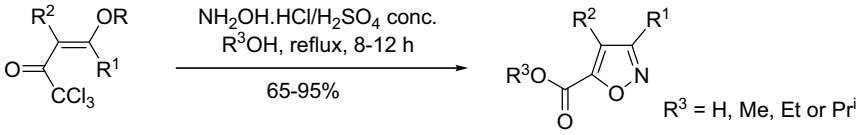
4 [91]



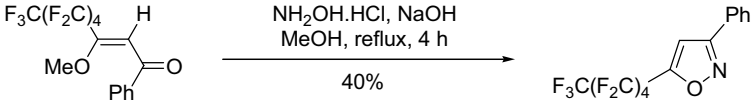
5 [104]



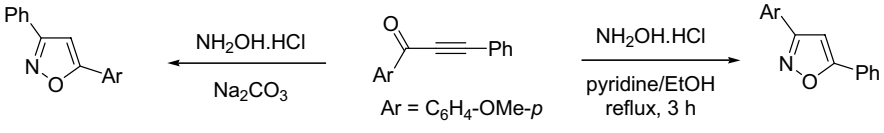
6 [108]

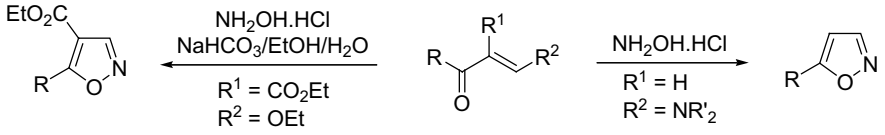


7 [109]



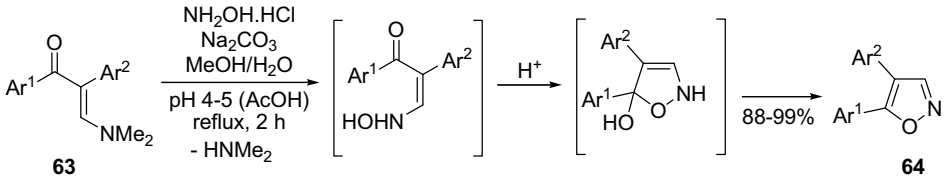
8 [110]





Scheme 9.4

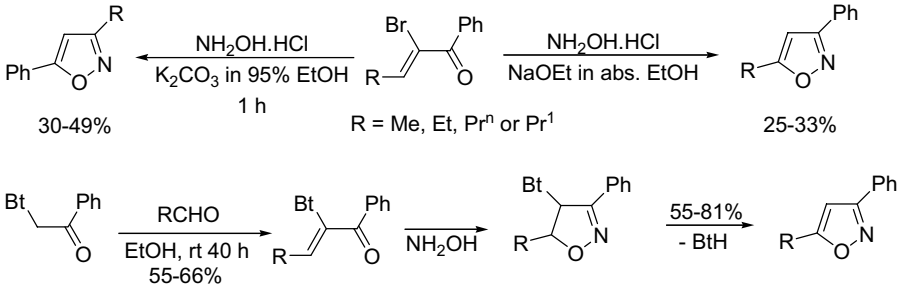
isoxazoles **64** (Scheme 9.5) [95]. This strategy has been applied to the synthesis of the cholinergic channel activator ABT-418 [99].



Scheme 9.5

The reaction of 2-acyl-3-(dimethylamino)propenoates with hydroxylamine in refluxing methanol leads to 5-substituted isoxazole-4-carboxylates in high yields (68–90%) [100] and open-chain and cyclohexane *syn*-2-(dimethylamino)ethylene-1,3-diones are converted into 5-substituted 4-acylisoxazoles [101]. A cellulose-based resin has also been used to prepare 5-substituted isoxazole-4-carboxylates via *in situ* generation of a polymer-bound enaminone [101–103]. The same strategy can be used to prepare tri-substituted isoxazoles. In fact, a β-enamino ketoester reacts with hydroxylamine hydrochloride in the presence of triethylamine to give a tri-substituted isoxazole (e.g., Table 9.5, entry 5) [104–107].

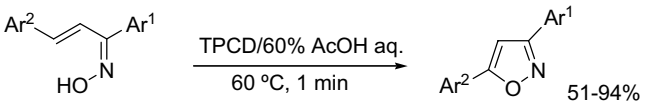
The reaction of vinyl ketones bearing a potential leaving group (bromo or benzotriazole) at the α position with hydroxylamine has also been reported (Scheme 9.6) [111, 112]. Depending on the leaving group or the experimental conditions 3(5)-substituted-5(3)-phenylisoxazoles are regioselectively obtained.



Scheme 9.6

Reaction conditions were found to allow the exclusive formation of isoxazole-5-carboxylic acid derivatives by conjugate addition, in acidic medium, of hydroxylamine to a β-alkoxyvinyl trichloromethyl ketone (Table 9.5, entry 6) [108]. The trichloromethyl group is the carboxyl group precursor: using water as solvent it leads to the formation of carboxylic acids whereas the use of an alcohol leads to ester derivatives. In contrast, the β-perfluoroalkyl-β-alkoxyvinyl phenyl ketone undergoes a selective attack on the carbonyl group upon reacting with hydroxylamine in basic medium, affording an isoxazole bearing a perfluoroalkyl substituent (Table 9.5, entry 7) [109].

Isoxazoles can be obtained via oxidative cyclization of α,β-unsaturated oximes with iodine/potassium iodide [113], with N-bromosuccinimide [114] or with palladium complexes in the presence of sodium phenoxide [115]. 3,5-Diarylisoxazoles can also be obtained using lead(IV) acetate as oxidant, although in moderate yields (24–28%) [116]. The method of preparation of 3,5-disubstituted isoxazoles by oxidative closure of α,β-unsaturated oximes can be carried out using tetrakis(pyridine)cobalt(II) dichromate (TPCD) as oxidant, under mild reaction conditions and very short reaction time (Scheme 9.7) [117]. A route to ABT-418 involving the same type of strategy for the isoxazole ring has been described [118].



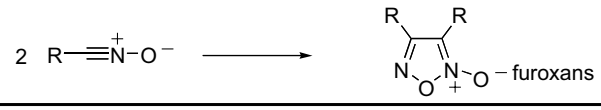
Scheme 9.7

The synthesis of isoxazoles attached to sugar moieties via oxidative cyclization of α,β-unsaturated oximes has been reported [119]. The isoxazoles were obtained by reacting the oximes with potassium iodide and sodium hydrogen carbonate at 100 °C (64–68% yield).

The reaction of α,β-alkynic ketones with hydroxylamine hydrochloride gives 3- or 5-substituted isoxazole isomers, depending on the conditions used (Table 9.5, entry 8) [110]. This route to isoxazoles has been applied to the synthesis of non-proteinogenic isoxazole substituted α-amino acids [120].

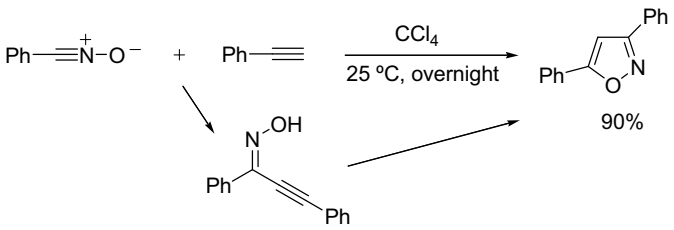
9.4.1.1.2 **[CNO + CC] Reactions: 1,3-Dipolar Cycloaddition of Nitrile Oxides** The study of Quilico *et al.* on the formation of isoxazoles from nitrile oxides and unsaturated compounds is a milestone in the chemistry of isoxazoles [7]. Since then, the 1,3-dipolar cycloaddition of nitrile oxides has became an important approach to isoxazoles [6, 10, 85, 86, 121, 122]. Nitrile oxides can undergo dimerization to give furoxans (1,2,5-oxadiazole-2-oxides), the rate of this process being strongly dependent on the nature of the nitrile oxide substituent. Thus, steric and electronic effects determine the stability of the nitrile oxides, as illustrated by the time required for complete dimerization of some derivatives (Table 9.6) [123]. To avoid dimerization, nitrile oxides are usually generated *in situ*.

Table 9.6 Stability of some nitrile oxides towards dimerization to furoxans [123].



R	Complete dimerization (at 18 °C)	R	Complete dimerization (at 18 °C)
Methyl	<1 min	*p*-Chlorophenyl	10 days
t-Butyl	2–3 days	*p*-Nitrophenyl	Very slow
Phenyl	30–60 min	2,4,6-Trimethylphenyl	Very stable

The 1,3-dipolar cycloaddition of nitrile oxides with mono-substituted alkynes (alkyl/aryl) gives the corresponding 3,5-disubstituted isoxazoles regioselectively and occurs in competition with the 1,3-addition to give acetylenic oximes, which in some cases can be isolated. These oximes can easily be converted into isoxazoles (Scheme 9.8) [124].



Scheme 9.8

A one-pot synthesis of isoxazoles from monosubstituted acetylenes with nitric acid under biphasic conditions (nitromethane–water, 1 : 1) in the presence of the catalyst $Bu_4N^+AuCl_4^-$ has been described (Table 9.7, entry 1) [125]. Nitrile oxide, generated from α-hydroxyimino carboxylic acids, in the presence of an alkyne furnishes the corresponding isoxazole (Table 9.7, entry 2) [126].

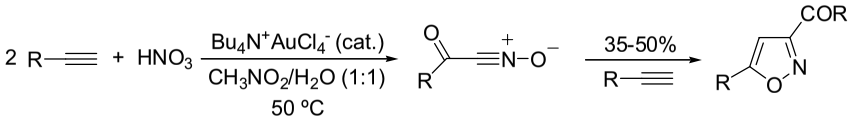
An efficient method for the *in situ* generation and cycloaddition of nitrile oxides from nitroalkanes, using 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium (DMTMM) chlorides and DMAP as catalyst through microwave irradiation has been reported. Carrying out the reaction in the presence of the appropriate alkynes, isoxazoles are obtained in high yields (Table 9.7, entries 3 and 4). This approach can also be applied to solid-phase synthesis [127].

Geometry constraints in the intramolecular 1,3-dipolar cycloaddition of nitrile oxides containing internal terminal alkynes leads to the exclusive formation of 4-substituted isoxazoles (Table 9.8).

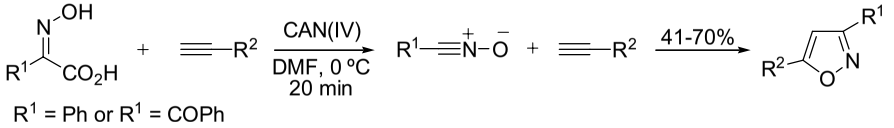
The reaction of nitrile oxides with disubstituted alkynes leads to isoxazoles exclusively via 1,3-dipolar cycloaddition when the alkyne contains at least one electron-withdrawing substituent [6, 134].

Table 9.7 1,3-Dipolar cycloaddition of nitrile oxides with mono-substituted alkynes.

1 [125]

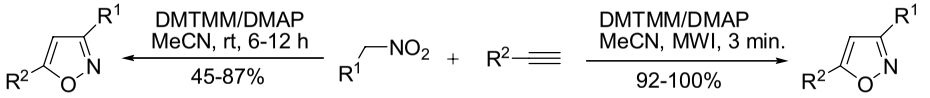


2 [126]



R^1 = Ph or R^1 = COPh

3 [127]



4 [127]

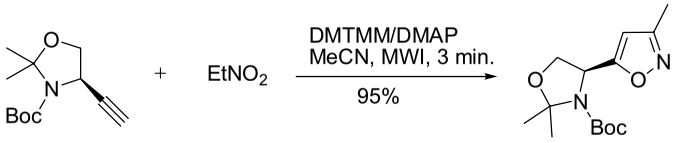
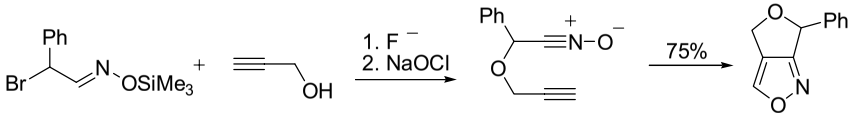
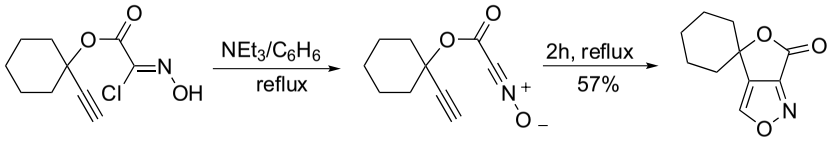
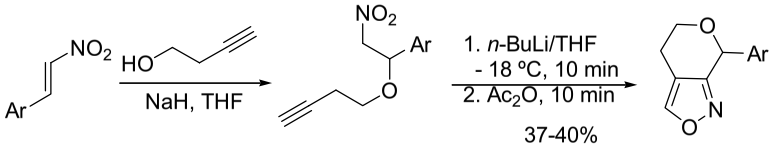
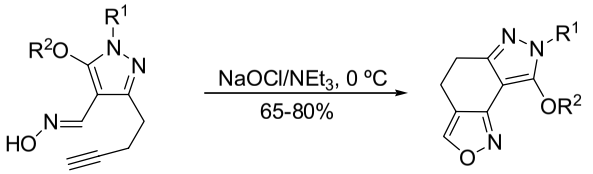
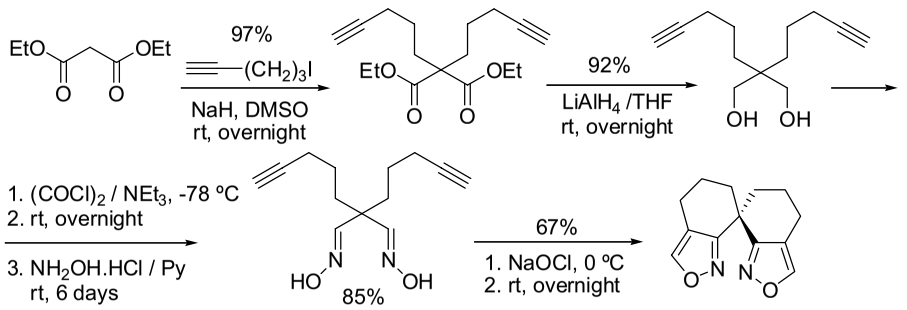
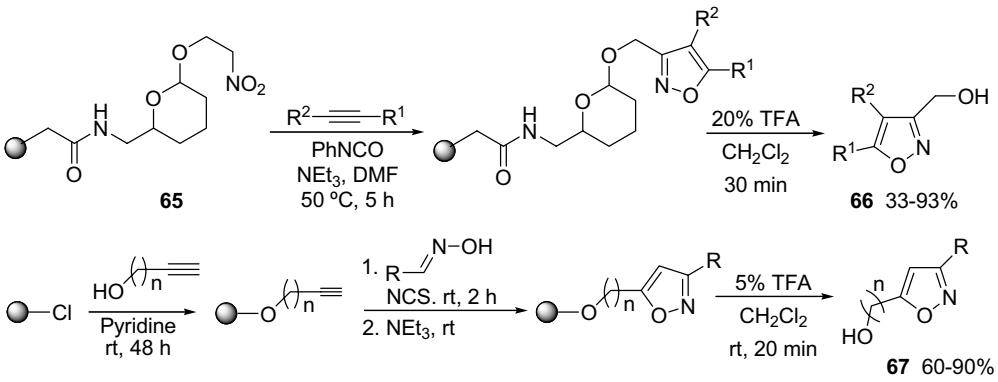


Table 9.8 Intramolecular 1,3-dipolar cycloaddition of nitrile oxides.

1 [128]	
2 [129]	
3 [130, 131]	
4 [132]	
5 [133]	

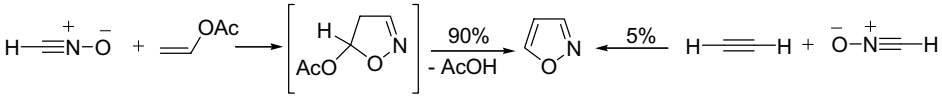
Solid-phase synthesis of 3-hydroxymethyl-4,5-disubstituted isoxazoles **66** has been achieved through a 1,3-dipolar cycloaddition of different alkynes to resin-bound nitrile oxide generated from nitro compound **65** under Mukaiyama conditions [135]. An alternative solid-phase 1,3-dipolar cycloaddition methodology allows the regioselective preparation of 5-hydroxyalkylisoxazoles **67** by anchoring acetylenic compounds on trityl chloride resin and carrying out the cycloaddition with nitrile oxides generated *in situ* from aldoximes (Scheme 9.9) [136].



Scheme 9.9

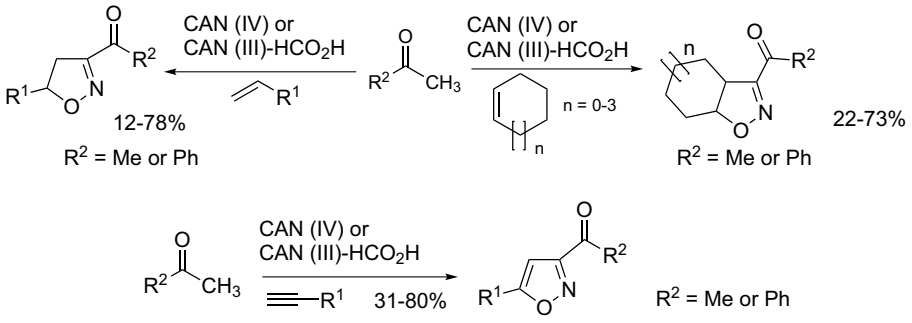
A soluble polymer-supported synthesis of 3-hydroxymethyl-5-arylisoxazole, where construction of the isoxazole ring was based on nitrile oxide cycloaddition reactions, has been reported [137–140]. An alternative route to solid-phase synthesis for the construction of a library of isoxazoles involves a solution phase combinatorial synthesis of isoxazoles via cycloaddition of nitrile oxides with alkynes followed by precipitation of the products as HCl salts [141].

The synthesis of isoxazoles via cycloaddition of nitrile oxides can also be achieved using easily available alkenes instead of alkynes and converting the resulting isoxazolines into the corresponding isoxazoles either by dehydrogenation or by elimination reaction in the case of derivatives bearing a potential leaving group. In many cases the cycloaddition of nitrile oxides to alkenes affords directly the isoxazoles due to the lability of the intermediate isoxazoline under the experimental conditions (Scheme 9.10) [10, 121, 142].



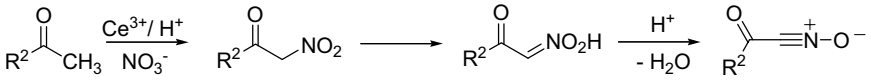
Scheme 9.10

The reaction of alkenes and alkynes with cerium ammonium nitrate (CAN) in acetone or acetophenone under reflux gives 4,5-dihydroisoxazoles or isoxazoles, respectively (Scheme 9.11) [143]. The reaction mechanism involves the nitration of



Scheme 9.11

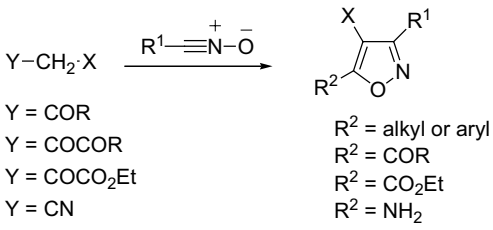
acetone or acetophenone mediated by CAN (IV) or CAN (III) followed by the generation of the corresponding nitrile oxide (Scheme 9.12). The 3-acetyl- and 3-benzoylisoxazole derivatives are obtained by 1,3-dipolar cycloaddition of this dipole with the alkenes or alkynes.



Scheme 9.12

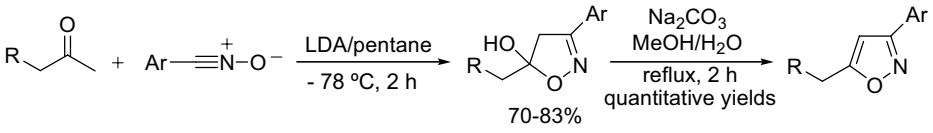
Further examples of the use of 1,3-dipolar cycloaddition of nitrile oxides with alkenes and alkynes for the synthesis of isoxazoles have been published [144–155].

An alternative approach to the regioselective construction of the isoxazole ring involves the reaction of nitrile oxides with doubly activated methylene groups containing at least one carbonyl or nitrile substituent. This group ends up in the 5-position of the isoxazole: an acyl group as an alkyl or aryl group, 2-oxoacyl group as an acyl group, an ethoxyoxoacyl as an ethoxycarbonyl group, and a nitrile as an amino group (Scheme 9.13) [10, 156–159].



Scheme 9.13

Several 3-aryl-5-alkylisoxazoles were synthesized in good yields by reacting arylnitrile oxides with free enolates, obtained from alkyl methyl ketones, followed by dehydration (Scheme 9.14) [160].

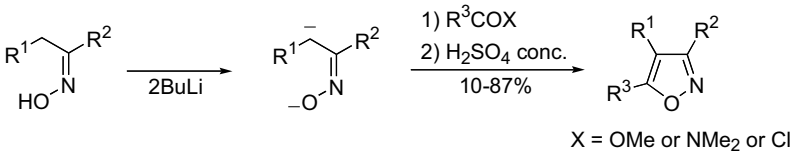


Scheme 9.14

Polyisoxazole systems containing two or more isoxazole rings can be constructed using the 1,3-dipolar cycloaddition of nitrile oxides. Starting from bisnitrile oxides the reaction with alkynes leads to 3,3′-linkage of the isoxazole rings whereas the cycloaddition of nitrile oxides with diynes produces a 5,5′-linkage [6, 161–165].

9.4.1.2 [4 + 1] Routes

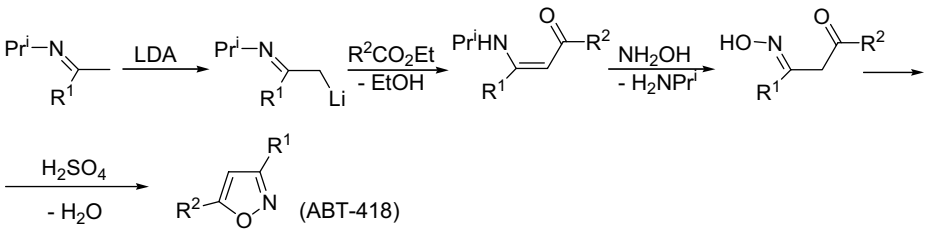
9.4.1.2.1 **[CCNO + C] Reactions: Reactions of Oxime Dianions with Carbonyl Compounds** The reaction of oxime dianions with carbonyl compounds (e.g., esters, amides or aroyl chlorides) is an alternative regioselective method for the construction of the isoxazole ring (Scheme 9.15). The anion is acylated on carbon followed by cyclization–dehydration to give the unsymmetrically substituted isoxazoles. The same type of reaction can be carried out with benzonitriles, benzaldehydes and benzophenones [6, 10]. The condensation of 1,4-dilithiooximes with amides usually leads to higher yields than the reaction with aromatic esters [166–168].



Scheme 9.15

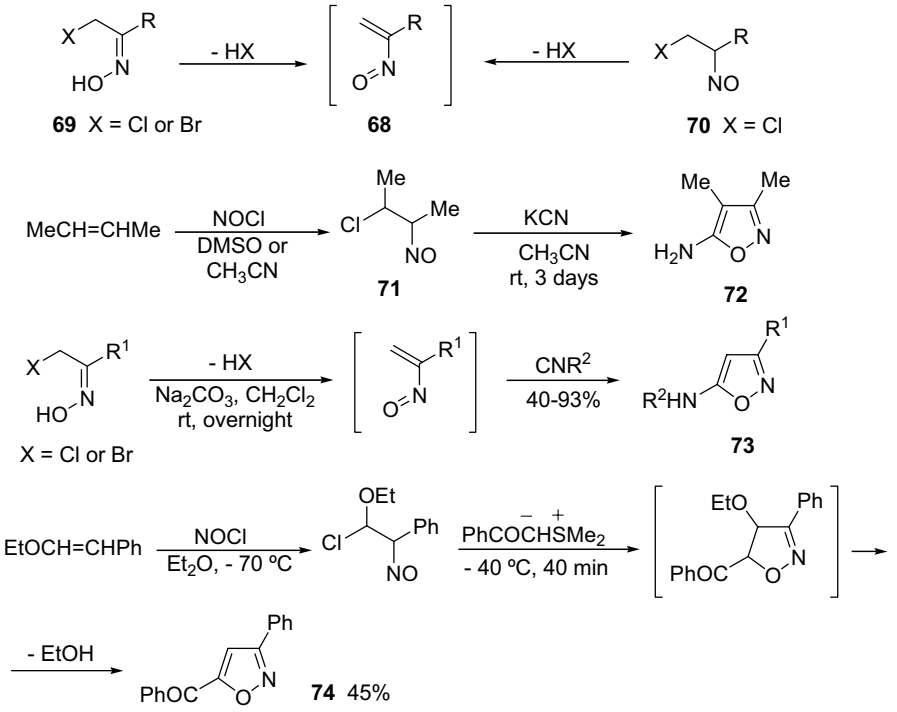
A regiocontrolled route to isoxazoles has been reported that is a modification of the oxime dianion method (Scheme 9.16) [169].

9.4.1.2.2 **[CCNO + C] Reactions: via Nitrosoalkenes** Isoxazoles can be obtained from the reaction of nitrosoalkenes **68**, generated *in situ* by dehydrohalogenation



Scheme 9.16

of α-halooximes **69** or of the isomeric nitroso compounds **70**, with a C synthon (Scheme 9.17). The formation of alkene-nitrosyl chloride adduct **71** followed by reaction with cyanide affords 5-aminoisoxazoles **72** [170]. N-Substituted 5-aminoisoxazoles are usually prepared through N-functionalization of 5-aminoisoxazoles. However, such derivatives can also be produced directly from oximes of α-haloketones and isocyanides in the presence of sodium carbonate [171]. The process is thought to involve a [4 + 1] cycloaddition of the transient nitrosoalkene with isocyanides to give **73**. The C synthon can also be a keto-stabilized sulfonium ylide, as illustrated by the reaction of benzoylsulfonium ylide with (2-chloro-2-ethoxy-1-nitrosoethyl)benzene leading to isoxazole **74** [172].

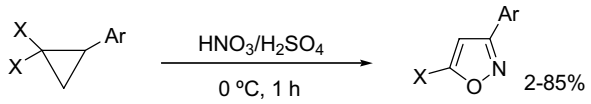


Scheme 9.17

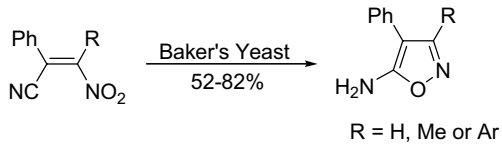
9.4.1.3 [5 + 0] Routes

9.4.1.3.1 **[CCCNO] Reactions** Reaction of 1,1-dihalo-2-arylcyclopropanes, bearing electron-accepting substituents in the aromatic ring, with a mixture of nitric acid and sulfuric acid leads to halogen-substituted isoxazoles (Scheme 9.18) [173–174].

A simple procedure for the synthesis of 5-aminoisoxazoles takes advantage of the biohydrogenation of nitroacrylonitriles (R=H, Me or Ar) with baker's yeast (Scheme 9.19) [175]. The reduction of nitroacrylonitriles as a route to isoxazoles



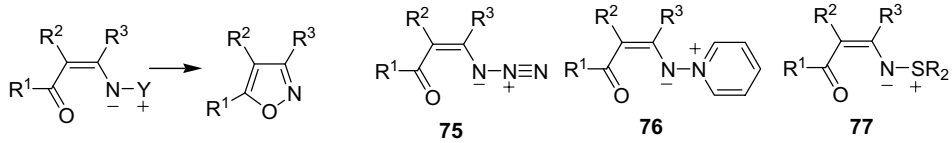
Scheme 9.18



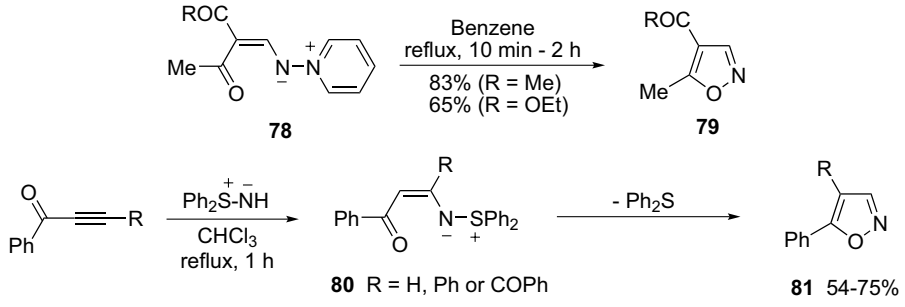
Scheme 9.19

can also be carried out electrochemically or by reduction or by treatment with thiophenol in basic medium [10].

9.4.1.3.2 **[OCCCN] Reactions** Cyclization of α,β-unsaturated ketones or esters bearing an appropriate nitrogen-containing substituent in the β-position can lead to the corresponding isoxazole derivatives (Scheme 9.20). The nitrogen atom can undergo a nucleophilic attack by the carbonyl oxygen atom if a good leaving group is present. However, the formation of an β-acylvinylnitrene as intermediate cannot be excluded. Examples of this type of isoxazole precursors are β-azidovinyl ketones or esters **75**, *N*-(1-pyridinio)acylvinylaminides **76** and acylvinylsulfinimines **77** [6, 10]. The *N*-(1-pyridinio)acylvinylaminides **78** undergo N−N bond cleavage upon heating in benzene to give isoxazoles **79** [176]. Acylvinylsulfinimines **80** [177], generated from the reaction of diphenylsulfilimine with benzoylacetylenes, allows the synthesis of isoxazoles **81** (Scheme 9.21).

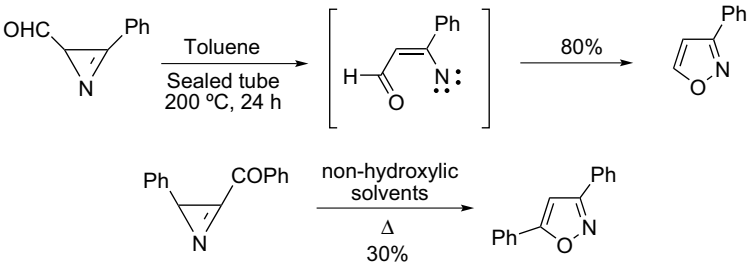


Scheme 9.20



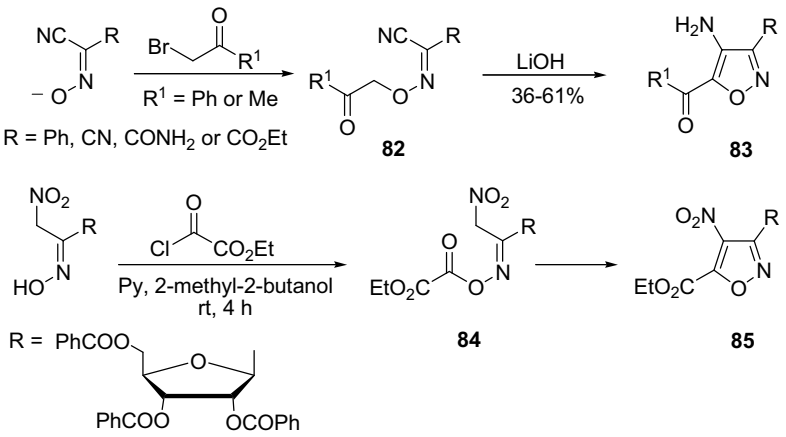
Scheme 9.21

The thermolysis of 3-phenyl-2*H*-azirine-2-carbaldehyde at 200 °C leads to 3-phenylisoxazole in high yield [178]. The same isoxazole can also be obtained in 90% yield by treatment of 3-phenyl-2*H*-azirine-2-carboxaldehyde at 25 °C with Grubbs' catalyst [179]. Furthermore, 2-benzoyl-3-phenyl-2*H*-azirine affords the corresponding isoxazole upon heating in non-hydroxylic solvents [180] (Scheme 9.22).



Scheme 9.22

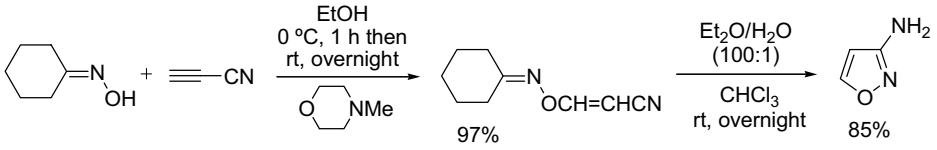
9.4.1.3.3 **[CONCC] Reactions** Lithium hydroxide-catalyzed cyclization of α-(acylmethoxyimino)nitriles **82** provides a route to 5-acyl-4-aminoisoxazoles **83** [181]. The α-nitro oximes **84** act as an CONCC synthon in the synthesis of benzoyl-protected 3-ribofuranosyl-4-nitroisoxazole-5-carboxylate **85** (Scheme 9.23) [182].



Scheme 9.23

9.4.1.3.4 **[NOCCC] Reactions** 3-Aminoisoxazole can be synthesized by the hydrolysis and ring closure of vinyl-substituted oximes under acidic conditions

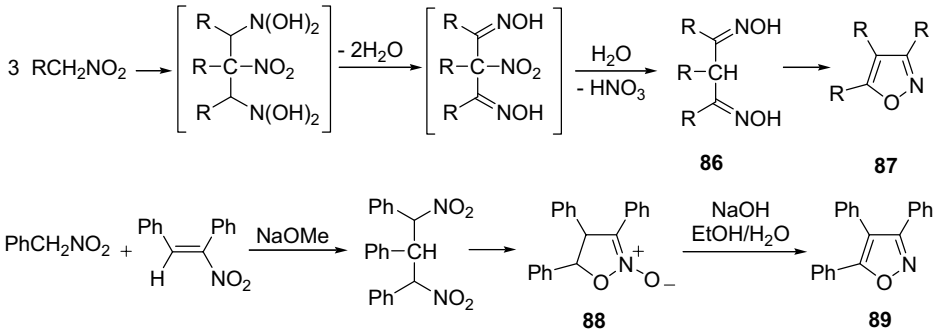
(Scheme 9.24) [183]. Similar results are obtained starting with other oximes (e.g., acetone oxime or ethyl acetate oxime) and the cyanoacetylene can also be replaced by β-chloroacrylonitrile [184].



Scheme 9.24

9.4.1.4 [3 + 1 + 1] Routes

9.4.1.4.1 **[ONC + C + C] Reactions** The reaction of primary nitroalkanes with organic bases affords dioximes **86** which are converted into trialkylisoxazoles **87** in high yields when heated in dilute acids [10]. In contrast, the reaction of phenylnitromethane with *cis*-α-nitrostilbene gives isoxazoline-*N*-oxide **88**. Treatment of **88** with aqueous alcoholic sodium hydroxide allows the synthesis of triphenylisoxazole **89** (Scheme 9.25) [185]. Trisubstituted isoxazoles can also be obtained from the reaction of nitroalkanes with aldehydes in the presence of a base [10, 186].

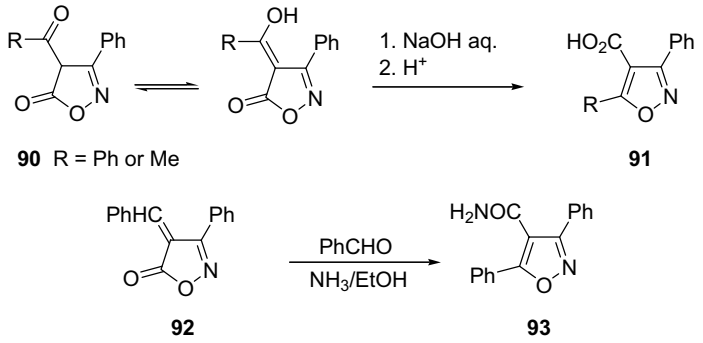


Scheme 9.25

9.4.1.5 Ring Transformations of Heterocycles Leading to Isoxazoles

4-Acylisoxazolin-5-ones **90** rearrange to the isomeric isoxazole-4-carboxylic acids **91** upon treatment with aqueous sodium hydroxide [187]. 4-Benzylidene-3-phenylisoxazolin-5-one (**92**) is converted into isoxazole **93** upon treatment with anhydrous ammonia in ethanol in the presence of benzaldehyde (Scheme 9.26) [188].

The reaction of hydroxylamine with 2-substituted or 3-substituted chromones gives exclusively the corresponding 5-(2-hydroxyphenyl)isoxazoles (Scheme 9.27) [10]. The reaction involves the opening of the chromone ring followed by the formation



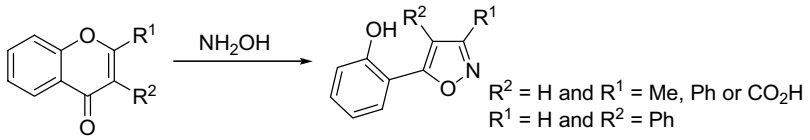
90 R = Ph or Me

91

92

93

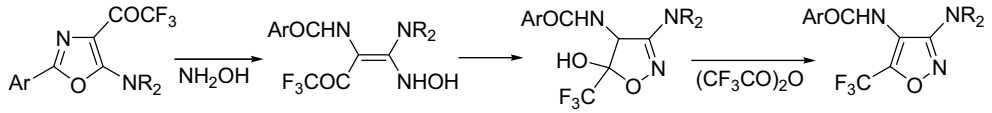
Scheme 9.26



Scheme 9.27

of 5-(2-hydroxyphenyl)isoxazole in 72% overall yield [189, 190]. Some of these isoxazole derivatives show anti-inflammatory related activity.

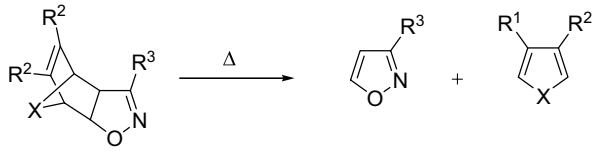
The 5-amino-4-trifluoroacetyloxazoles **94** can be used in a two-step synthesis of isoxazoles **96** (Scheme 9.28). Nucleophilic attack of hydroxylamine at the five position of **94** leads to ring opening followed by a cyclization to give isoxazoline **95**. Subsequent dehydration in the presence of trifluoroacetic anhydride allows the synthesis of isoxazoles in good yields [191].



94 **95** **96**

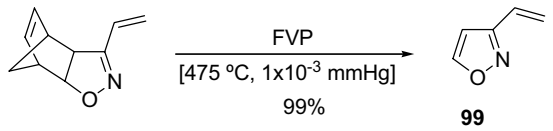
Scheme 9.28

Isoxazolines with the general structure **97** undergo cycloreversion to give isoxazoles **98** (Scheme 9.29) [6]. The parent isoxazole can be prepared in 37% yield by the thermolysis of the cycloadduct obtained from fulminic acid (HCNO) and norbornadiene [192]. This type of approach can also be used to the synthesis of 3-vinylisoxazole (**99**), which is unsubstituted at both the 4- and 5-positions. The two-step procedure involves initial 1,3-dipolar cycloaddition of acrylonitrile oxide to norbornadiene followed by retro-Diels–Alder fragmentation under flash vacuum pyrolysis [193].



97 X = CH, O, NH, CR=CR

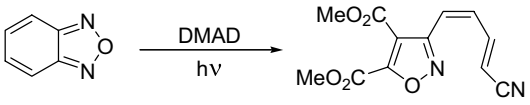
98



99

Scheme 9.29

Furazans (1,2,5-oxadiazoles) undergo fragmentation to nitrile and nitrile *N*-oxides by thermolysis or photolysis. Irradiation of benzofurazan in the presence of dimethyl acetylenedicarboxylate (DMAD) to give isoxazole **100** is an illustrative example of this approach (Scheme 9.30) [194, 195].



100

Scheme 9.30

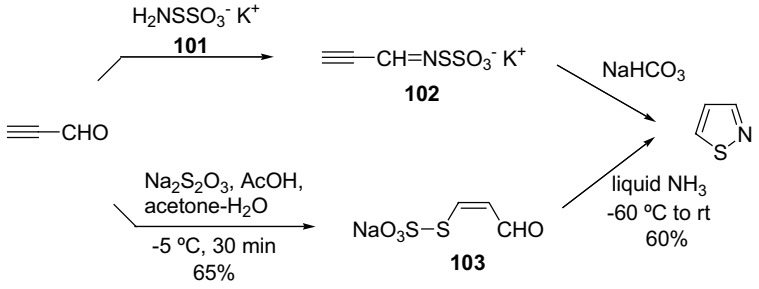
9.4.2 Isothiazoles

The first synthesis of a mononuclear isothiazole ring system was reported in 1956 [15]. Oxidation of 5-amino-1,2-benzisothiazole by alkaline permanganate gives isothiazole-4,5-dicarboxylic acid. Decarboxylation to isothiazole-4-carboxylic acid followed by functional group interconversion leads to the isothiazole itself and a range of monosubstituted isothiazoles [15].

The chemistry of isothiazoles has been reviewed [25–29]. The most convenient methods for the construction of the isothiazole ring involve: (i) oxidative cyclization of a γ-thio amine derivative (formation of the S–N bond), (ii) 1,3-dipolar cycloaddition of nitrile sulfides to alkynes or alkenes and (iii) conversion of other heterocycles into isothiazoles. Examples of such synthetic methodologies are described below.

9.4.2.1 Synthesis from Acyclic Compounds

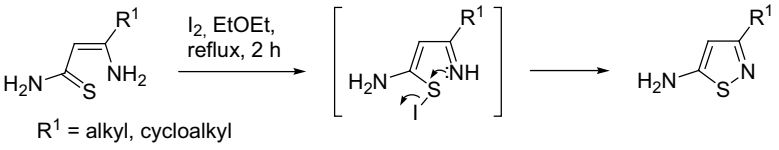
Isothiazole itself can be prepared from propynal by two distinct routes (Scheme 9.31). It reacts with thiohydroxylamino-*S*-sulfonate (**101**) to give the thiooxime intermediate



Scheme 9.31

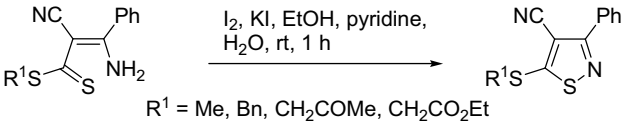
102, which, in the presence of $NaHCO_3$, cyclizes to isothiazole [21]. In the second route, propynal and sodium thiosulfate afford the intermediate **103**, which on treatment with ammonia cyclizes to isothiazole [196]. 3-Methylisothiazole can be obtained by a similar synthetic procedure, changing propynal by but-3-yn-2-one [196].

There are several routes to isothiazoles based on oxidative cyclization reactions in which the N–S bond is formed. A good leaving group attached to the sulfur atom is required, which frequently is introduced by reaction with iodine (Scheme 9.32) [197, 198].



Scheme 9.32

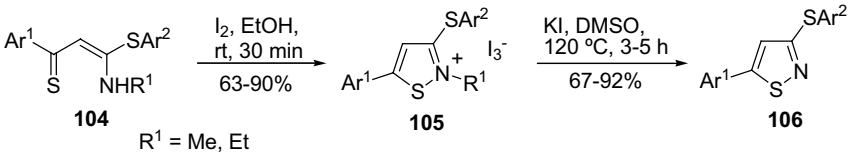
Oxidation of 3-amino-2-cyano-3-phenylpropenedithioates with iodine produces 3-phenyl-5-alkylthioisothiazole-4-carbonitriles in near-quantitative yield (Scheme 9.33) [199].



Scheme 9.33

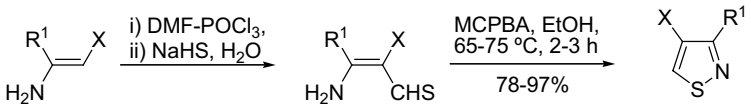
Ketene *S,N*-acetals **104** give the isothiazolium salts **105** in good yields when treated with iodine at room temperature. Dealkylation with KI in DMSO affords the corresponding 5-aryl-3-(arylthio)isoxazoles **106** (Scheme 9.34) [200].

Enamino thioaldehydes **108** can be converted in good yields into 3,4-disubstituted isothiazoles **109** by oxidation with *m*-chloroperbenzoic acid (Scheme 9.35) [201]. Oxidation of enamino thioaldehydes **108** (generated from **107a**) with iodine, at room



R^1 = Me, Et
Ar^1 = Ph, XC_6H_4 (X = Cl, 3-MeO, 4-MeO)
Ar^2 = Ph, XC_6H_4 (X = Cl, Br, MeO), 2-naphthyl

Scheme 9.34

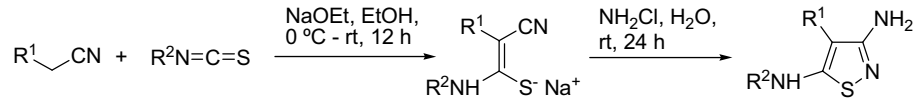


107a, X = CO_2R (R = Me, Et)
107b, X = CN
R^1 = alkyl, aryl

Scheme 9.35

temperature, also affords the corresponding isothiazoles **109** in moderate to good yields [202]. Thioaldehydes **108** may be synthesized from enamines **107** by solvolysis of the corresponding Vilsmeier salts with aqueous or methanolic sodium hydrogen sulfide [201, 202].

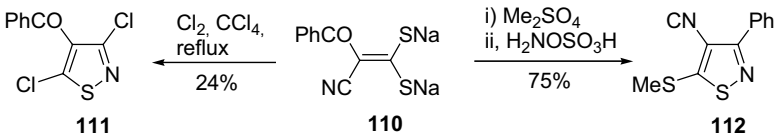
3,5-Diaminoisothiazole-4-carboxylate derivatives can be prepared in a one-pot reaction from active methylene nitriles, isothiocyanates and chloramine (Scheme 9.36) [203]. Reactions starting from malononitrile give the corresponding isothiazole in higher yields (41–65%).



R^1 = CN, CO_2R (R = Me, Et, ^{t}Bu); R^2 = alkyl, aryl

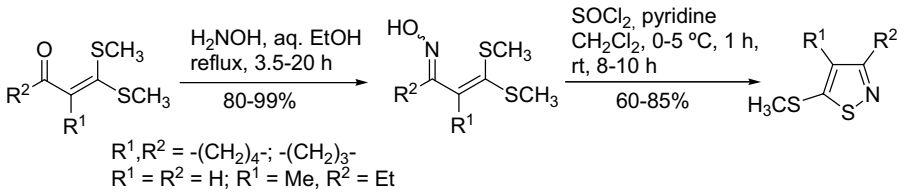
Scheme 9.36

Dithiolate disodium salt **110** reacts with chlorine to give 4-benzoyl-3,5-dichloroisothiazole (**111**) in low yield. However, the same compound can be monomethylated and reacted with hydroxylamine-*O*-sulfonic acid to afford isothiazole **112** in a global 75% yield (Scheme 9.37) [204].



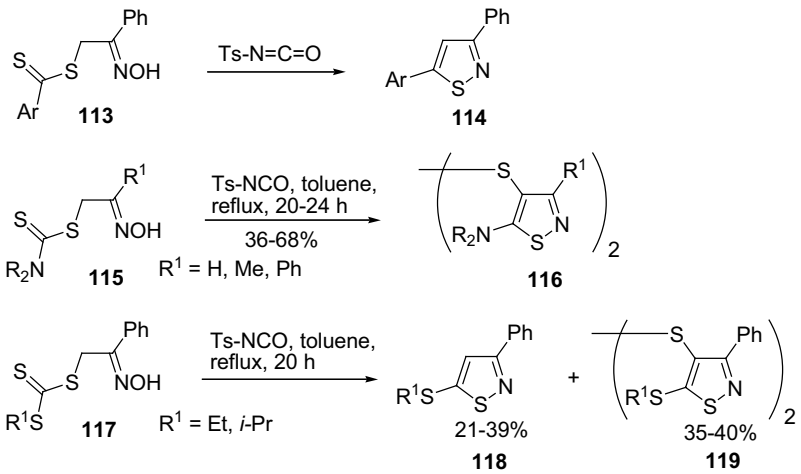
Scheme 9.37

Oximes are also useful intermediates in the synthesis of isothiazoles. For instance, oximes derived from α-oxoketene dithioacetals cyclize to 5-methylthioisothiazoles when treated with thionyl chloride in pyridine (Scheme 9.38) [205].



Scheme 9.38

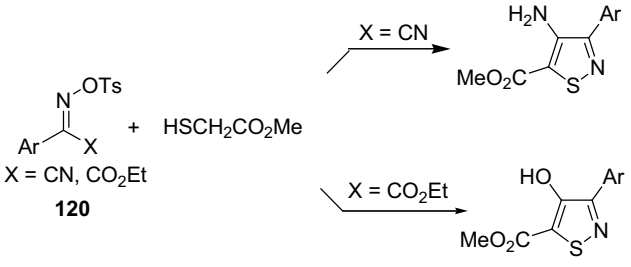
Oxime derivatives **113** are converted into isothiazoles **114** by reaction with a dehydrating agent, namely tosyl isocyanate [206]. Similarly, the 2-(hydroxyimino)alkyl *N,N*-dialkyldithiocarbamates **115** and the analogous trithiocarbonates **117** react with tosyl isocyanate to afford the bis(4-isothiazolyl) disulfides **116** or **119** and the disubstituted isothiazoles **118** (Scheme 9.39) [207].



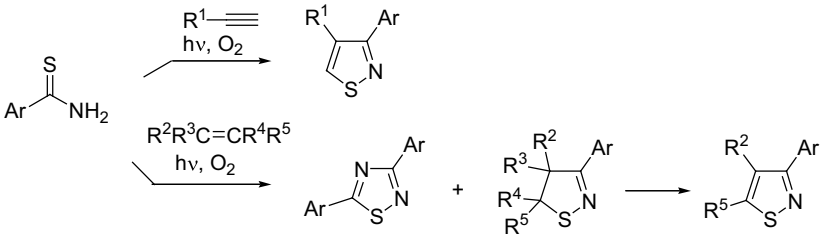
Scheme 9.39

Oxime tosylates of type **120** react with methyl thioglycolate to give 4-amino or 4-hydroxyisothiazole-5-carboxylate esters (Scheme 9.40) [208, 209]. This synthetic methodology has been used to prepare ethyl 4-aminoisothiazole-5-carboxylate *C*-nucleosides [210].

Photoreaction of arylthioamides with alkenes and alkynes, under aerobic conditions, yields isothiazoles and 1,2,4-thiadiazoles in low to moderate yields (Scheme 9.41). Nitrile sulfides are probable intermediates in these reactions [211].

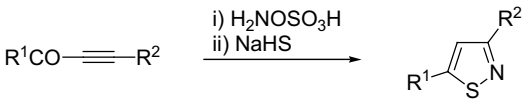


Scheme 9.40



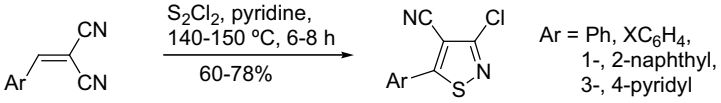
Scheme 9.41

α-Acetylenic aldehydes or ketones are converted into 4-unsubstituted isothiazoles by reaction with hydroxylamine-*O*-sulfonic acid and sodium hydrogen sulfide in buffered aqueous solution in a one-pot procedure (Scheme 9.42) [212].



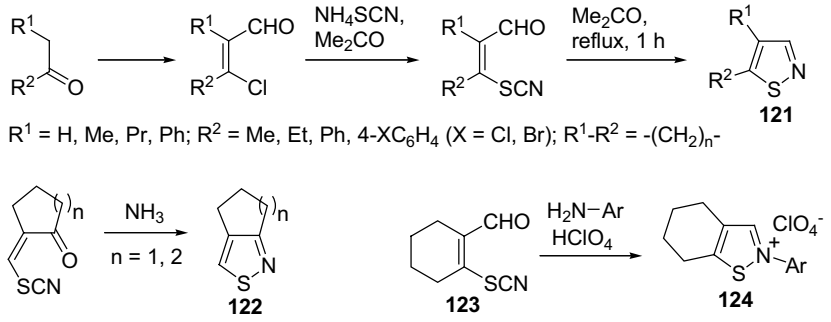
Scheme 9.42

Arylmethylene-malononitriles react with sulfur chloride in the presence of pyridine to give 5-aryl-3-chloroisothiazole-4-carbonitriles in high yields (Scheme 9.43) [213].



Scheme 9.43

3-Chloroalk-2-enals react with ammonium thiocyanate to afford 4,5-disubstituted isothiazoles **121** (Scheme 9.44) [214, 215]. Cycloalka[*c*]isothiazoles **122** can be prepared by a similar method [216]. 2-Thiocyanatocyclohex-1-ene carbaldehyde (**123**) reacts with anilines to afford isothiazolium salts **124** [217].



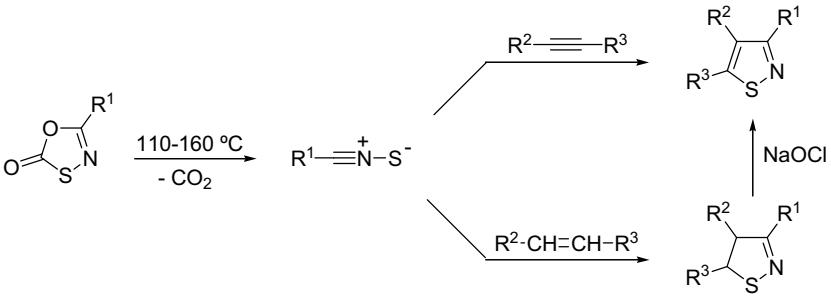
Scheme 9.44

Methacrylonitrile reacts with trithiazyl trichloride $(NSCl)_3$ in the presence of excess SO_2Cl_2, in refluxing chloroform, to give 4-cyanoisothiazole in 78% yield [218].

9.4.2.2 Ring Transformations of Heterocycles Leading to Isothiazoles

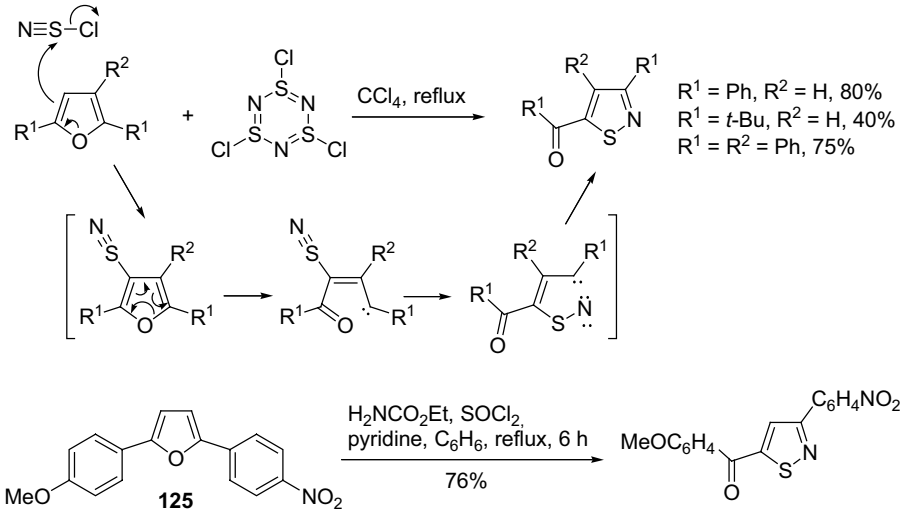
Several heterocyclic compounds can, by chemical modification, be converted into isothiazoles. Despite some synthetically interesting exceptions, in most cases the starting heterocycles are not readily available and the routes are unlikely to be general.

A synthetically useful method involves the generation of nitrile sulfides in the presence of alkynes or alkenes, affording isothiazoles or 4,5-dihydroisothiazoles, respectively (Scheme 9.45). The nitrile sulfides are conveniently generated *in situ* by thermal cycloreversion of five-membered heterocycles already containing the C=N-S unit [219]. Decarboxylation of 1,3,4-oxathiazol-2-ones in an inert solvent (e.g., xylene, chlorobenzene) in the presence of an excess of the dipolarophile is one of the most convenient routes [220–223]. Using dimethyl acetylenedicarboxylate as dipolarophile, the isothiazole-4,5-dicarboxylates are obtained in yields as high as 96% [221]. The low regioselectivity observed in the reactions of nitrile sulfides with unsymmetrical alkynes and alkenes is a major disadvantage of this method. Oxidation of 4,5-dihydroisothiazoles with sodium hypochlorite, under phase-transfer conditions, affords the isothiazoles in high yields [223].



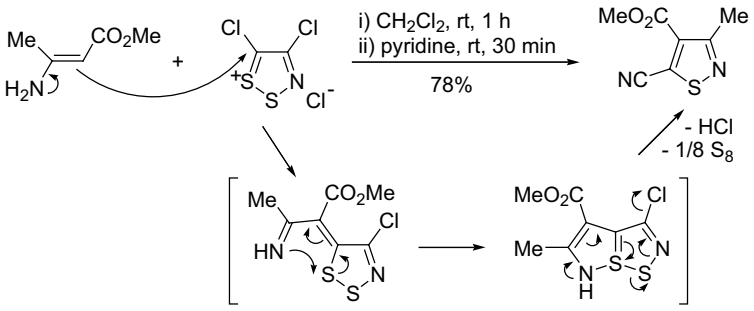
Scheme 9.45

Both 2,5- and 2,3,5-substituted furans react with trithiazyl trichloride $(NSCl)_3$ to afford 5-acylisothiazoles in good yield (Scheme 9.46) [224, 225]. A much simpler procedure makes use of a mixture of ethyl carbamate, thionyl chloride and pyridine in boiling benzene or toluene; this generates the reactive thiazyl chloride, NSCl, *in situ* [226, 227]. Highly polarized 2,5-disubstituted furans (such as **125**) yield only one isothiazole. However, when the electronic properties of the substituents are more balanced, two isomeric isothiazoles are formed [225, 227]. The thiazyl chloride reagent has been used for the direct conversion of calix[*n*]furans into macrocyclic isothiazoles [228].



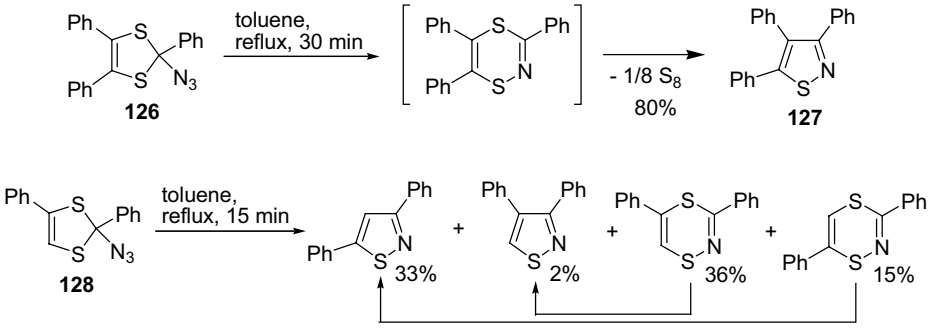
Scheme 9.46

4,5-Dichloro-1,2,3-dithiazolium chloride reacts with methyl 3-aminocrotonate at room temperature to give 5-cyano-3-methylisothiazole-4-carboxylate in 78% yield (Scheme 9.47) [229].



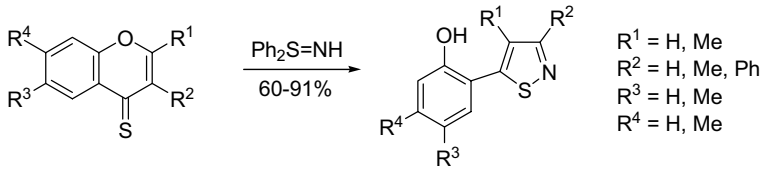
Scheme 9.47

Thermolysis of triphenyl-1,3-dithiol-2-yl azide (**126**) in refluxing toluene gives 3,4,5-triphenylisothiazole (**127**) in 80% yield. However, under identical conditions, the diphenyl analogue **128** affords a mixture of isothiazoles and 1,4,2-dithiazines (Scheme 9.48). These dithiazines, when refluxed in toluene, extrude the sulfur atom at the 4-position to give, selectively, one isothiazole [230].



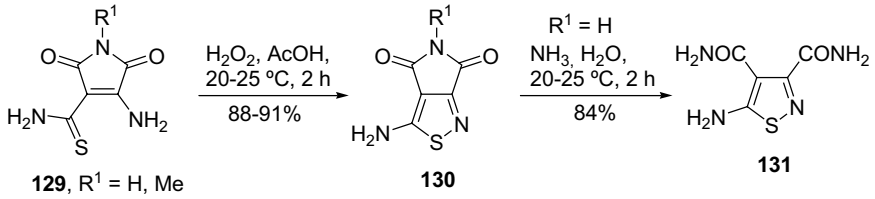
Scheme 9.48

Benzopyran-4-thiones react with diphenylsulfilimine to give the corresponding 5-(2-hydroxyphenyl)isothiazoles in high yields (Scheme 9.49) [231].



Scheme 9.49

Maleimide derivatives **129** undergo oxidative cyclization to give isothiazole-3,4-dicarboximides **130** (Scheme 9.50) [232]. By ammonolysis, the *N*-unsubstituted derivative affords 5-aminoisothiazole-3,4-dicarboxamide (**131**).

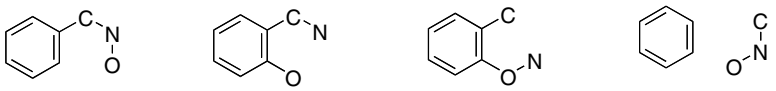


Scheme 9.50

9.5
Synthesis of Benzisoxazoles and Benzisothiazoles

9.5.1
1,2-Benzisoxazoles

Most synthetic approaches to 1,2-benzisoxazoles involve cyclization of a suitable benzene derivative and can be represented as follows:



1,2-Benzisoxazoles can also be obtained from 3-3a bond formation in the cyclization processes. The remaining methodology involves heterocyclic rearrangements.

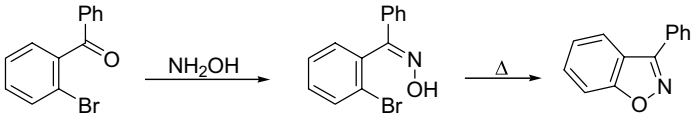
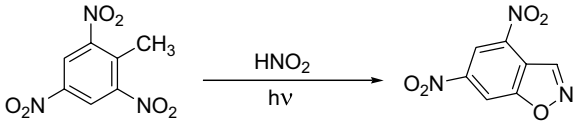
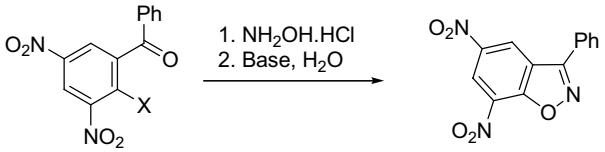
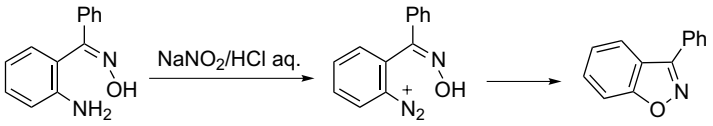
9.5.1.1 **Formation of Bond 7a-1**

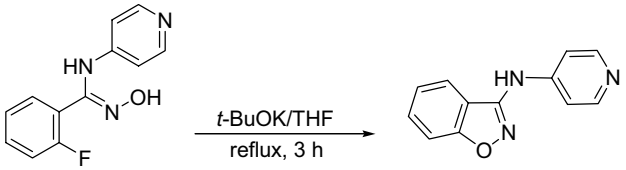
The first synthesis of a 1,2-benzisoxazole was reported in 1892, 3-phenyl-1,2-benzisoxazole **132**, and involved the reaction of hydroxylamine with *ortho*-bromobenzophenone in alkaline medium [30]. However, 1,2-benzisoxazole had been known since 1882, obtained from the reduction of *ortho*-nitrobenzaldehyde with tin and hydrochloric acid [233]. This base-promoted intramolecular displacement reaction for formation of the 7a-1 bond has became an important route to 1,2-benzisoxazoles. Other halogens also undergo this type of displacement, with the reactivity of iodide and fluoride comparable with bromide but chloride less reactive [10, 234]. The displaceable groups also include nitro, amino, methoxy and hydroxyl groups (Scheme 9.51 and Table 9.9).

Scheme 9.51

The course of the reaction is determined by the configuration of the oxime. A *syn* relationship of the OH to the aryl substituent bearing the leaving group allows cyclization to 1,2-benzisoxazole whereas the isomeric oximes usually produce Beckman rearrangement products [234]. Amidoximes are configurationally labile, allowing the use of the *anti* oxime as starting material for the synthesis of 1,2-benzisoxazoles. Thus, the amide oxime **133** cyclizes to 3-(4-pyridinylamino)-1,2-benzisoxazole **134** on reacting with potassium *tert*-butoxide via an isomerization/cyclization process (Scheme 9.52) [239].

Table 9.9 Base-promoted intramolecular displacement reactions for 1,2-benzisoxazole 7a-1 bond formation.

1 [235]		
2 [236]		Via photonitrosation of trinitrotoluene
3 [237]		X = OMe or OH Requires substantial activation such as the presence of nitro groups
4 [238]		Via diazonium salt



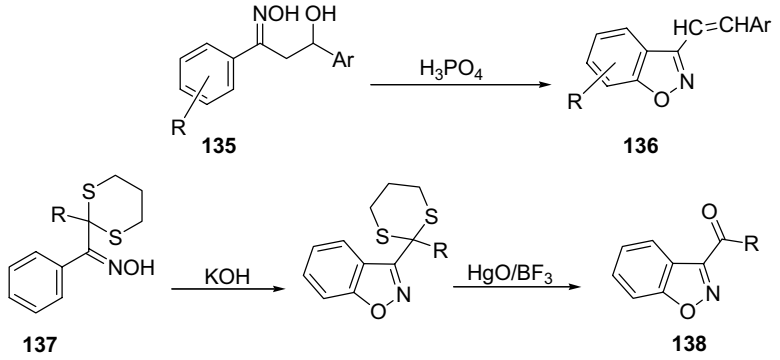
133 **134** 69%

Scheme 9.52

β-Hydroxyoximes **135**, bearing a phenyl group unsubstituted in the *ortho* positions, are converted into styrylbenzisoxazole **136** upon treatment with phosphoric acid [10]. The base cyclization of dithioacetal **137** followed by desulfurization leads to 3-acyl and 3-aroyl-1,2-benzisoxazoles (**138**) [240] (Scheme 9.53).

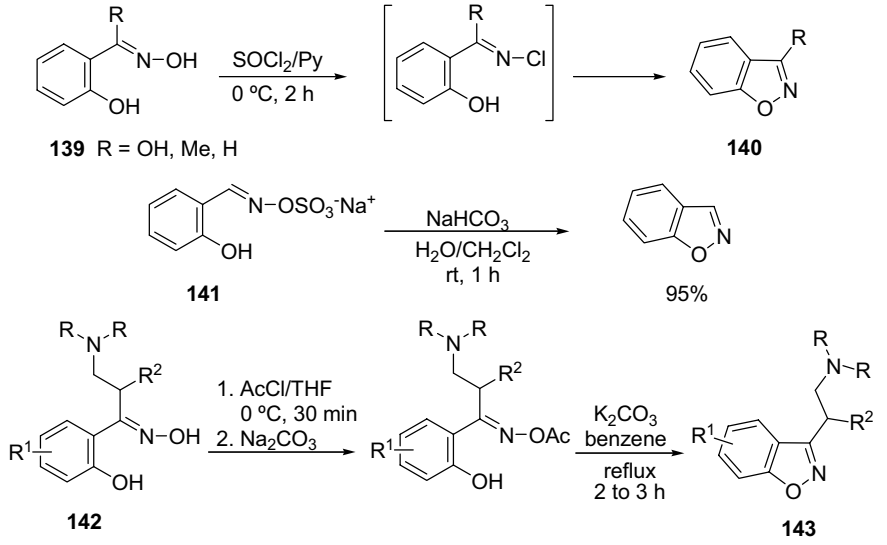
9.5.1.2 **Formation of Bond 1-2**

1,2-Benzisoxazoles can be obtained from 2-hydroxybenzophenone oximes by thermolysis, treatment with base or with dehydrating agents (e.g., sulfuric and phosphoric acid). By reacting oxime **139** with thionyl chloride/pyridine the



Scheme 9.53

1,2-benzisoxazole **140** can also be prepared [241]. The *O*-sulfonate oxime **141** is converted, in the presence of mild bases, into 1,2-benzoisoxazole in 95% yield [242]. A synthesis of 3-(2-dialkylaminoethyl)-1,2-benzisoxazoles **143** from oxime acetates of 2-hydroxyphenyl ketones **142** has also been reported [243] (Scheme 9.54). A similar synthetic approach has been applied to the synthesis of 3-[2-(1-pyrazolyl)ethyl]-1,2-benzisoxazoles [244].

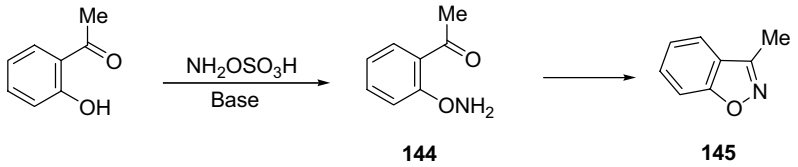


Scheme 9.54

9.5.1.3 **Formation of Bond 2-3**

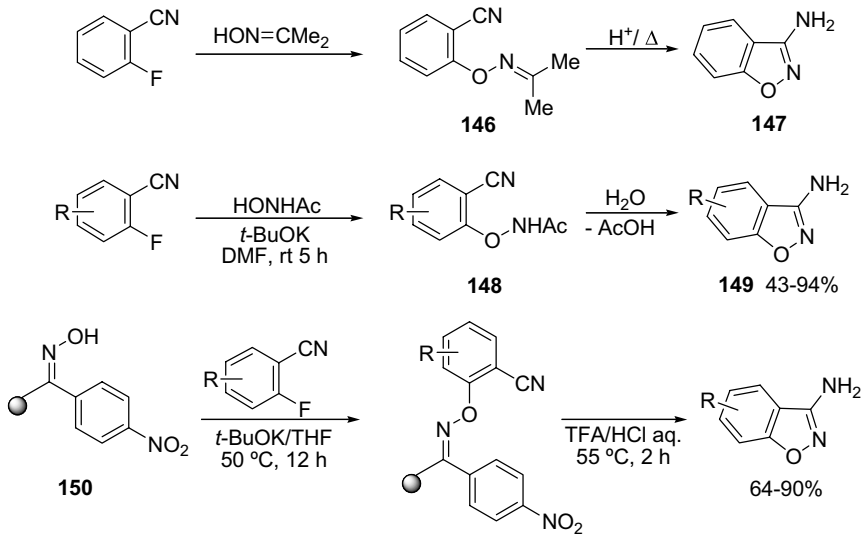
The synthesis of 3-methyl-1,2-benzisoxazole (**145**) from the reaction of 2-hydroxyacetophenone with hydroxylamine-*O*-sulfonic acid in diluted aqueous base is an

example of a 2–3 ring closure. The process occurs via the generation of intermediate **144**, which then undergoes the cyclization [9] (Scheme 9.55).



Scheme 9.55

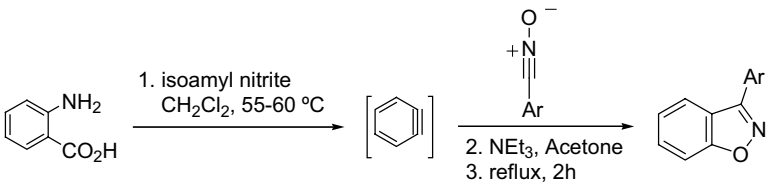
3-Amino-1,2-benzisoxazoles (**147** or **149**) can be obtained from 2-fluorobenzenonitrile [245, 246]. The synthesis involves an S_NAr reaction to give an intermediate (**146** or **148**, respectively) followed by ring-closure to give the 1,2-benzisoxazoles. A solid-phase synthesis of 3-amino-1,2-benzisoxazoles uses a similar synthetic strategy: the displacement of fluoride from 2-fluorobenzonitrile by the Kaiser oxime resin **150** followed by cyclization [247, 248] (Scheme 9.56).



Scheme 9.56

9.5.1.4 **Formation of Bonds 7a-1/3-3a**

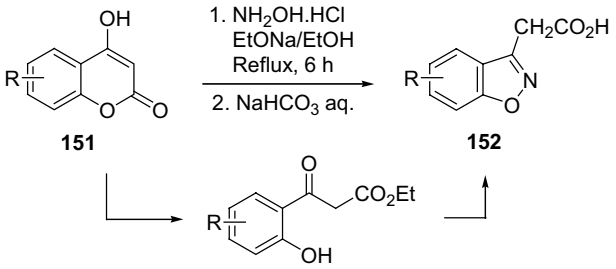
1,3-Dipolar cycloaddition of nitrile oxides to benzyne gives 3-substituted 1,2-benzisoxazoles in modest yield (Scheme 9.57) [249]. Other dipolarophiles can also be used for the synthesis of 1,2-benzisoxazole derivatives, namely 1,4-benzoquinones and enamines [9].



Scheme 9.57

9.5.1.5 **From Other Heterocycles**

The reaction of 4-hydroxycoumarin **151** (R=H) and 4-hydroxycoumarin substituted derivatives with hydroxylamine leads to 1,2-benzisoxazole-3-acetic acid **152** (Scheme 9.58) [250, 251].



Scheme 9.58

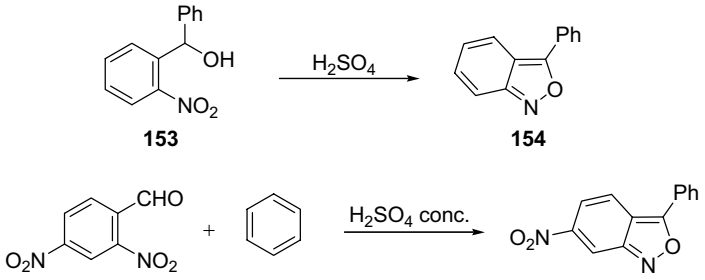
9.5.2
2,1-Benzisoxazoles

2,1-Benzisoxazoles are usually prepared by 1-2 or 2-3 bond formation in the cyclization step or by introduction of atom C3, resulting in the formation of bond 2-3.

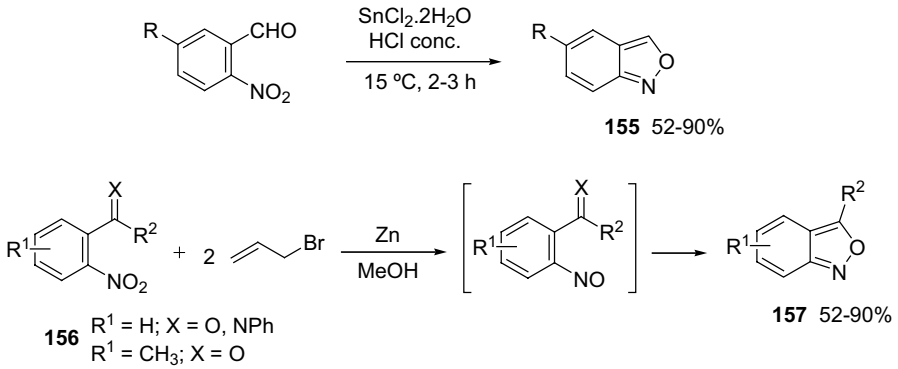
9.5.2.1 **Formation of Bond 1-2**

An important route to 2,1-benzisoxazoles involves reduction of *ortho*-nitrophenones or *ortho*-nitroalkylbenzenes containing an oxygen function on the α-carbon of the alkyl substituent. 3-Phenyl-2,1-benzisoxazole (**154**) can be obtained from **153** in the presence of sulfuric acid. 3-Aryl-2,1-benzisoxazoles are also prepared by the reaction of *ortho*-nitrobenzaldehydes and an aromatic hydrocarbon catalyzed by sulfuric acid (Scheme 9.59) [252].

5-Substituted-2,1-benzisoxazoles **155** have been prepared from 5-substituted-2-nitrobenzaldehydes by the reduction of the nitro group with stannous chloride dihydrate and *in situ* cyclization (Scheme 9.60) [253]. The allyl bromide/Zn mediated reductive cyclization of 2-nitrobenzaldehydes, 2-nitroacetophenone and *N*-(2-nitrobenzylidene)anilines (**156**) leads to 2,1-benzisoxazoles in good to excellent



Scheme 9.59



Scheme 9.60

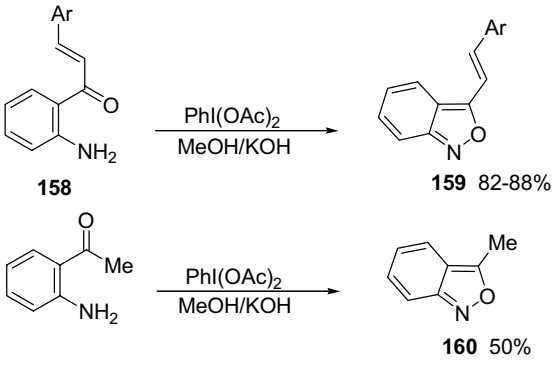
yields [254]. The reductive cyclization of *ortho*-nitrobenzaldehydes and *ortho*-nitroacetophenone can be carried out with 2-bromo-2-nitropropane/Zn in methanol at 50 °C to give 2,1-benzisoxazoles **157** in good yields [255]. Electrochemical synthesis of 2,1-benzisoxazole from nitroarenes by controlled potential cathodic electrolysis has been reported [256].

Many methods of oxidative cyclization of *ortho*-aminoaryl ketones to 2,1-benzisoxazoles are known [9]. An illustrative example is the hypervalent iodine oxidation of *ortho*-aminochalcones **158** to give styryl-2,1-benzisoxazole **159** in good yields (Scheme 9.61) [257]. Under similar reaction conditions, 3-methyl-2,1-benzisoxazole (**160**) is obtained from *ortho*-aminoacetophenone.

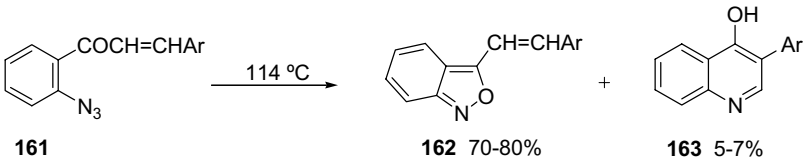
The thermolysis of *ortho*-azidoaryl ketones also produces 2,1-benzisoxazoles. For example, the thermal decomposition of azide **161** gives styryl-2,1-benzisoxazoles **162** along with a minor amount of hydroxyquinoline **163** (Scheme 9.62) [258].

9.5.2.2 Formation of Bond 2-3

The 2,1-benzisoxazole ring system can be constructed from the acid- or base-catalyzed dehydration of 2-nitrobenzyl compounds. In fact, sulfuric acid cyclization of *ortho*-nitrophenylacetic acid yields a mixture of 2,1-benzisoxazole and

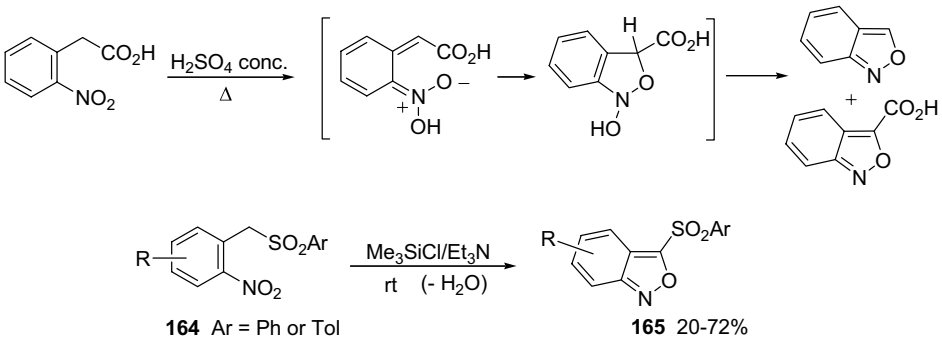


Scheme 9.61



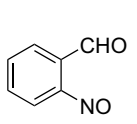
Scheme 9.62

2,1-benzisoxazole-3-carboxylic acid [259]. Me_3SiCl/Et_3N-mediated dehydration of 2-nitrobenzyl derivatives **164** gives sulfones **165** (Scheme 9.63) [260].

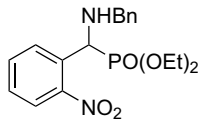


Scheme 9.63

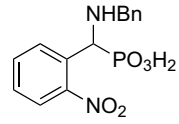
Two research groups claimed the synthesis of 2,1-benzisoxazoles from the reaction of *ortho*-nitrosobenzaldehyde with benzylamine [261] and from treatment of **167a** or **167b** with aqueous sodium hydroxide [262]. However, Kurth *et al*. have demonstrated that the products of these reactions were in fact indazalones [263].



166



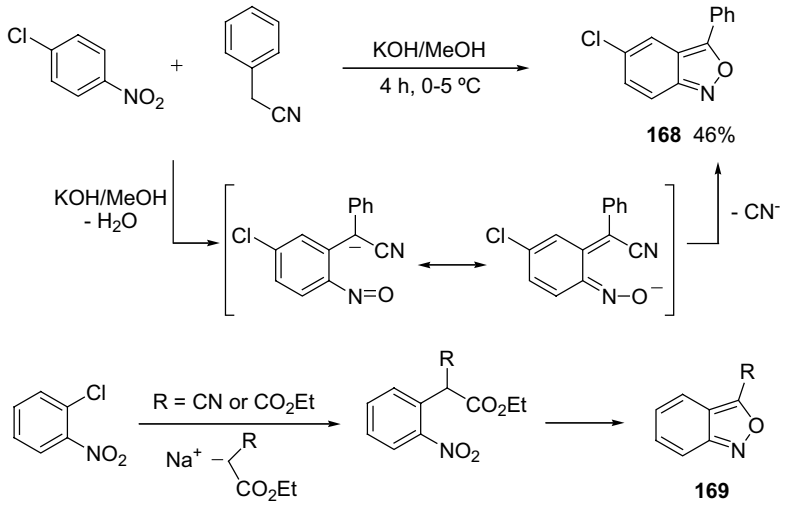
167a



167b

9.5.2.3 **By introduction of C-3**

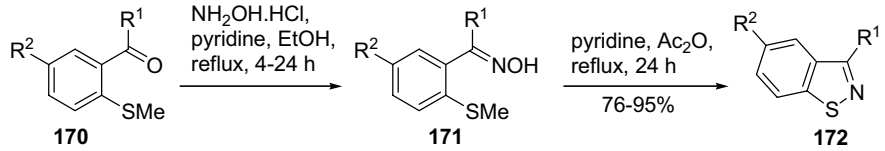
2,1-Benzisoxazole can be produced from the condensation of nitrobenzenes with benzyl cyanide in the presence of a base. Starting from *para*-chloronitrobenzene the reaction with benzyl cyanide gives 2,1-benzisoxazole **168** in 46% yield via an *ortho*-quinonoid intermediate [264]. The synthesis of 3-substituted 2,1-benzisoxazoles **169** from the reaction of *ortho*-chloronitrobenzene with the sodium salt of malonic ester or ethyl cyanoacetate occurs through an initial nucleophilic displacement (Scheme 9.64).



Scheme 9.64

9.5.3 **1,2-Benzisothiazoles**

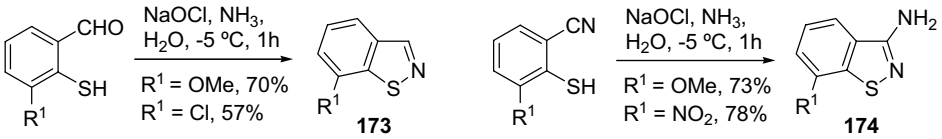
One of the most synthetically appealing methods for 3-substituted 1,2-benzisothiazoles involves the cyclization of the readily accessible oximes of 2-methylthiophenyl ketones **170**. Heating oximes **171** in an acetic anhydride/pyridine mixture converts them into 1,2-benzisothiazoles **172** (Scheme 9.65) [265]. This method has been used to prepare some benzo[*d*,*d*']diisothiazoles [266]. The oximes of



Scheme 9.65

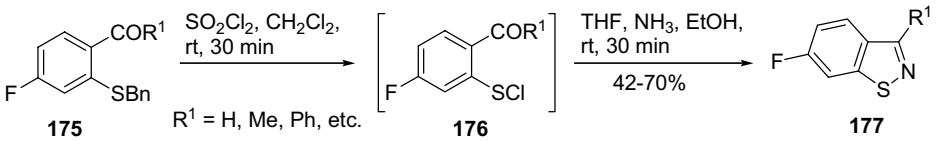
2-(*t*-butylthio)benzaldehydes cyclize to 1,2-benzisothiazoles (**172**, R^1=H) when treated with polyphosphoric acid [267].

1,2-Benzisothiazoles **173** and 3-amino-1,2-benzisothiazoles **174** are obtained, respectively, by treatment of 2-sulfanylbenzaldehydes or 2-sulfanylbenzonitriles with chloramine (Scheme 9.66) [268].



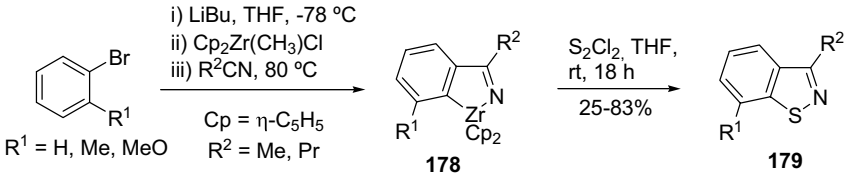
Scheme 9.66

The reaction of 2-benzylthio-4-fluorobenzaldehyde or ketones **175** with sulfuryl chloride gives the corresponding sulfenyl chlorides **176**, which by treatment with ethanol saturated with ammonia afford the 6-fluoro-1,2-benzisothiazoles **177** (Scheme 9.67) [269].



Scheme 9.67

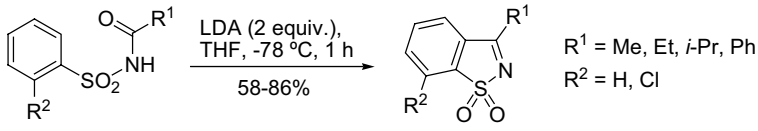
A one-pot procedure for the synthesis of 1,2-benzisothiazoles starting from simple bromobenzenes is shown in Scheme 9.68. It involves the generation of substituted



Scheme 9.68

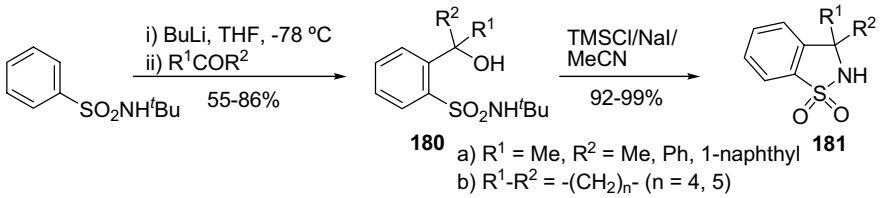
benzynes, formation of zirconium complexes and reaction with nitriles to form metallacyclic compounds **178.** These compounds react with sulfur monochloride to afford regioselectively the benzisothiazoles **179** in moderate to good yields [270].

3-Substituted 1,2-benzisothiazole 1,1-dioxides can be prepared by *ortho*-deprotonation–cyclization of *N*-acylbenzenesulfonamides with 2 equivalents of LDA (Scheme 9.69) [271]. A related method for the synthesis of 3-aryl-1,2-benzisothiazoles involves the ortho-lithiation of *N,N*-diphenylbenzenesulfonamides followed by the addition of aromatic nitriles [272].



Scheme 9.69

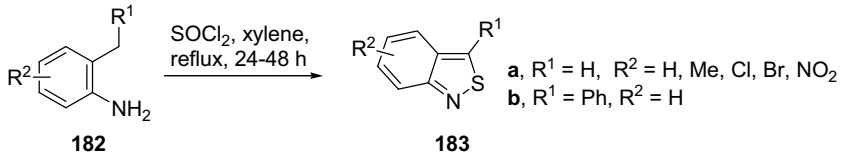
The ortho-lithiation of *N-tert*-butylbenzenesulfonamide followed by reaction with ketones gives the tertiary alcohols **180**, which undergo TMSCl-NaI-MeCN reagent mediated cyclization to afford 3,3-disubstituted 2,3-dihydrobenzisothiazole 1,1-dioxides **181** in high yields (Scheme 9.70) [273].



Scheme 9.70

9.5.4
2,1-Benzisothiazoles

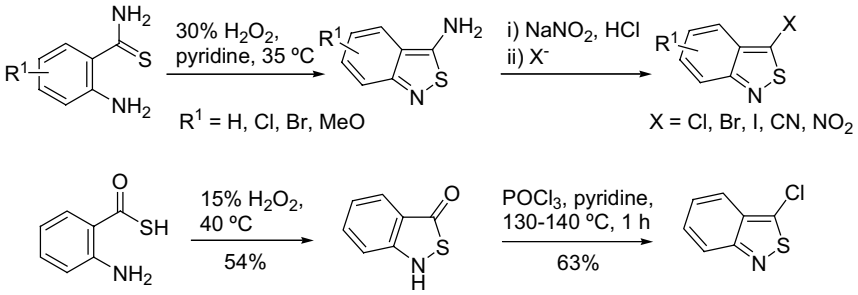
ortho-Toluidine and ring substituted *o*-toluidines **182** (R^1=H) react with thionyl chloride in xylene at reflux temperature to yield 2,1-benzisothiazoles **183a** [274]. Similarly, *o*-benzylaniline affords 3-phenyl-2,1-benzisothiazole (**183b**) (Scheme 9.71) [275]. *o*-Toluidines can also be converted into 2,1-benzisothiazoles



Scheme 9.71

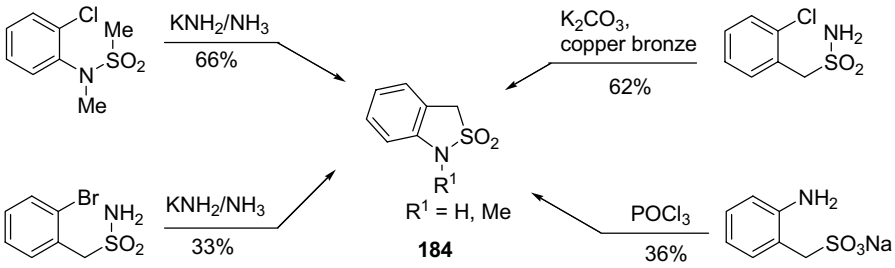
by reaction with *N*-sulfinylmethanesulfonamide (CH_3SO_2NSO) [276]. This method has been used for the synthesis of all the possible angular benzo[*c*] bisisothiazoles and the symmetrical benzo[*c*]trisisothiazole and also benzo[*c*:*d*′] bisisothiazoles [277, 278].

3-Amino-2,1-benzisothiazoles are easily prepared by the oxidative cyclization of *ortho*-aminothiobenzamides [279, 280]. These compounds can be converted into other 3-substituted derivatives by diazotization and replacement of the diazonium group by halogen atoms or cyanide or nitro groups (Scheme 9.72) [281]. Similarly, oxidative cyclization of *ortho*-aminothiobenzoic acid affords 2,1-benzisothiazol-3-one, which can be converted into 3-chloro-2,1-benzisothiazole (Scheme 9.72) [282]. The chlorine atom is easily and almost quantitatively displaced by nucleophiles, leading to several different 3-substituted 2,1-benzisothiazoles [282].

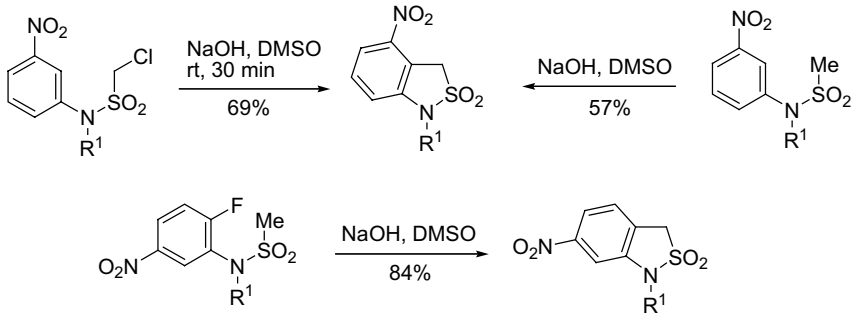


Scheme 9.72

2,1-Benzisothiazole 2,2-dioxides **184** can be prepared from a wide range of precursors (Scheme 9.73) [283]. The nitro derivatives are prepared in higher yields and under milder conditions (Scheme 9.74) [283]. Such compounds are used as precursors of aza-*ortho*-quinodimethanes (see Scheme 9.119).



Scheme 9.73



Scheme 9.74

9.6
Reactivity of 1,2-Azoles

9.6.1
Isoxazoles and Benzisoxazoles

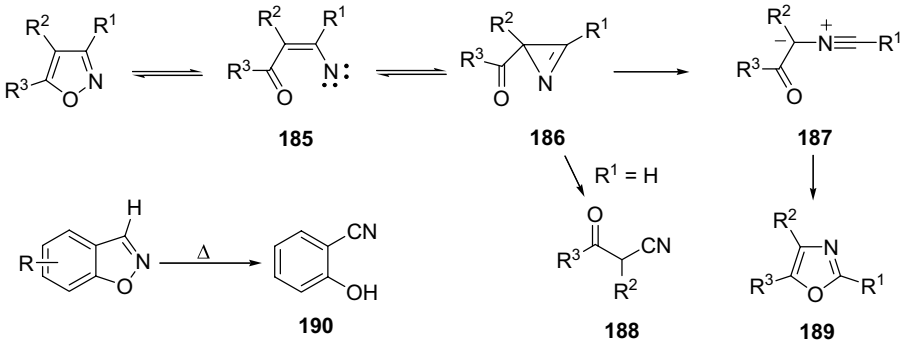
The key feature of these heterocycles is that they possess the typical properties of an aromatic system but contain a weak nitrogen–oxygen bond, which, under certain reaction conditions, particularly in reducing or basic conditions, is a potential site of ring cleavage. Thus, isoxazoles are very useful intermediates since the ring system stability allows the manipulation of substituents to give functionally complex derivatives, yet it is easily cleaved when necessary.

The ring opening provides difunctionalized compounds, namely 1,3-dicarbonyl, enaminoketone, γ-amino alcohol, α,β-unsaturated oxime, β-hydroxy nitrile or β-hydroxy ketone compounds, so that isoxazoles can be considered masked forms of these synthetic units. Consequently, isoxazoles have become an important synthetic tool.

The chemical behavior of benzisoxazoles can, in general, be compared with that of substituted isoxazoles. 1,2-Benzisoxazoles undergo electrophilic substitution in the benzo ring whereas the reaction with nucleophiles involves the isoxazole moiety. Benzisoxazoles readily undergo cleavage of the heterocyclic ring and this feature makes them suitable building blocks for the synthesis of other heterocyclic systems.

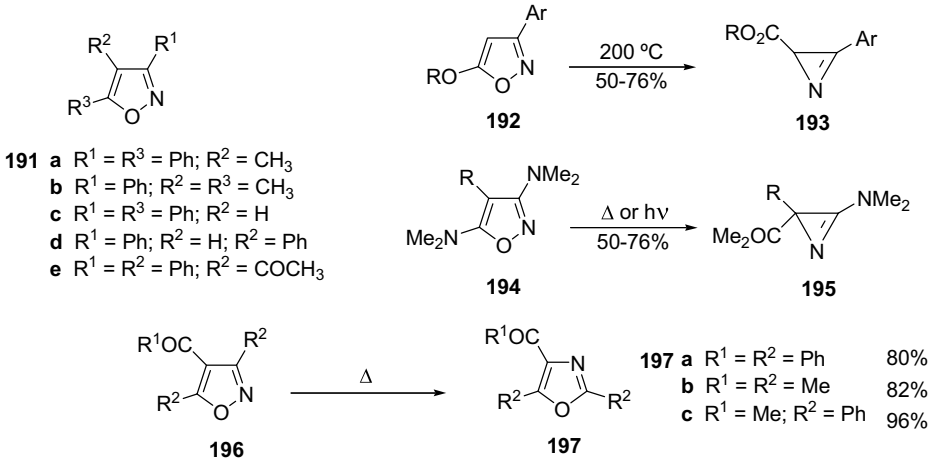
9.6.1.1 **Thermal and Photochemical Reactions**

Scheme 9.75 outlines the reactivity pattern of isoxazoles under thermal reaction conditions. N−O bond cleavage leads to the generation of vinylnitrenes **185**, which rearrange to the corresponding 2*H*-azirines **186**. The 2*H*-azirines can also undergo ring cleavage to give nitrile ylides **187** followed by recyclization to give oxazoles **189** as the final product. However, thermolysis of isoxazoles unsubstituted at C3 usually leads to nitriles **188** (Scheme 9.75) [284, 285]. Thermolysis of 3-unsubstituted 1,2-benzisoxazoles yields the corresponding salicylnitriles **190** [286].



Scheme 9.75

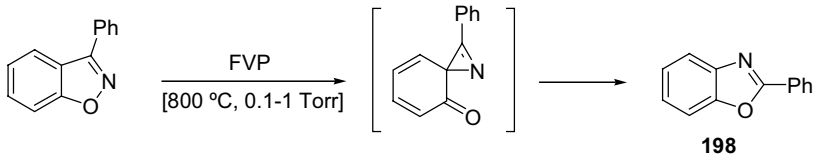
The thermal stability of alkyl or aryl substituted isoxazoles is relatively high. In fact isoxazoles **191** are stable on heating at 280 °C for 10 days [287]. However, isoxazoles having a heteroatom (O, S, N) substituent at C5 undergo ring cleavage at lower temperatures. In fact, 5-alkoxy-3-arylisoxazole **192** is converted into 2*H*-azirine **193** when heated at 200 °C (Scheme 9.76) [288]. High yields of 3-amino-2*H*-azirines **195** are also obtained by both thermolysis and photolysis of 3,5-bis(dimethylamino) isoxazoles **194** [289]. The presence of a carbonyl group in the isoxazole C4 position also favors the cleavage of the N−O bond [287, 290]. Thus, heating 4-acylisoxazoles **196** at 230–240 °C affords the isomeric 4-acyloxazoles **197** in good yields.



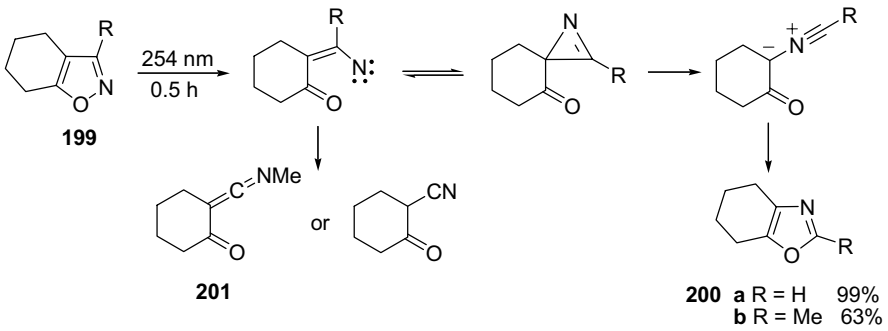
Scheme 9.76

Flash vacuum pyrolysis (FVP) of 3-phenyl-1,2-benzisoxazole allows the synthesis of 2-phenylbenzoxazole (**198**) in 80% yield (Scheme 9.77) [291].

Similar chemical behavior is observed when isoxazoles are subjected to photolysis instead of thermolysis (Scheme 9.78). The photochemical rearrangement of **199a**



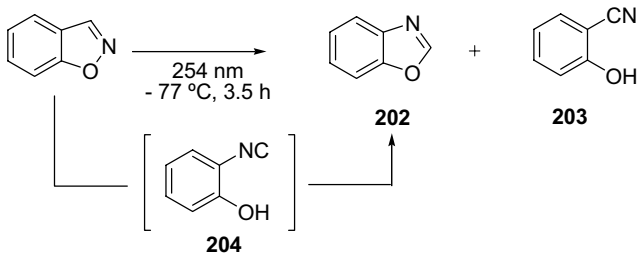
Scheme 9.77



Scheme 9.78

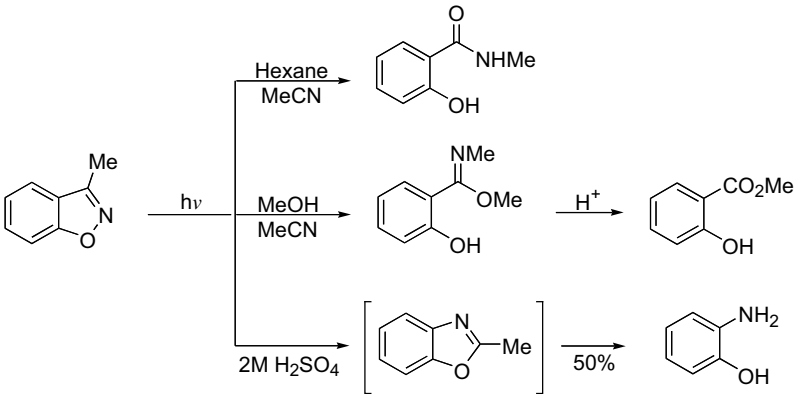
(R=H) furnishes **200a** in 99% yield. Irradiation of **199b** (R=Me) gives the corresponding oxazole **200b** in 63% yield. Photolysis of **199b** at −77 °C allowed the observation of an IR band at 2050 cm^{-1}, which is assigned to the ketoketenimine **201** [292]. The nature of the solvent used to promote the photochemical reactions can determine the product profile [293].

1,2-Benzisoxazole undergoes photochemical rearrangement to give benzoxazole **202** and salicylnitrile **203**. The synthesis of salicylnitrile can be rationalized by considering the direct cleavage followed by hydrogen transfer, while the formation of benzoxazole occurs via isocyanide intermediate **204**, which can be detected be IR and UV spectroscopy (Scheme 9.79) [294].



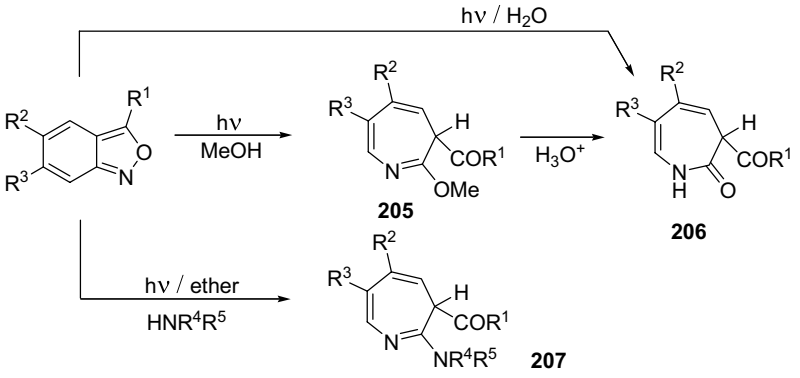
Scheme 9.79

The photolysis of 3-methyl-1,2-benzisoxazole in *n*-hexane/acetonitrile gives a salicylamide, whereas carrying out the irradiation in acetonitrile/methanol (95 : 5) gives an iminoester that is converted into methyl salicylate upon hydrolysis. Photolysis of 3-methyl-1,2-benzisoxazole in 2M H_2SO_4 affords 2-aminophenol via hydrolysis of the benzoxazole intermediate (Scheme 9.80) [10].



Scheme 9.80

2,1-Benzisoxazoles can undergo ring expansion reactions on photolysis (Scheme 9.81). Carrying out the photochemical reaction in methanol leads to the synthesis of 3-acyl-2-methoxy-3*H*-azepines **205**. The reaction in ether containing water or amines affords the corresponding 2-oxo- or 2-amino-3*H*-azepines (**206** or **207**) [295].



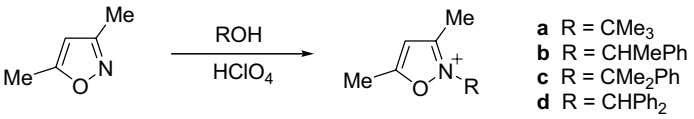
Scheme 9.81

9.6.1.2 **Reactions with Electrophilic Reagents**

Isoxazoles are quaternized by reaction with alkyl iodides or dialkyl sulfates, although special conditions are required due to the low basicity of isoxazoles and their susceptibility to nucleophilic attack. The reactivity of various azoles (1-methylimi-

dazole, thiazole, 1-methylpyrazole, oxazole, isothiazole and isoxazole) towards dimethyl sulfate has been studied and revealed that the parent isoxazole is the least reactive towards quaternization and is also 10^4 times less reactive than pyridine [296]. Thus, direct alkylation with alkyl iodides and sulfates requires relatively vigorous reaction conditions and long reaction times. The rates of quaternization of isoxazole, 1,2-benzisoxazole and 2,1-benzisoxazole with dimethyl sulfate show that 1,2-benzisoxazole is the least reactive towards *N*-methylation whereas 2,1-benzisoxazole reacts faster than isoxazole [297].

The reaction of isoxazoles with secondary and tertiary alcohols and perchloric acid, a efficient source of carbonium ions, is a more convenient route to isoxazolium salts with bulky *N*-substituents. Reaction of 3,5-dimethylisoxazole with a range of alcohols occurs at room temperature, affording isoxazolium salts in 50–90% yield (Scheme 9.82) [298].



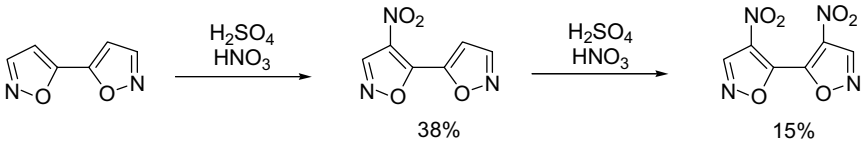
Scheme 9.82

4-Unsubstituted isoxazoles undergo electrophilic substitutions such as nitration, sulfonation, halogenation, chloromethylation and hydroxymethylation, Vilsmeier–Haack formylation and acetoxy mercuration at the 4-position of the ring. Isoxazoles are less reactive towards electrophilic attack than furan but more reactive than pyridine, as expected for a heterocycle having an activating oxygen and a pyridine-like *N*-atom.

The parent isoxazole is nitrated with great difficulty to give 4-nitroisoxazole in 3.5% yield under controlled conditions, with mixed nitric acid and sulfuric acid at 35–40 °C. However, nitration of 3,5-dimethylisoxazole at 100 °C affords the 4-nitro derivative in 86% yield. Both 3-methyl- and 5-methylisoxazole are nitrated regioselectively at the 4-postion. Aryl substituted isoxazoles can be nitrated under mild conditions, although competition between nitration at the C4 of the isoxazole ring and nitration at the aryl group can occur. Under controlled conditions, nitration of 3,5-diphenylisoxazole in Ac_2O/HNO_3 at 20 °C affords only 4-nitro-3,5-diphenylisoxazole. However, the same isoxazole in HNO_3 at 0 °C undergoes nitration at the phenyl groups [9, 10].

1,2-Benzisoxazoles undergo electrophilic substitutions, such as nitration, sulfonation and halogenation, preferentially at the 5-position [9, 10]. Nitration of the parent 1,2-benzisoxazole gives exclusively the 5-nitro-1,2-benzisoxazole [299] and 3-substituted 1,2-benzisoxazoles also lead to the synthesis of the 5-nitro derivatives as the major product.

Isoxazole can act as an activating substituent, as illustrated by the reaction of 5,5′-diisoxazole, which undergoes nitration at the 4-position of both rings (Scheme 9.83) [300].



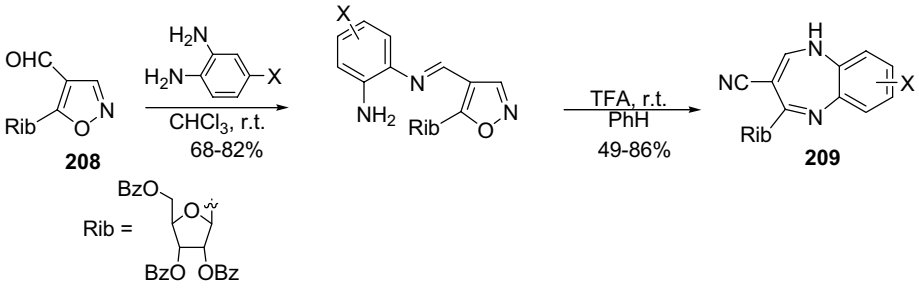
Scheme 9.83

Isoxazoles are rather resistant to sulfonation [6, 10]. This is illustrated by the reaction of 5-phenylisoxazole with chlorosulfonic acid, which undergoes sulfonation only at the phenyl substituent, to give a mixture of *m*- and *p*-phenylsulfonyl chloride isoxazole derivatives. However, on prolonged heating with chlorosulfonic acid, 3-methyl-, 5-methyl, and 3,5-dimethyl-isoxazoles are converted into the corresponding sulfonic and sulfonyl chlorides via electrophilic substitution at C4.

Isoxazoles can be halogenated with various reagents, leading to 4-haloisoxazole derivatives. Treatment of isoxazoles with chlorine or bromine leads to coordination compounds, which afford 4-chloro- or 4-bromoisoxazoles when heated or irradiated. An improved procedure for the C4 halogenation of 3,5-diarylisoxazoles with *N*-halosuccinimide (NBS, NCS and NIS) in acetic acid has been reported. The 4-haloisoxazoles are obtained in yields ranging from 37 to 97% [301].

Other examples of electrophilic substitution of isoxazoles have been reviewed [6, 10].

Ring-opening reactions of isoxazoles can be carried out under acidic conditions. This aspect of the isoxazoles' reactivity has been explored in the conversion of 5-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)isoxazole-4-carbaldehyde (**208**) into 3-cyano-1,5-benzodiazepine *C*-nucleosides **209** (Scheme 9.84) [302].

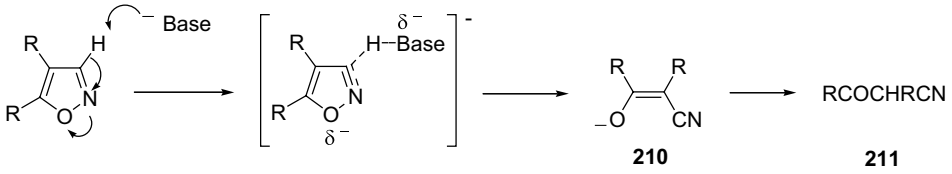


Scheme 9.84

9.6.1.3 **Reactions with Nucleophilic Reagents**

The lability of isoxazoles towards nucleophiles is a key feature of their reactivity. However, its reactivity depends on the nature and position of the substituents. In general, the stability increases with increasing substitution. In fact, the trisubstituted isoxazoles are usually stable and react with nucleophiles preferentially in the side-chains.

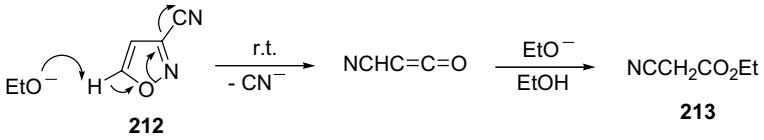
The 3-unsubstituted isoxazoles are cleaved by bases giving cyanoenolates via a one-step concerted E2 type mechanism [303]. Protonation of **210** followed by rearrangement affords β-ketonitriles **211**, which in some cases undergo further reactions (Scheme 9.85). The reaction can be carried out with strong bases such as alkoxides, sodium amide, lithium diisopropylamide, butyllithium and also with hydroxide ion or with weaker bases, such as ammonia and phenyl hydrazine, at higher temperature.



Scheme 9.85

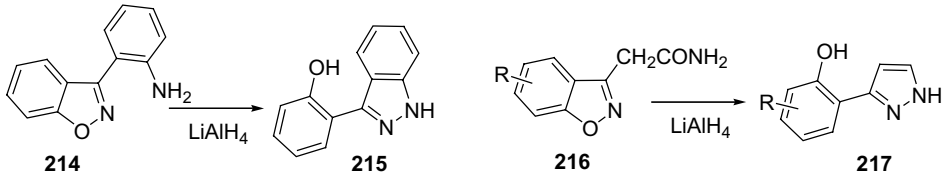
The 3-unsubstituted 1,2-benzisoxazoles present similar behavior, reacting with hydroxide ion and amines to yield 2-cyanophenolates [304]. Reactions of 1,2-benzisoxazoles with sodium borohydride and lithium aluminium hydride usually result also in N–O bond cleavage [9].

The ring opening of 5-unsubstituted 3-alkyl- or 3-arylisoxazoles requires more vigorous reaction conditions, for example heating with alkoxides or use of stronger bases, such as sodium amide or butyllithium. H5 deprotonation of these derivatives leads to N–O and C3/C4 bond cleavage with formation of a nitrile and an ethynolate [305]. The 5-unubstituted isoxazoles bearing a potential leaving group at C3 react with bases without the C3/C4 bond cleavage. This is the case with cyanoisoxazole **212**, which reacts with sodium ethoxide to give **213** as the final product (Scheme 9.86) [306].



Scheme 9.86

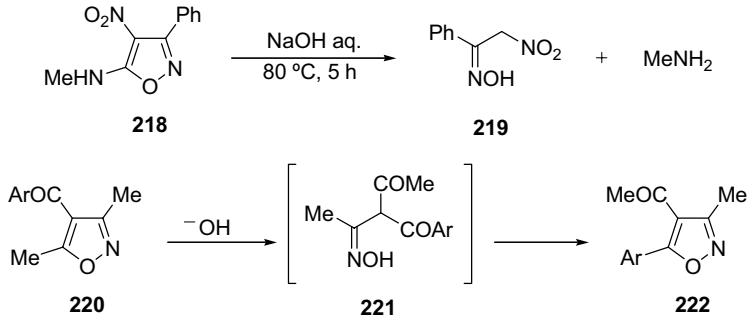
1,2-Benzisoxazoles can be used as a building block for the synthesis of other heterocycles via a reaction with bases [307, 308]; Scheme 9.87 shows two examples.



Scheme 9.87

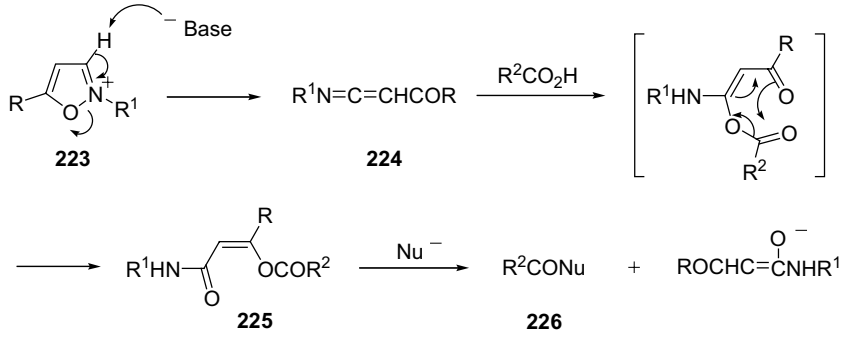
The 1,2-benzisoxazole amine derivative **214** is converted into 3-(2-hydroxyphenyl) indazole (**215**) by treatment with $LiAlH_4$ or NaH [307] and the 1,2-benzisoxazole amide derivatives **216** give 3-(2-hydroxyphenyl)pyrazoles **217** [308].

Trisubstituted isoxazoles with strong electron-withdrawing groups at the 4-position are susceptible to ring cleavage when reacting with nucleophiles (Scheme 9.88). For example, alkaline treatment of 5-methylamino-4-nitroisoxazole **218** leads to oxime **219** along with methylamine [309]. The process proceeds with initial nucleophilic attack at the 5-position of the isoxazole ring. 4-Aroylisoxazole **220** undergoes a rearrangement to give 4-acetylisoxazole **222** via an initial nucleophilic attack at the 5-position followed by cyclization of oxime **221** [310].



Scheme 9.88

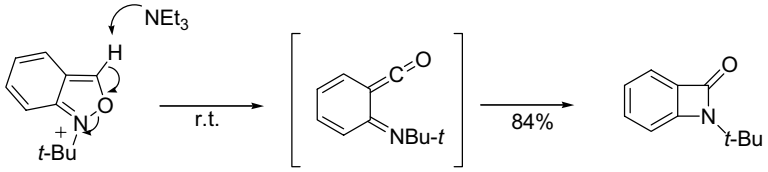
Isoxazolium salts are easily cleaved with nucleophiles. The quaternization of the nitrogen atom increases the lability of the isoxazole ring towards nucleophilic attack. The 3-unsubstituted isoxazolium salts undergo ring cleavage with mild nucleophiles, including carboxylate ions in aqueous solution, which makes these derivatives useful coupling reagents for peptide synthesis. This synthetic strategy is outlined in Scheme 9.89. Deprotonation of isoxazolium salts **223** at the 3-position is followed by ring opening and the ketoketenimines **224** formed react with a carboxylic acid to



Scheme 9.89

give **225**. Reaction of this enol ester with nucleophiles (e.g., an amino acid) gives the final product **226** [10].

1,2-Benzisoxazolium salts readily undergo ring opening to salicylnitrile derivatives upon treatment with bases [311, 312]. The 3-unsubstituted 2,1-benzisoxazoles show similar instability in the presence of bases, and easily undergo ring opening reactions to give anthranilic acid derivatives. The 2,1-benzisoxazolium salts are particularly reactive towards nucleophilic attack at the 3 position and stable adducts can be obtained from their reaction with a range of nucleophiles. The 3-unsubstituted 2,1-benzisoxazolium salts behave in an analogous manner to their 1,2-isomers. In the reaction of 2,1-benzisoxazolium salt **227** with triethylamine the deprotonation is followed by ring opening to the iminoketene **228**, which undergoes electrocyclization to give *N-tert*-butylbenzoazetinone **229** in 84% yield (Scheme 9.90) [313].



227 **228** **229**

Scheme 9.90

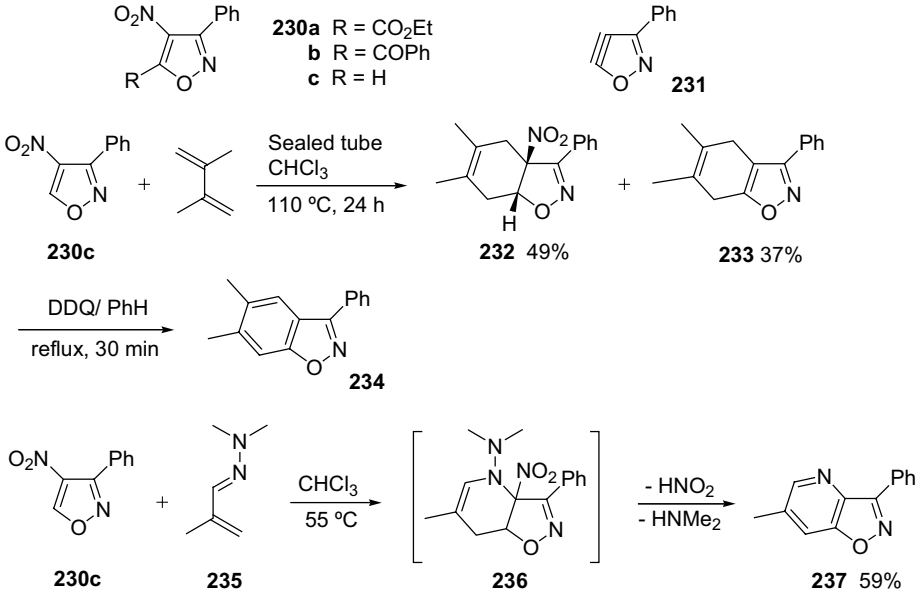
The reactivity profile of isoxazoles with nucleophiles also includes nucleophilic addition to the ring and nucleophilic replacement reactions. Halide displacement reactions can be carried out with 3-halo- and 5-haloisoxazoles bearing the appropriate substitution pattern to prevent ring opening. 4-Haloisoxazoles are very stable and their reactivity towards nucleophiles is similar to that of aryl halides.

9.6.1.4 **Cycloaddition Reactions**

4-Nitro-3-phenylisoxazoles **230** act as dienophiles towards 2,3-dimethylbutadiene (Scheme 9.92 below) [314, 315]. The activated C4/C5 double bond undergoes Diels–Alder reaction with 2,3-dimethylbutadiene, acting as a synthetic equivalent of the corresponding didehydro derivative **231** since the activating groups can be easily removed. Thus, isoxazole **230c** undergoes Diels–Alder reaction with 2,3-dimethylbutadiene to give the bicyclic derivatives **232** and **233** in 49 and 37% yields, respectively. The initial adducts **232** can be easily converted into **233** on treatment with DBU and both **232** and **233** are converted into benzisoxazole **234** either by prolonged heating or by oxidation with DDQ.

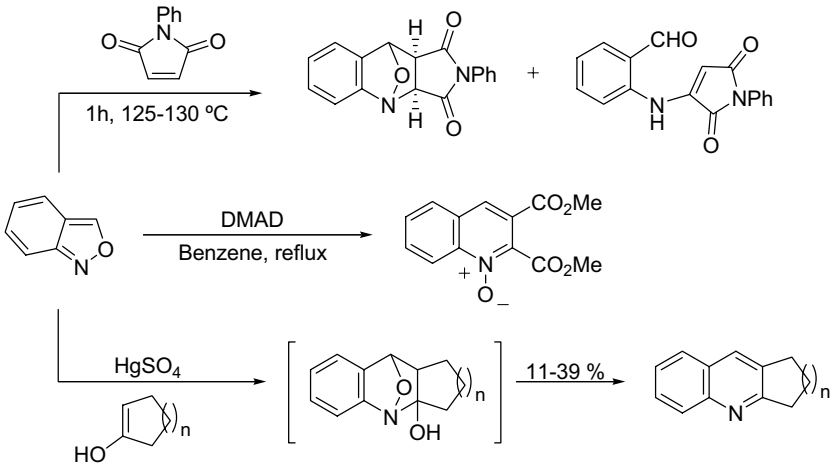
The reaction of nitroisoxazole **230c** with 1-azadiene **235** affords the isoxazolopyridine **237** in 59% yield, with loss of nitrous acid and dimethylamine from the initial cycloadduct **236** (Scheme 9.91) [315].

The nitroalkene moiety of 4-nitroisoxazoles undergo hetero-Diels–Alder reactions with enol ethers (e.g., ethyl vinyl ether) [316].



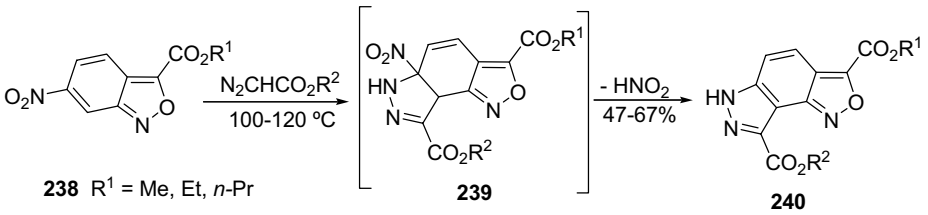
Scheme 9.91

2,1-Benzisoxazole participates in Diels–Alder reactions as a diene. Cycloaddition with *N*-phenylmaleimide gives the corresponding *exo* product together with a ring-opened product [317]. From the reaction of 2,1-benzisoxazole with dimethyl acetylenedicarboxylate (DMAD) in refluxing benzene the quinoline 1-oxide is obtained. The mercury sulfate-catalyzed cycloaddition of 2,1-benzisoxazole with cyclic ketones has also been reported (Scheme 9.92) [318].



Scheme 9.92

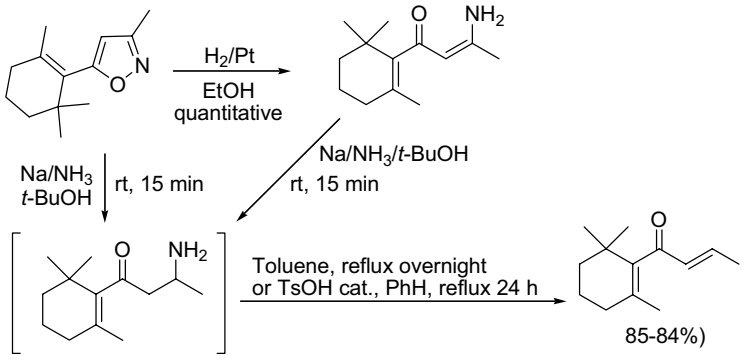
1,3-Dipolar cycloadditions of 2,1-benzisoxazole are also known, as illustrated by the example presented in Scheme 9.93 [319]. The reaction of 6-nitro-2,1-benzisoxazole-3-carboxylate **238** with excess of diazoacetic esters affords 6*H*-pyrazolo[3,4-*g*][2,1]benzisoxazoles **240** in good yield. The reaction proceeds via the formation of the 1,3-dipolar cycloadduct **239** followed by elimination of nitrous acid.



Scheme 9.93

9.6.1.5 **Reactions with Reducing Agents**

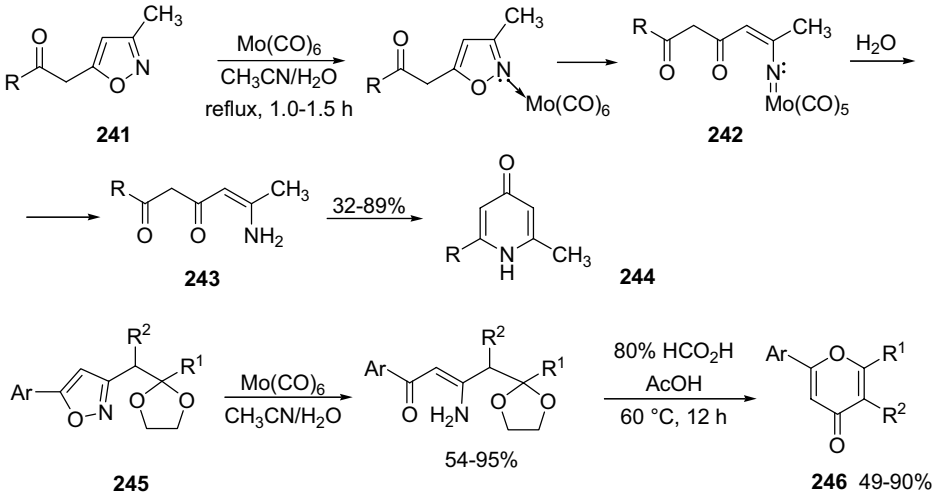
Isoxazoles are readily cleaved at the N–O bond under reducing conditions and many examples have been reported. Catalytic hydrogenolysis leads to β-enaminoketones or to the corresponding 1,3-diketone obtained by hydrolysis. The reduction with sodium in liquid ammonia in the presence of 3 equivalents of *tert*-butyl alcohol gives β-aminocarbonyl compounds, which are converted into α,β-unsaturated ketones on heating or under acidic conditions. Thus, isoxazoles can be considered masked forms of these important synthetic building blocks. The example shown in Scheme 9.94 illustrates this type of reactivity [113]. The use of isoxazoles as masked β-enaminoketones has been applied in a strategy for the total synthesis of vitamin B_{12} [320].



Scheme 9.94

Samarium diiodide [321] and transition-metal carbonyls [322, 323], such as molybdenum hexacarbonyl in the presence of water, are also efficient reagents for the reductive cleavage of isoxazoles. Nitta *et al.* have reported that 3-methyl-5-(2-oxoalkyl)isoxazoles **241** undergo a $Mo(CO)_6$-induced reductive cleavage to give pyridin-4(1*H*)-ones **244** in a single step [322]. Here, complex formation of isoxazole

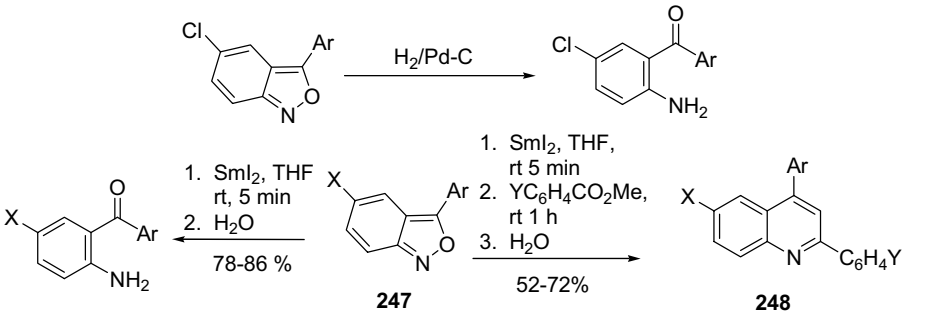
with $Mo(CO)_6$ is followed by the N–O bond cleavage to give the nitrene complex **242**. Hydrolysis of **242** gives the enamino ketone **243**, which cyclizes to the pyridin-4(1*H*)-ones **244**. Li *et al.* have shown that if the 2-oxoalkyl side-chain is at the 3-position of the isoxazole **245** the corresponding enamino ketone could be isolated after reduction with $Mo(CO)_6$ and could be cyclized to pyran-4-ones **246** under acidic conditions (Scheme 9.95) [323].



Scheme 9.95

Under reducing conditions the N–O bond of benzisoxazoles is readily cleaved and many examples have been reported. The catalytic hydrogenolysis of 1,2-benzisoxazoles gives 2-iminophenols and/or 2-ketophenols depending on the reaction conditions. The catalytic reduction of 2,1-benzisoxazoles results in the formation of 2-aminophenones.

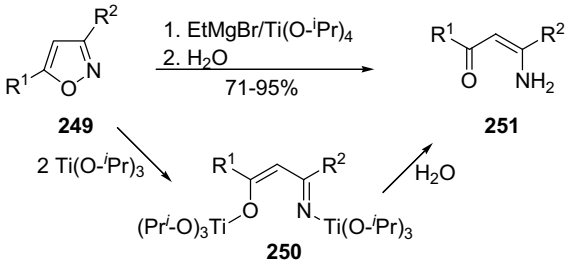
Hydrogenolysis of 3-aryl-2,1-benzisoxazoles is a useful route to 2-aminobenzophenones (Scheme 9.96) [324]. The efficient reductive cleavage of the N–O bond of



Scheme 9.96

5-substituted-3-aryl-2,1-benzisoxazoles **247** can also be achieved with samarium(II) iodide. If aryl methyl ketones are added to the reactive mixture 2,4-diarylquinolines **248** are obtained [325].

Reductive ring cleavage of isoxazoles to the corresponding β-enaminoketones under treatment with titanium(IV) isopropoxide and ethylmagnesium bromide has been reported (Scheme 9.97). The interaction of equimolar quantities of EtMgBr and $Ti(O\text{-}^iPr)_4$ leads to the formation of titanium(III) isopropoxide. This reagent assists the homolytic cleavage of the N–O bond in isoxazoles **249**, giving the alcoholates **250**, followed by hydrolysis to afford the enaminoketones **251**. From isoxazolines the corresponding β-hydroxyketones are obtained [326]. The isoxazole ring is also cleaved by reactions with LDA [327].

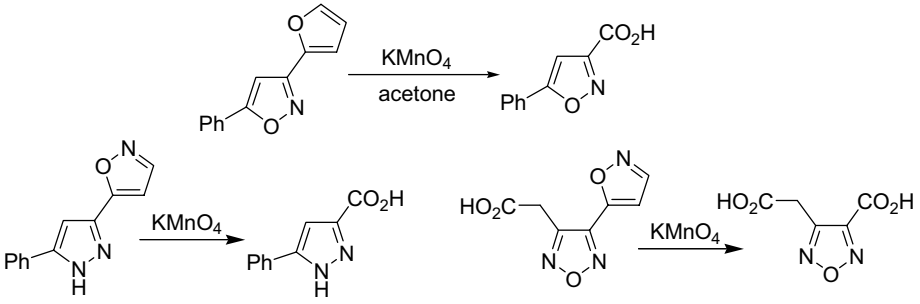


Scheme 9.97

9.6.1.6 **Reactions with Oxidizing Agents**

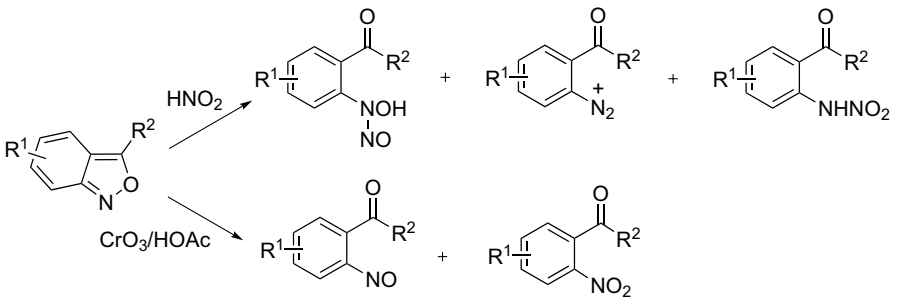
Isoxazoles are stable to acidic oxidizing reagents such as peroxyacids, chromic and nitric acids and acidic permanganate. The only general method of oxidation ring cleavage of substituted isoxazoles is ozonolysis. 3-Unsubstituted isoxazoles are also easily converted into cyanoketones with alkaline oxidizing reagents.

Oxidation reactions of isoxazoles bearing heterocyclic substituents allows us to redraw conclusions concerning the relative stability of various heterocyclic compounds under the reaction conditions used (Scheme 9.98) [10]. The isoxazole ring proved to be more stable than furan but less stable than pyrazole and furazan rings.



Scheme 9.98

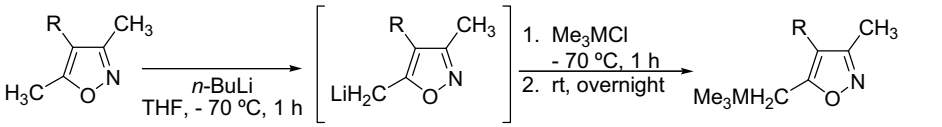
1,2-Benzoisoxazoles are also quite stable towards oxidizing reagents, allowing selective oxidation of substituents of the 1,2-benzisoxazole ring system. Substituted 2,1-benzisoxazole can be oxidized with nitrous acid or with CrO_3/AcOH to generate mixtures of ring-opened products, the rate of which is dependent on the amount of oxidant (Scheme 9.99) [9].



Scheme 9.99

9.6.1.7 **Reactions of Metallated Isoxazoles**

Protons at the α-position of alkylisoxazoles are relatively acidic and can be removed by strong bases (e.g., BuLi, LDA or $NaNH_2/NH_3$), giving carbanionic species. Reaction of these intermediates with electrophiles is an approach to side-chain functionalization and many examples are known [6, 328]. The α-deprotonation of an 5-alkyl substituent is favored over deprotonation of alkyl groups at 3- and 4-positions of the isoxazole ring, allowing regioselective reactions with electrophiles via lateral metallation. Thus, the 3,5-dimethylisoxazole **252a** reacts with BuLi to give specific metallation at C5 methyl group and the subsequent treatment with Me_3SiCl affords **253a** in 70% yield (Scheme 9.100). Regioselective metallation at the same position is observed for trimethylisoxazole **252b** [329, 330]. 4-Metalloisoxazoles are generally prepared by halogen–metal exchange reactions [330].

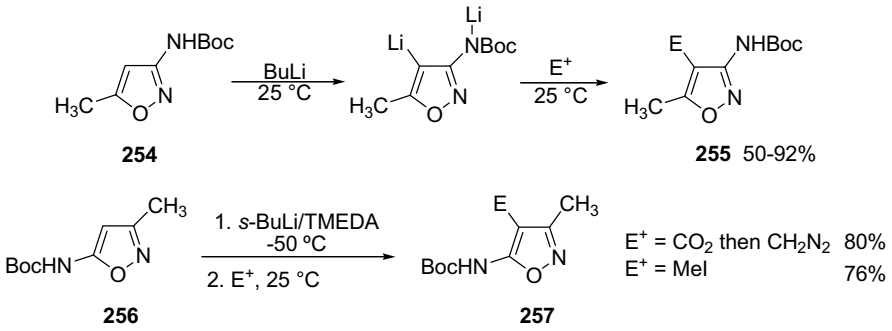


252a R = H
b R = CH_3

253 a R = H; M = Si 70%
b R = CH_3; M = Si 60%
c R = CH_3; M = Sn 75%

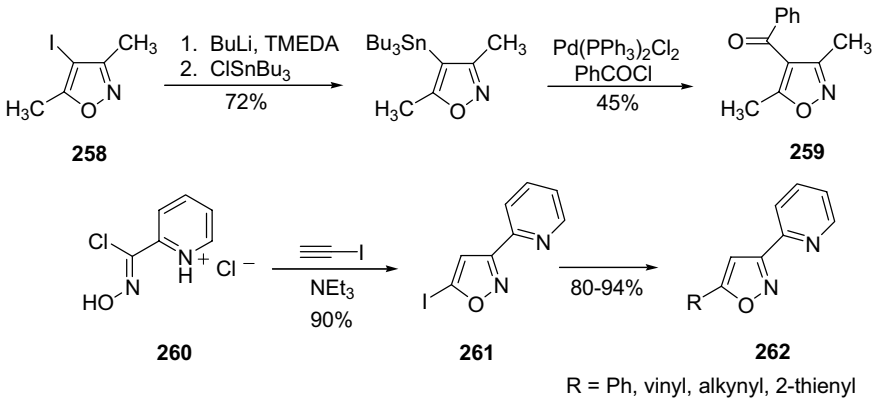
Scheme 9.100

Direct lithiation of 3-(Boc-amino)isoxazole **254** and 5-(Boc-amino)isoxazole **256** using BuLi or *s*-BuLi/TMEDA as the lithiating reagents, respectively, has been reported (Scheme 9.101) [331]. The anion intermediates undergo addition to electrophiles to give 4-substituted isoxazoles (**255** and **257**).



Scheme 9.101

Palladium-catalyzed coupling reactions (Suzuki–Miyaura, Stille or Heck reactions) of 3,5-disubstituted 4-iodoisoxazole afford in good yields the corresponding 4-substituted derivatives, bearing 4-aryl, 4-heteroaryl, 4-vinyl or 4-acetylenyl groups as substituents [332]. Tin 4-metallated isoxazoles are synthesized by stannylcupration of 4-haloisoxazoles **258** and can also be used as intermediates in the preparation of 4-substituted isoxazoles **259**. The 5-iodoisoxazolylpyridine **261**, obtained from **260** via 1,3-dipolar cycloaddition with iodoacetylene, also undergoes palladium-catalyzed coupling to give 5-substituted isoxazoles **262** (Scheme 9.102) [333, 334].



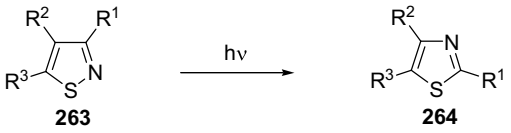
Scheme 9.102

3,4,5-Trisubstituted isoxazoles can also be prepared via cross-coupling reactions of isoxazolyl-4-sinanols and isoxazole-4-boronic esters with the appropriate halo-compounds [335, 336].

9.6.2 Isothiazoles and Benzisoxazoles

9.6.2.1 Photochemical Reactions

The photochemical reactions of isothiazoles have been reviewed [337]. Isothiazole photoisomerizes to thiazole **264a** (Scheme 9.103) [338]. This photorearrangement is also observed in methylisothiazoles. Each methylisothiazole **263b–d** isomerizes selectively to the corresponding methylthiazole **264**, indicating that the rearrangement occurs via a N2–C3 exchange process [339].

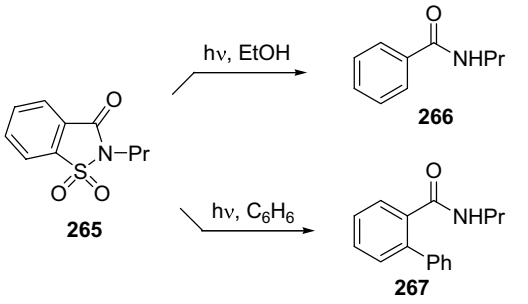


a, $R^1 = R^2 = R^3 = H$ **c**, $R^1 = R^3 = H$, $R^2 = Me$
b, $R^1 = Me$, $R^2 = R^3 = H$ **d**, $R^1 = R^2 = H$, $R^3 = Me$

Scheme 9.103

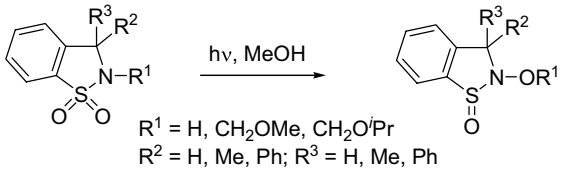
The photochemistry of phenyl substituted isothiazoles has been extensively studied. The resulting products are phenylthiazoles, phenylisothiazoles isomeric of the starting materials and ring-opened compounds. The relative proportions of these products are strongly dependent on the presence of a base or acid and, in some cases, on the polarity of the solvent used [340–342].

Saccharin derivatives undergo extrusion of sulfur dioxide when irradiated in solution. When irradiated in ethanol or propan-1-ol, the *N*-propyl derivative **265** is converted into *N*-propylbenzamide **266** by hydrogen uptake, while in benzene it gives the *N*-propylbiphenyl-2-carboxamide **267** (Scheme 9.104) [343].



Scheme 9.104

In contrast to that observed in the saccharin derivatives, in the 3-mono- and 3,3-disubstituted 2,3-dihydro-1,2-benzisothiazole 1,1-dioxides a net migration of one oxygen atom from sulfur to nitrogen is observed upon irradiation at 254 nm in acetonitrile or methanol (Scheme 9.105) [344].

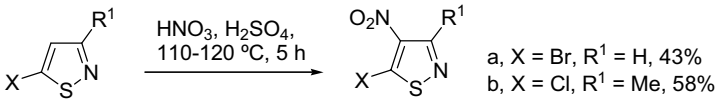


Scheme 9.105

9.6.2.2 **Reactions with Electrophilic Reagents**

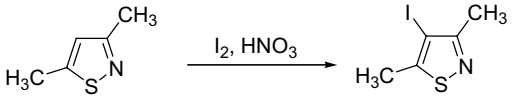
Isothiazoles are quaternized by iodoalkanes, dialkyl sulfate, trialkyloxonium tetrafluoroborate or diazomethane.

Mononuclear isothiazoles give electrophilic substitution at the 4-position, with the 3-position being relatively inert to attack. Nitration also occurs at C4, usually in good yield. 5-Haloisothiazoles give the 4-nitro derivatives in moderate yields by reaction with a mixture of concentrated sulfuric acid and 90% nitric acid (Scheme 9.106) [345].



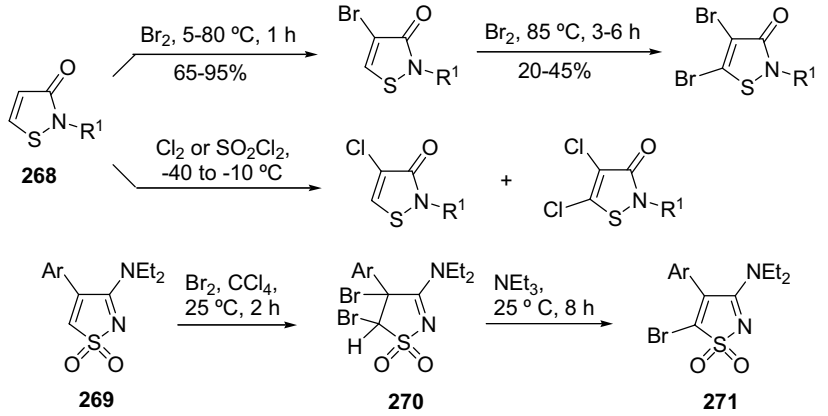
Scheme 9.106

Electron-releasing groups in the 3- or 5-position facilitate halogenation. For instance, 3,5-dimethylisothiazole reacts with iodine to give the 4-iodo derivative (Scheme 9.107) [346].



Scheme 9.107

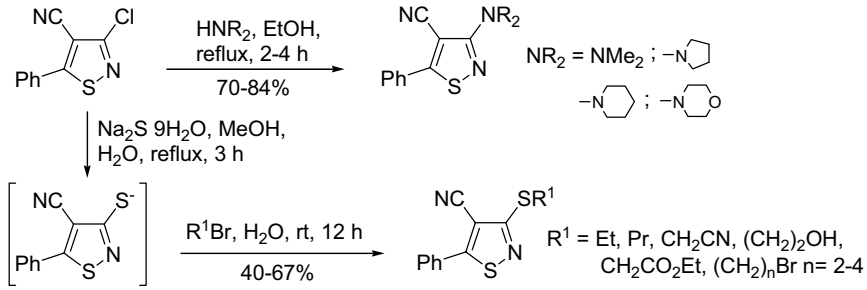
Bromination of 2-substituted isothiazolin-3-ones **268** affords the 4-bromo derivatives in good yields. The formation of 4,5-dibromo derivatives is much more difficult (Scheme 9.108) [347]. In contrast, even under mild conditions, chlorination of **268** gives primarily 4,5-dichloro derivatives and lesser amounts of the 4-chloro derivatives [347]. 3-Diethylamino-4-(4-methoxyphenyl)isothiazole 1,1-dioxide **269** reacts with bromine to afford the 4,5-dibromo derivative **270**, which, on heating or by treatment with triethylamine, gives the 5-bromoisothiazole **271** [348].



Scheme 9.108

9.6.2.3 **Reactions with Nucleophilic Reagents**

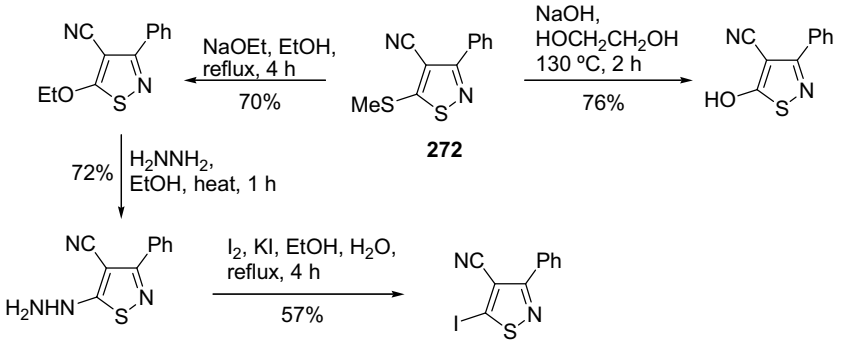
The displacement of a halogen atom from halo-isothiazoles by nucleophiles is a versatile route to new isothiazole derivatives. As shown in Scheme 9.109, substitution of the halogen by alkylthio groups can be conveniently performed by converting the halo-isothiazole into a thiolate followed by reaction with a suitable alkylating reagent (one-pot procedure) [213].



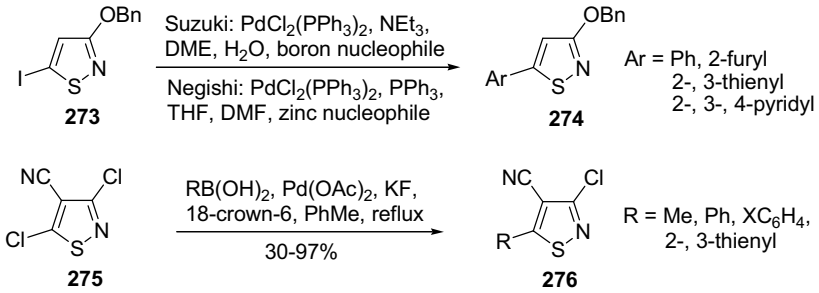
Scheme 9.109

Certain groups at the 5-position of the isothiazole ring can be easily displaced by nucleophiles, affording new functionalized isothiazoles. As an example, starting from 5-methylthioisothiazole **272**, four new isothiazoles have been prepared by successive nucleophilic substitutions (Scheme 9.110) [199]. 5-Unsubstituted isothiazole 1,1-dioxides give addition products with sulfur, oxygen, nitrogen [349] and phosphorus [350] nucleophiles. When 5-bromoisothiazole 1,1-dioxides are reacted with these nucleophiles, the substitution products are obtained [69, 70].

5-Iodoisothiazole **273** can be used as electrophile in Suzuki and Negishi cross-coupling reactions to afford 5-aryl and 5-hetarylisothiazoles **274** in good to excellent yields (48–95%) (Scheme 9.111) [351]. Similarly, 3,5-dichloroisothiazole-4-



Scheme 9.110

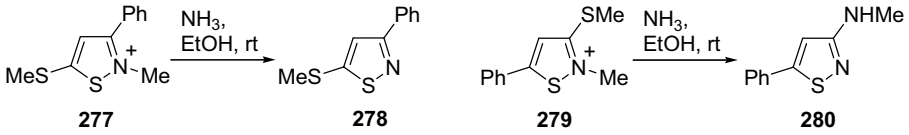


Scheme 9.111

carbonitrile (**275**) reacts with aryl- and methylboronic acids to give in high yields the 3-chloro-5-(aryl or methyl)-isothiazole-carbonitriles **276**. This reaction is totally regioselective [352].

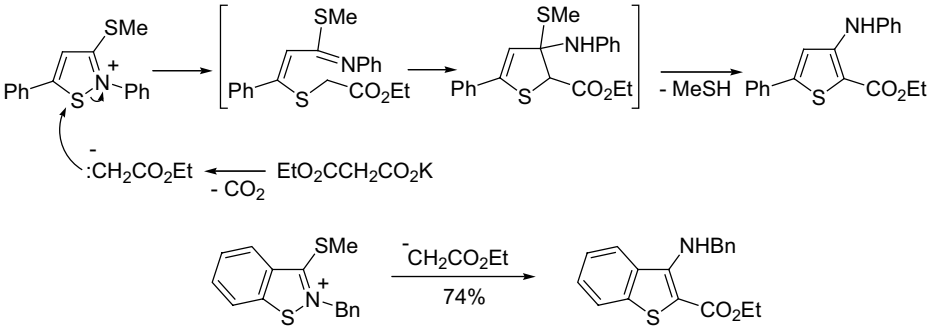
The palladium-catalyzed reaction of 5-bromo-3-diethylamino-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide with vinyl-, aryl-, heteroaryl- and alkynylstannanes provides a general and efficient method for the synthesis of 5-substituted isothiazole 1,1-dioxides [348].

2-Alkylisothiazolium salts are converted into polymeric products by alkali hydroxides or alkoxides. When treated with ethanolic ammonia, isothiazolium salt **277** yields the corresponding demethylated isothiazole **278**. However, under identical conditions, its isomeric compound **279** affords the 3-methylamino derivative **280** (Scheme 9.112) [353]. These transformations result from an initial nucleophilic attack on the ring S atom and recyclization of the initial intermediates.



Scheme 9.112

Isothiazolium salts react with other nitrogen nucleophilic reagents such as phenylhydrazine and hydroxylamine to give, respectively, pyrazoles, and isoxazoles; with benzylamine they afford acyclic thiones [21]. They also react with carbanions to give thiophene or benzo[*b*]thiophene derivatives (Scheme 9.113) [354].



Scheme 9.113

9.6.2.4 **Cycloaddition Reactions**

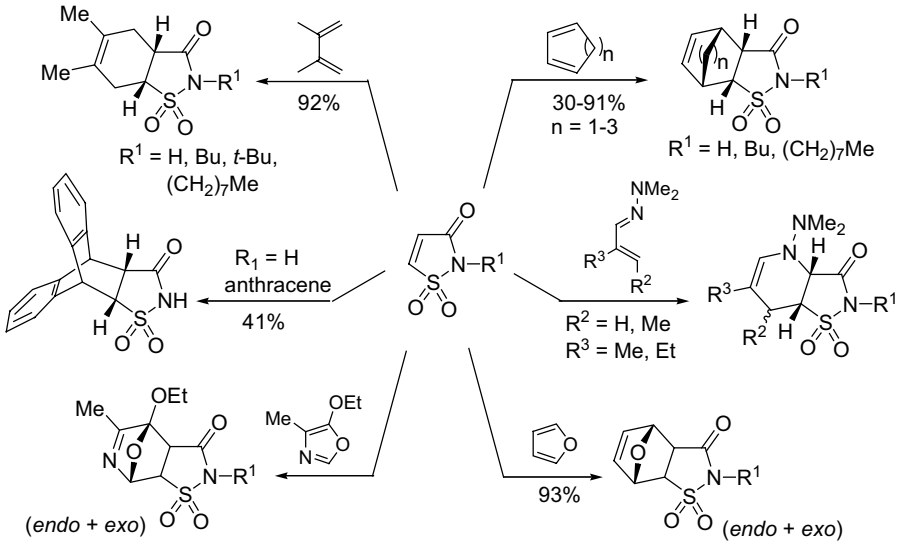
Isothiazoles participate in Diels–Alder reactions and in 1,3-dipolar cycloadditions as the 2π electrons component [355]. A few examples of their participation in $[2\pi + 2\pi]$ cycloadditions with diphenylketene or inamines have also been reported [356, 357]. Some isothiazole derivatives are used as precursors of reactive dienes (*ortho*-quinodimethanes) that can be trapped in Diels–Alder reactions (see below).

Isothiazol-3(2*H*)-one 1,1-dioxides react with buta-1,3-dienes [358, 359], cyclo-1,3-dienes [356], anthracene [356], 1-azadienes [360], furans [356, 361], 1,3-oxazoles [362] and so on to afford the Diels–Alder adducts in moderate to good yields (Scheme 9.114).

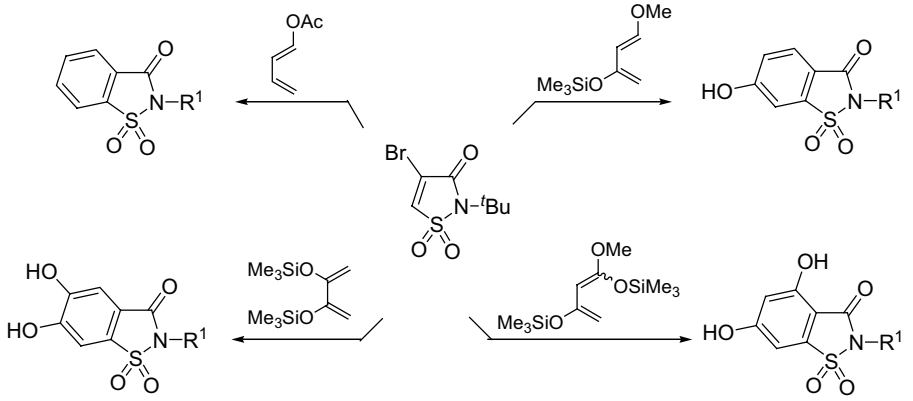
A general method for the synthesis of saccharin derivatives involves the Diels–Alder reaction of 4-bromo-2-*t*-butylisothiazol-3(2*H*)-one 1,1-dioxide with oxi-substituted buta-1,3-dienes (Scheme 9.115) [359]. Dehydrobromination of the cycloadducts and removal of the protecting groups leads to the saccharin derivatives.

Isothiazole derivatives, especially the 1,1-dioxides, undergo 1,3-dipolar cycloadditions with a wide range of dipoles under mild conditions [363]. For instance, isothiazol-3(2*H*)-one 1,1-dioxides react with nitrile imines and nitrile oxides to give the expected cycloadducts (Scheme 9.116) [364]. In the case of reaction with azides and diazo compounds, the presence of a substituent at 4-position makes all the difference in the outcome of the reaction (Scheme 9.117) [360].

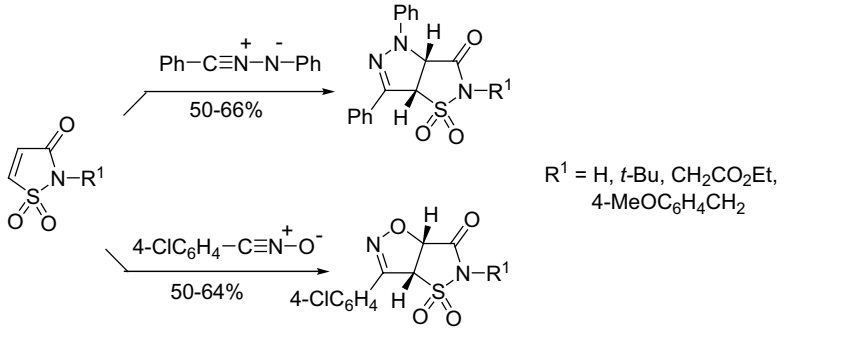
The 3-amino-4-arylisothiazole 1,1-dioxides are also very reactive in 1,3-dipolar cycloadditions. They react with a wide range of dipoles, such as oxazolones [365], diazo compounds [366], azides [367], and nitrile oxides [368]. The bicyclic cycloaddition products are versatile intermediates for monocyclic heterocycles by cleavage of one ring.



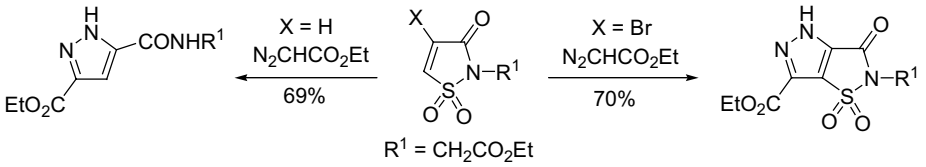
Scheme 9.114



Scheme 9.115

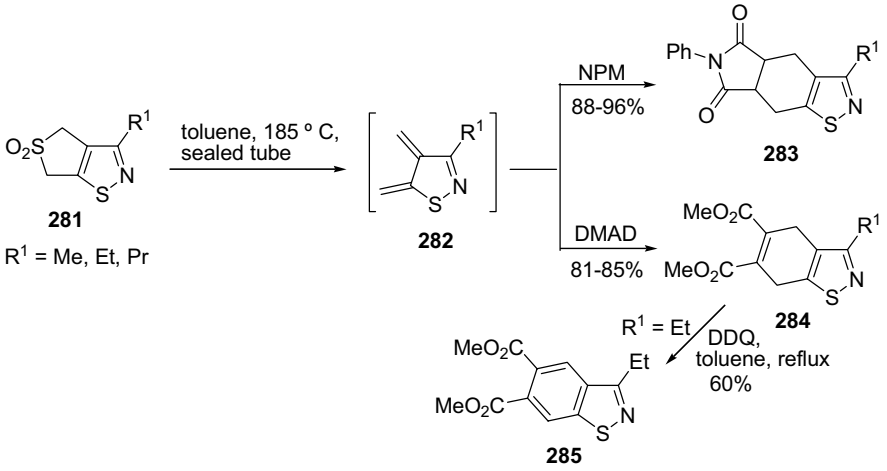


Scheme 9.116



Scheme 9.117

Isothiazole-fused 3-sulfolenes **281** extrude SO_2 when heated at 185 °C in a sealed tube, generating the isothiazole *o*-quinodimethanes **282**. Extrusion of SO_2 in the presence of *N*-phenylmaleimide (NPM) or dimethyl acetylenedicarboxylate affords the corresponding Diels–Alder adducts **283** and **284**, respectively, in good yields (Scheme 9.118) [369]. Benzisothiazole **285** is obtained by the oxidation of the corresponding adduct **284**.



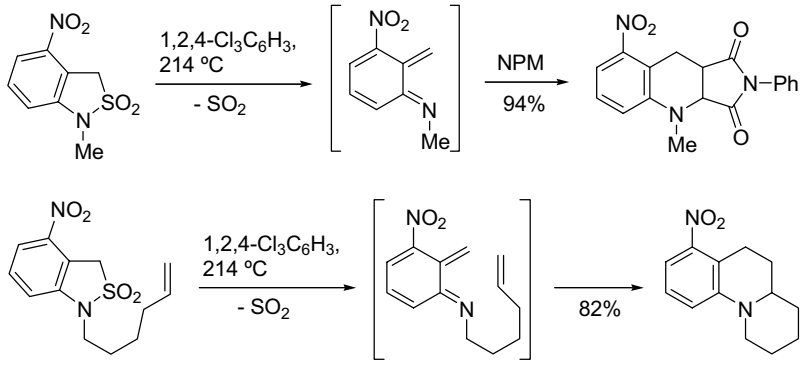
Scheme 9.118

2,1-Benzisothiazole 2,2-dioxides (see Schemes 9.73 and 9.74) extrude SO_2 when heated in refluxing 1,2-dichloro- or 1,2,4-trichlorobenzene to yield aza-*ortho*-quinodimethanes that can be trapped in inter- or intramolecular Diels–Alder cycloadditions (Scheme 9.119) [283, 370].

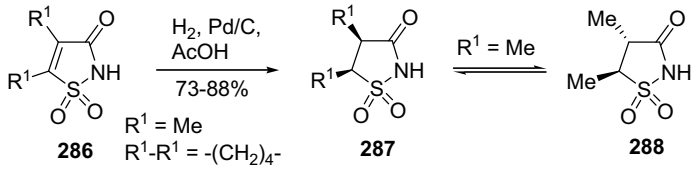
9.6.2.5 **Reactions with Reducing Agents**

Catalytic hydrogenation of isothiazol-3-ones **286** at 3.5 atm leads to the *cis*-dihydro derivatives **287** (Scheme 9.120) [214]. The dimethyl derivative **287**, however, isomerizes to the *trans*-isomer **288** via keto-enol tautomerism.

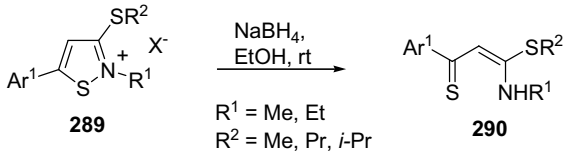
2-Alkyl-3-alkylthio-5-arylisothiazolium halides **289** are reduced to the S,N-acetals **290** by treatment with $NaBH_4$ in ethanol at room temperature (Scheme 9.121) [200, 371].



Scheme 9.119



Scheme 9.120



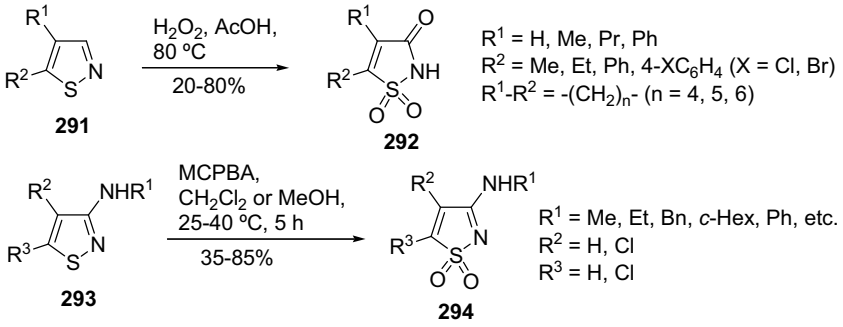
Scheme 9.121

9.6.2.6 Reactions with Oxidizing Agents

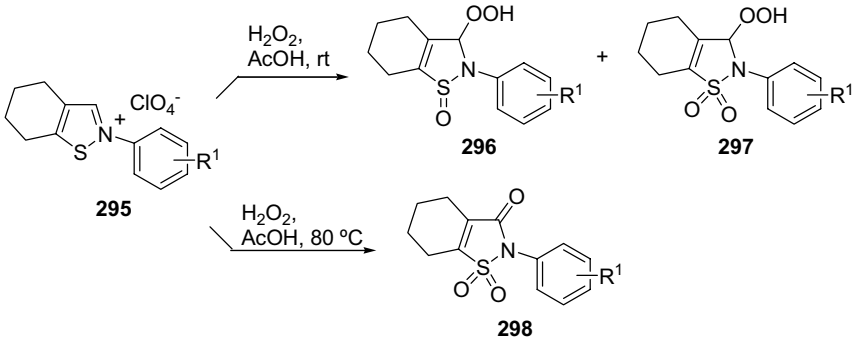
Isothiazoles unsubstituted at 3-position (**291**) are oxidized with 35% H_2O_2 in acetic acid to 1,2-isothiazol-3(2*H*)-one 1,1-dioxides **292** (Scheme 9.122) [214]. Oxidation of 3-aminoisothiazoles **293** with *m*-chloroperbenzoic acid affords the corresponding 1,1-dioxides **294** [372].

The oxidation of isothiazolium salts **295**, containing electron-withdrawing substituents in the *ortho*-position of the 2-aryl ring, with 30% H_2O_2 in acetic acid gives 3-hydroperoxy derivatives **296** in moderate to good yields (42–70%) and minor amounts of the corresponding 1,1-dioxides **297** (Scheme 9.123). When R^1 is an electron-donating group compounds **297** are the only products (40–63%) [372]. If the reaction is carried out at 80 °C the products are the isothiazol-3(2*H*)-one 1,1-dioxides **298** (up to 81% yield) [372].

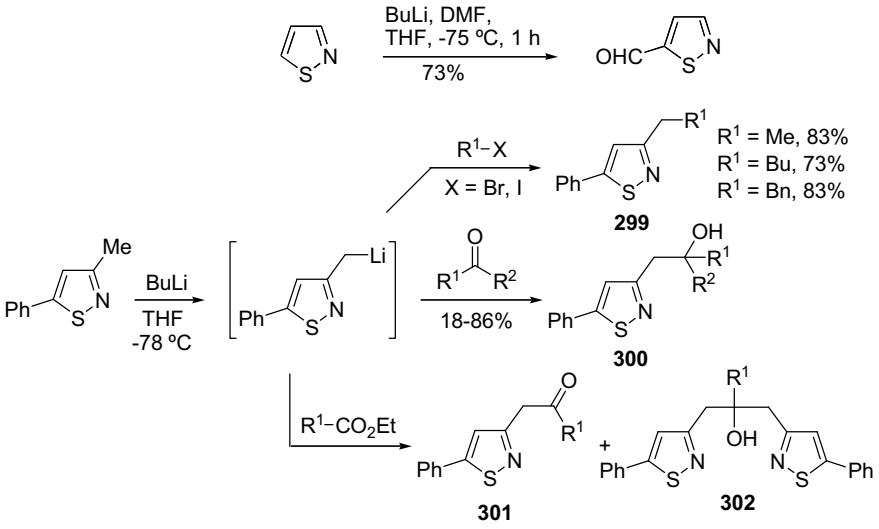
Oxidation of 1,2-benzisothiazoles with hydrogen peroxide [373, 374] or perphthalic acid [375] yields the corresponding 1,1-dioxides.



Scheme 9.122



Scheme 9.123



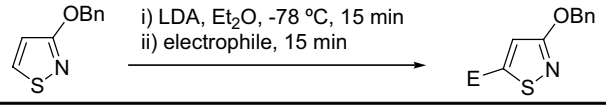
Scheme 9.124

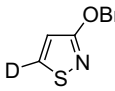
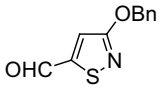
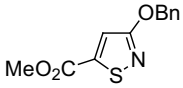
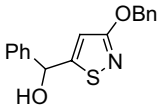
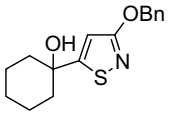
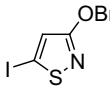
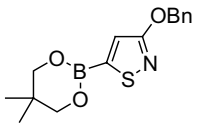
9.6.2.7 Reactions of Metallated Isothiazoles

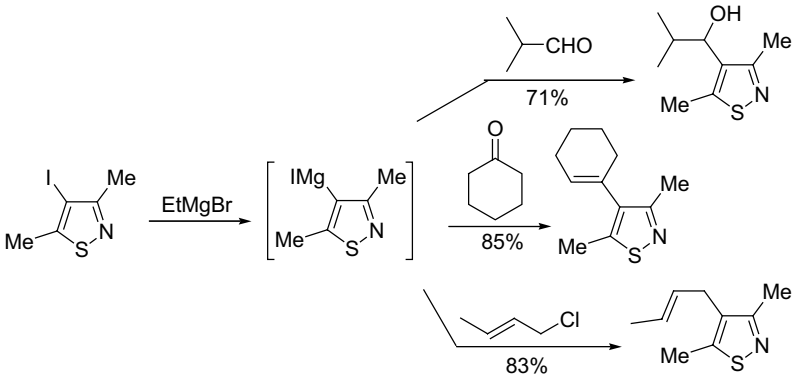
Isothiazole is selectively lithiated with BuLi at the 5-position. 5-Substituted isothiazoles can be prepared by reacting the 5-lithioisothiazole with electrophiles [376–379]. For instance, it reacts with DMF to afford selectively the isothiazole-5-carbaldehyde in good yield (Scheme 9.124) [196].

3-Benzyloxyisothiazole is also lithiated regioselectively in the 5-position using LDA in diethyl ether. Quenching the lithiated species with electrophiles leads to the corresponding 3,5-disubstituted isothiazoles (Table 9.10).

Table 9.10 Lithiation of 3-benzyloxyisothiazole and reaction with various electrophiles.



Electrophile	Product	Yield (%)	Reference
MeOD		57	[380]
DMF		54	[377]
MeOCOCN		56	[377]
PhCHO		65	[377]
		68	[377]
I_2		95	[351]
(i) $B(O\text{-}i\text{-}Pr)_3$		89	[351]
ii) 			



Scheme 9.125

Lithiation of 3-methyl-5-phenylisothiazole with butyllithium occurs selectively at the methyl group (Scheme 9.124). The lithiated species reacts with alkyl halides to give isothiazoles **299** in high yields [363]. It also reacts with a range of aldehydes and ketones to afford the corresponding secondary or tertiary alcohols **300** [381]. When esters are used as electrophiles, mixtures of ketones **301** and tertiary alcohols **302** are obtained [378].

3,5-Dimethylisothiazol-4-ylmagnesium iodide, generated *in situ* from 4-iodo-3,5-dimethylisothiazole and ethylmagnesium bromide, reacts with a range aldehydes, ketones and alkyl halides to afford 4-substituted 3,5-dimethylisothiazoles in good yields (Scheme 9.125) [382].

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10
Five-Membered Heterocycles: 1,3-Azoles

Julia Revuelta, Fabrizio Machetti, and Stefano Cicchi

10.1
Introduction

Imidazole, oxazole, and thiazole, known as 1,3-azoles, are planar five-membered ring systems with three carbons, one nitrogen, and an additional heteroatom (nitrogen, oxygen or sulfur). These compounds and their derivatives have been known since the nineteenth century.

The first reports on imidazoles were published in the 1840s concerning the 2,3,5-triphenylimidazoles [1, 2]. In 1858 Debus [3] reported the reaction between glyoxal and ammonia and pioneered the synthesis of imidazoles. Historically, the molecule was named "glyoxaline" and "iminazole," but imidazole is now used universally.

Oxazole (1,3-oxazole) was first prepared by Cornforth [4] in 1947, about 100 years after the first synthesis of a substituted oxazole, 1,4,5-triphenylisoxazole, reported by Zinin in 1840 [5]. In 1888, Hantzsch [6] gave the name of oxazoles to these class of compounds. Oxazole is not easily synthesized and has been unavailable in large quantities (because of high synthesis costs) and has only recently become commercially available in multigram scale at a reasonable cost. The Cornforth procedure was a lengthy route in which the oxazole was obtained in the final stage by decarboxylation–distillation of the corresponding oxazole-4-carboxylic acid from hot quinoline-CuO. Oxazole may be prepared in the laboratory following the practical method of Brederick and Bangert [7].

Modern oxazole chemistry was stimulated in the 1940s by the synthesis of penicillin, which was presumed to contain the oxazole nucleus. The next important development of oxazole chemistry came from the discovery by Kondrateva in the late 1950s that these compounds acts as dienes in the Diels–Alder reaction and by Huisgen's work on 1,3-dipolar cycloaddition reactions of mesoionic derivatives.

Wallach reported the synthesis of some thiazoles in the 1870s. One of the first thiazoles prepared was the 5-aminothiazole-2-carboxylic acid amide [8].

In terms of literature about imidazoles, oxazoles and thiazoles there are many reviews on specialized topics (chemistry, physicochemical, biological and pharma-

Modern Heterocyclic Chemistry, First Edition.
Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.

cological properties) but *Comprehensive Heterocyclic Chemistry* (1984 [9] updated in 1996 [10]) and *Science of Synthesis* [11] are the most exhaustive sources of information.

10.1.1 Nomenclature

The general name 1,3-azoles (**1**) indicates, according to the more recent IUPAC nomenclature rules, five-membered (stem -ole) heterocycles with one nitrogen atom (prefix aza-) bearing a second heteroatom in position 3 of the cycle. This name is generally used to indicate thiazole, oxazole and imidazole. The first two names correspond to the IUPAC nomenclature, whereas the name imidazole is a trivial one that is commonly preferred to 1,3-diazole. The state of hydrogenation is indicated either by the prefixes "dihydro-" or in the stem "-olidine". This chapter examines 1,3-oxazole, 1,3-thiazole and imidazole, as well as their saturated derivatives. Figure 10.1 gives an easy, exhaustive description of nomenclature and numbering of the structures.

These heterocyclic rings occur widely in nature, contained in the structure of several secondary metabolites. Some of these compounds are promising candidates as drugs and their synthesis has been performed. The oxazole ring is present in the backbone of diazonamide A (**3**), a complex macrocyclic molecule with anticancer properties, which was recently been synthesized [12]. Phorboxazole A (**4**), which possesses two isolated oxazole rings, is an extremely cytotoxic compound that is active towards numerous human tumor cell lines [13]. Other bis- and trisoxazole oxazole compounds are known, such as muscoride A (**5**) [14] and ulapualide A (**6**) [15]. The thiazole ring, in different degrees of saturation, is present in thiamine pyrophosphate (**7**), 6-aminopenicillanic acid (**8**) and other secondary metabolites such as dendroamide A (**9**) [16] and epothilone A (**10**) [17]. Histidine (**11**), which has an imidazole ring, is a very well known amino acid with a fundamental role in the metabolism and also in the family of alkaloids derived from it. The same ring, in reduced form, is also found in biotin (**12**) and in a large series of alkaloids, such as (−)-agelastatin A (**13**) [18] and fumiquinazoline A (**14**) [19] (Figure 10.2).

10.2 General Reactivity

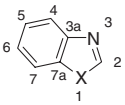
10.2.1 Relevant Physicochemical Data, Computational Chemistry and NMR Data

These compounds present an additional nitrogen atom in the ring with respect to pyrrole, thiophene and furan. This additional nitrogen atom contributes with one electron to the aromaticity of the ring while a lone pair of electrons remains in the plane of the molecule. This additional nitrogen atom lowers the energy levels of π orbitals, as verified by the ionization potentials, which are higher than those of pyrrole, thiophene and furan, respectively. At the same time the additional nitrogen

X = O 1,3-oxazole

X = S 1,3-thiazole

X = NH 1*H*-imidazole



X = O 1,3-benzoxazole

X = S 1,3-benzothiazole

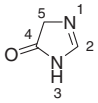
X = NH 1*H*-benzimidazole

X = O 1,3-oxazol-5(4*H*)-one

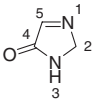
X = S 1,3-thiazol-5(4*H*)-one

X = O 1,3-oxazol-5(2*H*)-one

X = S 1,3-thiazol-5(2*H*)-one



3,5-dihydro-4*H*-imidazol-4-one



2,3-dihydro-4*H*-imidazol-4-one

X = O 4,5-dihydro-1,3-oxazole

X = S 4,5-dihydro-1,3-thiazole

X = NH 4,5-dihydro-1*H*-imidazole

X = O 2,5-dihydro-1,3-oxazole

X = S 2,5-dihydro-1,3-thiazole

X = NH 2,5-dihydro-1*H*-imidazole

X = O 2,3-dihydro-1,3-oxazole

X = S 2,3-dihydro-1,3-thiazole

X = NH 2,3-dihydro-1*H*-imidazole

X = O 1,3-oxazolidine

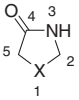
X = S 1,3-thiazolidine

X = NH imidazolidine

X = O 1,3-oxazolidin-2-one

X = S 1,3-thiazolidin-2-one

X = NH imidazolidin-2-one



X = O 1,3-oxazolidin-4-one

X = S 1,3-thiazolidin-4-one

X = NH imidazolidin-4-one

Figure 10.1 Nomenclature and numbering of 1,3-oxazole, 1,3-thiazole, imidazole, and their saturated derivatives.

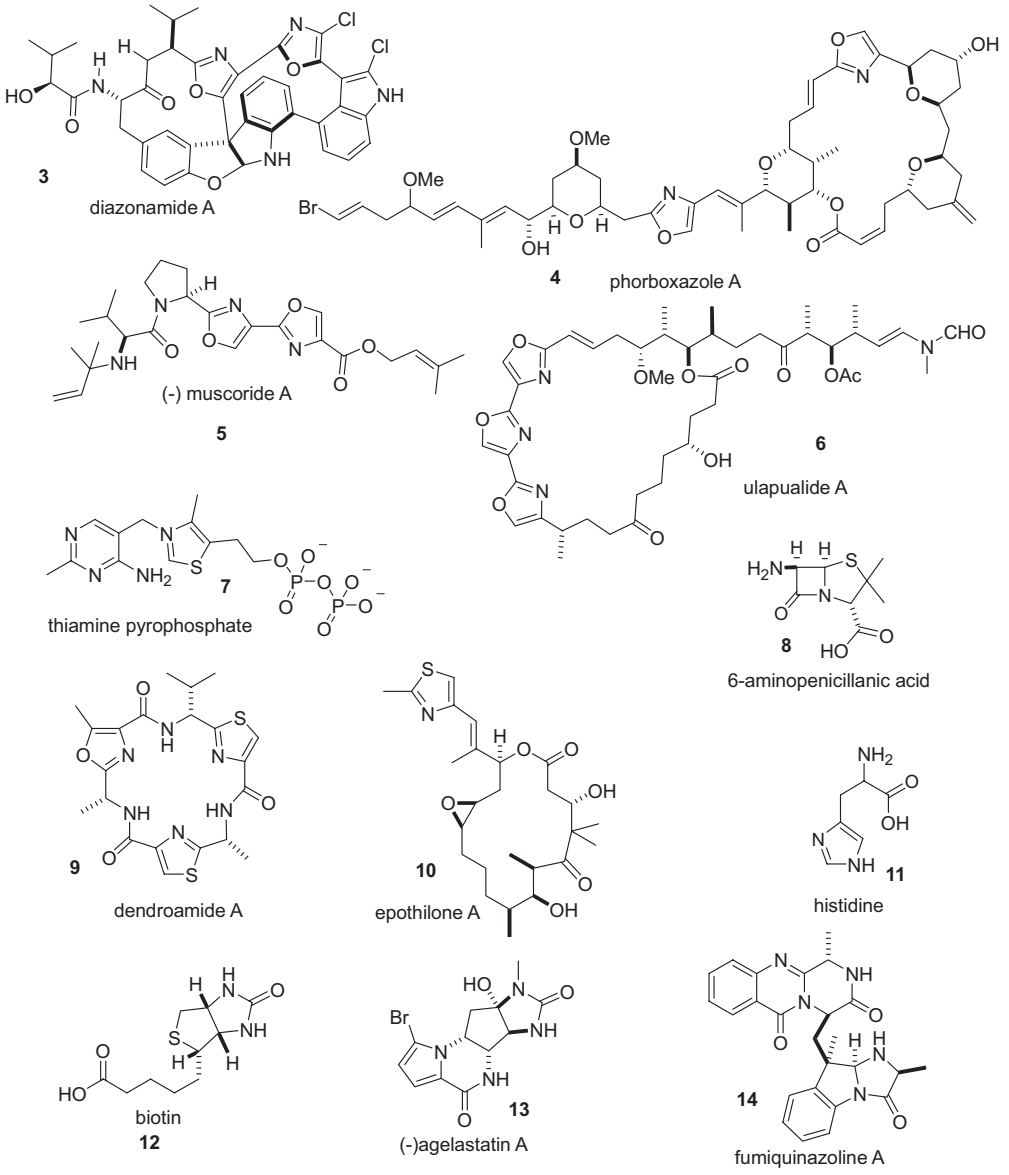
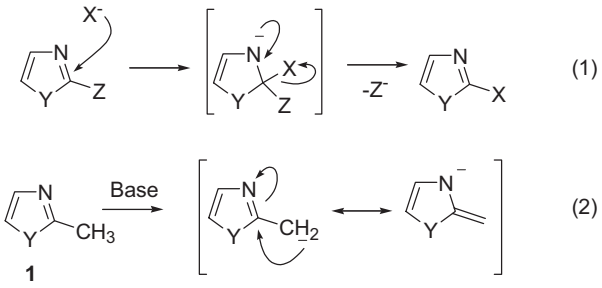


Figure 10.2 Some natural compounds containing the 1,3-azole structure.

atom has an inductive electron-withdrawing effect that provides stabilization to negatively charged reaction intermediates formed in reactions like nucleophilic substitution [Scheme 10.1 (1)] and deprotonation of the methyl group [Scheme 10.1 (2)]. A recent study, based on NMR data of the carbanions of 2-benzyl-1,3-azoles, ranked the π electron-withdrawing power of these heterocycles as thiazole > oxazole



Scheme 10.1

> imidazole in terms of charge demand, that is, the fraction of p-negative charge delocalized by the ring [20]

These compounds are aromatic, each carbon atom and one nitrogen atom participating with one electron to the conjugated π system while the other heteroatom participates with a lone pair of electrons. The NMR and UV spectra confirm the aromaticity of the ring (Table 10.1).

The π electrons are delocalized across the ring although the electron density is largely concentrated onto the two heteroatoms. The electron density map also indicates that these compounds are π excessive although this character decreases on passing from N to O to S. From the same map it can be predicted that electrophilic substitution is favored at C4 and C5, while the reduced electron density at C2 should favor nucleophilic attack onto this position (Table 10.2).

The effect of the additional nitrogen atom is evidenced also by the acid/base properties of these compounds. The lone pair on nitrogen atom provide a site for protonation and most azoles are stronger bases than pyrroles. However, the stability of the azolide anions makes imidazole a stronger acid than pyrrole (Figure 10.3).

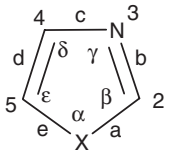
Outstanding, in this series, is the pK_a of imidazole and of the imidazolium ion. These values are justified by the predominance of a mesomeric effect. The two

Table 10.1 UV and NMR data for 1,3-azoles[a)].

X (Table 10.2)	UV (ethanol) λ (nm) (ε, $mol^{-1}\,dm^3\,cm^{-1}$)	^{1}H (δ, ppm)	^{13}C (δ, ppm)
N	207–208 (3.7)	H2: 7.73	C2: 135.4
		H4: 7.14	C4: 121.9
		H5: 7.14	C5: 121.9
O	205 (3.9)	H2: 7.95	C2: 150.6
		H4: 7.09	C4: 125.4
		H5: 7.69	C5: 138.1
S	207.5 (3.41) 233.0 (3.57)	H2: 8.77	C2: 153.6
		H4: 7.86	C4: 143.3
		H5: 7.27	C5: 119.6

For atom numbering see structure in Table 10.2.

Table 10.2 Physicochemical data for 1,3 azoles.



1

X	Bond angles (°)					Bond distances (Å)				
	α	β	γ	δ	«	a	b	c	d	e
N	107.2	111.3	105.4	106.3	109.8	1.349	1.326	1.378	1.358	1.369
O	103.9	115.0	103.9	109.7	108.1	1.357	1.292	1.395	1.353	1.370
S	89.3	115.2	110.1	115.8	109.6	1.713	1.304	1.372	1.367	1.713

	Electron densities				
X	1	2	3	4	5
N	1.502	0.884	1.502	1.056	1.052
O	1.730	1.021	1.115	1.058	1.076
S	1.970	0.870	1.190	0.960	1.010

identical resonance structures account for the high stability of these ions (Scheme 10.2). Oxazole, on the other hand, is the least basic of the three heterocycles due to the inductive effect of the oxygen atom.

10.2.2 Tautomerism

A peculiar behavior of *N*-unsubstituted imidazoles is their rapid equilibrium between the two possible tautomers. This rapid equilibrium hampers the separate isolation of 4- and 5-substituted imidazoles. Nevertheless the tautomeric equilibrium can be shifted mainly towards one of the two forms. Imidazoles substituted with electron-

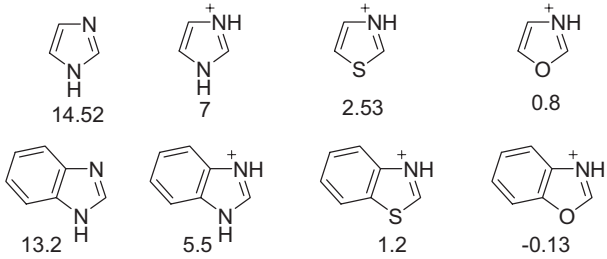
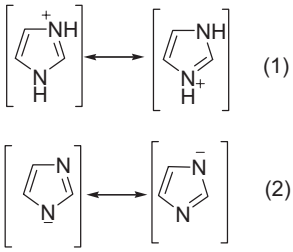


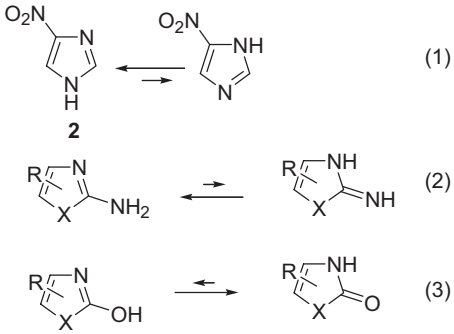
Figure 10.3 Values of pK_a for 1,3-azoles and azolium ions.



Scheme 10.2 Resonance structures of imidazolium and imidazolide ions.

withdrawing groups are predominantly present as 4-substituted tautomers (e.g., 4-nitroimidazole, **2**) [Scheme 10.3 (1)]. In neutral organic solvents this equilibrium can be an intermolecular process involving two or more imidazole molecules while in protic solvents the solvent itself is involved. The NH proton of imidazole exchanges rapidly in D_2O solution.

The tautomeric equilibrium of 2-amino substituted 1,3-azoles is shifted towards the amino form over the imino form [Scheme 10.3 (2)]. This assumption is confirmed by the basicity of the imino form, which is generally higher than that of the amino. Conversely, 2-hydroxy substituted 1,3-azoles behave as keto derivatives [Scheme 10.3 (3)]. These considerations can generally be extended to other amino and hydroxy derivatives.



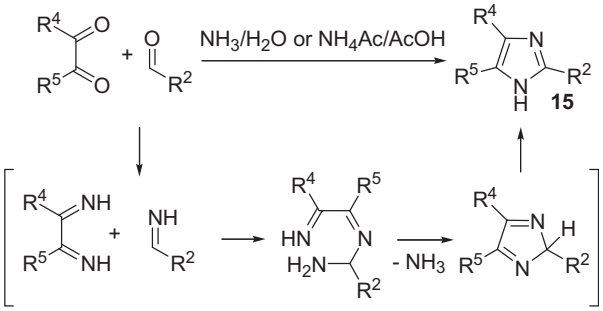
Scheme 10.3 Tautomeric equilibria of substituted 1,3-azoles.

10.3
Synthesis of Aromatic 1,3-Azoles

10.3.1
Synthesis of Imidazoles

A remarkable number of synthetic approaches have been developed for imidazoles, due to is prevalence in natural products and pharmacologically active compounds. Clearly, no a single general synthetic method fulfils all needs in the preparation of

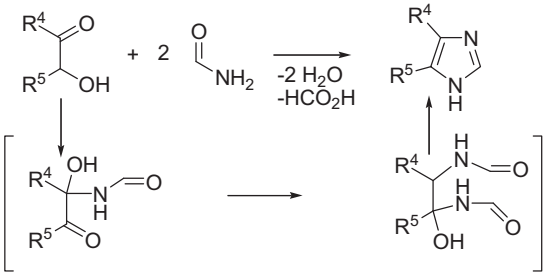
functionalized imidazoles, and various cyclization reactions are used to produce specifically substituted imidazoles [21–24]. A detailed compilation of known methods of synthesis of imidazoles has been published [25]. This brief section, while covering classical methods, focuses mainly both on their conceptual extensions and on new synthetic routes. Most classical preparation methods of imidazoles derive from the approach followed by Debus, who pioneered the use of 1,2-dicarbonyl compounds for the synthesis of substituted imidazoles (Scheme 10.4). The reaction was extended using α-ketoaldehydes or α-diketones as substrates. This route in general provides 2-monosubstituted and 2,(4,5- homo and hetero)trisubstituted imidazoles (Scheme 10.4).



Debus' reaction: $R^2=R^4=R^5=H$

Scheme 10.4

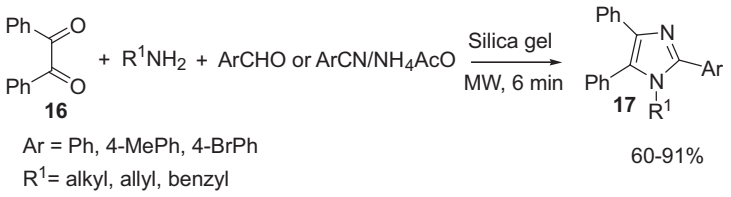
The Radziszewski reaction [26] is a modified version of this method using α-hydroxyketones. A similar synthetic methodology was introduced by Bredereck [27] in which an α-hydroxyketone or an α-haloketone is heated with formamide instead of ammonia or ammonium acetate. Bredereck's reaction provides 4-substituted and 4,5-disubstituted imidazoles (Scheme 10.5).



Scheme 10.5

The advent of microwave assisted organic synthesis (MAOS) has allowed the reinvestigation of the classical conditions of Debus synthesis of imidazoles. Thus, synthesis from 1,2-diketones and aldehydes in the presence of various catalysts has

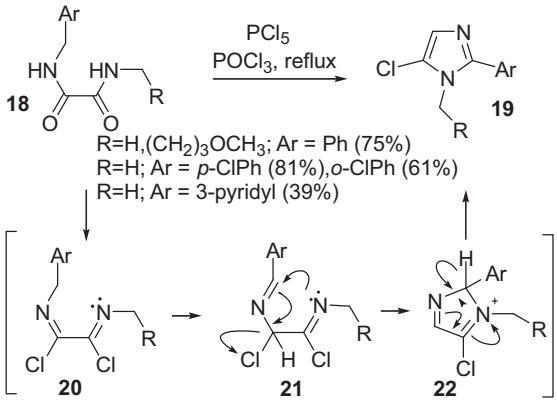
been reported. These include silica gel [28], silica gel/Zeolite HY [29], Al_2O_3 [30] and CH_3CO_2H [31]. These recent more reports, with some green chemistry related improvements, utilize solvent-free, silica-gel catalyzed condensation of aromatic aldehydes or benzonitrile derivatives with benzyl (**16**) (as well as other aromatic or heteroaromatic diketones) [31] in the presence of primary amines to obtain the corresponding tetrasubstituted imidazoles (**17**). The reactions proceed with high yields but the tolerated substitution pattern is restricted to symmetrical residues due to a lack of regiocontrol for the 4- and 5-positions (Scheme 10.6) [29].



Scheme 10.6

α-Hydroxyketones have also been used in MAOS procedures [32], and both diketones and α-hydroxyketones have found application in ionic-liquid promoted synthesis [33].

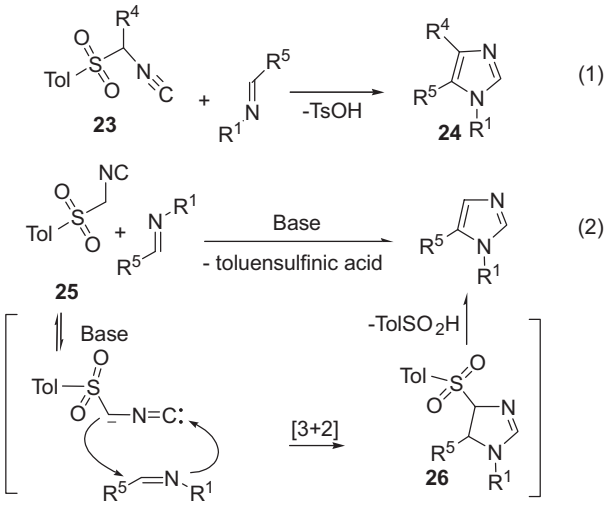
The cyclization of N,N′-disubstituted oxamides **18** with PCl_5 to afford 1-substituted 5-chloroimidazoles **19** is another classical method of imidazole ring preparation. This method was discovered by Wallach [34–36] and elaborated by Sarasin [37]. This approach, initially limited to methyl and ethyl symmetrical disubstituted oxamides, was extended to higher symmetrical [34, 38, 39] and unsymmetrical N,N′-disubstituted oxamides (Scheme 10.7) [40]. In the latter case, to obtain appreciable regioselectivity very dissimilar substituent (alkyl versus aryl) should be used. The reaction gives high yields for limited phenyl and chlorinated phenyl substituents but with a 3-pyridyl substituent the yield is low (Scheme 10.7).



Scheme 10.7

Wallach's reaction proceeds via a dichlorinate adduct (**20**), which after a double bond migration (hydride shift), cyclizes to the final 5-chlorosubsituted imidazole **19** (Scheme 10.7).

Another example of a classical approach to imidazole is represented by the Marckwald synthesis, involving the use of α-aminocarbonyl compounds with cyanates, thiocyanate and isothiocyanates. This approach allows the synthesis of 4,5-disubstituted imidazoles and will be described in more detail in Section 10.4.5 for the synthesis of 2-amino-1,3-azoles. TosMIC (tosylmethyl isocyanide) **25** and other isocyanides, **23**, are key reagents for the preparation of 1,5 substituted imidazole rings, providing the CNC fragment [Scheme 10.8 (1)] [41]. Different species like aldimines, imidoyl chlorides, isothiocyanates, nitriles and imino ethers can undergo cycloadditions with TosMIC giving imidazoles. This methodology provides densely functionalized imidazoles, as **24**, with various substitution patterns in a completely regioselective manner.

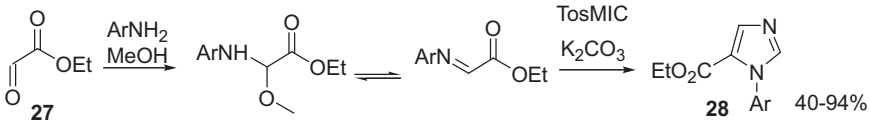


Scheme 10.8

The TosMIC molecule (which accommodates a reactive isocyanide carbon and an activated methylene) can cycloadd its $CH_2N{=}C$ moiety to polarized double bonds under basic conditions [Scheme 10.8 (2)]. When applied to aldimines, this type of reaction affords imidazoles by elimination of *p*-toluenesulfinic acid from the intermediate 4-tosyl-2-imidazolines **26** [42]. This methodology regioselectively provides 1,5 and a limited number of 1,4,5-trisubstituted imidazoles.

This methodology provides regioselectively 1-arylimidazole-5-carboxylates **28** by the addition of anilines to ethyl glyoxylate **27** in methanol followed by reaction with TosMIC (Scheme 10.9) [43].

The related reaction of ethyl glyoxylate or glyoxylic acid with primary amines or ammonia and aryl substituted TosMIC reagents **23** [44] is a versatile method for the synthesis of imidazole-5-carboxylates substituted at C4 (e.g., **29**, Figure 10.4) [45].



Scheme 10.9

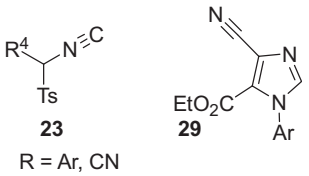
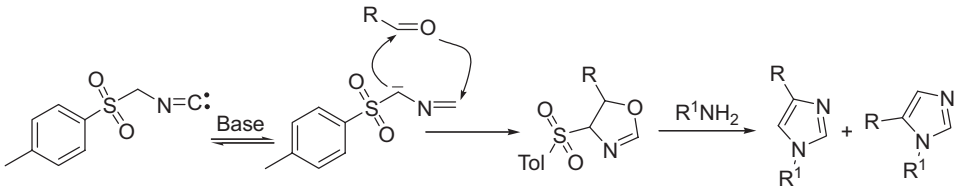


Figure 10.4 Structures of susbstitute TosMIC reagents and of imidazole-5-carboxylates substituted at C4.

The TosMIC chemistry can be extended utilizing an aldehyde as a partner (Scheme 10.10) [46]. Polysubstituted imidazoles are not easily made with this methodology and a mixtures of regioisomeric imidazoles are obtained.

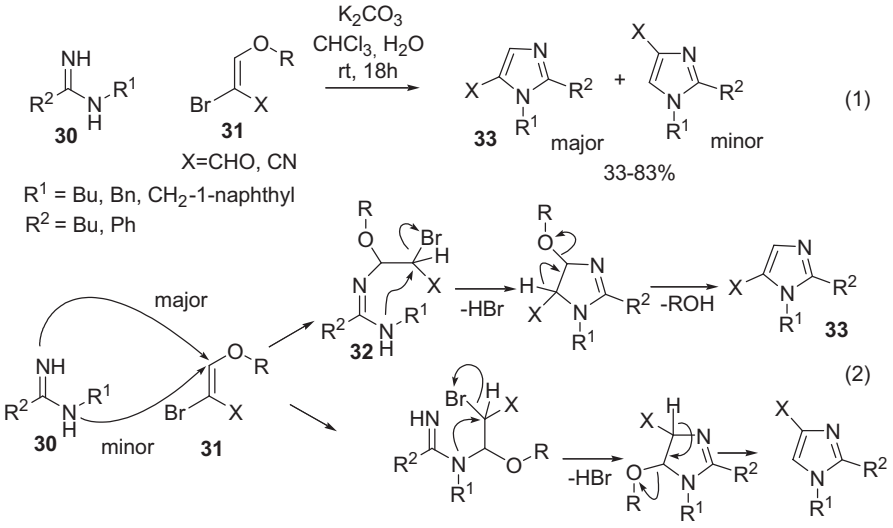


Scheme 10.10

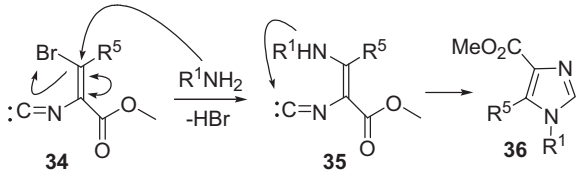
Amidines, guanidines, ureas and thioureas are the most common NCN synthons. With these synthons we can selectively synthesize 1,2,5 substituted imidazoles [47].

Bromo enol ethers **31** react with a range of monosubstituted amidines **30**, giving with high regioselectivity 1,2,5 imidazoles in moderate yields [Scheme 10.11 (1)]. The mechanism that explains the high regioselectivity of this reaction is shown in Scheme 10.11 (2). The unsubstituted nitrogen of amidine **30** adds in Michael fashion to the β-carbon of the ether. Intermediate **32** then cyclizes with extrusion first of HBr and then of ROH to afford imidazole **33**. Initial attack by the monosubstituted nitrogen is disfavored, particularly in cases where R^1 is a bulky group.

1,5 Disubstituted imidazole-4-carboxylates can be efficiently synthesized using the reactivity of BICA [3-bromo-2-isocyanoacrylate (**34**)] [48]. In this strategy, a Michael reaction of a primary amine with α,β-unsaturated ester **34** and subsequent β-elimination of hydrogen bromide occurs as the first step. The resulting enamine **35** undergoes an intramolecular nucleophilic addition to the isonitrile group, affording the final imidazole **36** (Scheme 10.12). This approach has been applied to the synthesis of imidazoles having a range of substituents at the 1- and 5-positions.



Scheme 10.11

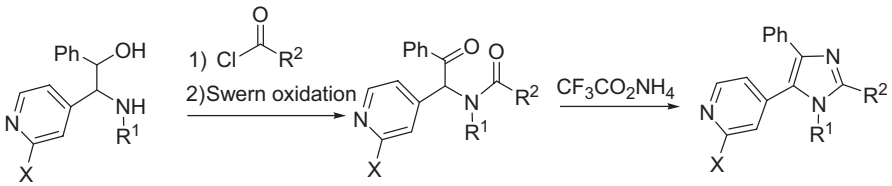


Scheme 10.12

A methodology for the preparation of 2-substituted-4,5-dicyanoimidazoles is the reaction of DAMN (diaminomaleonitrile) with carbonyl compounds under oxidative conditions [49]. A more recent variation is the reaction of DAMN with anhydrides to afford β-aminoenamides that dehydrates to afford the imidazole nucleus [50]. The commercial availability of this reagent gave impulse to its use in the synthesis. Its use and the mechanism of action are discussed in Section 10.5.6 for the synthesis of 2-amino derivatives.

Few methods for the direct construction of tetrasubstituted imidazoles are available and they are often restricted to a fixed pattern of substitution [28, 51, 52]. Popular methodologies for the construction of imidazole rings such as the aforementioned approaches based on van Leusen's TosMIC chemistry are not able to provide direct access to tetrasubstituted imidazoles, because do not allow to insert substituent on C2 of the imidazole ring. Further introduction of substituent requires activation/substitution (Section 10.3). In general the synthesis of tetrasubstituted imidazoles rely on the regiocontrolled synthesis of trisubstituted imidazoles followed by insertion of the fourth substituent [53–56]. This approach have some drawbacks. For example the *N*-alkylation of 2,4,5-trisubstituted imidazoles has as a major drawback the formation of both possible regioisomers that are often difficult to separate.

One of the more versatile intermediates for the synthesis of imidazoles and in particular tetrasubstituted imidazoles are 1,4 dicarbonyl compounds. This approach is limited for two main reasons: (i) the syntheses of these precursors are nontrivial and in many examples involve multistep sequences starting from 1,2-aminoalcohols [57–59]; (ii) the reaction conditions are often drastic. An efficient synthesis of tri- and tetra- substituted imidazoles starting from β-ketoamides under neutral reaction conditions has been reported (Scheme 10.13) [58]. Cyclization was carried out using ammonium trifluoroacetate as a solvent.



Scheme 10.13

The method tolerates a various array of substituents at N1 and C2. For bulky R^1 the substituent R^2 is limited to small groups due to the difficult synthesis of the corresponding keto amides. With this methodologies it is possible decorate the imidazole scaffold with sufficient flexibility (Figure 10.5) [60].

A very attractive method for the preparation of tetrasubstituted imidazoles is based on an hetero-Cope rearrangement followed by an amidine cyclization [61]. This procedure utilizes as starting materials oximes **37** (bearing R^4 and R^5 imidazole substituents) and imidoyl chlorides **38** (bearing R^1 and R^2 imidazole substituents) (Scheme 10.14). This reaction is highly regioselective, the main limitation being the aromatic nature of the C2 substituents.

Another direct approach towards 1-methyl-tetrasubstituted imidazoles involves the 1,3-dipolar cycloaddition of methylated mesoionic oxazolones (münchnones). The reaction of *N*-methyl-1,3-oxazolium-5-olates **39** with imines **40** involves a 1,3-dipolar cycloaddition to give an unstable primary bicyclic adduct **41** that loses carbon dioxide and benzenesulfinic acid and gains aromaticity (Scheme 10.15) [52]. The phenylsulfonyl leaving group enhances the tendency to aromatize. The yields reported for this reaction are low, at least partly due to self-condensation of münchnones.

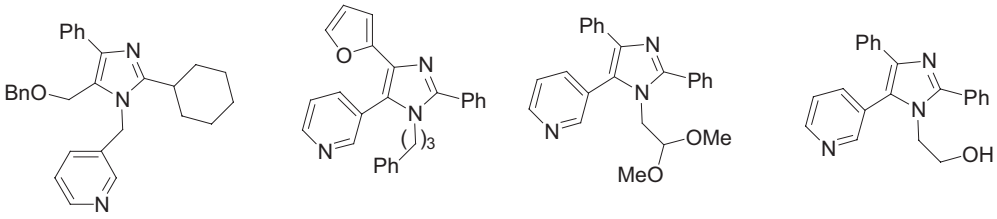
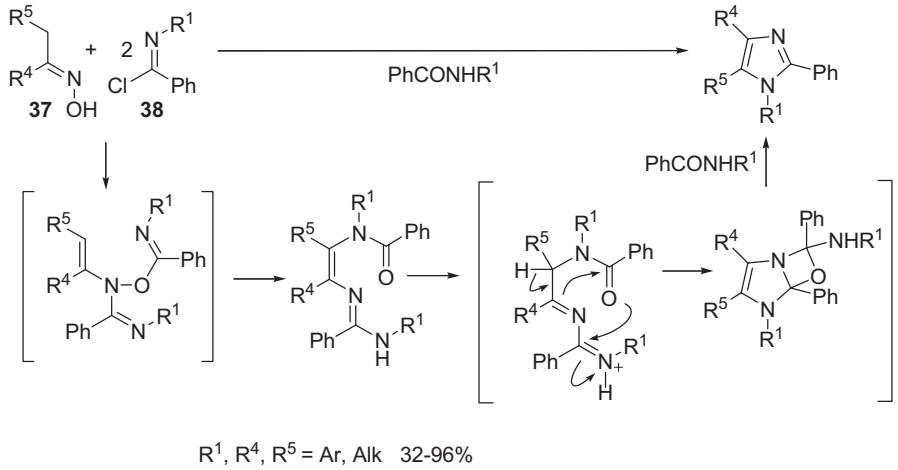
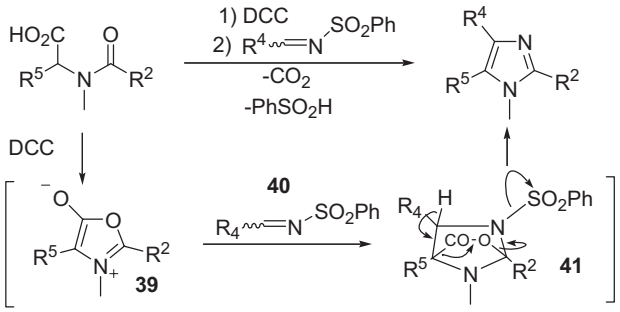


Figure 10.5 Structures of compounds obtained starting from 1,4-dicarbonyl reagents.



Scheme 10.14

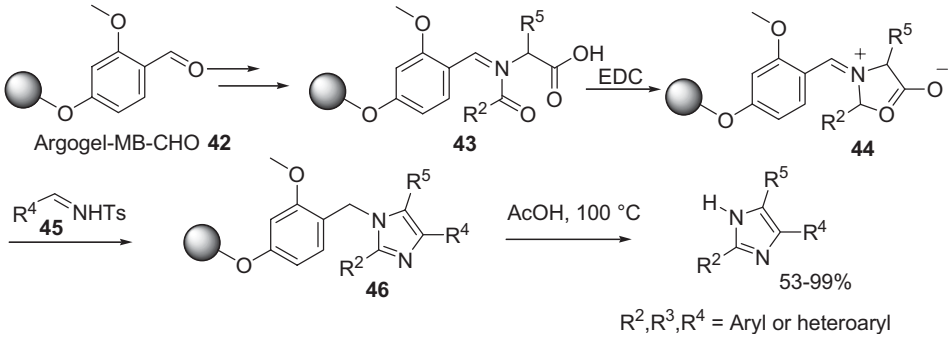


Scheme 10.15

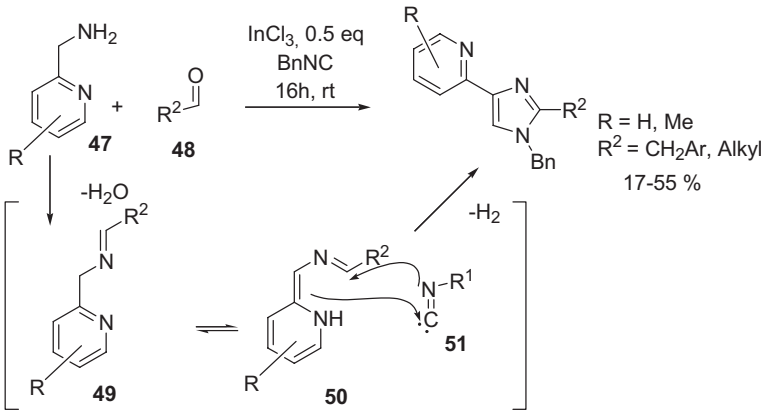
The problem of self-condensation can be suppressed by using a solid-phase approach towards preparation of imidazoles (Scheme 10.16) The precursor **43** prepared from commercially available resin **42** (ArgoGel-MB-CHO) and treated with ethyl-diisopropylcarbodiimide (EDC) led to the münchnone **44**. Subsequent cycloaddition with tosyl imine **45** followed by elimination of toluenesulfinic acid and CO provided the resin linked imidazoles **46**. The imidazoles were liberated from the resin by treatment with glacial acetic acid at 100 °C and obtained in good yield and purities [62].

There are a few examples that utilize the concept of a multicomponent reaction (MCR), especially the Ugi type reaction, for the synthesis of imidazoles. However, most syntheses have been performed in a stepwise fashion and were not set-up as MCR. A three component reaction utilizing aldehydes, *o*-picolilamines and isocyanides is shown in Scheme 10.17 [63].

The reaction proceeds through *in situ* formation of imine **49** from aldehyde **48** and amine **47** followed by the attack of the α-acidic isocyanide **51** and subsequent ring



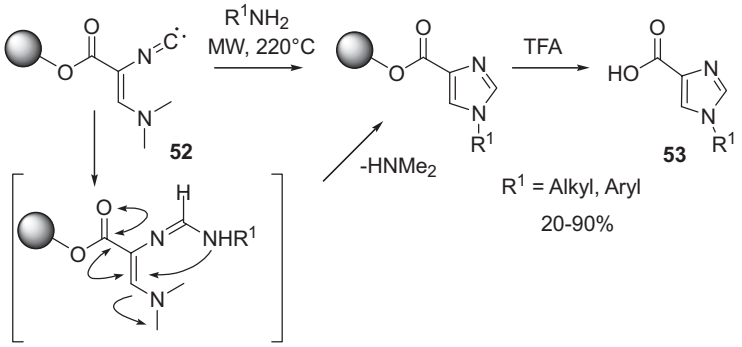
Scheme 10.16



Scheme 10.17

closure. Subsequent aromatization affords the final imidazole. The nucleophilicity of the (2-pyridyl)methyl carbon derives from the enamine tautomer **50**.

Scheme 10.18 depicts the synthesis of 1-substituted-4-carboxylic acid imidazoles **53** through a resin-bound isonitrile [64]. The solid supported isonitrile



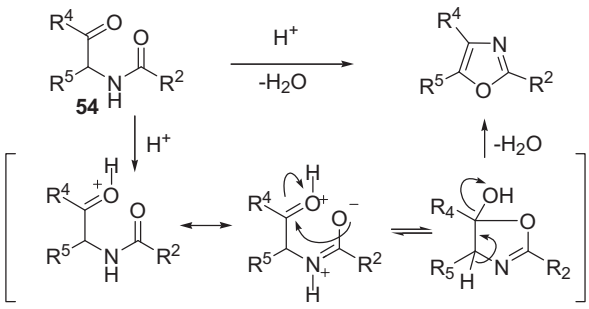
Scheme 10.18

(Wang resin) **52** was treated with alkyl and aryl amines to give, in variable yields, the imidazoles. The reactions can be speeded up using microwaves. The reaction proceeds with a mechanism involving α-addition of the amine to the isocyanide.

10.3.2
Synthesis of Oxazoles

Oxazole are common substructures in several biologically active compounds, synthetic intermediates and pharmaceuticals, and consequently there is a continuing stimulus for the development of more general and versatile synthetic methodologies for this class of compounds [65].

The cyclodehydration of 2-acylamino ketones **54**, known as the Robinson–Gabriel reaction, is one of the oldest and most widely used synthesis of 2,5-disubstituted and 2,4,5-trisubstituted oxazoles (Scheme 10.19) [66, 67].



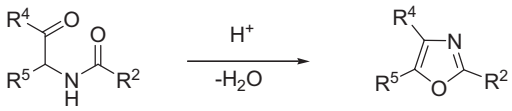
R^2,R^3,R^4= alkyl, aryl, heteroaryl

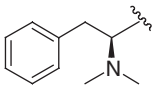
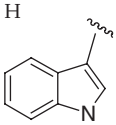
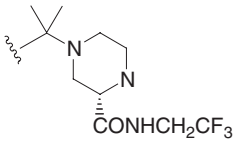
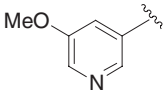
Scheme 10.19

As an extension of Robinson–Gabriel synthetic approach to oxazoles, *N*-acylamino acids, *N*-acylamino esters, *N*-acylamino nitriles and *N*-acyl peptides have been used as substrate for cyclodehydration. Classically, this transformation was carried out with relatively harsh dehydrating agents, including concentrated H_2SO_4, polyphosphoric acid, P_2O_5, $SOCl_2$, $POCl_3$ and anhydrous HF. These classical reagents continue to be used to prepare a wide variety of oxazole derivatives and some examples are shown in Table 10.3.

2-Monosubstituted and 2,4-disubstituted oxazoles are generally inaccessible by the Robinson–Gabriel method owing to the sensitivity of 2-acylamino aldehydes to oxidative and dehydrating conditions. In addition, the same problems can be suffered by α-acylamino ketones containing stereochemically sensitive side chains. However, milder dehydrating agent can be used, offering broader functional group compatibility [76]. A protocol based on triphenylphosphine/iodine in the presence of triethylamine has been introduced by Wipf and Miller (Scheme 10.20) [77].

Table 10.3 Robinson–Gabriel synthesis of substituted oxazoles.



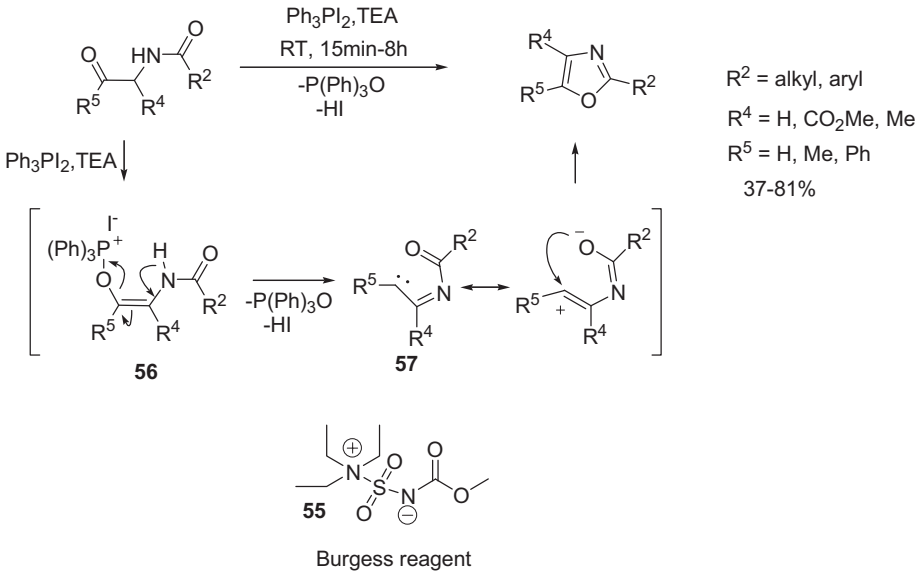
R^2	R^4	R^5	Yield (%)	Reference
CH_2Cl	Et	H	31[a)]	[68]
	H		77[a)]	[69]
Me	CO_2Me	CH_2CO_2Me	19[b)]	[70]
Pr	Ph	Ph	87[c)]	[71]
	H		82[c)]	[72]
$(CH_2)_6CO_2Me$	H	Ph	84[d)]	[73]
i-Pr	H	3,4-di-MeOPh	79[e)]	[74]
Me	*i*-Pr	$N(Bn)_2$	86[f)]	[75]

Dehydrating agents:
a) $POCl_3$.
b) $SOCl_2$.
c) H_2SO_4.
d) P_2O_5.
e) TFA/TFAA.
f) PPA.

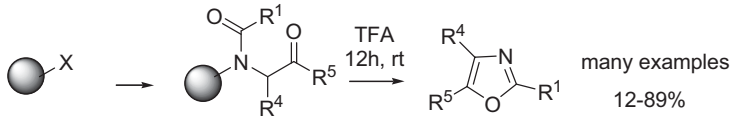
The authors have proposed a mechanism in which an enol phosphonium salt **56** loses Ph_3PO to generate acylimino carbene **57**, which cyclizes to the oxazole ring (Scheme 10.20). The same result can be obtained using the Burgess reagent **55** (Scheme 10.20), in combination with microwave irradiation [78].

The Robinson–Gabriel synthesis of oxazoles can be extended to solid-phase synthesis utilizing solid supported α-acylaminoketones with TFAA as dehydrating agent [79], (Scheme 10.21) or the Burgess reagent [80].

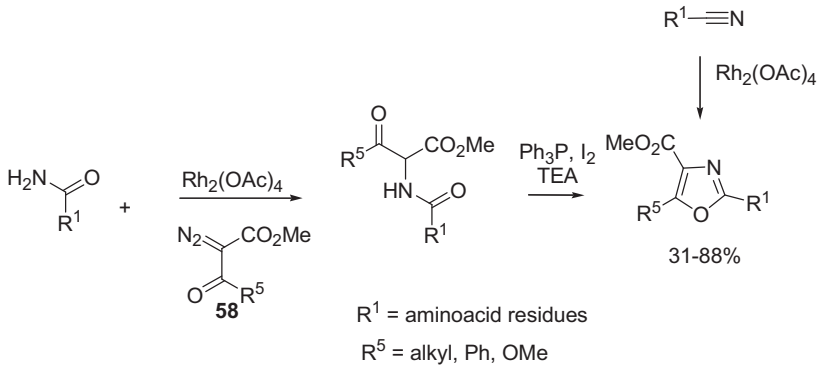
Following the Robinson–Gabriel [66, 67, 81] approach new methodologies have been developed mainly with the aim of improving the generation of the α-aminoacyl ketone precursors. A synthesis described by Moody and coworkers is based on Rh-catalyzed insertion of carbenoids. The use, as counterparts, of nitriles [82] affords directly the oxazole, while the use of primary amides goes through a preliminary insertion of the carbenoid in the N−H bond and subsequent cyclization following the methodologies introduced by Wipf [83]. The source of carbenoids are diazoesters **58** (Scheme 10.22).



Scheme 10.20 Wipf-Miller cyclodehydration synthesis.



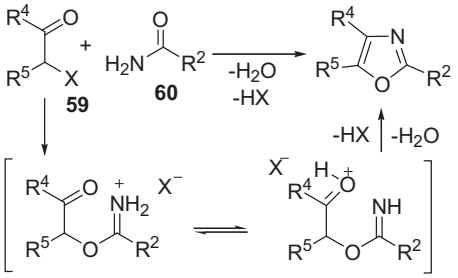
Scheme 10.21



Scheme 10.22

Another well established and widely used method to prepare oxazoles is the cyclocondensation of α-haloketones **59** with primary amides **60** (Hantzsch type reaction). The reaction is typically driven by heating the mixture of **59** and **60** in the presence of a buffer to remove the generated acid. Both 2,4-disubstituted oxazoles and

2-amino-4-substituted oxazoles can be accessed with this methodology (Scheme 10.23). This approach can be extended to synthesize 2-aminooxazoles using urea and its derivatives as the partner of α-haloketones (Section 10.4.4). Furthermore, this approach, using thioamides, is the most general method for the synthesis of thiazoles and it is discussed in details in the next section.



Scheme 10.23

As we have previously seen for the synthesis of imidazoles, TosMIC (**23**) is also a useful reagent for the synthesis of oxazoles [45]. Aldehydes condense, in presence of a base, with TosMIC to afford 4,5-disubstituted oxazolines that eliminate toluenesulfinic acid to yield 5-monosubstituted oxazoles, as already outlined for the imidazole series. The reaction can be extended to substituted TosMIC, giving 4,5-disubstituted oxazole (Table 10.4). The reaction proceeds with the nucleophilic addition of TosMIC to aldehyde followed by cyclization–aromatization.

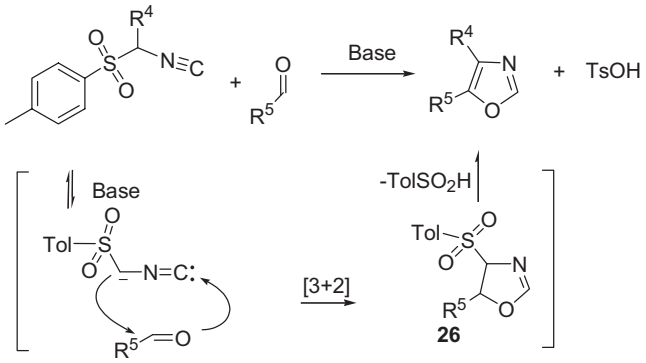
The TosMIC route has been extended to solid-phase synthesis. The use of a polymer-supported version of TosMIC offers the advantage, compared with the homogeneous counterpart, of easy recovery of pure products. Resins that are unstable in basic reaction conditions are avoided. Polystyrene-SO_2-CH_2-NC resin **61**, prepared from Merrifield resin, can be used as a solid-phase equivalent of TosMIC and has found application in the synthesis of 5-aryloxazoles using tetrabutylammonium hydroxide as base (Figure 10.6) [88].

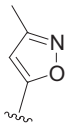
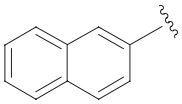
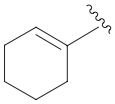
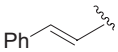
Resin **62** has also been used for the preparation of 5-aryloxazoles in conjunction with t-Bu-tetramethylguanidine [89].

An alternative method to the cyclodehydration of keto amide is the base-promoted [90] or palladium-catalyzed cycloisomerization of propargyl amides. The first reaction in Scheme 10.24 is an example of the latter, in which 2,5 disubstituted oxazoles **63** are prepared. The reaction proceeds through a palladium-catalyzed coupling step followed by cyclization [91]. In the same manner [Scheme 10.24 (2)], 2,4,5 trisubstituted oxazol-5-yl carbonyl derivatives **64** can be prepared using cheap and easily removable silica gel as the mediator of cycloisomerization. These oxazol-5-yl carbonyl compounds were inaccessible utilizing the base- or palladium catalyst-mediated procedure [92].

Oxazoles can also be prepared from β-(acyloxy)vinyl azides by reaction with phosphorous(III) reagents (Table 10.5). The intermediate iminophosphorane gives substituted oxazoles through an intramolecular version of the aza-Wittig reaction.

Table 10.4 Substituted oxazoles prepared using the van Leusen–TosMIC route.



R^4	R^5	Yield (%)	Reference	R^4	R^5	Yield (%)	Reference
H		65	[84]	H	*p*-CF_3Ph	79	[74]
	CO_2Et	80	[45]			90	[85]
3,4,5-$(MeO)_3$Ph	3-BnO-4-MeOPh	89	[86]	Me	*p*-NO_2Ph	96	[87]

This route is particularly useful for the synthesis of acid-labile oxazole derivatives (Table 10.5) [93].

An intermolecular version of the aza-Wittig reaction, using aroyl chlorides, affords imidoyl chloride derivatives **65** which easily cyclize to afford derivatives **66** (Scheme 10.25) [94, 95].

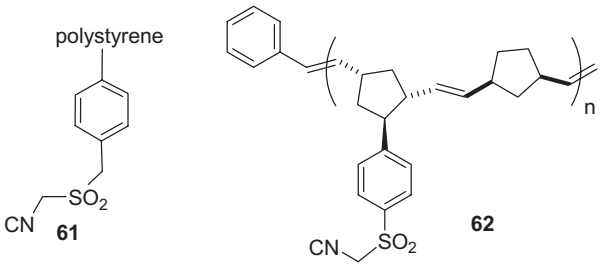
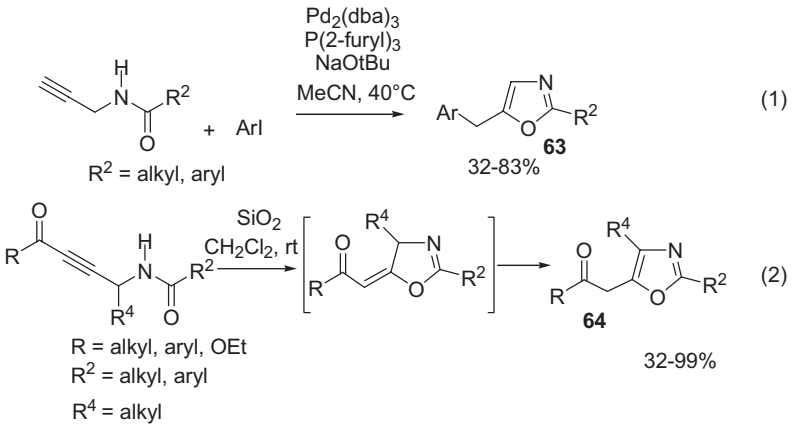


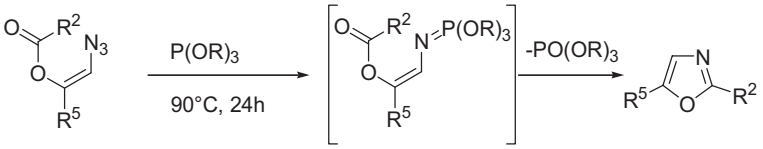
Figure 10.6 Resins used for the preparation of 5-aryloxazoles.

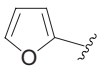
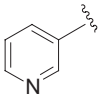
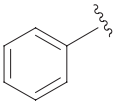
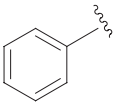


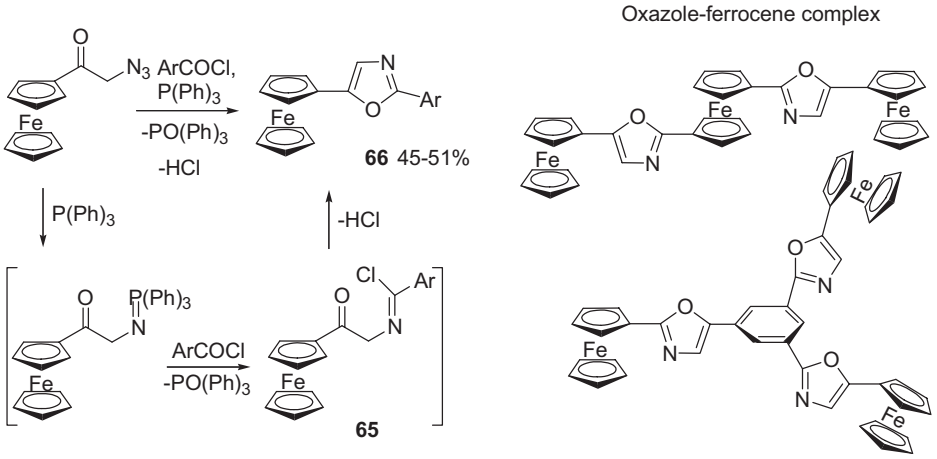
Scheme 10.24

Iminophosphorane joined with isothiocyanate are also useful intermediates for the synthesis of 2-amino substituted oxazoles. This tandem iminophosphorane/heterocumulene mediated annulation is described in Section 10.4.4 [96]

Table 10.5 Oxazoles via intramolecular aza-Wittig rearrangement.



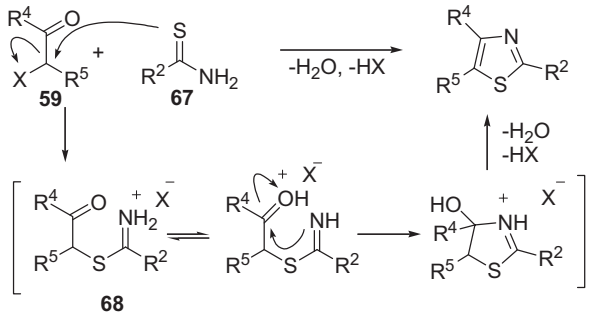
R^2	R^5	Yield (%)
		55
		74
		61
Me		61



Scheme 10.25

10.3.3 Synthesis of Thiazoles

The classical method for the synthesis of thiazole is the Hantzsch process in which an α-halocarbonyl compound **59** (or the corresponding α-haloacetal) is condensed with a primary thioamide **67** (or a thiourea for the 2-amino derivatives) [97, 98]. The reaction proceeds with the nucleophilic attack of sulfur on the carbon atom bearing the halogen. The acyclic intermediate (isolated in few cases) α-S-alkyliminium salt **68**, after a proton transfer, undergoes cyclization and subsequent acid-catalyzed elimination of water (Scheme 10.26).



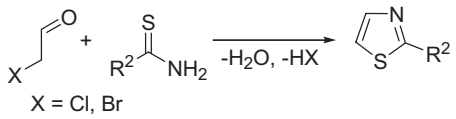
Scheme 10.26

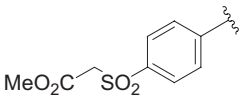
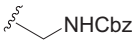
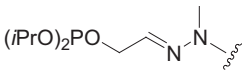
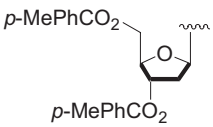
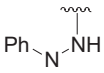
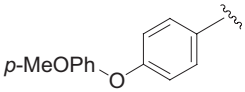
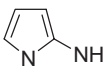
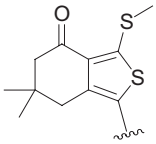
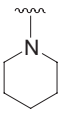
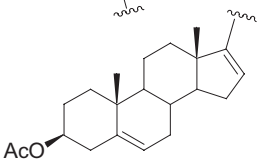
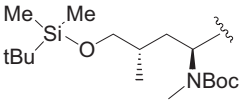
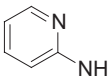
This reaction usually proceeds smoothly to yield the desired thiazole and excellent yields have been obtained for simple thiazoles. However, for some types of substituent the range of pattern is limited, and low yields occur, as a result of dehalogenation of the α-haloketone during the reaction. Using thioamides and unsubstituted

α-halocarbonyl it is possible to access 2-substituted thiazoles. In this case the range of substitution pattern is in almost every case abundant. Table 10.6 lists some examples.

Dimethyl and diethyl acetals as well as halohydrine derivatives frequently replace the aldehydes.

Table 10.6 2-Substituted thiazoles prepared following the Hantzsch procedure.

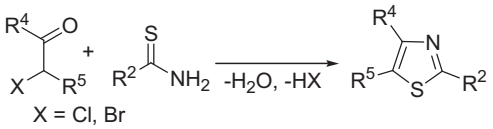


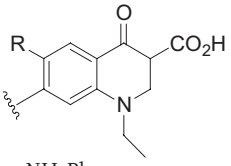
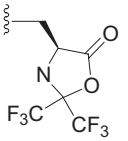
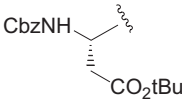
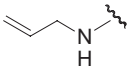
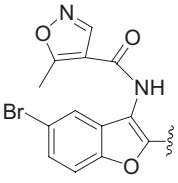
R^2	Yield (%)	Reference	R^2	Yield (%)	Reference
Me	49	[99]		33	[100]
Ph	79	[101]		71	[102]
NH_2	91	[103]		41	[104]
SH	50	[105]		70	[106]
SMe	88	[107]		78	[108]
Me_2N	85	[109]		50	[110]
	80	[111]		65	[112]
	50	[113]		15	[114]
	73	[115]		79	[116]

For the synthesis of 4-substituted thiazole the thioformamide is the reagent of choice, while using substituted thioamides and substituted α-haloketones affords 2,4,5-trisubstituted azoles (Table 10.7).

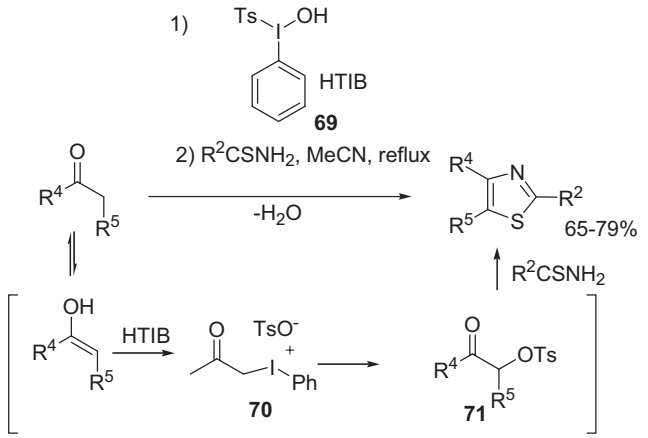
A modification of the Hantzsch synthesis utilizes α-tosylketones instead of α-halocarbonyl compounds [128]. One of the advantages of this modification is to

Table 10.7 Synthesis of 2,4,5-trisubstituted azoles.



R^2	R^4	R^5	Yield (%)	Reference
H	CH_2CH_2Phth	H	78	[117]
H	$CH_2CH_2CO_2Et$	H	40	[118]
H		H	83	[119]
H	*m*-NH_2Ph	H	84	[119]
H		H	52	[120]
Me	3,4-diOMe-Ph	CO_2Me	80	[121]
Bt	Me	Me	66	[122]
	Ph	Ph	50	
	Ph	Me	59	
	CO_2Et	Me	81	[123]
NH_2	Me	CO_2Me	53	[124]
	CO_2Me	CO_2Me	65	[125]
Ph		H	86	[126]
NH_2	CO_2Et	H	76	[127]

avoid the use of lachrymatory and toxic α-halocarbonyl compounds. This method involves a reaction of ketones with the hypervalent iodine reagent HTIB [hydroxy-(tosyloxy)iodobenzene] (**69**) to produce the α-tosylketone **71** through the intermediate formation of α-λ^3-iodanil ketone **70** (Scheme 10.27).

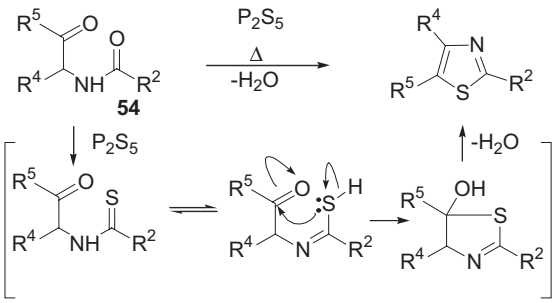


R^2 = NH_2, NHAr
R^4 = Ar
R^5 = H, COMe, CO_2Me

Scheme 10.27

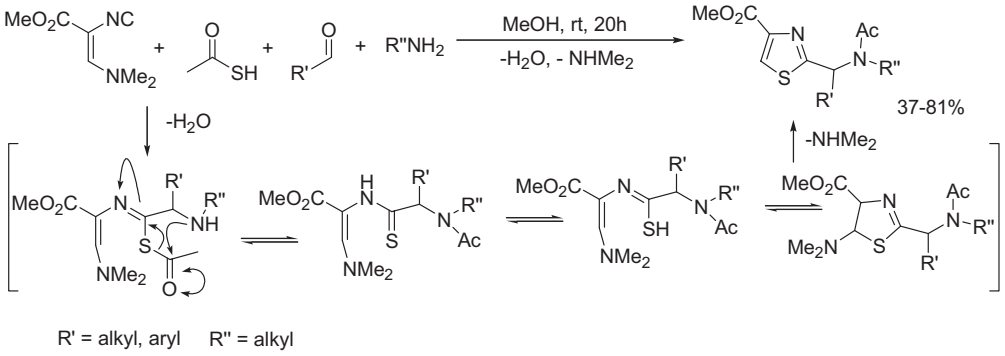
It was subsequently noted that α-λ^3-iodanil ketones, obtained *in situ*, could also undergo direct cyclization by the reaction with thioamides, avoiding the isolation of the α-tosylketone **71** [129].

Another important synthetic method for the synthesis of thiazoles involves treating α-acylamino ketones **54** with phosphorous pentasulfide or Lawesson reagent [130] (Gabriel synthesis) (Scheme 10.28).



Scheme 10.28

An alternative thiazole synthesis, which is applied to combinatorial chemistry, is shown in Scheme 10.29. These isocyanide based four-component reactions provides



Scheme 10.29

2,4-disubstituted thiazoles. The substituent on C4 is limited to carbomethoxy (Scheme 10.29) [131].

Methods involving a regioselective metal-catalyzed coupling reaction have also been utilized to construct highly substituted thiazoles in view of the fact that coupling reactions would be selective for the more electron-deficient C2 (see below).

10.4 Reactivity

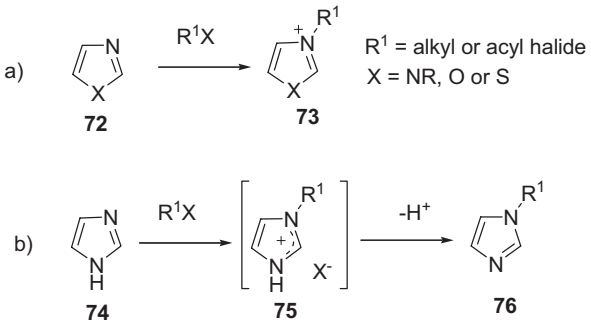
This section considers the reactivities of 1,3-azoles in detail and, when possible, the reactions of these heteroaromatic systems are compared among themselves. These reactions can be rationalized with reference to the tautomeric and acid–base equilibria shown by these compounds that are discussed in Section 10.1.

10.4.1 Reactions with Electrophilic Reagents

10.4.1.1 Electrophilic Attack at N3

Electrophilic attack at the azomethine nitrogen (pyridine-type) depends upon (i) the electron density on the pyridine-type nitrogen and (ii) the substituents present on the azole ring. The nature and position of the heteroatom other than azomethine nitrogen determine the electron density on the former. The interaction of pyridine-type nitrogen with pyrrole-type nitrogen, oxygen and sulfur atoms has a considerable influence due to the presence of two opposite electronic effects: (i) the mesomeric effect and (ii) the inductive effect. The balancing of both these effects determines the electron density at the pyridine-type nitrogen atom. The inductive effect is stronger when the second atom is oxygen or sulfur and thus lowers the electron density on nitrogen. In contrast, with two nitrogen atoms the mesomeric effect is stronger and increases the electron density at position 3. Imidazoles substituted at N1 [132], oxazoles [133], and thiazoles [134] **72** are alkylated/acylated with the formation of

quaternary salts **73** (Scheme 10.30a) and alkylation/acylation of imidazole **74** (with free NH group) produces protonated N-alkyl-/acyl-imidazolium salt **75** that can be deprotonated by a base to afford N-alkyl imidazole **76** [135]. In this case, if the electrophilic reagent is a proton, this reaction sequence is a simple tautomer interconversion (Scheme 10.30b).



Scheme 10.30

There are several examples of quaternizing alkylations of imidazoles using diverse reagents like alkyl, alkenyl or arylalkyl halides, ethyl chloroacetate, phenacyl bromide or dimethyl sulfate [136]. Although quaternization at the already substituted nitrogen atom has been reported and one of the products of the reaction of imidazole with 2,2-dichlorodiethyl sulfide was identified as **77**, it is more likely to be **78** or **79** (Figure 10.7). The observations of Pinner and Schwarz in 1902 that the quaternary salt obtained from 1-methylimidazole and 1-bromopentane was decomposed by alkali to give both aminomethane and 1-aminopentane was the first piece of evidence (more recently confirmed by NMR studies) to support the accepted view that quaternization takes places at the unsubstituted ring nitrogen [137].

The oxazole and thiazole nitrogen atom also reacts with various alkylating and acylating agents [138, 139]. Oxazoles react with bromine in methanol to give a mixture of products via initial attack of bromine on nitrogen atom to form the charged complex **80**. Subsequent rapid reactions with methanol lead to intermediates **81** or **82** depending on the C2 and C4 substituents ability to stabilize the C=N bond. Thus, a phenyl substituent on C2 favors the 2,5-dihydrooxazole structure **81**, whereas a phenyl group on C4 favors the 4,5-dihydrooxazole structure **82**. The intermediates give cyclic or ring-opened products **83–86** (Scheme 10.31) [140].

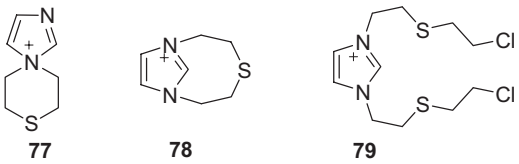
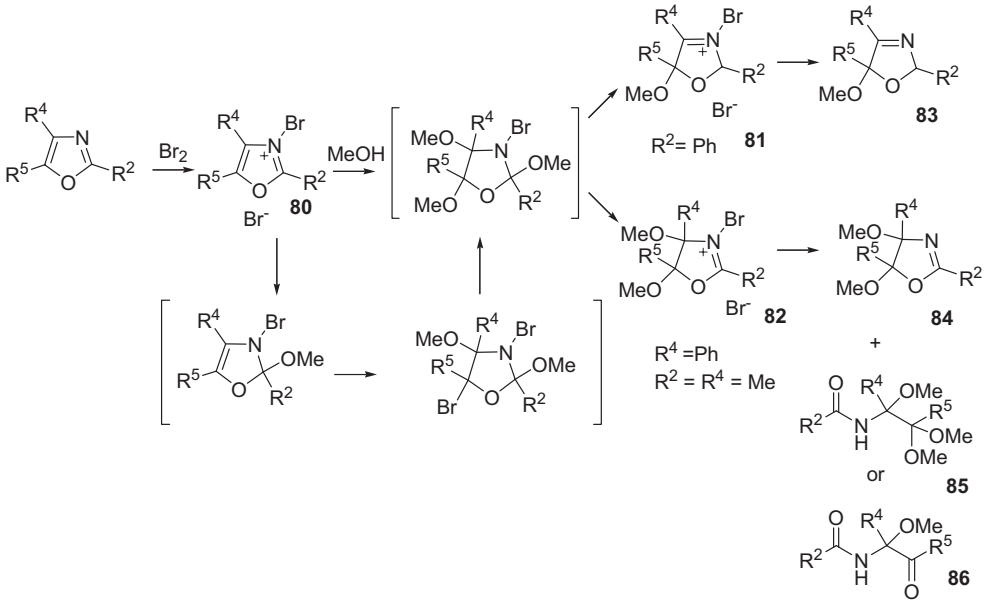


Figure 10.7 Possible products of the reaction of imidazole with 2,2-dichlorodiethyl sulfide.

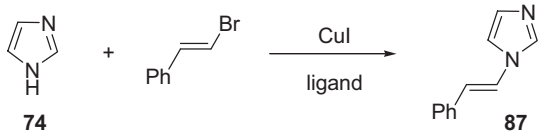


Scheme 10.31

The electronic density on pyridine-type nitrogen is also affected by the substituents on the azole ring and may be rationalized as follows:

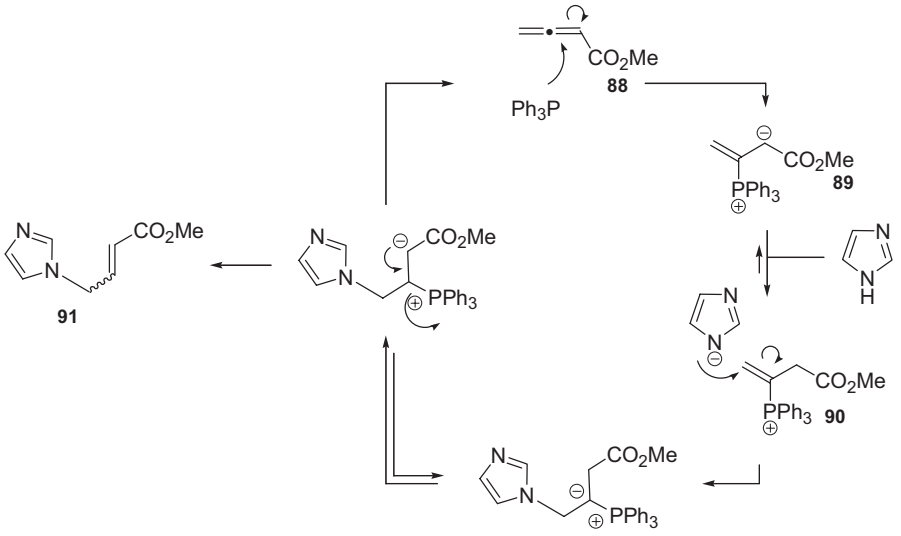
1) Strongly electron-withdrawing substituents (e.g., NO_2, COR, CHO) make these reactions less favorable by decreasing the electron density on the nitrogen atom(s). The effect is largely inductive and, therefore, is particularly strong for the α-position.
2) Strongly electron-donating substituents (e.g., NH_2, OR) facilitate electrophilic attack by increasing the electron density on the nitrogen atom. This is due to the mesomeric effect and is, therefore, strongest for the α- and γ-positions.
3) Groups with relatively weak electronic effects have a relatively small electronic influence.

More recently, an efficient and straightforward copper-catalyzed method allowing vinylation of imidazoles in high yields and selectivities with di- or trisubstituted vinyl bromides has been described. The reaction can be performed with catalytic amounts of copper iodide and inexpensive nitrogen ligands under very mild temperature conditions (35–110 °C) [141]. For example, the viynilation of imidazole **74** by β-bromostyrene afforded compound **87** with a yield of 93% (Scheme 10.32).



Scheme 10.32

In this context, triphenylphosphine has been used as nucleophilic catalyst for umpolung addition of azoles to electron-deficient allenes. This strategy offers a simple and efficient method for functional allylation of azoles under neutral conditions and affords heterocyclic substituted Michael olefins [142]. The catalytic cycle might be initiated by a nucleophilic addition of triphenylphosphine to the electron-deficient allene **88**. The enolate **89** then deprotonates the azole, generating the vinylphosphonium **90**. Subsequently, nucleophilic addition to vinylphosphonium **90** leads to the ylide. Finally, the enolate is obtained by prototropy and then undergoes a β-elimination, affording the final allylazole **91** and regenerating the nucleophilic catalyst. (Scheme 10.33).



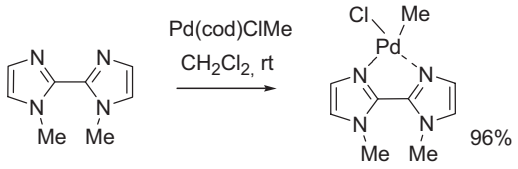
Scheme 10.33

Finally, many metal complexes with azoles or alkyl derivatives are known. The sulfur, oxygen and pyrrolidine-type nitrogen atoms are less nucleophilic than a pyridine-type nitrogen atom and the latter is expected to be the dominant donor. For example, a palladium(II) bisimidazole complex was obtained from the reaction of Pd(cod)ClMe (cod=cyclooctadiene) with equimolar amounts of **92** and proved to be an effective catalyst for the Heck reaction under phosphine-free conditions using ionic liquids as solvent (Scheme 10.34) [143].

10.4.1.2 **Electrophilic Attack at Carbon**

Figure 10.8 depicts the reactivity order in 1,3-azoles.

Imidazoles containing an unsubstituted NH group are easily chlorinated (Cl_2/H_2O or *N*-chlorosuccinimide/$CHCl_3$), brominated ($Br_2/CHCl_3$ or $KOBr/H_2O$) and iodinated (I_2/HIO_3). Substitution generally occurs first at the 4-position but further reaction at the other available positions takes place readily, providing



92

Scheme 10.34

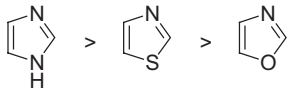
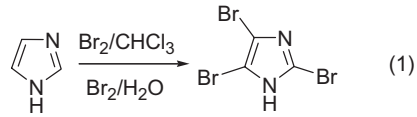
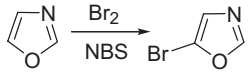


Figure 10.8 Order of reactivity in 1,3-azoles.

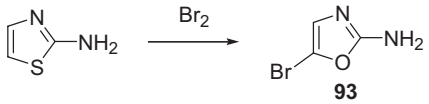
2,4,5-tribromoimidazole [Scheme 10.35 (1)] [144]. Ring bromination of oxazole **90** with bromine or NBS (*N*-bromosuccinimide) occurs preferentially at the 5-position to afford 5-bromooxazole and, if this is occupied, at the 4-position [Scheme 10.35 (2)] [145].





Scheme 10.35

Thiazole does not react with bromine or chlorine in an inert solvent, but thiazoles with an electron-releasing substituent in the 2 or 4-position are brominated at C5 [146]. For example, 2-aminothiazole afforded compound **93** in a bromination reaction (Scheme 10.36).

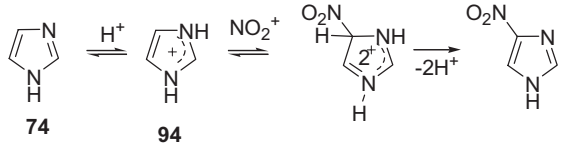


93

Scheme 10.36

Nitration of imidazoles [137] and thiazoles [139] has usually been carried out using either a mixture of concentrated (or fuming) nitric acid and concentrated sulfuric acid, or in some cases with concentrated nitric acid and acetic anhydride. Nitration

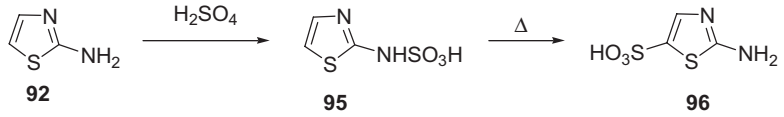
(HNO_3/H_2SO_4, 160 °C) and sulfonation (H_2SO_4/SO_3, 160 °C) of imidazoles proceeds at the 4-position very slowly, because the reaction takes places in acidic medium, with formation of imidazolium cations (e.g., **74** yields **94**) (Scheme 10.37) [137]. The deactivating effect of a protonated nitrogen atom is considerably greater than, for example, the two nitro groups in *m*-dinitrobenzene.



Scheme 10.37

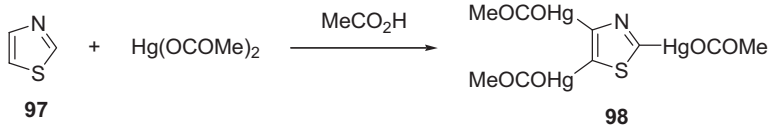
With the object of finding milder nitration conditions, the use of cerium (IV) ammonium nitrate [147], montmorillonite impregnated with bismuth nitrate [148], and nitrations with dinitrogen pentoxide [149, 150] have been studied. Direct nitration of various imidazoles and thiazoles with nitric acid/trifluoroacetic anhydride, which involves N_2O_5, affords mononitro derivatives with an average yield of 60% [151]. Finally, dinitrothiazoles have been obtained by direct nitration of the corresponding mononitro derivative with acetyl nitrate [152].

In the case of thiazole, the reaction only occurs at the 5-position under forcing conditions (H_2SO_4/SO_3 in the presence of $HgSO_4$, 250 °C). As expected, these reactions are facilitated by activating groups such as an amino group; for example, 2-aminothiazole **92** is sulfonated at low temperature with the formation of sulfamic acid **95**, which on heating rearranges to 2-aminothiazole-5-sulfonic acid **96** (Scheme 10.38) [153].



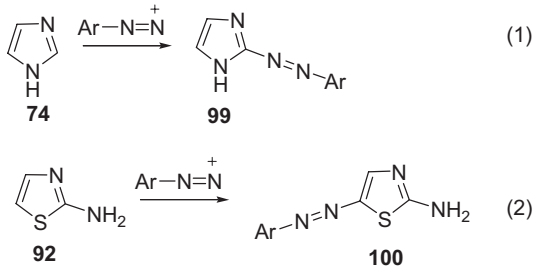
Scheme 10.38

Mercuration of oxazole with mercury(II) acetate occurs at C4 or C5 depending upon the available unsubstituted position. If both positions are substituted, mercuration occurs at the 2-position. Thiazole **97** is mercurated at positions 2, 4 and 5 in the order: C5 > C4 > C2, providing 2,4,5-tris(acetoxymercury)thiazole **98** on treatment with mercury acetate in the presence of aqueous acetic acid (Scheme 10.39) [153].



Scheme 10.39

Diazonium ions couple with the anions of N-unsubstituted imidazoles at the 2-position (e.g., **74** affords **99**) [Scheme 10.40 (1)]. In general, other azoles react only when they contain an amino or an hydroxy group. For example, 2-aminothiazole **92** undergoes diazo coupling with diazonium salts at C5 to afford **100** [Scheme 10.40 (2)] [154].

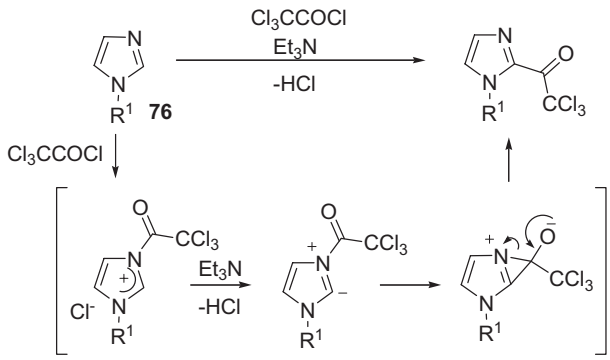


Scheme 10.40

Phosphorylation of 1-substituted imidazoles has been achieved under basic conditions by treatment with phosphorous(V) acid chlorides and provided good yields of the corresponding phosphinic acid salts after treatment with aqueous base [155].

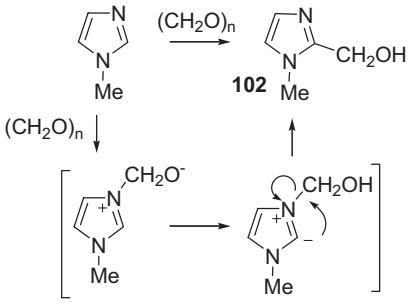
Direct electrophilic silylation of 1,3-azoles with silane (II) under basic conditions afforded C-trimethylsilylazoles in good yields. The silylation occur at C2 [156].

On the other hand, electrophilic substitution is by far the most common method for substitution at the 2-position of substituted 1,3-azoles [157]. With this aim the addition of electrophiles as acid chlorides [158] or aldehydes [159] has been studied. In general, the reactions are run with an amine base for acid chlorides and are proposed to proceed via an intermediate carbene/ylide species [160]. In this context, the addition of 2,2,2-trichloroacetyl chloride to **76** affords **101** (Scheme 10.41).



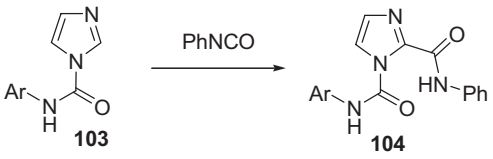
Scheme 10.41

Imidazoles are sufficiently nucleophilic to condense with aldehydes under thermal conditions in the presence of acid to give 2-hydroxymethylimidazoles. For example, the addition of formaldehyde to *N*-methylimidazole yields **102** (Scheme 10.42). The reaction, however, is highly variable and substrate dependent.



Scheme 10.42

The addition of imidazole-1-carboxamides **103** to phenyl isocyanate gives the corresponding amides **104** in modest yield (Scheme 10.43) [161].

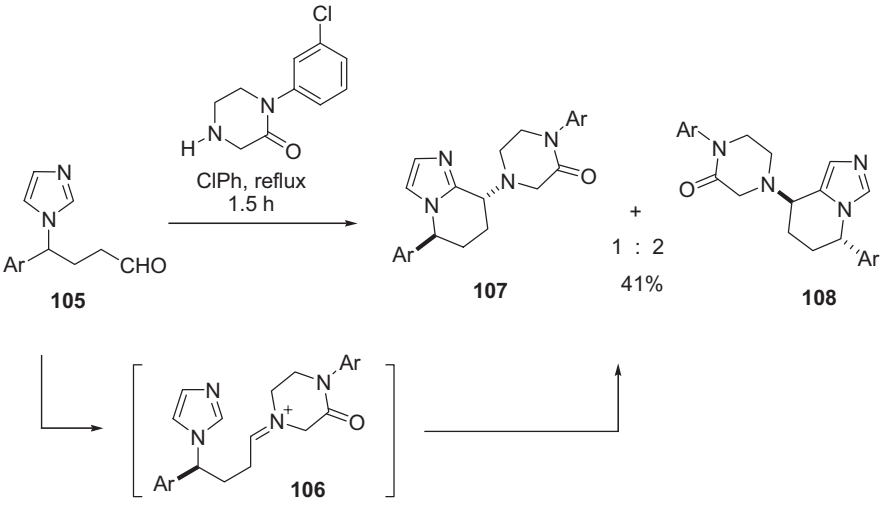


Scheme 10.43

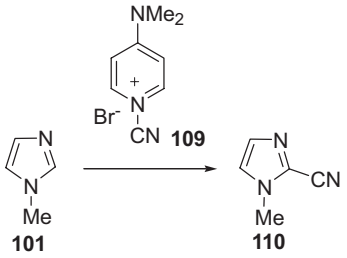
The intramolecular addition of azoles to iminium ions formed from aldehydes and secondary amines affords 2-substituted derivatives cleanly only when the 4- or 5-position is blocked. For example, the addition of the iminium ion **106** obtained from the azole-aldehyde **105** and an aryl-piperazinone affords a mixture of **107** and **108** in a 1 : 2 ratio, respectively (Scheme 10.44) [162]. When position 2 is substituted the reaction yields the 4-substituted product [137, 163].

The preformation of 1-cyano-4-(*N*,*N*-dimethylamino)-pyridinium bromide (**109**), from DMAP (4-*N*,*N*-dimethylaminopyridine) and BrCN, allows for the selective 2-cyanation of *N*-methylimidazole to yield **110** (Scheme 10.45). In the absence of DMAP, the 2-position is brominated [164].

Finally, although the Lewis acid-promoted Friedel–Crafts acylation is the most commonly used method for the acylation of an aromatic ring, it is impracticable for imidazoles, due to deactivation of the Lewis acids. Other azoles, such as oxazoles and thiazoles, are generally also not amenable, because of their electron-deficient aromatic character. This type of acylation, however, proceeds in the presence of strong activation from electron-donating groups, such as alkoxy, amino or arylthio groups, in the substrates [165].



Scheme 10.44



Scheme 10.45

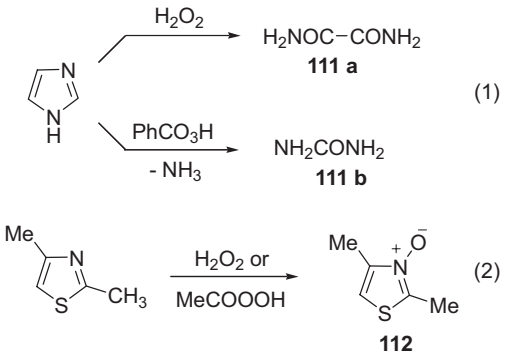
10.4.2
Reaction with Oxidizing Agents

Imidazoles and thiazoles are resistant to oxidation, but they can be oxidized by hydrogen peroxide and peracids as, for example, perbenzoic or peracetic acid. In the case of imidazoles the ring is degraded [166] to afford **111a** and **111b** [Scheme 10.46 (1)] and with thiazoles the 3-oxide **112** is obtained [Scheme 10.46 (2)] [167].

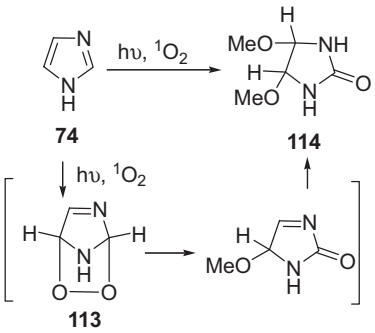
Photosensitized oxidation of imidazole (**74**) with singlet oxygen produces imidazolidin-2-one **114** via the cyclic peroxide **113** (Scheme 10.47) [168].

Trisubstituted imidazoles and thiazoles undergo photosensitized oxidation with the formation of ring cleaved products depending on the solvent and the sensitizer used [169].

The oxazole ring is cleaved by oxidizing agents such us permanganate, chromic acid or hydrogen peroxide to give acids or amides [170].



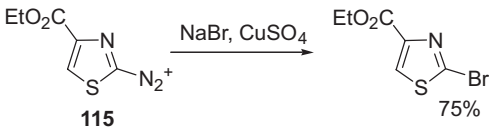
Scheme 10.46



Scheme 10.47

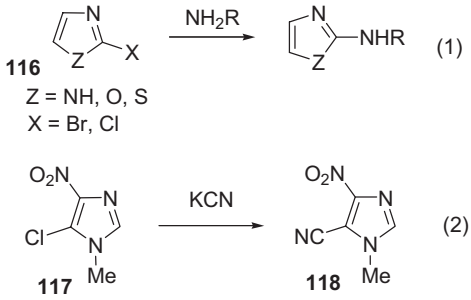
10.4.3
Reactions with Nucleophilic Reagents

Substitution at C2 of 1,3-azoles with a leaving group generates a heterocycle that can be functionalized via displacement of the C2 substituent. Heteroatom nucleophiles add either as the deprotonated species (e.g., alkoxides, thiolates) or under milder basic conditions. Diazo salts (e.g., **115**) can be displaced by bromide ion (Scheme 10.48) [171] or by alcohols [172].



Scheme 10.48

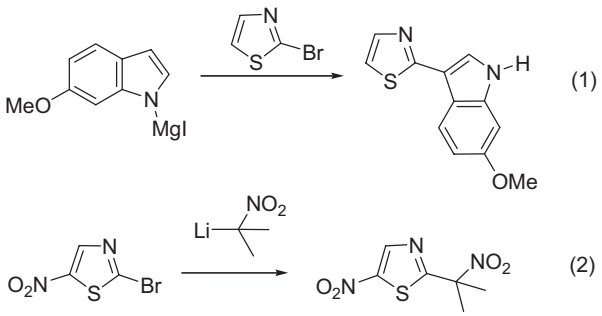
2-Haloazoles **116** undergo nucleophilic substitution reactions with replacement of the halogen atom by nucleophiles [Scheme 10.49 (1)]. Halogen atoms at the 4- and



Scheme 10.49

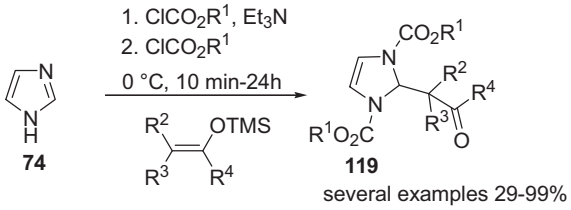
5- positions of imidazoles are normally unreactive but can be activated by an α- or γ- electron-withdrawing substituent (e.g., **117** yields **118**) [Scheme 10.49 (2)] [173].

Addition of carbon nucleophiles to halogenated thiazoles includes the use of sodium cyanide [174], indolyl Grignard reagent [Scheme 10.50 (1)] [175], 2-lithio-2-nitropropane [Scheme 10.50 (2)] [176] and ester enolates [177].



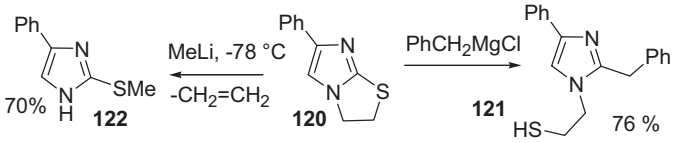
Scheme 10.50

Imidazole (**74**) has been used as electrophile with silyl enol ethers in the presence of alkyl chloroformates to provide the 2-substituted 2,3-dihydroimidazole **119** (Scheme 10.51) [178]. The same reaction can be performed with thiazole.



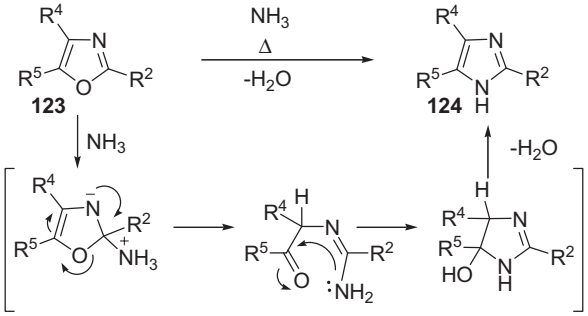
Scheme 10.51

Imidazo[1,2-*b*]thiazolines **120** undergo nucleophilic displacement with allylic, benzylic and alkyl Grignard reagents to yield **121** (Scheme 10.52) while alkyl or aryl lithium reagents result in nucleophilic attack on sulfur and loss of ethylene to afford 2-thioalkyl-1*H*-imidazoles **122** (Scheme 10.52) [179].



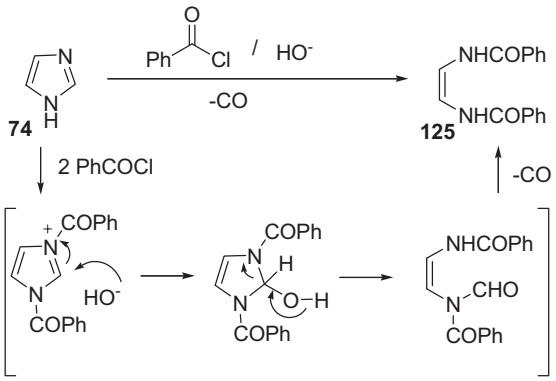
Scheme 10.52

In some cases nucleophilic attack results in the cleavage of the ring. For example, oxazoles **123** when treated with ammonia at 200 °C undergo nucleophilic attack at the 2-position and are transformed into the corresponding imidazoles **124** (Scheme 10.53) [180].



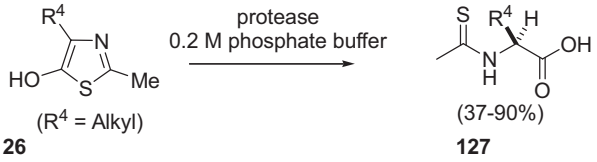
Scheme 10.53

Imidazole (**74**) reacts with acid chlorides to give salts that in the presence of alkali react to afford compound **125**, derived from the ring cleavage (Scheme 10.54) [181].



Scheme 10.54

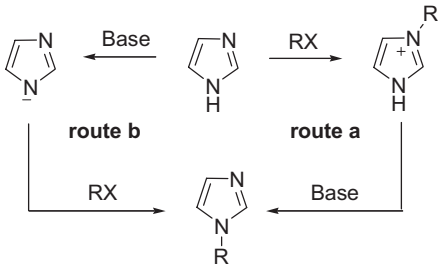
Finally, thiazoles are quite inert in the presence of hydroxide and alkaline ions. However, two proteases were found to catalyze the enantioselective hydrolysis of several 5-hydroxythiazoles (**126**) to give α-amino acids (**127**) (Scheme 10.55) [182].



Scheme 10.55

10.4.4
Reactions of N-Metallated Imidazoles

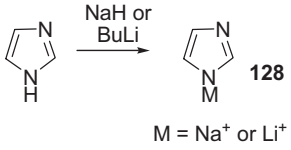
Although the direct alkylation of imidazoles at N3 affords the 1-substituted imidazoles through a tautomer interconversion (Scheme 10.56, route a), in some cases the synthesis of these compounds has been reported using N-metallated imidazoles (Scheme 10.56, route b).



Scheme 10.56

Route b can be considered as a complementary way for the preparation of 1-substituted imidazoles and has permitted the introduction of the imidazolyl unit in a large number of structures for the synthesis of natural products or analogues [183].

In general, N-metallated imidazoles **128** are obtained using a base such as NaH or BuLi (Scheme 10.57).



Scheme 10.57

10.4.5 Reactions of C-Metallated Azoles

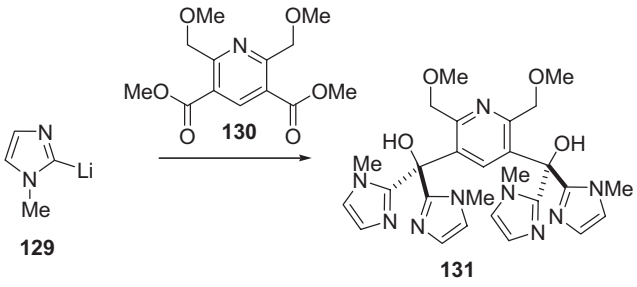
10.4.5.1 Lithium Azoles

These derivatives are prepared by direct deprotonation [184, 185] using strong bases or, particularly useful in the case of the less acidic sites in aromatic rings, by halogen exchange [186] between an halogenated heterocycle and an organolithium compound or lithium metal.

1,3-Azoles are prone to be lithiated at C2, but if this position is already occupied, lithiation occurs at C5. If a C4 metallation is required, usually the halogen–lithium exchange methodology is employed. The combination of all these techniques allows the selective lithiation at any position in the azole nucleus.

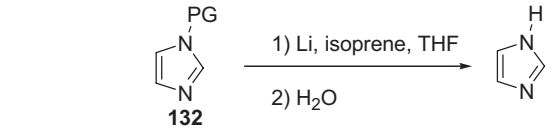
N-Substituted imidazoles tend to lithiate with alkyllithiums at C2, affording a carbenoid species that can be used as a bulky base, as in the case of 2-lithio-1-methylimidazole, which has been used in the stereoselective deprotonation of cyclohexene oxides when combined with a chiral lithium amide [187]. However, 2-lithioimidazoles are employed normally as nucleophiles, for instance in addition reactions to aldehydes [188], ketones [189], esters and isocyanates [190], as well as in silylation [191], sulfenylation [192], and cyclic sulfate ring-opening [193] reactions.

2-Lithiated N-substituted imidazoles such as 2-lithio-*N*-methylimidazole (**129**), prepared by direct deprotonation using *n*-butyllithium, has recently been used in the reaction with the diester **130** for the preparation of compound **131** as a zinc ligand (Scheme 10.58) [194].



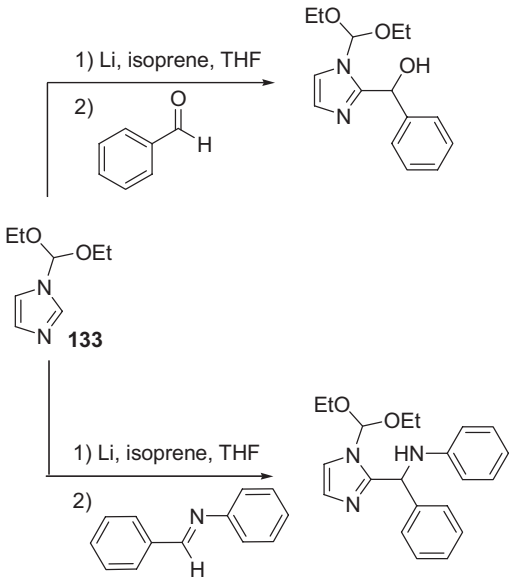
Scheme 10.58

2-Lithioimidazoles can also be generated by treatment of 1-substituted imidazoles with an excess of lithium powder in the presence of a catalytic amount of an electron-carrier [195] such as isoprene [196]. The isoprene-catalysed lithiation of different 1-substituted imidazoles **132** (PG = trityl, allyl, benzyl, vinyl, *N*,*N*-dimethylsulfamoyl, *para*-toluenesulfonyl, *tert*-butoxycarbonyl, acetyl, trimethylsilyl, *tert*-butyldimethylsilyl) leads to the cleavage of the protecting group producing 1*H*-imidazole (Scheme 10.59). However, the use of 1-(diethoxymethyl)imidazole (**133**) in the same lithiation reaction allows the preparation of the corresponding 2-lithio intermediate, which by reacting with different electrophiles such as, for example, benzaldehyde or *N*-phenyl-benzyl imine leads to 2-functionalized imidazoles (Scheme 10.60) [197].



PG = Tr, Allyl, Bn, vinyl, -SO_2NMe_2, Ts, Boc, Acetyl, -$SiMe_3$, -$SiBu^tMe_2$

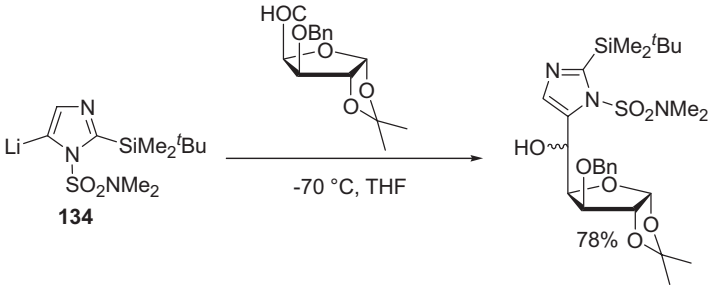
Scheme 10.59



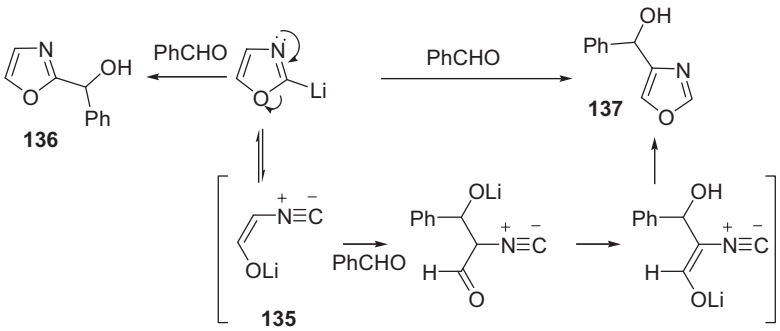
Scheme 10.60

As mentioned above, 5-lithiumimidazoles can be generated by direct deprotonation with an alkyllithium if the C2 position of the ring is blocked. When the substituent at C2 is a trialkylsilyl group, introduced by deprotonation and reaction with a trialkylsilyl halide, lithiation at C5 takes place. Examples of the use of these 2-sylilated imidazol-5-yllithiums (**132**) are in the synthesis of imidazolsugars **133** (Scheme 10.61) [198].

As in the case of any 1,3-azole, oxazoles are readily lithiated at C2. However, attempts to trap 2-lithioxazoles with electrophiles must contend with complications due to the ring opening of the anion that equilibriates by an elimination/ring-opening to produce the β-cyano enolate **135**, which, according to NMR data, is the dominant form. In many cases enolate **135** cyclizes back after the C-electrophilic attack, affording mixtures of C2 and C4 substituted oxazoles, **136** and **137** (Scheme 10.62) [200].

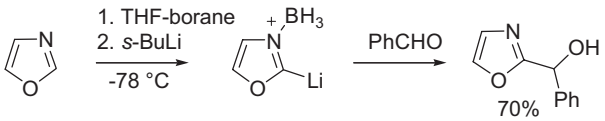


Scheme 10.61



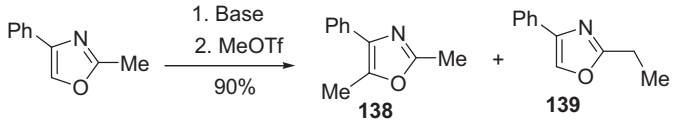
Scheme 10.62

In this electrophilic ring opening, it is possible to lock the electron pair at the oxazole nitrogen by complexation with a Lewis acid, such as borane, thus allowing C2-lithiation (Scheme 10.63) [201].



Scheme 10.63

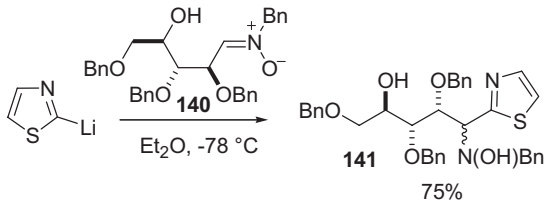
In 2-substitued oxazoles, direct C5-lithiation can be carried out, allowing further reaction with electrophiles [202], although the bromine–lithium exchange methodology has also been used [203]. Remarkably, in 2 methyl-4-substituted oxazoles, a selectivity for lithiation at C5 to give compound **138**, versus lithiation at the methyl group to give compound **139**, has been observed, depending on the lithium base (Scheme 10.64) [204]. 5-Lithiation of 2-substituted oxazoles has also been achieved by ortho-lithiation to a triflate group [205]. Concerning 5-bromo-2-phenyloxazole, 5-lithiation and further reaction with electrophiles has been achieved through an initial LDA-promoted 4-lithiation followed by halogen migration, leading to a 4-bromo-5-lithio-2-phenyloxazole intermediate [206].



base = nBuLi, **138:139**, 91:9
base = LDA, **138**:**139** 9:91

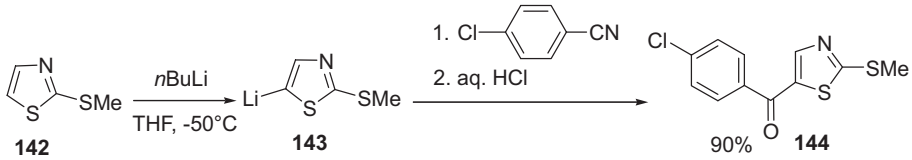
Scheme 10.64

2-Lithiothiazoles [207] have been used as nucleophiles, for instance addition to aldehydes [208], the thiazole moiety being considered as a formyl equivalent [209], for example in addition reactions to lactones [210], to benzyloxyacetaldoximes [211] or in reactions with nitrones **140** for the synthesis of amino sugars (e.g., **141**) (Scheme 10.65) [212].



Scheme 10.65

Lithiation at C5 in thiazoles takes place directly if the C2 position is blocked, an example being the lithiation of 2-(methylthio)thiazole (**142**) to give intermediate **143**, which can react further with a nitrile such as *p*-chlorobenzonitrile, affording 5-(arylcarbonyl)thiazole **144** after hydrolysis (Scheme 10.66) [213].



Scheme 10.66

5-Lithiation has also been achieved in 2-thiazolamines bearing a bromine atom at C5 through a halogen migration process starting from a LDA-promoted 4-lithiation [214].

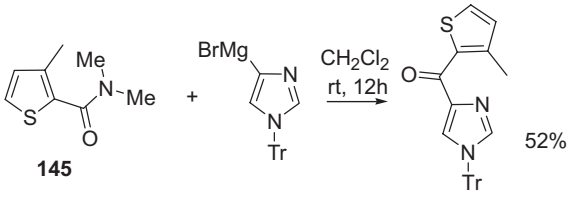
4-Lithiated thiazoles have usually been generated by bromine–lithium exchange, an example of their use being the synthesis of some photochromic dithiazolylethenes [215].

10.4.5.2 Magnesium Azoles

The direct preparation of azolic organomagnesium reagents using the standard reaction between a halogenated derivative and magnesium is rather difficult due to

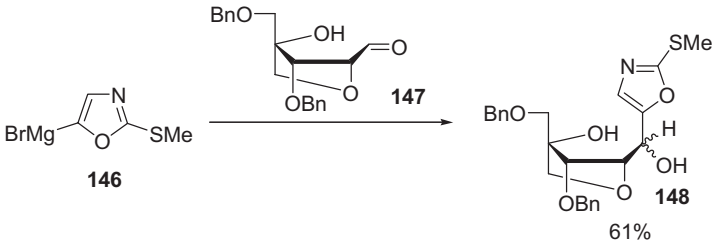
the presence of a basic nitrogen. In these cases, the usual preparative procedure is to treat the azole with an alkyl Grignard reagent (generally EtMgBr, *i*PrMgBr, or $i\text{Pr}_2\text{Mg}$) or to perform a halogen–magnesium exchange by treating bromo and iodo azoles with the mentioned alkyl Grignards [216]. This procedure tolerates the presence of other functionalities [217]. Furthermore, the preparation of the organolithium derivative followed by interchange using magnesium dibromide can also be used.

The generated imidazolylmagnesium halide has been employed in addition reactions to carbonyl compounds for the preparation, for example, of ligands for the α_{2D} adrenergic receptor [218], sugar-mimic glycosidase inhibitors [219] or C-nucleosides [220]. It has also been used in acylation reactions with esters in the synthesis of pilocarpine analogues [221] or with Weinreb amides such as **145** (Scheme 10.67) [222].



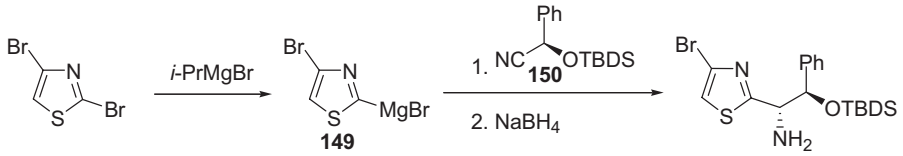
Scheme 10.67

In addition, examples of the use of oxazolylmagnesiums can be found in the addition of 2-(methylthio)-5-oxazolylmagnesium bromide (**146**) to the aldehyde **147** to give compound **148**, which has been employed for the synthesis of conformationally locked C-nucleosides (Scheme 10.68) [223].



Scheme 10.68

Finally, thiazolylmagnesiums metalated at C2 have been obtained by the usual bromine-magnesium exchange using alkyl Grignards, even regioselectively. For example, 2-thiazolylmagnesium bromide **149** has been obtained from 2,4-dibromothiazole. This reagent has been used in an addition reaction to the chiral nitrile **150**, affording, after reduction, the corresponding amine, which is a building block for the synthesis of thiazolyl peptides (Scheme 10.69) [224]. The lithium–magnesium transmetalation can also be used for the generation of thiazolylmagnesiums, an example being the preparation of 2-methylthiazol-4-ylmagnesium bromide, which is



Scheme 10.69

useful in the preparation of a fragment of epothilone via a copper(I)-catalyzed coupling to an allylic bromide [225].

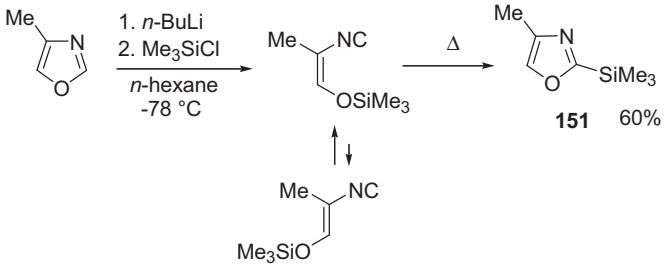
10.4.5.3 **Silicon Azoles**

Azole silanes are usually prepared by reaction of the corresponding heterocyclic organolithiums with alkylhalosilanes [226].

Imidazoles have been silylated at C2 using the conventional lithium–silicon exchange, although it has been observed that 2-*tert*-butyldimethylsilylimidazole can be obtained by reaction of *O*-*tert*-butyldimethylsilylimidazolyl aminals with organolithium reagents through a retro-[1,4]-Brook rearrangement [227]. Usually, 2-silylimidazoles are employed in a subsequent lithiation at the 3-position and further reaction with electrophiles such as aldehydes [228] or tosyl azide [229].

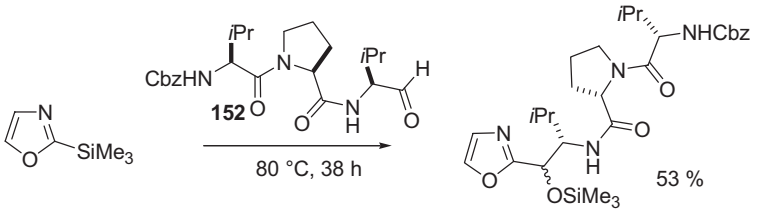
The introduction of a silyl group at the 2-position in N-protected imidazoles was used as a logical way of changing the acidic proton by an easily removable group, thus allowing deprotonation at C5 and further transformations (Section 10.4.5.1). Examples are 2-silylated imidazoles, which are lithiated at C5 and act as nucleophiles [230].

The preparation of 2-silylated oxazoles is not obvious, since the usual 2-lithiation–silylation sequence drives the above mentioned ring opening to give an isocyano enolate (Section 10.4.5.1) after the lithiation step. This problem was overcome by O-silylation of the isocyano enolate followed by a base-promoted insertion to give the corresponding 2-silyloxazole **151** (Scheme 10.70) [231]. The procedure can be simplified by a heat-induced cyclization in the final distillation step [232]. These derivatives have also been prepared by reaction with trimethylsilylbromide in the presence of triethylamine [233].



Scheme 10.70

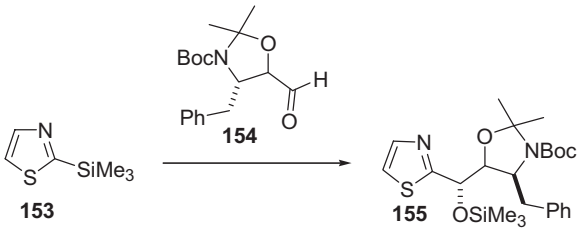
These 2-silylated oxazoles can be used as nucleophiles in additions to aldehydes [234], such as to the tripeptide-derived aldehyde **152** (Scheme 10.71) [232].



Scheme 10.71

Recently, 4-(triethylsilyl)oxazoles have been prepared, by treatment of (triethylsilyl) diazoacetates with rhodium(II) octanoate and nitriles, as precursors of 4-halogenated oxazoles after treatment with *N*-bromosuccinimides [235]. On the other hand, these derivatives have been used to perform a 4-litiation followed by reaction with electrophiles [236].

2-(Trimethylsilyl)thiazole (**153**), which is prepared by the conventional lithiation–-silylation sequence, has been frequently used for addition reactions to aldehydes [237], mainly for chain elongation due to consideration of the thiazole moiety as an equivalent of the formyl synthon. An example of the use of **153** is its diastereoselective addition to the chiral aldehyde **153**, yielding the corresponding protected alcohol **155**, an intermediate in the synthesis of the pseudopeptide microbial agent AI-77-B (Scheme 10.72) [238].



Scheme 10.72

In addition, 2-methylthiazole can be trimethylsilylated at C5 by lithium–silicon exchange, with the resulting 2-methyl-5-silylthiazole permitting, therefore, a subsequent lithiation at the 2-methyl substituent [239].

Although the addition to aldehydes is well documented, the less known reaction with ketones [240] and some acid chlorides [241] has also been reported. Other examples of the use of 2-(trimethylsilyl)thiazole are the ring expansion of a cyclopropanated carbohydrate [242], the copper(I) salt-mediated coupling to iodobenzene [243] and the *ipso*-substitution with iodine [244].

10.4.5.4 **Tin Azoles**

In general, azolic stannanes have been obtained by reaction of their corresponding azolic organolithiums with a chlorostannane [245, 246]. These metallated azoles have

found application mainly in palladium-catalyzed cross-coupling reactions (the so-called Stille coupling) (see Section 10.4.6.31).

2-Azolylstannanes and 2-substituted-5-stannylazoles have been prepared following the usual stanylation sequence. 5-Stannylimidazoles have also been prepared by a 2,5-dilithiation, followed by a double stannylation and a 2-hydrodestannylation sequence [247].

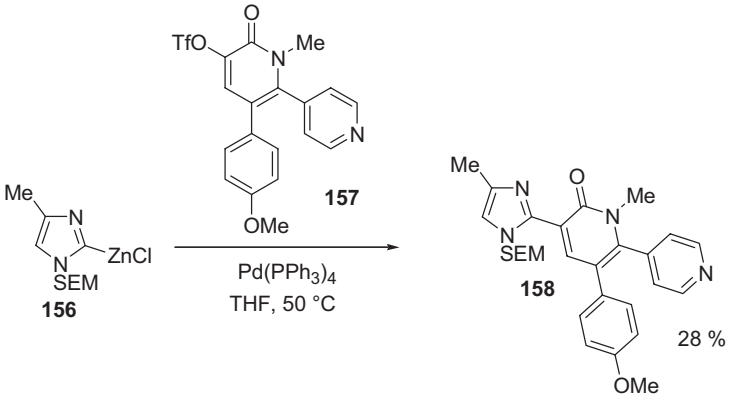
The preparation of 4-stannylated azoles is not obvious. 4-Stannylated thiazoles are usually obtained by a sequential halogen–lithium–tin interchange [248], although after lithiation of 4-bromo-2-stannylthiazoles, to give the 4-stannylated heterocycles, rearrangements were observed [249]. In some cases, 4-stannylthiazoles are prepared by palladium-catalyzed cross-coupling of the corresponding bromide using bis (trimethyltin) [250].

The same methodology has been employed when 4-stannylated oxazoles bearing labile groups are required [246].

10.4.5.5 Zinc Azoles

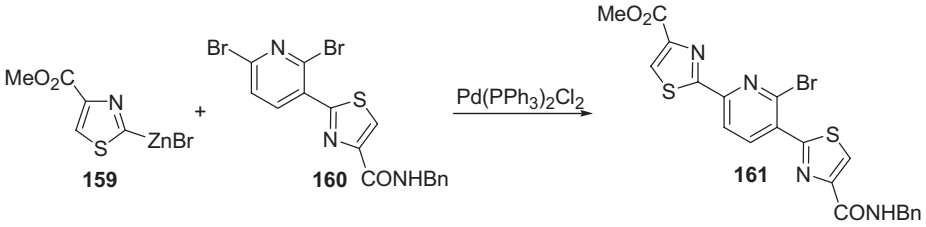
Organozincs are a useful class of organometallic reagents due to their tolerance of several functional groups [251]. Azolic zinc derivatives are generally prepared by exchange reactions of the corresponding organolithium or magnesium with zinc halides, being stable at higher temperatures than their precursors [251]. Other methods for their preparation employ zinc dust [251], active Rieke zinc [251] or electrochemical methods [252].

2-Zincated 1,3-azoles are used mainly in palladium-catalyzed Negishi cross-couplings, as in the reaction of the triflate **157** with the *N*-silylated imidazolylzinc chloride **156** to afford compound **158** (Scheme 10.73), in studies toward the synthesis of anxiolytics.



Scheme 10.73

More recently, the coupling of the organozinc reagent **159** with the bromopyridine **160** afforded compound **161**, which is an intermediate in the synthesis of the heterocycle core of the GE 2270 antibiotic (Scheme 10.74) [253].



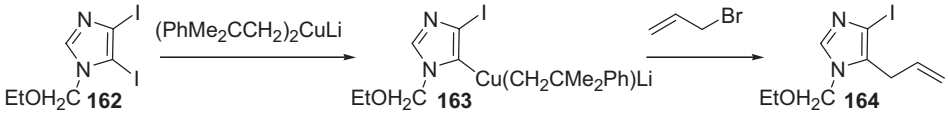
Scheme 10.74

Imidazol-4-yl-zinc chloride has been used in several synthesis [218], whereas oxazol-2-yl-zinc [254] and thiazol-2-yl-zinc [255] derivatives are also employed in Negishi cross-couplings. Furthermore, copper-catalyzed cross-coupling reactions have been performed using *N*-methylimidazol-2-yl-zinc iodide [256]. Finally, thiazol-4-yl-zinc bromide is used in additions to nitrones [209].

10.4.5.6 **Copper Azoles**

Azolyl copper reagents are usually obtained from the corresponding organolithium reagents (2 equivalents) by reaction with a copper(I) salt [239, 245].

For example, *N*-substituted 4,5-diiodoimidazole **162** has been regioselectively transformed into the 5-cuprated imidazole **163** after reaction with $(PhMe_2CCH_2)_2$-CuLi. These organocopper reagents reacted with electrophiles such as allyl bromide to give the corresponding 5-functionalized imidazole **164** (Scheme 10.75) [257].



Scheme 10.75

Examples of high order 5-oxazolyl cuprates in allylation and propargylation reactions have also been reported [258].

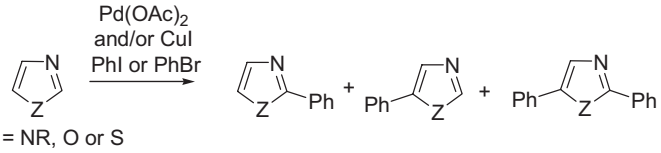
10.4.6
Transition Metal Mediated Reactions

10.4.6.1 **Metal-Mediated Functionalization**

Recently, several new methods for the functionalization of 1,3-azoles under selective conditions of C−H activation have been developed, particularly through the use of transition metal catalysts.

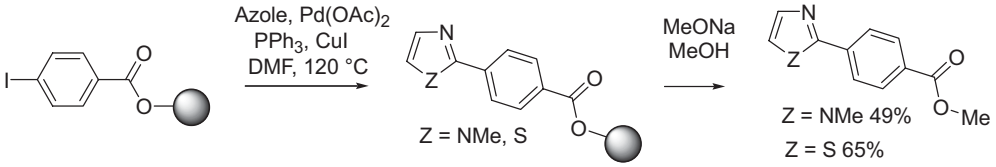
The arylation of 1,3-azole derivatives (oxazoles, thiazoles and protected imidazoles) proceeds using catalytic palladium, rhodium, and/or copper in the presence of an inorganic base [259]. However, these reactions often suffer from low yields and poor selectivity, and a major disadvantage is the need to apply a relatively high reaction

temperature. In general, the addition of copper(I) iodide facilitates the reactions and in specific cases can promote the reaction without a source of palladium (Scheme 10.76).



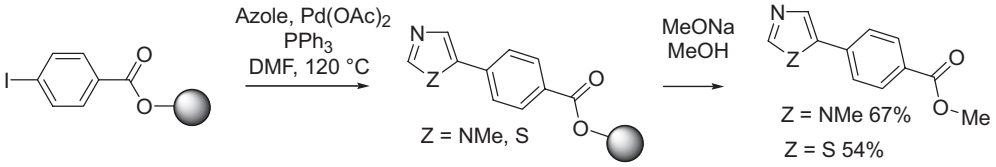
Scheme 10.76

Employing solid-supported aryl iodides, regioselective arylation at C2 is obtained (Scheme 10.77) [260]. The observed selective monofunctionalization can be attributed to the solid-phase pseudodilution effect which prohibits a second equivalent of the iodide interacting with the already coupled product.



Scheme 10.77

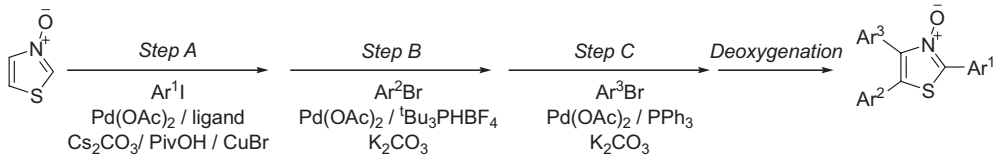
In contrast, in the absence of CuI the 5-arylated products are obtained (Scheme 10.78) [260].



Scheme 10.78

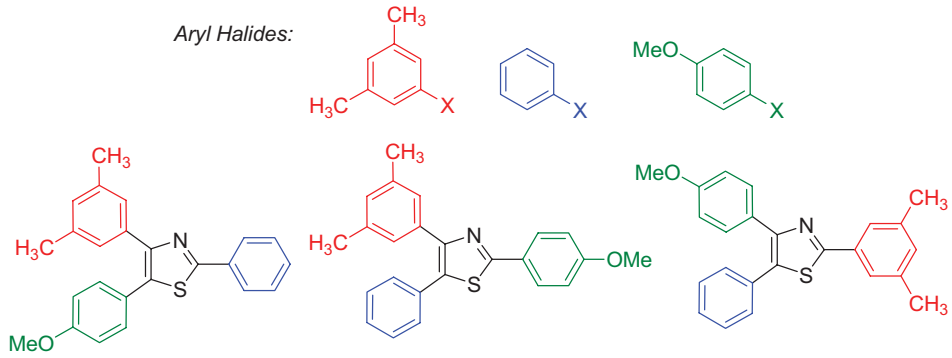
However, although in particular cases it is possible to obtain the arylation with palladium in a regioselective form, in general, non-fused azoles gave mixtures of substitution at the 2- and/or 5-position and the use of bulky phosphines as ligands gives improved yields of diarylation [261].

As an alternative to problematic organometallic azole functionalization, thiazole N-oxides have been investigated as alternatives [262].The N-oxide group not only imparts a dramatic increase in reactivity in direct arylation at all positions of the azole ring but also changes the weak azole bias for C5 > C2 arylation to a reliable C2 > C5 > C4 reactivity profile (Scheme 10.79). This permits high yielding, regioselective, and room temperature arylation at C2, high yielding arylation at C5, and the first



Scheme 10.79

examples of arylation at C4, providing a unique opportunity for exhaustive functionalization of the azole core (Scheme 10.80).



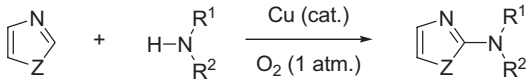
Scheme 10.80

In recent years, phosphine-free and even base-free conditions, palladium-catalyzed C–H bond arylation of azoles have been reported [263]. However, these methods are typically restricted to only one type of heterocycle, even under harsh conditions, such as elevated temperature and/or microwave assistance. Moreover, stoichiometric amounts of copper salts (1–3 equiv) or silver additives are generally required to improve these phosphine-free, Pd-catalyzed coupling reactions.

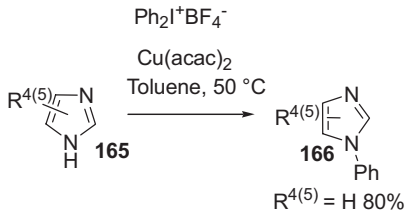
The direct C-arylation of azoles with a broad spectrum of aryl bromides without the presence of phosphines, the aid of CuI, or other metal additives has been described by using pivalic acid as a cocatalyst. Particularly noteworthy is than this protocol can tolerate an array of functional groups such as ester, nitrile, nitro, aldehyde, methoxy, trifluoromethyl, fluoro, and chloro substituents [264].

In addition to such carbon–carbon bond-forming reactions, carbon–heteroatom bond formation is also an important issue. Limited examples of intra- [265] and intermolecular [266] C–H funcionalization with amines have been described. For example, C–H, N–H coupling of azoles takes place with several amines in the presence of a copper catalyst to undergo amination at the 2-position (Scheme 10.81) [267].

Finally, several metal-promoted N−C cross-coupling reactions have been developed [268]. For example, copper-catalyzed N-phenylation of imidazoles **165** with diphenyliodonium tetrafluoroborate affords *N*-phenylimidazoles **166** (Scheme 10.82) [269].



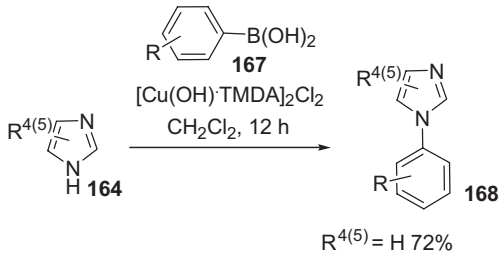
Scheme 10.81



Scheme 10.82

The N-arylation of azoles, in lower nitrile solvents, with aryl halides has been achieved efficiently in the presence of copper powder without any additional ligands. Thus, the first nitrile type of monodentate ligand-mediated, "ligand-free-like" copper catalyzed N-arylation procedure was established [270].

Arylboronic acids **167** react efficiently with imidazoles **165** in the presence of a novel diamine-copper complex to give various *N*-arylimidazoles **168** (Scheme 10.83) [271].



Scheme 10.83

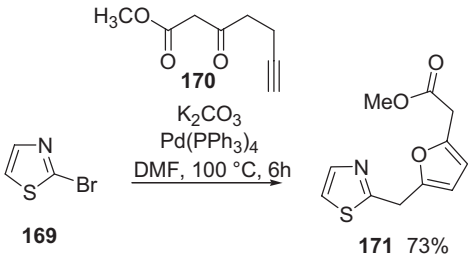
Alkoxydienyl and alkoxystynyl boronates have also been used in various copper acetate mediated cross-coupling reactions with imidazole, affording various *N*-alkoxydienyl- and *N*-styrylimidazoles in good yields under mild conditions [272].

10.4.6.2 Catalytic Transition-Metal Mediated Reactions of Halogenated Azoles

2-Halogenated azoles are among the most valuable synthons for further functionalization of 1,3-azoles using catalytic transition-metal mediated reactions. They are readily prepared by direct halogenation (Br_2, I_2, or *N*-halosuccinimides) or trapping of C2-metalated (Li, Mg, Zn) azoles. Numerous methods have therefore been made for their further functionalization. Coupling reactions mediated by transition-metal catalysts allow for bond formation between halogenated azoles and unsubstituted olefins and acetylenes, as well as dimerization reactions.

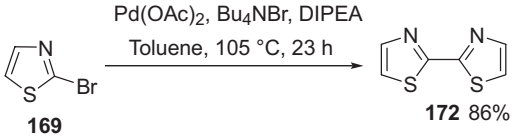
10.4.6.2.1 **Heck and Ullmann Couplings** Classical Heck-type couplings (using Pd-catalyst and a base) are one of the most common bond-forming reactions of aromatic halides. Its use in the chemistry of 1,3-azoles is also very common. A σ-azolylpalladium complex, generated *in situ* from 2-halogenated azole, undergoes an insertion with the alkene/alkyne cosubstrate, followed by β elimination to give the product.

A useful example of this reaction is the coupling of methyl 3-oxo-6-heptynoate **170** with 2-bromothiazole (**169**) in the presence of K_2CO_3 and catalytic amounts of Pd $(PPh_3)_4$ that provide the derivative **171** (Scheme 10.84) [273].



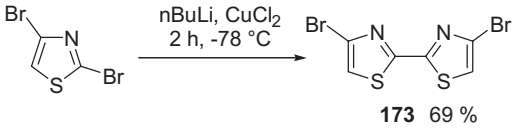
Scheme 10.84

This reaction has also been utilized to catalyze the dimerization of bromothiazole **169** [274], isolating the product **172** in an improved yield (Scheme 10.85).



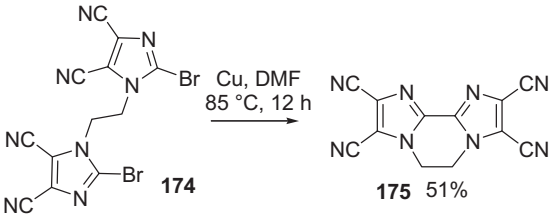
Scheme 10.85

One of the more common methods for forming 2,2′-azoles is to utilize copper as a coupling catalyst (Ullmann conditions). For example, selective lithium–bromine exchange followed by oxidative coupling with copper(II) chloride allows for the formation of dibromobithiazole **173** via a homodimerization (Scheme 10.86) [275].



Scheme 10.86

Another example of this reaction is the cyclization of the symmetric derivative **174** in modest yield utilizing copper to furnish a tetracyanobisimidazole **175** (Scheme 10.87) [276].



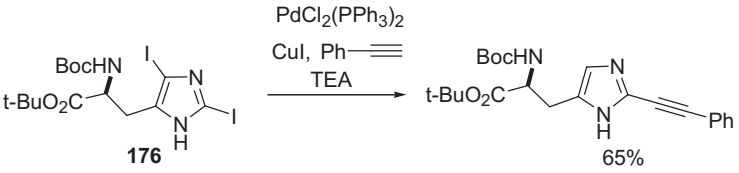
Scheme 10.87

However, despite extensive research in this area, the classical Ullmann reactions were invariably plagued by the need for large amounts of copper (in the form of salts, oxides, or finely divided metal) and for very harsh reaction conditions, most notably for a high reaction temperature. In this context, very recently it was shown that simple copper(I) complexes formed *in situ* with chelating nitrogen- and/or oxygen-containing ligands could effect N- and O-arylations of many different organic compounds with azol halides in good yields at temperatures in the range 80–150 °C [277].

The range of employed ligands is continuously increasing [278], and other kinds of copper-containing catalysts, such as Cu_2O-coated soluble copper nanoparticles [279], copper-exchanged apatites [280], and copper-containing perovskites [281] have been successfully tested as well.

10.4.6.2.2 **Sonogashira Reaction** The Sonogashira reaction [using Pd(0)/Cu(I)-catalyst] is a useful method for the cross-coupling of a terminal alkyne to an 2-halogenated azole. In this case the σ-azolylpalladium complex reacts with a copper acetylide, generated *in situ*, and after a β-elimination the final product is obtained.

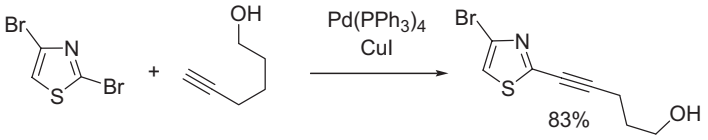
This reaction has been used, for example, to prepare histidine derivatives wherein diiodide **176** undergoes selective coupling as well as dehalogenation in the presence of excess phenylacetylene (Scheme 10.88) [282].



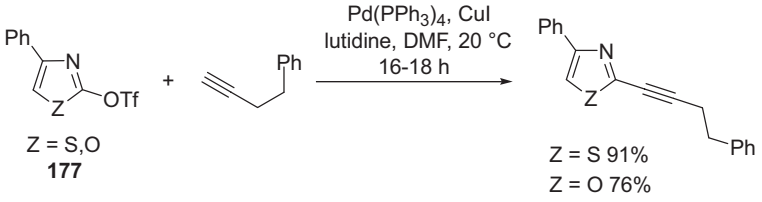
Scheme 10.88

Imidazole derivatives [283] and thiazole analogs (Scheme 10.89) [284] have been investigated, and regioselective alkynylation is often feasible.

Finally, although in general 2-halogenated azoles are employed as starting materials for this type of reaction, oxazolyl and thiazolyl triflates **177** are also effective substrates [285] for substitution (Scheme 10.90).



Scheme 10.89

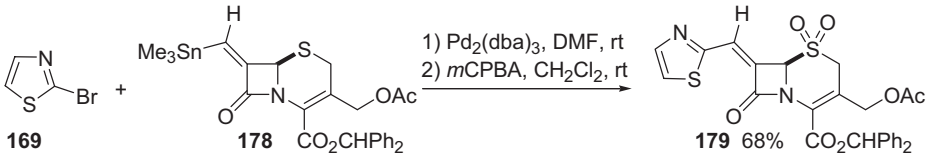


Scheme 10.90

10.4.6.3 **Stoichiometric Organometallic/Transition Metal Mediated Reactions**
Whereas the use of 1,3-azoles in coupling reactions with unsubstituted partners (Section 10.4.6.1) is somewhat limited, the use of stoichiometric organometallic reagents is very broad. The use of organostannanes, boronates and other metal-substituted reagents in transition-metal mediated coupling reactions has been widely examined.

10.4.6.3.1 **Stille Cross-Coupling Reactions** The availability of organostannanes and their well-understood cross-coupling reactions has been applied to the coupling with 2-halogenated azoles.

The cross-coupling of the organostannane **178** with 2-bromothiazole **169** has been used to construct alkylidene-cephalosporine derivatives **179** as β-lactamase inhibitors (Scheme 10.91) [241].

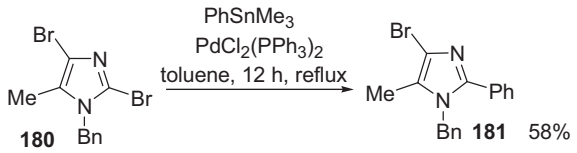


Scheme 10.91

Trialkylstannyl-1,3-azoles have also been utilized as partners in the Stille reaction with aromatic or heteroaromatic halides and triflates.

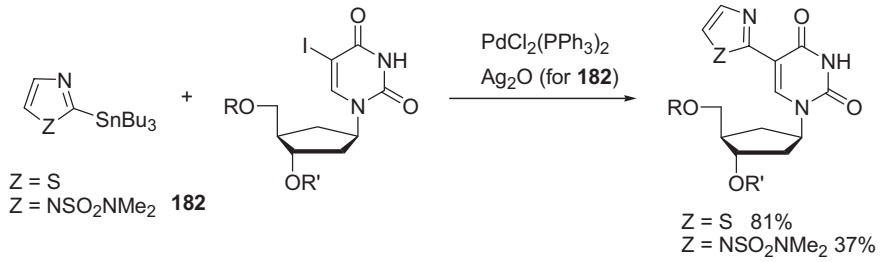
This reaction constitutes a useful solution for the selective arylation of azoles. For example, a good yield of the arylated imidazole derivative **181** is obtained from dibromide **180**, with good selectively for C2 substitution (Scheme 10.92) [287].

Examples using N-protected imidazolyl-stannanes or thiazolyl-stannanes can be found in the coupling with iodouracil derivatives [288]. Standard conditions were



Scheme 10.92

effective for incorporation of the thiazole moiety; however, the reaction of imidazole **182** required the use of stoichiometric silver(I) oxide (Scheme 10.93).



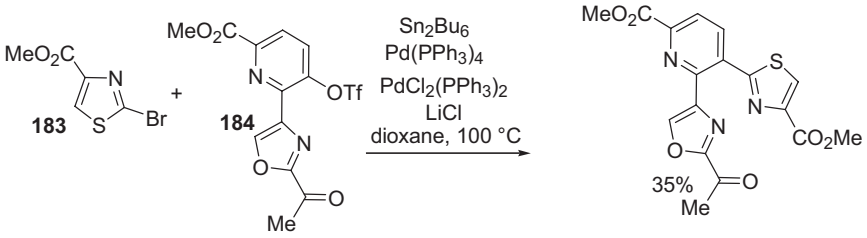
Scheme 10.93

More recently, these conditions have been employed in the synthesis of RNA containing imidazole attached directly to 5-position of uracyl heterocycles of tandem G–U wobble base pairs. The modified uridine was prepared using a palladium-catalyzed coupling of 5-iodouridine and 4-tributylstannyl imidazole [289].

Other examples of Stille couplings using 2-substituted 5-stannylimidazoles [290] are applicable to the synthesis of cytotoxic agents [291] and an imidazolyl isomer of the alkaloid didemnimide C [292]. 5-Stannylimidazoles have also been prepared by a 2,5-dilithiation, followed by a double stannylation and a 2-hydrodestannylation sequence [291]. In addition, the stannyl group on imidazoles has been employed for *ipso*-iodination reactions, as in the synthesis of inhibitors of phophodiesterase PDE4 [293].

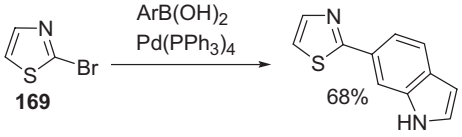
Finally, sometimes attempts to generate either coupling partner as a discrete stannane lead to dimeric or decomposition products. In some cases it is necessary to form the stannane *in situ*, such as in the synthesis of dimethyl sulfomycinamate, which was prepared via *in situ* stannane formation from triflate **184** followed by addition of bromide **183** to the reaction (Scheme 10.94) [294].

10.4.6.3.2 **Suzuki–Miyaura Cross-Coupling Reactions** Reactions of azole derivatives that take advantage of a boron-containing partner in the coupling reaction are also very common, but generally use an halogenated azole and an aryl or heteroaryl boronic acid, many of which are now commercially available. The Suzuki reaction is exceptionally tolerant of functional groups that often need protection under other coupling conditions.



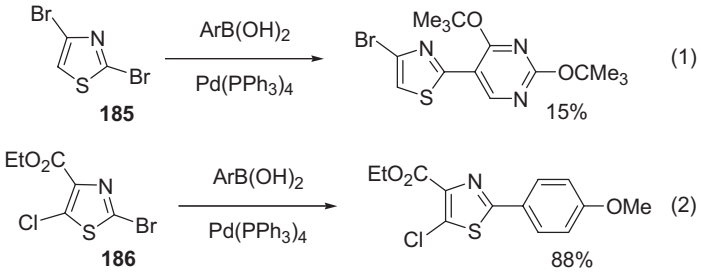
Scheme 10.94

Also in this case, 2-bromothiazole (**169**) [295a–c] is a common substrate for this type of reactions (Scheme 10.95) [295a].



Scheme 10.95

These cross-coupling reactions are a useful solution for the selective arylation of azoles. For example, chemoselective reaction of 2,4-dibromothiazole **185** proceeds selectively at C2 [Scheme 10.96 (1)] [296], as does the 2-bromo-5-chloro derivative **186** [Scheme 10.96 (2)] [297].

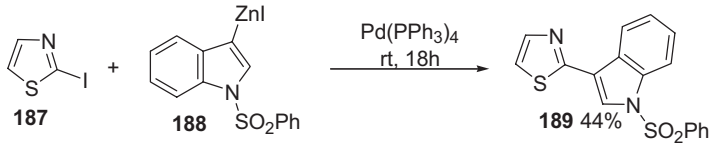


Scheme 10.96

10.4.6.4 Zinc, Magnesium and Other Metal Mediated Couplings

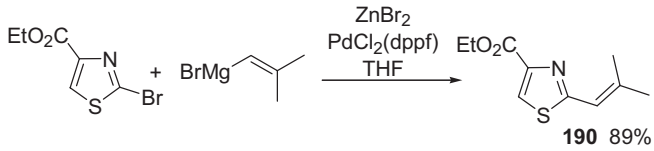
Metal-substituted coupling partners for transition-metal mediated reaction, other than tin and boron, are of interest for environmental (tin toxicity) or synthetic (availability of boronates) reasons.

Zinc-mediated couplings have been developed. For example, highly active zinc [298] generates **188**, which efficiently couples with 2-iodothiazole (**187**) to afford indolyl-thiazole adduct **189** (Scheme 10.97).



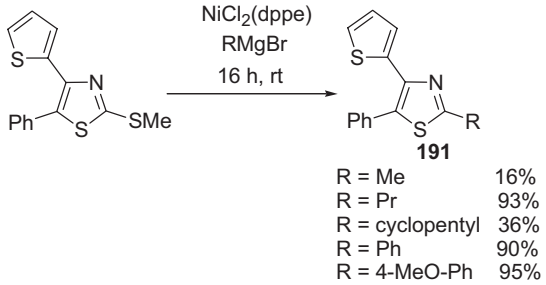
Scheme 10.97

Another class of cross-coupling reactions recently described are the Grignard couplings. For example, the combination of zinc bromide and a Grignard reagent allows for installation of the isobutylene fragment in thiazole **190** in the first step (Scheme 10.98) towards the fungicidal natural product hectochlorin [299].



Scheme 10.98

New methods for the coupling of thioether derivatives have been reported. Nickel catalysis in combination with both aryl and alkyl Grignard reagents affords derivative **191** (Scheme 10.99) [300].



Scheme 10.99

Finally, the use of other organometallic reagents has proven useful with halogenated azoles, and include organoaluminates [301] with palladium catalysis as well as Grignard reagents with the catalysis of nickel [302] and iron [303].

10.4.7
Reactions with Radicals

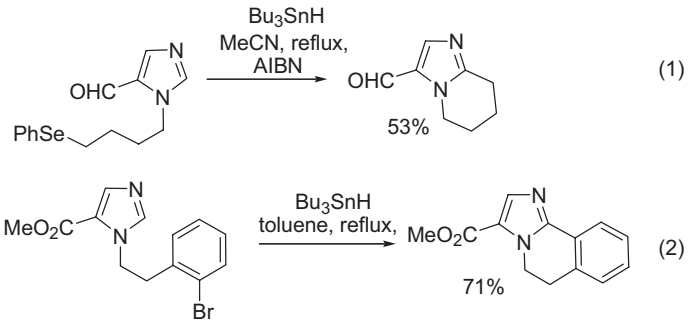
Free radical reactions are still very much less common in azole chemistry than those involving, for example, electrophilic or nucleophilic reagents. In reactions involving

free radicals, substituents have little orienting effect; however, rather selective radical reactions are now known.

Phenyl radicals attack azoles unselectively to form a mixture of phenylated products. The phenyl radicals may be prepared from the usual precursors: PhN(NO)COMe, $Pb(OCOPh)_4$, $(PhCO_2)_2$ or $PhI(OCOPh)_2$. For example, the three monophenylthiazoles are obtained in the practically constant ratio of 6 : 3 : 1 (2 : 5 : 4, respectively) using the photolysis of benzyl peroxide as source of radicals in the presence of thiazole. In the case of 1-methylimidazole, phenylation, using the decomposition of benzoyl peroxide at 118 °C, no change in the overall yield is reported whether the solvent is 1-methylimidazole itself or acetic acid. In acetic acid, however, only 1-methyl-2-phenylimidazole was formed, while with the excess of heterocycle 1-methyl-2-phenyl- and -5-phenyl-imidazoles were isolated in the ratio 79 : 21 [304].

In contrast, alkyl radicals produced by oxidative decarboxylation of carboxylic acids are nucleophilic and attack azoles at the most electro-deficient sites. Thus, imidazole and 1-alkylimidazoles are alkylated exclusively at the C2. Similarly, thiazoles are attacked in acidic media by methyl and propyl radicals to give 2-substituted derivatives in moderate yields, with smaller amounts of 5-substitution. Similar reactions occur with acyl radicals, for example with the $CONH_2$ radical from formamide [305].

Recently developed are alkyl [Scheme 10.100 (1)] and aryl [Scheme 10.100 (2)] radical cyclization onto azoles for the synthesis of bi-or tricyclic heterocycles [306].

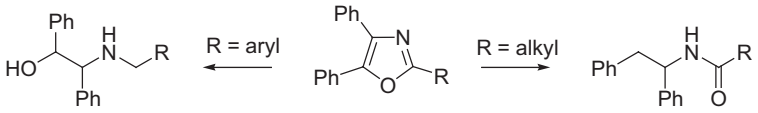


Scheme 10.100

10.4.8
Reactions with Reducing Agents

Oxazoles are readily reduced, usually with ring scission (Scheme 10.101). Only acyclic products have been reported from the reductions with complex metal hydrides of oxazoles. Similar results have been obtained using catalytic hydrogenation or reduction by dissolving metals [307].

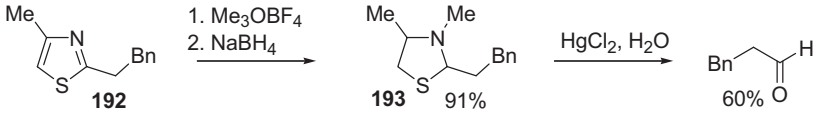
Imidazoles are generally resistant to reduction. Unless the NH of imidazole is substituted, the preferential reaction with a complex hydride will be salt formation,



Scheme 10.101

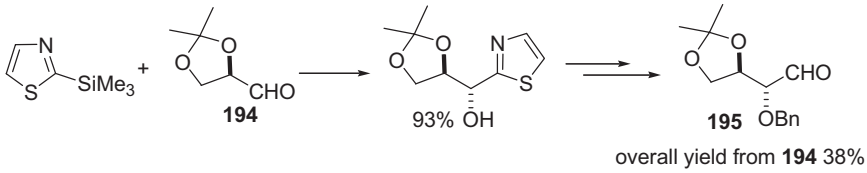
which leaves a negative charge on the ring nitrogen. Consequently, the species becomes resistant to reduction.

Finally, thiazole reduction is a very useful method for the synthesis of aldehydes [207]. The aldehyde is prepared via a three-step reaction sequence that consists of N-methylation of the thiazole ring **192**, reduction of the resulting *N*-thiazolium salt (not shown) to the thiazolidine **193** and, finally, $HgCl_2$-promoted hydrolysis of the heterocyclic nucleus of **193** (Scheme 10.102).



Scheme 10.102

One of the first examples of this reaction was the thiazole-based one-carbon homologation of 2,3-*O*-isopropylidine-D-glyceraldehyde **194** to protected D-erythrose **195** (Scheme 10.103) [308].



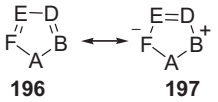
Scheme 10.103

10.4.9
Electrocyclic and Photochemical Reactions

10.4.9.1 Diels–Alder Reactions and 1,3-Dipolar Cycloadditions

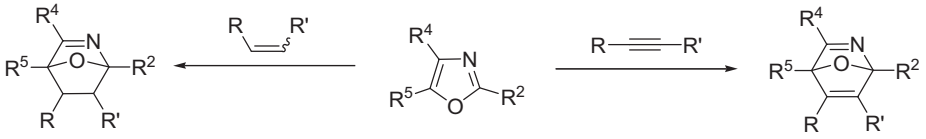
The distinction between these two classes of reactions is simply semantic for the five-membered rings: Diels–Alder reaction at the F/B positions in **196** (four-atom fragment) is equivalent to 1,3-dipolar cycloaddition in **197** across the three-atom fragment, both providing the four π-electron component of the cycloaddition (Figure 10.9) [309].

Oxazoles exhibit diene-type characteristics and undergo Diels–Alder reactions with alkenic and alkynic dienophiles (HOMO-oxazole, LUMO-dienophile) (Scheme 10.104) [310]. The presence of electron-releasing substituents on the oxazole ring facilitates the reaction with dienophiles.



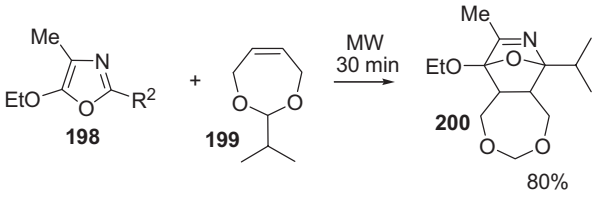
196 **197**

Figure 10.9 A Diels–Alder reaction at the F/B positions in **196** (four-atom fragment) is equivalent to 1,3-dipolar cycloaddition in **197** across the three-atom fragment.



Scheme 10.104

The primary adducts of oxazoles with alkenes and alkynes are usually too unstable to be isolated. An exception, for example, is compound **200**, obtained from 5-ethoxy-4-methyloxazole **198** and 4,7-dihydro-1,3-dioxepine **199**, which has been separated into its *endo* and *exo* components (Scheme 10.105) [310].



Scheme 10.105

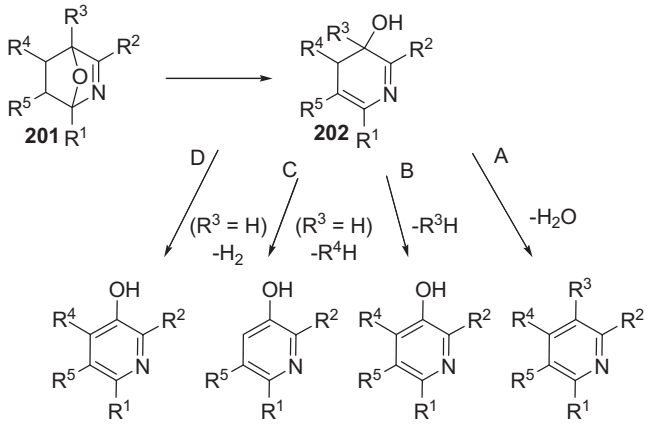
If the dienophile is unsymmetrical the cycloaddition can afford the two regioisomers. This is usually the case in the reactions of oxazoles with monosubstituted alkynes; while with alkenes regioselectivity is observed. A general rule for the reactions of alkyl- and alkoxy-substituted oxazoles is that in the adducts the more electronegative substituent of the dienophile R^4 occupies the position shown in Scheme 10.104.

Acid- or base-catalyzed cleavage of the ether bridge in primary cycloadducts leads to pyridine derivatives (Scheme 10.106) [312]. The intermediates **201** cleave to unstable dihydropyridinols **202**, which aromatize in four ways:

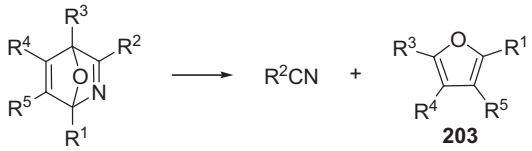
- path A: pyridines are formed by dehydration;
- path B: 3-hydroxypyridines results from elimination of R^3H;
- path C: elimination of R^4H if R^3 is hydrogen;
- path D: dehydrogenation if R^3 is hydrogen.

Generally, more than one path is followed and a mixture of products results.

However, the reaction of oxazoles with alkyne dienophiles affords furans **203** with the elimination of cyanide in a retro-Diels–Alder reaction (Scheme 10.107) [313].



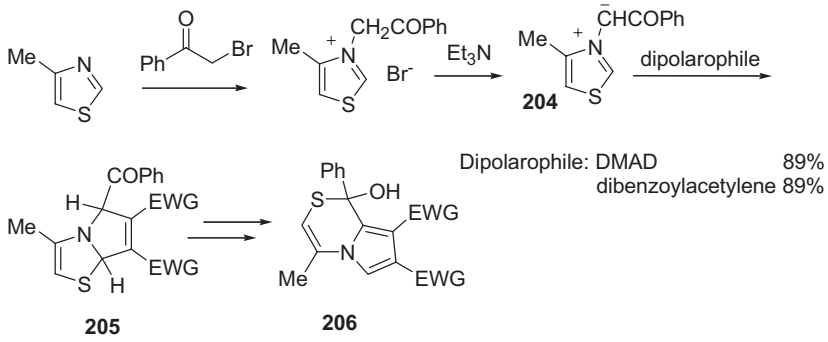
Scheme 10.106



Scheme 10.107

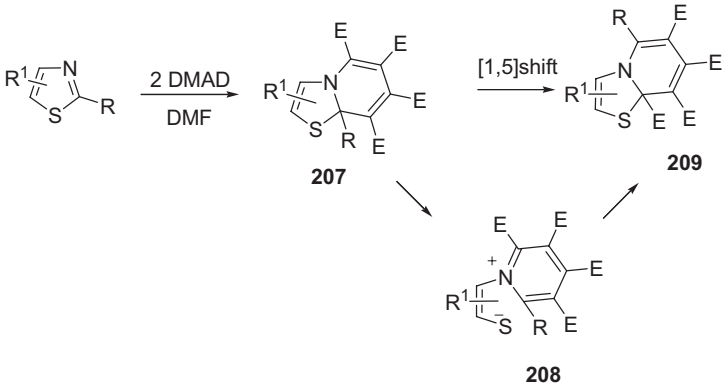
In contrast to oxazole, thiazole does not undergo Diels–Alder cycloaddition reaction. This behavior can be correlated with the more dienic character of oxazole relative to thiazole.

Dipolarophiles like DMAD (dimethyl acetylenedicarboxylate), dibenzoylacetylene and ethyl propiolate condense with ylides **204** resulting from quaternization of 4-methylthiazole with an α-bromo ketone or ester and subsequent deprotonation. The 1 : 1 molar adduct **205** rearranges to a pyrrolothiazine **206** (Scheme 10.108) [341].



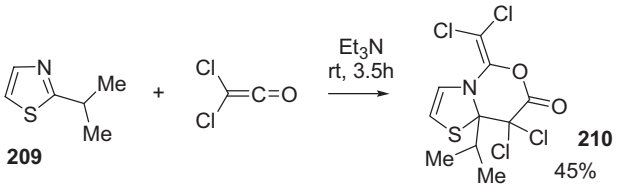
Scheme 10.108

Thiazoles itself reacts with DMAD at room temperature in DMF; the initially formed adduct **207** rearranges either via a concerted suprafacial 1,5-sigmatropic shift or by a non-concerted pathway proceeding via zwitterions **208** to **209** (R=R^1=H) (Scheme 10.109) [315].



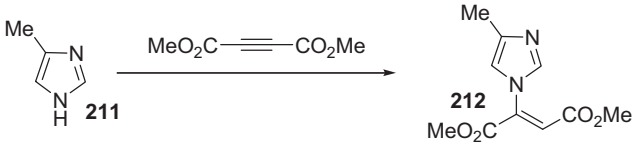
Scheme 10.109

2-Isopropylthiazole (**209**) reacts with dichloroketene in a [2 + 2 + 2] manner to give **210** as the major product (Scheme 10.110) [316].



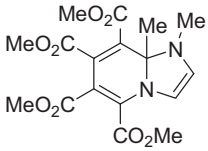
Scheme 10.110

Finally, reactions of imidazoles **211** with DMAD usually do not lead to normal Diels–Alder adducts but to products of N-alkylation (**212**) (Scheme 10.111) [317].



Scheme 10.111

There are instances, nevertheless, in which some form of addition takes place. For example, 1,2-dimethylimidazole gives the adduct **213** (Figure 10.10) [318].

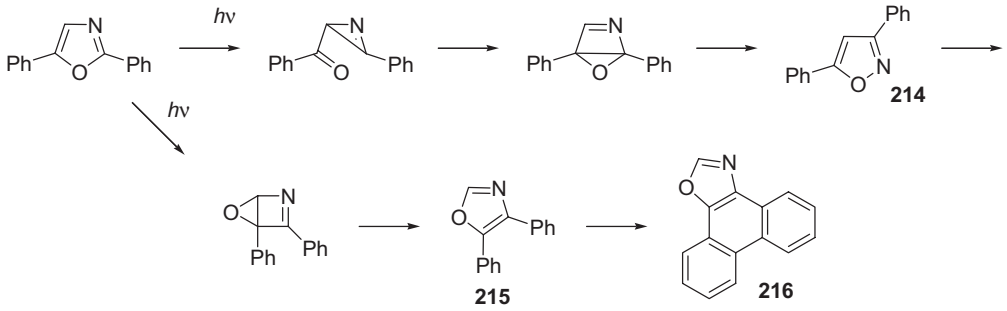


213

Figure 10.10 Diels–Alder adduct between 1,2-dimethylimidazole and DMAD.

10.4.9.2 **Photochemical Reactions**

Oxazoles are generally photostable and are, indeed, produced by light-induced rearrangements of isoxazoles [319]. However, irradiation of 2,5-diphenyloxazole in ethanol gives a mixture of 3,5-diphenylisoxazole (**214**), 4,5-diphenyloxazole (**215**), the phenanthrooxazole (**216**) and traces of benzoic acid. This reaction proceed by two distinct paths, which are rationalized as shown in Scheme 10.112.

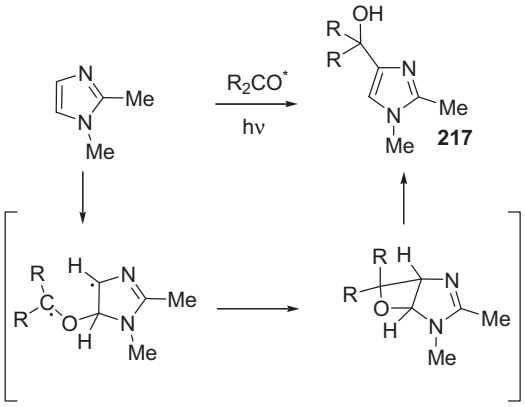


Scheme 10.112

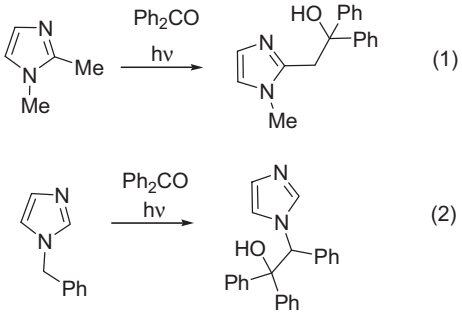
In the case of photoaddition of acetone and other ketones to 1-, 2- and 1,2-dimethylimidazoles the products are α-hydroxyalkylimidazoles **217**, which are derived from the selective attack of excited carbonyl oxygen at C5 (Scheme 10.113) [320]. Imidazole itself does not react.

Benzophenone reacts differently with 1,2-dimethylimidazole. The diarylketone adds at the 2-methyl group [Scheme 10.114 (1)]; 1-benzylimidazole reacts at the exocyclic methylene group [Scheme 10.114 (2)] [321].

More recently, a photoinduced procedure for the intermolecular hydroamination of alkenes using azoles has been described. This reaction occurs in modest to good yield for six- and seven-membered cyclic alkenes. Upon irradiation at 254 nm in the presence of methyl benzoate and a small amount of triflic acid as an additive (20 mol. %), imidazoles can react with the alkene to afford complex Markovnikov adducts [322].



Scheme 10.113



Scheme 10.114

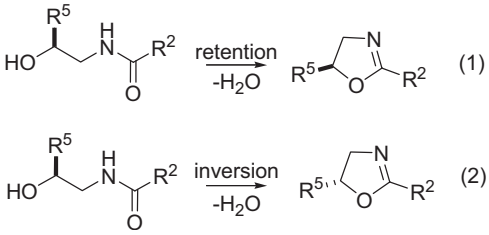
10.5 Derivatives

10.5.1 Dihydro-1,3-Azoles

The most important partially saturated derivatives of 1,3-azoles are 4,5-dihydroazoles, and several methods have been developed to obtain substituted derivatives both achiral and chiral. The impetus to this development was surely given by the wide use oxazolines (another common name for 4,5-dihydroxazoles) have found in homogeneous catalysis [323]. For this reason, synthetic approaches to 4,5-dihydrooxazoles are the blueprint of this section. The synthesis of 4,5-dihydroimidazoles and -thiazoles, which also have important application in catalysis [324] and natural compounds chemistry, are discussed in comparison with 4,5-dihydrooxazoles.

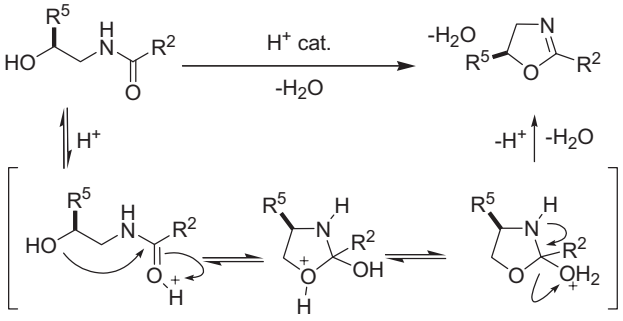
The most important and widely used approach is the cyclic dehydration of a β-hydroxyamide derivative. Several reagents are commonly used to obtain this dehydration and new ones are developed every year. Simple heating of the amide

can in some cases afford the final oxazoline derivative but a high temperature is generally required and efforts have been devoted to using milder reaction conditions. All known reactions can be divided into two main classes [Scheme 10.115 (1) and (2)]: (i) reactions that give retention of configuration on the stereocenter that bears the hydroxyl group; (ii) reactions that cause inversion of configuration on the same stereocenter [325]. The first class of reactions resembles the biosynthetic process.



Scheme 10.115

In the first class the common mechanism is the activation of the carbonyl group of the amide moiety to nucleophilic attack of the hydroxyl group, followed by elimination of water. The activation is performed through the use of Lewis or Brønsted acids (Scheme 10.116).

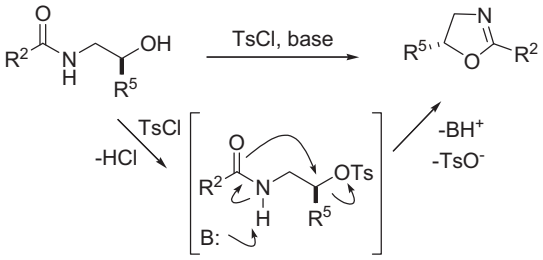


Scheme 10.116

This class of reagents includes $TiCl_4$ [326], TsOH [327], Ph_3PO-Tf_2O [328] and recently also Mo(IV) and Mo(VI) oxides [325].

The second class of reagents is instead based on the transformation of the hydroxyl group into a good leaving group to perform a nucleophilic substitution by the amide oxygen through an S_N2 mechanism. This mechanism is described, using TsCl as reagent, in Scheme 10.117.

This class of reagents includes Martin's sulfrane [329], the Burgess reagent [330], Mitsunobu reagents [331], DAST (diethylaminosulfur trifluoride) [332], polymer-supported TsCl [333] and $SOCl_2$ [334].

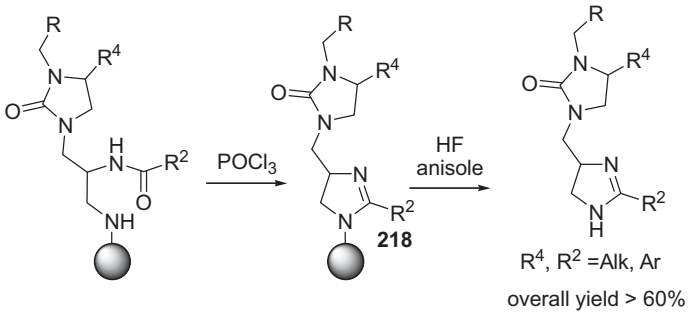


Scheme 10.117

In a similar process, a solid-phase supported synthesis of 4,5-dihydrooxazoles has been performed, transforming the hydroxyl group into a iodide through the use of PPh_3, I_2, imidazole [335].

Several of these methods can be extended to the synthesis of 4,5-dihydrothiazoles. Thiazoles derivatives can be obtained by cyclodehydration of β-hydroxythioamides with $SOCl_2$-Py [336], and with $MsCl/NEt_3$ [337], as well as by $TiCl_4$-induced dehydration of amides derived from vicinal aminothiols [338], cyclization of a serine-derived thiolamide with [339] or without [340] the use of Burgess' reagent, dehydrocyclization of thioamides with deoxofluor or DAST [332, 341] or with Mitsunobu reagents [342], and reaction of aminothiols with carboxylic acids [346].

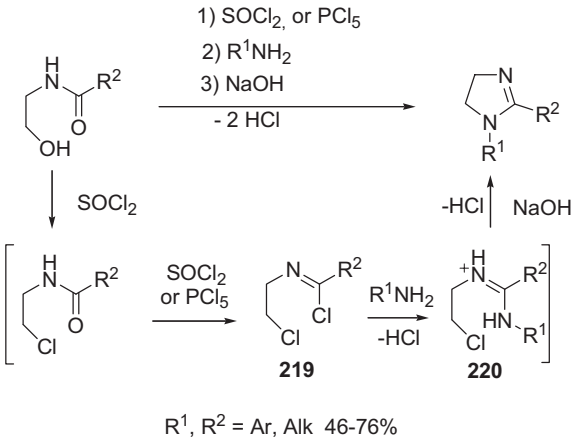
Concerning 4,5-dihydroimidazoles, *N*-aminoethyl amides dehydrocyclize in the presence of $POCl_3$ [343], and this procedure has been applied also for the solid-phase synthesis of imidazoline **218** (Scheme 10.118) [344].



Scheme 10.118

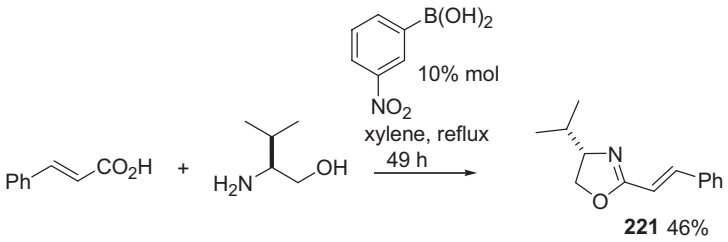
A somewhat related procedure is used to produce imidazoline derivatives. N-hydroxyethylamides are treated with excess thionyl chlorides, or thionyl chlorides followed by PCl_5, to afford N-chloroethylimidoyl chlorides **219**. These intermediates are treated with amines and anilines to produce *N*-chloroethylamidines **220**, which are converted into imidazolines upon workup with aqueous sodium hydroxide (Scheme 10.119) [345].

Direct condensation of carboxylic acids with β-aminoalcohols is quite a drastic procedure but works nicely with substituted aminoalcohols in the presence of acid



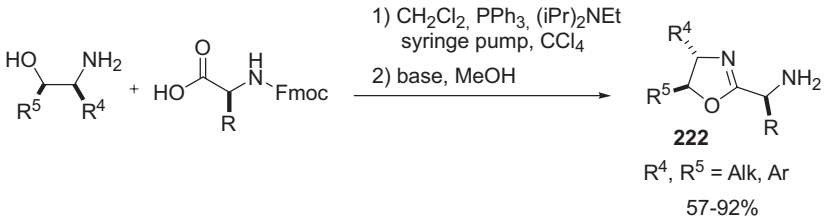
Scheme 10.119

catalysts, such as boric acids, to afford polysubstituted oxazolines such as **221** (Scheme 10.120) [346].



Scheme 10.120

The use of a combination of PPh_3, a base and CCl_4 [347] allows the one-pot condensation and cyclic dehydration of amino acids and β-aminoalcohols, in a process that affords 2-aminomethyl-4,5-dihydrooxazoles **222** (Scheme 10.121) [348].



Scheme 10.121

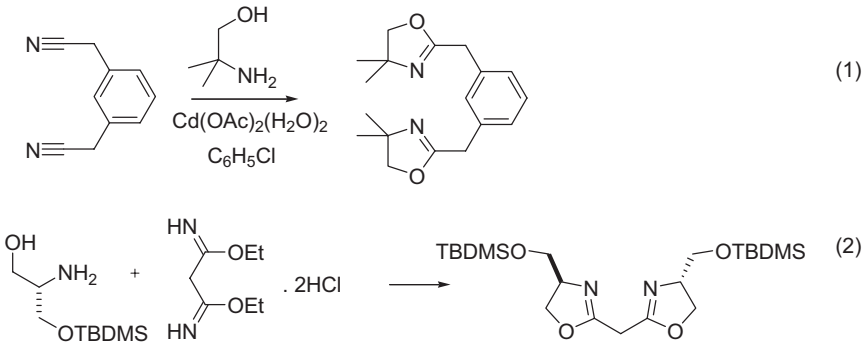
A microwave accelerated two-step, one-pot procedure has been proposed, using 1-acyl benzotriazole, $SOCl_2$ and the aminoalcohol. The $SOCl_2$ was needed to

complete the cyclization of the intermediate amide formed. This procedure is also convenient for the synthesis of thiazoline derivatives [349].

Several other derivatives of carboxylic acids can be used for the synthesis of oxazoline. The reaction of esters with vicinal diamines affords the expected imidazolines and, in the same way, also thiazolines and oxazolines. The reaction conditions are refluxing toluene and $Al(Me)_3$ [350].

Vicinal diamines, as well as aminoalcohols and aminothiols, also react with orthoesters in the presence of HCl to afford the corresponding heterocycles. Often the orthoester is the solvent [351].

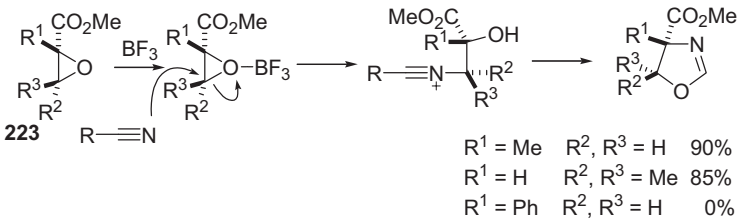
The cyano group reacts with aminoalcohols in the presence of metal catalysts, such as Cd salts [352] or $ZnCl_2$ [Scheme 10.122 (1)] [353]. The same reaction can be performed using aminothiols to afford thiazoline derivatives [354].



Scheme 10.122

Much milder reaction conditions are needed when employing imidates and vicinal aminoalcohols [355], aminothiols [356] and diamines [Scheme 10.122 (2)] [357].

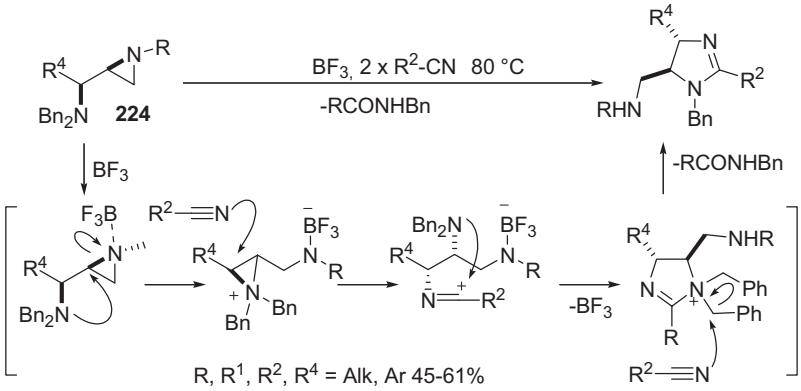
Oxiranes and aziridines are converted, in a Ritter reaction, into 4,5-dihydrooxazoles and 4,5-dihydroimidazoles by treatment with cyanides in the presence of Lewis acids. The reaction occurs with inversion and, for substrate **223**, is completely regiospecific (Scheme 10.123) [358].



Scheme 10.123

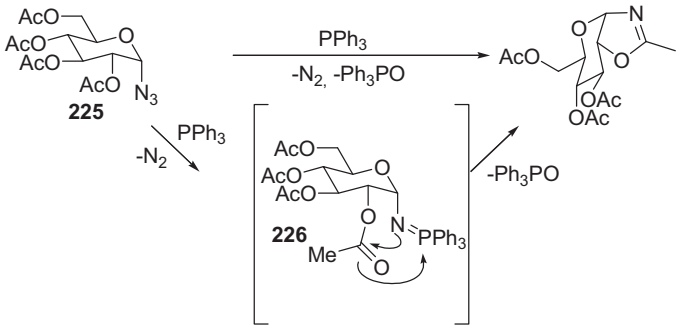
Analogously the Ritter reaction of enantiopure 2-(1-aminoalkyl)aziridines **224** with different nitriles affords enantiopure tetrasubstituted imidazolines. Again the

opening of the aziridine ring takes place with total regio- and stereoselectivity, by the mechanism proposed in Scheme 10.124 [359].



Scheme 10.124

A very general route to 1,3-azolines is represented by the cyclization obtained by the aza-Wittig reaction of substituted azides. The reaction occurs under very mild conditions and the synthesis appears particularly versatile. Triphenylphosphine reacts with the azido group of **225** to afford the corresponding iminophosphorane **226**, which then react with the vicinal ester group to give the ring closure (Scheme 10.125) [360].

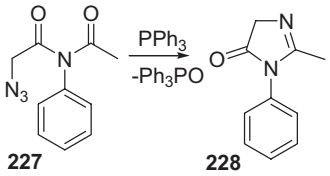


Scheme 10.125

The use of polymer-supported triphenylphosphine makes the purification easier.

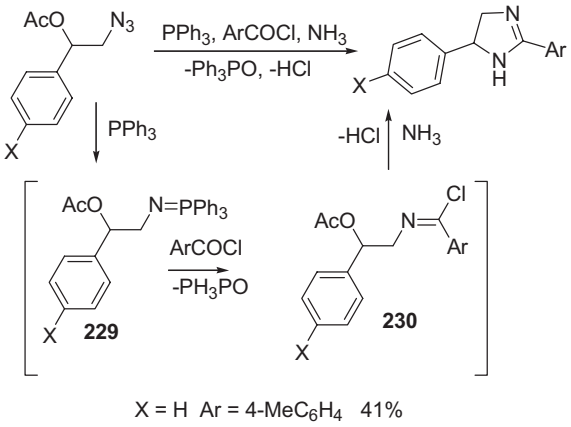
The same reaction can be performed using thioester to obtain the corresponding thiazolidine [361].

The equivalent reaction for the synthesis of imidazolidine is more limited since it is necessary to use activated amides to obtain the ring closure. For example, azido imide **227** reacts to give the corresponding imidazolinone **228** (Scheme 10.126) [362].



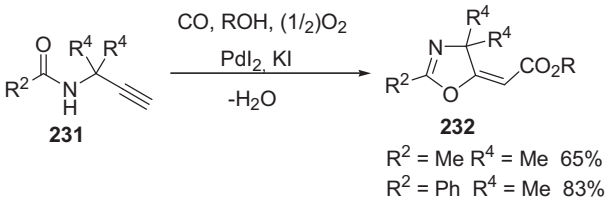
Scheme 10.126

A more general route to imidazoline is obtained by treating the intermediate iminophosphorane **229** with an acyl chloride and subsequently with NH_3. Imidoyl chloride **230** is the proposed reactive intermediate (Scheme 10.127) [363].



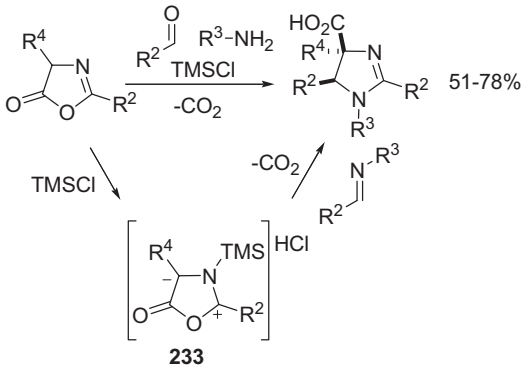
Scheme 10.127

Propargylamides **231** are transformed into the correspondent 5-carboxymethylene-4,5-dihydrooxazoles **232** in a Pd-catalyzed process in the presence of CO, an alcohol and molecular oxygen (Scheme 10.128) [364].



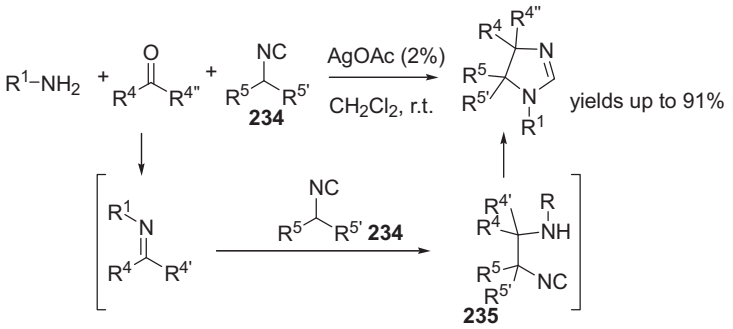
Scheme 10.128

A multicomponent reaction of oxazolones with aldehydes, primary amines and TMSCl affords diastereoselectively highly substituted imidazolines. The proposed mechanism proceeds through a 1,3-dipolar cycloaddition reaction of the mesoionic intermediate **233** (Scheme 10.129) [365].



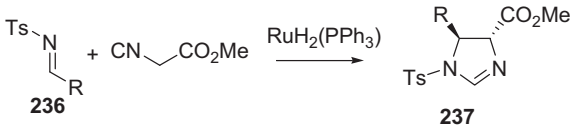
Scheme 10.129

Another multicomponent reaction (MCR) has been developed using aldehydes, primary amines and isonitriles with AgOAc as catalyst. This MCR probably involves an aldol-type addition of the isocyanide **234** to the *in situ* generated imine followed by ring closure of the intermediate **235** (Scheme 10.130). The role of AgOAc is to increase the acidity of the proton α to the isonitrile group through complexation [366].



Scheme 10.130

Isonitrile derivatives have also found application in reactions with N-sulfonylimines, as **236**, catalyzed by Ru or Gd complexes to afford stereoselectively the corresponding *N*-sulfonyl-2-imidazolines **237** (Scheme 10.131).

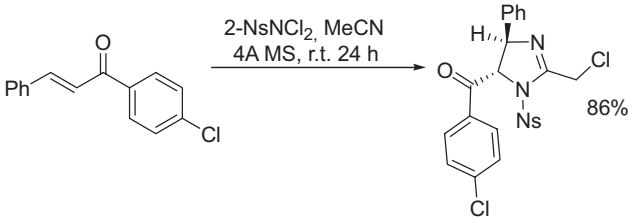


Scheme 10.131

The salt derived from Ph_3PO/Tf_2O is effective in the dehydrocyclization of N-aminoethyl amides obtained by condensation of amino acids. This procedure

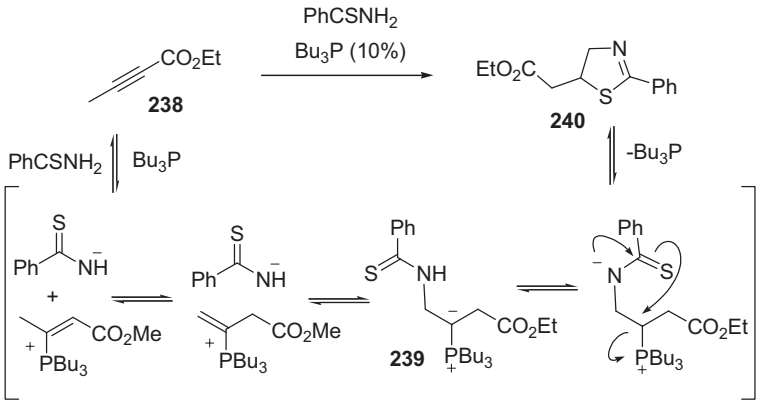
affords imidazolines that still contain the amino acid functionality and preserves the stereochemical integrity [367]. The same procedure has been used by the same authors for the biomimetic synthesis of thiazoline starting from cystein-containing dipeptides [368].

N,N-Dichloro-*o*-nitrobenzenesulfonamide (2-NsNCl$_2$) is an effective electrophilic nitrogen source for the direct diamination of α,β-unsaturated ketones in the presence of acetonitrile, without the use of any metal catalysts (Scheme 10.132) [369].



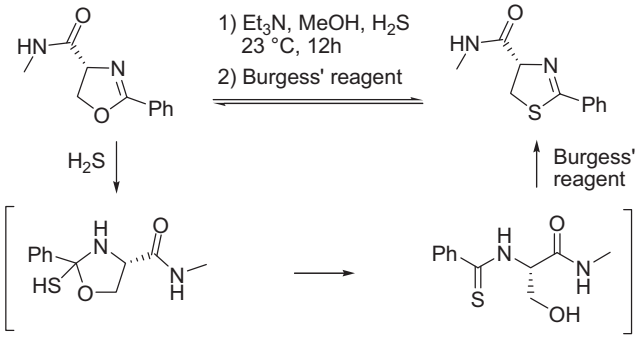
Scheme 10.132

Peculiar to the synthesis of thiazolines is the phosphine-induced annulation of thiolamides and 2-alkynoates. The proposed mechanism, depicted in Scheme 10.133, is based on the bielectrophilic character imparted by the phosphine to the triple bond [370]. The addition of tributylphosphine to the polarized triple bond of **238** induces, after migration of the double bond, the formation of the ylide **239**, which undergoes cyclization to afford thiazoline **240**.



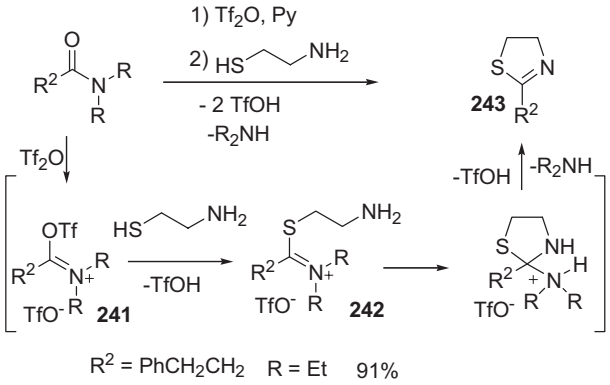
Scheme 10.133

Direct oxazoline–thiazoline conversion can be realized by thiolysis of oxazolines with H_2S in methanol/triethylamine, followed by cyclodehydration with Burgess reagent **55** (for structure see Scheme 10.20). This protocol is high yielding, chemoselective and essentially free of racemization for C(5)-unsubstituted and trans-4,5-disubstituted peptide oxazolines (Scheme 10.134) [371].



Scheme 10.134

A very mild transformation of secondary and tertiary amides into thiazolines has been described using iminium triflates. The reaction proceeds at very low temperature and is tolerant towards several functional groups [372]. The iminium triflate **241** undergoes nucleophilic addition–elimination by 2-aminoethanthiol to afford **242**, which subsequently cyclizes with loss of the secondary amine to give **243** (Scheme 10.135).



Scheme 10.135

10.5.2
Benzo-1,3-Azoles

The synthesis of this class of compounds presents peculiar approaches, since the structure forces the syntheses towards cyclization reactions on a preformed 1,2 disubstituted benzene ring. Extremely rare are synthesis in which the benzene ring is formed during the synthesis. However, this implies that many synthetic approaches are common for benzoimidazoles, benzoxazoles and benzothiazoles. For this reason all the procedures presented here are applied to the three different kinds of

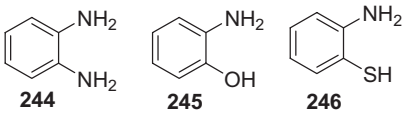


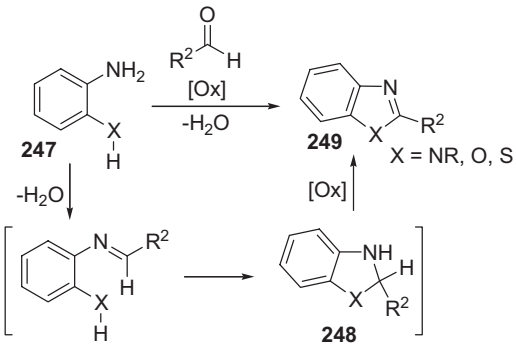
Figure 10.11 Starting materials used for the formation of benzo-1,3-azoles.

derivatives. Special syntheses that concern just one heterocycle are presented together with similar generic procedures.

The starting material are usually the ortho-substituted anilines **244–246** (Figure 10.11).

These compounds, as well as their derivatives bearing other substituents on the benzene ring, are generally available and stable. Only 2-aminobenzenethiol and its derivatives are not very stable since they are oxygen sensitive. To circumvent this problem they are often used in the form of derivatives such as acid salts, alkaline salts, zinc salts or disulfides [373].

A general synthetic approach is the intramolecular nucleophilic addition of the heteroatom substituent onto an imine moiety followed by oxidation to afford the aromatic derivative. The imine can be used as starting material but often the reaction is performed on a mixture of the 2-substituted aniline **247** and the aldehyde. The saturated intermediate **248** is subsequently oxidized to afford the final benzo-derivative **249** (Scheme 10.136).

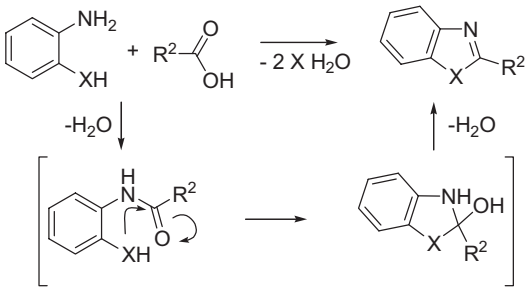


Scheme 10.136

Several oxidants have been used, such as DDQ or the simple 1,4 benzoquinone [374, 375], MnO_2 [376], $Mn(OAc)_3$ [377], NBS [378], Ag_2O [379], and oxone [380]; however, reactions in which the mixture of reagents is heated at high temperature in DMSO [381], or even under solvent-free conditions with Yb catalyst have also been described [382]. Remarkable is the reported synthesis of substituted benzoxazoles by heating the aniline and the aldehyde in xylenes in the presence of activated carbon is; the oxidant is presumed to be atmospheric oxygen [383]. Benzimidazoles can be obtained at room temperature by condensing *ortho*-phenylenediamine and aldehydes with silica-supported thionyl chloride [384]. Examples of reactions performed under

microwave irradiation, optimizing the time and the yields [385], have been reported, as have several examples of reactions applied on the solid phase for the production of libraries [374, 376, 386, 387] as well as for the synthesis of libraries in solution phase [388].

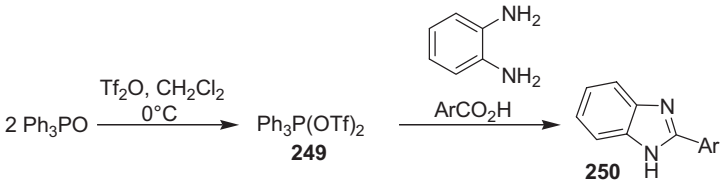
The most important synthetic methods for the preparation of a wide range of benzoazoles is the condensation of 2-substituted anilines with carboxylic acids or derivatives (Scheme 10.137). Benzimidazole can be made in 80% yield by merely standing a mixture of *o*-phenylenediamine and formic acid at room temperature for 5 days; however, at 100 °C the process takes only 2 h and it is applicable to a wide range of 2-substituted benzimidazole. Careful choice of reaction conditions is, however, essential to obtain good yield for each substrate [389]. The most widely used conditions (Phillip's method [390]) involve heating the reagents in the presence of hydrochloric acid, usually around 4 M concentration. However, the range of reaction conditions that has been used is wide: from merely heating the diamines with a carboxylic acid [391], to heating in the presence of acids such as HCl [392], PPA [393], and $POCl_3$ [394].



Scheme 10.137

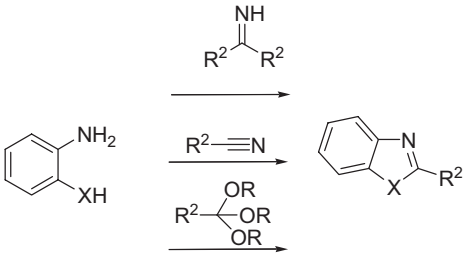
If the *o*-diaminoarene has one of the amino groups substituted by an alkyl or aryl group, 1-substituted benzimidazoles are formed [395].

As described in Section 10.5.1 the complex $Tf_2O/POPh_3$ acts as a dehydrating agent favoring the formation of the benzoimidazole **250** in common solvents, giving high yields in 30–60 min at room temperatures (Scheme 10.138) [344].



Scheme 10.138

A range of acid derivatives can substitute for carboxylic acids (Scheme 10.139): esters [397], orthoesters [398], nitriles [399], imidates [400], acid chlorides (including

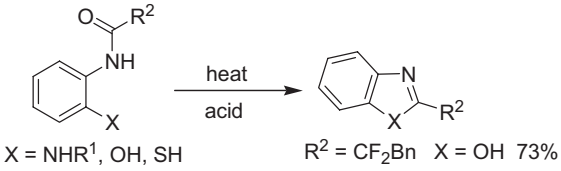


Scheme 10.139

phosgene) [401] and anhydrides [402]. Concerning the use of orthoester the reaction conditions may vary considerably depending on the reactivity of the 2-substituted aniline. In many cases an excess of orthoester is used – it is often the solvent – and the reaction is conducted in the presence of catalytic TsOH [402], of a base [404] or of KSF clay [405].

A few examples of the synthesis of benzimidazoles using amides have been reported in the literature. Usually, these reactions occur at high temperature [406].

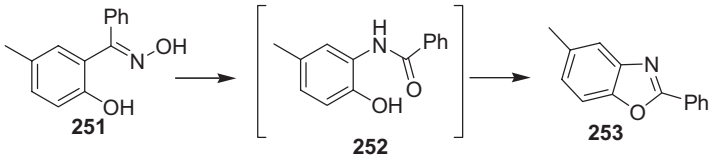
A procedure strictly related to the previous method is the reaction of N-acyl derivatives of **244**–**246**, which undergo thermal dehydration to afford the corresponding benzoazoles (Scheme 10.140) [407–410].



Scheme 10.140

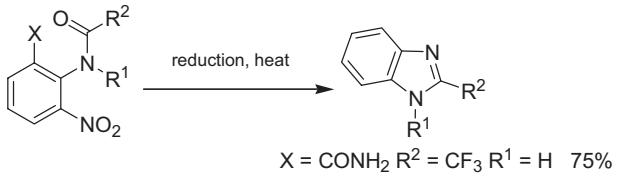
The cyclization may occur by simple uncatalyzed thermolysis or with aqueous or ethanolic acid as well as phosphoryl chloride. Recently, Mitsunobu reaction conditions were also used [411].

Since the amide intermediate **252** is formed, the Beckmann rearrangement of *o*-hydroxybenzophenone oxime **251** leads directly to benzoxazole **253** (Scheme 10.141) [412].



Scheme 10.141

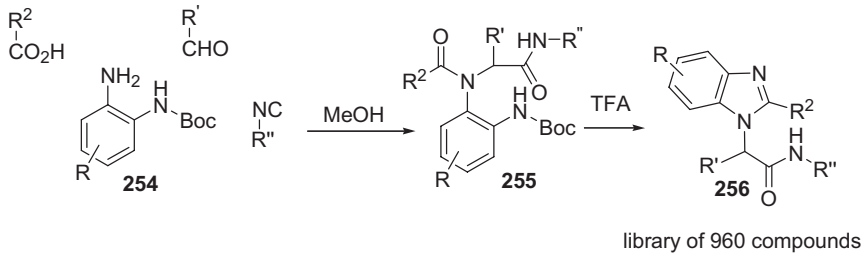
In situ reduction (tin and acetic or hydrochloric acids, hydrogen/palladium carbon, hydrogen/Raney nickel/hydrochloric acid) of *o*-nitroacylaminoarenes is followed by cyclization to afford 1,3-benzoimidazoles usually in good yields (Scheme 10.142) [413].



Scheme 10.142

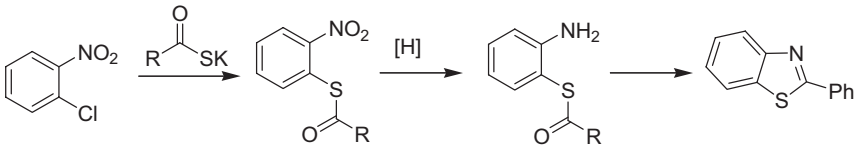
This general method can be applied to the synthesis of 2-unsubstituted benzimidazoles by cyclization of an *o*-formamidoarylamine and to 1-aminobenzidimazoles when *o*-acylaminophenylhydrazines are the substrates.

An example of a MCR can be included in this methodology since the reaction of *o*-phenylenediamine derivative **254** affords, in the Ugi reaction, compound **255**, which upon deprotection cyclizes to afford benzimidazole derivatives **256** (Scheme 10.143) [414].



Scheme 10.143

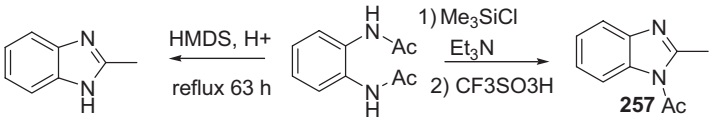
o-Nitrochlorobenzene easily undergoes nucleophilic substitution reactions with sulfurated reagents. The adducts can successively cyclize, after reduction of the nitro group, to afford the corresponding benzothiazole derivative (Scheme 10.144).



Scheme 10.144

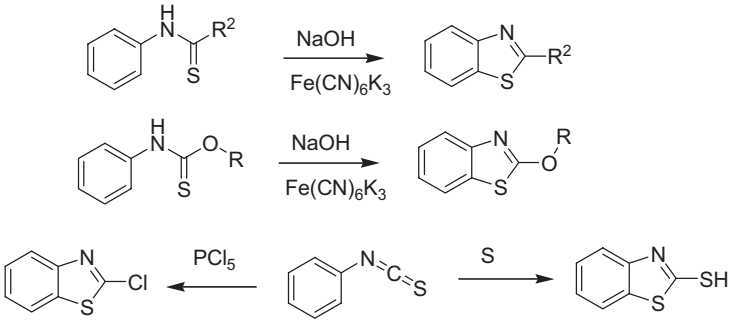
O,N- [415], N, N′-, S,N- [416] diacylated compounds can also cyclize under different conditions, ranging from simple heating at 200 °C [417] to microwaves irradiation of mixtures with montmorillonite K10 [418].

A modification has been introduced to prepare 1-acetyl-2-methylbenzimidazole (**257**) in quantitative yield (Scheme 10.145) [419].



Scheme 10.145

Simple aniline derivatives, such as thioanilides (Jacobson method) [420] or arylmonothiocarbamates (Jacobson–Hunter method) [421], cyclize to afford the corresponding 2-substituted benzothiazole derivative in the presence of potassium ferricyanide (Scheme 10.46).



Scheme 10.146

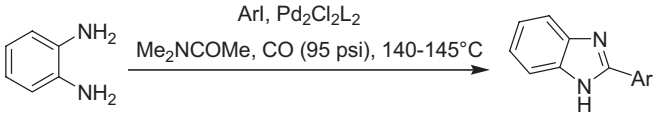
Aryl isothiocyanate can be cyclized by heating with PCl_5 to 2-chlorobenzothiazoles (Hunter's method) or with sulfur to 2-mercaptobenzothiazoles.

o-Halothioanilides undergo ring closure, presumably through an intermolecular aromatic nucleophilic substitution, under basic conditions [422, 423] in the presence of catalysts. The thioamide can also be formed *in situ* (Scheme 10.147) [424].

Scheme 10.147

A novel palladium-catalyzed carbonylation of iodobenzene has recently been linked to base-induced coupling and cyclization with *o*-phenylenediamine, to give 2-arylbenzimidazoles without having to use an aryl carboxylic acid (Scheme 10.148).

Provided that bases with pK_a values around 6.6 are used, the yields of 2-arylbenzimidazole lie in the range 70–98%. This route is tolerant of various functional



Scheme 10.148

groups and complements the classical approaches where the required benzoic acid is not readily available [425].

The presence of a fused aromatic ring on the five-membered ring induces some modification of the reactivity.

As expected from the nature of the heterocyclic portion, nucleophilic reaction concerns essentially the five-membered ring in the lone reactive position, that is, 2. Conversely, electrophiles attack the benzenoid ring. The fused aryl ring appears to exhibit less aromatic stability than the hetero-ring, as evidenced by the easy oxidation of benzimidazole to imidazole-4,5-dicarboxylic acid, and by its catalytic reduction over platinum oxide to give 4,5,6,7-tetrahydrobenzimidazole.

Benzimidazole is subject to N-alkylation and N-acylation as imidazoles, although the benzene ring reduces the reactivity as well as the basicity (Section 10.5.1). Furthermore, the electron-withdrawing nature of the benzene ring increases the facility with which nucleophilic substitution occurs at C2.

Since most electrophilic substitution reactions involve Lewis acids it is the benzoazolium species that is involved and in this substrate it is the benzene ring that is the more reactive.

Only a few electrophilic substitutions take place at the C2 of benzoazoles, for example acylation in the presence of triethylamine (compare reactivity of 1,3-azoles, Section 10.4).

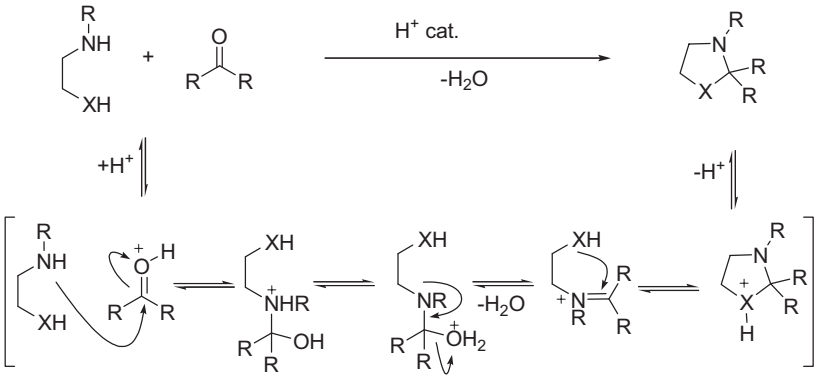
Sulfonation with oleum at 100 °C affords 4-, 6- and 7-benzothiazole sulfonic acids in the ratio 70 : 25 : 5%, respectively, while bromination at 100 °C in acetic acid gives 4,6-dibromobenzothiazole. Nitration of 2-methylbenzoxazole gives a 4 : 1 mixture of 6- and 5-nitro derivatives.

10.5.3
Tetrahydro-1,3-Azoles

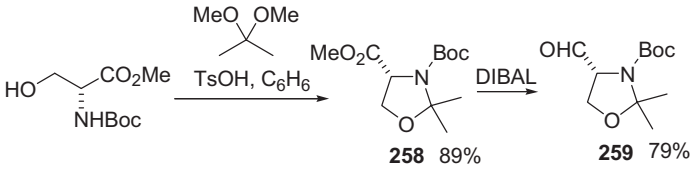
Imidazolines, oxazolidines, and thiazolidines are easily obtained by reactions of vicinal diamines, aminoalcohols and aminothiols, respectively, with carbonyl compounds (Scheme 10.149).

The typical condensation is conveniently conducted in boiling benzene with continuous removal of water [426] as described for the synthesis of oxazolidine **258**, which was then transformed into the Garner aldehyde **259** (a useful synthetic intermediate) (Scheme 10.150) [427].

However, the most recent syntheses can be achieved at rt. For example, imidazolidine **262** is obtained by simply reacting at rt the aldehyde **260** with the vicinal

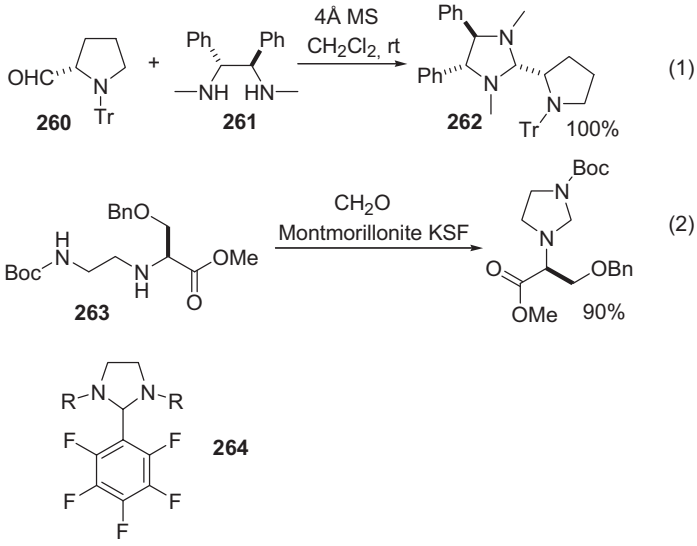


Scheme 10.149



Scheme 10.150

diamine **261** in the presence of molecular sieves [Scheme 10.151 (1)] [428]. In some cases less reactive substrates, such as **263**, may require activation, for example, the use of montmorillonite KSF [Scheme 10.151 (2)] [429].

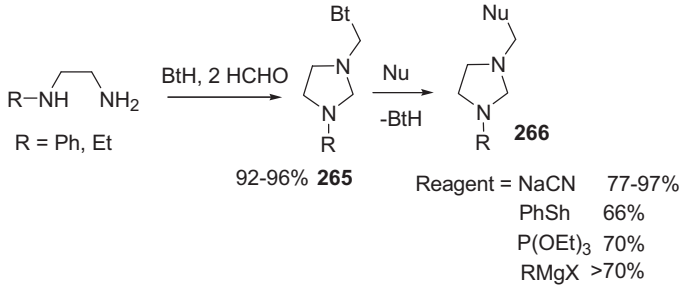


Scheme 10.151

Oxazolidines have also been obtained by these procedures [430], although an application to the production of a library of 96 oxazolidines through a parallel solid-phase synthesis required $MgSO_4$ as dehydrating agent and a temperature of 60 °C [431].

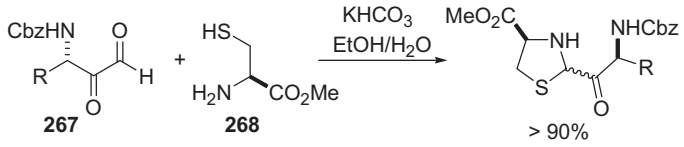
Particularly interesting is the synthesis under acid catalysis of substituted imidazolidines bearing a perfluorinated phenyl ring on C2, such as **264** (Scheme 10.151). On heating at temperatures ranging from 65 to 144 °C these compounds afford the corresponding carbene even the in absence of any transition metal [432].

The easy nucleophilic substitution of a benzotriazolyl group by C-nucleophiles allows the ready synthesis of unsymmetrical imidazolines. The process proceeds through Mannich reactions between 1,2-ethanediamines, benzotriazole (BtH) and formaldehyde at rt to produce imidazolidine **265**. Finally, reaction of **265** with different nucleophiles affords the products of general structure **266** (Scheme 10.152) [433].



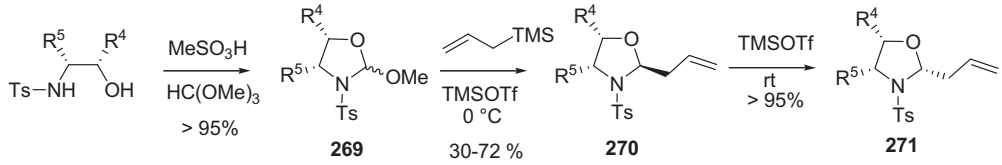
Scheme 10.152

Simple thiazolidine has been obtained by reacting at rt cysteamine hydrochloride with formaldehyde. Under these reaction conditions cysteamine can be replaced by aziridine and hydrogen sulfide [434]. Diastereomeric mixtures have obtained by reacting N-protected amino glyoxals **267** with L-cysteine methyl ester (**268**) (Scheme 10.153) [435].



Scheme 10.153

Several derivatives of carbonyl compounds can be used, such as acetals [436], hemiacetals [437], Schiff bases and orthoesters. The reaction of N-tosylaminoalcohols with orthoformates affords 2-methoxy-oxazolidines **269** that react with allyltrimethylsilane or trimethylsililenolether at 0 °C in a zinc chloride or trimethylsilyl triflate-catalyzed reaction to afford new oxazolidine derivatives [438]. The kinetic derivative



Scheme 10.154

270 isomerizes to the all-cis oxazolidine **271** when treated at room temperature with TMSOTf (Scheme 10.154).

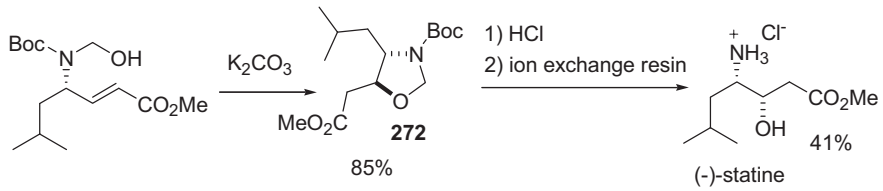
Similar reactivity is found with titanium enolates [439].

Similar substrates, in the enantiopure form, have been obtained in the solid phase by reaction of enantiopure aminoalcohols with solid-supported aldehydes and subsequent reaction with a sulfonyl chloride [440].

A new procedure for the formation of oxazolidines derived from ketones has been reported. It is based on the use of isopropoxytrimethylsilane and a catalytic amount of trimethylsilyl trifluoromethanesulfonate and has found application in the synthesis of a polymer-supported oxazolidine aldehyde [441].

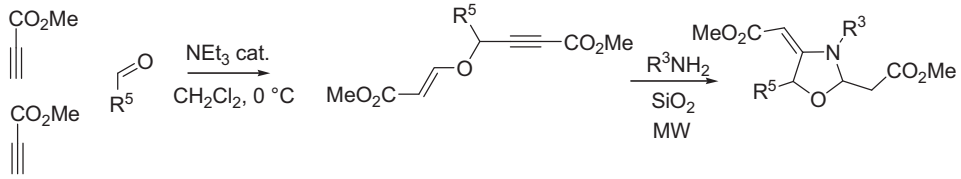
A vicinal aminoalcohol moiety is a perfect starting point for the construction of an oxazolidine ring; however, if the oxazolidine ring is built up in a different manner, hydrolysis of the ring is an efficient way to obtain aminoalcohols in stereoselective fashion.

Intramolecular conjugate addition of the N-hydroxymethyl moiety onto an α,β-unsaturated ester affords the corresponding oxazolidine **272** with high stereoselectivity. Finally, the oxazolidine ring was cleaved (Scheme 10.155) [442].



Scheme 10.155

Recently, a novel MCR has been developed using four components for the synthesis of highly substituted 1,3-oxazolidines. The reaction may be catalyzed by transition metals; however, the use of microwaves can efficiently substitute the metal catalysis (Scheme 10.156) [443].



Scheme 10.156

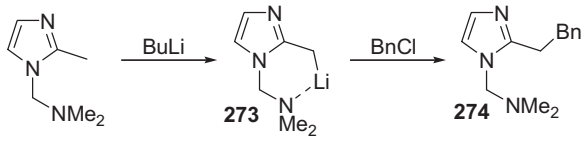
10.5.4
Alkyl-1,3-Azoles

The synthesis of alkyl-1,3-azoles is described throughout Section 10.3, for this reason this short section will deal only with the most characteristic reactivity of the alkyl residues linked to the heteroaromatic nuclei.

Alkyl groups attached to heterocyclic systems undergo many of the same reactions as those on benzenoid rings. For example, free radical bromination with NBS is often performed on these substrates. Bromination with NBS of 2-alkylthiazoles affords α-dibromothiazoles in good yields. The hydrolysis of these compounds leads to 2-acylthiazoles [444]. The side chains can, under certain circumstances, be oxidized. For example, methyl thiazoles with SeO_2 give thiazolecarbaldehydes but oxazole derivatives cannot be easily oxidized since the oxazole itself is reactive towards strong oxidants. However, it is stable to the Sharpless oxidation conditions with certain precautions [445].

In addition to these reaction, alkyl groups in the 2-positions of imidazole, oxazole and thiazole rings show reactivity that results from the easy loss of a proton from the carbon atoms of the alkyl group adjacent to the ring [compare Scheme 10.1 (2)]. Very strong bases, such as sodamide, LDA or butyllithium convert 2-methyl-oxazole and -thiazole and 1,2-dimethylimidazole essentially completely into the corresponding anions, although this transformation is not always straightforward since it is very sensitive to reaction conditions and the nature of the substituents [446].

Butyllithium reacts with 1,2-dimethylimidazole at −80 °C to lithiate the 2-methyl group, but at higher temperatures some 5-metalation also occurs [447], while treatment with LDA at −78 °C gives 84 % of 2-methyllithiation and 18% of 5-lithiation [448]. Much better control was obtained with 1-dimethylaminomethyl-2-methyl-imidazole, which was converted by butyllithium into the stabilized anion **273**, which reacted with benzyl chloride to form **274** (Scheme 10.157) [449].



Scheme 10.157

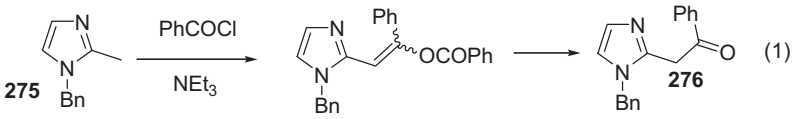
BuLi reacts at −78 °C with 2-methylthiazole to give a mixture of 2-lithiomethyl and 5-lithio derivatives in a ratio of 1 : 4 [450], while when the 2-position is blocked 4-or 5- methyl groups can be lithiated [451]. These anions all react readily even with mild electrophilic reagents; thus the original alkyl groups can be modified through alkylation, acylation, carboxylation and reaction with aldehydes [452].

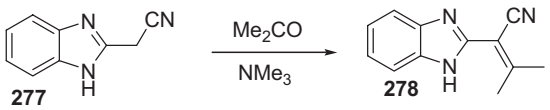
Extremely useful are the reactions of alkyl-1,3-azoles in which traces of the reactive anion is involved.

In aqueous or alcoholic solutions, many 2-alkyl-1,3-azoles react with bases to give traces of anions. With suitable electrophilic reagents these anions undergo reasonably

rapid and essentially non-reversible reaction. 2-Methyl and 2-ethylbenzothiazoles condense with aromatic aldehydes at room temperatures in 50% aqueous sodium hydroxide under phase-transfer catalysis conditions to afford secondary carbinols [453], while 2-methyl thiazole heated at 150°C with $ZnCl_2$ and benzaldehyde gives the styryl derivatives. To confirm the peculiar reactivity of the 2-alkyl group, neither 4- nor 5-methyl thiazole undergo such condensation.

1-Benzyl-2-methylimidazole **275** reacts with benzoyl chloride in the presence of a tertiary amine to give the phenacyl derivative **276**, but with 1-benzyl-5-methylimidazole the product is the 2-benzoyl derivative due to the substitution at C2 (Section 10.4.1.2) [454]. The reaction has also been extended to 2-methylimidazole [Scheme 10.158 (1)] [455].



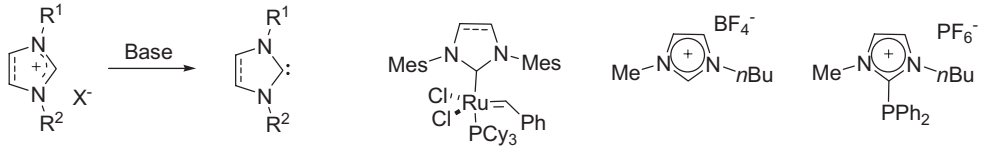


Scheme 10.158

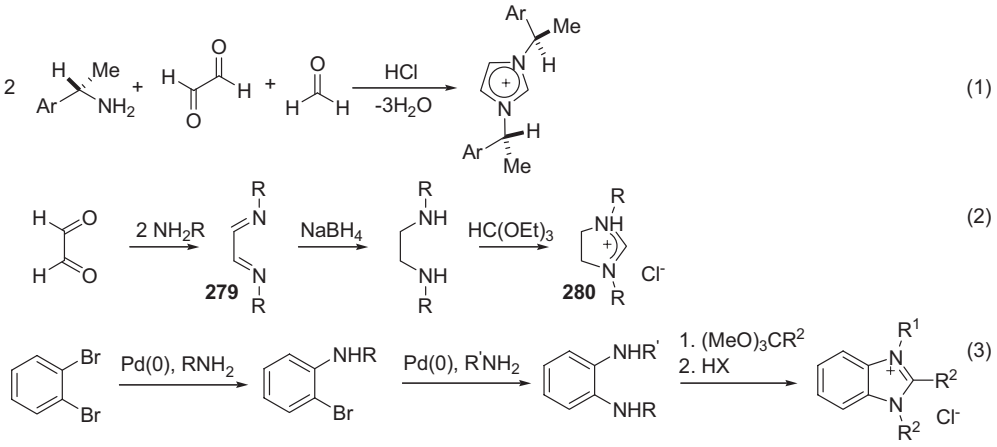
The presence of other activating group makes the condensation reaction even easier. In the presence of trimethylamine, 2-cyanomethylbenzimidazole (**277**) condenses with acetone to give the unsaturated derivative **278** [Scheme 10.158 (2)] [456].

10.5.5
Quaternary 1,3-Azolium Salts

In the past literature methods for the synthesis of azolium and azolinium salts have generally focused on N-alkylation reactions (Section 10.4.1.1). However, these reactions are limited to reactive halides and are inappropriate for introduction of chiral substituents. Since this class of compounds has very important applications, new general synthesis of them are of substantial interest. In this context, imidazolium salts are precursors of carbene ligands used for the synthesis of metathesis catalysts [457] and have been used also as ionic liquids (Scheme 10.159) [458].



Scheme 10.159



Scheme 10.160

Chiral imidazolium salts have been synthesized in one step (Scheme 10.160). Starting from racemic amines the *meso*-forms were produced. In contrast, only the C_2-symmetric imidazolium salts are formed when enantiomerically pure amines are employed [Scheme 10.160 (1)] [459].

In a similar reaction, starting from glyoxal, 1,3-diarylimidazolium chlorides are obtained in a three-step sequence via the diimine **279**, which is then reduced. Finally, cyclization of the diamines afforded the imidazolinium salt **280** [Scheme 10.160 (2)] [460].

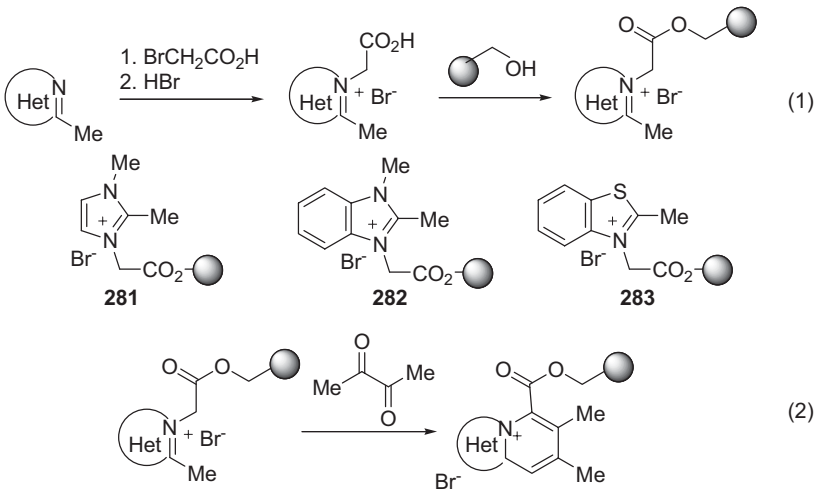
Benzimidazolium salts have been prepared through a subsequent Buchwald–Hartwig amination and ring closure. This method is suitable for the preparation of 2-substituted salts and benzimidazolium salts that bear chiral substituents on one or both the nitrogen atoms [Scheme 10.160 (3)] [409].

Solid-supported azolium and benzoalium salts have been prepared. Azole derivatives react with bromoacetic acid to give azolium acetic acids that have been anchored to a Wang resin [Scheme 10.161 (1)].

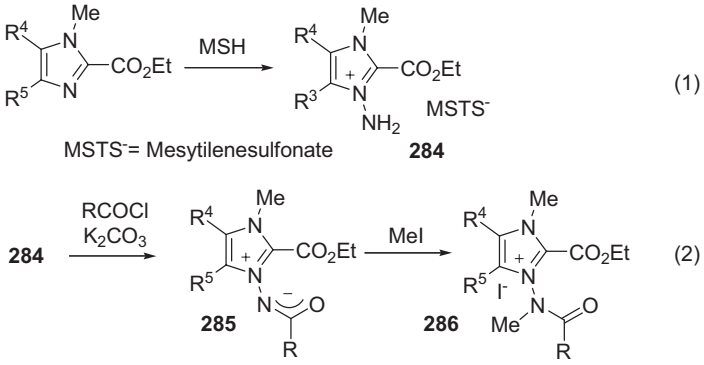
Compounds **281**–**283** have been employed in the Westphal reaction, obtaining cycloiminium salts [Scheme 10.161 (2)].

The synthesis of 1-amino-3-alkylimidazolium **284** [461] and *N*-imidazolium-*N*-methyl-amides **286** [462] has been reported. In the first case, the salts are obtained by direct amination of the corresponding alkoxycarbonylazoles using mesitylenesulfonylhydroxylamine (MSH) as the aminating agents (Scheme 10.162).

In the second case, the amino derivatives **284** are acylated with acyl chlorides, and the resulting betaines **285** are alkylated with methyl iodide to give the salts **286**. Azolium *N*-aminides **287**, generated from the corresponding salts in the presence of *N*-ethyldiisopropylamine, and cycloimmonium N-ylides are 1,3-dipoles, usually involved in 1,3-dipolar cycloaddition reactions (Figure 10.12) [463]. 2-Alkyl- and 2-amino-substituted structures **288** have the potential to function as 1,4-dinucleophiles through deprotonation and can react



Scheme 10.161



Scheme 10.162

with 1,2-dicarbonyl compounds to afford a great variety of derivatives [464]. 2-Alkoxycarbonylazolium *N*-ylides-*N*-aminides **289** are species that have the potential to act as efficient 1,4-dipole equivalents when they react with heterocumulenes such as iso(thio)cyanates and carbodiimides [465].

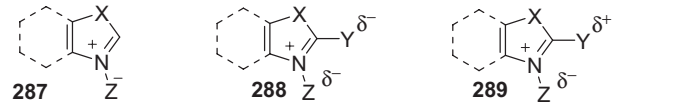
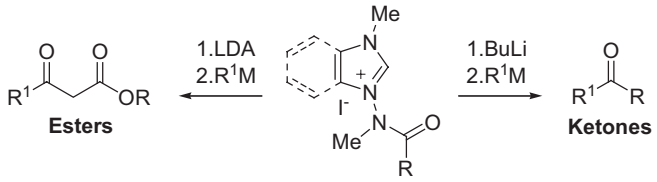


Figure 10.12

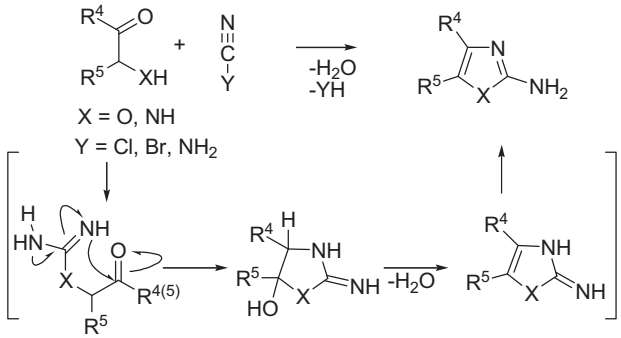


Scheme 10.163

N-Imidazolium-*N*-methylamides and bis-amides behave as highly selective acylating reagents towards organometallics, leading to ketones [462] and diketones. The metallation of alkoxycarbonyl-*N*-imidazolium-*N*-methyl amides with LDA followed by the addition of a Grignard reagent affords 4-oxo and homologous esters (Scheme 10.163).

10.5.6
Oxy- and Amino-1,3-Azoles

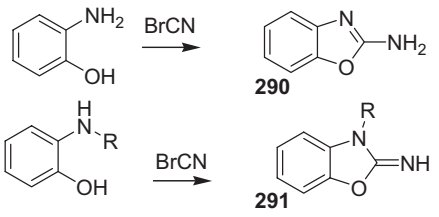
Cyanogen chloride (or bromide) as well as cyanamide are the reagents of choice for the synthesis of 2-aminoderivatives. These reagents have found application in the synthesis of the simple heterocycles as well as their benzofused derivatives by reaction with α-hydroxy [466] or α-amino ketones (an extension of the Marckwald synthesis in which cyanamide replaces cyanate, thiocyanate and isothiocyanate as a counterpart of α-aminoaldehydes or ketones) (Scheme 10.164) [467, 468].



Scheme 10.164

An application of this routes allows the synthesis of 2-aminoimidazole-containing natural products, demonstrating the usefulness and power of this methodology [469]. Another application of cyanogen chloride (or isocyanide dichlorides) for the synthesis of 2-aminoimidazoles is the reaction with DAMN, in which the nucleophilic addition of DAMN proceeds through a mechanism analogous to that reported above [470].

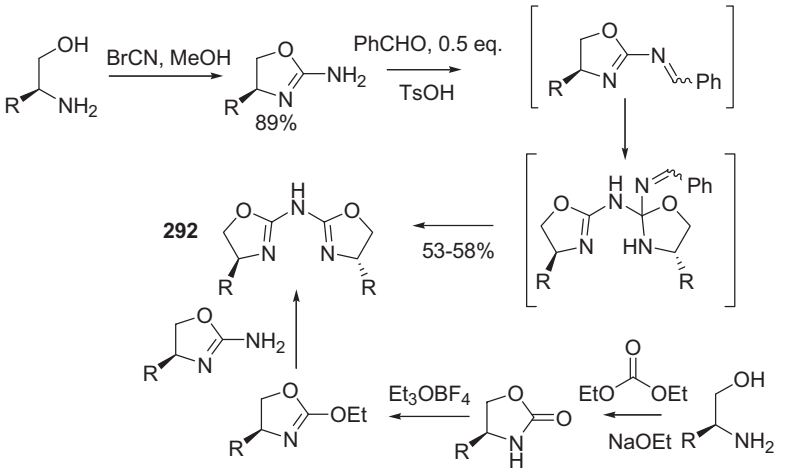
The reaction of *o*-aminophenols with cyanogen bromide or cyanamide affords 2-aminobenzoxazoles **290** or benzoxazoleimines **291**; yields are high and the general method can be adopted to give 2-substituted amino derivatives (Scheme 10.165).



Scheme 10.165

Alternatively, the reactivity of 2-bromo derivatives towards amines in the presence of CuBr can be used as well as the direct nucleophilic amination of benzimidazole by sodium amide.

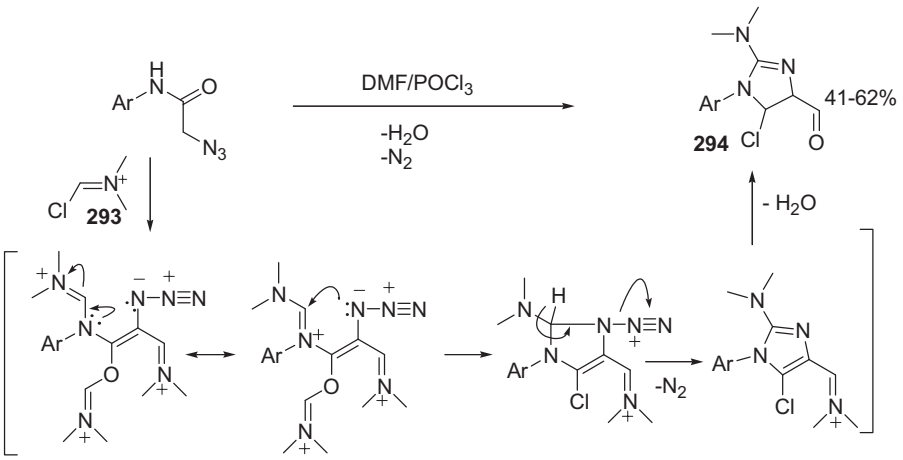
The reaction of a β-aminoalcohol with BrCN affords the correspondent 2-amino-oxazoline, whose reactivity is nicely exploited in the synthesis of the bis-oxazoline **292** (Scheme 10.166) [471].



Scheme 10.166

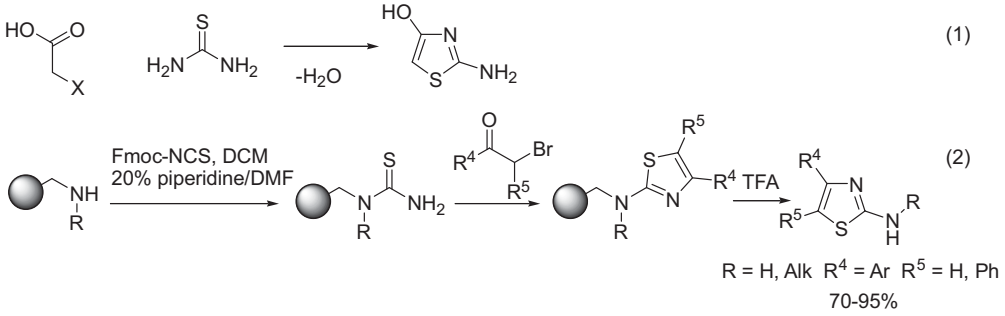
The cycloaddition of azides across a double bond provides another method of imidazole preparation. In this reaction an iminium species, **293**, generated *in situ* under Vilsmeier conditions, attacks an azide functionality [472]. The method is intrinsically limited to 2-dimethylamino substituted imidazoles **294** (Scheme 10.167).

A variation of the Hantzsch procedure uses thiourea with α-halocarbonyl compounds to produce 2-aminothiazoles, while α-halocarboxylic acids afford the correspondent 2-amino-4-hydroxythiazoles [Scheme 10.168 (1)].



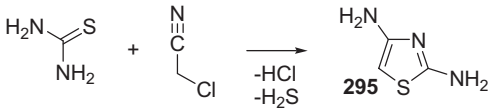
Scheme 10.167

This reaction has found application for the development of a solid-supported synthesis of 2-aminothiazole using the amino group as a convenient, traceless point of attachment to acid-sensitive resins [Scheme 10.168 (2)] [473].



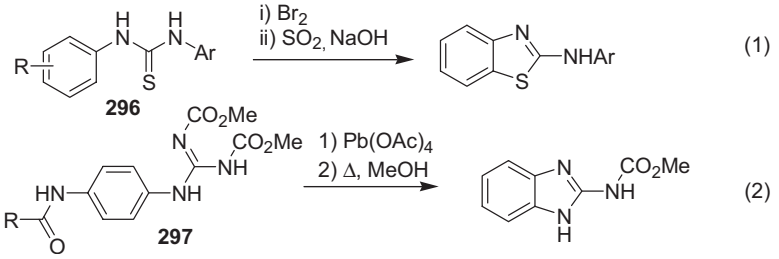
Scheme 10.168

2,4-Diaminothiazole (**295**) can be prepared by the reaction of thiourea with chloroacetonitrile (Scheme 10.169).



Scheme 10.169

Mono-, di-, and tri-substituted arylthioureas **296** are very easily cyclized to 2-aminobenzothiazoles by the action of bromine in a solvent such as $CHCl_3$, CCl_4

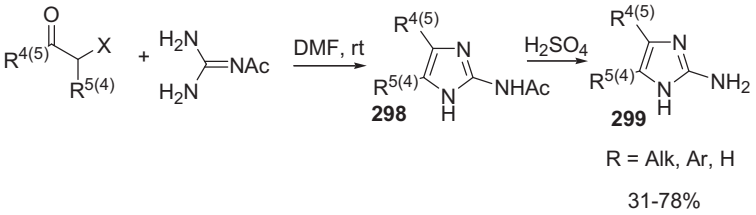


Scheme 10.170

(Hugershoff's method) followed by a treatment with SO_2 and with a base [Scheme 10.170 (1)].

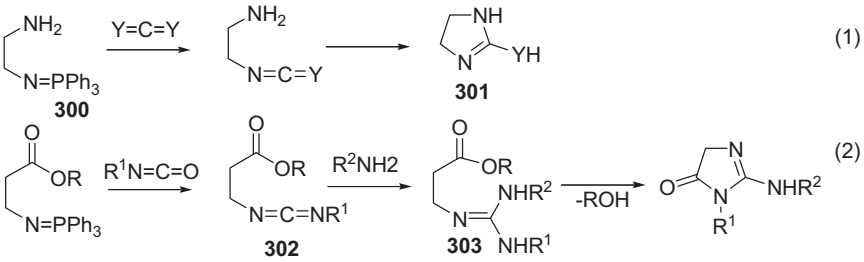
Under oxidative or acidic conditions, or merely by heating the reagents, appropriately functionalized guanidines **297** cyclize to 2-aminobenzimidazoles [Scheme 10.170 (2)] [474].

A variation of the Hantzsch synthesis has been introduced for the preparation of 2-aminoimidazoles using α-haloketones and *N*-acetylguanidines to afford the corresponding 4(5)-substituted *N*-(1*H*-imidazol-2-yl)acetamides **298**. These compounds are then hydrolyzed to their corresponding 2-aminoimidazoles **299** (Scheme 10.171) [475].



Scheme 10.171

Iminophosphoranes have found several applications in the synthesis of 2-aminoimidazole derivatives and particularly for the synthesis of natural product [476]. Aza-Wittig-type reactions of properly substituted iminophosphorane **300** with CO_2, isocyanates or isothiocyanates afford heterocumulenes that undergo

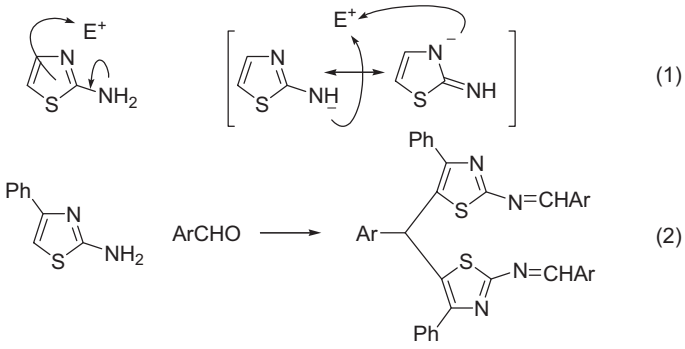


Scheme 10.172

nucleophilic attack of the amino group to give the five-membered heterocycles **301** [Scheme 10.172 (1)].

A variation to this method is the use of azido esters in combination with isocyanates. The intermediate carbodiimide **302** reacts with a primary amine to afford the guanidine derivative **303** that finally cyclizes on the ester group [Scheme 10.172 (2)] [476].

Concerning the reactivity of 2-aminoazoles, some general points can be made. In aminoazoles with the amino group α to C=N, the imino resonance structure justifies the increased reactivity of the pyridine-like nitrogen atom towards electrophilic reagents, but decreases that of the amino group. Consequently, protons, alkylating agents and metal ions usually react with amino azoles at the annular nitrogen. This is exemplified by the behavior of 2-aminothiazole. If the thiazole reacts in its neutral form, the ring nitrogen atom is the more reactive center, except when bulky substituents are present at the C4 position. If the thiazole reacts in the form of its conjugate base, the ambident anion leads to a mixture of products resulting from N-ring and N-exocyclic reactivity [Scheme 10.173 (1)].



Scheme 10.173

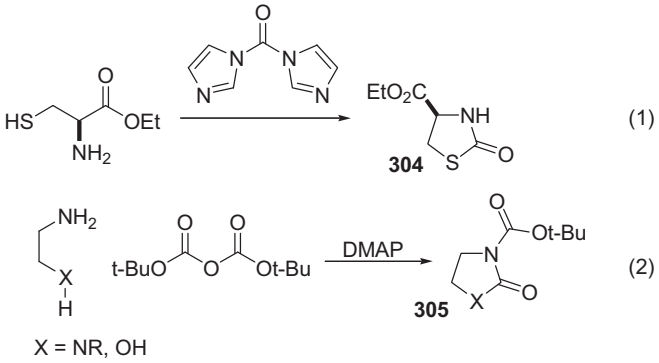
Under mild conditions, 2-aminothiazoles react at their exocyclic nitrogen atom with aromatic aldehyde, yielding Schiff bases. Under more forcing conditions, however, the 5 position can also react [Scheme 10.173 (2)].

Acylation of 2-, 4- and 5-aminothiazoles takes place on the exocyclic nitrogen atom. Acetic anhydrides acetylate aminothiazoles and benzothiazoles on the exocyclic nitrogen atom. The reaction of 2-aminothiazoles with alkyl or aryl isocyanates or isothiocyanates gives the corresponding thiazolylureas or thioureas.

Alkylation of Δ^4-thiazolin-2-ones may yield O−R or N−R derivatives according to experimental conditions. With diazomethane in ethanol, *O*-methylation takes place whereas *N*-methylation occurs when a basic solution of the thiazolinone reacts with methyl iodide. Alkylation of 2-amino imidazole occurs at the exocyclic N atom.

Azolidin-2-ones are popular tools in asymmetric synthesis and as synthetic intermediates, and new methods for their synthesis are described in the literature. Azolidin-2-ones are commonly prepared from aminoalcohols, vicinal diamines and aminothiols by incorporation of a carbonyl unit. Additions to the list of reagents that effect the transformation are bis(trichloromethylcarbonate) [477, 478] and

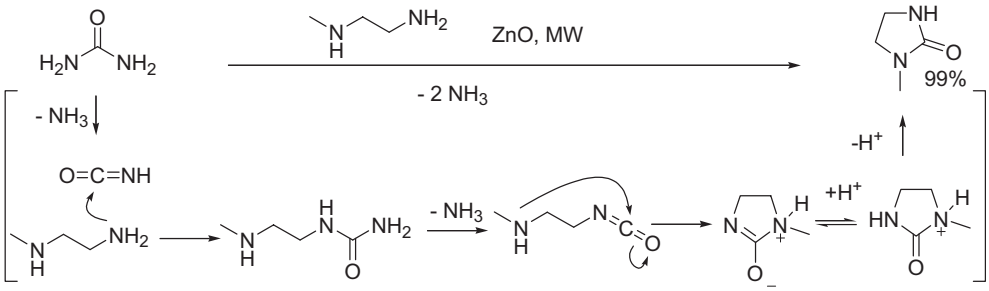
trichloromethyl chloroformate [479], which offer the advantages of easier handling and reduced risk of exposure compared to phosgene [480]. Another reagent of choice is carbonyldiimidazole, which by reaction with cysteine affords derivative **304** [Scheme 10.174 (1)] [481].



Scheme 10.174

Vicinal aminoalcohols and diamines react with Boc_2O/DMAP to afford the corresponding azolidinones **305** substituted on the N atom with Boc groups, while aminothiols are less efficient in this transformation [Scheme 10.174 (2)] [482].

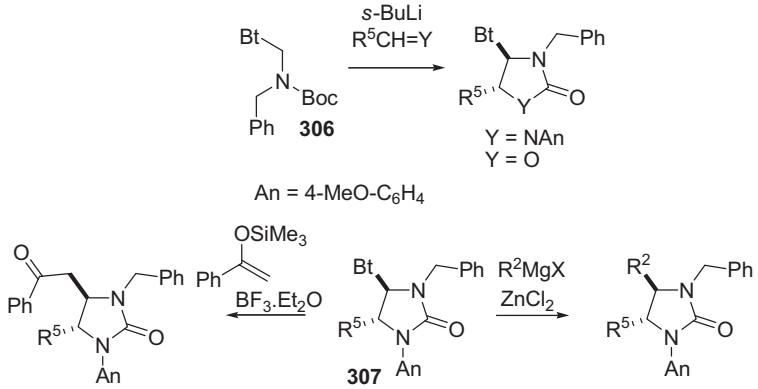
A recent method for the effective synthesis of imidazolidinones and oxazolidinones is MW irradiation. The proposed mechanism is shown in Scheme 10.175 [483].



Scheme 10.175

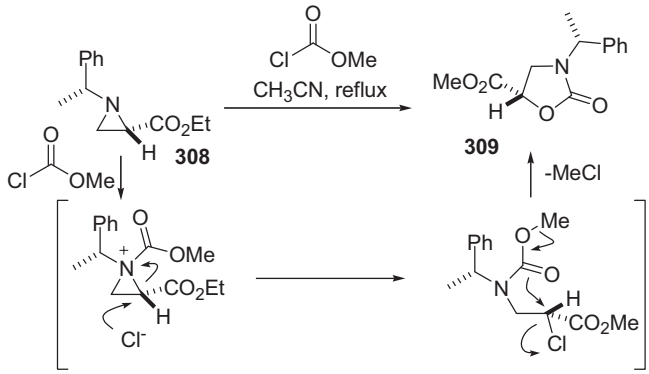
The ability of the benzotriazole nucleus to act as a good leaving group has found another application in the synthesis of polysubstituted imidazolidinones. Treating amine **306** with *s*-BuLi and subsequently with an aldimine or an aldehyde, affords imidazolidinones or oxazolidinones bearing a benzotriazolyl group on C4.

With imidazolidinones **307** it is possible to substitute the benzotriazolyl group with various *C*-nucleophiles to obtain differently substituted imidazolinones (Scheme 10.176) [484].



Scheme 10.176

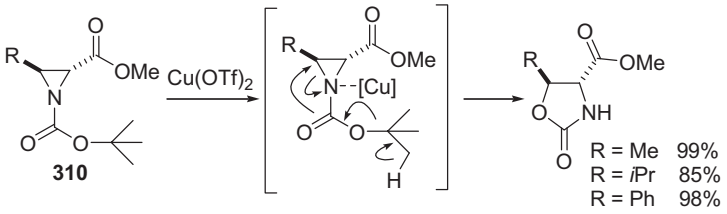
Aziridines in the presence of Lewis acids rearrange to afford substituted oxazolidinones. This approach has found interesting application for the production of enantiopure 4- and 5-carboxymethyl oxazolidinones, which are important precursors for the synthesis of amino acid analogs or as starting material for the synthesis of natural products. In the first case, aziridine **308** was treated with methyl chloroformate to afford the corresponding oxazolidinone **309** with retention of configuration on the reacting stereocenter due to a double inversion of configuration as described in Scheme 10.177 [485].



Scheme 10.177

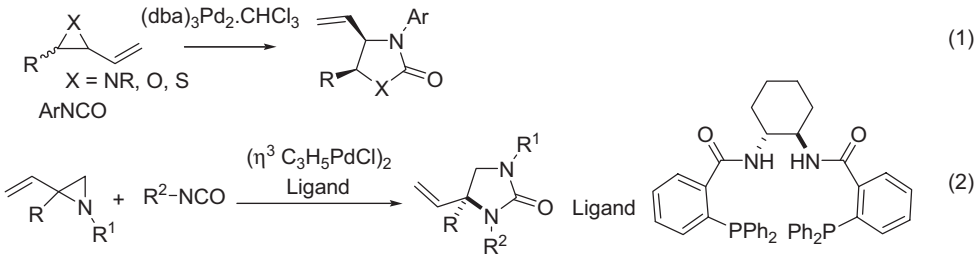
In contrast, treating aziridine **310** with Lewis acids induces a rearrangement in which it is the carbonyl group of the carbamoyl moiety, activated by the exit of

isobutene, that induces the enlargement of the three-membered ring (Scheme 10.178) [486].



Scheme 10.178

The reaction of vinyl epoxides with aryl isocyanates is facilitated by Pd catalysis [487]. The intermediate π-allyl complex equilibrates to afford stereoselectively the cis derivative from either isomer of the epoxide [Scheme 10.179 (1)].



Scheme 10.179

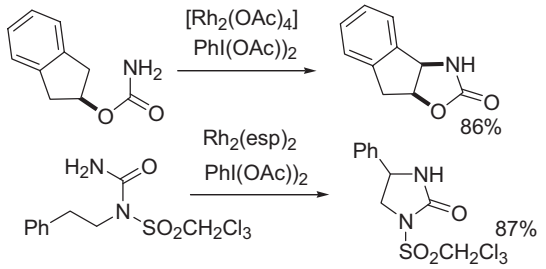
The same reactivity has been extended to aziridines [488] and to thiiranes [489]; for every substrates the enantioselective version of the transformation has also been described [Scheme 10.179 (2)].

Oxazolidinones can be obtained also through a palladium-catalyzed oxidative carbonylation of β-aminoalcohols [490]. In an analogous procedure vicinal diamines are converted into imidazolidinones through an oxidative carbonylation catalyzed by $W(CO)_6$ [491].

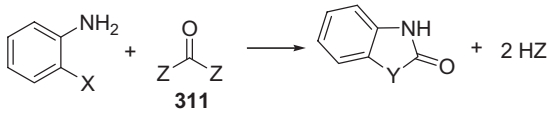
Particularly important, especially for the breakthrough that it allowed in the synthesis of tetrodotoxin [492], is the Rh-catalyzed C−H insertion reaction for the oxidative conversion of carbamates into oxazolidinones [493] and the more recent expansion to the synthesis of imidazolidines (Scheme 10.180) [494].

Some specific reported syntheses for the obtainment of benzo-1,3-azol-2-ones have found recent application. The most direct approach to these derivatives is the reaction of a 2-substituted aniline with the general reagent **311** (Scheme 10.181).

The reagent of general formula **311** stands for a series of different reagents in which the Z groups represents good leaving groups. For this reason, good reagents



Scheme 10.180

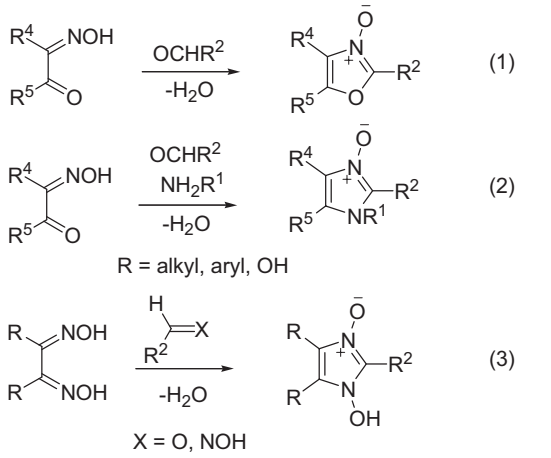


Scheme 10.181

are phosgene [495], urea [496],carbonyldiimidazole [497], dimethyl carbonate [498], *N,N*-diethylcarbamyl chloride and carbon dioxide [499].

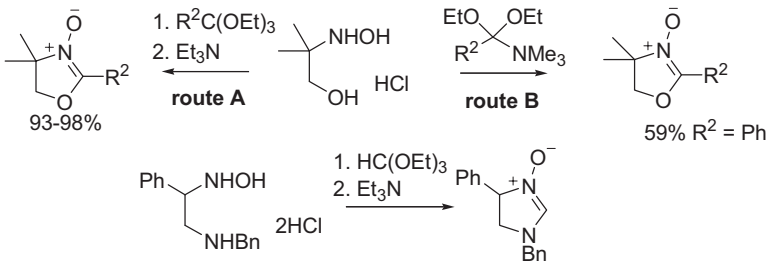
10.5.7
Azole N-Oxides and Azoline N-Oxides

Oxazole and imidazole N-oxides cannot be synthesized by oxygenation of oxazoles or imidazoles, respectively. The only method described for the synthesis of oxazole *N*-oxides is the condensation of monooximes of 1,2-dicarbonyl compounds with aldehydes in acidic medium [Scheme 10.182 (1)]. The aldehyde may be aromatic or aliphatic (including formaldehyde) and the oxime may be derived from an aromatic



Scheme 10.182

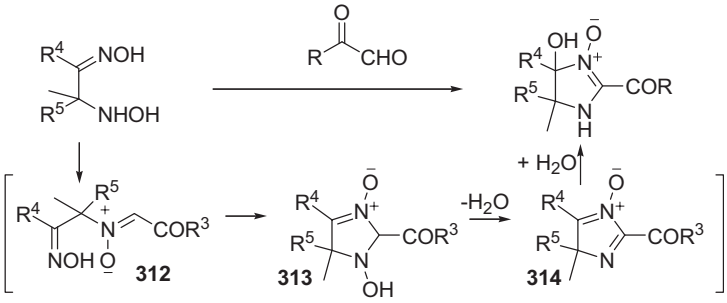
diketone or it may be an α-keto aldoxime, leading to a 2,5-disubstituted oxazole *N*-oxide. For imidazole N-oxides the most common approach is the condensation of an α-oximinoketone with an aldehyde and a primary amine. The use of an hydroxylamine in this condensation [Scheme 10.182 (2)] or the reaction of the aldehyde oxime or aldehyde with a 1,2-dioxime [Scheme 10.183 (3)] afford 1-hydroxyimidazole-3-oxides.



Scheme 10.183

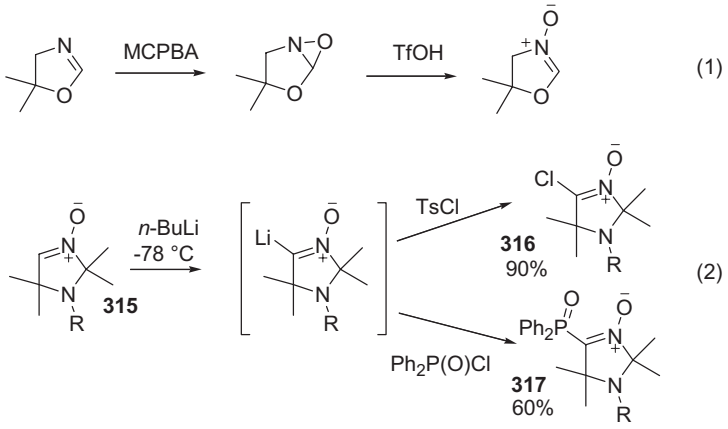
A similar method has been used for the synthesis of 4,5-dihydrooxazole-3-oxides (cyclic *C*-alkoxynitrones). In this case the condensation of an β-hydroxyamino alcohol hydrochloride with an ortho ester (Scheme 10.183, route A) [500] or an amide acetal (Scheme 10.183, route B) [501] affords the desired compound. 4,5-Dihydro-1*H*-imidazole-3-oxides (cyclic *C*-aminonitrones) have been prepared using route A with N-(2-aminoethyl)hydroxylamine dihydrochloride as starting material.

Treatment of 2-(hydroxyamino)alkan-1-one oximes with phenyl or methylglyoxal affords 4,5-dihydro-1*H*-imidazole 3-oxides. The reaction is occurs through the formation of intermediates **312–314** (Scheme 10.184).



Scheme 10.184

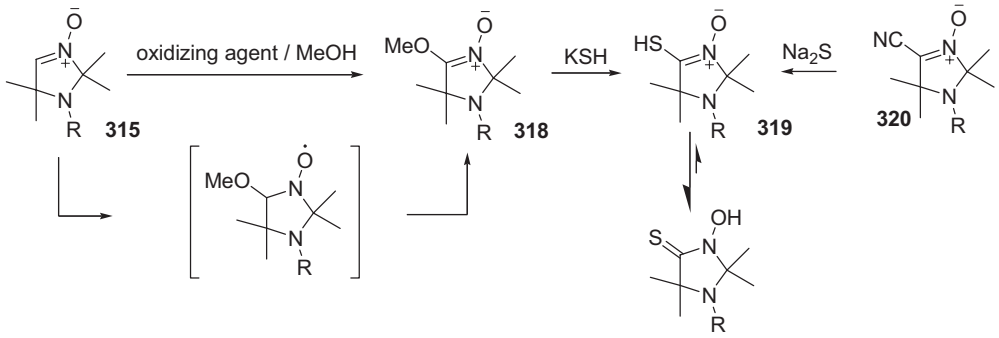
On the other hand, oxidation of 4,5-dihydrooxazoles with 3-chloroperoxybenzoic acid (MCPBA) produces oxaziridines that undergo isomerization to the corresponding nitrones upon treatment with trifluoromethanesulfonic acid (TfOH) [Scheme 10.185 (1)] [502].



Scheme 10.185

Lithiation of **315** followed by treatment with 4-toluensulfonyl chloride or diphenylphosphoryl chloride [503] affords the *C*-chloronitrone or the *C*-phosphorylnitrone, **316** and **317**, respectively [Scheme 10.185 (2)].

Oxidation of **315** in methanol with lead(IV) acetate or manganese(IV) or lead(IV) oxides affords predominantly the corresponding *C*-methoxynitrones **318** [504], which react with potassium hydrosulfide to afford the thiohydroxamic acids **319** [505]. Compound **319** has also been obtained by treatment of the nitrone **320** with sodium sulfide (Scheme 10.186) [506].



Scheme 10.186

Finally, the reactivity of azole-*N*-oxides is somewhat similar to that of the azolonium ions, particularly when the cationic species is involved. In the case of imidazoline-*N*-oxides (cyclic *C*-amino nitrones) and oxazoline-*N*-oxides (cyclic *C*-hydroxy nitrones) the reactivity is well known. These compounds are versatile synthetic intermediates that readily undergo 1,3-dipolar cycloaddition [507] and addition of nucleophiles [508] and are also useful as radical spin traps [509].

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11
Five-Membered Heterocycles with Two Heteroatoms: O and S Derivatives

David J. Wilkins

11.1
Introduction

A general review of chemistry for all the derivatives described in this chapter covering the period up to 1995 can be found in *Comprehensive Heterocyclic Chemistry* first edition (Volume 6) and second edition (Volume 3).

11.2
1,2-Dioxoles and 1,2-Dioxolanes

11.2.1
Introduction

Most work on 1, 2-dioxole systems has been on derivatives of the fully saturated 1, 2-dioxolane (**1**) and as cyclic peroxides these have been the subject of three major reviews [1–3]. 1,2-Dioxoles are unstable and they have only been detected spectroscopically at temperatures below −60 °C [4].

1

11.2.2
Relevant Physicochemical Data

11.2.2.1 NMR Spectroscopy

^{1}H and ^{13}C NMR data for *trans*- and *cis*-3, 5-dimethyl-1,2-dioxolane **2**, **3** have been published [5]; proton resonances appear (in ppm) at $\delta_H = 4.25$ cis and 4.3 trans for H3, at $\delta_H = 2.77$ cis and 2.19 trans for H4, and at $\delta_H = 4.25$ cis and 4.30 trans for H5.

Modern Heterocyclic Chemistry, First Edition.
Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.

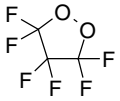
The cis and trans isomers are readily identified by ^{13}C NMR, which shows cis δ 19.25 Me, 49.34 C4 and 77.30 C3,5; trans δ 18.40 Me, 48.61 C4 and 77.04 C3,5.

2

3

11.2.2.2 Electron Diffraction Studies

Electron diffraction has been used to obtain the following dimensions for the heterocyclic ring of perfluorinated 1,2-dioxolane (**4**) [6]: O−O, 1.443 Å; C−O, 1.377 Å and C−C, 1.531 Å; C−C−C, 98.1°; C−C−O, 107.3° and C−O−O, 102.9°.

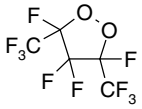


4

11.2.3 Synthesis

11.2.3.1 Synthesis by Ring Construction

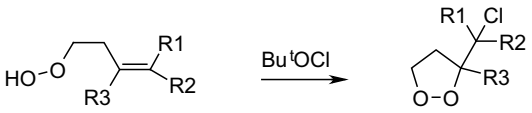
Oxidative addition of elemental fluorine to appropriate 1, 3-dicarbonyl compounds provides a convenient synthesis of perfluorinated 1,2-dioxolanes. Compound **4** can be synthesized by treatment of difluoromalonyl difluoride with fluorine [6] and **5** is similarly prepared from either hexafluoroacetylacetone or the copper(II) or nickel(II) chelate of trifluoroacetylacetone [7].



5

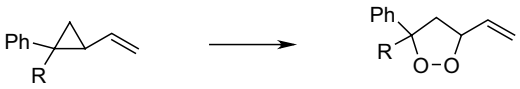
Several studies have appeared on the formation of 1, 2-dioxolanes either by *endo* cyclization of allylic hydroperoxides [8] or by *exo* cyclization of homoallylic hydroperoxides upon treatment with various electrophilic reagents [9]. For example, cyclization of the homoallylic peroxide **6** with Bu^{t}OCl affords the 1, 2-dioxolane **7** (Scheme 11.1) [10].

Photooxygenation of arylcyclopropanes **8** (R = Ph) provides direct access to the corresponding 1,2-dioxolanes **9** (R = Ph), although the reaction is non-stereospecific [11]. The addition can also be radical mediated, as in the conversion of **8** (R = H) to **9** (R = H) by treatment with O_2 in the presence of PhSeSePh and AIBN (Scheme 11.2) [12].



6 **7**

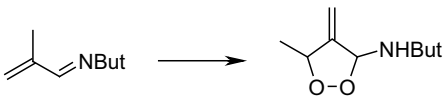
Scheme 11.1



8, R = H or Ph **9, R = H or Ph**

Scheme 11.2

α,β-Unsaturated imines **10** react directly with singlet oxygen to give 3-amino-1,2-dioxolanes **11** (Scheme 11.3) [13].

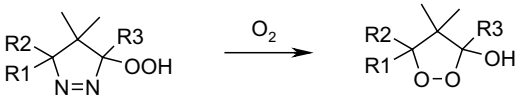


10 **11**

Scheme 11.3

11.2.3.2 Ring Transformations of Heterocycles Leading to 1,2-Dioxoles and 1,2-Dioxolanes

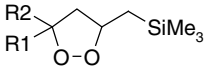
3-Hydroperoxypyrazolines **12** react readily with oxygen with the loss of N_2 to give 3-hydroxy-1,2-dioxolanes **13** (Scheme 11.4) [14].



12 **13**

Scheme 11.4

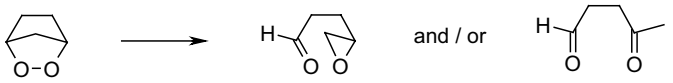
Lewis acid treatment of 1,2,4-trioxolanes gives metallated carbonyl oxides that may be trapped by cycloaddition to allylsilanes to give 1,2-dixolanes **14** [15].



14

11.2.4
Reactivity of 1,2-Dioxoles and 1,2-Dioxolanes

Solution thermolysis of the bicyclic dioxolane **15** gives epoxy aldehyde **16** in non-polar solvents and the diketone **17** in polar solvents [16]. Flash vacuum pyrolysis of **15** at 450 °C and 10^{-3} Torr gave only **16** [17]. Monocyclic dioxolanes such as **18** [17] and **19** [18] give under similar conditions a mixture of epoxide and carbonyl compounds (Scheme 11.5).



15 **16** **17**

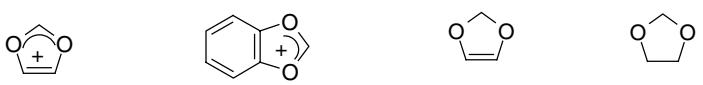
18 **19**

Scheme 11.5

11.3
1,3-Dioxoles and 1,3-Dioxolanes

11.3.1
Introduction

There has been relatively little work published on the fully conjugated system, 1,3-dioxolium salts **20** and their benzo analogues **21**, but there are reviews on these compounds [19, 20]. More recently a comprehensive review chapter on 1,3-dioxolium salts has appeared [21]. A much larger volume of work has been published on 1,3-dioxoles **22**, although most work published in this area is on the fully saturated compounds, 1,3-dioxolanes **23**. A major review of these compounds has been published [22].



20 **21** **22** **23**

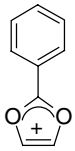
Table 11.1 X-ray structural data for **24**.

Bond length (Å)				
O1–C2	C2–O3	O3–C4	C4–C5	C5–O1
1.281	1.282	1.472	1.505	1.480
Internal angle (°)				
O1	C2	O3	C4	C5
108.1	103.4	103.1	108.6	116.8

11.3.2 Relevant Physicochemical Data

11.3.2.1 X-Ray Diffraction Studies

X-Ray diffraction studies on the 1,2-dioxolan-2-yl cation **24** have given molecular dimensions (Table 11.1). The data show the structure to be essentially planar at C2 [23].



24

11.3.2.2 NMR Spectroscopy

Table 11.2 presents the ^{1}H NMR spectra of 1,3-dioxolane derivatives.

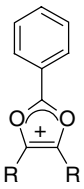
^{13}C NMR data for 1,3-dioxolium salts **24**–**26** and 1,3-dioxolane **27** are shown in Table 11.3. The high frequency for C2 signals in 1,3-dioxolium salts is notable when compared to the dioxolane **27**.

Table 11.2 ^{1}H NMR data for ring protons of 1,3-dioxolane derivatives.

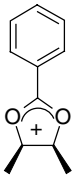
Compound	δ_H (ppm)			
	2H	4H	5H	Reference
4,4-Dimethyl-1,3-dioxolane	4.9		3.51	[24]
2-Imino-1,3-dioxolane		4.40	4.40	[25]
cis-2,2,4,5-Tetramethyl-1,3-dioxolane		4.15	4.15	[26]
trans-2,2,4,5-Tetramethyl-1,3-dioxolane		3.38	3.38	[26]

Table 11.3 ^{13}C NMR data for ring carbons of 1,3-dioxole derivatives.

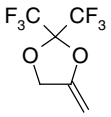
Compound	δ_C (ppm)			
	C2	C4	C5	Reference
24	174.7	146.6	146.6	[27]
25	175.4	147.9	147.9	[27]
26	181.9	90.6	90.6	[27]
27	101.5	153.2	69.1	[28]



24, R = Ph
25, R = Me



26



27

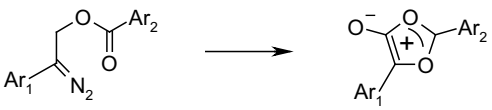
^{17}O NMR studies have been carried out on 1,3-dioxolanes **28** and a few simple derivatives. The chemical shift for the parent compound has been given variously as δ_O (with respect to $H_2{}^{17}O$): $+34$ [29], $+35.8$ [30] and $+34.8$ [31].

28

11.3.3 Synthesis

11.3.3.1 Synthesis by Ring Construction

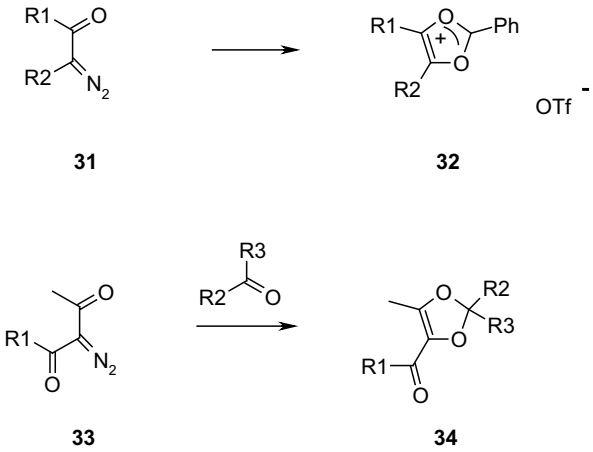
1,3-Dioxolium salts have been prepared from α-diazoanhydrides **29** by palladium-catalyzed decomposition to give a carbene intermediate that undergoes electrocyclization to give **30** (Scheme 11.6) [32].



29 **30**

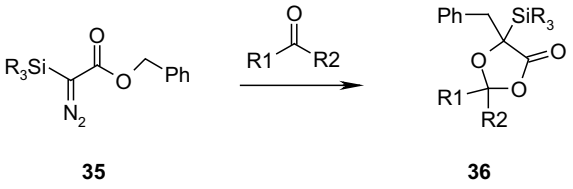
Scheme 11.6

Other methods that involve the decomposition of diazo compounds include the reaction of the diazoketone **31** with $PhCO_2Tf$ to afford the diazolium salt **32** [27] and the copper-catalyzed decomposition of the 2-diazo-1,3-dicarbonyl compound **33**, which in the presence of aldehydes or ketones gives 4-acyl-1,3-dioxoles **34** (Scheme 11.7) [33].



Scheme 11.7

Rhodium-catalyzed reaction of the diazo esters **35** with carbonyl compounds, R^1COR^2, provides a new route to silyl dioxolanones **36** in a process involving an intermediate carbonyl ylide (Scheme 11.8) [34].

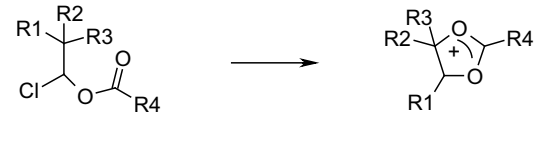


Scheme 11.8

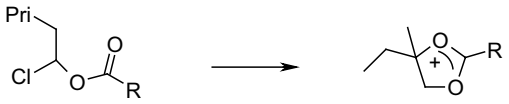
The treatment of chloroesters **37** and **38** with $SbCl_5$ results in cyclization with rearrangement of the carbon skeleton to give, respectively, the salts **39** [35] and **40** [36] (Scheme 11.9).

Vinyl esters such as **41** react with benzoyl or *t*-butyl hexachloroantiminoate to give the 1,3-dioxolium salt **42** (Scheme 11.10) [37, 38].

A simple preparation of 2-methyl-1,3-dioxolane (**44**) involves heating the vinyl ether **43** with KOH to give **44** in 66% yield [39]. A similar preparation involving enol ethers starts with **45**, which reacts with either EtMgBr or Bu_2^iAlH followed by benzaldehyde to give hydroxyalkyldioxolanes **46** (Scheme 11.11) [40].

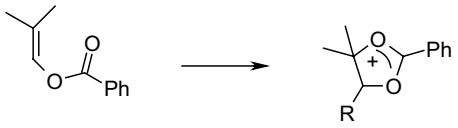


37 **39**



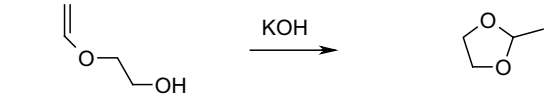
38 **40**

Scheme 11.9

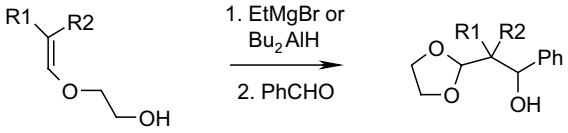


41 **42**

Scheme 11.10



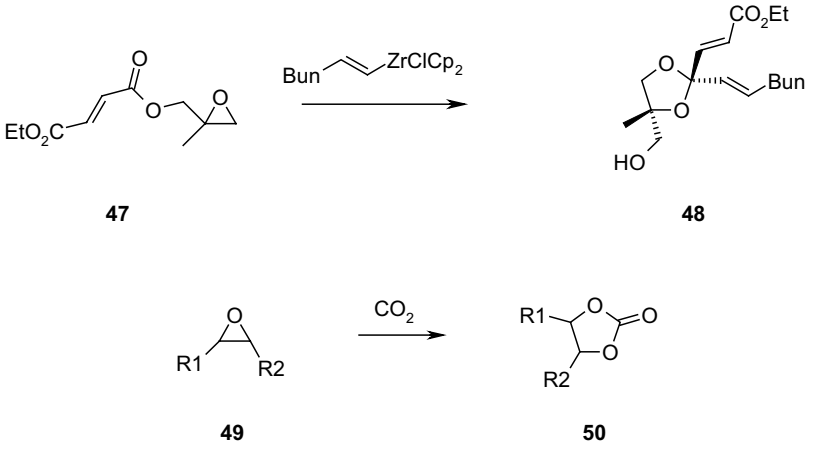
43 **44**



45 **46**

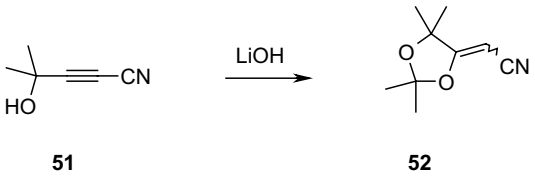
Scheme 11.11

Treatment of glycidic esters like **47** with cationic zirconium species and $AgClO_4$ affords the dioxolane **48** [41]. Epoxides like **49** react with CO_2 to give dioxolanones **50** (Scheme 11.12) The reaction may be catalyzed either by mixed alkali metal or manganese halides [42] or alkali metal/lead/indium halides [43]. The use of ionic liquids to catalyze this reaction has also been described [44].



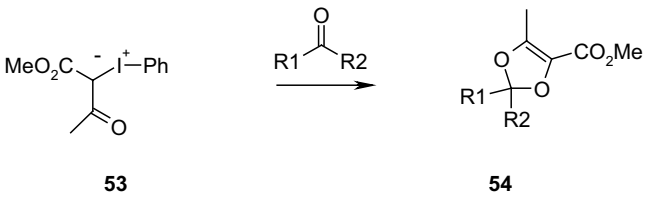
Scheme 11.12

Treatment of the acetylenic alcohol **51** with aq LiOH affords the dioxolane **52**; the yield of this reaction is increased by the addition of acetone (Scheme 11.13) [45].



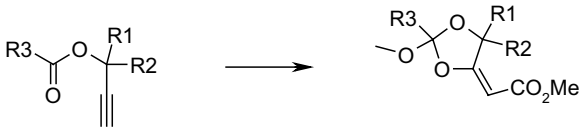
Scheme 11.13

Reaction of the stabilized iodonium ylide **53** with ketones affords 1,3-dioxoles **54** (Scheme 11.14) [46].



Scheme 11.14

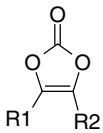
The palladium-catalyzed reaction of propargyl acetates with CO in methanol results in cyclization to give dioxolanes **55** (Scheme 11.15) [47].



55

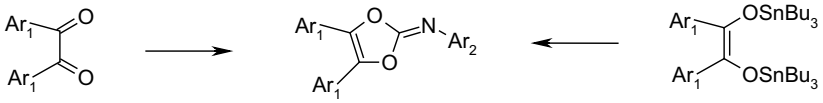
Scheme 11.15

Treatment of α-hydroxyketones, $R^1CH\ OH\ COR^2$, with triphosgene, Cl_3CO_2CO, gives the 1,3-dioxol-2-ones **56** in moderate yield [48].



56

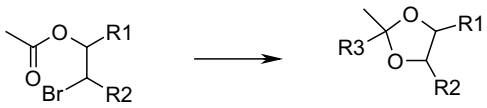
2-Imino-1,3-dioxoles **57** can be prepared either by electrochemical reduction of benzils **58** in the presence of $Ar_2N{=}CCl_2$ [49] or by the treatment of bis tin derivatives such as **59** with Ar_2NCS (Scheme 11.16); **59** also reacts with CS_2 to give 1,3-dioxole-2-thiones [50].



58 **57** **59**

Scheme 11.16

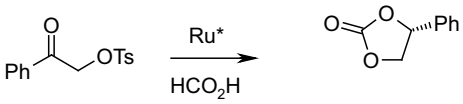
2,2-Disubstituted-1,3-dioxolanes **61** may be formed by nucleophilic attack with stabilized carbanions on 2-haloalkyl esters **60** (Scheme 11.17) [51].



60 **61**

Scheme 11.17

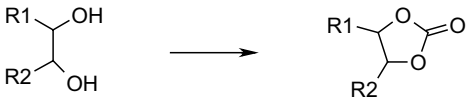
The transfer hydrogenation of the tosylacetophenone **62** using a chiral ruthenium catalyst and formic acid as the hydrogen source unexpectedly gives the chiral dioxolanone **63** in 94% ee (Scheme 11.18) [52].



62 **63**

Scheme 11.18

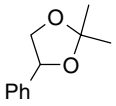
1,2-Diols like **64** react with oxalyl chloride and triethylamine to give the 1,3-dioxolanone **65** rather than the expected six-membered ring products (Scheme 11.19) [53].



64 **65**

Scheme 11.19

The treatment of styrene oxide with ruthenium trichloride in acetone gives the dioxolane **66** [54]. Titanium-based catalysts for the reaction of epoxides with acetone to give 2,2-dimethyl-1,3-dioxolanes are TiO CF_3CO_2 and TiCl CF_3SO_3 [55].



66

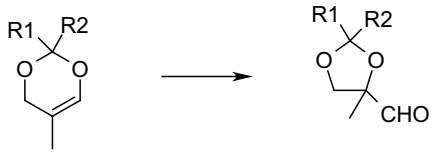
The most widely used method for the preparation of 1,3-dioxolanes involves the reaction of carbonyl compounds with 1,2-diols. A wide range of catalysts has been used in this reaction, trimethylsilyl triflate in the presence of a trimethylsilyl ether [56], K_{10} montmorillonite under solvent-free conditions [57, 58], scandium triflate [59] and *N*-benzoylhydrazinium salts [60].

11.3.3.2 Ring Transformations of Heterocycles Leading to 1,3-Dioxoles and 1,3-Dioxolanes

The treatment of 1,3-dioxane **67** with mCPBA provides an interesting route into 1,3-dioxolane aldehydes **68**, presumably via an epoxide rearrangement (Scheme 11.20) [61].

11.3.4 Reactivity of 1,3-Dioxoles and 1,3-Dioxolanes

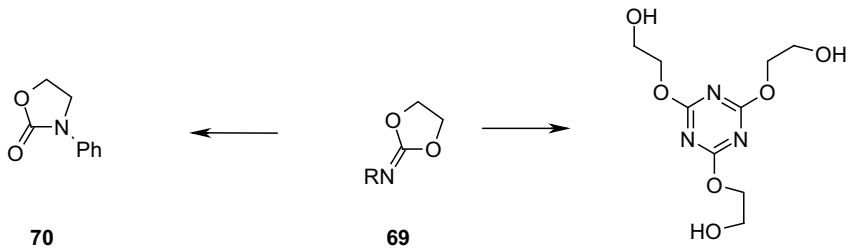
The phenyliminodioxolane **69** (R=Ph) undergoes isomerization to the oxazolidinone **70** upon heating at 200 °C with LiCl [62]. The parent compound **69** (R=H) undergoes



67 **68**

Scheme 11.20

spontaneous isomerization and trimerization to give the 1,3,5-triazine **71** (Scheme 11.21) [63].



70 **69** **71**

Scheme 11.21

11.3.4.1 Reactions with Nucleophiles

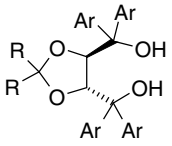
There has been several studies on stable cations such as **72** and their reactions with nucleophiles; **72** reacts with NaOMe at C2, but with $NaHCO_3$ or LiCl at C4 to give ring open 2-hydroxyethyl or 2-chloroethyl methyl carbonates, respectively [64]. The reaction of salts like **73** with acetylenic Grignard reagents takes place at C2 [65].

72 **73**

Efficient hydrolysis of 2,2-disubstituted-1,3-dioxolanes to carbonyl compounds has been an area of much interest. Methods for the hydrolysis of 2,2-dimethyl-1,3-dioxolanes include cerium ammonium nitrate and oxalic acid [66] and a polymer-supported dicyanoketene acetal [67]. Cleavage may also be achieved using Ph_3P/CBr_4 [68] or $CpTiCl_3$ [69], other reagents used include DDQ in aq. CH_3CN [70] and $TeCl_4$ [71].

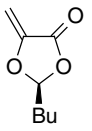
11.3.4.2 Uses in Asymmetric Synthesis

There has been a large volume of work published on the use of 1,3-dioxolanes in asymmetric synthesis. TADDOL complexes **74** have been used widely in asymmetric synthesis and have been the subject of a major review [72]. Further developments in this area involve the synthesis of polymer-supported TADDOLs [73] and TADDOL crown ethers [74]. Benzylcyclohexanone has been deracemized by the formation of an inclusion complex with TADDOL compound **74**, R,R=cyclohexyl. The X-ray structure of this complex has also been published [75]. The TADDOL complex **74**, R,R=cyclopentyl, has been used to direct enantioselective Diels–Alder reactions in aqueous solution [76].

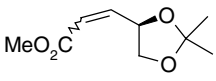


74

There has also been considerable work on C−C bond formation by attack on suitable dioxolane systems by carbanions, and of particular interest has been the use of chiral dioxolanes in asymmetric synthesis. Conjugate addition of organozinc compounds to chiral dioxolanes such as **75** and **76** affords adducts with a high degree of enantioselectivity [77, 78].



75

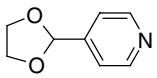


76

11.3.4.3 Reactions with Carbenes and Radicals

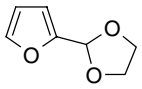
Treatment of 1,3-dioxolane (**23**) with ferrous sulfate and a peroxide in the presence of pyridine gives predominantly **77** together with small amounts of products resulting from reaction at the 4-position of the dioxolane and the 2-position of the pyridine [79].

23

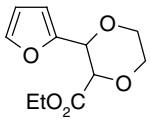


77

The reaction of 1,3-dioxolanes with carbenes generally proceeds by insertion into the C2−H bond and this has been examined for phase-transfer generated Cl_2C: and Br_2C: [80, 81] and for various arylchlorocarbenes (ArClC:) [82, 83]. Ethoxycarbonylcarbene behaves differently and reacts with **78** by insertion into the C2−O bond to give **79** [84].



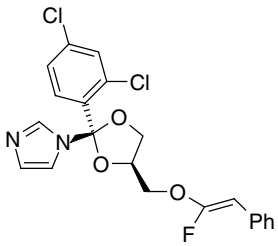
78



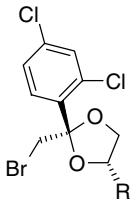
79

11.3.5
Compounds of Interest

1,3-Dioxolane derivatives such as **80** have been used as a fungicide [85] and related derivatives have anti-fungal activity [86–88]. The structurally related compounds **81** and **82** have been prepared as intermediates for ketoconazole synthesis by lipase-catalyzed kinetic resolution [89].

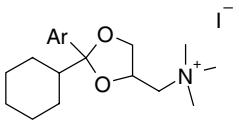


80



81, R = CH_2OH
82, R = CO_2H

Tertiary ammonium salts containing a 1,3-dioxolane ring (**83**) have been described as muscarinic acetylcholine antagonists [90].



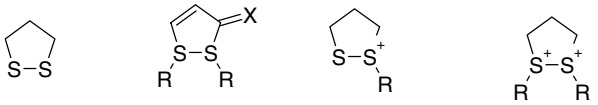
83

11.4
1,2-Dithioles and 1,2-Dithiolanes

11.4.1
Introduction

The 1,2-dithiolane system **84** is known but the partially unsaturated 1,2-dithiole system **85** is very common, along with its derivatives **85** (X=O, S, NR). There are only

a few references to systems where X=H,H or alkyl. Cationic species such as **86** and **87** are also known. 1,2-Dithiolanes have a greater reactivity than acyclic disulfides, which is attributed to some repulsion between the lone pairs on the adjacent sulfur atoms [91]. 1,2-Dithiolium cations are aromatic 6π systems and are very stable except to nucleophilic reagents. A comprehensive review of 1,2-dithiolium salts has been published [92].



84 **85** **86** **87**

11.4.2
Relevant Physicochemical Data

X-Ray methods for 1,3-dithiolanes have shown the S−S bond distances to be in the range of acyclic disulfides [91]. Figure 11.1 shows the bond lengths and angles of 1,2-dithiol-3-thione [93].

The ^{1}H NMR spectrum of 1,2-dithiolane **84** has signals at δ2.09 ppm for H4 and δ3.36 ppm for H3 and H5 [91]. Protons in 1,2-dithiole-3-ones absorb at higher field than the corresponding 1,2-dithiole-3-thiones. In the unsubstituted 1,2-dithiolium ion **88**, the H3 and H5 protons absorb at δ10.7 ppm and the H4 proton at δ8.88 ppm [91].

88

The ^{13}C NMR chemical shifts for 1,2-dithiolanes are ∼41 ppm for C3 and C5 and 56 ppm for C4; the chemical shifts for 1,2-dithiole-3-one are 216 ppm for C3, 140.2 ppm for C4 and 155.1 ppm for C5 [94].

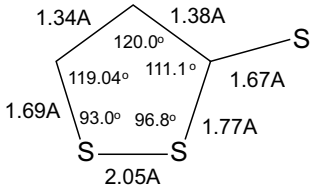


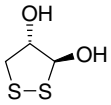
Figure 11.1 Geometry of 1,2-dithiol-3-thione.

11.4.3 Synthesis

11.4.3.1 Synthesis by Ring Construction

The synthesis of 1,2-dithioles and 1,2-dithiolanes has been the subject of a review [95]. The most practical method for the synthesis of 1,2-dithiols involves direct S−S bond formation, usually via oxidation or displacement of a leaving group on one of the sulfur atoms. For example, treatment of dithiols with bromine on hydrated silica has affords 1,2-dithiolanes **84** and **89** [96].

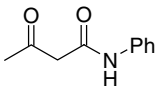
84



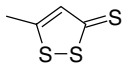
89

A mild method for the preparation of 1,2-dithiolanes involves the treatment of 1,3-dithiocyanates with $Bu^n{}_4N^+F^-$ [97].

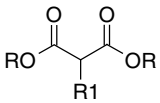
Treatment of β-ketoamides such as **90** with Lawesson's reagent gives the 1,2-dithiole-3-thione **91** [98]. In a similar preparation, treatment of malonates **92** with Lawesson's reagent and sulfur in xylene in the presence of a catalytic amount of 2-mercaptobenzothiazole and ZnO affords the 1,2-dithiol-3-thione **93** [99].



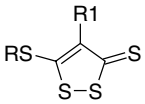
90



91

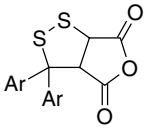


92

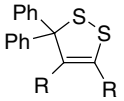


93

Dicyclic 1,2-dithiolane **94** has been prepared by treating either the ylide $Ph_3{=}Ar_2$ or the thione $Ar_2C{=}S$ with sulfur in boiling xylene in the presence of maleic anhydride [100]. The cycloaddition of thiocarbonyl sulfides with reactive alkynes gives access to 1,2-dithioles **95** [101].

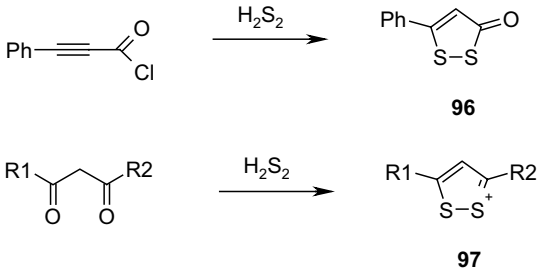


94



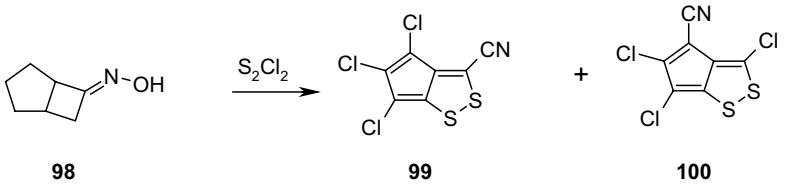
95

1,2-Dithiolanes are formed by the reaction of 1,3-halopropanes or haloalkenes with disulfide ions. Hydrogen disulfide provides the source of disulfide ion and it readily condenses with phenylpropynyl chloride to form 5-phenyl-1,2-dithiol-3-one (**96**) [102]. Similarly 1,3-diketones condense with hydrogen disulfide to give 1,2-dithiolium salts **97** (Scheme 11.22) [102].



Scheme 11.22

α-Thioderivatives of enamines or enol ethers react with carbon disulfide to form 5-amino or 5-alkoxy-1,2-dithiole-3-thiones [103]. An interesting reaction of the oxime **98** with S_2Cl_2 gives the bicyclic 1,2-dithiole isomers **99** and **100** (Scheme 11.23) [104].



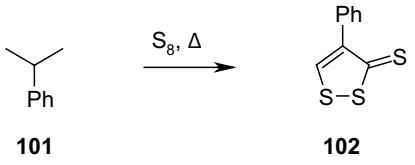
Scheme 11.23

A common method for the synthesis of 1,2-dithioles is the sulfurization of various 3-carbon units by elemental sulfur. The conversion of **101** into **102** and **103** into **104** is usually carried out under thermal conditions (180–250 °C) (Scheme 11.24) [105].

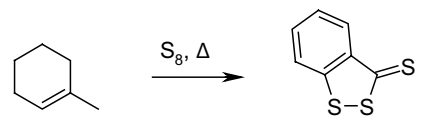
11.4.3.2 Ring Transformations of Heterocycles Leading to 1,2-Dithioles and 1,2-Dithiolanes

The synthesis of 1,2-dithioles by the transformation of other heterocyclic rings is a common method of preparation. Thiophene derivative **105**, when reacted with Na_2S in air affords the 1,2-dithiole **106** (Scheme 11.25) [106].

Ring contraction of 1,3-dithianes or 1,3-dithienes is also a well reported method for the preparation of 1,3-dithioles and 1,3-dithiolanes. The reaction is usually carried out under oxidizing conditions in the presence of acid or from 1, 3-dithiane-S-oxides with acids. Bromine has been used to transform the 1, 3-dithiane **107** into the 1,2-dithiolane **108** (Scheme 11.26) [107].

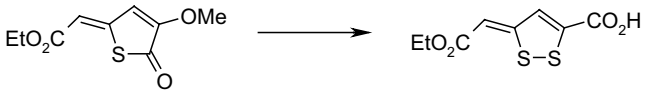


101 **102**



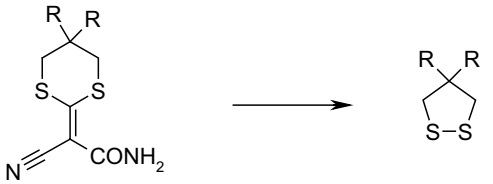
103 **104**

Scheme 11.24



105 **106**

Scheme 11.25



107 **108**

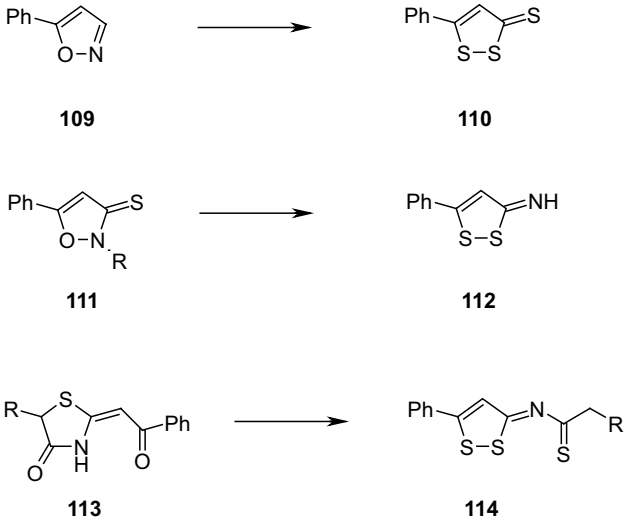
Scheme 11.26

Isoxazoles possess a three-carbon unit suitable for conversion into the 1,2-dithiole skeleton. Thus, 5-phenylisoxazole (**109**) is thionated to afford 5-phenyl-1,2-dithiole-3-thione (**110**) [108] and isoxazoline-3-thiones **111** affords 1,2-dithiole-3-imines **112** on treatment with H_2S (Scheme 11.27) [109]. Thiazolidinones **113** react with Lawesson's reagent to give 3-imino-1,2-dithioles **114** [110].

11.4.4 Reactivity of 1,2-Dithioles and 1,2-Dithiolanes

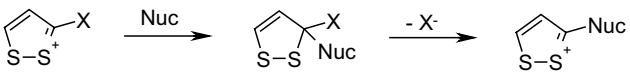
11.4.4.1 1,2-Dithiolium Salts

11.4.4.1.1 **Reactions with Nucleophiles** 1,2-Dithiolium salts react readily only with nucleophiles and often at the least hindered 3 or 5 position to form 1,2-dithioles.



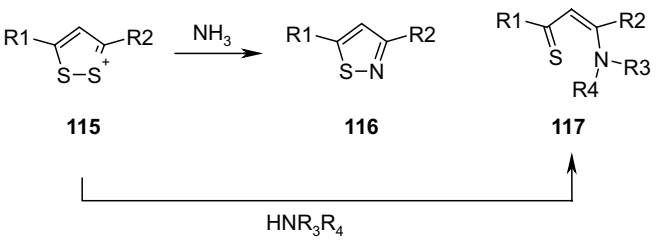
Scheme 11.27

These 1,2-dithioles may reform 1,2-dithiolium salts if there is a suitable leaving group at the 3-position Scheme 11.28.



Scheme 11.28

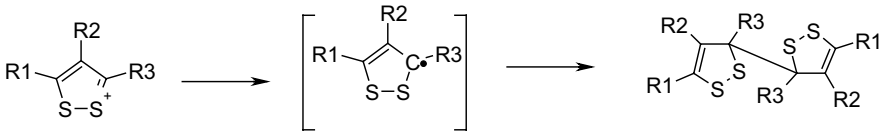
Oxygen and sulfur nucleophiles react in a similar fashion to give 3-alkoxy or 3-alkylthio substituted 1,2-dithioles, again if there is a suitable leaving group at the 3-position the products obtained are 1,2-dithiolium salts [111]. 1,2-Dithiolium salts react with nitrogen nucleophiles at the 3-position but the final product depends on the substitution pattern on the dithiolium ring. Dithiolium salts **115**, without a leaving group at C3, react with ammonia to form isothiazoles **116** [111] and with primary and secondary amines to form aminothiones **117** (Scheme 11.29) [111].



Scheme 11.29

The reaction of 1,2-dithiolium salts with carbon nucleophiles usually leads to ring opening and recyclization to give thiopyrans or thiophenes – these reactions are similar to those involving nitrogen nucleophiles by attack at C3 or it may involve an initial attack of the carbanion on a ring sulfur [112, 113].

11.4.4.1.2 **Reduction** Electrochemical reduction of 1,2-dithiolium salts **118** gives bis-1,2-dithiole dimers **120** via radical intermediates **119** whose stability depends on the substitution pattern (Scheme 11.30) [114].



118 **119** **120**

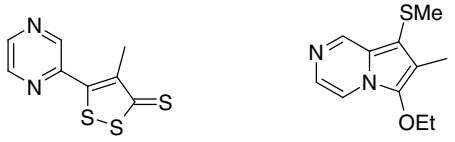
Scheme 11.30

11.4.4.2 **1,2-Dithioles**

To a certain extent 1,2-dithioles behave like acyclic disulfides in their reactions. 1,2-Dithioles with exocyclic double bonds are potentially aromatic and readily undergo reactions that result in the formation of 1,2-dithiolium salts.

11.4.4.2.1 **Reactions with Electrophiles** 1,2-Dithioles react with electrophiles at the ring sulfur atoms; thus chlorine, sulfuryl chloride and sulfenyl chlorides react at the ring sulfur to afford acyclic products [115].

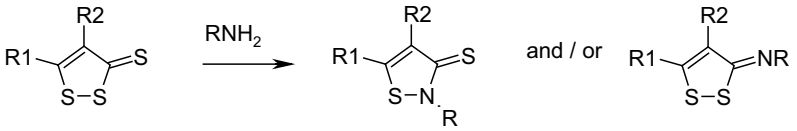
11.4.4.2.2 **Reactions with Nucleophiles** 1,2-Dithiole-3-thiones react with nucleophiles at S2, C3, C4 or C5, the exact position depending on the substitution pattern on the ring and on the hard/soft character of the nucleophile [116–118]. 1,2-Dithioles are attacked at C3 by hydroxide ion. Ethoxide ion attacks Oltipraz (**121**) at C5; subsequent ring opening and recyclization forms pyrrolodiazine **122** [116].



121 **122**

1,2-Dithiole-3-ones and 3-thiones behave like acyclic ketones and thiones, forming imines such as **125**, oximes and hydrazones with nitrogen nucleophiles [119]. 1,2-Dithioles **123** can also undergo ring opening and recyclization to afford isothiazoles **124** (Scheme 11.31). This pathway is dependant on the substituents at R1 and R2 and is particularly common with fused dithioles [120].

1,2-Dithioles react with carbon nucleophiles at a range of sites. Grignard reagents react as thiophiles, attacking at S2 of 1,2-dithiol-3-ones. Phosphonium ylides and

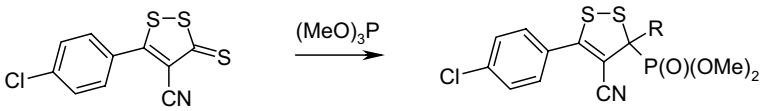


123 **124** **125**

Scheme 11.31

other carbanions attack at C3 of 1,2-dithiole-3-ones and 3-thiones to form 3-alkylidene-1,2-dithioles [121].

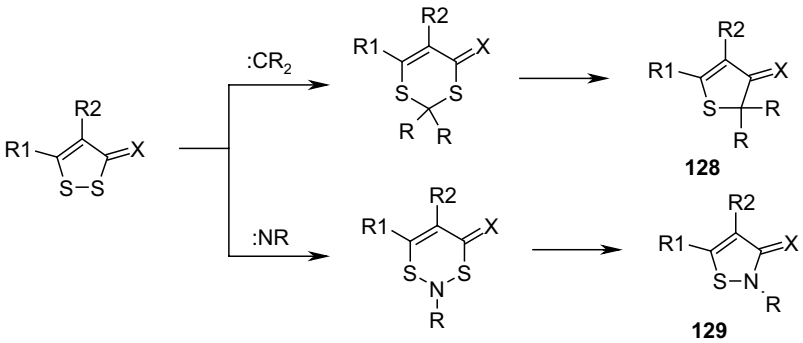
Reaction of the 1,2-dithiole-3-thione **126** with trimethyl phosphate affords some of the desired coupling product but also the phosphonate derivative **127** (Scheme 11.32) [122].



126 **127, R = H or Me**

Scheme 11.32

11.4.4.2.3 **Reactions with Carbenes and Nitrenes** 1,2-Dithioles react with carbene and nitrenes at the S−S bond, leading to insertion and sometimes with loss of one sulfur atom to form thiophenes (**128**) or isothiazoles (**129**), respectively, Scheme 11.33 [123, 124].



Scheme 11.33

11.4.4.3 1,2-Dithiolanes

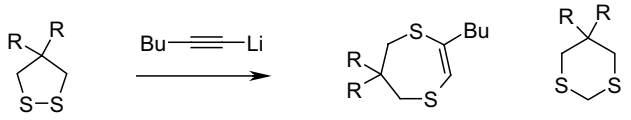
11.4.4.3.1 **Reaction with Electrophiles** Reactions of 1,2-dithiolanes all occur at the ring sulfur atoms. The sulfur is nucleophilic and is readily alkylated to form 1,2-dithiolium salts **130** (Scheme 11.34) [125].

84 **130**

Scheme 11.34

11.4.4.3.2 **Reaction with Nucleophiles** Alkyl lithium reagents, Grignard reagents and cyanide ion attack 1,2-dithiolanes at a sulfur atom to form ring open products [126, 127].

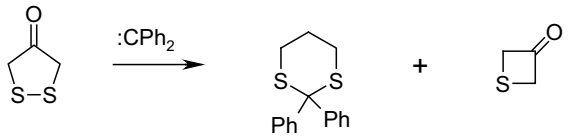
1,2-Dithiolanes **131** react with lithium acetylides to give the ring expanded product **132** [128]. If the 1,2-dithiolane **131** is reacted with dimethylsulfoxonium methylide the 1,3-dithiane **133** is formed (Scheme 11.35) [129].



131 **132** **133**

Scheme 11.35

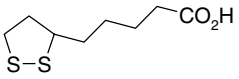
11.4.4.3.3 **Reactions with Carbenes** Carbenes react with 1,2-dithiolanes to afford insertion products at the S−S bond. The 1,2-dithiolane **134** reacts with diphenylcarbene to afford a mixture of the 1,3-dithiane insertion product **135** and the desulfurization product **136** (Scheme 11.36) [130].



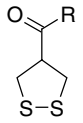
134 **135** **136**

Scheme 11.36

11.4.4.3.4 **Compounds of Interest** 1,2-Dithiolane-4-carboxylic acid (asparagusic, **137**) is thought to act in biological systems as a substrate of a dehydrogenating enzyme and to stimulate pyruvate oxidation. Lipoic acid **138** is involved in the oxidative decarboxylation of 3-ketoacids, oxidative phosphorylation and in photosynthesis [91]. The sulfonamide derivative of lipoic acid (**139**) is a glutathione reductase enhancer [131]. Oltipraz (**121**) has schistosomicidal activity [116].



137

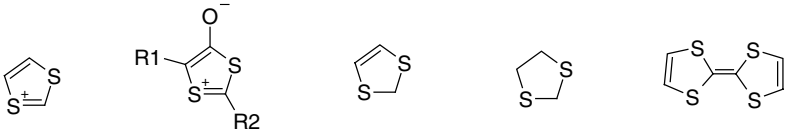


138, R = OH
139, R = $NHSO_2Me$

11.5
1,3-Dithioles and 1,3-Dithiolanes

11.5.1
Introduction

This section deals with 1,3-dithioles derivatives such as 1,3-dithiolylium ions **140**, mesoionic 1,3-dithiol-4-ones **141**, 1,3-dithioles **142**, 1,3-dithiolanes **143** and the tetrathiafulvalene (TTF) system **144**. The latter system has been the subject of a large number of publications because of its organic conducting properties.



140 **141** **142** **143** **144**

A comprehensive review chapter on 1,3-dithiolium salts has appeared [132]. The synthesis and reactions of 1,3-dithioles and dithiolanes have also been reviewed [95]. There have also been several reviews on the properties of TTFs [133–135].

11.5.2
Relevant Physicochemical Data

11.5.2.1 X-Ray Diffraction Studies

Several X-ray crystal structure determinations on 1,3-dithioles and 1,3-dithiolanes have been published; bond lengths and angles are presented in Tables 12.4 and 12.5, respectively.

Interestingly, the TTF system **144** is not planar but is slightly distorted into a chair conformation [136].

11.5.2.2 NMR Spectroscopy

^{1}H NMR data of variously substituted 1,3-dithiolylium ions have been published [113, 138].

Table 11.6 contains ^{1}H NMR data for several derivatives.

Table 11.4 Bond lengths (Å) for 1,3-dithiolane derivatives.

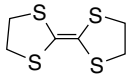
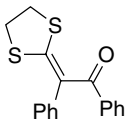
Bond		
S1–C2	1.756	1.72
S3–C2	1.758	1.76
S3–C4	1.729	1.80
C4–C5	1.314	1.54
S1–C5	1.732	1.83
Reference	[136]	[137]

Table 11.5 Bond angles (°) for 1,3-dithiolane derivatives.

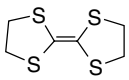
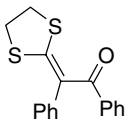
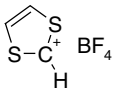
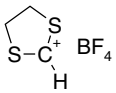
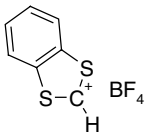
Bond		
S1–C2–S3	114.5	115.5
C2–S3–C4	94.3	96.7
S3–C4–C5	118.6	115.4
C4–C5–S1	118.0	108.3
C5–S1–C2	94.5	94.6
Reference	[136]	[137]

Table 11.6 ^{1}HNMR data for 1,3-dithiole derivatives.

Compound	H2 (δ, ppm)	H4 & 5 (δ, ppm)	Reference
	11.65	9.67	[139]
		7.2	[138]
		6.74	[138]

Table 11.7 ^{13}C NMR data for 1,3-dithiole derivatives.

Compound	C2 (δ, ppm)	C4 (δ, ppm)	Reference
	179.5	146.2	[140]
	221.2	46.4	[140]
	182.4	146.0	[140]
	140.7	133.7	[141]

^{13}C NMR data for 1,3-dithiole derivatives are presented in Table 11.7. Calculated electron densities have been correlated with observed ^{13}C chemical shifts for the benzo-1,3-dithiolylium ion [140].

11.5.2.3 Theoretical Methods

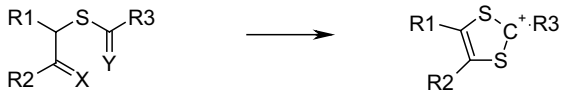
Simple LCAO-MO calculations for 1,3-dithiole-2-thione, benzo-1,3-dithiolylium ion,1,3-dithiole-2-one and 1,3-dithiolylium ions indicate that the lowest electron density is found at the 2-position of the 1,3-dithiolylium cation and showed that the C4–C5 bond order corresponded approximately to that of an isolated double bond [138].

11.5.3 Synthesis

11.5.3.1 1,3-Dithiolium Salts, 1,3-Dithiolones and 1,3-Dithioles

Several methods are known for the preparation of 1,3-dithiolylium salts from acyclic precursors by the formation of one bond. Acid-catalyzed cyclization of thioesters **145**, dithioesters **146** or thio analogues **147** using either mixtures of perchloric acid and glacial acetic acid or sulfuric acid in the presence of H_2S [138] or H_2S/BF_3 [113] results in the formation of **148** (Scheme 11.37).

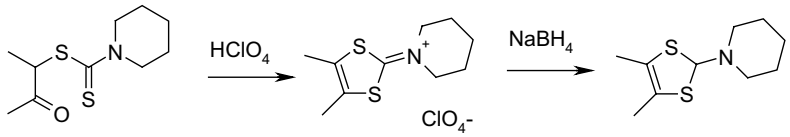
Dithiocarbamates like **149** afford the perchlorate salt **150** upon reaction with perchloric acid (Scheme 11.38). Reduction of **150** with sodium borohydride gives the 1,3-dithiole **151**, which can then be treated again with perchloric acid to afford the 1,2-dithiolylium salt **152** [142].



145, X = O, Y = O
146, X = O, Y = S
147, X = S, Y = O

148

Scheme 11.37

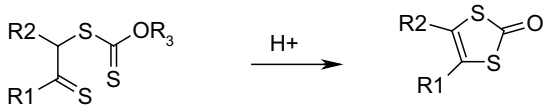


149 **150** **151**

152

Scheme 11.38

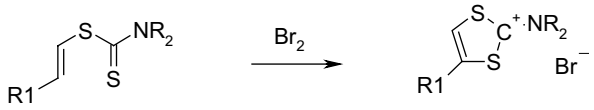
1,3-Dithiol-2-ones **154** are also obtained by acid-catalyzed cyclization of thioxodithiocarbamates **153** (Scheme 11.39) [143].



153 **154**

Scheme 11.39

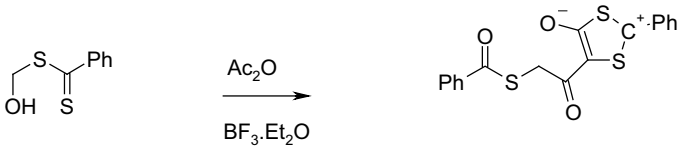
In a similar approach *S*-vinyl-*N,N*-dialkyldithiocarbamates **155** afford, upon reaction with bromine, the 1,3-dithiolylium bromides **156** (Scheme 11.40) [144, 145].



155 **156**

Scheme 11.40

Thiobenzoylthioglycolic acid **157** reacts with acetic anhydride in the presence of boron trifluoride results to form dithiolylium salt **158** (Scheme 11.41) [146].

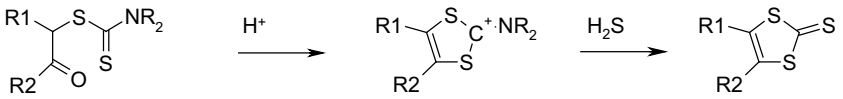


157 **158**

Scheme 11.41

Various methods have been described for the synthesis of 1,3-dithiole-2-thiones, which are widely used as precursors for the preparation of 1,3-dithiole derivatives.

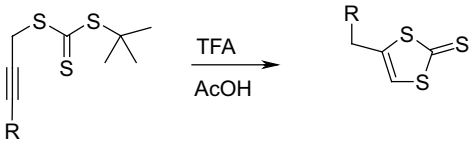
Dithiocarbamates **159** are easily cyclized with conc. sulfuric acid or 70% perchloric acid to yield the 1,3-dithiolylium salts **160**, which upon treatment with H_2S afford the 1,3-dithiole-2-thiones **161** (Scheme 11.42) [147].



159 **160** **161**

Scheme 11.42

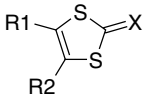
An alternative approach uses propargyl-*t*-butyltrithiocarbamates **162**, which afford mono substituted 1,3-dithiole-2-thiones **163** on treatment with trifluoroacetic acid/glacial acetic acid (Scheme 11.43) [148].



162 **163**

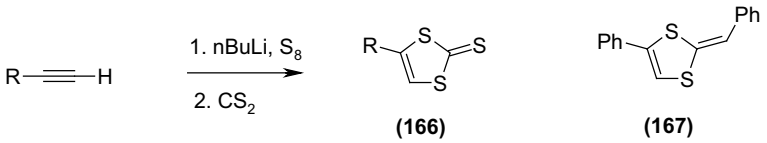
Scheme 11.43

A two-step conversion of alkynes into dithiolones **164** and dithiolethiones **165** has been reported. The initial step involves palladium-catalyzed addition of $Pr^i_3Si\text{-}S\text{-}S\text{-}SiPr^i_3$ followed by treatment with fluoride ion and either PhSOCl or $CSCl_2$ [149].



164, X = O
165, X = S

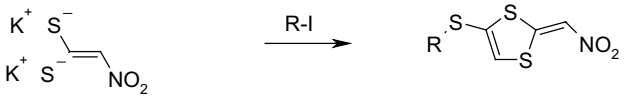
A convenient synthesis of 1,3-dithiole-2-thiones **166** involves the treatment of a terminal alkyne with butyllithium, sulfur and then CS_2 (Scheme 11.44) [150]. In similar fashion, the reaction of phenylacetylene with sulfur and KOH in DMSO leads to direct formation of the dithiole **167**, albeit in low yield [151].



(166) **(167)**

Scheme 11.44

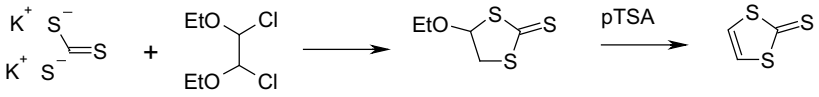
The bis-dithiole salt **168** reacts with long-chain alkyl iodides to give dithioles **169** (Scheme 11.45) [152].



168 **169**

Scheme 11.45

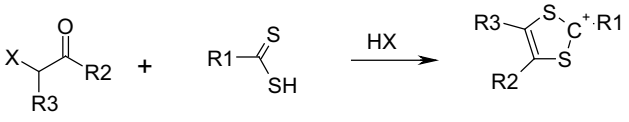
Unsubstituted 1,3-dithiole-2-thione (**172**) can be prepared from 1,2-dichloroethyl ethyl ether (**170**) and potassium trithiocarbonate (Scheme 11.46). The intermediate 4-ethoxy-1,3-dithiolane-2-thione **171** is treated with *p*-toluene sulfonic acid to give **172** [153].



170 **171** **172**

Scheme 11.46

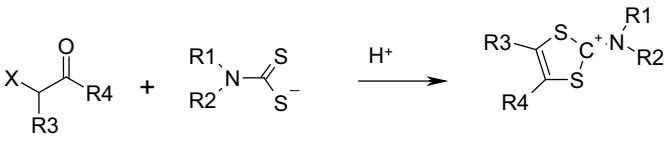
1,3-Dithiolylium salts **175** have also been prepared by the reaction of α-haloketones **173** with an excess of dithio-carboxylic acids **174** in the presence of strong mineral acids at 60–80 °C (Scheme 11.47) [154].



173 **174** **175**

Scheme 11.47

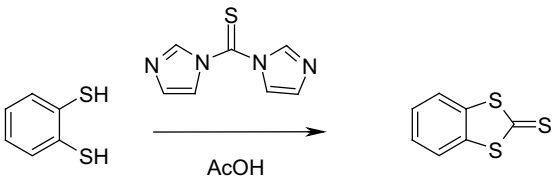
α-Haloketones **176** also react with N,N-dialkyldithiocarbamidates **177** in the presence of strong acid to afford 2-alkylamino-1,3-dithiolylium salts **178** (Scheme 11.48) [155, 156].



176 **177** **178**

Scheme 11.48

Benzo-annellated 1,3-dithiole-2-thiones (**180**) can be prepared by the reaction of benzene-1,2-dithiol (**179**) with thiocarbonyldiimidazole in glacial acetic acid (Scheme 11.49) [157].

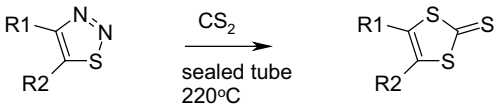


179 **180**

Scheme 11.49

11.5.3.2 **Ring Transformations of Heterocycles Leading to 1,3-Dithiole Derivatives**

Thermolysis of 1,2,3-thiadiazoles **181** in carbon disulfide provides a useful route to 1,3-dithiole-2-thiones **182** (Scheme 11.50) [158].

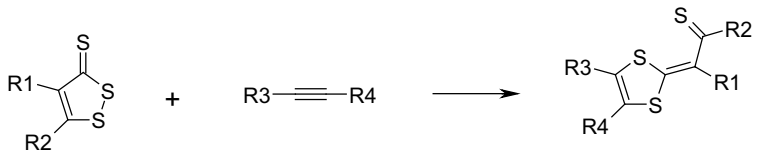


181 **182**

Scheme 11.50

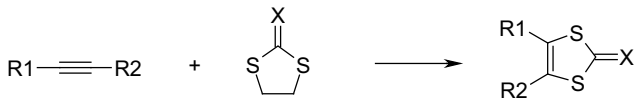
1,2-Dithiole-3-thione derivatives can also be used as starting compounds for 1,3-dithiole synthesis. 1,2-Dithiole-3-thiones **183** react with alkynes or even benzyne to afford 1,3-dithioles **184** (Scheme 11.51) [159].

Alkynes bearing electron-withdrawing groups also react with O,S-ethylene dithiocarbonate **185** (X=O) or ethylene trithiocarbonate **185** (X=S) to afford 1,3-dithiole-2-ones **186** (X=O) or 1,3-dithiole-2-thiones **186** (X=S) (Scheme 11.52) [160, 161].



183 **184**

Scheme 11.51



185 **186**

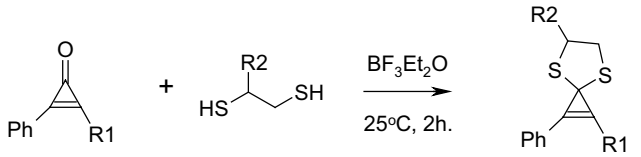
Scheme 11.52

11.5.3.3 **Ring Synthesis of 1,3-Dithiolanes**

The most widely used method for the synthesis of 1,3-dithiolanes involves the condensation reaction of an aldehyde or ketone with suitably substituted 1,2-dithiols in the presence of a catalyst. Catalysts for the conversion of aldehydes and ketones into 1,3-dithiolanes with ethanediol include HCl [162], BF_3Et_2O [162], iodine [163], $MoCl_5$ [164], indium triflate [165] and $Cu(CF_3SO_3)_2$ [166].

Iodine and indium triflate and indium chloride are also good catalysts for effecting the transthioacetalization of 1,3-dioxolanes [167]. $ZrCl_4$ has also been used in this transformation [168].

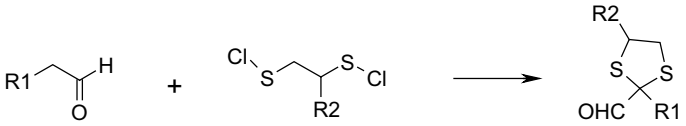
The use of $BF_3{\cdot}Et_2O$ as a catalyst allows the synthesis of some very sensitive systems; the cyclopropanone **187** reacts with 1,2-dithiols **188** in 24–58% yield to give the spiro derivatives **189** (Scheme 11.53) [169].



187 **188** **189**

Scheme 11.53

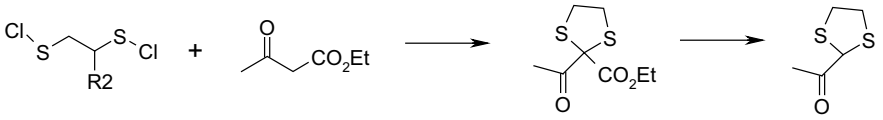
Carbonyl compounds possessing an α-methylene group (**190**) react with 1,2-bis(chlorosulfenyl)alkanes **191** to give 2- formyl-1,3-dithiolanes **192** (Scheme 11.54) [170].



190 **191** **192**

Scheme 11.54

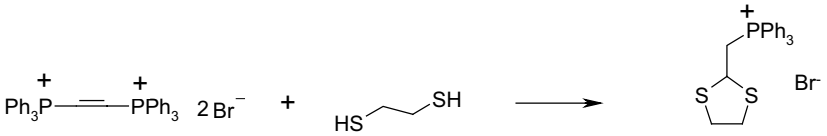
Compound **191** also reacts with ethyl acetoacetate to give 2-acetyl-2-ethoxycarbonyl-1,3-dioxolanes **193**, which are readily hydrolyzed and decarboxylated to give 2-acetyl-1,3-dioxolanes **194** (Scheme 11.55) [170].



191 **193** **194**

Scheme 11.55

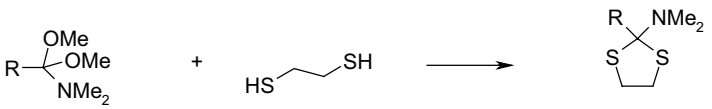
1,2-Bis(triphenylphosphonium)ethane dibromides **195** react with 1,2-ethanedithiol in the presence of a base to give an almost quantitative yield of 2-triphenylphosphoniomethyl-1,3-dithiolane (**196**), which can then undergo Wittig reactions (Scheme 11.56) [171].



195 **196**

Scheme 11.56

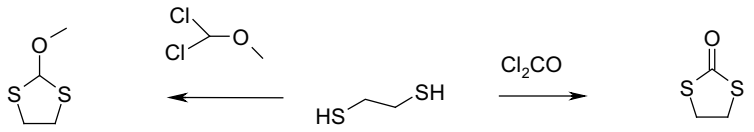
2-Amino substituted 1,3-dithiolanes **198** can be obtained from amide acetals such as **197** and 1,2-ethanedithiol (Scheme 11.57) [172].



197 **198**

Scheme 11.57

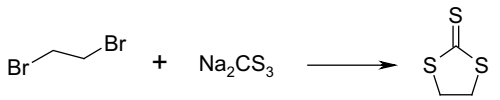
Ethane-1,3-dithiol also reacts with dichloromethyl methyl ether in the presence of sodium to give 2-methoxy-1,3-dithiolane **199** (Scheme 11.58) [173]. It also reacts with phosgene to give 1,3-dithiolan-2-one **200** [174].



199 **200**

Scheme 11.58

The reaction of ethylene dibromide with sodium trithiocarbonate affords 1,3-dithiolan-2-thione (**201**) (Scheme 11.59) [175].

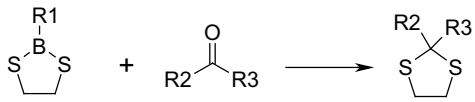


201

Scheme 11.59

11.5.3.4 **Ring Transformations of Heterocycles Leading to 1,3-Dithiolane Derivatives**
2-Substituted 1,3-dioxolanes react with ethanediol in an ionic liquid – transthioacetalization occurs to afford the corresponding 2-substituted 1,3-dithiolanes [176]. The asymmetric synthesis of various nucleoside analogues in which the ribose base is replaced by a 1,3-dithiolane ring has been described [177].

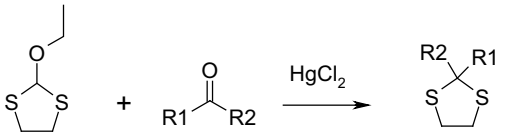
The transformation of complex and sensitive carbonyl compounds under neutral conditions into 1,3-dithiolanes **203** can be achieved using 2-phenyl or 2-halogeno 1,3,2-dithiaborolanes **202** (Scheme 11.60) [178].



202, R1 = Ph or Cl **203**

Scheme 11.60

An alternative method for the synthesis of 1,3-dithiolanes **205** from acid-sensitive carbonyl compounds involves the reaction of 2-ethoxy-1,3-dithiolane (**204**) in the presence of mercury(II) chloride or other Lewis acids (Scheme 11.61) [179].



204 **205**

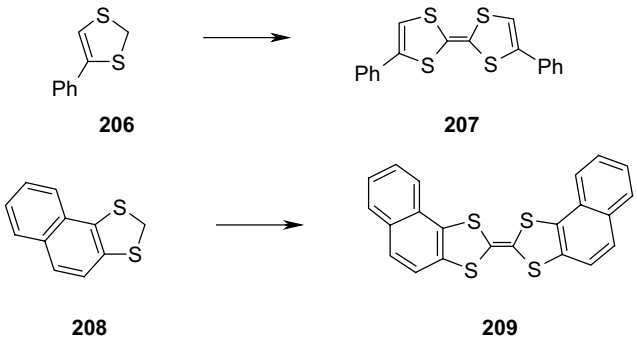
Scheme 11.61

11.5.3.5 Synthesis of Tetrathiafulvalenes

Tetrathiafulvalenes (TTFs) are electron donors that easily form charge-transfer complexes with electron acceptors such as radical salts. The discovery of the exceptional electron conductivity of TTFs has encouraged a great deal of research into their synthesis.

The vast majority of syntheses of TTFs involve the preparation of the π-bond in between the two 1,3-dithiole rings as the final step. This bond can be formed via an elimination reaction involving either two-proton electrochemical oxidation or the σ- and π- bonds can be formed simultaneously by a coupling reaction between two carbenes.

The electrochemical oxidation of the 1,3-dithioles **206** and **208** in the presence of pyridine has been described. The respective TTFs **207** and **209** were obtained in low yield, 30 and 40%, respectively (Scheme 11.62) [180].

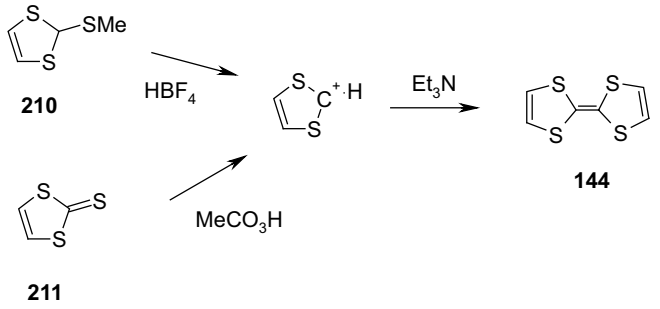


206 **207**

208 **209**

Scheme 11.62

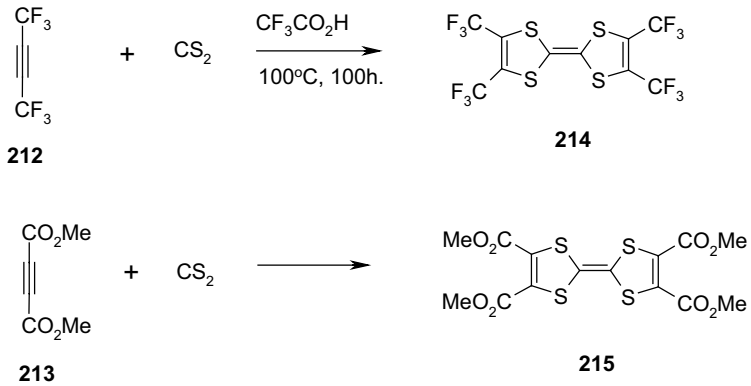
The synthesis of TTF via elimination of a proton from 1,3-dithiolylium salts in the final synthetic step involves the reaction of a carbene or phosphonium ylide on a 1,3-dithiolylium salt bearing a hydrogen at C2. These precursors can be prepared either by an alkylation of 2-alkylthio-1,3-dithioles **210** [181] or by oxidation of 1,3-dithiole-2-thiones **211** either with peracid or hydrogen peroxide (Scheme 11.63) [182]. Treatment of these precursors with a tertiary amine base affords TTF (**144**). The presence of alkyl groups in the 4 or 5 position does not interfere with this reaction; however, electron-withdrawing groups in these positions can lead to no reaction.



210 **211** **144**

Scheme 11.63

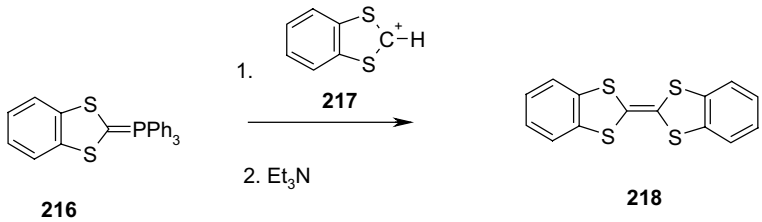
The reaction of carbon disulfide with either a strained or electron-rich acetylene derivatives in the presence of an acid or under high pressure is another common method for the preparation of TTFs. This method can be used to afford TTFs with electron-withdrawing substituents in the ring. Acetylenes **212** and **213** react with CS_2 to give the TTFs **214** [183] and **215** (Scheme 11.64) [184].



212 **214** **213** **215**

Scheme 11.64

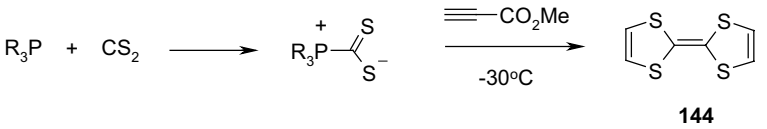
1,3-Dithiolylium salts **217** react with 2-triphenylphosphino-1,3-dithioles **216** to afford an intermediate that eliminates a proton and triphenylphosphine on treatment with base to give the TTF **218** (Scheme 11.65) [185].



216 **218**

Scheme 11.65

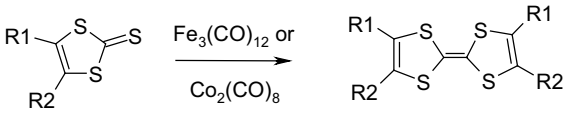
Similarly, TTF (**144**) is obtained from a mixture of trialkylphosphanes and alkynes in the presence of carbon disulfide (Scheme 11.66) [186].



144

Scheme 11.66

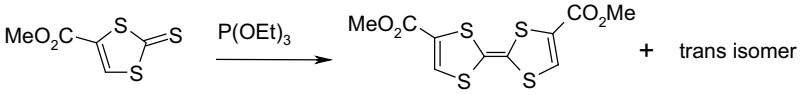
TTF may be obtained by dethioxygenation of 2-thioxo-1,3-dithioles by transition metal complexes. The reaction of 2-thioxo-1,3-dithioles **219** with $Fe_3(CO)_{12}$ or $Co_2(CO)_8$ furnishes TTFs **220** with aryl, alkyl or electron-withdrawing groups in the 4- and 5-positions of the dithiole ring (Scheme 11.67) [187, 188].



219 **220**

Scheme 11.67

2-Thioxo-1,3-dithioles bearing electron-withdrawing groups such as in **221** also react with trivalent phosphorus compounds to form the corresponding TTFs (**222**) as a mixture of regioisomers (Scheme 11.68) [189].

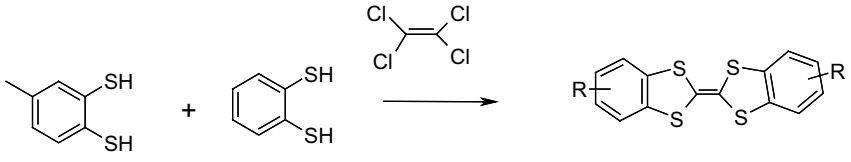


221 **222**

Scheme 11.68

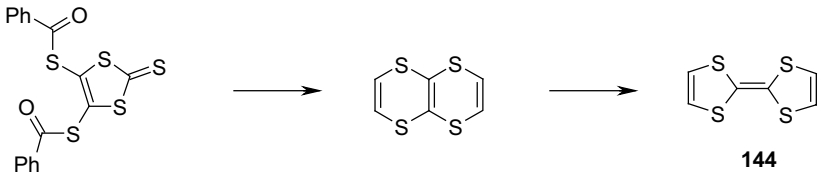
Tetrachloroethylene has also been used as a central building block for TTF synthesis. This method is suitable for the synthesis of symmetrical and unsymmetrical TTFs. The reaction of tetrachloroethylene with 1,2-benzenethiols **223** and **224** leads to a mixture of benzotetrathiafulvalenes **225** (Scheme 11.69) [190].

TTF (**144**) has been synthesized in two steps (85% overall yield), starting from 4,5-bis(benzoylthio)-1,3-dithiole-2-thione (**226**) (Scheme 11.70). The intermediate tetrathianaphthalene **227** is treated with base to afford TTF. This method is suitable for the large-scale synthesis of TTF as no chromatography is required [191].



223 **224** **225; R = H or Me**

Scheme 11.69



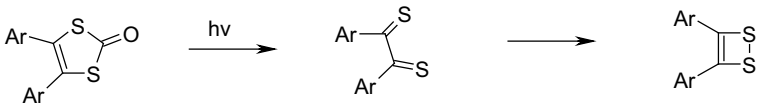
226 **227** **144**

Scheme 11.70

11.5.4
Reactivity of 1,3-Dithiolylium Ions, Mesoionic 1,3-Dithiol-4-ones and 1,3-Dithioles

11.5.4.1 Thermal and Photochemical Reactions

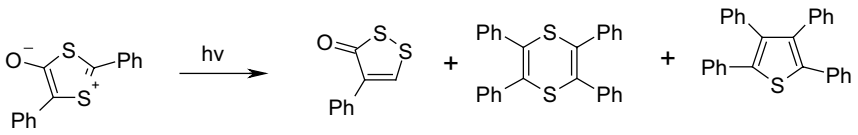
1,3-Dithiole-2-one **228** undergoes a photochemically induced decarbonylation to afford the dithione derivative **229**, which may react further to give the dithiete **230** (Scheme 11.71) [192].



228 **229** **230**

Scheme 11.71

Photolysis of the 1,3-dithiolylium-4-oate **231** gives a mixture of the 1,2-dithiol-3-one **232** along with diazine **233** and thiophene **234** (Scheme 11.72) [193].



231 **232** **233** **234**

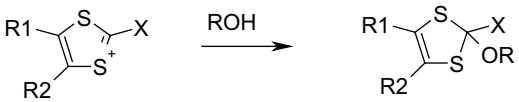
Scheme 11.72

11.5.4.2 Reactions with Electrophiles

The attack of electrophiles at the ring carbons of 1,3-dithiolylium ions is seldom observed. 1,3-Dithiole-2-thiones can be alkylated on the ring sulfur atom to give a 1,3-dithiolylium system – strong alkylating agents such as triethyloxonium tetrafluoroborate must be used [194].

11.5.4.3 Reactions with Nucleophiles

1,3-Dithiolylium salts react with nucleophiles at the 2-position while 1,3-dithiolylium-4-oates undergo nucleophilic attack at the 4-position. 1,3-Dithiolylium cations are hydrolyzed to the corresponding 2-hydroxy-1,3-dithioles, which upon treatment with acid reform the 1,3-dithiolylium cation [195]. The reaction of 1,3-dithiolylium salts **235** with alcohols leads to stable 2-alkoxy-1,3-dithioles **236** (Scheme 11.73) [196]. These alkoxy derivatives are useful precursors of 2-aryl-1,3-dithioles [197]. Sulfur nucleophiles react in a similar fashion to alcohols with 1,3-dithiolylium salts to afford 2-alkylthio or 2-arylsulfanyl-1,3-dithioles [196].

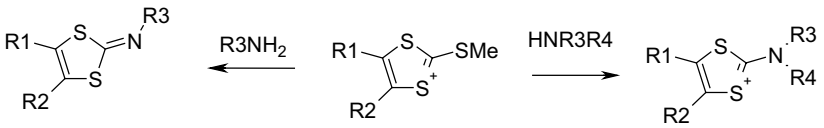


235 **236**

Scheme 11.73

Secondary amines react with 1,3-dithiolylium salts that are unsubstituted at the 2-position (**237**) to afford 2-amino-1,3-dithioles **238** (Scheme 11.74) [196]. 2-Methylsulfanyl-1,3-dithiolylium salts **239** give the corresponding 2-amino-1,3-dithiolylium salts **240** with secondary amines [198]. Primary amines react with **239** to afford 2-imino-1,3-dithioles **241** [199].

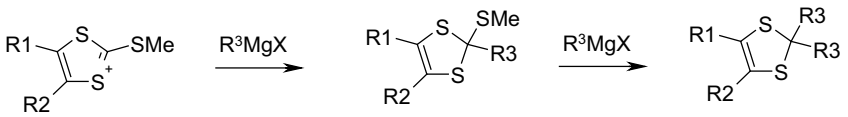
237 **238**



241 **239** **240**

Scheme 11.74

2-Methylsulfanyl-1,3-dithiolylium salts **239** also react with Grignard reagents to form 2-alkyl-2-methylsulfanyl-1,3-dithiolylium salts **242**, which may react with excess Grignard reagent to give 2,2-dialkyl-1,3-dithioles **243** (Scheme 11.75) [200].

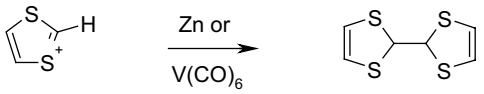


239 **242** **243**

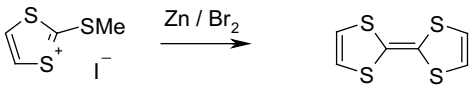
Scheme 11.75

11.5.4.4 **Reductions**

1,3-Dithiolylium salts are easily reduced by $NaBH_4$, $LiAlH_4$ or NaSH to give the corresponding 1,3-dithiole [196]. If 1,3-dithiolylium salts **244** are reduced with zinc [201] or $V(CO)_6$ [202] the dimer **245** is formed (Scheme 11.76). 2-Methylsulfanyl-1,3-dithiolylium iodide (**246**) forms TTF (**144**) when reduced with zinc in the presence of bromine [203].



244 **245**



246 **144**

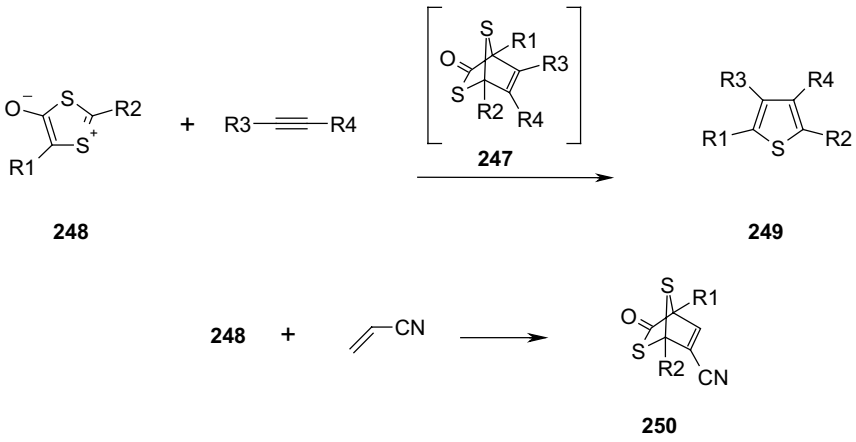
Scheme 11.76

1,3-Dithiolylium-4-olates **248** can be regarded as masked 1,3-dipole thiocarbonyl ylides; they react with dipolarophiles to give cycloadducts. Thiophenes **249** are obtained when **248** are reacted with alkynes (Scheme 11.77) [204].

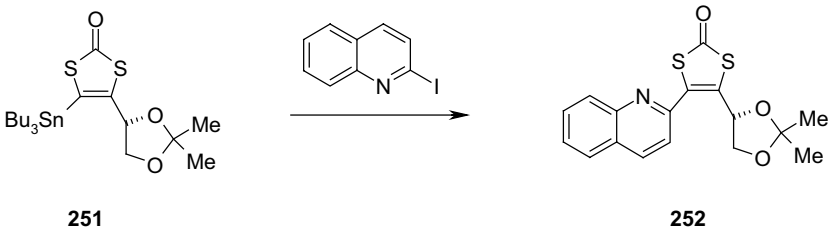
Stable adducts such as **250** are formed when **248** is reacted with electron-deficient alkenes [205].

11.5.4.5 **Coupling Reactions**

The palladium-catalyzed coupling of the tributyl tin 1,3-dithiole derivative **251** with 2-iodoquinoline to give the coupled product **252** has been described (Scheme 11.78) [206].



Scheme 11.77



Scheme 11.78

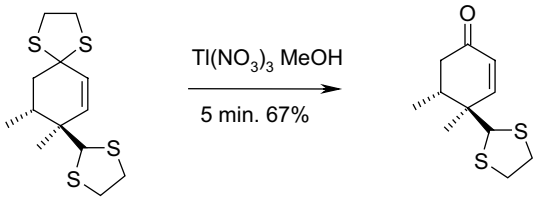
11.5.5 Reactivity of 1,3-Dithiolanes

1,3-Dithiolanes are resistant to both acid and alkaline hydrolysis, they are also resistant to nucleophilic attack by nucleophiles such as hydride ions.

11.5.5.1 Cleavage Reactions

A review of methods for cleaving 1,3-dithiolanes to aldehydes or ketones has been published [207]. The ring can be cleaved by a mixture of $HgCl_2/CdCO_3$ quite effectively [208]; alternatively, sodium in ethanol in liquid ammonia [209], NBS in acetone [210], or thallium(III) nitrate in methanol can be used. The latter method has been used for the selective cleavage of a mixture of thioketals **253** to afford the unsaturated ketone **254** (Scheme 11.79) [211].

$SOCl_2$-treated silica and DMSO is a good combination with which to cleave 2-substituted-1,3-dithiolanes; however, under similar conditions 2,2-disubstituted-1,3-dithiolanes undergo ring expansion to give dihydro-1,4-dithiins [212].



253 **254**

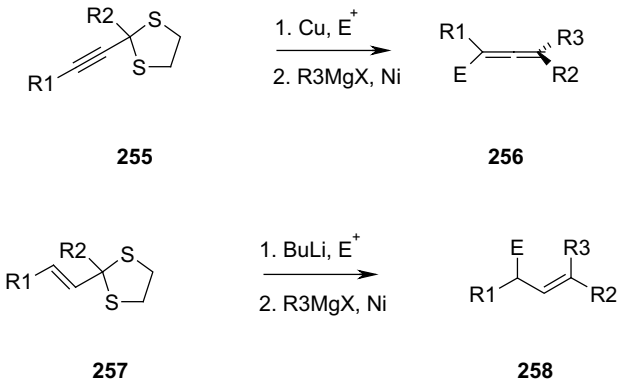
Scheme 11.79

Recent methods for the cleavage of 1,3-dithiolanes include the use of 2,4,6-trichlorotriazine and DMSO [213], oxone on wet alumina [214] and ferric nitrate on K-10 montmorillonite clay [215].

Treatment of 2-substituted-1,3-dithiolanes with NBS followed by 1,2-ethanediol affords 1,3-dioxolanes [216].

11.5.5.2 Electrophilic Attack at Carbon

1,3-Dithiolanes can be deprotonated at C2 with equimolar amounts of butyllithium. The resultant carbanions can then be trapped by various electrophiles [217]. 2-Alkynyl-1,3-dithiolanes **255** affords allenes **256**when treated with an organocuprate compound followed by an electrophile and then a Grignard reagent with nickel catalysis (Scheme 11.80) [218]. Similarly, the reaction of 2-alkenyl-1,3-dithiolanes **257** with Bu_2CuLi or BuLi and an electrophile followed by treatment with a Grignard reagent under nickel catalysis affords alkenes **258** [219].



255 **256**

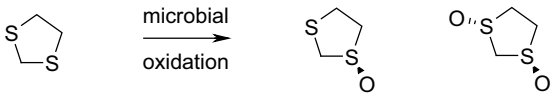
257 **258**

Scheme 11.80

11.5.5.3 Oxidations

1,3-Dithiolanes can be oxidized to afford 1,3-dithiolane-1-oxides by photooxidation [220], while oxidation under more vigorous conditions leads to mono and bis

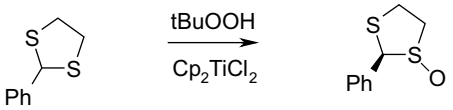
sulfones [221]. Enantioselective oxidations of 1,3-dithiolane (**143**) by microbial oxidation gives the corresponding *S*-oxide **259** in high enantiomeric excess (Scheme 11.81) [222]. A review of the preparation and use of the C2 symmetric bis-sulfoxide **260** has been published [223].



143 **259** **260**

Scheme 11.81

On a similar theme the 2-phenyl monosulfoxide derivative **262** has been prepared in a diastereoselective manner by the reaction of 2-phenyl-1,3-dithiolane (**261**) with Bu^tOOH and Cp_2TiCl_2 (Scheme 11.82) [224].

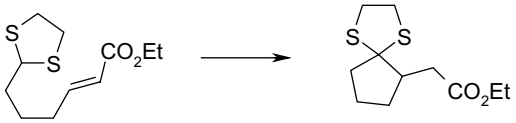


261 **262**

Scheme 11.82

11.5.5.4 **Radical Reactions**

Intramolecular addition of the 1,3-dithiolan-2-yl radical generated from **263** by photolysis affords the spirocyclic derivative **264** (Scheme 11.83) [225].



263 **264**

Scheme 11.83

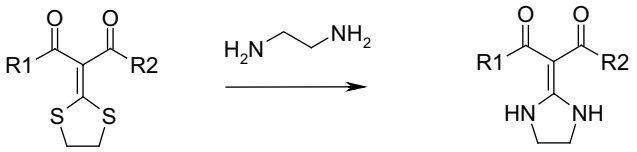
11.5.5.5 **Ring Transformation Reactions**

Treatment of dithiolane **265** with WCl_6 in DMSO gives the ring-expanded dithiin **266** (Scheme 11.84) [226].

265 **266**

Scheme 11.84

Ethylenediamine reacts with 1,3-dithiolane derivatives **267** to give imidazolines **268** (Scheme 11.85) [227].



267 **268**

Scheme 11.85

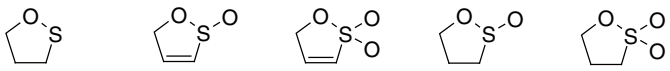
11.5.6
Compounds of Interest

TTF derivatives have been the focus of scientific interest since the mid-1970s. Indeed, their organic metal properties and superconductivity has prompted the publication of several reviews discussed earlier in this section [133–135].

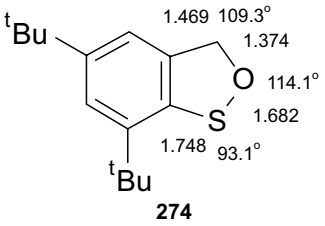
11.6
1,2-Oxathioles and 1,2-Oxathiolanes

11.6.1
Introduction

The parent oxathiolone **269** is known but most work published has been on the S-oxidized derivatives like **270** and **271**. The corresponding saturated derivatives **272** and **273** have also been described. A comprehensive review of 1,2-oxathiolium salts has been published [228].



269 **270** **271** **272** **273**



274

Figure 11.2 Geometry of a 1,2-oxathiolone derivative.

Table 11.8 ^{1}H NMR data for 1,2-oxathiolanes derivatives.

Compound	3-H (δ, ppm)	4-H (δ, ppm)	5-H (δ, ppm)	Reference
1,2-Oxathiolan-2-oxide (**272**)	1.35	1.35	3.45	[230]
1,2-Oxathiolan-2,2-dioxide (**273**)	3.1	2.5	4.82	[231]

11.6.2 Relevant Physicochemical Data

11.6.2.1 X-Ray Diffraction

The X-ray structure of **274** has been published to give the dimensions [229] shown in Figure 11.2.

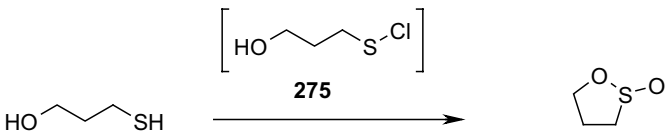
11.6.2.2 NMR Spectroscopy

Table 11.8 gives ^{1}H NMR data for S-oxidized 1,2-oxathiolane systems **272** and **273**.

11.6.3 Synthesis

11.6.3.1 Ring Synthesis of 1,2-Oxathioles

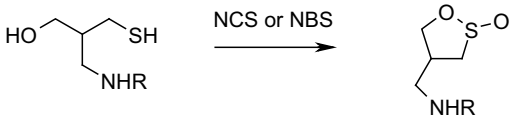
Chlorination of 1,3-thioalcohols using either Cl_2 or SO_2Cl_2 affords 1,2-oxathiolan-2-oxide **272** by way of an intermediate 3-hydroxysulfinyl chloride (**275**) (Scheme 11.86) [232].



275 **272**

Scheme 11.86

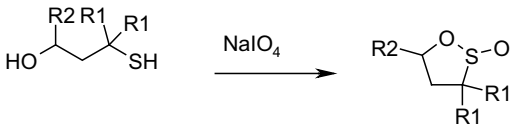
Oxathiolane **277** is prepared by treatment of *N*-alkylcystinol **276** with NCS or NBS (Scheme 11.87) [233].



276 **277**

Scheme 11.87

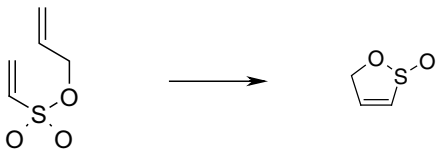
Substituted 1,3-thioalcohols **278** can also be oxidized with $NaIO_4$ to give the corresponding 1,2-oxathiolane-2-oxides **279** (Scheme 11.88) [234].



278 **279**

Scheme 11.88

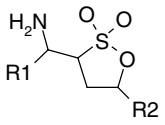
A ring-closing metathesis reaction of the allylvinyl sulfonate **280** using a second-generation Grubb's catalyst gives the oxathiole **270** (Scheme 11.89) [235].



280 **270**

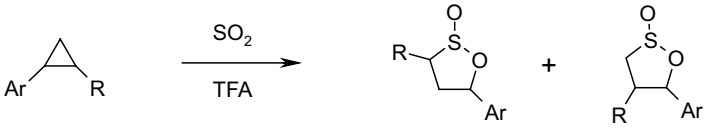
Scheme 11.89

Full details of the asymmetric synthesis of chiral γ-sultones **281** have been described [236].



281

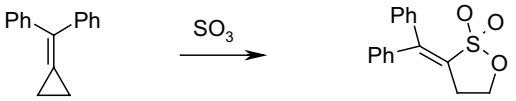
The direct reaction of cyclopropanes **282** with SO_2 in TFA to give 1,2-oxathiolane-2-oxides **283** and **284** has been studied extensively to determine the regioselectivity of this reaction (Scheme 11.90) [237].



282 **283** **284**

Scheme 11.90

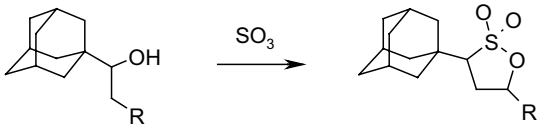
Similarly, treatment of the methylene cyclopropane **285** with SO_3 affords **286** directly (Scheme 11.91) [238].



285 **286**

Scheme 11.91

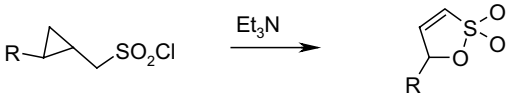
The adamantyl alcohols **287** can also be treated with SO_3 to afford 1,2-oxathiolane-2,2-dioxides **288** (Scheme 11.92) [239].



287 **288**

Scheme 11.92

The epoxide **289** can be cyclized with triethylamine to give the 1,2-oxathiolane-2,2-dioxides **290** (Scheme 11.93) [240].

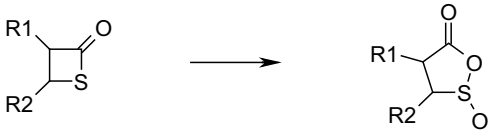


289 **290**

Scheme 11.93

11.6.3.2 **Ring Transformations of Heterocycles Leading to 1,2-Oxathiole Derivatives**

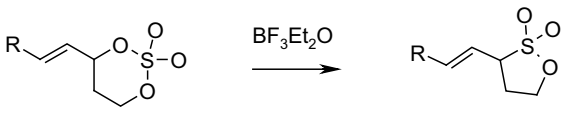
Oxidative ring expansion of thietan-2-ones **291** by treatment with chlorine or SO_2Cl_2 and acetic anhydride gives the 1,2-oxathiolan-5-one **292** (Scheme 11.94) [241].



291 **292**

Scheme 11.94

Cyclic sulfides **293** undergo ring contraction upon treatment with $BF_3{\cdot}Et_2O$ to give the 1,2-oxathiolane-2,2-dioxides **294** (Scheme 11.95) [242].



293 **294**

Scheme 11.95

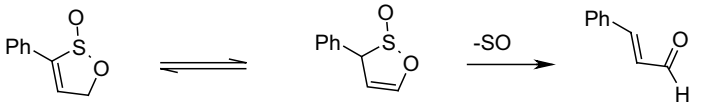
11.6.4

Reactivity of 1,2-Oxathioles and 1,2-Oxathiolanes

Most reactions in this area have involved either 1,2-oxathiolane 2-oxides or 2,2-dioxides. The type of reactions involve either thermal extrusion of SO or SO_2 or nucleophilic attack at the cyclic sulfinate or sulfonate functions.

11.6.4.1 **Thermal or Photochemical Reactions**

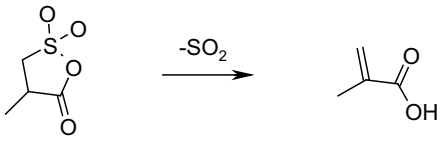
1,2-Oxathiolane 2-oxides **295** readily undergo thermal extrusion of SO to afford α,β-unsaturated carbonyl compounds. The reaction is most likely to proceed via an initial tautomerization from the 5H to the 3H form **296**, which then undergoes an electrocyclic process to give cinnamaldehyde (Scheme 11.96) [243].



295 **296**

Scheme 11.96

1,2-Oxathiolan-5-one 2,2-dioxide derivative **297** undergoes thermally induced elimination of SO_2 at 180 °C to give methacrylic acid (Scheme 11.97) [244].

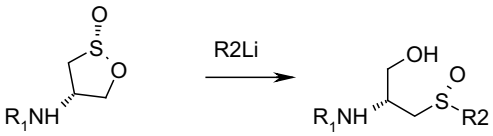


297

Scheme 11.97

11.6.4.2 **Nucleophilic Attack**

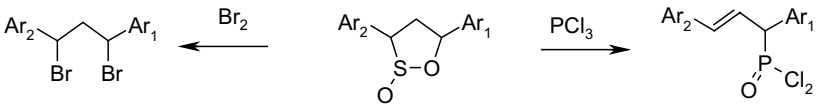
Nucleophilic attack on the cysteine-derived chiral 4-amino-1,2-oxathiolane 2-oxide **298** by alkyllithiums takes place on the sulfur atom with inversion of configuration to give **299** (Scheme 11.98) [245].



298 **299**

Scheme 11.98

Reaction of the 1,2-oxathiolane 2-oxide **300** with bromine results in the loss of SO_2 to give the 1,3-dibromo derivative **301** (Scheme 11.99) [246]. Compound **300** also reacts with PCl_3 to give the ring open product **302** [247].



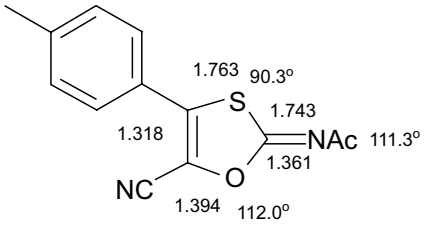
301 **300** **302**

Scheme 11.99

11.7
1,3-Oxathioles and 1,3-Oxathiolanes

11.7.1
Introduction

Little work has been published on 1,3-oxathiolium salts **303** and their mesoionic system **304** [20]. A review on 1,3-oxathiolium salts has appeared [248]. A larger amount of material has been published on 1,3-oxathioles **305.** Most studies have been



307

Figure 11.3 Geometry of a 1,3-oxathiolone derivative.

carried out on the fully saturated systems, 1,3-oxathiolanes (**306**), and reviews covering this system have appeared [249, 250].

303 **304** **305** **306**

11.7.2 Relevant Physicochemical Data

11.7.2.1 X-Ray Diffraction

The X-ray structure of **307** has been published to give the dimensions [251] shown in Figure 11.3.

11.7.2.2 NMR Spectroscopy

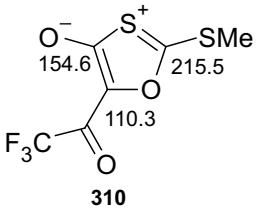
Table 11.9 gives ^{1}H NMR data for 1,3-oxathiolane systems **308** and **309**.

308 **309**

^{13}C NMR data for the mesoionic 1,3-oxathiolium 4-oxide compound **310** has been published (Figure 11.4) [254].

Table 11.9 ^{1}H NMR data for 1,3-oxathiolane derivatives.

Compound	2-H	4-H	5-H	Reference
5-Methyl-1,3-oxathiolane (**308**)	4.72/4.89	2.5/3.0	3.96	[252]
1,3-Oxathiolan-2-one (**309**)		3.59	4.53	[253]



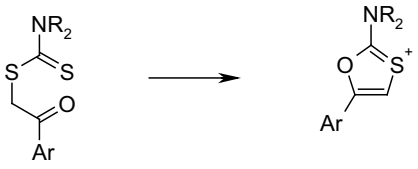
310

Figure 11.4 ^{13}C NMR data for a mesoionic 1,3-oxathiolium-4-oxide compound.

11.7.3
Synthesis

11.7.3.1 **Ring Synthesis of 1,3-Oxathioles and 1,3-Oxathiolanes**

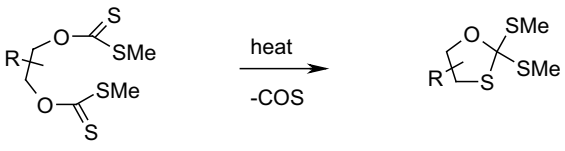
An important method for the preparation of 1,3-oxathiolium salts has been published. Phenacyldithiocarbamates **311** can be desulfurized with a silver, mercury or copper salt to afford 2-amino-1,3-oxathiolium salt **312** (Scheme 11.100) [255].



311 **312**

Scheme 11.100

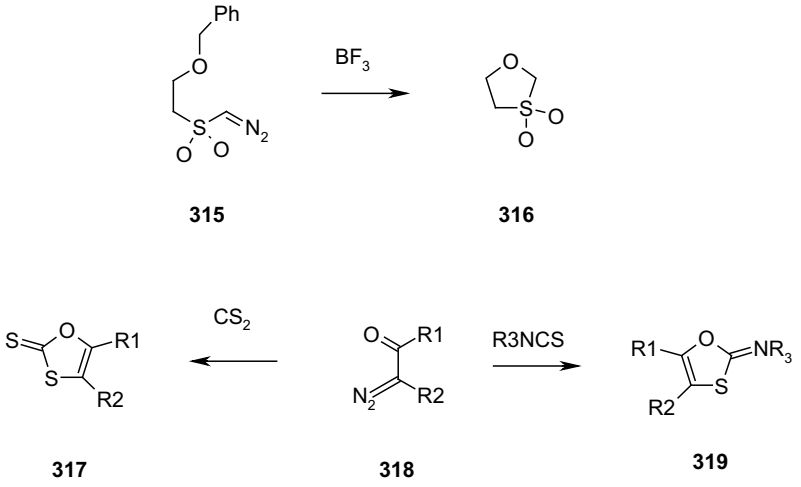
Thermolysis of the bis-dithiocarbonates **313** results in loss of COS to afford the 1,3-oxathiolane **314** in up to 90% yield (Scheme 11.101) [256].



313 **314**

Scheme 11.101

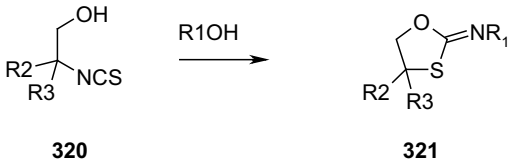
The 1,3-oxathiolane 2,2-dioxide **316** has been prepared by treatment of the diazosulfone **315** with BF_3 (Scheme 11.102) [257]. Similarly, rhodium-catalyzed decomposition of α-diazoketones **318** in the presence of CS_2 affords the 1,3-



Scheme 11.102

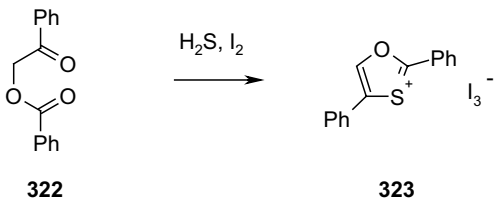
oxathiolane-2-thione **317** [258]. If the decomposition is carried out in the presence of an isothiocyanate then 2-imino derivatives **319** are formed [259].

The reaction of hydroxyethylthiocyanates **320** with a tertiary alcohol in sulfuric acid gives the 2-iminooxathiolane **321** (Scheme 11.103) [260].



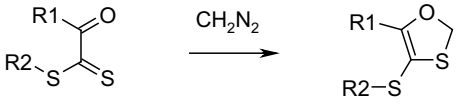
Scheme 11.103

Routes to fully conjugated systems include the reaction of the phenacyl benzoate **322** with H_2S and iodine to give the oxathiolium salt **323** in 88% yield (Scheme 11.104) [261].



Scheme 11.104

The addition of diazomethane to an α-oxothioester **324** affords 4-alkylthio substituted 1,3-oxathioles **325** (Scheme 11.105) [262].

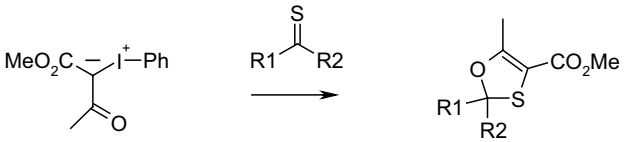


324 **325**

Scheme 11.105

The standard method of preparation of 1,3-oxathiolanes is to condense a carbonyl compound with 2-thioethanol. Several catalysts have been used for this reaction – the most common is $BF_3{\cdot}Et_2O$ [263]. More recently, other catalysts used for this reaction include triisopropyl triflate [264], indium triflate [265], NBS [266], tetrabutylammonium tribromide [267] and scandium triflate [268]. A catalyst that is selective for aldehydes in the presence of acyclic ketones is $LiBF_4$ [269]. A catalyst that is suitable for α,β-unsaturated ketones is an aminopropyl functionalized silica [270]. Dimethyl acetals can also be used in place of the carbonyl component for this reaction [271].

The iodonium salt **326** reacts with either carbon disulfide or a thioketone to form 2-thione 1,3-oxathiolane derivative **327** (Scheme 11.106) [46].



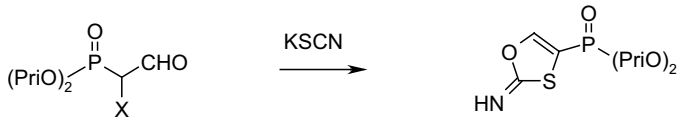
326 **327**

Scheme 11.106

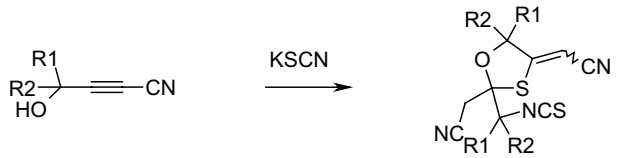
The phosphonate derivative **329** is prepared by the condensation of the α-haloaldehyde **328** with KSCN (Scheme 11.107) [272]. Acetylenic alcohols **330** also react with KSCN by a more complex course to give the 1,3-oxathiolane derivative **331** [273].

The standard method for the preparation of 2-imino-1,3-oxathioles **333** is to condense a phenacyl bromide with either a dithiocarbamate **332** (X=SR) [274] or a thiourea **332** ($X{=}NMe_2$) (Scheme 11.108) [275].

Silyl enol ethers **334** and α-halosulfonyl bromides when treated with DBN afford 1,3-oxathiole 3,3-dioxide **335** (Scheme 11.109) [276].

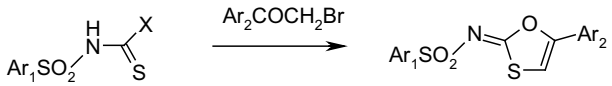


328 **329**



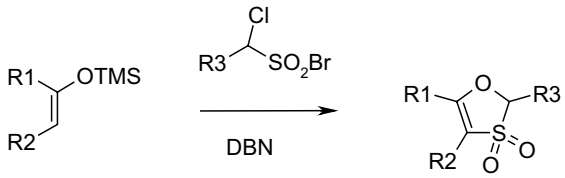
330 **331**

Scheme 11.107



332 **333**

Scheme 11.108



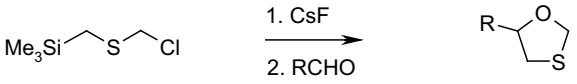
334 **335**

Scheme 11.109

Treatment of the silyl derivative **336** with CsF generates a thiocarbonyl ylide that can then be trapped by addition of aldehydes to give 5-substituted 1,3-oxathiolanes **337** (Scheme 11.110) [277].

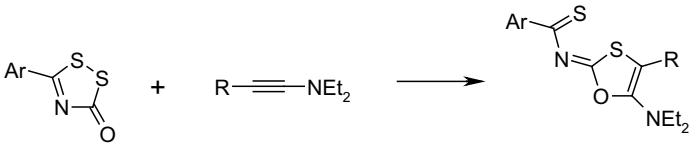
11.7.3.2 **Ring Transformations of Heterocycles Leading to 1,3-Oxathiole Derivatives**

The 1,2,4-dithiazol-3-one **338** undergoes cycloaddition to ynamines **339** to give 2-imino-1,3-oxathioles **340** (Scheme 11.111) [278]. Similarly, the 1,2,4-thiadiazol-3-one **341** reacts with enolates **342** to also give 2-imino-1,3-oxathioles **343** [279].

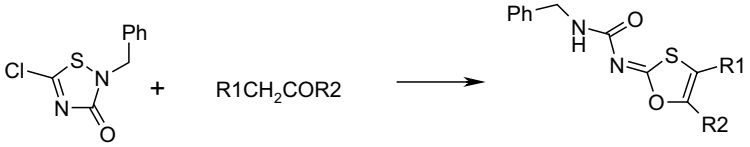


336 **337**

Scheme 11.110



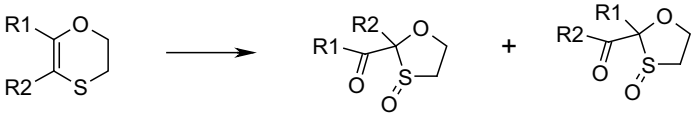
338 **339** **340**



341 **342** **343**

Scheme 11.111

The 1,4-oxathiane **344** undergoes rearrangement to the 2-acyl-1,3-oxathiolane 3-oxide derivatives **345** and **346** on treatment with singlet oxygen (Scheme 11.112) [280].



344 **345** **346**

Scheme 11.112

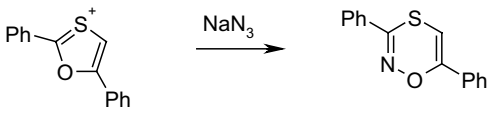
11.7.4 Reactivity of 1,3-Oxathioles

11.7.4.1 Reactions with Electrophiles

Electrophilic substitution on the heterocyclic ring of 1,3-oxathioles is essentially unknown.

11.7.4.2 Reactions with Nucleophiles

1,3-Oxathiolium salts **347** react with NaN_3 by attack at C2, followed by loss of nitrogen and rearrangement to give the 1,4,2-oxathiazine **348** (Scheme 11.113) [281].

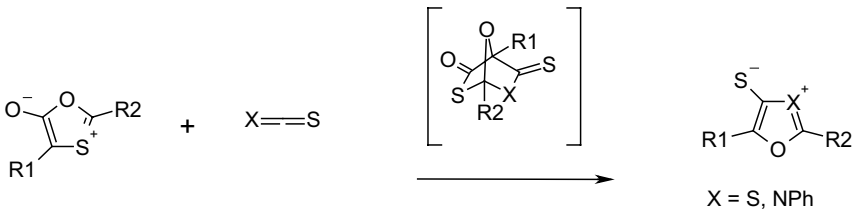


347 **348**

Scheme 11.113

11.7.4.3 Cycloaddition Reactions

Mesoionic 1,3-oxathiolium-4-olates **349** undergo ready cycloadditions with alkene and alkyne dipolarophiles. Addition of **349** to CS_2 or PhNCS proceeds by formation of a bicyclic adduct that then loses COS to give a new mesoionic system (**350**) (Scheme 11.114) [282].



349 **350**

Scheme 11.114

11.7.5 Reactivity of 1,3-Oxathiolanes

11.7.5.1 Thermal Reactions

Pyrolytic extrusion of CO_2 from both 1,3-oxathiolan-2-ones and 5-ones affords thiiranes. 2-Imino-1,3-oxathiolanes **351** rearrange to the isomeric thiazolidinones **352** at 80 °C where R=alkyl; where R=Ph an alternative pathway leads to the formation of RNCO and a thiirane (Scheme 11.115) [283].

11.7.5.2 Reactions with Electrophiles

Oxidation of 1,3-oxathiolanes to the corresponding 3-oxides is readily achieved in high yield using peroxyacetic acid [284]; *m*CPBA can also be used [285]. Asymmetric 3-oxidation using $Bu^tOOH/TiOPr^i_4$ and diethyl tartrate has been examined. The diastereoselectivity observed was moderate but the enantioselectivity observed was very poor [286].

R = Ph or alkyl

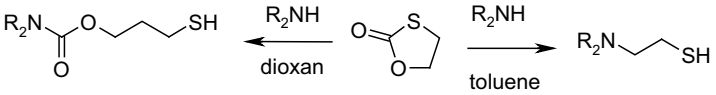
351 **352**

Scheme 11.115

11.7.5.3 Reactions with Nucleophiles

New catalysts for the efficient hydrolysis of 1,3-oxathiolanes to the corresponding aldehydes or ketones include H_2O_2/CH_3CN [287], $NaNO_2$/AcCl [288] and Amberlyst-15/glyoxylic acid under solvent-free conditions [289]. A method that is selective for 1,3-oxathiolanes in the presence of 1,3-dioxolanes is NBS in aqueous acetone [290].

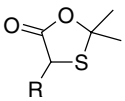
The 1,3-oxathiolan-2-one (**353**) reacts with secondary amines in toluene to afford, by loss of CO_2, thioethylamines **354** [291], when the same reaction is performed in dioxan the thiopropyl carbamate is formed (Scheme 11.116) [292].



355 **353** **354**

Scheme 11.116

1,3-Oxathiolane-5-ones such as **356** can be deprotonated and alkylated with reactive electrophiles at C4 when R=Me but not when R=H [293].



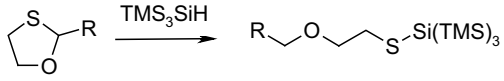
356

11.7.5.4 Radical, Electrochemical Reactions

2-Substituted 1,3-oxathiolanes **357** can undergo reductive cleavage when treated with trimethylsilyl hydride. Reduction occurs at the C2−S bond to give **358** (Scheme 11.117) [294]. 2-Substituted 1,3-oxathiolan-5-ones react in a similar way. They also undergo selective anodic fluorination to give the 4-fluoro derivatives [295].

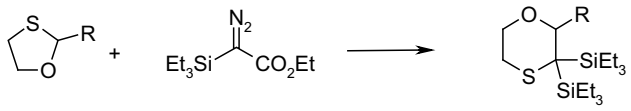
11.7.5.5 Ring Expansion

2-Substituted 1,3-oxathiolanes **357** react with carbenes to give ring-expanded 1,4-oxathianes **359** via insertion into the C2−S bond (Scheme 11.118) [296].



357 **358**

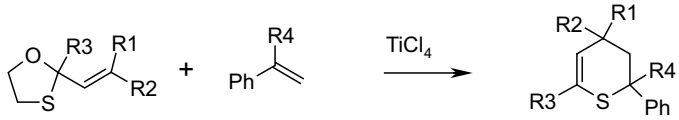
Scheme 11.117



357 **359**

Scheme 11.118

The titanium tetrachloride mediated reaction of α,β-unsaturated oxathiolanes **360** with styrene or α-methylstyrene gives the ring-expanded dihydrothiapyrans **361** (Scheme 11.119) [297].

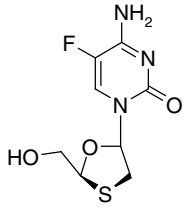


360 **361**

Scheme 11.119

11.7.6
Other Compounds of Interest

1,3-Oxathiolanes bearing a 2-propenyl, 2-furyl- or 2-phenyl group have been used as flavorings [298]. Anti-viral activity has been claimed for the nucleoside analogue **362** [299].



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12
Five-Membered Heterocycles with Three Heteroatoms: Triazoles

Larry Yet

12.1
1,2,3-Triazoles

12.1.1
Introduction

The chemistry of 1,2,3-triazoles is reviewed extensively elsewhere [1]. This chapter will focus on the general synthesis and reactivity of the monocyclic 1,2,3-triazole system with recent methods, which include solid-phase and microwave-assisted reactions.

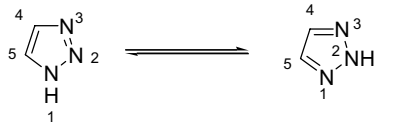
12.1.2
General Reactivity

12.1.2.1 Relevant Physicochemical Data and NMR Data

N-Unsubstituted 1,2,3-triazole can be shown as either 1*H*- or as 2*H*-triazoles since these two tautomeric forms are in equilibrium in the solution phase (Figure 12.1). In this chapter, for simplication, this type of compound will be represented as 1*H*-triazoles, independent of the predominant tautomer. In the gas phase, the 2*H*-tautomer of the 1,2,3-triazole represents more than 99.9% of the equilibrium mixture [2]. 1*H*-1,2,3-Triazole is both a weak base ($pK_a = 1.17$) and a weak acid ($pK_a = 9.40$). The basicity of *N*-unsubstituted and *N*-methyl-1,2,3-triazoles in the gas phase, in solution, and in the solid state has been determined [3].

The ^{1}H and ^{13}C NMR spectra of the parent 1,2,3-triazole for the protons and carbons at the 4- and 5-positions are identical because the compound exists as both 1*H*- and 2*H*-triazoles in solution at room temperature (Table 12.1). Other ^{1}H and ^{13}C NMR data of the methyl group attached to the 1,2,3-triazole in the 1- and 2-positions are listed for comparison.

Modern Heterocyclic Chemistry, First Edition.
Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.



1*H*-1,2,3-triazole **2*H*-1,2,3-triazole**

stable, water-soluble, colorless crystals

mp 120-121 °C

$pK_a = 9.40$

$pK_a = 1.17$ of the protonated species

Figure 12.1 Tautomeric structures of 1,2,3-triazoles.

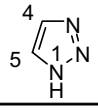
12.1.3
Relevant Natural and/or Useful Compounds

1,2,3-Triazoles are not present in natural products and are remarkably stable to metabolic transformations such as oxidation, reduction, and both basic and acidic hydrolysis. 1,2,3-Triazoles have found broad use in industrial applications such as dyes and brighteners for fibers, corrosion inhibitors for many metals and alloys, light stabilizers for organic materials and polymers, and agrochemicals such as herbicides, fungicides, and antibacterial agents [1d]. They have been considered as an interesting component from the viewpoint of biological activity and are seen in many drugs such as potent HIV-inhibitors [6], antimicrobial agents [7], and selective β_3-adrenergic receptor agonists [8]. Figure 12.2 shows the structures of β-lactam antibiotics tazobactam [9] and cefatrizine [10].

12.1.4
Synthesis of 1,2,3-Triazoles

The most important general approach to the synthesis of 1,2,3-triazoles involves the use of azide reagents. Azides that have been employed in these syntheses can be alkyl,

Table 12.1 ^{1}H and ^{13}C NMR data (ppm) of 1,2,3-triazoles.



	^{1}H NMR (DMSO-d_6)		Reference	^{13}C NMR (DMSO-d_6)		Reference
Substituents	H4	H5		C4	C5	
—	7.91	7.91	[4]	130.3	130.3	[5]
1-Me	7.72	8.08	[4]	134.3	125.5	[5]
2-Me	7.77	7.77	[4]	133.2	133.2	[5]

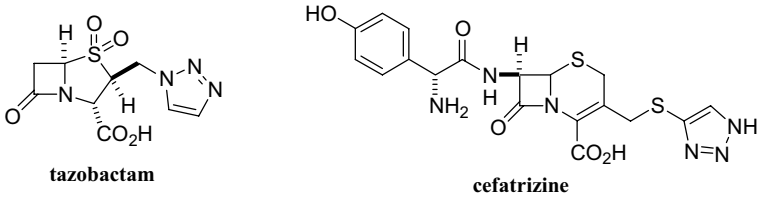


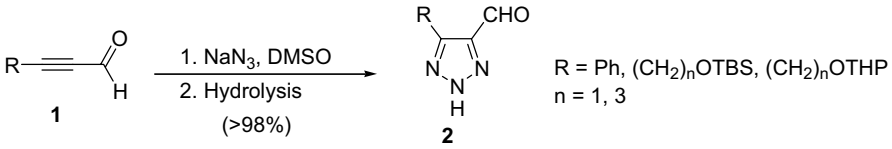
Figure 12.2 Structure of β-lactam antibiotics containing 1,2,3-triazole rings.

aryl, heteroaryl, acyl, alkoxycarbonyl and sulfonyl azides, trimethylsilyl azide, hydrazoic acid, and sodium azide. Azides can react with substituted alkynes and alkenes and with activated methylene compounds to yield various 1,2,3-triazoles.

12.1.4.1 1,3-Dipolar Cycloadditions of Alkynes with Azide Reagents

1,3-Dipolar cycloaddition of azides to alkynes is the most popular method for the syntheses of various 1,2,3-triazoles since it provides the desired product directly. A review on 1,2,3-triazole formation via 1,3-dipolar cycloaddition of acetylenes with azides under mild conditions has been published [11]. When unsymmetrical alkynes are used, two possible regioisomers are usually obtained. Isomers with the electron-withdrawing groups at the C4 position and the electron-donating groups at C5 are usually the major products.

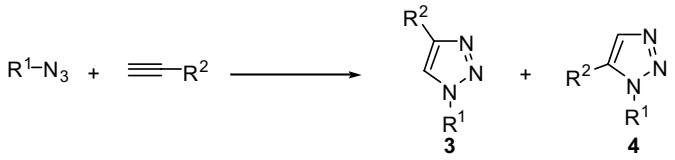
N-Unsubstituted-1,2,3-triazoles are prepared by direct addition of hydrazoic acid [12] or with azide ions [13] to alkynes, such as the reaction of α,β-acetylenic aldehydes **1** with sodium azide in dimethyl sulfoxide (DMSO) followed by hydrolysis to give 5-substituted-4-carbaldehyde-1,2,3-triazole derivatives **2** (Scheme 12.1) [14]. The major disadvantage of this method is that often thermal conditions are required for these reactions and that sodium azide can be explosive.



Scheme 12.1

The most prominent method employed for the synthesis of 1,2,3-triazoles is the addition of alkyl, aryl, and heteroaryl azides to alkynes. Azides can add to acetylene [15] and symmetrically substituted alkynes [16] to give only 4,5-unsubstituted- and 4,5-disubstituted-1,2,3-triazoles, respectively. Addition of azides to monosubstituted alkynes afford mixtures of 1,4- and 1,5-disubstituted 1*H*-1,2,3-triazoles **3** and **4**, respectively (Table 12.2). The ratio of the two products depends on the structure of the monosubstituted alkyne; alkynes with the electron-withdrawing groups preferentially give products substituted at C4 like **3**, while alkynes with electron-donating groups provide major products substituted at C5 like **4**.

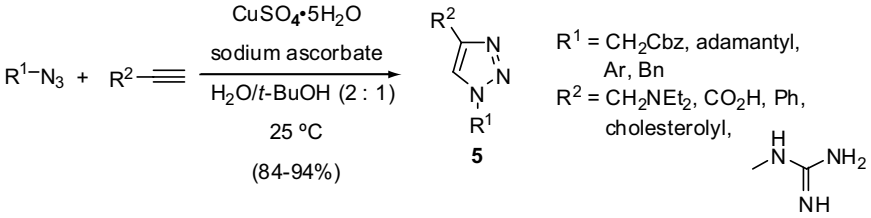
Table 12.2 Addition of azides to monosubstituted alkynes.



		Yield (%)		
R^1	R^2	3	4	Reference
Ph	Ph	43	52	[17]
Ph	CO_2Me	88	12	[18]
Bn	CONHBn	65	22	[19]
CF_2CFHCF_3	Bu	37	58	[20]
$CH_2PO(OEt)_2$	CH_2OH	30	69	[21]
4-Tol	Bz	60	11	[22]
Benzotriazolylmethyl	Ph	40	60	[23]

Recent advances in this area are the acceleration and regioselectivity of these azide additions to alkynes, which can sometimes be slow. "Click chemistry" is a recently coined term to denote a growing family of powerful chemical reactions that are based on "spring-loaded" energy-intensive substrates that can, under the right conditions, unload their energy to form stable products in high selectivity [24]. A microreview on copper(I)-catalyzed alkyne–azide "click" cycloadditions from a mechanistic and synthetic perspective has been written [25]. A mini-review has been published on the 1,3-dipolar cycloadditions of azides and alkynes as a universal ligation tool in polymer and materials science [26]. A highlight has been published on the click reaction in the luminescent probing of metal ions and its implications on biolabeling techniques [27]. A perspective on the Cu(I)-catalyzed 1,3-dipolar cycloaddition of azides and alkynes in carbohydrate chemistry, highlighting developments in the preparation of simple glycoside and oligosaccharide mimetics, glyco-macrocycles, glycopeptides, glyco-clusters, and carbohydrate arrays has been reported [28]. A review titled "Click chemistry – What's in a name? Triazole synthesis and beyond" has been published [29]. A highlight on the copper-free azide–alkyne cycloadditions with new insights and perspectives has been written [30]. Substituent effects in the 1,3-dipolar cycloadditions of azides with alkenes and alkynes have been investigated with the high accuracy CBS-QB3 method [31].

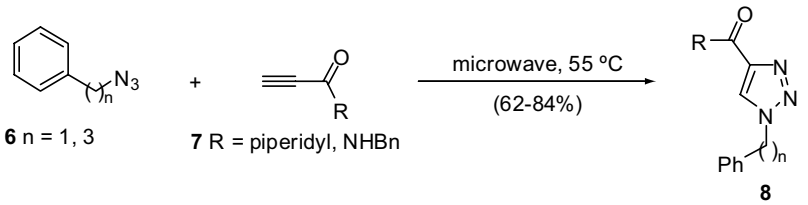
For example, a high-yielding copper-catalyzed reaction, which involves the reaction of azides to terminal alkynes in the presence of copper(II) sulfate with ascorbic acid or sodium ascorbate, gave 1,4-disubstituted-1,2,3-triazoles **5** regardless of the group on the alkynes or azides (Scheme 12.2) [32]. The mechanism of the ligand-free Cu(I)-catalyzed azide–alkyne cycloaddition reaction has been proposed in a literature report [33]. Triazole-linked glycopeptides have been obtained by Cu(I)-catalyzed cycloadditions of either azide-functionalized glycosides and acetylenic amino acids



Scheme 12.2

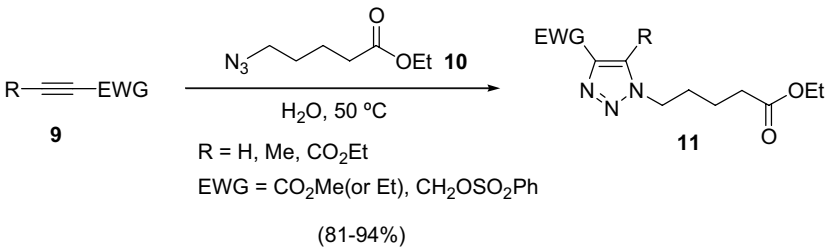
or acetylenic glycosides and azide-containing amino acids in the presence of sodium ascorbate [34]. A highly efficient one-pot synthesis of 1,2,3-triazole-linked glycoconjugates involving a Cu(I)-catalyzed 1,3-dipolar cycloaddition as a key step has been reported [35].

Microwave irradiation has also become a recent method for the synthesis of 1,2,3-triazoles under solvent-free conditions. For example, 1,3-dipolar cycloaddition of organic azides **6** with acetylenic amides **7** under solvent-free microwave irradiation produced *N*1-substituted-4*C*-carbamoyl-1,2,3-triazoles **8** (Scheme 12.3) [19]. Microwave irradiation allowed a substantial decrease in reaction times and offered greater simplicity in the purification step.



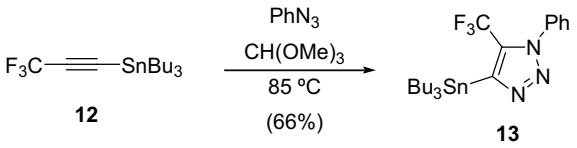
Scheme 12.3

Addition of azides to unsymmetrical disubstituted alkynes often yields mixtures of isomeric 1,2,3-triazoles. The relative ratios of the two products depend strongly on the nature of the substituents on the alkyne. A more recent example showed the 1,3-dipolar cycloadditions of azido ester **10** with electron-deficient alkynes **9** to give 1,4,5-trisubstituted 1,2,3-triazoles **11** under mild conditions in water (Scheme 12.4) [36]. 1,3-Dipolar cycloaddition of tributyl(3,3,3-trifluoro-1-propynyl)stannane (**12**) with

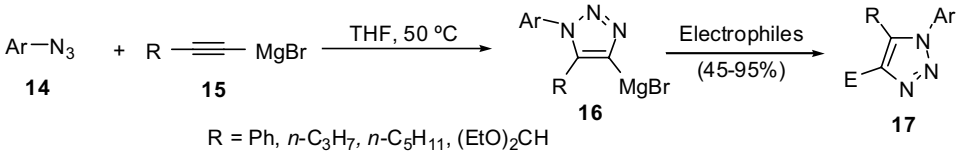


Scheme 12.4

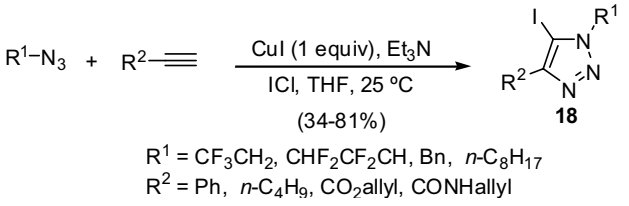
phenyl azide gave the corresponding 1,2,3-triazole **13**, which was a useful building block for further functionalization (Scheme 12.5) [37]. An interesting approach to prepare regiospecifically 4,5-disubstituted-1,2,3-triazoles is the addition of bromomagnesium acetylides **15** to aryl azides **14** to yield 1,5-disubstituted-1,2,3-triazoles **16**, which could be trapped with various electrophiles to form 1,4,5-trisubstituted 1,2,3-triazoles **17** (Scheme 12.6) [38]. In addition, copper(I) iodide promoted reaction of alkyl azides and terminal alkynes in the presence of iodine monochloride led to a regiospecific synthesis of 5-iodo-1,4-disubstituted-1,2,3-triazole **18**, which could be further elaborated to a range of 1,4,5-trisubstituted-1,2,3-triazole derivatives (Scheme 12.7) [39]. A series of 4,5-disubstituted-1,2,3-triazoles has been regiospecifically prepared directly from propargyl halides and sodium azide via the Banert cascade [40].



Scheme 12.5

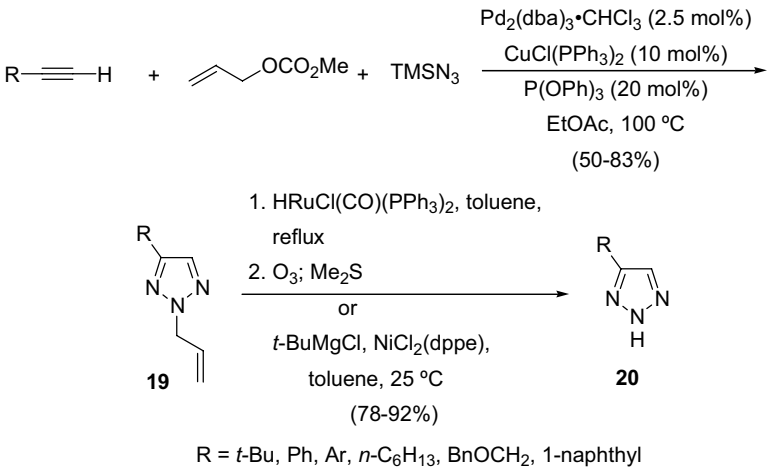


Scheme 12.6



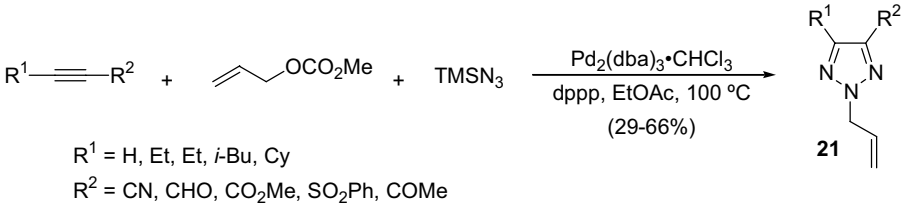
Scheme 12.7

Recently, metal-mediated methodologies have been published where 1,2,3-triazoles can be prepared regiospecifically, with non-activated terminal alkynes and trimethylsilyl azide as the safe synthetic equivalent of the highly explosive hydrazoic acid or sodium azide. Various triazoles (**19**) were synthesized from non-activated terminal alkynes, allyl methyl carbonate, and trimethylsilyl azide ($TMSN_3$) in a [3 + 2] cycloaddition with the use of a Pd(0)-Cu(I) bimetallic catalyst (Scheme 12.8) [41]. The



Scheme 12.8

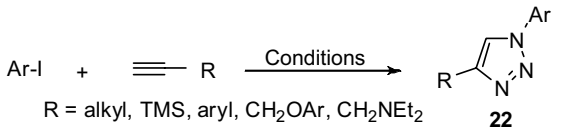
allyl group of **19** is efficiently deprotected by ruthenium-catalyzed isomerization followed by ozonolysis or by nickel-catalyzed Grignard addition reaction to give 4-substituted triazoles **20** [42]. 2-Allyl-1,2,3-triazoles **21** have been prepared regiospecifically by the palladium-catalyzed three-component coupling reaction of alkynes, allyl methyl carbonate, and trimethylsilyl azide (Scheme 12.9) [43]. Similarly, the four-component coupling reactions of silylacetylenes, allyl carbonates, and trimethylsilyl azide catalyzed by a Pd(0)-Cu(I) bimetallic catalyst led to trisubstituted 1,2,3-triazoles [44]. The [3 + 2] cycloaddition of non-activated terminal alkynes and trimethylsilyl azide proceeded smoothly in the presence of copper catalyst and *N,N*-dimethylformamide and methanol to give the corresponding *N*-unsubstituted-1,2,3-triazoles in good to high yields [45]. [3 + 2]-Cycloadditions of alkyl azides with various unsymmetrical internal alkynes in the presence of $Cp^*RuCl(PPh_3)_2$ as catalyst in refluxing benzene led to 1,4,5-trisubstituted-1,2,3-triazoles, whereas alkyl phenyl and dialkyl acetylenes underwent cycloadditions to afford mixtures of regioisomeric 1,2,3-triazoles and acyl-substituted internal alkynes reacted with complete regioselectivity [46]. In the presence of catalytic $Cp^*RuCl(PPh_3)_2$ or $Cp^*RuCl(COD)$, primary and secondary azides reacted with a broad range of terminal alkynes containing a range of functionalities to produce selectively 1,5-disubstituted-1,2,3-triazoles [47]. 1,3-Dipolar



Scheme 12.9

cycloaddition of trifluoromethylated propargylic alcohols with azides in the presence of catalytic $[Cp^*RuCl_2]_n$ afforded exclusively 4-trifluoromethyl-1,4,5-trisubstituted-1,2,3-triazoles in high yields [48]. Copper-catalyzed [3 + 2] cycloaddition of azides to mono- and disubstituted alkynes with N-heterocyclic carbene ligands has been found to be a versatile and highly efficient reaction in which an internal alkyne was successfully shown to work for the first time [49].

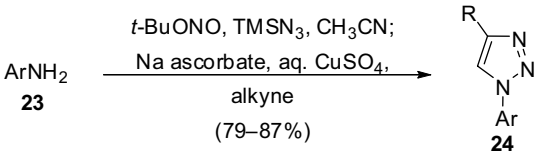
Azides can be prepared *in situ* from their respective halides and then reacted with their alkyne partners. 1,4-Disubstituted-1,2,3-triazoles **22** have been obtained in excellent yields by a convenient one-pot procedure from various aryl and alkyl iodides and terminal alkynes without isolation of potentially unstable organic azide intermediates (Scheme 12.10) [50]. The microwave-assisted synthesis of this version has been published by the same group [51]. A similar one-pot procedure uses benzyl and alkyl halides for generation of the azides with a series of terminal and disubstituted alkynes [52]. A one-pot sequential and cascade sequence involving the formation of allylic azides, from aryl/heteroaryl/vinyl halides, allene, and sodium azide, by palladium-catalyzed anion capture, and cyclization-anion capture, followed by 1,3-dipolar cycloaddition provided various 1,2,3-triazoles in good yields [53]. A copper(I)-catalyzed three-component reaction with amines, propargyl halides and azides in water affords 1-substituted-1*H*-1,2,3-triazol-4-ylmethyl)dialkylamines [54]. Terminal alkynes reacted with benzyl- or alkyl halides and sodium azide in the presence of a copper(I) catalyst immobilized on 3-aminopropyl- or 3-[(2-aminoethyl)amino]propyl-functionalized silica gel in ethanol to generate exclusively the corresponding regiospecific 1,4-disubstituted-1,2,3-triazoles in good to excellent yields [55]. An efficient and improved procedure for the preparation of aromatic azides from the corresponding aromatic amines **23** is accomplished under mild conditions with *tert*-butyl nitrite and trimethylsilyl azide and their application in the Cu(I)-catalyzed azide–alkyne 1,3-dipolar cycloaddition gives 1,4-disubstituted-1,2,3-triazoles **24** without the need for isolation of the azide intermediates (Scheme 12.11) [56].



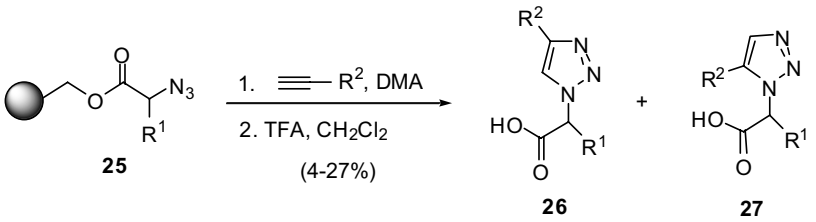
Condition A: NaN_3, L-Proline, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, Na_2CO_3, DMSO/H_2O (9 : 1), 60 °C (66-98%)
Condition B: NaN_3, *trans*-1,2-(methylamino)cyclohexane, CuI, sodium ascorbate, DMSO/H_2O (5 : 1), 25 °C (38-99%)

Scheme 12.10

Many recent reports have shown that polymer-supported azides and alkynes can be employed in the synthesis of 1,2,3-triazole derivatives. Functionalized 1,2,3-triazoles **26** and **27** were prepared by [3 + 2] cycloaddition of resin-bound α-azido esters **25** with terminal alkynes (Scheme 12.12) [57]. Polystyrene resin-bound azide **28** reacted

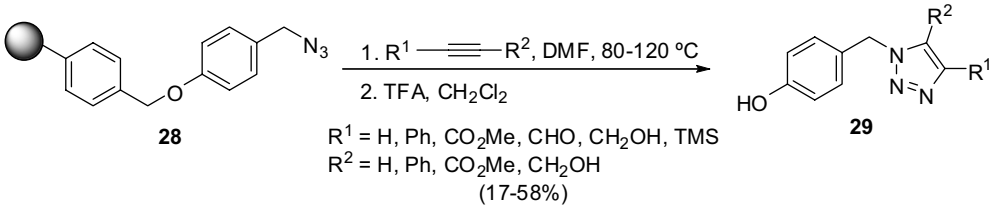


Scheme 12.11

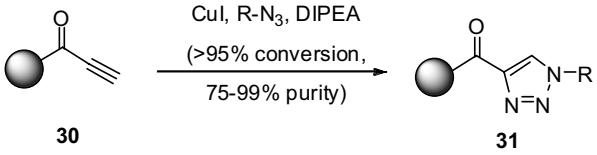


Scheme 12.12

with disubstituted alkynes followed by acidic cleavage to give 1,2,3-triazoles **29** (Scheme 12.13) [58]. Regiospecific copper(I)-catalyzed 1,3-dipolar cycloadditions of resin-bound alkynes **30** to azides afforded solid-supported 1,2,3-triazoles **31**, which were ligated further to give 1,4-substituted-1,2,3-triazole-peptide compounds (Scheme 12.14) [59]. Immobilized REM resin azides have provided a regioselective method for the preparation of 1,5-trisubstituted-1*H*-1,2,3-triazoles via a 1,3-dipolar cycloaddition of trimethylsilyl-propynoic acid [60]. A library of peptidotriazoles have been prepared by solid-phase peptide synthesis combined with a regiospecific copper (I)-catalyzed 1,3-dipolar cycloaddition between resin-bound alkynes and protected amino azides [61].

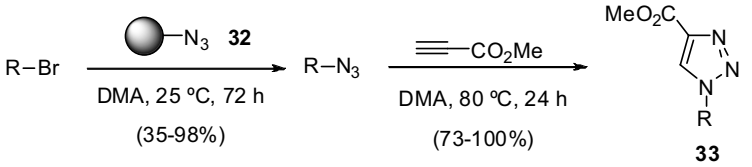


Scheme 12.13

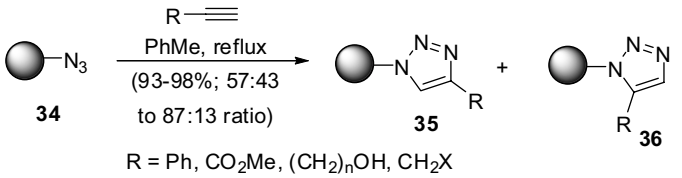


Scheme 12.14

There are published reports on the use of polymer-supported azide reagents in the 1,3-dipolar cycloadditions of alkynes. Different alkyl bromides reacted with Merrifield resin supported ammonium azide (**32**) to give various alkyl azides, which were reacted with methyl propiolate to give 1,2,3-triazoles **33** in excellent yields (Scheme 12.15) [62]. The monomethyl ether of poly(ethylene glycol) (PEG)- or MeOPEG-bound azide **34** has been utilized in the 1,3-dipolar cycloadditions with various alkynes to afford regioisomeric mixtures of **35** and **36** (Scheme 12.16) [63]. The 1,2,3-triazoles could be cleaved with formic acid in dioxane in one example (R = CO_2Me). 1,3-Dipolar cycloaddition of poly(ethylene glycol)-supported azide with various dipolarophiles followed by acidic cleavage afforded 4- and 5-substituted-1,2,3-triazoles [64].



Scheme 12.15

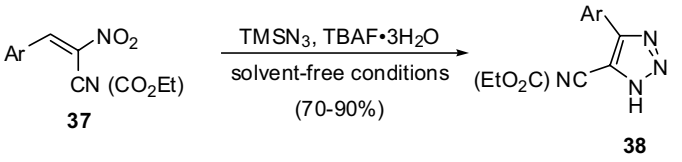


Scheme 12.16

12.1.4.2 Reactions of α,β-Unsaturated Systems with Azide Reagents

α,β-Unsaturated systems are good substrates for azide additions to prepare 1,2,3-triazole derivatives. Frequently, the azides undergo addition to unactivated or activated alkenes with electron-withdrawing or electron-rich substituents, such as enamines, enamides, enol ethers, and ketene acetals, to give 4,5-dihydro-1*H*-1,2,3-triazoles, which are unstable and by elimination of a stable fragment functional group aromatizes to 1,2,3-triazoles. Generally, the addition of azides to alkenes is regioselective and only one isomer is obtained.

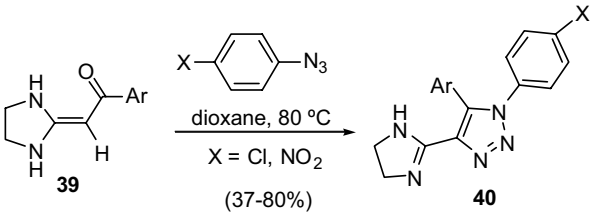
Several reports have been published on sodium azide additions to alkenes with strongly electron-withdrawing substituents to give *N*-unsubstituted-1,2,3-triazoles [65]. For example, tetrabutylammonium fluoride-catalyzed [3 + 2] cycloaddition reactions of 2-aryl-1-cyano(or carbethoxy)-1-nitroethenes **37** with trimethysilyl azide under solvent-free conditions provided 4-aryl-5-cyano(or carbethoxy)-1*H*-1,2,3-triazoles **38** in good to excellent yields under mild conditions (Scheme 12.17) [66a].



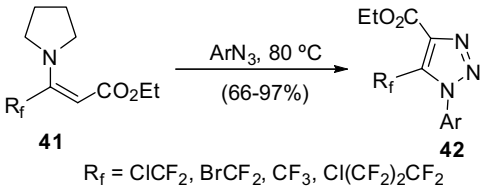
Scheme 12.17

Similarly, nitroalkenes or vicinal acetoxy nitro derivatives underwent a clean reaction with sodium azide in hot dimethyl sulfoxide to give the corresponding 1,2,3-triazoles in good yield [66b]. There are reports of additions of azide reagents to enol ethers [67], vinyl acetates [68], α-acylphosphorus ylides [69], allenes [70], and alkenes with very strong electron-withdrawing groups like nitro and sulfonyl [71] to produce the corresponding 1,2,3-triazoles.

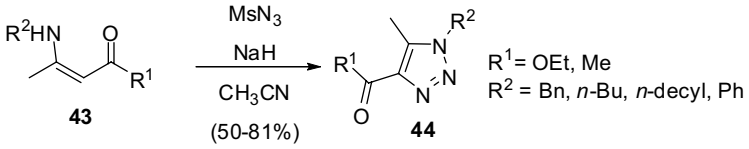
There are several interesting reports on the additions of various azide additions to enamine-type alkenes to give 1,2,3-triazoles where the amine portion either becomes part of the product or is eliminated as a fragment via the unstable 4,5-dihydro-1*H*-1,2,3-triazole intermediate. For example, aroyl-substituted ketene aminals **39** react with aryl azides to provide polysubstituted 1,2,3-triazoles **40** (Scheme 12.18) [72]. A series of 5-fluoroalkylated 1*H*-1,2,3-triazoles **42** have been prepared in good yield by the regiospecific 1,3-dipolar cycloaddition reaction of (*Z*)-ethyl-3-fluoroalkyl-3-pyrrolidinoacrylates **42** with aryl azides (Scheme 12.19) [73]. Benzyl azides also participated in these reactions but sodium carbonate was required to provide good yields of the triazoles. Condensation of enaminones **43** with mesyl azide (MsN_3) gave 1,4,5-trisubstituted-1,2,3-triazoles **44** (Scheme 12.20) [74]. A solid-phase version of this reaction has also been reported [75].



Scheme 12.18

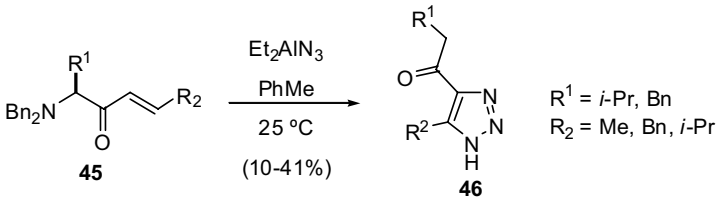


Scheme 12.19



Scheme 12.20

4-Acyl-1*H*-1,2,3-triazoles **46** have been formed from diethylaluminium azide and α,β-unsaturated ketones **45** by [3 + 2] cycloaddition of azide, followed by 1,5-hydride transfer to the β carbon of the triazoline side chain and fragmentation of the tertiary amino group (Scheme 12.21) [76].

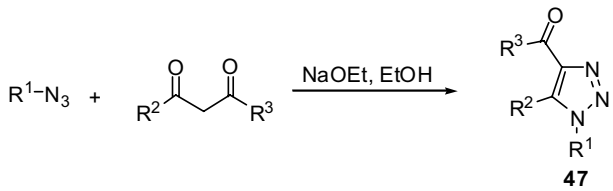


Scheme 12.21

12.1.4.3 Reactions of Azides and Hydrazines with Active Methylene Compounds

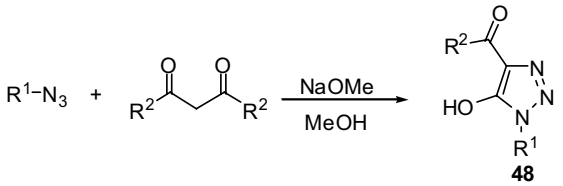
Base-catalyzed condensation of azides with active methylene compounds, known as the Dimroth reaction, is a versatile method for the preparation of 1,2,3-triazoles regioselectively. The 5-position of the 1,2,3-triazole can be an alkyl, aryl, hydroxyl, alkoxycarbonyl, or an amino group depending on the functional group of the active methylene compound used. Various azides can react with 1,3-diketones, 3-oxoesters, and 3-oxoamides to give 4-carboxy-1,2,3-triazoles **47** in good yields (Table 12.3) [77–79].

Table 12.3 Reactions of azides with active methylene compounds to give 4-carboxy-1,2,3-triazoles.



R^1	R^2	R^3	Yield (%)	Reference
4-$O_2NC_6H_4$	Me	Me	83	[77]
3,5-$Cl_2C_6H_3CH_2$	Me	OEt	89	[78]
2-O_2N-4-ClC_6H_3	Me	NHPh	80	[79]

Table 12.4 Reactions of organic azides with malonic esters and amides to give 1*H*-1,2,3-triazol-5-ols.



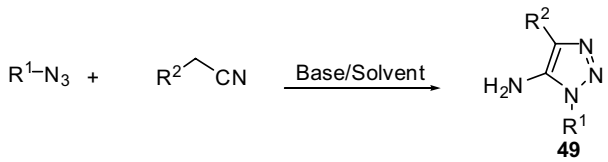
48

R^1	R^2	Yield (%)	Reference
Bn	OEt	88	[80]
4-pyridyl	OEt	75	[81]
Ph	NHPh	72	[82]

Furthermore, the base-catalyzed reaction of organic azides with malonic esters and malonamides gave the best synthesis of 1*H*-1,2,3-triazol-5-ols **48** with an alkyloxy(or aryloxy)carbonyl or carbamoyl functions at C4 (Table 12.4) [80–82]. Similarly, reactions of azides under base-catalyzed conditions with acetonitrile derivatives yielded 1-substituted-1*H*-1,2,3-triazol-5-amines **49** (Table 12.5) [83–85].

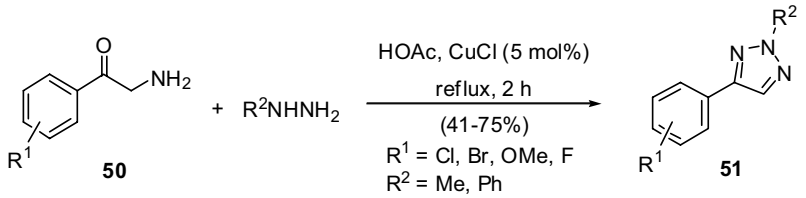
There are also reports where activated acyl compounds can react with hydrazines instead of azides to give substituted 1,2,3-triazoles. For example, α-aminoacetophenones **50** react with hydrazines in acetic acid to give an efficient preparation of 2,4-disubstituted-1,2,3-triazoles **51** (Scheme 12.22) [86]. Various phenacyl halides **52** react with excess tosyl hydrazide in refluxing methanol to provide 4-aryl-1-(*p*-toluenesulfonylamido)-1,2-3-triazoles **53** (Scheme 12.23) [87]. A general and efficient

Table 12.5 Reactions of organic azides with acetonitrile derivatives to give 1*H*-1,2,3-triazol-5-amines.

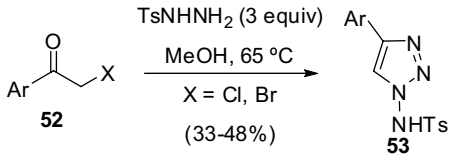


49

R^1	R^2	Base/solvent	Yield (%)	Reference
$PhSCH_2$	2-FC_6H_4	K_2CO_3/DMSO	29	[83]
Bn	Ph	K_2CO_3/DMSO	84	[84]
Bn	CN	K_2CO_3/DMSO	48	[84]
Bn	$CONH_2$	K_2CO_3/DMSO	84	[84]
2-$O_2NC_6H_4$	$CONH_2$	NaOEt/EtOH	55	[85]

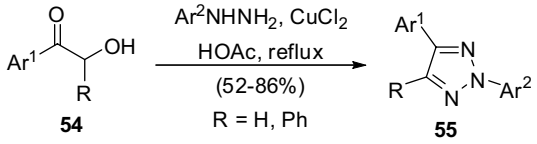


Scheme 12.22



Scheme 12.23

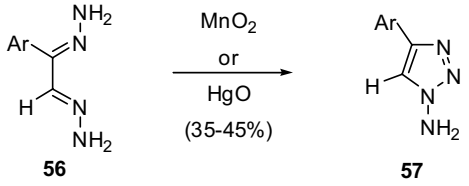
method for the preparation of 2,4-diaryl-1,2,3-triazoles **55** from α-hydroxyacetophenones **54** and arylhydrazines has been reported (Scheme 12.24) [88].



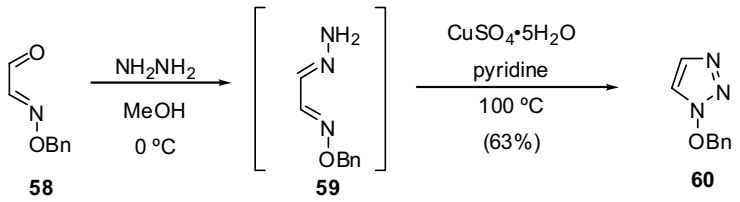
Scheme 12.24

12.1.4.4 Oxidation/Cyclization of Hydrazones

Oxidation of bis(hydrazones) **56** with manganese dioxide or mercury(II) oxide affords 4-aryl-1*H*-1,2,3-triazol-1-amines **57** as the only regioisomer (Scheme 12.25) [89]. However, other vicinal bis(hydrazones) have generated regioisomeric 1*H*-1,2,3-triazoles [90, 91]. Unsymmetrical vicinal bis(arylsulfonylhydrazones) have been cyclized either with acid or base to give 1-(arylsulfonylamino)-1*H*-1,2,3-triazoles as a mixture of regioisomers [92].

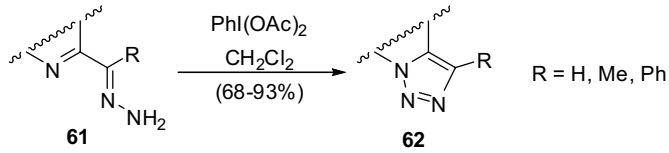


Scheme 12.25

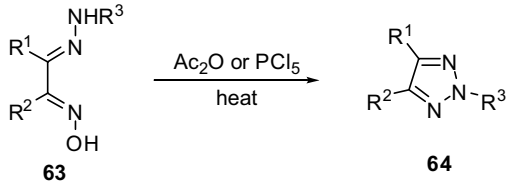


Scheme 12.26

Imine hydrazones can be cyclized in the presence of oxidants to give 1,2,3-triazole derivatives. Glyoxal *O*-benzyloxime hydrazone **59**, which is generated *in situ* from the reaction of glyoxal *O*-benzyloxime **58** with excess hydrazine, afforded 1-(benzyloxy)-1*H*-1,2,3-triazole (**60**) by oxidative cyclization (Scheme 12.26) [93]. Similarly, iodobenzene diacetate-mediated oxidation of hydrazones **61** furnished fused 1,2,3-triazoloheterocycles **62** (Scheme 12.27) [94]. α-Hydroxyimino hydrazones **63** undergo intramolecular cyclization with elimination of water to generate 2*H*-1,2,3-triazole derivatives **64** in the presence of acetic anhydride or phosphorus pentachloride (Scheme 12.28) [95].



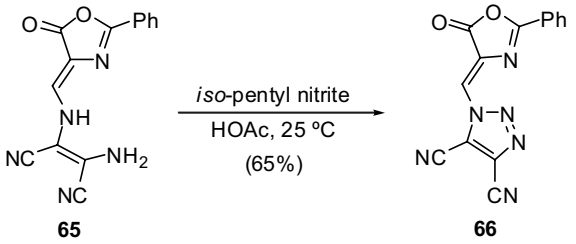
Scheme 12.27



Scheme 12.28

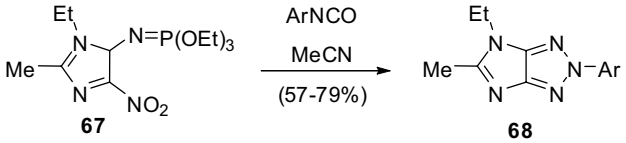
12.1.4.5 **Other Methods for Preparations of 1,2,3-Triazoles**

Several other recent methods for preparation of 1,2,3-triazoles do not fall into the above categories. Treatment of oxazolone **65** with *iso*-pentyl nitrite in the presence of acetic acid gives 1,2,3-triazole **66**, a precursor to β-(*N*-1,2,3-triazolyl)-substituted-α,β-unsaturated-α-amino acid derivatives (Scheme 12.29) [96]. 2-Aryl-2*H*,4*H*-imidazo[4,5-*d*][1,2,3]triazoles **68** have been prepared from the reaction of triethyl *N*-1-ethyl-2-methyl-4-nitro-1*H*-imidazol-5-yl phosphoramidate (**67**) with aryl isocyanates (Scheme 12.30) [97]. *N*-(Uracil-6-yl)-*S*,*S*-diphenylsulfilimine (**69**) reacted with aryldiazonium salts to give arylsulfilimines **70**, which were thermolyzed to the 1,2,3-



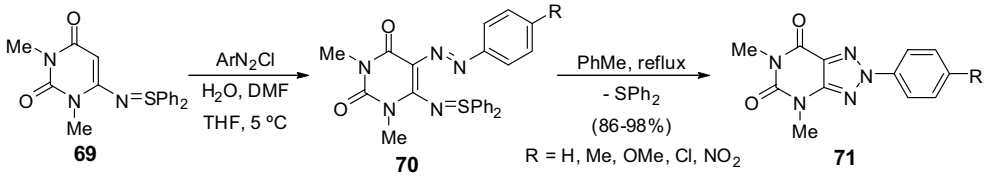
65 66

Scheme 12.29



67 68

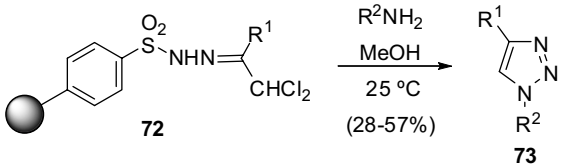
Scheme 12.30



69 70 71

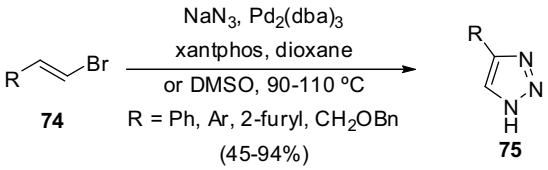
Scheme 12.31

triazolopyrimidine diones **71** in good yields (Scheme 12.31) [98]. Polystyrene-sulfonyl hydrazide resins **72** reacted with various amines to give regiospecifically 1,4-disubstituted-1,2,3-triazoles **73** via traceless cleavage reactions (Scheme 12.32) [99]. Palladium-catalyzed synthesis of 1*H*-triazoles **75** from alkenyl bromides **74** and sodium azide in the presence of xantphos ligand has been reported (Scheme 12.33) [100]. A new one-pot procedure has been developed to synthesize 1-aryl- and 1-vinyl-1,2,3-triazoles directly from boronic acids and alkynes, which avoids the need to isolate unstable azide intermediates [101].



72 73

Scheme 12.32



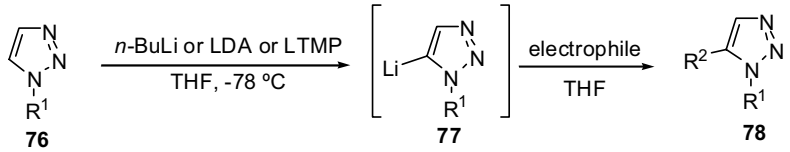
Scheme 12.33

12.1.5 Reactions of 1,2,3-Triazoles

12.1.5.1 Reactions of Carbon of 1,2,3-Triazoles

In general, the 1,2,3-triazole ring system is relatively resistant to both oxidation and reduction conditions but many synthetically useful reactions can still be achieved with this system. For example, lithiation of *N*-protected 1,2,3-triazoles is one of the most general methods for introduction of carbon or hetero substituents onto the C5 position of the ring. 1-Substituted-1,2,3-triazoles **76** react easily with *n*-butyllithium, lithium diisopropylamide (LDA), or with lithium tetramethylpiperidine (LTMP) to generate lithio species **77**, which are quenched with various electrophiles to give 1,5-disubstituted-1,2,3-triazoles **78** (Table 12.6) [93, 102, 103]. Low temperatures must be maintained, otherwise cycloreversion to the alkyne species can result. Alkyl, alcohol,

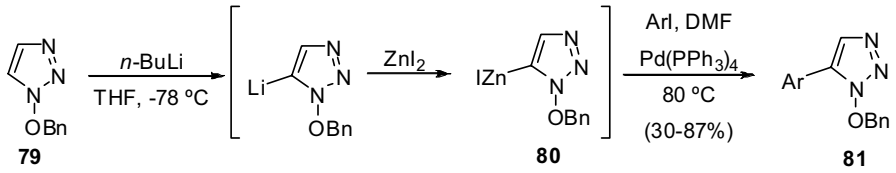
Table 12.6 Lithiation of 1*H*-1,2,3-triazoles and quenching with electrophiles.



R^1	R^2	Electrophile	Yield (%)	Reference
SEM	CH(OH)Ph	PhCHO	45	[102]
SEM	Me	MeI	30	[102]
SEM	Cl	Cl_3CCCl_3	50	[102]
SEM	SPh	PhSSPh	80	[102]
OBn	Me	MeI	93	[93]
OBn	CHO	DMF	87	[93]
OBn	Cl	Cl_3CCCl_3	88	[93]
OBn	Br	Br_2	86	[93]
OBn	$SnBu_3$	Bu_3SnCl	91	[93]
OBn	CO_2Me	$ClCO_2Me$	76	[93]
OBn	TMS	TMSCl	93	[93]
Me	Me	MeI	56	[103]
Me	CH(OH)Ph	PhCHO	61	[103]
Me	PhC(O)	$PhCONMe_2$	78	[103]
Me	$PhCOCH_2$	$PhCOCH_2Br$	66	[103]

halogen, sulfur, silicon, tin, aldehyde, and ester products can be formed from these reactions. The 2-(trimethylsilyl)ethoxymethyl (SEM) and benzyloxyl (OBn) N-protecting groups both stabilize the intermediate triazol-5-yllithium species by intramolecular coordination. The SEM group can be deprotected easily with dilute hydrochloric acid or with tetrabutylammonium fluoride to give the 5-substituted-1*H*-1,2,3-triazoles, while the Bn group can be deprotected with catalytic hydrogenation to give the corresponding 5-substituted-1*H*-1,2,3-triazol-1-ols. From Table 12.6, higher yields are generally obtained for the same type of reaction (Cl, Me) when the nitrogen was protected with the benzyloxy group [93]. Lithiation of 1-methyl-1*H*-1,2,3-triazole with *n*-butyllithium or with LTMP followed by addition of electrophiles gives moderate yields of 5-alkyl- or 5-acyl-1-methyl-1,2,3-triazoles [103]. Bromine–lithium exchange can be carried out on 4,5-dibromo-1-(methoxymethyl)-1*H*-1,2,3-triazole with *n*-butyllithium and subsequent quenching with various electrophiles gives high yields of the corresponding 5-substituted-1,2,3-triazoles [104].

1-(Benzyloxy)-1*H*-1,2,3-triazoles **79** have been lithiated followed by transmetalation to the zinc species **80**, which undergoes Negishi cross-coupling with aryl iodides to generate 5-aryl-1,2,3-triazoles **81** (Scheme 12.34) [105].



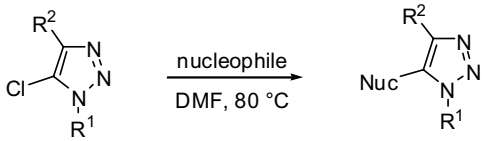
Scheme 12.34

Substitution of halogens by nucleophiles is possible in *N*-substituted-1,2,3-triazoles. Displacement of the chloro group in *N*-substituted-1,2,3-triazoles **82** by nucleophiles, such as cyanide, phenolates, arene, and furylthiolates, gave moderate to good yields of derivatives **83** (Table 12.7) [106–109]. Heating 1-aryl-5-chloro-1*H*-1,2,3-triazoles with hydrazine gave 5-substituted-1*H*-1,2,3-triazol-1,5-diamines, via the 5-hydrazinotriazole intermediates which spontaneously rearrange under the reaction conditions [110]. 5-Bromo-1-methyl-1*H*-1,2,3-triazole reacts with aniline to give the corresponding 5-anilino derivative [111].

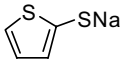
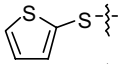
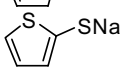
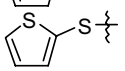
12.1.5.2 Reactions of Nitrogen of 1,2,3-Triazoles

1*H*-1,2,3-Triazoles can be N-alkylated with alkyl halides in the presence of bases such as sodium alkoxide, sodium hydride, or sodium hydroxide to give mixtures of 1- and 2-alkylated-1*H*-1,2,3-triazoles [112]. Selectivity for alkylation at the 1-position has been achieved in the presence of silver or thallium salts of 1,2,3-triazoles on reaction with alkyl halides [113]. Reaction of 2-(trimethylsilyl)-2*H*-1,2,3-triazoles with primary alkyl halides afforded products of selective alkylation at N1 [103]. 1*H*-1,2,3-Triazoles can be N-acylated with acyl halides and anhydrides to give exclusively 1-acyl-1*H*-1,2,3-triazoles; however, the acyl group can migrate to the 2-position on heating or on treatment with base [114].

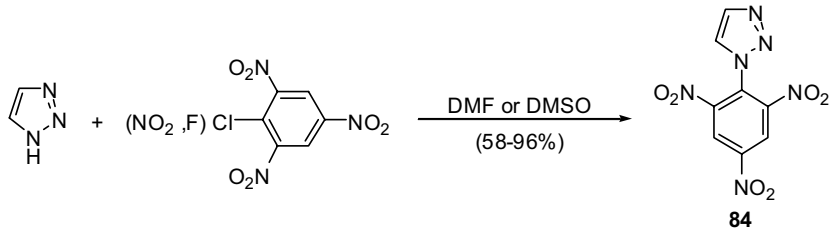
Table 12.7 Nucleophilic displacement of 5-chloro-*N*-substituted-1,2,3-triazoles with nucleophiles.



82 **83**

R^1	R^2	Nucleophile	Nuc	Yield (%)	Reference
PMB	CO_2Et	NaCN	CN	66	[106]
PMB	CO_2Et	4-$OMeC_6H_4SNa$	4-$OMeC_6H_4S$	74	[106]
Ph	Ph	NaCN	CN	75	[107]
Bn	CO_2Et	NaOPh	OPh	82	[108]
Bn	CO_2Me			48	[109]
PMB	CO_2Me			34	[109]

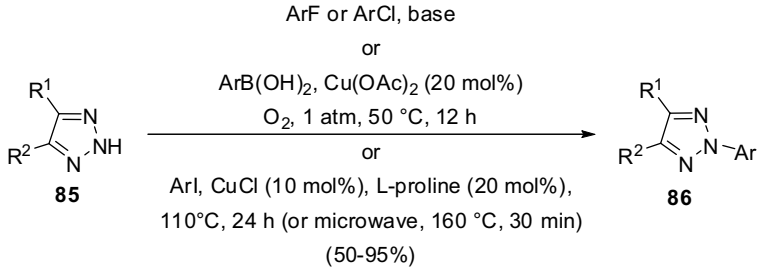
N-Arylation of 1,2,3-triazoles is possible with activated aryl halides. Activated aryl halides such as 1-fluoro-2-nitrobenzene and 1-fluoro-4-nitrobenzene with 1*H*-1,2,3-triazoles afforded mixtures of the corresponding 1- and 2-nitrophenyl-1,2,3-triazoles [115, 116]. However, reactions with even more activated halides such as 1-fluoro-2,4-dinitrobenzene and 2-chloro(or fluoro)-1,3,5-trinitrobenzene provided only 1-substituted-1*H*-1,2,3-triazoles **84** (Scheme 12.35) [116]. The copper-catalyzed arylation of 1,2,3-triazole with iodobenzene proved to be problematic as competitive *N*-1/*N*-2 arylation products were observed [117]. Efficient post-triazole regioselective *N*-2 arylation to give **86** has been developed from C4, C5 disubstituted-1,2,3-NH-triazoles **85** (Scheme 12.36) [118].



84

Scheme 12.35

1*H*-1,2,3-Triazoles can also N-substituted with heteroatoms. For example, 4,5-diphenyl-1*H*-1,2,3-triazole has been aminated with hydroxylamine-*O*-sulfonic acid to yield mixtures of *N*-aminotriazoles substituted in the 1- and 2-positions [119]. 1*H*-1,2,3-Triazoles can be oxidized by peracids such as 3-chloroperoxybenzoic acid and hydrogen peroxide to give 1*H*-1,2,3-triazol-1-ols [92, 120], which are also obtained by catalytic hydrogenation of 5-substituted-1-(benzyloxy)-1*H*-1,2,3-triazoles [92, 121].

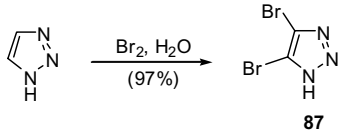


Scheme 12.36

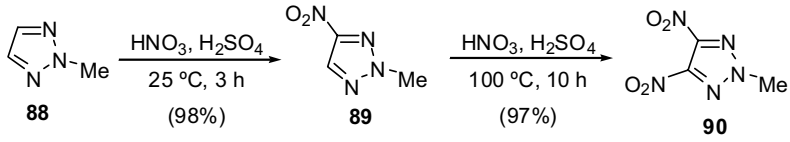
12.1.5.3 Electrophilic Reactions of 1,2,3-Triazoles

Halogenations are the most common type of electrophilic reactions of 1,2,3-triazoles. For example, 1*H*-1,2,3-triazole reacts with bromine to afford 4,5-dibromo-1*H*-1,2,3-triazoles (**87**) in almost quantitative yield (Scheme 12.37) [122]. 4-Bromo- and 5-bromo-1*H*-1,2,3-triazoles are obtained indirectly by bromination of a triazole with a protecting group at N1 [123]. In general, most halogens are introduced into the carbons of the ring system by a lithiation/electrophilic sequence (Section 12.1.5.1).

Direct nitration of 1*H*-1,2,3-triazole is not possible. Nitration of 1-phenyl and 4-phenyl-1*H*-1,2,3-triazole was also unsuccessful as nitration occured only on the phenyl ring [124]. However, nitration of 2-methyl-2*H*-1,2,3-triazole (**88**) with a mixture of fuming nitric acid and concentrated sulfuric acid afforded 2-methyl-4-nitro-2*H*-1,2,3-triazole (**89**), which can be nitrated further to **90** under more vigorous conditions (Scheme 12.38) [125].



Scheme 12.37



Scheme 12.38

12.2 Benzotriazole

12.2.1 Introduction

12.2.2 General Reactivity

12.2.2.1 Relevant Physicochemical Data and NMR Data

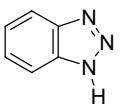
The parent benzotriazole is a weak base with a pK_a of 8.2, which is a stronger NH acid than indazole, benzimidazole, or 1,2,3-triazole (Figure 12.3). The 1-substituted 1*H*-benzotriazole is remarkably stable to strong acid and bases and to oxidative and reductive conditions. The two tautomeric forms of benzotriazole (Figure 12.4) are in equilibrium, but 1*H*-benzotriazole is the predominant species (99.9%) in both the gas and solution phases [2].

The ^{1}H and ^{13}C NMR spectra of the parent benzotriazole for the protons and carbons at the 4-/7- and 5-/6-positions are identical because benzotriazole undergoes rapid proton exchange between the tautomeric forms at room temperature (Table 12.8). Other ^{1}H and ^{13}C NMR data of the methyl group attached to the benzotriazole in the 1- and 2- positions are listed for comparison.

12.2.3 Synthesis of Benzotriazoles

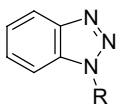
12.2.3.1 Synthesis by Ring-Closure Reactions

Diazotization of benzene-1,2-diamine derivatives is the most common synthetic route to 1-substituted benzotriazoles. Diazotization is mostly commonly performed with nitrous acid, generated *in situ* from sodium nitrite and a mineral acid source such as nitric, sulfuric, or acetic acids. A range of various 1-substituted benzotriazoles **92** can be prepared from the corresponding benzene-1,2-diamine derivatives **91** (Table 12.9).



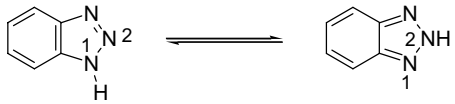
acid pKa 8.2 for proton loss
very weak Bronsted base (pKa for proton addition)
Lewis base of appreciable strength
non-volatile, crystalline, odorless, nontoxic
almost insoluble in water, soluble in sodium carbonate solution

Chemical Stability of Benzotriazole Ring System



Stable: thermally to 400 °C
to hot strong sulfuric acid
to fused potassium hydroxide
to oxidation
to reduction

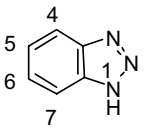
Figure 12.3 Physical and chemical properties of the parent and 1-substituted 1*H*-benzotriazole.



1*H*-benzotriazole **2*H*-benzotriazole**

Figure 12.4 Tautomerisim in benzotriazoles.

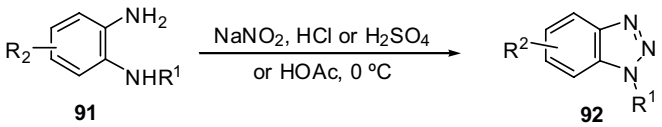
Table 12.8 ^{1}H and ^{13}C NMR data (ppm) of benzotriazoles.



Substituents	^{1}H NMR (DMSO-d_6)					^{13}C NMR (DMSO-d_6)				Reference
	H4	H5	H6	H7	Reference	C4	C5	C6	C7	
—	8.00	7.44	7.44	8.00	[126]	130.3	130.3	130.3	130.3	[128]
1-Me	8.02	7.47	7.47	7.36	[127]	119.3	123.4	126.8	108.8	[129]
2-Me	7.85	7.34	7.34	7.85	[127]	117.5	125.9	125.9	117.5	[129]

1-Substituted benzotriazoles can be prepared from various azides with a benzyne intermediate generated *in situ* from 2-aminobenzoic acid (Table 12.10). 1-Chloro-2-nitrobenzenes **93** react with hydrazine to yield benzotriazol-1-ols **95** via the 2-nitrophenylhydrazines **94** (Table 12.11). The polymer-supported synthesis versions of benzotriazol-1-ols has also been published [141, 142]. These benzotriazol-1-ols can be readily deoxygenated to their NH derivatives by reductive cleavage with either phosphorus trichloride or samarium(II) iodide [142]. Various substituted benzotria-

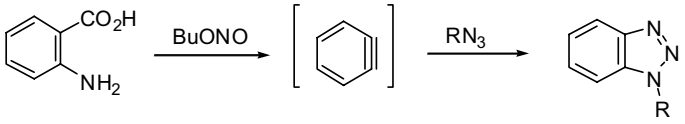
Table 12.9 Diazotization of benzene-1,2-diamine derivatives to give 1-substituted benzotriazoles.



91 **92**

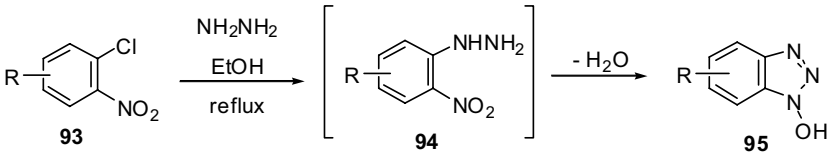
R^1	R^2	Yield (%)	Reference
H	H	81	[130]
Me	5,6-$(NO_2)_2$	83	[131]
Ac	5-6-Me_2	63	[132]
CO_2Et	7-Cl-4-OEt-5-CO_2Me	68	[133]
SO_2Ph	5-Me	100	[134]
Benzotriazol-2-yl	H	63	[135]

Table 12.10 Synthesis of 1-substituted benzotriazoles from azides and a benzyne intermediate.



R	Yield (%)	Reference
Ph	52	[136]
4-$O_2NC_6H_4$	62	[137]
Bz	63	[137]
SO_2Ph	52	[137]
4-$OMeC_6H_4CO$	60	[137]
1-Naphthalenyl	75	[138]

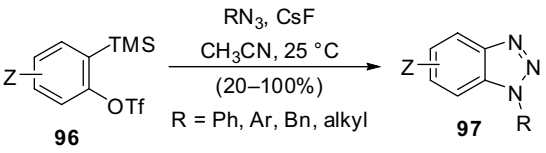
Table 12.11 Benzotriazol-1-ols from 1-chloro-2-nitrobenzenes and hydrazines.



R	Yield (%)	Reference
H	90	[139]
4,5,6-Cl_3	67	[139]
6-CF_3	90	[140]
6-OMe	6	[140]
6-$CONH_2$	39	[140]
6-SO_2NHBn	96	[135]

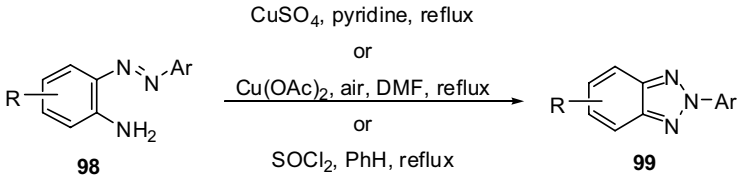
zoles **97** have been prepared by the [3 + 2] cycloaddition of azides to benzynes generated from aryl triflates **96** and cesium fluoride (Scheme 12.39) [143].

2-Substituted benzotriazoles can be prepared by several methods. For example, 2-aminoazobenzenes **98** can be converted into their 2-aryl-2*H*-benzotriazoles **99**

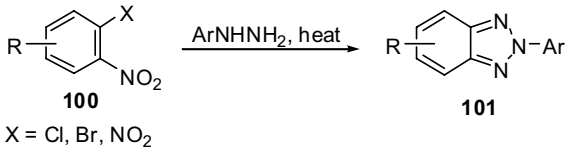


Scheme 12.39

by oxidation with copper(II) sulfate in refluxing pyridine [144], copper(II) acetate in air [145], or by refluxing the azo compound in thionyl chloride (Scheme 12.40) [145a]. 2-Aryl-2*H*-benzotriazoles **101** can be prepared directly by reaction of 1-halo(or nitro)-2-nitrobenzenes **100** with an excess of an arylhydrazine (Scheme 12.41) [146].



Scheme 12.40



Scheme 12.41

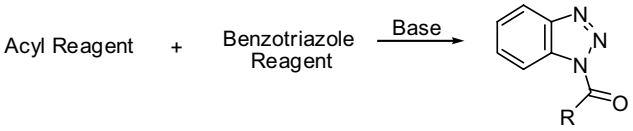
12.2.4
Reactions of Benzotriazoles

The growing applications of benzotriazole methodology as a versatile synthetic tool have been reviewed extensively [147]. Practically all the chemistry occurs on the N1-position of the benzotriazole. The benzotriazole group conveys multiple activating influences such as a leaving group, proton activator, ambident anion directing group, cation stabilizer, radical precursor, and anion precursor. The benzotriazole group can also easily be eliminated by radical-type reactions, by hydrolysis, by palladium-catalyzed S_N2' substitution, and by reductive metal reductive reactions. This section will not describe the chemistry needed to give the benzotriazole derivatives; however, the intermediates of these substitution reactions will be used to explain the myriad of useful synthetic reactions.

12.2.4.1 Acylation of 1-Benzotriazoles and Benzotriazole Methodology

The classical preparation of *N*-acylbenzotriazoles uses the corresponding acid chlorides (Table 12.12) [148]. More recently, two methods have been developed for the preparation of *N*-acylbenzotriazoles directly from carboxylic acid without the necessity of isolating the acid chlorides. Carboxylic acids are converted into the mixed carboxylic sulfonic anhydride, which is then attack by the benzotriazole anion with methanesulfonylbenzotriazole as the reagent [149]. Treatment of carboxylic acids

Table 12.12 Synthesis of *N*-acylbenzotriazoles.

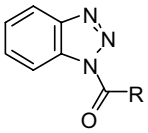


Acyl reagent	Benzotriazole reagent	Reference
RCOCl	BtH	[148]
RCO_2H	$BtSO_2Me$	[149]
$RCO_2H/SOCl_2$	BtH (4 equiv)	[150]
CO/iodonium salts	BtH	[151]

with thionyl chloride in the presence of excess benzotriazole provided *N*-acylbenzotriazoles in high yields [150]. *N*-Acylbenzotriazoles can be synthesized by palladium-catalyzed carbonylation of benzotriazole and hypervalent iodonium salts [151].

N-Acylbenzotriazoles are useful intermediates in several synthetically valuable reactions (Table 12.13) [152]. *N*-Acylbenzotriazoles can react with ammonia and primary and secondary amines to give high yields of their respective amides [149]. *O*-Alkyl, *N*-alkyl, and *O,N*-dialkylhydroxamic acids have been synthesized from *N*-acylbenzotriazoles [153]. C-Acylation of *N*-acylbenzotriazoles with furan, thiophene, pyrrole, and indole under Friedel–Crafts conditions gave products in high yields [154]. β-Diketones have been prepared from monoketones and *N*-acylbenzotriazoles in the

Table 12.13 Benzotriazole-mediated methodology of *N*-acylbenzotriazoles.



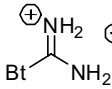
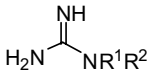
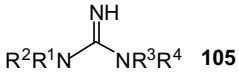
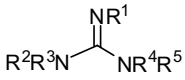
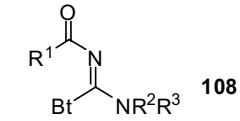
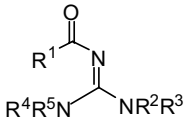
Reactants	Products	Reference
Amines (ammonia, primary, secondary)	Amides (primary, secondary, tertiary)	[149]
$R^1NHOR\ ^2HCl$	*O*-Alkyl, *N*-alkyl, *O,N*-dialkylhydroxamic acids	[153]
Five-membered heterocycles	C2-acylated heterocycles	[154]
Cyclic and acyclic ketones	β-Diketones	[155]
Nitriles (primary, secondary)	α-Substituted β-ketonitriles	[156]
Sulfones	β-Ketosulfones	[157]
Acetoacetic esters	β-Ketoesters/β-diketones	[158]
Grignards/heteroaryllithiums	Ketones	[159]
Sodium azide	Acyl azides	[160]
Indoles	Aroylindoles	[161]

presence of base [155]. α-Substituted β-ketonitriles have been synthesized from *N*-acylbenzotriazoles with primary and secondary alkyl nitriles [156]. C-Acylation of sulfones with *N*-benzotriazoles affords β-keto sulfones [157]. β-Ketoesters and β-diketones have been prepared by an acylative-deacylative sequence [158]. Stable and easily accessible *N*-acylbenzotriazoles, derived from various aliphatic, unsaturated, (hetero)aromatic, and *N*-protected-*R*-amino carboxylic acids, have been reacted with Grignard and heteroaryllithium reagents to afford the corresponding ketones [159]. A general synthesis of acyl azides from the corresponding *N*-acyl benzotriazoles have been described [160]. Stable and easily accessible *N*-aroylbenzotriazoles react with indoles in the presence of a base to afford the corresponding *N*-aroylindoles [161].

12.2.4.2 **Benzotriazole-Mediated Imidoylation**

N-(Imidoyl)benzotriazoles have found synthetic applications in the syntheses of various substituted guanidines. For example, benzotriazole-1-carboxamidinium tosylate (**102**) was found to be an efficient reagent for the synthesis of mono- and disubstituted guanidines **103** in moderate to good yields and offers advantages over previous procedures (Table 12.14) [162]. Introduction of Boc groups on both nitrogens of the amidine moiety and nitro or chloro group on the benzotriazole enhances the ability of the benzotriazole moiety as a leaving group [163]. Bis(benzotriazolyl) carboximidamide (**104**) has been developed as a new guanylating agent for the synthesis of tri- and tetrasubstituted guandines **105** [163, 164]. Benzotriazolyl carboximidoyl chlorides (**106**) are stable, colorless, and conveniently handled reagents for the synthesis of unsymmetrical guanidines **107** [165]. Polysubstituted acylguanidines and guanylureas **109** [166] have been prepared from *N*-acyl-*N*,*N*-disubstituted benzotriazolyl carboximidates **108**.

Table 12.14 Synthesis of substituted guanidines with various benzotriazole imidates.

Benzotriazole imidate	Reagents	Products	Reference
 **102**	R^1R^2NH	 **103**	[162]
 **104**	R^1R^2NH, R^3R^4NH	 **105**	[163, 164]
 **106**	R^2R^3NH, R^4R^5NH	 **107**	[165]
 **108**	R^4R^5NH	 **109**	[166]

R^1 = aryl, alkyl, NHAr

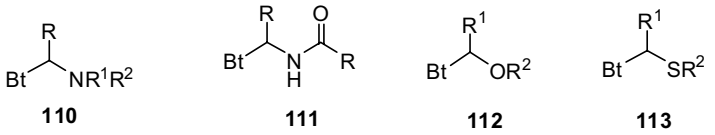


Figure 12.5 Structures of amino- (**110**), amido- (**111**), alkoxy- (**112**), and alkylthio- (**113**) methylbenzotriazoles [167].

12.2.4.3 **Benzotriazole-Mediated Amino-, Amido-, Alkoxy-, and Alkylthio-Alkylations**

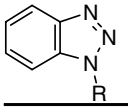
A very detailed recent review describes extensively the synthesis and the broad utility of aminomethylbenzotriazoles **110**, amidomethylbenzotriazoles **111**, alkoxymethylbenzotriazoles **112**, and alkylthiomethylbenzotriazoles **113** (Figure 12.5) and so this chemistry will not be presented here [167].

12.2.5

Benzotriazole-Containing Reagents

Substituents located in the N1 position of 1,2,3-benzotriazoles have become useful reagents in various reactions (Table 12.15). 1-Hydroxybenzotriazole (**114**) is a useful co-reagent in peptide coupling reactions in the activation of carboxylic acids [168]. Aminium-based **115** [169] and phosphonium-based **116** [170] benzotriazoles are currently utilized as peptide coupling reagents. 1-Aminobenzotriazole (**117**) is a useful reagent in the generation of benzyne intermediate, which can be trapped with various dienes [171]. 1-Cyanobenzotriazole (**118**) has been found to participate in electrophilic cyanations of sp^2 and sp carbanions [172]. 1*H*-Benzotriazole-1-yl methanesulfonate (**119**) has been explored as a regioselective *N*-mesylating reagent [173]. Reagent **119** mesylated molecules containing both primary and secondary amines on the primary amino position and mesylation occurred on the amino group in molecules containing both amino and hydroxy groups. 1*H*-Benzotriazole-1-yl alkyl carbonates (**120**) are convenient and inexpensive coupling agents in the preparation of active esters for the synthesis of amides [174]. A general and efficient route to thionoesters via thionoacyl nitrobenzotriazoles **121** has been reported [175]. The Vilsmeier-type reagent **122** with β-enaminonitriles provides a regioselective route to the preparation of nicotinonitriles [176] and was employed in the direct and efficient synthesis of dimethylformamidrazones from hydrazines [177]. 1-(Chloromethyl)benzotriazole reacted with sodium dialkyl phosphites to give dialkyl-(1-benzotriazolmethyl)phosphonates **123**, which are potential Horner–Emmons reagents [178] for the stereoselective preparation of (*E*)-1-(1-alkenyl)benzotriazoles [179]. 2-Benzotriazolyl-1,3-dioxolane (**124**) has been utilized as a novel formyl cation equivalent [180]. The novel three-carbon synthon 1-(1*H*-1,2,3-benzotriazol-1-yl)-3-chloroacetone (**125**) has been used for the synthesis of benzothiazoles, pyrido[1,2-*a*]indoles, styryl-substituted indolizines, and imidazo[1,2-*a*]pyridines [181]. Various functionalized *N*-allylamines and *N*-allylsulfonamides have been synthesized by Pd(II)-catalyzed intermolecular amination of the corresponding *N*-allylbenzotriazoles **126** [182]. *S*-(1*H*-1,2,3-Benzotriazol-1-ylmethyl)-*O*-ethylcarbo-

Table 12.15 Synthetic utility of 1-substituted benzotriazole reagents.



R	Number	Synthetic utility	Reference
OH	**114**	Co-reagent in peptide coupling	[168]
$\overset{\oplus}{C}HNR_2\ X^{\ominus}$	**115**	Peptide coupling agent	[169]
$\overset{\oplus}{O}P(NHR_2)_3\ \overset{\ominus}{X}$	**116**	Peptide coupling agent	[170]
NH_2	**117**	Benzyne intermediate	[171]
CN	**118**	Electrophilic cyanations	[172]
OMs	**119**	N-Mesylating reagent	[173]
OCO_2R	**120**	Synthesis of active esters	[174]
$C(S)R^*$	**121**	Synthesis of thioesters	[175]
$\overset{\oplus}{C}H{=}\overset{\oplus}{N}Me_2\ \overset{\ominus}{Cl}$	**122**	Vilsmeier-type reagent	[176, 177]
$CH_2P(O)(OR)_2$	**123**	Horner–Emmons reagent	[178, 179]
	**124**	Formyl cation equivalent	[180]
$CH_2C(O)CH_2Cl$	**125**	Three-carbon synthon	[181]
$CHRCH=CH_2$	**126**	*N*-Allylating reagent	[182]
$CH_2SC(S)OEt$	**127**	Benzotriazolylmethyl radical	[183]
CH_2TMS	**128**	One-carbon synthon	[184]
SO_2R	**129**	Sulfonylating reagents	[185]
C(S)X X = R, OR, SR, HetNH	**130**	Thioacylating reagents	[186]
$PhC(OCH_3)(CF_3)C(O))$	**131**	Mosher-Bt reagent	[187]
CH_2OH	**132**	Formaldehyde generation	[188]
$CONH_2$	**133**	Carbamoyl chloride reagent	[189]

nodithioate (**127**) has been used to generate the benzotriazolylmethyl radical, which was trapped by various olefins [183]. 1-(Trimethylsilylmethyl)benzotriazole (**128**) has been utilized as a one-carbon synthon in the conversion of alkyl and aryl carboxylic acids into their corresponding homologated acids or esters [184]. *N*-Alkane-, *N*-arene-, and *N*-heteroenesulfonylbenzenetriazoles **129** have been exploited as efficient sulfonylating agents [185]. Several benzotriazole sulfur reagents **130** have been prepared and used for thioacylations, thiocarbamoylations, alkyl/alkoxythioacylations, and aryl/alkylthioacylations [186]. Benzotriazole of 3,3,3-trifluoro-2-methoxy-2-phenylpropionic acid (**131**) reacted with water-soluble amino acids and peptides in an acetonitrile/water (2 : 1) mixture to give the corresponding Mosher derivative in quantitative yield [187]. Anionic *in situ* generation of formaldehyde from benzotriazolylmethanol **132** has proved to be a very useful and versatile tool in synthesis [188]. Carbamoyl-1*H*-benzotriazole **133**, an effective carbamoyl

chloride substitute, and a range of its analogs have been synthesized in good yields in two very simple steps from 1,2-diaminobenzene [189].

12.3
1,2,4-Triazoles

12.3.1
Introduction

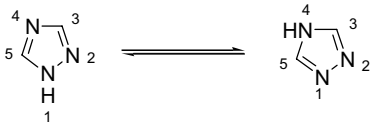
The chemistry of 1,2,4-triazoles is extensively reviewed elsewhere [190]. A comprehensive review on the chemistry of mercapto- and thione- substituted 1,2,4-triazoles and their utility in heterocyclic synthesis has been published [191]. This section will focus on methods for the synthesis of the monocyclic 1,2,4-triazole system, including solid-phase and microwave-assisted reactions.

12.3.2
General Reactivity

12.3.2.1 Relevant Physicochemical Data and NMR Data

The parent 1,2,4-triazole consists of a five-membered aromatic ring containing three nitrogen atoms, two of which are adjacent; it is a stable, water-soluble solid. Two tautomeric forms, 1*H*-tautomer and 4*H*-tautomer, can be envisaged (Figure 12.6). Theoretical and analytical methods show that the 1*H*-tautomer is the preferred structure. Every carbon atom in 1,2,4-triazole is linked to two nitrogen atoms and, thus, this ring system is electron deficient. The ring is deactivated towards electrophilic attack so nitration and other reactions at carbon typical of aromatic chemistry do not apply to the parent compound. However, electrophilic attack at nitrogen is found in abundance in the literature and this will be discussed later. The parent compound has a pK_a of 10.26 and so alkali metal salts form readily at the N1 position. The pK_a of the protonated species is 2.19 and the weakly basic nature allows electrophilic attack at the N4 position in 1-substituted-1,2,4-triazoles.

The ^{1}H NMR spectrum of the parent 1,2,4-triazole in HMPT is temperature dependent; the H3 and H5 protons show one broad singlet at slightly above or below room temperature due to the rapid proton exchange between the tautomeric forms

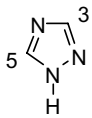


1*H*-tautomer **4*H*-tautomer**

stable, water-soluble, colorless crystals
mp 120-121 °C
pK_a = 10.26
pK_a = 2.19 of the protonated species

Figure 12.6 Tautomerism of 1,2,4-triazoles.

Table 12.16 ^{1}H and ^{13}C NMR data (ppm) of 1,2,4-triazole.



	^{1}H NMR (HMPT)		^{13}C NMR (CD_3OD-d_4)	
Temperature (°C)	H3	H5	C3	C5
37	8.03	8.03	147.4	147.4
10	8.17	8.17		
−34	7.92	8.85		

(Table 12.16) [192]. However, at −34 °C, the H3 protons and H5 protons are observed separately. The ^{13}C NMR spectrum shows a single peak for the parent triazole.

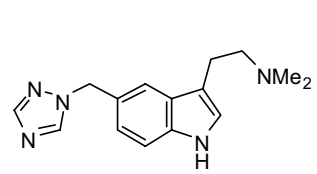
12.3.3 Relevant Natural and/or Useful Compounds

1,2,4-Triazoles have several applications in analytical chemistry, in industrial, and in molecular recognition processes [190d,190f]. The 1,2,4-triazole ring is also a component of a wide range of biologically active pharmaceutical products. For example, rizatriptan benzoate, marketed as Maxalt™, was launched in 1998 by Merck & Co. as an antimigraine medication (Figure 12.7) [193]. Voriconazole is sold as Vfend™ by Pfizer for treatment of fungal infections [194]. Aprepitant is sold as Emend™ for the treatment of chemotherapy-induced nausea and vomiting [195].

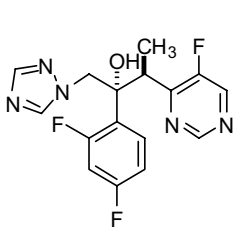
12.3.4 Synthesis of 1,2,4-Triazoles

12.3.4.1 Reactions of Acylhydrazines with Various Nitrogen-Containing Reagents

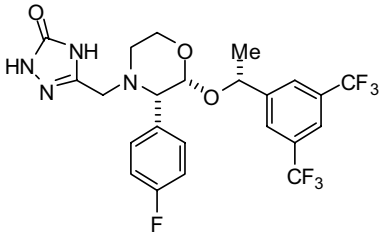
One of the most common methods of preparing 1,2,4-triazoles is the reaction of acylhydrazines with various nitrogen-containing reagents. For example, reactions of



rizatriptan benzoate (Maxalt™)
Merck & Co.



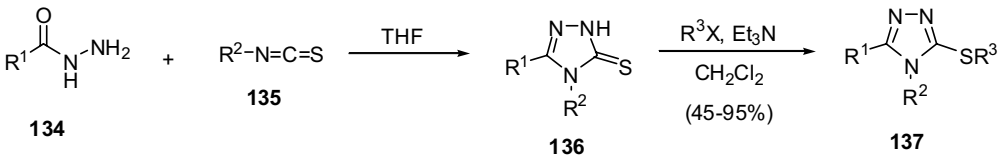
voriconazole (Vfend™)
Pfizer



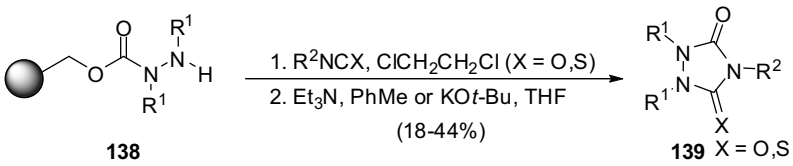
aprepitant (Emend™)
Merck & Co.

Figure 12.7 Some biologically active pharmaceutical products that contain a 1,2,4-triazole ring.

acylhydrazines with isothiocyanates or isocyanates to give 1,2,4-triazoles can be seen in the following examples. Acylhydrazines **134** and isothiocyanates **135** afforded 1,2,4-triazole-3-thiones **136**, which were intercepted by alkyl halides to give substituted 3-thio-1,2,4-triazoles **137** (Scheme 12.42) [196]. Solid-supported acylhydrazines **138** react with isocyanates or isothiocyanates followed by base-induced cyclization/cleavage to provide 1,2,4-trisubstituted urazoles and thiourazoles **139** (Scheme 12.43) [197]. A traceless liquid-phase synthesis of 3-alkylamino-4,5-disubstituted-1,2,4-triazoles on poly(ethylene glycol)-supported thioureas and acylhydrazines has been reported [198].

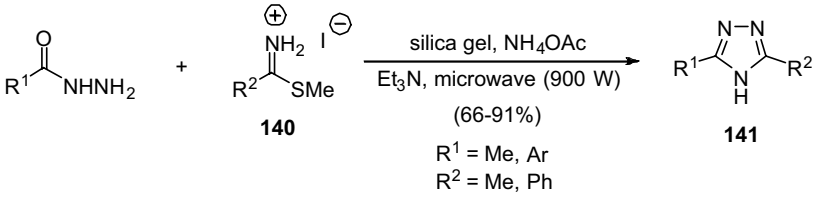


Scheme 12.42



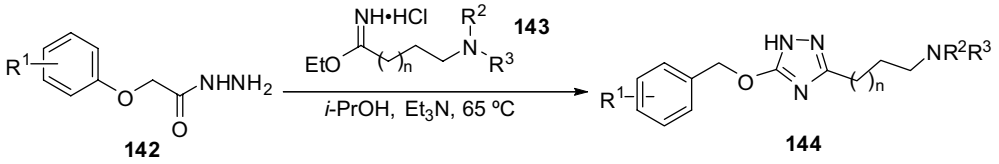
Scheme 12.43

Acylhydrazines can also be used in conjunction with substituted imidates to give 1,2,4-triazole derivatives. The three-component condensation of acylhydrazines in the presence of *S*-methyl isothioamide hydroiodide **140**, silica gel, and ammonium acetate under microwave irradiation afforded 1,2,4-triazoles **141** in good yields (Scheme 12.44) [199]. Acylhydrazines **142** react with imidates **143** to yield 1,2,4-triazoles **144** (Scheme 12.45) [200].



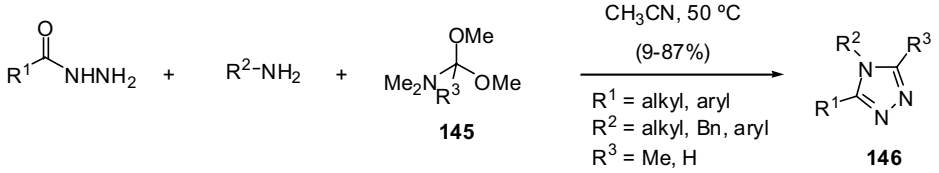
Scheme 12.44

Other non-traditional reactions of acylhydrazines with nitrogen reagents for the synthesis of 1,2,4-triazoles are also available. An efficient one-pot, three-component synthesis of substituted 1,2,4-triazoles **146** has been prepared from primary acylhy-

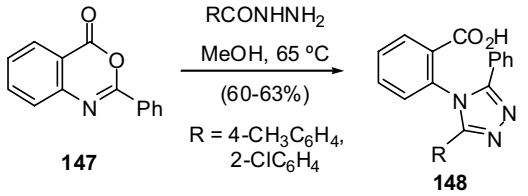


Scheme 12.45

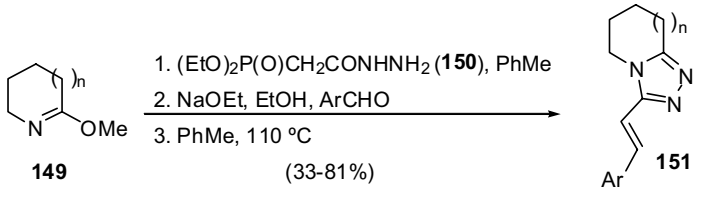
drazines, dimethylamino acetals **145**, and amines (Scheme 12.46) [201]. 1,3-Benzoxazine **147** reacts with acylhydrazines in refluxing methanol to give 1,2,4-triazoles **148** (Scheme 12.47) [202]. Diethoxyphosphinyl acetic acylhydrazine **150** was found to be a unique reagent that provided a convenient and efficient process to prepare fused [5,5]-, [5,6]-, and [5,7]-3-[(*E*)-2-(arylvinyl)]-1,2,4-triazoles **151** from aldehydes and alkoxyimines **149** (Scheme 12.48) [203]. A convenient and efficient one-step, base-catalyzed microwave-assisted synthesis of 3,5-disubstituted-1,2,4-triazoles by condensation of a nitrile and acyl hydrazide has been reported [204].



Scheme 12.46



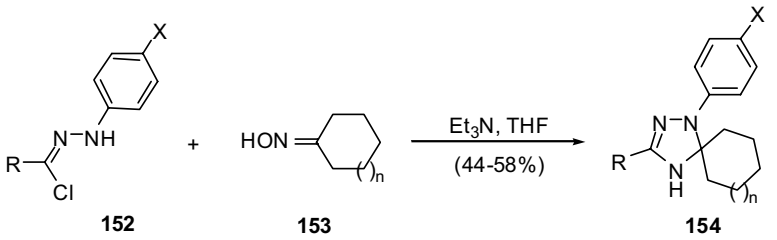
Scheme 12.47



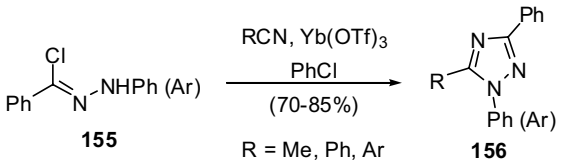
Scheme 12.48

12.3.4.2 **Reactions of Hydrazones**

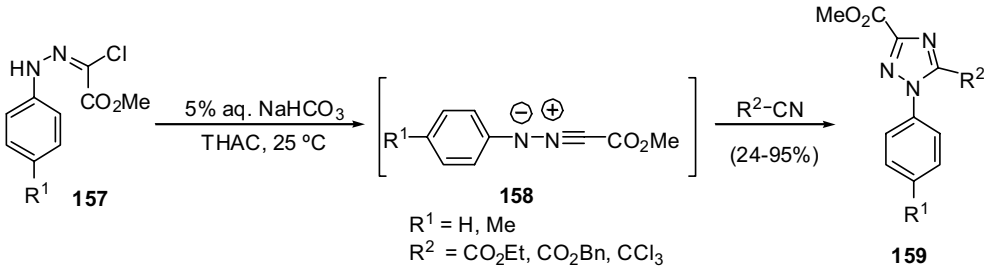
Substituted hydrazones are a rich source of precursors for the syntheses of 1,2,4-triazoles. For example, hydrazonyl chlorides can be used as partners in reactions with compounds containing a C–N multiple bond that lead to 1,2,4-triazoles. Aryl-substituted hydrazonyl chlorides **152** reacted with cycloalkanone oximes **153** to give 1,2,4-triazolospiro compounds **154** (Scheme 12.49) [205]. Intermolecular cyclization of hydrazonyl chlorides **155** with nitriles catalyzed by ytterbium(III) triflate afforded a series of 1,3,5-trisubstituted-1,2,4-triazoles **156** in good yields (Scheme 12.50) [206]. Dipolar cycloadditions between hydrazonyl chlorides **157** and nitriles in aqueous sodium bicarbonate in the presence of a surfactant provided mild conditions for the synthesis of 1-aryl-5-substituted-1,2,4-triazoles **159** via intermediate **158** (Scheme 12.51) [207]. A series of 1,2,4-triazoles have been prepared by oxidative intramolecular cyclization of heterocyclic hydrazones with copper dichloride [208]. Other C–N multiple partners include aryl cyanides [209], amidines [210], and cyanamides [211].



Scheme 12.49

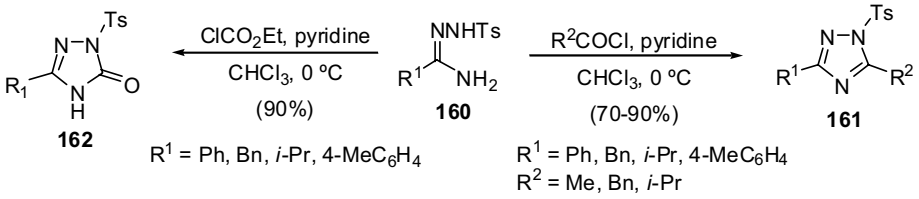


Scheme 12.50

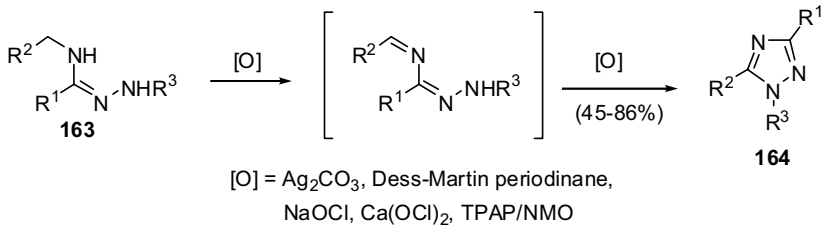


Scheme 12.51

Aminohydrazones or amidrazones are versatile reagents that can react with various electrophilic carbon compounds to give 1,2,4-triazoles. As an example, *N*-tosylamidrazones **160** can react either with acid chlorides or with ethyl chloroformate to give tosylated 1,2,4-triazoles **161** or 1,2,4-triazole-3-ones **162**, respectively (Scheme 12.52) [212]. Other amidrazone reactions can occur with carboxylic acids [213], cyanogen bromide [214], aldehydes [215], and orthoesters [215, 216]. Amidrazones **163** have been oxidized to 1,3,5-trisubstituted 1,2,4-triazoles **164** in good yields by silver carbonate, Dess–Martin periodinane, sodium and calcium hypochlorites, and tetrapropylammonium perruthenate (TPAP)/*N*-methylmorpholine *N*-oxide (NMO) combination (Scheme 12.53) [217–219].

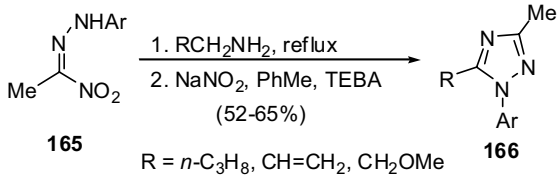


Scheme 12.52

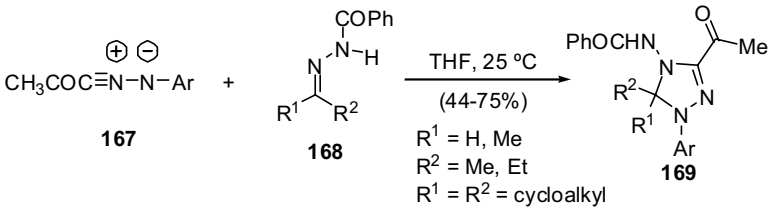


Scheme 12.53

Other hydrazone intermediates have been utilized in the synthesis of 1,2,4-triazoles. Addition of primary amines to α-nitrohydrazones **165** followed by addition of sodium nitrite affords 1,3,5-trisubstituted-1,2,4-triazole **166** (Scheme 12.54) [220]. 1,3,-Dipolar cyclocondensation of *C*-acetyl-*N*-arylnitrilimines **167** with benzoylhydrazones **168** furnished 1,2,4-triazoles **169** (Scheme 12.55) [221]. Iodobenzene

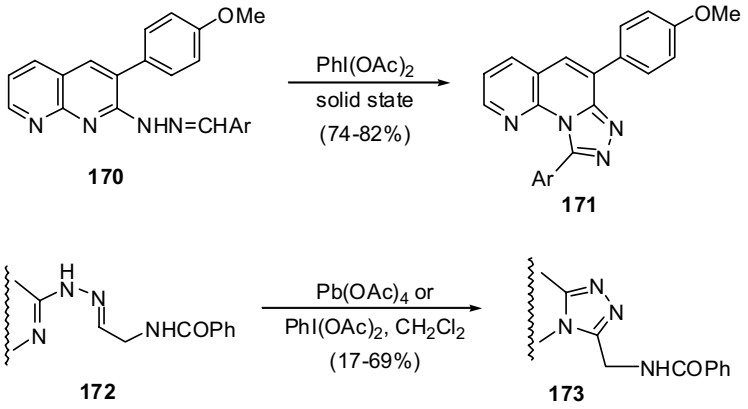


Scheme 12.54



Scheme 12.55

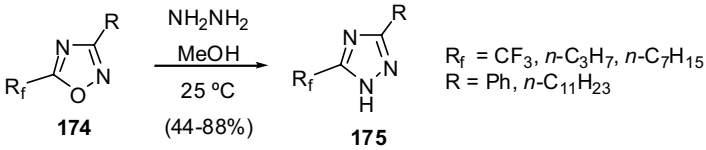
diacetate or lead tetraacetate cyclization of hydrazones **170** [222] or **172** [223] afforded fused 1,2,4-triazoles **171** and **173**, respectively (Scheme 12.56).



Scheme 12.56

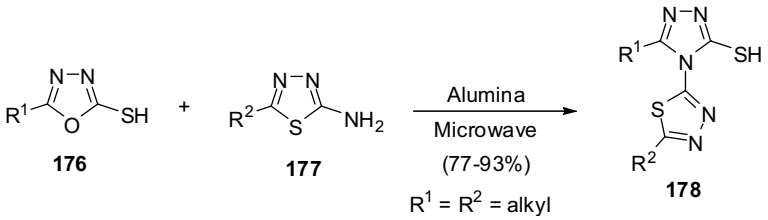
12.3.4.3 **Reactions of Oxadiazoles or Thiadiazoles**

1,2,4-Triazoles can be synthesized from oxadiazoles. Photolysis of 1,2,4-oxadiazoles in the presence of nucleophiles led to 1,2,4-triazole products [224] and 1,3,4-oxadiazoles can undergo ring-cleavage with nitrogen nucleophiles followed by recyclization of the intermediates to give 1,2,4-triazoles. For example, the unusual hydrazinolysis of 5-perfluoroalkyl-1,2,4-oxadiazoles **174** provided an expedient route to 5-perfluoroalkyl-1,2,4-triazoles **175** (Scheme 12.57) [225]. Similarly, 3,5-bis(trifluoromethyl)-1,3,4-oxadiazole is particularly activated towards nucleophilic



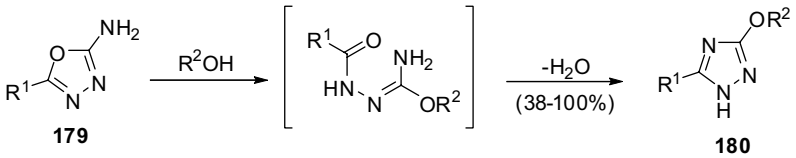
Scheme 12.57

attack by primary amines to yield 4-substituted-1,2,4-triazoles [226]. Microwave-assisted rate acceleration of reactions between 2-aminothiadiazoles **177** with oxadiazoles **176** on alumina support affords thiadiazolyl-substituted-1,2,4-triazoles **178** (Scheme 12.58) [227]. Photochemistry of some fluorinated oxadiazoles gives rise to mixtures of fluorinated 1,3,4-oxadiazoles and 1,2,4-triazoles [228]. 2-Amino-1,3,4-oxadiazoles **179** reacted with alcohols followed by subsequent ring-cleavage and ring-cyclization to give 3-alkoxy-1,2,4-triazoles **180** (Scheme 12.59) [229], while amines and hydrazines react with 2-amino-1,3,4-oxadiazoles to afford 3-amino- and 3,5-diamino-1,2,4-triazoles, respectively [230]. Condensation of highly reactive chloromethyloxadiazoles with ethylenediamines provides a concise synthesis of [1,2,4]triazolo[4,3-*a*]piperazines [231]. Reaction of some fluorinated 1,2,4-oxadiazoles in the presence of methylamine or propylamine under photochemical irradiation in methanol or acetonitrile led to the corresponding fluorinated 1-methyl- or 1-propyl-1,2,4-triazoles [232].



176 177 178

Scheme 12.58

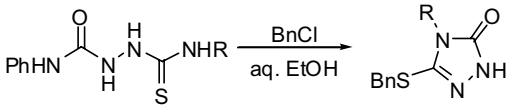


179 180

Scheme 12.59

12.3.4.4 **Synthesis of 1,2,4-Triazoles from Thioureas, Thiocyanates, and Thioamides**

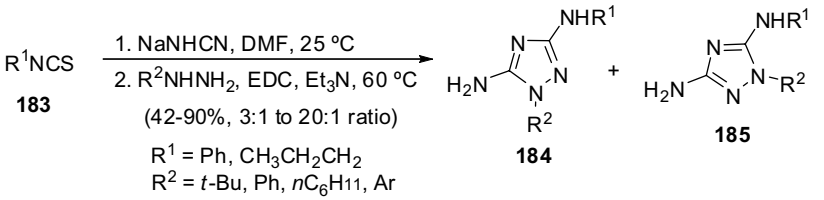
Unsaturated and saturated thio compounds have been employed in the syntheses of 1,2,4-triazoles. Δ^2-1,2,4-Triazolin-5-ones **182** have been prepared from 1-aryl/alkyl-6-phenyl-2-thiobioureas **181** in the presence of benzyl chloride and aqueous ethanol (Scheme 12.60) [233]. A novel one-pot synthesis of 1,2,4-triazole-3,5-diamine derivatives **184** and **185** from isothiocyanates **183** and monosubstituted hydrazines has



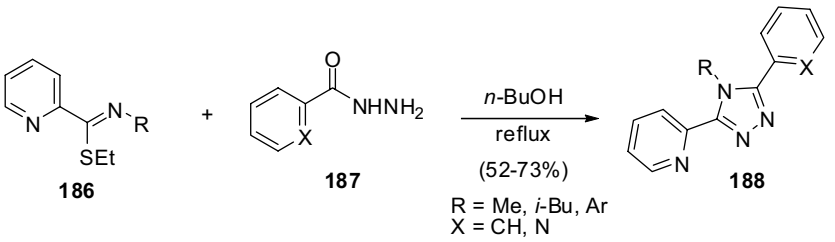
181 182

Scheme 12.60

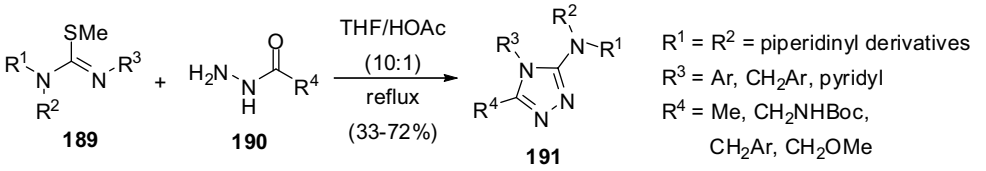
been reported; derivatives **185** were obtained with higher regioselectivity when aromatic and sterically bulky hydrazines were used (Scheme 12.61) [234]. *S*-Ethyl thioamides **186** react with acyl hydrazides **187** in refluxing *n*-butanol to give 3,4,5-trisubstituted 4*H*-1,2,4-triazoles **188** (Scheme 12.62) [235]. An efficient synthesis of substituted 1,2,4-triazoles involved condensation of benzoyl hydrazides with thioamides under microwave irradiation [236]. 3-*N*,*N*-Dialkylamino-1,2,4-triazoles **191** have been synthesized from *S*-methylisothioureas **189** and acyl hydrazides **190** in moderate to good yields (Scheme 12.63) [237].



Scheme 12.61

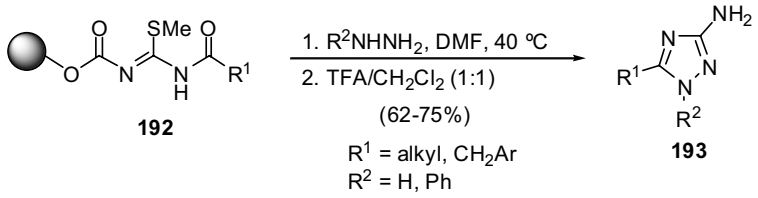


Scheme 12.62

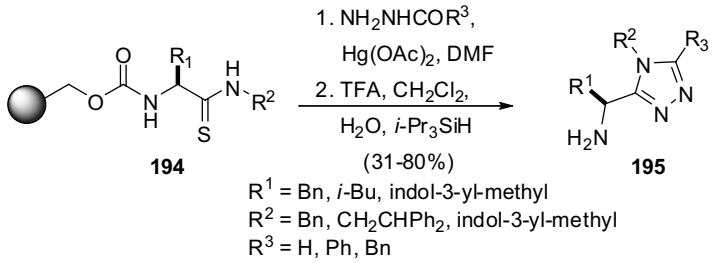


Scheme 12.63

Combinatorial solid-phase reactions have been used in the synthesis of libraries of 1,2,4-triazole compounds. Reaction of resin bound *S*-methyl-*N*-acylisothioureas **192** with hydrazines followed by acidic cleavage yielded 3-amino-1,2,4-triazoles **193** under mild conditions (Scheme 12.64) [238]. 3,4,5-Trisubstituted 1,2,4-triazoles **195** have been synthesized on solid-phase from various thioamides **194** and hydrazides, leading to peptidomimetic scaffolds (Scheme 12.65) [239]. A robust "catch,



Scheme 12.64

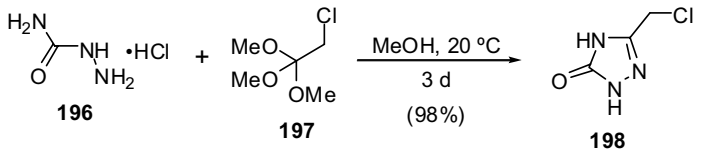


Scheme 12.65

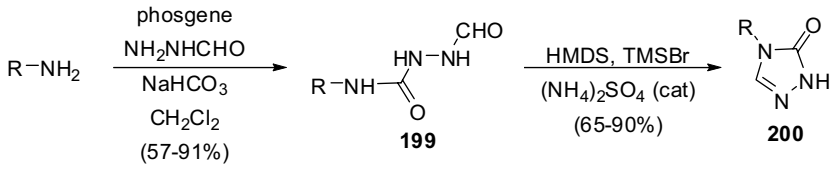
cyclize, and release" preparation of 3-thioalkyl-1,2,4-triazoles mediated by the polymer-bound base P-BEMP has been described [240].

12.3.4.5 Reactions of Semicarbazides

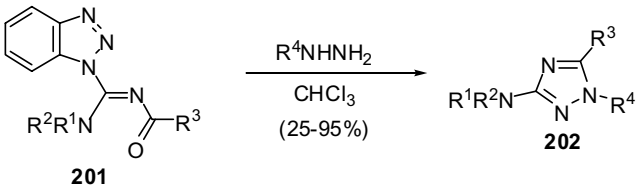
A couple of reports present the use of semicarbazides in the synthesis of 1,2,4-triazolones. Condensation of semicarbazide hydrochloride **196** with orthoester **197** resulted in a simple synthesis of chlorotriazolinone **198** (Scheme 12.66), and the method was applied to the convergent synthesis of an NK_1 antagonist [241]. Amines have been converted into 1-formyl semicarbazides **199**, which were cyclized smoothly to 2,4-dihydro-3*H*-1,2,4-triazolin-3-ones **200** with hexamethyldisilazane (HMDS), bromotrimethylsilane, and a catalytic amount of ammonium sulfate (Scheme 12.67) [242].



Scheme 12.66



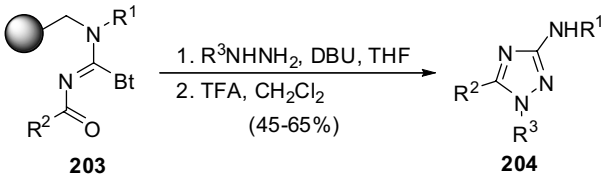
Scheme 12.67



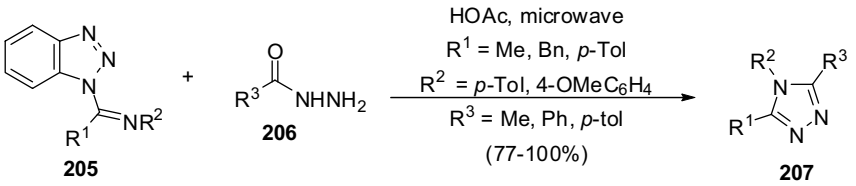
Scheme 12.68

12.3.4.6 **Synthesis of 1,2,4-Triazoles via Benzotriazole Methodology**

Solution- and solid-phase benzotriazole-mediated methodologies are employed in the synthesis of 1,2,4-triazoles. Acyl 1*H*-benzotriazol-1-carboximidamides **201** and hydrazines have been employed in a general synthesis of *N,N*-disubstituted 3-amino-1,2,4-triazoles **202** (Scheme 12.68) [243]. Polymer-supported *N*-acyl-1*H*-benzotriazole-1-carboximidamides **203** reacted with hydrazines followed by acidic cyclizative release to give 3-alkylamino-1,2,4-triazoles **204** (Scheme 12.69) [244]. Reaction of acyl hydrazides **206** with imidoylbenzotriazoles **205** in the presence of catalytic amounts of acetic acid under microwave irradiation afforded 3,4,5-trisubstituted triazoles **207** (Scheme 12.70) [245].



Scheme 12.69

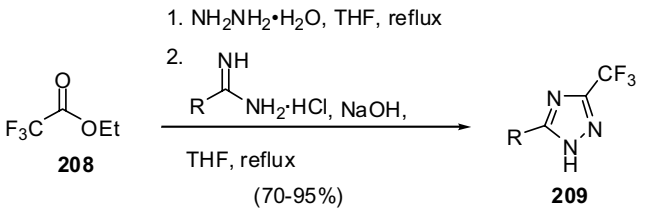


Scheme 12.70

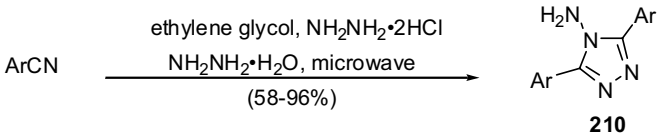
12.3.4.7 **Other Synthesis of 1,2,4-Triazoles**

Three-component condensation of ethyl trifluoroacetate (**208**), hydrazine, and amidines in the presence of sodium hydroxide gave 3-trifluoromethyl-5-substituted-1,2,4-triazoles **209** (Scheme 12.71) [246, 247]. The amidine supplies a C–N bond to the new ring system while the other two nitrogen atoms are derived from hydrazine. Reaction of aromatic nitriles with hydrazine dihydrochloride in the presence of hydrazine hydrate in ethylene glycol under microwave irradiation gave 3,5-disubstituted-4-amino-1,2,4-triazoles **210** (Scheme 12.72) [248]. 1,3-Dipolar cycloadditions

between poly(ethylene glycol) supported münchnones and diethyl azodicarboxylate led to synthesis of 3,5-disubstituted-1,2,4-triazoles [249].



Scheme 12.71



Scheme 12.72

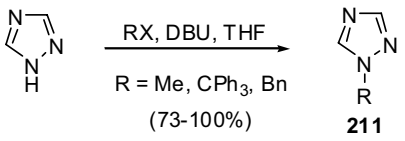
12.3.5 Reactions of 1,2,4-Triazoles

12.3.5.1 Reactions on the Nitrogen of 1,2,4-Triazoles

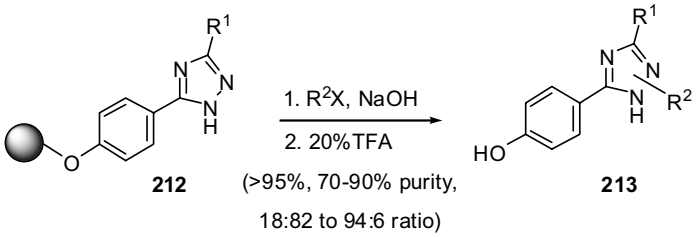
12.3.5.1.1 **N-Alkylation of 1,2,4-Triazoles** 1,2,4-Triazoles that are unsubstituted on nitrogen can be readily alkylated. 1-Substituted-1,2,4-triazoles are the predominant products of these base-catalyzed alkylation reactions; 4-substituted-1,2,4-triazoles are rarely isolated after purification. DBU is found to be a mild and convenient base for the alkylation of 1,2,4-triazole with alkyl halides in the high-yielding syntheses of 1-substituted-1,2,4-triazoles **211** (Scheme 12.73) [250]. Sodium hydroxide [251], sodium methoxide [252], and sodium hydride [253] are other bases that have been successfully employed in these reactions.

The synthesis of 1,2,4-triazole-functionalized solid-support **212** and its use in the solid-phase synthesis of various N1 and N2 trisubstituted-1,2,4-triazoles **213** has been reported (Scheme 12.74) [254].

1,2,4-Triazoles can be alkylated at N4 by using a removable protecting group at N1 and then forming a quaternary salt with the 1-substituted triazole. 1-Acetyl and 1-cyanoethyl groups have been used as removable protecting groups [255].

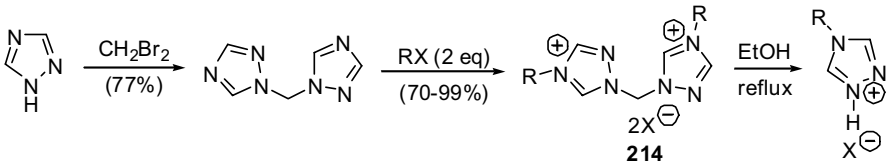


Scheme 12.73

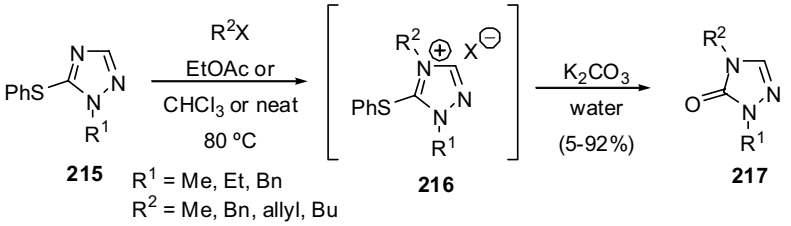


Scheme 12.74

The sequence involving quaternization/dealkylation with 1,1′-methylenebis(triazolium) salts **214** linked at the N1 position is shown in Scheme 12.75 [256]. Other similar sequences have also been reported [257]. Alternatively, 3-phenylthio-1,2,4-triazoles **215** were alkylated to their triazolium salts **216**, which under aqueous basic conditions provided 2,4-disubstituted-1,2,4-triazol-3-ones **217** (Scheme 12.76) [258].



Scheme 12.75

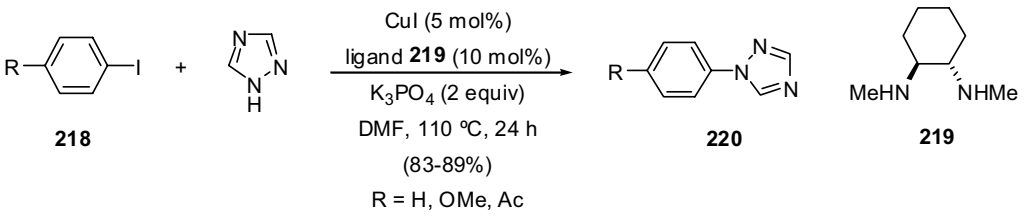


Scheme 12.76

12.3.5.1.2 **N-Acylation of 1,2,4-Triazoles** N-Unsubstituted-1,2,4-triazoles can be readily acylated at N1 by common acylating reagents such as acetyl chloride or acetic anhydride under standard conditions to give 1-acyl-1,2,4-triazoles [259]. 1*H*-1,2,4-Triazol-3-amines are acetylated first on N1 and then on the 3-amino group [260].

12.3.5.1.3 **N-Arylation of 1,2,4-Triazoles** 1,2,4-Triazole can be N-arylated at the 1-position by activated aryl halides such as 1-fluoro-2-nitrobenzene or 1-chloro-2-nitro-4-(trifluoromethyl)benzene [261]. N1-Phenylation can be achieved with triphenylbismuth diacetate and copper(II) acetate [262].

Recent protocols of copper-catalyzed N-arylations of aryl iodides with 1,2,4-triazoles represent a new landmark in the field of Ullmann-type arylation couplings of nitrogen-containing heterocycles. The aryl iodides **218** reacted efficiently and regioselectively at the N1 position with 1,2,4-triazole in the presence of copper(I) iodide and *trans*-diamine ligand **219**, with potassium phosphate as a base, to give **220** (Scheme 12.77) [117]. Another similar procedure employs copper(I) oxide, Chxn-Py-Al as the ligand, and cesium carbonate as the base [263]. However, these procedures are limited to aryl iodides; aryl bromides and aryl chlorides are not efficiently cross-coupled under these conditions.

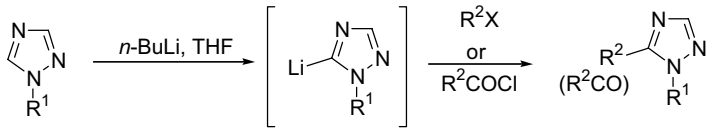


Scheme 12.77

12.3.5.2 Reactions on the Carbons of 1,2,4-Triazoles

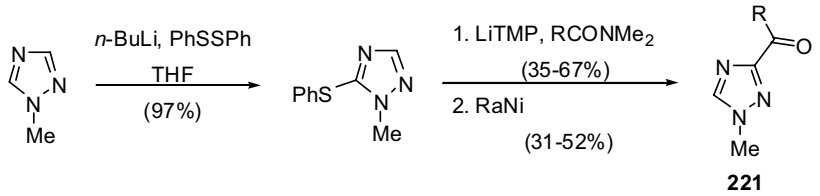
1,2,4-Triazoles are electron-deficient aromatic systems and so conventional electrophilic substitution reactions are not a practical method for the introduction of carbon substituents at C3 or C5. The most common methods for introduction of groups to C3 or C5 are by triazolyllithium intermediates or more recently by radical or carbene species.

12.3.5.2.1 **C-Substitution by Triazolyllithium** Hydrogen–metal exchange by *n*-butyllithium can occur at C5 if N1 is substituted to give organolithium species, which then react quickly with alkylating agents or with other electrophiles (Scheme 12.78) [264]. If the N1 is a removable protecting group, then monosubstituted 1,2,4-triazoles can be prepared by this method [264b,264c]. 1-(Methoxymethyl)-1*H*-1,2,4-triazole is converted directly into 5-acyl derivatives by reaction with acyl chlorides and triethylamine and the methoxymethyl protecting group could be removed in a subsequent step [265].



Scheme 12.78

Methods are available for preparation of 3-substituted-1,2,4-triazoles. A C5 removable group such as a phenylthio is employed in a protection/deprotection sequence to give 1-substituted 3-acyl-1,2,4-triazoles **221** (Scheme 12.79) [266]. 1*H*-1,2,4- and

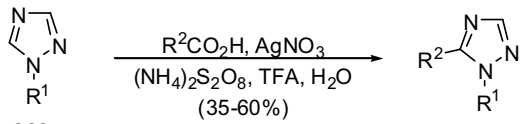


221

Scheme 12.79

1-methyl-1*H*-1,2,4-triazoles have been transformed directly into their 3(5)-arylcarbamyoyl derivatives by heating with aryl isocyanates [267]. These C-acylations are suggested to proceed by formation of N-acylated triazoles, followed by thermal rearrangements.

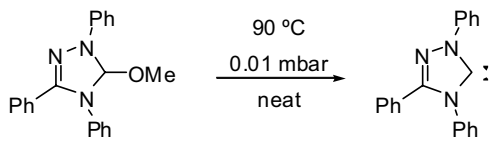
12.3.5.2.2 **Radical Reactions of 1,2,4-Triazoles** Reaction of 1-*N*-alkyl triazoles **222** with an alkyl radical generated from the corresponding secondary carboxylic acid in the presence of silver nitrate affords the triazole ring **223** alkylated selectively in the 5-position (Scheme 12.80) [268].



222 **223**

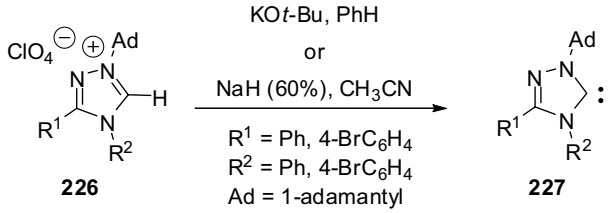
Scheme 12.80

12.3.5.2.3 **Carbene Reactions of 1,2,4-Triazoles** There are two published reports on the syntheses of stable 1,2,4-triazolyl carbenes. Thermal decomposition *in vacuo* of 5-methoxytriazoline **224** provided in quantitative yield 1,2,4-triazol-5-ylidene **225**, a stable carbene in the absence of oxygen and moisture (Scheme 12.81) [269]. Nucleophilic carbene **225** could react with various alcohols, thiols, amines, oxygen, sulfur, selenium, isocyanantes, and metal carbonyls to form a myriad of addition products. Reactions of 1,2,4-triazolyl perchlorate salts **226** with base afforded stable nucleophilic 1,2,4-triazol-5-ylidenes **227**, which could react with acetonitrile and elemental sulfur and selenium to yield addition products (Scheme 12.82) [270].



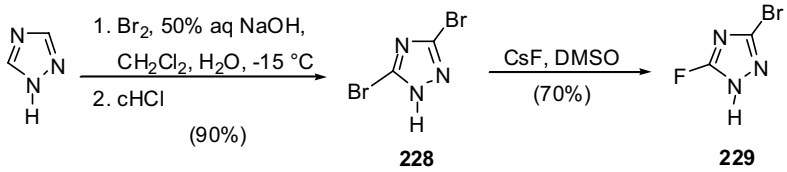
224 **225**

Scheme 12.81



Scheme 12.82

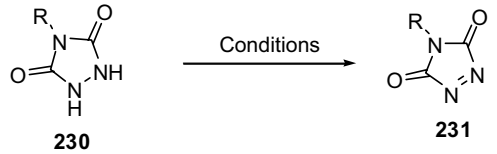
12.3.5.2.4 **Halogenations of 1,2,4-Triazoles** Most halogenation reactions of 1,2,4-triazoles are *N*-chlorotriazoles, kinetic products that rearranges to 3-halo-1,2,4-triazoles slowly upon storage or heating in water [271]. 5-Chloro derivatives of 1-substituted-1,2,4-triazoles have been obtained by C5-lithio derivatives [272]. *C*-Halo-1,2,4-triazoles can be prepared more directly without isolation of the *N*-halo-1,2,4-triazoles. For example, bromination of 1*H*-1,2,4-triazole in excess aqueous sodium hydroxide afforded 3,5-dibromo-1*H*-1,2,4-triazole (**228**), which selectively exchanges a bromine with a fluorine to give **229** (Scheme 12.83) [273].



Scheme 12.83

12.3.5.2.5 **Other Reactions of 1,2,4-Triazoles** Urazoles **230** can be converted into the corresponding 1,2,4-triazol-3,5-diones **231** by various oxidizing reagents (Table 12.17). Trichloroisocyanuric acid [274], a silica gel/sodium nitrite combination [275], an ionic complex, obtained from N_2O_4 and 18-crown-6 [276], Oxone/

Table 12.17 Dehydrogenation of urazoles to 1,2,4-triazol-3,5-diones with various oxidants.

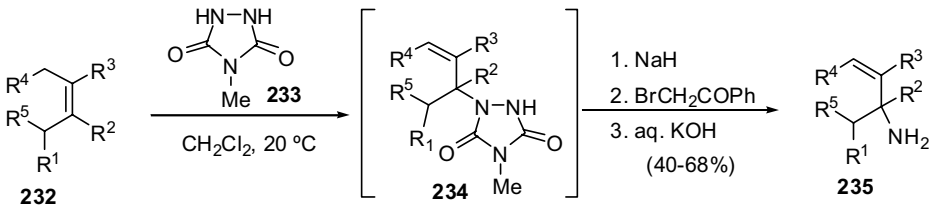


Conditions	Reference
Trichloroisocyanuric acid	[274]
Silica gel/$NaNO_2$	[275]
N_2O_4/18-crown-6	[276]
Oxone/$NaNO_2$/wet silica gel	[277]
Silica sulfuric acid/$NaNO_2$	[278]

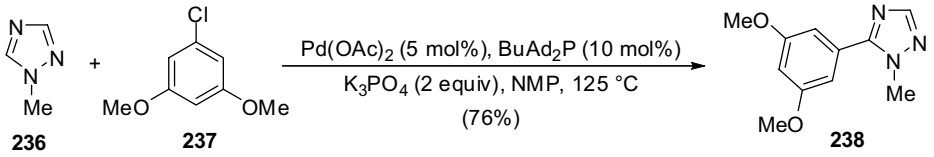
sodium nitrite in the presence of wet silica [277], and silica sulfuric acid/sodium nitrite [278] have all been reported as oxidants in this reaction.

1,2,4-Triazoline-3,5-dione **233** underwent an ene reaction with olefins **232** to yield trialkylated allylic urazoles **234**, which were further elaborated into allylic amines **235** (Scheme 12.84) [279].

1-Methyl-1,2,4-triazole **236** participated in a palladium-catalyzed C–H arylation reaction with 3,5-dimethoxychlorobenzene (**237**) to give coupled product **238** (Scheme 12.85) [280].



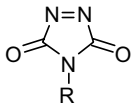
Scheme 12.84



Scheme 12.85

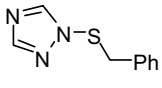
12.3.6
1,2,4-Triazole-Containing Reagents

Monocyclic 1,2,4-triazole-containing structures have found synthetic utility. For example, 4-phenyl-1,2,4-triazole-3,5-dione (**239**) was found to be a novel and reusable reagent for the aromatization of 1,4-dihydropyridines under mild conditions [281] and to be an efficient and chemoselective reagent for the oxidation of thiols to their corresponding symmetrical disulfides [282]. *N*-4-(*p*-Chloro)phenyl-1,2,4-triazole-3,5-dione **240** has been used as an effective oxidizing agent for the oxidation of 1,3,5-trisubstituted pyrazolines to their corresponding pyrazoles under mild conditions at room temperature [283]. 1-Benzylsulfanyl-1,2,4-triazole (**241**) is a useful electrophilic sulfur source in the organocatalyzed α-sulfenylation of aldehydes [284]. Catalyst **242** catalyzed the oxidation of allylic alcohols to allylic esters with manganese(IV) oxide in excellent yields [285] and the oxidation of unactivated aldehydes to esters with manganese(IV) oxide in excellent yields [286]. The asymmetric synthesis of hydrobenzofuranones via desymmetrization of cyclohexadienones using the intramolecular Stetter reaction has been accomplished with 1,2,4-triazolium salt catalyst **243** [287].

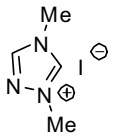


239 R = Ph

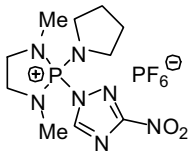
240 R = 4-ClC$_6$H$_4$



241

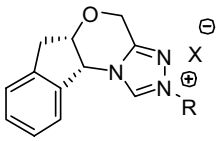


242



243

1,2,4-Triazolium salt catalysts **244** and **246** have been employed in the highly enantioselective azadiene Diels–Alder reactions [288]. Chiral catalyst **245** promoted the intramolecular Stetter cyclization of an aldehyde onto a vinylphosphine oxide or vinylphosphonate Michael acceptor [289]. Chiral triazolium salt **246** has been employed successfully in the hetero Diels–Alder reactions of α-chloroaldehyde bisulfite adducts with various oxodienes under biphasic reaction conditions with high levels of enantioselectivity [290] and in the highly enantioselective *cis*-cyclopentene-forming annulation reactions [291].

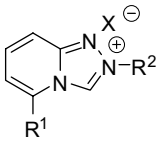


244 R = 4-OMeC$_6$H$_4$, X = BF_4

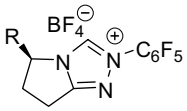
245 R = C_6F_5, X = BF_4

246 R = Mes, X = Cl

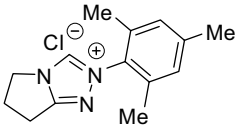
Bicyclic 1,2,4-triazolium salts have varied synthetic utility in a host of reactions. 1,2,4-Triazolium salts **247** have been identified as a new family of stable annulated N-heterocyclic carebenes that found applications in catalytic benzoin condensations and transesterifications at ambient temperature [292]. *N*-Pentafluorophenyl triazolium tetrafluoroborate salts **248** were found to be useful catalysts in the macrocyclization of α,ω-dialdehydes to α-hydroxyketones [293] and in the synthesis of 1,2-amino alcohols via azidation of epoxy aldehydes (where modest asymmetric induction was achieved) [294]. *N*-Pentafluorophenyl triazolium tetrafluoroborate salt **249** was found to be useful catalyst in the asymmetric intermolecular Stetter reaction of glyoxamides with alkylidenemalonates [295]. Chiral catalyst **250** has been utilized in the N-heterocyclic carbene-catalyzed redox amidations of α-functionalized aldehydes with amines [296]. The N-heterocyclic catalyst **251** promoted *O* to *C* carboxyl transfer on a range of indolyl and benzofuranyl carbonates [297] and also promoted the formal [2 + 2] cycloaddition of ketenes with *N*-tosyl imines to give the corresponding β-lactams [298]. Chiral triazolium catalyst **252** has been found to be efficient in the formal [2 + 2] cycloaddition reactions of alkyl(aryl)ketenes with 2-oxoaldehydes to afford β-lactones with α-quaternary-β-tertiary stereocenters in high yields with good diastereoselectivities and excellent enantioselectivities [299]. The asymmetric Michael addition of aromatic heterocyclic aldehydes to arylidenemalonates catalyzed



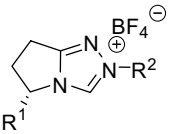
247 X = BF_4, PF_6



248 R = H
249 R = Bn



250



251 R^1 = H, R^2 = Ph
252 R^1 = CPh_2OTBS, R^2 = Ph
253 R^1 = $CH_2OTBDPS$, R^2 = Bn

by N-heterocyclic carbene **253** has been disclosed [300]. Catalyst **253** was also effective in an intermolecular Stetter reaction to give 1,4-diketones [301].

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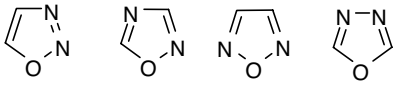
13
Oxadiazoles

Giovanni Romeo and Ugo Chiacchio

13.1
Introduction

There are four isomeric types of oxadiazoles (**1–4**).



1 **2** **3** **4**

Examples of all these ring derivatives are reported; the 1,2,3-oxadiazole system is well represented by the mesoionic sydnones (**5**, X = O) and sydnonimines (**5**, X = NR). In fact, potential 1,2,3-oxadiazoles **6** are not known: when formed in some reactions, they isomerize, instantaneously, into the open α-diazoketone tautomeric forms **7** (Figure 13.1).

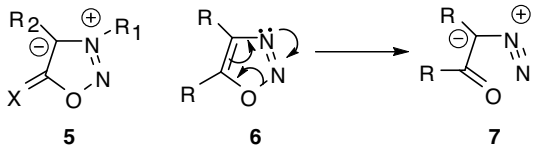
Arguments concerning the existence of **6** and **7** have been summarized [1], but the firmly established 1,2,3-oxadiazole ring system is of the sydnone type.

Ring systems of type **2** are commonly termed azoximes and the 1,2,5-oxadiazoles **3** are often referred to by the trivial name furazan, while 1,2,5-oxadiazole-2-oxide, a well-known derivative, has the trivial name furoxan.

Notably, 1,2,4-oxadiazoles have received great attention in the pharmaceutical industry. In contrast, 1,3,4-oxadiazoles have recently found extensive application in the field of new materials for the development of electric as well as optical devices.

The chemistry of 1,2,3- [2], 1,2,4- [3], 1,2,5- [4], and 1,3,4-oxadiazoles [5] has been widely reported in a series of books and reviews. We refer here to the cited references for general aspects of reactivity of these heterocycles. Particular attention is paid to the literature published after 1995.

Modern Heterocyclic Chemistry, First Edition.
Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.



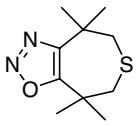
5 **6** **7**

Figure 13.1 Mesoionic sydnones (**5**, X = O) and sydnone imines (**5**, X = NR) are well represented, while potential 1,2,3-oxadiazoles **6** are not known since when formed in some reactions they isomerize instantaneously into the open α-diazoketone tautomeric forms **7**.

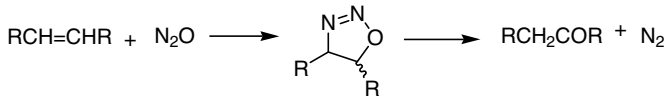
13.2 1,2,3-Oxadiazoles

These are the least common of the oxadiazole group of heterocycles and the literature relating to them is rather sparse. With a very limited and still not perfectly defined number of exceptions, simple 1,2,3-oxadiazoles **6** are not isolable because they isomerize immediately to the their more stable open-chain tautomers, the α-diazoketones **7**. The sterically protected 1,2,3-oxadiazole **8** is the only known oxadiazole, bearing alkyl substituents, which exists in the cyclic form in the crystalline state but as diazoketone in chloroform solution [6].

1,2,3-Oxadiazoles have been proposed [7] as not-isolated intermediates in the oxidation of alkenes with nitrous oxide: a recent DFT analysis predicts that the reaction consists of two steps, with the formation of 1,2,3-oxadiazole in the first and its decomposition in the second, leading to carbonyl compounds [8] (Scheme 13.1).

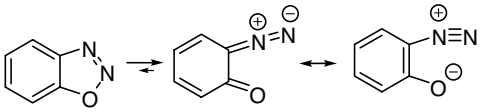


8



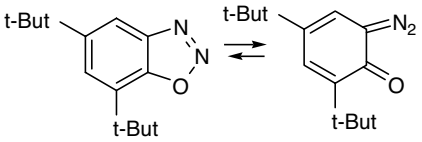
Scheme 13.1

Fusion with an aromatic ring does not stabilize the system. 1,2,3-Benzoxadiazole (**9**) is more stable as an *o*-quinone diazide (**10**↔**11**): the ionization potentials, measured by MS for **10** and **11** and estimated for **9**, indicate that the stabilizing influence of the zwitterionic structures is more important than the gain in aromaticity [9, 10].



9 **10** **11**

Some substituted 1,2,3-benzoxadiazoles have been shown to exist in equilibrium with their open chain tautomers. The relative concentration of the species at the equilibrium is strongly dependent upon solvent and substitution effects: the diazoketone structure is stabilized by hydrogen bonding and polar interactions. The most stable of these compounds is 5,7-di-*t*-butyl-1,2,3-benzoxadiazole (**12**) which is 6.3 kJ mol^{-1} more stable than its diazocyclohexadienone valence isomer **13** in the vapor phase.



12 **13**

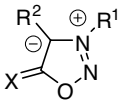
Several examples in the literature report on compounds that have been incorrectly formulated as 1,2,3-oxadiazoles [11]: the previously formulated diazoesters **14** were successively established as non-cyclic **15**.

14 **15**

13.2.1
Sydnones and Sydnonimines

The 1,2,3-oxadiazole ring system is present in the stable mesoionic sydnones (**5a**, X = O and sydnone imines (**5b**, X = NR). The trivial term "sydnone" comes from the University of Sidney, where the first example of these compounds, the 3-phenylsydnone **16**, was synthesized (by Earl and Mackney) by cyclodehydration of *N*-nitroso-*N*-phenylglycine with acetic anhydride [12] (Scheme 13.2).

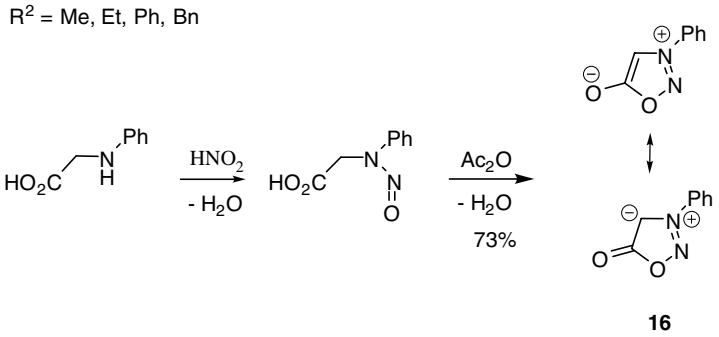
Baker and Ollis coined the term mesoionic [13] to describe the structure of such compounds, for which a totally covalent structure cannot be written, and which cannot be represented satisfactorily by any one polar structure. The term was then extended to several compounds that can be depicted only as resonance hybrids of dipolar structures. Structure **17**, in which the positive charge is delocalized, can be represented as the summary of three canonical forms **18**–**20** [14]. The formal positive charge is associated with the ring atoms, and the formal negative charge is associated



5a: X = O

5b: X = NR_1

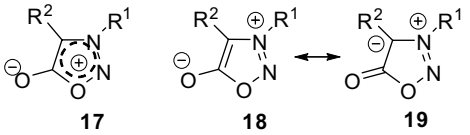
R^1 = Me, Ph, Bn
R^2 = Me, Et, Ph, Bn



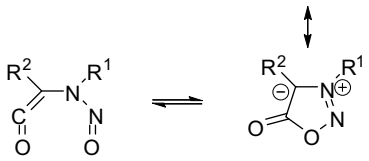
16

Scheme 13.2

with ring atoms or an exocyclic nitrogen or chalcogen atom. X-Ray evidence shows that the valence tautomer **21** should also be considered in discussions of the structure of the sydnones [15].



17 **18** **19**

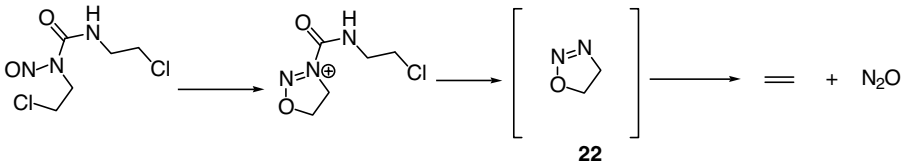


21 **20**

13.2.2
1,2-3-Oxadiazolines

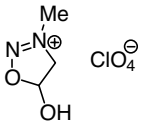
The partially reduced 4,5-dihydro-1,2,3-oxadiazole system, theoretically assemblable by dipolar cycloaddition of diazoalkanes to carbonyl compounds, has never been detected directly in such reactions, although dihydro-1,2,3-oxadiazoline structures

have been proposed in the literature [16]. *Ab initio* and DFT calculations indicate that, in the reaction of diazomethane with formaldehyde, the kinetically most favorable cycloadduct is less stable than the reactants and has a lower barrier for nitrogen elimination [17]. Derivative **22** has been postulated as intermediate in the metabolism of some (2-hydroxyethyl)- or (2-haloethyl)nitrosoureas, a class of highly active antitumor agents (Scheme 13.3) [18].



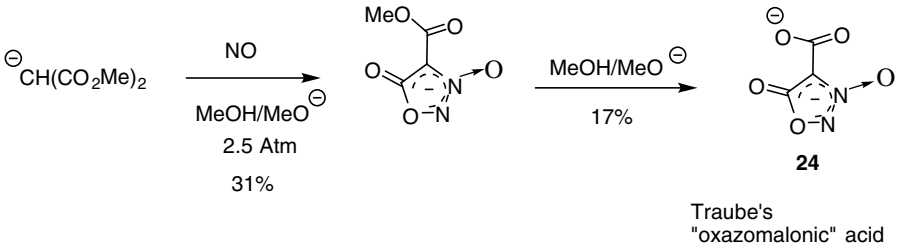
Scheme 13.3

One derivative, the salt **23**, has been isolated as a crystalline solid [19].



23

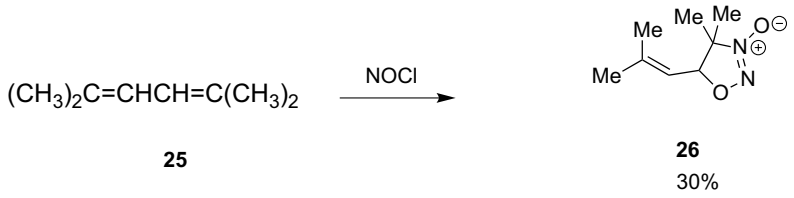
An unambiguous characterization of the so-called "Traube's oxazomalonic acid," obtained from the condensation of dimethyl malonate with nitric oxide, has demonstrated that the compound is really an unusual five-membered heterocycle and corresponds to 3-hydroxy-2-carboxysydnone dianion **24** (Scheme 13.4): the synthesis, structure and spectroscopic analysis of the potassium salt and methyl ester have also been reported [20].



Scheme 13.4

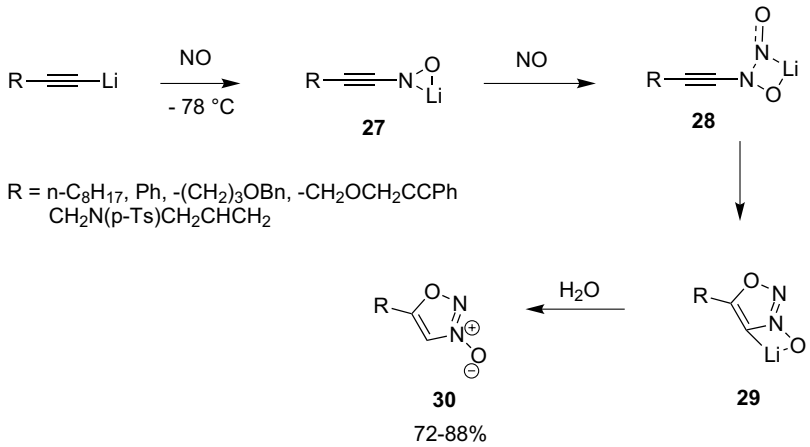
The oxidation state represented by an N-oxide lends stability to the 1,2,3-oxadiazole system [21]. Thus, the reaction of diene **25** with nitrosyl chloride afforded 4,4-dimethyl-5-(2-methylpropenyl)-Δ^2-1,2,3-oxadiazoline 3-oxide **26**, whose structure was confirmed by chemical and spectroscopic data (Scheme 13.5).

A wide variety of 1,2,3-oxadiazole 3-oxides, valuable candidates for drug frameworks, have been synthesized by the reaction of nitric oxide with functionalized



Scheme 13.5

alkynyllithium derivatives [22]. A theoretical study [23] indicates that the overall reaction is stepwise and is considered to include two processes. In the first, the nitrogen atom in nitric oxide at first attacks the C1 atom in alkynyllithium to afford the intermediate **27**. In the second, another nitric oxide reacts with **27** to produce **28**. Then, attack of the oxygen atom at C2 to form a five-membered-ring geometry (**29**) is followed by addition of water, leading to the final 5-alkyl-1,2,3-oxadiazole 3-oxides **30** (Scheme 13.6).

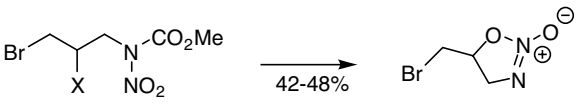


Scheme 13.6

The structure of some of the obtained compounds was confirmed by X ray crystallography and spectroscopic data.

The isomeric 2-oxide system is present in **32**, isolated as a crystalline solid from the reaction of the nitroazo-compounds **31** with bases [24]. As a general process, the intramolecular alkylation of 2-halo- or 2-cyano-substituted nitramines proceeds through an O-alkylation and leads to 4,5-dihydro-1,2,3-oxadiazole 2-oxides **32** (Scheme 13.7) [25].

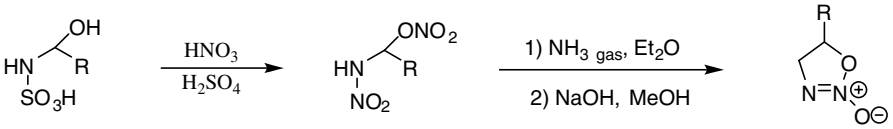
Recently, a new synthetic approach to functionally substituted 4,5-dihydro-1,2,3-oxadiazolo 2-oxides **34** has been described, starting from sulfamic acid derivatives **33** (Scheme 13.8) [26].



31 **32**

X = Cl, Br, CN

Scheme 13.7



33 - 30°C 45- 50 °C **34** 26-63%

a: R = H
b: R = CH_2OMe
c: R = CH_2Cl

Scheme 13.8

Stable derivatives of the 1,2,3-oxadiazolidine ring system **35** are unknown.

35

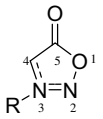
13.2.3 Theoretical Aspects

Ab initio theoretical studies and semiempirical MNDO calculations [27], performed on 1,2,3-oxadiazoles, indicate that the heterocycle is too unstable to be isolated and predict a major stability for its tautomer the diazoacetaldehyde. MNDO calculations on substituted 1,2,3-benzoxadiazoles and the isomeric diazocyclohexadienones reach the same conclusion [10].

Ab initio methods have also been used to calculate the geometry and the energy of 4,5-dihydro-1,2,3-oxadiazole (**22**): the molecule is predicted to be unstable, its most favorable mode of decomposition being a retro 1,3-dipolar addition to diazomethane and formaldehyde [28].

Several theoretical studies have addressed the structure and aromaticity of sydnones [20–34]. Sydnones could be regarded as aromatic because their structures could be represented as cyclic arrays of p-orbitals containing six p-electrons, with four from the C=N−N system and two from the lone pair on oxygen. However, sydnones are not a delocalized "aromatic" ring system, as confirmed by their chemical reactivity: the reactions of sydnones include both substitutions and additions

Semiempirical and *ab initio* calculations provide the same overall description of the bond lengths. The bond from C5 to the exocyclic oxygen atom is essentially a double bond, while the bonds O1–N2, O1–C5, and C4–C5 are approximately single bonds. N2–N3 and N3–C4 are partial double bonds (**36**). On this basis, these compounds could be regarded as 1,3-dipolar azomethyne imines bearing a conjugative carbonyl group at C5 [29].



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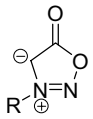


37

X-Ray structural measurements confirm that the exocyclic C–O bond is close in length to that of a normal carbonyl group [35–38]. Therefore, according to the values of the net atomic charges on the ring, determined by semiempirical methods, the resonance structure **37** appears to be the best single representation. The large dipole moments of sydnones (>6 D) are consistent with their strongly polar character and the charge separation shown in structure **37** [29, 36].

Frontier orbital energies and coefficients for sydnones and for some substituted sydnones, performed by the MINDO/3 method, show that the HOMO is a pure p-orbital with a large coefficient on N2 and C4 (Figure 13.2) [29, 33]. On this basis, 1,3-dipolar cycloadditions of sydnones to electron-deficient alkenes should be controlled by the HOMO of the sydnone and the LUMO of the dipolarophile.

13.2.4
Structural Aspects

Structural parameters, IR spectra, ionization potentials, relative energies, isomerization barriers, and solvation energies have been calculated for sydnones and for the aromatic benzo-1,2,3-oxadiazole (prevalent tautomer in the gas phase) and zwitterionic 6-diazocyclohexa-2,4-dienone (prevalent tautomer in a polar solvent) molecules. The calculations indicate that unsubstituted 1,2,3-oxadiazole is unstable in all solvents [39].

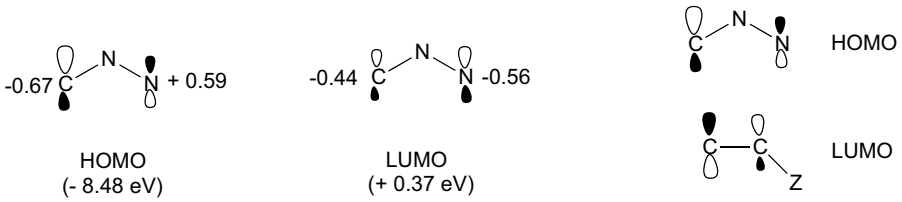
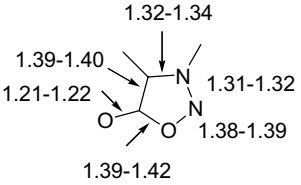


Figure 13.2 Frontier orbital energies and coefficients for sydnones and for some substituted sydnones show that the HOMO is a pure p-orbital with a large coefficient on N2 and C4.

13.2.4.1 X-Ray Diffraction

Crystal structure data of several sydnones have been reported [34, 40]. The ring is nearly planar and the values for bond lengths are in the range illustrated in structure **38**. The exocyclic carbonyl bond length is 1.21 Å; the N2−N3 and N3−C4 bonds are somewhat shorter than a single bond, while the only C−C bond present is longer than a double bond.



38

13.2.4.2 UV and IR Spectra

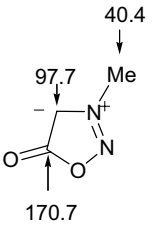
UV and IR spectroscopy have afforded useful information in studies of the equilibrium between 1,2,3-benzoxadiazole and *o*-quinone diazide structures. The IR spectra of 1,2,3-benzoxadiazoles show absorptions at 1626, 1611, 1464, and 1457 cm^{-1}, whereas the isomeric quinone diazides show strong absorptions at 2090 and 1718 cm^{-1} [41]. The UV spectrum of 1,2,3-benzoxadiazole in an argon matrix shows maxima at 201, 243, and 289 nm [10].

Carbonyl stretching frequencies of sydnones are in the range 1720–1790 cm^{-1}. Alkylsydnones show a single maximum at 290 nm in the UV spectrum.

13.2.4.3 NMR Spectra

The ^{1}H and ^{13}C spectra of several sydnones and sydnonimines have been reported [42]. In accord with the dipolar structure **5**, the H4 proton resonates upfield in the range 6.2–6.8 ppm. Analogously, for the strong deshielding effect of positively charged N3 atom, the 3-alkyl protons are shifted downfield (4.10–4.40 ppm) with respect to 4-alkyl protons (2.20–2.50 ppm).

For 3-methylsydnone, the ^{14}N and ^{17}O spectra have also been determined and a complete set of chemical shift values for all the atoms have been reported [45]. The ^{13}C chemical shifts are reported on structures **39** and **40**.



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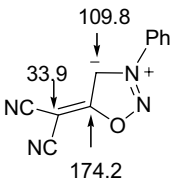


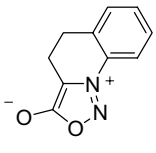
40

According to a synthetic approach that allowed for the independent labeling of the nitrogen atoms (Section 13.2.5.1), the NMR chemical shift for each ^{15}N has been determined unambiguously.

13.2.4.4 Mass Spectra

Electron impact mass spectra of the sydnone ring are characterized by the loss of NO (M–30) and CO (M–28) fragments, which can occur consecutively or simultaneously. The fragment M-58 represents generally the base peak and the molecular ion is often distinguishable [44].

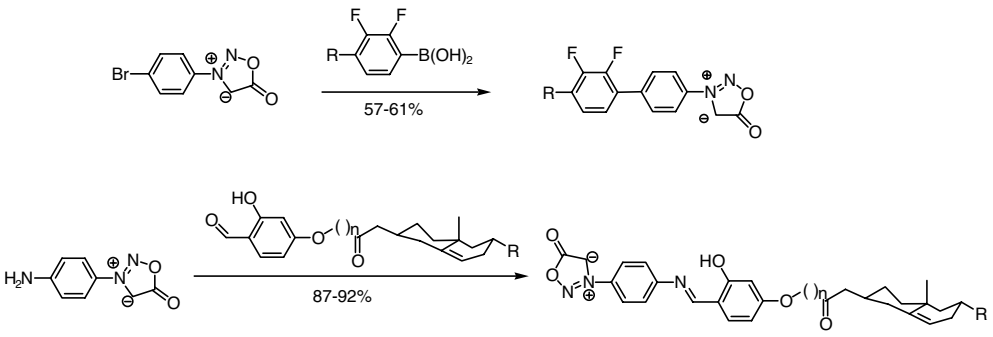
Reported CI spectra indicate the same pattern of fragmentation. In the fused sydnone **41**, the initial loss of NO is followed by CO, HCN, acetylene, and finally Ph, as the principal fragment ion [45].



41

13.2.4.5 Other Properties

The highly polarized yet neutral electrical character and the high dipolar moments of sydnones have been exploited for the design of technologically interesting thermotropic liquid crystals (LCs) with properties between those of covalent and ionic LC. The molecular design, synthesis, and characterization of the first examples of both classical and non-conventional chiral mesoionic (mesomeric + ionic) liquid crystals derived from sydnones have been reported (Scheme 13.9) [46, 47].



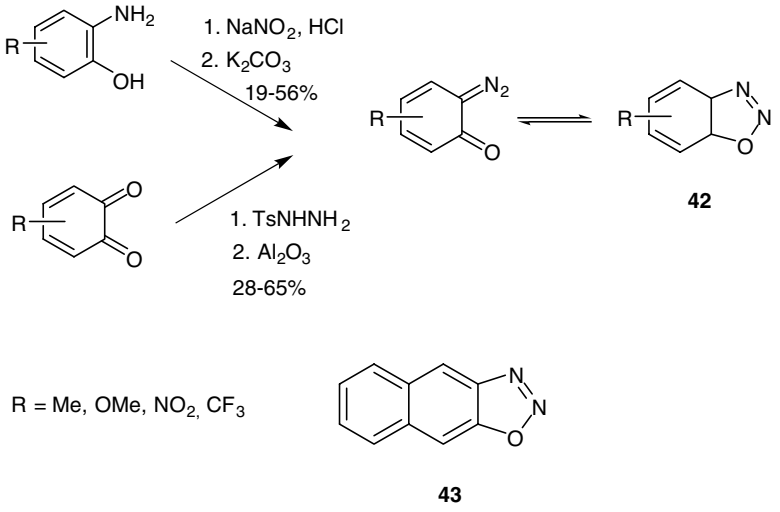
Scheme 13.9

The occurrence of chiral smectic phases in these novel compounds was evidenced by optical microscopy, calorimetry, and X-ray studies.

A side-chain polysiloxane containing 3-(4-aminophenyl)sydnone moieties at terminal and aliphatic spacer has been prepared and its structure was confirmed by IR and NMR measurements. By introducing sydnone into polysiloxane, the polymer displays a high electrorheological effect due to the increased interaction between sydnone moieties [48].

13.2.5
Synthesis of 1,2,3-Oxadiazoles

The synthetic approach towards substituted 1,2.3-benzoxadiazoles is based on the synthesis of the tautomeric open-chain 6-diazo-1,2-cyclohexadienones [49, 50]. Thus, the diazotization of 2-aminophenols by treatment with sodium nitrite or isoamyl nitrite, followed by careful neutralization with potassium carbonate, afforded the diazoketones (Scheme 13.10), which is in equilibrium with the cyclic tautomer benzoxadiazole (**42**) (Section 13.2). An alternative route exploited the reaction of a substituted *o*-benzoquinone with tosyl hydrazine [43]. Naphthoxadiazole (**43**), stable in the solid state at −19 °C, has been prepared according to this synthetic route.

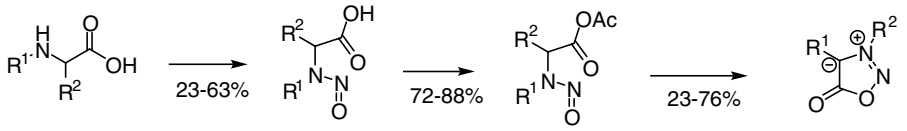


Scheme 13.10

13.2.5.1 Sydnones and Sydnonimines

Despite extensive studies of the sydnone ring, practically only one general synthetic entry is available [51]. The method involves (a) nitrosation of amino acids to give **44;** (b) formation of a mixed anhydride **45** and (c) cyclization to the sydnone ring **46** (Scheme 13.11).

The nitrosation step has been carried out under neutral conditions, using isoamyl nitrite. Among the dehydrating agents, trifluoroacetic anhydride gives the most rapid



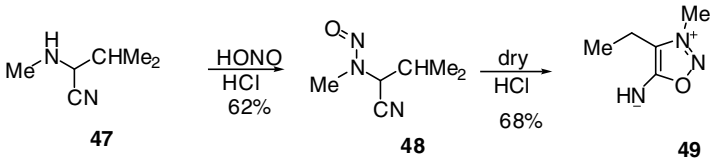
R^1 = Me, Et, Ph, Bn
R^2 = Me, Ph, Bn

Scheme 13.11

results; thionyl chloride, phosphorus oxychloride, phosphoric anhydride, and carbodiimides have also been used successfully.

The cyclization step can be aided by ultrasonic irradiation [52, 53]: in this way, functionalized 3-aryl sydnones have been prepared in good yields.

A similar general method towards sydnonimines involves the nitrosation of the corresponding α-aminonitriles **47** and cyclization of the intermediate **48** (Scheme 13.12) [54]. Substituents can be introduced at the exocyclic nitrogen atom by normal methods in acidic or buffered solutions: sydnone imines are more stable in acid and less stable in base than sydnones.



Scheme 13.12

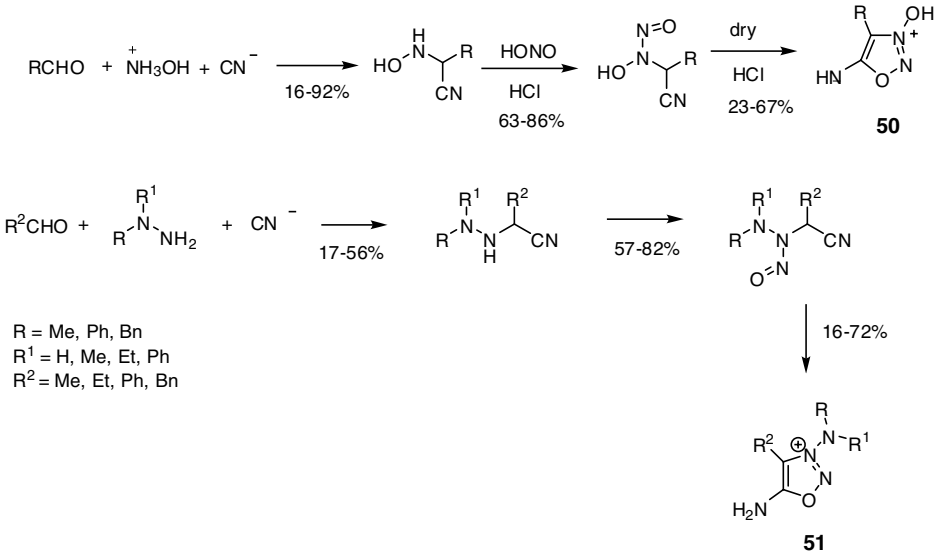
A three-component reaction of the Mannich type has been exploited to prepare 3-*N*-hydroxy- (**50**) and 3-*N*-amino- (**51**) substituted sydnone imines (Scheme 13.13) [55–57].

13.2.5.2 4,5-Dihydro-1,2,3-Oxadiazolines

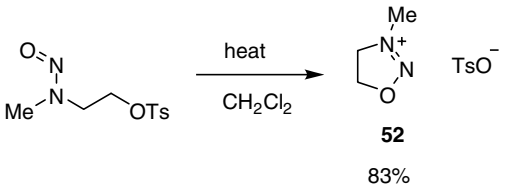
Methods for the synthesis of the few reported compounds of this type have been described in Section 13.2.2. Scheme 13.14 describes the synthesis of 4,5-dihyro-3-methyl-1,2,3-oxadiazolium tosylate (**52**) [58]. Accordingly, 5-alkoxy-substituted derivatives can be prepared by cyclization of 2,2-dialkoxy-*N*-methyl-*N*-nitrosoethylamines [59].

13.2.6 Reactivity of 1,2,3-Oxadiazoles

With the exception of some benzo-fused derivatives and 4,5-dihydro-1,2,3-oxazolidinium salts, the chemistry of the 1,2,3-oxadiazole system is nearly confined to the mesoionic sydnones or sydnonimines.



Scheme 13.13



Scheme 13.14

13.2.6.1 Benzo-1,2,3-Oxadiazoles

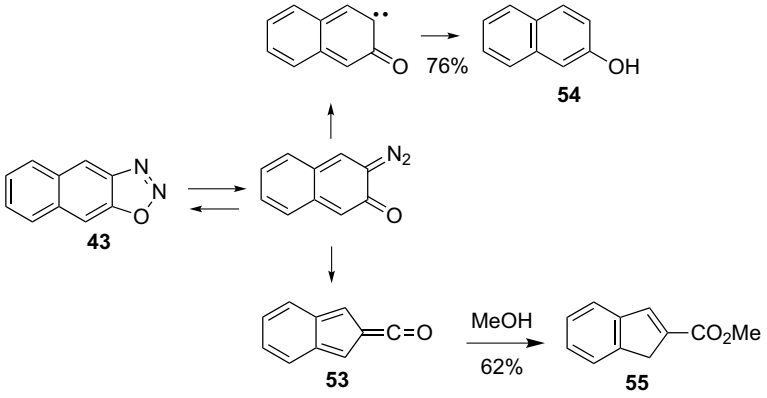
UV irradiation cleaves the benzoxadiazole ring to 2-diazocyclohexadienones: subsequent loss of nitrogen and Wolff rearrangement leads to ketene **53** (Scheme 13.15) [10]. The formation of 2-naphthol **54** and methyl indene-2-carboxylate **55** by irradiation of naphthoxadiazole **43** is amenable to the loss of nitrogen from the diazocarbonyl tautomer [60].

13.2.6.2 4,5-Dihydro-1,2,3-Oxadiazoles

The known chemistry is limited to 4,5-dihydro-3-methyl-1,2,3-oxadiazolinium salts. The cation reacts with nucleophiles at the methyl group (methylation of the nucleophile) or at C5, with opening of the ring.

13.2.6.3 Sydnones

13.2.6.3.1 **General Aspects** Sydnones are crystalline compounds that are sensitive to hydrolysis, especially in basic media where they are rapidly cleaved. The ring is also



Scheme 13.15

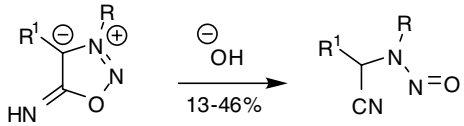
cleaved by catalytic reduction and, oxidatively, by reaction with nitric acid, potassium permanganate, and other oxidants.

The chemical reactivity of the sydnone system is displayed in ring cleavage reactions and in processes in which the ring system is retained such as substitution or addition reactions (at the 4-position). Substituents can be introduced into the 4-position by conventional electrophilic substitution or after metallation at C4. Standard transformation of functional groups at C4 of sydnone have also been investigated extensively and targeted to the synthesis of various 4-substituted sydnones.

Sydnones can act as 1,3-dipoles in dipolar cycloaddition reactions.

13.2.6.3.2 Ring Cleavage

Hydrolysis (Acid and Basic Ring Cleavage) The alkaline hydrolysis of sydnonimines (Scheme 13.16) proceeds through an experimentally ascertained third-order kinetics, and leads to ring cleavage that affords the nitrosonitrile **56** [61].

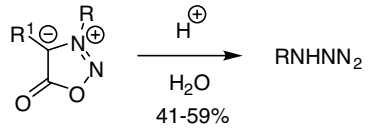


R = Me, Ph
R^1 = Me, Et, Bn

Scheme 13.16

Acid hydrolysis of sydnones, which occurs at elevated temperatures, has been exploited as a synthetic path to alkyl- and arylhydrazines (Scheme 13.17) [62–64].

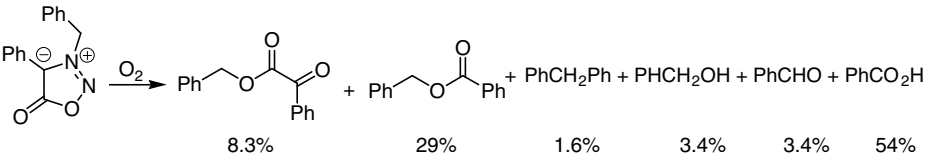
Oxidative Ring Cleavage Ring cleavage of sydnones with oxygen in the dark affords a mixture of products; thus, oxidation of 3-phenylsydnone gives benzaldehyde, benzyl



R = Ph, Pyridyl
R^1 = Me, Ph, Bn

Scheme 13.17

alcohol, and benzyl formate, while 3-benzyl-4-phenylsydnone affords benzyl phenylglyoxylate, benzyl benzoate, diphenylmethane, benzyl alcohol benzaldehyde, and benzoic acid (Scheme 13.18) [65].



Scheme 13.18

The proposed mechanism, which implies radical intermediates, arises from an initial electron-transfer reaction of the sydnone with oxygen. Recombination of the radical ion with $^{\bullet}O_2^-$ would lead to the hydroxyperoxy zwitterion **57**, which could then cyclize at the 3- or 2-position to give **58** and **59**, respectively. Further collapse of **58** and **59** afforded the obtained mixtures of compounds (Scheme 13.19).

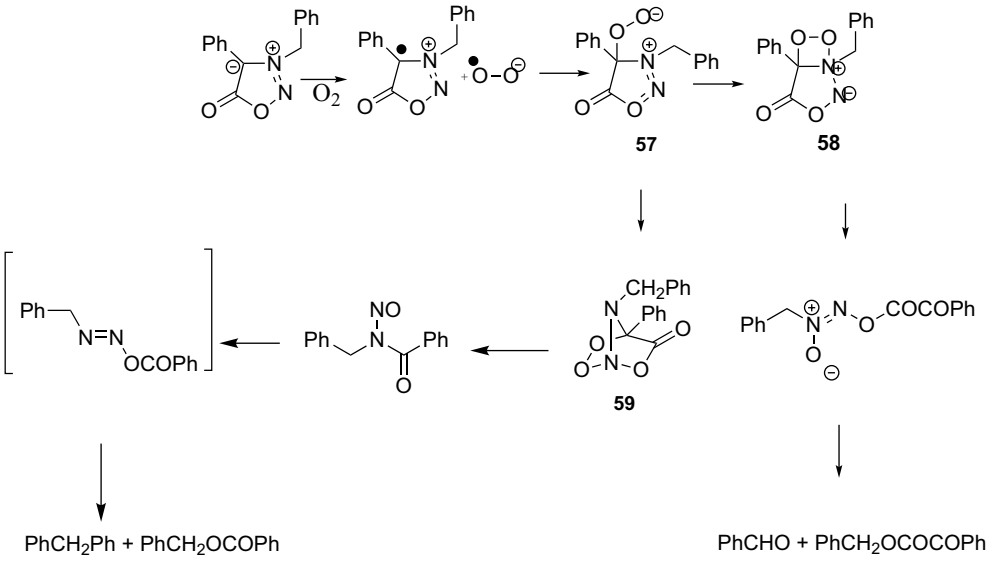
Oxidation with ozone of 4-methylsydnones leads to pyruvate esters (Scheme 13.20) [66].

Thermal and Photochemical Ring Cleavage Thermochemical and photoinduced decomposition of sydnones give different products as a function of the nature of substituents present in the ring.

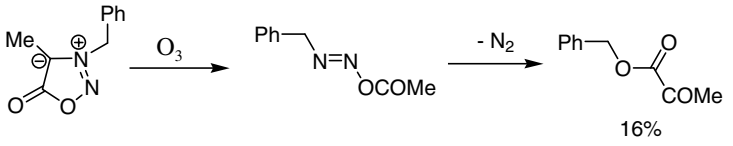
3,4-Diarylsydnones lose carbon dioxide by UV irradiation or by flash photolysis and give transient nitrile imines, which can be intercepted by external or internal dipolarophiles [67, 68]. For example, the photochemically induced reaction of 3,4-diphenylsydnone affords, in the presence of DMAD, the dimethyl 2,5-diphenylpyrazole-3,4,dicarboxylate (**61**) (Scheme 13.21), which originates from the loss of CO_2 and the addition of the dipolarophile to the dipolar intermediate **60** (Scheme 13.21) [69].

In the thermochemically induced process, the addition of DMAD occurred first to give **62**, followed by elimination of carbon dioxide to form the dimethyl 1,5-diphenylpyrazole-3,4-dicarboxylate **63**.

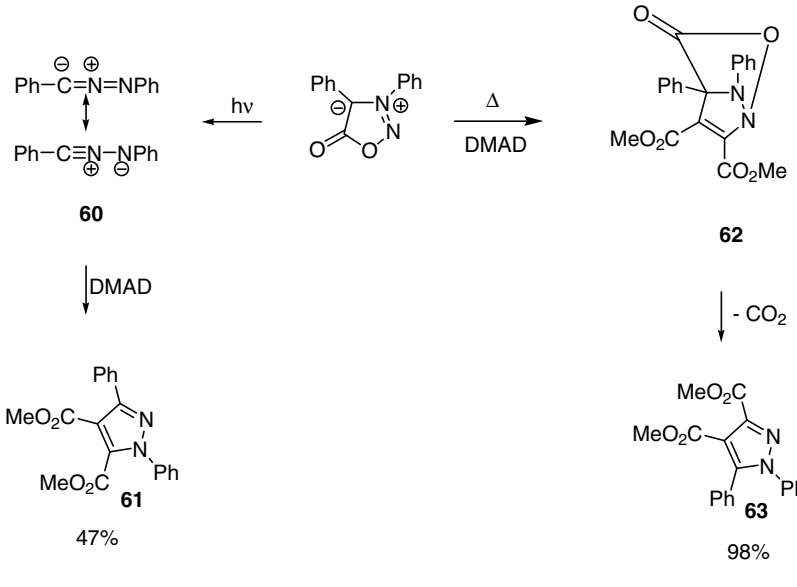
Alkenes and other trapping agents have been used to capture the dipolar nitrilimine [70–72]. When 1,3-butadiene was used as a dipolarophile, 1,3-diphenyl-5-vinylpyrazole (**64**) was obtained, so confirming that **60** is the trapped fragment (Scheme 13.22) [73].



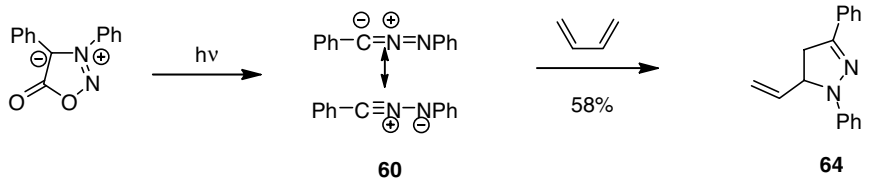
Scheme 13.19



Scheme 13.20

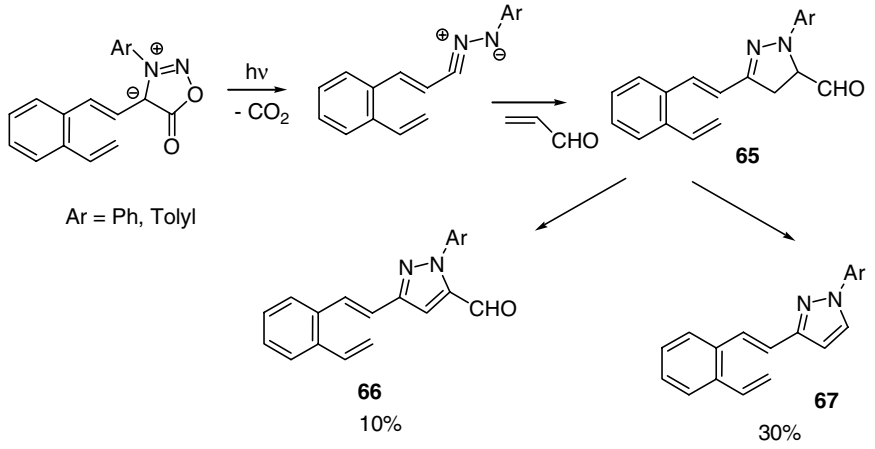


Scheme 13.21



Scheme 13.22

3-Aryl-4-[2-(2-vinylphenyl)ethenyl]sydnones undergo fast isomerization to the trans isomer and competitive photolysis of the sydnone moiety, giving the corresponding nitrile imine, which cannot react intramolecularly. In the presence of acrolein, a [3 + 2] cycloaddition takes place to give the *trans*-styrylpyrazoline derivative **65**, which during isolation aromatizes to the pyrazoles **66** and **67** (Scheme 13.23) [74].

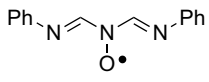


Scheme 13.23

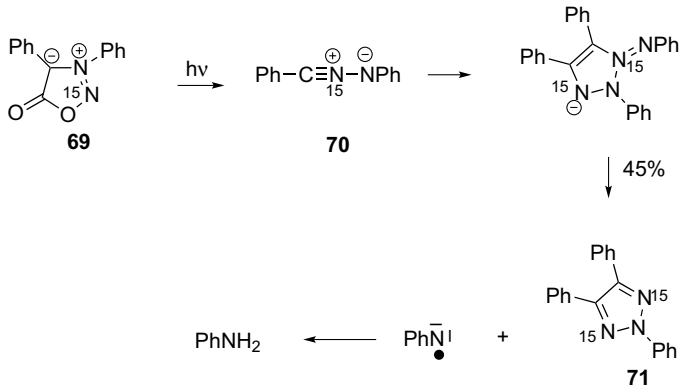
Nitrile imines have not been detected from 3-arylsydnones unsubstituted at C4; ESR techniques have, however, revealed the presence of the radical species **68**, which originates from the photolysis of 3-phenylsydnone [75].

Nitrile imines have also been claimed as intermediates in the formation of triazole derivatives by photochemical decomposition of a sydnone in dioxane. By labeling the nitrogen atoms in **69**, the mechanism for the formation of the triazole **71**, based on **70** as key intermediate, has been supported (Scheme 13.24) [76].

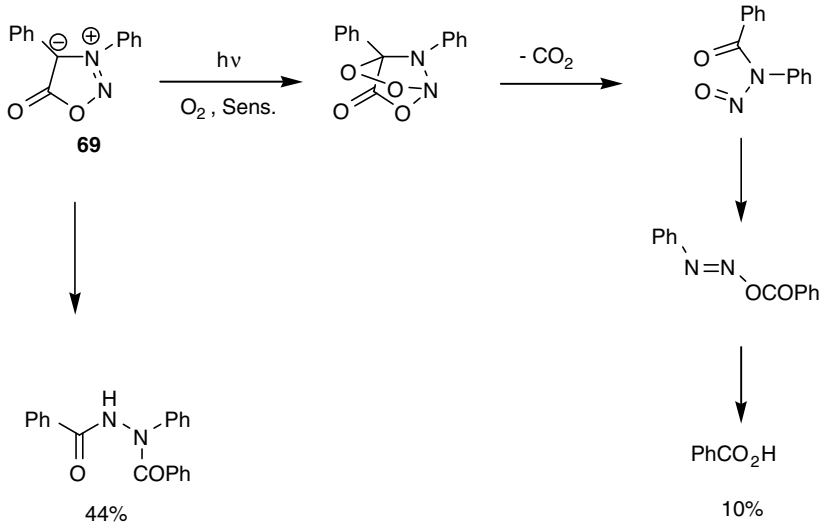
The photosensitized oxidation of sydnones with singlet oxygen has also been reported to give a mixture of products. In the presence of Rose Bengal as a sensitizer, singlet oxygen adds to a sydnone as a dipolarophile. The identification of benzoic acid and dibenzoylphenylhydrazine among the reaction products has been rationalized on the basis of two simultaneous reaction pathways (Scheme 13.25) [77].



68

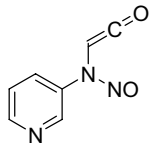


Scheme 13.24



Scheme 13.25

Several sydnones develop a color when irradiated by UV light; for instance, a blue color has been observed by irradiation of the 3-(3-pyridyl)sydnone. The phenomenon has been explained through the formation of diketene **72**, which has been identified as the blue species [78].



72

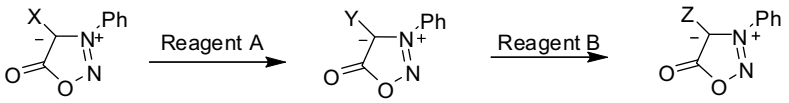
13.2.6.3.3 **Nucleophilic Substitution at C4** Replacement reactions at C4 in sydnones have been reviewed. Butyllithium has been exploited to displace the bromine atom from a 3-phenylsydnone [46b]: the resulting organometallic compound has been carbonylated, added to ketones and converted into a silyl derivative [79]. Grignard compounds have also been prepared from 3-bromosydnones, and subsequently reacted with ketones to give the corresponding alcohols (Table 13.1) [80].

Metallation reactions have been exploited as a synthetic tool for effecting electrophilic substitution at C4 (Section 13.2.6.3.4) [81].

13.2.6.3.4 **Electrophilic Substitution at C4** Electrophiles can be directly introduced at C4 in the sydnone ring. Table 13.2 summarizes a series of such reactions reported in literature [82, 83].

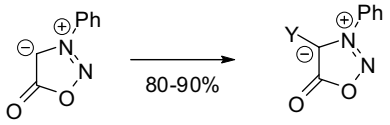
With 4-unsubstituted 3-alkyl- or 3-phenylsydnones, substitution occurs only at the electron-rich C4, while when aryl substituents are present at C3 the position of the electrophilic attack depends upon the nature of the aryl group, Exclusive aryl ring nitration occurs with electron donors on the aryl group [84]. Thus, 3-(2-aminophenyl) sydnone is brominated in the benzene ring *para* to the amino group [85] while the nitration of 3,4-diphenylsydnone affords the 4-nitrophenyl derivative. As further

Table 13.1 Nucleophilic replacement reactions at C4 in sydnones.



X	Reagent A	Y	Reagent B	Z
Br, H	BuLi	Li	CO_2	COOH
			$COCl_2$	$(CO)_{1/2}$
			$MeCOCHMe_2$	$MeC(OH)CHMe_2$
Br	Mg, ether, MeI	MgBr	I_2	I
			Ac_2O	COMe
			RCHO	CH(OH)R
SMe	H_2O_2	SO_2Me	$NaBH_4$	H

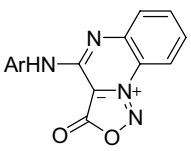
Table 13.2 Electrophilic replacement reactions at C4 in sydnones.



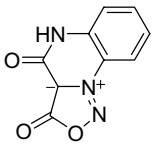
Reagent	Y
(a) Br_2, ether, $NaHCO_3$	Br
(b) $HONO_2$ + $HOSO_3H$, O °C	NO_2
(c) SO_3 (dioxane)	SO_3H
(d) $ClSO_3H$ + H_3PO_4	SO_2Cl
(e) Ac_2O + BF_3 (ether)	COMe
(f) $HCONMe_2$ + $POCl_3$	CHO
(g) $Hg(OAc)_2$	HgOAc
(h) DMSO + AcCl	SMe

examples, the sydnone ring is brominated in preference to a pyrazolyl system at C3, while nitration of 3-methyl-4-phenyl sydnone affords the 4-nitrophenyl substituted derivative.

Intramolecular electrophilic substitutions at C4 provide a route to fused sydnones such as **73** [86] and **74** [87].

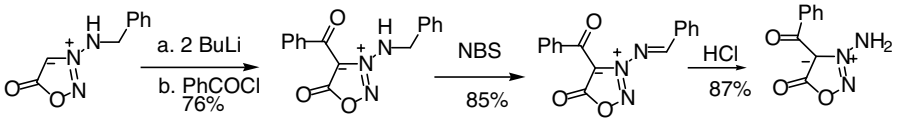


73



74

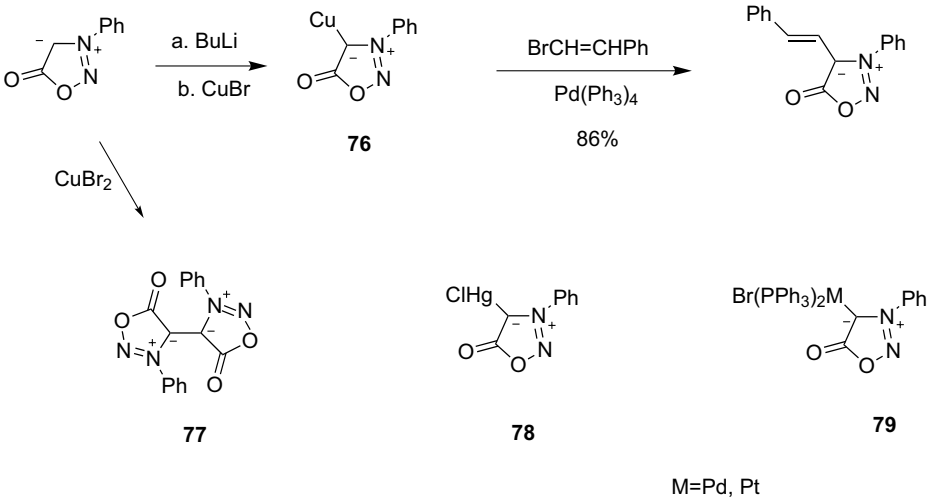
Electrophiles have also been introduced at the 4-position through organometallic derivatives. 4-Lithio intermediates [46b] (Section 13.2.6.3.3) have been used to introduce several S, Se, and Te electrophiles [88, 89], and also formyl or acetyl substituents (Scheme 13.26) [90]. This strategy has been exploited for the synthesis of 3-amino-4-benzoylsydnone (**75**), the first example of a sydnone containing an amino group at C3 [91].



75

Scheme 13.26

Vinyl and aryl substituents at C4 have been introduced by means of other organometallic species. Thus, the reaction of 4-lithio-3-phenylsydnone with copper(I) bromide affords the stable copper derivative **76**, which gives palladium (0)-catalyzed coupling to iodobenzenes and vinyl bromides [92]. The reaction of the lithium intermediate with copper(II) bromide leads to the dimer **77** (Scheme 13.27).

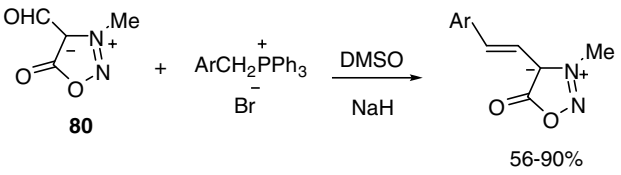


Scheme 13.27

Various 4-arylethynyl sydnones have been prepared in good yields by the reaction of 4-bromo-3-phenylsydnone with aryl acetylenes under palladium catalysis [93].

Chloromercuro derivatives **78** have also been used in Heck coupling reactions with vinyl halides, and sydnones with platinum or palladium substituents **79** have been prepared from 4-bromo-3-phenylsydnone and $M(PPh)_3$ [94].

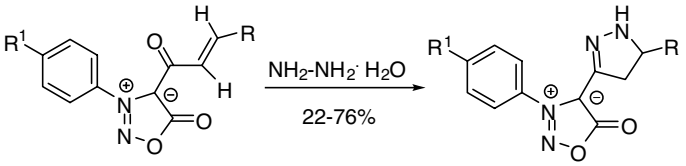
13.2.6.3.5 **Reactions of Substituents** Standard transformations occur in various functional groups present on the sydnone ring. Thus, 3-phenylsydnone-4-carboxylic acids can be easily converted into the corresponding esters, amides, and hydrazides; tertiary alcohols can be dehydrated to alkenes and ketones can be condensed with benzaldehyde. Aldehyde **80** can be converted into the corresponding *(E)*- and *(Z)*-alkenes by a Wittig reaction (Scheme 13.28) [95].



Scheme 13.28

Sydnonyl-substituted α,β-unsaturated ketones have been synthesized by Claisen–Schmidt condensation of 4-acetyl-3-arylsydnones with aryl aldehydes. An easy, eco-friendly synthetic version has also been reported that involves grinding 4-acetyl-3-aylsydnones with aryl aldehydes in a mortar [96].

Further reaction of sydnonyl-substituted α,β-unsaturated ketones with hydrazine hydrate afforded sydnonyl-substituted pyrazolines **81**, which possess useful applications in medicine (Scheme 13.29) [97].

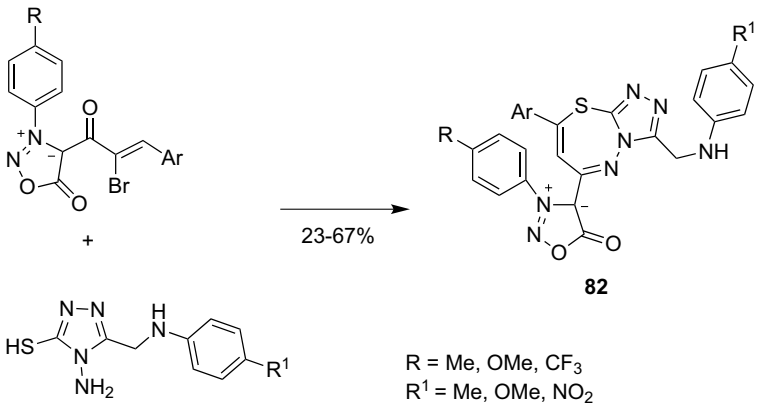


R = Me, Et, Ph, Bn
R^1 = Me, OMe, NO_2

81

Scheme 13.29

Moreover, the reaction of 3-aryl-2-bromo-1-sydnonylpropenones with 3-arylaminomethyl-4-amino-5-mercapto-1,2,4-triazoles gives 3-arylaminomethyl-6-(3-arylsydnon-4-yl)-8-aryl-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazepines **82** with antibacterial activity (Scheme 13.30) [98].

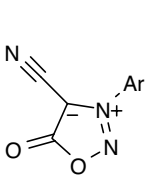


82

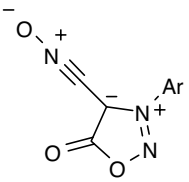
R = Me, OMe, CF_3
R^1 = Me, OMe, NO_2

Scheme 13.30

4-Aryl-3-formylsydnones can be easily converted into their oximes, from which other functionalized sydnones such as the nitrile **83** [99] and the nitrile oxide **84** [100] can be obtained.

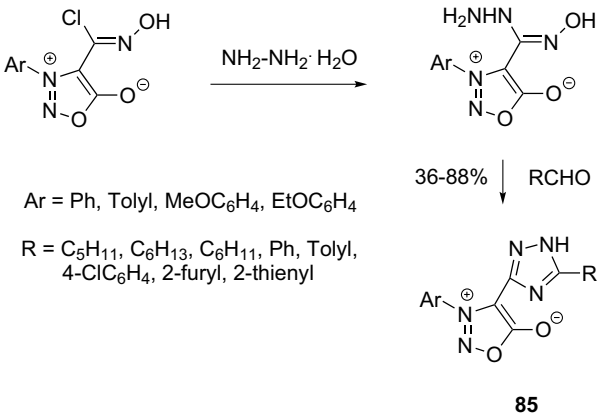


83



84

The reaction of 3-aryl-4-carbohydroximic acid chlorides with hydrazine hydrate gives hydrazino(3-arylsydnon-4-yl)methanone oximes, which by reaction with aldehydes are good precursors of 4-triazolyl-sydnones (**85**, Scheme 13.31) [101].



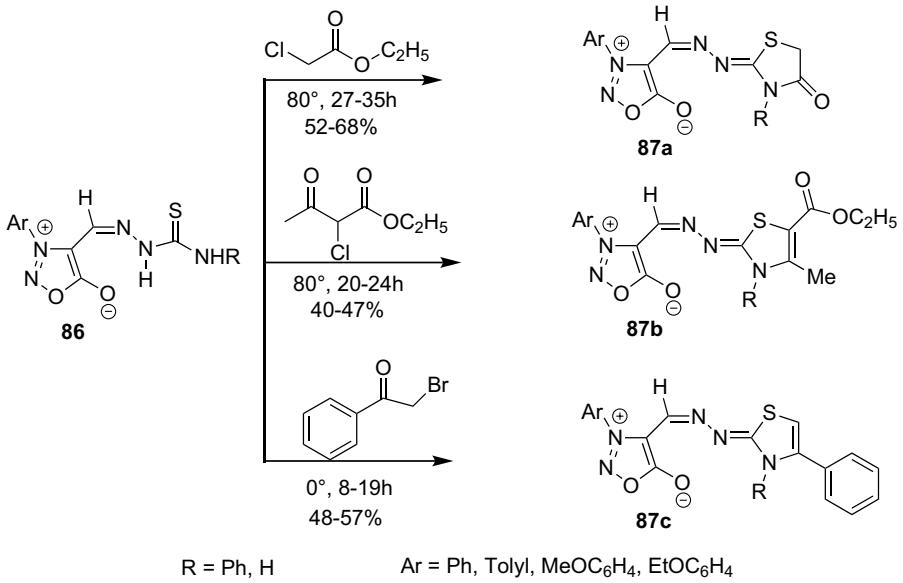
85

Scheme 13.31

4-Formylsydnones undergo reduction, Claisen condensation with acetophenone, and condensation with nitroalkanes and active methylene compounds. Thus, the Knoevenagel reaction of 3-aryl-4-formylsydnones affords multifunctional derivatives [102].

3-Aryl-4-formylsydnone-4′-phenyl-thiosemicarbazones and 3′ aryl-4-formylthiosemicarbazones **86** react with ethyl chloroacetates, ethyl 2-chloroacetoacetate, and 2-bromoacetophenone to produce heterocyclic substituted sydnone derivatives **87a–c** that possess 4-oxo-thiazolidine and thiazoline groups (Scheme 13.32) [103]. The antioxidant activity of the synthesized compounds was evaluated. Among these compounds, 4-methyl-2-[(3-arylsydnon-4-yl-methylene)hydrazono]-2,3-dihydro-thiazole-5-carboxylic acid ethyl ester and 4-phenyl-2-[(3-arylsydnon-4-yl-methylene) hydrazono]-2,3-dihydro-thiazoles exhibit potent DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging activity, comparable to that of vitamin E.

A suitable substituent at C4 can be used as a temporary blocking group to allow reaction to take place at another side of the sydnone. For example, 4-acetyl-



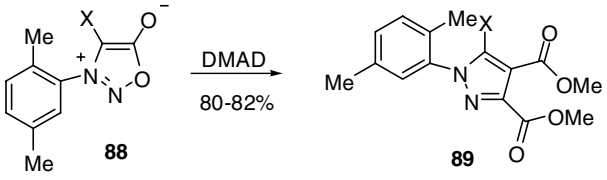
Scheme 13.32

or 4-formyl-3-phenylsydnones can be nitrated in the aromatic ring (in the *meta* position) and subsequently the acyl group can be removed under basic conditions.

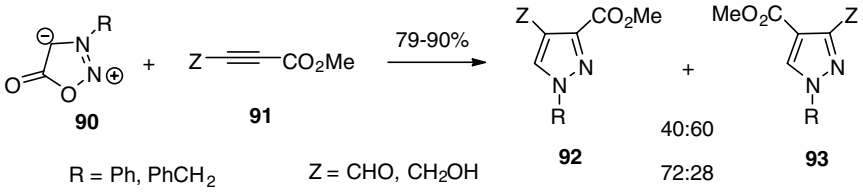
Similarly, a thioether group at C4 can be removed by oxidation to sydnone sulfone and subsequent reduction with sodium borohydride.

13.2.6.3.6 **1,3-Dipolar Cycloaddition Reactions** Sydnones can be regarded as cyclic azomethine imines and as such they undergo thermal cycloaddition reactions with a range of dipolarophiles. As previously discussed (Section 13.2.6.3.2), on photolysis 3,4-diaryl-sydnones lose carbon dioxide and afford transient nitrile imines, which can be trapped by alkynes to give pyrazole derivatives.

Thermal reactions with acetylenic dipolarophiles also lead to pyrazoles by spontaneous loss of carbon dioxide from the cycloadducts. According to this reaction route, a series of 5-halopyrazoles (**89**) with potential pharmacological activity has been synthesized in good yields by 1,3-dipolar cycloaddition of 4-halogenated sydnones **88** with dimethyl acetylenedicarboxylate (DMAD) (Scheme 13.33) [104].



Scheme 13.33

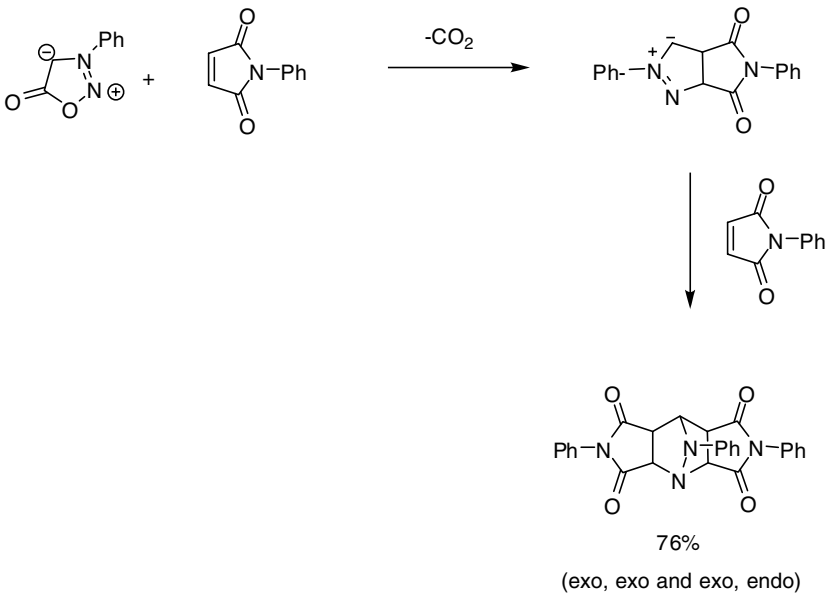


Scheme 13.34

With unsymmetrical alkynes **91**, the cycloaddition reactions of sydnones **90** rarely show a good regioselectivity (Scheme 13.34) [105].

With monosubstituted alkenes bearing conjugative electron-withdrawing groups, the regioselectivity of the reaction is that predicted by frontier orbital analysis (Figure 13.2), that is, with the carbon bearing the electron-withdrawing group next to nitrogen. The obtained products are usually dihydropyrazoles or pyrazoles formed by oxidation of the intermediate dihydropyrazoles.

The unstable species formed by loss of carbon dioxide are also azomethine ylides: thus, in the reaction of 3-phenylsydnone with *N*-phenylmaleimide, a second dipolar cycloaddition reaction can take place (Scheme 13.35) [106].

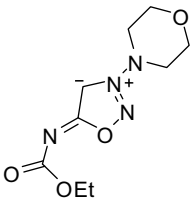


Scheme 13.35

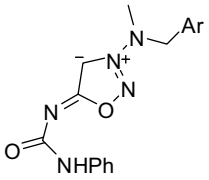
The tandem 1,3-dipolar cycloaddition between sydnones and 1,5-cyclooctadiene afforded 9,10-diazatetracyclo[6.3.0.0.^{4,11}0.^{5,9}]undecanes (Weintraub reaction) [107].

13.2.7
Important Compounds and Applications

1,2,3-Oxadiazole derivatives show a wide range of biological activities. In particular, two most important and studied compounds are the sydnonimines molsidomine (**94**) and sydnocarb (**95**).



94

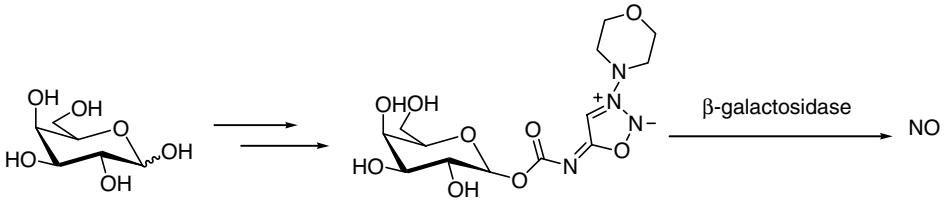


95

Molsidomine (**94**), endowed with very low toxicity, has a long-term effect in vasodilation, thus exerting a positive effect in cases of ischemic heart diseases. In combination with the β-blocker propanolol, molsidamine has shown a high efficacy for the treatment of portal hypotension [108].

Molsidomine is also used in treating angina pectoris [109].

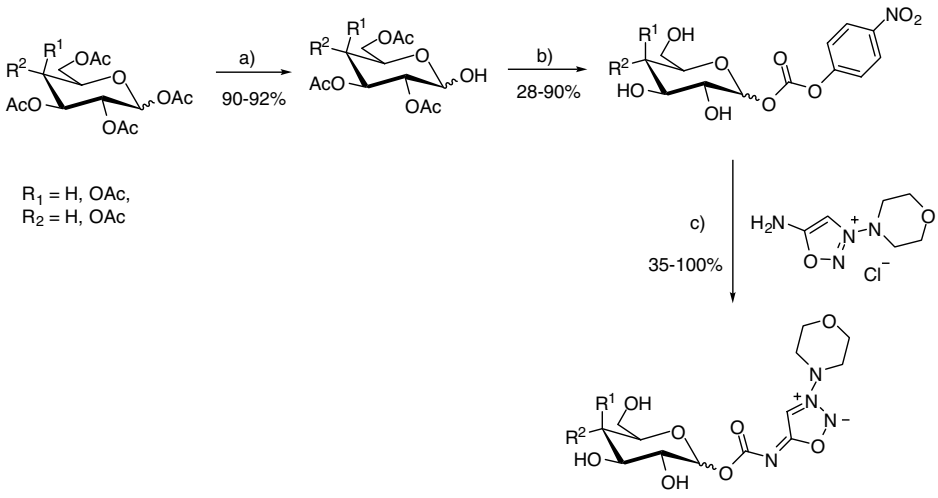
The pharmacological activity is correlated to the formation of a metabolite, the *N*-morpholino-*N*-nitrosoaminoacetonitrile, which acts as a nitric oxide donor (Scheme 13.36) [110].



Scheme 13.36

Accordingly, to achieve site-specific delivery of nitric oxide (NO), a new class of glycosidase activated NO donors has been developed, in which glucose, galactose, and *N*-acetylneuraminic acid were covalently coupled to 3-morphorlinosydnonimine, via a carbamate linkage at the anomeric position [111]. The β-glycosides were successfully prepared for these conjugates, while the α-glycosidic compounds were very unstable. The new stable sugar–NO conjugates could release NO in the presence of glycosidases (Scheme 13.37). Such NO prodrugs may be used as enzyme-activated NO donors in biomedical research.

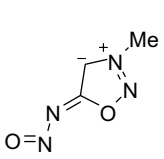
With analogous aim, conjugates of cephalosporin with 3-morpholinosydnonimine have been designed and evaluated [112]. The obtained compounds demonstrated promising β-lactamase dependent NO releasing ability.



a) $BnNH_2$, THF, rt, 30h; b) p-$NO_2C_6H_4OCOCl$, Et_3N, CH_2Cl_2, rt, 4.5h; c) pyridine, rt, 12h.

Scheme 13.37

Sydnocarb acts on the central nervous system and has been used as a psychostimulant and an antidepressive. Nitrososydnonimines **96** and **97** showed potent antithrombotic activity [113, 114].



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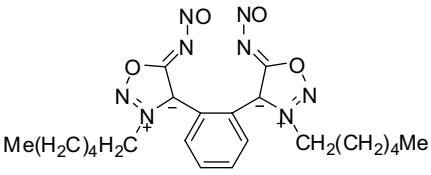
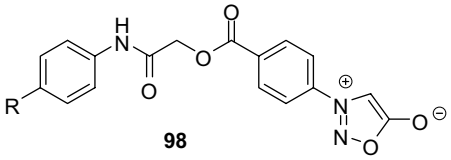


97

A series of derivatives – **98** and **99** – prepared by manipulation of the carboxylic group of 3-(3-carboxyphenyl)- and 3-(3-carboxyphenyl)sydnones, or by Claisen–Schmidt condensation of 3-(4-acetylphenyl)sydnone with aldehydes or malononitrile, showed high antibacterial activity against both Gram-positive and Gram-negative organisms [115].



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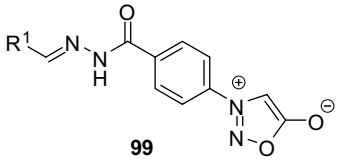
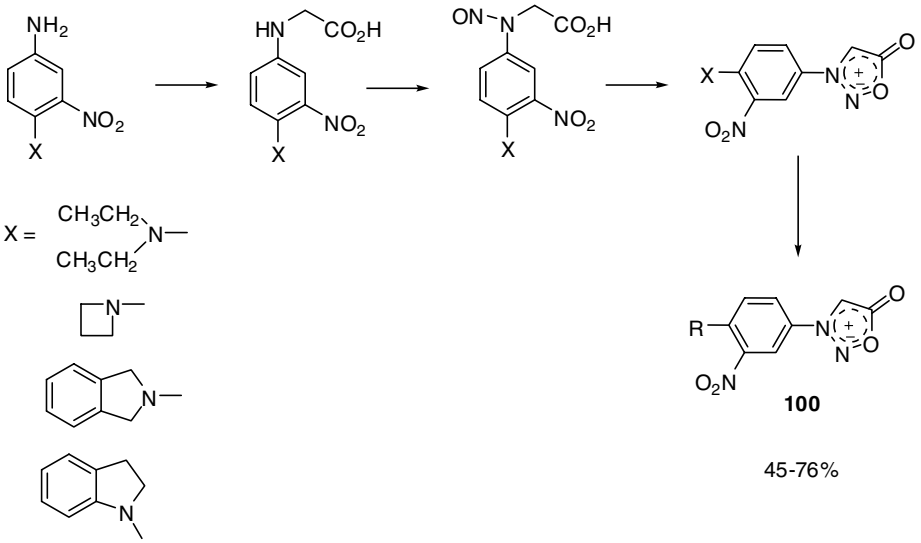


99

R = H, EtO, Ac, CO_2H, CO_2Et R^1 = Ph, 2-Furyl, 4-Cl-C_6H_4, 4-NO_2-C_6H_4, 2-Cl-4-NO_2-C_6H_3

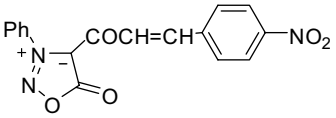


Scheme 13.38

A series of 4′-substituted-3′-nitrophenylsydnones **100** have been synthesized (Scheme 13.38) and evaluated [116, 117] for anticancer activity and it was found that the 4′-chloro, 4′-fluoro and 4′-pyrrolidino compounds significantly enhanced the survival of Sarcoma 180 (S180), Ehrlich carcinoma (Ehrlich), and Fibrous histiocytoma (B10MCII) tumor bearing mice.

Many other sydnones have been tested for antioxidant, antimicrobial, antifungal, analgesic, anti-inflammatory, and antipyretic activities [118].

4-Styrylcarbonyl-3-phenylsydnone derivatives **101** and **102** showed activity similar to that of aspirin, at the same dosage [119].



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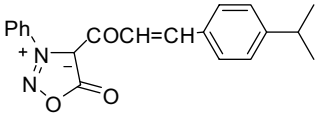


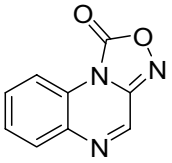
102

13.3 1,2,4-Oxadiazoles

The chemistry of 1,2,4-oxadiazoles **103** has been extensively reported [120]. Research on this class of heterocycles has registered great interest in medicinal chemistry. Many derivatives possess diverse biological activities [121–123]. Some 1,2,4-oxadiazoles can reduce pain and inflammation in rats and mice [124, 125]; for example, *N*-[3-aryl-1,2,4-oxadiazol-5-yl-methyl]phthalimides have been found to be analgesic, and one of them, namely, *N*-[3-phenyl-1,2,4-oxadiazol-5-yl-methyl]phthalimide, possesses highly enhanced analgesic activity compared to aspirin [124].

103

Furthermore, the 1,2,4-oxadiazole ring has been exploited as a peptidomimetic, as a stable ester and amide isostere; specific 1,2,4-oxadiazoles have been used as inhibitors in several biological systems [126, 127]. In particular, numerous papers deal with applications of the soluble guanylyl cyclase inhibitor 1*H*-[1,2,4]-oxadiazole[4,3-*a*] quinoxalin-1-one (ODQ) (**104**) and with applications of the neuroexcitatory quisqualic acid (**105**), the only naturally occurring 1,2,4-oxadiazole known hitherto [128].



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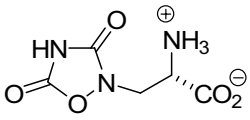
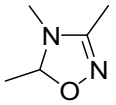


105

Partially or fully saturated 1,2,4-oxadiazoles (**106–109**) have also been reported. In particular, 4,5-dihydro-1,2,4-oxadiazoles **106** have been evaluated very little for biological activities compared to 1,2,4-oxadiazoles, but some of them have shown interesting pharmacological results. For example, some are fungicides [129, 130], and other 3,4,5-triaryl-4,5-dihydro-1,2,4-oxadiazoles demonstrated bronchodilator, anticholinergic, hypertensive, analgesic, anti-inflammatory, diuretic, antiulcer, vasodilatatory, and sedative properties [131]. Some 4-adamantyl-5-aryl-3-phenyl-1,2,4-oxadiazolines have been evaluated *in vitro* for antiviral activity against human immunodeficiency virus (HIV), where the 5-phenyl substituent produced a reduction of more than 50% of viral cytopathic effects [132]. The present chapter updates the previous work and reviews the literature published since, with reference to new advances, preparations, reactions, and uses.



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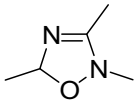

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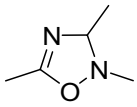

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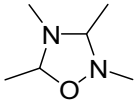


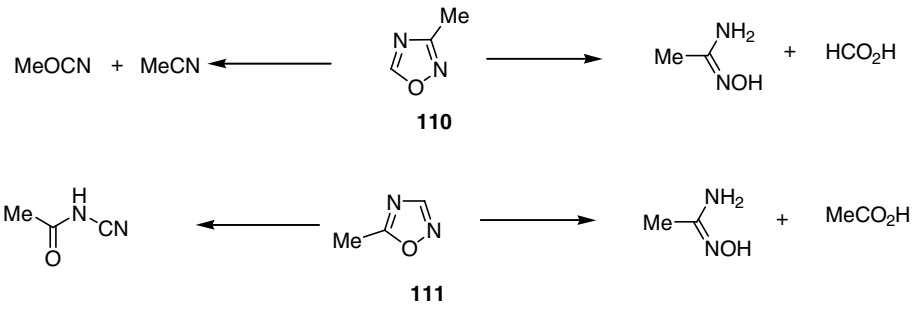
109

13.3.1 Structure

The 1,2,4-oxadiazole ring is planar and described as having little aromatic character [133] – lower than furan on the Bird index [134]. Dipole moments and Kerr constants of certain oxadiazoles seem to indicate some ability of the ring oxygen atom to donate π electrons into the ring. This heterocyclic system has an appreciable heterodiene character, as suggested by X-ray analysis, which indicates, for both C−N distances, conjugated double bond character. The low aromaticity manifests itself by allowing rearrangement to more thermodynamically stable ring systems, thus making 1,2,4-oxadiazoles good substrates for ring-to-ring transformations [135].

The ring of 4,5-dihydro-1,2,4-oxadiazoles, according to CNDO/2 calculations, is nonplanar, adopting an envelope conformation with one atom sitting above the plane described by the four others, and, in contrast to the 1,2,4-oxadiazole ring, it is quite polar [136].

The parent compound **103** is an extremely volatile liquid, very soluble in water and organic solvents, but it is unstable at room temperature. 3,5-Dialkyl and 3,5-diaryl 1,2,4-oxadiazoles are thermally stable and do not hydrolyze by treatment with aqueous sodium hydroxide or hydrochloric acid. In contrast, **103** and monosubstituted oxadiazoles **110** and **111** are thermally and hydrolytically markedly less stable (Scheme 13.39) [137].



Scheme 13.39

Tautomerism of 3- and 5-hydroxy, 3- and 5-amino, and 3- and 5-sulfur analogues has been recently reviewed [138]. In 5-hydroxy-3-phenyl-1,2,4-oxadiazole (**112a**), the keto forms **112b** and **112c** predominate according to NMR data [139]. The tautomer **113b** is more important in the 5-phenyl isomer in solution, but in acetone and oxygenated solvents **113a** allows for an effective hydrogen bonded dimer **114** (Figure 13.3).

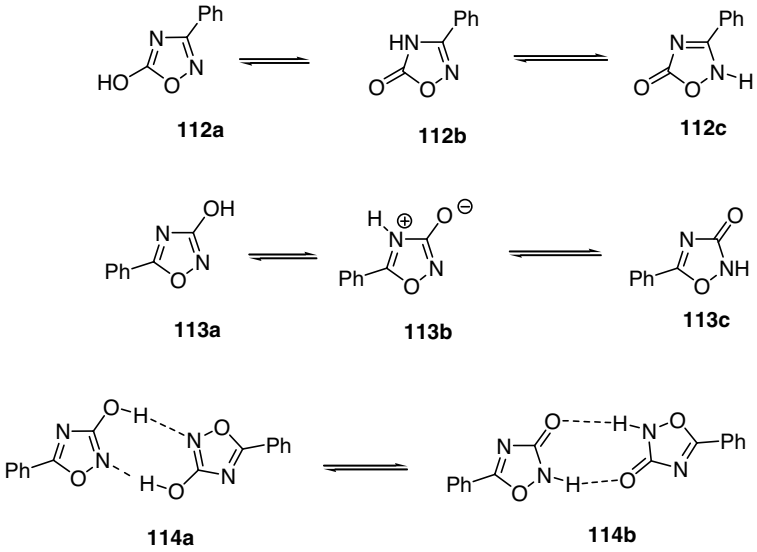
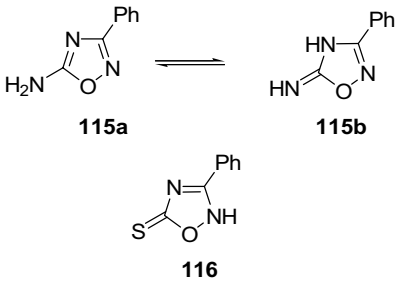


Figure 13.3 Tautomerism exhibited by hydroxy derivatives.

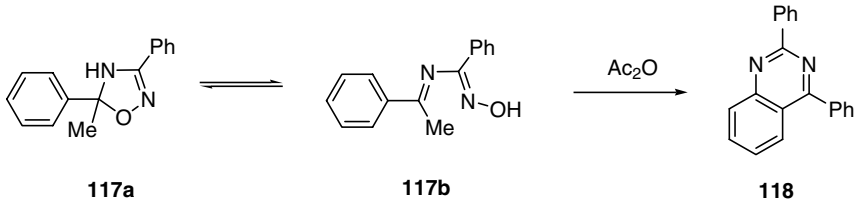
In aminooxadiazole derivatives the tautomeric imino form **115b** is less significant, since **115a** is more basic; in the corresponding sulfur analog there is only evidence for the thione form **116** with the hydrogen at N2.



Interestingly, the 5-aryl-4,5-dihydro-1,2,4-oxadiazole **117a** undergoes formal tautomerism with the 4-aryl-1,3-diaza-1,3-butadiene **117b**, which in turn can undergo ring closure with loss of water to form the quinoxaline **118** (Scheme 13.40) [140].

13.3.2
Theoretical Aspects

Theoretical studies on the structure and properties of 1,2,4-oxadiazoles have been reported. Semiempirical (PM3 and AM1) and *ab initio* molecular orbital



117a **117b** **118**

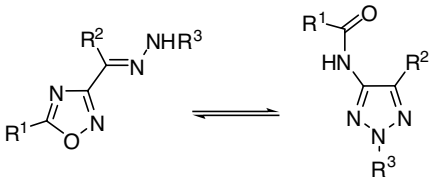
Scheme 13.40

calculations have been performed for diaryl-1,2,4-oxadiazoles and 4,5-dihydro-1,2,4-oxadiazoles to determine bond orders, total energies, ionization potentials, and dipole moments [141]. In particular, *ab initio* molecular calculations give values close to those obtained by crystallographic techniques and NMR spectroscopy. Proton affinities and pK_a values of amino-substituted oxadiazoles have been calculated [142]. INDO studies on 3-phenyl-1,2,4-oxadiazole and its 5-methyl analog suggest that nucleophilic attack should occur on C3 and C5 [143]. In connection with pharmacological structure–activity relationships, semiempirical and *ab initio* molecular orbital calculations have been reported for a series of analgesic compounds, leading to new suggestions for their mechanism of activity [120, 144]. A new model of interaction between the drug and the enzyme has been proposed that involves an electron transfer from the amino acid residue of the enzyme to the drug.

A theoretical study of photoinduced ring-isomerization of 3-amino-5-methyl- and 3-amino-5-phenyl-1,2,4-oxadiazoles has been reported. The results agree well with experimental data and explain the ring-photoisomerization into the corresponding 2-amino-1,3,4-oxadiazoles through a ring contraction–ring expansion route [145] (see Scheme 13.19 in 1,3,4-oxadiazoles). On the same basis a theoretical study of degenerate Boulton–Katritzky rearrangements concerning the anion of the 3-formylamino-1,2,4-oxadiazole has been carried out by using semiempirical MNDO and *ab initio* Hartree–Fock procedures [146].

A combined kinetic and theoretical study of the monocyclic rearrangements of the *(Z)*-hydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole into the corresponding triazole (Scheme 13.41) has been investigated at the DFT level [147].

The synthetic approach towards 1,2,4-oxadiazoles, based on the BH_3- or BF_3-mediated cycloaddition of benzonitrile oxide to nitriles, has been investigated theoretically according to quantum chemical methods (MP2 and B3LYP) together with a topological analysis of the charge density (Section 13.3.4.2) [148]. Activation by the Lewis acid occurs via two different mechanisms: if the Lewis acid is coordinated to the nitrile oxide, the reactant is activated, so that the reaction is expected to be catalytic. If the Lewis acid is coordinated to the nitrile and strong enough, the process requires a stoichiometric amount of Lewis acid and forms a stable Lewis acid–product complex.



119 **120**

R^1 = Ph, H R^2 = Ph R^3 = Ph, 2,4-NO_2-C_6H_3

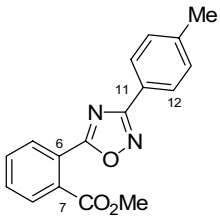
Scheme 13.41

13.3.3 Structural Aspects

13.3.3.1 X-Ray Diffraction

X-Ray data of many 1,2.4-oxadiazoles confirms that the ring is planar [149–154]. Values of C—N bond lengths are consistent with a heterodiene character and account for the low aromaticity of the system. Table 13.3 shows the reported bond lengths and bond angles for methyl 2-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]benzoate (**121**), a compound used as spacer in the synthesis of a potential non-peptide angiotensin receptor antagonist [155].

Table 13.3 Molecular dimensions for methyl 2-[3-(4-methylphenyl)-1,2,4-oxadiazol-5-yl]benzoate (**121**).

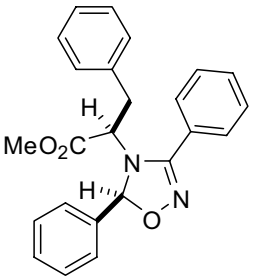


121

Bonds	Distances (Å)	Bond angles	(°)
O1—N2	1.415	O1—N2—C3	103.51
N2—C3	1.310	N2—C3—N4	114.10
C3—N4	1.325	C3—N4—C5	102.83
N4—C5	1.298	N4—C5—O1	113.30
C5—O1	1,347	C5—O1—N2	106.25

The 3,5-diphenyl-oxadiazole fragment is almost coplanar. The angles between the planes of the rings C5−N4/C6−C7 and C5−N4/C11−C12 are 11.13 and 2.28°, respectively. The phenyl rings are tilted to the same side with respect to the oxadiazole ring and the angle between them is 8.86°. An interesting aspect of the crystal structure is the presence of two weak C−H−O bonds between two neighboring molecules in the same layer. Each molecule behaves as both donor and acceptor, leading to a dimer formation [155].

Crystal structures for a series of 2,3-dihydro-1,2,4-oxadiazoles have been reported [156–158]. The 4,5-dihydro-1,2,4-oxadiazole ring in compounds **122** [156] and **123** [151] are in an envelope conformation, with the oxygen atom above the plane occupied by other atoms.



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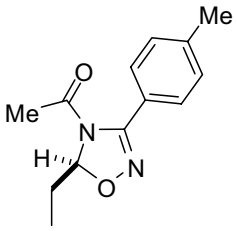
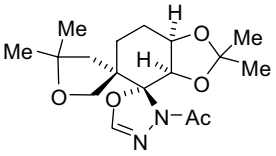


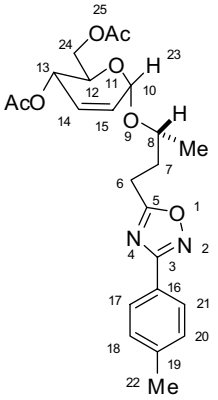
123

Yu and coworkers have reported the preparation and spectroscopic and X-ray diffraction studies of two diastereoisomeric Δ^2-1,2,4-oxadiazolines (**124**, showing the assigned configuration of the diastereoisomer) having a spiral junction at C3 of fructopyranose. These compounds show extensive applications as drugs [159, 160].



124

According to the biological activities of 1,2,4-oxadiazole derivatives, the combination of an oxadiazole moiety with a sugar framework has been performed. Unsaturated glycosides having an 1,2,4-oxadiazole part as an aglycone, **125** and **126**, have been reported [153]: crystallographic data, providing precise information regarding the configuration at C8 and also about the molecular conformation, have shown that compound **125** has a torsion angle H(15)–C(15)–C(10)–H(10) of −43.2°, which clearly shows that the anomeric proton is disposed equatorially. The ring oxygen atom is a little above the C(10)-C(15)-C(14)-C(13) plane; the C(12) atom is slightly below this plane. The *p*-tolyl ring and the 1,2,4-oxadiazole rings are coplanar [torsion angle N(2)–C(3)–C(16)–C(17)Z10.618°]. The bond distances C(13)–C(12) and C(12)–O(11) are 1.54 and 1.43 Å, respectively.



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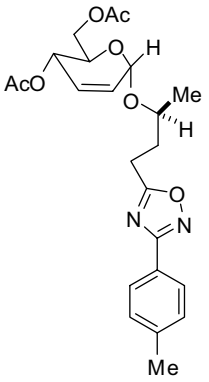
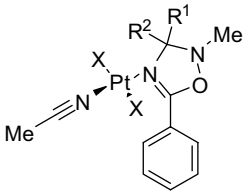


126

Based on the recent observation that Pt(II) mono- and bis-1,2,4-oxadiazoline complexes exhibit *in vitro* cytotoxicity against a series of platinum-sensitive and resistant human cancer cell lines, with a potency comparable to that of cisplatin and superior to carboplatin [161], a series of PtX2(nitrile)(oxadiazoline) (**127**) and PtX2 bis-1,2,4-oxadiazoline (**128**) complexes have been prepared.



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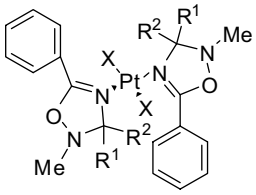


128

13.3.3.2 NMR Spectroscopy

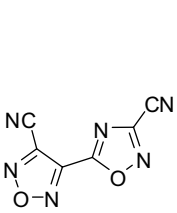
Protons on the 1,2,4-oxadiazole ring are shifted downfield with respect to protons in benzene, according to the electron deficiency of the heterocyclic ring. In the parent compound **103**, the signal for the C3 proton is at 8.99 ppm, while the C5 proton resonates at 9.49 ppm. The presence of an alkyl or aryl substituent shifts the resonance upfield; for 3-phenyl-1,2,4-oxadiazole, the H5 in CCl_4 is at 8.70 ppm [120]. Resonances for H5 of 4-unsubstituted 5-alkyl-4,5-dihydro-1,2,4-oxadiazoles appear at 5.4–5.7 ppm [125, 162]. Chemical shifts for H5 of 5-alkyl-2,5-dihydro-1,2,4-oxadiazoles have been found at 6.1–6.3 ppm [163].

For 3-substituted 2,3-dihydro-1,2,4-oxadiazoles, the H3 shift is in the range 5.7–6.2 and 7.2–7.6 ppm, according to the presence of N-alkyl or N-aryl substituents, respectively [164].

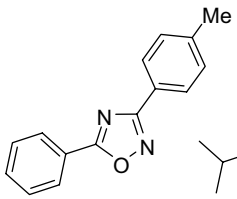
Many fully assigned ^{13}C data for C3/C5 disubstituted 1,2,4-oxadiazoles have been reported [165–168]. C3 resonances are in the range 148–169, while chemical shifts for

Table 13.4 ^{13}C NMR shifts (ppm) for C3/C5-disubstituted 1,2,4-oxadiazoles **129–132**.

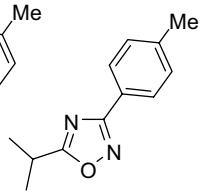
1,2,4-Oxadiazole	129	130	131	132
C3	148.6	168.8	176.9	169.3
C5	164.1	174.7	182.7	173.4
Solvent	CD_3CN	$CDCl_3$	$CDCl_3$	DMSO



129



130



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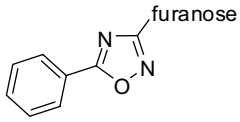


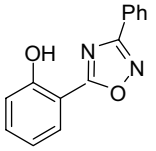
132

C5 are downfield, in the range 165–185 ppm. Table 13.4 summarizes the data for oxadiazoles **129–132**.

13.3.3.3 UV and IR Spectroscopy

UV spectra of aryl-substituted 1,2,4-oxadiazoles have been reported [162, 169]; non-aryl 1,2,4-oxadiazoles have no UV absorption. UV and fluorescence spectra of Cu(II) complexes of 5-(2-hydroxyphenyl)-3-phenyl-1,2,4-oxadiazole (**133**) have been reported [170]: Cu (II) binds to monodentate oxadiazole via N4 and the OH group in a 2 : 1 complex.

A detailed IR analysis exists for the parent compound and a series of fully conjugated 1,2,4-oxadiazoles [162]. Diagnostic absorptions are at 1590–1560 (C=N), 1119–1218 (C−O) and 895–910 (N−O) cm^{-1} [171, 172]. For 4,5-dihydro-1,2,4-oxadiazole **134**, the C = N absorption is shifted to around 1600 cm^{-1} [162, 173]. 2,3-Dihydro-1,2,4-oxadiazoles exhibit a $\nu_{C=N}$ between 1670 and 1676 cm^{-1} [156, 183], while in 2,5-dihydro the same absorption is at 1622–1640 cm^{-1} [162, 173].



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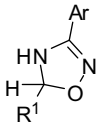
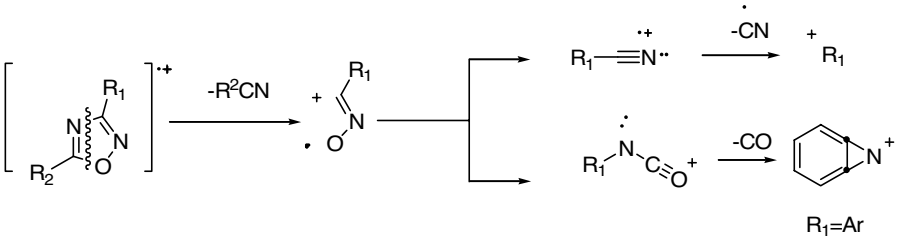


134

13.3.3.4 Mass Spectrometry

The diagnostic fragmentation pattern of 1,2,4-oxadiazoles is a 1,3-dipolar cycloreversion process, which proceeds via initial cleavage of the 1,5 (C−O) and 3,4 (C−N)

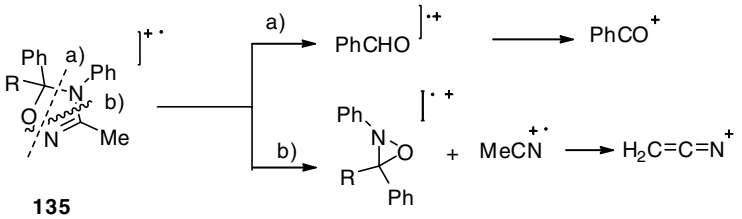
bonds: the positive charge is retained in the predominant nitrile oxide fragment (Scheme 13.42) [175, 176].



Scheme 13.42

The nitrile oxide fragment itself fragments further, either by expulsion of oxygen to give a nitrile, which may then lose a CN fragment, or via rearrangement and expulsion of CO.

A recent review reports a detailed mass spectrometric analysis of a series of 1,2,4-oxadiazoles and 4,5-dihydro-1,2,4-oxadiazoles [177]. The fragmentation mode of the latter compounds differs from that of 1,2,4-oxadiazoles. For example, the electron impact dissociation of compounds **135** is reported in Scheme 13.43.



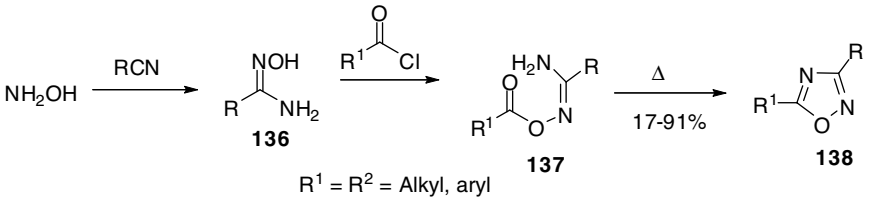
Scheme 13.43

13.3.4
Synthesis

Many synthetic routes for the 1,2,4-oxadiazole system have been reported [120]. 1,2,4-Oxadiazoles can be achieved from open-chain precursors through conventional heterocyclization reactions: the best represented approach exploits the cyclodehydration of *O*-acyl-amidoximes, a method first used by Tiemann and Kruger [178], or N-acylamidoximes, a method developed by Beckmann and Sandel (amidoxime route) [179]. Another different general synthetic route is based on the 1,3-dipolar cycloaddition of nitrile oxides to nitriles, developed by Leandri (cycloaddition route) [180].

13.3.4.1 Amidoxime Route

13.3.4.1.1 **Cyclization of O-Acylamidoximes** According to the most represented route, 1,2,4-oxadiazoles **138** can be prepared by cyclization of *O*-acylamidoximes **137**, which are obtained from the appropriate amidoxime **136** (easily prepared by reaction of the corresponding nitrile with hydroxylamine) and an acylating reagent [120] (generally acyl halides [181, 182], esters [183], or anhydrides [184]) (Scheme 13.44).



Scheme 13.44

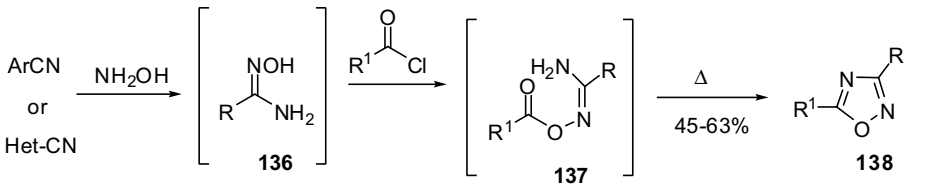
The cyclization of *O*-acylamidoximes is performed by heating them at their melting point [185], or at reflux in a high-boiling solvent (DMF [186], toluene [187], pyridine [188], ethanol [189], acetonitrile [190], glacial acetic acid at reflux) [191, 192], eventually in the presence of a dehydrating agent (phosphorous pentoxide, phosphorus oxychloride, or acetic anhydride).

The experimental conditions required to realize the ring closure of the corresponding *O*-acylamidoximes vary as a function of their structures. In some cases, depending on the substrates, the cyclodehydration reaction occurs under the same conditions as the acylation reaction and the open-chain intermediate is not isolated.

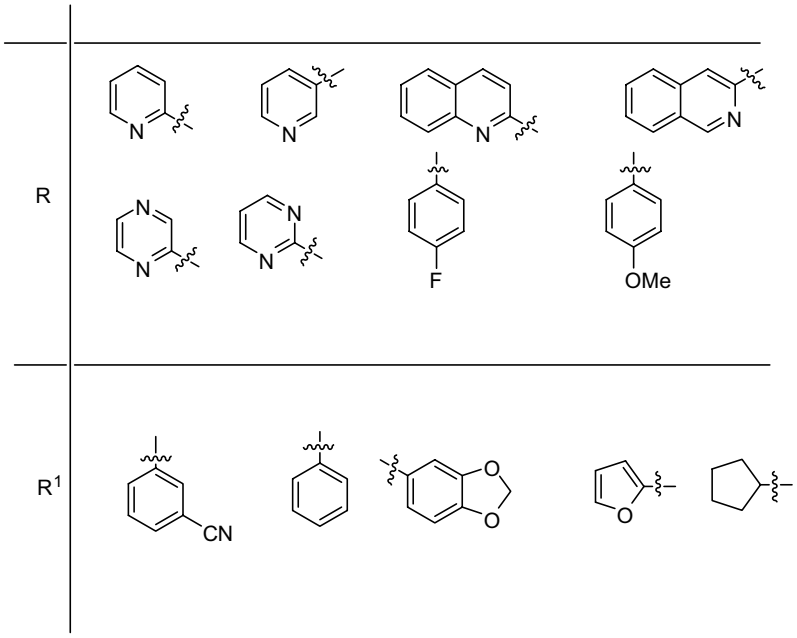
An efficient one-pot method based on the reaction of nitriles with hydroxylamine hydrochloride in the presence of magnesia-supported sodium carbonate, followed by reaction with acyl halides under solvent-free conditions and microwave irradiation, has been reported [193a]. The use of microreactors (microfluidic chips) as an alternative to "in flask" chemistry has been exploited for a rapid synthesis of bis-substituted 1,2,4-oxadiazoles from aryl nitriles and acyl chlorides or succinic anhydride in a single continuous microreactor sequence. In this way, a multiday, multistep sequence has been amended to a highly efficient procedure lasting less than 30 min (Scheme 13.45) [193b].

Cyclization can be performed under mild conditions if the weak nucleophilic amide group is converted into the more nucleophilic amide ion. Thus, 1,2,4-oxadiazoles **140** have been obtained by treatment of **139** with DBU at 70 °C [205]. A significant advance is the use of TBAF at room temperature as a cyclization media, a process that occurs in high yields in the presence of 0.1–1 eq of TBAF, with the fluoride ion acting as both a homogeneous and strongly basic reagent (Scheme 13.46) [194, 195].

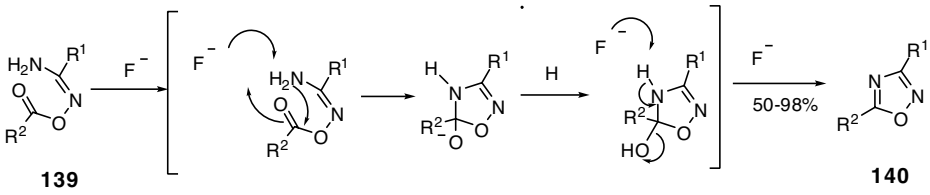
A wide variety of carboxylic acid derivatives can be used for the formation of *O*-acylated amidoximes, such as esters [196], acid chlorides [152, 154, 171, 175, 187, 197],



R = Ar, Het



Scheme 13.45

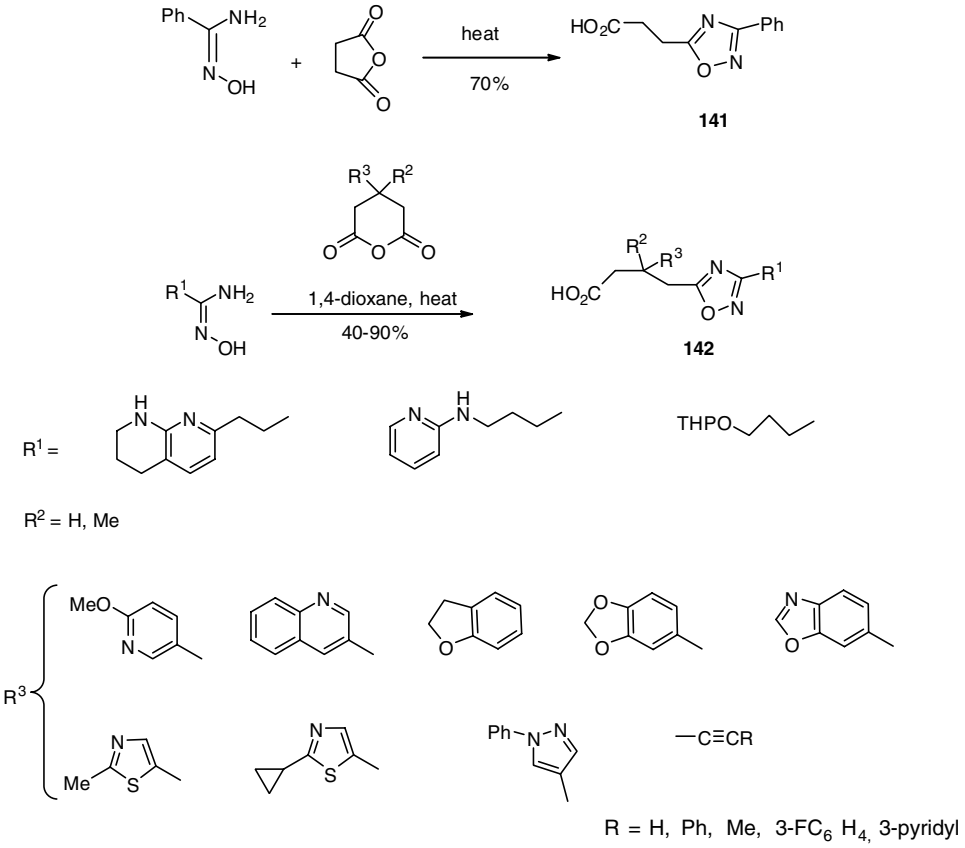


R^1 = Ph,2-,3- or 4-Tol,2-,3- or 4 $MeOC_6H_4$,2-,3-, or 4-$NO_2C_6H_4$, Me, 4-$BocHNC_6H_4$, 2-Cl, 5-1,4-$BocHNC_6H_2$
R^2 = Me, Ph, OMe, Bu^t, CH_2Cl, $CH_2OCH_2CH_3$, CF_3, Pr^i, 2-, 3-, or 4-$NO_2C_6H_4$, CH_2Ph

Scheme 13.46

acid anhydrides [197b, 152, 171, 198], including symmetrical acid anhydrides derived from amino acids [184c], and amino-acid activated as succinimides [183].

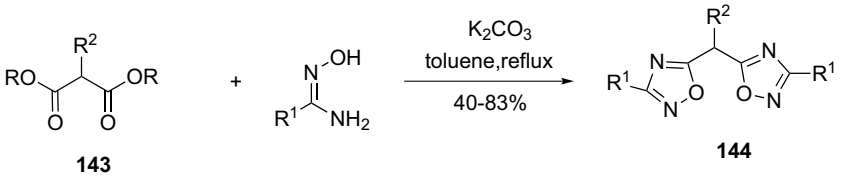
Succinic [199] and glutaric anhydrides [200] are excellent substrates for reaction with amidoximes, giving 1,2,4-oxadiazol-5-yl carboxylic acids **141** and **142**, respectively: the obtained compounds are excellent substrates for coupling to amino acid derivatives (Scheme 13.47).



Scheme 13.47

Examples of the amidoxime route, by which two 1,2,4-oxadiazole moieties can be linearly joined by alkyl chains through the annular 5,5′-positions, have been reported. Thus, the 5,5′-bis-1,2,4-oxadiazolyl system **144** has been obtained by reaction of malonates **143** with two equivalents of an amidoxime in the presence of potassium carbonate (Scheme 13.48) [196f].

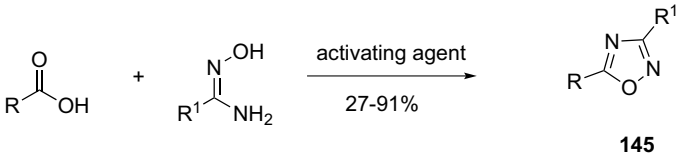
The use of carboxylic acids, activated *in situ* and reacted with an amidoxime, has also been exploited, using various coupling reagents, including dicyclohexylcarbodiimide (DCC) [184a–f], 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide(EDC) [184a,d, 201c], (EDC)/HOBt [201b,c, 202], bis(2-oxo-3-oxazolidinyl)phosphinic



R^1 = Me, Et, Bn, 4-FC_6H_4, 4-$MeOC_6H_4$, cyclopropylmethyl, CH_2CH_2OMe
R^2 = H, Bn
R = Me, Et

Scheme 13.48

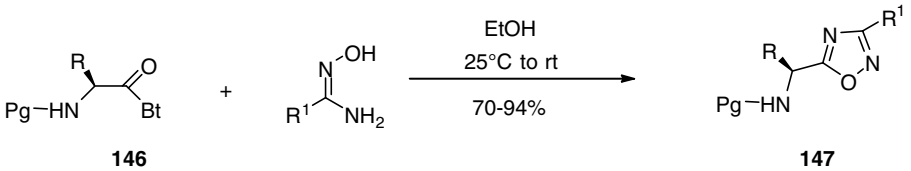
chloride (BOP-Cl) [184a], 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyl-uronium tetrafluoroborate (TBTU) [186, 201c], 1,1′-carbonyldiimidazole (CDI) [184a, 203], and/or high-speed microwave irradiation (Scheme 13.49) [186,197a, 201].



R^1 = 4-MeC_6H_4, Me, 4-FC_6H_4, 3-pyridyl
R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-$EtOC_6H_4$, 3-$MeOC_6H_4$

Scheme 13.49

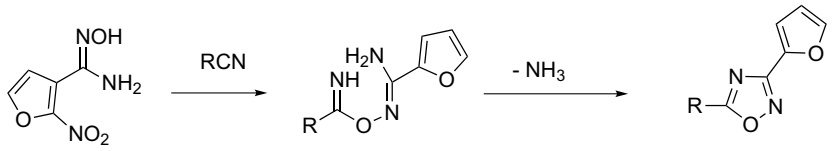
Chiral 1,2,4-oxadiazoles **147** have been synthesized from amino acids by reaction of the readily available *N*-protected (α-aminoacyl)benzotriazoles **146** with amidoximes in ethanol (Scheme 13.50) [189].



R^1 = 4-Tol, 4-pyridyl, Bn
R = Me, Me_2CH, $PhCH_2$, $MeSCH_2CH_2$, $NH_2COCH_2CH_2$, $C_8H_6NCH_2$
Pg = Boc, Fmoc

Scheme 13.50

In some cases, nitriles can be used as acylating reagent for amidoximes, and the subsequent heterocyclization involves loss of ammonia in the final step, with formation of 1,2,4-oxadiazoles **148** (Scheme 13.51) [204].



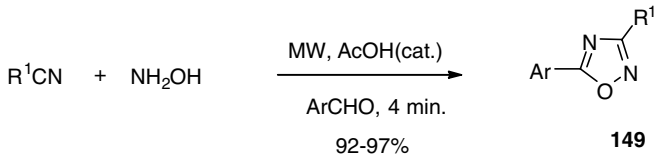
R = Alky, Aryl

Scheme 13.51

For this purpose the reaction is carried out in the presence of an ammonia acceptor reagent (a carboxylic acid or an excess of the nitrile). For example, from the reaction of benzamidoximes with perfluoroalkyl nitriles, a series of fluorinated 5-alkyl-1,2,4-oxadiazoles can be obtained [205].

Disubstituted 1,2,4-oxadiazoles have been synthesized in good yields and good purity in a one-pot procedure by reaction of aromatic nitriles, hydroxylamine hydrochloride, and sodium carbonate in ethylene glycol under heating at 195 °C [168].

Microwave irradiation of nitriles in the presence of hydroxylamine and different aromatic aldehydes, under solvent-free conditions, affords fully conjugated 1,2,4-oxadiazoles **149** in high yields (Scheme 13.52) [206].

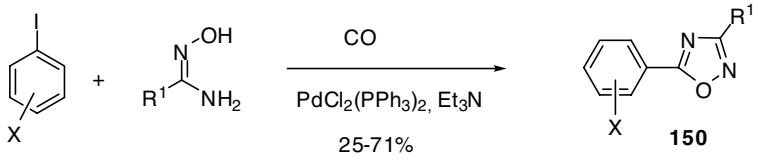


R^1 = Ph, 4-MeC_6H4, 3-ClC_6H_4

Ar = Ph, 4-MeC_6H4, 4-ClC_6H_4, 4-$MeOC_6H4$

Scheme 13.52

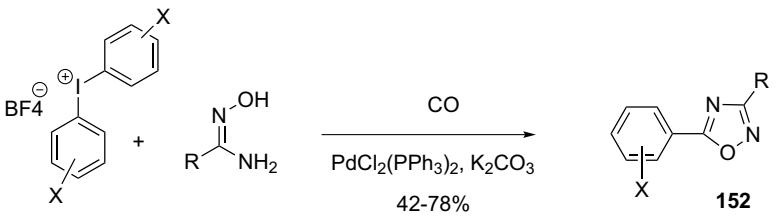
Other methods to obtain 1,2,4-oxadiazoles **150** include the palladium-mediated coupling of an aryl iodide with an amidoxime in the presence of carbon monoxide (Scheme 13.53) [207].



R^1 = Me, CO_2Et X = 2-OMe, 4-OMe, 4-Br, 4-NO_2, 4-CO_2Me

Scheme 13.53

Similarly, 1,2,4-oxadiazoles **152** have been prepared by palladium-catalyzed reactions of diaryliodonium salts (**151**) with amidoximes in the presence of carbon monoxide (Scheme 13.54) [208].



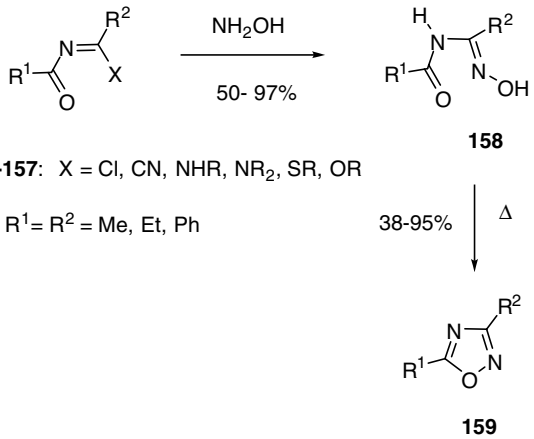
151 **152**

X = H, 4-Me, 4-Cl, 4-OMe, 3-NO_2

R = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, $PhCH_2$

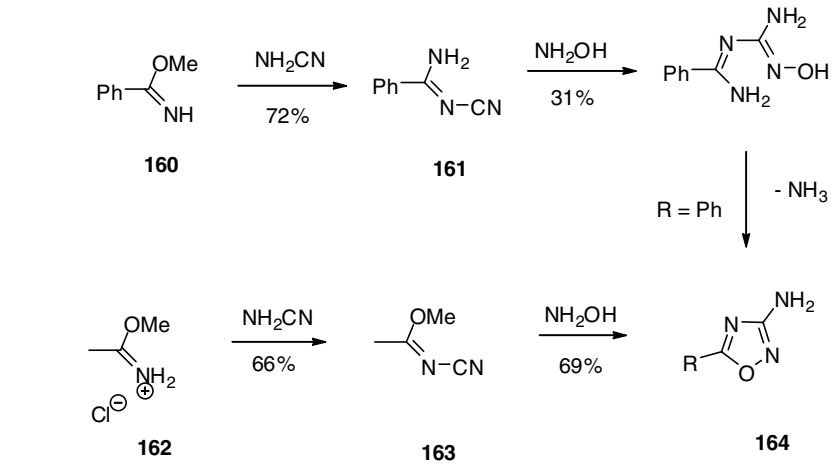
Scheme 13.54

13.3.4.1.2 **Cyclization of N-Acylamidoximes** N-Acylamidoximes **158** cannot be prepared by acylation of amidoximes because O-acylation is faster. Suitable starting materials for N-acylamidoximes can be found in *N*-acylimidic chlorides **153** (X = Cl), cyanides **154** (X = CN), acylamidines **155** (X = NHR, NR_2), *N*-acyl(alkylthio)imides **156** (X = SR), or *N*-acyl(alkoxy)imides **157** (X = OR), which, by reaction with hydroxylamine, lead to 1,2,4-oxadiazoles **159** (Scheme 13.55) [209].



Scheme 13.55

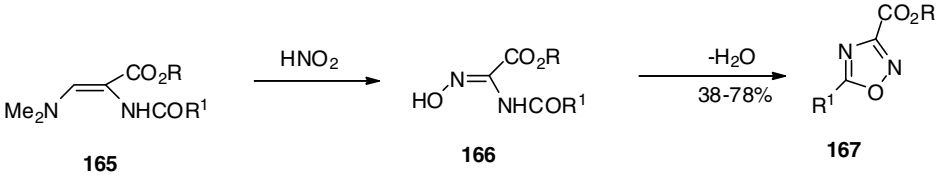
Imidates such as **160** react with cyanamide to give *N*-cyanoamidines **161**, while the hydrochloride **162**, is transformed into **163** [210]. Both **161** and **163** give 3-amino-1,2,4-oxadiazoles **164** on treatment with hydroxylamine (Scheme 13.56).



160 161 164 162 163

Scheme 13.56

A different approach involves the nitrosation of dimethylaminopropenoates **165**, with formation of the corresponding oximes **166**, which undergo cyclization to give the 5-substituted 1,2,4-oxadiazoles 3-carboxylates **167** (Scheme 13.57) [211].



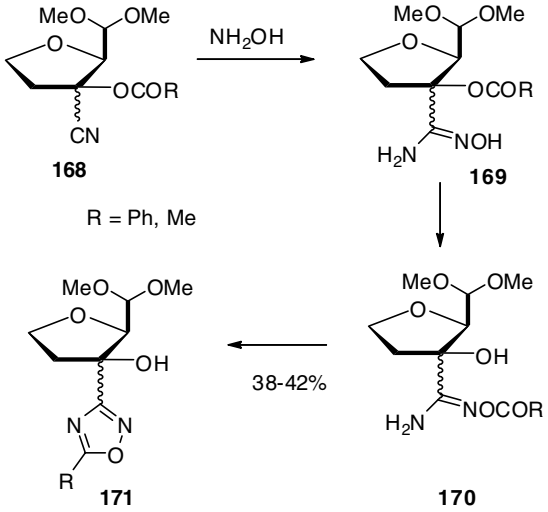
165 166 167

R = Me, Et; R^1 = Ph, 2-ClC_6H_4, 4-ClC_6H_4, 4-Tol, 4-$MeOC_6H_4$, Me, styryl, 2,6-dichlorostyryl, 2-methystyryl, 2-methoxystyryl

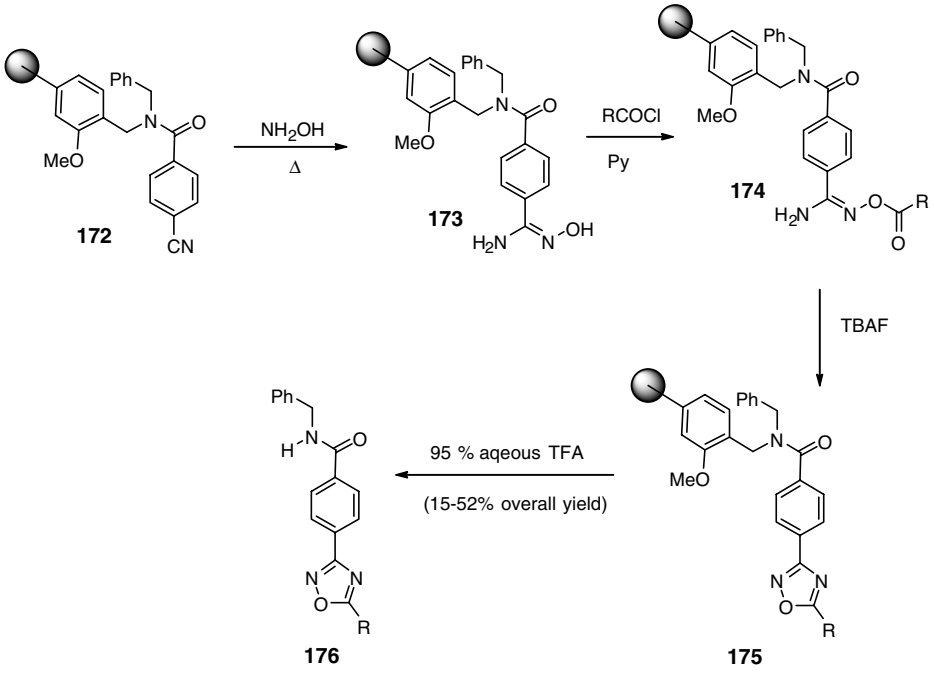
Scheme 13.57

The reaction of cyanohydrines **168** with hydroxylamine leads to the non-isolable amidoximes **169**, which, through intramolecular acylation to **170**, cyclize to epimeric 1,2,4-oxadiazoles **171** (Scheme 13.58) [212].

A series of substituted 1,2,4-oxadiazoles **176** have been synthesized through a new and versatile solid-phase synthesis protocol using resin-bound nitriles (**172**). This resin was treated with hydroxylamine and converted into resin-bound amidoximes **173**, which were transformed into the polymer supported *O*-acylamidoximes **174** upon treatment with acyl chloride. These compounds were subsequently converted into immobilized 1,2,4-oxadiazoles **175**, and then to **176** by treatment with 95% aqueous TFA in 15–52% overall yield (Scheme 13.59) [213].



Scheme 13.58

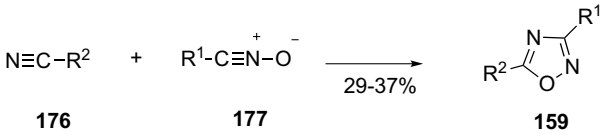


R = Me, *t*-butyl, Ph, 1-Naphthyl, 2-Naphthyl, 2-furyl, 2-thienyl, 4-pyridyl, 3-pyridyl, 2-MeO-C_6H_4, 3-MeO-C_6H_4, 4-MeO-C_6H_4, 2-F-C_6H_4, 3-F-C_6H_4, 4-F-C_6H_4, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, Phenylacetyl, hydrocinnamyl

Scheme 13.59

13.3.4.2 Cycloaddition Route

Another general and well-established route to 1,2,4-oxadiazoles **159** relies on the 1,3-dipolar cycloaddition between a nitrile **176** and a nitrile oxide **177** (Scheme 13.60) [120]. Aromatic and electron-deficient nitriles showed good reactivities, while aliphatic nitriles do not undergo cycloaddition to the oxadiazole derivative. However, under Lewis acid catalysis even aliphatic nitriles form cycloadducts [148].

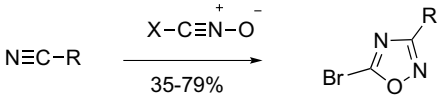


176 **177** **159**

R^2 = Methyl-tetrazolyl ring R^1 = 3-NO_2-C_6H_4, 4-NO_2-C_6H_4

Scheme 13.60

Non-activated nitriles undergo cycloaddition with especially reactive nitrile oxides such as bromo- and chlorocyanogen oxide (Scheme 13.61) [214].



178

X = Cl, Br

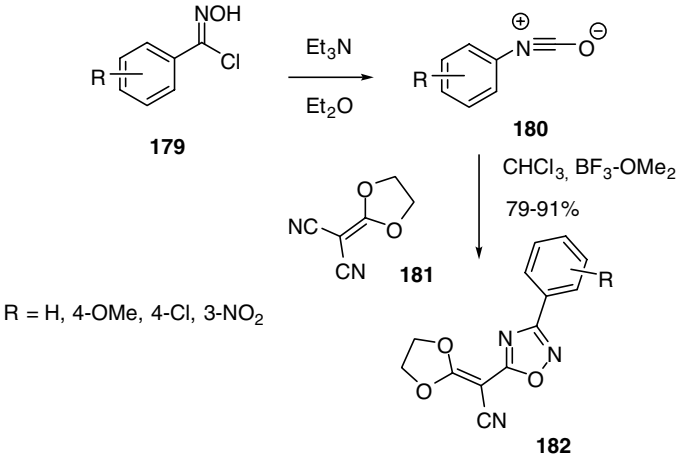
R = *i*-propyl, $ClCH_2$, $BrCH_2$, $PhCH_2$

Scheme 13.61

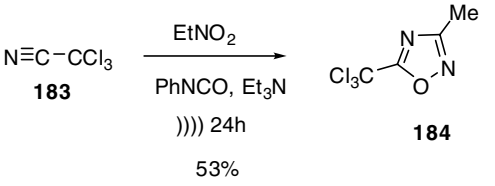
Several methods are reported in the literature for the *in situ* generation of nitrile oxides. Huisgen's base-induced dehydrohalogenation of hydroximoyl chlorides [215] and Mukaiyama's dehydration of primary nitro compounds, using phenyl isocyanate with a catalytic amount of triethylamine [216], are the most frequently used routes to generate nitrile oxides. Thus, the loss of HCl from imidoyl chloride **179** leads to the nitrile oxide **180**, which undergoes cycloaddition to the dicyanoketene acetal **181**, producing the 1,2,4-oxadiazole **182** (Scheme 13.62) [217].

The ultrasound cycloaddition of nitrile oxide, formed by Mukaiyama's dehydration of nitroethane, with trichloroacetonitrile **183** affords the 1,2,4-oxadiazole **184** whose remarkable reactivity towards nucleophilic substitution by amines has been widely exploited (Scheme 13.63) [218].

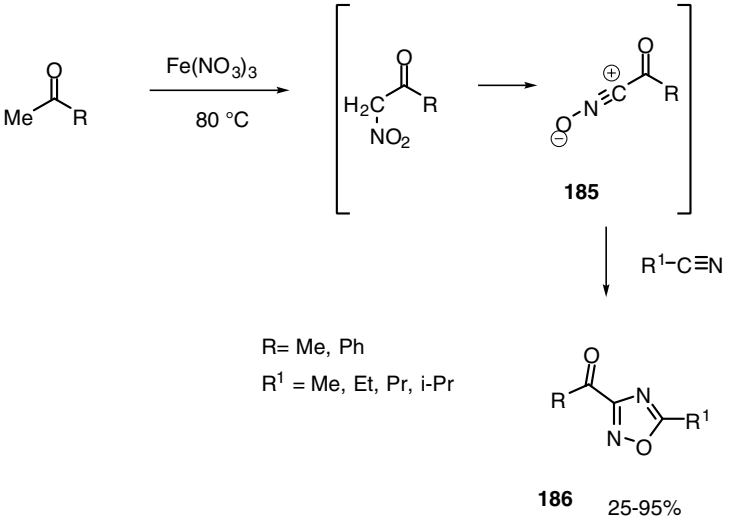
Treatment of nitriles with acetone or acetophenone in the presence of iron(III) nitrate affords 3-acetyl- or 3-benzoyl-oxadiazoles **186;** the reaction proceeds through enolization and nitration to give an α-nitroketone, which undergoes an acid-catalyzed dehydration to the intermediate nitrile oxide **185** (Scheme 13.64) [219].



Scheme 13.62

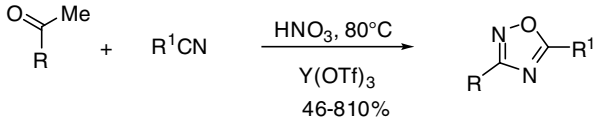


Scheme 13.63



Scheme 13.64

A similar reaction leading to 1,2,4-oxadiazoles from ketones, nitriles, and nitric acid has been described using yttrium triflate as catalyst (Scheme 13.65) [220].

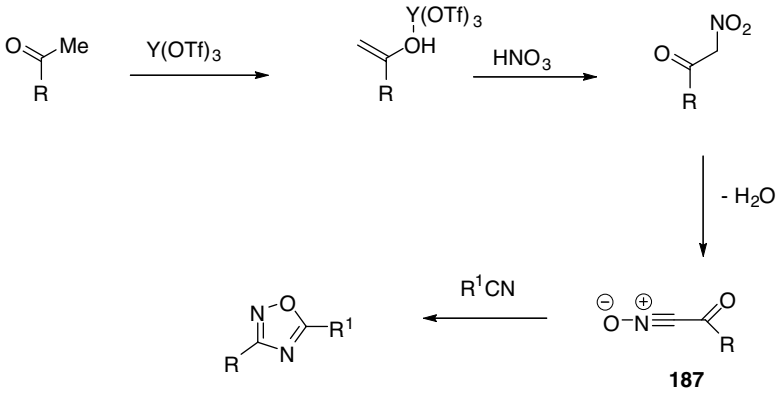


R = Me, 4-FC_6H_4, 4-ClC_6H_4, 3-$NO_2C_6H_4$, 2,4-Cl_2-5FC_6H_2, 3-NO_2-4MeC_6H_3

R^1 = Me, Ph, 2-FC_6H_4

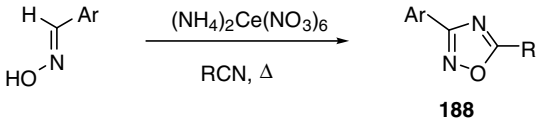
Scheme 13.65

The reaction mechanism involves the 1,3 dipolar cycloaddition of nitriles with nitrile oxide **187**, which is obtained by enolization of the ketones promoted by yttrium triflate, followed by nitration and subsequent dehydration (Scheme 13.66).



Scheme 13.66

A less common method for the formation of nitrile oxides is the oxidation of aromatic aldoximes with ceric ammonium nitrate (Scheme 13.67) [221]; the subsequent cycloaddition to nitriles leads to 1,2,4-oxadiazoles **188**.

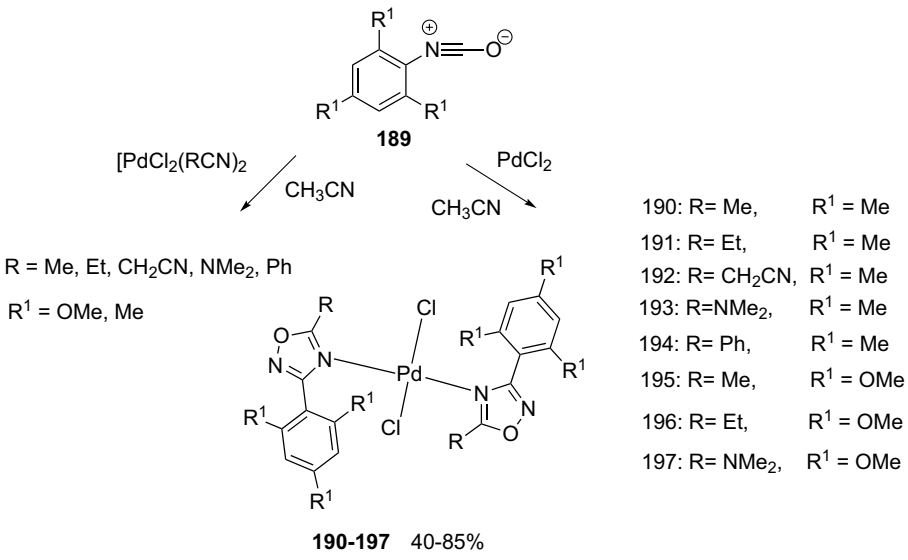


R = Me, Et

Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-Cl, 4-$NO_2C_6H_4$

Scheme 13.67

The cycloaddition methodology has been employed for the synthesis of complex systems. The reaction between nitrile oxides **189** and *trans*-[$PdCl_2(RCN)_2$], or RCN (R = Me, Et, CH_2CN, NMe_2, Ph) in the presence of $PdCl_2$, proceeded smoothly under mild conditions and allowed isolation of the *trans*-[-$PdCl_2$]-1,2,4-oxadiazole complexes (**190–197**) in 40–85% yields. (Scheme 13.68) [222].



Scheme 13.68

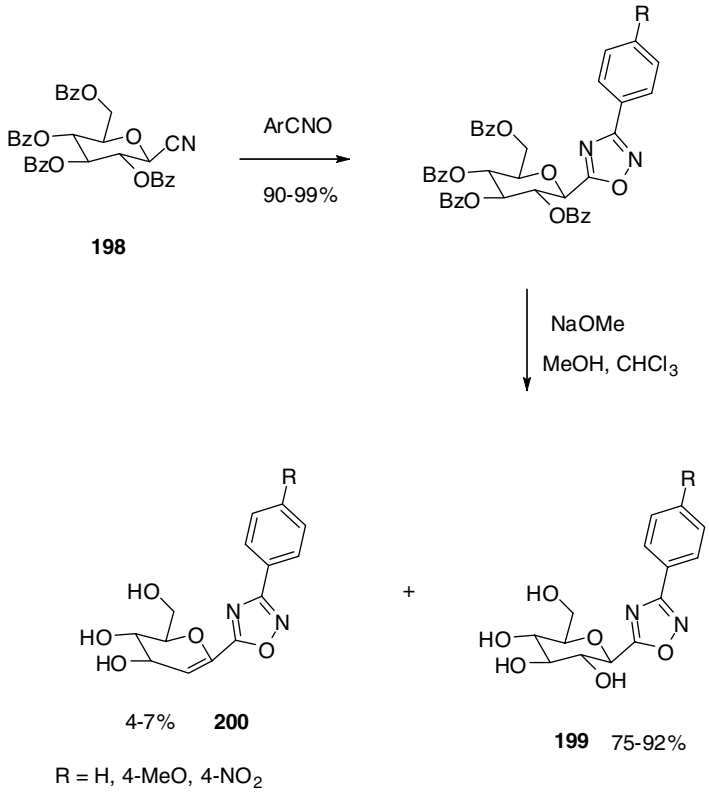
3-Aryl-5-*C*-glucosyl-1,2,4-oxadiazoles **199** and **200**, assayed as glycogen phosphorylase inhibitors, have been prepared in high yield by 1,3-dipolar cycloaddition of aryl nitrile oxides to benzoylated glucosyl cyanide **198** and subsequent cleavage of the protecting group (Scheme 13.69) [223].

1,2,4-Oxadiazoles have been prepared by cycloaddition of nitrile oxides to different dipolarophiles. Thus, the cycloaddition of nitrile oxides to amidoximes **201** proceeds with loss of diethylamine to give the 1,2,4-oxadiazole-4-oxide **202**, which can be deoxygenated with trimethyl phosphite to give 1,2,4-oxadiazole **203** (Scheme 13.70) [224].

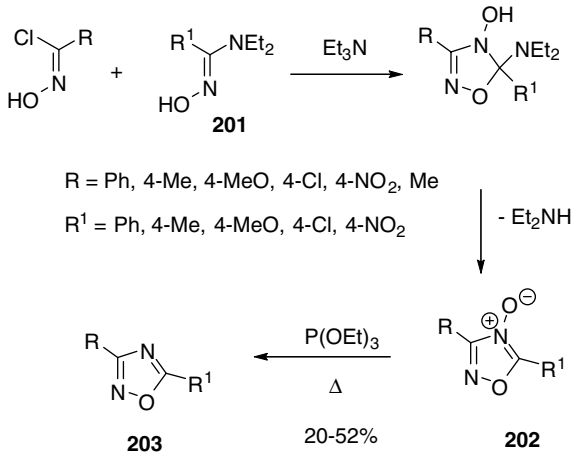
The reaction of nitrile oxide **204** with imine **205** affords the 1,2,4-oxadiazole **207** via the non-isolable intermediate **206** (Scheme 13.71) [225].

13.3.4.3 Miscellaneous Synthesis of 1,2,4-Oxadiazoles

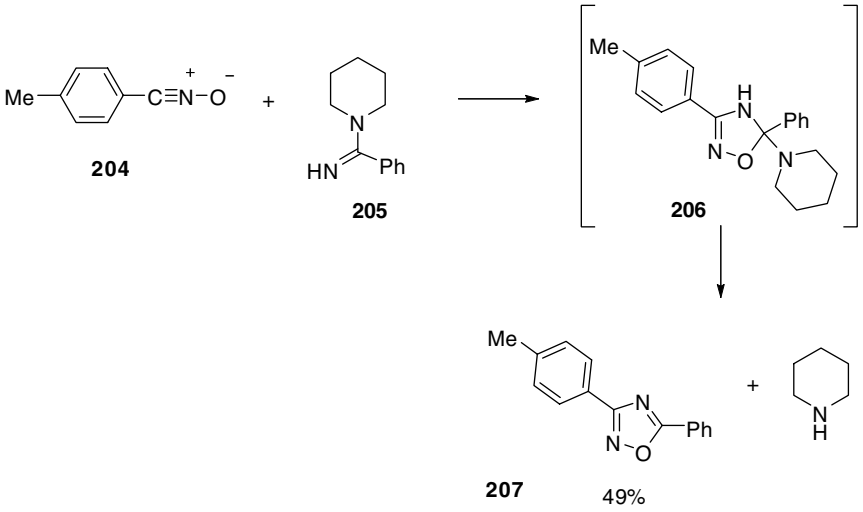
Fully conjugated 1,2,4-oxadiazoles have been prepared by oxidation of 4,5-dihydro-1,2,4-oxadiazoles **208** (Section 13.3.4.4.1), containing hydrogen atoms in the 4- and 5-positions: the oxidation can be performed by MnO_2 [125], nitric acid [125], NaOCl [162], or *N*-chlorosuccinimide (NCS) [169] (Scheme 13.72).



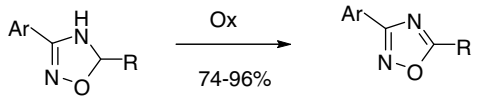
Scheme 13.69



Scheme 13.70



Scheme 13.71



208

Ox=MnO_2, HNO_3, NaOCl, NCS

R=Pr, *i*-Pr

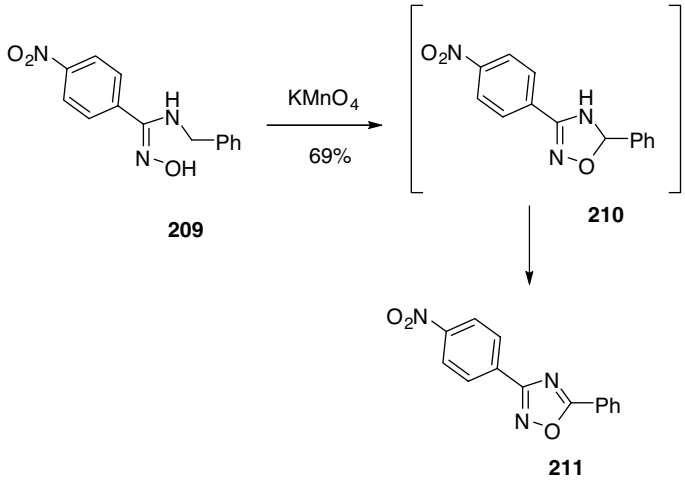
Ar=Ph,4-MeO-C_6H_4, 4-Cl-C_6H_4, 4-NO_2 -C_6H_4

Scheme 13.72

Oxidation of *N*-benzylamidoxime **209** with $KMnO_4$ affords 1,2,4-oxadiazole **211**, through the intermediate 4,5-dihydro-1,2,4-oxadiazole **210** (Scheme 13.73) [226].

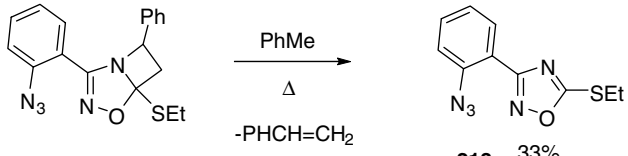
Bicyclic 4,5-dihydro-1,2,4-oxadiazole **212** leads to **213** through a retro-[2 + 2] cycloaddition via loss of styrene in toluene at reflux (Scheme 13.74) [227].

Some recent synthetic procedures concern ANRORC-like reactions that consist of the Addition of a Nucleophile to a π-deficient heterocycle, followed by Ring-Opening and Ring-Closure steps. By this approach, a heterocycle can be transformed into a different one containing the heteroatoms originally belonging to the nucleophilic reagent. Thus, the reaction of 5-fluoroalkyl-1,2,4-oxadiazoles **214** with hydroxylamine furnishes high yields of 3-fluoroalkyl-1,2,4-oxadiazole **217** in a virtual C5–C3 annular shift (Scheme 13.75) [228]. The reaction is promoted by nucleophilic attack of the hydroxylamine to the electron-deficient C5 to produce **215**. Heterocyclization of the dioxime intermediate **216** and removal of hydroxylamine leads to the more stable oxadiazole **217**, in an irreversible ring-degenerate process.



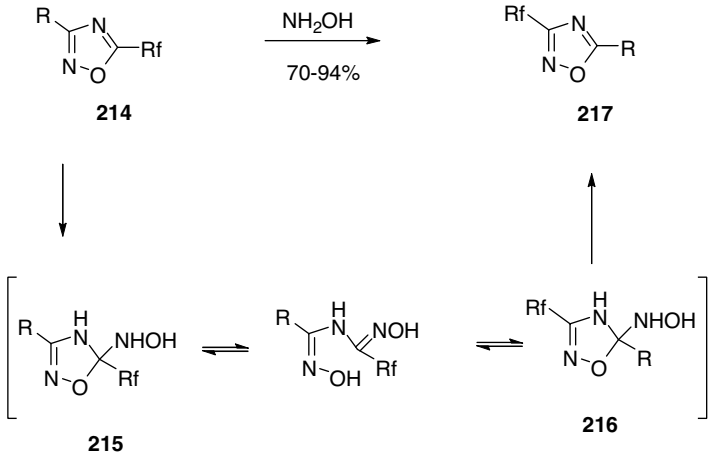
209 **210** **211**

Scheme 13.73



212 **213** 33%

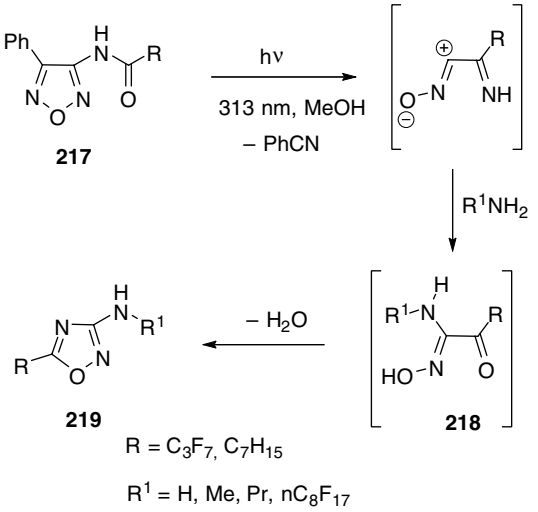
Scheme 13.74



214 **217** **215** **216**

Scheme 13.75

Accordingly, photoinduced rearrangements of O–N bond containing azoles can be useful for the synthesis of 3-amino-5-alkyl-1,2,4-oxadiazoles [229]. This procedure exploits the photofragmentation pattern of the furazan heterocycle into a nitrile and a nitrile oxide. Thus, irradiation of 3-alkanoylamino **217** at $\lambda = 313$ nm in methanol and in the presence of ammonia or primary aliphatic amines gives the corresponding 3-amino- or 3-*N*-alkylamino-5-alkyl-1,2,4-oxadiazoles **219** as a result of the heterocyclization of the intermediate **218** (Scheme 13.76) [230, 231].



Scheme 13.76

Unfortunately, yields of isolated products (about 30–40%) were not very good because of the photoreactivity of oxadiazoles under irradiation conditions; this, however, appears to be the only method that allows these derivatives to be obtained.

13.3.4.4 Synthesis of Dihydro-1,2,4-Oxadiazoles

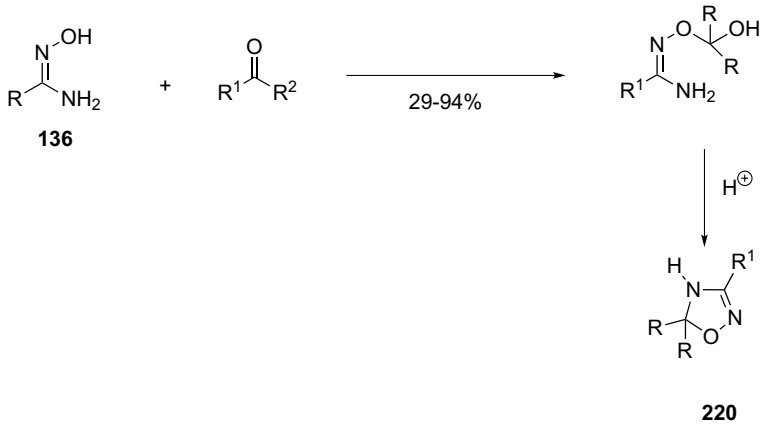
13.3.4.4.1 **4,5-Dihydro-1,2,4-Oxadiazoles** The main methodology towards the synthesis of 4,5-dihydro-1,2,4-oxadiazoles **220** relies on the reaction of carbonyl compounds with amidoximes **136** under acidic conditions (Scheme 13.77) [120, 162, 232].

The use of chloroformate or diethyl carbonate leads to 4,5-dihydro-1,2,4-oxadiazolones **222** via an intermediate acetamidoxime, which cyclizes under base treatment (Scheme 13.78) [233].

The reaction with phosgene or thiophosgene constitutes an alternative route towards the 4,5-dihydro-1,2,4-oxadiazol-5-ones or -5-thiones **223** (Scheme 13.79) [234].

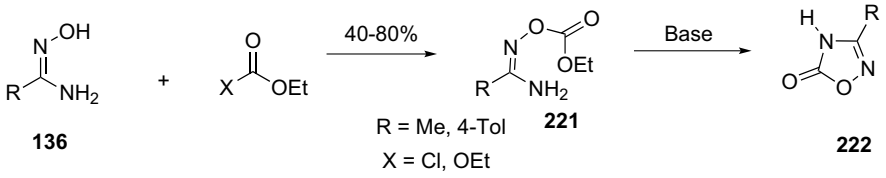
A widely exploited route to 4,5-dihydro-1,2,4-oxadiazoles is the 1,3-dipolar cycloaddition of nitrile oxides to azomethines [120, 235].

Thus, the reaction of imines **224** with hydroxyimoyl chlorides **225** in the presence of triethylamine gives 4,5-dihydro-1,2,4-oxadiazoles **226** (Scheme 13.80) [236].

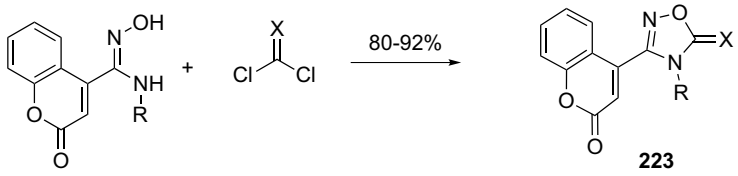


R = Ph, Bn, 2-furyl, 2-thienyl, 2-Tol, 3-Tol, 4-Tol, 4-pyridyl, 2-MeO-$C_6H_4CH_2$,
R^1 = H, Me, Me_2CH, Et, 4-MeO-C_6H_5,
R^2 = H, Me;
R^1, R^2 = -$(CH_2)_5$-

Scheme 13.77

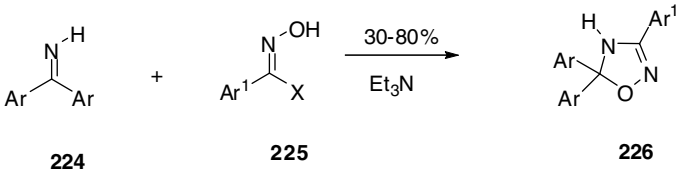


Scheme 13.78



R = H, Ph, 4-Tol,
X = O, S

Scheme 13.79



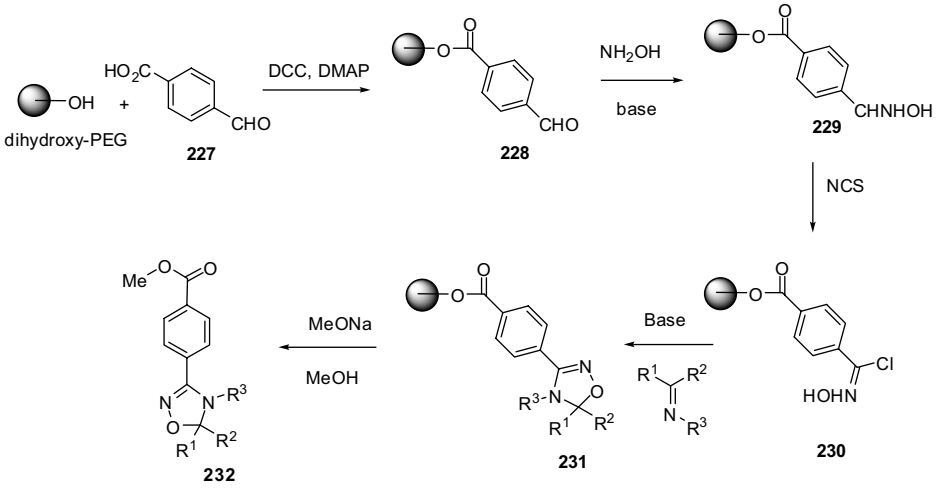
224 **225** **226**

Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 3NO_2-C_6H_4, 4-C_6H_4, 4-C_6H_4, 4-C_6H_4,

Ar^1 = Ph, 4-MeC_6H_4

Scheme 13.80

Scheme 13.81 reports a parallel synthesis of 4,5-dihydro-1,2,4-oxadiazoles, through a cycloaddition reaction of imines with poly(ethylene glycol) (PEG) supported nitrile oxide. 4-Formylbenzoic acid (**227**) was attached to the dihydroxylated PEG by esterification in the presence of DCC. The PEG-bound derivative **228** was converted into oxime **229** by treatment with hydroxylamine hydrochloride, in the presence of trioctylamine, which with *N*-chlorosuccinimide afforded the PEG-bound chlorooxime **230**. This derivative was then treated with several imines to give the corresponding cycloadducts **231**, which were released from the PEG by treatment with sodium methoxide in methanol, to afford 1,2,4-oxadiazolines **232** in 71–91% overall yield [237].



227 **228** **229** **230** **231** **232**

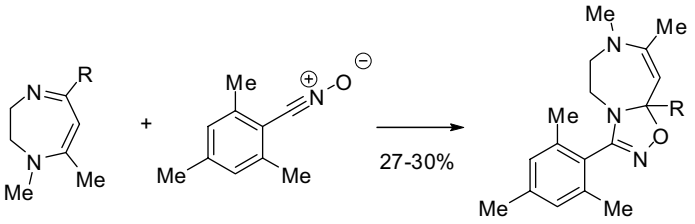
R^1 = H, Me

R^2 = Ph, 4-MeO-C_6H_4, 4-F-C_6H_4, 4-Me-C_6H_4, 3-NO_2-C_6H_4, 4-$C_7H_5O_2$,

R^3 = Ph, 4-F-C_6H_4, 4-Me-C_6H_4, $PhCH_2$, butyl

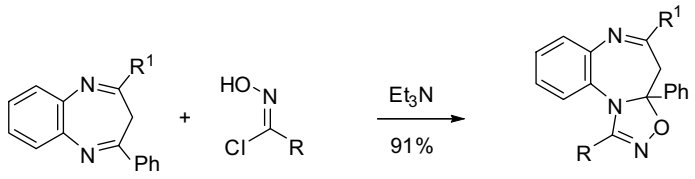
Scheme 13.81

The use of cyclic imines in the cycloaddition reaction is a useful route to various fused 4,5-dihydro-1,2,4-oxadiazoles. In this way, oxadiazolo-1,4-diazepines, **233** [238], oxadiazole-1,5-benzodiazepines **234** [239], and oxadiazolotriazole-1,5-benzodiazepines **235** have been prepared [240] (Scheme 13.82).



R = Ph, Me

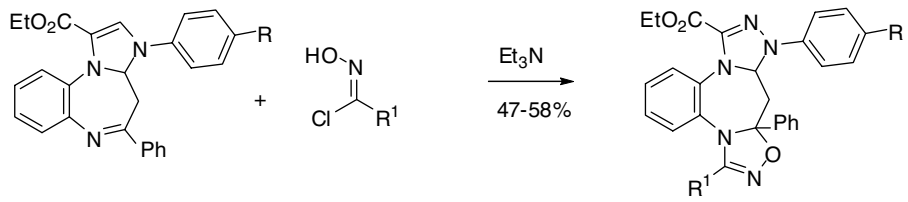
233



R = 3-Cl,4-Me-C_6H_3,

R^1 = SMe

234



R = NO_2, Cl,

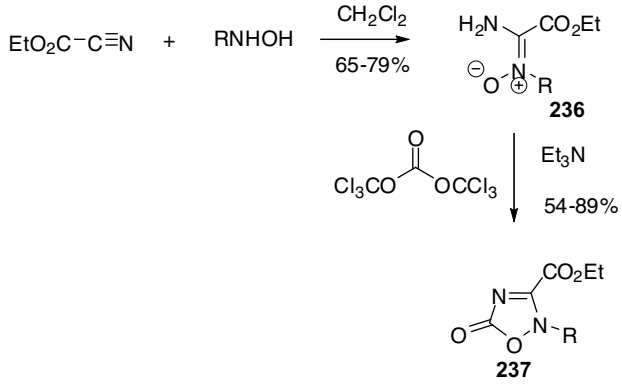
R^1 = 4- NO_2-C_6H_4, 4- Me-C_6H_4,4- Cl-C_6H_4

235

Scheme 13.82

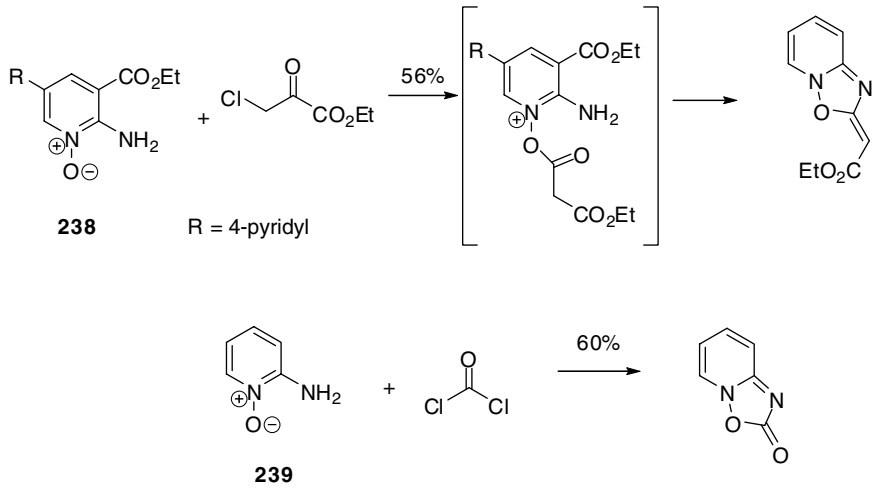
13.3.4.4.2 **2,5-Dihydro-1,2,4-Oxadiazoles** Aminonitrones **236**, prepared by reaction of hydroxylamines with ethyl cyanoformate, cyclize by treatment with triphosgene to 2,5-dihydro-1,2,4-oxadiazin-5-ones **237** (Scheme 13.83).

A related reaction involves the acylations of 2-aminopyridine *N*-oxides **238** and **239** with ethyl chloropyruvate or phosgene, respectively (Scheme 13.84) [241].



R = Me, i-propyl, Ph, 4-BrC_6H_4, 4-MeC_6H_4, 3-MeC_6H_4

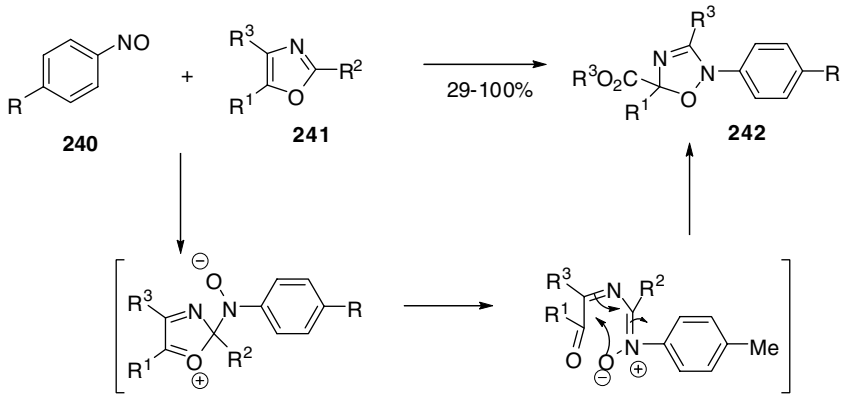
Scheme 13.83



Scheme 13.84

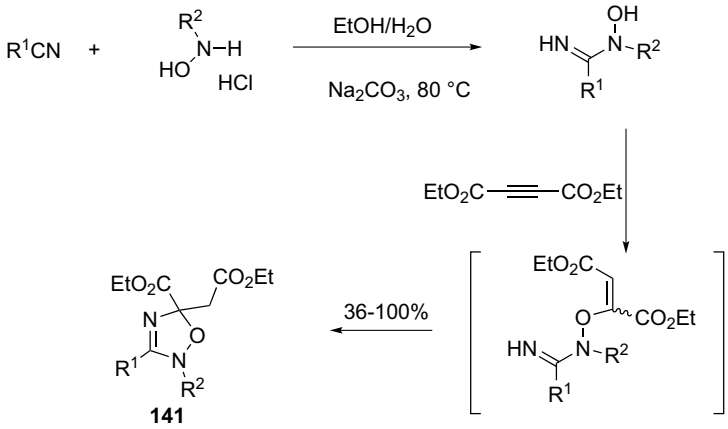
The reaction of substituted oxazoles **241** with arylnitroso derivatives **240** affords 2-aryl-2,5-dihydro-1,2,4-oxadiazoles **242** regioselectively, through a formal [3 + 2] cycloaddition, proceeding via a ring opening of oxazoles promoted by a nucleophilic attack of the nitroso compound at the 2-position of the penta-atomic ring (Scheme 13.85) [242].

A facile one-pot synthesis of 2,3,5-substituted 1,2,4-oxadiazolines from nitriles in aqueous solution has been reported [243]. Thus, alkyl/aryl amidoximes, prepared from the corresponding nitriles and *N*-alkylhydroxylamines, readily undergo consecutive double Michael additions to electron-deficient alkynes and provide highly



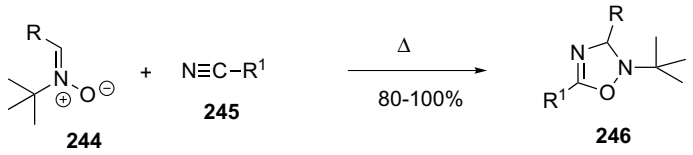
Scheme 13.85

substituted 1,2,4-oxadiazolines **243** in good yields in homogeneous aqueous solution (Scheme 13.86).



Scheme 13.86

13.3.4.4.3 **2,3-Dihydro-1,2,4-Oxadiazoles** A general route to 2,3-dihydro-1,2,4-oxadiazoles is based on the 1,3-dipolar cycloaddition of nitrones to nitriles. Thus, 3-*t*-butyl-2,3-dihydro-1,2,4-oxadiazoles **246** have been prepared through cycloaddition between butylnitrone **244** and different activated nitriles **245** (Scheme 13.87) [244].



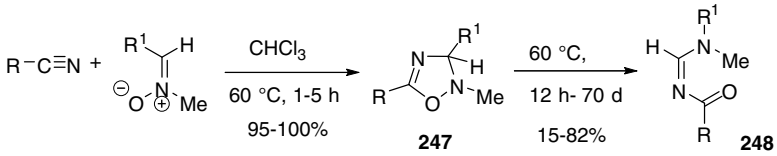
R = Ph, 4-NO_2-C_6H_4

R^1 = $ClC(CN)_2$, $Br_2(CN)$, $C(CN)_3$, CCl_3

Scheme 13.87

The cycloadditions have been performed in the absence of solvent, under microwave irradiation within 2–10 min [245].

Recently, a series of 5-trichloro- and 5-(2-methylpropanenitrile)-Δ^4-1,2,4-oxadiazolines **247** have been synthesized by 1,3-dipolar cycloaddition of nitrones to trichloroacetonitrile and 2,2-dimethylmalononitrile, respectively. These oxadiazolines rearrange into formamidine derivatives **248** by prolonged heating, via ring opening and a 1,2-aryl shift from carbon to the adjacent amino nitrogen (Scheme 13.88) [246].



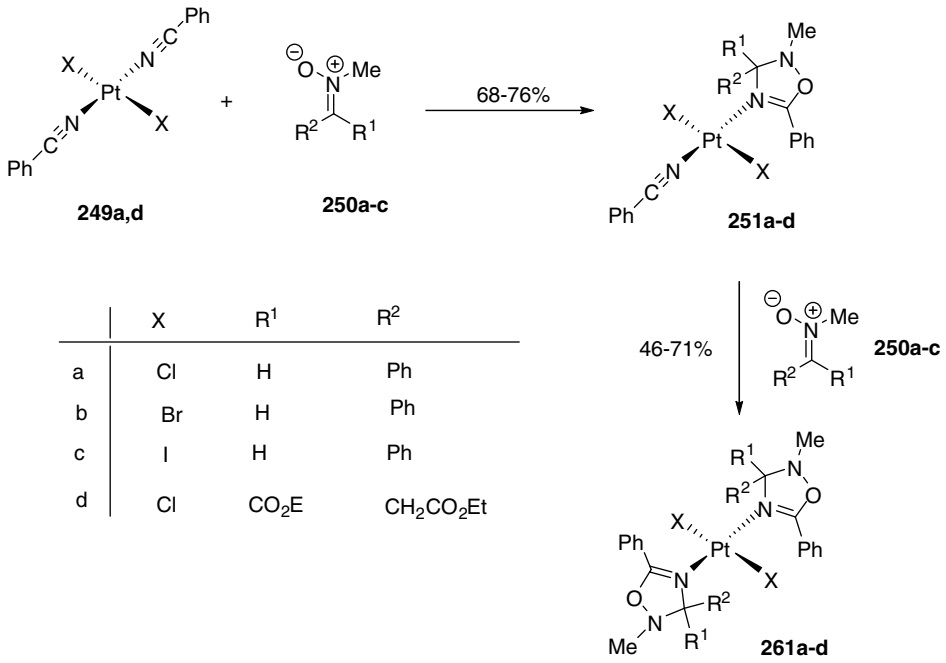
R = CCl_3, Me_2CCN

R^1 = 2-$MeOC_6H_4$, 2,3-$(MeO)_2C_6H_3$, 2,4-$(MeO)_2C_6H_3$, 2,5-$(MeO)_2C_6H_3$, 2,6-$(MeO)_2C_6H_3$, 3,4-$(MeO)_2C_6H_3$, 2,3,4-$(MeO)_3C_6H_2$, 3,4,5-$(MeO)_3C_6H_2$, 2,4,5-$(MeO)_3C_6H_2$, 2,4,6-$(MeO)_3C_6H_2$

Scheme 13.88

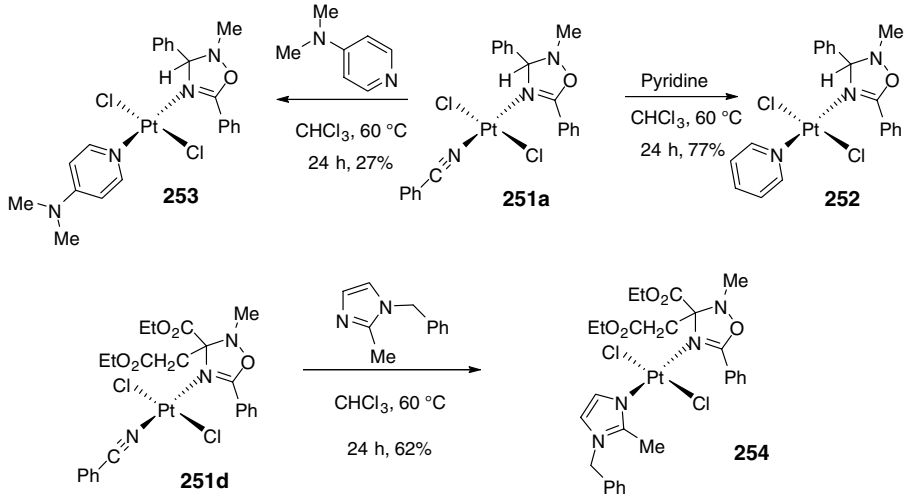
Based on a recent observation that Pt(II) mono- and bis-oxadiazoline complexes exhibit *in vitro* cytotoxicity against a series of platinum-sensitive and resistant human cancer cell lines with a potency comparable to that of cisplatin and superior to carboplatin [247] a series of 2,3-dihydro-1,2,4-oxadiazoles have been synthesized by 1,3-dipolar cycloaddition of coordinated dinitriles **249a,d** to nitrones **250a–c** (Scheme 13.89). Moreover, Pt(II)oxadiazoline complexes **251a** and **251d**, having only one of the coordinated nitriles, have been used for various new mixed ligand complexes. Thus, **252–254** have been obtained by reaction of the corresponding oxadiazolines with pyridine, 4-*N*-dimethylpyridine, and 1-benzyl-2-methylimidazole, respectively (Scheme 13.90) [248].

A novel type of heterocycle, 2,3a-disubstituted 5,6-dihydro-3aH-[1,3]oxazolo[3,2-*b*][1,2,4]oxadiazoles **258a–g,** has been generated by an intermolecular Pt(II)-mediated 1,3-dipolar cycloaddition between the oxazoline *N*-oxide **256** and coordinated nitriles



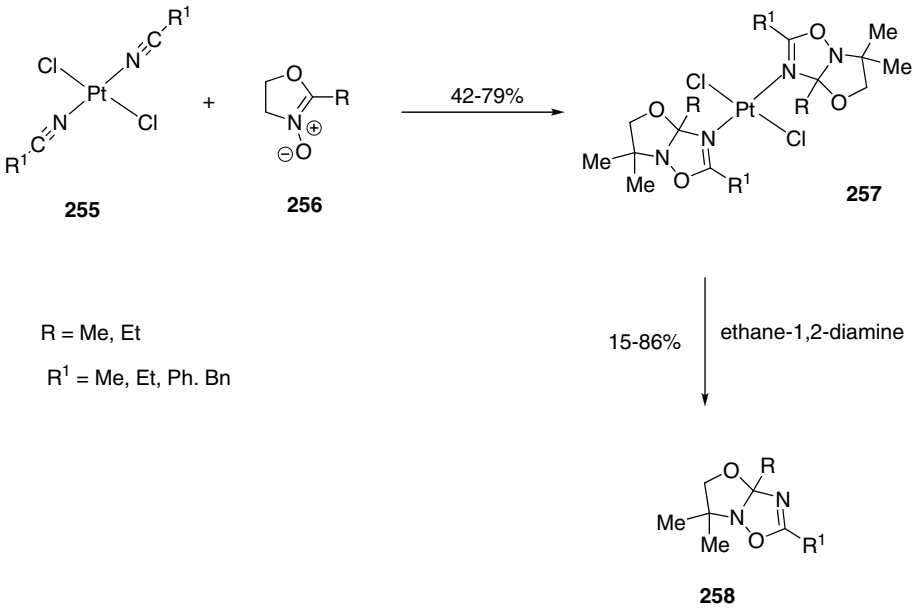
	X	R^1	R^2
a	Cl	H	Ph
b	Br	H	Ph
c	I	H	Ph
d	Cl	CO_2E	CH_2CO_2Et

Scheme 13.89



Scheme 13.90

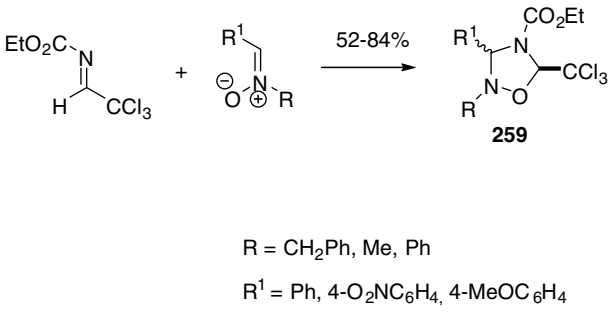
in the complexes *trans*/*cis*-[$PtCl_2$(R-CN)$_2$] **255**. The reaction is unknown for free RCN and oxazoline *N*-oxides, but under PtII-mediated conditions the reaction proceeds smoothly and gives pure complexes **257a–g** in 42–79% yields (Scheme 13.91) [249].



Scheme 13.91

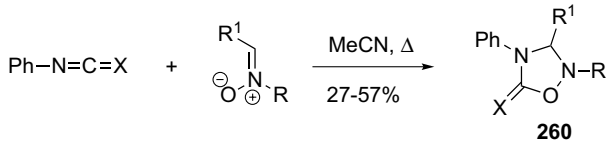
13.3.4.5 **Synthesis of 1,2,4-Oxadiazolidines**

A general synthetic approach to 1,2,4-oxadiazolidines **259** exploits the 1,3-dipolar cycloaddition of nitrones to a C=N double bond, a method first used by Beckmann (Scheme 13.92) [250].



Scheme 13.92

The use of isocyanates and isothiocyanates as dipolarophiles affords an easy entry to 1,2,4-oxadiazolidinones and thiones **260** (Scheme 13.93) [251].

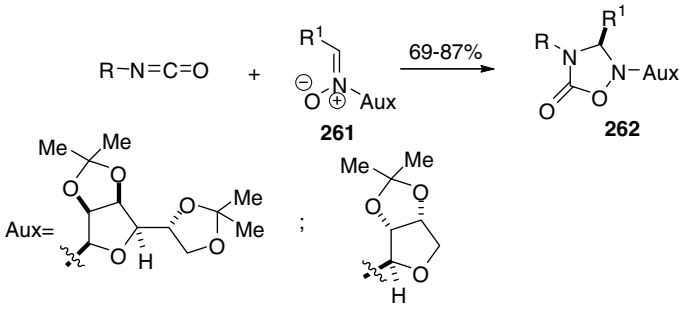


R= Me, $PhCH_2$, 4-$O_2NC_6H_4$, 2,3-$(MeO)_2C_6H_3CH_2$ X = O, S

R^1 = Ph, 2-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 2,3-$(MeO)_2C_6H_4$, 3,4-$(MeO)_2C_6H_4$

Scheme 13.93

On this basis, 1,2,4-oxadiazolidinones as stable chiral building blocks have been prepared by 1,3-dipolar cycloaddition of isocyanates with mannosyl- or erythrosyl derived nitrones **261**. The reaction proceeds with a good diastereoselectivity, giving enantiopure 1,2,4-oxadiazolidin-5-ones **262** after removal of the auxiliary (Scheme 13.94) [252].



R= Ph, $PhCH_2$, PhCO, 4-$O_2NC_6H_4$, 4-$CF_3C_6H_4$, 4-FC_6H_4, 4-$MeOC_6H_4$, 2,6-$Cl_2C_6H_3$,

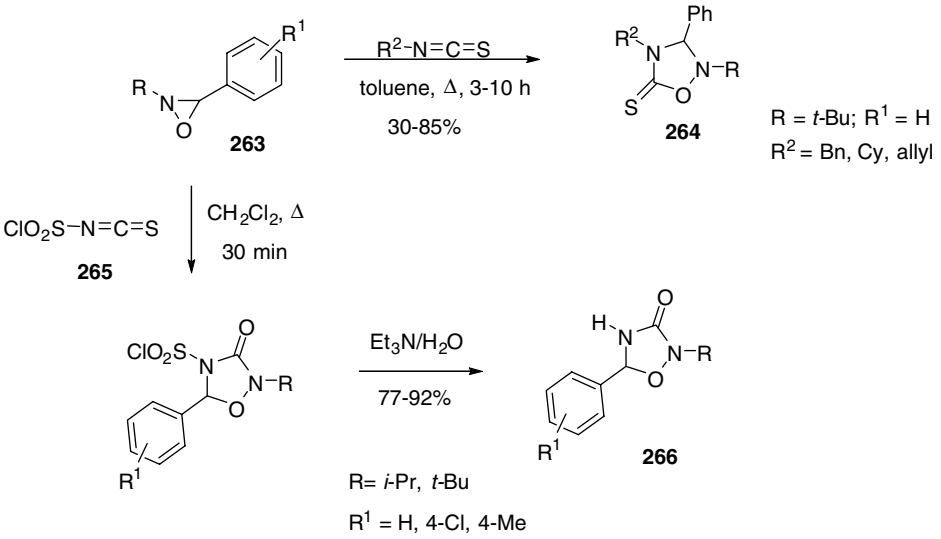
R^1 =Me, Cy, *t*-Bu, Ph, 3-Py, 2-furyl, 1- Naph, 4-$O_2NC_6H_4$, 4-$CF_3C_6H_4$, 4-BrC_6H_4, 4-$MeOC_6H_4$

Scheme 13.94

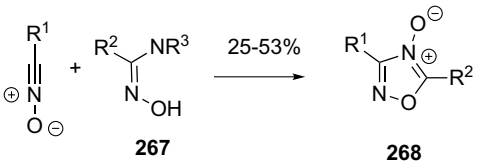
The reaction of oxaziridines **263** with isothiocyanates affords 1,2,4-oxadiazolidin-5-thiones **264**; interestingly, the reaction of **263** with chlorosulfonyl isocyanate **265** leads to 1,2,4-oxadiazolidin-3-ones **266**, as established by X-ray crystallography (Scheme 13.95) [253].

13.3.4.6 Synthesis of 1,2,4-Oxadiazole-N-Oxides

The 1,3-dipolar cycloaddition of amidoximes **267** with nitrile oxides affords an easy entry to 1,2,4-oxadiazole-*N*-oxides **268**, through elimination of an amine (Scheme 13.96). A version of this approach exploited the use of Wang-supported nitrile oxide [224, 254].



Scheme 13.95



R^1 = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$O_2NC_6H_4$, 4-MeC_6H_4

R^2= Me, Ph, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$, 4-ClC_6H_4

R^3 = H, Et

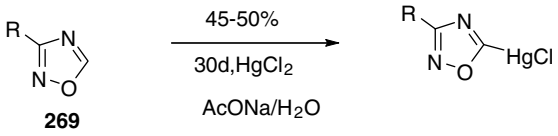
Scheme 13.96

13.3.5 Reactivity of 1,2,4-Oxadiazoles

13.3.5.1 Reactions with Electrophiles

1,2,4-Oxadiazoles are rather inert against electrophilic attack. Halogenation, nitration, Friedel–Crafts alkylation, and acylation do not occur in this ring system. However, electrophilic mercuration of 5-unsubstituted oxadiazoles **269** is possible (Scheme 13.97) [120].

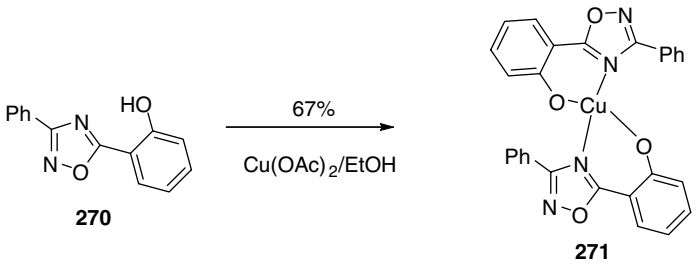
3,5-Diaryl-substituted 1,2,4-oxadiazoles serve as monodentate ligands for some transition metal complexes. The reaction of 1,2,4-oxadiazole **270** with Cu(II)acetate, to give **271**, occurs selectively on N4 (Scheme 13.98) [170].



269

R=Me,Ph

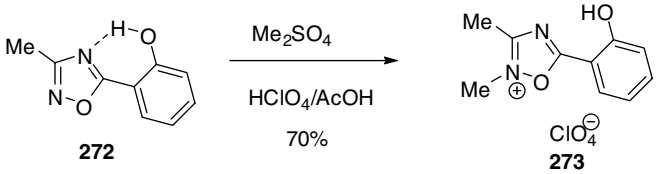
Scheme 13.97



270 271

Scheme 13.98

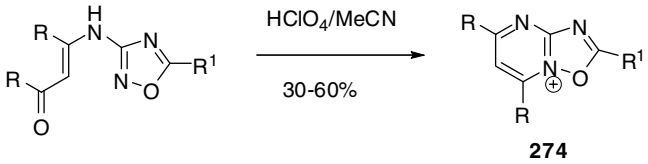
The closely correlated oxadiazole **272** is, by treatment with dimethyl sulfate and perchloric acid, methylated at N2 to give the 1,2,4-oxadiazolium salt **273** (Scheme 13.99).



272 273

Scheme 13.99

An interesting example of an intramolecular electrophilic attack at the N2, reported in Scheme 13.100, yields oxadiazolopyrimidinium salts **274** [255].



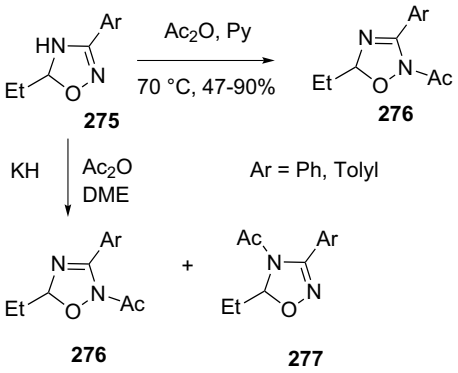
274

R = H, Me, CF_3

R^1 = Me, Ph

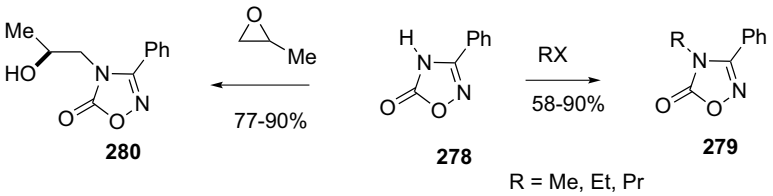
Scheme 13.100

Acetylation of 1,2,4-oxadiazoline **275** with acetic anhydride in pyridine furnishes the N2-acetylated compound **276**, while the treatment with potassium hydride in 1,2-dimethoxyethane (DME) gives mixtures of the N2 and the N4-acetylated heterocycles **276** and **277**, respectively (Scheme 13.101) [120b].



Scheme 13.101

4,5-Dihydro-1,2,4-oxadiazol-5-one **278** can be N-alkylated with alkyl halides or with epoxides in the presence of bases to give **279** and **280**, respectively (Scheme 13.102) [256].



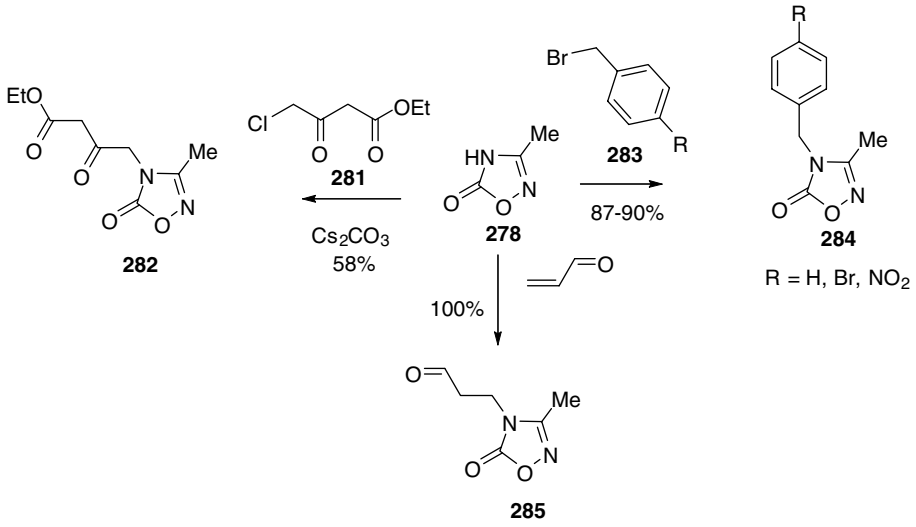
Scheme 13.102

Similarly, 4,5-dihydro-1,2,4-oxadiazol-5-one **278** reacts with alkyl halides **281** and **283** to give the N4 substituted derivatives **282** and **284**, respectively. Compound **278** also reacts with acrolein, via Michael addition, to give **285** (Scheme 13.103) [257].

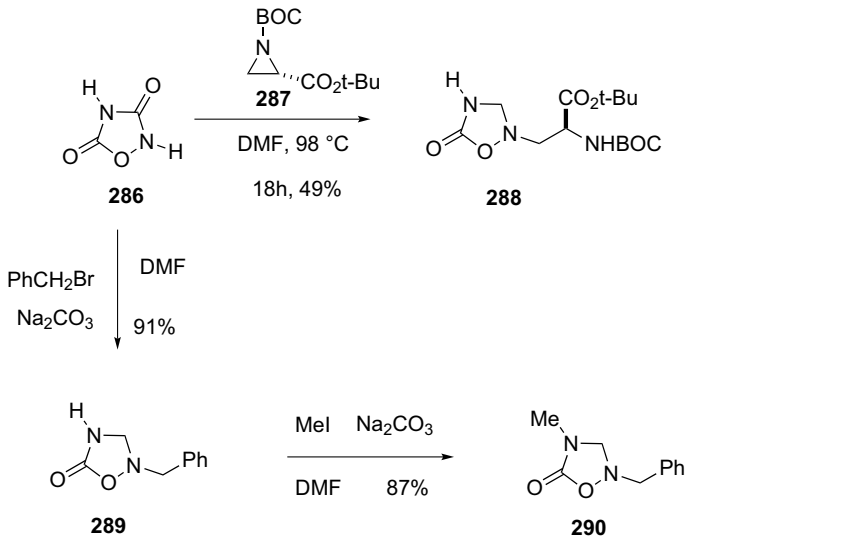
Unsubstituted 1,2,4-oxadiazolidine 3,5-dione (**286**) undergoes alkylation preferentially at N2. Thus, the reaction with benzyl bromide leads to 2-benzyl derivative **289**, which can be further methylated at *N*-4 to give **290** [258]. Similarly, the reaction with (*S*)-aziridine **287** produced the protected (*S*)-quisqualic acid **288** (Scheme 13.104) [259].

13.3.5.2 Reactions with Nucleophiles

Nucleophilic attack on 1,2,4-oxadiazole systems occurs mainly at C5 with nucleophilic displacements of good leaving groups. Table 13.5 summarizes some of these reactions [120, 121, 198, 218, 260].



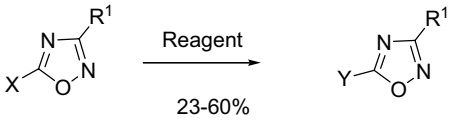
Scheme 13.103



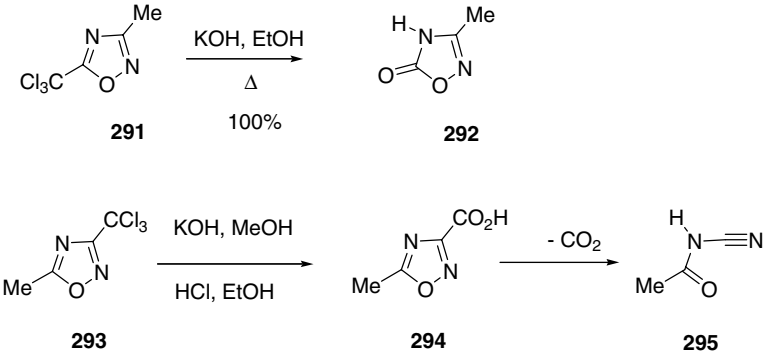
Scheme 13.104

The 3-position is remarkably stable to nucleophilic attack. While the 5-trichloromethyl group of **291** leads, by treatment with KOH, to the 5-oxo compound **292**, the 3-trichloromethyl isomer **293** gives carboxylic acid **294**, which rearranges with loss of CO_2 to acetyl cyanamide **295** (Scheme 13.105) [261].

Table 13.5 Nucleophilic displacements on 1,2,4-oxadiazoles.



R^1	X	Reagent	Y
Me	Cl	OH	OH
Me	Cl	$MeNH_2$	MeNH
Me	OEt	Me_2NH	Me_2N
C_6H_4-*p*-NO_2	S-C_6H_2-[2-Cl-4,6-$(NO_2)_2$]	$(CH_2)_5NH$	$(CH_2)_5N$
C_6H_4-*p*-Me	Cl	$PhCH_2ONa$	$PhCH_2O$
C_6H_4-*p*-NO_2	CCl_3	NH_3	NH_2



Scheme 13.105

Nucleophilic addition of hydrazine or hydroxylamine to the 5-position of 5-fluoroalkyl-1,2,4-oxadiazoles leads to triazole or oxadiazole derivatives **296** and **297** (Scheme 13.106) [135, 228, 262].

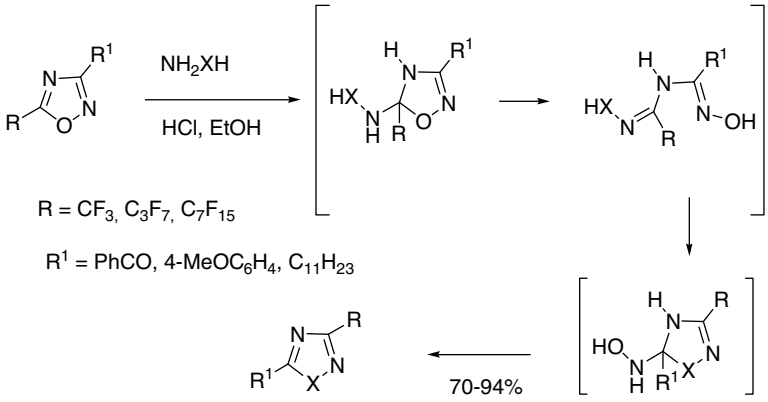
The reaction of fully conjugated 3,5-diaryl-1,2,4-oxadiazoles **298** with butyllithium allows facile access to 5-butyl-3,5-diaryl-4,5-dihydro-1,2,4-oxadiazoles **299** (Scheme 13.107) [263].

A similar reaction occurs with 3-methyl derivative **300** to produce **301** [120a], while the 5-methyl of **302** is deprotonated by butyllithium to afford the anion **303**, which produces, after CO_2 treatment, the corresponding acid **304** (Scheme 13.108) [264].

4,5-Dihydro-1,2,4-oxadiazol-5-one **305** hydrolyzes by treatment with NaOH to give amidoximes **306** (Scheme 13.109) [153].

13.3.5.3 Reductions and Oxidations of 1,2,4-Oxadiazoles

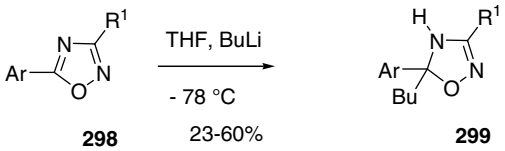
Catalytic hydrogenation of 1,2,4-oxadiazoles **307** have been reported, and begins with N-O fission, leading to the corresponding iminoamides intermediates **308** that under



296 : X = NH, NMe

297 : X = O

Scheme 13.106

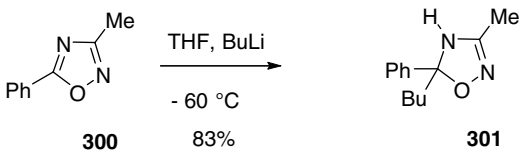


298 **299**

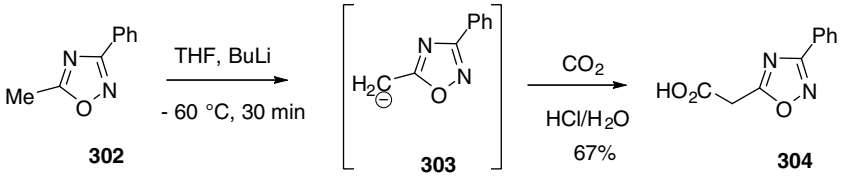
Ar = Ph. 2-ClC$_6$H$_4$, 2-OHC$_6$H$_4$,

R^1 = Ph, 2-ClC$_6$H$_4$

Scheme 13.107

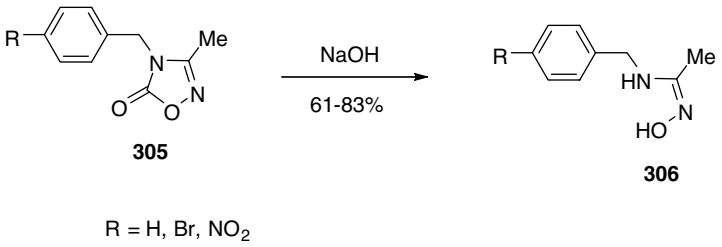


300 **301**



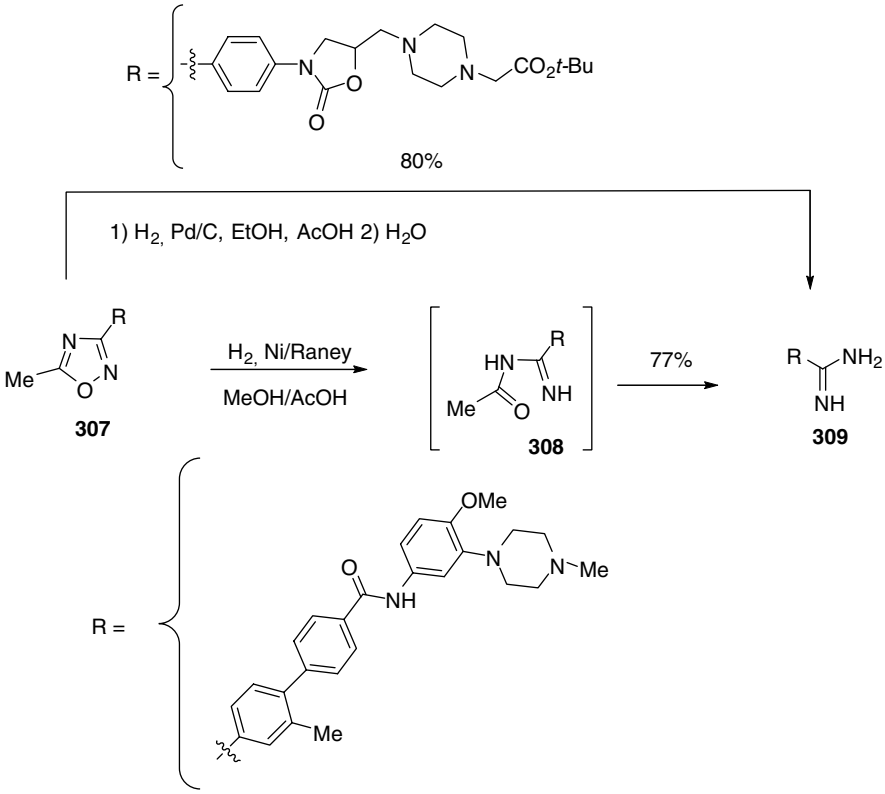
302 **303** **304**

Scheme 13.108



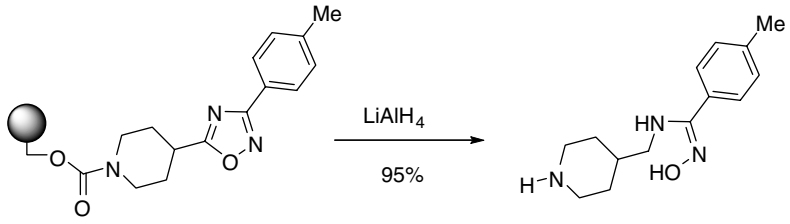
Scheme 13.109

the reaction conditions adopted are converted into amidines **309** (Scheme 13.110) [265].



Scheme 13.110

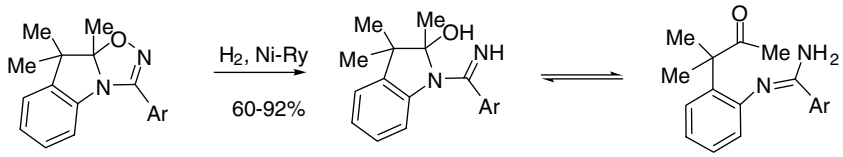
$LiAlH_4$ reduction furnishes N-substituted amidoximes [121, 266]. An application of this reaction concerns the reduction of the Wang resin-bound 1,2,4-oxadiazole **310** to furnish directly the amidooxime **311** via a reductive cleavage from the resin followed by a reductive ring opening of the 1,2,4-oxadiazole ring (Scheme 13.111) [267].



310 **311**

Scheme 13.111

Amidines are also obtained by catalytic hydrogenation of 4,5-dihydro-1,2,4-oxadiazoles. Thus, 1,2,4-oxadiazolo[4,5-*a*]indolines **312** are catalytic hydrogenated over Raney nickel to furnish the corresponding amidines **313** that under tautomerization reaction lead to the opened structures **314** (Scheme 13.112) [268].

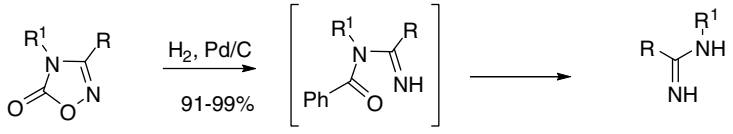


312 **313** **314**

Ar= Ph, 4-Cl-C_6H_4,2-Cl-C_6H_4, 2,6-Cl_2-C_6H_3, 2,4,6-Me_3-C_6H_2

Scheme 13.112

Similar reactions have been reported for 4,5-dihydro-1,2,4-oxadiazole 5-ones **315** (Scheme 13.113) [269].



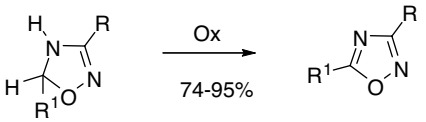
315

R = Me, 4-Me-C_6H4

R^1 = H, Me

Scheme 13.113

Oxidation of 4,5-dihydro-1,2,4-oxadiazoles **316** leads to fully conjugated 1,2,4-oxadiazoles **317;** the oxidation has been performed with different oxidants such as *N*-chlorosuccinimide, manganese dioxide, and concentrated HNO_3 (Scheme 13.114) [125, 162, 169].



316 **317**

R = Me, 4-Me-C_6H4

R^1 = H, Me

Scheme 13.114

13.3.5.4 Thermal and Photochemical Ring Cleavage

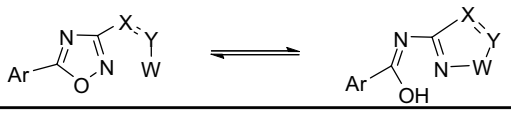
Owing their low aromaticity, 1,2,4-oxadiazoles undergo, by thermal or base-treatment, an easy ring rearrangement known as the Cusmano–Ruccia or Boulton–Katritzky rearrangement. This rearrangement involves a nucleophilic attack on N2 by the oxygen, sulfur, selenium, nitrogen atoms, or carbon anion of a side chain (W) linked at the 3-position of the heterocycle. The generalized rearrangement is reversible only when atom W is oxygen. Table 13.6 summarizes the more common rearrangements [270].

The ring degenerate version of the process has also been reported and investigated as a function of substituent effects and experimental conditions [271]. Thus, for the interconversion **318–319**, mixtures enriched in compound **318** are obtained, while in neutral conditions compound **319** predominates. The effect of substituent X is significant in basic media (Scheme 13.115).

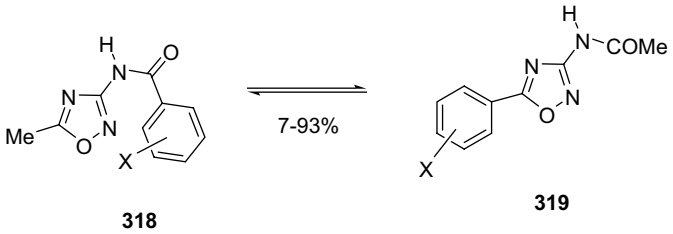
The rearrangement has been used for a synthesis of a series of 3-amino-5-aryl-, 3-amino-5-alkyl-, and 3-amino-5-polyfluorophenyl-1,2,4-oxadiazoles **321** starting from 3-amino-5-methyl-1,2,4-oxadiazoles **320** (Scheme 13.116).

Detailed studies of experimental and theoretical aspects of the rearrangement of phenylhydrazones of 3-benzoyl-1,2,4-oxadiazoles **322** and **323** into the corresponding triazoles **324** and **325** have been performed (Scheme 13.117) [272].

Table 13.6 Rearrangement reactions of 1,2,4-oxadiazole rings.



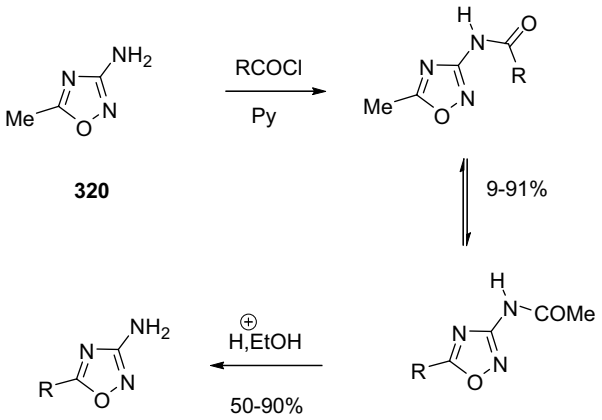
Sequence atoms XYW	Rearranged products	Sequence atoms XYW	Rearranged products
NCC	Imidazole	CNN	1,2,3-Triazole
CNO	1,2,5-Oxadiazole	NCN	1,2,4-Triazole
NCS	1,2,4-Thiadiazole	CCO	Isoxazole
NCSe	1,2,4-Selenadiazole	CNC	Imidazole



318 **319**

X=H, *p*-Me, *p*-OMe, *p*-Cl, *p*-CF_3, *p*-CN, *p*-NO_2, *m*-NO_2, *m*-Me, *m*-Cl, *m*-CF_3, *p*-CN, *m*-OMe

Scheme 13.115



320 **321**

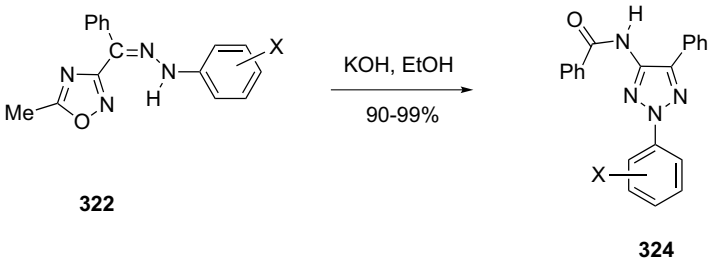
R = *n*-Pr, *t*-Bu, *n*-$C_{11}H_{23}$, Ph, 4-CF_3-C_6H_4, 2-NO_2-C_6H_4, 2-CF_3-C_6H_4, 3-CF_3-C_6H_4, 2-Furyl, 2-Thienyl, 2,3,4,5-Tetrafluorophenyl, 2,3,4-Trifluorophenyl

Scheme 13.116

1,2,4-Oxadiazoles undergo photochemically induced azole to azole interconversions, similar to the previously mentioned thermal rearrangements (Scheme 13.118) [273].

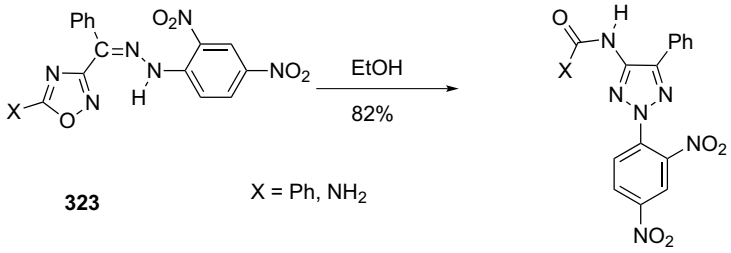
Thus, photolysis of the 3-acetamino-1,2,4-oxadiazole **326** involves cleavage of the N—O bond and the formation of the new oxadiazole **327** (Scheme 13.119).

Similarly, the irradiation of 3-(*o*-aminophenyl)-1,2,4-oxadiazole **328** affords the indazole **331** from the photolytic species **329** and the benzimidazole **332** as



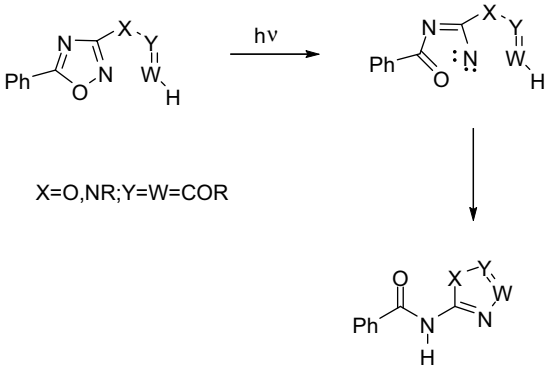
322 **324**

X= H, *p*-Me, *p*-OMe, *p*-Cl, *p*-CF_3, *p*-CN, *p*-NO_2, *m*-NO_2, *m*-Me, *m*-Cl, *m*-CF_3, *p*-CN, *m*-Me, *m*-Et, *p*-Et, *p*-Fl, *m*-Fl, *m*-Br, *p*-Br



323 X = Ph, NH_2 **325**

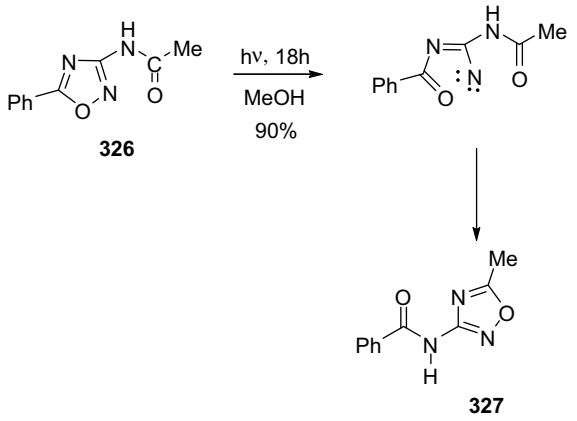
Scheme 13.117



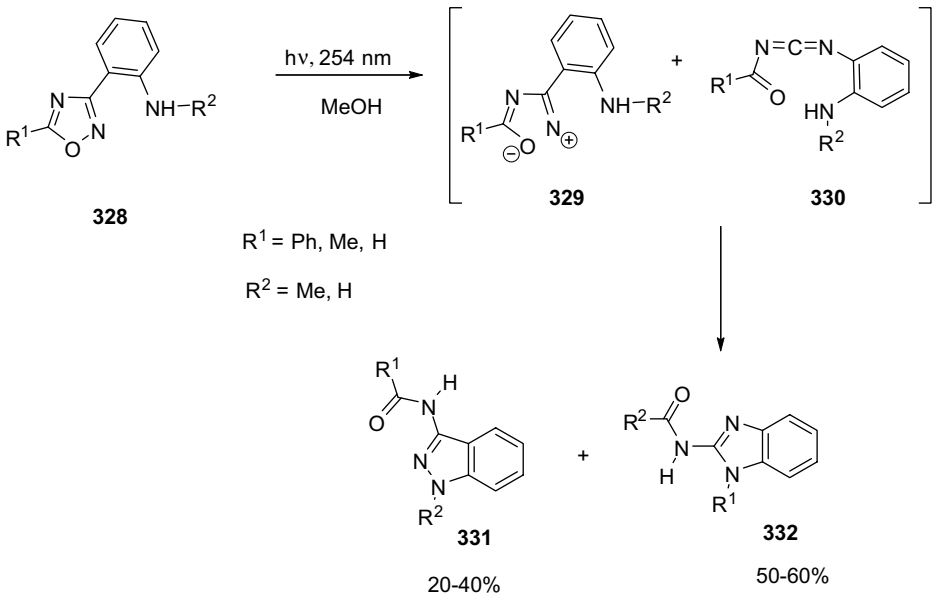
Scheme 13.118

a byproduct originating from the carbodiimide **330**, the rearrangement product of **329** (Scheme 13.120) [274].

UV irradiation of 1,2,4-oxadiazoles **333** in the presence of nucleophilic nitrogen sources (primary amines, ammonia, hydrazine) affords triazoles **335**, via cleavage of the N–O bond and addition of the nucleophile to the intermediate **334** (Scheme 13.121) [275].



Scheme 13.119

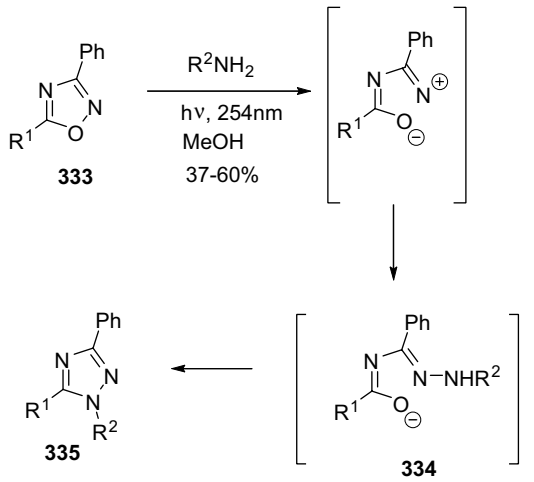


Scheme 13.120

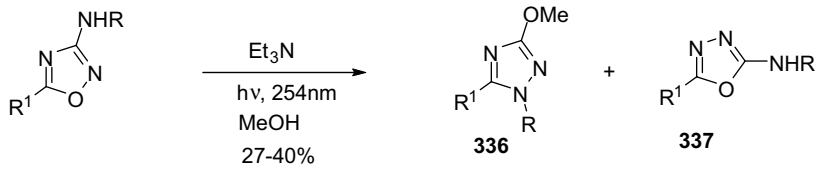
The use of methanol as nucleophile leads to a 1 : 1 mixture of 1,3,4-oxadiazole **337** and triazole **336** (Scheme 13.122).

When an amino group is present at C5, the reaction with a sulfur nucleophile leads to 1,2,4-thiadiazoles **338** (Scheme 13.123) [276].

Irradiation of 1,2,4-oxadiazoles-4-oxides **339** in methanol causes the initial formation of an isolable nitrile together with the nitrosocarbonyl derivative **340**, which



Scheme 13.121



R=Me,Pr

R^1 =C_7F_{15}, C_3F_7

Scheme 13.122

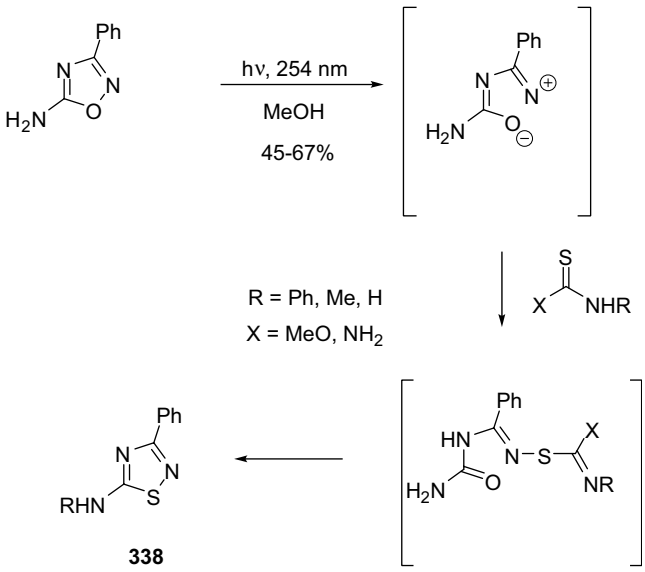
can be trapped by cyclohexadiene to give the hetero-Diels–Alder adducts **341** in good yields (Scheme 13.124) [277].

The intermediate nitrosocarbonyls **340** can also be trapped in ene reactions to give adducts **342** and **343** [254, 278].

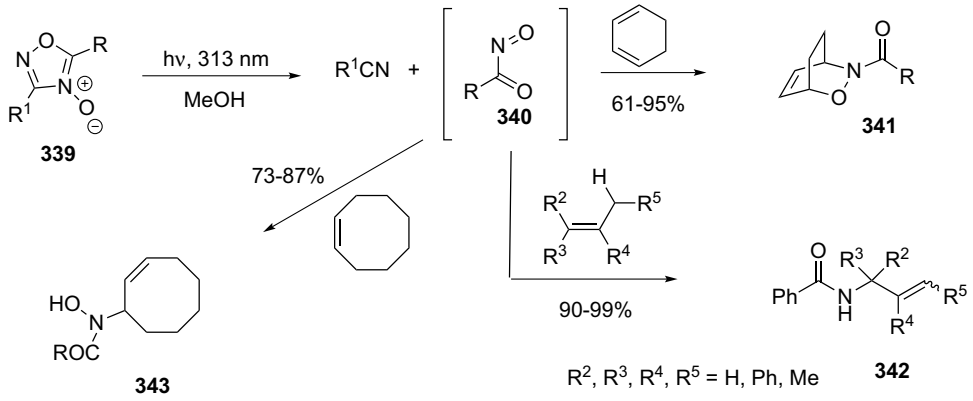
The 1,2,4-oxadiazol-5-ones **344** undergo, when heated in vacuum, a retro-1,3-dipolar cycloaddition to give nitrones **345** (Scheme 13.125) [251].

13.3.5.5 **Reactivity of Substituents**

Reactions involving substituents attached to ring carbons reveal the particular stability of the heterocyclic system. A series of examples are related to the formation and reactivity of α-anions. Thus, 5-methyl-3-phenyl-1,2,4-oxadiazole (**302**) is deprotonated by bases to the corresponding anion, which adds to carbonyl group of ketones or CO_2 [264]. Conversely, the methyl group of 3-methyl-5-phe-



Scheme 13.123



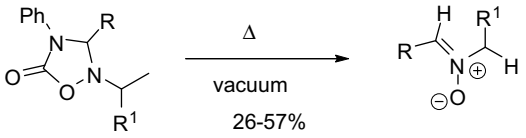
R = Ph, 2,4,6-MePh, p-Cl-Ph, p-MeOPh

R^1 = Ph, 2,4,6-MePh, p-Cl-Ph

Scheme 13.124

nyl-1,2,4-oxadiazole (**300**) by treatment with butyllithium does not form the anion: the reagent adds to the 4,5-bond (Scheme 13.108) [120a].

1,2,4-Oxadiazole **302** also undergoes the aldol condensation with benzaldehyde (Scheme 13.126) [120a].

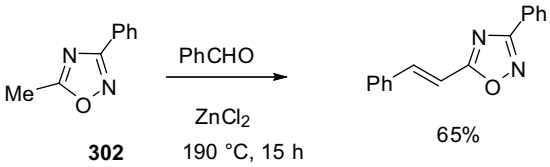


344 **345**

R = Ph,2,3-$(MeO)_2$Ph, 2-NO_2 Ph,3,4-$(MeO)_2$Ph

R^1 =H, Ph, 2,3-$(MeO)_2$ Ph

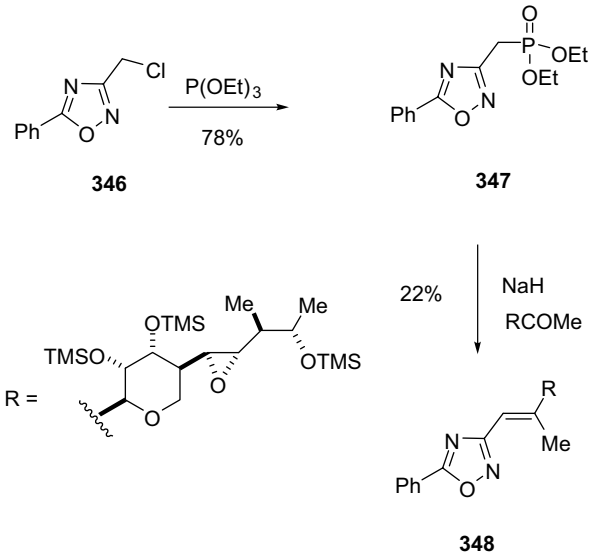
Scheme 13.125



302

Scheme 13.126

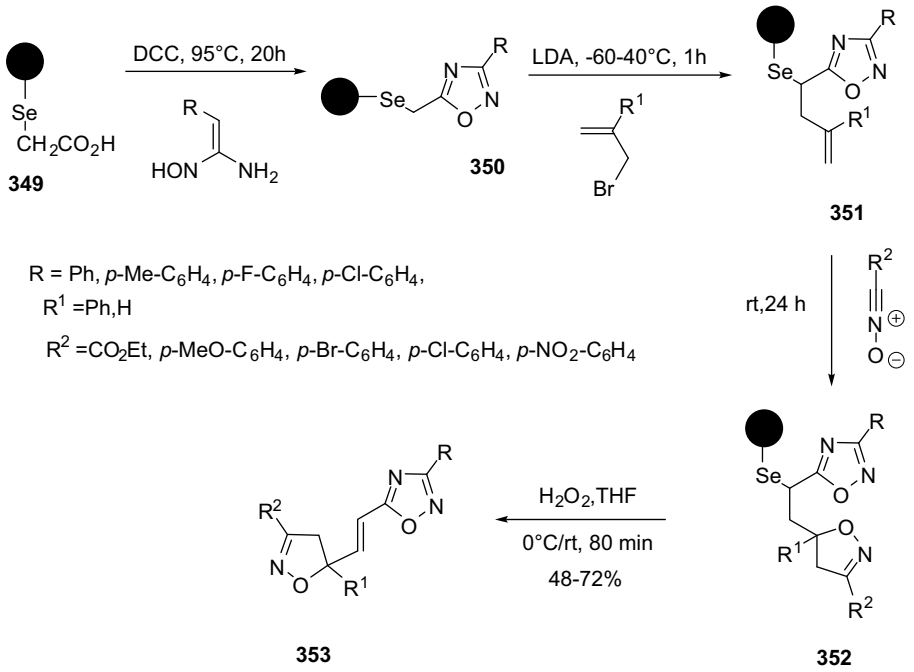
Phosphonate **347**, obtained by Arbuzov reaction of 3-chloromethyl-1,2,4-oxadiazole **346**, has been used in Wadsworth–Emmons reactions: the methodology provides useful access to 3-alkenyl-1,2,4-oxadiazoles **348** (Scheme 13.127) [264].



346 **347** **348**

Scheme 13.127

The formation of α-anions has been exploited for the synthesis of a library of 5-alkenyl-substituted 1,2,4-oxadiazoles **353**. Compounds **353** have been prepared starting from a polystyrene-supported oxadiazolyl-substituted selenium resin **350**, prepared by reaction of polystyrene-supported selenyl acetic acid **349**, with amidoxime and DDC through Porco's two-step, one-pot condensation. Alkylation of **350** by base treatment and addition of allyl bromides produced the α-alkylated selenium resins **351**, which were used as dipolarophiles in a 1,3-dipolar cycloaddition to furnish polystyrene-supported oxadiazolyl- and isoxazolinyl-substituted selenium resins **352**. Oxadiazolyl and isoxazolinyl substituted olefins **353** were then obtained stereoselectively through selenoxide *syn*-elimination from resins **352** by H_2O_2 treatment (Scheme 13.128) [279].

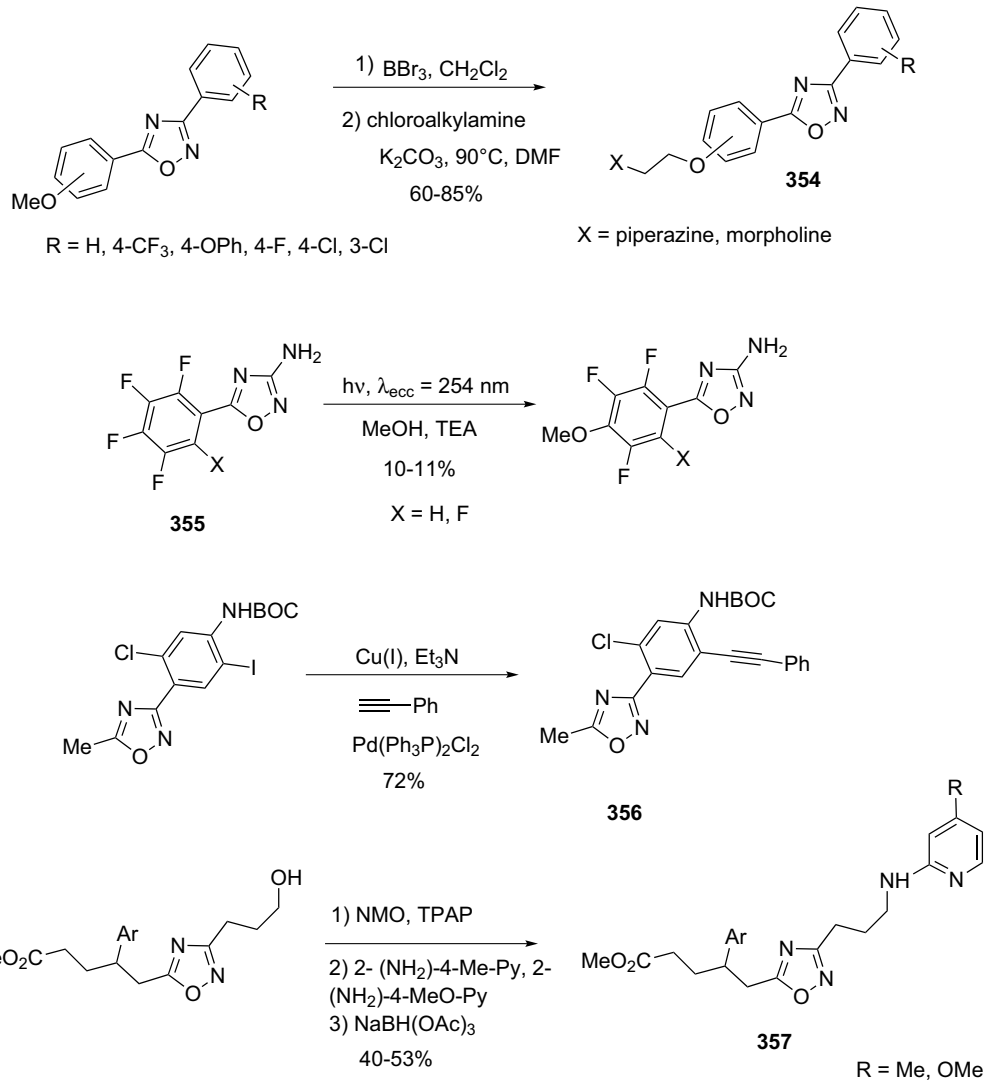


Scheme 13.128

The stability of the oxadiazole ring is pointed out in many reactions that substituents at C3 or C5 undergo. Among the more recent reactions, Scheme 13.129 shows the synthesis of aryl ethers **354** [280], the nucleophilic attack of methanol to a pentafluorophenyl or tetrafluorophenyl 1,2,4-oxadiazole (**355**) [275b], a Sonogashira coupling to afford **356** [195a], and the synthesis of amino compounds **357** by tetrapropylammonium perruthenate (TPAP) oxidation of the hydroxyl group followed by reductive amination of the resulting aldehyde [200].

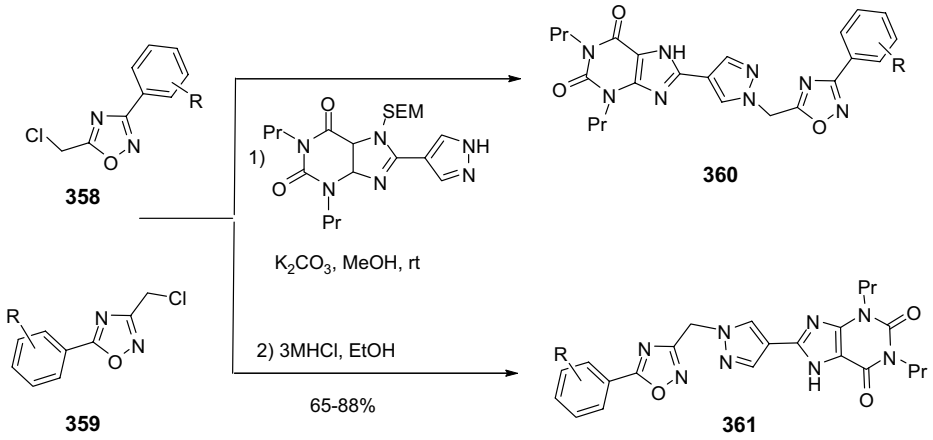
The reaction of 5- and 3-chloromethyl-1,2,4-oxadiazoles **358** and **359**, respectively, with pyrazolyl-purine affords the corresponding derivatives **360** and **361** (Scheme 13.130) [187].

Analogously, the polymer supported-1,2,4-oxadiazole **362** reacts with primary amines to give 5-aminomethyl oxadiazoles **363** (Scheme 13.131) [281].

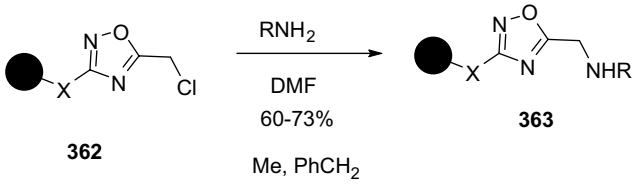


Scheme 13.129

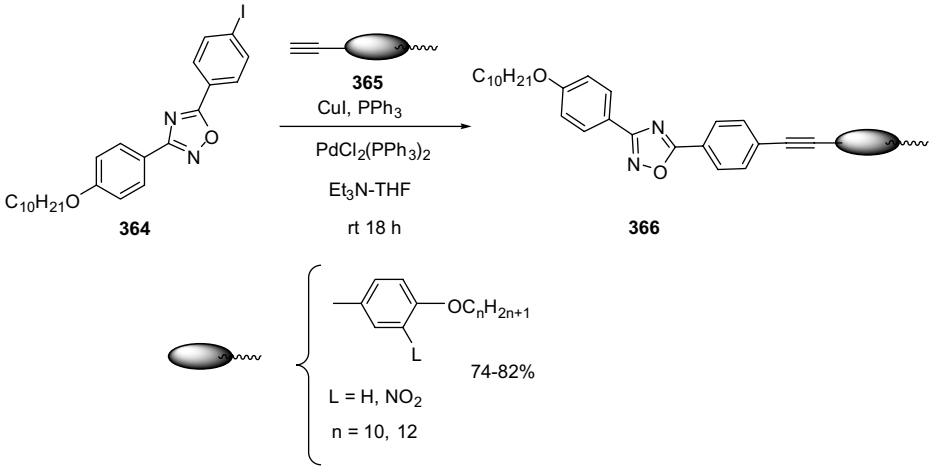
A series of highly π-conjugated nonsymmetrical liquid crystals, based on the core 3,5-(disubstituted)-1,2,4-oxadiazole with a shape similar to a hockey stick, have been synthesized by Sonogashira coupling reaction. Thus, compounds **366** were prepared in 74–82% yield, by reaction of an aryl iodide containing the 1,2,4-oxadiazole ring (**364**) with the terminal arylacetylenes **365**, using 10 mol.% of dichlorobis(triphenylphosphine)palladium, 5 mol.% of the co-catalyst copper(I) iodide, in a triethylamine–tetrahydrofuran mixture (7 : 3). The obtained compounds showed liquid crystal phases, in particular smectic and nematic typical of calamitic structures, and moreover exhibit strong blue fluorescence in solution (Scheme 13.132) [282].



Scheme 13.130



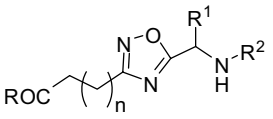
Scheme 13.131



Scheme 13.132

13.3.6
1,2,4-Oxadiazoles in Medicine

1,2,4-Oxadiazole ring occurs widely in biologically active synthetic compounds, and is often used in drug discovery as a hydrolysis-resisting bioisosteric replacement for amide or ester functionalities [283] because of its electronic properties. Its derivatives can be found in a vast number of compounds exerting biological activity, such as ligands of benzodiazepine receptors [284, 285], anti-inflammatory agents [131, 199, 234], antiviral agents [283], inhibitors of protein tyrosine phosphatases [286], agonists of muscarinic receptors [287], inhibitors of Src SH2 [183], antagonists of histamine H_3-receptors [288], integrin receptor antagonists [200], angiotensin II receptor antagonists [289], and HIV-1 reverse transcriptase inhibitors [290]. 1,2,4-Oxadiazole moieties have been used in the design of dipeptidomimetics as peptide building blocks [184a,b]. Compounds **367** contain, at C5 of the 1,2,4-oxadiazole nucleus, a residue of an amino group linked to peptide moieties, and a carboxyl or ester functionality attached at C3 directly or through a methylene chain [291]



367

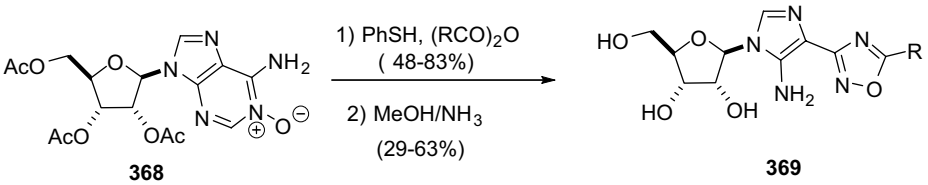
n =0, 1,2

R = OH, OEt, NHMe R^1 = $PhCH_2$, Me, *i-P*rop

R^2 = Ac, Boc, H-Tyr-D-Ala, H-Arg-Pro--Lys-Pro-Gln-Gln-Phe

Numerous 1,2,4-oxadiazoles have been suggested as potential agonists for cortical muscarinic [292], benzodiazepine [293], and 5-HT1D (5-hydroxytryptamine) receptors [294], and as antagonists for 5-HT [295] or histamine H3 receptors [296]. They show activity as antirhinoviral agents [297], growth hormone secretagogues [298], anti-inflammatory agents [234], and antitumor agents [183, 188, 299]. They also inhibit the SH2 domain of tyrosine kinase [300], monoamine oxidase [301], human neutrophil elastase [302], and human DNA topoisomerases. Finally, tropane derivatives of 1,2,4-oxadiazoles display high affinity for the cocaine binding site of the dopamine transporter [303].

More recently, it has been reported that the ring opening of N-oxides of adenosines **368**, followed by exocyclic ring closure, in the presence of carboxylic anhydrides and thiophenol, followed by ammonia treatment, generates 1,2,4-oxadiazolyl imidazoles **369** (Scheme 13.133) [304]. The so-obtained separation of the fused imidazole and pyrimidine rings of purine nucleosides increases the conformation flexibility: these shape-modified analogues have been used to investigate triple helix formation and as probes for the study of enzyme interactions [305a].

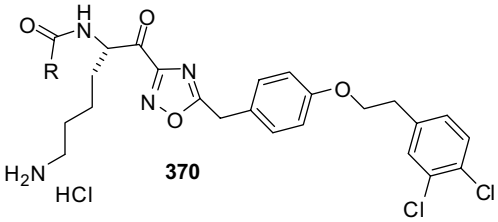


368 369

R = Me, Et, pr, *i*-pr, *t*-bu, C_5H_{11}, C_7H_{15}, C_9H_{19}, Ph

Scheme 13.133

Furthermore, a series of keto-1,2,4-oxadiazoles (**370**) have been prepared that have been shown to be potent inhibitors of human mast cell tryptase and useful in the treatment of asthma and allergic diseases.

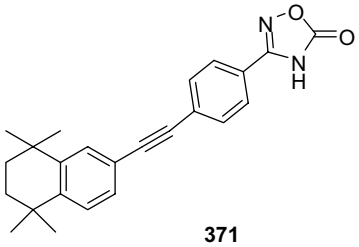


370

R = CF_3, C_3H_5, OEt, $N(CH_2)_4O$, *t*-bu, *i*-pr, *n*-pentyl, 2,4-$F_2C_6H_3$, 3,4-$F_2C_6H_3$, 4-FC_6H_4, 4-ClC_6H_4

The 1,2,4.oxadiazol-5-one moiety can act as a bioisostere of the carboxylic acid function in retinoid structures. Recently, the solid-phase or solution-phase syntheses of a new series of non-carboxylic acid retinoic acid receptor ligands (RARs) bioisosteres of Am580 or tazarotene-like retinoids has been reported [305b].

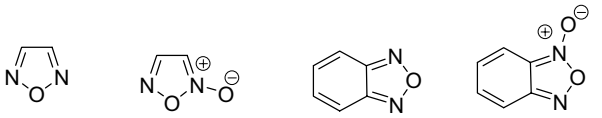
In particular, the retinoidal activity of compound **371** (RAR-β,γ selective) is significant. These non-carboxylic acid type RAR ligands may exhibit different pharmacological behaviors from classical carboxylic acid compounds, as well as unique biological activity, and they may provide further scope for clinical applications.



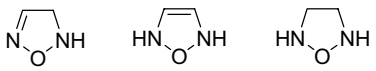
371

13.4
1,2,5-Oxadiazoles

1,2,5-Oxadiazole (**372**) is often referred to by the trivial name furazan; for 1,2,5-oxadiazole-2-oxide (**373**), a common derivative, the trivial name furoxan is still in wide usage. The first report on a 1,2,5-oxadiazole ring system appeared in the 1850s: the parent compound **1** was prepared in 1964 by treatment of glyoxime with succinic anhydride [306]. For 2,1,3-benzoxadiazoles (**374**) and the corresponding N-oxide **375**, the terms benzofurazan and benzofuroxan are commonly used. The partially reduced dihydro- (Δ^2, Δ^3) and tetrahydro-derivatives **376–378** are very rare.



372 **373** **374** **375**



376 **377** **378**

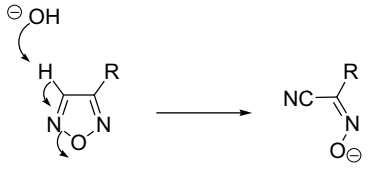
1,2,5-Oxadiazoles, their N-oxides, as well as their benzo-fused systems are biologically active compounds. Some of their derivatives are important because of their anthelmintic, fungicidal, bactericidal, and herbicidal action. They have also been found to possess antitumoral activity.

Several reviews have been published on 1,2,5-oxadiazoles [307–311]: the most comprehensive account of the chemistry of furoxans and benzofuroxans is that by Gasco and Boulton [312], and the more recent one by Paton [313].

13.4.1
Structure

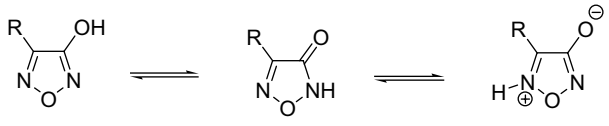
1,2,5-Oxadiazole is a heteroaromatic compound; strictly, it should be regarded as a π-excessive heterocycle with six electrons distributed over five atoms. However, the π-electron density on the heteroatoms is so great that the values for the C-atoms are smaller than one, where π-deficiency prevails, thereby influencing the reactivity [314]. Despite low π-electron density on the C-atoms, 1,2,5-oxadiazoles do not react at all or only slowly with nucleophiles: treatment with strong bases, such as NaOH in methanol, causes ring opening to form sodium salts of α-oximinonitriles **380** (Scheme 13.134).

The 1,2,5-oxadiazole ring is a stable system and annular-group tautomerism is not favored [308]. Thus, the two theoretically possible tautomeric forms **381a** and **381b** for 3-hydroxyfurazans **381** can be discarded on the basis of IR and NMR data, which show the exclusive presence of the hydroxy compound in chloroform solution (Scheme 13.135).



379 **380**

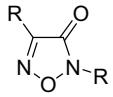
Scheme 13.134



381 **381a** **381b**

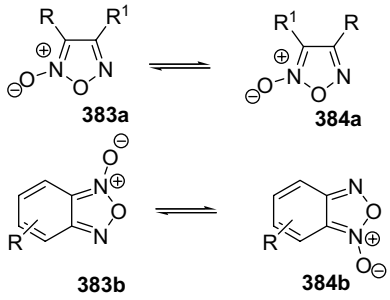
Scheme 13.135

However, the formation of 2-alkyl-1,2,5-oxadiazol-3(2*H*)-ones **382** by alkylation of trimethylsilyl derivatives of 3-hydroxyfurazans using triethyl orthoformate has been reported [315]. The compounds were characterized by NMR and MS measurements.



382

The N-oxide structure for furoxans and their benzo-derivatives was ascertained by Wieland [316] and Werner [317]. Ring-chain tautomerism is a distinctive feature of furoxan chemistry, as evidenced in the interconversion of 2-oxide **383** and 5-oxide isomers **384** (Figure 13.4: see Section 13.4.2).



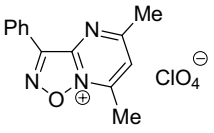
383a **384a**

383b **384b**

Figure 13.4 Example of ring-chain tautomerism shown by the interconversion of 2-oxide **383** and 5-oxide isomers **384**.

A furazan fused to a five-membered heterocycle was first described in 1908 [318]: annelation in 5/5-byciclic systems suggests the presence of strain energy in the molecules, which is manifested in the difficulty to form these compounds. Destabilization of the distorted aromatic oxadiazoles results not only from bond stretching, angular distortion, and torsional effects, but also from the decreased resonance stabilization [319].

5,7-Dimethyl-3-phenyl-furazano- and –furoxano[5,4-*a*]pyridinium perchlorates (**385** and **386**), a new type of condensed system, have been obtained by cyclocondensation of aminophenylfuroxan and aminophenylfurazan with acetylacetone in the presence of $HClO_4$. The structure of these compounds is supported by crystallographic analysis and CNDO/2 calculations [320].



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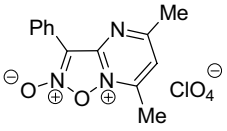
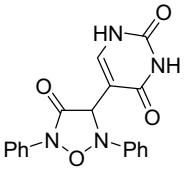


386

Very few partially or totally reduced 1,2,5-oxadiazole ring systems has been reported. For instance, a Japanese patent [321] describes the synthesis of 5-(4-oxo-2,5-diphenyl-1,2,5-oxadiazolidine-3-yl)-2,4(1*H*,3*H*)-pyrimidinedione (**387**), the first representative of 1,2,5-oxadiazolidines.

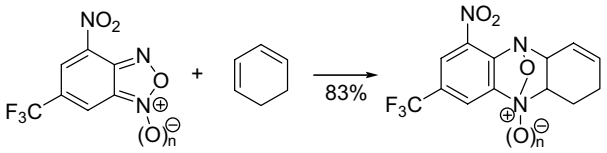


387

As a result of the low aromatic character of the benzofuroxan system, recent studies have revealed that nitrobenzofuroxan acts as very versatile Diels–Alder reagent, with the carbocyclic ring being capable of acting as a dienophile [322], a heterodiene [322], or a carbodiene [323], depending upon the experimental conditions. Thus, treatment of 4-nitro-6-trifluoromethylfurazan (**388**) and -furoxan (**389**) with 1,3-cycloexadiene afforded a mixture of fused derivatives **390** and **391**, respectively (Scheme 13.136) [324].

13.4.2
Theoretical Aspects

Theoretical studies on the structure and properties of 1,2,5-oxadiazoles have been reported. Molecular orbital calculations [325, 326] and *ab initio* quantum mechanical methodologies have been used to determine bond orders, total energies, ionization potentials, and dipole moments [327]: a good match with experimental data has been obtained.



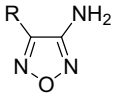
388 n = 0 **390**

389 n = 1 **391**

Scheme 13.136

Dipole moments for a set of substituted 1,2,5-oxadiazoles and 1,2,5-oxadiazole 2-oxides have been measured in benzene solution [328]. The dipole moment of furazans is oriented with the negative end towards the oxygen atom, while in furoxans the data revealed a strong electron shift from the exocyclic oxygen back into the heterocyclic system, corresponding to a mesomeric moment of approximately 3 D. The molecule of furoxan is well characterized as electron-overcrowded, particularly near the nitrogen atom N2.

Dipole moments of 3-amino-4R-furazans **392** have been determined experimentally and also calculated by HF *ab initio* (STO-3G, 3-21G, 4-31G, 6-31G, 6-31G**/4-31G, 6-31G** levels) and semiempirical (MNDO, AM1, PM3) quantum chemical methods; good agreement with the experimental values has been found.

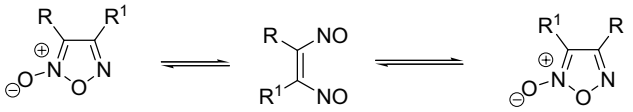


392

R = H, NH_2, OMe, N_3, COOH, COOMe, NO_2

For these compounds, the amino–imino tautomeric equilibrium is strongly shifted towards the amino-form [329].

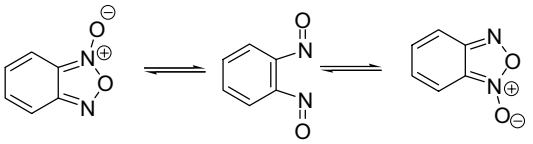
A great deal of interest has been taken in the 2-oxide and 5-oxide tautomers and the pathway of their interconversion (**393**↔**395**) has been studied in some detail [330–335]. Structures and relative stabilities of furoxan and its open-chain tautomers have been calculated by semiempirical and *ab initio* procedures. The obtained results support a mechanism that involves the *cis*-1,2-dinitroethene **394** as intermediate/transition state, with an energy about 120 kJ mol^{-1} above that of furoxan.



393 **394** **395**

Analogously, in the benzofuroxan series, MP2 calculations afford a correct prediction of the structure [336]: the most likely intermediate in the interconversion

396↔**398** is *anti*-1,2-dinitrosobenzene (**397**) with an energy of 50 kJ mol^{-1} above that of benzofuroxan [337].



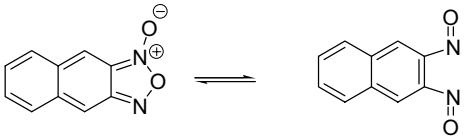
396 **397** **398**

The involvement of 1,2-nitrosoarenes as intermediates in the equilibration process has been established by matrix isolation experiments [338–340]: photolysis (360 nm) of benzofuran in an argon matrix at 14 K generated 1,2-nitrosobenzene, which was characterized by UV and IR spectroscopy, and subsequent thermolysis or photolysis (320 nm) afforded benzofuroxan. The gain of resonance energy of the benzene ring does not compensate for the energy needed to open the furoxan ring, and therefore dinitrosobenzene is less stable than benzofuroxan.

More recently, the first experimental evidence for the formation of 2,3-dinitroso-2-butene as a reactive intermediate, during the photolytically induced decomposition of dimethylfuroxan, has been reported by matrix isolation experiments [341a]. DFT calculations gave the geometry of the dinitrosoalkene intermediate [341b]. However, this species is photolabile and decomposes upon prolonged photolysis time to give acetonitrile *N*-oxide as the final, photostable product. The two photoproducts were characterized using a combination of experimental and quantum chemical results.

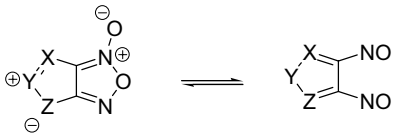
Factors influencing the equilibrium constants and rates have been reviewed [312, 342–344].

The equilibrium between annelated furoxans and the isomeric dinitroso derivatives, for example, **399** and **400**, has been investigated theoretically by semiempirical (AM1, PM3) and *ab initio* methods (MP2/6-31G*//6-31G* and RHF/6-31G*) [345]. For both 1,2- and 2,3-dinitrosonaphthalene, several conformers exist as minimum on the potential energy surface (PES). Calculations of the energy difference between [1,2,5]thiadiazolo[3,4-*e*]benzoxadiazole-1-oxide and -3-oxide are in agreement with experimental data.



399 **400**

Ab initio and density functional theoretical studies on non-classical furoxans **401** (Y = O, NH, S for each of the following combinations of X,Z: CH,CH; N, CH; CH,N; and N,N) and their open-chain *anti*-1,2-dinitroso isomers **402** have been reported [346, 347]. Calculations indicate that, in all cases considered, the non-classical furoxans are less stable than the corresponding open-chain isomers.



401 402

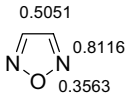
Density functional theory (DFT) has been used to calculate the heats of formation and IR active vibrational frequencies of 12 furazan compounds [348]. The assignments of the vibrational motions to IR frequencies based on a force field analysis are given to clarify the complex coupling in these molecules.

Dissociation enthalpies of terminal (N−O) bonds, ΔH°(N−O), in furoxans have been calculated from enthalpy of formation, enthalpy of sublimation, and enthalpy of vaporization data [349].

13.4.3 Structural Aspects

13.4.3.1 X-Ray Diffraction

X-Ray crystal structures have been reported for various furazans and furoxans [350–357]. Bond lengths and bond angles have been determined also by double resonance modulation microwave spectroscopy [358]. For furazans, crystallographic data show that the heterocyclic ring is essentially planar and possess C_{2v} symmetry. π-Bond orders are 0.72–0.82 for N2−C3 and C4−N5 and 0.45–0.52 for C3−C4. These data suggest a significant π-delocalization; in contrast, O1−N2 and N5−O1 are essentially single bonds (0.32–0.36). Benzofurazans show similar parameters and a significant double bond fixation in the fused ring. The molecular geometry for the parent furazan (**403**) has been determined by microwave spectroscopy.



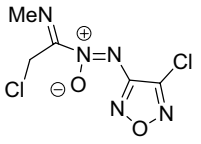
403

As for furazans, the oxadiazole ring of furoxans in nearly planar, but the exocyclic oxygen at N2 causes substantial distortion, lying 0.05 Å out of the plane of the heterocycle. Structures are characterized by the long O1−N2 and the short N2−O_{exo} bonds. Moreover, C3−C4 is shortened, with about 30% double bond-character, while N2−C3 is longer than C4−N5.

Benzofuroxans show a similar pattern of bond lengths and angles. In the homocyclic ring, significant bond localization is supported by the consideration that the C4−C5 and C6−C7 bonds are notably shorter than C5−C6, in accord with their chemical reactivity (Section 13.4.5.2).

Crystal structure simulations for three azoxyfurazans, 4,2′-dichloroazoxyfurazan (**404**), 4,4′-di(morpholin-1-yl)azoxyfurazan (**405**), and 4,4′-dimethylazoxyfurazan (**406**), have been carried out to test the reliability of standard force fields for

furazan derivatives [359]. The predicted crystal structures were compared with experimental ones, obtained by X-ray diffraction analysis.



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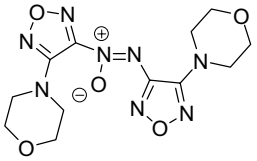

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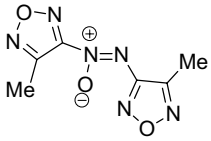
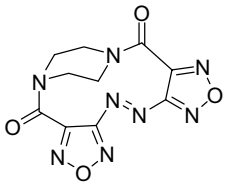


406

X-Ray data for 1,2,5-oxadiazoles fused with a pyrazine ring have been reported recently [360].

Azofurazan annulated macrocycles **407** [361], **408** [362], and **409** [363] have been synthesized and then characterized by X-ray analysis. Lactam **407** show two furazan rings linked to a piperazine system, while compound **408** contains four furazan rings bonded by three azo bonds. The ion binding ability of compounds **409** was tested.



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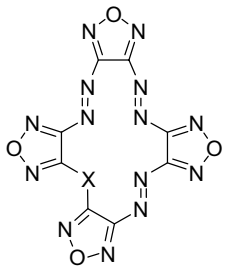
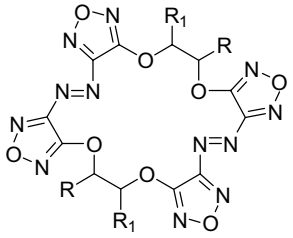


408 X = O, S, $O(CH_2)_2O$



409

13.4.3.2 **NMR Spectroscopy**

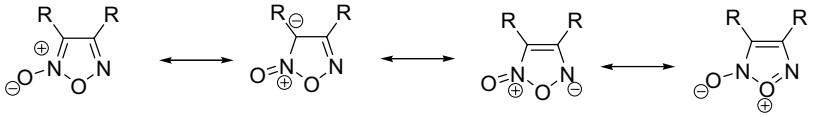
Monosubstituted furazans [364], phenylfurazans [365], azoxyfurazans [366], and hydroxy-, alkoxy- and phenoxyfurazans [367] have been studied by NMR spectroscopy. Additive schemes have been developed and spectrum–structure correlations have been elucidated.

Table 13.7 reports the NMR chemical shifts (^{1}H, ^{13}C, ^{15}N, and ^{17}O) of furazan, furoxan, and their benzo derivatives [308].

Table 13.7 NMR chemical shifts (ppm) for furazan, furoxan, and their benzo-fused derivatives.

Compound	H3	H4	C3	C4	N2	N5	O1	O-exo
Furazan	7.92	7.92	142.0	142.0	−33.5	−33.5	450	
Benzofurazan			148.6	148.6	−35.6	−35.6		
Furoxan	7.44	8.50	105.2	146.8	−15.4	3.9	507.5	364.0
Benzofuroxan			113.7	152.2	−25.3	−13.2		

In the furoxan series the lower chemical shifts of 3H with respect to 4H is due to the contribution of the resonance structure **411**.



410 **411** **412** **413**

The strong shielding effect exerted by the exocyclic oxygen atom on the proton attached to the substituents at C3 allows one to identify the individual isomer **383a** and **384a.** Thus, for dimethylfuroxan the resonance at 2.16 ppm is assigned to the 3-methyl group, while that at 2.38 ppm is attributable to the 4-methyl group [368].

In benzofuroxans, the shielding effect exerted by N-oxide shifts all the signals to higher frequency with respect to the resonances of benzofurazans, with the larger shifts for H7 and for H4 [369]. The ring-chain tautomerism of these compounds has been investigated by ^{1}H spectroscopy. The unsymmetrical ABCD pattern for the homocyclic protons, observed at $-40\,^{\circ}C$, changes into a symmetrical A_2B_2 pattern at $100\,^{\circ}C$, as a consequence of the rapid equilibration of two isomers. In this way, exchange rates over a range of temperatures have been determined and thermodynamic activation parameters calculated [344, 370].

The most noteworthy feature of the ^{13}C NMR of furoxans is the large difference in chemical shifts of C3 and C4 resonances. As indicated in Table 13.7, C3 resonates at higher field in the range 100–123 ppm, while C4 appears in the range 140–160 ppm [368].

The chemical shifts and multiplicities of the two bridgehead carbons in the ^{13}C NMR spectra of various fused furoxans have been shown to provide a general method for assigning structure in these tautomeric systems [371].

3-Methylfurazans with nitrogen-containing substituents at C4 have been studied by ^{1}H, ^{13}C and ^{14}N NMR spectroscopy [372]. A correlation between the chemical shifts in ^{13}C NMR spectra of these furazans and monosubstituted benzenes with the same substituents was found. The influence of substituents on the NMR data of the iodofurazans was also investigated [356].

The ^{15}N NMR spectra of furazan and benzofurazan show a single absorption at -33 and -36 ppm, respectively [373, 374]. The nitrogen atoms of furoxans show distinct signals in the range -26 to -15 for N2 and -14 to $+4$ ppm for N5: these resonances coalesce on heating.

The parent furoxan **373** has ^{17}O signals at 508 and 364 ppm, while furazan **372** shows a single resonance at 450 ppm [368]. The corresponding figures for dimethylfuroxan are 460 and 350 ppm, and 475 ppm for dimethylfurazan.

13.4.3.3 **UV and IR Spectroscopy**

Characteristic peaks in the IR spectra of furazans are in the ranges 1525–1560 (C=N−O), 1430–1385 (N−O), and 1040–1030 and 890–880 cm^{-1} (heterocyclic ring). Furoxans show diagnostic peaks at 1625–1600 (CN−O), 1490–1400 ($C{=}NO_2$),

1360–1280 (N−O), and at 1190–1150, 1030–1000, and 890–875 cm^{-1} (heterocyclic ring) [308].

MINDO/3 and DFT methods have been used to calculate the IR active vibrational frequencies of a series of furazans and furoxans [348]. The 1605 cm^{-1} band of furoxans was assigned to vibrations of the C:N(O) group [326].

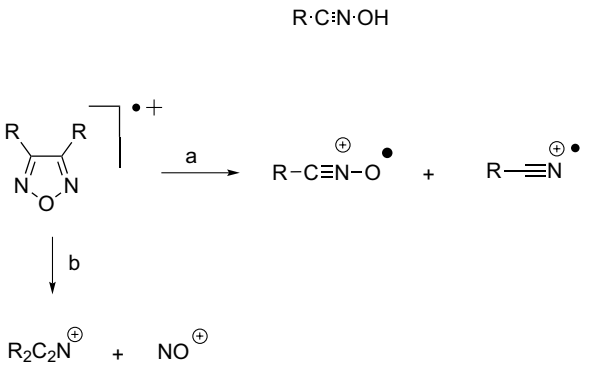
Monocyclic furazans and dimethylfurazan have UV absorption bands at 228–241 nm, while typical monocyclic furoxans have a peak at 255–295 nm [375].

The extended conjugation in the chromophores of benzofurazans and benzofuroxans results in a shifts of λ_{max} to longer wavelengths (350–410 nm); the energy band can extend into the visible region when conjugating groups are present.

7-Halo-4-nitro and 7-halodinitrobenzofurazans are used as analytical reagents because of the strong visible fluorescence in the region 525–545 nm when reacted with ethers, thioethers, and amines. Thus, tyrosil, cysteinyl, and amino residues of proteins can be labeled by this method, providing access to a fluorescence probe incorporating various biological interesting molecules [376].

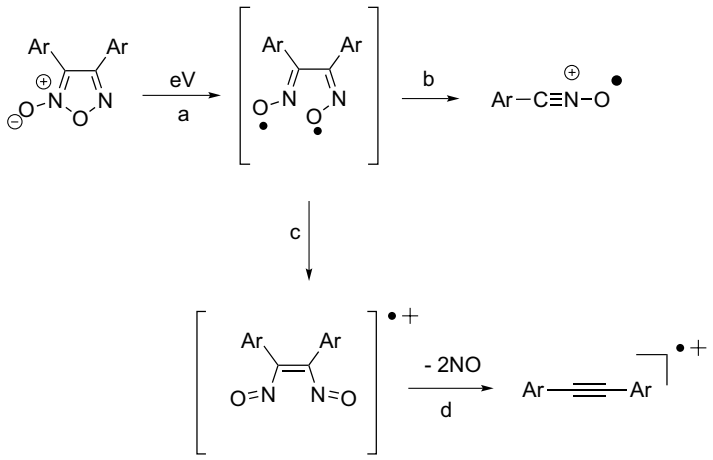
13.4.3.4 **Mass Spectrometry**

Two general patterns of fragmentation under ionizing radiation characterize monocyclic furazans (Scheme 13.137) [377–379]. Initial ring opening by cleavage of the weak O1−N2 bond is followed by the C3−C4 bond breaking to yield nitrile and nitrile oxide (path a) or by the extrusion of NO (path b) [380]. Peaks attributable to RC^+ are usually observed.



Scheme 13.137

Unlike many aromatic N-oxides, the $(M–16)^+$ peak for furoxans is weak. The electron impact mass spectra of furazans are characterized by diagnostic peaks at $(M–30)^+$ and $(M–60)^+$, due to the loss of NO and two NO molecules, respectively [381, 382]. The fragmentation pattern (Scheme 13.138) is consistent with the O1−N2 bond cleavage, with formation of the 1,2-dinitrosoethene tautomers, followed by sequential expulsion of NO. In parallel with this route, cleavage of the C3−C4 bond yields two nitrile oxides.



Scheme 13.138

The acetylenic structure of the $(M–60)^+$ fragment has been ascertained by mass-analyzed ion kinetic energy (MIKE) spectroscopy performed under high energy collision activation conditions [312].

The direct generation of NO by a chemical decomposition suggests that the furoxan derivatives can be utilized as a potential NO-related biological probe [381].

13.4.4 Synthesis

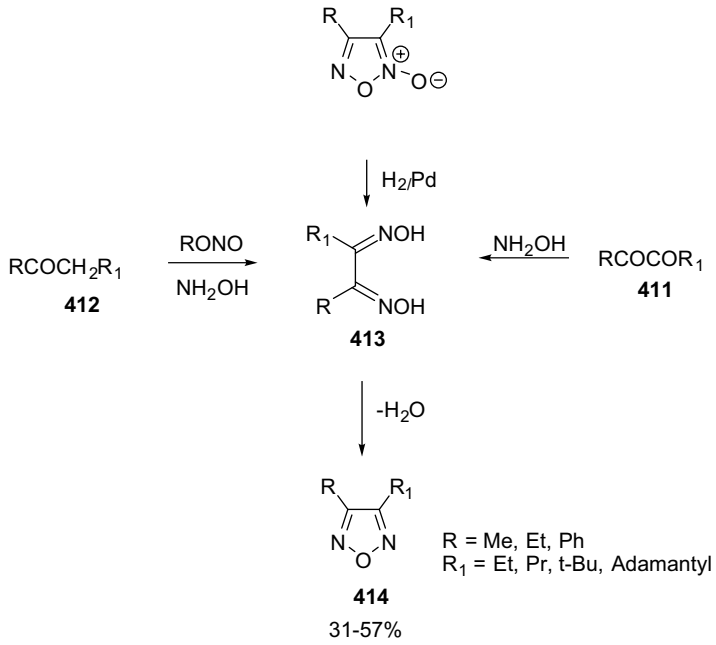
Many synthetic routes for the 1,2,5-oxadiazole system have been reported [308, 313, 384]. Different approaches are generally required for furazans, furoxans, and their benzo-fused analogues; thus separate subsections are devoted to the synthesis of furazans, benzofurazans, furoxans and benzofuroxans.

Moreover, according to the stability of the heterocyclic ring, numerous different 1,2,5-oxadiazole derivatives can be generally prepared by exploiting appropriate interconversion reactions of the substituents present on the five-membered ring.

13.4.4.1 Furazans

Three main routes have been designed for the synthesis of furazans: (i) dehydrative cyclization of 1,2-dioximes, (ii) deoxygenation of furoxans, and (iii) Boulton–Katritzky rearrangement of other five-membered heterocycles.

13.4.4.1.1 **Dehydration of 1,2-Dioximes** Furazan **372** was first prepared in 1964, by melting glyoxime with succinic anhydride, in 57% yield [306]. Cyclization of substituted glyoximes **413** is the most exploited methodology for the preparation of mono and disubstituted furazans **414** (Scheme 13.139). The starting material is prepared by reaction of 1,2-diketones **411** with hydroxylamine or by α-nitrosation of an alkylketone **412**, followed by oximation of the resulting 1,2-dione monooxime. A "one-pot" method for the synthesis of 3-alkyl-, 3-aryl-, and 3-hetaryl-4-aminofurazans



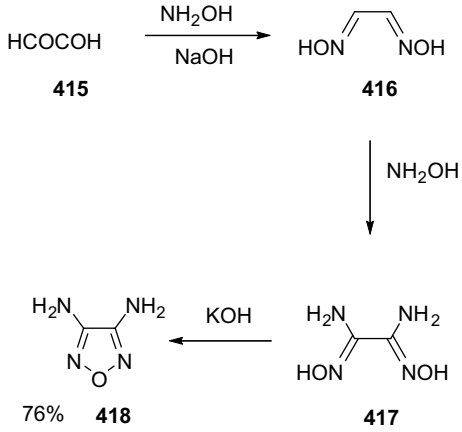
Scheme 13.139

from β-alkyl- or β-aryl and β-hetaryl-β-oxoesters has been reported recently. The multistep process involves hydrolysis of the ester, nitrosation at the activated methylene group, and treatment of the resulting intermediate with an alkaline solution of hydroxylamine in the presence of urea [385].

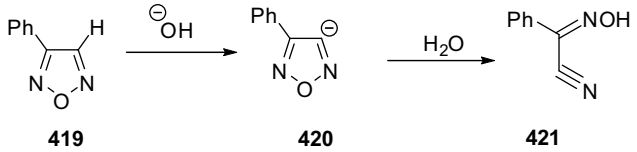
Dioximes can be also obtained by reduction of furoxans with H_2, Pd/C (Section 13.4.4.1.2); thus, when furoxan is easily available, as for example by dimerization of nitrile oxides, the sequence furoxan–glyoxime–furazan constitutes a valuable synthetic route for symmetrically substituted furoxans. Various dehydrating agents have been utilized, such as acetic, succinic and phthalic anhydrides, sulfuric acid, dicyclohexylcarbodiimide, phosphorus oxychloride, thionyl chloride, and alcoholic sodium hydroxide. According to this procedure, diaminofurazan **418** has been prepared in good yield by reaction of glyoxime **416** and hydroxylamine hydrochloride in aqueous NaOH, to give diaminoglyoxime **417**, followed by KOH mediated dehydration; the reaction has also been performed under microwave irradiation in 2/3 min (Scheme 13.140) [386].

For monosubstituted furazans such as **419**, basic dehydrating agents must be avoided because most of these compounds are isomerized to oximes of α-ketonitriles (**421**), according to a sequence that originates from the initial deprotonation at C4 (Scheme 13.141) [387]. Thus, in these cases, dehydration of the corresponding dioximes is conveniently carried out with anhydrides or sulfuric acid.

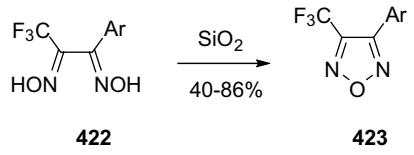
In contrast, disubstituted furazans are stable to both heat and chemical conditions and a wide range of dehydrating agents may be used. An unusual synthesis of



Scheme 13.140



Scheme 13.141



Ar =Ph, Tolyl

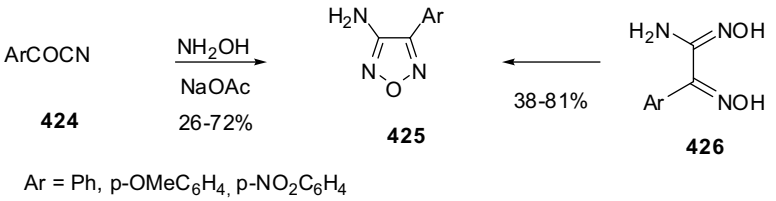
Scheme 13.142

3-(trifluoromethyl)-4-aryl-furazans **423** has been reported (Scheme 13.142) [388]: dehydration of 1,1,1-trifluoromethyl-2,3-dione dioximes **422**, which failed with traditional methods, was performed on heating with silica gel.

A modification of the dehydration route involves the conversion of dioximes into diesters, followed by cyclization via distillation or reaction with alkali [389].

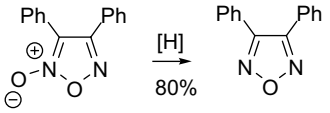
The 1,2-dioxime dehydration route is compatible with various substituents, such as alkyl, aryl, acyl, carboxyl, and amino groups. For example, 3-amino-4-phenylfurazans (**425**) are obtained by treatment of aroyl cyanides **424** with hydroxylamine and sodium acetate in ethanol or on heating N-hydroxy-2-(hydroxyimino)-2-arylacetimidamide (**426**) with sodium acetate in ethanol (Scheme 13.143) [390].

13.4.4.1.2 **Deoxygenation of Furoxans** Furazans have been prepared by deoxygenation of furoxans: this method is suitable for furazans bearing different substituents, including alkyl, aryl, acyl, cyano, and amino groups (Scheme 13.144) [313].



Ar = Ph, p-$OMeC_6H_4$, p-$NO_2C_6H_4$

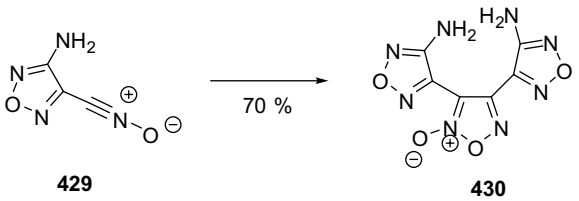
Scheme 13.143



Scheme 13.144

However, the reduction process must be carried out so as to avoid over-reduction and, when the furazan is thermally labile, the formation of by-products by ring opening [319]. The most employed reducing agents include trialkyl and triarylphosphites and phosphines, phosphorous pentachloride, stannous chloride in acetic acid, and Zn/acetic acid [308].

The strategy is particularly efficient for the preparation of symmetrical substituted furazans because the corresponding furoxans can be easily prepared via dimerization of the appropriate nitrile oxides (Section 13.4.4.3.3) (Scheme 13.145) [391].

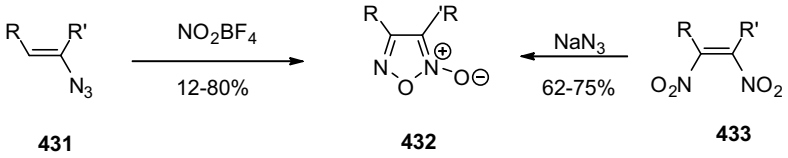


Scheme 13.145

Vinyl azides **431** [392] and vicinal vinyl nitro compounds **433** [393] can be precursors for furoxans and furazans (Scheme 13.146).

13.4.4.1.3 **Boulton–Katritzky Rearrangement** Oximes of several classes of 3-acyl-1-oxa-2-azoles, such as isoxazoles, 1,2,4-oxadiazoles, and furazans, undergo a thermal or base-catalyzed rearrangement, known as the Boulton–Katritzky rearrangement, which leads to furazans (Scheme 13.147) [342, 394].

The reaction can proceed by a concerted electrocyclic mechanism or, in the presence of a base catalyst, in two steps by an intramolecular nucleophilic attack at the nitrogen atom of an anionic intermediate.



431 **432** **433**

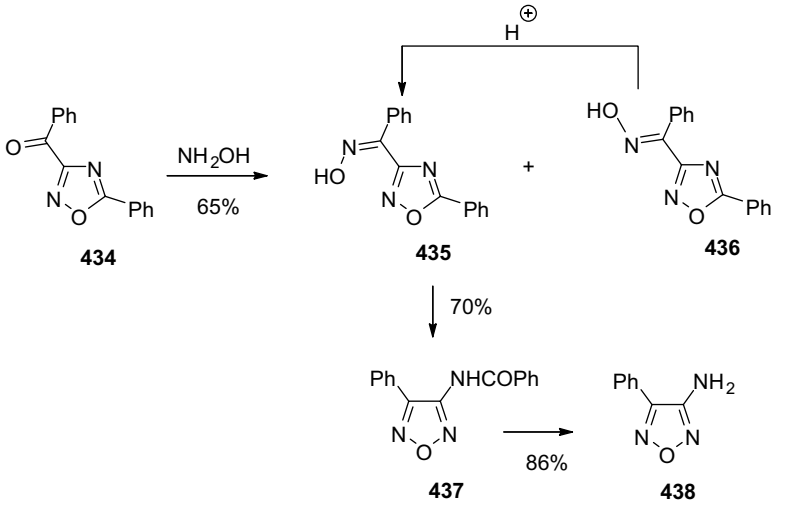
R = H, Me, n-Bu
R' = H, Me, Ph

Scheme 13.146

A) Z=Y=CH; B) Z=N, Y=CH; Z=CH, Y=N

Scheme 13.147

The process is geometry dependent, with the *(Z)*-isomer rapidly transformed, while the *(E)*-isomer is generally stable. Thus, the reaction of 3-benzoyl-5-phenyl-1,2,4-oxadiazole (**434**) with hydroxylamine gives rise to a mixture of *(E)*-oxime **436** and the amido furazan **437** resulting from the rearrangement of *(Z)*-oxime **435** [395]. The addition of an acid improves the process because of the *(Z/E)*-oxime isomerization. Under this condition the amidofurazan **437** is hydrolyzed to its amino derivative **438** (Scheme 13.148).

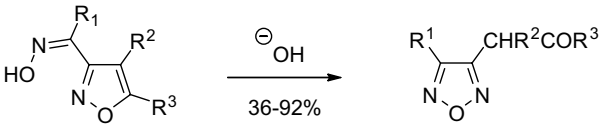


434 **435** **436** **437** **438**

Scheme 13.148

The transformation is not limited to oximes, but also amidoximes and hydrazidoximes can give the corresponding furazans [396].

The *(Z)*-oximes of 3-acylisoxazoles **439**, which are more stable than the corresponding 1,2,4-oxadiazole derivatives, do not react in the absence of a catalyst; the rearrangement occurs easily by treatment with bases, leading to the formation of β-ketoalkylfurazans **440** (Scheme 13.149).

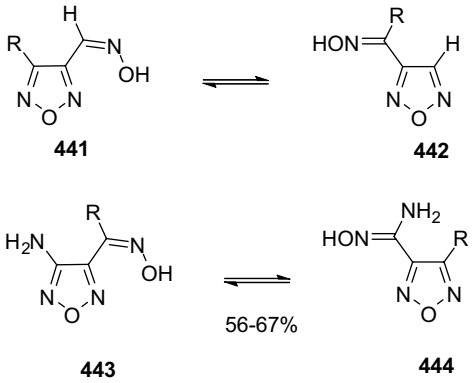


439 **440**

R^1 =H,Me,Et,Ph
R^2 =H,Me,Ph,Bn
R^3 =Me,Et,i-Pr

Scheme 13.149

Various oximes of 3-acyl-substituted furazans **441** undergo the Boulton–Katritzky rearrangement in which the oxadiazole ring is converted into a new furazan system bearing a hydroxyiminoalkyl group (**442**). Several examples of *N*-mono and *N,N*-dialkylfurazanamidoximes (**443**↔**444**) have been reported (Scheme 13.150) [397].

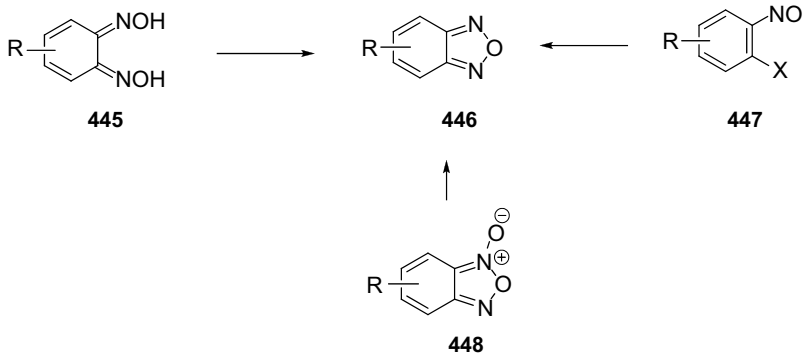


R = PhNH,$PhCH_2NH$, $(CH_2)_5N$, $(CH_2)_4ON$, Me_2N, Me_2CHN, $(Me_2CH)_2N$

Scheme 13.150

13.4.4.2 **Benzofurazans**

The main synthetic routes towards benzofurazans are (i) dehydration of *o*-quinone dioximes, (ii) cyclization of *o*-substituted nitrosoarenes, and (iii) deoxygenation of benzofuroxans (Scheme 13.151) [307, 309].



Scheme 13.151

Various dehydration conditions have been used for the conversion of *o*-quinone dioximes into benzofurazans, such as the use of acetic anhydride, thionyl chloride, sulfuric acid, phenyl isocyanate, and alcoholic sodium hydroxide. Alternatively, cyclization may be performed by thermolysis of the corresponding dioxime diacetates or dibenzoates [307, 309].

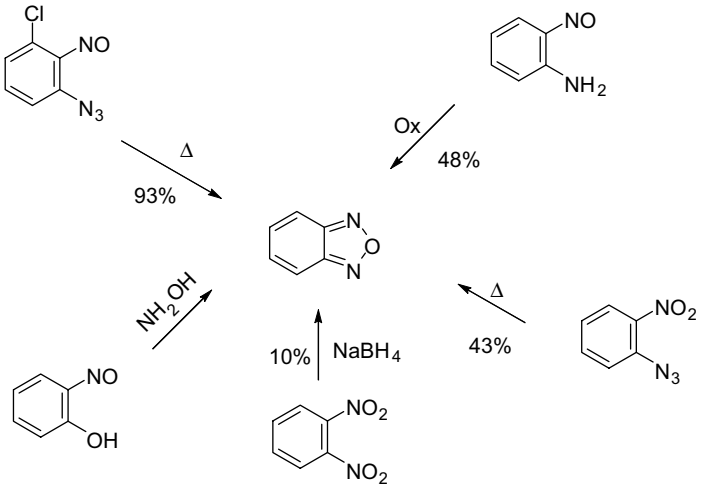
The utility of this synthetic approach is linked to the availability of dioxime precursors, which can be prepared by direct oximation of *o*-quinones or by reduction of the corresponding benzofuroxans, although, in many cases, direct deoxygenation to benzofurazans can occur.

A different widely exploited methodology starts from *o*-nitrosoarenes: thus, *o*-azido nitroso derivatives, generated from the *o*-chloro analogues, can be converted into benzofurazans by thermolysis [398], while 1-amino-2-nitrosoarene affords benzofurazan by oxidation with ferricyanide or hypochlorite, probably through an *o*-quinone dioxime intermediate. In addition, *o*-nitrosophenol heated in the presence of hydroxylamine leads to furazans, presumably by oximation of the tautomeric *o*-quinone monooxime followed by dehydration. Other approaches involve the thermolysis of *o*-nitroanilines or the reaction of *o*-dinitroarenes with sodium azide [399] and the reduction of *o*-dinitroarenes with sodium borohydride [400] (Scheme 13.152)

Moreover, benzofurazans can be synthesized by a Boulton–Katritzky rearrangement. Thus, 7-nitrosobenzofuroxan or 3-methyl-7-nitroso-2,1-benzisoxazole afford the corresponding 4-nitrofurazan [398] and 4-acetylbenzofurazan [401]. Analogously, benzofurazan is formed by photolysis of 2,1,3-benzoselenadiazole *N*-oxide. This reaction involves cleavage of the heterocyclic ring, and the extrusion of selenium followed by ring closure [402].

13.4.4.3 **Furoxans**

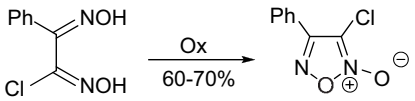
The most exploited routes towards furoxans are (i) oxidative cyclization of 1,2-dioximes, (ii) dehydration of α-nitroketoximes, and (iii) dimerization of nitrile oxides for symmetrically substituted furoxans. For unsymmetrical furoxans, the possibility



Scheme 13.152

of formation of mixtures of 2- and 5-isomers must be taken in account in choosing a suitable synthetic strategy. No data have been reported on the direct oxidation of furazans to furoxans.

13.4.4.3.1 **Oxidation of 1,2-Dioximes** The oxidation of 1,2 dioximes offers a valuable route towards furoxans. The oxidation can be carried out with *t*-butyl hypochlorite [403], lead tetraacetate, dinitrogen tetroxide [404], as well as electrochemically [405]; as an example, Scheme 13.153 shows the oxidation reaction of compound **449** to give **450**.



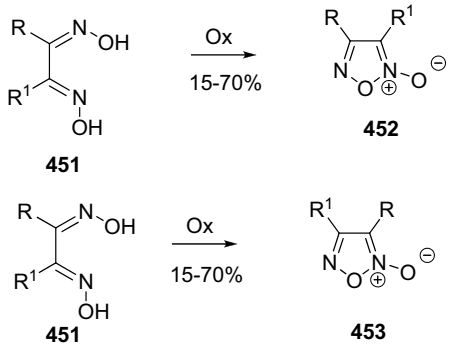
449 **450**

Scheme 13.153

Ring closure can be achieved stereospecifically, thus allowing the formation of individual isomers for asymmetrically substituted furoxans **452** and **453** (Scheme 13.154) [406].

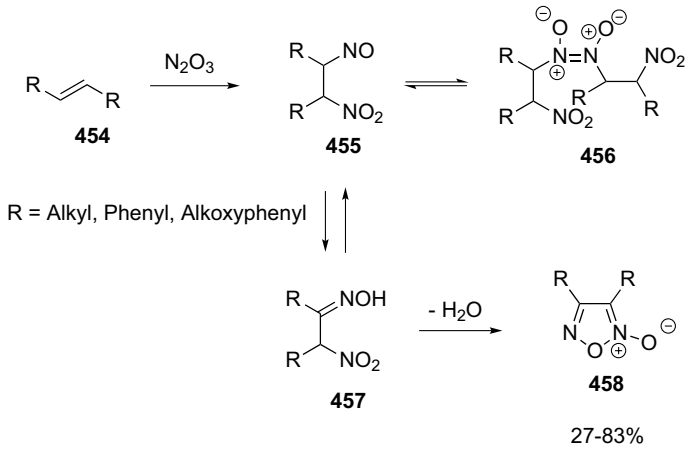
This approach is suitable for the synthesis of 1,2,5-oxadiazoles fused to other carbocyclic and heterocyclic systems [406, 407].

13.4.4.3.2 **Dehydration of α-Nitro Ketoximes** Mono- and polycyclic furoxans have been easily prepared by a synthetic strategy that starts from readily available alkenes [312, 408]. The process involves the initial reaction of alkenes **454** with



Scheme 13.154

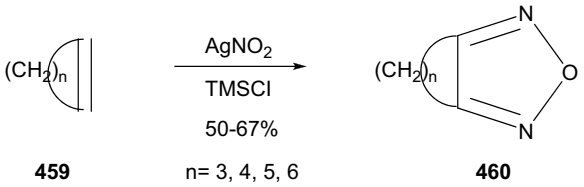
nitrogen trioxide to afford the 1-nitro-2-nitroso adduct **455** – isolable as its nitroso dimer **456** – followed by thermal isomerization to the α-nitro ketoxime tautomer **457** and dehydration with cyclization to the target furoxans **458** (Scheme 13.155).



Scheme 13.155

Mixtures of isomers are obtained from non-symmetrical alkenes. The reaction route is compatible with a wide range of functional groups; thus, nitrosation of crotonoaldehyde leads to 4-formyl-3-methylfuroxan [409] and similarly the reaction of β-nitrostyrene with N_2O_3 yields the corresponding aryl nitrofuroxan isomers [410].

Recently, it has been reported that $AgNO_2$/TSMCl reacts with olefins to afford nitrosonitrates that are then converted into furoxans in high yields (Scheme 13.156): the reaction of $AgNO_2$ with TSMCl furnishes first hexamethylsiloxane and N_2O_3

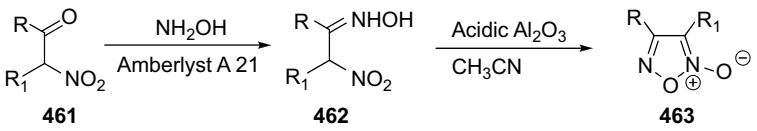


459 460

Scheme 13.156

which *in situ* add to alkenes **459** [411]. The approach has been applied to the synthesis of furoxans fused to penta-, six-, seven-, and eight-membered saturated rings **460**.

A general method for the synthesis of furoxans **463** starts from α-nitro-ketones **461** [412], by conversion into the corresponding α-nitro-ketoximes **462**, followed by treatment with acidic alumina (Scheme 13.157) [413].



461 462 463

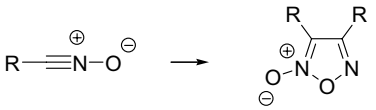
R = Et, Ph(CH2)2, i Pr
R1 = Me, Et, n-Pr

83-91%

Scheme 13.157

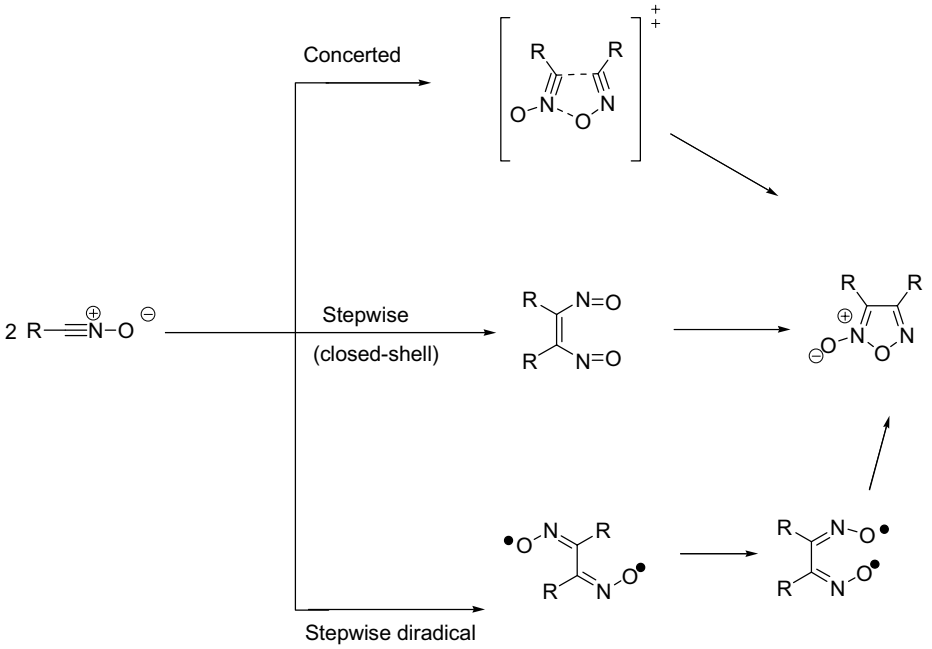
A number of symmetrically substituted dibenzoylfuroxans have been synthesized by treating substituted acetophenones with nitric acid distilled from sulfuric acid [414].

13.4.4.3.3 **Dimerization of Nitrile Oxides** Besides their characteristic and synthetically important 1,3-dipolar cycloaddition reactions, nitrile oxides undergo spontaneous [3 + 2] dimerization, usually regarded as an unwanted side reaction, which can be exploited for the preparation of furoxans (Scheme 13.158).



Scheme 13.158

Two paths have been proposed for the dimerization of nitrile oxide to furoxans, but the detailed mechanism is unknown. The most widely accepted mechanism is a concerted 1,3-dipolar cycloaddition process, where one nitrile oxide acts as a dipole, while the C−N multiple bond in the other nitrile oxide acts as a dipolarophile (Scheme 13.159) [415, 416]. A (closed-shell) stepwise mechanism, often called the carbene mechanism, has also been proposed [417–419]. In the carbene mechanism, the first step corresponds to bond formation between the carbenoid carbons of



Scheme 13.159

two nitrile oxides to form a dinitroso alkene intermediate, which then cyclizes to the furoxan.

DFT calculations performed at the B3LYP/6-31G* level on the dimerization reactions of acetonitrile oxide and *para*-chlorobenzonitrile oxide to form furoxans indicate that these processes are stepwise, involving dinitrosoalkene intermediates that have considerable diradical character (stepwise diradical mechanism in Scheme 13.159). The rate-determining steps for these two reactions correspond to C−C bond formation [420].

The retardation of dimerization in aromatic nitrile oxides arises from the interruption of conjugation between the nitrile oxide and aryl groups in the C−C bond formation step. The reluctance of aromatic nitrile oxides to dimerize with respect to aliphatic nitrile oxides is attributed to conjugative stabilization of the former. The dimerization processes in solution are slower than in the gas phase, and polar solvents retard the reaction rates.

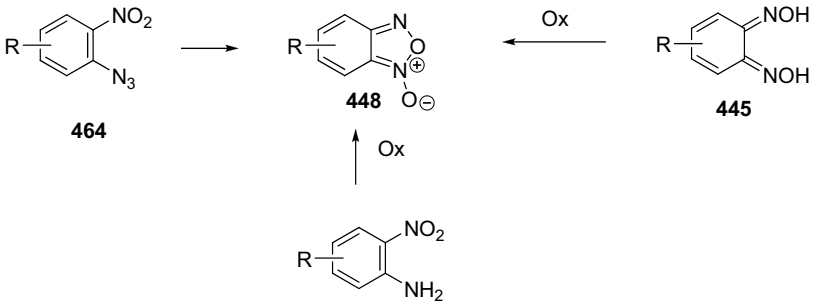
The method is not appropriate for bicyclic furoxans; a few examples of intramolecular dimerization have been reported. The bimolecular dimerization competes with the unimolecular rearrangement to the isomeric isocyanate, with the latter dominant at higher temperature. Therefore, the preparation of furoxans from nitrile oxides is carried out in concentrated solution at room temperature.

Nitrile oxides are conveniently accessible from many compounds such as oximes, hydroximoyl halides, nitromethyl compounds, alkyl esters of α-nitroalkanoic acids, and others.

The most useful methods have been widely reported in reviews and specialized books [421, 422].

13.4.4.4 **Benzofuroxans**

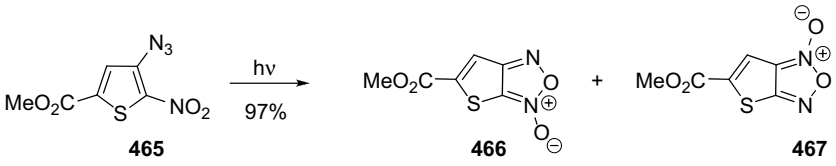
The benzofuroxan system can be constructed by suitable modification of the synthetic methods used to synthesize benzofurazans. Thus, the main routes involve the thermolysis of *o*-nitroaryl azides, the oxidation of *o*-quinone dioximes, the oxidation of *o*-nitroanilines (Scheme 13.160), and the Boulton–Katritzky rearrangement.



Scheme 13.160

The most exploited methodology for the synthesis of benzofuroxans and hetero-substituted analogues is the thermolysis or photolysis of *o*-nitroarylazides, which can be easily generated from the *o*-nitrohaloarene and sodium azide [423]. The reaction mechanism involves the intramolecular displacement of the nitrogen by the oxygen of the adjacent nitro group.

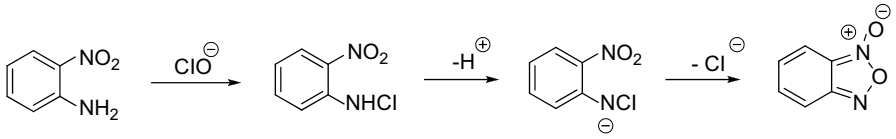
The method can be used to prepare various hetero-substituted analogues, such as thieno-, imidazo-, oxadiazolo-, thiadiazolo-, pyrido-, quinilino-, pyridazino-, and pyrimidino-derivatives. Thus, photolysis of 4-azido-5-nitrothiophene-2-carboxylic acid ester **465** gives a mixture of thieno[2,3-*c*]furoxan isomers **466** and **467** (Scheme 13.161) [424].



Scheme 13.161

In analogy with the formation of furoxans by oxidation of 1,2-dioximes, benzofurazans can be prepared by oxidation of *o*-quinone dioximes. The method is, however, limited by the availability of the starting materials.

Oxidative ring closure of *o*-nitroanilines constitutes a preferable and commonly used alternative route towards benzofuroxans [425, 426]. Alkaline hypochlorite is the most used reagent: the mechanism involves an initial N-chlorination, followed by deprotonation and loss of chloride ion (Scheme 13.162).



Scheme 13.162

13.4.5 Reactivity of the Heterocyclic Ring

The parent 1,2,5-oxadiazole, with pK_a about −5, is less basic than isoxazole ($pK_a = -2.97$). 1,2,5-Oxadiazoles are aromatic in nature and are to be considered as π-excessive heterocycles with relatively π-deficient C-atoms. Despite the electron deficiency of carbon atoms, nucleophilic substitution reactions are not common; however, when good leaving groups are present, then reactions can take place. Generally, electrophilic substitutions at the C-atoms cannot be achieved.

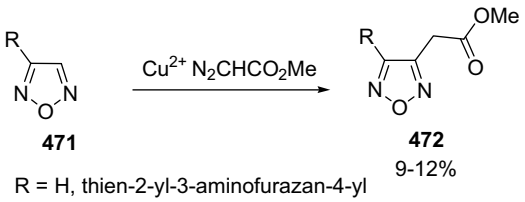
13.4.5.1 Furazans and Benzofurazans

13.4.5.1.1 Reactions with Electrophiles and Oxidizing Agents The heterocyclic ring of 1,2,5-oxadiazoles is particularly resistant to attack by electrophilic reagents; thus, halogenation, nitration, and oxidation take place at substituent groups. Electrophilic substitutions in benzofurazan and phenylfurazan occur on the aromatic ring, predominantly at the 4-position and in ortho–para positions, respectively. For example, bromination of phenylfurazan with bromine in the presence of Ag_2SO_4/H_2SO_4 gave the *p*-bromophenyl derivative in 82% yield [427].

Similar results have been obtained on nitration with fuming nitric acid, which gives 4-nitro- or 2,4-dinitro products [428, 429].

There is a single example of an electrophilic reaction at the ring carbon of furazans: insertion of methoxymethylcarbene in the C−H bond of a furazan occurred on thermolysis of furazans **471** with methyl diazoacetate in the presence of copper stearate to give the corresponding methoxycarbonylmethylfurazans **472** in 9–12% yield (Scheme 13.163) [430, 431].

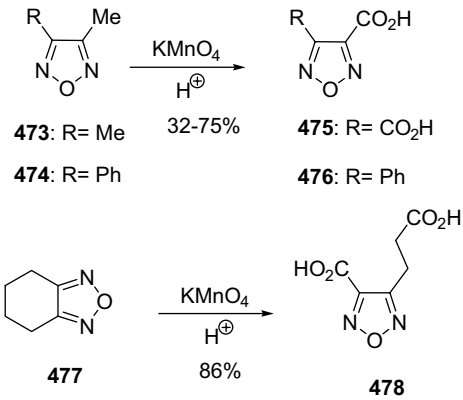
For benzofurazans and benzofuroxans the most facile electrophilic substitution is nitration, which occurs preferentially at the 4-position; a second nitro group can sometimes be inserted at C6. Other electrophiles react less readily, with nitrosation and diazo-coupling occurring only in the presence of activating groups. 5-Methylbenzofurazan reacts with bromine to give substitution at the 4-position; however,



Scheme 13.163

bromine in the presence of sun light undergoes electrophilic addition to the 4,5,6,7-tetra-adduct rather than substitution.

Direct oxidation of furazans to furoxans has not been achieved, as can be expected from the high ionization energy. For instance, oxidation of 3,4-dimethyl-1,2,5-oxadiazole (**473**) [432] and 3-methyl-4-phenylfurazan (**474**) [433] with potassium permanganate occurs at the alkyl substituents, giving rise to 1,2,5-oxadiazole-3,4-dicarboxylic acid (**475**) and 4-phenylfurazan-3-carboxylic acid (**476**), respectively. Under mild conditions, oxidation of fused furazan **477** afforded the dicarboxylic acid **478** (Scheme 13.164) [434].

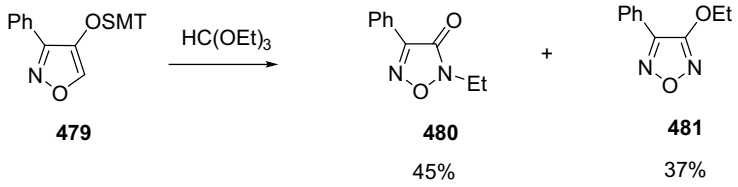


Scheme 13.164

The heterocyclic ring is also resistant to acid attack; pK_a values for protonation of methylphenylfurazan and benzofurazan are −4.9 and −8.4, respectively.

Quaternization with dimethyl sulfate in sulfolane proceeds under forcing conditions, more slowly than that of isoxazoles with iodomethane, to give the corresponding N-methylfurazinium salt [435]. N-Ethyl salts of furazan and 3-phenylfurazan have been obtained by reaction with triethyloxonium tetrafluoroborate.

The reaction of the silyloxy-furazan derivative **479** with triethyl orthoformate led to a mixture of 2-ethyl-1,2,5-oxadiazole-3(2*H*)-one (**480**) and O-ethyl compound **481** (Scheme 13.165). Compound **480** is a rare example of a tricoordinate N-substituted 1,2,5-oxadiazole [436].



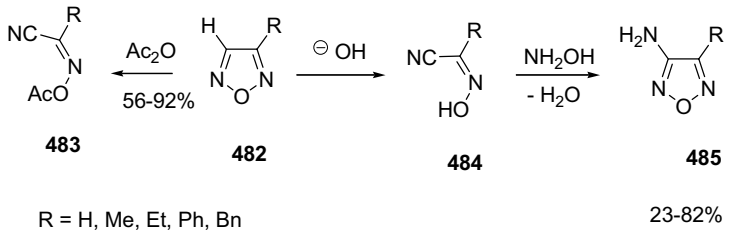
479 **480** **481**

45% 37%

Scheme 13.165

13.4.5.1.2 **Reactions with Nucleophiles and Reducing Agents** Furazans and benzofurazans are generally resistant to attack by nucleophiles. As reported in Scheme 13.134, treatment of the parent compound and monosubstituted furazans with strong bases, as NaOH in methanol, causes the ring opening to form sodium salts of α-oximinonitriles. Disubstituted furazans are comparatively inert.

Furazan ring cleavage occurs also when **482** is treated with Ac_2O at elevated temperatures to produce acylated derivatives **483** [387]. Ring opening with subsequent recyclization has been observed by nucleophilic attack of hydroxylamine on monosubstituted furazans **482**, leading to aminofurazans **485** (Scheme 13.166) [437].



483 **482** **484** **485**

R = H, Me, Et, Ph, Bn

23-82%

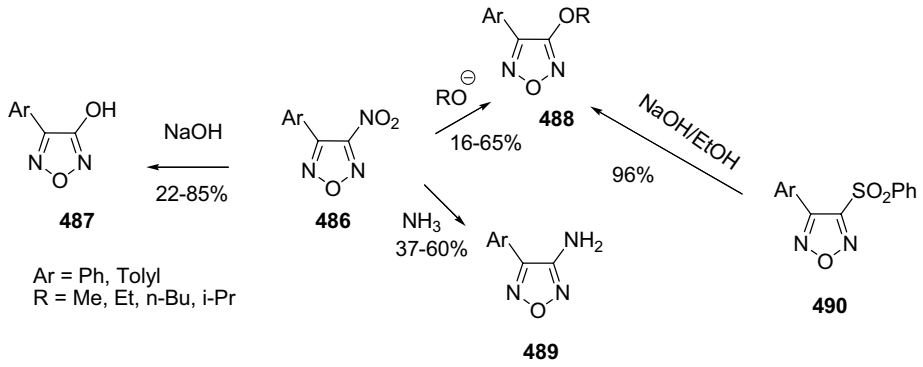
Scheme 13.166

However, when a good leaving group is present, then substitution can occur. Thus, displacement of the nitro group by a hydroxy group has been observed on heating 3-nitro-4-phenylfurazan **486** with sodium hydroxide (Scheme 13.167) [436]; displacement of nitrite or phenylsulfonyl group by alkoxy nucleophiles and by ammonia [438] has also been reported.

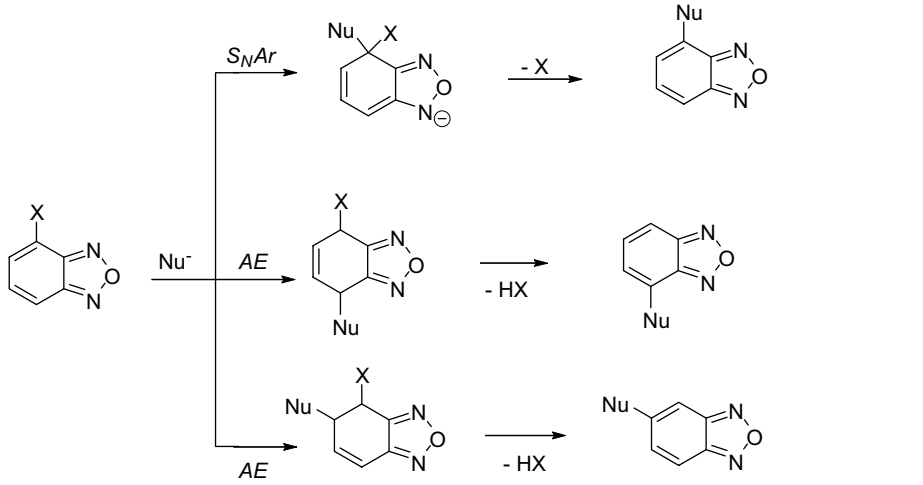
Similarly, the homocyclic ring of benzofurazans is susceptible to analogous nucleophilic substitutions. Thus, halides are displaced by various nucleophiles such as alkoxides, fenoxides, cyanide, amines, and thiolates. 4-Halogenobenzofurazans give 4- or 5-substitued products generated from normal *ipso* or *cine* reactions; the *cine* products are amenable to an addition–elimination mechanism (AE), while *ipso* substitution can result from both *AE* and S_NAr (Scheme 13.168) [439].

However, substitution reaction on the homocyclic ring can take place even in the absence of a leaving group: benzofurazan has been converted into its 4-formyl derivative by treatment with LDA in DMF.

The furazan ring is susceptible to reduction. Thus, benzofurazans give 1,2-diaminoarenes by treatment with tin and hydrochloric acid, while catalytic reduction



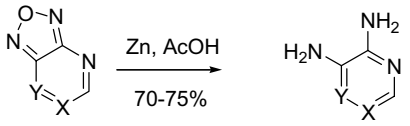
Scheme 13.167



Scheme 13.168

takes place at the homocyclic ring to afford tetramethylenefurazans. 1,2-Diamines are also formed by reduction of furazans with sodium borohydride, whereas $LiAlH_4$ causes fragmentation of the C3—C4 bond, yielding primary amines as final products. Treatment with phosphites results in both fragmentation and deoxygenation to nitriles. Zinc and acetic acid can lead to a selective reduction of the oxadiazolo moiety in the presence of other heterocyclic systems: furazano[3,4-*d*]pyrimidines **491** and furazano[3,4-*e*]pyrazines **492** have been converted into the corresponding *o*-amino compounds (Scheme 13.169) [440].

4,6-Dinitrobenzofurazan, which is strongly electrophilic, undergoes facile σ-complexation with weak nucleophiles to form stable Meisenheimer complexes (Section 13.4.5.3).



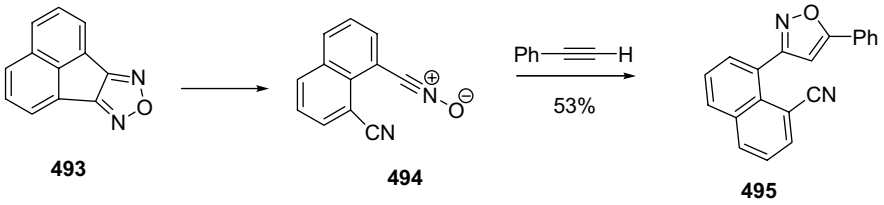
491: X= N, Y=CH

492: X= CH, Y=N

Scheme 13.169

13.4.5.1.3 **Thermal and Photochemical Ring Cleavage** Thermolysis and photolysis of 1,2,5-oxadiazoles proceeds by cleavage of the O1−N2 and C3−C4 bonds to give nitrile and nitrile oxides, together with products derived therefrom.

The thermal process requires temperatures above 200 °C, except for ring-strained derivatives, where less drastic conditions are needed. Thus, diphenylfurazan decomposes at 250 °C to give benzonitrile, phenyl isocyanate, and 3,5-diphenyl-1,2.4-oxadiazole, with the latter two products arising from the rearrangement and 1,3-dipolar cycloaddition with benzonitrile of the initially formed benzonitrile oxide. In contrast, the ring-strained acenaphthofurazan **493** fragments at 120–150 °C to produce the transient **494**, which in the presence of phenylacetylene gives **495** in 53% yield (Scheme 13.170) [441].



493 **494** **495**

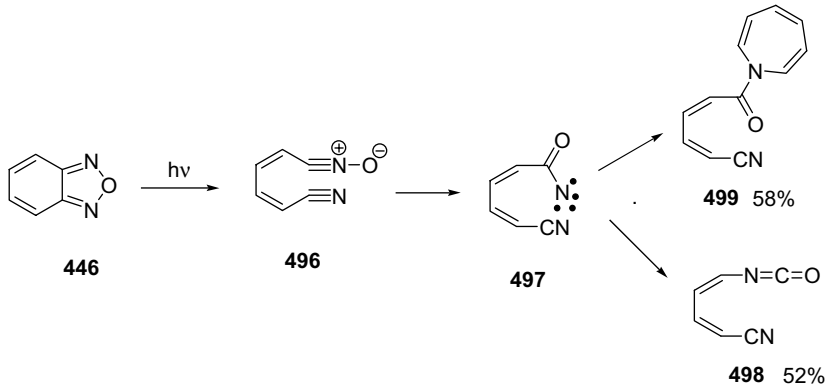
Scheme 13.170

The kinetics of the gas-phase thermolysis of several furazans to phenyl isocyanate and 3,5-diphenyl-1,2.4-oxadiazole have also been examined [442], and a biradical mechanism has been proposed.

Benzofurazans, which are thermally more stable, may be cleaved photochemically. For example, benzofurazan **446** in benzene affords cyanoisocyanate **498** and azepine **499** (Scheme 13.171). Compound **499** probably originates from the reaction of the solvent with the acylnitrene intermediate **497** [443].

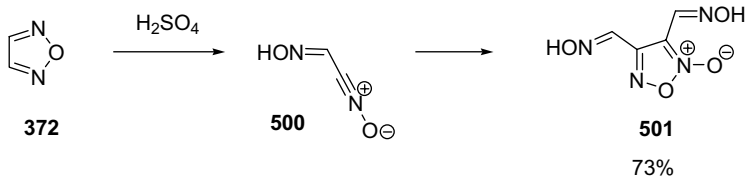
13.4.5.2 Furoxans and Benzofuroxans

13.4.5.2.1 **Reactions with Electrophiles and Oxidizing Agents** As reported for furazans, the furoxan nucleus shows low reactivity towards electrophiles; reactions occur at the substituents or at the homocyclic ring of benzofuroxans [444]. Reaction with acids is also slow: benzofuroxans have pK_a values of about −8, similar to those of



Scheme 13.171

benzofurazans. Treatment of the parent furoxan **372** with concentrated H_2SO_4 proceeds with ring-cleavage to (hydroxyimino)acetonitrile oxide **500**, followed by dimerization to bis(hydroxyiminomethyl)furoxan **501** in nearly quantitative yield (Scheme 13.172) [375].



Scheme 13.172

Quaternization is difficult for all furoxans: benzofuroxan does not react with triethyloxonium tetrafluoroborate.

The heterocyclic ring of furazans is also resistant to attack by oxidizing agents, with reactions occurring preferentially at the substituents groups. However, benzofuroxan is oxidized by persulfuric or trifluoroperacetic acid to 1,2-dinitrobenzene, while the 4,6-dinitro compound affords the 1,2,3,4-tetranitrobenzene [445].

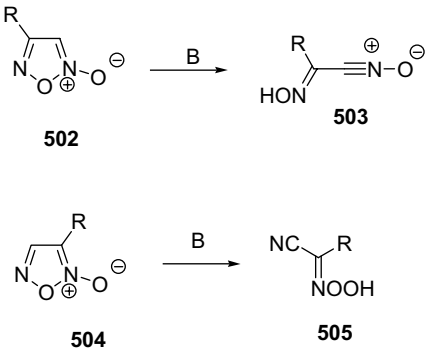
13.4.5.2.2 **Reaction with Nucleophiles and Reducing Agents** The reactivity of furoxans with nucleophiles and reducing agents is good. In fact, Grignard reagents react with disubstituted furoxans, primarily at C3, leading to nitrile and nitronate fragments, which, in the presence of an excess of Grignard reagent, yield the corresponding ketones. Monosubstituted furoxans give glyoximes.

Nucleophilic substitution of substituents at C3 and C4 is an easy and valuable pathway towards the synthesis of a wide series of derivatives. The nitro group in particular is readily displaced by numerous nucleophiles such as amines, alkoxides, thiols, azide, halides, and sulfonyl groups [375, 446]. In the benzofuroxans series, nucleophilic reactions take place preferentially at the homocyclic ring; the reactivity is

enhanced by the presence of nitro groups [447]. Numerous biologically interesting applications of this kind of reaction have recently appeared in the literature (Section 13.4.6).

In the absence of a good leaving group, nucleophilic attack occurs at N5 of the oxadiazole ring: in this case, the reaction with secondary amines proceeds via ring opening to furnish *o*-nitroarylhydrazines. However, a substitution reaction on the homocyclic ring can take place even in the absence of a leaving group: with 4-nitrobenzofuroxan, carbanions of the form RSO_2ClCH^- cause the displacement of the hydrogen at C5 and at C7 [448].

All monosubstituted furoxans are quite sensitive to bases, which causes ring-opening reactions, with the formation of nitrile oxides **503** from 4-substituted furoxans **502** and *aci*-nitro compounds **505** from 3-substituted furoxans **504** (Scheme 13.173) [313].



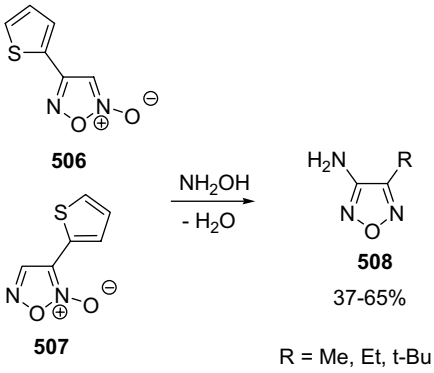
Scheme 13.173

Base attack is favored at the position adjacent to the more highly electron-withdrawing substituent.

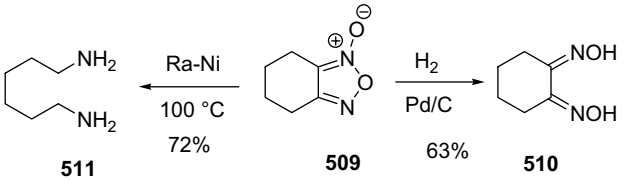
Ring opening with subsequent recyclization has been observed by nucleophilic attack of hydroxylamine in aqueous KOH on 3-thien-2-yl and 4-thien-2-yl furoxans (**506**, **507**), leading to aminofurazans **508** (Scheme 13.174) [449].

Furoxans and benzofuroxans can be reduced by various reagents to yield furazans α-dioximes, 1,2-diamines, and nitriles, according to the experimental conditions. Catalytic hydrogenation usually leads to dioximes, but, under forcing conditions, ring cleavage at C3−C4 and N1−O2 can occur. For example, tetramethylenefuroxane **509** affords cyclohexane-1,2-dione dioxime (**510**) by treatment with H_2 and Pd/C at room temperature, while the use of Raney nickel at 100 °C leads to 1,6-diaminohexane (**511**) (Scheme 13.175).

$NaBH_4$ behaves in a similar way, while $LiAlH_4$ reduction is accompanied by ring cleavage to give primary amine fragments. Benzofuroxans are reduced to *o*-nitroaniline derivatives by ferrous salts [450] and to *o*-phenylenediamines by ammonium sulfate–sodium borohydride [451].



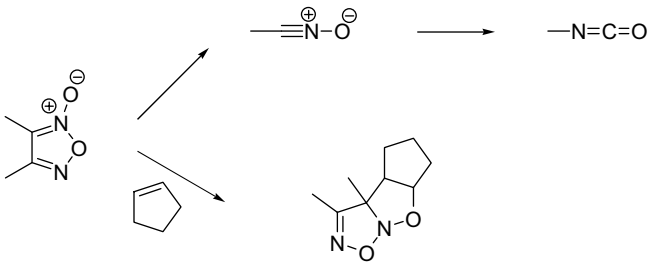
Scheme 13.174



Scheme 13.175

Reduction with tervalent phosphorus compounds, such as trialkyl and triaryl phosphites and phosphines, causes deoxygenation of furoxans and benzofuroxans to give furazans and benzofurazans, respectively, leaving the heterocycle intact.

13.4.5.2.3 **Thermal and Photochemical Ring Cleavage** Monocyclic furoxans undergo by thermolysis ring cleavage at the O1−N2 and C3−C4 bonds to give two nitrile oxides fragments, in a formal retro 1,3-dipolar cycloaddition reaction. In the presence of a dipolarophile, the nitrile oxide can be trapped as its 1,3-dipolar cycloadduct; otherwise, the nitrile oxide rearranges to the isomeric isocyanate (Scheme 13.176).

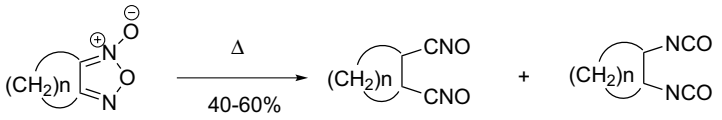


Scheme 13.176

Under flash vacuum pyrolysis conditions, the nitrile oxides can be isolated [452a].

Bicyclic furoxans afford bisnitrile oxides and diisocyanates. The process is sensitive to the ring strain: for decamethylenefuroxan **513** a temperature above 200 °C is required, while the trimethylene analog **512** reacts at 80–100 °C (Scheme 13.177) [452b,c].

In general, benzofuroxans are much less susceptible to decomposition.



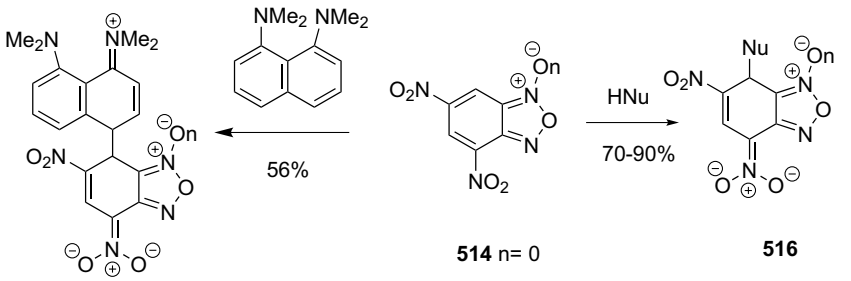
512 n= 3

513 n= 10

Scheme 13.177

13.4.5.3 Meisenheimer Complex Formation

4,6-Dinitro compounds **513** and **514** are strongly electrophilic and form stable Meisenheimer complexes when treated even with weak nucleophiles under mild conditions. In particular, **514** is regarded as a super-electrophile – more powerful than 1,3,5-trinitrobenzene. Thus, **514** reacts with methanol, enols, phenols, anilines, thiophenes, pyrroles and indoles, and nitroalkanes to form, in the absence of base, stable C-bonded σ-adducts **516**. Moreover, the electrophilic character of **515** is also confirmed by its reaction with 1,8-bis(dimethylamino)naphthalene, the so-called "proton sponge," yielding carbon-linked compound **517** (Scheme 13.178) [453].



514 n= 0

515 n= 1

516

517

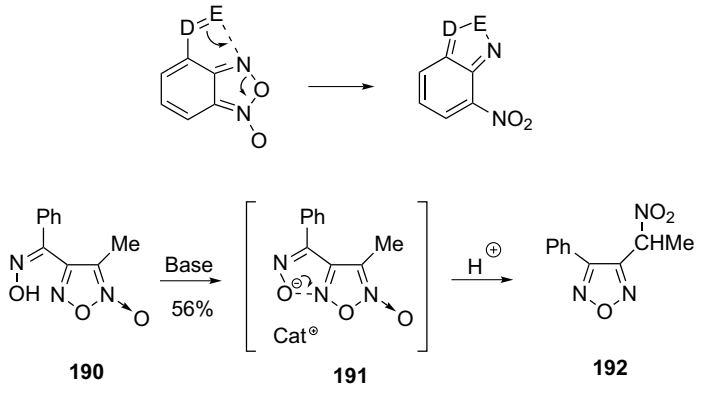
Scheme 13.178

13.4.5.4 Heterocyclic Ring Rearrangements of Furoxans and Benzofuroxans

Furoxans have been extensively used as starting material for synthetic conversions into various other heterocyclic systems, some of which show interesting biological activity. The Boulton–Katritzky rearrangement is the most exploited reaction route, affording an easy entry towards isoxazoles, pyrazoles, and furazans. Other conversion reactions give access to isoxazolines, quinaxoline, and benzimidazole *N*-oxides.

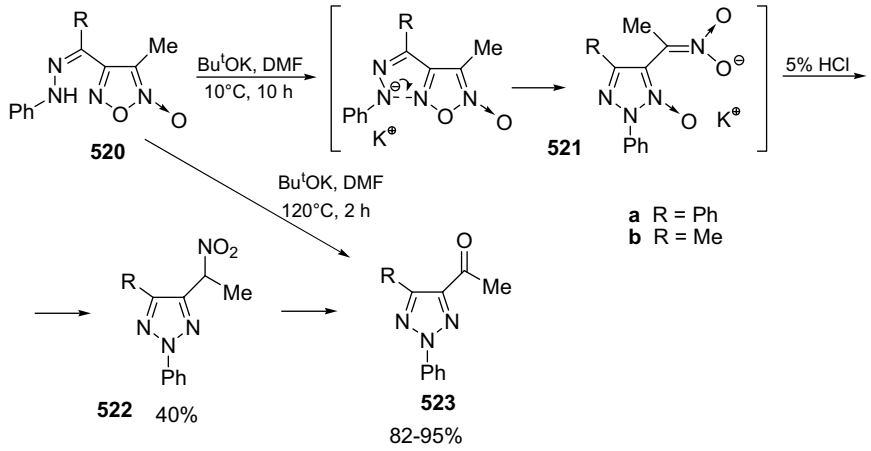
13.4.5.5 **Rearrangements of Furoxans**

The Boulton–Katritzky rearrangement [342, 393] of non-condensed furoxan derivatives has been reported for oximes of 4-furoxanylcarbonyl compounds [454]; in particular, the base-catalyzed rearrangement of the *(Z)*-isomer of 4-benzoyl-3-methylfuroxan oxime (**518**) leads to 3-(1-nitroethyl)-4-phenyl-1,2,5-oxadiazole **519** (Scheme 13.179).



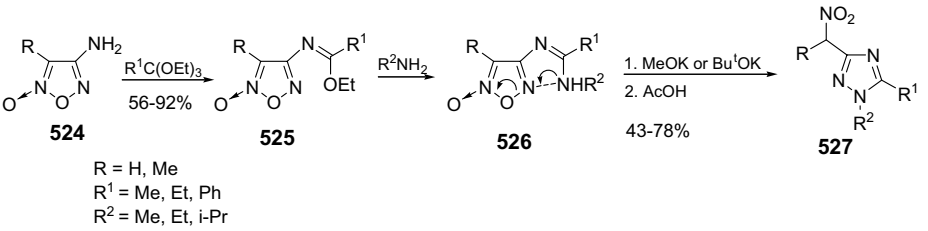
Scheme 13.179

Other variants of rearrangement of monocyclic furoxans have been performed for derivatives involving different side chains: C-N-N (phenylhydrazones), N-C-N (amidines), and N-C-S (thioureides) [455]. Thus, treatment of *(Z)*-isomers of phenylhydrazones **520** with Bu^{t}OK and heating yielded 1,2,3-triazoles **523**, formed with a Nef-type [456] reaction via 5-(1-nitroethyl)-1,2,3-triazole **522** intermediate (Scheme 13.180).



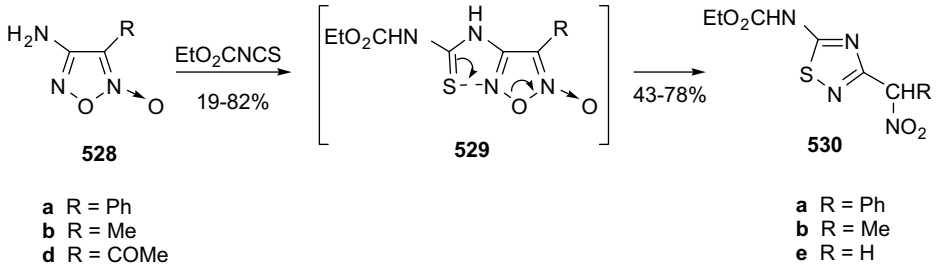
Scheme 13.180

Analogously, the rearrangement of 3-aryl(alkyl)-1-(3-R-furoxan-4-yl)amidines **526** – synthesized by reaction of aminofuroxans **524** with triethyl orthoformate or triethyl orthoacetate, followed by the action of various amines on the resulting iminoethers **525** – afforded the 1,5-disubstituted 3-[1-nitroethyl(benzyl)]1,2,4-triazoles **527** (Scheme 13.181) [455].



Scheme 13.181

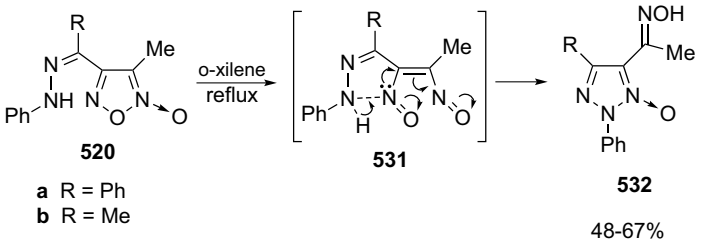
5-Ethoxycarbonylamino-3-(1-nitroalkyl)-1,2,4-thiadiazole derivatives **530** have been obtained by refluxing a mixture of aminofuroxans and ethoxycarbonyl isothiocyanate in various solvents: the reaction proceeds through a not-isolated 4-(3-ethoxycarbonylthioureido)-3-substituted-furoxan intermediate (**529**) (Scheme 13.182) [456].



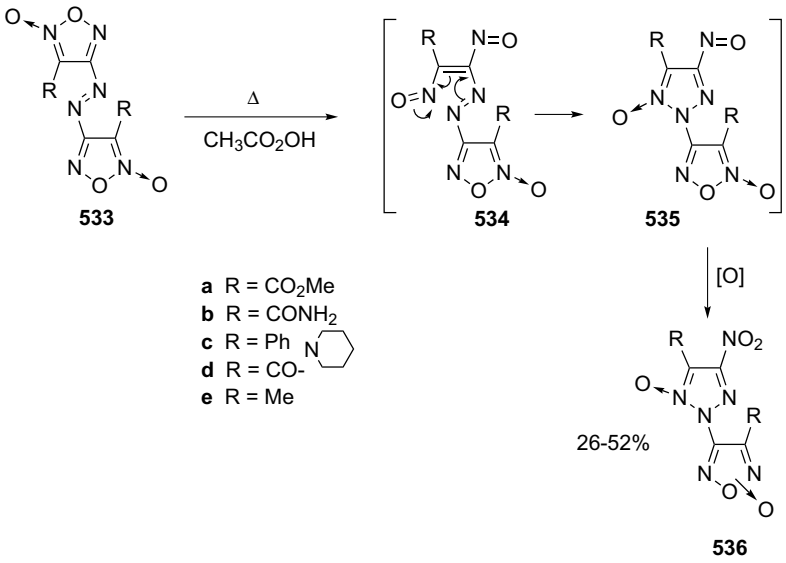
Scheme 13.182

A different kind of rearrangement has been described that proceeds through a dinitrosoethylene intermediate. In particular *(Z)*-isomers of 4-benzoyl or 4-acetyl-3-methylfuroxan phenylhydrazones **520**, thermally or in the presence of various bases, give oximes of 5-acetyl-4-phenyl(methyl)-2-phenyl-2*H*-1,2,3-triazole 1-oxide **532** (Scheme 13.183) [457]. It has been suggested that the reaction starts with rupture of the O1–N2 bond in the furoxan ring, which results in formation of dinitrosoethylene intermediates **531**, followed by the reaction of one nitroso group with the phenylhydrazone moiety and transformation of the second nitroso group into the oxime group.

Another example of this rearrangement is represented by the thermally induced transformation of 3,3′-disubstituted-4,4′-azofuroxans **533** in an oxidizing medium into triazole 1-oxide derivatives **536** (Scheme 13.184) [458].

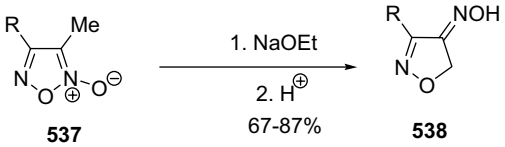


Scheme 13.183



Scheme 13.184

Furoxans **537** bearing a methyl group at C3 give hydroximino derivatives of isoxazolines **538** on treatment with alkoxides or alcoholic alkali hydroxides (the so-called isoxazoline transposition or Angeli rearrangement) (Scheme 13.185) [459].

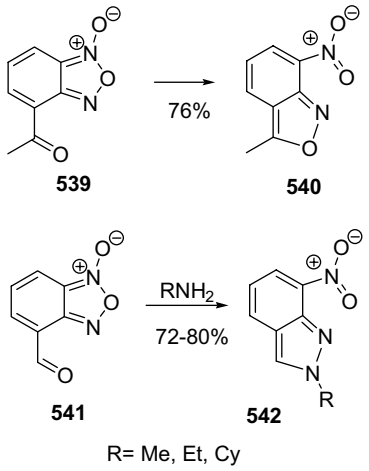


R = Ph, $PhCH_2$, Cl-C_6H_4, MeO-C_6H_4

Scheme 13.185

13.4.5.6 Rearrangements of Benzofuroxans

The Boulton–Katritzky rearrangement of benzofuroxans bearing at the 4-position a ring-conjugated side chain has been studied in detail from both a synthetic and mechanistic point of view [342, 370, 393, 460–465]. As a rule, rearrangements are initiated thermally, photochemically or in the presence of bases; the first example of acid catalysis has been published [466]. Several types of unsaturations can constitute the X = Y group, such as C=O, N=N, C=N, and N=N, so allowing the construction of a series of new heterocyclic systems. Thus, 4-acetylbenzofuraxan **539** rearranges spontaneously to 3-methyl-7-nitrobenzo[*c*]isoxazole **540**, while nitroindazoles **542** are formed from 4-formylbenzofurazan **541** and primary amines (Scheme 13.186).

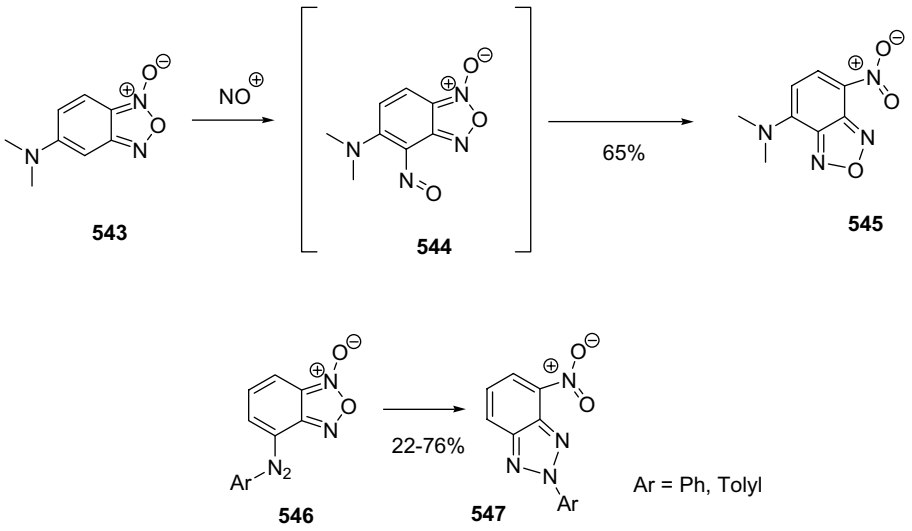


Scheme 13.186

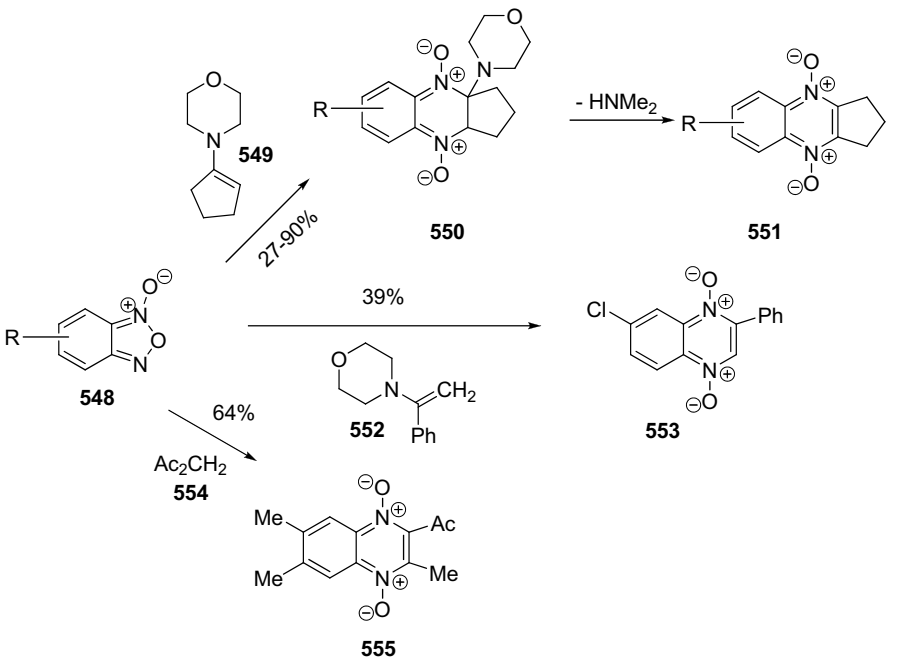
Analogously, nitrosation of 5-(dimethylamino)benzofuroxan (**543**) affords 4-(dimethylamino)-7-nitrobenzofurazan (**545**) through the rearrangement of the intermediate 4-nitroso compound **544**. Similar behavior has been observed for 4-arylazobenzofuroxans **546** yielding 4-nitrobenzo-1,2,3-triazoles **547** (Scheme 13.187).

Quinoxaline-1,4-dioxides **551**, **553**, and **555** are readily obtained from the reaction of benzofurazans with enamines or carbonyl compounds in the presence of ammonia or amines (Beirut reaction) (Scheme 13.188) [467]. In the absence of the α-hydrogen required for the elimination, the 2,3-dihydroquinoxaline intermediate **550** can be isolated. Enolates derived from β-diketones react in an analogous way, affording 2-acylquinoxalines [468].

This process formally involves the insertion of a two-carbon fragment between the N−O groups of the furoxan (Scheme 13.188). Various quinoxalines are endowed with interesting biological activity: this feature has considerably extended the scope of this reaction. In the same context, the reaction also gives ready access to polycyclic compounds: for example, phenazine derivatives result from benzofuroxans and phenolates, *p*-benzoquinone, or hydroquinone [312, 469].



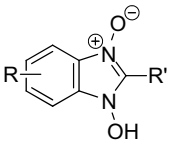
Scheme 13.187



R = H, 5(6)Cl, 4,7-Cl_2, 5,6-Cl_2, 4(7)-Me, 5(6)Me, 5,6-Me_2, 5(6)-CF_3, 4(7)-MeO, 5(6)-MeO, 5(6)-Ac

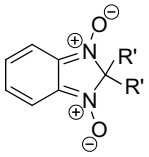
Scheme 13.188

Benzimidazole oxides, in 25–90% yields, are also accessible from benzofuroxans. The reaction with primary nitroalkanes leads to 2-substituted-1-hydroxybenzimidazole-3-oxides **556** via displacement of the NO_2 group; similarly, the nitrile group of α-cyanoacetamides is removed with formation of 2-amide derivatives **557** ($R' = CONR_2$). Secondary nitroalkyl compounds afford 2,2-disubstituted-2*H*-benzimidazole-1,3-dioxides **558**.



556 : R' = Alkyl

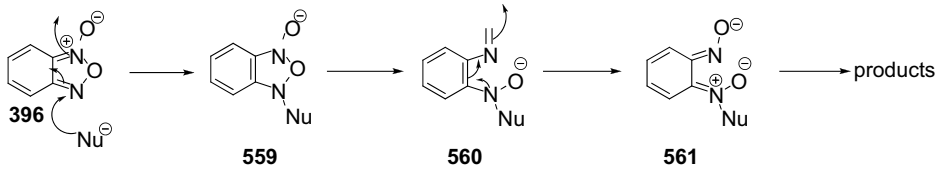
557 : R' = $CONR_2$



558

Benzimidazoles are also obtained from the reaction of benzofuroxans with phosphorus ylides [470], nitrones [471], and diazo compounds [472].

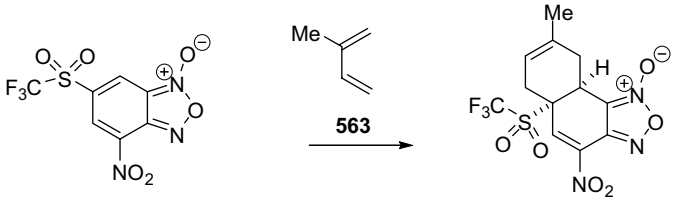
A mechanism has been suggested that involves the nucleophilic attack at N3 of the benzofuroxan **396** (or at one of the nitroso groups of the *o*-dinitroso tautomer), followed by cleavage of the O2–N3 bond to give the di-N-oxide **561**, with subsequent cyclization to five- or six-membered ring products, according to the nature of the nucleophile (Scheme 13.189).



Scheme 13.189

13.4.5.7 Cycloaddition Reactions of Benzofuroxans

The double bonds at the 4,5- and 6,7-positions in benzofuroxans are sufficiently localized and activated to undergo [3 + 2] and [4 + 2] cycloaddition reactions. Thus, isoprene (**563**) gives in 80% yield the 1:1 Diels–Alder adduct **562** with 4-nitro-6-trifluoromethansulfonylbenzofuroxan (**564**) (Scheme 13.190) [473].

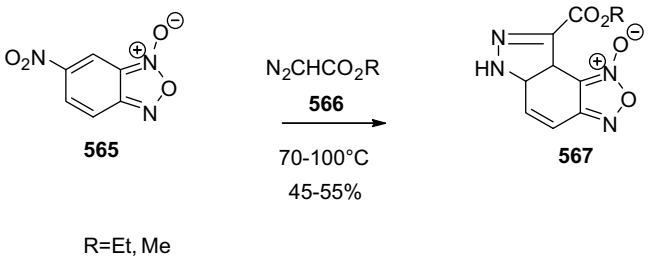


564

562

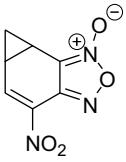
Scheme 13.190

Similarly, alkyl diazoacetates **566** afford pyrazolo derivatives **567** by reaction with 6-nitrobenzofuroxan (**565**) (Scheme 13.191) [474].



Scheme 13.191

Mesitonitrile oxide gives mixtures of 1 : 1 and 2 : 1 adducts [475], and diazomethane reacts at C5—C6 of 4-nitrobenzofuroxan to give the 5-6-cyclopropa-fused derivative **568**, probably by loss of nitrogen from the initial pyrazoline cycloadduct [476].



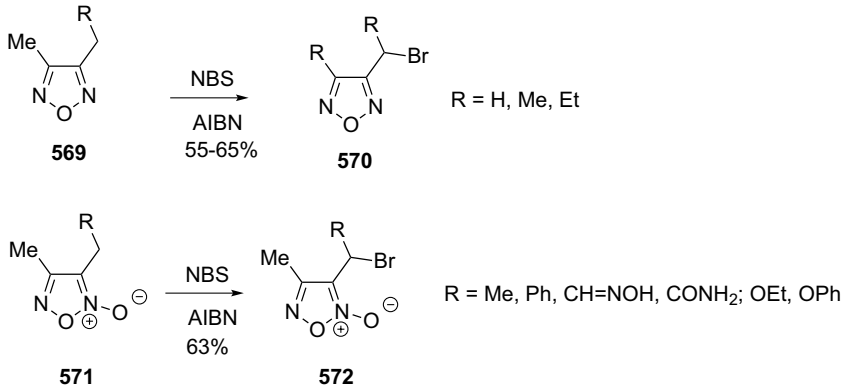
568

13.4.5.8 **Alkyl and Aryl Furazans and Furoxans**

Reactions of aryl furazans and furoxans have been studied in detail. The heterocyclic ring exerts an *ortho–para*-directing influence with the predominant formation of *para* products. For example, nitration or chlorosulfonation of phenylfurazan and phenylfuroxan take place at the phenyl group, at the 4′-position, leaving the heterocycle intact. In benzofurazans and benzofuroxans, electrophilic attack occurs, as previously reported (Section 13.4.5.1.1), at the 4-position; a second group can be sometimes inserted at the 6-position.

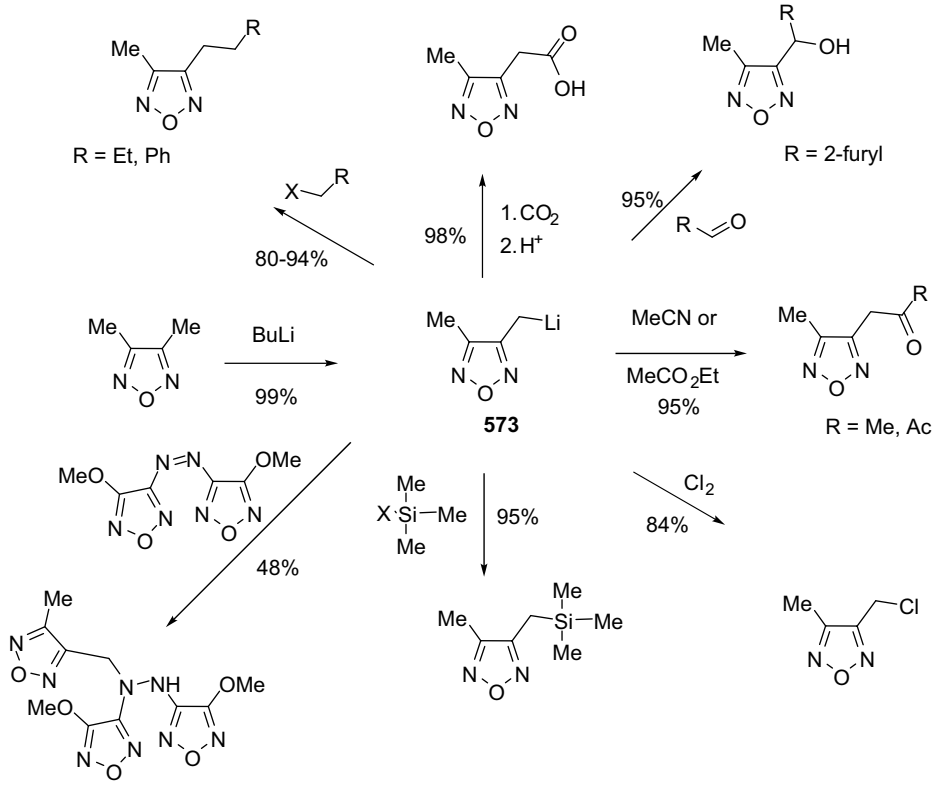
Alkyl groups on the furazan or furoxan ring can undergo functional transformations that depend on the electron-withdrawing properties of the rings. Treatment of alkylfurozans **569** with NBS in the presence of BPO or AIBN gives α-bromoalkyl derivatives **570** (Scheme 13.192) [477]. Similar results were obtained with 3-methylfuroxans **571** [478].

These α-haloyl derivatives are excellent starting materials for side-chain substituted furazans and furoxans through classical nucleophilic substitution reactions. The halogen atom is readily displaced by a wide range of oxygen, sulfur, nitrogen, phosphorus, and carbon nucleophiles to give the corresponding products in good yields [477–483].



Scheme 13.192

α-Metalation offers an alternative approach to functionalization of the methyl compounds. 3,4-Dimethylfurazan readily undergoes lithiation by treatment with *n*-butyllithium: the lithiated intermediate **573** reacts with electrophiles at –55°C to give various α-functionalized alkylfurazans (Scheme 13.193) [484–486]. The electrophile



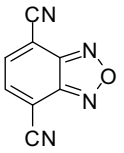
Scheme 13.193

can be an alkyl halide, a chlorosilane, a carbonyl compound, a nitrile, or an ester, an azo compound, and chlorine.

A similar procedure using two equivalents of BuLi and two equivalents of the electrophile offers access to α,α′-difunctionalized derivatives.

13.4.6
Furazans, Furoxans, and Benzo-Related Compounds in Medicine

Furazans, benzofurazans, and in particular furoxans and benzofuroxans are very important bioactive compounds. They have shown anti-microbial, anti-parasitic, anti-viral; mutagenic, anticancer and immunosuppressive, anti-aggregating, and vasorelaxant activity. Moreover, compounds containing the furoxan or benzofuroxan moiety inserted in a classical active principle have produced hybrid compounds that have been used, very recently, as new anti-ulcer drugs, calcium channel modulators, and vasodilatators. Several furoxan and furazan derivatives have been evaluated as antibacterial (Gram-negative and Gram-positive), antiprotozoal (*Trichomonas vaginalis* and *Entamoeba histolytica*), and antifungal compounds. 4,7-Dicyanobenzofurazan (**574**) presents a bacteriostatic effect in *Escherichia coli*, due to inactivation of 2,3-dihydroisovalerate [487]. 3-Nitro-4-phenylfuroxan (**575**) and its tautomer **576** displayed anti-infective properties, but with mutagenic activity; 3-bromo-4-phenylfuroxan (**577**) shows strong antimicrobial activity [488].



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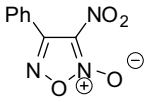

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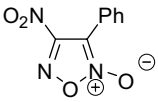

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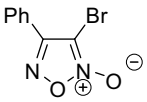
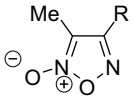


577

Furoxans and benzofuroxan **578–580** have been reported to inhibit *in vitro* the growth of *Trypanosoma cruzi*, the etiologic agent of Trypanosomiasis americana, the so-called Chagas' disease, and their activity is in the order **580** > **579** > **578**.



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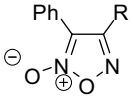

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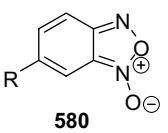
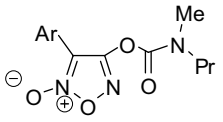


580

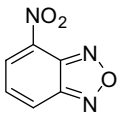
R = CH=NNHCONH-butyl

Anti HIV-1 reverse transcriptase activity has been described for compounds **581** and **582**. In particular, compound **582** has shown the best anti-viral activity with a selectivity index (ratio of cytotoxic concentration to effective concentration) ranked in the order of **582** > **581**.



581 Ar = Ph
582 Ar = 2,6-di-Cl-Ph

4-Nitro (**583**), 4-thio (**585**) or 4-phenoxy- (**587**) benzofurazans and 4-nitro- (**584**), 7-thio (**586**) or 7-phenoxy (**588**) benzofuroxans present optimal drug activity as inhibitors of RNA synthesis in sheep lymphocytes [489].



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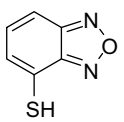

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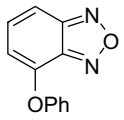

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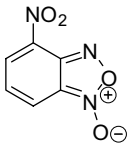

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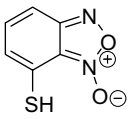

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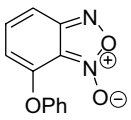
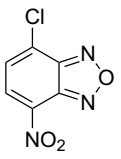


588

Since the first report indicating that some nitrobenzofurazans displayed anti-leukemic properties, numerous 7-nitro-2,1,3-benzoxadiazole derivatives have been evaluated as anticancer agents. In particular, 7-nitro-2,1,3-benzoxadiazoles such as **589** [R_1 = alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, etc.; X = O, S] have been prepared recently and used as agents able to inhibit glutathione S-transferase (GST). These compounds are useful in the production of pharmaceutical drugs to be used in anticancer therapy, and may be employed either alone or in combination with other chemotherapeutic agents. Thus, 4-[(7-nitro-2,1,3-benzoxadiazol-4-yl)sulfanyl]butanol **590**, prepared by reacting 4-chloro-7-nitro-2,1,3-benzoxadiazole with 4-mercapto-1-butanol in EtOH and potassium phosphate buffer, has shown a relevant activity against different cancer cell lines, such as K562 human myeloid leukemia, HepG2 human hepatic carcinoma, CEM1.3 human T-lymphoblastic leukemia, and GLC-4 human small cell lung carcinoma [490].



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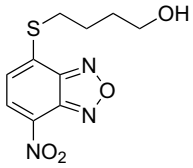
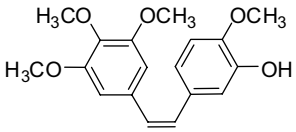
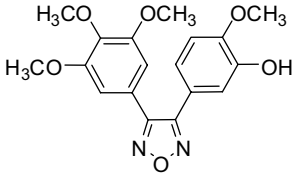


590

Combretafurazan (**592**), obtained from combretastatin A-4 (**591**), an antitumoral and antitubulin agent that is active only in its cis configuration, has shown to be a potent *in vitro* cytotoxic compound compared to combretastatin in neuroblastoma cells, while maintaining a similar structure–activity relationship and pharmacodynamic profiles [492].

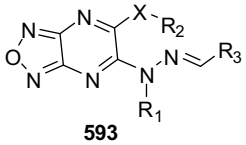


Combrestatin A-4 **(591)**



Combretafurazan **(592)**

Recently, another class of furazans, and in particular the furazano[3,4-*b*]pyrazines **593** have been prepared and used as antitumoral agents. Their activity is not limited to sarcomas, melanomas, neuroblastomas, carcinomas (including but not limited to lung, renal cell, ovarian, liver, bladder, and pancreatic carcinomas), and mesotheliomas. Moreover, specific assays, conduced for compound **594**, have demonstrated that it exhibited an IC_{50} of 0.00834 nM against sarcoma tumors [492].



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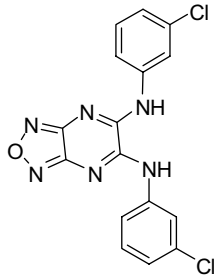


594

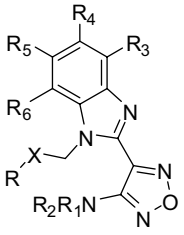
X = O, S, NH

R_1 = H, Alkyl

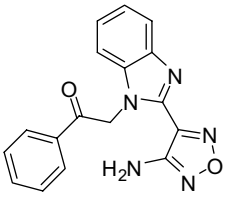
R_2 = H, Aryl, Heteroaryl, alkyl

R_3 = H, Ary, Heteroaryl, alkyl

Some furazanobenzimidazoles **595** (R = aryl, haloaryl, etc.; R_1, R_2 = H, alkyl, cycloalkyl, etc.; R_3, R_4, R_5, R_6 = H, alkyl, haloalkyl, cycloalkyl, etc.; X = O, C:Y; Y = O, NOH, etc.) and their salts have been synthesized as apoptosis inducers for the treatment of neoplastic and autoimmune diseases. In particular, compound **596** exhibits a strong apoptotic activity in the Hoechst 33342 nuclear staining assay [493].

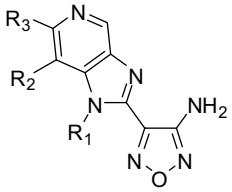


595



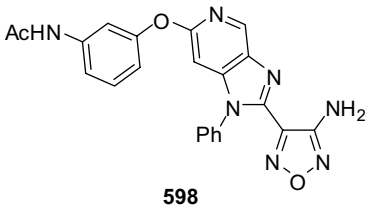
596

It has also been found that azabenzimidazoles **597** – in which R_1 is H or C_{1-6} alkyl; R_2 is halo or optionally substituted Ph, heteroaryl, or carboxamide; R_3 is halo, (un) substituted C_{1-6} alkoxy, (un)substituted phenoxy, heteroaryloxy, or heterocyclyloxy – are inhibitors of Rho-kinases. Rho-kinase is implicated in the phosphorylation of myosin light chain downstream of Rho, which is thought to induce smooth muscle contraction and stress fiber formation in non-muscle cells [494].



597

Moreover, compound **598** is useful for the treatment of diseases such as hypertension, heart failure, and ischemic angina [495].



598

Many other furoxans and furazans have been synthesized to improve their cytotoxic activity; their biological assays have established that the furazan analogues are, usually, less active than the corresponding furoxans. These results indicate the relevance of N-oxide in terms of the bio-response.

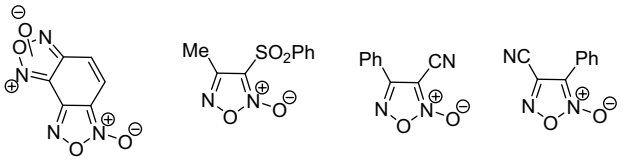
One of the most interesting pharmacological properties of furoxans and benzofuroxans is the nitric oxide (NO) releasing capacity. NO displays diverse potent physiological actions. As regards the cardiovascular system, it plays a crucial role in vascular homeostasis through several mechanisms, including vasodilation, inhibition of platelet aggregation, and modulation of platelet and leukocyte adherence. In the central nervous system, it plays roles in learning and memory formation. In the peripheral nervous system, it regulates several gastrointestinal, genitourinay, and respiratory functions as neurotransmitter at the endings of nonadrenergic, noncholinergic nerves. NO is also potentially toxic and can induce genomic alterations.

Figure 13.5 gives some examples of these drugs.

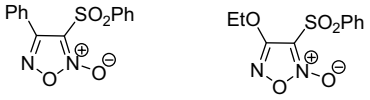
13.5
1,3,4-Oxadiazoles

1,3,4-Oxadiazole (**599**) is a partially aromatic and thermally stable molecule [496]. Exocyclic-conjugated mesoionic 1,3,4-oxadiazoles (**600**), 1,3,4-oxadiazolium cations

Vasodilating agents:



Human platelet-SGS activators:



Hybrid Antiulcer agents:

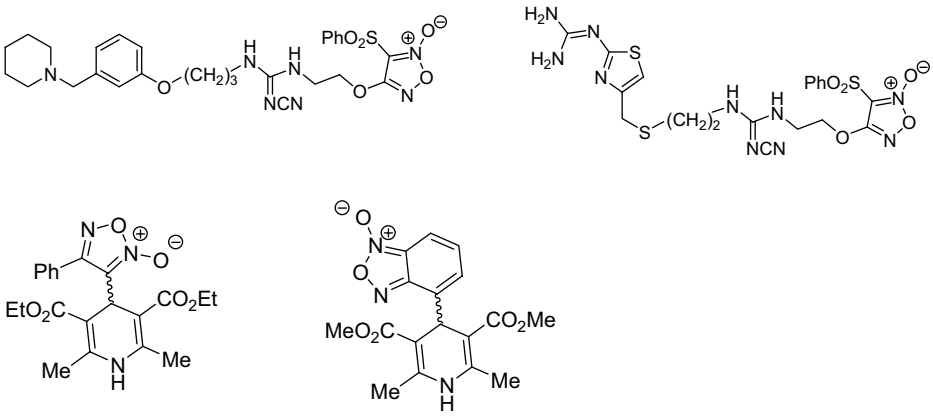
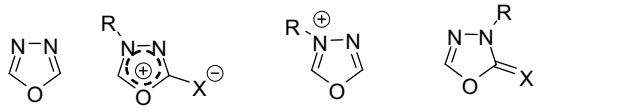
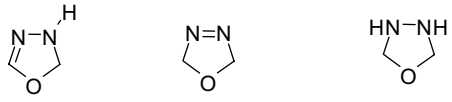


Figure 13.5 Examples of drugs that contain a furoxan moiety.

(**601**), and 1,3,4-oxadiazolines (**602**) are also stable molecules. The partially and fully reduced systems designated as 4,5-dihydro-(Δ^2) (**603**), 2,5-dihydro-(Δ^3) (**604**), and 2,3,4,5-tetrahydro-1,3,4-oxadiazole (**605**) are also known.



599 **600** X = O, S, NR **601** **602** X = O, S, NR



603 **604** **605**

1,3,4-Oxadiazoles are of great practical importance. In particular, these compounds are used in medicine, as leprostatics, tuberculostatics, antibacteric, antiproteolytic, and anticonvulsants. They also possess analgesic, antipyretic, antiphlogistic, bactericides, insecticides, fungicidal, and several other biological activities [496]. More recently, compounds containing the 1,3,4-oxadiazole motif have been used as HIV integrase and angiogenesis inhibitors [497]. 1,3,4-Oxadiazoles have also been used in agriculture, in the production of polymers, laser dyes, photographic materials, or scintillators. Furthermore, they show a combination of interesting properties, which makes them suitable for the development of new electrical and electro-optical devices.

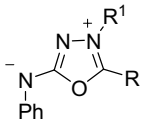
A good number of reviews on the chemistry of the 1,3,4-oxadiazoles are present in the literature [496]: the most recent report covers the literature up to the early part of 2007.

13.5.1 Structure

13.5.1.1 Theoretical Aspects

1,3,4 Oxadiazole is not fully aromatic; it has an aromaticity index of 50 (43 and 66 for furan and thiophene, respectively), while the bond orders for O−C, C−N, and N−N bonds are 1.3124, 1.9062, and 1.3348, respectively.

Theoretical studies on the structure and properties of 1,3,4-oxadiazoles are numerous [496]. In particular, MNDO and STO-3G *ab initio* methods have been used to calculate the proton affinities; CNDO/2 methods have been used to calculate the total energies, ionization potentials, and net atomic populations; INDO/S has been used to calculate the electron distribution of ground and excited states. Diels–Alder reactions of several 1,3,4-oxadiazoles used as dienes with alkenes have been investigated through molecular orbital calculations at the B3LYP/6-31G(d)AM1 theory level [498]. MNDO-PM3 calculations have been used to calculate the geometry and electronic structure of mesoionic 1,3,4-oxadiazolium-2-aminides **606** (R = 4-MeO-3-$O_2NC_6H_3$, R^1 = Me, Ph; R = 4-Cl-3-$O_2NC_6H_3$, R^1 = Me; R = Me, R^1 = Ph) and 1,3,4-oxadiazolium-2-olates **607** (Ar = 4-Cl-3-$O_2NC_6H_3$, 4-MeO-3-$O_2NC_6H_3$) [499].



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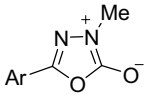
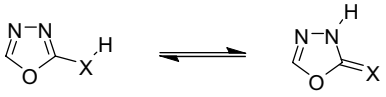


607

2-Hydroxy, 2-amino and 2-thiol derivatives **608** are in tautomeric equilibrium with Δ^2-1,3,4-oxadiazolin-5-ones, 5-imino, and 5-thiones **609**, respectively. Usually, one of the forms distinctly predominates.



608 **609**

X = O, NH, NR, S

Most of 1,3,4-oxadiazoles are solids, apart from the parent compound (bp 150 °C) and its lower alkyl derivatives, which are liquids. Some of them are soluble in water, with a solubility that decreases with increasing molecular weight.

13.5.1.2 Structural Aspects

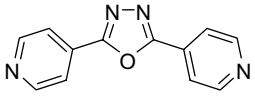
13.5.1.3 X-Ray Diffraction

Many papers related to the X-ray structures of 1,3,4-oxadiazoles have been reported [500]. The oxadiazole ring has a nearly flat structure: all the atoms of the ring lie in the same plane with very slight deviation from it.

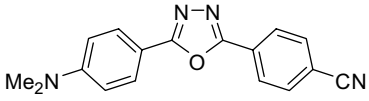
Table 13.8 shows the reported bond lengths and bond angles for 2,5-di(4-pyridyl)-1,3,4-oxadiazole **610** and for 2-(4-cyanophenyl)-5-(4-dimethylaminophenyl)-1,3,4-oxadiazole **611**.

In the crystal, compound **610** has an almost planar structure. All three rings of the molecule are planar but they show a slight torsion relative to each other. The deviation of the planes of the two pyridyl rings relative to the plane of the oxadiazole ring is $+3.3°$ for one ring and $-3.4°$ for the other. Owing to the absence of significant steric hindrance the torsion angle between the neighboring rings is small and, therefore, the conjugation is not lost. Compound **611** is almost planar. The planarity of the three single rings is nearly perfect but again the rings show a slight torsion relative to each other. The rotation of the inter-ring bond between the oxadiazole ring and the benzonitrile is $+6.5°$ and between the oxadiazole ring and the dimethylaniline is $+4.2$. In this molecule the two substituents are tilted in the same direction relative to the oxadiazole ring whereas in **610** the rings are tilted in opposite directions [501].

Table 13.8 Molecular dimensions for 2,5-di(4-pyridyl)-1,3,4-oxadiazole (**610**) and for 2-(4-cyanophenyl)-5-(4-dimethylaminophenyl)-1,3,4-oxadiazole (**611**).



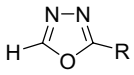
610



611

Compound 610				Compound 611			
Bond lengths (nm)		**Bond angles (°)**		**Bond lengths (nm)**		**Bond angles (°)**	
O1–C2	0.1365	O1–C2–N3	112.50	O1–C2	0.1368	O1–C2–N3	111.36
C2–N3	0.1292	C2–N3–N4	106.20	C2–N3	0.1292	C2–N3–N4	106.97
N3–N4	0.1409	N3–N4–C5	106.20	N3–N4	0.1407	N3–N4–C5	106.13
N4–C5	0.1292	N4–C5–O1	112.50	N4–C5	0.1294	N4–C5–O1	112.36
C5–O1	0.1365	C2–O1–C5	102.50	C5–O1	0.1374	C2–O1–C5	102.82

Table 13.9 Proton NMR data (ppm) for ring hydrogens of 1,3,4-oxadiazoles.



R	Solvent	δ
H	$CDCl_3$	8.73
Me	$CDCl_3$	8.53
Et	$CDCl_3$	8.48
$PhCH_2$	$CDCl_3$	8.26
Ph	$CDCl_3$	8.50
MeS	d_6-DMSO	9.42

13.5.1.4 NMR Spectroscopy

The ^{1}H NMR spectrum of the parent compound **599** shows the relative signals at 8.73 δ in $CDCl_3$ [496, 502]. The presence of alkyl groups or phenyl group moves the proton of the ring upfield, while the shift is downfield for 2-alkylthio derivatives (Table 13.9).

The ^{13}C chemical shift for C2, or C5 carbon in the parent compound is centered at 152.1 ppm. The presence of a phenyl ring at C2 moves this carbon to 164 δ [502]. The chemical shifts of the ring carbon atoms in several 1,3,4-oxadiazoles have also been reported. For example, in 2-methoxy-1,3,4-oxadiazole the C2 signal is shifted downfield in comparison with signal of C5. The same trend has been observed for the oxadiazolinone and oxadiazolinethione derivatives where the C2 carbons resonate downfield with respect to C5 carbon [496]. Recently the structure of some 2,5-disubstitued-1,3,4-oxadiazoles has been elucidated by spectral (IR, ^{1}H NMR, ^{13}C NMR) analysis. The ^{13}C NMR analysis revealed that the presence of alkyl groups attached to C2 and C5 of the ring induced a downfield shift of both carbons by at least about 20–22 ppm in comparison with the relative signal present in **599** [503].

The ^{15}N and ^{17}O data of different 1,3,4-oxadiazoles have also been used to elucidate their structures. In particular, the ^{17}O resonances registered for the 1,3,4-oxadiazolium-2-olate have demonstrated that the value centered at 181 ppm, relative to exocyclic oxygen, is that expected for an enolate form instead of that for a carbonylic function [496].

13.5.1.5 UV and IR Spectroscopy

The electronic spectrum of the 1,3,4-oxadiazole system is equivalent to that of benzene and the maxima are only slightly hypsochromically shifted. Substituted 2,5-diaryl- derivatives show strong fluorescence in solution on stimulation by UV or β-irradiation, and some of them are electroluminescent with irradiation of blue light [504]. The electronic effects of conjugated rings on 1,3,4-oxadiazoles are maintained and the absorption and emission spectra of these compounds have been extensively studied and reported [499, 505].

The IR absorption spectra for 1,3,4-oxadiazoles show bands at 1640–1560 (ν_{CN}), 1030–1020 (ν_{CO}), and 970 cm^{-1} [496, 503, 506]. These bands occur at longer

wavelengths in the spectra of 2,5-dialkyl-1,3,4-oxadiazoles and at shorter values in 5-thione derivatives [496]. A band in the range 1785–1740 cm^{-1} is reported for C=O absorption in the case of oxazolidin-5-ones [496].

13.5.1.6 Mass Spectrometry

The electron impact mass spectra of most 1,3,4-oxadiazoles exhibit a very intense signal for the molecular ion [496, 503, 506]. Moreover, the predominant fragment is represented by R-C = $O^{+\bullet}$. In the case of 2-substituted 1,3,4-oxadiazoles, diagnostic fragments derive from loss of CO and HCO. Loss of HNCO is fundamental in the spectrum of 2-amino-5-phenyl-1,3,4-oxadiazole. Oxazolidin-5-ones easily lose CO_2 to give the corresponding ions of general formula R-C=N=NH^+.

A study regarding the electron-spray ionization mass spectra of 2,5-diaryl and 2-arylamino-5-aryl-1,3,4-oxadiazoles together with their complexes with copper cations has been reported [507]. In this latter case, loss of NH_3 and HNCO was observed. In some protonated 2,5-diaryl derivatives an unusual elimination of HNCO was also detected [508].

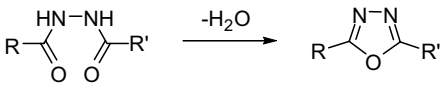
13.5.2 Synthesis of 1,3,4-Oxadiazoles

The common synthetic routes to these compounds involve:

1) cyclization of diacylhydrazines with various anhydrous reagents such as $BF_3{\cdot}OEt_2$ [503], thionyl chloride [509], phosphorous pentoxide [510], phosphorous oxychloride [511], triflic anhydride [512], triphenylphosphine [513], polyphosphoric acid [514], and sulfuric acid [515];
2) cyclization of acylhydrazones [516], semicarbazones, and thiosemicarbazides;
3) ring transformations [517].

13.5.2.1 Cyclization of Diacylhydrazines

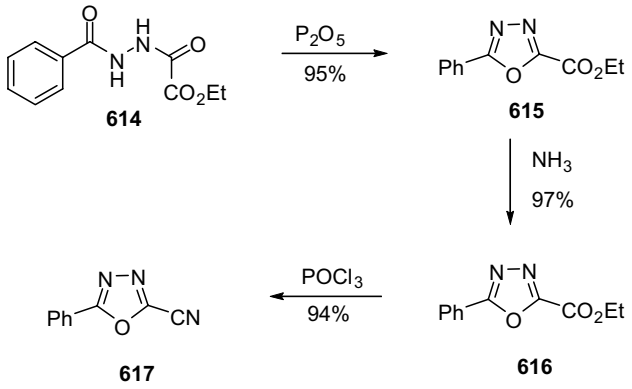
The first synthesis of this ring, reported by Robert Stolle, exploits a condensation reaction of *N,N′*-diacid hydrazides **612** under vigorous conditions to produce in variable yields 2,5-diaryl(alkyl)-1,3,4-oxadiazoles **613** (Scheme 13.194) [518].



612 **613**

Scheme 13.194

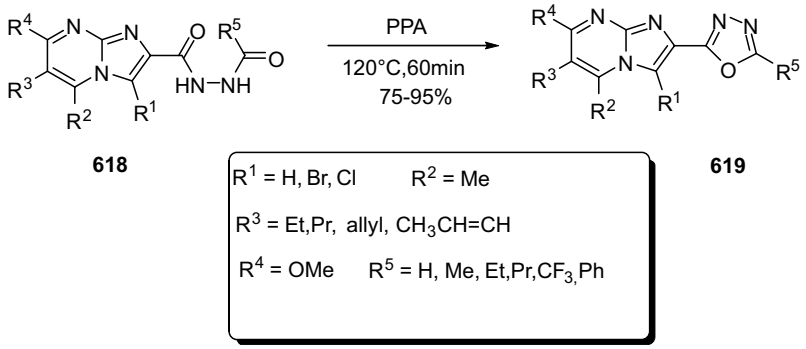
Useful as agricultural fungicide, Boesch has reported the synthesis of 2-cyanooxadiazole **617** by cyclocondensation of ethyl 2-(2-benzoylhydrazinyl)-2-oxoacetate **614** with P_2O_5 followed by NH_3 treatment and dehydration with $POCl_3$ (Scheme 13.195) [519].



614 615 616 617

Scheme 13.195

Using hot polyphosphoric acid (PPA) 5-substituted [1,3,4]oxadiazol-2-yl compounds **619** have been obtained in good yield (75–95%) (Scheme 13.196).



618 619

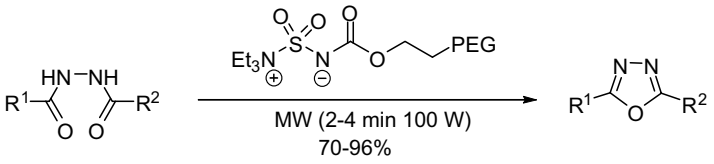
Scheme 13.196

The 2-(oxadiazolyl)imidazo[1,2-*a*]pyrimidines (**619**) thus obtained are a class of compounds that bind to benzodiazepine receptors with moderate to weak affinity, and yet display antianxiety properties of similar potency to chlordiazepoxide in animal models, while demonstrating reduced or negligible myorelaxant effects [514].

A polymer-supported Burgess reagent under microwave conditions has been efficaciously used for the cyclodehydration of 1,2-diacylhydrazines **620** to provide 1,3,4-oxadiazoles **621** in excellent yields (Scheme 13.197) [520].

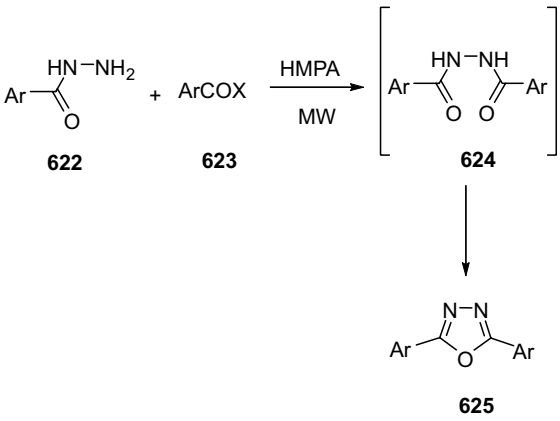
A convenient, one-pot procedure has been reported by Mashraqui and coworkers for the synthesis of various 2,5-disubstituted-1,3,4-oxadiazoles **625** by condensing mono-aryl hydrazides **622** with acid chlorides **623** in HMPA solvent under microwave heating (involving as intermediates diaroylhydrazines **624**) (Scheme 13.198) [521].

The yields are good to excellent; the process is rapid and does not need any added acid catalyst or dehydrating reagent.



R^1	R^2	Yield	HPLC Purity (%)
Ph	Ph	96	91
2-Methoxyphenyl	Me	89	>99
2-Chlorophenyl	Me	70	97
2-Nitrophenyl	Me	95	>99
2-Tyhiophenyl	Ph	95	97
3-Pyridyl	Ph	95	>99
4-Pyridyl	NHPh	95	>99
4-Chloro-3-Nitroamminophenyl	Ph	90	92

Scheme 13.197

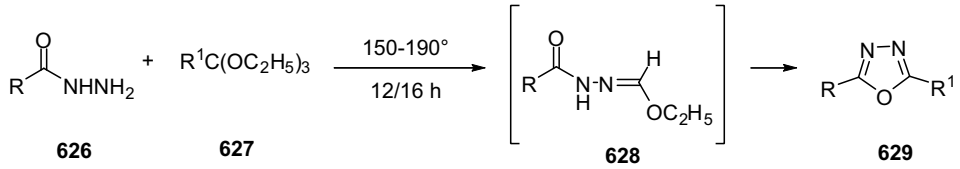


Scheme 13.198

13.5.2.2 **Cyclization of Acylhydrazones, Semicarbazones, and Thiosemicarbazides**

Mono and disubstituted 1,3,4-oxadiazoles **629** have been prepared by oxidation of acylhydrazones **628** prepared *in situ* by the condensation of aryl carboxylic acid hydrazides **626** with orthoesters **627** (Scheme 13.199). In two examples, the 1-acyl-2-ethoxymethylenehydrazine **628** intermediate was isolated [522]. This reaction has been used to prepare the parent 1,3,4-oxadiazole (**599**) [523].

The above reaction has been revised recently by Varma *et al.*, who have used a green protocol to synthesize 1,3,4-oxadiazoles **629** [502]. In particular, various

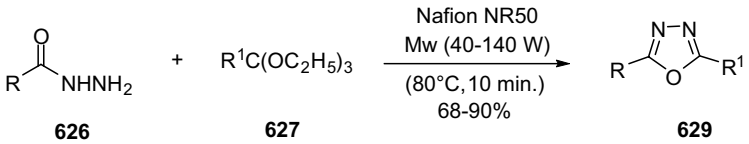


626 627 628 629

R	R^1	Yield (%)
Phenyl	H	70
o-Methoxyphenyl	H	79
p-Chlorophenyl	H	78
p-Nitrophenyl	H	79
α-Naphthyl	H	63
4-Pyridyl	H	82
3-Pyridyl	H	68
2-Quinolyl	H	70
Phenyl	Me	70
4-Pyridyl	Me	70
Phenyl	Et	80
o-Methoxyphenyl	Et	79
p-Chlorophenyl	Et	86
p-nitrophenyl	Et	92
α-Naphthyl	Et	80
4-Pyridyl	Et	84

Scheme 13.199

hydrazides **626** have been reacted with triethyl orthoalkanates or triethyl orthobenzoate (**627**), in the presence of Nafion NR50, under microwave irradiations and in the absence of any solvents to afford the desired 1,3,4-oxadiazoles **629** in good yields (68–90%) (Scheme 13.200).



626 627 629

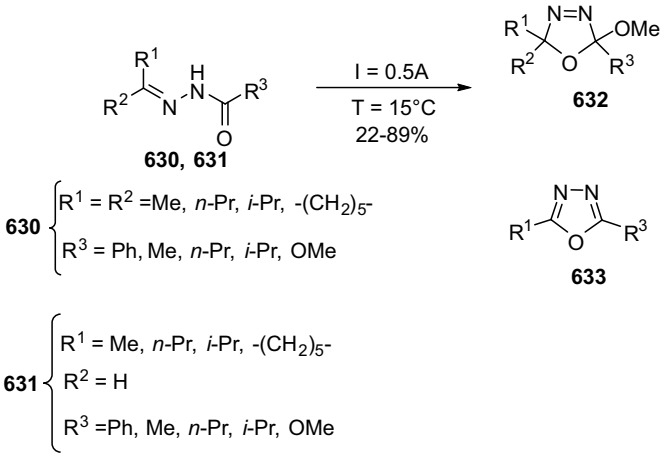
R = Ph, p-F-C_6H_4, p-OMe-C_6H_4, 2-furyl, 2-thienyl, 4-pyridyl, $PhCH_2$

R^1 = H, Et, Ph

Scheme 13.200

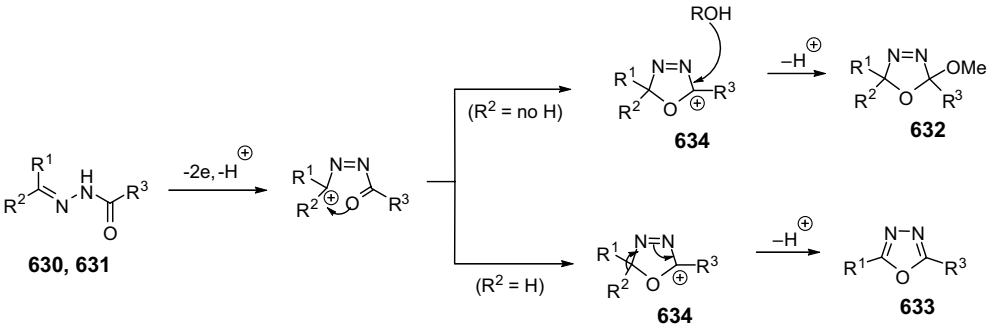
Owing to the selective absorption of catalyst, the reaction rate is strongly accelerated (10 min). Moreover, Nafion NR50 is easy to handle because it involves a simple addition of Nafion beads in a reaction vessel, which can be physically removed by forceps after completion of the reaction.

Electrolytic oxidation of ketone *N*-acylhydrazones **630** and aldehyde *N*-acylhydrazones **631** in methanolic sodium acetate affords, through their intramolecular cyclization, the corresponding 2-methoxy-Δ^3-1,3,4-oxadiazolines **632** and oxadiazoles **633**, respectively (Scheme 13.201) [524].



Scheme 13.201

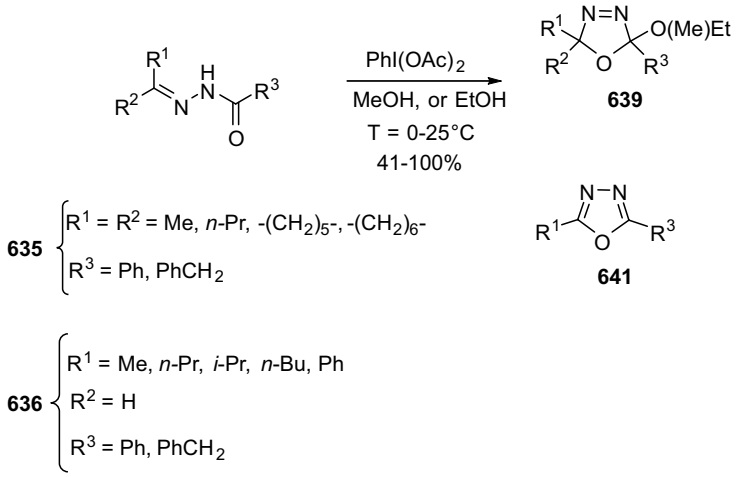
The formation of heterocycles **632** and **633** has been rationalized according to a three-step process. The first step involves the formation of a cationic intermediate generated from **630** or **631** by the loss of two electrons and one proton. In the second step, a 1,3,4-oxazolidinyl carbocation (**634**) is formed by an intramolecular cyclization promoted by the oxygen of the carbonyl group; and the third step consists of attack by methanol followed by expulsion of a hydrogen in the case of compound **630** or hydrogen extrusion in the case of **631** (Scheme 13.202).



Scheme 13.202

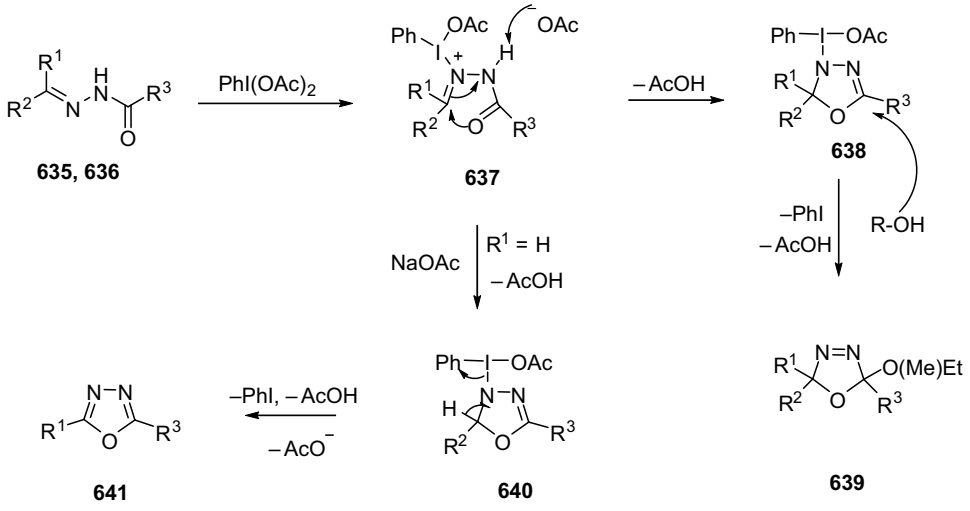
Another method of oxidation of *N*-acylhydrazones **635** and **636** involves a hypervalent iodine reagent. Thus, Dai *et al.* have reported the synthesis of 2-alkoxy-Δ^3-1,3,4-

oxadiazolines **639** and 2,5-disubstitued-1,3,4-oxadiazoles **641** in good to excellent yield by means of phenyl-iodine(III) diacetate (Scheme 13.203). The yields in 1,3,4-oxadiazoles was improved by the use of 2 mmol of NaOAc [525].



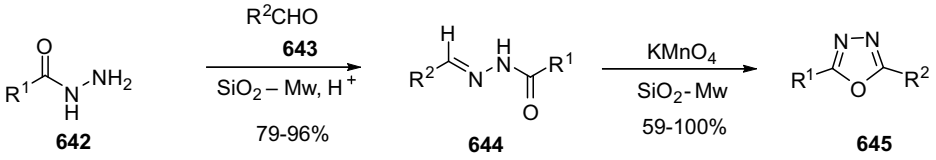
Scheme 13.203

Scheme 13.204 explains the formation of these compounds.



Scheme 13.204

More recently, starting from 1-aroyl-2-arylidene hydrazines **644**, a microwave assisted synthesis of 2,5-disubstituted 1,3,4-oxadiazoles **645** has been reported using as oxidizing agent potassium permanganate supported by montmorillonite K10. The reaction was more efficient when acetone/H_2O (20 : 5) was used as solvent, and occurs in only 10 min, with a yield in the range 59–100%. Interestingly, the starting hydrazines **644** have been prepared in good yields under microwave irradiation, mixing in ethanol 6 mmol of acid hydrazide **642**, 6 mmol of aldehyde **643**, and three drops of phosphoric acid (Scheme 13.205) [526].



R^1 = Me, Ph, 4-Cl-C_6H_4

R^2 = Ph, 4-NO_2-C_6H_4, 3-NO_2-C_6H_4, 4-Cl-C_6H_4, 3-Cl-C_6H_4, Me, 4-I-C_6H_4, 4-Br-C_6H_4, 4-Cl-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-CN-C_6H_4, 4-Cl-C_6H_4, 4-MeOOC-C_6H_4, 4-$(NMe)_2$-C_6H_4,

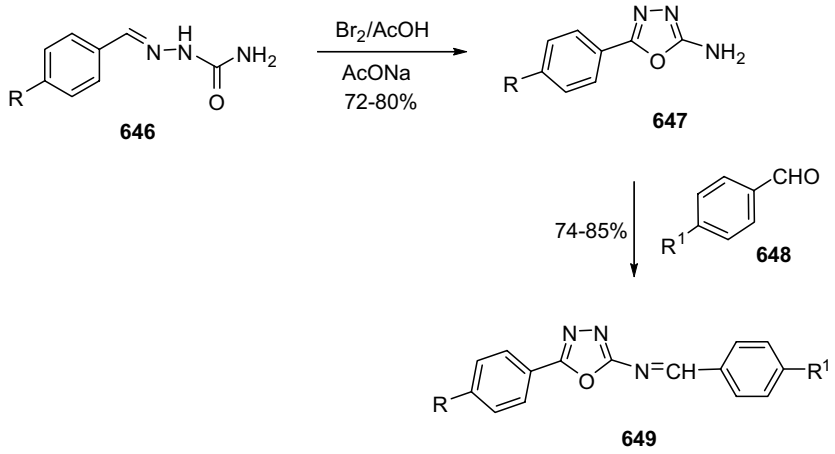
Scheme 13.205

Semicarbazones have also been used for the synthesis of 2-amino-1,3,4-oxadiazoles, through their cyclization performed with a mixture of sodium acetate, bromine, and glacial acetic acid. In fact, this procedure was used recently to prepare some Schiff bases of 2-amino-5-aryl-1,3,4-oxadiazoles (**649a–t**) that posses antibacterial activities. In particular, semicarbazones **646** have been reacted with a mixture of sodium acetate, bromine, and glacial acetic acid, and transformed into the corresponding 2-amino-5-aryl-1,3,4-oxadiazoles **647** that in turn have been condensed with aldehydes **648** to give the expected 1,3,4-oxadiazole derivatives **649a–t** (Scheme 13.206). The antibacterial properties of the compounds were investigated against *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, and *Staphylococcus aureus*. The most active compounds were **649c**,**649f**,**649m**, and **649q** with a MIC in the range 62–68 μg ml^{-1}. Antifungal activity against *Aspergillus niger* and *Candida albicans* were also found for compounds **649g**,**h**,**i**,**m.** The corresponding MICs are in the range 52–60 μg ml^{-1}. The biocidal activities of these compounds were attributed to the toxophoric C=N linkage [527].

The mixture of sodium acetate, bromine, and glacial acetic acid has also been used to prepare several antibacterial 1,2-bis(1,3,4-oxadiazol-2-yl)ethanes **651** from the corresponding diacylhydrazones **650** (Scheme 13.207) [528].

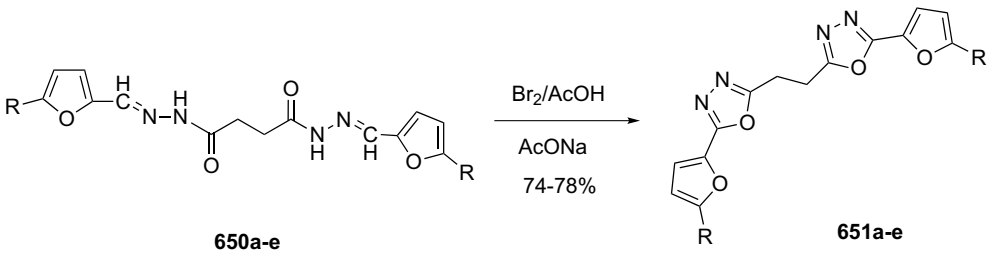
In particular, compounds **651c–e** show a good antibacterial activity against *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Staphylococcus aureus*, and *Escherichia coli*, with a MIC of 6 μg ml^{-1}.

Another cyclization method towards the synthesis of 1,3,4-oxadiazoles involves the cyclodesulfurization of thiosemicarbazides **652** using either dicyclohexylcarbodii-



a: R =–OMe R^1 = –OMe	f: R =– NO_2 R^1 = –OMe	k: R =–Cl R^1 = –OMe	p: R =–Me R^1 = –OMe
b: R =–OMe R^1 = – NO_2	g: R =– NO_2 R^1 = – NO_2	l: R =–Cl R^1 = –NO_2	q: R =–Me R^1 = –NO_2
c: R =–OMe R^1 = –Cl	h: R =– NO_2 R^1 = –Cl	m: R =–Cl R^1 = –Cl	r: R =Me R^1 = –Cl
d: R =–OMe R^1 = –Me	i: R =– NO_2 R^1 = –Me	n: R =–Cl R^1 = –Me	s: R =–Me R^1 = –Me
e: R =–OMe R^1 = –OH	j: R =–NO_2 R^1 = –OH	o: R =–Cl R^1 = –OH	t: R =–Me R^1 = –OH

Scheme 13.206

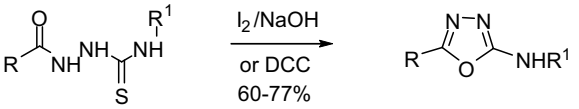


R = **a**: NO_2; **b**: *p*-nitrophenyl; **c**: *p*-chlorophenyl; **d**: *p*-bromophenyl; **e**: 2,4-dichlorophenyl

Scheme 13.207

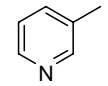
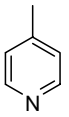
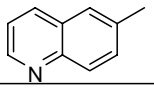
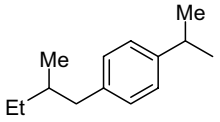
mide (DCC), or a mixture of I_2/NaOH. By this procedure 2-amino-substituted-1,3,4-oxadiazoles **653**, having anti-inflammatory activity, have been synthesized (Scheme 13.208) [529]. The anti-inflammatory activity was investigated by determining the inhibitory effect of the oxadiazole derivatives **653a–p** on histamine-induced edema in rat abdomen. Compounds **653a**,**653c**,**653e**,**653j**, and **653n** proved to be more potent anti-inflammatory agents at 200 mg kg^{-1} p.o. than Ipobrufen, the standard reference drug.

2-Amino-5-aryl-1,3,4-oxadiazoles **656** have also been prepared, in good yield, by cyclodesulfurization of thiosemicarbazides **654** using 1,3-dibromo-5,5-dimethylhydantoin (**655**) as primary oxidant in the presence of potassium iodide (Scheme 13.209) [530].

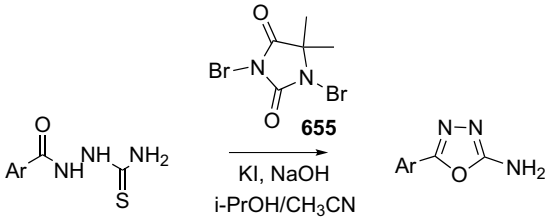


652a-p

653a-p

R	R^1 = Et	Cyclohexyl	Ph	Me-C_6H_4
	**652a** **653a**	**652b** **653b**	**652c** **653c**	**652d** **653d**
	**652e** **653e**	**652f** **653f**	**652g** **653g**	**652h** **653h**
	**652i** **653i**	**652j** **653j**	**652k** **653k**	**652l** **653l**
	**652m** **653m**	**652n** **653n**	**652o** **653o**	**652p** **653p**

Scheme 13.208



654

655

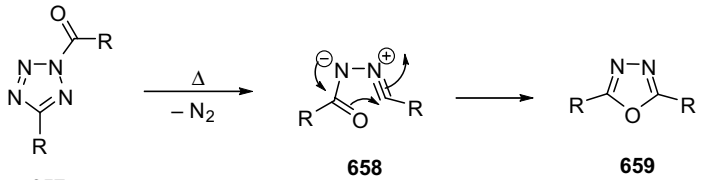
656

Ar: Ph, 4.Cl-Ph, 4-OMe-Ph, 2-Furyl, $PhCH_2CH_2$, PhCH=CH

Scheme 13.209

13.5.2.3 **Ring Transformations**

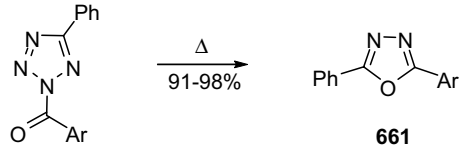
Thermal decomposition of *N*-acyl-tetrazoles **657** is a common way to obtain 1,3,4-oxadiazoles **659** [496]. This reaction has been easily explained by the loss of nitrogen, formation of the corresponding nitrilimines **658**, and an intramolecular 1,5-cycloaddition (Scheme 13.210).



657 658 659

Scheme 13.210

The mechanism of the process was demonstrated by labeling with ^{15}N the atoms N1 and N4 in 5-phenyltetrazole. Half of the ^{15}N was found in the 2,5-diphenyl-1-3-4-oxadiazole, obtained by the breakdown of the *N*-benzoyl-5-phenyltetrazole. Therefore, either the atoms N1 and N2 or N3 and N4 were eliminated as N_2 [531]. Scheme 13.211 shows that the thermolysis of *N*-aroyl-5-phenyltetrazoles **660** affords oxadiazoles **661** [532].

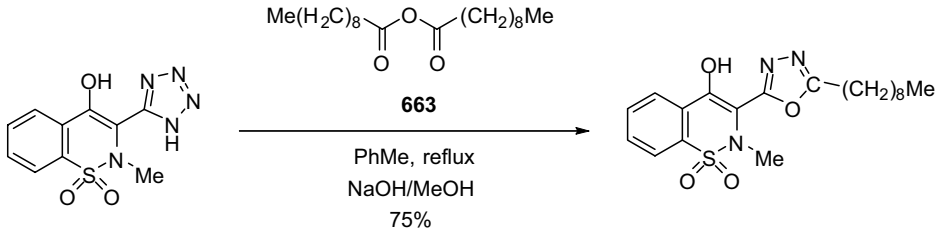


660 661

Ar = Ph, 2-Cl-C_6H_4; 2-Br-C_6H_4; 4-NO_2-C_6H_4; 4-Me-C_6H_4

Scheme 13.211

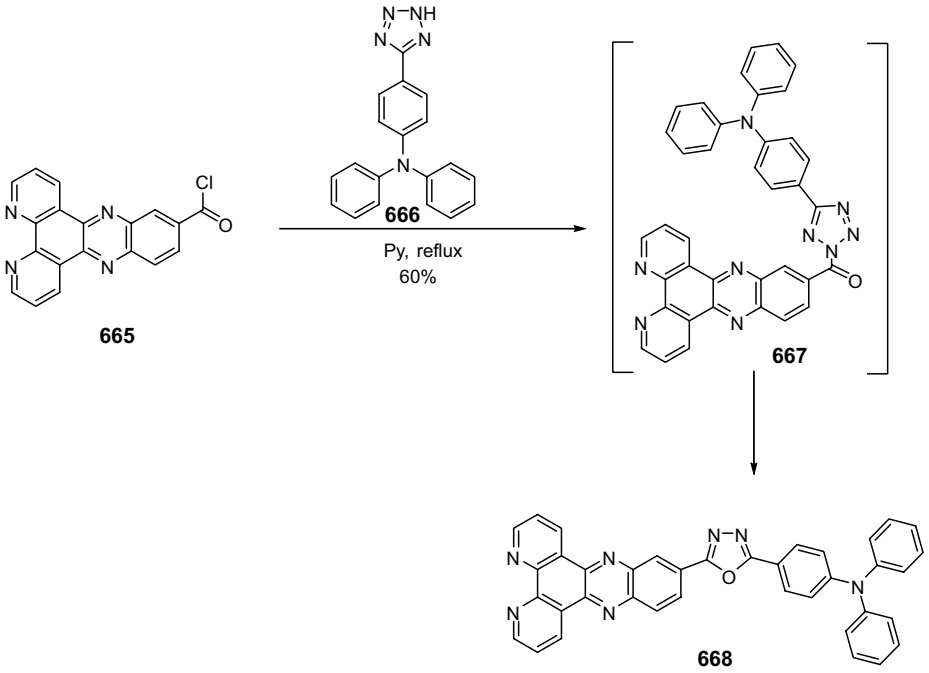
(5-Nonyl-1,3,4-oxadiazol-2-yl)benzothiazine dioxide **664**, a compound that shows anti-inflammatory properties by virtue of its inhibition of arachinodate 5-lipoxygenase [533], has been prepared starting from tetrazol-5-yl derivative **662**, which undergoes a Huisgen rearrangement on refluxing with decanoic anhydride **663** in toluene, followed by saponification (Scheme 13.212).



662 664

Scheme 13.212

By exploiting the thermal decomposition of alkoxycarbonyl tetrazoles, the 4-[5-(dipyrido[3,2-a:2′,3′-c]phenain-11-yl)-1,3,4-oxadiazol-2-yl]-N,N-diphenylaniline **668** has been prepared. Thus, the dipyrido[3,2-*a*,2′,3′-*c*]phenazine 8-carboxyl chloride **665** in dry pyridine was refluxed for 72 h with triphenylamine tetrazole **666** to afford **668** via the corresponding alkoxycarbonyl tetrazole intermediate **667**, in 60% yield (Scheme 13.213) [534].

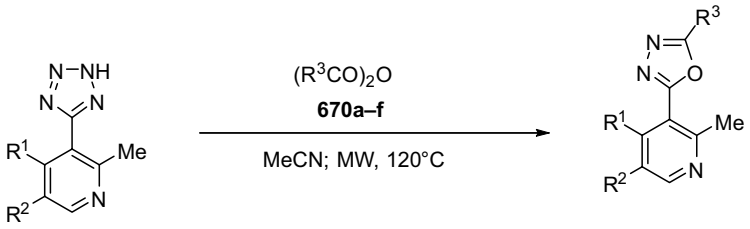


Scheme 13.213

The above compound, which contains a hole-transporting triphenylamine and an electron-transporting 1,3,4-oxadiazole unit, is an efficient light-emitting material. In particular, the absorption spectrum of **668** is extended into the visible region and shows a typical CT band around 416 nm and a broad π–π^* transition band around 347 nm. This is the result of the extended conjugation of the phenanthroline moiety. The emission maximum of **668** is at 635 nm (red) with λ_{ex} at 416 nm, and a quantum yield of 40%. Moreover, preliminary studies performed on this compound showed that it can be used as anorganic light emitting diode (OLED).

Microwave methodology has also been used to prepare various 3-(1,3,4-oxadiazol-2-yl)pyridines **671** in good to excellent yields, by reaction of 3-(5-tetrazolyl)pyridines **669** with different acid anhydrides (**670**) (Scheme 13.214) [535].

1,3,4-Oxadiazoles can also be obtained by photo-isomerization of 1,2,4-oxadiazoles. Irradiation of 5-alkyl-3-amino-1,2,4-oxadiazoles **672** at 254 nm in methanol and in presence of Et_3N, even if in moderate yields, leads to 2-amino-5-alkyl-1,3,4-

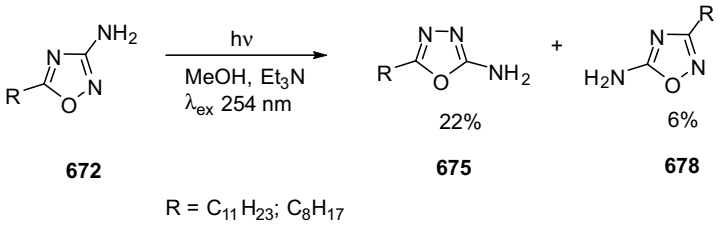


	R[1]	R[2]	R[3]	Yield (%)
a:	Ph	H	Me	95
b:	Ph	H	CF_3[a]	100
c:	–*o*–C_6H_4–$(CH_2)_2$–		*t*-Bu	96
d:	–*o*–C_6H_4–OCH_2–		$MeO(CH_2)_2$	80
e:	–$(CH_2)_3$–		*i*-Pr	99
f:	–$(CH_2)_5$–		4–Cl– C_6H_4	68

[a] The reaction was performed at room temperature for 2 h.

Scheme 13.214

oxadiazoles **675**. A small amount of the ring-degenerate isomers 3-alkyl-5-amino-1,2,4-oxadiazoles **678** (Scheme 13.215) was also obtained [536].

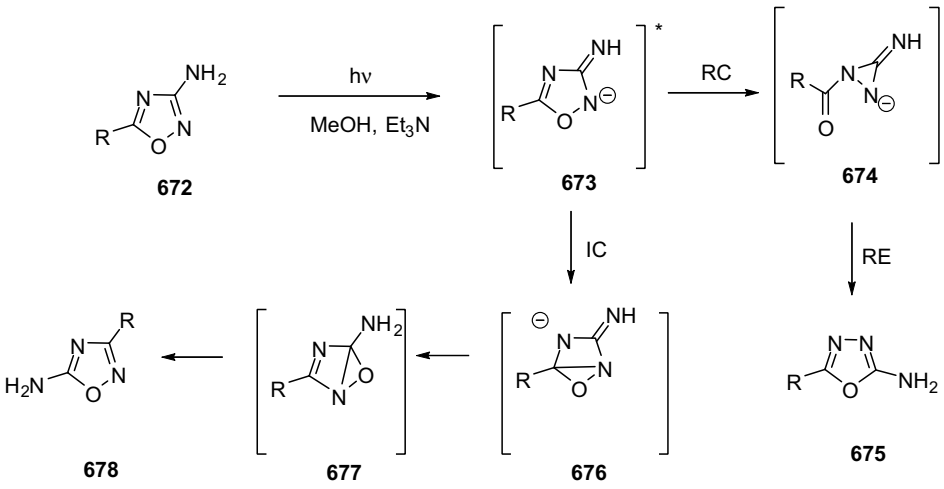


Scheme 13.215

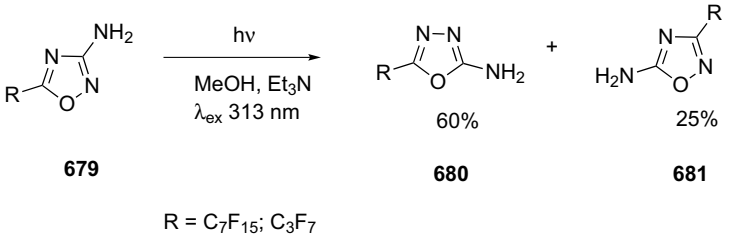
The formation of **675** has been explained according to the ring contraction–ring expansion (RCRE) route, while **678** originates via a competing internal cyclization (IC)–isomerization mechanism, with an anionic species (**673**) as a common precursor (Scheme 13.216).

By a similar approach, 2-amino-5-alkylfluorinated-1,3,4-oxadiazoles **680** have been prepared utilizing the photochemical interconversion of 3-*N*-alkylamino-5-perfluoalkyl-1,2,4-oxadiazoles **679** in the presence of triethylamine. A moderate yield of 5-amino-3-alkyl-1,2,4-oxadiazoles **681** was also obtained, as a rearrangement product (Scheme 13.217) [537].

In this context, the same authors have reported that 1,2,5-oxadiazoles containing an acetylamino moiety are able to photochemically interconvert into 1,3,4-oxadiazoles. Thus, irradiation of 2,2,2-trifluoro-*N*-(4-phenyl-1,2,5-oxadiazol-3-yl)acetamide

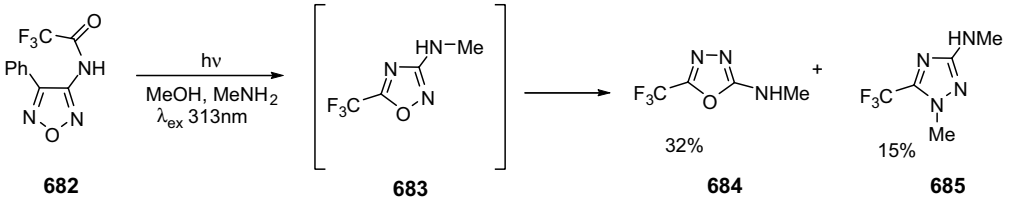


Scheme 13.216



Scheme 13.217

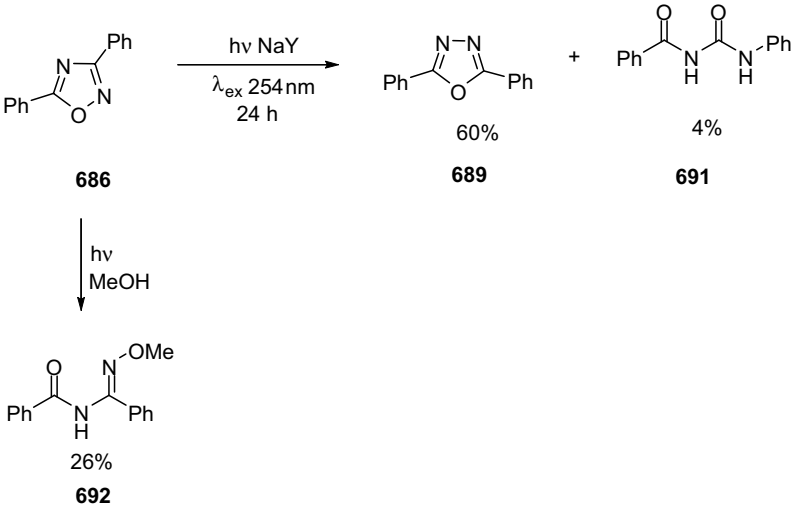
682, in methanol in the presence of methylamine, produces, via 3-*N*-methylamino-5-trifluoromethyl-1,2,4-oxadiazole (**683**), a mixture of 2-*N*-methylamino-5-trifluoromethyl-1,3,4-oxadiazole (**684**) and 1-methyl-3-*N*-methylamino-5-trifluoro-methyl-1,2,4-triazole (**685**) in 32% and 15% yield respectively (Scheme 13.218) [538].



Scheme 13.218

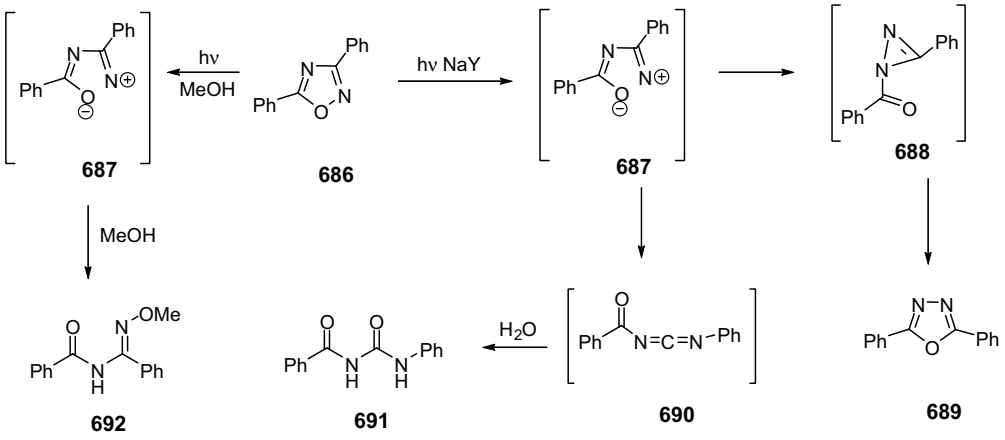
The study of organic transformations within constrained media is a research topic that has received considerable attention in recent years. In this regard the

first intrazeolite-photoinduced rearrangement of 1,2,4-oxadiazoles leading to 1,3,4-oxadiazoles has been reported. Irradiation of a perfluorohexane slurry of 3,5-diphenyl-1,2,4-oxadiazole (**686**) in zeolite (NaY) at 254 nm for 24 h furnished 2,5-diphenyl-1,3,4-oxadiazole (**689**) in 60% yield together with *N*-benzoyl-*N*′-phenylurea (**691**) (4%) and unreacted starting compound (35%). The formation of **689** and **691** is unknown in solution (Scheme 13.219) [539].



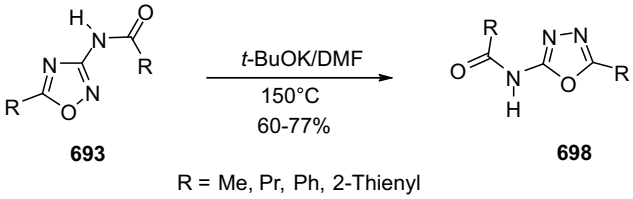
Scheme 13.219

In fact, a photochemical study performed on **686** in MeOH afforded product **692**. This dramatic difference of photo-behavior is explainable through a common intermediate (**687**), which in the zeolite cage leads to compounds **689** and **691**, via intermediates **688** and **690**, respectively, while **687** in methanol undergoes a nucleophilic addition of the solvent, giving rise to **692** (Scheme 13.220).



Scheme 13.220

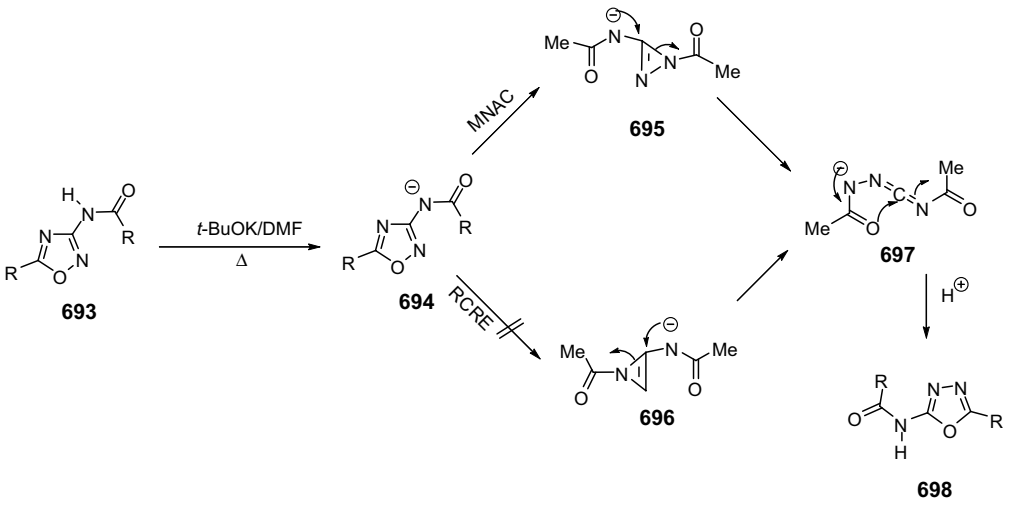
It was found recently that a thermal rearrangement promoted by base is also effective in the formation of 1,3,4-oxadiazoles **698** starting from 3-acylamino-1,2,4-oxadiazoles **693** (Scheme 13.221) [540].



Scheme 13.221

The reaction consists of a one-atom side-chain rearrangement that is base activated, occurs at higher temperature, and irreversibly leads to the corresponding 2-acylamino-1,3,4-oxadiazoles.

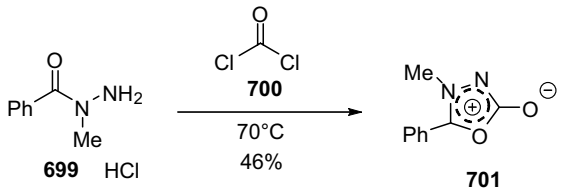
The reaction mechanism has been studied in depth by computational methods, using the hybrid DFT B3LYP method and the 6-31 + + G(d,p) basis set. Following these computational studies, the proposed mechanism is that reported in Scheme 13.222, where the route involving migration–nucleophilic attack–cyclization (MNAC) is the activated route, while the ring contraction–ring expansion route (RCRE) is ruled out.



Scheme 13.222

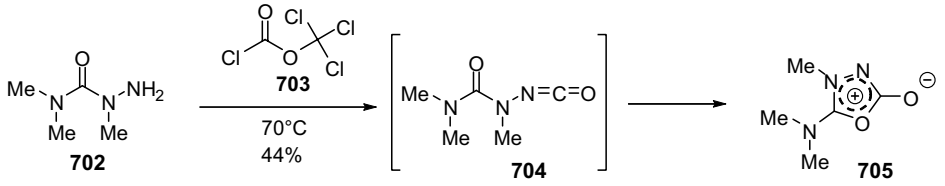
13.5.2.4 Synthesis of Mesoionic 1,3,4-Oxadiazoles (600), and 1,3,4-Oxadiazolium Cations (601)

The simplest way to prepare mesoionic 1,3,4-oxadiazoles **600** is by the thermal cyclization of 1-carbonyl-substituted-1-substituted hydrazine hydrochloride and phosgene [541]. Thus, the 4,5-dihydro-3-methyl-5-oxo-2-phenyl-1,3,4-oxadiazolium inner salt **701** has been synthesized from 1-benzoyl-1-methylhydrazine hydrochloride (**699**) and phosgene (**700**) (Scheme 13.223) [541].



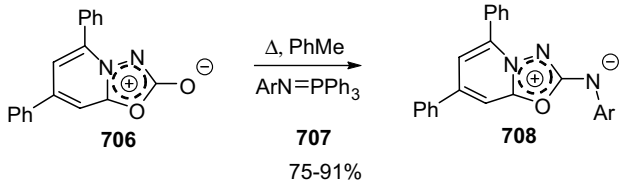
Scheme 13.223

In the same way, 5-(dimethylamino)-4-methylisosydnone **705** has been prepared, via the aminoisocyanate **704** intermediate, by heating at 70 °C the 2,4,4-trimethylsemicarbazide **702** with trichloromethyl chloroformate (**703**) (Scheme 13.224) [542].



Scheme 13.224

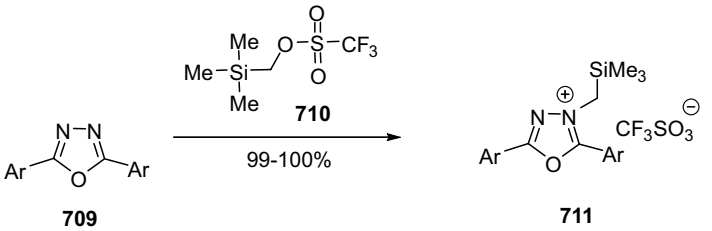
1,3,4-Oxadiazolo[3,2-*a*]pyridylium-2-aminides **708** are available in 75–91% yield by reaction, in refluxing toluene, of 1,3,4-oxadiazolo[3,2-*a*]pyridylium-2-olate **706** with *N*-aryliminotriphenyl-phosphoranes **707** (Scheme 13.225) [543].



Ar = Ph, 4-BrC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, α-$C_{10}H_7$

Scheme 13.225

1,3,4-Oxadiazolium cations **601** are easily obtained by treatment of 1,3,4-oxadiazoles with several alkylating agents to give in about 100% yield the corresponding salts. A recent example is the synthesis of 2,5-diaryl-3-trimethylsilylmethyl-1,3,4-oxadiazolium trifluoromethanesulfonates (**711**) [544]. These compounds have been prepared in 99–100% yield by mixing a solution of 2,5-diaryl-1,3,4-oxadiazoles **709** with trimethylsilylmethyl trifluoromethanesulfonate **710** in dry CH_2Cl_2 at 50 °C under reflux condenser for 24 h (Scheme 13.226).

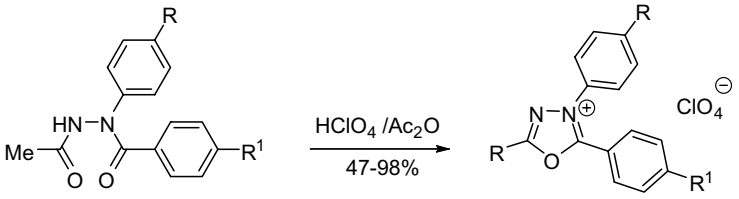


709 **711**

Ar = Ph; 4-BrI-C_6H_4, 4-Me-C_6H_4,

Scheme 13.226

Another method involves the cyclization reaction of N-substituted diacylhydrazides with a mixture of $HClO_4$–Ac_2O. Thus, cyclization of $RCONR^1NHAc$ **712** with $HClO_4$–Ac_2O gave 47–98% yields of 1,3,4-oxadiazolium salts **713** (Scheme 13.227) [545].



712 **713**

R= F, Me, Cl, NO_2, OMe

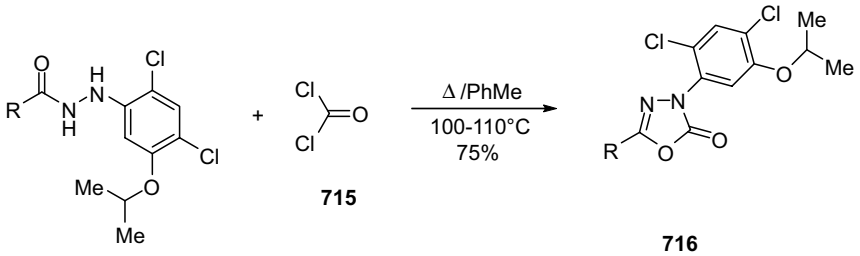
R^1= F, Me, NO_2, OMe, Cl, SMe, H, NH_2, SO_2Me

Scheme 13.227

13.5.2.5 **Synthesis of Oxadiazolinones, Oxadiazolinethiones, and Oxadiazolimines (602)**

1,3,4-Oxadiazolin5-ones are, usually, synthesized by reaction of substituted acid hydrazide with phosgene or by thermal cyclization of acylcarbazates.

5-*tert*-Butyl-3-(2,4-dichloro-5-isopropoxyphenyl)-1,3,4-oxadiazolin-2-one – a very active herbicide, that goes under the commercial name of Oxadiazon (**716**, R = CMe_3), commonly used in rice production for controlling weeds and increasing seed yield in soya beans, containing the oxadiazolinones ring – has been prepared by reaction of 1-trimethylacetyl-2-(2,4-dichloro-5-isopropoxyphenyl)hydrazide **714** with phosgene (**715**) in toluene at 100–110 °C (Scheme 13.228) [546].



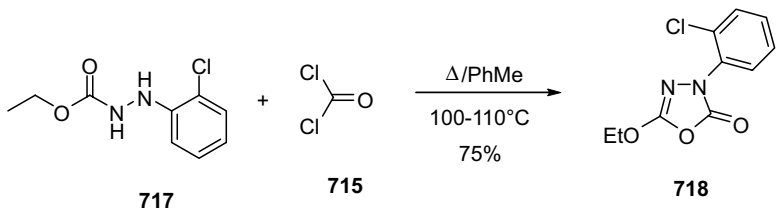
714 **715** **716**

R = CMe_3, OMe, OEt, O-*n*-Pr, OBu, O-*sec*-Bu, O-*iso*-Bu

Scheme 13.228

Similarly, 5-substituted-3-(2,4-dichloro-5-isopropoxyphenyl)-1,3,4-oxadiazolin-2-ones have been prepared (R = MeO, EtO, *n*-PrO, BuO, *sec*-BuO, *iso*-BuO).

Condensation of ethyl 2-(2-chlorophenyl)hydrazine-carboxylate **717** with phosgene has furnished 5-ethoxy-3-(2-chlorophenyl)-1,3,4-oxadiazolin-2-one **718**, which is active orally against gastrointestinal nematodes of domestic animals and man (Scheme 13.229) [547].

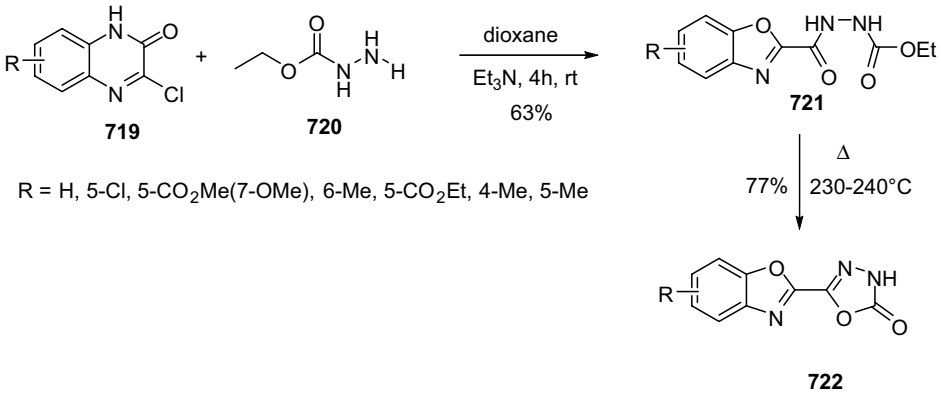


717 **715** **718**

Scheme 13.229

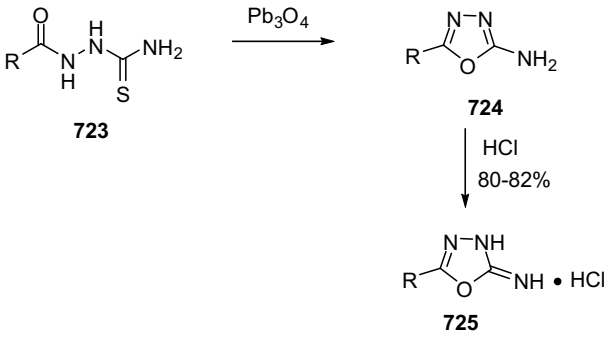
Cyclization of acylcarbazates has been utilized fruitfully for the synthesis of 2-(2,3-dihydro-2-oxo-1,3,4-oxadiazol-5yl)benzoxazoles, a class of compounds that are potent inhibitors of anaphylactically induced histamine release from rat peritoneal mast cells and are orally active as inhibitors of IgE-mediated passive cutaneous anaphylaxis in the rat [548]. The 2-(2,3-dihydro-2-oxo-1,3,4-oxadiazol-5-yl)benzoxazole **722a** (R = H), chosen as an example, was synthesized by heating ethyl 3-(2-benzoxazolyl)hydrazine-carboxylate (**721**) in Dowtherm at 230–240 °C for 1 h. Intermediate **721** was prepared by treating 3-chloro-1,4-benzoxazin-2-one **719** with ethyl carbazate **720**

in dioxane and triethylamine at room temperature for 4 h. In a similar manner, compounds **722b–g** have been prepared (Scheme 13.230).



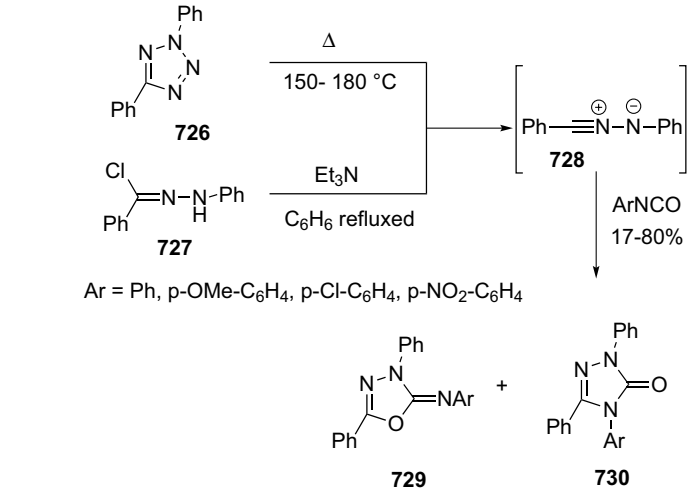
Scheme 13.230

5-Imino-2-substituted Δ^2-1,3,4-oxadiazolines **725**, as hydrochloride salts, which are able to produce a profound flaccid paralysis in rats, have been prepared by hydrochloric reaction of 2-amino-5-aryl-1,3,4-oxadiazoles **724**, in DMF/H_2O or in ethanol–ether as solvents. These latter compounds have been synthesized by reaction of 1-acyl-3-thiosemicarbazide **723** with Pb_3O_4 (Scheme 13.231) [549].



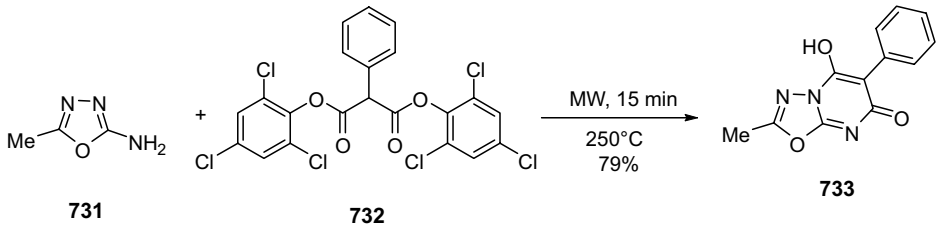
Scheme 13.231

Diphenylnitrilimine **728**, prepared from 2,5-diphenyltetrazole (**726**) or by triethylamine treatment of diphenylchlorohydrazone **727**, adds to C=O and C=N double bond of aryl isocyanate to give 2,4-diphenyl-1,3,4-oxadiazol-5-phenylimino **729**, and 1,3-diphenyl-4-aryl-1,2,4-triazolin-5-ones (**730**) in a 2 : 1 ratio respectively (Scheme 13.232) [550].



Scheme 13.232

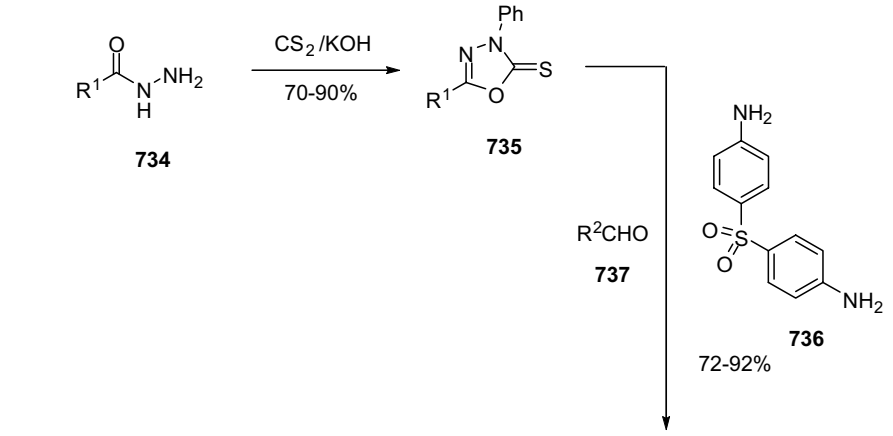
5-Hydroxy-2-methyl-6-phenyl-7*H*-[1,3,4]oxadiazolo[3,2-*a*]pyrimidin-7-one (**733**) has been obtained in 79% yield via a solvent-free microwave cyclocondensation reaction using di(2,4,6-trichlorophenyl) 2-phenylmalonate (**732**) and 2-methyl-5-amino-1,3,4-oxadiazole (**731**) in a 1 : 2 ratio under heating at 250 °C for 15 min (Scheme 13.233) [551].

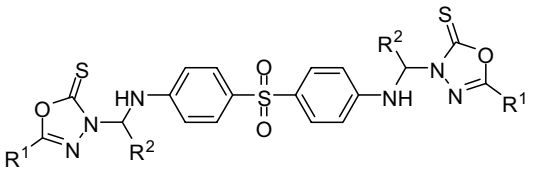


Scheme 13.233

The synthetic procedure based on the ring closure of substituted acid hydrazide **734** with carbon disulfide leads to 5-aryl-2,3-dihydro-1,3,4-oxadiazole-2-thiones **735** in excellent yield (Scheme 13.234).

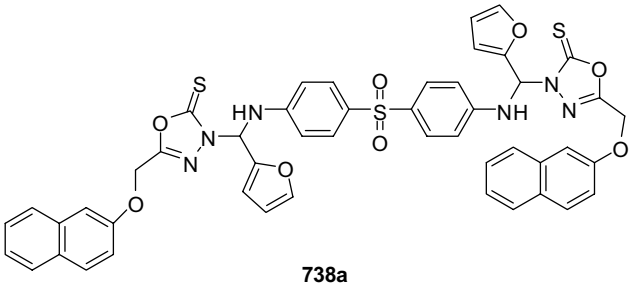
The obtained compounds have been conveniently transformed into 3,5-disubstituted-2,3-dihydro-1,3,4-oxadiazole-2-thiones **738** in 72–92% yield, by reaction with dapsone (**736**) and aromatic aldehydes **737** in methanolic solution. Compound **738a** has been shown to be very active against *Mycobacterium tuberculosis* H37Rv and isoniazid (INH) resistant *M. tuberculosis* with MIC of 0.1 and 1.10 μM respectively [552].





738

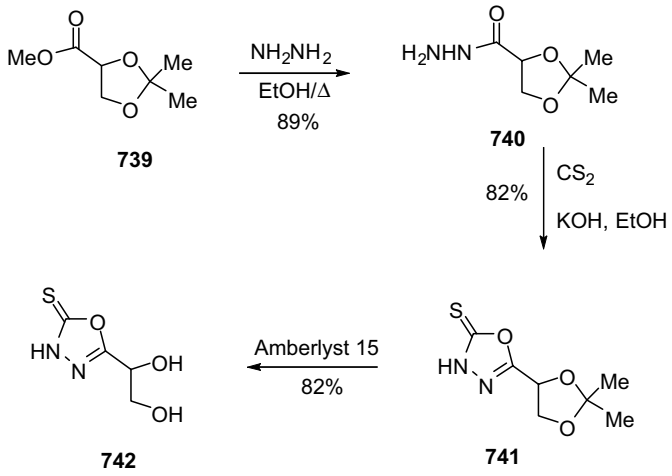
Scheme 13.234



738a

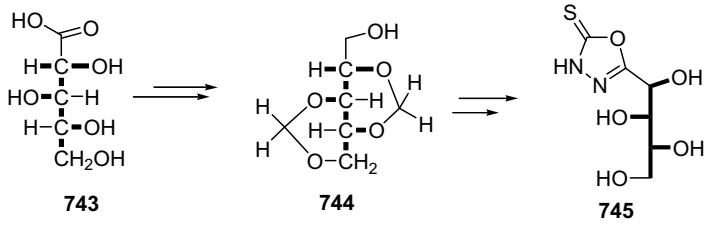
Acyclic C-nucleoside 5-(1,2-dihydroxyethyl)-*3H*-[1,3,4]oxadiazole-2-thione **742**, containing an 1,3,4-oxadiazolinethione ring, as mimic of ribose unit, has been synthesized starting from (±)-2,2-dimethyl-[1,3]dioxolan-4-carboxylic acid methyl ester **739** via reaction with hydrazine to give the corresponding hydrazide **740**, followed by CS_2 treatment and subsequent deacetonation with Amberlyst 15 (Scheme 13.235) [553].

The synthesis of this optical active compound has been performed by the same common route using as chiral source the D-mannitol. Furthermore, the use of D-xylose **743**, via (tetrahydro-[1,3]dioxino[5,4-d][1,3]dioxin-4-yl)-methanol **744**, leads



Scheme 13.235

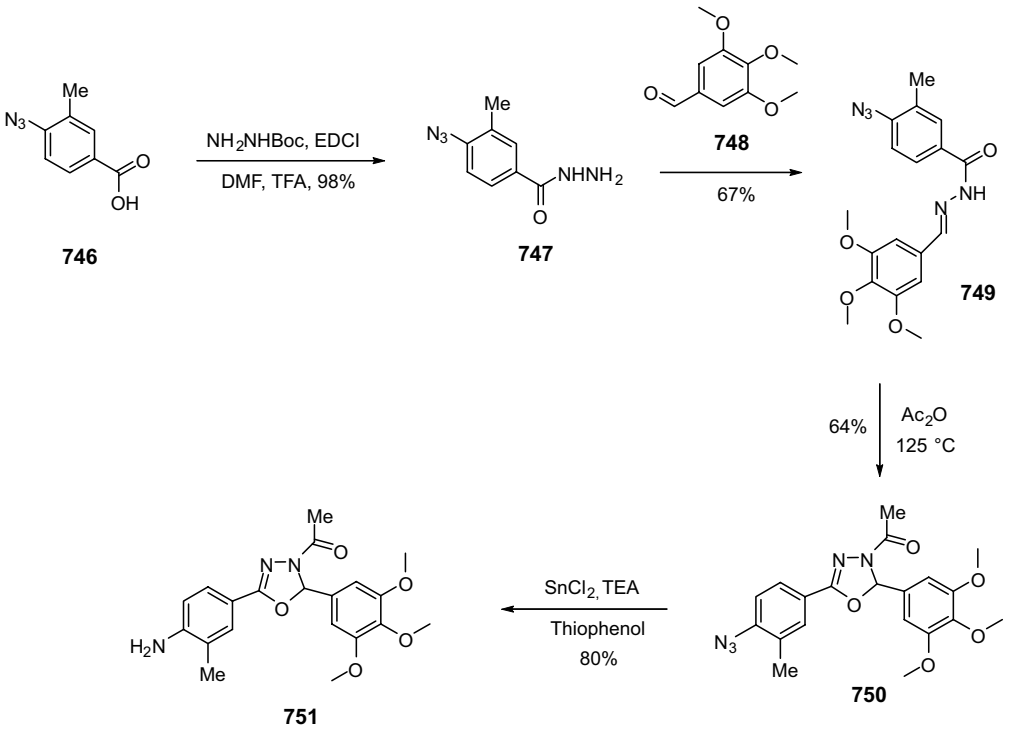
to 5-(1,2,3,4-tetrahydroxybutyl)-3*H*-[1,3,4]oxadiazole-2-thione **745** in enantiomerically pure form, in 8.5% total yield (Scheme 13.236).



Scheme 13.236

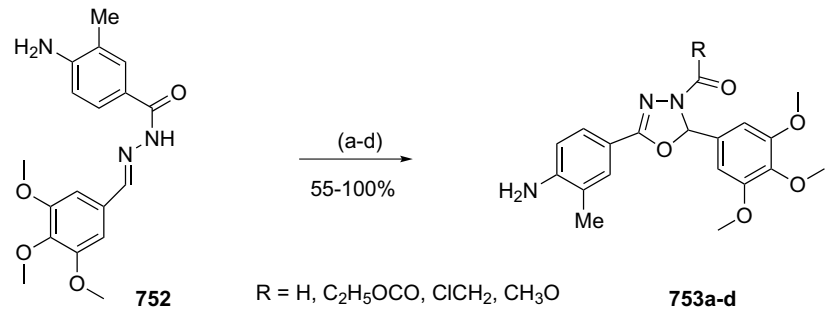
13.5.2.6 Synthesis of (Δ^2) (603), (Δ^3) (604), and 2,3,4,5-Tetrahydro-1,3,4-Oxadiazoles (605)

The Δ^2-1,3,4-oxadiazoline **751**, which inhibits cell proliferation and binds to tubulin, has been synthesized, as reported in Scheme 13.237, according to a process that involves as the key reaction the cyclization of acylhydrazone **749** with acetic anhydride [554]. The synthesis starts from the 4-azido-3-methylbenzoic acid (**746**), which was reacted with *tert*-butylcarbazate in the presence of 1-[3-(dimethylamino) propyl]-3-ethylcarbodiimide hydrochloride (EDCI) and a small amount of 4-(*N,N,*-dimethylamino)pyridine as base, to give, after trifluoroacetic acid (TFA) treatment, 98% of 4-azido-3-methylbenzoylhydrazide (**747**). This compound was condensed with 3,4,5-trimethoxybenzaldehyde (**748**) to give in 67% yield the corresponding acylhydrazone **749**, which was then cyclized to 2-(4-azido-3-methlphenyl)-4-acetyl-5-(3,4,5-trimethoxyphenyl)-Δ^2-1-3-4-oxadiazoline (**750**). Compound **750** was converted into the target compound **751** by reduction of the azido group with a suspension of $SnCl_2$, thiophenol, and triethyl amine, in 80% yield (total overall yield 32%).



Scheme 13.237

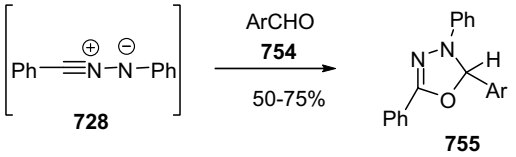
The method has been exploited to prepare various 2-[4-(*N,N*-dimethylaminophenyl]-4-substituted-(3,4,5-trimethoxyphenyl)-Δ^2-1-3-4-oxadiazolines **753**, which present interesting antitumoral activity (Scheme 13.238)[555].



(a) Ac_2O/HCO_2H; (b) ethyl oxalyl chloride; (c) chloroacetic anhydride; (d) dimethylpyrocarbonate

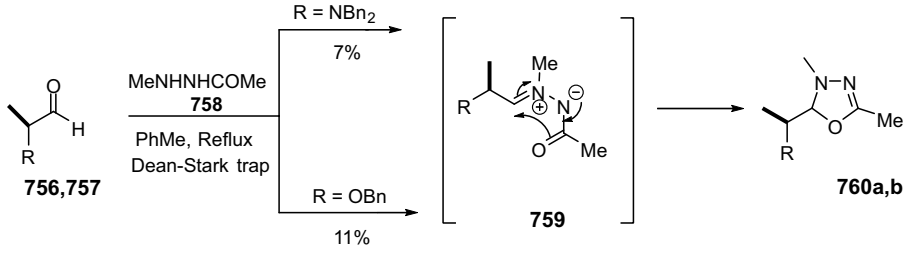
Scheme 13.238

C,*N*-Diphenyl nitrilimine **728** reacts, by 1,3-dipolar cycloaddition, with aldehydes **754** to produce in 50–75% yield 5-aryl-substituted-2,4-diphenyl-1,3,4-oxadiazolines (**755**) (Scheme 13.239) [555, 556].



Scheme 13.239

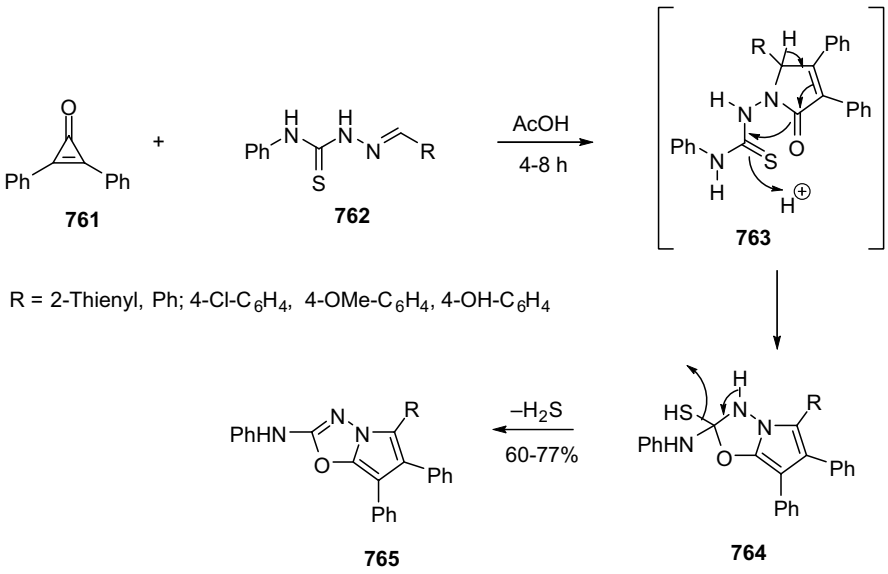
N-Substituted 2,3-dihydrooxadiazoles have been prepared recently by intramolecular cyclization of protected amino-aldehydes (1,5-dipolar cycloaddition) [557]. Thus, the *N*,*N*-dibenzylated aldehyde **756** after heating at reflux for 72 h, in toluene, with N^1-acetyl-N^2-methylhydrazine **758**, for 16 h, gave rise to the 2,3- dihydro-1,3,4-oxadiazole **760a** (7%), through a cyclization involving the hydrazine N-acetyl group of the not-isolable intermediate **759** (Scheme 13.240). 2-Benzyloxypropanal **757** gave the analogous product **760b** (11%).



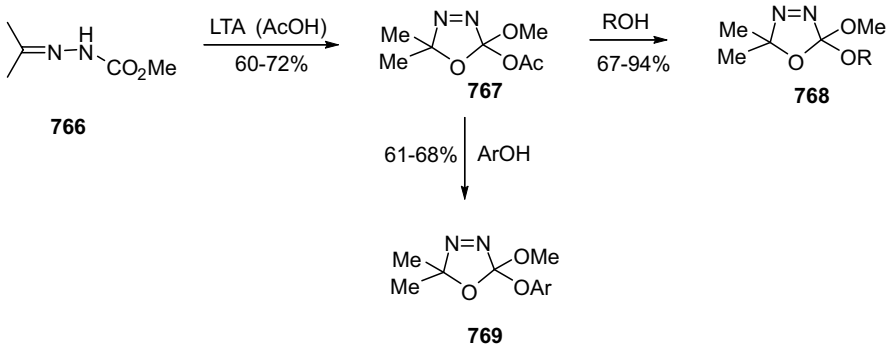
Scheme 13.240

Ylidine-*N*-phenylhydrazine-carbothioamides **762** react, in glacial acetic acid at reflux temperature, with 2,3-diphenylcyclopropenone (**761**) by way of an initial [2 + 3] cycloaddition to give **763**, which undergoes a cyclization process with extrusion of H_2S to afford the pyrrolo[2,1-*b*]-1,3,4-oxadiazoles **764a–e** in 60–77% yield (Scheme 13.241) [558].

Δ^3-1,3,4-Oxadiazolines (**604**) can be easily prepared by oxidation of acylhydrazones (see Schemes 13.201 and 13.203) [524, 525]. Thus, the oxidation of methoxycarbonyl hydrazone of acetone (**766**) with lead tetraacetate (LTA) furnishes the 2-acetoxy-2-methoxy-5,5-dimethy-Δ^3-1,3,4-oxadiazoline (**767**) in 60–72% yield (Scheme 13.242). This reaction route was further developed, transforming **767** into various Δ^3-1,3,4-oxadiazolines **768** and **769** by reaction with alcohols or phenols. Notably, these compounds have been used as a carbene source, because they fragment quite cleanly in solution at about 100 °C to give as by-products acetone and N_2 [559].



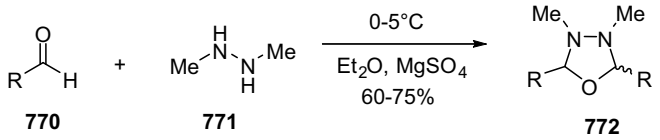
Scheme 13.241



R	Me	Et	Pr	i-Pr	Bu	t-Bu	CH_2CF_3	But-3ynyl	Pent-4ynyl
Ar	Ph	4-CN-C_6H_4	4-OMe-C_6H_4	—	—	—	—	—	—

Scheme 13.242

2,3,4,5-Tetrahydro1,3,4-oxadiazoles are obtained by reaction of 1,2-disubstituted hydrazines with aldehydes. Zwanesburg *et al.* have reported the synthesis of a series of 2,3,4,5-tetraalkyl-1-3-4-oxadiazolidines (**772**) by reaction of 1,2-dimethylhydrazine (**771**) with aliphatic aldehydes **770**. Thus, the appropriate aldehyde (2 equivalents) in 50 ml of dry ether and a few grams of $MgSO_4$ treated drop-wise during 15 min, below 5 °C, with one equivalent of aldehyde gave after 1 h the corresponding 1,3,4 oxadiazolines in 60–75% yield (Scheme 13.243) [560].

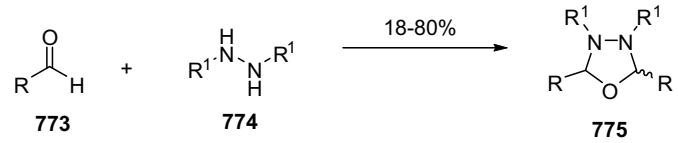


770 **771** **772**

R = Me, Et, Pr, Bu

Scheme 13.243

In a similar way Zinner and Kliwing have prepared other 1,3,4-oxadiazolines (**775**) using different hydrazines (**774**) (Scheme 13.244) [561].



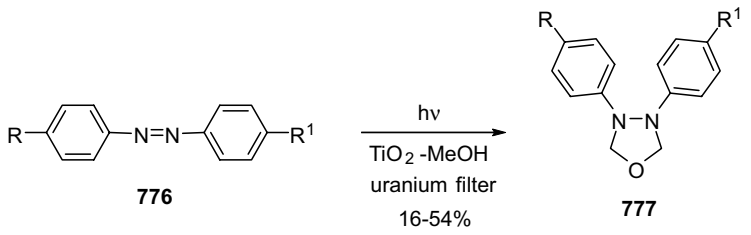
773 **774** **775**

R = H, Me, Et, Pr, *i*-Pr, *t*-Bu, Ph

R^1 = Me, i-Pr, Cyclohexyl, -$CH_2CHMeCH_2$-

Scheme 13.244

3,4-Diaryl substituted 1,3,4-oxadiazolidines **777** have been synthesized in moderate to good yields (16–54%) by TiO_2-photocatalyzed reaction of azobenzenes **776** in methanol through a uranium glass filter ($\lambda_{ex} > 320$ nm). The reaction probably involves a photoreduction of azobenzenes to 1,2-diarylhydrazine, an oxidation of methanol to formaldehyde, and the subsequent cyclization to 1,3,4-oxadiazolidines (Scheme 13.245) [562].



776 **777**

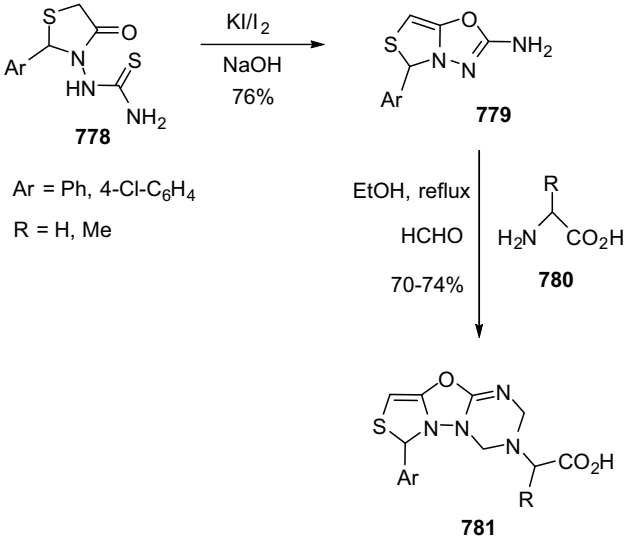
R = H, Ph

R^1 = 4-Cl-C_6H_4, 4-Me-C_6H_4, 3-Cl-C_6H_4

Scheme 13.245

Tricyclic fused-1,3,4-oxadiazole systems that display *in vitro* fungitoxicity comparable to that of fungicide Dithane M45 at 1000 ppm concentration against *Aspergillus niger* and *Fusarium oxysporum* have been obtained starting from 2-aryl-3-thioureido-4-

thiazolidinones **778**. These compounds were treated with a mixture of KI/I_2 under basic conditions to afford bicyclic compounds containing the Δ^2-1,3,4-oxadiazoline core (**779**) that were then converted into the target compounds by reaction with formaldehyde and various α-amino acids **780** (Scheme 13.246) [563].



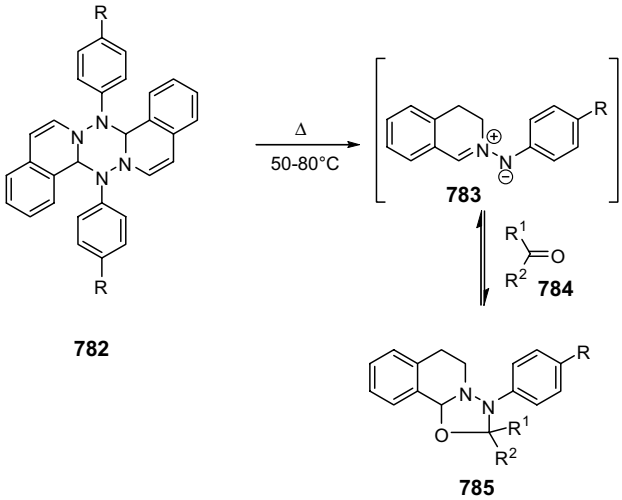
Scheme 13.246

Another versatile method for the synthesis of 1,3,4-oxadiazolidines (**605**) is the 1,3-dipolar cycloaddition of azomethinimines to carbonyl compounds. In particular, thermal decomposition of 8,8a,16,16a-tetrahydro-8,16-diphenyl-[1,2,4,5]tetrazino[6,1-*a*:3,4-*a*′]diisoquinoline (**782**) at 50–80 °C gave the 3,4-dihydroisoquinolineazomethinimine **783** that in presence of various carbonyl compounds (**784**) gave rise to substituted 1,3,4-oxadiazolidines **785** (79–100% yield) (Scheme 13.247) [564].

The obtained compounds, at high temperature, are thermolabile and decompose to azomethinimines and carbonyl compounds. This is recognizable by a color change to reddish-brown. Moreover, the azomethinimines thus obtained can be trapped with a wide range of dipolarophiles [565].

Hydrazide **786** (R = Me) and semicarbazides **787** (R = NHAr) have been used for the synthesis of azomethine imines **789** that, *in situ*, react with methyl glyoxylate hemiacetal **788** to give the corresponding 1,3,4-oxadiazolidines **790** in good yields (60–70%) (Scheme 13.248) [566].

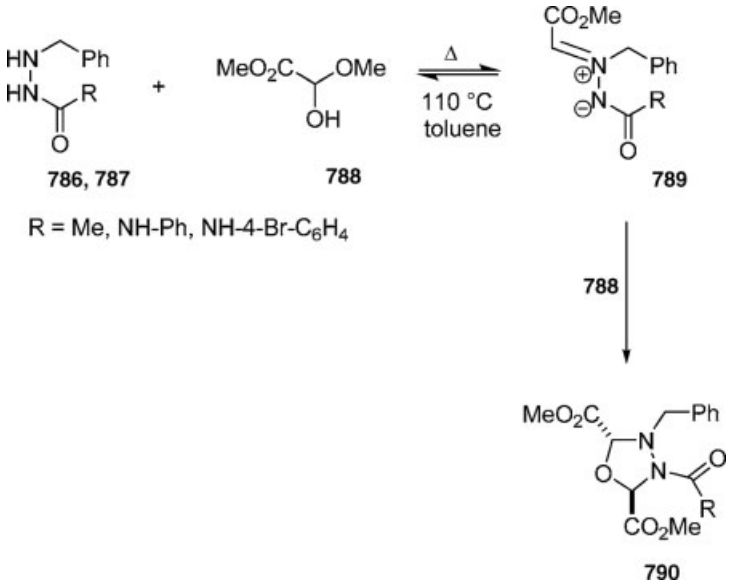
Similarly, the cyclic hydrazine **791** reacts with ethyl glyoxylate (**792**) in the presence of $MgBr_2 \cdot Et_2O$ in THF at 65 °C to give in 71% yield the bicyclic 1,3,4-oxadiazolidine **794** with a diastereomeric ratio of 46/38/16, via the azomethinimine intermediate **793** (Scheme 13.249) [567].



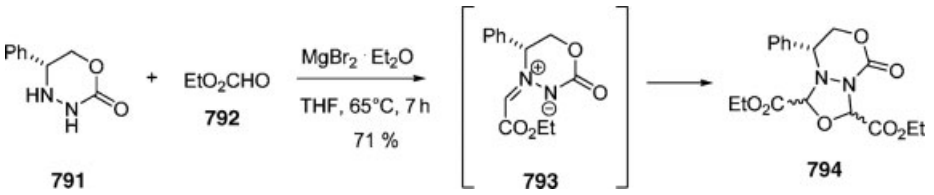
782

R	R^1	R^2	Yield
H	H	H	88
H	Me	H	79
H	CCl_3	H	84
NO_2	CCl_3	H	99
H	Ph	H	93
H	p-MeO-C_6H_4	H	92
H	p-Cl-C_6H_4	H	92
H	2-pyridyl	H	98
H	2-furyl	H	85
H	CO_2Et	H	93
NO_2	CO_2Et	H	100

Scheme 13.247



Scheme 13.248



Scheme 13.249

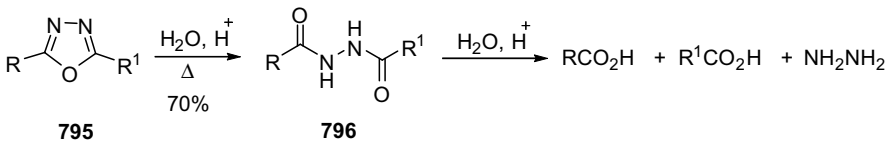
13.5.3 Reactivity

The reactivity of the 1,3,4-oxadiazole system is expressed in a series of different chemical transformations that can be amenable to (i) ring cleavage reactions, (ii) reactions due to the reactivity of heterocycle ring, and (iii) reactions of substituents.

13.5.3.1 Ring Cleavage Reactions

Ring-opening reactions of 1,3,4-oxadiazoles can be achieved by the action of nucleophilic reagents; in some cases the ring opening occurs by thermolysis or photolysis.

2,5-Dialkyl-1,3,4-oxadiazoles are cleaved by water in basic or acid conditions to produce diacylhydrazines that suffer further hydrolysis under vigorous conditions to give carboxylic acids and hydrazine (Scheme 13.250).

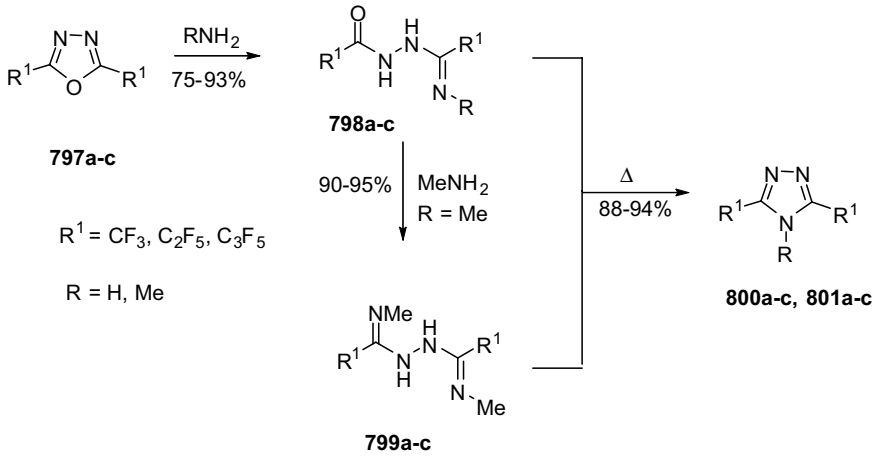


Scheme 13.250

This ring cleavage is dependent on the solubility. In fact, no hydrolysis was observed for 2,5-diphenyl-1,3,4-oxadiazole, which has a solubility in water of 0.03% [568].

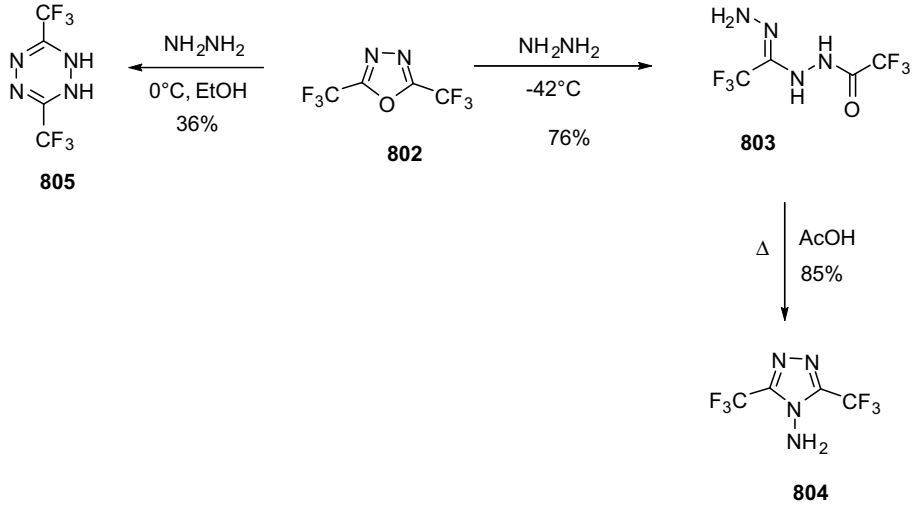
The presence of an electron-withdrawing group at C2 and C5 of the ring increases the reactivity towards nucleophiles. Thus, 2,5-bis(perfluoroalkyl)-1,3,4-oxadiazoles **797a–c** are very sensitive to nucleophilic attack. They react with ammonia to give the corresponding 1-(perfluoroalkylimidoyl)-2-(perfluoroacyl)hydrazines **798a–c** (R = H). The reaction occurs by attack of nucleophiles on the electron-deficient oxadiazole ring carbon to afford the **798a–c.** The reaction with the more nucleophilic methylamine provides 1,2-bis(*N*-alkyl)perfluoroalkylimidoyl)hydrazines **799a–c** via the hydrazine intermediates **798a–c** (R = Me) (Scheme 13.251) [569].

Interestingly, thermal dehydration or deamination of these hydrazine derivatives **798** and **799** produces the corresponding 4-substituted-3,5-bis(perfluoroalkyl)-4*H*-1,2,4-triazoles **800a–c** or **801a–c** in 88–94% yield (Scheme 13.251).



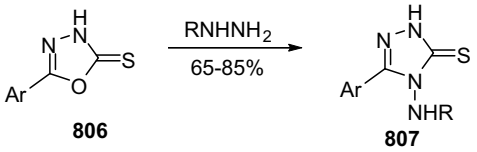
Scheme 13.251

In a similar fashion 3,5-bis(trifluoromethyl)-1,3,4-oxadiazole **802** reacts with hydrazine in methanol at −42 °C to afford the N^2-(α-hydrazonotrifluoromethyl)-N^1-(trifluoroacetyl)hydrazine **803**, which under heating is converted into the 4-amino-3,5-bis(trifluoromethyl)-4*H*-1,2,4-triazole (**804**) (85%). Dihydrotetrazine **805** in 36% yield is, instead, obtained if the reaction is performed in ethanol at 0 °C (Scheme 13.252) [570].



Scheme 13.252

2-Aryloxadiazolinethiones **806** also react with hydrazines, giving rise to triazoline thione derivatives **807** (Scheme 13.253) [571].

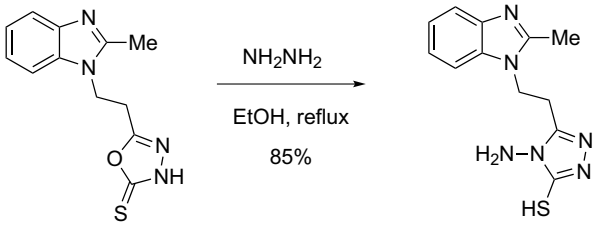


806 **807**

Ar = Ph, 4-MeO-C_6H_4, 4-NO_2-C_6H_4, 4-Pyridyl R = H, Ph, Me

Scheme 13.253

The ring-opening reaction promoted by hydrazine has been used by El-masry *et al.* to prepare, starting from 5-[2-(2-methylbenzimidazol-1-yl)ethyl-[1,3,4]-oxadiazole-2(3*H*)thione (**808**), 1-[(1-amino-2-mercapto-1,3,4-triazol-5-yl)ethyl]-2-methylbenzimidazole **809**, a biologically active compound, which possesses a moderate activity against *Bacillus cereus* (Scheme 13.254) [572].



808 **809**

Scheme 13.254

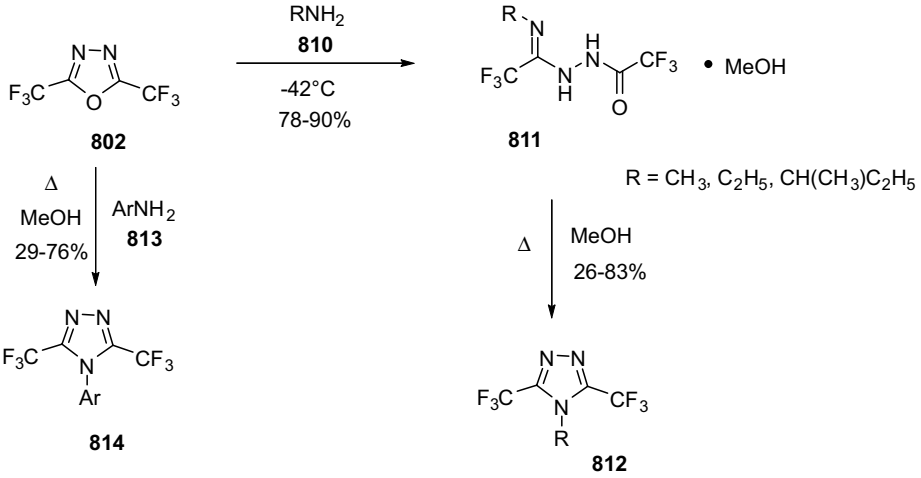
The reaction of **802** with primary alkyl amines **810** in methanol at −42 °C leads to complexes **811** whose structure has been elucidated by X-ray crystal analysis. These complexes can be conveniently transformed into 4-substituted-3,5-bis(trifluoromethyl)-4*H*-1,2,4-triazoles **812** by heating in methanol. The reaction of **802** with aromatic amines **813**, performed at reflux, provides directly the triazole derivatives **814** in moderate to good yields (Scheme 13.255) [573].

1,3,4-Oxadiazol-2-ones **815** react with water to form 1,5-diacylcarbohydrazides **819**. The pathway of this reaction appears to be the hydrolytic ring opening to form the hydrazide **818**, via either an acylhydrazinoformic acid **816** or the acyl hydrazonoformic acid **817**, followed by loss of carbon dioxide to produce **818**, which, in turn, attacks the remaining oxadiazolone **815** to form the observed product **819** (Scheme 13.256) [574].

Oxadiazolones **815** also react with hydrazine and amines to give semicarbazides **820** and carbohydrazides **821**, respectively (Scheme 13.257) [575].

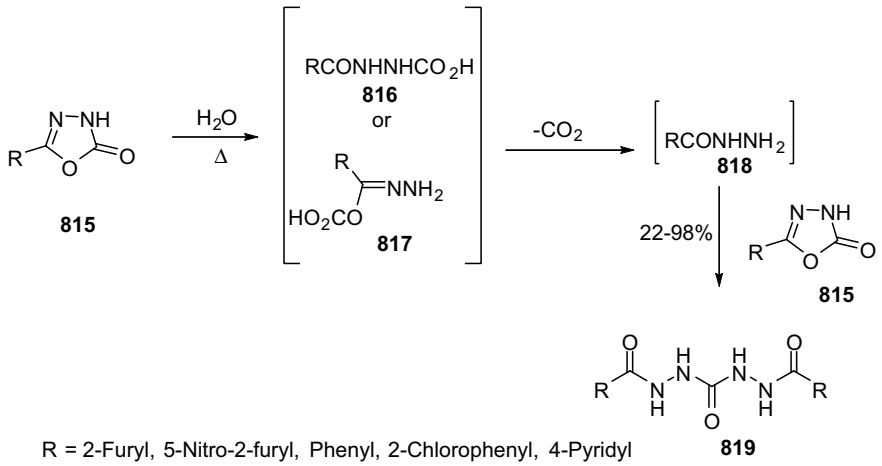
This reaction is quite general and similar to the above reported reactions. The reaction with NaOMe promotes the formation of **822** (Scheme 13.258) [575].

3-Substituted 5-trifluoromethyl-1,3,4-oxadiazolones **823a–d** are attacked by N and S-nucleophiles to give, as initial products, compounds deriving from the ring-opening reaction. In some cases, ring-enlargement products are formed. The



Ar = Ph, 4-Cl-C_6H_4, 4-Me-C_6H_4, 3-F-C_6H_4, 4-CF_3-C_6H_4, 4-MeO-C_6H_4

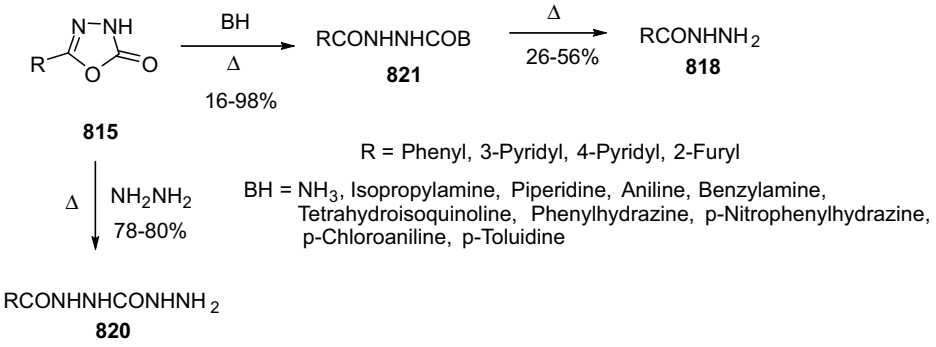
Scheme 13.255



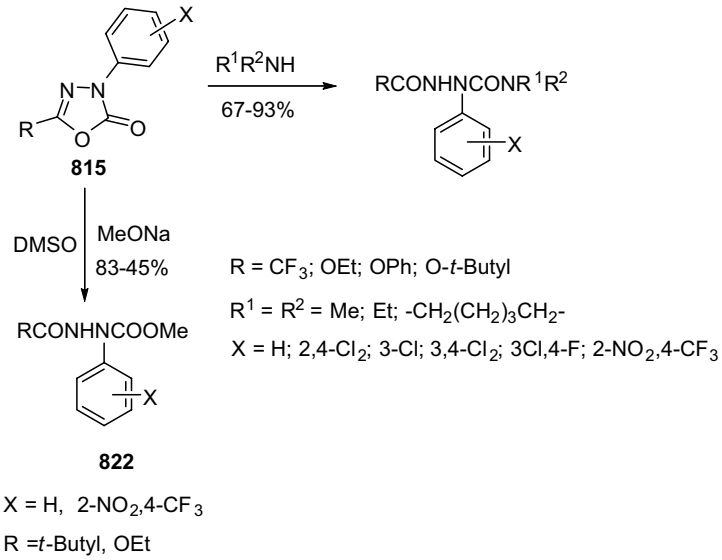
Scheme 13.256

reaction of 3-iodomethyl-5-trifluoromethyl-1,3,4-oxadiazol-2-(3*H*)-one (**823d**) with thiols (**827**) produces **830** through a Grob-type fragmentation (Scheme 13.259) [576].

2-Methyl-6-phenylimidazo[2,1-*b*]oxadiazole **831**, a cyclic oxadiazolimine, is cleaved with concentrated HCl or an 8% solution of KOH to give **832** and then **833** in quantitative yield. The reaction of **831** with 48% HBr gives **834** in 40% yield. In addition, **833** has been transformed into **834** by reaction with HBr (Scheme 13.260) [577].

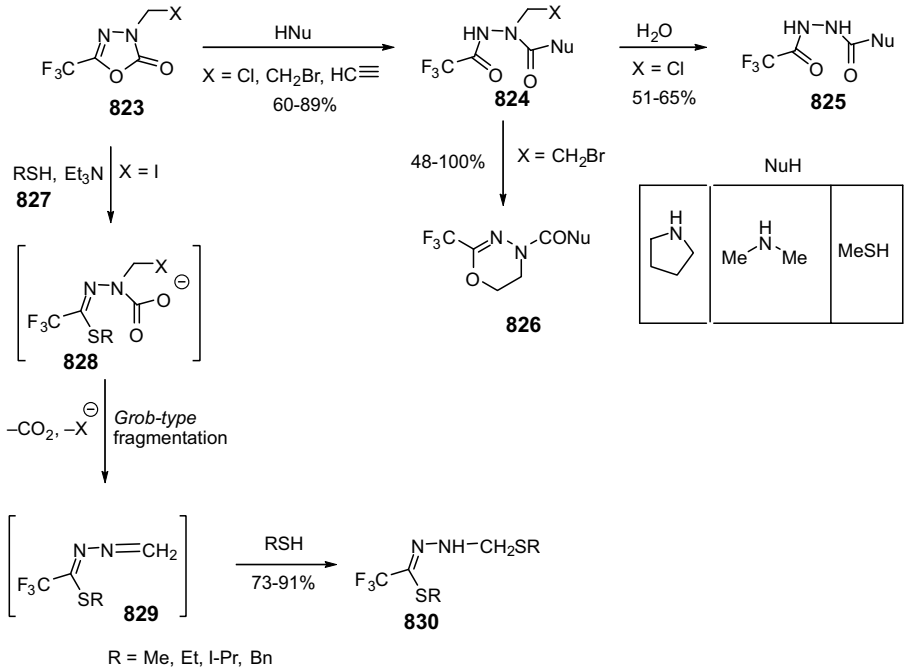


Scheme 13.257

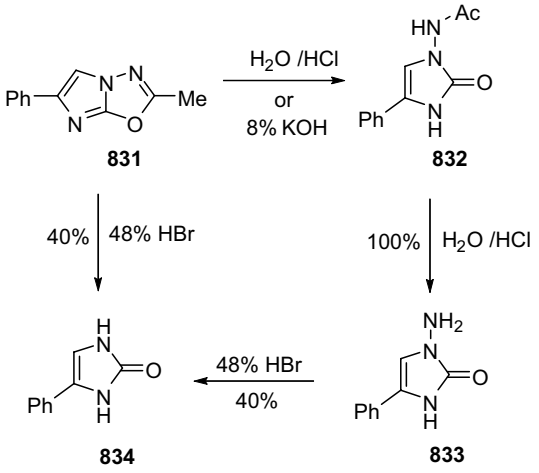


Scheme 13.258

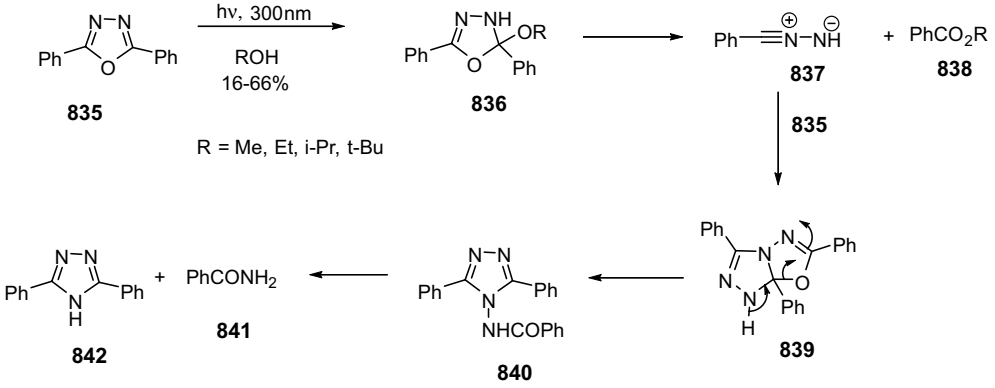
2,5-Diphenyl-1,3,4-oxadiazole **835** is cleaved under photolytic conditions in the presence of alcohols to yield benzonitrile imine **837** and benzoic acid esters **838** in moderate yields [578]. These compounds are produced by an initial nucleophilic attack of alcohols on the C=N bond of the oxadiazole ring, followed by cycloelimination. Moreover, as expected, the benzonitrile imine **837** undergoes a 1,3-dipolar cycloaddition with the unreacted 1,3,4-oxadiazole **835** to furnish the bicycloadduct **839**. This compound is then transformed into benzamide (**841**) and 3,5-diphenyl-1,2,4-triazole (**842**), via 4-benzamido-3,5-diphenyl-1,2,4-triazole (**840**) produced by ring opening of **839** and concurrent hydrogen shift (Scheme 13.261).



Scheme 13.259

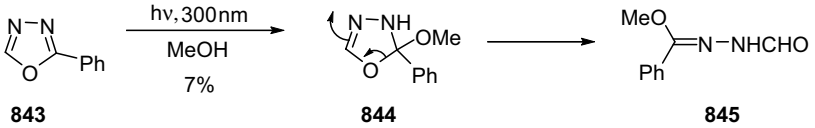


Scheme 13.260



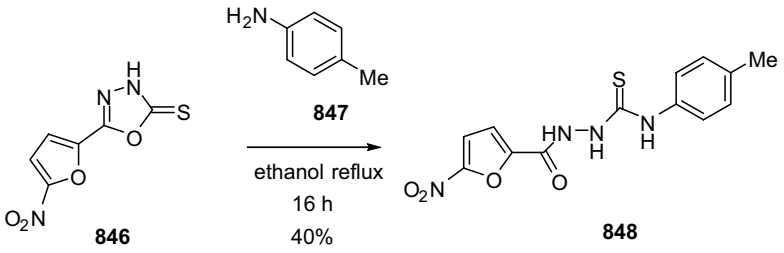
Scheme 13.261

In the case of 2-phenyl-1,3,4-oxadiazole (**843**), the regioselective addition of methoxy group at C2 of 1,3,4-oxadiazole ring affords, as the only detectable compound, 1-(α-methoxybenzylidene)-2-formylhydrazine **845** in 7% yield, produced by an initial nucleophilic attack of methanol followed by a ring opening reaction (Scheme 13.262).



Scheme 13.262

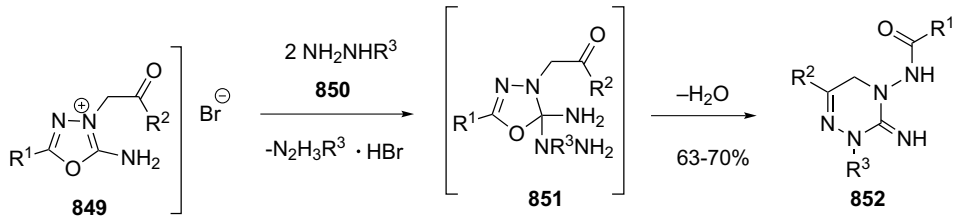
Thione **846** forms a stable salt with *p*-toluidine (**847**), which gives rise to ring-open product **848** on heating (Scheme 13.263) [579].



Scheme 13.263

Alkylhydrazine and arylhydrazines **850** react with 1,3,4-oxadiazolium bromides **849** to produce 2-methyl or 2-phenyl-4-acylamino-3-imino-6-aryl-2,3,4,5-tetrahydro-1,2,4-triazines **852**. These compounds are probably obtained via inter-

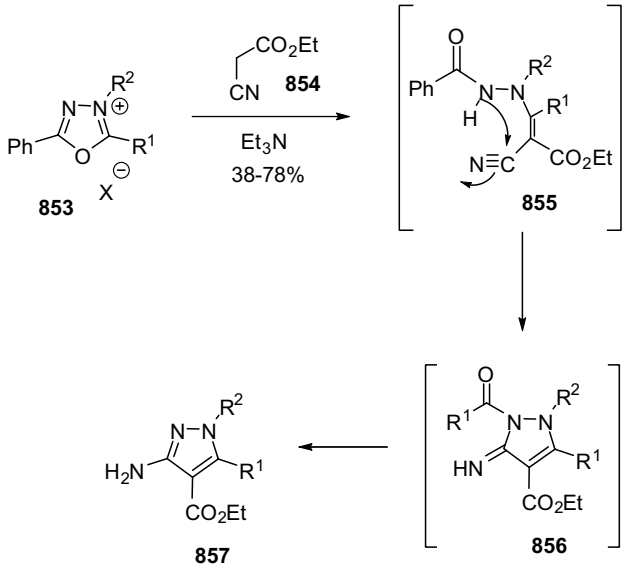
mediate **851**, which rearranges to **852** through a ring opening reaction followed by a ring closure (Scheme 13.264) [580].



R^1 = Me, Et, Ph, Ph-CH_2 R^2 = Ph, 4-Cl-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4 R^3 = Me, Ph

Scheme 13.264

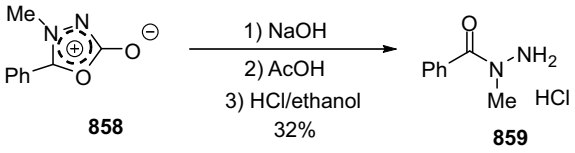
1,3,4-Oxadiazolium salts **853** react with ethyl cyanoacetate (**854**) in the presence of triethylamine to yield 1,5-substituted 3-aminopyrazole-4-carboxylic esters **857**. An open chain intermediate **855** was isolated and the reaction involves an initial attack at C2 of the oxadiazole ring (Scheme 13.265) [581].



R^1 = Ph, Me, Et, i-Pr R^2 = Ph, Et, 4-NO_2-C_6H_4, 2,4-$(NO_2)_2$-C_6H_3

Scheme 13.265

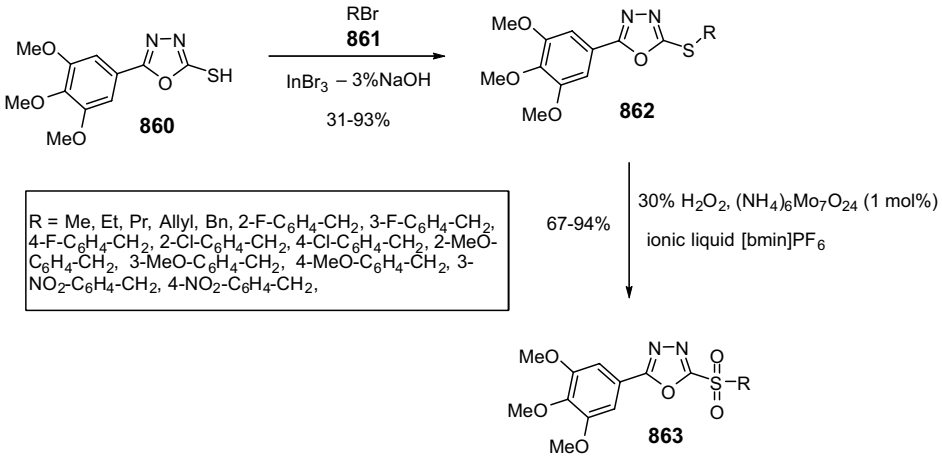
Isosydnone **858** undergoes a ring-opening reaction by treatment with sodium hydroxide followed by addition of an ethanol–hydrogen chloride mixture to give 1-benzoyl-1-methylhydrazine hydrochloride (**859**) (Scheme 13.266) [541].



Scheme 13.266

13.5.3.2 Oxidative and Reductive Processes

1,3,4-Oxadiazoles are very stable to strong oxidizing and reducing agents. However, some oxidations or reductions involving atoms linked to the heterocycle ring have been performed. Thus, recently, sulfonyl derivatives **863**, with antifungal activity, containing trimethoxyphenyl substituted 1,3,4-oxadiazoles have been synthesized, in 67–94% yield, by hydrogen peroxide oxidation, catalyzed by ammonium molybdate in ionic liquid ([bmim]PF6), of substituted 1,3,4-oxadiazole sulfide **860** [582]. In particular, 1,3,4-oxadiazole sulfides **862** have been prepared, in 31–93% yield, by thioetherification, catalyzed by indium tribromide, of 5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole-2-thiol (**860**) with organic halides (Scheme 13.267).

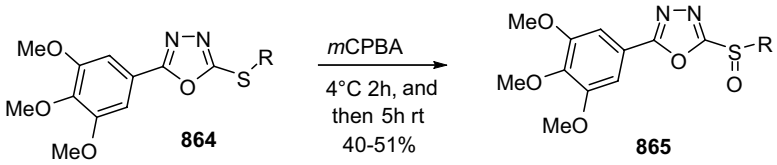


Scheme 13.267

The oxidation of sulfides **864** with m-CPBA furnishes, in contrast, the corresponding sulfoxides **865** (Scheme 13.268) [583].

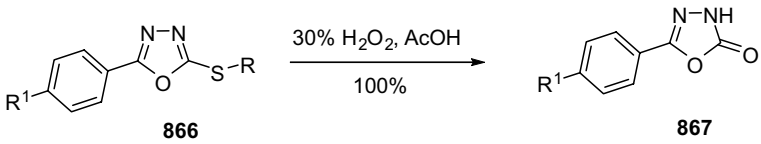
It has also been reported that the oxidation of **866** with hydrogen peroxide and no catalyst affords oxadiazolone derivatives **867** (Scheme 13.269) [584].

Oxidation of 2,5-di *m*- or *p*-tolyl-1,3,4-oxadiazoles **868** with potassium permanganate/pyridine leads to the corresponding dicarboxylic acids **869** (78–94%) [585]; if the oxidation is performed with chromium trioxide/acetic anhydride, diacetoxymethyl derivatives **870** are obtained. These latter compounds can be conveniently transformed by acid hydrolysis into dialdehydes **871** (Scheme 13.270) [586].



R = Me, Et, Pr, Allyl, Bn, 2-F-C_6H_4-CH_2, 3-F-C_6H_4-CH_2, 4-F-C_6H_4-CH_2, 2-Cl-C_6H_4-CH_2, 4-Cl-C_6H_4-CH_2, 2-MeO-C_6H_4-CH_2, 3-MeO-C_6H_4-CH_2, 4-MeO-C_6H_4-CH_2, 3-NO_2-C_6H_4-CH_2, 4-NO_2-C_6H_4-CH_2,

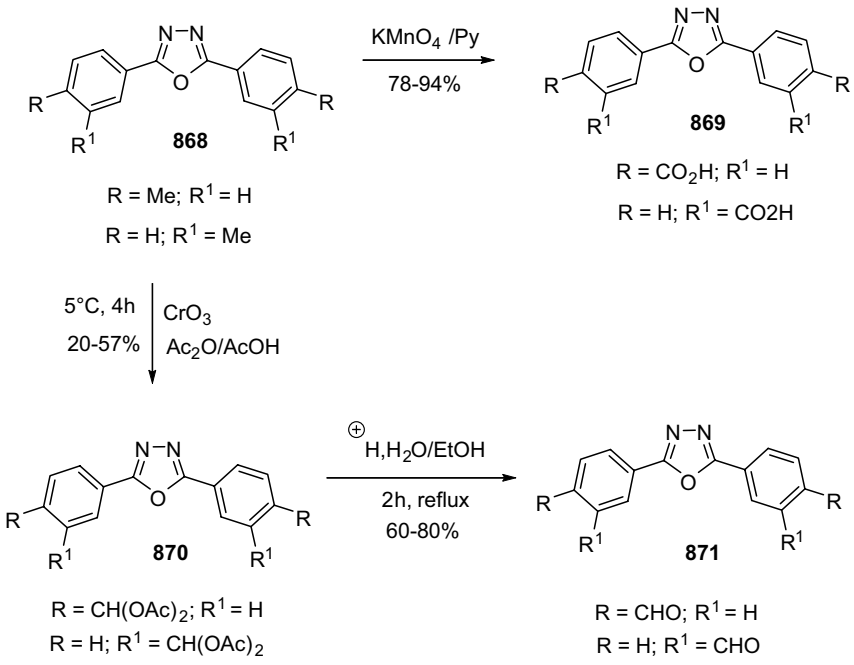
Scheme 13.268



R = CH_2=$CHCH_2$, $HC{\equiv}C{-}CH_2$, $HOH_2C{-}C{\equiv}C{-}CH_2$,

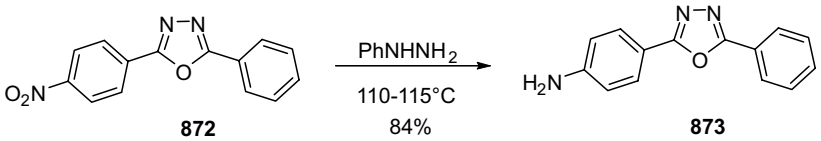
R^1 = H, Me, Br

Scheme 13.269



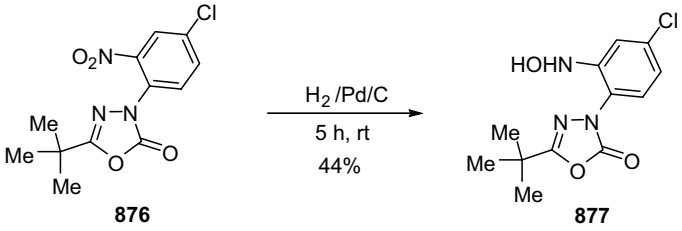
Scheme 13.270

Reduction of the nitro group linked to phenyl moiety of 1,2,4-oxadiazoles with phenylhydrazine or hydrogen/palladium has been reported to give aminoaryl 1,3,4-oxadiazoles in good yield [587]. Thus, 2-phenyl-5-(*p*-nitrophenyl)-1,3,4-oxadiazole (**872**), carefully heated to 110–15 °C for 75–90 min, gives 2-phenyl-5-(*p*-aminophenyl)-1,3,4-oxadiazole **873** in 84% yield (Scheme 13.271) [588]. Similar results have been obtained with nitrophenyl derivatives such as **874**, which upon hydrogenation with Pd/C yields **875** [589].



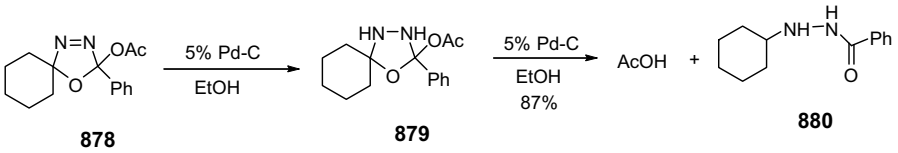
Scheme 13.271

Hydrogenation, performed on 5-*tert*-butyl-3-(4-chloro-2-nitrophenyl)-1,3,4-oxadiazolin-2-one (**876**) in AcOEt, conversely, leads to a partial reduction of nitro group with the formation of the 4-chloro-2-(hydroxyamino)phenyl derivative **877** in 44% yield (Scheme 13.272) [590].



Scheme 13.272

It has been reported that the hydrogenation of Δ^3-1,3,4-oxadiazoline **878**, performed in ethanol over Pd/C, gives acetic acid and *N*-cyclohexyl-*N*-benzoylhydrazine (**880**) via the corresponding 2,3,4,5-tetrahydro-1,3,4-oxadiazole derivative **879** (Scheme 13.273) [591].



878 879 880

Scheme 13.273

13.5.3.3 Reactions due to the Reactivity of the Heterocyclic Ring

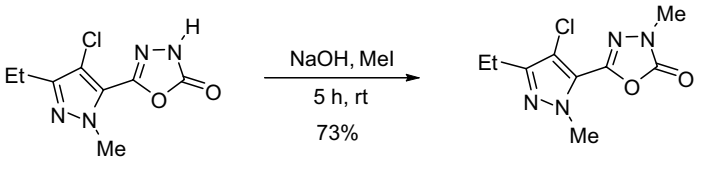
1,3,4-Oxadiazoles are weak bases. The pK_a values of 2,5-diaryl-1,3,4-oxadiazoles measured by the method of Yates and MacClelland in aqueous solution of sulfuric acid are in the range of −1.15 to −2.49. 2-Amino derivatives ($pK_a = 2.3-2.7$) are more basic and form stable salts. As already reported, some hydrochloride salts have been obtained by hydrochloric reaction of 2-amino-5-aryl-1,3,4-oxadiazoles, in DMF/H_2O or in ethanol–ether as solvents, giving rise to compounds having muscle relaxant properties (Scheme 13.230) [549]. In the same context, 5-imino-2-phenyl-Δ^2-1,3,4-oxadiazoline-maleate, -citrate, -sulfate, and -nitrate, together with 5-imino-2-(*p*-aminophenyl)-Δ^2-1,3,4-oxadiazoline dihydrochloride, 5-imino-2-(1-ethylpropyl)-Δ^2-1,3,4-oxadiazoline hydrochloride, 5-imino-2-(1-ethylbenzyl)-Δ^2-1,3,4-oxadiazoline hydrochloride, and 1-ethyl-3-(5-phenyl-1,3,4-oxadiazol-2-yl)urea have also been prepared.

Electrophilic substitution on the C-atoms of the ring is difficult, because protonation of the nuclear nitrogen in acidic media reduces strongly the possibility of electrophilic attack. Thus, no nitrations, sulfonations, or halogenations of unsubstituted oxadiazoles are known. Mono-substituted derivatives are not able to react with electrophiles because they are sensitive to acid conditions. In fact, for example, 2-phenyl 1,3,4-oxadiazole is easily hydrolyzed by acids at room temperature to give benzohydrazide and formic acid [588]. In addition, the mono- and 2,5-dialkyl-derivatives undergo a ring-opening reaction on treatment with acids [592].

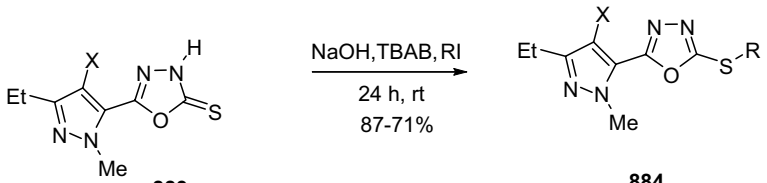
There are several examples of reactions of alkyl halides with 1,3,4-oxadiazole derivatives. The alkylation reactions occur preferentially at the N3 ring atom, except for amino and thio derivatives, where the alkylation, essentially, occurs at the sulfur or the exo-nitrogen atom.

Thus, it has been reported that the reaction of 5-(4-chloro-3-ethyl-1-methyl-1H-pyrazole-5-yl)-1,3,4-oxadiazole-2-one (**881**) with methyl iodide in the presence of NaOH gives rise to the corresponding *N*-methyl derivative **882**, while alkylation of the 2-thioxo derivatives **883** with NaOH, tetrabutylammonium bromide (TBAB), and alkyl iodide leads to the corresponding thioalkylated derivatives **884** in good yield. In the same context, it has been noted that the 2-alkylthio derivatives so obtained are active against rice sheath blight, which is a major disease of rice in China (Scheme 13.274) [593].

Analogously, a series of bis-oxadiazolyl sulfides **887** (R = Ph, substituted Ph) have been synthesized via alkylation reaction of 5-[[2-(trifluoromethyl)-1H-benzimidazol-1-yl]methyl]-1,3,4-oxadiazole-2(3)thione(2-trifluoromethylbenzimidazol-1-ylmethyl)-5-mercapto-1,3,4-oxadiazoles **885** with 2-aryl-5-chloromethyl-1,3,4-oxadiazoles **886**. Interestingly, the relative oxidation of these sulfides performed at 0 °C



881 882

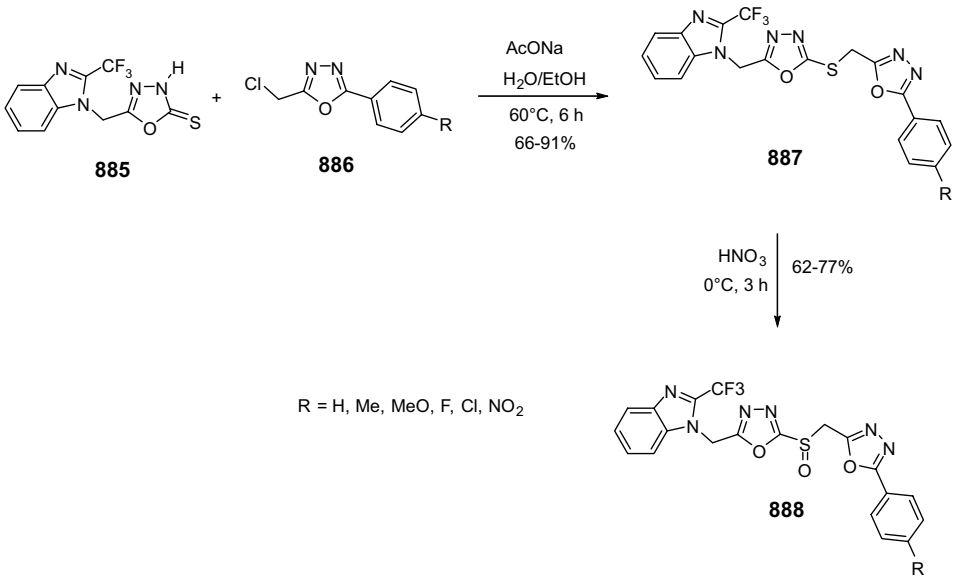


883 884

X = H, Cl
R = Me, *n*-Pr, *n*-C_5H_{11}, *n*-C_7H_{15}, *n*-C_8H_{17}, $CH(CH_3)CO_2Et$

Scheme 13.274

with HNO_3 produces the sulfoxide derivatives **888** in good yield (Scheme 13.275) [594].

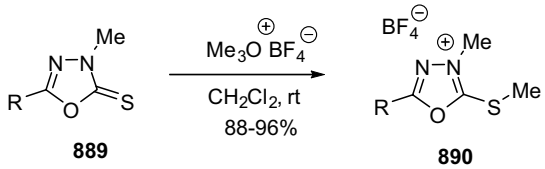


885 886 887 888

Scheme 13.275

Methylation of 5-methyl or 5-aryl-2-thioxo-2,3-dihydro-1,3,4-oxadiazoles **889** with trimethyloxonium tetrafluoroborate in CH_2Cl_2 at room temperature furnishes, as

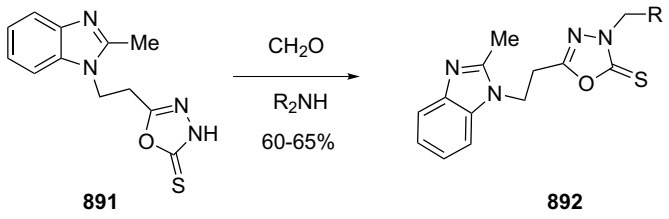
expected, the corresponding methyl(methylthio)oxadiazolium tetrafluoroborates **890** in 86–96% yield (Scheme 13.276) [595].



R = Me, Ph, 4-Me-C_6H_4, 4-MeO-C_6H_4

Scheme 13.276

The Mannich reaction of 1,3,4-oxadiazole-2-thione derivatives **891** with different secondary amines and paraformaldehyde in absolute ethanol occurs at the N3 ring atom and leads to 5-[2-(2-methylbenzimidazol-1-yl)ethyl-3-*N*-methylamino-1,3,4-oxadiazole-2-thiones (**892**) in 60–65% yield (Scheme 13.277). In particular, the diethylamino derivative **892** has shown to exhibit moderate antimicrobial activity against one strain of Gram-positive bacteria (*Bacillus cereus*) [596].



R = $N(C_2H_5)_2$, $N(C_4H_8O)$, $N(C_4H_8)NMe$

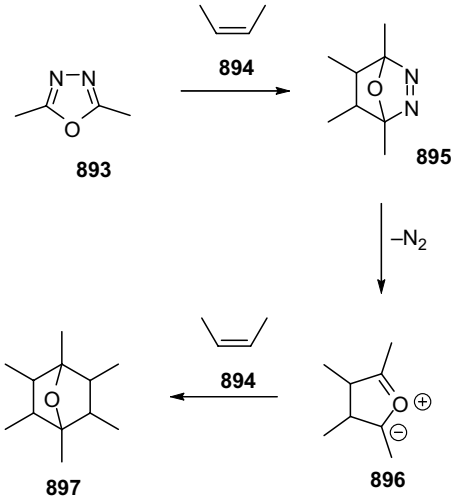
Scheme 13.277

The 1,3,4-oxadiazole ring **893** has been, recently, used as 4π component in a Diels–Alder reaction. This ring is considered an electron poor diaza-diene and reacts with extremely electron rich (aminoacetylenes) or strained dienophiles in an inverse electron demand reaction. Unfortunately, the mono cycloadduct **895** thus obtained has never been isolated, but it extrudes N_2 and generates a carbonyl ylid **896**, which further reacts with olefin in a 1,3-dipolar cycloaddition to give the final product **897** (Scheme 13.278).

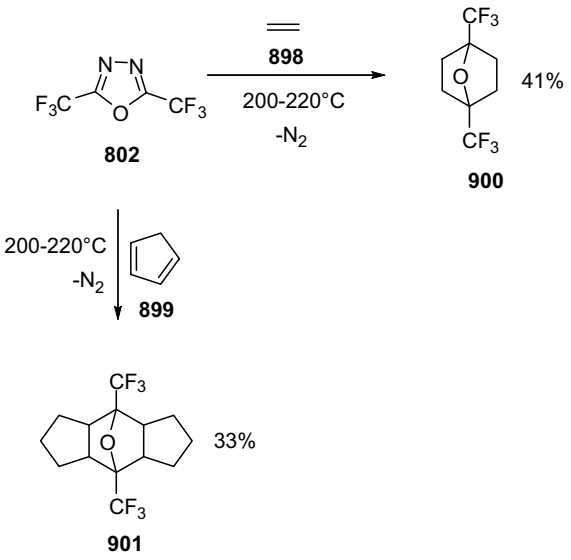
The first example of such a cycloaddition cascade was reported by Vasiliev *et al.* Heating at 200–220 °C of the 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole **802** with ethylene (**898**) or cyclopentadiene (**899**) affords the oxabicycloheptane **900** in 41%, or oxatetracyclotridecane **901** in 33% yield respectively (Scheme 13.279 [597].

Other examples of this cycloaddition have been reported, giving rise to the formation of strained structures (Scheme 13.280) [598].

In some cases, the intramolecular version of this reaction is more productive and leads to bicyclic or monocyclic derivatives (Scheme 13.281) [599].

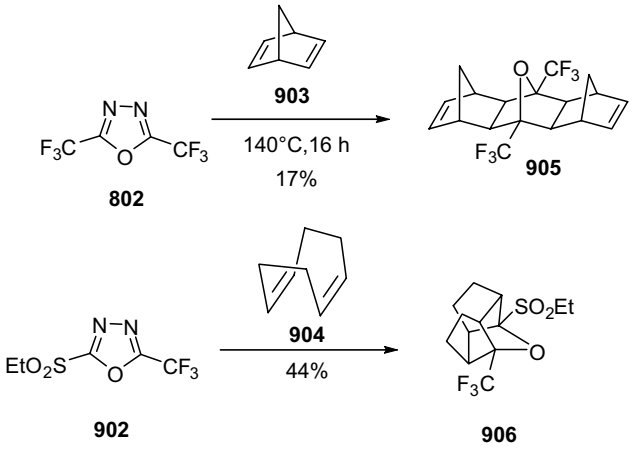


Scheme 13.278

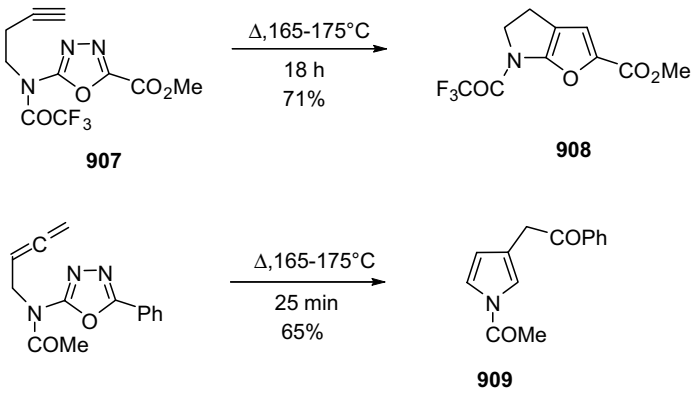


Scheme 13.279

The synthetic efficiency of the process can be improved through the development of domino reactions that allow the formation of complex compounds, starting from simple substrates, in a single transformation consisting of several steps. A domino reaction can be defined as a process involving two or more bond-forming transformations that take place under the same reaction conditions, without adding



Scheme 13.280

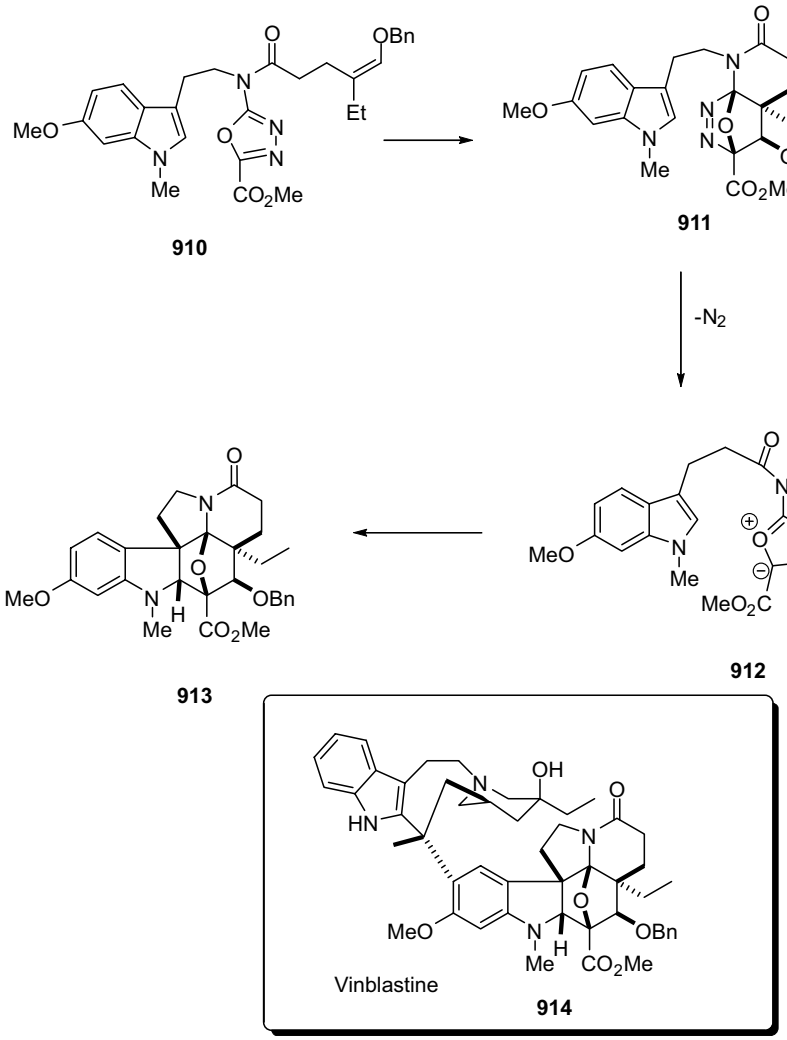


Scheme 13.281

additional reagents and catalysts and in which the subsequent reactions result as a consequence of the functionalities obtained in the previous step.

Thus, the intramolecular Diels–Alder (DA)/1,3-dipolar cycloaddition (1,3-DC) cascade of 1,3,4-oxadiazoles has became a powerful tool for the rapid generation of molecular complexity. Specifically, this methodology has been featured in the construction of the pentacyclic ring systems and ultimately in the total syntheses of vindoline and several structurally related natural products [600]. Vindoline (**913**) constitutes the most complex half of vinblastine (**914**), a member of the bisindole alkaloid family that is used as an antineoplastic drug. The method is based on a combination of a DA and 1,3-DC. The synthesis proceeds by a diastereoselective tandem [4 + 2]/[3 + 2]-cycloaddition of a substituted 1,3,4-oxadiazole. The reaction leading to vindoline is initiated by an intramolecular [4 + 2]-cycloaddition of 1,3,4-oxadiazole **910** with the tethered enol ether. Loss of N_2 from the initially formed

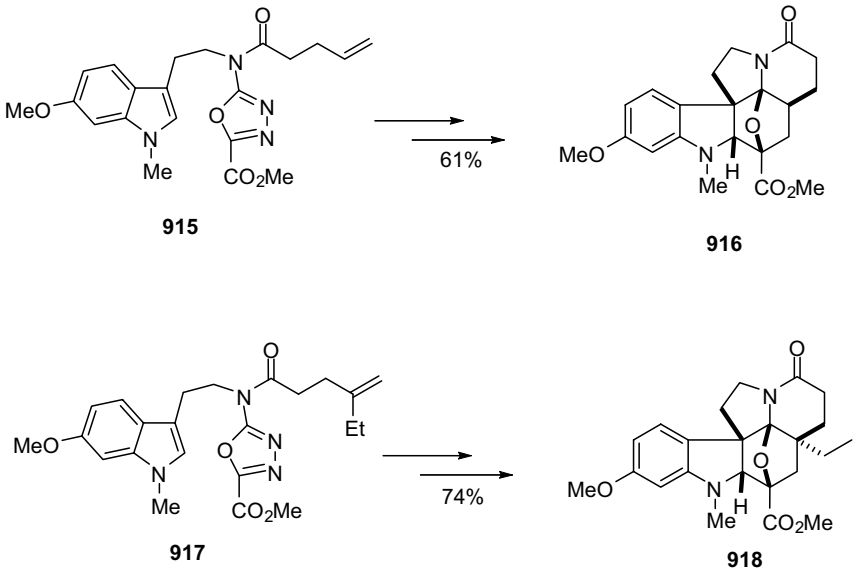
cycloadduct **911** provides the carbonyl ylid dipole **912**, which undergoes a subsequent 1,3-dipolar cycloaddition across the proximal indole moiety (Scheme 13.282) [601].



Scheme 13.282

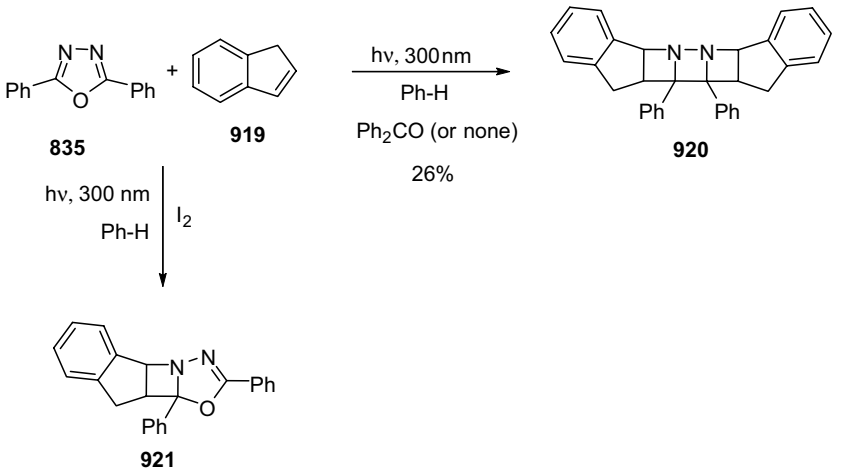
Some other examples of this methodology (**916**, **918**) are reported in Scheme 13.283 [599].

The double bond of the 1,3,4-oxadiazole ring has also been used as 2π component in a [2 + 2] photochemical cycloaddition. Thus, it has been reported that 2,5-diphenyl-1,3,4-oxadiazole (**835**) with indene (**919**), with or without benzophenone as a sensitizer, affords the bis adduct diazetidine derivative **920**, while if the reaction is



Scheme 13.283

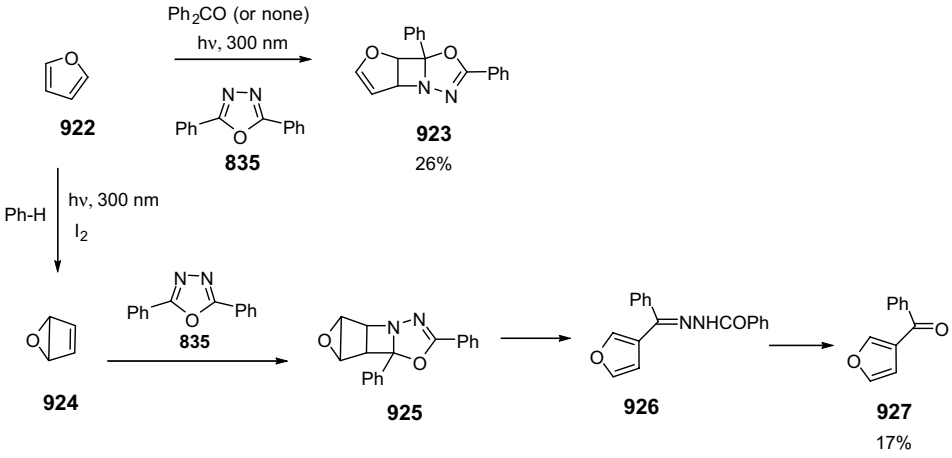
performed in the presence of iodine the photoreaction leads to the mono-adduct **921** (Scheme 13.284) [602].



Scheme 13.284

A 1 : 1 adduct with **923** (26%) was obtained when a solution of **835** was irradiated with an excess of furan (**922**) in the presence or absence of benzophenone used as sensitizer. The reaction did not occur in the presence of a triplet quencher such as piperylene, indicating that the photoaddition takes place from an

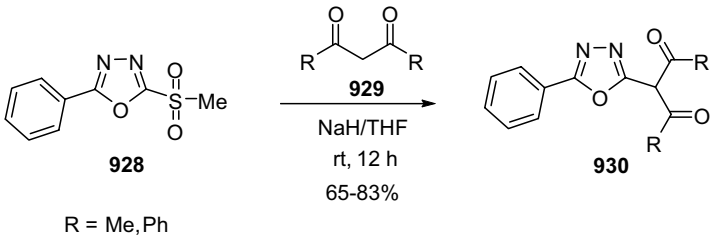
excited triplet state [603]. The presence of iodine promotes a different reaction pathway, leading to the formation of 3-benzoylfuran (**927**) (17%). This product has been rationalized by an initial valence tautomerization of furan into cyclobutadiene oxide **924**, which undergoes a [2 + 2] cycloaddition with a double bond of 1,3,4-oxadiazole ring, leading to monoadduct **925**. This compound, via ring opening and photoisomerization reaction, produces the *N*′-[3-furyl(phenyl)methylene]phenylhydrazide (**926**) that is easily hydrolyzed with trace amounts of water to give **927** (Scheme 13.285).



Scheme 13.285

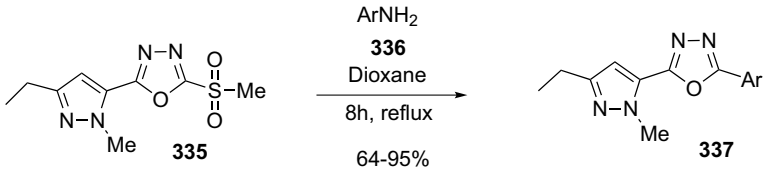
13.5.3.4 **Reactions with Nucleophiles**

Direct nucleophilic substitutions of ring C-substituents in 1,3,4-oxadiazoles are seldom. These reactions occur only for compounds containing a good leaving group, via addition–elimination reaction. Thus, for example, 3-(5-phenyl-[1,3,4]oxadiazol-2-yl]pentane-2,4-dione (**930**, R = Me) and 3-(5-phenyl-[1,3,4]oxadiazol-2-yl]-dibenzoylmethane (**930**, R = Ph) have been synthesized, in 63% and 85% yield, respectively, by nucleophilic substitution of 2-methylsulfonyl-5-phenyl-1,3,4-oxadiazole (**928**) with β-diketone anions, formed by the corresponding carbonyl compounds **929** with NaH (Scheme 13.286) [604].



Scheme 13.286

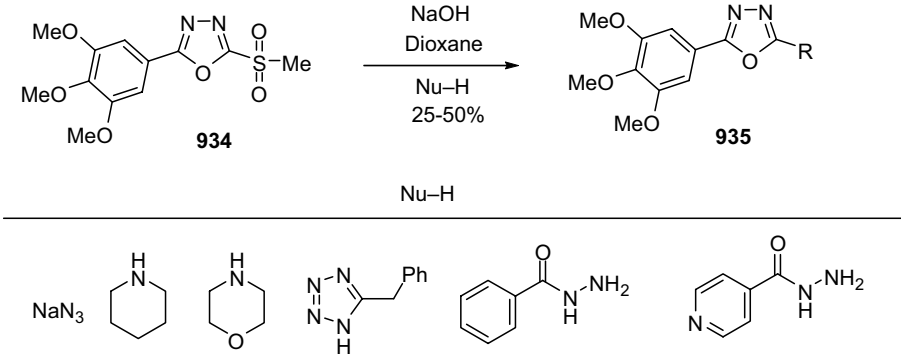
A similar displacement reaction has been performed with 2-methylsulfonyl-5-pyrazolyl-1,3,4-oxadiazole **931** that by reaction with arylamines **932** produces bioactive 2-substituted-amino-5-pyrazolyl-1,3,4-oxadiazoles **933**, which exhibit moderate fungicidal activity (Scheme 13.287) [605].



Ar = Ph, 4-Cl-C_6H_4, 3-Cl-C_6H_4, 4-Br-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4,

Scheme 13.287

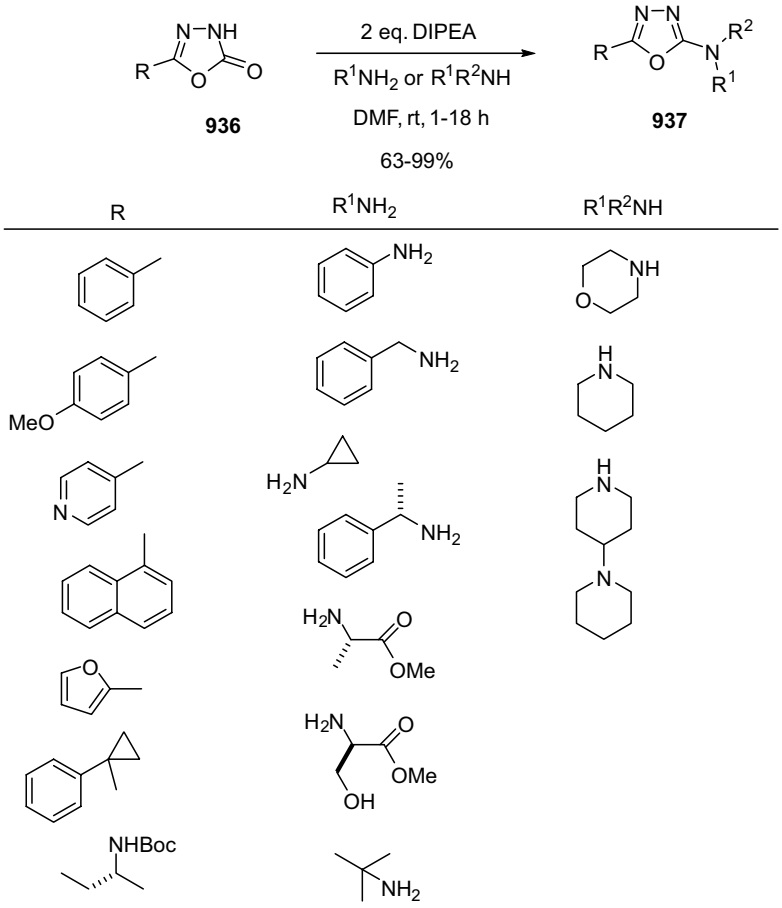
Nucleophilic substitution of 2-methylsulfonyl-1,3,4-oxadiazoles **934** has been reported to occur with other nucleophiles, such as sodium azide, amines, and acylhydrazines (Scheme 13.288). The compounds containing the acylhydrazine group have shown to posses strong antibacterial activity against *Bacillus subtilis* and *Escherichia coli* (2.0×10^{-4} mol l^{-1}) [606].



Scheme 13.288

Recently an efficient conversion of 5-substituted-1,3,4-oxadiazolin-2-ones **936** into 2-amino-1,3,4-oxadiazoles **937**, via a nucleophilic aromatic substitution, appeared in the literature (Scheme 13.289) [607].

The reaction is activated from benzotriazol-1-yloxytris(dimethylamino)-phosphonium PF_6^- (**938**), and occurs according to Scheme 13.290, using as co-reagent 2 equivalents of base. The key step of the reaction is the attack of the oxygen atom of the carbonyl group on the phosphonium salt, promoted by base. The intermediate **939** thus obtained undergoes a facile reaction with the nucleophile **940** at C2 of the oxadiazole ring, followed by extrusion of HMPA (**941**).

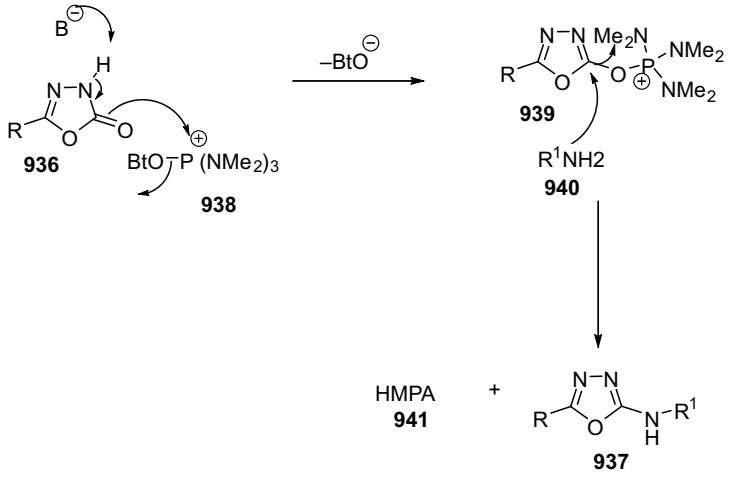


Scheme 13.289

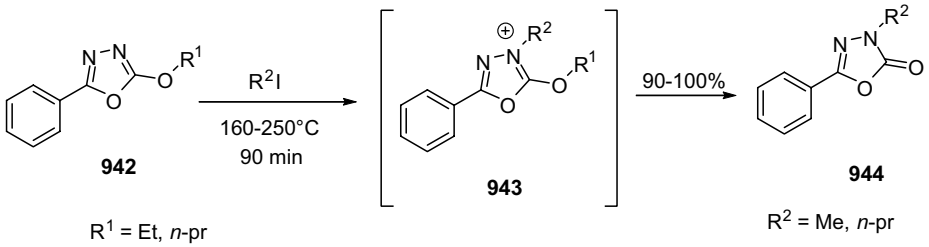
A nucleophilic substitution has also been reported for quaternary intermediate salts obtained by reaction of alkyl iodide with phenylalkoxyoxadiazoles. The reaction produces the corresponding 3-alkyl-5-phenyl-1,3,4-oxadiazol-2-ones via a nucleophilic attack promoted by iodine ion on the R^1 group of quaternary salts (Scheme 13.291) [608].

13.5.3.5 Reactions of Substituents

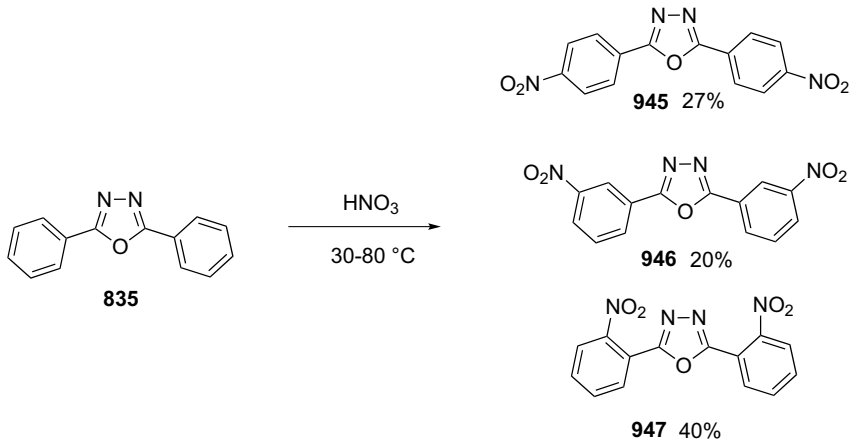
Electrophilic reaction can occur on diphenyl derivatives. Thus, 2,5-bis(4-nitrophenyl)-, bis(3-nitrophenyl)- and bis(2-nitrophenyl)-1,3,4-oxadiazoles have been obtained in 27%, 20%, and 40% yield, respectively, by mixing 2,5-diphenyl-1,3,4-oxadiazole (**835**) with HNO_3 at 30 °C and then at 80 °C for 4 h (Scheme 13.292). The addition of HNO_3 to the oxadiazole in concentrated H_2SO_4 at 50 °C and subsequent heating for 6 h at 100 °C gave bis(3-nitrophenyl)-1,3,4-oxadiazole (38%) and 2-phenyl-5-(*m*-nitrophenyl)-1,3,4-oxadiazole (31%) [609].



Scheme 13.290

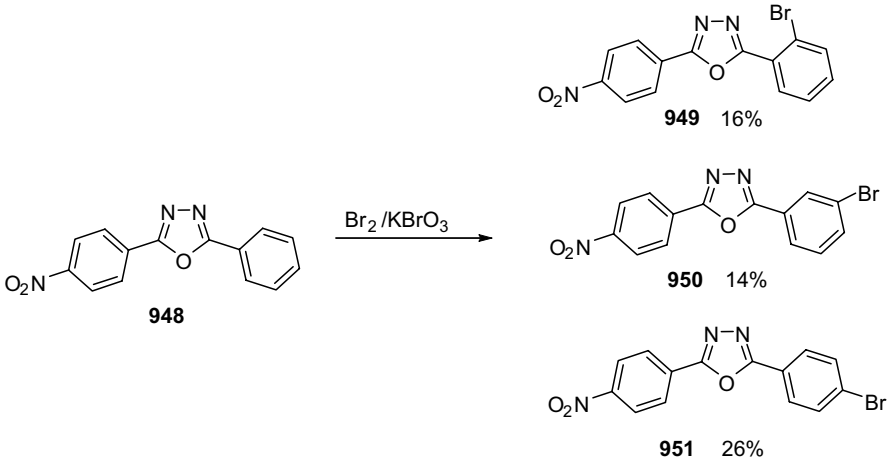


Scheme 13.291



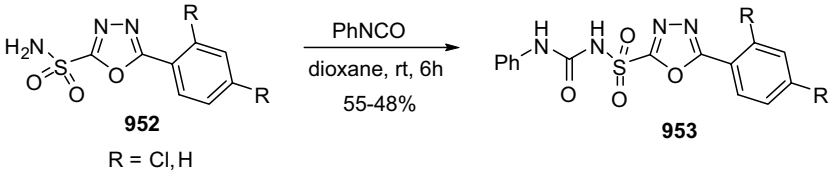
Scheme 13.292

2-(4-Nitrophenyl)-5-phenyl-1,3,4-oxadiazole undergoes selective electrophilic bromination of the phenyl ring in the presence of potassium bromate to produce *o*-, *m*-, and *p*-derivatives in 16%, 14%, and 26% yield, respectively (Scheme 13.293) [610].



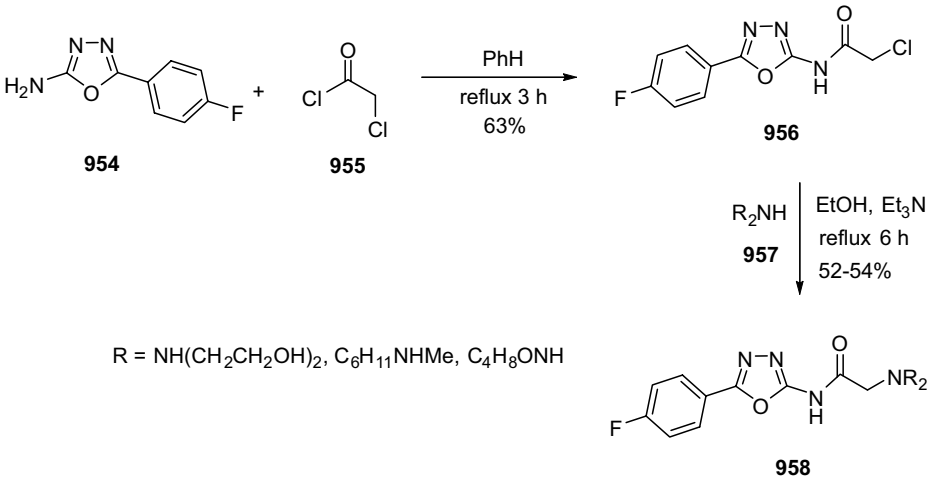
Scheme 13.293

A sulfonamide group directly linked to 1,3,4-oxadiazole ring has been utilized to synthesize *N*-(anilinocarbonyl)-5-(2,4-dichlorophenyl)-1,3,4-oxadiazole-2-sulfonamide **953** (R = Cl) and *N*-(anilinocarbonyl)-5-phenyl-1,3,4-oxadiazole-2-sulfonamide **953** (R = H) with aim of preparing potential pesticides. These compounds have been obtained by reaction of phenyl isocyanate with 5-(2,4-dichlorophenyl)-1,3,4-oxadiazole-2-sulfonamide (**952**, R = Cl) or with 5-phenyl-1,3,4-oxadiazole-2-sulfonamide (**952**, R = H) respectively (Scheme 13.294). The compounds so obtained have been tested for fungicidal activity against the fungal species *Cephalosporium saccharii* and *Helminthosporium oryzae*, and have been shown to possess a good level of activity [611].



Scheme 13.294

Some acetamides carrying a substituted-1,3,4-oxadiazole moiety with local anesthetic activity have synthesized by reaction of 5-aryl-2-chloroacetamido-1,3,4-oxadiazoles **956** with different secondary amines (Scheme 13.295). Compound **956** was easily prepared in 63% yield from the reaction of 5-(4-fluorophenyl)-1,3,4-oxadiazol-



Scheme 13.295

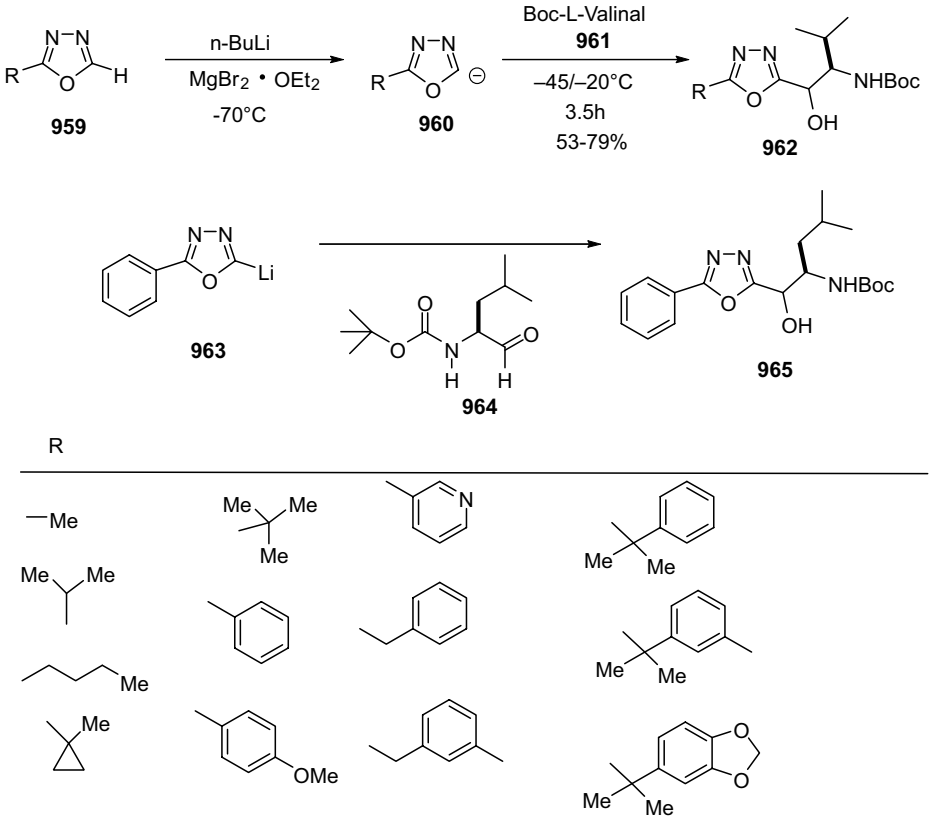
2-amine (**954**) with chloroacetyl chloride (**955**). The local anesthetic activity was investigated using the rabbit corneal reflex method and guinea pig's wheal derm method, using lidocaine as standard drug [612].

Monosubstituted oxadiazoles are deprotonated at the ring carbon atom to give the corresponding anion, which has been subsequently alkylated with various alkylating agents. Thus, for example, 2-substituted-1,3,4-oxadiazoles **959** after treatment with butyllithium in the presence of $MgBr_2$ diethyl etherate in THF, followed by the addition of *N*-[(1*S*)-1-(methylethyl)-2-oxoethyl](*tert*-butoxy)carboxamide (*N*-Boc-L-valinal) (**961**), affords the corresponding *N*-Boc alcohols **962** in 53–79% yield. Similar treatment of (5-phenyl-1,3,4-oxadiazol-2-yl)lithium (**963**) with Boc-leucinal (**964**) produces [1-[(*R*/*S*)-hydroxy-(5-phenyl-[1,3,4]oxadiazol-2-yl]-(*S*)-methyl]-3-methylbutyl]carbamic acid *tert*-butyl ester (**965**) in 70% yield (Scheme 13.296) [613, 614].

In addition, the methyl group attached at carbons of 1,3,4-oxadiazoles shows a marked acidity when it is treated with strong bases. Thus, when 2,5-dimethyl- or 2-methyl-5-phenyl-1,3,4-oxadiazoles **966** and **971** were treated with isopropylmagnesium bromide (**967**) or NaH, followed by addition of alkyl carboxylates, 5-substituted 1,3,4-oxadiazol-2-ylmethyl ketones **969**, **970**, and **972** were obtained. The yield in ketones has been shown to depend on the nature of substituents present in the carboxylate moiety (Scheme 13.297) [615].

Interestingly, when the lithium anion of **971** was allowed to warm from −78 °C to room temperature, the *N*-benzoylated hydrazone **973** was isolated from the reaction mixture in 34% yield (Scheme 13.298) [616]. The formation of this latter compound is easily rationalized as the nucleophilic attack of the lithium anion to the not de-protonated **971** still present in solution.

1,3-4 Oxadiazoles containing a good leaving group at the methylene moiety are able to give nucleophilic substitutions. Thus, 2-aryl-5-chloromethyl-1,3,4-oxadiazoles **974**,

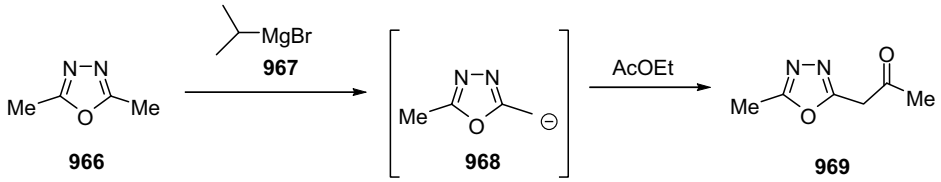


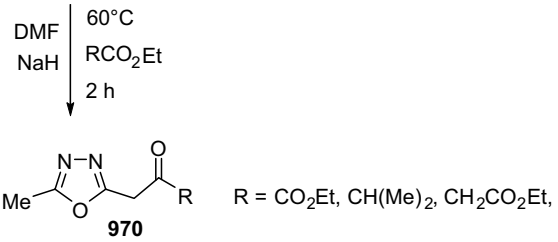
Scheme 13.296

via condensation of piperazine (**975**), give 1,4-bis[(5-aryl-1,3,4-oxadiazol-2-yl)methyl] piperazines **976** that *in vitro* displayed relatively potential antibacterial activities (Scheme 13.299) [617].

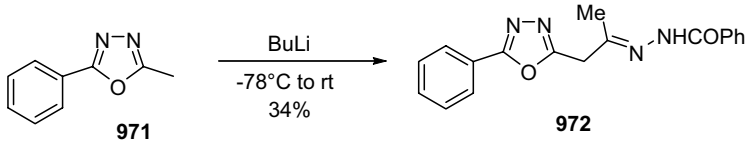
5-(*p*-Cyanomethylphenyl)-2-*n*-nonyl-1,3,4-oxadiazole **979**, useful precursor for organic light-emitting diodes (OLEDS), has been synthesized in 82% yield, by reaction of the bromide derivative **978** with tetraethylammonium cyanide. The 5-(*p*-bromomethylphenyl)-2-*n*-nonyl-1,3,4-oxadiazole (**978**) was easily prepared by the reaction of 5-(*p*-methylphenyl)-2-*n*-nonyl-1,3,4-oxadiazole (**977**) with *N*-bromosuccinimide(NBS) (Scheme 13.300) [618].

Substituents linked to 1,3,4-oxadiazoline moiety have also been involved in the synthesis of compounds having interesting properties. Thus, the herbicide 5-*tert*-butyl-3-(2,4-dichloro-5-isoprooxyphenyl)-1,3,4-oxadiazol-2-one (**981**) has been obtained starting from **877** via 5-*tert*-butyl-3-(2-amino-4-chloro-5-hydroxyphenyl)-1,3,4-oxadiazolin-2-one (**980**) (Scheme 13.301) [590].

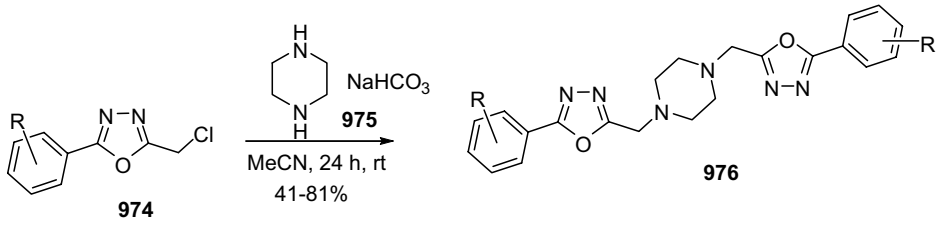




Scheme 13.297

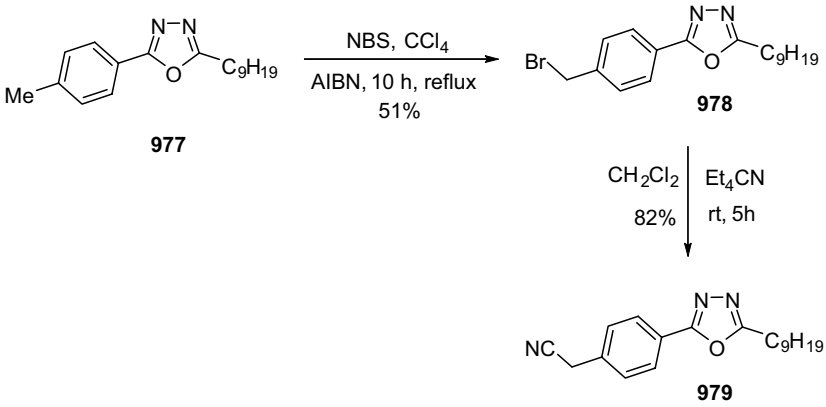


Scheme 13.298

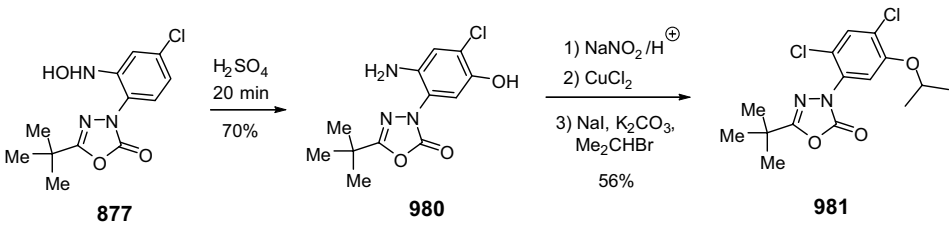


Scheme 13.299

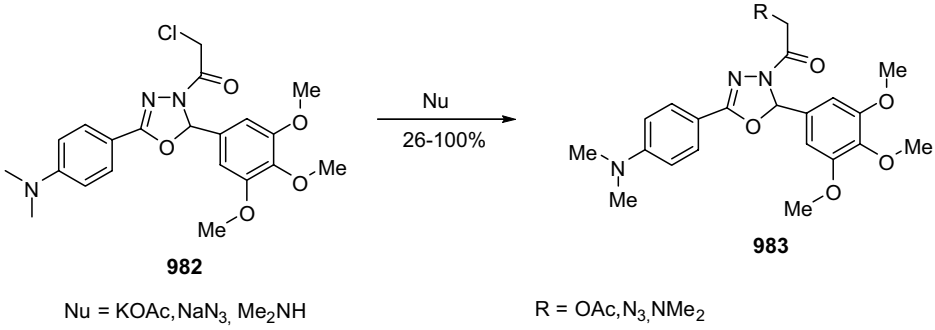
Some 3-acyl-1,3,4-oxadiazoline derivatives **983**, having antitumoral activity, have been prepared by nucleophilic displacement of the chlorine atom in **982** (Scheme 13.302).



Scheme 13.300



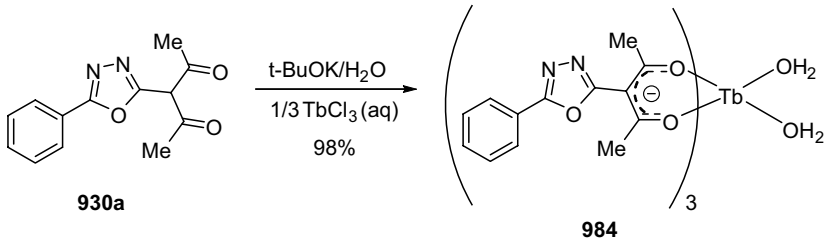
Scheme 13.301



Scheme 13.302

13.5.3.6 **Metal Complexes**

1,3,4-Oxadiazole derivatives are widely used as electron-transporting groups due to their high electron deficiency and good thermal stability [619]. According to these properties, compounds containing the 1,3,4-oxadiazole core have prepared and used



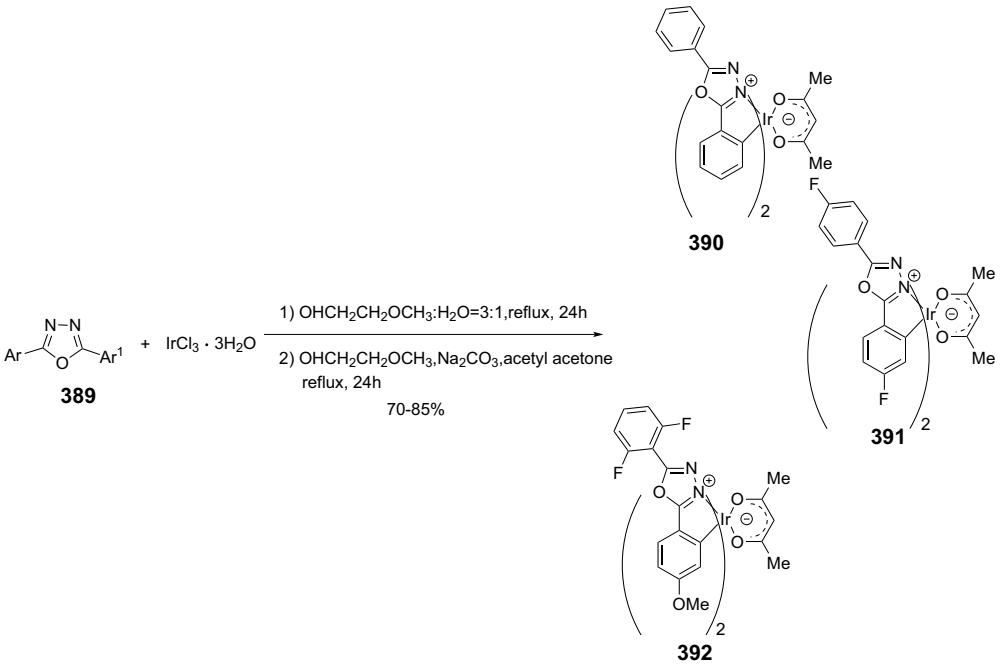
930a

984

Scheme 13.303

in the production of organic light-emitting diodes (OLEDs). An OLED converts electrical energy into light and it is formed by an emissive chromophore, an electron-transporting group, and a hole-transporting unit. Recently, heavy metal ions have been incorporated in OLEDs as a cyclometalated ligand to increase the phosphorescence at room temperature, because these ions are able to increase the efficiency of the intersystem crossing from the singlet to triplet excited state. Based on the above consideration, here are two reported examples of 1,3,4-oxadiazole metalated complexes together with their syntheses.

The first synthesis of 1,3,4-oxadiazole-functionalized terbium (III) β-diketonate for organic electroluminescence has been reported by Zheng *et al.* The synthesis was performed by treating compound **930** with a suspension of *t*-BuOK and an aqueous solution of $TbCl_3$ (Scheme 13.303). The crystal structure of **984** was



389

390

391

392

Scheme 13.304

established by X-ray diffraction. The Tb(III) ion is surrounded by eight oxygen atoms, six of which are from the bidentate β-diketonate ligands and the other two from the coordinated water molecules. The coordination polyhedron is best described as square antiprismatic. This compound was used as an emitting material, and a bright and highly efficient green-emitting LED was fabricated [604].

An interesting series of iridium(III) complexes linked to 1,3,4-oxadiazole systems has been synthesized and utilized to prepare three organic light emitting diodes devices, which showed stable green-yellow luminescence. The synthetic procedure involved two steps. In the first step, $IrCl_3 \cdot 3H_2O$ was allowed to react with an excess of 2,5-diaryl-1,3,4-oxadiazoles **985** in a 2-ethoxyethanol–water mixture. In the second step, the resulting iridium compounds were treated with sodium carbonate and acetyl acetone in 2-ethoxyethanol as solvent to afford the cyclometalated derivatives **986–988** in 70–85% yield (Scheme 13.304) [620].

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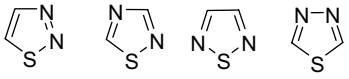
14
Thiadiazoles

Ugo Chiacchio and Giovanni Romeo

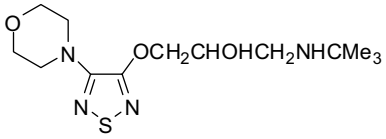
14.1
Introduction

There are four isomeric types of thiadiazoles (**1–4**).



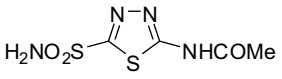
1 **2** **3** **4**

Many biologically active derivatives of this ring system have been synthesized and incorporated into commercial drugs and pesticides. For instance, the 1,2,5-thiadiazole timolol (**5**), is used as maleate salt to treat glaucoma; the sulfonamide derivative, acetazolamide **6**, is a diuretic.



5

Timolol



6

Acetazolamide

14.2
1,2,3-Thiadiazoles

1,2,3-Thiadiazoles are heterocycles of great practical and theoretical interest. Most of the literature has been devoted to thermal and photochemical reactions of the 1,2,3-thiadiazole ring, whose cleavage and rearrangement allow easy access to a series of functionalized compounds. Derivatives of this heterocyclic system are important in industry, medicinal chemistry, and agriculture. However, although interest in

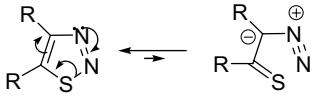
Modern Heterocyclic Chemistry, First Edition.
Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.

isomeric thiadiazoles is continuously increasing, there is a gap of knowledge in the area of 1,2,3-thiadiazoles, which still account for the fewest literature citations.

A good number of reviews on the chemistry of 1,2,3-thiadiazoles are present in literature [1]: one of the most recent reports cover the literature up to the early part of 2004 [2].

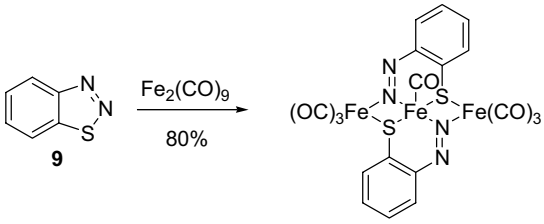
14.2.1 Structure

While the 1,2,3-oxadiazole system occurs nearly exclusively as open-chain tautomers, 1,2,3-thiadiazoles are stable compounds: the neutral aromatic structure **7** is preferred with respect to α-diazothiaketone species **8**.



7 **8**

However, it has been suggested that α-diazothiaketones **8** are involved as intermediates in some reactions [3]. The existence of these intermediates has been supported by the isolation of the complex of 2-diazothione **10** with iron nonacarbonyl, obtained by reaction of 1,2,3-benzothiazole (**9**) with $Fe_2(CO)_9$ (Scheme 14.1) [4].

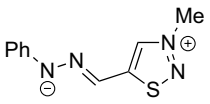


9 **10**

Scheme 14.1

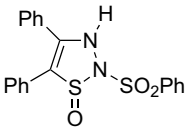
The parent compound is a yellow liquid with a boiling point of 157 °C at atmospheric pressure, and is soluble in alcohol, diethyl ether, and water. Other 1,2,3-thiadiazoles are soluble in methylene chloride and chloroform. Benzo-fused analogues of 1,2,3-thiadiazoles **7** have also been reported [5]. Fully aromatic mesoionic compounds have been synthesized [6], but information is limited. More recently, mesoionic 1,2,3-thiadiazoles as **11** have been obtained by methylation at N3 of 1,2,3-thiadiazoles containing an oxime or phenylhydrazone function at the 5-position [7].

Very few examples of non-aromatic 1,2,3-thiadiazoles such as **12** and **13** have appeared in the literature [8].



11

12



13

14.2.2 Theoretical Aspects

Theoretical studies on the structure and properties of 1,2,3-thiadiazoles are not numerous, probably due to the difficulty associated with calculating sulfur-containing organic compounds [9]. Bond angles and lengths have been determined by *ab initio* methods for the parent compound (Table 14.1) [10, 11].

The distribution of the electronic charge density shows that the largest negative values are adjacent to the nitrogen atoms [10, 11].

The relative stabilities of 1,2,3-thiadiazolines and 1,3,4-thiadiazolines, which are formed as a mixture of regioisomers in the cycloaddition reaction of aliphatic diazo compounds to thioketones (Pechmann synthesis), have also been determined by semiempirical and *ab initio* [12] 1,2,3-Thiadiazoline is 0.9 kcal mol^{-1} more stable than 1,3,4-thiadiazoline. The reverse trend has been found for alkyl-substituted derivatives.

According to frontier molecular orbital theory, the reaction between diazomethane and thioformaldehyde can be classified as HOMO-CH_2N_2/LUMO-CH_2S controlled: the formation of two regioisomeric adducts is predicted (Figure 14.1) [12].

The aromaticity of 1,2,3-thiadiazole 1,1-dioxide has been studied by *ab initio* calculations [13] and compared with that of isomeric thiadiazoles: the heteroaromaticity of 1,2,3-thiadiazole 1,1-dioxide is higher than that of 1,3.4-thiadiazole 1,1-dioxide, but lower than that of 1,2,5-isomer.

Table 14.1 Calculated geometry of 1,2,3-thiadiazole.

Bond	Length (Å)	Bond	Angle (°)
S–C	1.6872	C–S–N	92.11
S–N	1.7357	S–N–N	110.27
N–N	1.2786	N–N–C	115.45
C–C	1.3809	C–C–S	106.67
C–H	1.0937	S–C–H	124.01
		N–C–H	119.93

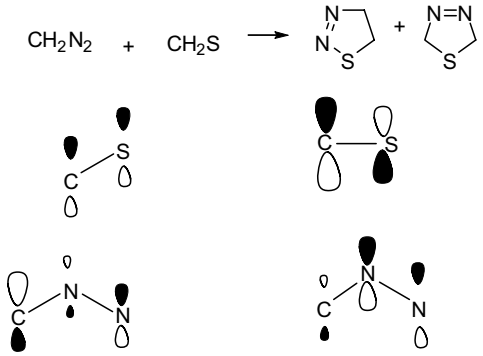


Figure 14.1 Frontier molecular orbital theory prediction of the reaction between diazomethane and thioformaldehyde.

14.2.3 Structural Aspects

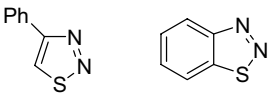
14.2.3.1 X-Ray Diffraction

Many papers related to X-ray structures of 1,2,3-thiadiazoles have been reported [14]. The thiadiazole ring is essentially flat: all atoms of the ring lie in the same plane, with a very slight deviation of less than 0.02° from the plane.

Table 14.2 shows the reported bond lengths and bond angles for 1,2,3-benzothiadiazole (**9**) and for 4-phenyl-1,2,3-thiadiazole (**14**).

For compound **14**, the N2–N3 and C4–C5 bond lengths show a nearly double bond character, while the bond lengths of S–N2 and S–C5 indicate partial double bond character for both sulfur bonds; an aromatic behavior has been ascribed to this ring. The distance between C4–C6, 0.14 nm as expected for a sp^2–sp^2 carbon–carbon bond,

Table 14.2 Molecular dimensions for 1,2,3-benzothiadiazole (**9**) and 4-phenyl-1,2,3-thiadiazole (**14**).

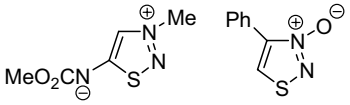


14 **9**

Compound 14				Compound 9			
Bond lengths (nm)		**Bond angles (°)**		**Bond lengths (nm)**		**Bond angles (°)**	
S–N	0.1666	C–S–N	93.2	S–N	0.1706	C–S–N	92.6
N–N	0.1286	S–N–N	111.2	N–N	0.1279	S–N–N	112.7
N–C	0.1378	N–N–C	114.4	N–C	0.1384	N–N–C	113.4
C–C	0.1363	N–C–C	112.2	C–C	0.1397	N–C–C	114.2
C–S	0.1670	C–C–S	109.0	C–S	0.1708	C–C–S	107.1
C–Ph	0.1469						

indicates that there is a little conjugation between the two rings [15]. Similar values of bond angles and bond lengths have been reported for benzo-1,2,3-thiadiazole **9** [5].

X-Ray data have also been reported for the mesoionic 5-(methoxycarbonyl)amino-3-methyl-1,2,3-thiadiazole (**15**) and for 4-phenyl-1,2,3-thiadiazole 3-oxide (**16**) [6].



15 **16**

14.2.3.2 NMR Spectroscopy

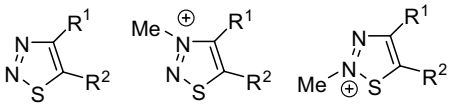
^{1}H NMR spectroscopy confirms the aromatic character of the 1,2,3-thiadiazole ring. Proton chemical shifts are found in the region 7.44–9.37 ppm. N-Alkylation of the ring shifts these signals 1.0–1.5 ppm downfield (Table 14.3).

^{13}C NMR spectroscopy is a useful tool for the elucidation of heterocyclic structures where few or no ring protons are present. For symmetrically substituted 1,2,3-thiadiazoles, the carbon adjacent to the nitrogen atom resonates at lower field than the carbon atom adjacent to the sulfur atom. The body of ^{13}C reported data allows us to predict accurately the chemical shift of ring carbons, assuming the tabulated incremental effects of substituents at C4 and C5 (Table 14.4) [16].

Very few references are present in the literature for the ^{14}N and ^{15}N NMR of 1,2,3-thiadiazoles. One paper, regarding solvent effects on the ^{14}N NMR spectra of isomeric thiadiazoles, suggests that an increase in solvent polarity favors the delocalization of the lone electronic pair from the sulfur atom into the ring, thus leading to an increase of electronic charge at the nitrogen atom [17].

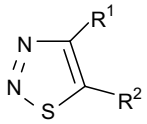
The ^{15}N NMR spectra of a series of 1,2,3-thiadiazoles reveal the strong influence of substituents on the N2 resonance, which can be rationalized by the conjugation

Table 14.3 Proton NMR data for ring hydrogens of 1,2,3-thiadiazoles (see text for details).



R^1	R^2	N2	N3	δ (ppm)
Methyl	H			8.20
Phenyl	H			8.60
H	Methyl			8.35
H	Phenyl			8.70
H	Acetyl			9.04
H	Formyl			9.20
H	Diethylamino			7.44
Phenyl	H	Methyl		9.93
Phenyl	H		Methyl	10.17

Table 14.4 ^{13}C NMR spectral data (ppm) for ring carbons of 1,2,3-thiadiazoles.



R^1	R^2	C4	C5
H	H	147.3	135.8
Phenyl	H	163.9	130.9
H	Phenyl	144.2	152.2
Phenyl	Phenyl	157.5	150.8

effect. Conversely, little influence on the chemical shifts is exerted by substituents at position 4.

The ^{15}N chemical shifts of some mesoionic compounds have also been determined and explained by the dual effect of 5-substitution and salt formation [18].

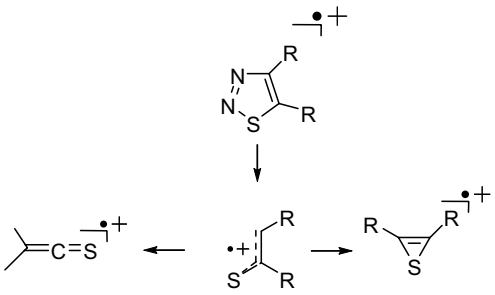
14.2.3.3 UV and IR Spectroscopy

Data on IR [19] and UV [20] spectroscopy have been reported for some 1,2,3-thiadiazoles. Characteristic infrared absorptions are at 1560–1475 and 1350–1280 cm^{-1} (ring skeletal).

Simple 1,2,3-thiadiazoles show three absorption bands in the UV spectra: 211–217, 249–253, and 290–294 nm.

14.2.3.4 Mass Spectrometry

The electron-impact mass spectra of the most 1,2,3-thiadiazoles exhibit a very intense signal for the molecular ion [21]. Moreover, the predominant fragmentation is represented by the loss of N_2 $(M–28)^+$, which gives rise the most intense peak in the spectrum (Scheme 14.2). Other types of molecular ion fragmentations are negligible and are of some interest only for complex structures [22].



Scheme 14.2

The structure of the $[M–N_2]^+$ fragment has been investigated and found to depend on the substitution pattern. For the unsubstituted 1,2,3-thiadiazole, the fragment shows the thioketene and the distonic $^{\bullet}CH{=}CH{-}S^+$ structure, while for 5-amino-1,2,3-thiadiazoles the ion exists in the thiirene form [23].

14.2.4 Synthesis

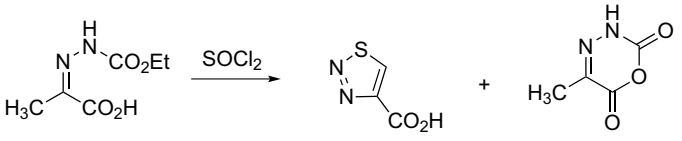
The synthetic approaches towards the 1,2,3-thiadiazole system can be classified according to five methodologies:

1) cyclization of hydrazones with thionyl chloride: the Hurd–Mori reaction [24];
2) heterocyclization of α-diazocarbonyl compounds: the Wolff synthesis [25];
3) 1,3-dipolar cycloaddition of diazo compounds **3** to isothiocyanates: the Pechmann and Nold synthesis [26];
4) ring transformation of other sulfur-containing heterocycles;
5) elaboration of preformed 1,2,3-thiadiazoles.

14.2.4.1 Hurd–Mori Synthesis

Hydrazone derivatives, possessing a methylene moiety and an electron-withdrawing group (CO_2Et, SO_2R) at N2, give rise to 1,2,3-thiadiazoles upon treatment with thionyl chloride [27]. Retrosynthetically, the Hurd–Mori reaction is a [4 + 1] approach where four atoms come from hydrazone and one (the sulfur atom) from the thionating agent.

Thus, the reaction of 2[(ethoxycarbonyl)hydrazono]propanoic acid (**17**) with $SOCl_2$ affords 1,2,3-thiadiazole-4-carboxylic acid (**18**) in 53% yield, accompanied by traces of 5-methyl-2*H*-1,3,4-oxadiazine-2,6(3*H*)-dione (**19**) (Scheme 14.3) [24].

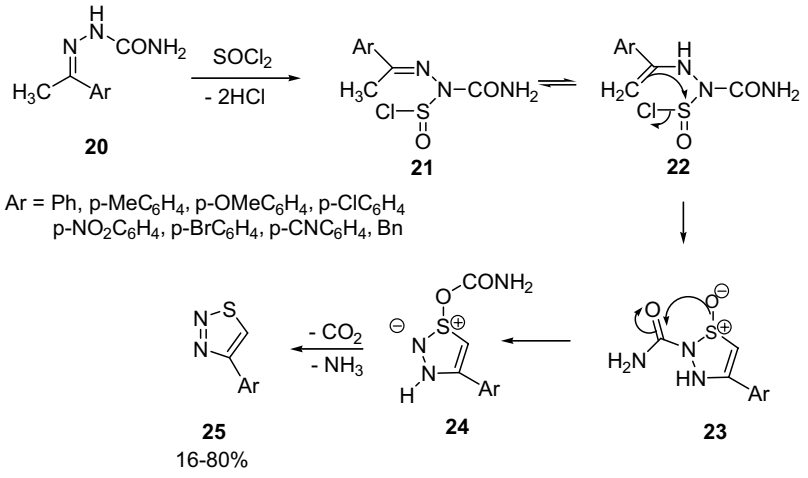


17 **18** 53% **19** trace

Scheme 14.3

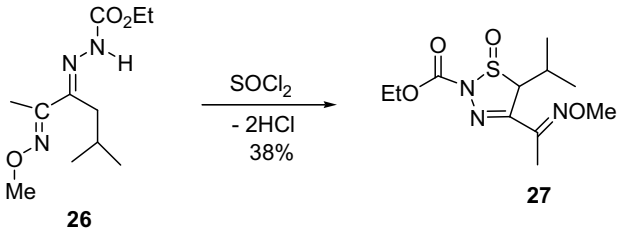
The obtainment of 1,2,3-thiadiazoles has been interpreted according to the initial formation of intermediate **21**, which originates from the nucleophilic attack of **20** to the sulfur atom [28]. A fast ene–hydrazine tautomerism promotes the cyclization to the sulfoxide **23**, which, probably through a Pummerer-type rearrangement [2], evolves towards the 1,2,3-thiadiazole system **25**, with extrusion of NH_3 and CO_2 (Scheme 14.4).

The presence of intermediate thiadiazoline-1-one **23**, isolated and characterized in some cases [29], was also ascertained by the crystallographic investigation of the



Scheme 14.4

compound **27** isolated by Kobori *et al.* [30] in the reaction of **26** with $SOCl_2$ (Scheme 14.5).

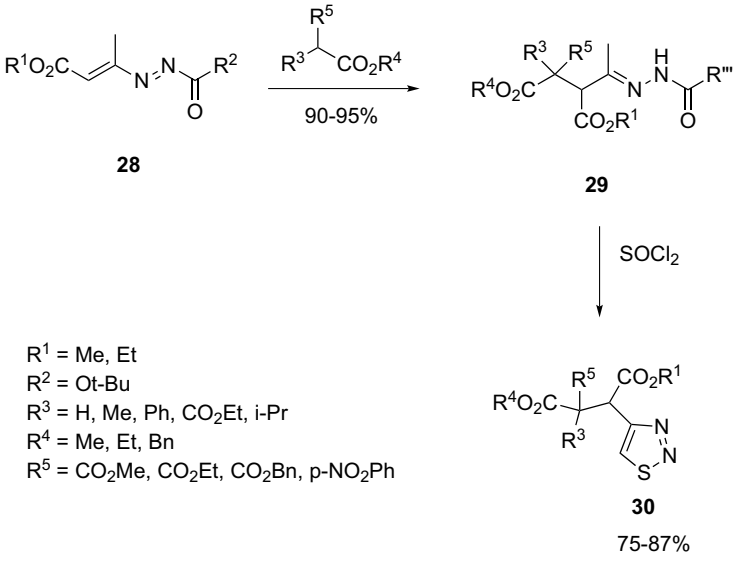


Scheme 14.5

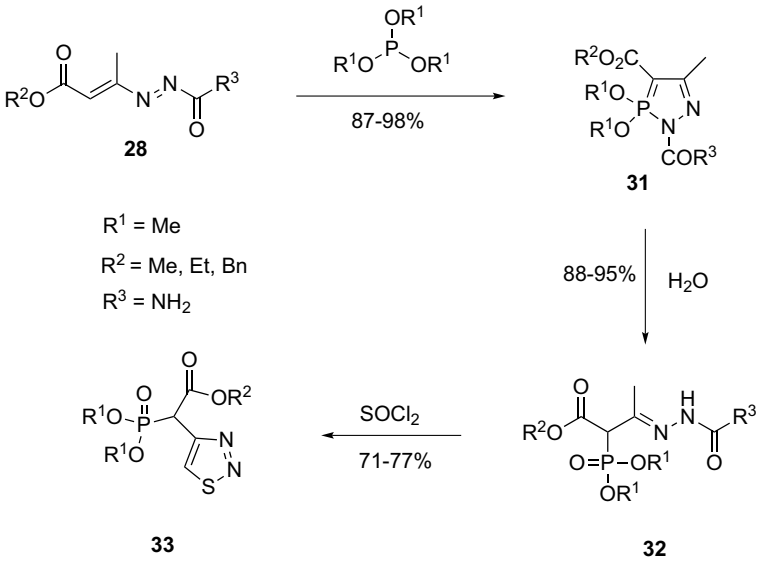
Substituted hydrazones **29**, obtained from 1,2-diaza-1,3-butadienes **28** and methylenic or methinic activated substrates, afford, in the presence of thionyl chloride as solvent-reagent, functionalized 1,2,3-thiadiazoles **30** in good yields (Scheme 14.6) [31].

Similarly, the reaction of 1,2-diaza-1,3-butadienes **28** and trialkyl phosphites, under solvent-free conditions, leads to alkyl 3,3-dialkoxy-2*H*-1,2,3,λ^5-diazaphosphole-4-carboxylates **31** that are easily converted into the corresponding *(E)*-hydrazinophosphonates **32** by treatment with water. Subsequent reaction with thionyl chloride affords 4 substituted 1,2,3-thiadiazoles **33** (Scheme 14.7) [32].

The Hurd–Mori reaction is by far the most widely exploited synthetic methodology for 1,2,3-thiadiazoles. The reaction is especially suitable for alkyl- and (het)aryl-substituted 1,2,3-thiadiazoles; in the same way, fused 1,2,3-thiadiazoles have been prepared from cyclic ketones. Several substituted thiadiazoles, possessing halide [33],



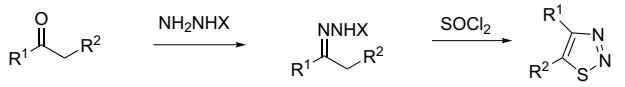
Scheme 14.6



Scheme 14.7

ester [34], carboxy [24], aldehyde [35], sulfide [36], and amino groups [37], have also been obtained.

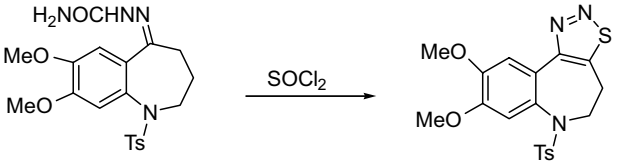
4,5-Diaryl and 4-aryl-substituted 1,2,3-thiadiazoles **36**, with potential antithrombotic activity, have been prepared starting from aldehydes and ketones **34** (Scheme 14.8) [38].



R^1 = Ph, 4-MeO-C_6H_4, 4-Me-C_6H_4, 4-NO_2-C_6H_4, 4-NO_2-C_6H_4, 4-MeS-C_6H_4, 4-Cl-C_6H_4,3,4-Cl_2-C_6H_3, 3,4,5-$(MeO)_3$-C_6H_2,
R^2 = H, Ph, 4-MeO-C_6H_4, 4-NO_2-C_6H_4, 2-(C_4H_3S), 3,4-(-OCH_2O-)C_6H_3

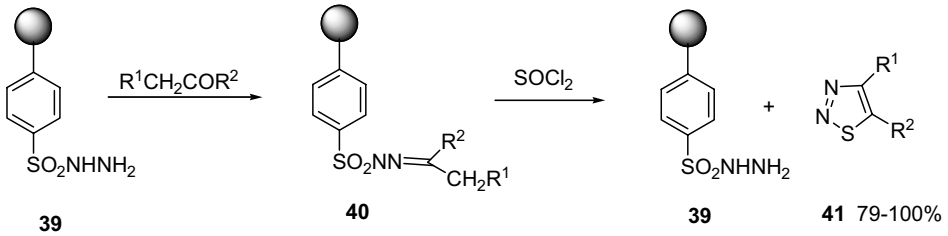
Scheme 14.8

The 1,2,3-thiadiazole ring annelated to the benzazepine ring **38** was obtained by the Hurd–Mori reaction of hydrazonobenzazepine **37** (Scheme 14.9) [39].



Scheme 14.9

An interesting solid-phase synthesis of 1,2,3-thiadiazoles **41** has also been reported. A Merrifield type resin functionalized with sulfonhydrazide groups (**39**) was used to capture ketones from the reaction mixtures (Scheme 14.10) [40].



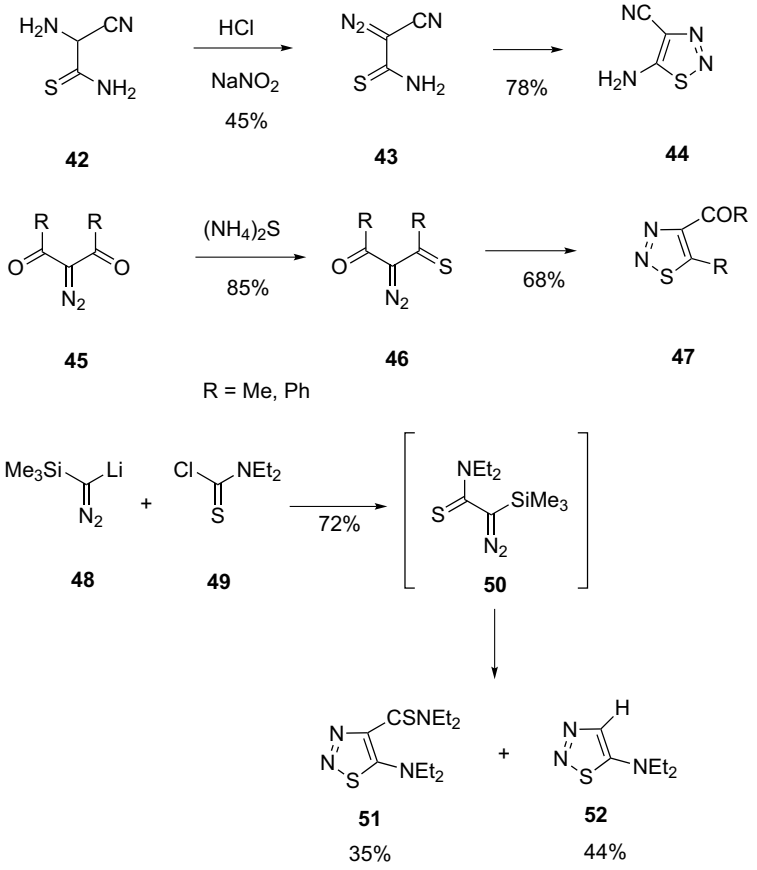
R^1 = Me, Et, n-Bu, *iso*-Bu, Bn
R^2 = p-$OMeC_6H_4$, p-ClC_6H_4, pPhC_6H_4, o-BrC_6H_4, m-BrC_6H_4p-BrC_6H_4

Scheme 14.10

14.2.4.2 Wolff Synthesis

Wolff's synthesis of 1,2,3-thiadiazoles is one of the earliest methods [25]; it implies the heterocyclization of α-diazothiocarbonyl compounds, which can be prepared via different routes. According to this methodology, 5-alkyl and 5-aryl-1,2,3-thiadiazoles have been prepared by reaction of 2-diazo-1,3-dicarbonyl compounds with ammonium sulfide [41]. The method has been exploited to prepare various 5-amino- and

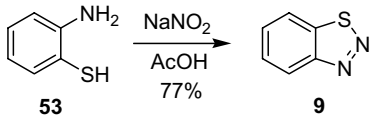
5-mercapto-1,2,3-thiadiazoles bearing different functional groups at the 4-position (Scheme 14.11) [41, 42]. Diazothiocarbonyl compounds **43**, **46** and **50** may be generated: (i) by introducing the diazo group into compounds containing a C=S bond, (ii) by constructing a C=S group into the α-position of a diazo compound, or (iii) by simultaneous introduction of both these functions.



Scheme 14.11

Thiadiazole **44** has been prepared by diazotation of 2-amino-2-cyano-thioacetamide (**42**) [41, 43]. The method requires the presence of two electron-withdrawing groups at the α-carbon atom, which stabilize the intermediate diazothiocarbonyl compounds **43**.

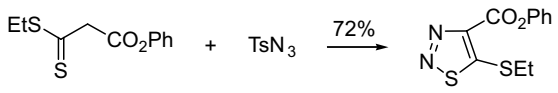
The same stabilization can be achieved by including the carbon atom attached to the diazo function onto an aromatic ring. In this way, benzo-1,2,3-thiadiazole **9** has been synthesized in 77% yield by reaction of *ortho*-aminothiophenol (**53**) with sodium nitrite in acetic acid (Scheme 14.12) [44].



53 9

Scheme 14.12

An alternative way to generate α-diazothiocarbonyl compounds exploits the reaction of species bearing an active methylene group such as compound **54**, with azides (Scheme 14.13) [45].

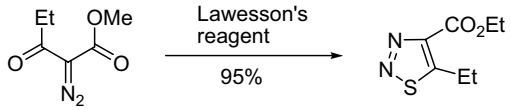


54 55

Scheme 14.13

2-Diazo-1,3-dicarbonyl derivatives **45** react with thionating reagents to give diazocarbonyl intermediates that spontaneously cyclize to 4-carbonyl-5-alkyl- or 5-aryl-1,2,3-thiadiazoles **47** (Scheme 14.11) [41].

As an example, 5-ethyl-4-ethoxycarbonyl-1,2,3-thiadiazole has been prepared from an α-diazoketone via its thioketone intermediates using Lawesson's reagent (Scheme 14.14) [46].



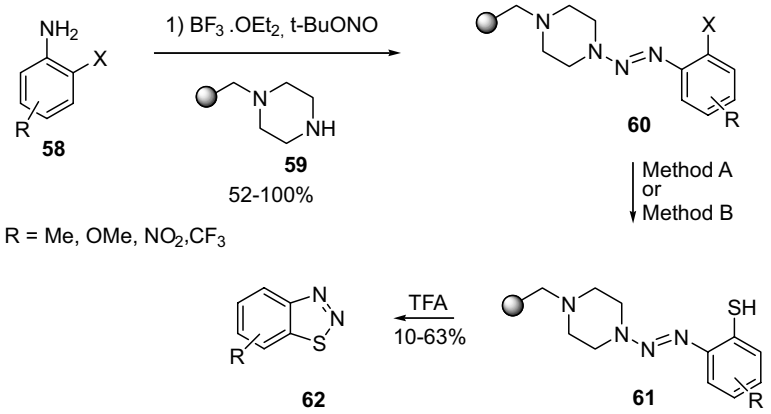
56 57

Scheme 14.14

Lithium trimethylsilyldiazomethane (**48**) reacts with thiocarbamoyl chloride **49** to give a mixture of 5-amino-1,2,3-thiadiazoles **51** and **52**. The proposed mechanism involves the formation of a diazothioacetamide that undergoes a rapid cyclization (Scheme 14.16) [47].

Wolff's methodology has been exploited in the first solid-phase synthesis of benzo-1,2,3-thiadiazoles and related structures, starting from resin bound chloro, bromo, or iodo triazenes and using a functionalization on cleavage [48]. In particular, the synthesis was realized employing two different, synergetic methods: an anionic approach, via a halide metal exchange, and a cross-coupling approach, via an innovative palladium catalyzed C–S bond forming reaction. Anilines **58** were diazotated with *tert*-butyl nitrite and subsequently coupled with piperazine resin **59**. The resulting triazene aryl halides **60** have been converted into the corresponding thiol **61** bonded to the resin by two alternative methods: (A) reaction with *n*-BuLi and

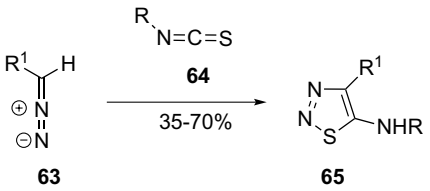
TMEDA, followed by treatment with elemental sulfur; (B) reaction with triisopropylsilylthiol in the presence of palladium acetate. Cleavage from the resin with dilute trifluoroacetic acid (TFA) resulted spontaneously in the desired cyclization reaction, yielding benzo[1,2,3]thiadiazoles **62** in good yields (Scheme 14.15).



Scheme 14.15

14.2.4.3 **Pechmann and Nold Synthesis**

One of earliest synthesis of 1,2,3-thiadiazoles is the Pechmann and Nold synthesis [26], which involves the 1,3-dipolar cycloaddition between diazoalkanes **63** and isocyanates **64** (Scheme 14.16) [1].

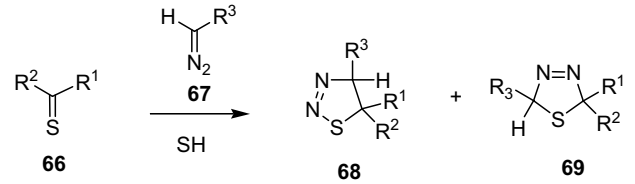


Scheme 14.16

This method includes the reactions of diazo compounds with various thiocarbonyl derivatives, such as thioketones, thioesters, thioamides, and carbon disulfide [49].

The reaction of diazoalkanes **67** with thioketones **66** gives a mixture of 1,2,3- **68** and 1,3,4-thiadiazolines **69**[50]: the regioisomeric distribution depends on the solvent polarity and steric effects (Scheme 14.17) [12].

The reaction has been studied in detail by *ab initio* RHF and CASSCF calculations (3-21G*, 6-31G*, CAS/3-21G*) and semiempirical calculations (AM1 and MNDO-PM3). In particular, *ab initio* calculations, in accord to experimental data, show that



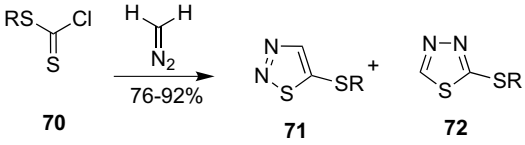
R^1 = Et, n-Pr, i-Pr, t-Bu
R^2 = Et, n-Pr, i-Pr, t-Bu
R^3 = H, Me, Ph

SH = $(Et)_2O$, MeOH

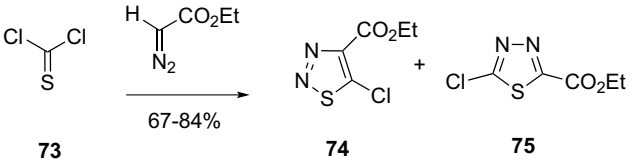
Scheme 14.17

1,2,3-thiadiazoline products are formed in higher ratio in more polar solvents and that this is explainable by the higher dipole moment (about 5 D as compared to circa 2 D) of the transition structure [12].

If the cycloaddition reaction is performed with chlorodithioformates **70** or thiophosgene (**73**) as dipolarophiles, the initial thiazolidines undergo elimination of HCl and form a mixture of 1,2,3- (**71** and **74**) and 1,3,4-thiadiazoles (**72** and **75**) (Scheme 14.18) [41, 50, 51].



R = Et, Pr

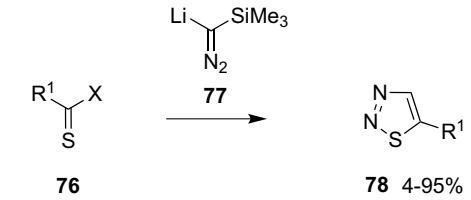


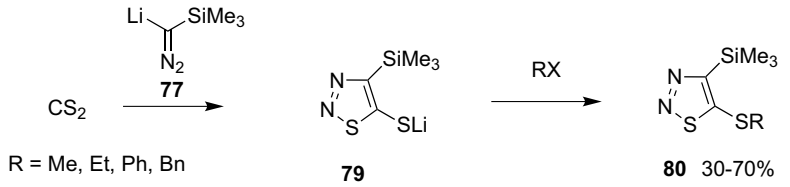
Scheme 14.18

A variation of this method, which probably does not proceed through a concerted [3 + 2] cycloaddition, involves the reaction of lithium (trimethylsilyl)diazomethane (**77**) with thioesters or dithioesters **76** and with carbon disulfide to afford various 5-substituted-1,2,3-thiadiazoles **78** and **80** (Scheme 14.19) [52].

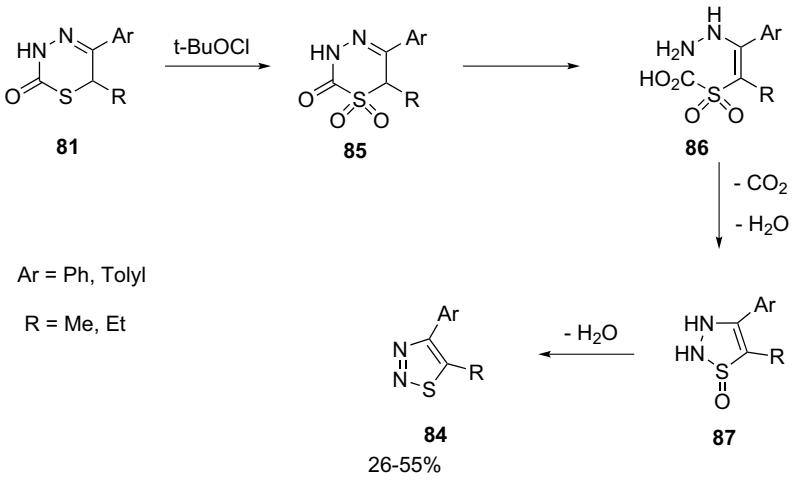
14.2.4.4 Transformations of Other Heterocycles

The 1,2,3-thiadiazole ring can also be obtained by chemical transformation of other sulfur-containing heterocycles. Thus, treatment of 1,3,4-thiadiazin-2-ones **81** with *tert*-butyl hypochlorite gives rise to 1,2,3-thiadiazole **84**, probably via the intermedis **82** and **83**, as reported in Scheme 14.20 [41].





Scheme 14.19

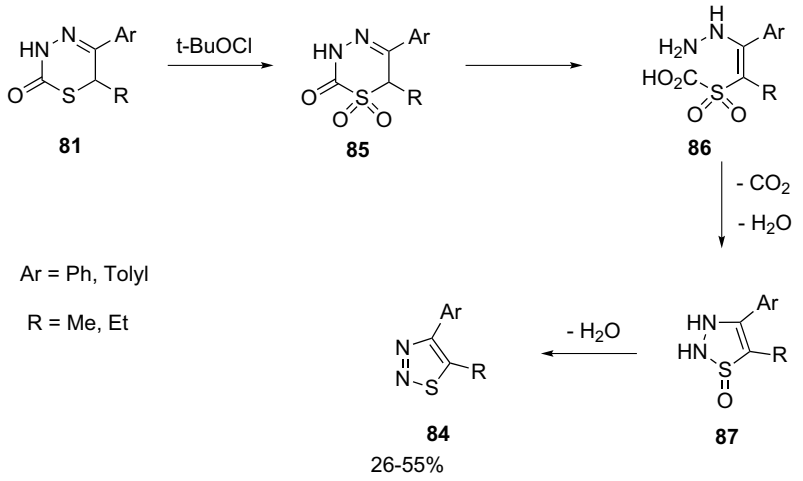


Scheme 14.20

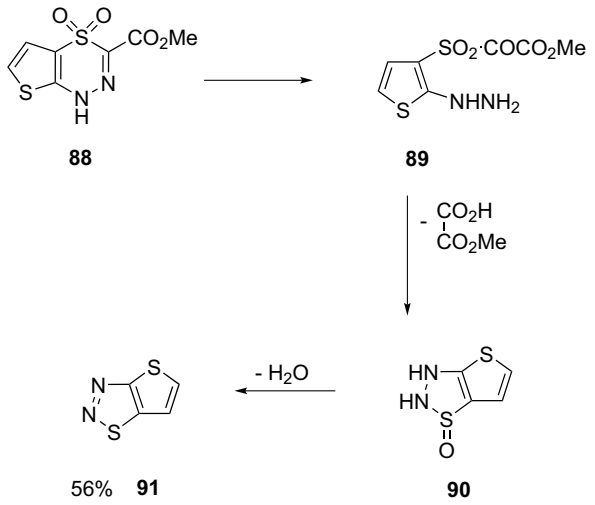
A different mechanism has been proposed for this reaction, based on the oxidation of **81** to thiadiazine dioxide **85**, which undergoes hydrolysis of the imine double bond. Subsequent loss of CO_2 and H_2O leads to the final product **84** (Scheme 14.21) [2].

As support, a suspension of thieno thiadiazine dioxide **88** in acid media affords thienothiadiazole **91** (Scheme 14.22) [53].

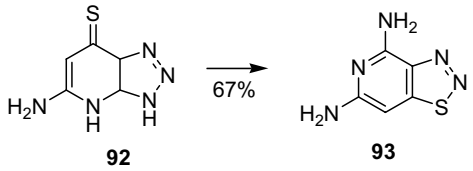
Another interesting conversion is represented by the rearrangement reaction of 1,2,3-triazoles containing a thiocarbonyl group. Thus, 1,2,3-triazolo[4,5-*b*]pyridin-4(7*H*)-thione (**92**) rearranges by thermolysis into 1,2,3-thiadiazolo[4,5-*c*]pyridine **93** (Scheme 14.23) [41, 54].



Scheme 14.21



Scheme 14.22



Scheme 14.23

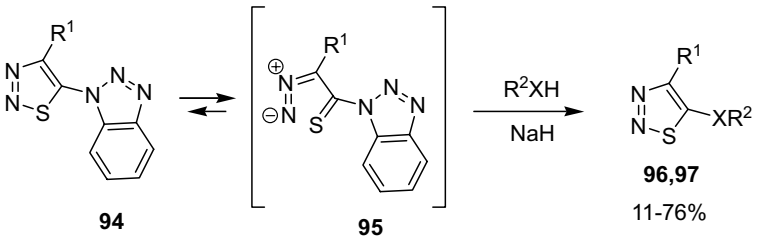
14.2.4.5 Elaboration of Preformed 1,2,3-Thiadiazoles

Various 1,2,3-thiadiazole derivatives have also been easily prepared by chemical modification of substituents present at C4 or C5 in a preformed 1,2,3-thiadiazole system. Thus, 1,2,3-thiadiazole carboxylic acids have been obtained by oxidation of 4- or 5-methyl-1,2,3-thiadiazole [55], or by hydrolysis of the corresponding esters [56]. The acids can be easily converted by standard procedures into the corresponding esters, chlorides, amides, hydrazides, azides, thioamides, and nitriles [36, 57].

The carbaldehyde function has been introduced by oxidation of a hydroxymethyl group [58] or by acid-catalyzed hydrolysis of the corresponding hydrazones and oximes [7, 35, 59].

4- and 5-Amino- [1, 3, 41, 42], 5-halo- [3, 42], 5-mercapto- [36], and 5- and 4-alkenyl 1,2,3-thiadiazoles [60–62] have been prepared following the same synthetic approach.

In particular, different 5-substituted derivatives have been synthesized by Katritzky *et al*. [63] following a procedure that exploits the chemistry of the benzotriazole system. Thus, the 1-(1,2,3-thiadiazol-5-yl)-1*H*-1,2,3-benzotriazole **94** has been transformed into 5-[(4-methylphenyl)thio]-1,2,3-thiadiazoles **96** (X = S) and 5-phenoxy-4-phenyl-1,2,3-thiadiazoles **97** (X = O). The reaction mechanism includes the known ring-chain tautomerism of substituted 1,2,3-thiadiazoles, involving cleavage of 1,2-bond to afford 2-diazoethanethione tautomers **95**. This intermediate then undergoes a direct nucleophilic substitution of the benzotriazole moiety and sequential ring closure to give 5-substituted 1,2,3-thiadiazoles **96** and **97** in yields ranging from 11% to 76% (Scheme 14.24).



X = S,O R^1 = H, Ph, Thiophen-2-yl, Furan-2-yl

R^2 = Ph, *p*-CH_3-C_6H_4, 2-Naphthyl, Bn, *p*-Cl-C_6H_4, *p*-CH_3O-C_6H_4

Scheme 14.24

14.2.5 Reactivity

The reactivity of the 1,2,3-thiadiazole system is expressed in a series of different chemical transformations: (i) ring cleavage reactions, (ii) base-catalyzed decompositions, (iii) rearrangement processes, (iv) oxidative and reductive processes, (v) reactions due to the reactivity of the heterocycle ring, and (vi) reactions of nucleophiles.

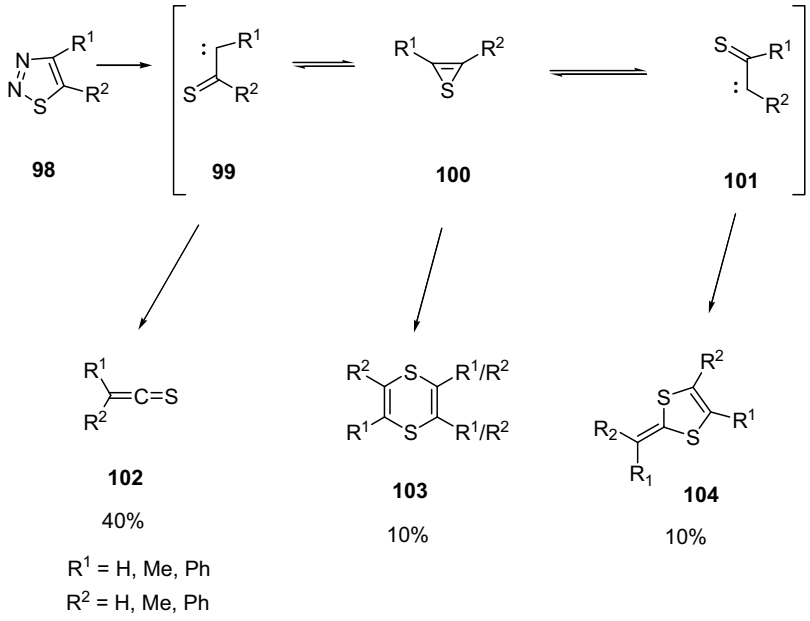
14.2.5.1 Ring Cleavage Reactions

The easy ring cleavage of the 1,2,3-thiadiazole system, which produces highly reactive fragments, affords a useful synthetic access to different functionalized compounds.

The most important reaction pathways are:

1) loss of the nitrogen molecule with production of α-thioxocarbene which, in turn, can rearrange to thioketenes;
2) simultaneous loss of a molecule of nitrogen and the sulfur atom.

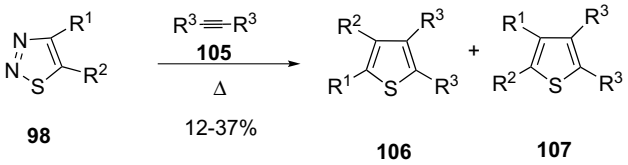
As an example of the first case, compounds **98** upon thermolysis extrude nitrogen, leading to transients α-thioxocarbenes **99** and **101** and thiirenes **100**, which can follow different reaction routes [64–66]: (i) rearrangement to thioketenes **102**, (ii) dimerization to 1,4-dithiins **103**, or (iii) cycloaddition of the intermediate α-thioxocarbenes with the rearranged thioketene **102** to give 4-dithiafulvenes **104** (Scheme 14.25).



Scheme 14.25

Formation of thioketenes **102** from **99** and **101** involves a 1,2-shift of the substituent at the carbon atom of the thiocarbonyl group. The structure of thioketenes has been confirmed by NMR [67] and IR spectra [68].

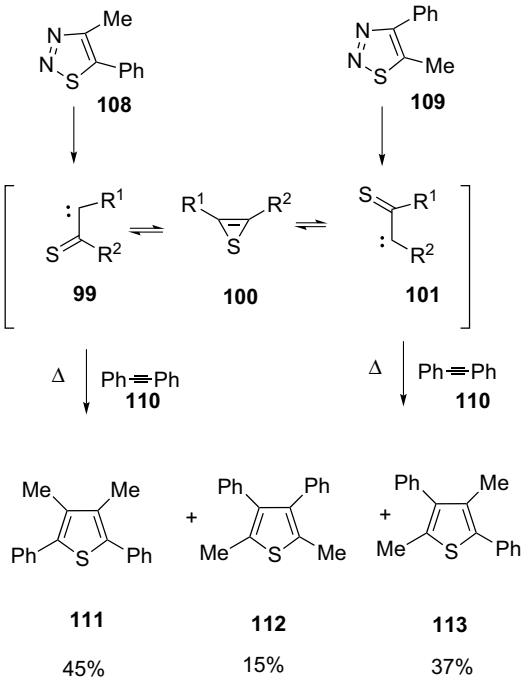
The intermediate four-electron systems **99–101** have been trapped by reaction with acetylenes **105** [69–72], affording a mixture of isomeric thiophenes **106** and **107** in a ratio of 1 : 1 (Scheme 14.26).



R^1 = H, Me
R^2 = H, Me
R^3 = CF_3

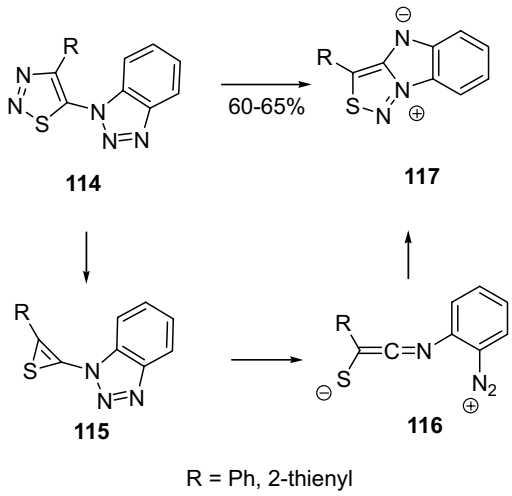
Scheme 14.26

The formation of the same product distribution (**111–113**) from regioisomeric thiadiazoles supports the suggested equilibrium between the two isomeric 1,3-diradicals **99** and **101** via thiirene **100** (Scheme 14.27) [73].



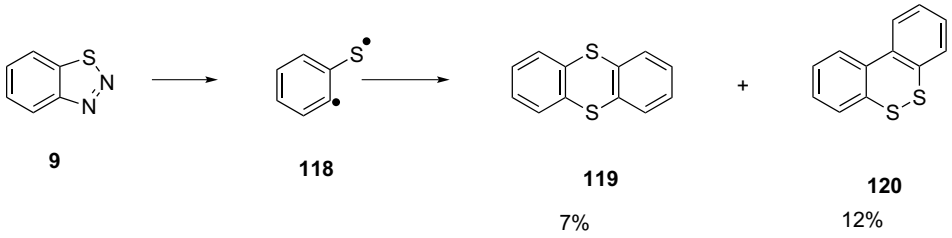
Scheme 14.27

Capture of the thiirene intermediate by an intramolecular reaction has been reported by Katritzky *et al.* [74] in the thermal rearrangement of 5-benzotriazolyl-1,2,3-triazoles **114** to zwitterionic 3-phenyl-[1,2,3]thiadiazolo[3,4-a]benzimidazol-9-ium-4-ide **117** (Scheme 14.28).



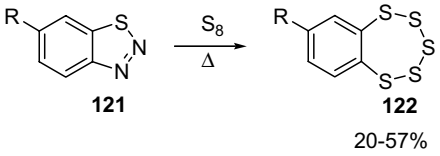
Scheme 14.28

Thermolysis of 1,2,3-benzothiazole **9** gives, as main products, thianthrene (**119**) [64, 65] and dibenzo[1,2]dithiin (**120**). The formation of these compounds can be explained on the basis of the dimerization of biradical **118**, formed after the nitrogen extrusion (Scheme 14.29).



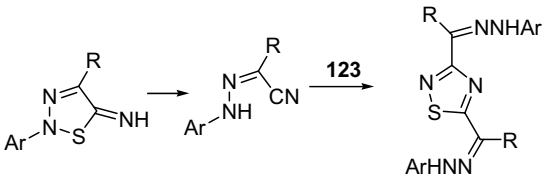
Scheme 14.29

When heated in the presence of sulfur, 1,2,3-benzothiadiazole **121** loses nitrogen and produces benzopentathiepine **122** (Scheme 14.30) [75]. In this way several heterocycles fused to the pentathiepine nucleus have been obtained by starting from the corresponding thiadiazoles [76].



Scheme 14.30

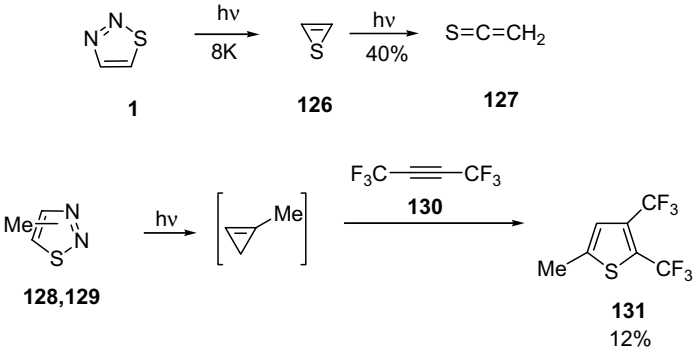
2-Aryl-1,2,3-thiadiazole-4*H*-5-imines **123**, when heated in boiling pyridine, undergo extrusion of sulfur to form hydrazones **124**, which by reaction with the starting thiazolidin-5-imines give 1,2,4-thiadiazoles **125** (Scheme 14.31) [77].



Ar =Ph, Tolyl
R = Me, Ph, Bn

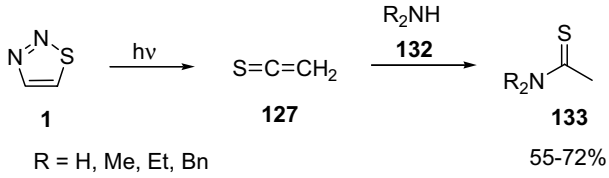
Scheme 14.31

In analogy to thermolysis, photolysis of 1,2,3-thiadiazoles proceeds with extrusion of nitrogen and leads to many products, all of which correspond with the above reported intermediates (Scheme 14.25) [78, 79]. Thus, thioketenes **102**, 1,4-dithins **103** and 1,4-dithiafulvenes **104** have been obtained. Photolysis of 1,2,3-thiadiazole **1** in an argon matrix at 8 K produced thiirene **126**, as seen by the appearance of its IR spectrum [80]. Upon further irradiation, this intermediate affords the corresponding thioketene **127**. Evidence for the thiirene intermediate has been obtained during the photolysis of 5-phenyl-1,2,3-thiadiazole by ^{13}C NMR spectroscopy [81]. Further support of thiirene intermediates has been given by the photolysis of either **128** or **129**, which in the presence of hexafluoro-2-butyne (**130**) lead to the thiophene **131** (Scheme 14.32) [72].



Scheme 14.32

The photochemical decomposition of 1,2,3-thiadiazole **1** in the presence of amines **132** leads to thioamides **133** in yields of 60–75% (Scheme 14.33) [82, 83].

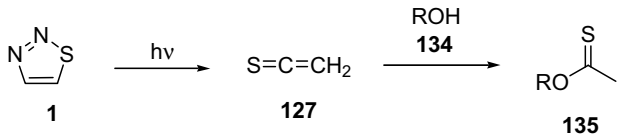


1 **127** **133**

R = H, Me, Et, Bn 55-72%

Scheme 14.33

In the presence of alcohols (**134**), photolysis or thermolysis leads to thioesters **135** (Scheme 14.34) [64, 65, 84].

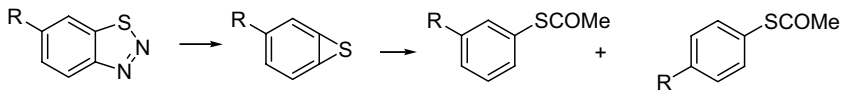


1 **127** **135**

R = Me, Et, *i*-Pr, t-Bu, Bn 12-72%

Scheme 14.34

The photochemical decomposition of benzothiadiazoles, followed by acylation of the obtained products, affords thioesters of acetic acid (**138** and **139**) (Scheme 14.35) [85].

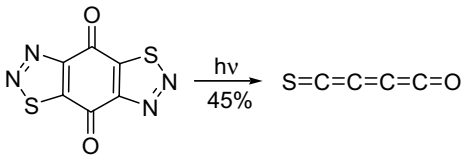


136 **137** **138** **139**

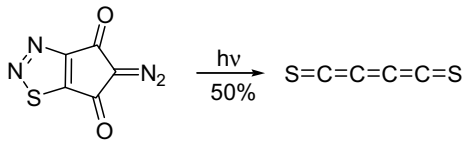
R = Me, OMe, NO_2, Cl, -Br 19-42% 16-56%

Scheme 14.35

Photolysis of substituted 1,2,3-thiadiazoles has also been used to generate highly reactive intermediates such as heterocumulenes [86]. Heterocumulenes **142** and **143** have been obtained by photolysis of quinone **140** and indandione **141**, respectively (Scheme 14.36) [87, 88].



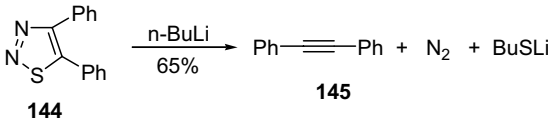
140 **142**



141 **143**

Scheme 14.36

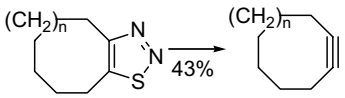
An example of the simultaneous loss of a molecule of nitrogen and the sulfur atom arises upon treatment of 4,5-disubstituted 1,2,3-thiadiazoles with strong bases, which results in ring cleavage. Thus, treatment of 4,5-diphenyl-1,2,3-thiadiazole (**144**) with *n*-butyllithium at −60 °C gives 1,2-diphenylacetylene (**145**) with evolution of nitrogen and extrusion of the sulfur atom (Scheme 14.37) [1].



144 **145**

Scheme 14.37

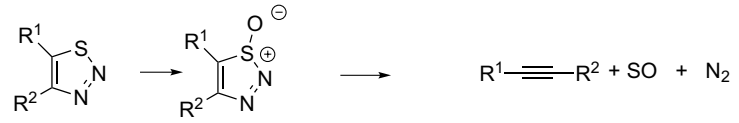
Upon irradiation, fused compounds like **146**, through the simultaneous loss of nitrogen and sulfur, give acetylene derivatives **147** (Scheme 14.38) [89, 90].



146 **147**

Scheme 14.38

Monocyclic 1,2,3-thiadiazoles **148**, acting as heme ligands, are oxidized by cytochrome P450 and oxygen to give acetylenic derivatives **150**. The formation of these compounds has been rationalized by the production of an unstable S-oxide (**149**), which loses nitrogen and SO (Scheme 14.39) [91].



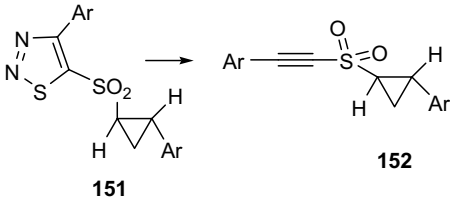
148 **149** **150**

19-65%

R^1 = Me, Et, i-Pr, Ph, Bn
R^2 = Me, i-Pr, Ph

Scheme 14.39

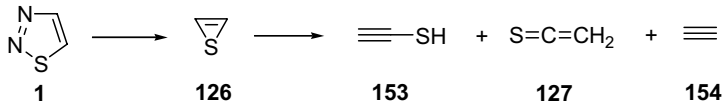
Pyrolysis of 1,2,3-thiadiazole **151** produces the arylethynyl sulfone **152** in satisfactory yields via N_2 and S displacement (Scheme 14.40) [92].



151 **152**

Scheme 14.40

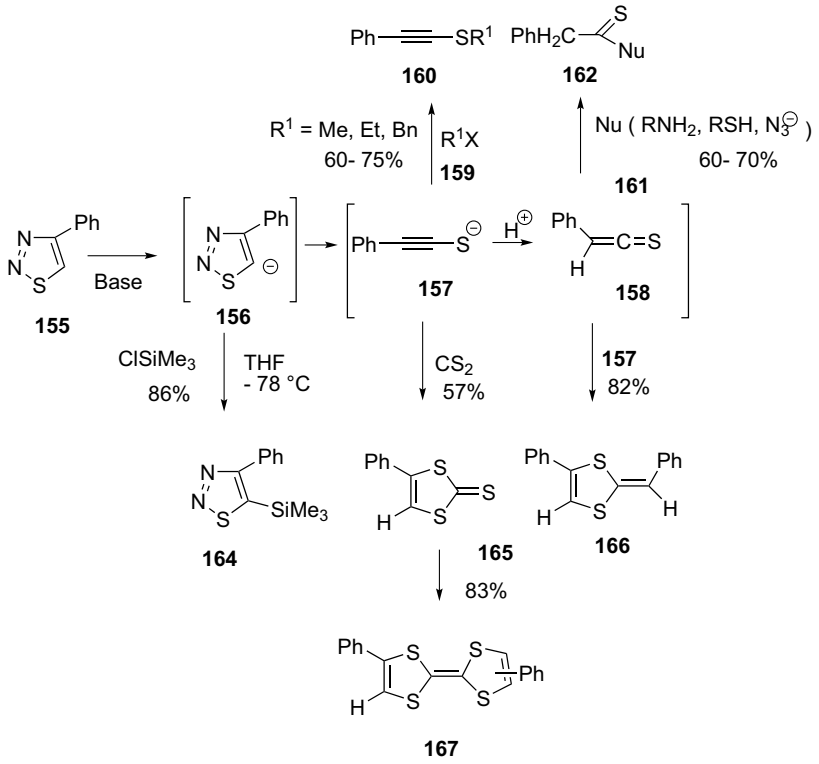
A study of the thermal decomposition of unsubstituted 1,2,3-thiadiazole has suggested the formation of alkynethiol, thioketene, and acetylene. *Ab initio* calculations indicate that thioketene **127** is 74 kJ mol^{-1} more stable than ethynethiol **153** and 552 kJ mol^{-1} more stable than thiirene **126** (Scheme 14.41) [93, 94].



Scheme 14.41

14.2.5.2 **Base-Catalyzed Decompositions**

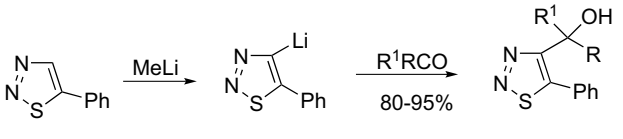
The ring cleavage of 4-monosubstituted 1,2,3-thiadiazoles in the presence of strong bases affords reactive alkynethiolates **157** [95, 96]. The alkynethiolate can be alkylated to give sulfide derivatives **160**, or acylated, reacted with nucleophiles to give **162**, dimerized to 1,4-dithiafulvenes **166**, cyclized with CS_2 to give 1,3-dithiole-2-thiones **165**, which are useful intermediates towards tetrathiafulvalenes **167** (Scheme 14.42) [97–99].



Scheme 14.42

Thomas and Zimmerman have trapped the anion **157** *in situ*, by reaction with chlorotrimethylsilane, giving rise to the formation of compound **164** [100].

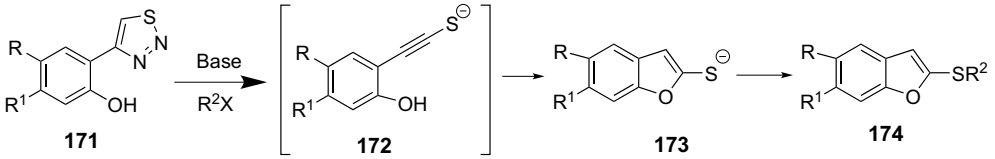
In contrast to 4-monosubstituted thiadiazoles, 5-derivatives produce stable anions that can react with many electrophiles to give various 4,5-disubstitued 1,2,3-thiadiazoles. For example, the metallation of 5-phenyl-1,2,3-thiadiazole (**168**) with methyllithium gives 4-lithio-5-phenyl-1,2,3-thiadiazole (**169**), which is stable and can react with aldehydes or ketones at −70 °C in tetrahydrofuran to produce 4-oxymethyl-1,2,3-thiadiazoles **170** in good yields (Scheme 14.43) [100].



R = H, Me,
R^1 = Me, Et, cycloexyl,cyclopentyl, Bn, n-Pr, n-eptyl

Scheme 14.43

4-(*o*-Hydroxyaryl)-1,2,3-thiadiazoles **171** have proven to be susceptible to relatively weak bases such K_2CO_3 and give, in the presence of alkylated agents, the unexpected benzofuran-2-sulfides **174** instead of the O-alkylated 1,2,3-thiadiazoles (Scheme 14.44) [101, 102].

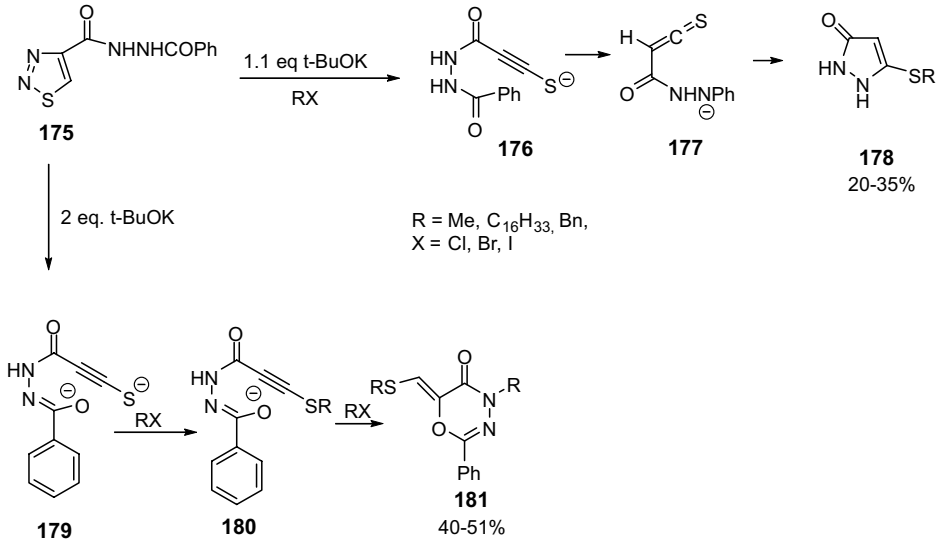


R = H, OH
R^1 = H, OH
R^2 = Me, Bn, $C_{16}H_{33}$
X = Cl, Br, I

Scheme 14.44

^{1}H NMR data proved that the benzofuran-2-thiolate **173** is really the intermediate of the reaction.

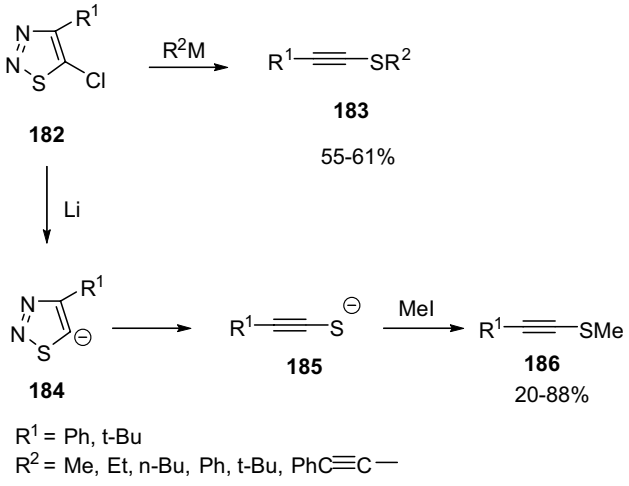
This methodology has been exploited to produce nitrogen heterocycles: thus base-catalyzed ring cleavage of derivatives of 1,2,3-thiadiazole-4-carbonylhydrazide **175**, followed by alkylation, affords the pyrazoles **178** (Scheme 14.45) [103].



Scheme 14.45

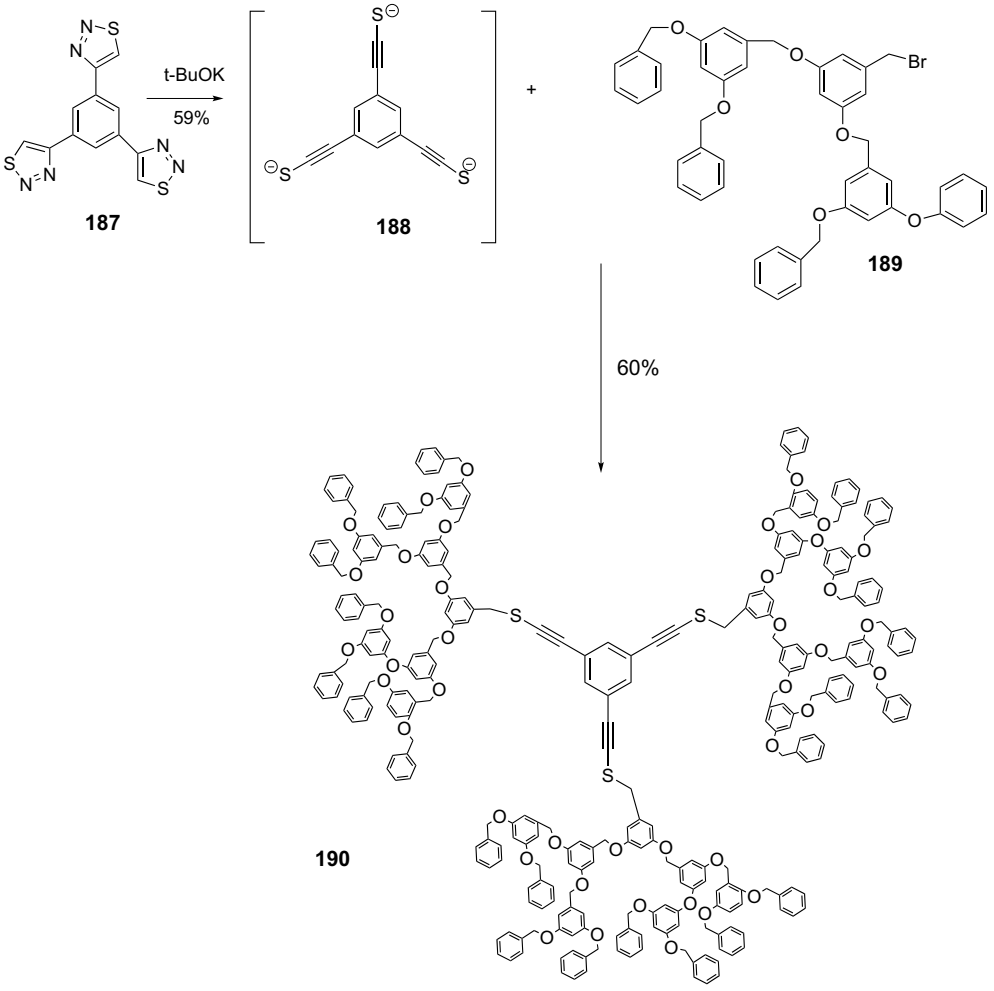
The presence of two or more equivalents of base promotes a different reaction course that leads to the formation of the 1,3,4-oxadiazine structure **181**.

5-Chloro-1,2,3-thiadiazoles **182**, which are stable in the presence of weak or moderately strong bases, react with organometallic reagents to give alkyne sulfides **183** as a consequence of the ring cleavage. Metallation of **182** with lithium affords the unstable 1,2,3-thiadiazol-5-yllithium **184**, which loses nitrogen to give the alkynethiolate **185**, which in turn can be easily transformed into **186** (Scheme 14.46) [104].



Scheme 14.46

The formation of alkynethiolates, by decomposition of the 1,2,3-thiadiazole ring in the presence of bases, has been used for the synthesis of a series of dendrimers. Thus, 1,3,5-tris(1,2,3-thiadiazolyl-4-yl)benzene **187**, prepared from 1,3,5-triacetylbenzene by the Hurd–Mori reaction, upon treatment with potassium *t*-butoxide gives the trithiolate anion **188**, which can be coupled with dendron **189** to afford the second generation dendrimer **190** (Scheme 14.47) [105].



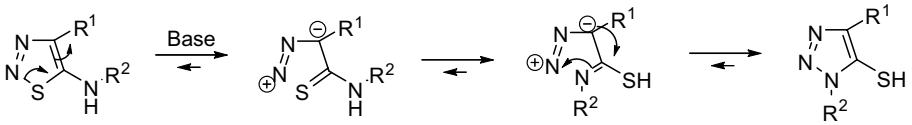
Scheme 14.47

14.2.5.3 **Rearrangement Processes**

The chemistry of the 1,2,3-thiadiazole system has found extensive application in organic synthesis as a useful approach to a series of functionalized five-, six-, and seven-membered heterocyclic systems. The reaction routes starting from 1,2,3-thiadiazoles are promoted by (i) the cleavage of the weak N–S bond, (ii) the

equilibrium between 1,2,3-thiadiazole and α-diazothiocarbonyl structures, and (iii) the cyclization of these functionalities onto electrophilic and nucleophilic substituents [3].

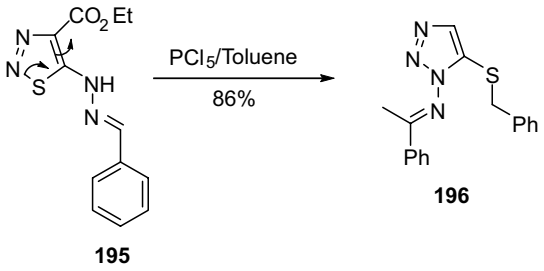
14.2.5.3.1 **Dimroth-Type Rearrangement** The Dimroth rearrangement [106] has been observed in a series of heterocyclic derivatives possessing several N-atoms. In the 1,2,3-thiadiazole system, this rearrangement occurs through cleavage of the N–S bond to give the corresponding diazothiocarbonyl compound **193**. 5-Amino-1,2,3-thiadiazoles **191** easily undergo this type of rearrangement, upon treatment with base, to form 5-mercapto-1,2,3-triazoles **194** (Scheme 14.48). In this rearrangement, the nitrogen atom of the chain at position-5 takes part in the process.



Scheme 14.48

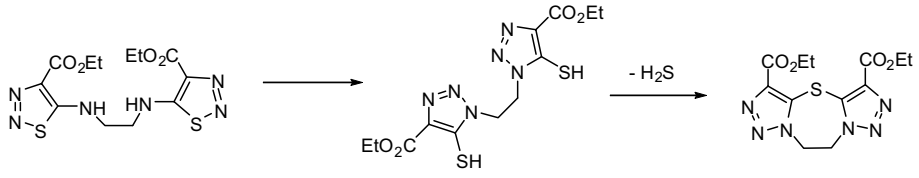
The suggested mechanism is supported by the kinetics of the process and by the influence of the solvent polarity. The acidity of the mercapto group shifts the reaction forward with the formation of thiolate salts in basic conditions.

The transformation of hydrazones **195** into 1,2,3-triazoles **196** by treatment with PCl_5 could proceed by the same reaction route, although the mechanism has not been perfectly elucidated (Scheme 14.49) [107, 108].



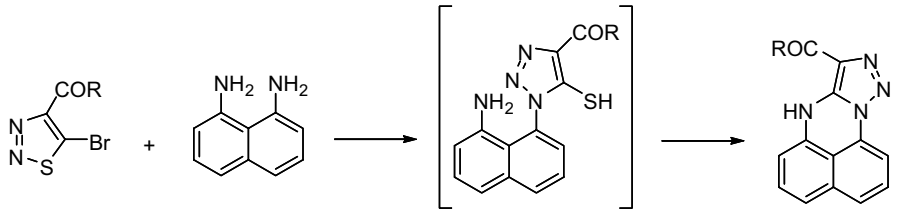
Scheme 14.49

A double Dimroth rearrangement has been reported for the conversion of ethylene bis(thiadiazol-5-amine) (**197**) into the intermediate bis thiol, which undergoes an intramolecular nucleophilic substitution reaction with loss of H_2S to give tricyclic triazole **199** (Scheme 14.50) [108].



Scheme 14.50

By the same reaction route, 5-halo-1,2,3-thiadiazole **200** reacts with 1,8-diaminonaphthalene (**201**) to afford the tetracyclic derivative **203** (Scheme 14.51) [27, 109].

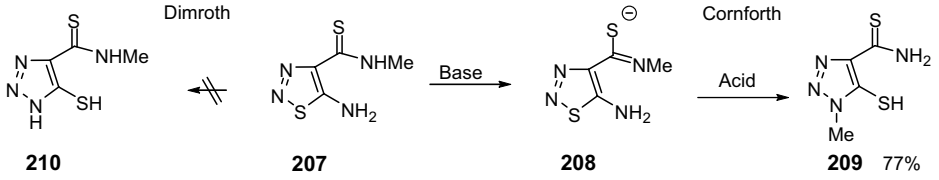


Scheme 14.51

14.2.5.3.2 **Cornforth-Type Rearrangement** 1,2,3-Thiadiazoles, bearing a C=N and or C=S function at the 4-position, when treated with base, rearrange to give 1,2,3-triazoles (X = NR) or isomeric 1,2,3-thiadiazoles (X = S). The process, in contrast to the Dimroth rearrangement, involves two atoms of the 4-substituent and is similar to the interconversion reactions of isomeric 4-acyl-substituted oxazoles via the dicarbonyl nitrile ylides discovered by Cornforth in 1949 [110]. The rearrangement has been rationalized on the basis of a 1,3-dipolar intermediate diazo compound **205** bearing two nucleophilic groups (two thiocarbonyl functions or a thiocarbonyl and an iminocarbonyl function) (Scheme 14.52).

Scheme 14.52

The example reported in Scheme 14.53 shows the different course of the Cornforth rearrangement with respect to the Dimroth reaction. Treatment of 5-amino-1,2,3-thiadiazole-4-carbothioamide (**207**) with bases involves two atoms of the side chain to give 5-mercapto-1,2,3-triazoles **209** rather than the isomeric product **210** resulting from the Dimroth rearrangement [111].

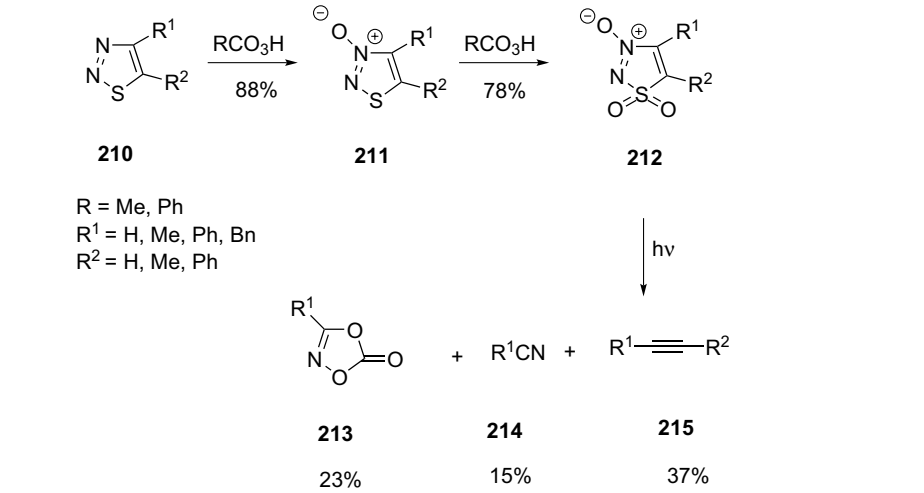


210 **207** **208** **209**

Scheme 14.53

14.2.5.4 Oxidative and Reductive Processes

1,2,3-Thiadiazoles are very stable to strong oxidizing and reducing agents. However, oxidation with peracetic acid gives 1,2,3-thiadiazole 3-oxides **211** and, with an excess of oxidizing agent, 1,2,3-thiadiazole 1,1,3-trioxides **212**. Photolysis of **212** produces several products such as dioxazoles **213**, nitriles **214**, and acetylenes **215** (Scheme 14.54) [112].



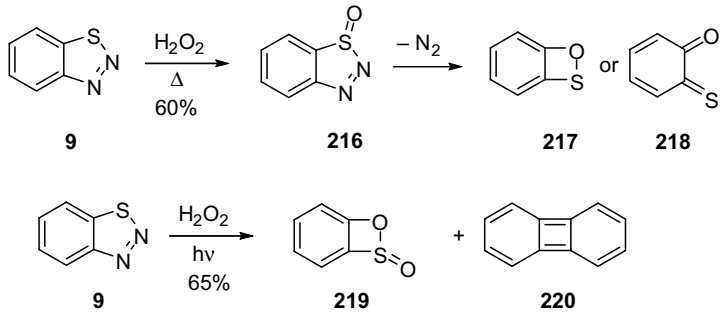
210 **211** **212**

213 **214** **215**

23% 15% 37%

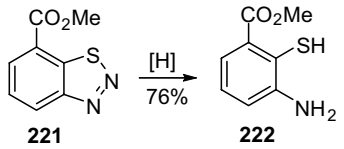
Scheme 14.54

Oxidation of 1,2,3-benzothiadiazole **9** with hydrogen peroxide leads to 1-oxo-1,2,3-benzothiadiazole (**216**), which thermally decomposes into benzoxathiete **217** or its valence tautomer **218**. Photochemical oxidation of **9** affords the benzoxathiete *S*-oxide **219** and biphenylene (**220**) (Scheme 14.55) [113].



Scheme 14.55

Reduction of benzothiadiazole **221** with hydrogen on palladium gives methyl 3-amino-2-mercaptobenzoate (**222**) (Scheme 14.56) [114].



Scheme 14.56

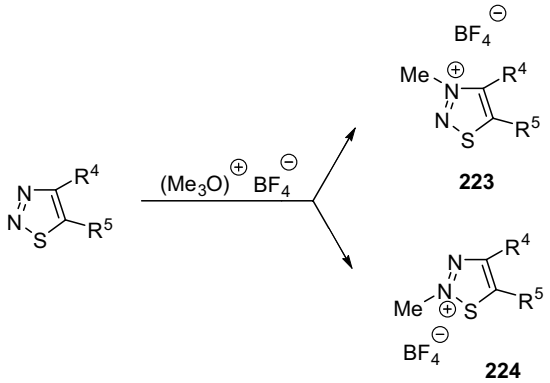
14.2.5.5 **Reactions due to the Reactivity of Heterocyclic Ring**

Electrophilic substitution on the C-atoms is difficult, while nucleophiles prefer to attack the 5-position. 1,2,3-Thiadiazoles are weak bases and form a deliquescent hydrochloride salt that is decomposed by water. There are several examples of reactions of alkyl halides at the nitrogen atoms of 1,2,3-thiadiazoles to give salts or mesoionic compounds [5]. Alkylation reactions occur preferentially at N3 ring atom; Table 14.5 shows the effect exerted by substituents at the 4 and 5-position of the ring with the relative formation of compounds **223** and **224**. The presence of a bulky group at the 4-position directs alkylation towards the preferential formation of the 2-alkyl derivative [18].

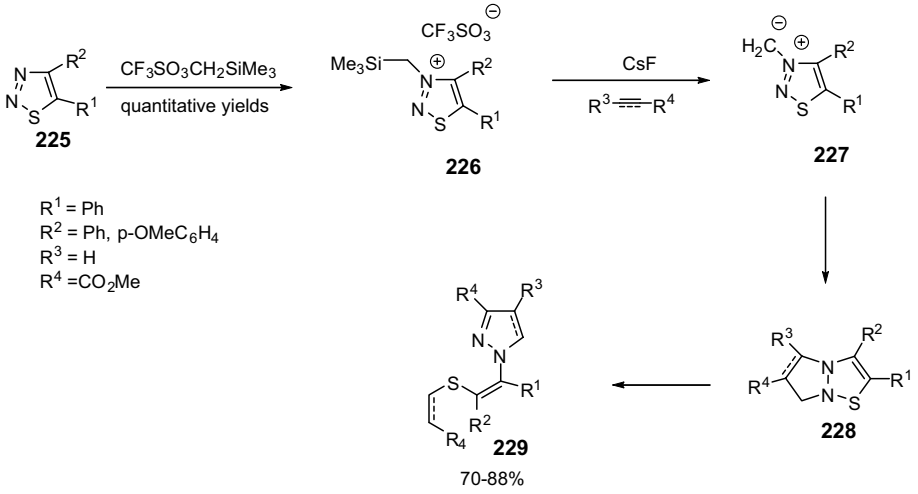
The alkylation of 1,2,3-thiadiazoles with trimethylsilylmethyl-trifluoromethanesulfonate occurs at N3 to produce the corresponding thiadiazolium salts **226**, which, when treated with CsF, give rise to 1,2,3-thiadiazol-3-ium-3-methanides **227** [115]. These non-stabilized azomethine ylides react *in situ*, via 1,3-dipolar cycloaddition, with electron-deficient alkynes or alkenes to give pyrazolo-thiadiazole systems **228**. The fused bicyclo compounds can in turn undergo a ring-opening reaction to form pyrazole or pyrazoline derivatives **229**, depending on the nature of the dipolarophiles (Scheme 14.57).

1,2,3-Thiadiazoles are not easily halogenated. It has been reported that 5-phenylureido-1,2-3-thiadiazole **230** reacts with chlorine or bromine to give the compound **231**, produced by halogenation on both the thiazole and phenyl rings (Scheme 14.58) [116].

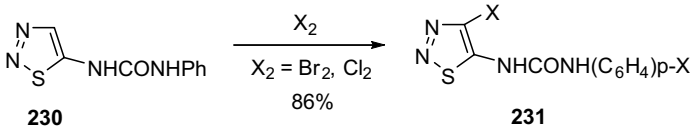
Table 14.5 Product distribution in the methylation of 1,2,3-thiadiazoles with Meerwein's reagent.



R^4	R^5	**223** (%)	**224** (%)
H	H	96	4
H	Cl	100	
Ph	H	19	81
t-Bu	H	13	87
CO_2Me	H	92	8

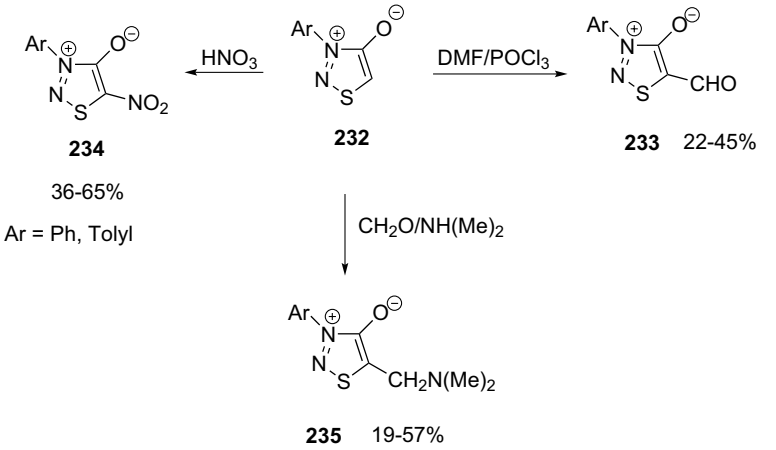


Scheme 14.57



Scheme 14.58

Mesoionic 3-phenyl-1,2,3-thiadiazoles **232** can be nitrated, formylated, and aminomethylated, as a result of the influence of the olate moiety (Scheme 14.59) [37].

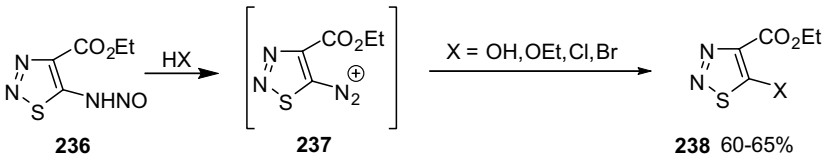


Scheme 14.59

With 1,2,3-benzothiadiazoles, electrophilic substitution occurs on the benzene ring. For instance, the reaction with nitric acid leads to 4- and 7-nitro-1,2,3-benzothiadiazoles [1].

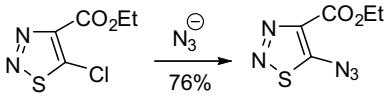
14.2.5.6 **Reactions with Nucleophiles**

1,2,3-Thiadiazoles containing a good leaving group at the C5 atom are able to give nucleophilic substitutions. Thus 5-nitrosoamino-1,2,3-thiadiazoles **236** in presence of acid, via the intermediate diazonium salt, react with nucleophiles to give, through a nucleophile displacement, the corresponding derivatives (Scheme 14.60) [2].



Scheme 14.60

Moreover, 5-chloro and 5-bromo-1,2,3-thiadiazoles in turn can react with different nucleophilic reagents to give a large variety of 5-substituted 1,2,3-thiadiazole derivatives [117]. For example, the reaction of the 5-chloro derivative **239** with sodium azide affords in good yield the 5-azide derivative **240** [118] (Scheme 14.61).

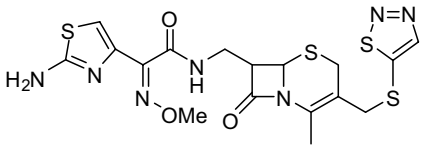


239 **240**

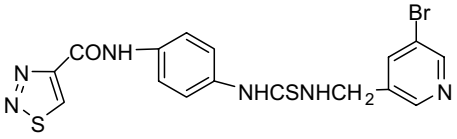
Scheme 14.61

14.2.6
1,2,3-Thiadiazoles in Medicine and Agriculture

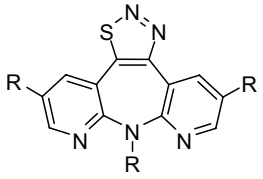
1,2,3-Thiadiazoles exhibit various types of biological activities and some of these compounds are useful pharmacophores. This nucleus is found in some cephalosporin derivatives such as **241** (cefuzonam), which show antibiotic properties, in compounds that are antipsychotic agents, in derivatives such as **242** and **243**, which exhibit activity against herpes viruses, herpes simplex viruses, varicella-zoster, human cytomegalovirus, and HIV-1 [119].



241
Cefuzonam



242

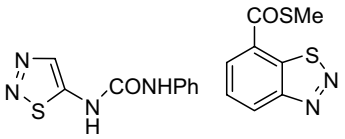


243

In general, it is interesting to note that the introduction of the 1,2,3-thiadiazole nucleus in molecules of known biological activity leads to an increase of their pharmacological profiles.

1,2,3-Thiadiazoles are also used in agriculture as pesticides. In particular, the 5-phenylureido-1,2,3-thiadiazole **244** (thidiazuron) is a very active cotton defoliant, while the *S*-methyl ester of 1,2,3-benzothiadazole-7-thiocarboxylic acid **245** (Bion), introduced by Novartis, has been shown to induce disease resistance in wheat,

tobacco, melons, maize, and *Arabidopsis*. Moreover, compounds showing antibacterial, antiviral, and antifungal activities have also been reported.

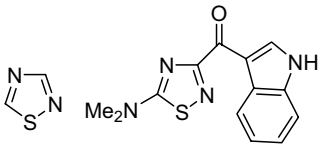


244 Thidiazuron

245 Bion

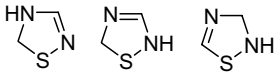
14.3 1,2,4-Thiadiazoles

The parent compound **246** was prepared in 1955 and the first natural product containing the 1,2,4-thiadiazole system (dendroine, **247**, a cytotoxic compound isolated from marine tunicate *Dendrodoa grassularia*) was reported in 1984 [120].



246 **247**

The partially reduced ring systems **248–250** are designated as 4,5-dihydro- (Δ^2), 2,5-dihydro- (Δ^3), and 2,3-dihydro-1,2-4- (Δ^4) thiadiazole; the fully reduced ring is termed thiadiazolidine.



248 **249** **250**

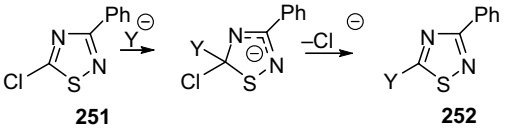
Many synthetic 1,2,4-thiadiazole derivatives are biologically active compounds and find use as insecticides, fungicides, herbicides, and antibacterials. As an example, 5-ethoxy-3-trichloromethyl-1,2,4-thiadiazole (ethridiazole) is used to combat or prevent fungal infestation of plants, fruit, cotton, and soil [121]. Azodyes derived from diazotized 5-amino-1,2,4-thiadiazoles are used as dyestuffs for polyester and polyacrylonitrile fibers.

During the last decade, very interesting therapeutic applications have been explored: the 1,2,4-thiadiazole nucleus is a fundamental constituent of several synthetic products with biological activities concerning the central nervous system (CNS), G-protein coupled receptors, cardiovascular system, or antibiotic activity.

Extensive reviews have been published on 1,2,4-thiadiazoles [120, 122, 123].

14.3.1 Structure

1,2,4-Thiadiazole is a heteroaromatic compound. It is a π-excessive heterocycle, but the presence of two nitrogen atoms exerts a considerable effect on its properties, leading to a relative π-deficiency on the carbon atoms. Electrophilic substitution reactions on carbon atoms are extremely rare, while nucleophilic substitution reactions are common and take place very readily in this ring system, because both nitrogen atoms can assist in stabilizing the intermediates. An example is provided by the high reactivity of 5-chloro-3-phenyl-1,2,4-thiadiazole (**251**) towards nucleophiles: the compound reacts faster than many activated six-membered heteroaromatics (Scheme 14.62).

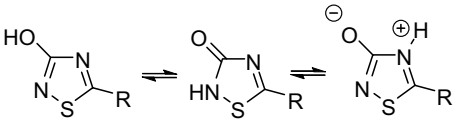


251 **252**

Scheme 14.62

The inductive effect of the sulfur undoubtedly contributes to the stabilization. This effect is selective, since the 3-chlorine in 3,5-dichloro-1,2,4-thiadiazole is much more difficult to displace than the 5-chlorine.

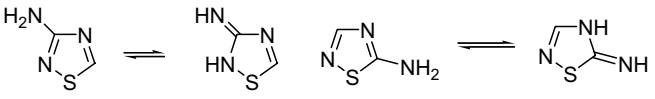
For 3-hydroxy-1,2,4-thiadiazoles three tautomeric forms are possible (**253a–c**).



253a **253b** **253c**

UV data suggest that the lactam form **253b** is the major tautomer in ethanol [120]; however, 3-hydroxy-5-phenyl-1,2,4-thiadiazole has been shown by X-ray studies to exist as the OH tautomer **253a** [124].

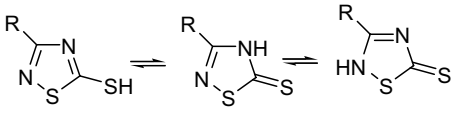
3-Amino and 5-amino-1,2,4-thiadiazoles exist predominantly in the amino forms (Figure 14.2), as supported by spectroscopic methods and *ab initio* MO calculations [125].



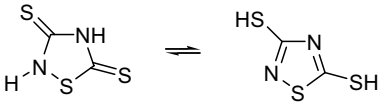
254 **255** **256** **257**

Figure 14.2 3-Amino and 5-amino-1,2,4-thiadiazoles exist predominantly in the amino forms.

The IR spectrum of 5-mercapto-1,2,4-thiadiazole does not show the SH absorption of structure **258**, thus suggesting the thione tautomers **259** and **260**. On the same basis, IR experiments indicated that perthiocyanic acid exists as dithione **261** and not in tautomeric form **262** [120].

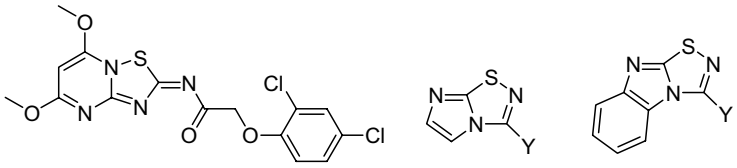


258 **259** **260**



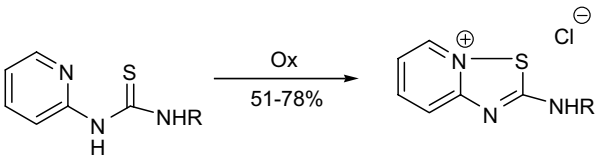
261 **262**

1,2,4-Thiadiazoles fused with heteroaromatic systems have also been reported: the 5,7-dimethoxy-2-(2,4-dichlorophenoxyacetylimino)-2*H*-1,2,4-thiadiazolo[2,3-*a*] pyrimidine (**263**) [126] shows interesting herbicidal properties. Bicyclic imidazo[1,2-*d*][1,2,4]thiadiazoles **264** and tricyclic benzo[4,5]imidazo[1,2-*d*][1,2,4]thiadiazoles **265** have been described as compounds able to react with enzyme cysteine residues to form a disulfide adduct, thus inhibiting the enzyme [127–129].



263 **264** **265**

The structure of the 1,2,4-thiadiazole[2,3-*a*]pyridinium salts **267** (Scheme 14.63), obtained from the oxidation of *N*-alkyl-*N*-benzylthiourea or *N*-benzyl-*N*′-(2-pyridyl) thiourea **266** with sulfuryl chloride in toluene, has been confirmed by ^{1}H and ^{13}C NMR spectroscopy [130].

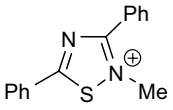


266 **267**

R= Me, Et, Bn

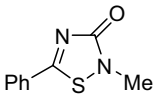
Scheme 14.63

The *N*-methyl-1,2,4-thiadiazolium salt **268** has been proposed as an interesting pharmacophore in the design of inhibitors targeting the cysteine residues of proteins [131].

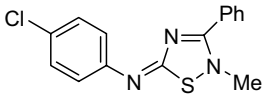


268

As mentioned above, the partially reduced 1,2,4-thiadiazoles (1,2,4-thiadiazolines) can exist in three tautomeric forms **248–250**, depending on the position of the double bond. The tautomer **248**, with the double bond between the α-nitrogen and the β-carbon, is the one with the lowest energy, lying 3.3 and 4.6 kcal mol^{-1} off the other forms, and thus is the more stable geometric structure [132]. Stable N-substituted Δ^4-**269** [133] and Δ^3-thiadiazolines **270** [134] have been suggested as scaffolds for structure–activity investigation as N-S cysteine thiol trapping agents in enzyme systems [135].

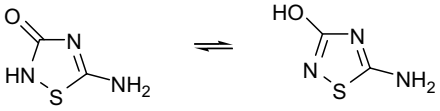


269



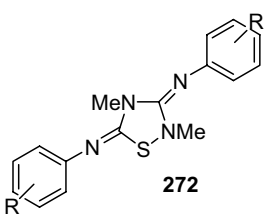
270

The 5-amino-1,2,4-thiadiazolin-3-one **271**, analog of cytosine, can exist in two stable tautomeric forms: lactam (oxo) **271a** and lactim (enol) **271b**. ^{13}C and ^{1}H NMR spectra and *ab initio* molecular orbital calculations support the idea that **271** exists in the lactam rather than in the lactim form [136, 137].

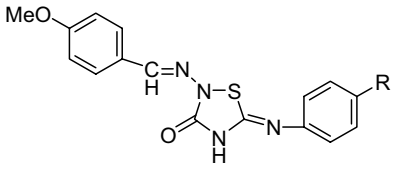


271a **271b**

The fully saturated 1,2,4-thiadiazole system (1,2,4-thiadiazolidine) is present in a series of compounds endowed with important biological activities. Compounds **272** and **273** are characterized by interesting antibacterial, antifungal, anti-inflammatory, and analgesic activities [138, 140].

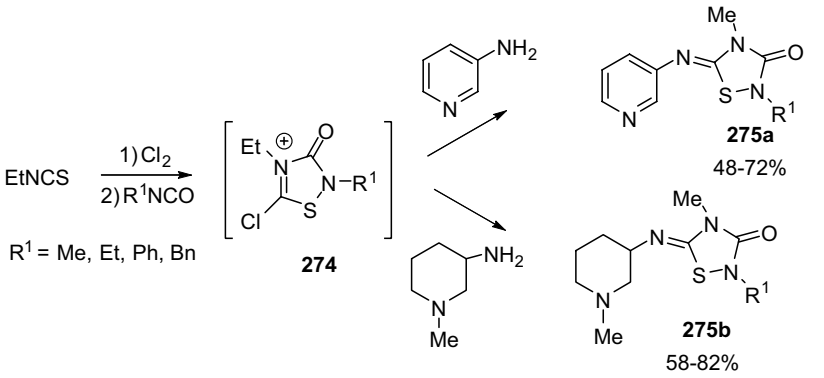


272



273

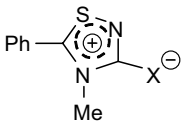
Thiazolidinones **275** have been obtained by reaction of oxathiadiazolium salt **274** with aromatic and cycloalkyl amines (Scheme 14.64). The (*Z*) configuration for **275** was assigned by AM1 calculations and ^{1}H NMR data [139].



Scheme 14.64

Synthetic approaches towards 1,2,4-thiadiazolidine systems are reported in Section 14.3.4.1.

The synthesis and chemistry of two classes of meso-ionic 1,2,4-thiadiazoles (**276**, X = O, X = $SO_2C_6H_4Me$-*p*) have also been reported [133].



276

14.3.2 Theoretical Aspects

Theoretical studies on the structure and properties of 1,2,4-thiadiazoles are not numerous, because of the difficulties linked to the presence of the sulfur atom. AM1 calculations have been performed on the parent compound to predict the degree of aromaticity and to calculate some energetic and magnetic parameters [141]. With the view to establishing structure–activity relationships, the charge densities of 3,5-disubstituted 1,2,4-thiadiazoles have been calculated and possible conformations estimated [142]. The reactivity of the 5-position in nucleophilic substitution reactions for non-protonated 1,2,4-thiadiazoles has been supported by a molecular orbital method with the LCAO approximation [120].

Electrostatic potentials at N2 and N4 have been calculated for 3,5-dimethyl-1,2,4-thiadiazole and other 5-substitued-3-methyl-1,2,4-thiadiazoles and correlated with the relative binding to cortical muscarinic receptors [143].

Table 14.6 Equilibrium geometry parameters performed at the B3LYP with a 6-31G** basis set for the 1,2,4-thiadiazoline nucleus.

Bond	Length (Å)	Bond	Angle (°)
S–N(1)	1.746	N(1)–S–C(1)	93.9
S–C(1)	1.862	S–N(1)–C(2)	108.3
N(1)=C(2)	1.280	S–C(1)–N(2)	101.6
C(1)–N(2)	1.463	N(1)–C(2)–N(2)	121.1
C(2)–N(2)	1.386	C(1)–N(2)–C(2)	112.7
C(1)–H(3)	1.093	S–C(1)–H(3)	110.1
N(2)–H(2)	1.011	C(1)–N(2)–H(2)	117.6

Geometrical bond lengths and bond angles for the 1,2,4-thiadiazoline nucleus have been estimated by density functional theory (DFT) methods (Table 14.6) [132].

Dipole moments, ionization potentials, and electron affinities as a measure of aromaticity have also been calculated to determine the reactivity of different sites within the molecules studied. The results were compared with existing experimental evidence on thiazolidines and related compounds.

Ab initio calculations performed on thiadiazoline **271** confirm that the lactam form **271a** is more stable than lactim form **271b** by 9.82 kcal mol^{-1} at the HF/3-21G* level. On the same basis, bond lengths and angles have been estimated (Figure 14.3) [144].

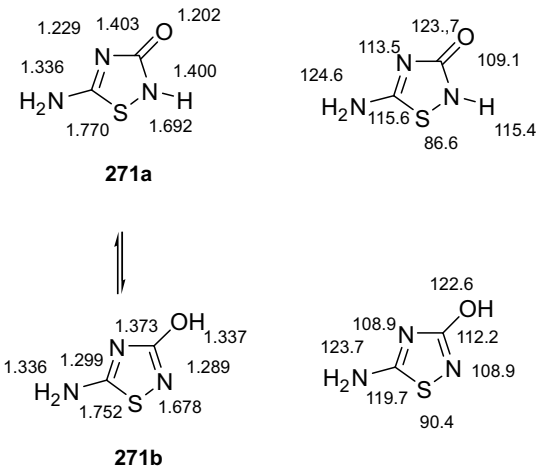


Figure 14.3 According to *ab initio* calculations performed on thiadiazoline **271**, lactam form **271a** is more stable than lactim form **271b**.

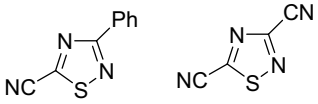
Figure 14.4 Bond lengths and angles determined by double resonance modulation microwave spectroscopy.

14.3.3 Structural Aspects

14.3.3.1 X-Ray Diffraction

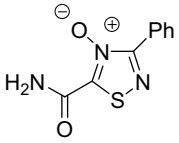
X-Ray diffraction measurements of several 1,2,4-thiadiazoles and 1,2,4-thiadiazolidines have been reported; [122, 126, 145–149] bond lengths and angles have been determined by double resonance modulation microwave spectroscopy (Figure 14.4) [122].

The X-ray analysis of 5-cyano-3-phenyl-1,2,4-thiadiazole (**277**) shows the molecule to be almost planar with only ca 2° torsional twist about the bond linking the thiadiazole and the phenyl system. The experimental data are consistent with the presence of a formal N=C double bond for the N2–C3 and N4–C5 linkages, though there is some evidence for delocalization that extends from S1 via C3 to C5 [150]. The pattern of bonding is similar to that observed for 1,2,4-thiadiazole-3,5-dicarbonitrile (**278**) [151], indicating that the nature of the substituent on C3 has little effect on the bonding within the ring.



277 **278**

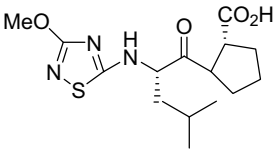
The X-ray structure of 5-carboxamide-3-phenyl-1,2,4-thiadiazole 4-oxide (**279**), the first 1,2,4-thiadiazole *N*-oxide reported [150], shows that this molecule too has a nearly planar conformation, the torsional twists about the C(3)–C(Ph) and C(5)–C(O) bonds being only ca 8° and 5°, respectively. The conformation is stabilized by intramolecular NH...O and CH(Ph)...O hydrogen bonds, with the former producing the *syn* relationship between the N-oxide oxygen and the amido nitrogen. The bonding in the thiadiazole ring differs noticeably from that observed in **277**, where a pattern of delocalization is present extending from C3 via S1 to N4.



279

More recently, the X-ray crystal structure of the bicyclic imidazo[1,2-*d*][1,2,4] thiadiazole **264** was obtained: some of the salient features include the C1–S1 and N1–S1 bond lengths of 1.730 and 1.693 Å, respectively, which are slightly longer than the C–S (1.707 Å) and N–S (1.649 Å) bond lengths of monocyclic [1,2,4] thiadiazole [152].

The crystal structure of the adduct of cathepsin B and Apo501 (**280**), a member of a series of 1,2,4-thiadiazole analogues designed as inhibitors of cysteine proteases, clearly indicates that the cysteine thiol reacts with the N–S bond of the thiadiazole moiety, thus resulting in the inactivation of the enzymes [127].



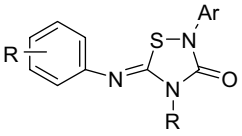
280

14.3.3.2 **NMR Spectroscopy**

^{1}H NMR spectral data on several 1,2,4-thiadiazole derivatives have been reported [126, 153, 154, 158]. In general, the resonances of protons in the 1,2,4-thiadiazoles are shifted downfield with respect to benzene protons, with the proton at C3 more deshielded than the proton at C5. In 3-phenyl-1,2,4-thiadiazole, H3 resonates at 9.9 δ, while H5 appears at 8.55 δ [125].

The solvent effect on the ^{1}H NMR spectral data of a series of 1,2,4-thiadiazole derivatives has been determined by measuring the chemical shift differences observed in various solvents. For methyl and methylene groups linked to a sp^2-hybridized nitrogen, Δν shows a linear correlation with Hammett σ constants, while the same groups attached to a sp^3-hybridized nitrogen correlate with Taft σ^0 constants [122, 155].

^{1}H and ^{13}C NMR data have been reported for 1,2,4-thiadiazolidines **281** [156].



281

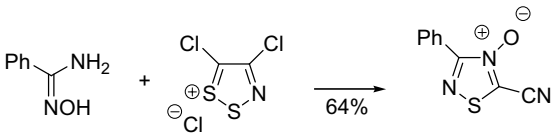
^{13}C NMR spectroscopy has been widely used to elucidate the structures of various 1,2,4-thiadiazoles and thiadiazolines [159–163]. More recently, ^{13}C chemical shifts of 3,4-disubstituted-1,2,4-thiadiazole-5-ones were determined [164]. Exceptionally good Hammett correlations of ^{13}C chemical shifts with σ were obtained. The negative ϱ values observed indicate π-polarization of C=N, and C=O bonds.

Unequivocal assignment of all chemical shifts (^{1}H and ^{13}C NMR) has been performed using two-dimensional experiments such as HMQC for one-bond correlations and HMBC for long distance proton/carbon correlations [171].

Solvent and concentration effects in ^{14}N NMR spectroscopy have been investigated [165, 166]. High precision ^{14}N NMR measurements are reported for all possible thiadiazole isomers in various solvents. Both solvent polarity and hydrogen bonding effects produce an increase in the nitrogen shielding. Analysis of the experimental data and molecular orbital studies indicates that an increase in the polarity of the solvent favors the delocalization of the lone pair electrons from the sulfur atom into the conjugated ring, thus leading to an increase in electronic charge at the nitrogen atoms.

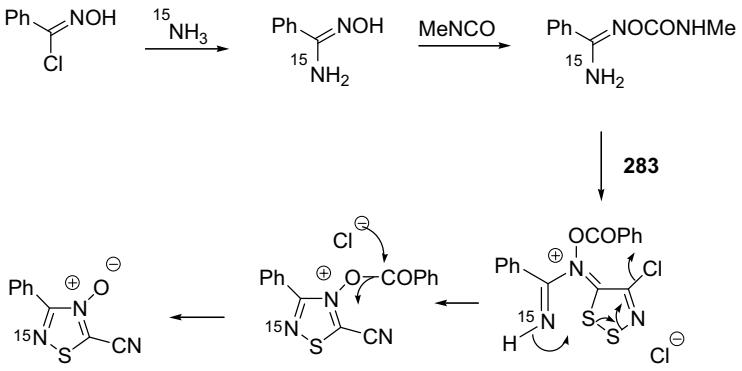
In the case of 1,2,4-thiadiazoles, nitrogen shielding ranges from 11 to 20 ppm, with the range for N3 approximately twice that for N2.

The mechanism of the reaction and the formation of 1,2,4-thiazolidine N-oxide **284** by reaction of O-substituted benzamidoxime **282** with 4,5-dichloro-1,2,3-dithiazolium chloride (**283**) (Scheme 14.65) has been investigated by analysis of ^{13}C and ^{14}N NMR spectra of ^{15}N-labeled and unlabeled precursors (Scheme 14.66) [150].



282 **283** **284**

Scheme 14.65



Scheme 14.66

The signal at δ −110.9, corresponding to the unoxidized nitrogen atom, in the ^{15}N NMR spectrum of the N-oxide – and the signal at δ −70.7, characteristic of heterocyclic N-oxides, in the ^{14}N NMR spectrum – clearly suggests that all the ^{15}N labels are on the unoxidized nitrogen atom.

14.3.3.3 UV and IR Spectroscopy

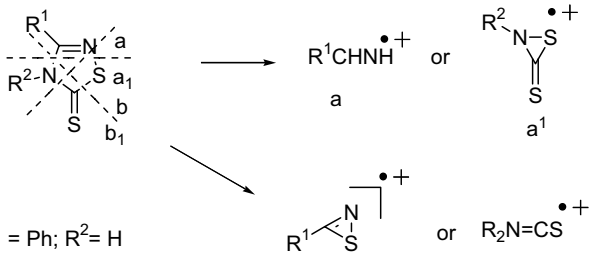
Data on IR and UV spectroscopy have been reported for some 1,2,4-thiadiazoles [120].

Characteristic infrared absorptions are seen at 1560–1590 and 1490–1550 cm^{-1} (ring skeletal vibrations), 1215–1270, 1080–1185, and 1020–1050 cm^{-1} (CH in plane deformations), and 735, 795–860 cm^{-1} (CH out-of-plane deformations) [167].

1,2,4-Thiadiazoles show an absorption band in the UV spectra at 229 nm: the presence of amino groups in the ring induces a bathochromic shift (247 nm for 5-amino- and 256 nm for 3,5-diamino-1,2,4-thiadiazole).

14.3.3.4 Mass Spectrometry

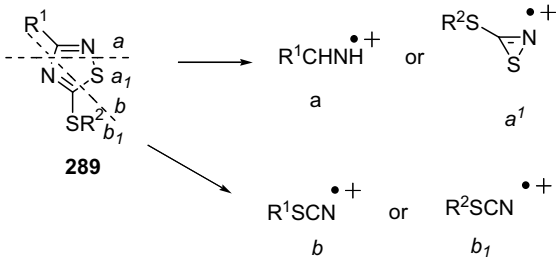
The electron-impact mass spectra of 1,2,3-thiadiazoles exhibit an intense signal for the molecular ion [139]. Moreover, the predominant fragmentation pattern follows two general pathways (a and b) as reported in Scheme 14.67. 3-Aryl-1,2,4-thiadiazole-5-thiones **285** and **286** fragment much less than 3,4-disubstituted compounds **287**, **288** [168].



285 :R^1 = Ph; R^2= H
286 :R^1= *p*.MeC_6H_4; R^2= H
287 :R^1= *p*.ClC_6H_4; R^2= *o*.MeC_6H_4
288 :R^1= *p*.$NO_2C_6H_4$; R^2= *n*.propyl

Scheme 14.67

3-Aryl-5-alkyl- or arylthio-1,2,4-thiadiazoles **289** have been shown to exhibit rather stable $M^{+\bullet}$ ions and relatively simple fragmentation patterns (Scheme 14.68), which are usually dominated by the $R^1CNS^{+\bullet}$ ion, which is even the base peak.



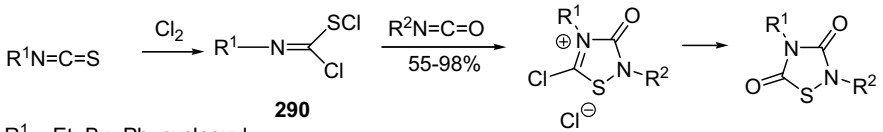
Scheme 14.68

The mass spectra of 1,2,4-thiadiazole 4-oxides **279** and **284** show as first fragmentation the loss of the oxygen atom, followed by the fragmentation observed for the corresponding deoxygenated compounds, which is the usual fragmentation of the 1,2,4-thiadiazole ring [150].

14.3.4 Synthesis

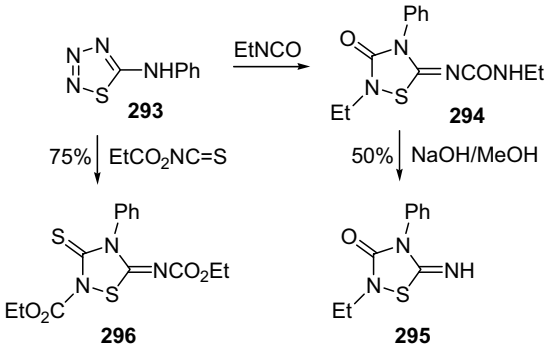
14.3.4.1 1,2,4-Thiadiazolidines

The most general synthetic entry to thiadiazolidinediones **292** starts from N-alkyl- or N-aryl-S-chloroisothiocarbamoyl chlorides **290**, obtained by treatment of alkyl or aryl isothiocyanate with chlorine. Thus, the reaction of **290** with aliphatic or aromatic isocyanates gives the sparingly soluble 3-oxothiadiazolium salts **291**, which, in the presence of moist air, hydrolyzes to 1,2,4-thiadiazolidine-3,5-diones **292** with evolution of hydrogen chloride (Scheme 14.69) [169, 170].



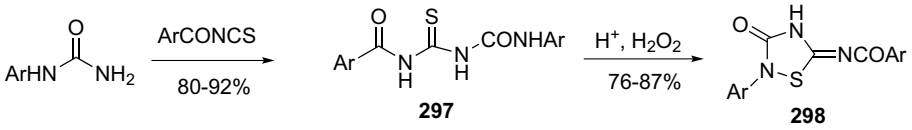
Scheme 14.69

Introduction of an imino moiety at the 5-position of the thiadiazolidine framework, leading to compound **295**, has been achieved by the basic hydrolysis of urea derivative **294** (Scheme 14.70). This last compound was easily obtained following a described procedure of 5-aminophenyl-1,2,3,4-thiatriazole **293** rearrangement with isocyanates and isothiocyanates [171]. Treatment of **293** with ethoxycarbonyl isothiocyanate leads to thiadiazolidine **296**.



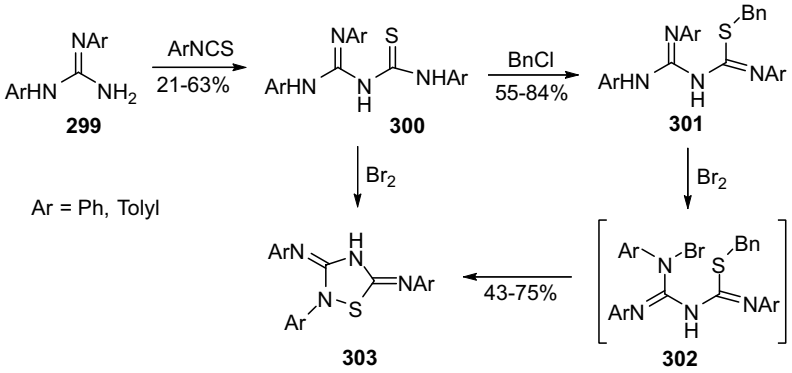
Scheme 14.70

Alternatively, 5-imino-3-oxo-1,2,4-thiadiazolidines **298** have been obtained in good yields by addition of arylureas to benzoyl isothiocyanate and oxidation of intermediate 2-thiobiourets **297** with hydrogen peroxide (Scheme 14.71) [172].



Scheme 14.71

Similarly, amidinothioureas **300**, obtained by reaction of aryl isothiocyanates with guanidines **299**, have been converted into 3,5-diarylimino-1,2,4-thiadiazoles **303** by reaction with bromine in ethanol or by reaction with benzyl chloride followed by bromine treatment (Scheme 14.72) [173].

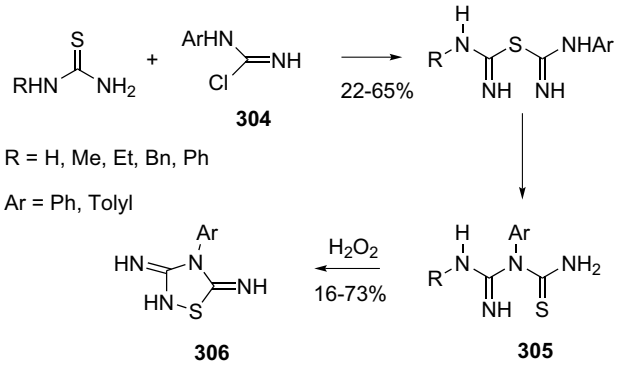


Scheme 14.72

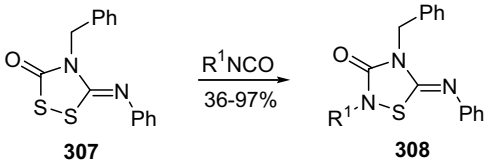
An alternative synthesis of amidinothioureas **305** involves the reaction of α-chloroformamidines **304** with substituted thioureas: oxidation of **305** with hydrogen peroxide leads to thiadiazolidine **306** (Scheme 14.73) [174].

The 1,2,4-thiadiazolidone system has also been prepared starting from other heterocycles by a cycloaddition–elimination sequence. The reaction of 5-benzylimino-1,2,4-dithiadiazolidin-3-one **307** with isocyanates leads to the corresponding 1,2,4-thiadiazolidinone **308** with elimination of carbonyl sulfide (Scheme 14.74) [175].

An alternative way to obtain 5-imino-1,2,4-thiadiazole-3-ones **310** is based on the reaction of 5-imino-1,2,3,4-thiatriazolines **309**, as masked 1,3-dipoles, with isocyanates via a cycloaddition–elimination process (Scheme 14.75) [176].

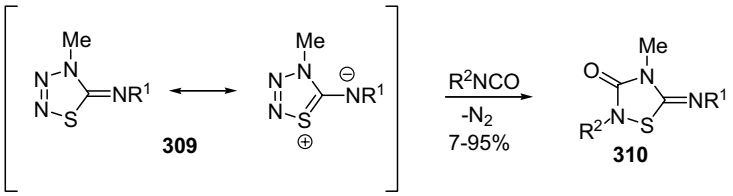


Scheme 14.73



R^1 = Ph, p-ClC_6H_4, $PhSO_2$, $PhCH_2$

Scheme 14.74

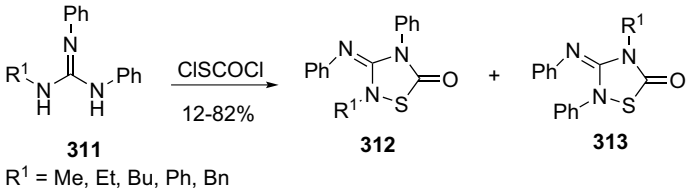


R^1 = Me, Ph,$CHMe_2$, CMe_3
R^2 = Et, n-Bu, t-Bu, Ph, $PhCH_2$, $PhSO_2$, p-ClC_6H_4, p-$NO_2C_6H_4$, p-$MeOC_6H_4$

Scheme 14.75

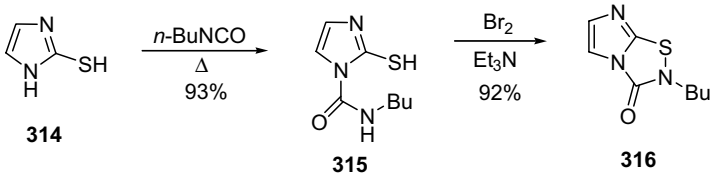
Finally, 3-(phenylimino)-1,2,4-thiadiazolidin-5-ones **312** and **313** can be synthesized by reaction of substituted guanidines **311** with chlorocarbonylsulfenyl chloride (Scheme 14.76) [177].

Bicyclic imidazo[1,2-*d*][1,2,4]thiadiazol-3(2*H*)-one (**316**) was prepared by condensation of 2-amino- or 2-mercaptoimidazole (**314**) [152] with alkyl isocyanates, to give compound **315**, followed by oxidative ring closure with bromine in triethylamine at ice cold temperature (Scheme 14.77). Tricyclic benzimidazo derivatives have been obtained by a similar pathway.



R^1 = Me, Et, Bu, Ph, Bn

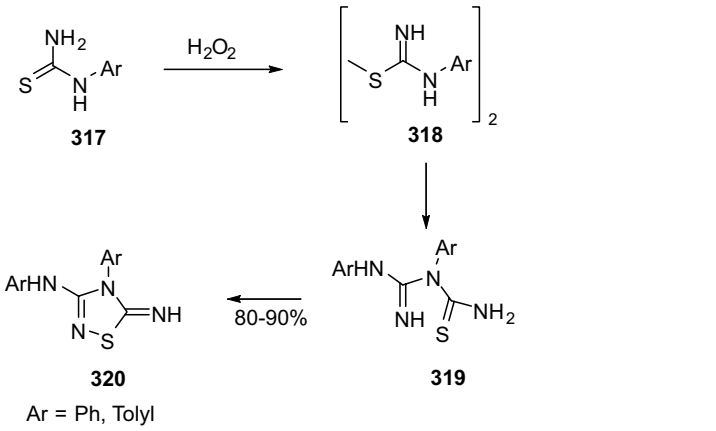
Scheme 14.76



Scheme 14.77

14.3.4.2 Δ^n1,2,4-Thiadiazolines

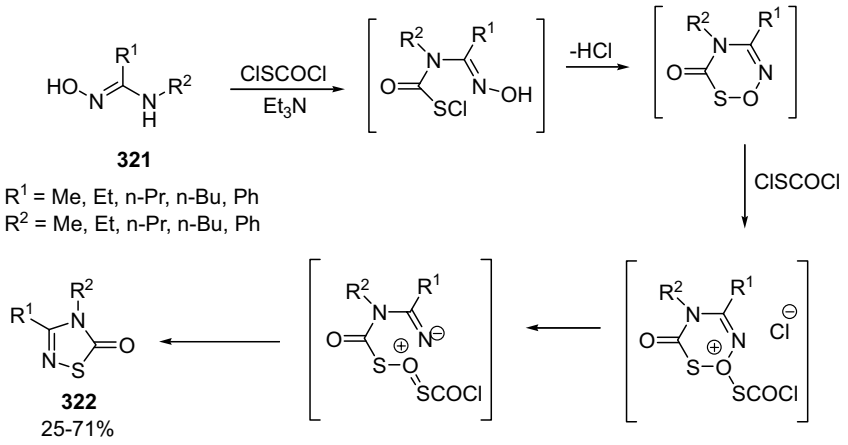
14.3.4.2.1 **Δ^2-1,2,4-Thiadiazolines** Δ^2-1,2,4-Thiadiazolines **320**, the so-called Hector's bases, have been synthesized in good yields by oxidation of N-arylthioureas **317**, with hydrogen peroxide or other oxidizing reagents, via the intermediate dithioformamidines **318** and N-arylamidinothioureas **319** (Scheme 14.78) [178].



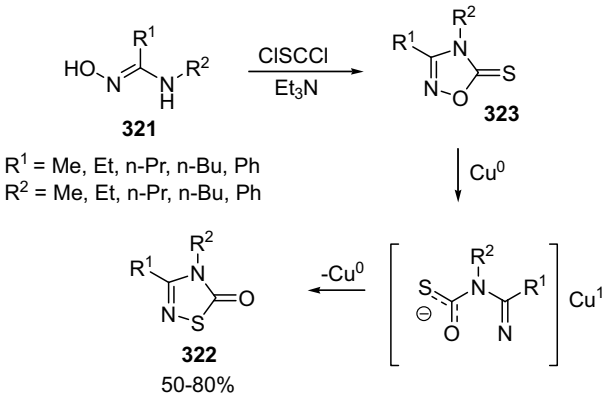
Ar = Ph, Tolyl

Scheme 14.78

Usually, the preparation of 3,4-disubstituted-1,2,4-thiadiazole-5-ones **322** includes the reaction of amidoximes **321** with chlorocarbonylsulfenyl chloride in the presence of base as a catalyst (Scheme 14.79) [179] or the reaction with thiophosgene to afford 3,4-disubstituted 1,2,4-oxadiazoline-5-thiones **323**, which, in the presence of a catalytic amount of copper powder, is converted into **322** (Scheme 14.80) [180].



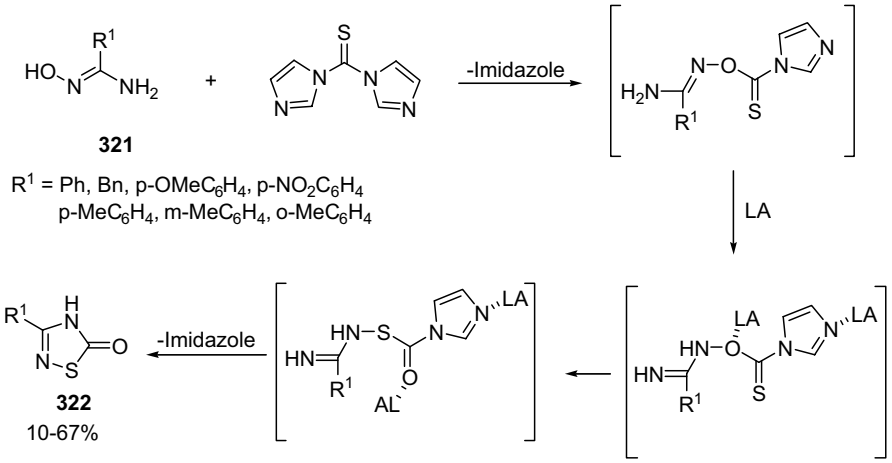
Scheme 14.79



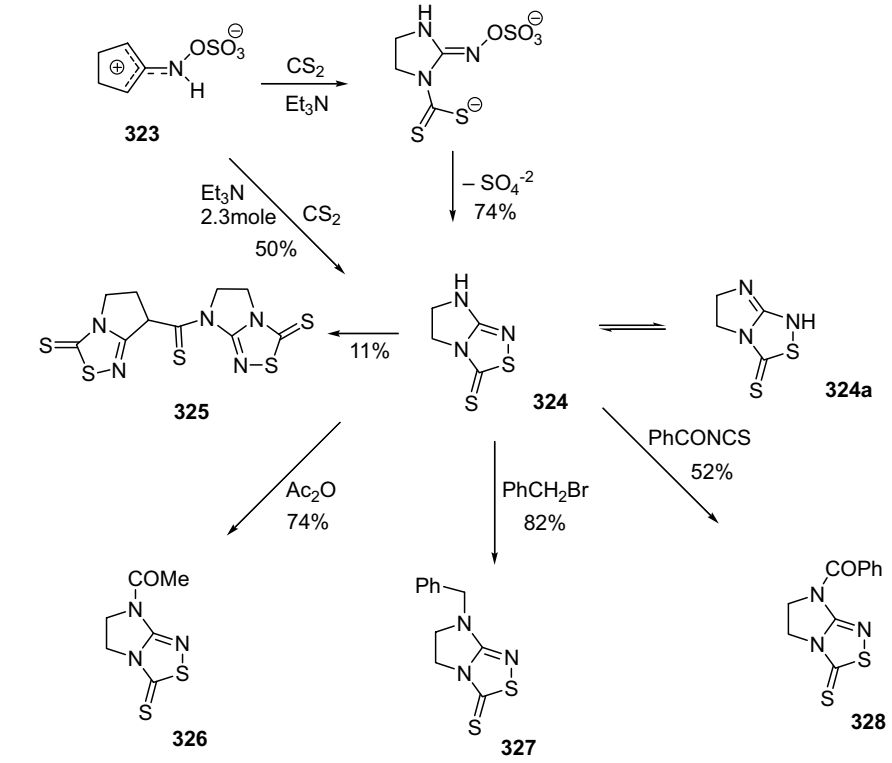
Scheme 14.80

However, these methods require highly toxic reagents and often lead to a mixture of products. New methods have been developed from amidoximes **321** by a Lewis acid-mediated rearrangement (Scheme 14.81) [181].

The reaction of 2-hydroxylamino-4,5-dihydroimidazolium-*O*-sulfonate (**323**) with carbon disulfide took two different courses, dependent on the base–solvent combination. Thus, when the reaction of **323** was performed in DMF in the presence of an equimolar amount of triethylamine, 6,7-dihydro-5*H*-imidazo[2,1-*c*][1,2,4]thiadiazole-3-thione **324** was produced in 50% yield as a result of a tandem nucleophilic addition–electrophilic amination. In the presence of an excess of triethylamine, **324** underwent subsequent reaction with a second molecule of carbon disulfide to give di(5,6-dihydro-7*H*-imidazo[2,1-*c*][1,2,4]thiadiazole-3-thione-7-yl)methanethione **325**. The resulting mixture contained **324** and **325** in a ratio of about 7 : 1 (Scheme 14.82) [182].



Scheme 14.81

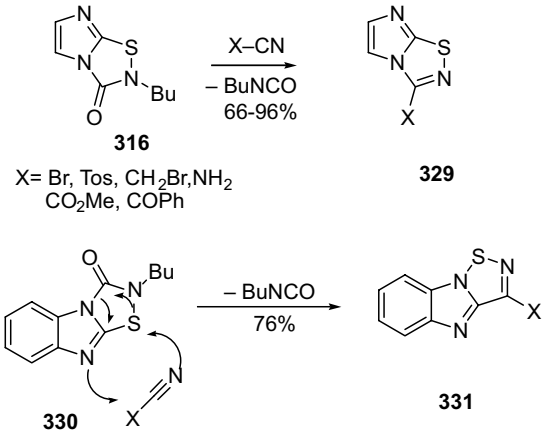


Scheme 14.82

The imidazothiadiazole **324** can exist in two likely (i.e., low-energy) tautomeric forms, the N7–H tautomer **324** and the N1–H tautomer **324a**, which can interconvert via a 1,3-prototropic shift. Calculations [135] indicated that **324** has a relative energy 12.9 kcal mol^{-1} below that of **324a**. NMR spectroscopy showed that the low-energy tautomer **324** is also present in DMSO-d_6 solution. The methylene groups of the imidazoline moiety are non-equivalent, and a NOE was observed between an upfield-shifted C6–H proton and the N–H proton.

Compound **324** reacted in the normal manner with acetic anhydride and benzyl bromide (Scheme 14.82) to afford **326** and **327**, respectively. The structure of 7-benzyl-6,7-dihydro-5*H*-imidazo[2,1-*c*][1,2,4]thiadiazole-3-thione (**327**) was confirmed by an X-ray crystallographic study. The reaction of **324** with benzoyl isothiocyanate carried out in THF in the presence of Et_3N at room temperature led to the formation of the N7-benzoyl derivative **328** [182].

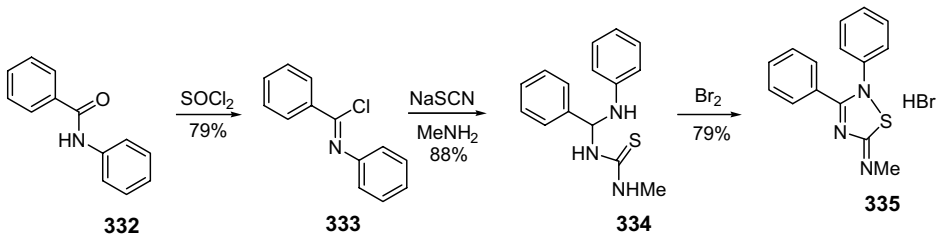
Bicyclic and tricyclic [1,2,4]thiadiazolines **329** and **331**, respectively, have been synthesized starting from the corresponding [1,2,4]thiadiazol-3(2*H*)ones **316** and **330**, by an exchange reaction with cyanogen bromide at room temperature, with extrusion of alkyl isocyanate (Scheme 14.83) [152].



Scheme 14.83

14.3.4.2.2 **Δ^3-1,2,4-Thiadiazolines** *N*-(2,3-Diphenyl-1,2,4-thiadiazol-5-(2*H*)-ylidene methanamine **335**, SCH-202676, is a Δ^3-thiadiazoline, identified in 2001 as an inhibitor of both agonist and antagonist binding to G protein-coupled receptors [183]. The synthetic approach moves from benzamide **332**, which was converted into benzimidoyl chloride **333** by reaction with thionyl chloride. Substitution of chlorine with NCS, followed by addition of methylamine, afforded thiourea **334** in good yield. Finally, oxidation with bromine led to the target 2,3-diphenyl-5-methylimino-*2H*-[1,2,4]thiadiazole hydrobromide **335** (Scheme 14.84) [184].

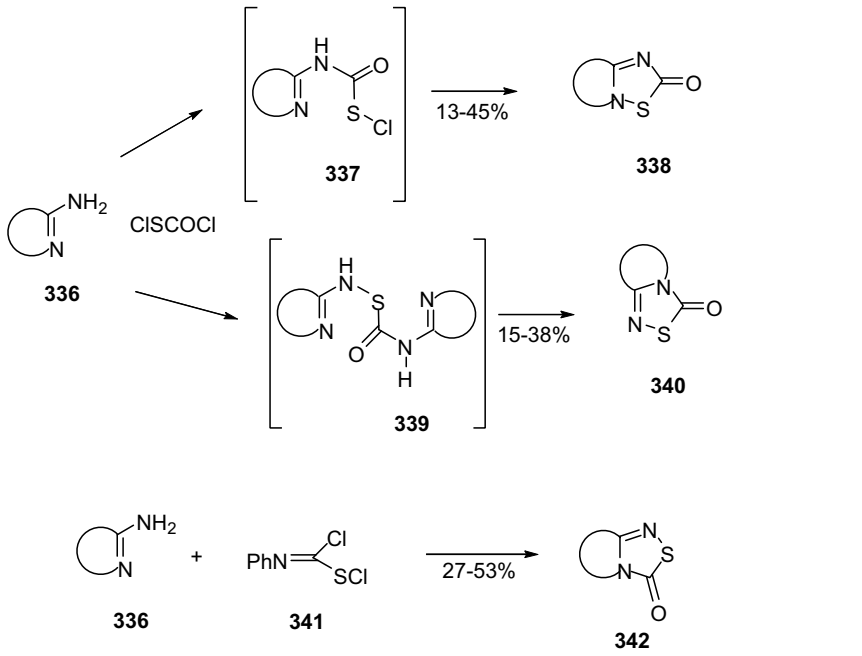
More recently, a new series of **335** were synthesized with different N-imino substituents [185]. Receptor–ligand binding experiments and stability studies



Scheme 14.84

showed that these compounds are highly reactive sulfhydryl modifying agents rather than allosteric inhibitors.

Bicyclic Δ^3-1,2,4-thiadiazolines are formed in moderate yields by treatment of cyclic amidines **336** as 2-aminopyridine, 3-aminopyridazine, 2-aminobenzothiazole, 2-aminopyrimidine, and 2-aminothiazole with chlorocarbonylsulfenyl chloride (Scheme 14.85) [186].

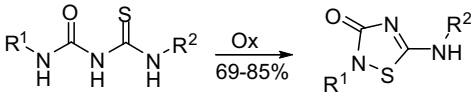


Scheme 14.85

The products obtained depend on the mode of addition. When **336** is added to chlorosulfenyl chloride, derivatives **338** are isolated via the intermediate **337**. Addition of chlorocarbonylsulfenyl chloride to **336** leads to 5-oxo derivatives **340**, via the bis(intermediate) **339**.

Treatment of amidine **336** with 1-chloro-1-phenylimonomethanesulfenyl chloride (**341**) affords 3*H*-1,2,4-thiadiazoles **342**.

14.3.4.2.3 **Δ^4-1,2,4-Thiadiazolines** The most general synthetic approach to Δ^4-1,2,4-thiadiazolines is based on the ring closure of thiobiourets in the presence of different oxidizing agents. In this way, 5-amino-1,2,4-thiadiazole-3-ones **344** have been synthesized from **343** via N–S bond formation by treatment with hydrogen peroxide in alkaline solution (Scheme 14.86) [136, 158, 187].



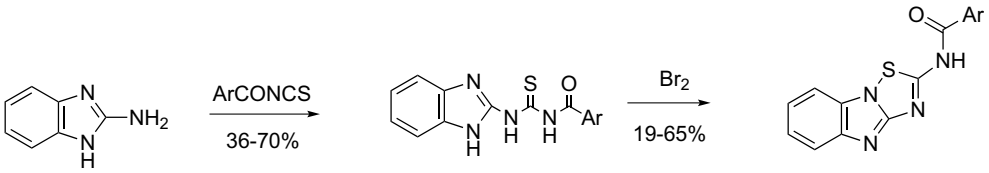
343 **344**

R^1 = Me, Ph, C(O)Ar
R^2 = H, Me

Scheme 14.86

Other oxidizing agents such as molecular bromine [136] or *N*-bromosuccinimide [188] have been used for cyclization.

Analogously, the oxidation with bromine of amidinothioureas **345**, derived from 2-aminobenzimidazole, afforded the tricyclic benzimidazole[1,2-*b*]-1,2,4-thiadiazoline **346** (Scheme 14.87) [189].

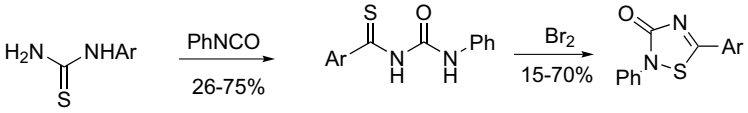


345 **346**

Ar = Tolyl, 4-$MeOC_6H_4$

Scheme 14.87

The reaction of arylthioamides **347** with phenyl isocyanate leads to arenethiocarboxamide **348**, which can be converted into 5-aryl-3-oxo-2-phenyl-1,2,4-thiadiazoline (**349**) by direct oxidation with bromine (Scheme 14.88) [190].



347 **348** **349**

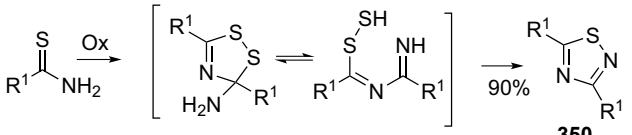
Ar = $MeOC_6H_4$, $EtOC_6H_4$

Scheme 14.88

14.3.4.3 1,2,4-Thiadiazoles

In general, 1,2,4-thiadiazoles are prepared by the appropriate intra- or intermolecular ring closure reactions, starting from different compounds containing nitrogen and/or sulfur atoms.

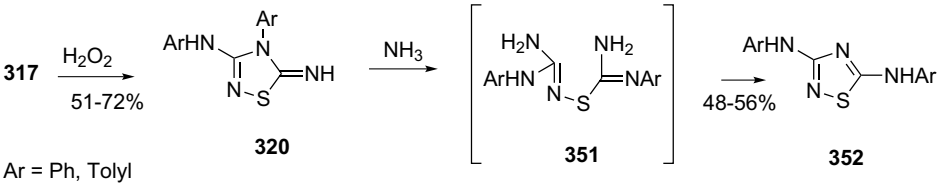
The main synthetic route towards 3,5-diaryl- or dialkyl-1,2,4-thiadiazoles is based on the oxidation of thioamides derivatives [170, 191]: various oxidizing agents as halogens, hydrogen peroxide, or thionyl chloride promote the oxidative cyclization in moderate yields. More recently, the condensation reactions of thioamides (as well as thionicotinamide and isothionicotinamide) have been performed in the presence of an oxidative DMSO–HCl mixture to give symmetrically substituted 1,2,4-thiadiazoles **350** (Scheme 14.89) [192].



R^1 = Ph, 3-pyridyl

Scheme 14.89

Under oxidative cyclization conditions, N-substituted thioureas have also been converted into 1,2,4-thiadiazole derivatives [192]. Thus, 3,5-diamino-1,2,4-thiadiazoles **352** (Dost's bases) [193] have been obtained in 48% yield, as a result of isomerization, by heating a suspension of 5-imino-4-phenyl-3-phenylamino-4*H*-1,2,4-thiadiazoline **320** (Ar = Ph, Hector's base) in ammonia alcohol solution at 135 °C (Scheme 14.90) [194].



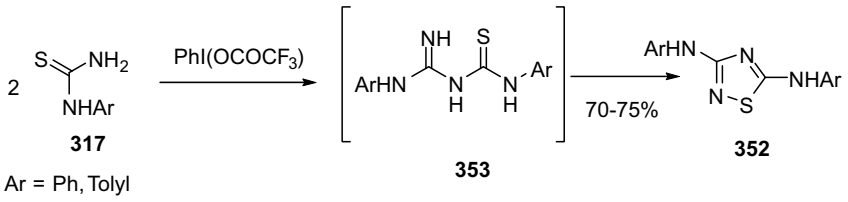
Ar = Ph, Tolyl

Scheme 14.90

The appropriate Hector's base has been obtained by oxidation of 1-phenyl-1-phenylamidinothiourea bromohydrate **319** (Scheme 14.78) with molecular bromine (73% yield) [178] or by oxidation of phenylthiourea **317** with hydrogen peroxide (70%) [195], *tert*-butyl hypochlorite (46%) [196], dioxane dibromide (85%) [197], or diaryl telluroxide (97%) [198]. Compound **352** has also been synthesized by reaction of 3,5-dichloro-1,2,4-thiadiazole with boiling aniline for 100 h [199].

In comparison with all these oxidative processes needing preliminary, often labor-intensive synthesis of precursors, a recent method affords **352** starting from arylthioureas **317** at room temperature by a single-step reaction [200]. The process

uses [bis(acyloxy)iodo]arenes as a more specific oxidant reagent than the traditional ones (Scheme 14.91).



317

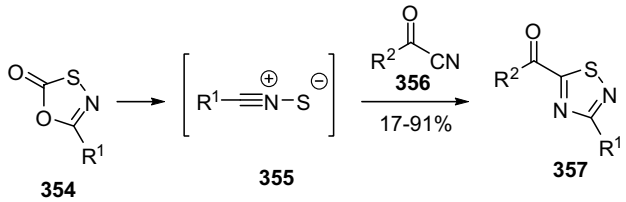
Ar = Ph, Tolyl

353

352

Scheme 14.91

Reaction of nitrile sulfides **354** with acyl cyanides **356** provides a useful access to 5-acyl-1,2,4-thiadiazoles **357** [201]. The synthetic route is based on the 1,3-dipolar cycloaddition of short-life nitrile sulfides **355**, generated *in situ* by thermal decarboxylation of 1,3,4-oxathiazol-2-ones **354** [202], to strongly activated dipolarophiles such as the acyl cyanide (Scheme 14.92).



354

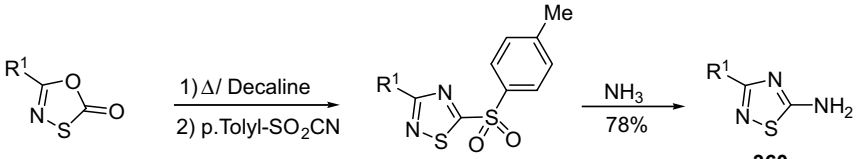
355

357

R^1 = Me, Ph, 4-MeC_6H_4, 2-furoyl, $CH_3(CH_2)_5$
R^2 = Ph, Tolyl

Scheme 14.92

Analogously, the reaction of **354** with tosyl cyanide (**358**) leads to the key intermediate **359**, which, by displacement of the tosyl group with ammonia, provides the 5-amino-1,2,4-thiadiazoles **360** (Scheme 14.93) [203].



354

358

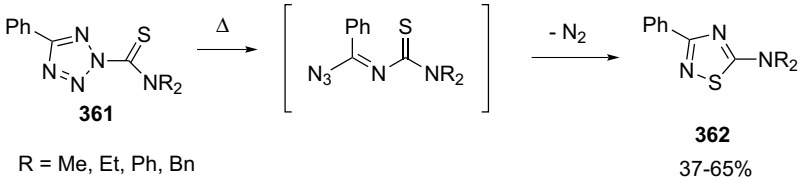
359

360

R^1 = 2,6-di-*tert*-butylphenol

Scheme 14.93

5-Amino-1,2,4-thiadiazoles **362** have also been generated by thermolysis of 2-thiocarbamoyl-5-phenyltetrazoles **361** (Scheme 14.94) [204].



361

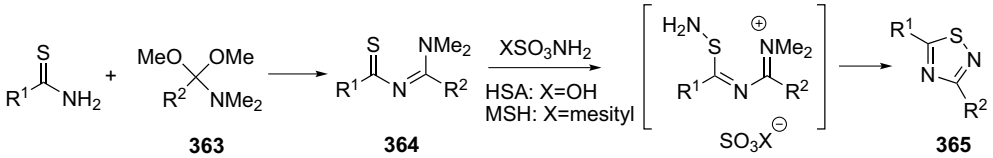
R = Me, Et, Ph, Bn

362

37-65%

Scheme 14.94

A more recent synthetic strategy towards 3,5-dialkyl 1,2,4-thiadiazoles **365** involves the amination-cyclization of *N′*-(thioaroyl)-*N,N*-dimethylamidines **364** with an aminating agent such as hydroxylamine-*O*-sulfonic acid (HSA) or *O*-(mesitylenesulfonyl) hydroxylamine (MSH) (Scheme 14.95).



363 **364** **365**

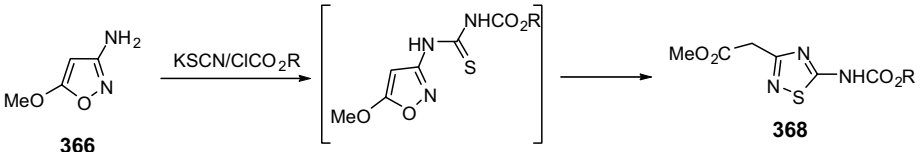
$R^1 = R^2$ = Me, Et, Ph

19-66%

Scheme 14.95

Amidines **364** are prepared by reaction of thioamides with *N,N*-dimethylformamide dimethyl acetal or *N,N*-dimethylacetamide dimethyl acetal (**363**) [205].

1,2,4-Thiadiazole derivatives have also been synthesized by skeletal rearrangements of different five-membered rings. In this way, methyl 2-(5-alkoxycarbonylamino-1,2,4-thiadiazol-3-yl)acetates **368** have been prepared by reaction of 3-amino-isoxazole **366** with isothiocyanates, following skeletal (Dimroth) rearrangement of the intermediate thiourea derivative **367** (Scheme 14.96) [206].



366

R = Me,Et

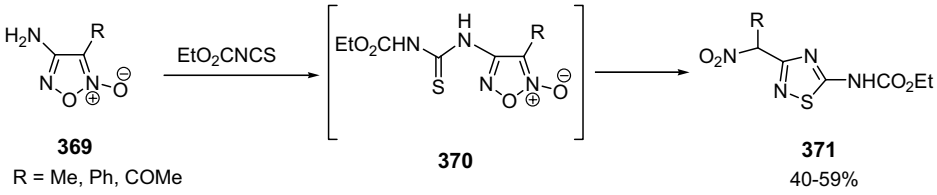
367

368

17-69%

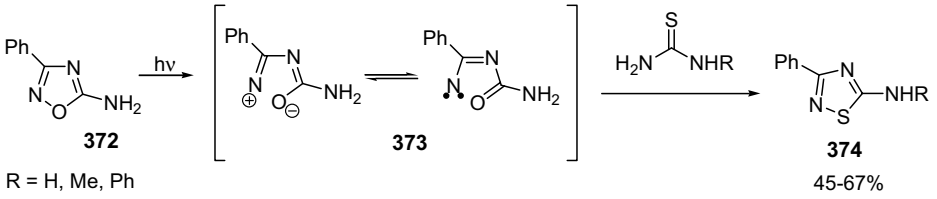
Scheme 14.96

5-Amino-3-(α-nitroalkyl)-1,2,4-thiadiazoles **371** have been obtained by thermal rearrangements of 3-substituted 4-(3-ethoxycarbonylthioureido)-1,2,5-oxadiazole 2-oxides **370** (Scheme 14.97). The reaction was performed by refluxing a mixture of aminofuroxans **369** with ethoxycarbonyl isothiocyanate [207].



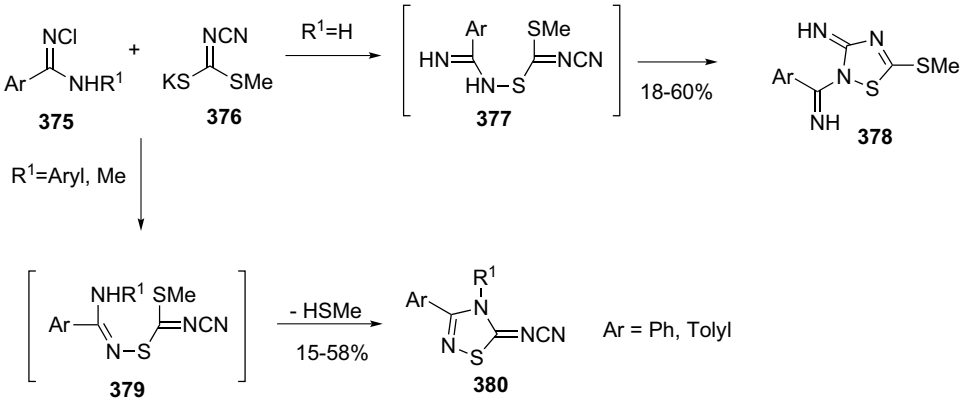
Scheme 14.97

An interesting access to 3-phenyl-5-substituted-1,2,4-thiadiazoles **374** has been exploited by the photoinduced molecular rearrangement of five-membered heterocycles containing a N–O bond. In fact, photolytic species, which originates from the ring cleavage of 1,2,4-oxadiazoles, react with sulfur reagents by forming a new N–S bond. Thus, irradiation of 5-amino-3-phenyl-1,2,4-oxadiazole (**372**) in the presence of thiourea leads to 1,2,4-thiadiazole **374**, through the intermediate **373** (Scheme 14.98) [208].



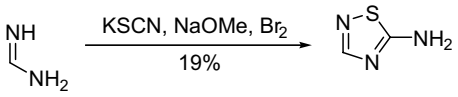
Scheme 14.98

N-Unsubstituted-*N*′-chlorobenzamidines (**375**, $R^1 = H$), by treatment with potassium *S*-methyl cyanimidodithiocarbonate **376**, afford 2-arylimidoyl-3-imino-5-methylthio-1,2,4-thiadiazoles **378** [209]. In contrast, substituted amidines (**375**, R = aryl and methyl) give 5-cyanimino-4,5-dihydro-3-aryl-1,2,4-thiadiazoles **380** containing in the ring both the nitrogen atoms of amidines (Scheme 14.99) [210].



Scheme 14.99

At the same time, aminothiadiazole **382** has been obtained by cyclization of amidine **381** with potassium thiocyanate and bromine (Scheme 14.100) [211, 212].



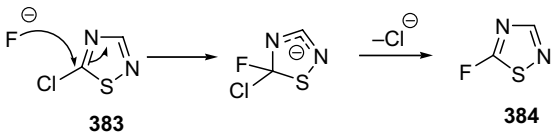
381 **382**

Scheme 14.100

14.3.5 Reactivity

1,2,4-Thiadiazoles are aromatic in nature and are to be considered as π-excessive heterocycles with relatively π-deficient C-atoms. Electrophilic substitutions at the C-atoms could not be achieved.

The π-electron density at the 5-position, calculated by the HMO method, is markedly lower than that at the 3-position, thus influencing many of the properties of substituted derivatives. As an example, 5-halo derivatives are susceptible to replacement of halogen by nucleophiles, whereas 3-halo derivatives are relatively inert. Thus, 5-chloro-1,2,4-thiadiazole (**383**) undergoes nucleophilic substitution with silver fluoride to give the 5-fluoro derivative **384** (Scheme 14.101).



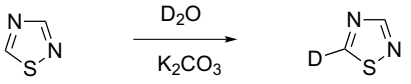
383 **384**

Scheme 14.101

In the case of 3-chloro-1,2,4-thiadiazole, delocalization of the negative charge in the intermediate with involvement of both nitrogen atoms is not possible; for this reason, it does not react or reacts only slowly with nucleophiles.

The parent compound **246** is quite sensitive to acid and bases, as well to oxidizing and reducing agents. It reacts rapidly with cold alkali hydroxides, undergoing ring opening with formation of ammonia, hydrogen sulfide, and sulfur. Treatment of **246** with a weak base (K_2CO_3) in D_2O gives the 5-deuteroderivative **385** (Scheme 14.102) [122].

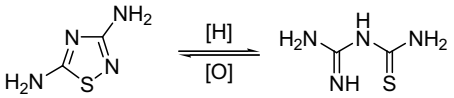
With hydrochloric acid, hydrolytic ring-opening occurs via the 1,2,4-thiadiazolium ion. Substituents in the 3- and 5-positions of 1,2,4-thiadiazoles exert a marked stabilizing influence: for example, the 3,5-diphenyl derivative resists the action of hot mineral acids and prolonged boiling is required for attack by alkalis [178].



246 **385**

Scheme 14.102

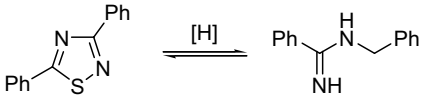
Catalytic and dissolving metal reductions usually cleave the nucleus at the N–S bond by a reaction that can be considered as the reverse of its synthesis by oxidative cyclization of amidinothio-derivatives (Section 14.3.4). For example, reduction of the diamino derivative **386** affords amidinothiourea (**387**), from which **386** may be prepared by oxidation (Scheme 14.103).



386 **387**

Scheme 14.103

Reduction of 3,5-diphenyl-1,2,4-thiadiazole (**388**) results in the loss of sulfur and formation of benzamidine **389** (Scheme 14.104)

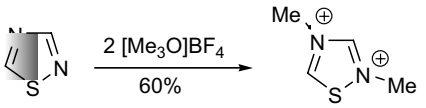


388 **389**

Scheme 14.104

14.3.5.1 **Aromatic Ring Reactivity**

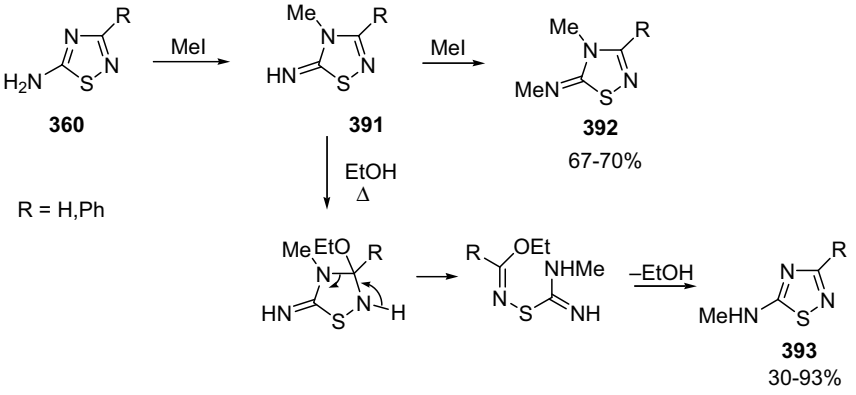
1,2,4-Thiadiazoles are weak bases. Methylation with iodomethane occurs at N4; when trimethyloxonium tetrafluoroborate is used as methylating agent, the reaction takes place at both nitrogen atoms, leading to the diquaternary salt **390** (Scheme 14.105) [213].



246 **390**

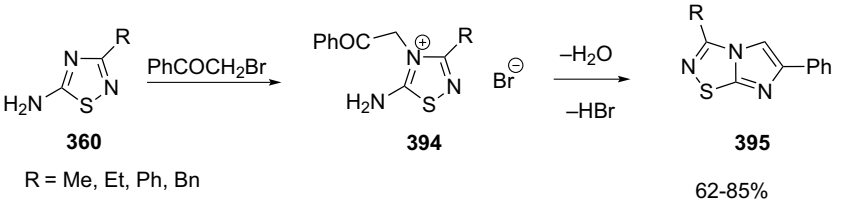
Scheme 14.105

Methylation of 5-amino-1,2,4-thiadiazoles **360** (R = H, Ph) affords the N4 derivatives **391**; further methylation gives 4-methyl-5-methylimino-3*H*-1,2,4-thiadiazolines **392** (Scheme 14.106) [214]. On warming in ethanol, compound **391** (R = H) undergoes a Dimroth rearrangement to give **393**.



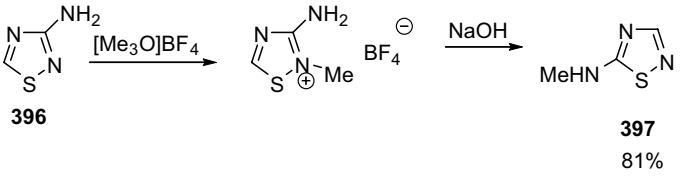
Scheme 14.106

The N4 derivatives **394**, obtained by reaction of phenacyl bromide with 5-amino-1,2,4-thiadiazoles **360**, spontaneously cyclizes to the fused imidazolothiadiazoles **395** (Scheme 14.107) [178].



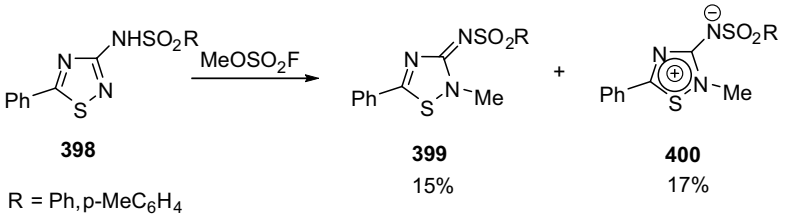
Scheme 14.107

Reaction of 3-amino-1,2,4-thiadiazole (**396**) with trimethyloxonium tetrafluoroborate occurs at N2 to yield the thiadiazolium salt, which, on basification, undergoes a Dimroth rearrangement to give the 5-methylamino derivative **397** (Scheme 14.108) [215].



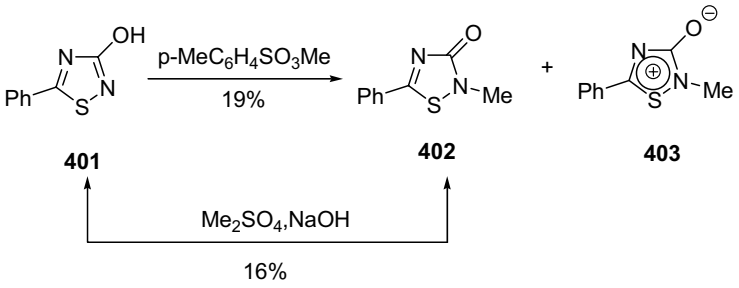
Scheme 14.108

Analogously, the sulfonamide **398** by reaction with methyl fluorosulfonate gives the N2 derivative **399**, together with the mesoionic compound **400** (Scheme 14.109) [133].



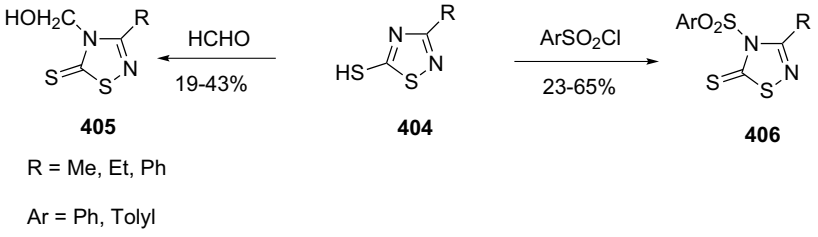
Scheme 14.109

Similar behavior has been observed for 3-hydroxy-5-phenyl-1,2,4-thiadiazole (**401**). The reaction with dimethyl sulfate and sodium hydroxide leads to N2 methylated derivative **402**; when methylation was carried out with toluene-4-sulfonate, **402** was obtained together with the meso-ionic compound **403** (Scheme 14.110) [133].



Scheme 14.110

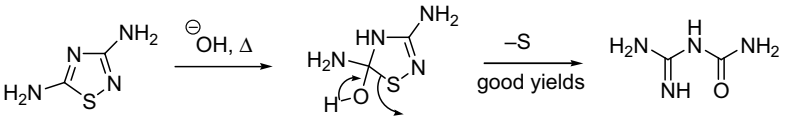
The reaction of 3 substituted 1,2,4-thiadiazole-5-thiols (**404**) with formaldehyde and with arylsulfonyl chlorides leads to N4 derivatives **405** and **406** (Scheme 14.111) [216].



Scheme 14.111

In general, hard nucleophiles attack at the C5 carbon atom of 1,2,4-thiadiazoles, while soft nucleophiles react at the sulfur atom.

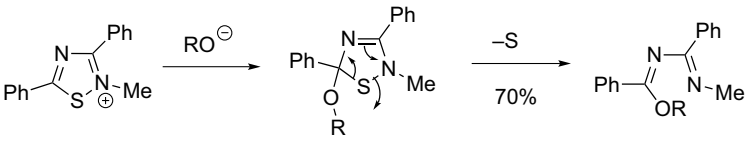
For examples, nucleophilic attack at C5 has been suggested as the initial step in many ring-opening reactions leading to linear products that, according to the substituents, can recyclize to other heterocyclic systems [120]. Thus, 3,5-diamino-1,2,4-thiadiazole (**386**) upon treatment with hot alkali undergoes a nucleophilic attack at C5 to give the proposed intermediate **407**, which affords, by extrusion of sulfur, the amidinourea (**408**) (Scheme 14.112). The stability of 5-alkylamino and 5-arylamino homologues is considerably higher; thus, the reaction does not occur even after several hours refluxing in 3N sodium hydroxide solution.



386 **407** **408**

Scheme 14.112

2-Methyl-3,5-diphenyl-1,2,4-thiadiazolium chlorosulfate (**409**) is cleaved by alkoxides to give the benzimidate **410** (Scheme 14.113) [167].



409 **410**

R = Me, Et

Scheme 14.113

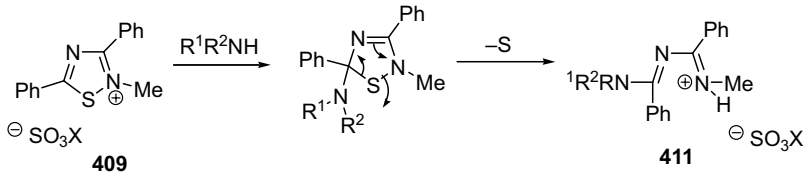
Primary and secondary amines also function as hard nucleophiles and attack at the C5 position of **409** to yield the open-chain salts **411**; when hydrazines and hydroxylamines are used, the initially formed salts cyclize to give a 1,2,4-triazole or oxadiazole **412** (Y = N or O) (Scheme 14.114) [131].

A carbon nucleophile, the dicyanomethanide ion, also attacks at the C5 position of **409**; the open-chain product **413** cyclizes to the dihydropyrimidine **414**. On further treatment with dicyanomethanide ion or aqueous base, a Dimroth rearrangement occurs to pyrimidine **415** (Scheme 14.115) [131].

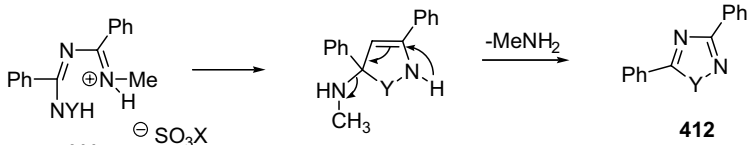
Soft nucleophiles attack at the sulfur atom. For example, 3-hydroxy-5-phenyl-1,2,4-thiadiazole (**402**) reacts with acetic anhydride in the presence of DBU at 130 °C to give thiazole **417** (Scheme 14.116) [215].

When the reaction is carried out at room temperature, acetylation occurs at the N2 position to give compound **418** in low yields (Scheme 14.117) [215].

However, the most important nucleophilic attack at the sulfur atom is related to the ability of 1,2,4-thiadiazoles to act as a class of small heterocyclic thiol trapping agents. In fact, heterocyclic compounds possessing a N–S bond are cleaved by thiolates to form compounds such as **419** via a disulfide intermediate (Scheme 14.118) [131].

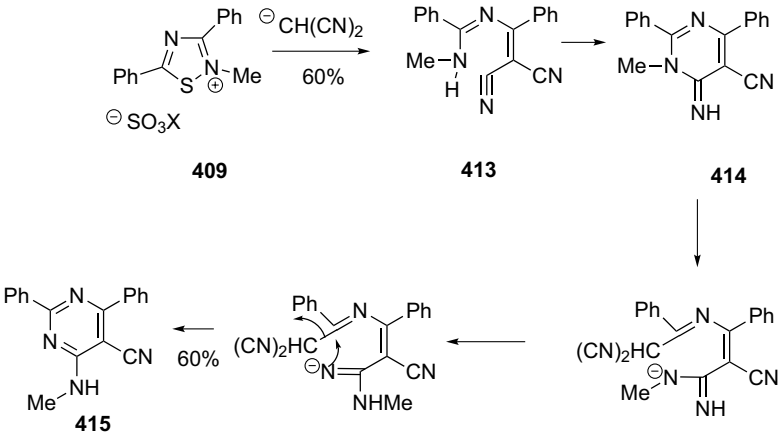


R^1 = H, $(CH_2)_5$
R^2 = Ph, CH_2Ph, $(CH_2)_5$

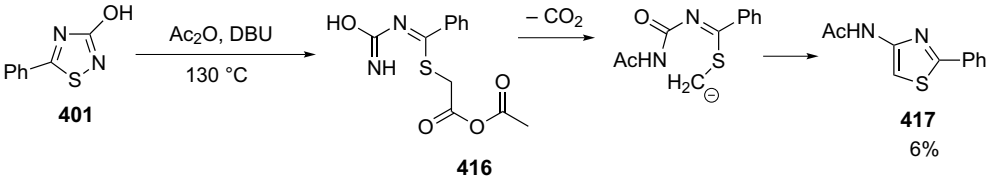


Y= NH, NPh, O

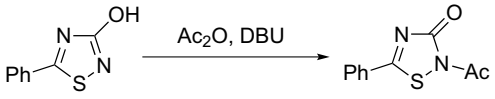
Scheme 14.114



Scheme 14.115

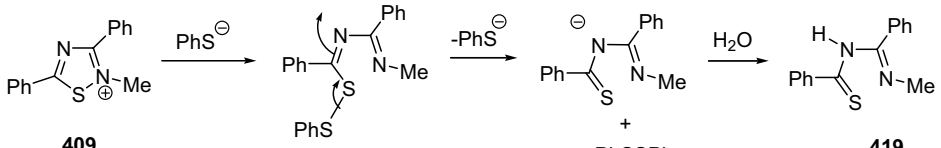


Scheme 14.116



401 **418** 3%

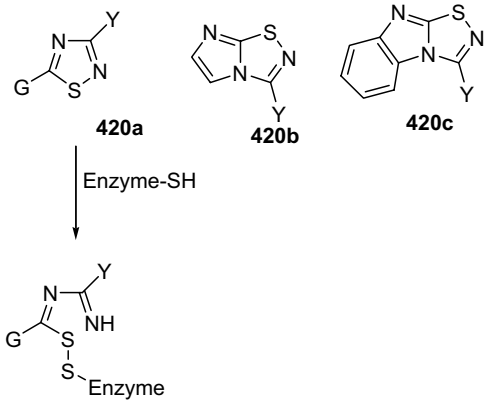
Scheme 14.117



409 **419** 63%

Scheme 14.118

It has been widely reported that three different families of 1,2,4-thiadiazoles are able to react with enzyme cysteine residues to form a disulfide adduct, thus inhibiting the enzyme (Scheme 14.119) [127–129].

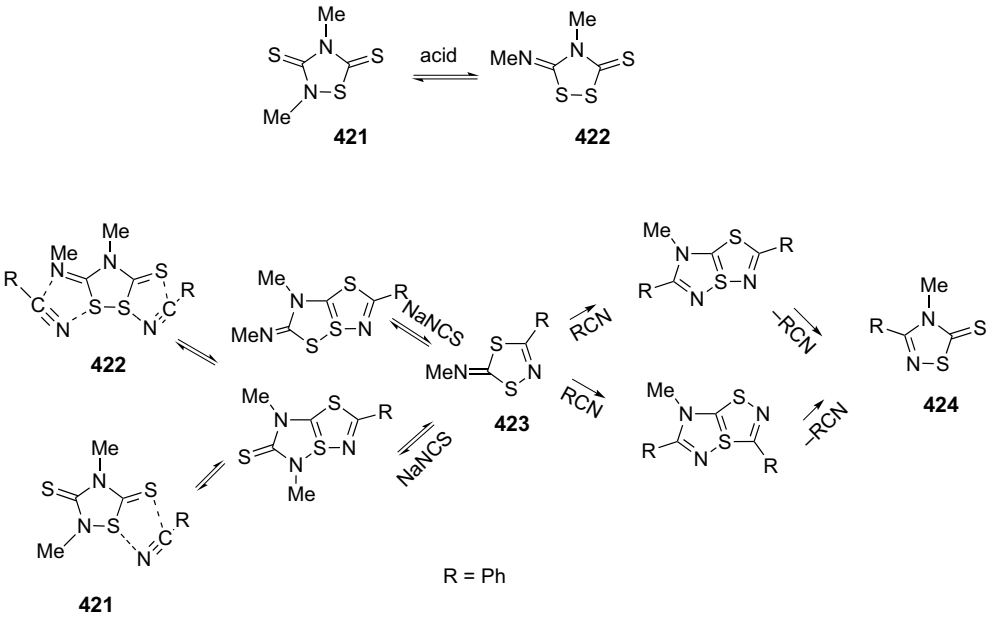


Scheme 14.119

The design of inhibitors based on the monocyclic 1,2,4-thiadiazole scaffold **420** involves the use of substituent G as a recognition arm for the enzyme binding, and the substituent Y for tuning the reactivity of the ring opening. The presence of a fused ring in bicyclic **420b** and tricyclic **420c** derivatives is preferred for the inhibition of certain enzymes such as H^+/K^+ ATPase.

14.3.5.2 Reactions of 1,2,4-Thiadiazolidines

2,4-Dimethyl-1,2,4-thiadiazolidine-3,5-dithione (**421**) isomerizes in acid solution to 4-methyl-5-(methylimino)-1,2,4-dithiazolidine-3-thione (**422**): the reverse reaction occurs in alkaline media [163]. Compounds **421** and **422** are interconvertible also in the presence of electrophilic nitriles and give 1,2,4-thiadiazoline-5-thiones **424** as final products. The interconversion has been rationalized on the basis of a cycloaddition–elimination mechanism that involves hypervalent sulfur intermediates (Scheme 14.120).



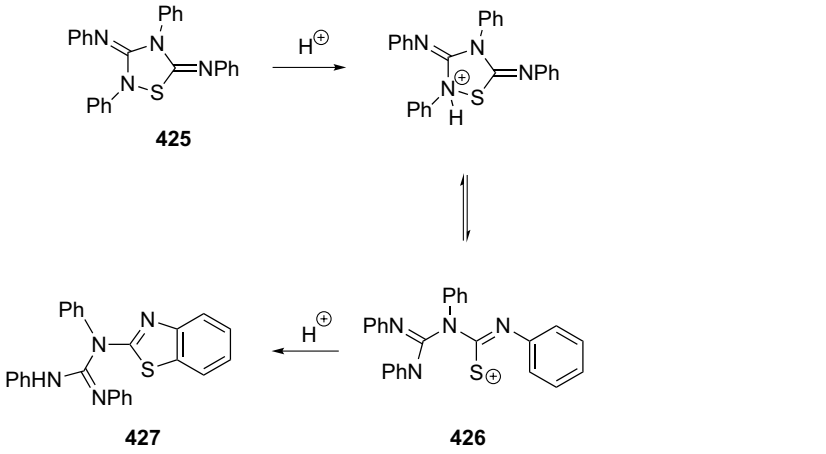
Scheme 14.120

Substituted 2,4-diimino-1,2,4-thiadiazolidines **425** isomerize under acidic conditions to 2-guanidinobenzothiazoles **427**. The suggested mechanism involves the protonation of **425** at N2, followed by the N–S bond cleavage to **426** and subsequent electrophilic attack of the sulfur at the aromatic ring (Scheme 14.121) [167].

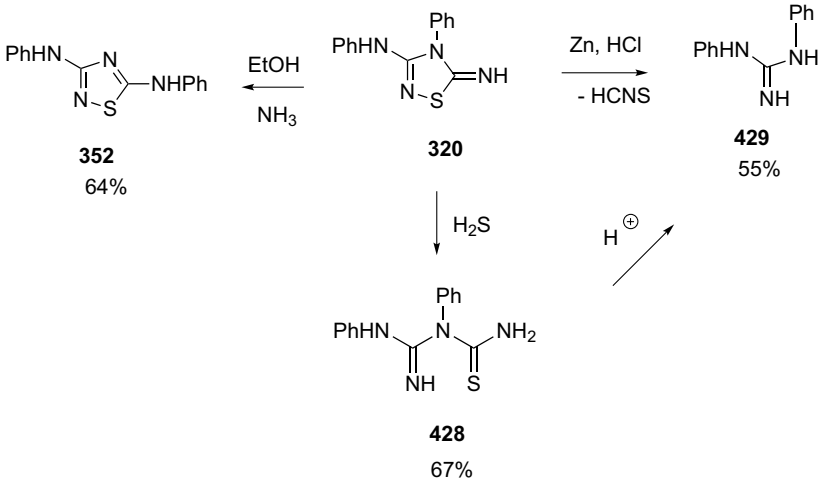
14.3.5.3 Reaction of Δ^2-1,2,4-Thiadiazolines

Hector's base, 3-arylamino-4-aryl-5-imino-1,2,4-thiadiazole (**320**), undergoes a base-catalyzed Dimroth rearrangement to give Dost's base **352** (Scheme 14.90); the reduction of **320** under mild conditions (H_2S/25 °C) gives amidinothiourea **428**, which hydrolyzes to diphenylguanidine (**429**). Compound **429** can be obtained directly from **320** by reduction under drastic conditions (Scheme 14.122) [178].

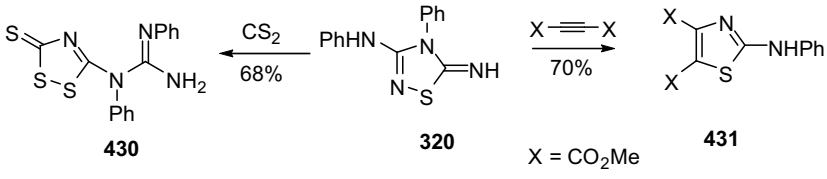
Hector's base forms a 1 : 1 adduct (**430**) with CS_2 [217], while reaction with electron-deficient alkynes gives 2-arylaminothiazoles **431** (Scheme 14.123) [120].



Scheme 14.121

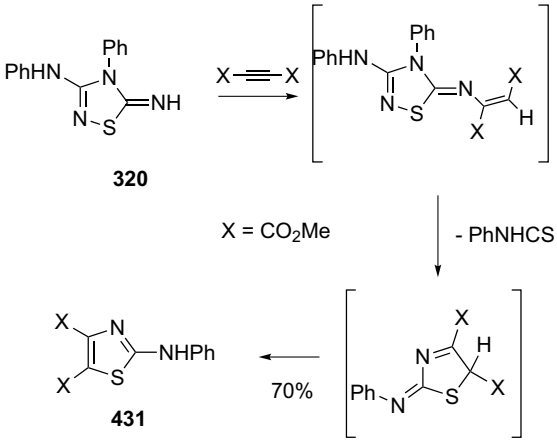


Scheme 14.122



Scheme 14.123

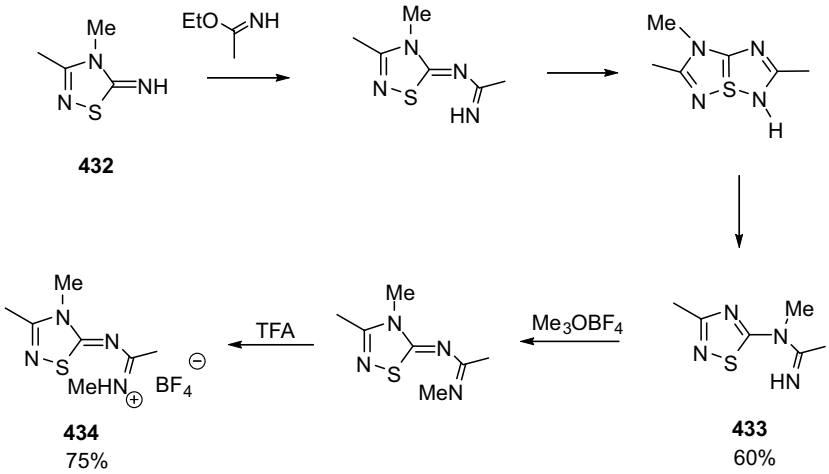
It has been suggested [120] that these reactions proceed via a stepwise mechanism (Scheme 14.124).



Scheme 14.124

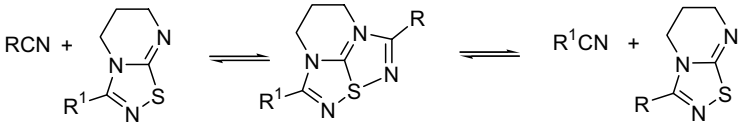
An analogous nucleophilic substitution pattern has been proposed for the reaction of 3,4-disubstituted 5-imino-Δ^2-1,2,4-thiadiazolines with arylcyanamides and imidates. These reactions give rearranged products that result from bond switching at hypervalent sulfur intermediates [218].

Thus, treatment of **432** with ethyl acetimidate leads to derivative **433**, which on methylation with Meerwein's reagent ($Me_3O^+BF_4^-$) affords the salt **434**. The structure of compounds **433** and **434** has been confirmed by X-ray analysis (Scheme 14.125) [219].



Scheme 14.125

Bond switching rearrangement using the propensity of sulfur to assume a hypervalent state has been observed in the reactions of bicyclic thiadiazolines **435** with nitriles: an exchange of nitrile units has been observed to give **436** (Scheme 14.126) [220].



435 **436**

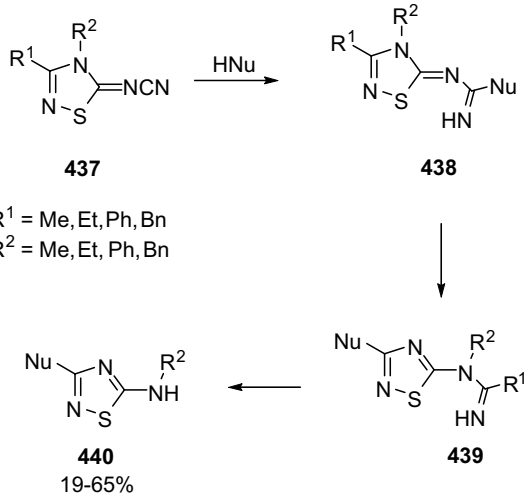
R = Me

R^1 =H, Me, Ph, 4-NO_2 C_6H_4, 4-pyridyl, CH_2OMe, 2-OHC_6H_4, CD_3, CH=CHCN

62-82%

Scheme 14.126

The products **438** of the addition of nucleophiles (i.e., alcohols, amines) to the cyano group of 5-(cyanoimino)thiadiazolines **437** undergo a Boulton–Katritzky rearrangement, followed by the elimination of a nitrile from the intermediate **439** to give thiadiazoles **440** (Scheme 14.127) [221].



437 **438**

R^1 = Me, Et, Ph, Bn

R^2 = Me, Et, Ph, Bn

439

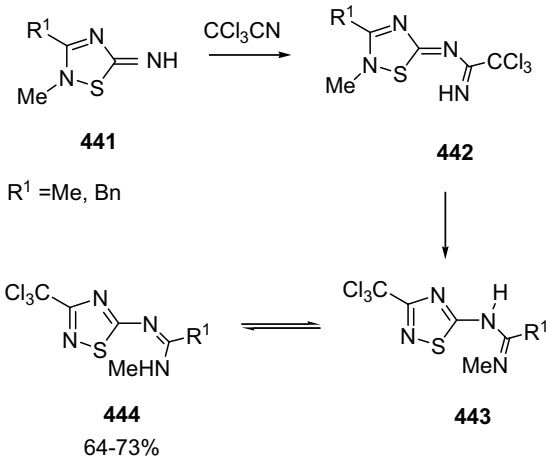
440

19-65%

Scheme 14.127

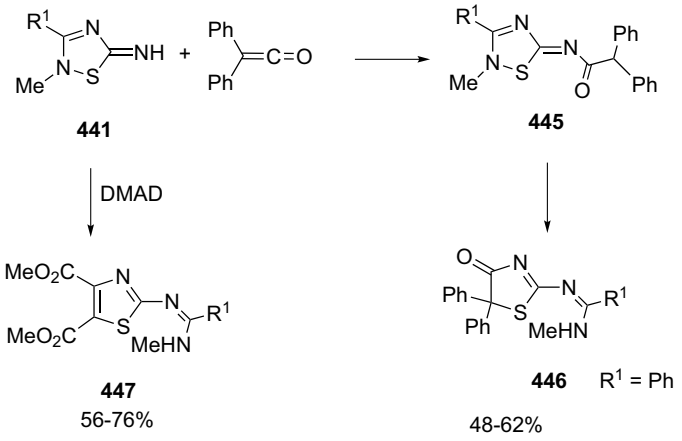
14.3.5.4 **Reaction of Δ^3-1,2,4-Thiadiazolines**

Δ^3-1,2,4-thiadiazolines react with electrophilic reagents to give rearrangement products. As an example, treatment of thiadiazoline **441** with trichloroacetonitrile affords a mixture of tautomers **443** and **444**, through the intermediacy and rearrangement of imine **442** (Scheme 14.128) [222].



Scheme 14.128

Thiadiazolines **441** have been acylated in the presence of triethylamine [223]. The use of diphenylketene as acylating agents leads to **445** which, by heating in polar solvents, rearranges to Δ^2-thiazolin-4-one **446**, whose structure has been confirmed by X-ray analysis. A similar rearrangement is observed when **441** is reacted with DMAD to give **447** (Scheme 14.129).



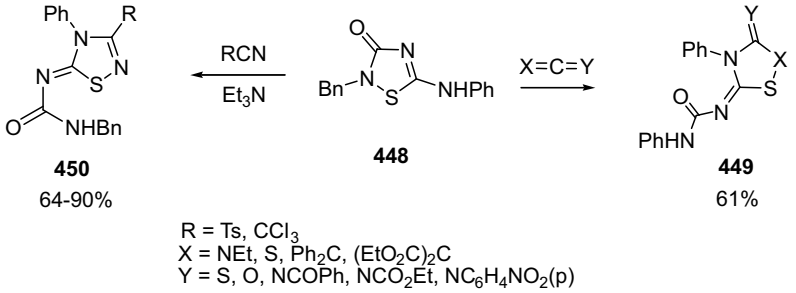
R^1 = Me, Ph, p-MeC_6H_4, p-$MeOC_6H_4$, $CH(CH_3)_2$

Scheme 14.129

14.3.5.5 **Reaction of Δ^4-1,2,4-Thiadiazolines**

Bond-switching rearrangement via hypervalent sulfur occurs when 5-anilino-2-benzyl-3-oxo-Δ^4-1,2,4-thiadiazoline (**448**) reacts with ketenes (or isothiocyanates or

carbon disulfide) and nitriles to give the products **449** and **450**, respectively (Scheme 14.130) [224].



450
64-90%

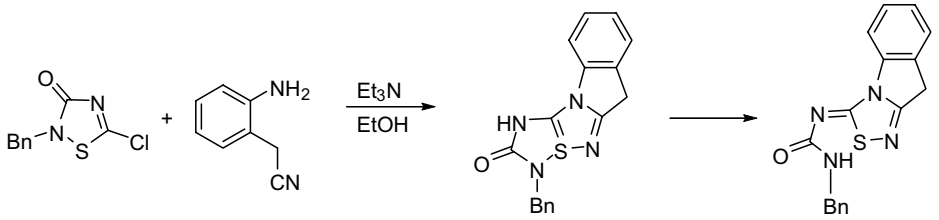
448

449
61%

R = Ts, CCl_3
X = NEt, S, Ph_2C, $(EtO_2C)_2C$
Y = S, O, NCOPh, NCO_2Et, $NC_6H_4NO_2(p)$

Scheme 14.130

2-Benzyl-5-chloro-1,2,4-thiadiazole-3-one (**451**) and 2-aminobenzyl cyanide (**452**) in ethanol containing triethylamine react to afford the intermediate **453**, which, through yet another example of bond switching, gives the indolinothiadiazolone **454** (Scheme 14.131) [225].



451 **452** **453** **454**
60%

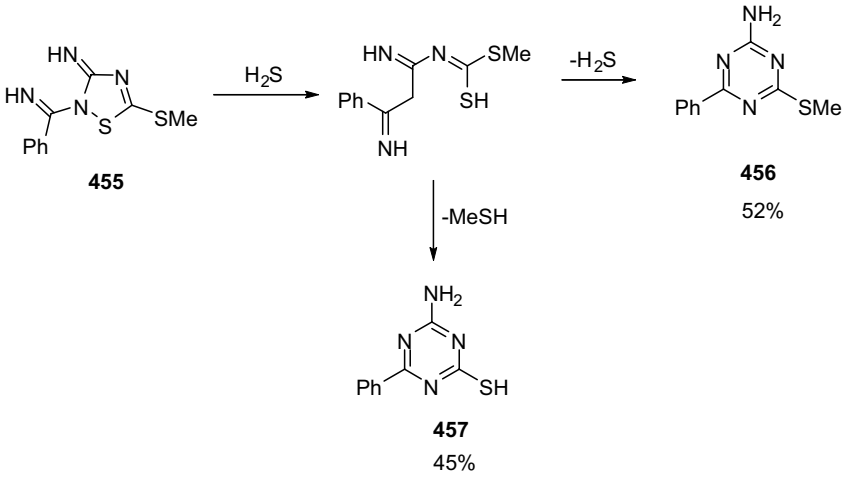
Scheme 14.131

Δ^4-1,2,4-Thiadiazolines are readily cleaved at the N–S bond under very mild conditions to give thiobiouret by a reaction that is inverse to that reported in Scheme 14.86.

3-Imino-1,2,4-thiadiazoline provides example of reductive ring cleavage in which the products immediately recyclize to new heterocyclic system. Thus, the Δ^4-1,2,4-thiadiazoline **455** is cleaved with H_2S to give triazines **456** and **457** (Scheme 14.132) [167].

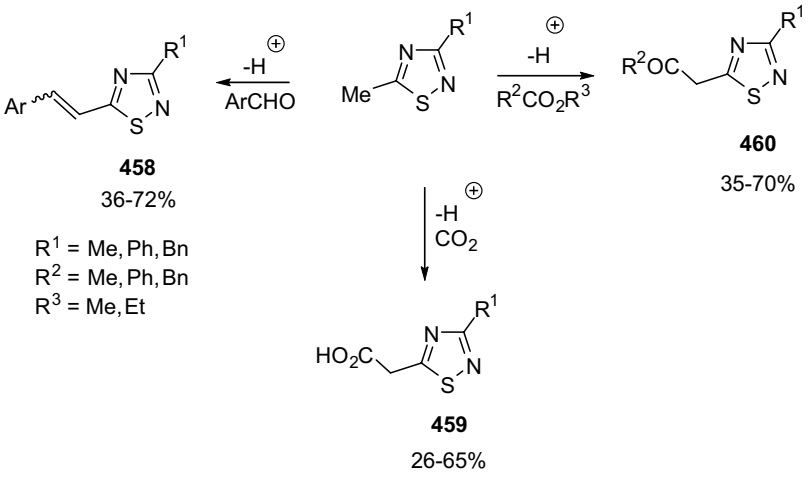
14.3.5.6 Reactions of Substituents

Owing to the lower electron density at the 5-position of the 1,2,4-thiadiazole ring with respect to the 3-position, methyl or methylene groups attached at C5 show a marked acidity, which promotes different reactions patterns, following hydrogen abstraction by bases. In fact, the resulting carbanions, stabilized by conjugation, react, for



Scheme 14.132

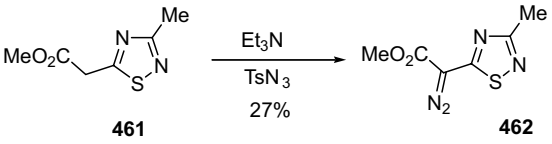
example, with aromatic aldehydes to give 5-styrylthiadiazoles **458**, with CO_2 to yield the carboxylic acids **459**, and with carboxylic acid esters to afford the keto derivatives **460** (Scheme 14.133) [120].



Scheme 14.133

Analogously, treatment of the methyl ester **461** with triethylamine and tosyl azide leads to diazoester **462** through the formation of an intermediate carbanion (Scheme 14.134) [226].

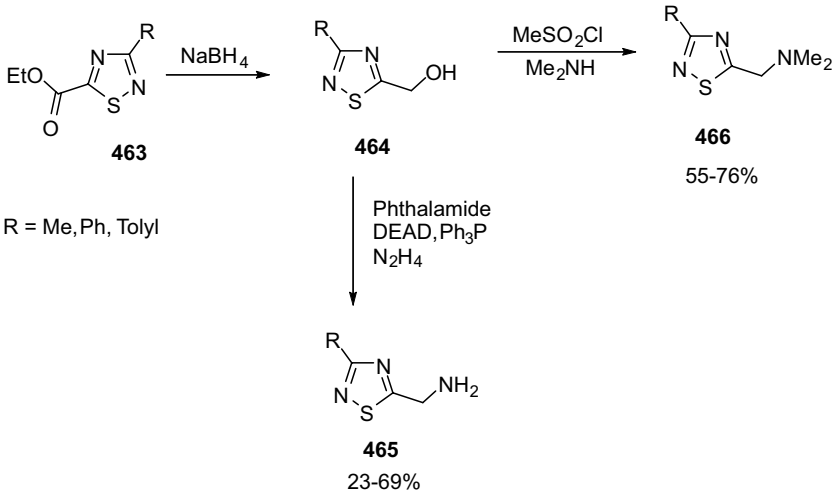
3-Methyl-1,2,4-thiadiazole is less acidic and will not undergo the above reported reactions.



461 **462**

Scheme 14.134

According to standard procedures, 3-alkyl-1,2,4-thiadiazole-5-carboxylates **463** are transformed into hydroxymethyl derivatives **464**, primary amines **465**, and tertiary amines **466** (Scheme 14.135) [226].



463 **464** **466**

55-76%

465

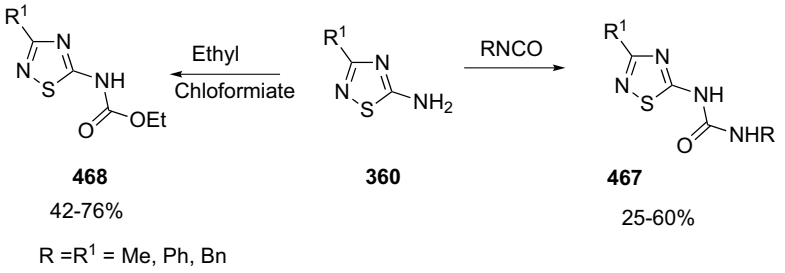
23-69%

Scheme 14.135

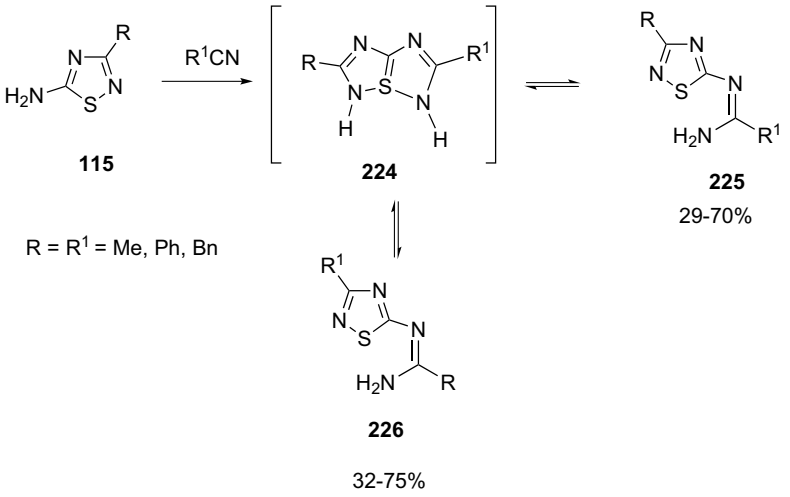
3-Amino-1,2,4-thiadiazoles are alkylated at N4 by treatment with MeI, while methylation of 3-amino derivatives with trimethyloxonium tetrafluoroborate produces the N4 quaternary salt (Section 14.5.5.1): the obtained compounds can undergo a Dimroth rearrangements (Schemes 14.106 and 14.108). In contrast, harder electrophiles, such as benzydryl and thrityl chlorides, alkylate 3-amino and 5-amino derivatives at the amino functionality [227].

3-Amino and 5-amino-1,2,4-thiadiazoles are acylated under the usual conditions at the amino group. Moreover, they easily react with isocyanates, carbamates, and chloroformates (Scheme 14.136); the 5-amino derivatives **467** and **468** are used as herbicides and bactericides [120].

A bond-switching reaction, already described in the Section 14.3.5.2 (Scheme 14.120) for 1,2,4-thiadiazolidines, can occur at the π-hypervalent sulfur atom of 5-amino derivatives. In fact, when compounds **360** were reacted with aliphatic or aromatic nitriles, a mixture of 1,2,4-thiadiazoles **470** and **471** via the intermediate **469** were obtained (Scheme 14.137) [167].



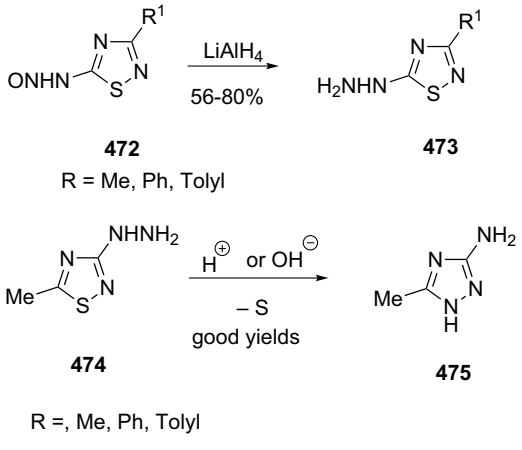
Scheme 14.136



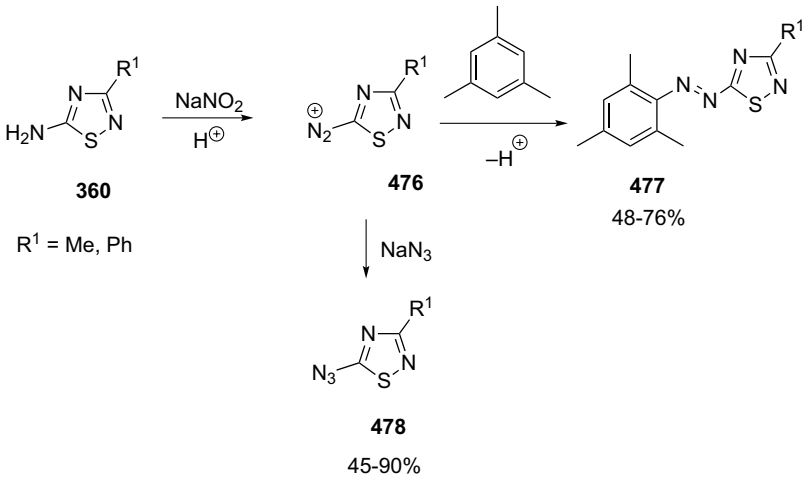
Scheme 14.137

5-Nitrosoamino-1,2,4-thiadiazoles are moderately reactive and can be converted into different functional groups by reaction with the appropriate reagents [120]. For example, the 5-hydrazino-1,2,4-thiadiazoles **473** can be easily prepared by simple reduction with $LiAlH_4$ of the corresponding nitrosoamine **472**. Compounds **473** are stable in acidic or basic conditions and can be transformed into the corresponding hydrazones by reaction with suitable carbonyl compounds. In contrast, the 3-hydrazino derivatives **474**, obtained by ring closure procedures, are very sensitive to both acids and bases, giving 1,2,4-triazoles **475** by sulfur extrusion (Scheme 14.138).

5-Amino-1,2,4-thiadiazoles **360** can be diazotized, by treatment with sodium nitrite, to give the diazonium salts **476**. These compounds, because of the strong electron attraction of the 1,2,4-thiadiazole ring, are particularly reactive and can even couple with the hydrocarbon mesitylene, leading to the monoazo dye **477** [227], or can be transformed into the 5-azido derivatives **478** by treatment with sodium azide (Scheme 14.139).



Scheme 14.138

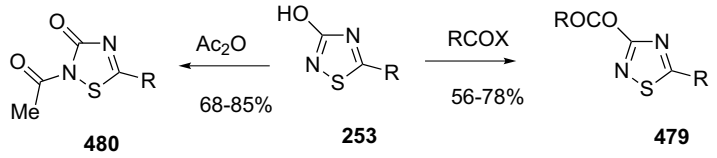


Scheme 14.139

Both 3- and 5-hydroxy-1,2,4-thiadiazoles are generally acidic compounds, comparable to phenol and nitrophenol, respectively. The mercapto-1,2,4-thiadiazoles are even more acidic [178].

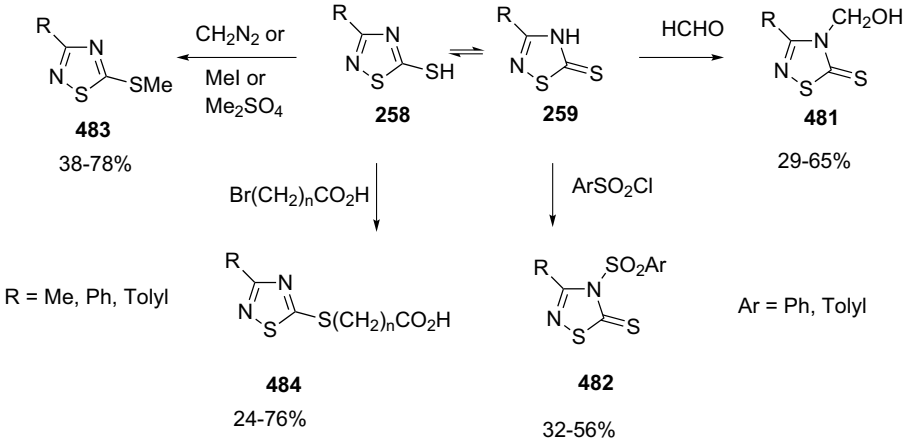
3-Hydroxy-1,2,4-thiadiazoles **253** react with electrophiles either at the hydroxylic function or at N2. Normally, hard electrophiles (acyl chlorides) attack the oxygen of the hydroxyl group, giving rise to 3-acyl derivatives **479**, while soft reagents (acid anhydrides) attack the N2 position, giving rise to 1,2,4-thiadiazolin-3-ones **480** (Scheme 14.140) [167].

As already reported in Section 14.3.1, 5-mercapto-1,2,4-thiadiazoles **258** do not show any SH absorption, thus suggesting that the position of the equilibrium is



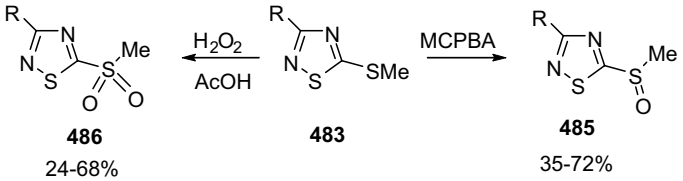
Scheme 14.140

shifted towards the thione tautomers **259** and **260**. The presence of **259** at the equilibrium is confirmed by the reaction with either formaldehyde or with sulfenyl chlorides, which give rise to N4 derivatives **481** and **482**, respectively. In contrast, treatment with diazomethane, methyl iodide, methyl sulfate, and bromoacetic and 3-bromopropionic acids gives only the S- derivatives **483** and **484** (Scheme 14.141), so indicating that the 5-mercapto form **258** contributes to tautomeric equilibrium [227].



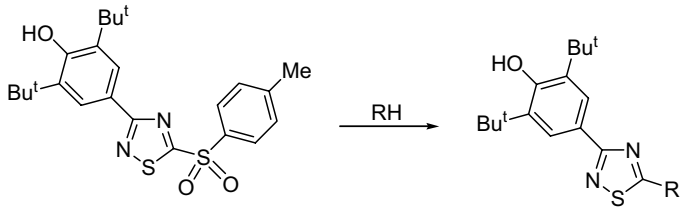
Scheme 14.141

The sulfide derivatives **483** can be oxidized to the corresponding sulfoxides **485** and sulfones **486** using *m*-chloroperbenzoic acid (MCPBA) and hydrogen peroxide respectively (Scheme 14.142) [216].



Scheme 14.142

The 5-sulfonyl group can be easily removed by nucleophilic displacement: for example, the reaction of **486a** with various amines gives **487** (Scheme 14.143) [228].



486a **487** 72%

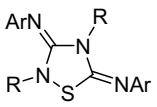
R = NH_2, $HNC(NH)NH_2 \cdot HCl$, $HNC(NH)Me \cdot HCl$, $HNC(NH)SMe \cdot HCl$

Scheme 14.143

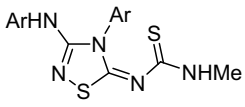
14.3.6 Thiadiazoles in Medicine

1,2,4-Thiadiazoles constitute a distinctive class of small heterocycles exhibiting various types of biological activities and some of these compounds are useful pharmacophores. Furthermore, they have found use as dyestuffs, lubricant additives, and vulcanization agents [120].

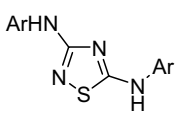
The 1,2,4-thiadiazole nucleus is found in some compounds that show analgesic and anticonvulsant properties, such as **488**–**490** [227]. More recently, it has been reported that 3-arylamino-4-aryl-5-(*N*-arylthiocarbamoyl)-4,5-dihydro-1,2,4-thiadiazoles block strychnine seizures [228].



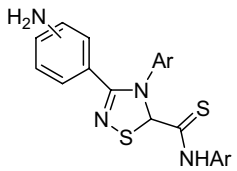
488



489

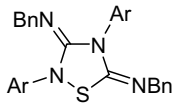


490

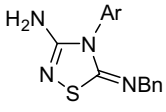


491

Anti-inflammatory activity has been described for compounds **492**–**494** [229]. In particular, several 1,2,4-thiadiazoles containing a di-*tert*-butyl-phenol substituent have been identified as active and selective cyclooxygenase (COX-2) inhibitors [230].



492



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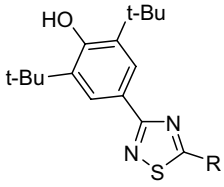
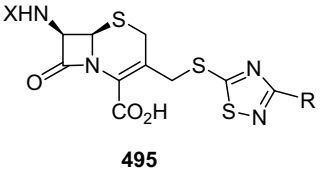


494

Cephalosporins incorporating the 1,2,4-thiadiazole system have been prepared and shown to possess good antibiotic activity. Thus, compounds of type **495** have been the subject of patent specifications [167]. With the aim of developing a broad-spectrum cephalosporin, new β-lactams bearing various condensed-heterocycles have been reported [231]. In particular, improvement of anti-pseudomonal and anti-MRSA (methicillin-resistant *Staphylococcus aureus*) activities was obtained by introducing a 5-amino-1,2,4-thiadiazol-3-yl moiety and a hydroxyimino group as C7 substituent (as in compound **496**) [231, 232].



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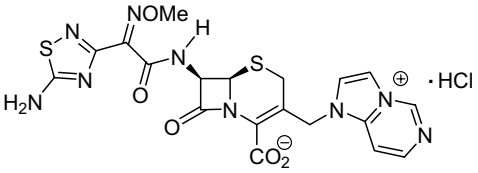
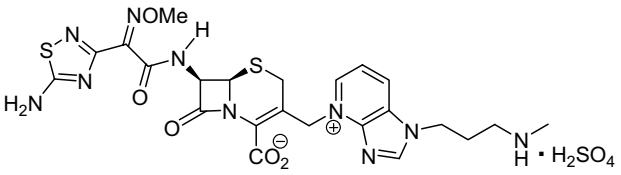


496

The novel cephalosporin **497** showed an extremely potent activity against Gram-positive and Gram-negative bacteria [233, 234]. Novel C3′ condensed-heterocyclic pyridinium cephems have also been prepared to enhance the antibacterial spectrum and water solubility [235, 236].



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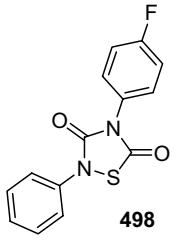
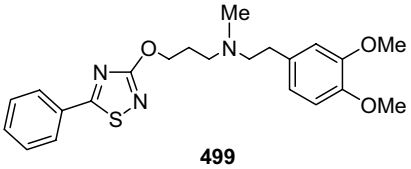


498

Thiadiazolidinediones such as **498** are the first examples of potent and selective inhibitors of bacterial dihydroorotate dehydrogenase (DHO), a critical enzyme of the pyrimidine biosynthesis [237].

During the last decade, several 1,2,4-thiadiazoles have been reported with relevant biological activities concerning the central nervous system, G-protein coupled receptors, and cardiovascular system.

Among the thiadiazoles that act on the cardiovascular system, KC 12 291 (**499**) has shown cardioprotective actions due to the inhibition of voltage-gated Na^+ channels [238].



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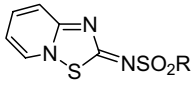
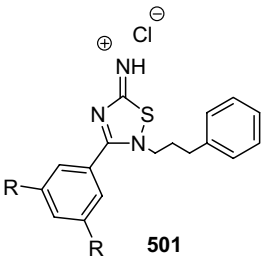


500

The 2-sulfonylimino-2*H*-1,2,4-thiadiazolo[2,3-*a*]pyridine derivatives **500** have been described as possessing platelet aggregation inhibitory and cardiotonic actions, although the mechanism of action at the molecular level has not been disclosed [239].

Remarkable antiplatelet and anticoagulant activities have also been observed in 1,2,4-thiadiazol-5(2H)-iminium chlorides **501** [240]. In addition, 5-oxo-1,2,4-thiadiazoles **502** have shown efficient oral bioavailability as angiotensin II receptor antagonists [241].



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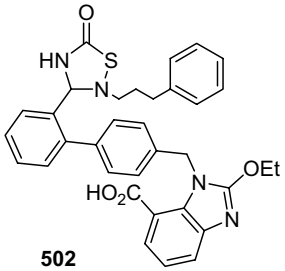
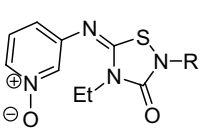


502

Some 1,2,4-thiadiazoles have been described as potential drugs for the treatment of Alzheimer's disease. Thus, 3-(thiadiazolyl)pyridine-1-oxides **503** are endowed with antioxidant and muscarinic receptor binding properties [242], while a series of 1,2,4-thiadiazolidinones containing the *N*-benzylpiperidine fragment (**504**) have revealed acetylcholinesterase inhibitory activity [243]. Furthermore, it has been stated that in a series of 1,2,4-thiadiazoles bearing a mono-or bicyclic amine at C5 (**505**), the ring can be regarded as an ester mimic in the binding of muscarinic ligands capable of displaying high receptor affinity [143]. More recently, the thiadiazolidin-3,5-diones **506** were described as the first non-ATP competitive inhibitors of glycogen synthase kinase 3β [171], an interesting target for the development of new promising drugs for the treatment of Alzheimer's disease, stroke, cancer, and diabetes type II.



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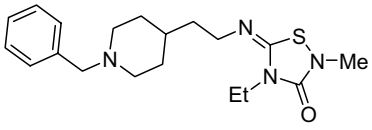

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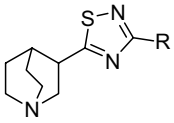

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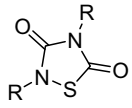
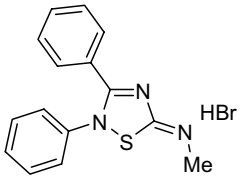


506

Compound **507** has been found to be a general allosteric modulator of both agonist and antagonist binding to a wide series of G-protein coupled receptors such as the human μ-, δ-, and κ-opioid, α- and β-adrenergic, muscarinic M_1 and M_2, and dopaminergic D_1 and D_2 receptors [183, 244].

Some 2,3,5-substituted-1,2,4-thiadiazoles of general formula **508** were able to inhibit at a final concentration of 1 μM the [3H]CCPA (2-chloro-N_6-cyclopentyladenosine) agonist binding to human A_1 adenosine receptors. At the same concentration, the same compounds were able to increase [^{3}H]DPCPX(1,3-dipropyl-8-cyclopentylxanthine) antagonist binding [184, 185].



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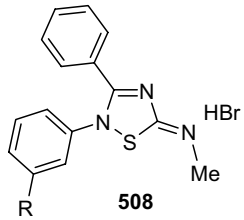
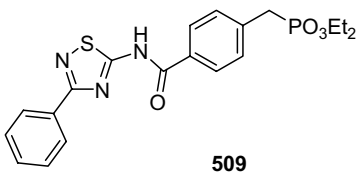


508

Thiadiazoles with different N-imino substituents have been synthesized; the results of receptor–ligand binding showed that these compounds are best described as protein modifiers (sulfhydryl modifying agents) rather than allosteric modulators.

4-(Diethoxyphosphoryl)methyl-*N*-(3-phenyl[1,2,4]thiadiazol-5-yl)benzamide (**509**) acts as a potent mesangial cell proliferation inhibitor [245], 6-(1,2,4-thiadiazol-5-yl)-3-aminopyridazine derivatives **510** are novel angiogenesis inhibitors [246], and 2,3-diaryl-5-anilino-1,2,4-thiadiazolium bromide **511** has been identified as a melacortin-4 receptor agonist [247].



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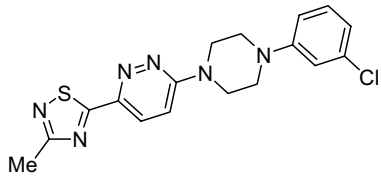

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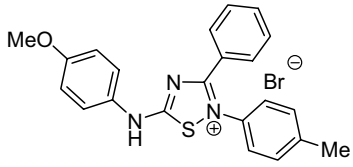
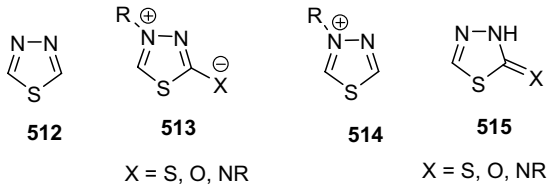


511

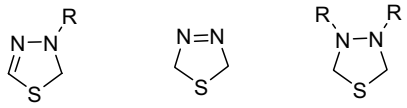
14.4 1,3,4-Thiadiazoles

1,3,4-Thiadiazole ring systems include aromatic derivatives such as the parent compound **512**, the mesoionic systems **513**, the 1,3,4-thiadiazolium cation **514** and the non-aromatic forms such as the tautomeric compounds **515**, the 1,3,4-thiadiazolines **516** and **517**, and the tetrahydro-1,3,4-thiadiazolidines **518**. All the structures are well known.



512 **513** **514** **515**

X = S, O, NR X = S, O, NR



516 **517** **518**

The chemistry of 1,3,4-thiadiazoles has attracted continued interest over the years because of the great practical importance of these compounds. Several thiadiazoles have been broadly applied in agriculture, industry, polymer chemistry, and, especially, in the pharmaceutical field, because some compounds have shown to be active as fungicides, bactericides, herbicides, and plant-growth regulators. In particular, 1,3,4-thiadiazoles are used in medicine, as antimicrobial [248], antituberculosis [249], anti-inflammatory [250], anticonvulsant [251], antihypertensive [252], local anesthetic [253], anticancer [254], and hypoglycaemic compounds [255]. This ring system has been the subject of several reviews [256–258]; this chapter will be essentially devoted to the recent published reports (2000–2008).

14.4.1 Structure

14.4.1.1 Theoretical Aspects

The structure and electronic parameters have been obtained by means of theoretical calculations using the computational methodologies of quantum chemistry [259].

Reported DFT and *ab initio* calculations of the molecular geometry of the parent compound **512** (Table 14.7) are in agreement with experimental data

Table 14.7 DFT/6-31G computational method versus experimental bond lengths (Å), angles (°), and dipole moment (Debye) of 1,3,4-thiadiazole (**512**).

Coordinates	DFT/6-31G*	Microwave spectroscopy	Electron diffraction	X-ray
C–S (Å)	1.747	1.720	1.722	1.74
C=N (Å)	1.300	1.303	1.304	1.31
N–N (Å)	1.373	1.371	1.381	1.38
C–H (Å)	1.082	1.077	1.081	0.98
C–S–C (°)	85.6	86.4	86.4	87
S–C=N (°)	114.7	114.6	114.8	114
C=N–N (°)	112.5	112.2	112.0	113
S–C–H (°)	122.1	122.5	124.1	123
N=C–H (°)	123.3	122.9	121.1	123
μ (Debye)	3.43	3.28	—	—

Table 14.8 Net charges and condensed Fukui functions for 1,3,4-thiadiazole (**512**) obtained through BLYP-DFT calculations.

Atom	Net charges	f^+	f^-	f^0
S	0.818	0.2445	0.2633	0.2539
C	−0.3275	0.2153	0.1233	0.1693
N	−0.0308	0.0930	0.1740	0.1335
H	0.2673	0.0694	0.0711	0.0703

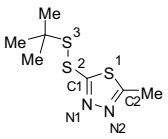
(electron diffraction, microwave spectroscopy, dipole moment, and X-ray spectroscopy) [260].

DFT methods have also been used to calculate the net atomic charges and the Fukui functions f^+, f^-, and f^0 for 1,3,4-thiadiazole **512** (Table 14.8) [261].

The obtained data show that **512** is reactive towards nucleophiles, with the sulfur atom as the favorite position. In particular, the sulfur atom, which has the largest f^+ value (0.2445) is the preferred site of soft nucleophiles, while the carbon atom is the preferred site of hard nucleophiles.

More recently, the molecular geometry of 2-*tert*-butyldithio-5-methyl-1,3,4-thiadiazole (**519**) has been investigated by Hartree–Fock (HF) and density functional methods (B3LYP and BLYP), with the 6-31G(d) basis set, and compared with experimental data (Table 14.9) [262]. The best agreement with the experimental

Table 14.9 DFT/6-31G(d) and Hartree–Fock computational methods versus experimental bond lengths (Å) and angles (°) of 2-*tert*-butyldithio-5-methyl-1,3,4-thiadiazole (**519**) in the ground state.

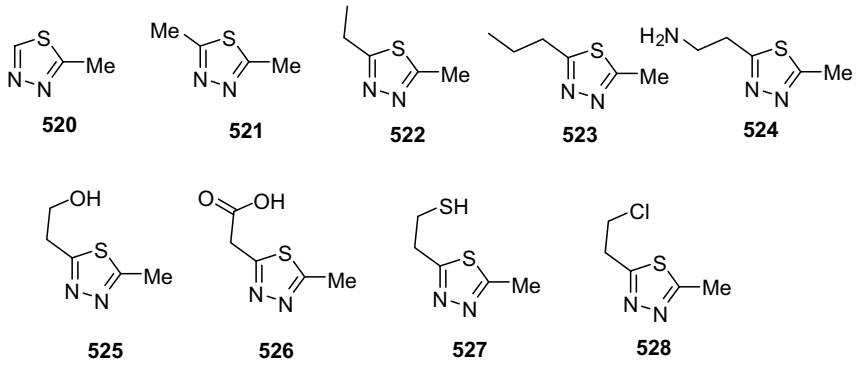


519

Coordinate	Experimental	HF	B3LYP	BLYP
S1–C1 (Å)	1.732	1.738	1.760	1.741
S1–C2 (Å)	1.736	1.736	1.761	1.741
S2–C1 (Å)	1.760	1.771	1.779	1.779
N1–C1 (Å)	1.299	1.271	1.304	1.309
N1–N2 (Å)	1.383	1.361	1.372	1.378
N2–C2 (Å)	1.294	1.275	1.302	1.313
C1–S1–C2 (°)	86.7	86.2	86.4	87.1
N1–C1–S1 (°)	107.1	104.9	107.0	106.3
C1–N1–N2 (°)	119.0	116.1	117.4	117.7
C2–N2–N1 (°)	109.9	111.4	110.0	111.1
S2–C1–S1 (°)	127.2	123.6	124.9	123.0
S2–C1–N1 (°)	125.7	123.5	123.3	123.8
C3–C2–S1 (°)	122.7	120.0	123.7	120.1
C1–N1–N2–C2 (°)	−0.1	0.1	0.6	1.3

values has been reached using the optimized bond lengths by HF and bond angles by DFT (B3LYP) methods.

Fukui functions, the HOMO and a Mulliken population analysis of 1,3,4-thiadiazoles **520–528** have been calculated by using the B3LYP functionals and a STO-3G* basis set [259].



520 **521** **522** **523** **524**

525 **526** **527** **528**

According to these calculations the most susceptible sites for electrophilic attacks are the N3 and N4 atoms of the thiadiazole ring. These sites present the highest values in f_k^- with a range of 0.0839–0.2144. Derivatives **524**, **527**, and **528** show other sites susceptible to electrophilic attack, corresponding to the atoms of nitrogen, sulfur, and chlorine present as substituents in the alkyl chain. Nevertheless, in compound **527** the sulfur atom of the thiole group was demonstrated to be much more reactive than atoms N3 and N4 with a f_k^- equal to 0.2931. In all the cases studied the site prone to nucleophilic attack was shown to be the sulfur atom of the ring that possesses the highest values of f_k^+ falling in a range 0.1983–0.2520.

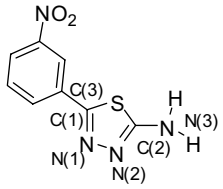
14.4.2 Structural Aspects

14.4.2.1 X-Ray Diffraction

A gas-phase electron diffraction investigation of the molecular structure of 1,3,4-thiadiazole **512** has been reported by Markov *et al.* [263]. The compound is planar and has a C_{2V} symmetry with the following bond lengths (Å) and bond angles (°): C–H = 1.081 ± 0.028, N–C = 1.304 ± 0.010, N–N = 1.381 ± 0.016, S–C = 1.722 ± 0.006; C–S–C = 86.4 ± 0.4, S–C–N = 114.8 ± 0.5, C–N–N = 112.0 ± 0.4, S–C–H = 124.1 ± 3.0, and H–C–N = 121.1 ± 3.0. The technique has been largely used to determine the structure of 1,3,4-thiadiazoles.

The X-ray structure of 2-amino-5-(*m*-nitrophenyl)-1,3,4-thiadiazole (**529**) shows that this compound is also planar [264]. The single crystals are monoclinic, $a = 11.832$ Å, $b = 9.862$ Å, $c = 8.353$ Å, $\beta = 110.40(3)°$, $V = 913.6(3)$ Å^3, $d_{calcd} = 1.212$ g cm^{-3},

Table 14.10 Bond lengths (Å) and angles (°) in the structure of 2-amino-5-(*m*-nitrophenyl)-1,3,4-thiadiazole (**529**).



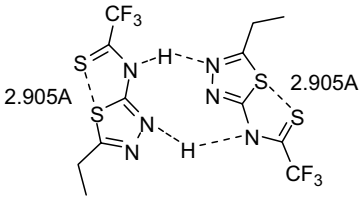
529

Bond	*d* (Å)	Bond	Angle (°)
S–C1	1.742	C1–S1–C2	86.8
S–C2	1.730	N1–C1–S	113.7
N1–C1	1.285	C1–N1–N2	113.6
N1–N2	1.380	C2–N2–N1	112.0
N2–C2	1.311	N1–C1–C3	124.5
N3–C2	1.353	C3–C1–S	121.8
C1–C3	1.471	N2–C2–N3	124.7
—	—	N2–C2–S	113.9

$\mu(\mathrm{Mo}K_\alpha) = 0.253\,\mathrm{mm}^{-1}$, $Z = 4$, and space group $P2_1/c$. Table 14.10 gives the relative bond lengths and angles.

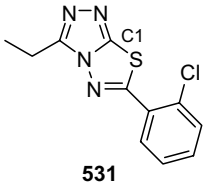
The lone pairs of nitrogen and sulfur atoms are conjugated with the double bonds of the five-membered ring. This is indicated by the N2–C2 (1.311 Å), N1–C1 (1.285 Å), and N1–N2 (1.380 Å) bond lengths. The lengths of two endocyclic N–C bonds are intermediate between the standard lengths of the sesqui-bond and double bond. The planes of the thiadiazole and benzene rings form a dihedral angle of 27.7°. The angle between the benzene ring and the nitro group is 8.3°.

The X-ray analysis of 2-trifluoro-N-1,3,4-thiadiazole-2-yl)ethanethioamide (**530**) shows that this molecule is a dimer and exhibits intermolecular hydrogen bonds and intramolecular nonbonding 1,5-type S….S interactions. The distance between the thiocarbonyl sulfur and the thiadiazole ring sulfur is 2.905 Å [265].



530

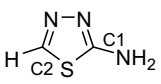
The crystal structure of 6-(2-chlorophenyl)-3-ethyl-[1,2,4]triazole[3,4-*b*]1,3,4-thiadiazole (**531**) has been reported recently [266]. The compound crystallizes in monoclinic space group $P2_1/c$ with a cell parameters $a = 11.879$ Å, $b = 15.112$ Å, $c = 13.95$ Å, $Z = 8$, and the final R factor is $R1 = 0.0524$. The five-membered and phenyl rings are planar with a maximum deviation of 0.021 Å for C1. The structure exhibits both intra- and intermolecular hydrogen bonds of the type C–H. . .N.



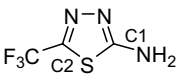
531

14.4.2.2 NMR Spectroscopy

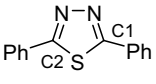
The ^{1}H NMR signals of 1,3,4-thiadiazoles are usually shifted downfield with respect to protons in benzene, according to the electron deficiency of the heterocyclic ring. In the parent compound **512**, the protons are equivalent and resonate at 9.12 ppm as singlet. The presence of alkyl or aryl substituents shifts the resonance upfield, similarly to amino and alkoxy groups. In particular, the 2-amino-1,3,4-thiadiazole (**532**) shows the H5 proton as singlet at 7.06 δ and the NH_2 protons at 8.54 ppm; for 2-amino 5-trifluoromethyl-1,3,4-thiadiazole (**533**), the NH_2 resonance appears as singlet at 7.71 δ [267].



532



533



534

The ^{13}C chemical shift for C1, or C2 carbon, in the parent compound is at 153.1 ppm. The presence of phenyl substituents in **534** moves these carbons to 167.7 δ [268].

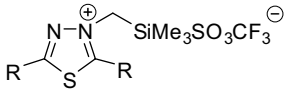
In the case of compounds **532** and **533**, the C2 signals are shifted upfield compared with C1 carbons, which, respectively, resonate in the range 144.8–146.8 δ and 171.2–173.8 δ [267].

Many fully assigned ^{1}H and ^{13}C data for disubstituted 1,3,4-thiadiazoles have been reported [269]. Table 14.11 summarizes the ^{1}H and ^{13}C NMR spectra of 2,5-disubstituted-3-trimethylsilymethyl-1,3,4-thiadiazolium trifluoromethanesulfonates **535–537**, which are useful starting materials for the preparation of 1,3,4-thiadiazolium-3-methanide species used as 1,3-dipoles [270].

14.4.2.3 UV, ESR, and IR Spectroscopy

The electronic spectra of 1,3,4-thiadiazoles containing substituents with lone pairs are bathochromically shifted. Substituted alkylthio- derivatives show a greater bathochromic shift than the amino derivatives. *p*-Nitrophenyl groups cause large bathochromic shifts, while *m*-nitrophenyl groups cause hypsochromic shifts.

Table 14.11 ^{1}H and ^{13}C NMR data (ppm) of 2,5-disubstituted-3-trimethylsilymethyl-1,3,4-thiadiazolium trifluoromethanesulfonates (**535–537**).

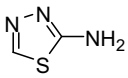


535–537 R = H, Me, Ph

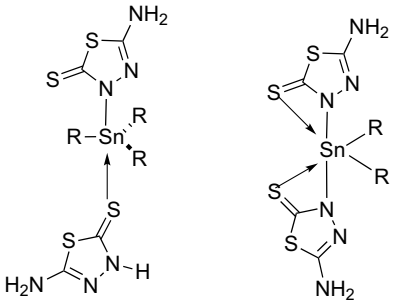
Salts	Me_3Si	Me-2/Me-5	NCH_2	Aromatic protons	H2/H5
δ ^{1}H ppm ($CDCl_3$)					
535	0.21	—	4.48	—	10.63/9.78
536	0.10	2.90/2.71	3.98	—	—
537	0.19	—	4.34	7.55–10.96 (10H)	—
δ ^{13}C ppm ($CDCl_3$)					
Salts	Me_3Si	Me-2/Me-5	NCH_2	Aromatic carbons	C2/C5
535	−3.0	—	51.0	—	158.7/158.6
536	−2.6	15.8/14.8	46.9	—	171.6/166.0
537	−2.2	—	48.9	122.1–134.1 (8C)	170.4/168.6

Unconjugated 1,3,4-thiadiazoles have no selective absorption above 220 nm. The electronic spectra of some 2-arylazo-5-phenyl-1,3,4-thiadiazole derivatives, made in pure and mixed organic solvents with different polarities, display two bands in the UV region: the first one at 204–238 nm was ascribed to the π–π^* transition in the benzenoid system, while the second one, at 237–313 nm, was attributed to a π–π^* transition of the 1,3,4-thiadiazole moiety [271].

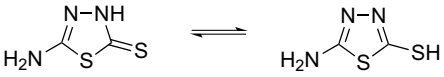
Electron spin resonance (ESR) spectroscopy has also been used to study the surface complexes of CuX (X = Cl^-, Br^-, ClO_4^-) on silica gel chemically modified with 2-amino-1,3,4-thiadiazole (**532**) [272]. ESR indicated a tetragonal distorted structure with low degrees of metal loading on the silica gel. Recently, the electronic spectra of some organotin(IV) derivatives of 5-amino-3*H*-1,3,4-thiadiazole 2-thione **538**, together with the uncoordinated thiazole-2-thione **539**, have been reported (Figure 14.5) [273]. These spectra show two absorption bands, at 256 ± 2 and 318 ± 4 nm, which may be assigned to π–π^* and n–π^* transitions, respectively, of the chromophore (C=N) present in thiadiazole ring. These bands undergo a hyperchromic shift upon complexation, indicating the participation of C=N group in coordination. The infrared spectra of these compounds have also been reported. In particular, the uncoordinated ligand **539** exhibits two bands, at 2622 and 1240 cm^{-1}, assigned to ν(SH) and ν(C=S), indicating the coexistence of both thione and thiol forms in the solid state.



532



538: R =n-Pr, N-Bu



539a **539b**

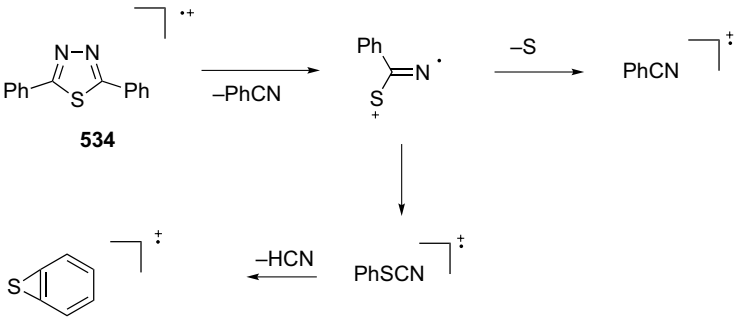
Figure 14.5 Organotin(IV) derivatives of 5-amino-3*H*-1,3,4-thiadiazole 2-thione (**538** and **539**) and the uncoordinated thiazole-2-thione (**540**).

In the IR spectra of the organotin(IV) compounds **538**, ν(SH) is not observed, indicating the deprotonation of the thiol form. The ν(C=S) band shifts downward by $53 \pm 13\,cm^{-1}$, thus indicating the coordination of thione sulfur to tin. The other significant signals for compound **539** are at 3347 (NH_2), 3244 (NH_2), 3180 (N3–H), 1604 (N–H + C=N), 1547 and 1476 (C=N/ring mode), 1058(N–N), and 672 (C–S–C).

Some other IR absorption spectra for 1,3,4-thiadiazoles show bands at 1230–1165, 1190–1120, 1075–1045, 1040, 975–905, 905–875, 850, and 775–750 cm^{-1} [257].

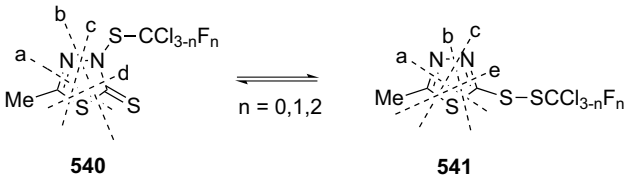
14.4.2.4 Mass Spectrometry

The main fragmentation of 1,3,4-thiadiazoles is the loss of a nitrile group. Thus, 2,5-diphenyl-1,3,4-thiadiazole (**534**) shows intense ions due to the loss of PhCN, S, and HCN (Scheme 14.144).



534

Scheme 14.144



540 **541**

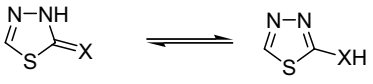
Figure 14.6 Fragmentation pattern of trihalomethylsulfenyl derivatives of 5-methyl-1,3,4-thiadiazole-2-thiols.

In the presence of a methylthio substituent, such as 5-(methylsulfanyl)-1,3,4-thiadiazol-2-amine, the major process is the loss of $^{\bullet}SH$ and the fragmentation at the heterocyclic sulfur atom. In the case of 3,5-diphenyl-2,3-dihydro-1,3,4-thiadiazole, the predominant fragment is represented by $PhS^{\bullet}$, while 1,3,4-thiadiazolidine-thione **515** decomposes by fragmentation of the ring [257].

More recently, fragmentation studies of several trihalomethylsulfenyl derivatives of 5-methyl-1,3,4-thiadiazole-2-thiols **540** and **541** have been reported [274]. The diagnostic fragments are characterized by the loss of the halogenated substituents, and in all cases cleavage via fragmentation "a" (Figure 14.6) generated the base peak of m/z 59 Da $[CH_3C{=}S]^{+\bullet}$. Other fragmentations of the substituent occur, producing Cl_3C^+, Cl_2FC^+, and ClF_2C^+. Fragments and losses common to all derivatives were also $[M–CCl_nF_{3-n}]^+$, $[M–SCCl_nF_{3-n}]^+$, $[M–(S–SCCl_nF_{3-n})]^+$, $[CS]^+$, and $[CH_3CN]^{+\bullet}$.

14.4.2.5 **Thermodynamic Aspects**

The parent compound **512** does not show tautomerism in its fully conjugated form. Nevertheless, in the presence of some substituents tautomerism is possible.



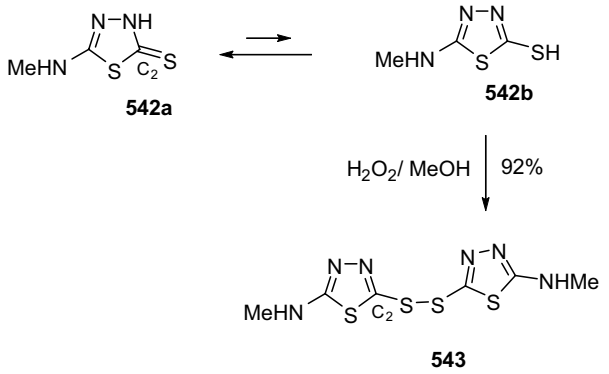
515a **515b**

X = O, S

1,3,4-Thiadiazolin-2-ones (X = O) and -2-thiones (X = S) exist, in the oxo and thione forms **515a**.

This result is confirmed by ^{13}C NMR spectra of 5-methylamino-1,3,4-3*H*-thiadiazoline-2-thione **542a**, where the C2 signal appears at 180.6 ppm, while the oxidized species, the bis(5-methylamino-1,3,4-thiadiazol-2-yl)disulfide **543**, obtained from **542** with aqueous hydrogen peroxide, shows the same carbon (C2) resonating at 148.6 ppm (Scheme 14.145) [275].

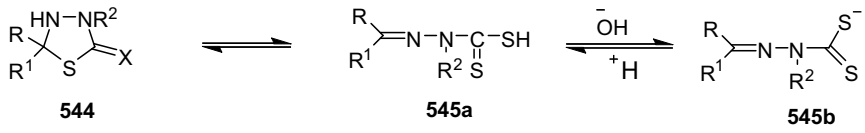
Tautomeric energy differences also calculated for **515**, using the HF/6-31G**, B3LYP/6-311G**, and B3LYP/6-311 + + G** levels of approximation, confirm that these compounds are oxo or thione compounds rather than hydroxyl and mercapto tautomers [276].



Scheme 14.145

2-Amino-1,3,4-thiadiazoles **532** exist in the amino form, in solution and in the solid state, while the presence of the sulfonamido group shifts the equilibrium towards the imido tautomer [256, 257].

1,3,4-Thiadiazolidine-2-thiones **544** are in equilibrium with the open-chain hydrazone tautomers **545**; under basic conditions, the hydrazone salt is the predominant form (Scheme 14.146) [277].



R = Ph, 2-pyridyl R^1 = H R^2 = Me

Scheme 14.146

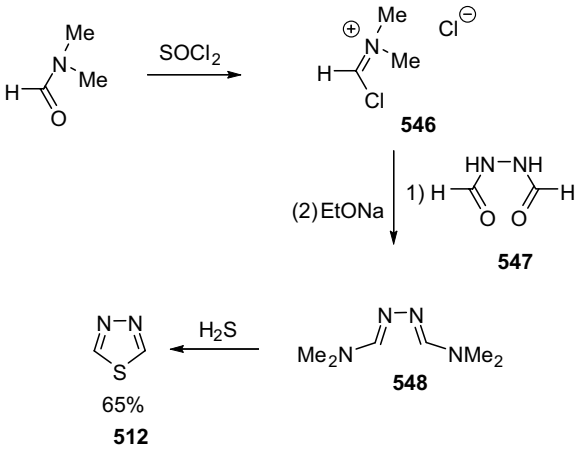
1,3,4-Thiadiazoles are solids; some of them are soluble in water, with a solubility decreasing with increasing molecular weight.

14.4.3 Synthesis

14.4.3.1 Synthesis of 1,3,4-Thiadiazoles

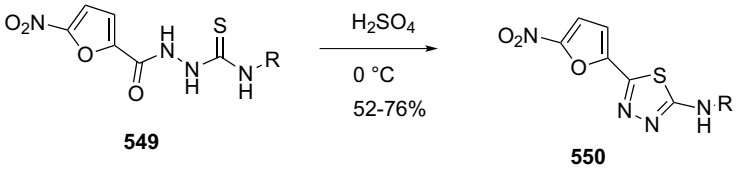
The parent compound, described in 1956 by Goerdeler *et al.*, was obtained by hydrogenation of 2-bromo-1,3,4-thiadiazole with Adams catalyst in 90% yield [278]. Compound **512** was also obtained by cyclization, in the presence of hydrogen sulfide, of *N*′-[(dimethylamino)methylidene]-*N*,*N*-dimethylhydrazonoformamide (**548**), prepared in a two-step sequence by reaction of DMF with thionyl chloride,

followed by treatment with *N,N'*-diformylhydrazine (**547**) and sodium ethoxide (Scheme 14.147) [279].



Scheme 14.147

A general procedure for the preparation of 1,3,4-thiadiazoles is the cyclization of 1-acylthiosemicarbazides by cold concentrated sulfuric acid. Using this method, several 5-(5-nitro-2-furyl)-1,3,4-thiadiazoles (**550**) have been obtained from **549** (Scheme 14.148) [280].

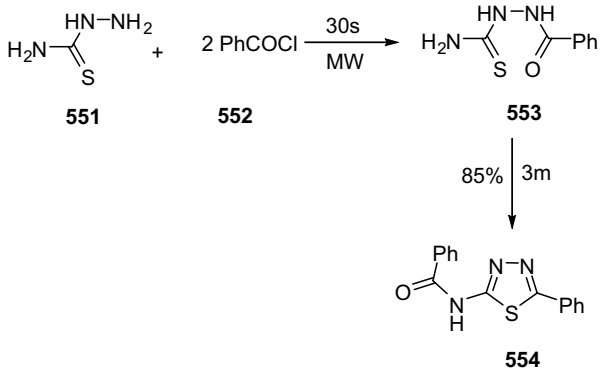


Scheme 14.148

A convenient procedure has been reported by Nami and coworkers for the synthesis of *N*-(5-phenyl-1,3,4-thiadiazol-2yl)benzamide (**554**), by condensing thiosemicarbazide **551** with benzoyl chloride (**552**) under microwave irradiation, involving as intermediate the 2-benzoylhydrazinecarbothioamide (**553**) (Scheme 14.149) [281].

Compound **553** can also be cyclized into compound **554** with H_3PO_4 under conventional heating at 120 °C for 10 min [282]. This cyclization is quite general and other dehydrating agents have been used such as polyphosphoric acid [283] and phosphorus oxychloride [284].

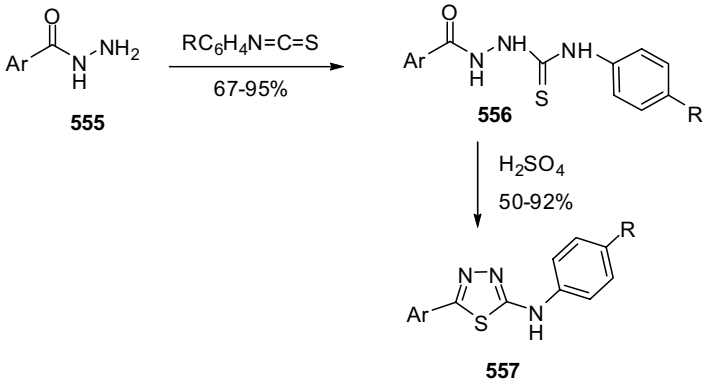
Different 2-amino-1,3,4-thiadiazoles, screened for the antituberculosis activity against *Mycobacterium tuberculosis* H37Rv, have been synthesized from the reaction



551 552 553 554

Scheme 14.149

of various 1-acylthiosemicarbazides (**556**) with sulfuric acid. Compounds **556** were prepared by reaction of 4-substituted benzoic acid hydrazides **555** with different aryl isothiocyanates (Scheme 14.150). Among the tested compounds, 2-phenylamino-5-(4-fluorophenyl)-1,3,4-thiadiazole showed the highest inhibitory activity (69%) [285].



555 556 557

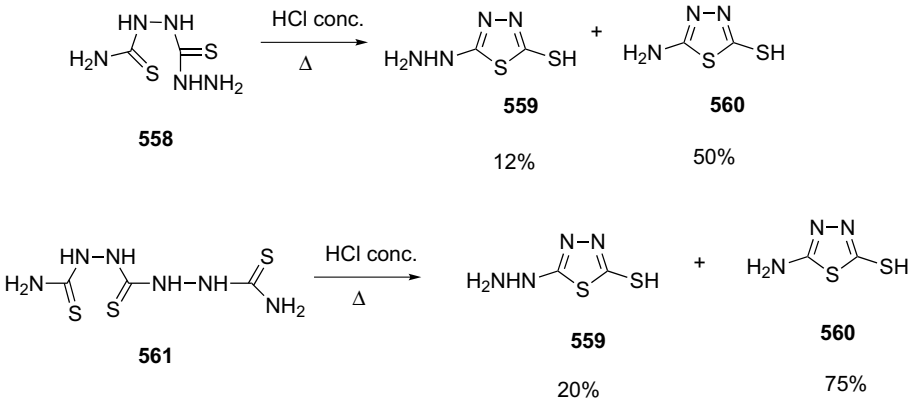
Ar = Ph, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-$NO_2C_6H_4$, C_5H_4N

R = H, F, Cl, Br, Me, NO_2

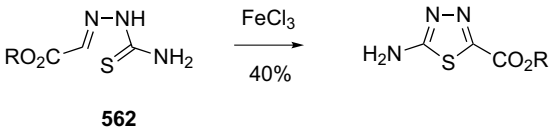
Scheme 14.150

5-Hydrazinyl- and 5-amino-1,3,4-thiadiazole-2-thiols (**559** and **560**) have been prepared in 50% and 12% yields, respectively, starting from 2-(hydrazinylcarbonothioyl)hydrazinecarbothioamide (**558**), by reaction with hydrochloric acid; a better yield of both compounds was obtained starting from 2,2′-carbonothioyldihydrazinecarbothioamide (**561**) (Scheme 14.151) [286].

Oxidation of ethyl or butyl (2-carbamothioylhydrazinylidene)ethanoate **561** with ferric chloride leads to ethyl 5-amino-1,3,4-thiadiazole-2-carboxylates showing that the electron-donating group increases the stability of 1,3,4-thiadiazole carboxylic acids (Scheme 14.152) [287].



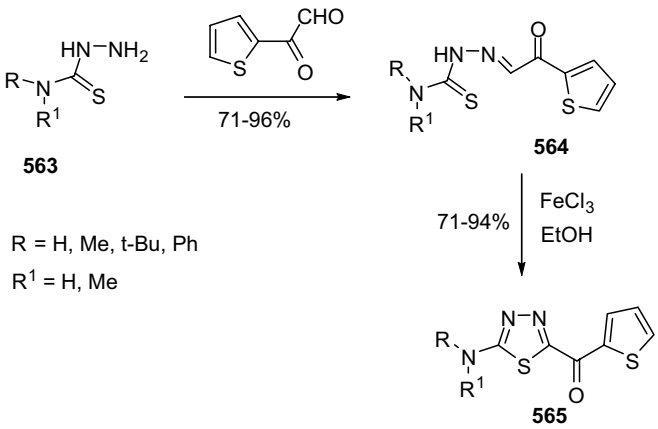
Scheme 14.151



R = Et, Bu

Scheme 14.152

Oxidative cyclization has also been performed with substituted thiosemicarbazones [288]. Thus, the reaction of substituted thiosemicarbazides **563** with aldehydes yields the corresponding thiosemicarbazones **564**, which by oxidative cyclization, achieved with iron(III) chloride or $K_3Fe(CN)_6$, lead to substituted 1,3,4-thiadiazoles **565** in good yields (Scheme 14.153) [289].

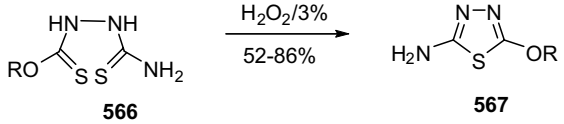


R = H, Me, t-Bu, Ph

R^1 = H, Me

Scheme 14.153

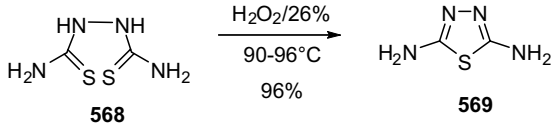
2-Alkoxy-2-amino-1,3,4-thiadiazoles **567** have been prepared, in good yields, by oxidation of the corresponding *O*-alkyl 2-carbamothioylhydrazinecarbothioate **566** with hydrogen peroxide (Scheme 14.154) [290].



R = Me, Et, n-Pr, i-Pr, n-Bu

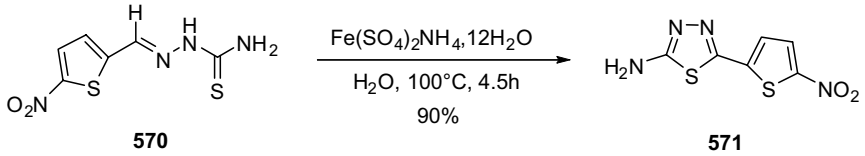
Scheme 14.154

The oxidation method has also been applied to 1,2-hydrazinedicarbothioamide **568** (dithiobiurea), using iodine, ferric chloride and hydrogen peroxide, to produce 2,5-diamino-1,3,4-thiadiazole (**569**) (Scheme 14.155) [291].



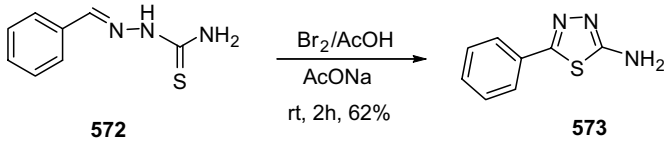
Scheme 14.155

Ammonium ferric sulfate dodecahydrate has been used to prepare, in 90% yield, 2-amino-5-(5-nitro-2-thienyl)-1,3,4-thiadiazole (**571**), starting from 5-nitrothiophene-2-carboxaldehydethiosemicarbazone (**570**) (Scheme 14.156) [292].



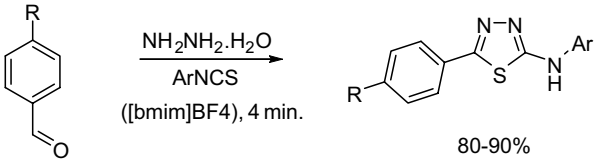
Scheme 14.156

A similar oxidation has been accomplished using a mixture of sodium acetate, bromine, and glacial acetic acid, which is useful in preparing 2-amino-5-phenyl-1,3,4-thiadiazole (**573**) starting from 2-benzylidenehydrazinecarbothioamide (**572**) (Scheme 14.157) [293].



Scheme 14.157

An efficient one-pot procedure for the preparation in excellent yields of 1,3,4-thiadiazoles **575** in ionic liquid, as dual solvent and catalyst, has been reported recently [294]. The reaction involves a one-pot, three-component condensation of hydrazine hydrate with substituted phenyl isothiocyanates, followed by the addition of substituted benzaldehydes **574** in the presence of the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) and in the absence of any other catalyst, under mild conditions (Scheme 14.158). The reaction workup is simple, and the ionic liquid is easily recovered from the reaction and reused.

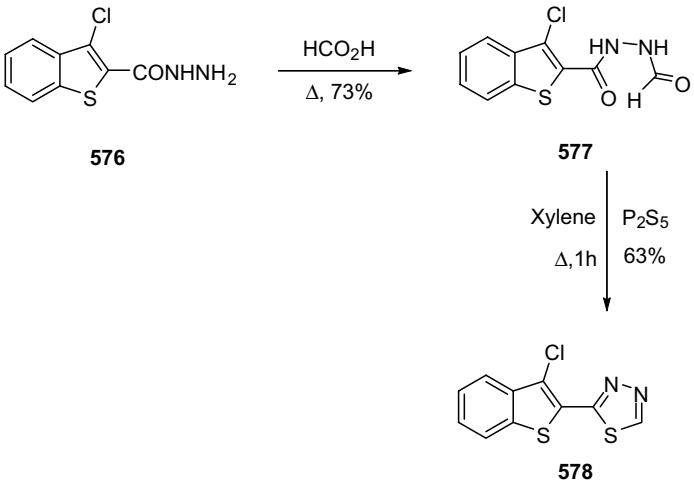


574 **575**

R = H, Br, Cl, F, NO_2
Ar = Ph, 4-$NO_2C_6H_4$, 4-MeC_6H_4, 3-MeC_6H_4

Scheme 14.158

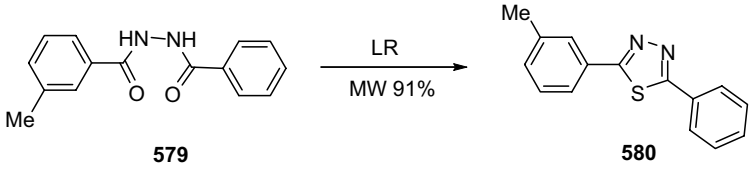
1,3,4-Thiadiazoles can be also obtained from the reaction of diacylhydrazines with a sulfur source. Thus, *N′*-formyl 1-benzothiophene-2-carbohydrazide derivative **577**, prepared by condensation of 3-chlorobenzo[*b*]thiophene-2-carboxylic acid hydrazide **576** with formic acid, reacts with phosphorous pentasulfide in xylene at reflux to give the corresponding 2-(3-chloro-1-benzothien-2-yl)-1,3,4-thiadiazole (**578**) in 63% yield (Scheme 14.159) [295].



576 **577** **578**

Scheme 14.159

Moreover, some 2,5-diaryl-1,3,4-thiadiazoles have been prepared in 74–91% yields using Lawesson's reagent and microwave irradiation in the absence of solvent for 3–8 min [296]. Thus, for example, 2-phenyl-5-*m*-tolyl-1,3,4-thiadiazole (**580**) was prepared in 91% yield from of a mixture of **579** and Lawesson's reagent (LR) (Scheme 14.160) [297].



579 **580**

Scheme 14.160

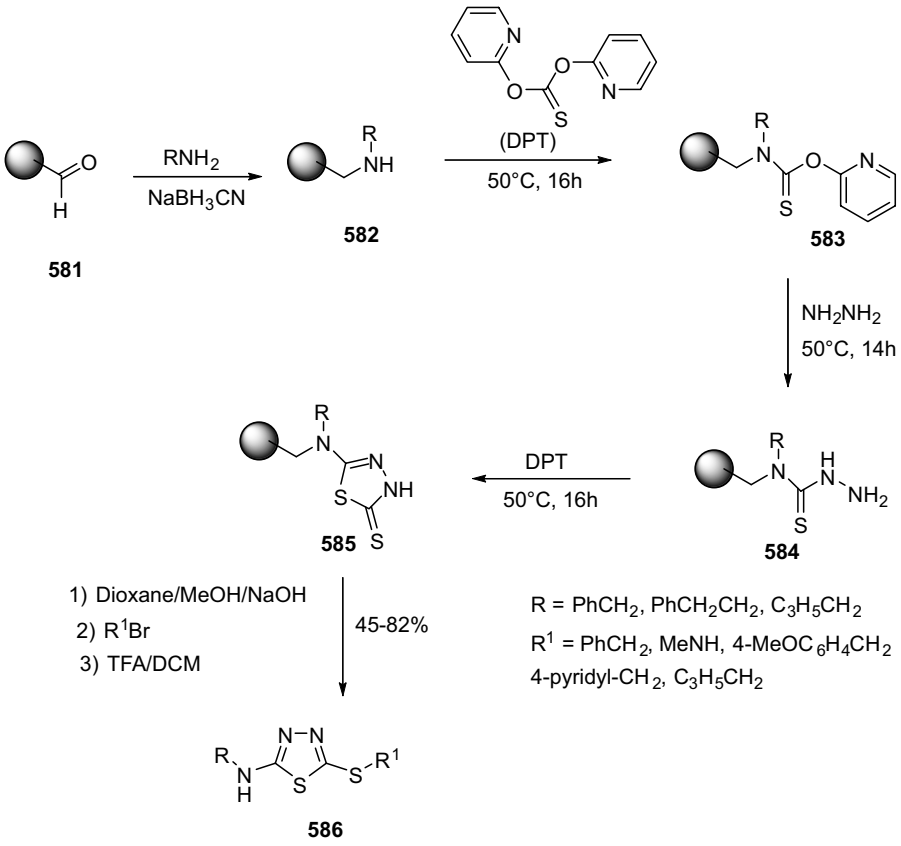
A series of 2-alkylthio-5-alkylamino-1,3,4-thiadiazoles have been synthesized through a new and versatile solid-phase synthesis protocol using the commercially available 2-(3,5-dimethoxy-4-formylphenoxy)ethoxymethyl polystyrene (**581**). This resin was treated with a range of primary amines under standard reductive amination conditions to yield the respective resin bound derivatives **582**, which were transformed into resin bound benzyl-thiocarbamic acid *O*-pyridin-2-yl esters **583** upon treatment with di-(2-pyridyl)-thionocarbonate (DPT). These compounds were subsequently converted into thiosemicarbazides **584** by reaction with hydrazine, and then treated with 10 equivalent of DPT in dichloromethane (DCM) to give immobilized thiones **585**. Alkylation of thione **585** with primary alkyl- or benzyl bromides in a mixture of 1,4-dioxane–methanol and aqueous sodium hydroxide, followed by TFA/DCM treatment, yielded 1,3,4-thiadiazoles **586** in 45–82% yield (Scheme 14.161) [298].

Some benzaldehyde *N*′-(5-benzoylmethyl-1,3,4-thiadiazol-2-yl)hydrazone hydrobromides **590**, subsequently converted into the free bases **591** by treatment with aqueous ammonia, have been synthesized by the reaction of 1-benzylidenethiocarbohydrazones **587** with 3-bromo-1-phenylprop-2-yn-1-one (**588**). This reaction involves, presumably, a nucleophilic replacement of the bromine atom with the formation of benzoylethynyl sulfide intermediate **589** and intramolecular cyclization of the NH_2 group at the electron-deficient β-carbon of the triple bond (Scheme 14.162) [299].

Varma *et al.* have used a green protocol to synthesize in a single step several 1,3,4-thiadiazoles **594** [300]. In particular, various hydrazides **592** have been reacted with triethyl orthoalkanates or triethyl orthobenzoate (**593**), in the presence of phosphorous pentasulfide in alumina under microwave irradiations and in the absence of any solvents, to afford the target 1,3,4-thiadiazoles **594** in good yields (65–70%) (Scheme 14.163).

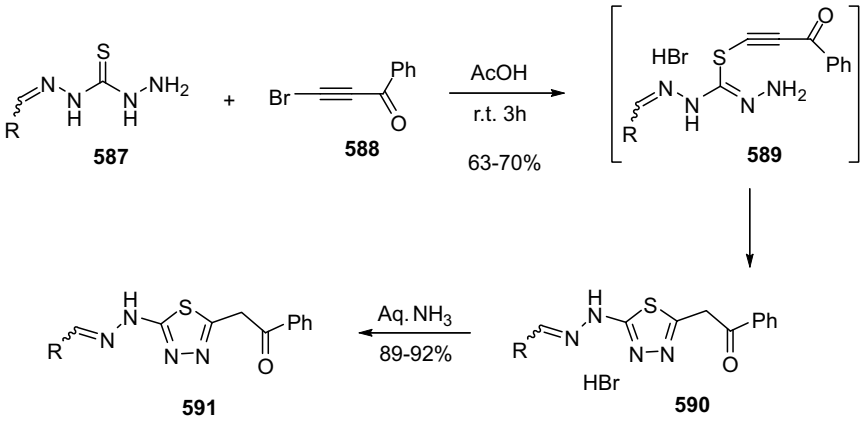
N-alkylhydrazinecarbothiamides **595** can react with triethyl orthoformate (**596**) in the presence of a small amount of concentrated hydrochloric acid to yield unsubstituted alkylamino-1,3,4-thiadiazoles **597** (Scheme 14.164) [301].

Triethyl orthoformate (**596**) has been used to prepare in good yield 5-amino-3-(methylthio)-1-(1,3,4-thiadiazol-2-yl)-1*H*-pyrazole-4-carbonitrile (**600**). Thus, starting



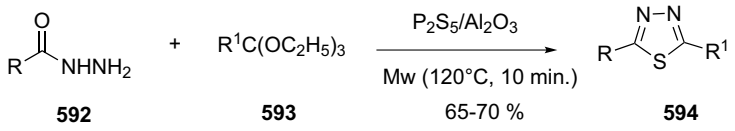
581 **582** **583** **584** **585** **586**

Scheme 14.161



587 **588** **589** **590** **591**

Scheme 14.162

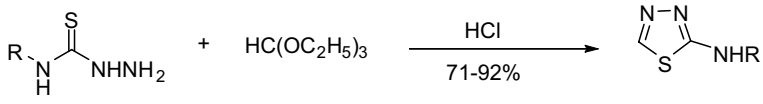


592 **593** **594**

R = Ph, p-F-C_6H_4, p-OMe-C_6H_4, 2-furyl, 2-thienyl, 4-pyridyl, $PhCH_2$

R^1 = H, Et, Ph

Scheme 14.163

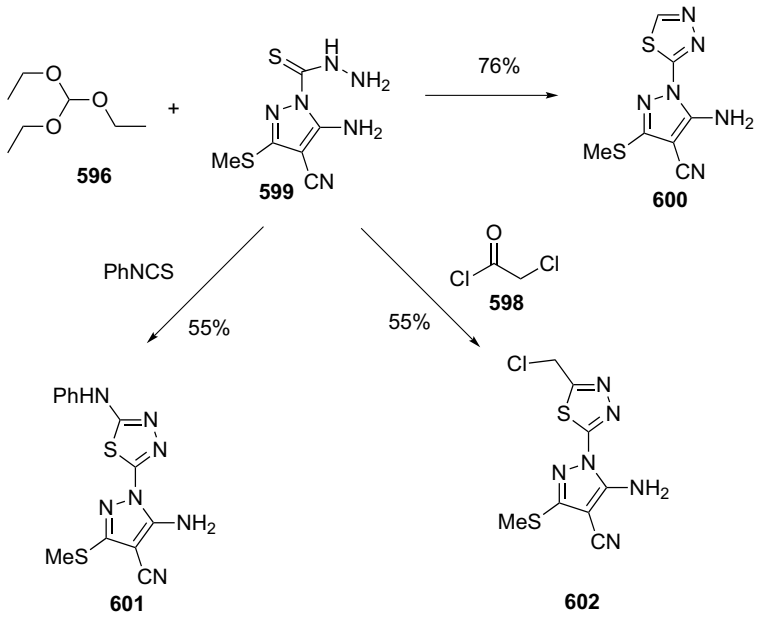


595 **596** **597**

R = Me, Et, nPr, $PhCH_2$, t-C_8H_{17}, 1-Adamantyl

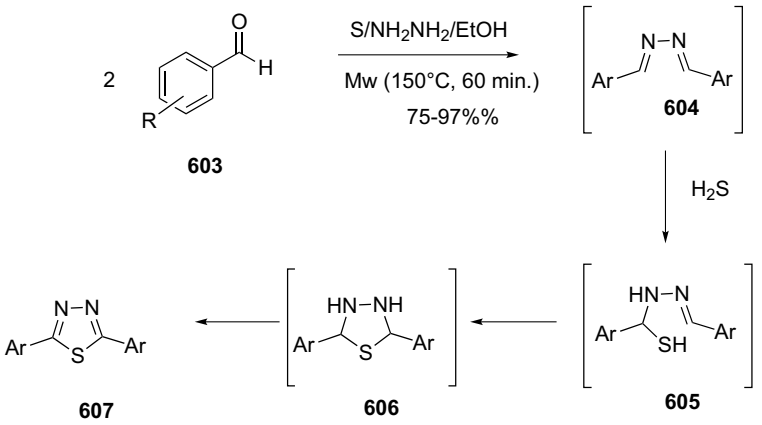
Scheme 14.164

from 5-amino-4-cyano-3-(methylthio)-1*H*-pyrazole-1-carbothiohydrazide (**599**), **600** was synthesized in 76% yield. Compound **599** was also used to generate **601** and **602** in 55% yield (Scheme 14.165) [302].



Scheme 14.165

2,5-Disubstituted-1,3,4-thiadiazoles **607**, in high yields and good purity, have been prepared in a one-pot three-component condensation of aromatic aldehydes **603**, hydrazine, and sulfur in ethanol under microwave irradiation (300 W, 1 h) [303]. The reaction involves as intermediates the corresponding azines **604**, which can be isolated in good yield if the reaction is stopped after 15 min. The same reaction performed with aromatic aldehydes under conventional heating led to 2,5-diaryl-1,3,4-thiadiazoles **607** (Scheme 14.166) [304].



Ar = Ph, *p*-OH-C_6H_4, m-OH-C_6H_4, o-OH-C_6H_4, *p*-OMe-C_6H_4, *o*-OMe-C_6H_4, *m*-OMe-C_6H_4, 3-thienyl, 2-thienyl, 3-pyridyl, 2-pyridyl, *p*-Me-C_6H_4, *p*-Me_2N-C_6H_4,

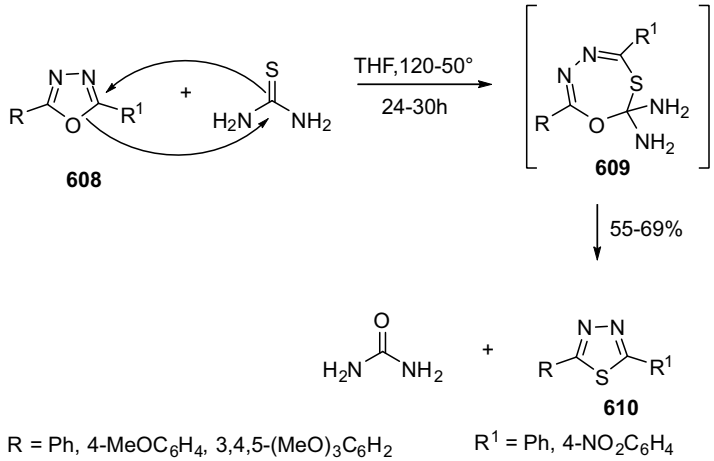
Scheme 14.166

2,5-Diaryl-1,3,4-thiadiazoles **610** can be also prepared in relatively good yield starting from the corresponding 1,3,4-oxadiazoles **608** by reaction with thiourea. The reaction involves an initial nucleophilic attack of the sulfur of thiourea on the carbon atom of 1,3,4-oxadiazole ring, followed by formation of an oxathiadiazepine intermediate **609**, and subsequent ring contraction and extrusion of urea (Scheme 14.167) [305].

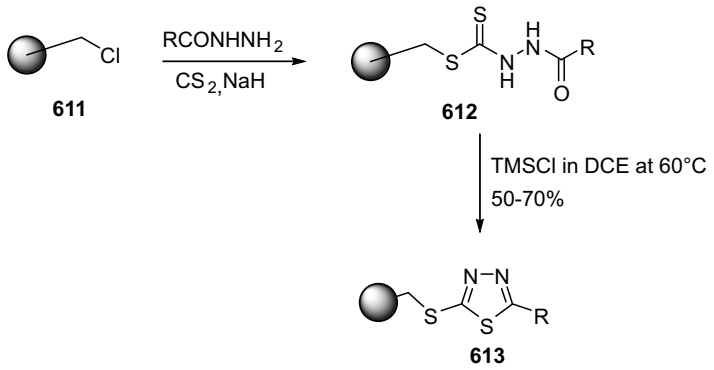
Recently, a solid-phase synthetic route using the Merrifield resin (**611**) has been utilized to prepare various substituted-1,3,4-thiadiazoles **613**, by a dehydrative cyclization of acyldithiocarbazate resins **612** with TMSCl in DCE at 60 °C [306]. Acyldithiocarbazate resins **612** have been prepared by reaction of the Merrifield resin **611** with carbon disulfide, various hydrazides, and NaH (Scheme 14.168).

14.4.3.2 Synthesis of Exocyclic-Conjugated Mesoionic 1,3,4-Thiadiazoles (513) and of 1,3,4-Thiadiazolium Cations (514)

The simplest way to prepare 2-oxo or 2-thio mesoionic 1,3,4-thiadiazoles **513** is the thermal cyclization of 1-thioacyl hydrazine with phosgene or thiophosgene. Thus,



Scheme 14.167

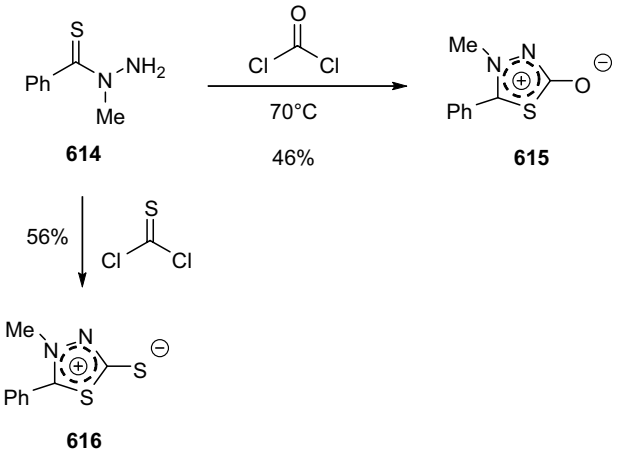


Scheme 14.168

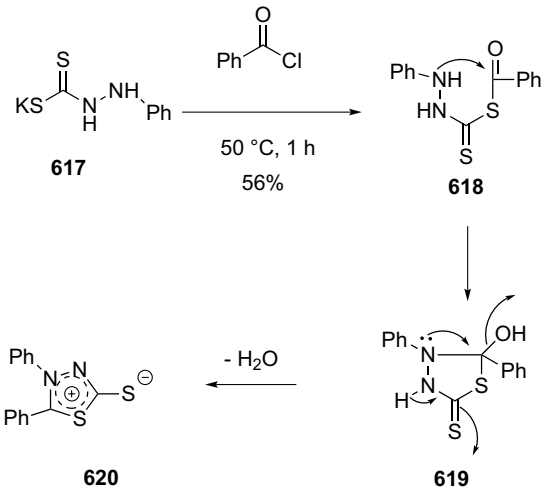
mesoionic 1,3,4-thiadiazolium-2-olate **615** and 1,3,4-thiadiazolium-2-thiolate **616** have been synthesized from thiocarboxylic acid hydrazide hydrochloride **614** with phosgene or thiophosgene (Scheme 14.169) [307].

Potassium 2-phenylhydrazinecarbodithioate (**617**), warmed at 50 °C in benzene for 1 h with benzoyl chloride, has afforded a 56% yield of 4,5-diphenyl-1,3,4-thiadiazolium-2-thiolate **620**, most probably involving as intermediates the species **618** and **619** (Scheme 14.170) [308].

Mesoionic 2-methylene-1,3,4-thiadiazole **623** has been synthesized from thiocarboxylic acid hydrazide (**614**) and 3,3-dichloroacrylonitrile **622**, while the reaction of **614** with carbon disulfide leads to 4,5-disubstituted-1,3,4-thiadiazolium 2-thiolate **624** [309]. Starting from **625**, it is possible to obtain in good yield the corresponding mesoionic compounds **624** (Scheme 14.171).



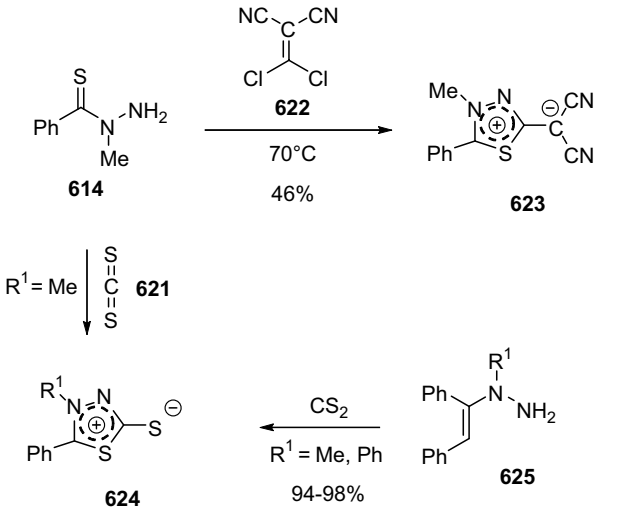
Scheme 14.169



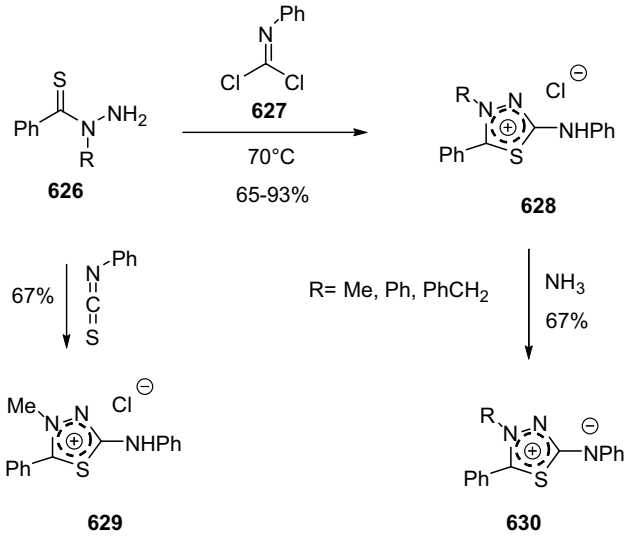
Scheme 14.170

A similar reaction performed with thiohydrazides **626** and isonitrile dichloride (**627**) or isothiocyanate leads to 2-amino-1,3,4-thiadiazolium salts **628** and **629**, respectively [310]; treatment of **628** with a chloroform solution of anhydrous ammonia yielded the mesoionic compounds **630** (Scheme 14.172) [311].

2-Substituted 5,7-diphenyl-1,3,4-thiadiazolo[3,2-*a*]pyridilyum derivatives **633** and **634** have been prepared by reaction of 1-amino-4,6-diphenylpyridine-2-thione (**631**) with phenyl isothiocyanate, in 65% and 78% yield, respectively. This transformation presumably involves the corresponding thioureas **632** as highly reactive intermediates, which easily undergo cyclodehydrosulfuration. Iminophosphorane **635**,



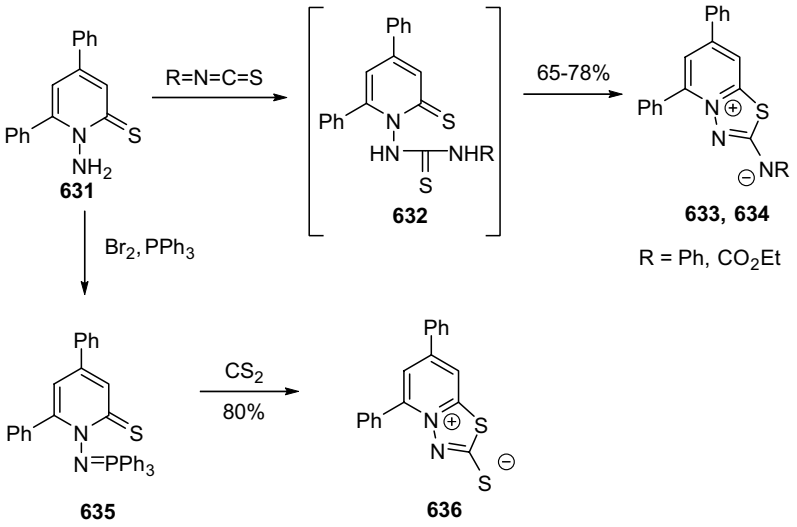
Scheme 14.171



Scheme 14.172

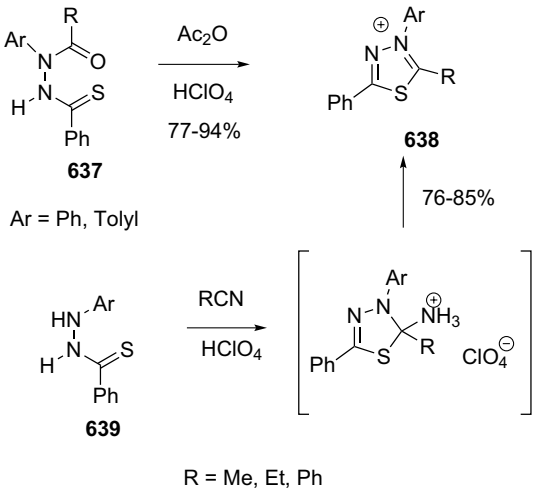
obtained by reaction of **631** with Br_2 and triphenylphosphine, alternatively produces, by reaction with carbon disulfide, 5,7-diphenyl-1,3,4-thiadiazolo[3,2-*a*]pyridinium-2-thiolate (**636**) in 80% yield (Scheme 14.173) [312].

Some 1,3,4-thiadiazolium perchlorates **638** have been prepared by reaction of *N*′-acyl-*N*′arylbenzenecarbothiohydrazide **637** with acetic anhydride–perchloric



Scheme 14.173

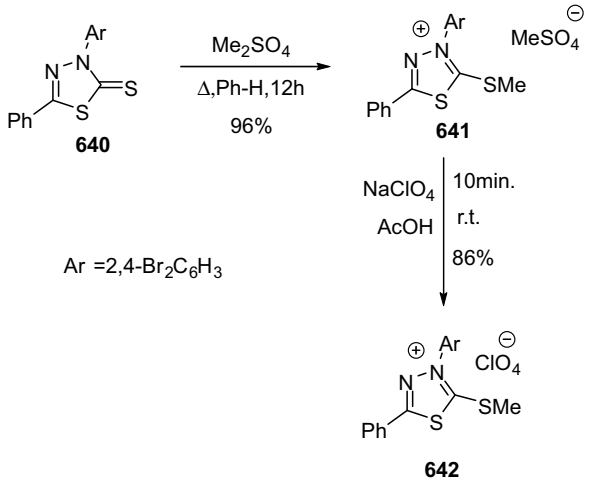
acid [313]. Moreover, these compounds have also been synthesized starting from benzenecarbothiohydrazide **639**, by reaction with a nitrile–perchloric acid mixture (Scheme 14.174) [314].



Scheme 14.174

3-(2,4-Dibromophenyl)-2-methylthio-5-phenyl-1,3,4-thiadiazolium methosulfate (**641**) can be prepared by reaction of 3-(2,4-dibromophenyl)-5-phenyl-1,3,4-thiadiazole-2-thione (**640**) with dimethyl sulfate in dry benzene at reflux for 12 h. The

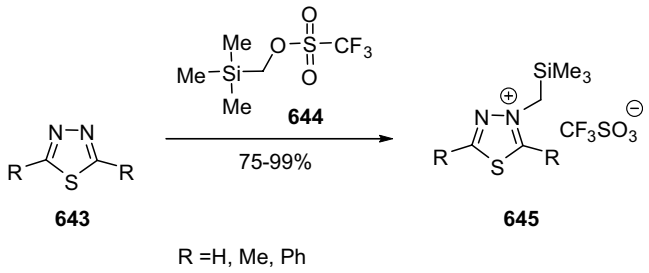
corresponding perchlorate **642** is synthesized by treatment of the methosulfate salt with a solution of sodium perchlorate in acetic acid (Scheme 14.175) [315].



Scheme 14.175

1,3,4-Thiadiazolium cations **514** are easily obtained by treatment of 1,3,4-thiadiazoles with several alkylating agents to give, in about 100% yield, the corresponding salts.

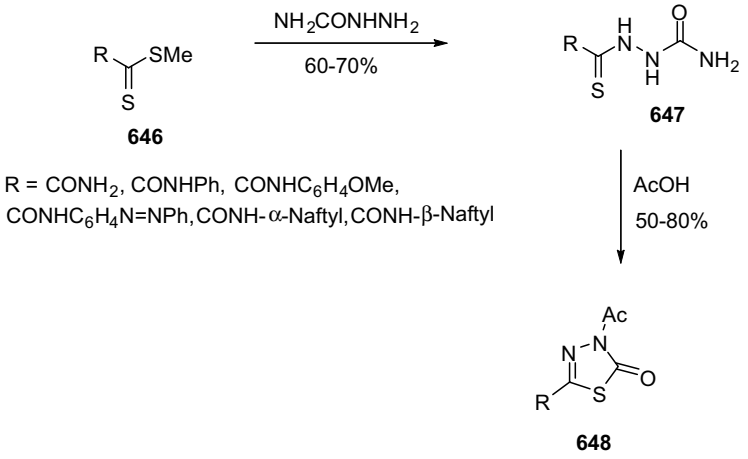
A recent example is the synthesis of 3-trimethylsilylmethyl-1,3,4-thiadiazolium trifluoromethanesulfonates **645**. These compounds have been prepared in 75–99% yields by mixing a solution of 1,3,4-thiadiazoles **643** with trimethylsilylmethyl trifluoromethanesulfonate (**644**) in dry CH_2Cl_2 at 50 °C under reflux for 24 h (Scheme 14.176) [270].



Scheme 14.176

14.4.3.3 Synthesis of Thiadiazolinones, Thiadiazolinethiones, and Thiadiazolimines (515)

1,3,4-Thiadiazolin-2-ones can be prepared in good yields by acidic thermal cyclization of substituted thioylhydrazinecarboxamides **647**. Thus, the reaction of substituted dithioate **646** with semicarbazide gave **647**, which on cyclization furnished the substituted 3-acetyl-1,3,4-thiadiazol-2-ones **648** (Scheme 14.177) [316].

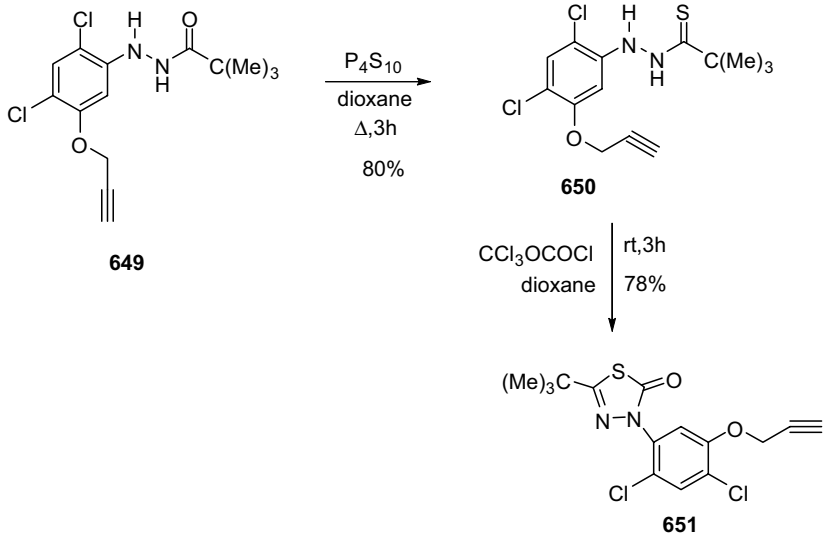


Scheme 14.177

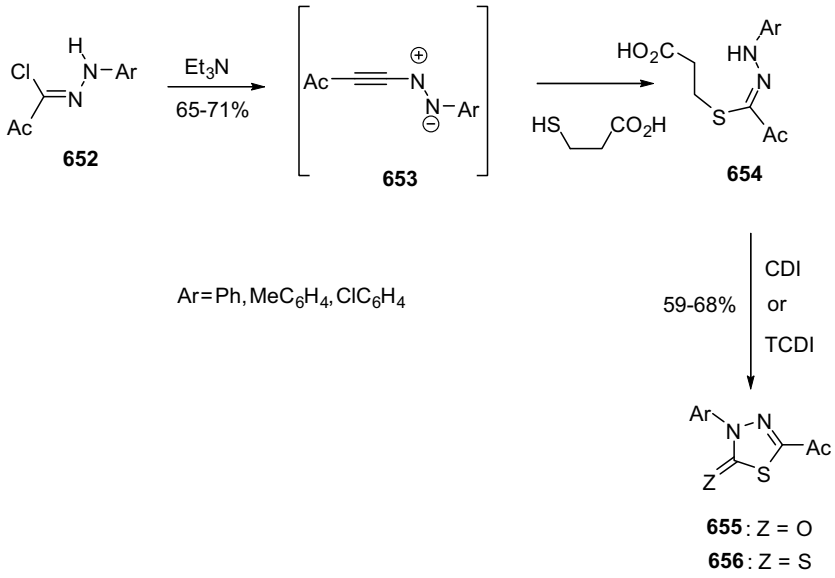
5-*tert*-Butyl-3-[2,4-dichloro-5-(2-propynyloxy)phenyl]-1,3,4-thiadiazol-2(3*H*)-one (**651**), an arylthiadiazolone herbicide structurally related to oxadiargyl and oxadiazon, has been prepared in high yield in a two-step synthesis starting from *N*-2,4-dichloro-5-(2-propynyloxy)phenyl]-*N*′-pivaloylhydrazine (**649**). Thus, **649** was transformed into the corresponding *N*-thiopivaloylhydrazine **650** by reaction with tetraphosphorus decasulfide and then converted into **651** by reaction with trichloromethyl chloroformate in dioxane at room temperature for 3 h (Scheme 14.178) [317].

1,3,4-Thiadiazol-2-(3*H*)-ones **655** and -2(3*H*)-thiones **656** can be prepared in good yield by 1,1′-carbonyldiimidazole or 1,1′-thiocarbonyldiimidazole induced cyclization of 3-mercaptopropanoic acid derivatives **654**. The reaction starts from 2-oxo-*N*-arylpropanehydrazonoyl chloride **652**, which in the presence of triethylamine is converted into the corresponding nitrile imines **653**, which *in situ* undergo a nucleophilic attack of 3-mercaptopropionic acid leading to 3-[[2-oxo-1-(arylhydrazono)propan-1yl]mercapto]propanoic acids **654** (65–71% yield). These propanoic acids were then treated with 1,1′-carbonyldiimidazole (CDI) or 1,1′-thiocarbonyldiimidazole (TCDI) to afford the corresponding 1,3,4-thiadiazole derivatives **655** and **656** (Scheme 14.179) [318].

The cyclization reaction is explained as reported in Scheme 14.180, in which CO_2, ethylene, and imidazole are simultaneously formed.

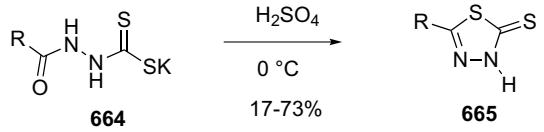


Scheme 14.178



Scheme 14.179

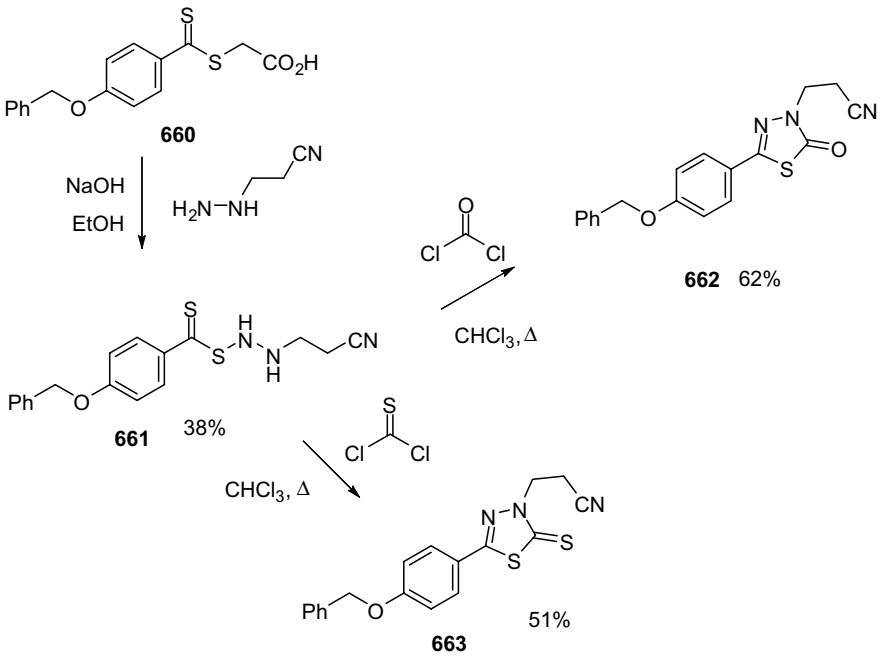
5-[4-(Benzyloxy)phenyl]-3-(2-cyanoethyl)-1,3,4-thiadiazol-2(3*H*)-one (**662**) and 5-[(4-benzyloxy)phenyl]-3-(2-cyanoethyl)-1,3,4-thiadiazole-2(3*H*)-thione (**663**), used as monoamine oxidase inhibitors of type B (8 and 16 μM), have been synthesized starting from ({[4-(Benzyloxy)phenyl](thiocarbonyl)}thio)acetic acid (**660**). In



R = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, n-C_7H_{15}, 2-furyl, 3-pyridyl

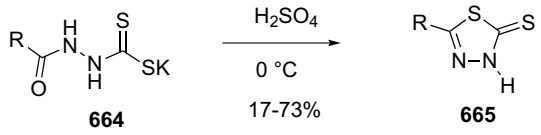
Scheme 14.180

particular, compound **660** was treated with NaOH and (2-cyanoethy1)hydrazine in EtOH at 0 °C to give 1-{[4-(Benzyloxy)phenyl](thiocarbonyl)}-2-(2-cyanoethyl)hydrazine (**661**), which by subsequent reaction with phosgene or thiophosgene gave the resulting 1,3,4-thiadiazole derivatives **662** and **663** in 62% and in 51% yield, respectively (Scheme 14.181) [319].



Scheme 14.181

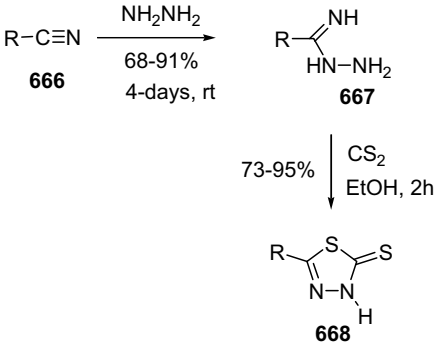
5-Substituted-1,3,4-thiadiazole-2-thiones **665** are obtained in moderate–good yields from potassium 2-acyl- or 2-aroylhydrazinecarbodithioate **664** and cold concentrated sulfuric acid (Scheme 14.182) [320].



R = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, n-C_7H_{15}, 2-furyl, 3-pyridyl

Scheme 14.182

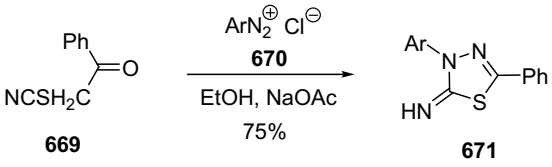
Another method for preparing 5-substituted-1,3,4-thiadiazole-2-thiones is the reaction of carbon disulfide with amidrazones. Thus, starting from aromatic and heterocyclic amidrazones **667**, obtained from the reaction of corresponding nitriles **666** with hydrazine, a series of 5-substituted-1,3,4-thiadiazole-2-thiones (**668**) were obtained in excellent yields (Scheme 14.183) [321].



R = Ph, α-naphthyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolyl, 1-isoquinolyl

Scheme 14.183

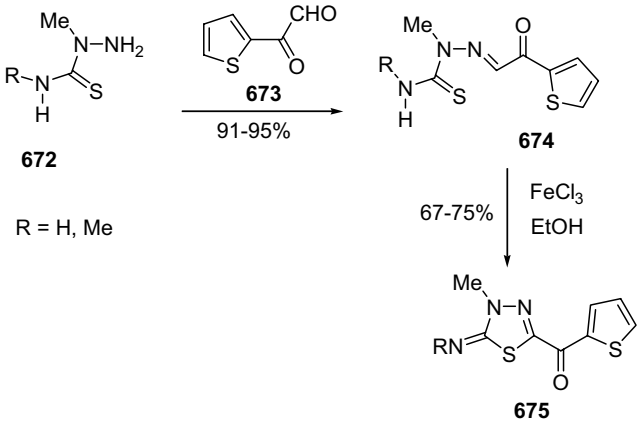
Various 5-imino-Δ^2-1,3,4-thiadiazolines have been synthesized from activated thiocyanates and benzenediazonium chloride. The reaction has been performed in NaOAc buffered solution of EtOH to yield 5-imino-4-aryl-2-phenyl-Δ^2-1,3,4-thiadiazolines (**671**) in 75% yield (Scheme 14.184) [322].



Ar = Ph, ClC_6H_4, $NO_2C_6H_4$

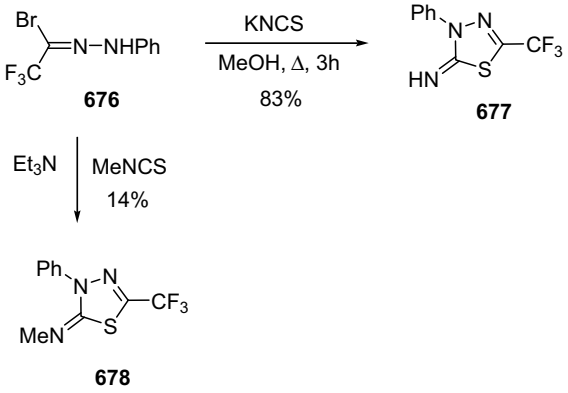
Scheme 14.184

4-Methyl-5-imino-2-thienoyl-Δ^2-1,3,4-thiadiazolines (**675**) have also been prepared by condensation of thienylglyoxal (**673**) with suitable thiosemicarbazides (**672**) followed by oxidation of the resulting **674** with $FeCl_3$ (Scheme 14.185) [288].



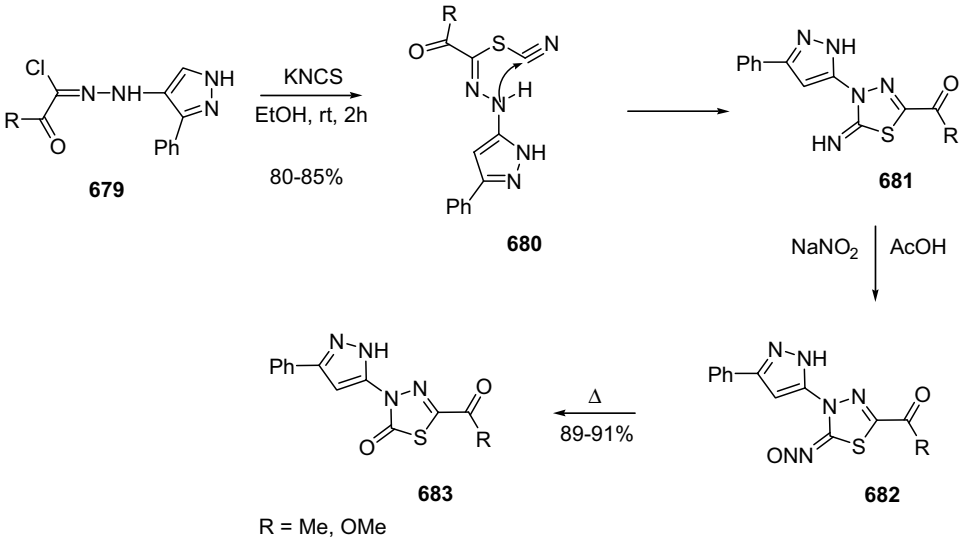
Scheme 14.185

Hydrazonoyl halides offer a versatile tool in the synthesis of azoles. Thus, 5-imino-4-phenyl-2-trifluoromethyl-Δ^2-1,3,4-thiadiazoline (**677**) has been prepared in 83% yield by the reaction of *N*-phenyltrifluoroacetohydrazonoyl bromide (**676**) with potassium isothiocyanate [323]. If the reaction is performed with methyl isothiocyanate, the analogous *N*-methylthiadiazoline **678** was obtained, but in low yield (Scheme 14.186).



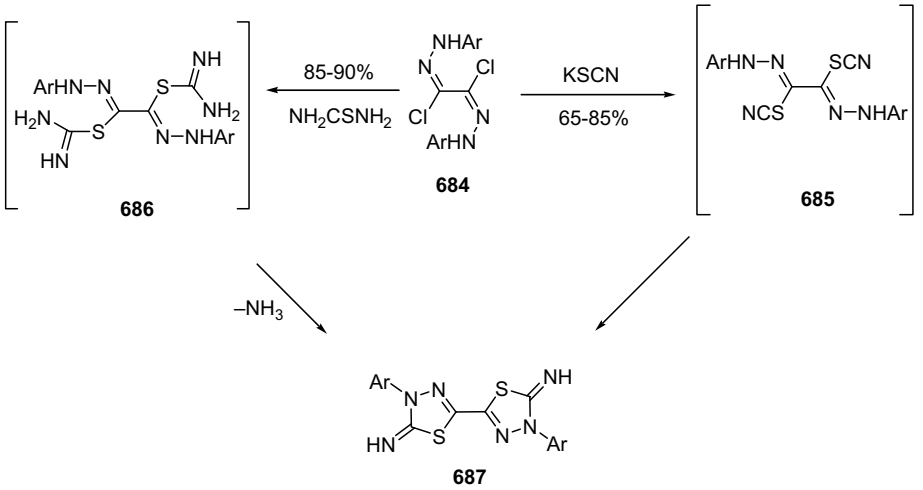
Scheme 14.186

A similar reaction has been reported for the synthesis of some 5-acyl-2,3-dihydro-2-imino-3-(3-phenyl)pyrazol-5-yl)-1,3,4-thiadiazoles **681**. Thus, phenylpyrazolylhydrazonoyl chlorides **679** undergo cyclocondensation with potassium thiocyanate to give **681** in 80–85% yield. At the same time, treatment of **681** with sodium nitrite in acetic acid, followed by heating, provided the thiadiazolones **683** in good yield (Scheme 14.187) [324].



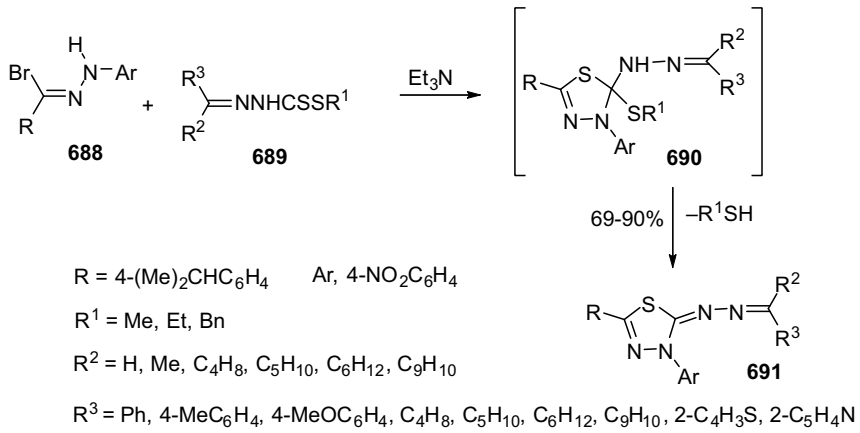
Scheme 14.187

Bi(4,5-dihydro-1,3,4-thiadiazol-5-imines) have been prepared in good yield by the reaction of *N,N'*diaroyldihydrazonoyl dihalides with potassium thiocyanate. The formation of **687** is assumed to proceed via a nucleophilic attack of the thiocyanate anion to afford intermediates **685**, followed by an intramolecular cyclization. Compounds **687** were also obtained from the reaction of dihalides **684** with thiourea, through the formation of the non-isolable intermediates **686**, which cyclized readily via loss of ammonia (Scheme 14.188) [325].



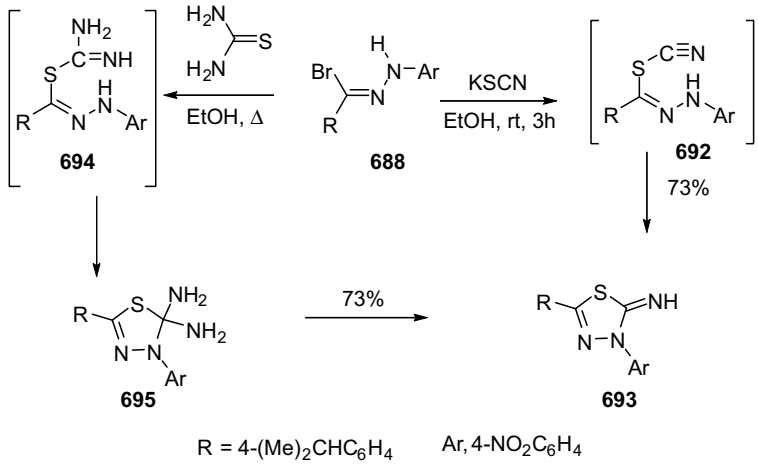
Scheme 14.188

1,3,4-Thiadiazole derivatives **691** and **693** have been synthesized via reactions of hydrazonoyl bromide **688** with alkyl carbodithioates **689**, potassium thiocyanate, or thiourea, according to Schemes 14.189 and 14.190 [326].



688 **689** **690** **691**

Scheme 14.189

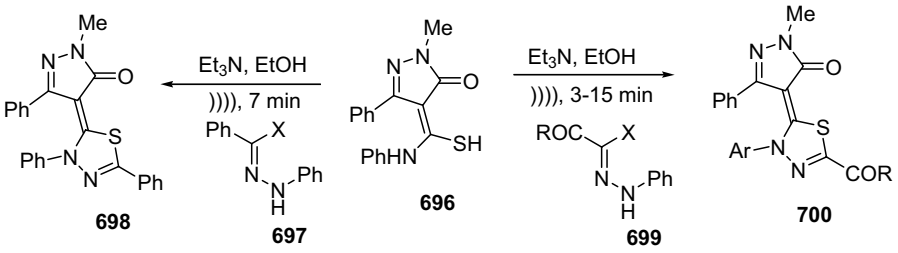


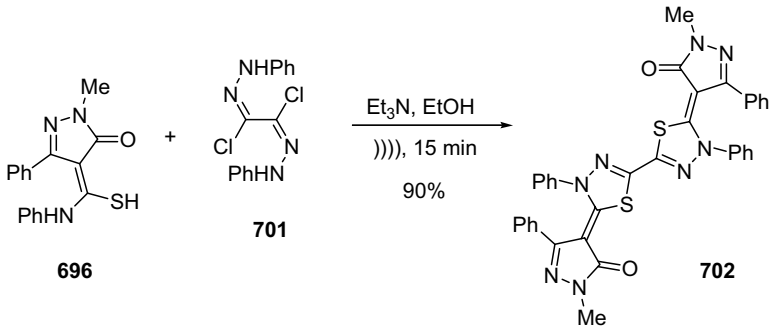
694 **688** **692** **695** **693**

Scheme 14.190

14.4.3.4 Synthesis of 2,3-Dihydro-(Δ^2) (516), 3,4-Dihydro-(Δ^3) (517), and 2,3,4,5-Tetrahydro-1,3,4-Thiadiazoles (518)

Under ultrasonic irradiation conditions a series of 2,3-dihydro-1,3,4-thiadiazole derivatives **698** and **700** and 5,5′-bi(3*H*-3-phenyl-2-(1-methyl-5-oxo-3-phenyl-1*H*,4*H*-pyrazol-4-ylidene)-1,3,4-thiadiazole **702** have been synthesized from reaction of 1-methyl-5-oxo-3-phenyl-2-pyrazolin-4-thiocarboxanilide (**696**) with different hydrazonyl halides [**697**, **699**], or *N*,*N*′-diphenyl-oxalodihydrazonoyl dichloride





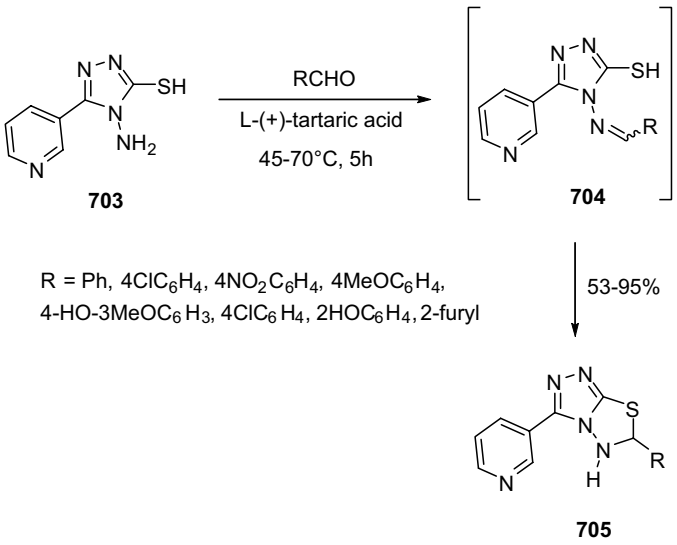
Scheme 14.191

(**701**). This technique reduces the time of reaction from several hours to minutes and increases the yields of the obtained products (Scheme 14.191) [327].

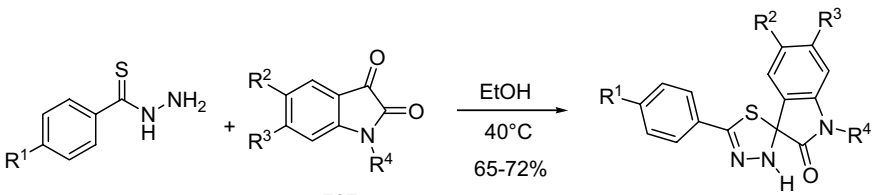
A general method for the synthesis of 1,3,4-thiadiazolines is the reaction of carbonyl compounds with substituted thiohydrazides. Thus, chiral 1,2,4-triazolo [3,4-*b*]-1,3,4-thiadiazoles **705** have been synthesized by the Mannich reaction of 3-pyridyl-4-amino-5-mercapto-1,2,4-triazole (**703**) (synthetic equivalent of a thiohydrazide), with aromatic aldehydes or furaldehyde in the presence of a catalytic amount of tartaric acid. Some of the obtained products have shown significant antibacterial activities against *Staphylococcus aureus*, and *Escherichia coli* at 500 and 100 ppm concentrations (Scheme 14.192) [328].

Another recent application of this methodology is the synthesis of 5′-phenyl-3′*H*-spiro[indoline-3,2′-[1,3,4]thiadiazol]-2-ones **708**, compounds that are able to inhibit the aggrecanase-2 with a selectivity in the sub-micromolar range. In particular, the reaction involves a condensation between arylthiohydrazides **706** and isatins **707** (Scheme 14.193) [329].

4,5-Dihydro-1,3,4-thiadiazole-2-carboxamides **712** have been synthesized by acylation of hydrazones of thiooxamic acid hydrazides **711**, which were obtained from thiooxamic acid hydrazides **709** with different aldehydes **710**. Oxidation of



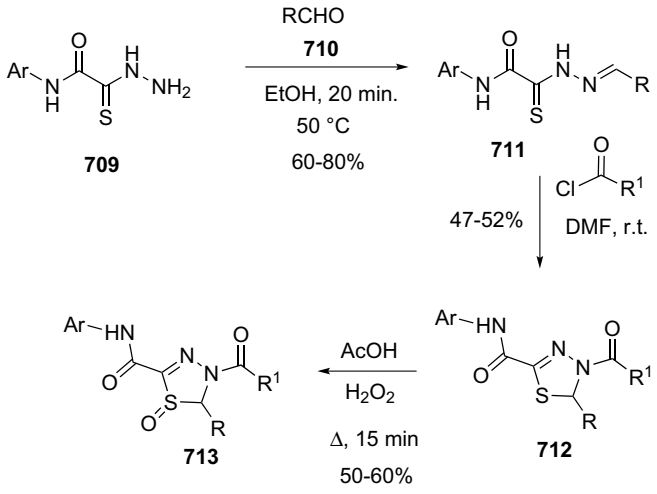
Scheme 14.192



Scheme 14.193

712 with hydrogen peroxide in acetic acid leads to 2-carbamoyl-4,5-dihydro-1,3,4-thiadiazole 1-oxides **713** in good yields (Scheme 14.194) [330].

2-Amino-5-aryl-5-hydrothiazolo[4,3-*b*]-1,3,4-thiadiazoles **715a,b** have been prepared in 78–80% yield by treating 2-aryl-3-thioureido-4-thiazolidines **714a,b** with cold concentrated sulfuric acid. These compounds were then transformed into unnatural α-amino acids **716a–d**, containing the 1,3,4-thiadiazole core, by condensation with HCHO and α-amino acids (74–80%) (Scheme 14.195). Fungitoxicity has also been evaluated *in vitro* against *Aspergillus niger* and *Fusarium oxysporium* and it was found that compounds **716c,d** (Ar = ClC_6H_4, R = H, Me) displayed activities comparable with that of the commercial fungicide Dithane M-45 [331].

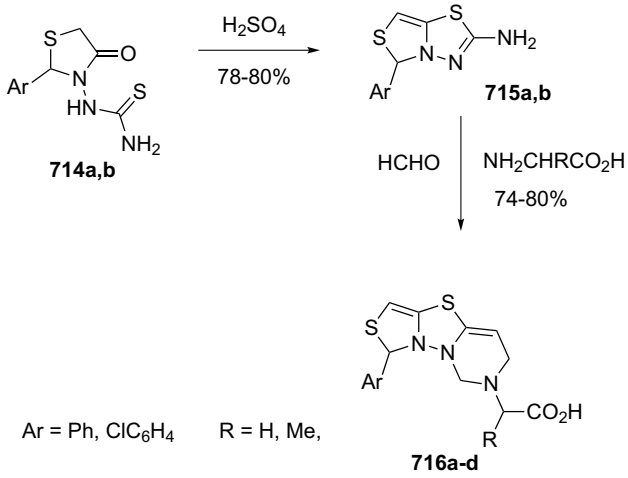


Ar = Ph, 3,4-$Cl_2C_6H_3$, 2,3-$Me_2C_6H_3$, 3-MeC_6H_4

R = 2-Thienyl, Ph; 4-$NO_2C_6H_4$, 5-methy-2-Thienyl

R^1 = Me, Et, Ph, 2-Thienyl

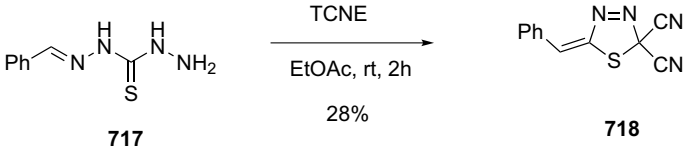
Scheme 14.194



Ar = Ph, ClC_6H_4 R = H, Me,

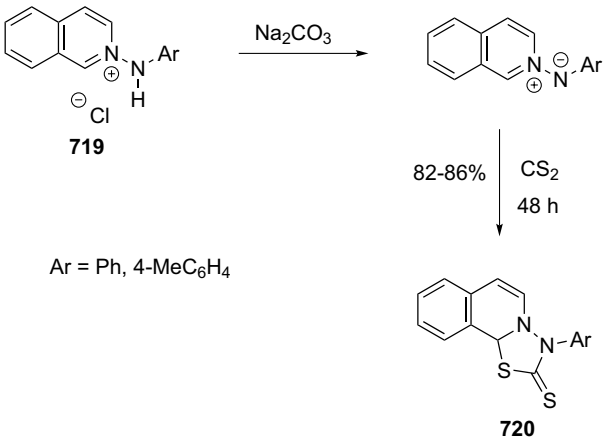
Scheme 14.195

5-Benzylidene-1,3,4-thiadiazole-2,2(5*H*)-dicarbonitrile (**718**), in 28% yield, has been synthesized through the cyclization of *N*′(phenylmethylidene)thicarbonohydrazide (**717**) promoted by tetracyanoethylene (TCNE) (Scheme 14.196) [332].



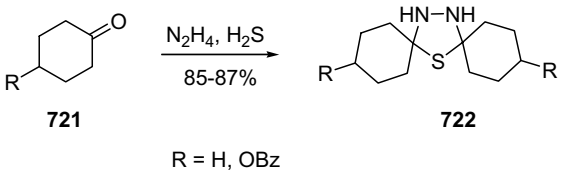
Scheme 14.196

3-Phenyl- and 3-(*p*-tolyl)-10b*H*-1,3,4-thiadiazolo[2,3-*a*]isoquinoline-2(3*H*)-thiones (**720**) have been prepared in 86% and 82% yield, respectively, by 1,3-dipolar cycloaddition of *N*-phenyl or *N*-*p*-tolylimides, obtained by sodium carbonate treatment of 2-anilino or 2-(*p*-toluidino)isoquinolinium chlorides **719**, with carbon disulfide (Scheme 14.197) [333].



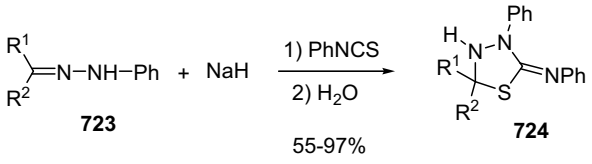
Scheme 14.197

2,3,4,5-Tetrahydro-1,3,4-thiadiazoles **722** have been prepared by treating cyclohexanones **721** with hydrazine and H_2S in ethanol at reflux for 12 h (Scheme 14.198) [334].



Scheme 14.198

Phenyl isothiocyanate in the presence of sodium hydride reacts with different phenyl hydrazones **723** to afford 1,3,4-thiadiazolidines **724** in good yields (Scheme 14.199).



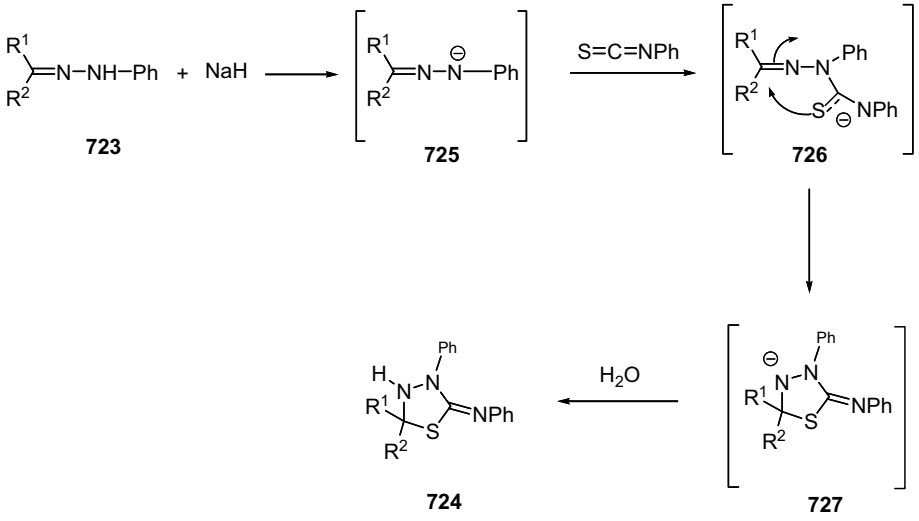
723 724

R^1 = Me, Ph $R^1 = R^2 = (CH_2)_5$

R^2 = Me, Et, Ph, H

Scheme 14.199

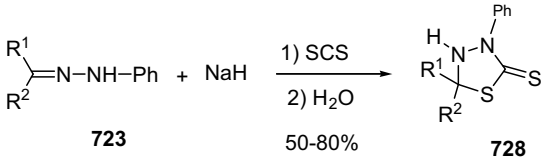
It is presumed that the anion of the hydrazones **725**, formed initially, attacks the isothiocyanate and gives an intermediate ion **726** that cyclizes to **727**, producing after water treatment the 1,3,4-thiadiazolidine **724** (Scheme 14.200).



723 725 726 727 724

Scheme 14.200

Alternatively, the reaction of **723** with carbon disulfide yields 3-phenyl-1,3,4-thiadiazolidine-2-thiones **728** (Scheme 14.201) [335].



723 728

R^1 = Me, Ph $R^1 = R^2 = (CH_2)_5$

R^2 = Me, Et, Ph

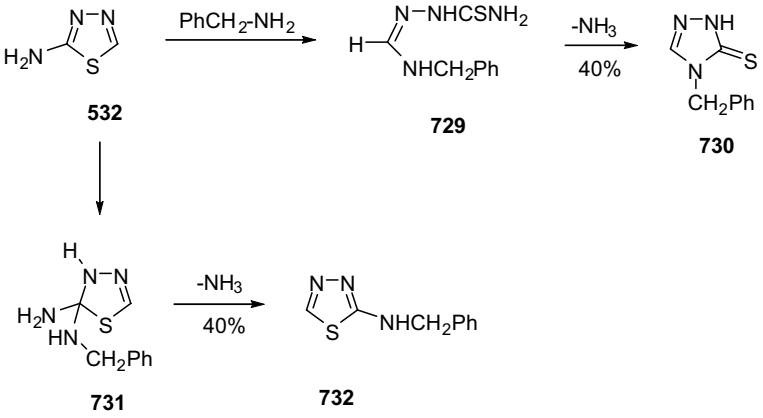
Scheme 14.201

14.4.4 Reactivity

The reactivity of the 1,2,3-thiadiazole system is expressed in a series of different chemical transformations: (i) ring cleavage reactions and rearrangements, (ii) reductive and oxidative processes, (iii) reactions due to the reactivity of heterocycle ring, and (iv) reactions of substituents.

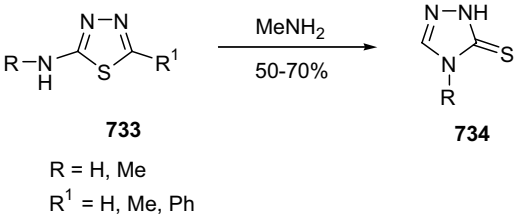
14.4.4.1 Ring Cleavage Reactions and Rearrangements

The 1,3,4-thiadiazole system is cleaved by bases. In particular, Goerdeler and Galinke have shown that 2-amino-1,3,4-thiadiazole (**532**) on heating with benzylamine gives mixtures of triazoline thione **730** and 2-benzylamino-1,3,4-thiadiazole (**732**) in a 1 : 1 ratio (80%) [336]. Formation of **730** most probably occurs via the ring-opened amidrazone intermediate **729** (Scheme 14.202).



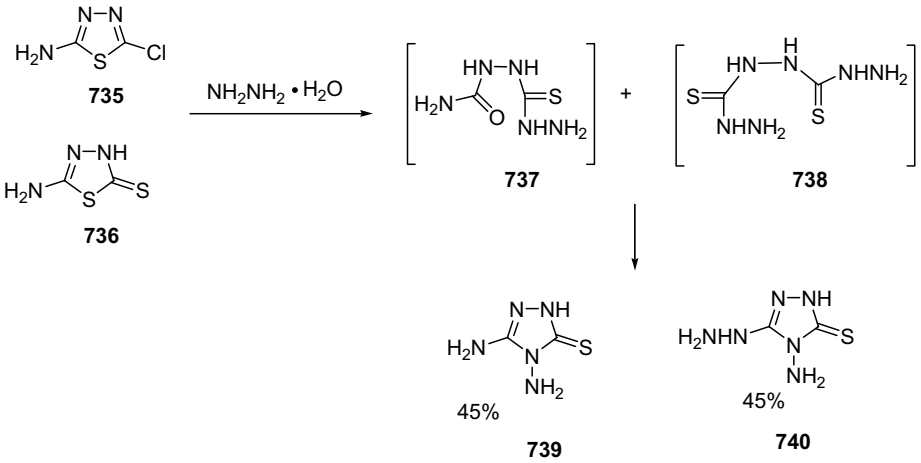
Scheme 14.202

Under the same conditions, 2-methylamino-, 2-amino-, and 2-amino-5-phenyl-1,3,4-thiadiazoles **733** react with methylamine to produce the corresponding triazoline-thiones **734** (Scheme 14.203).



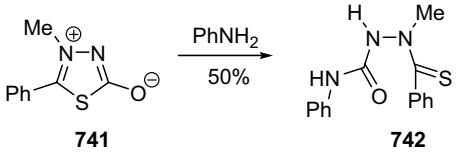
Scheme 14.203

2-Amino-5-chloro-1,3,4-thiadiazole (**735**) and 5-amino-1,3,4-thiadiazole-2(3*H*)-thione (**736**) react with a large excess of hydrazine hydrate on heating to give a mixture of 3,4-diamino-1*H*-1,2,4-triazole-5(4*H*)-thione (**739**) and 4-amino-3-hydrazinyl-1*H*-1,2,4-triazole-5(4*H*)-thione (**740**). This rearrangement probably arises from the ring-opened intermediates **737** and **738** (Scheme 14.204) [337].



Scheme 14.204

Mesoionic thiadiazoles undergo ring fission at C2 to give open chain compounds. Thus, 5-phenyl-4-methyl-1,3,4-thiadiazolium-2-olate (**741**) produces by reaction with aniline compound **742** (Scheme 14.205) [256].

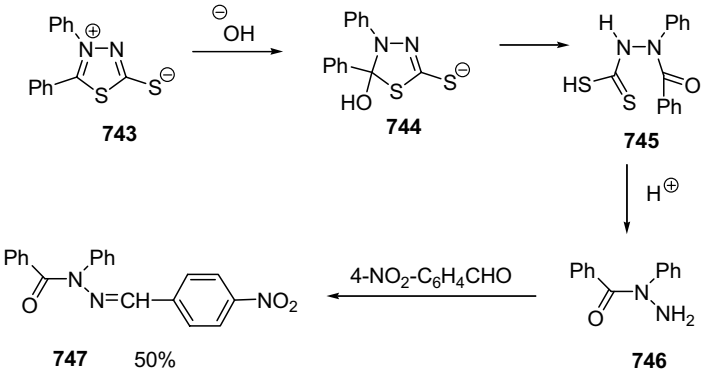


Scheme 14.205

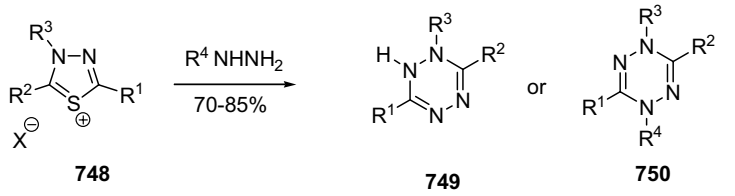
Similarly, compound **743** on treatment with alkali hydrolyzes to *N*-benzoyl-*N*-phenyldithio-carbamate **745**. This compound was gently warmed on a steam bath and transformed into **746** by extrusion of CS_2; subsequent reaction with *p*-nitrobenzaldehyde furnishes hydrazone derivate **747** in 50% yield (Scheme 14.206) [338].

Hydrazine or alkylhydrazines cleave and recyclize the 1,3,4-thiadiazolium salts **748** to 1,2- dihydro-1,2,4,5-tetrazines **749** or 1,4-dihydro-1,2,4,5-tetrazines **750**, respectively, in high yields (Scheme 14.207) [339].

The action of phenylhydrazine on **748** results in an alternative cyclization to yield 4-amino-1,2,4-triazolium salts **752**, most probably via the ring opened intermediate **751** (Scheme 14.208).



Scheme 14.206



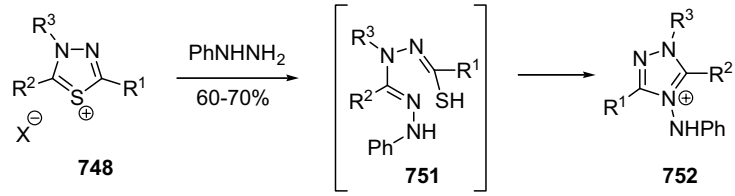
R^2 = Ph, 4-$MeOC_6H_4$, 1-naphthyl, 2-furanyl, 2-thienyl

R^3 =Me, Ph, 4-BrC_6H_4, 4-$O_2NC_6H_4$;

R^1 = Me, Ph, 4-$MeOC_6H_4$

R^4 = H, Me, Et X = ClO_4, 4-$MeC_6H_4SO_3$

Scheme 14.207



R^2 = Ph, 4-$MeOC_6H_4$, 1-naphthyl, 2-furanyl, 2-thienyl

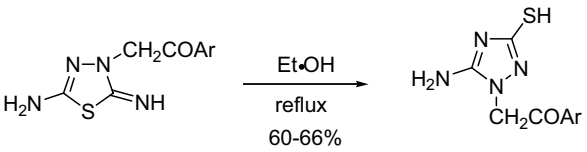
R^3 =Me, Ph, 4-BrC_6H_4, 4-$O_2NC_6H_4$;

R^1 = Me, Ph, 4-$MeOC_6H_4$

X = ClO_4, 4-$MeC_6H_4SO_3$

Scheme 14.208

Under mild, neutral conditions, 5-amino-2-imino-3-phenacyl-1,3,4-tiadiazolines **753**, in accord with to the Dimroth rearrangement, isomerize to 5-amino-3-mercapto-1-phenacyl-1,2,4-triazoles **754** in good yields (Scheme 14.209) [340].

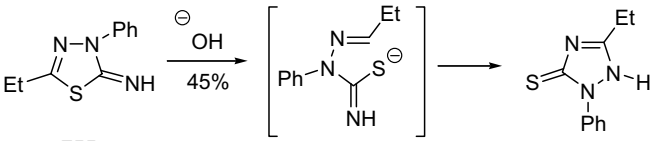


753 **754**

Ar = Ph, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-$O_2NC_6H_4$;

Scheme 14.209

A Dimroth rearrangement is also found when a solution of 5-ethyl-3-phenyl-1,3,4-thiadiazol-2(3*H*)-imine (**755**) in aqueous NaOH is heated at 80 °C for 5 h, to afford the triazole derivative **757** in 45% yield (Scheme 14.210) [341].



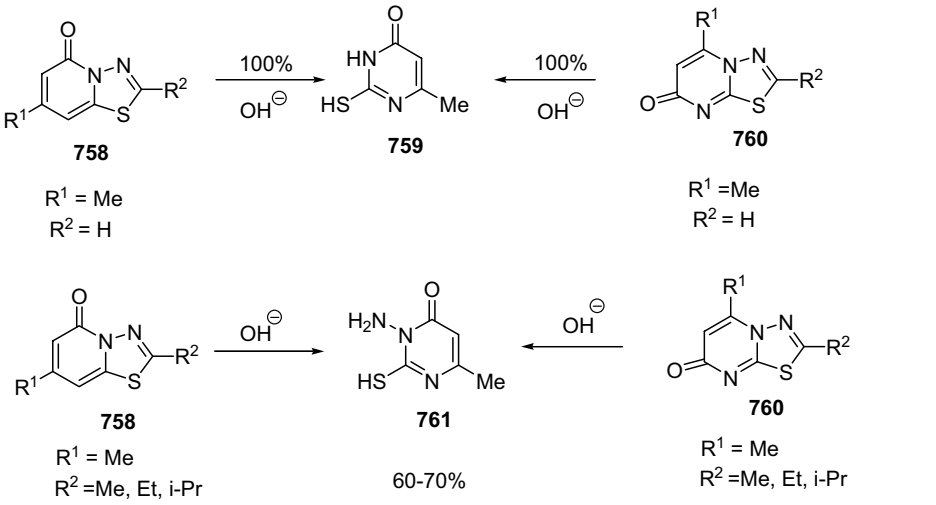
755 **756** **757**

Scheme 14.210

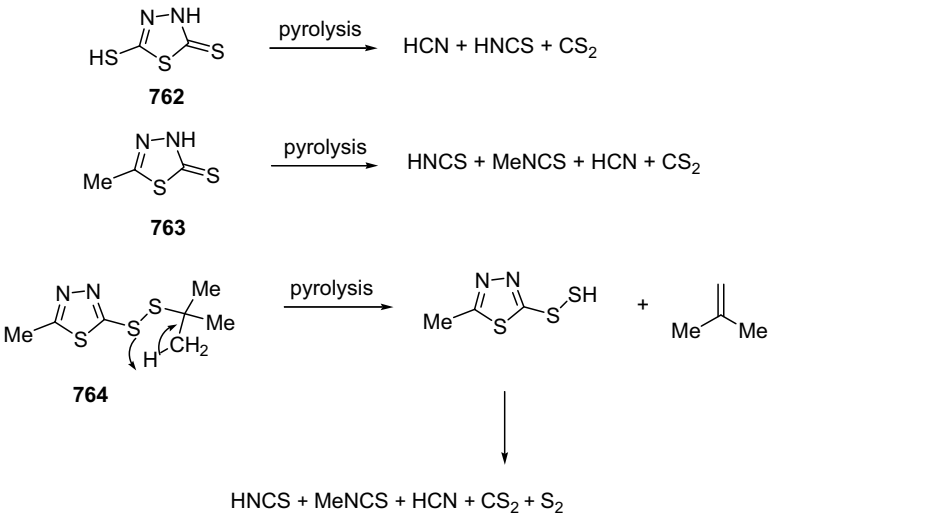
Ring cleavage has also been reported for 1,3,4-thiadiazolo[3,2-*a*]pyrimidines. The substituent R^2 influences the site of ring scission. Thus, isomers **758** and **760** react with 5% sodium hydroxide to give quantitative yields of methyl-thiouracil **759** by N–N bond cleavage. When R^2 is an alkyl group (Me, Et, i-Pr), however, the S–C is broken, giving rise to **761** (Scheme 14.211) [342].

1,3,4-Thiadiazoles, according to the substitution pattern, undergo thermal or photochemical fragmentation processes similar to that observed in a mass spectrometer. Thus, it was found that pyrolysis of 5-sulfanyl-1,3,4-thiadiazole-2 (3H)-thione (**762**) gave HNCS, CS_2, and HCN, while the 5-methyl-1,3,4-thiadiazole-2(3H)-thione (**763**) yielded HCNS, MeNCS, HCN, and CS_2 [343]. Analogous pyrolysis of 2-(*tert*-butyldisulfanyl)-5-methyl-2,3-dihydro-1,3,4-thiadiazole (**764**) produces, besides the expected fragmentation products, 2-methylpropene by an initial β-hydrogen elimination Scheme 14.212) [344].

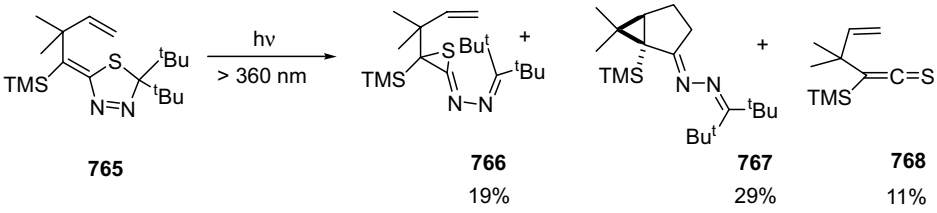
2-Alkylidene-1,3,4-thiadiazolines **765** irradiated in benzene solution at a wavelength greater than 360 nm produces a mixture of **766–768** in 19%, 29%, and 11% yield, respectively. The formation of these compounds can be explained by several different reactions, all of which are amenable to an initial cleavage of the 1,3,4-thiadiazole ring (Scheme 14.213) [345].



Scheme 14.211

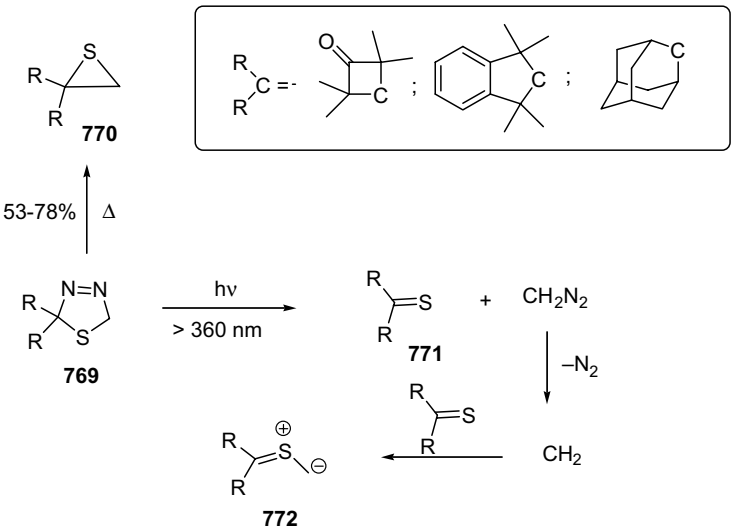


Scheme 14.212



Scheme 14.213

Thermolysis of 1,3,4-thiadiazolines **769** yields the corresponding thiiranes **770**. In contrast, matrix photolysis in an organic glass at 77 K or in solid Ar at 10 K allows the detection of the thiocarbonyl ylides **772**, which were characterized by intense UV maxima at $\lambda = 350$ nm. The thiocarbonyl ylides are formed in a stepwise manner, and not directly from the thiadiazolines, by elimination of N_2. In the first step, compounds **769** are cleaved into the thioketones **771** and diazomethane. This latter compound generates methylene as carbene that, reacting with thioketones **771**, produces the corresponding thiocarbonyl ylides **772** (Scheme 14.214) [346].

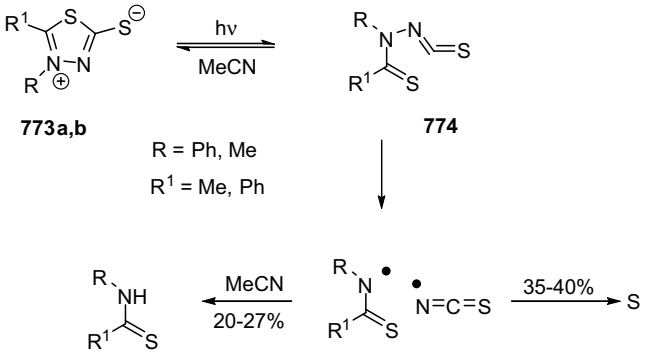


Scheme 14.214

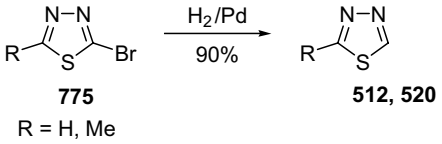
4,5-Diphenyl-1,3,4-thiadiazolium 2-thiolate (**773a**) is cleaved on irradiation at 253.7 nm, in acetonitrile as solvent, to give *N*-phenylthiobenzamide in 27% yield and sulfur 35%. Similarly, irradiation of 1,3,4-thiadiazolium 2-thiolates **773b** gives *N*-phenylthiacetoamide and *N*-methylthiobenzamide in 20% and 21%, respectively, together with elemental sulfur (35–40%). This fragmentation has been rationalized through an initial valence tautomerization to *N*-isothiocyanatothioamide **774**, which undergoes homolytic fission of N–N bond to yield the radical precursor of the thioamide and isothiocyanate radicals. The latter radical loses elemental sulfur, while the former abstracts a hydrogen from the solvent and produces the corresponding thioamide (Scheme 14.215) [347].

14.4.4.2 **Reductive and Oxidative Processes**

1,3,4-Thiadiazoles are stable to reducing and oxidizing agents. However, some reductions have been reported. In particular, reduction with hydrogen/palladium of 2-bromo- and 2-bromo-5-methyl-1,3,4-thiadiazoles **775** produced, in about 90% yield, the corresponding debrominated 1,3,4-thiadiazoles **512** and **520**, respectively (Scheme 14.216) [278].

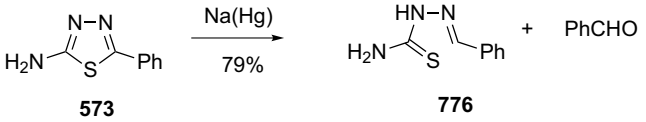


Scheme 14.215



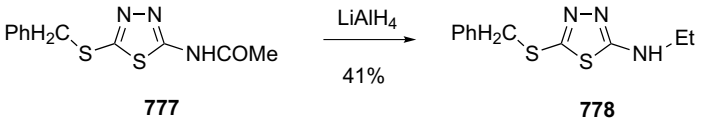
Scheme 14.216

2-Amino-5-phenyl-1,3,4-thiadiazole **573** has been reduced with sodium amalgam to benzaldehyde and thiosemicarbazone **776** (Scheme 14.217) [256].



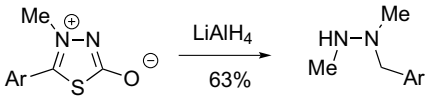
Scheme 14.217

2-Acetylamino-5-benzylmercapto-1,3,4-thiadiazole (**777**) is reduced to 2-ethylamino-5-benzylmercapto-1,3,4-thiadiazole **778** in 41% yield by reaction with lithium aluminum hydride (Scheme 14.218) [348].



Scheme 14.218

Lithium aluminum hydride also reduces the mesoionic compound **779** to hydrazine derivative **780** with loss of sulfur (Scheme 14.219) [256].

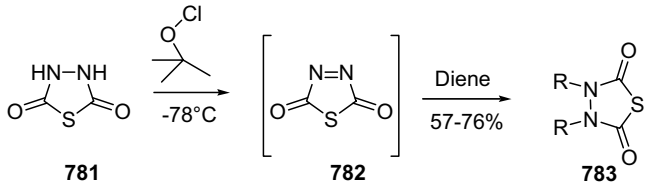


779 **780**

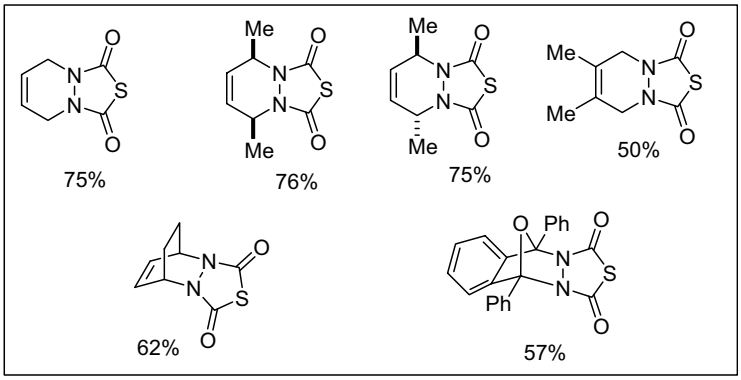
Ar = Ph, Tolyl

Scheme 14.219

Oxidation of 1,3,4-thiazolidine-2,5-dione **781** with *tert*-butyl hypochlorite gives at −78 °C thiadiazolinedione (**782**), which *in situ* undergoes Diels–Alder reactions with several dienes to provide the corresponding cycloadducts **783** in good to excellent yield (Scheme 14.220) [349].



783:

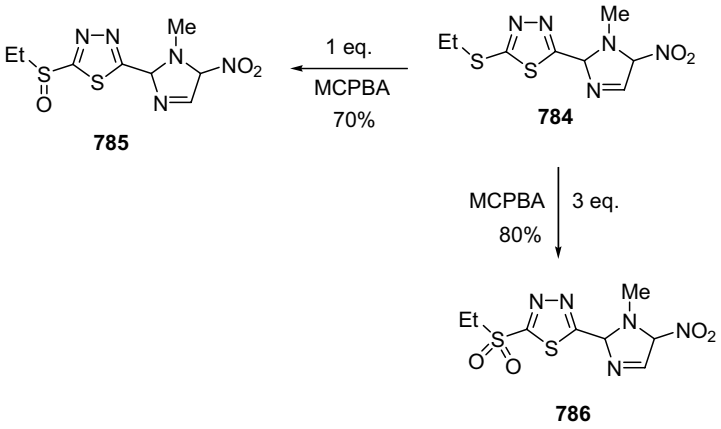


Scheme 14.220

Sulfoxide **785** and sulfone **786** derivatives have been obtained by oxidation of 2-(ethylsulfanyl)-1,3,4-thiadiazole- **784** with *m*-chloroperbenzoic acid (MCPBA) (Scheme 14.221) [350].

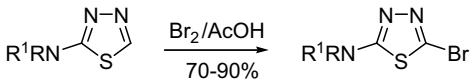
14.4.4.3 Reactions due to the Reactivity of the Heterocyclic Ring

Electrophilic substitution on the C-atoms of the ring is very difficult owing to two main problems: (i) the presence of two nitrogen atoms in the ring, which leaves these carbons with a very low electron density, and (ii) the protonation of nuclear nitrogen in acidic media, which reduces strongly the possibility of this type of reactions. Thus, reactions such as nitration, sulfonation, acetylation, halogenation, and so on normally do not take place.



Scheme 14.221

However, it has been reported that the presence of amino groups linked to position-2 allow the bromination reaction; thus, and 2-amino-substituted-5-bromo-1,3,4-thiadiazoles **788** have been prepared in good yield, starting from 2-amino-1,3,4-thiadiazoles **787** (Scheme 14.222) [351].



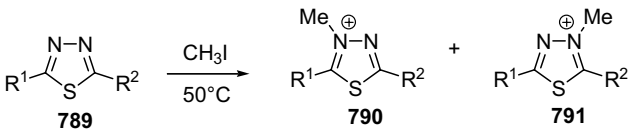
787 **788**

R = H, Me

R^1 = H, Me, NO, COMe, COPh

Scheme 14.222

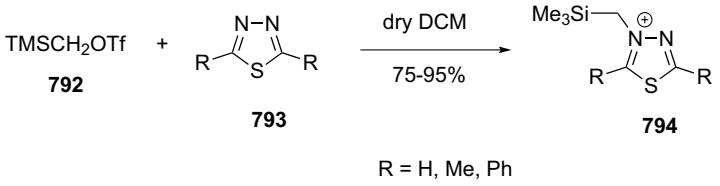
The alkylation reaction occurs easily on the annular nitrogen atoms; thus, quaternary salts are formed. In the case of mono- or dialkyl-1-3,4-thiadiazoles **789**, the alkylation is regioselective and the product distribution **790** versus **791** depends on the bulky group present at C2. When this carbon is substituted with a *tert*-butyl group, quaternization occurs almost exclusively at N4 (Scheme 14.223) [352].



R^1 = H, Me, Et, i-Pr, t-Bu R^2 = Me, Et, i-Pr

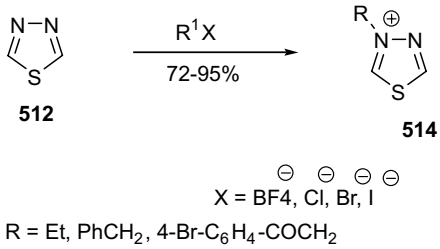
Scheme 14.223

Trimethylsilylmethyl trifluoromethanesulfonate **792** is an efficient alkylating agent for 2,5-disubstituted-1,3,4-thiadiazoles. In fact, 2,5-diphenyl- and 2,5-dimethyl-1,3,4-thiadiazoles **793** react in dry dichloromethane (DCM) with **792** to give in high yield the corresponding salts **794** (Scheme 14.224) [270].



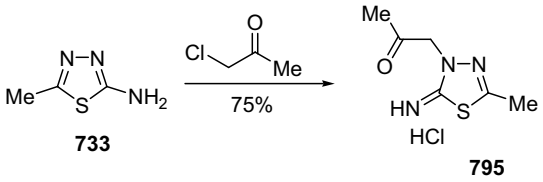
Scheme 14.224

Other alkylating agents have been used, such as triethyloxonium tetrafluoroborate, benzyl chloride, *p*-bromophenacyl bromide, octyl iodide, and so on (Scheme 14.225) [353].



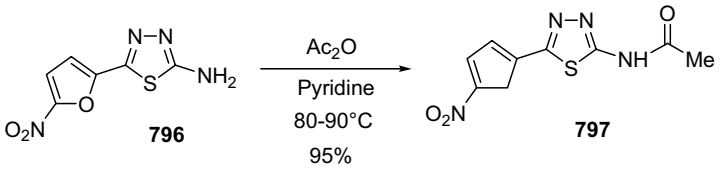
Scheme 14.225

In most cases, 2-amino-1,3,4-thiadiazoles are also alkylated at the N3 atom of the ring [354]. Thus, 2-amino-5-methyl-1,3,4-thiadiazole (**733**) reacts with chloroacetone to afford the N-alkylated thiadiazolimine **795** in 75% yield (Scheme 14.226).



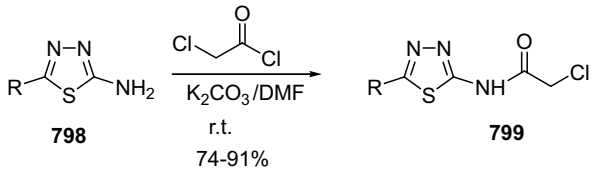
Scheme 14.226

Amino derivatives are acylated at the amino group. Thus, it has been reported that 2-amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole **796** by reaction with acetic anhydride is transformed into 2-acetylamino derivative **797** in 95% yield (Scheme 14.227) [355].



Scheme 14.227

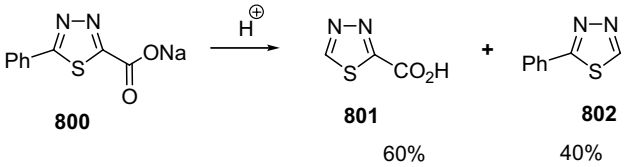
A similar reaction is observed with chloroacetyl chloride. Thus, starting from **798**, a series of 2-chloro-*N*-(5-aryloxymethylene/aryl-1,3,4-thiadiazol-2-yl)acetamides **799** have been synthesized in 81–91% yield (Scheme 14.228) [356].



R = $PhOCH_2$, 2-$ClC_6H_4OCH_2$, 2-Me-$C_6H_4OCH_2$, 4-Me-$C_6H_4OCH_2$, 4-Cl-$C_6H_4OCH_2$, 4-MeO-$C_6H_4OCH_2$, 2-MeO-$C_6H_4OCH_2$, 3-Me-$C_6H_4OCH_2$, 3-NO_2-$C_6H_4OCH_2$, 4-NO_2-$C_6H_4OCH_2$, 2,4-Cl_2-$C_6H_3OCH_2$, Ph, 2-ClC_6H_4, 3-MeC_6H_4, 3-$NO_2C_6H_4$

Scheme 14.228

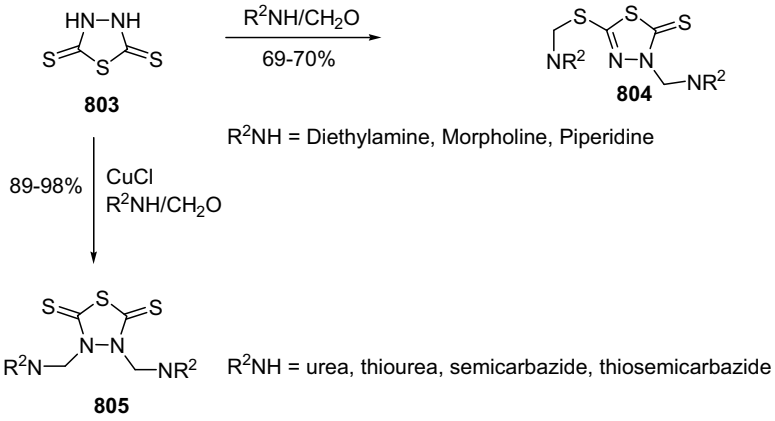
Owing to the strong electron-withdrawing effect of the thiadiazole ring, carboxylic acids with the carboxyl group attached to the ring are rather unstable. Thus, Holmberg, on acidification of the sodium salt of 5-phenyl-1,3,4-thiadiazole-2-carboxylic acid (**800**), obtained a mixture of the acid **801** (40%) and 2-phenyl-1,3,4-thiadiazole (**802**) (60%) (Scheme 14.229) [357].



Scheme 14.229

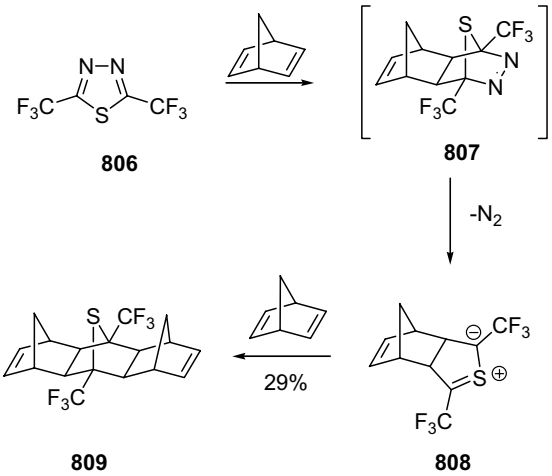
The Mannich reaction of 1,3,4-thiadiazole derivatives with different amino groups occurs at the N3 ring atom. Thus, it has been reported that 1,3,4-thiadiazolidine-2,5-dithione **803** with dialkylamines and formaldehyde give *N,S*-aminomethylated thiadiazoles **804**. With urea, thiourea, semicarbazide, or thiosemicarbazide *N,N*-aminomethylated thiadiazoles **805** have been obtained (Scheme 14.230) [258].

Cycloaddition reactions have been reported for the 1,3,4-thiadiazole moiety. In particular, 2,5-bis(trifluoromethyl)-1,3,4-thiadiazole (**806**) has been used as 4π



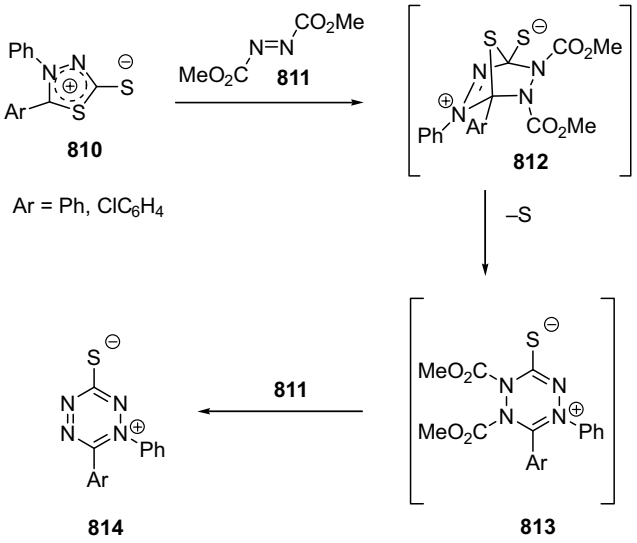
Scheme 14.230

component in a Diels–Alder reaction, giving rise with norbornadiene to bicycloadduct **809**. The formation of this compound was rationalized via the initial cycloadduct **807**, which loses molecular nitrogen to generate a thiocarbonyl ylide (**808**) that reacts with a second molecule of norbornadiene (Scheme 14.231) [358].



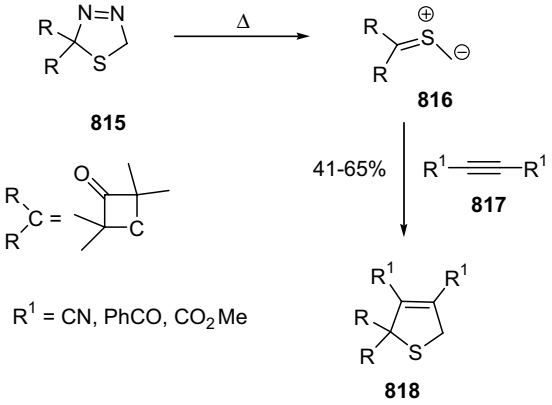
Scheme 14.231

A Diels–Alder reaction has also been reported for mesoionic 1,3,4-thiadiazoles. Thus, treatment of 4,5-diphenyl-1-thia-2-thio-3,4-diazolium thiols **810** with a twofold molar excess of dimethyl azodicarboxylate (**811**) in benzene under reflux for 12 h yields the corresponding adducts **812**, which undergo subsequent sulfur extrusion to intermediates **813**, which with a concomitant oxidation reaction produce the final products **814** in 62–65% yield (Scheme 14.232) [359].



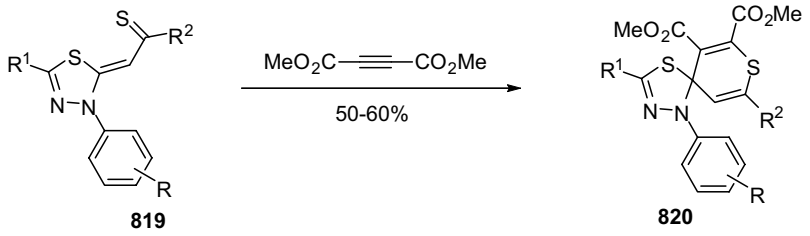
Scheme 14.232

2,5-Dihydro-1,3,4-thiadiazoles are able to produce under thermal conditions thiocarbonyl ylides that can be trapped with suitable dipolarophiles. Thus, as already reported [346], compound **815** gave **816** and then 2,5-dihydrothiophenes **818** by reaction with different acetylenic derivatives **817** (Scheme 14.233).



Scheme 14.233

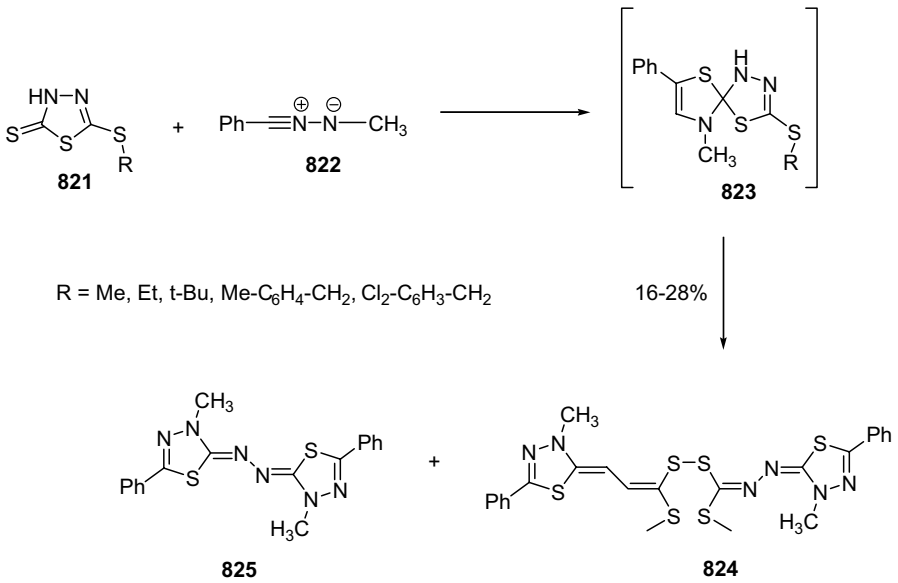
2,3-Dihydro-[(thioacyl)methylene]thiadiazoles **819** undergo cycloaddition reaction with acetylenedicarboxylate to furnish spiro cycloadducts **820** in 50–60% yield. The reaction was carried out in chlorobenzene solution under reflux. Surprisingly, the reaction rates were strongly enhanced upon UV irradiation ($\lambda > 300$ nm), which allowed the reaction to occur at room temperature in dichloromethane solution (Scheme 14.234) [360].



R^1	Ph	COMe	CO_2Et
R^2	Ph	Me	Me
R	H	H	3,5-dimethyl

Scheme 14.234

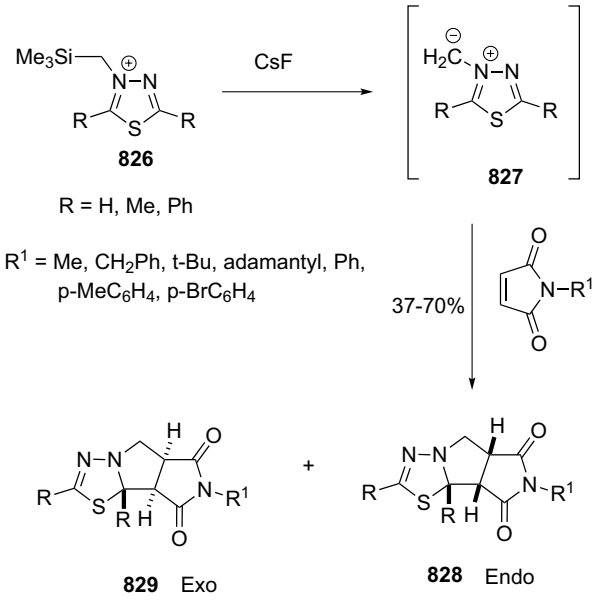
The thiocarbonyl moiety of 1,3,4-thiadiazole-2(3*H*)-thiones **821** reacts as 2π component in a 1,3-dipolar cycloaddition reaction with *N*-methyl-*C*-phenylnitrilimine (**822**) to give, via the intermediate cycloadduct **823**, the rearranged products **824** and **825** in 16–28% yields (Scheme 14.235) [361].



Scheme 14.235

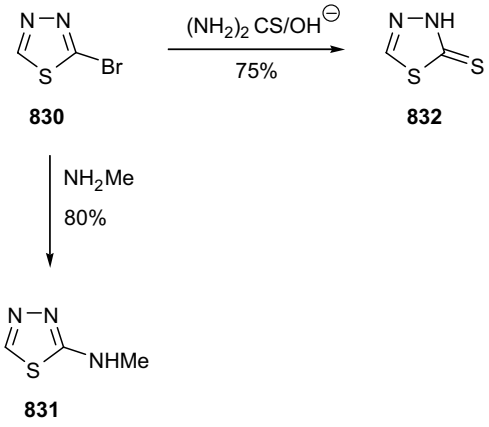
1,3,4-Thiadiazolium-3-methanide 1,3-dipoles **827**, generated *in situ* from 3-trimethylsilylmethyl-1,3,4-thiadiazolium trifluoromethanesulfonates **826** with CsF at −60 °C, afforded by reaction with substituted alkenes the substituted pyrrolo[2,1-*b*][1,3,4]-thiadiazole systems with *endo* selectivity. In particular, the reaction performed with N-substituted maleimide is the first example of bowl-shaped tricyclic

nitrogen–sulfur (**828** and **829**) analogues of the tripentagon bowl, a 3,4,10-triaza-6-thiatricyclo[6,3,0,$0^{3,7}$]undecane ring system (*endo* selectivity range 6.6–1.1) (Scheme 14.236) [270].



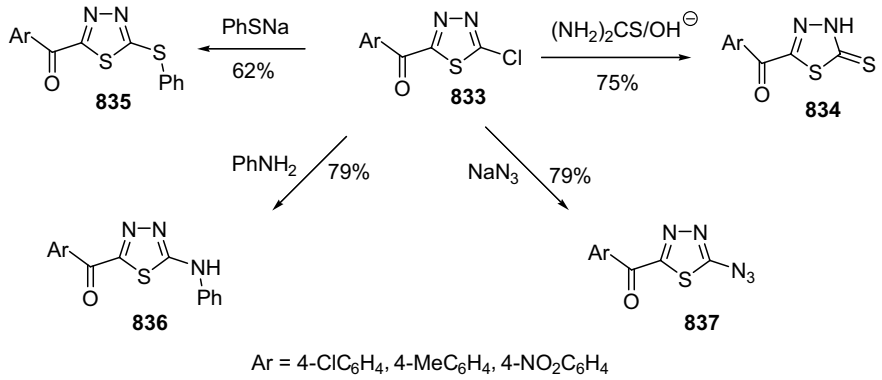
Scheme 14.236

1,3,4-Thiadiazoles containing a good leaving group at the carbon atoms of the ring can undergo nucleophilic substitutions. Thus, it has been reported that 2-bromo-1,3,4-thiadiazole (**830**), by reaction with methylamine or thiourea, affords the *N*-methylamino and 2-mercapto-1,3,4-thiadiazoles **831** and **832** in 80% and 75% yield respectively (Scheme 14.237) [278].



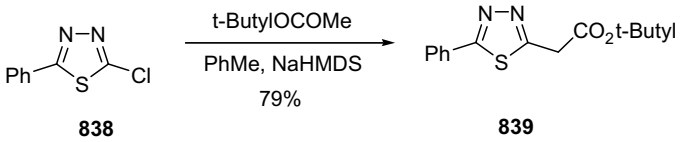
Scheme 14.237

Some other nucleophilic reactions, involving 2-chloro-5-aroyl-1,3,4-thiadiazoles **833** (Scheme 14.238) lead to the corresponding thiadiazoles **834–837** [362].



Scheme 14.238

A chlorine atom can be easily displaced in reactions involving simple esters as anion. Thus, *tert*-butyl 2-(5-phenyl-1,3,4-thiadiazol-2-yl)acetate **839** in 79% yield has been recently prepared by reaction of 2-chloro-5-phenyl-1,3,4-thiodiazole (**838**) with *tert*-butyl acetate in the presence of sodium hexamethyldisilazide (Scheme 14.239) [363].



Scheme 14.239

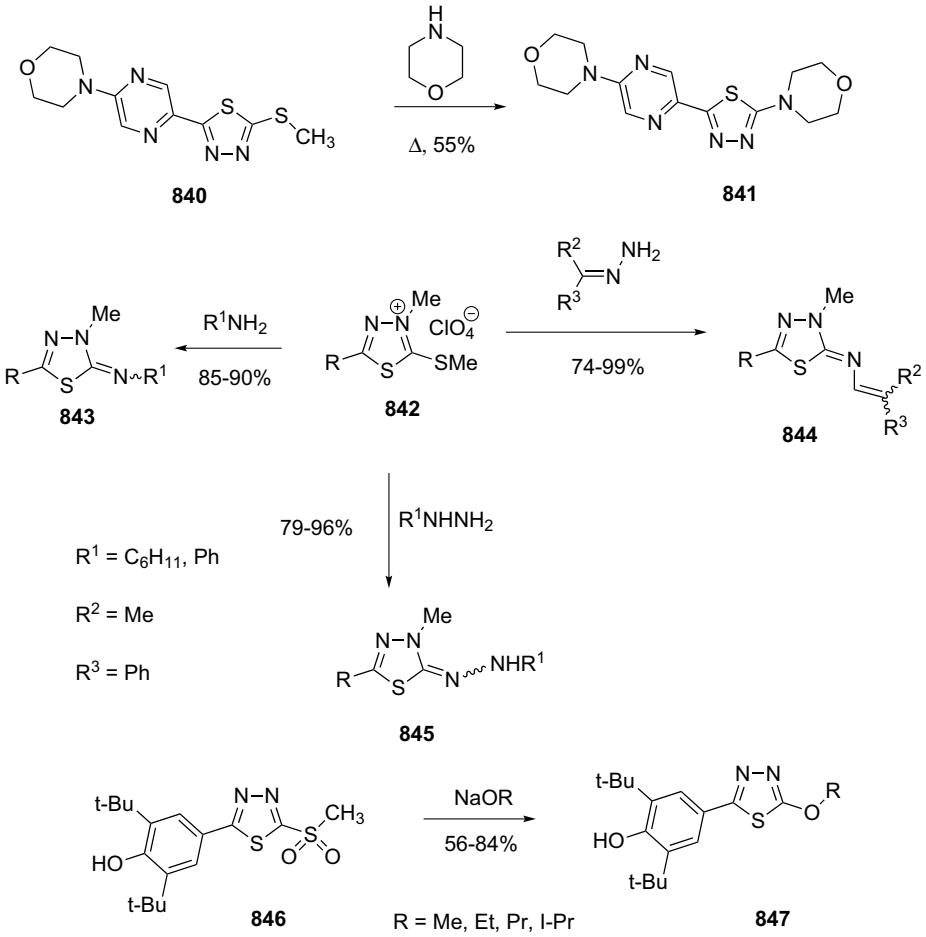
Thioalkyl or sulfonyl substituents, which are good leaving groups, can be substituted by a range of nucleophiles. Scheme 14.240 shows several examples of such reactions, leading to different 1,3,4-thiadiazoles **841**, **843–845**, and **847** [364].

A solid-phase synthetic route, from Merrifield resin, has been exploited to prepare various 2-amino-5-substituted-1,3,4-thiadiazoles (**849**) by nucleophilic displacement of the sulfonyl group (Scheme 14.241) [306].

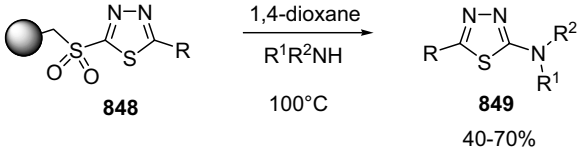
14.4.4.4 Reactions of Substituents

2-Amino-1,3,4-thiadiazoles are easily diazotated using strongly acid solutions. The intermediate diazonium salts have been used to prepare various substituted 1,3,4-thiadiazoles (Scheme 14.242) [278].

2-Halo-1,3,4-thiadiazoles can be also prepared according to Sandmeyer reactions. Thus, 2-chloro-5-phenyl-1,3,4-thiadiazole (**853**) has been synthesized in 85% yield by reaction of 2-amino-5-phenyl-1,3,4-thiadiazole (**573**) with amyl nitrite in the presence of CuCl generated *in situ* (Scheme 14.243) [363].



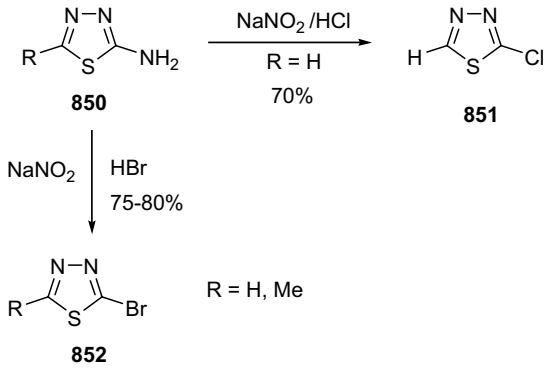
Scheme 14.240



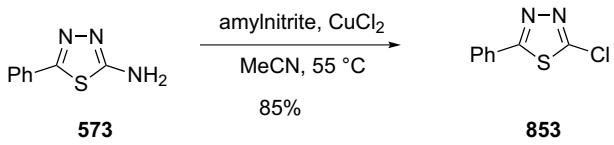
R^1R^2NH = Piperidine, Isobutylamine, Morpholine, Cyclohexylamine, Dibenzylamine

Scheme 14.241

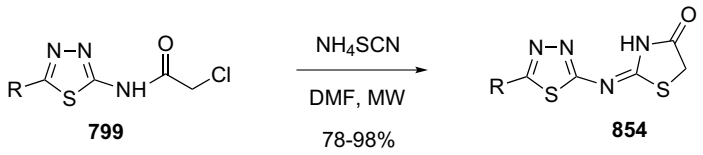
2-Chloro-*N*-(5-aryloxymethylene/aryl-1,3,4-thiadiazolo-2-yl)acetamides **799** treated with ammonium thiocyanate under microwave irradiation provide, in only 5 min, 2-(5-aryloxyme-thylene/aryl-1,3,4-thiadiazolo-2-ylimino)thiazolidin-4-ones **854** in optimal yields (Scheme 14.244) [356].



Scheme 14.242



Scheme 14.243

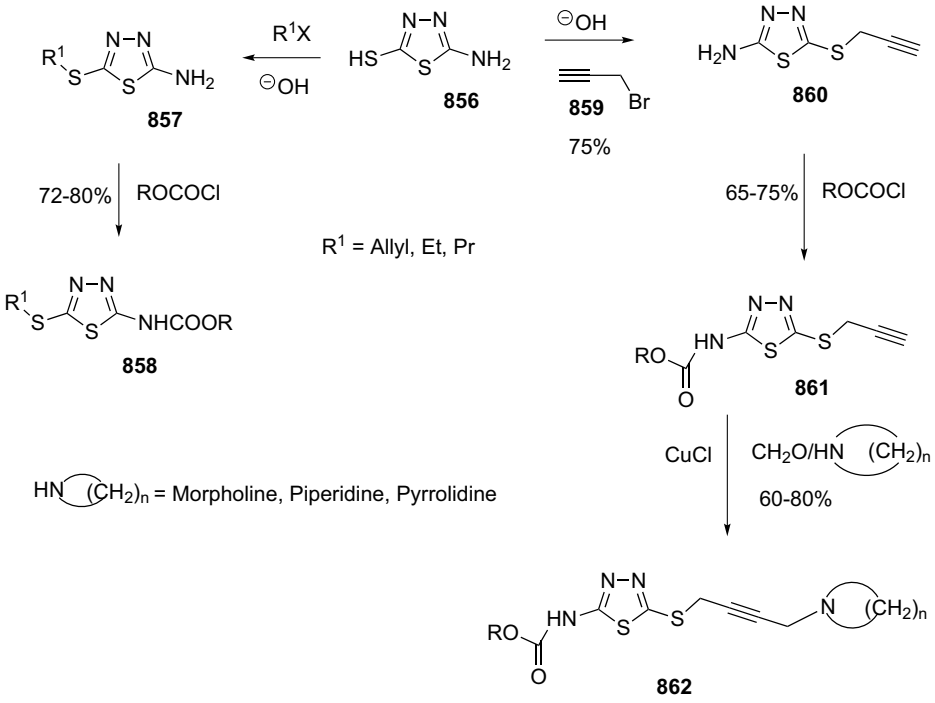


R = $PhOCH_2$, 2-$ClC_6H_4OCH_2$, 2-Me-$C_6H_4OCH_2$, 4-Me-$C_6H_4OCH_2$, 4-Cl-$C_6H_4OCH_2$, 4-MeO-$C_6H_4OCH_2$, 2-MeO-$C_6H_4OCH_2$, 3-Me-$C_6H_4OCH_2$, 3-NO_2-$C_6H_4OCH_2$, 4-NO_2-$C_6H_4OCH_2$, 2,4-Cl_2-$C_6H_3OCH_2$, Ph, 2-ClC_6H_4, 3-MeC_6H_4, 3-$NO_2C_6H_4$

Scheme 14.244

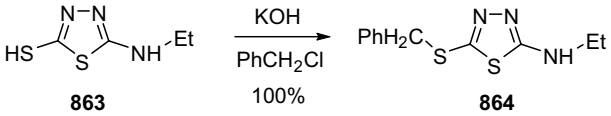
A series of 5-thiosubstituted-1,3,4-thiadiazo-2-yl-2-carbamates **858** and **862** as potential antimicrobial agents has been synthesized starting from 2-amino-5-mercapto-1,3,4-thiadiazole (**856**), according to standard procedures. In particular, the corresponding 5-alkyl or alkenylthio derivatives **858** have been prepared via **857** by reacting **856** with alkyl or allylic halides, followed by treatment with ethyl or allyl chloroformate in 72–80% yield. The butynylamino derivatives **862** have been prepared by reaction of **856** with propargyl bromide (**859**), via the propynylthio analog **860** (75%), followed by reaction with chloroformates to give **861** and subsequent reaction with formaldehyde and secondary amines (Scheme 14.245).

Most of the thiadiazoles so obtained exhibited some activity against *Pseudomonas aeruginosa* and *Candida albicans*. The thiadiazole containing the perhydroazepino moiety was more active against *C. albicans* than phenol (used as standard) [365].



Scheme 14.245

5-(Benzylthio)-*N*-ethyl-1,3,4-thiadiazol-2-amine (**864**) can prepared in similar way in 100% yield by reaction of 2-ethylamino-5-mercapto-1,3,4-thiadiazole (**863**) with KOH and benzyl chloride (Scheme 14.246) [348].

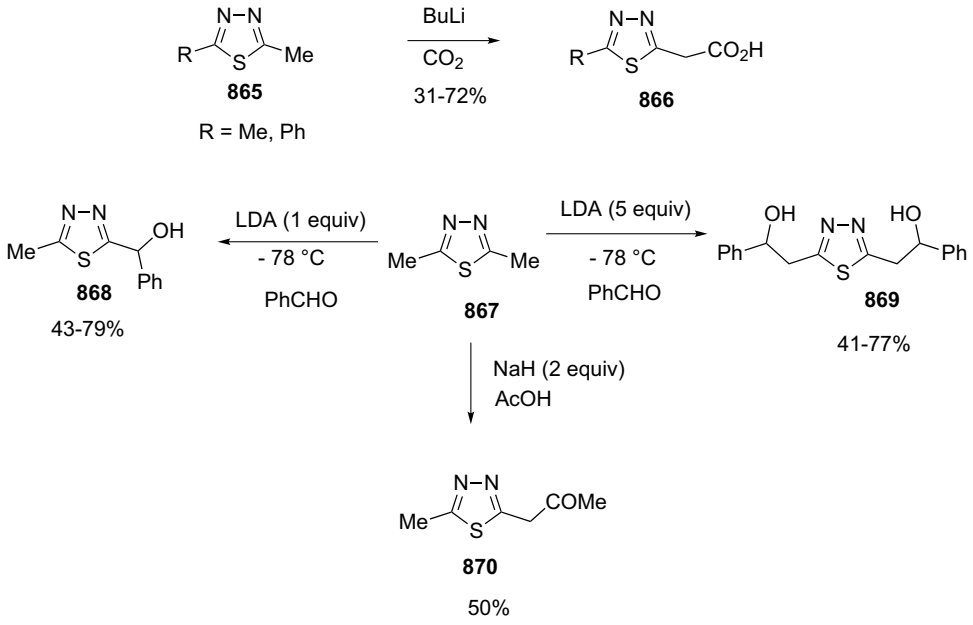


Scheme 14.246

It was found that the methyl group attached at carbons of 1,3,4-thiadiazoles shows fair acidity when treated with a strong base. Thus, when 2-methyl-5-phenyl- or 2,5-dimethyl-1,3,4-thiadiazoles **865** and **867** were reacted with butyllithium, or NaH, or lithium diisopropylamide, followed by addition of CO_2, aldehydes, ketones, or acetic acid, 5-substituted derivatives were obtained (**866** and **868–870**) (Scheme 14.247) [366].

14.4.5
1,3,4-Thiadiazoles in Medicine and Agriculture

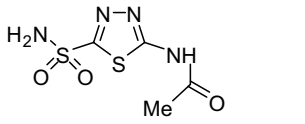
One of the best known drugs based on a 1,3,4-thiadiazole is acetazolamide (**871**, acetazolam), a carbonic anhydrase inhibitor launched in 1954. Compound **871** has



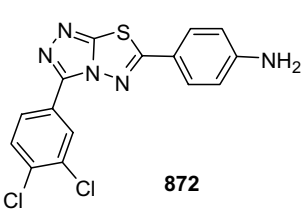
Scheme 14.247

many indications, including the treatment of glaucoma, epilepsy, and congestive cardiac failure [367].

1,3,4-Thiadiazoles exhibit various types of biological activities and some of these compounds are useful pharmacophores. This nucleus is found in some antiviral derivatives such as **872** (anti HIV-1 and HIV-2) [368] and **873** (anti HIV-1) [369], and also in the treatment of neurodegenerative diseases and cancer (such as **874** [370] and **875** [371]).



871



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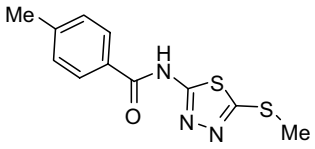
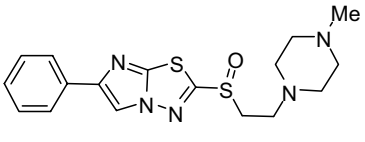


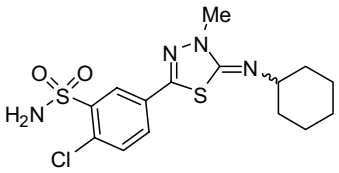
873

Anticancer activity has also been found for 2-amino-1,3,4-thiadiazole (ATDA, NSC-4728) and related compounds (EATDA, NSC-143 019) [372]. Recently several *N*-substituted-2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles have shown

a marked antiproliferative activity *in vitro*. In particular, the highest antiproliferative activity was found for 2-(2,4-dichlorophenylamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole (**876**), with an ID_{50} two times lower (human cell lines SW707 and T47D) than cisplatin studied comparatively as the control compound [373].



874



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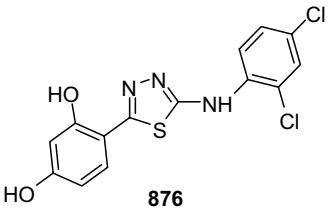
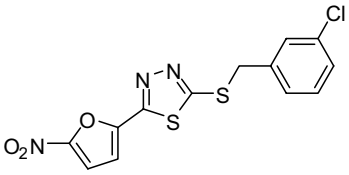
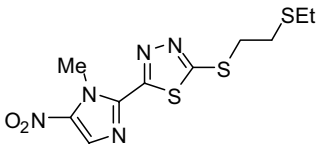


876

It is also used as bactericidal; compounds **877** and **878** are active against *Helicobacter pylori* [374].

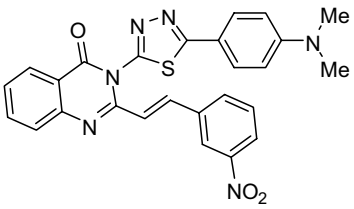


877



878

Some compounds posses muscle relaxant properties. Thus, recently, Bhandari *et al*. have shown that derivatives **879** and **880** have significant anticonvulsant activity against maximal electronic shock model compared to standard drugs phenytoin, diazepam, and phenobarbital [375].



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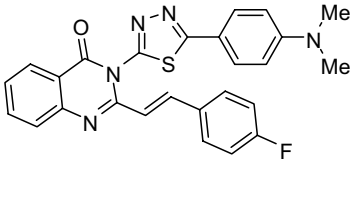
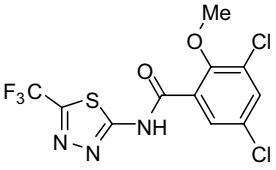


880

Moreover many 1,3,4-thiadiazole derivatives have also been patented in the agricultural field as pesticides, herbicides, insecticides, fungicides, and so on. Two examples are reported here: in particular compound **881**, which shows fungicidal

activity against *Venturia inaequalis* [376], and compound **882**, which is an anti-tobacco mosaic virus agent [377].



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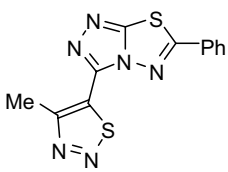

882

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15
Five-Membered Heterocycles with Four Heteroatoms: Tetrazoles

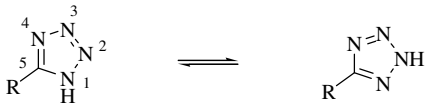
Ulhas Bhatt

15.1
Introduction

Tetrazoles are five-membered ring aromatic compounds composed of one carbon atom and four nitrogen atoms such that the four nitrogen atoms are linked contiguously to each other. Tetrazoles have 6π electrons and exist as either the 1*H*- or the 2*H*-tautomer (Figure 15.1). In solution, the 1*H* tautomer is the predominant form, but in the gas phase the 2*H*-tautomer is more stable. Disubstituted tetrazoles can be prepared by substituting the ring hydrogen, producing both 1,5- and 2,5-disubstituted tetrazoles. Various substitutions can adorn the tetrazole ring, from heteroatoms like N, O and S, to alkyl, aryl and heteroaryl groups. In addition, the tetrazole ring can be part of a fused ring system.

X-Ray structures have confirmed the planarity of the ring system with N−N bond lengths being of nearly equal length. The cyclic C−N=N and N−N=N groups' vibrational frequencies are observed at 1000–1100 cm^{-1} in their infrared (IR) spectra. Weak to medium intensity bands occur in the 1200–1300 cm^{-1} region due to N−N vibrations and a strong N−N stretching band can be seen at 1270–1300 cm^{-1}. The C=N band occurs at 1450–1500 cm^{-1}. The 5-CH stretching frequency of tetrazole is at 3146 cm^{-1} and in several N-alkyl compounds this is shifted to below 3138 cm^{-1}. ^{15}N and ^{13}C NMR spectroscopy are useful tools in the determination of the substitution pattern. The C5 signal in 2-substitued tetrazoles is usually up to 10 ppm deshielded when compared to the 1-substitued tetrazoles. Although tetrazoles are an important compound class in their own right, they are used extensively as surrogates for carboxylic acids in medicinal chemistry. They have similar pK_a values (tetrazole has a pK_a of 4.76) and generally exhibit greater metabolic stability than carboxylic acids. Tetrazoles are also weak bases, exhibiting a pK_a in the range of −3. The hydrogen at position 1 (N1) can participate in intermolecular hydrogen bonding with the other pyridine-type nitrogen atoms. Tetrazoles carrying an N1 substituent are unable to create these strong hydrogen bonds and thus exhibit significantly lower melting and boiling points than N1 unsubstituted tetrazoles. The tetrazole ring exhibits a strong electron-withdrawing inductive effect (−I effect) that is more

Modern Heterocyclic Chemistry, First Edition.
Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.



1*H*-tautomer 2*H*-tautomer

Figure 15.1 Tautomers of tetrazoles.

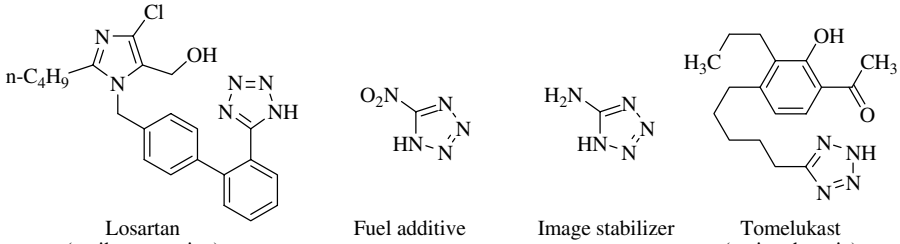
effective than its weaker mesomeric effect (+M effect). The tetrazole ring thus has a deactivating effect, especially when substituted with a strong activating group.

Tetrazoles are useful in various applications like pharmaceuticals, agriculture, photography, polymers and explosives (Figure 15.2). In medicinal chemistry, biphenyl tetrazoles have shown potential as stimulators of growth hormone release, metalloprotease inhibitors and chloride channel blockers.

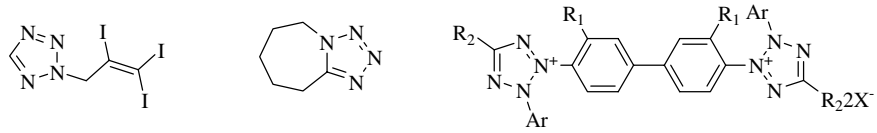
Tetrazole chemistry has been extensively reviewed and so this chapter will cover the latest advances in the field [1]. Special attention has been paid to syntheses performed using newer technologies like solid-phase and microwaves.

15.2 Synthetic Methods

Many methods for the synthesis of tetrazoles utilize an azide as the source of three of the four nitrogen atoms. A range of compounds, like acid chlorides, amides, amidines, carbodiimides, carbonimidic dichlorides, cyanates, imines, isocyanates, isothiocyanates, isocyanides, ketones, nitriles, nitrilium salts, orthoesters, oximes, oxazolones, and thiocyanates, react with inorganic azides (e.g., sodium azide) to produce tetrazoles. This is by far the most popular and extensively studied route for



Losartan (antihypertensive) Fuel additive Image stabilizer Tomelukast (anti-asthmatic)



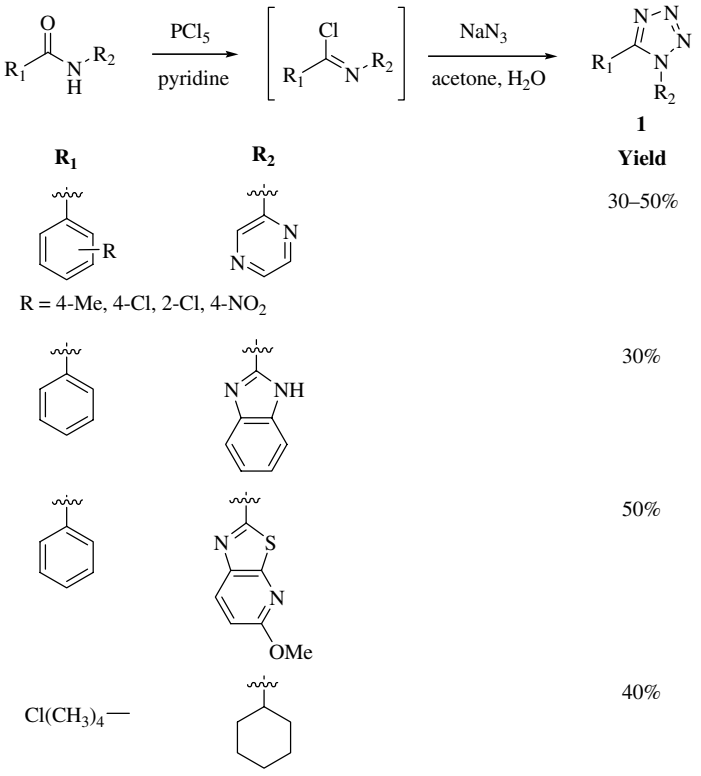
Fungicide PTZ (CNS agent) electronic display component

Figure 15.2 Useful tetrazole compounds.

the synthesis of tetrazoles. The most commonly used azide sources are sodium azide (as a suspension in DMF or acetone or under phase-transfer conditions), ammonium azide (generated *in situ*) and trimethylsilyl azide. Tetrazoles can also be prepared from azidoaziridines, triazoles, and triazines.

15.2.1 Amides as Substrates

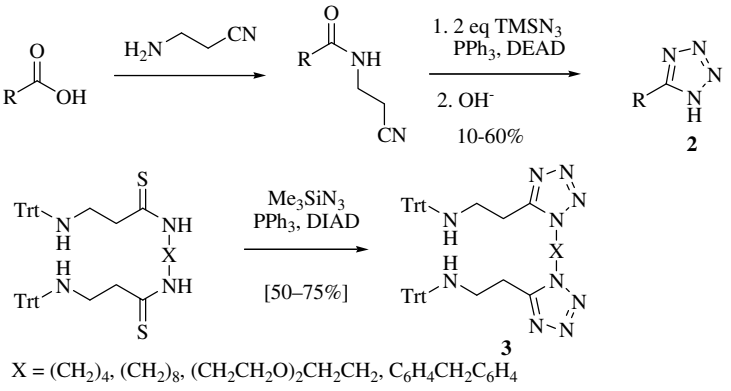
Amides react with sodium azide in presence of reagents like PCl_5, $POCl_3$ or $SOCl_2$ to generate the corresponding 5-substituted tetrazoles. This reaction proceeds through the chlorination of the amide to generate the imidoyl chloride, which reacts with the azide to produce the tetrazole. When PCl_5 is the chlorinating reagent, the reaction is called the von Braun–Rudolph reaction, but product yields are usually moderate. This methodology has been utilized to prepare tetrazole derivatives **1** (Scheme 15.1) [2].



Scheme 15.1 Synthesis of tetrazoles from amides [2].

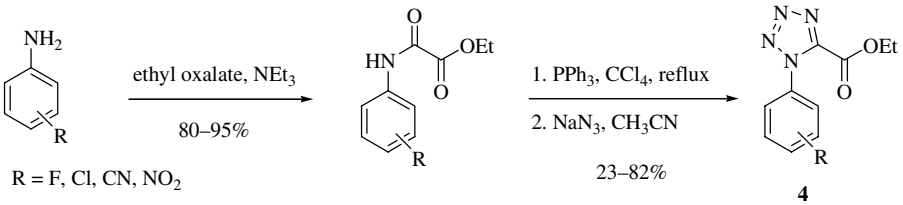
In a Mitsunobu-type variation of this reaction, an amide is treated with excess triphenylphosphine, trimethylsilyl azide and diethylazodicarboxylate (DEAD) to generate the corresponding tetrazoles [3]. This methodology was utilized in the

synthesis of a series of tetrazole-ring containing growth hormone secretagogues. It was also used successfully to prepare compound **2** (Scheme 15.2) where the cyanoethyl group does not react under these conditions with $TMSN_3$ to produce the second tetrazole ring and can be removed later under basic conditions. When poor yields of tetrazole products are observed using this route, it may be worthwhile treating the amides with Lawesson's reagent and then subjecting the resulting thioamides to Mitsunobu conditions to produce the tetrazole products. This strategy has been cleverly utilized to convert linear N^{ω}-tritylated ω-amino thiobenzylamides and N^{α},N^{ω}-ditritylated polyamino mono- or bisthioamides into the corresponding tetrazole derivatives **3** [4].



Scheme 15.2 Synthesis of tetrazoles from amides and thioamides under Mitsunobu conditions [3, 4].

In a related reaction sequence, substituted anilines are reacted with ethyl oxalate and triethylamine to produce the corresponding ketoamides (Scheme 15.3) [5]. These were treated with triphenylphosphine in refluxing carbon tetrachloride followed by reaction with sodium azide to produce the tetrazole compounds **4**. Recently, the conversion of amide into tetrazole has been reported by using tributyltin chloride and sodium azide [6].



Scheme 15.3 Synthesis of tetrazoles from ketoamides [7].

The tetrazole ring has also been proposed as a replacement of the cis-amide bond in peptides (Figure 15.3) [7]. Peptides that contain the tetrazole group in place of a

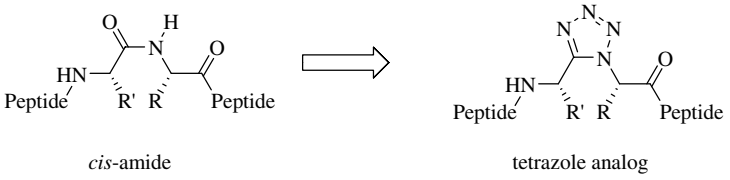
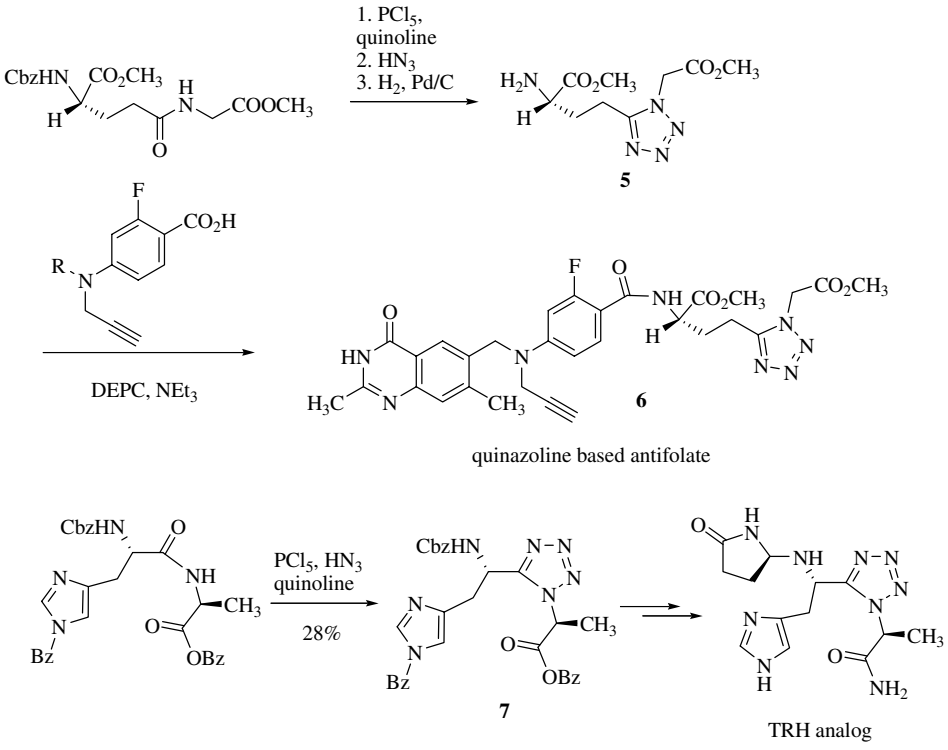


Figure 15.3 Tetrazole ring as a replacement for cis-amide bond [6, 7].

cis-amide bond are able to adopt most of the conformations available to the original peptide.

Tetrazolyl analogs of bradykinin and scyliorhinin I were among the first few peptides studied. More recently, quinoxaline-based antifolates, with tetrazole modified glutamate side chain peptidomimetics, have been synthesized (Scheme 15.4) [8]. The reaction of a glutamate derivative with quinoline, phosphorus pentoxide and hydrazoic acid provided the corresponding tetrazole derivative **5**. The Cbz group was removed under hydrogenating conditions and the resulting amine was coupled with a pteroic acid derivative to produce the desired analogs **6**. These analogs exhibited potent thiamidyl synthase and L1210 cell growth inhibitory activities. Along similar lines, an analog of thyrotropin releasing hormone (TRH) containing the tetrazole



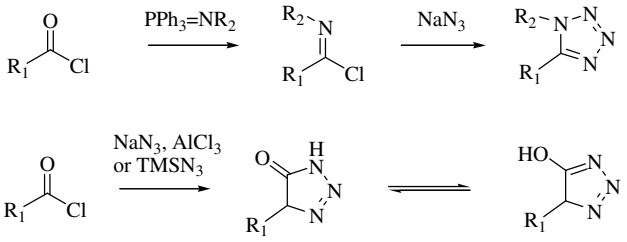
Scheme 15.4 Tetrazole ring as a replacement for the cis-amide bond in peptides [9, 10].

ring as a mimic for the cis amide bond has been prepared (Scheme 15.4) [9]. Cbz-His-Ala-OBz dipeptide derivative was treated with PCl_5, quinoline and hydrazoic acid to produce the tetrazole product **7** that was later transformed into the desired tripeptide TRH analog. The lack of binding for this particular analog suggests that the amide bond geometry was not a critical factor in the binding of TRH with its receptor.

In a recent development, an interesting methodology was reported for the synthesis of tetrazole ring compounds starting from an amide [10]. The amide substrate was first converted into an oxazoline and then treated with hydrazine hydrochloride in methanol to yield an amidrazone. Subsequent reaction with sodium nitrite formed the desired tetrazole via a nitrosation process. This procedure avoided the use of azides altogether and was amenable to scale-up.

15.2.2
Acid Chlorides as Substrates

Acid chlorides react with sodium azide and phosphine imide to generate tetrazoles (Scheme 15.5) [11]. This reaction proceeds through the formation of imidoyl chloride that, in some cases, can be isolated prior to its reaction with the azide source. These reactions occur by the displacement of the chlorine by the azide anion. Other leaving groups can also be displaced by the azide anion and examples of such substrates include imidates, thioimidates, and amidines. Aromatic and aliphatic acid chlorides react with Lewis acids and two equivalents of metal azide to produce 1-substituted tetrazolols. Trimethylsilylazide has been used in place of the metal azide and the Lewis acid with excellent results. This reaction proceeds via the formation of the isocyanate followed by reaction of the second equivalent of the azide anion to complete the formation of the tetrazole ring.

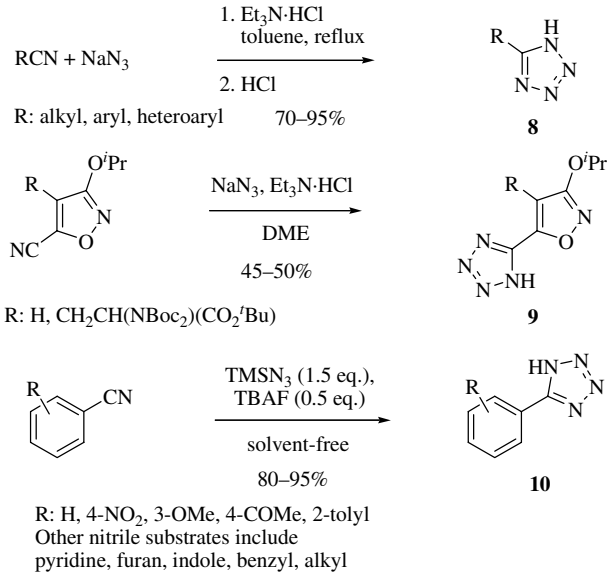


Scheme 15.5 Synthesis of tetrazoles from acid chlorides [11].

15.2.3
Nitriles as Substrates

Nitriles react with azides to generate tetrazoles and this method is widely used as a large number of nitriles are either commercially available or easily prepared. Earlier procedures used hydrazoic acid generated *in situ* from sodium azide and acid, but were often slow and gave poor yields. Use of polar solvents like DMF and DME and

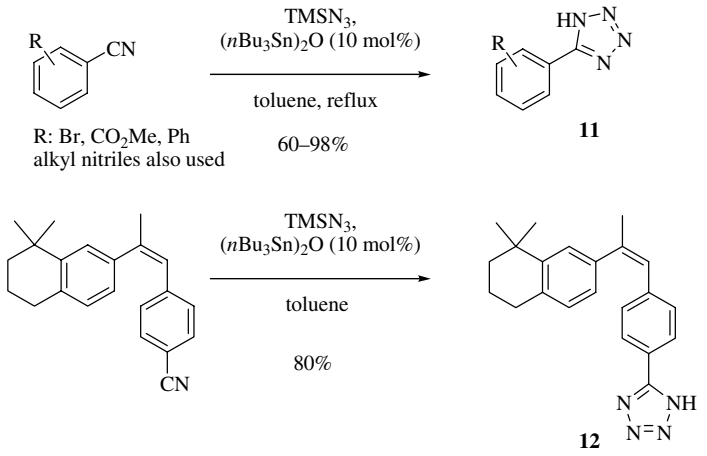
the addition of ammonium chloride or alkylammonium salts tends to shorten reaction times considerably and give better yields. Various 5-substituted tetrazoles **8** have been prepared by reacting nitriles with sodium azide in an aromatic solvent like toluene in the presence of an amine salt like triethylammonium chloride (Scheme 15.6) [12]. Several different conditions have been studied, including the effect of the number of equivalents of sodium azide used, the type of salt and the solvent. Following this protocol, the synthesis and pharmacological characterization of 1- and 2-alkyltetrazolyl analogs of 2-Me-Tet-AMPA (*(RS)*-2-amino-3-[3-hydroxy-5-(2-methyl-2*H*-5-tetrazolyl)-4-isoxazolyl]propionic acid), a highly potent and selective agonist at AMPA receptors, has been described recently [13]. These tetrazole derivatives (**9**) have been synthesized by reacting nitriles with sodium azide and triethylamine hydrochloride in DME. Similarly, tetrabutylammonium fluoride has been used as the catalyst to prepare tetrazoles **10** from nitriles and trimethylsilyl azide under solvent-free conditions [14].



Scheme 15.6 Synthesis of tetrazoles from nitriles and sodium azide [12–14].

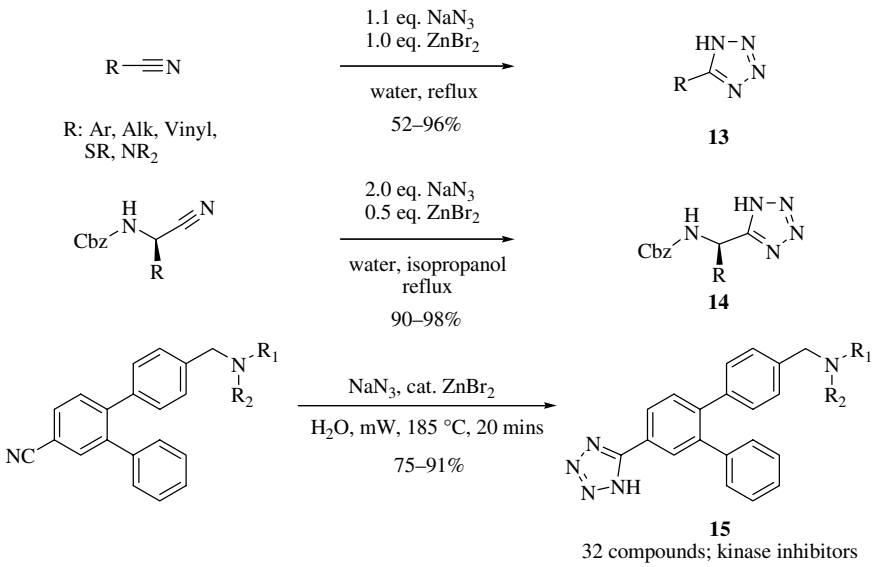
Bis(tributyltin) oxide has also been used as a catalyst in the reaction between nitriles and trimethylsilyl azide to produce tetrazoles **11** and **12** (Scheme 15.7) [15]. Excellent yields of both alkyl and aryl tetrazoles are usually obtained by this method, which avoids the use of hydrazoic acid and also minimizes exposure to toxic tin compounds.

Sharpless's group has disclosed that the reaction of sodium azide with nitriles proceeds nicely in presence of zinc salts to give 1*H*-tetrazoles [16]. This has been called click-chemistry and these reactions are performed in water with or without an organic co-solvent. For example, the synthesis of compound **13** proceeded readily



Scheme 15.7 Further syntheses of tetrazoles from nitriles and sodium azide. [15].

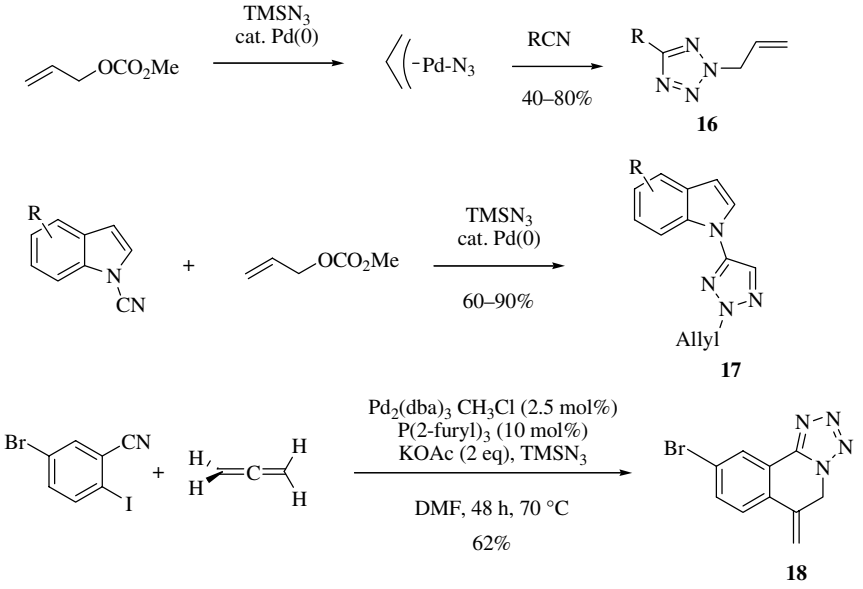
in water with zinc salts as catalysts (Scheme 15.8). The scope of the reaction is quite broad; various aromatic nitriles, activated and unactivated alkyl nitriles, substituted vinyl nitriles, thiocyanates and cyanamides are all viable substrates under these conditions. However, this method works best for electron-deficient nitriles. The authors have extended this methodology by using a mixture of water and 2-propanol at reflux to transform N-Cbz amino nitriles into the corresponding tetrazole compounds **14** using sodium azide and half-an-equivalent of zinc bromide (Scheme 15.8) [17]. This methodology has found wide acceptance [18]. For instance,



Scheme 15.8 Synthesis of tetrazoles from nitriles and azides using zinc bromide [16–19].

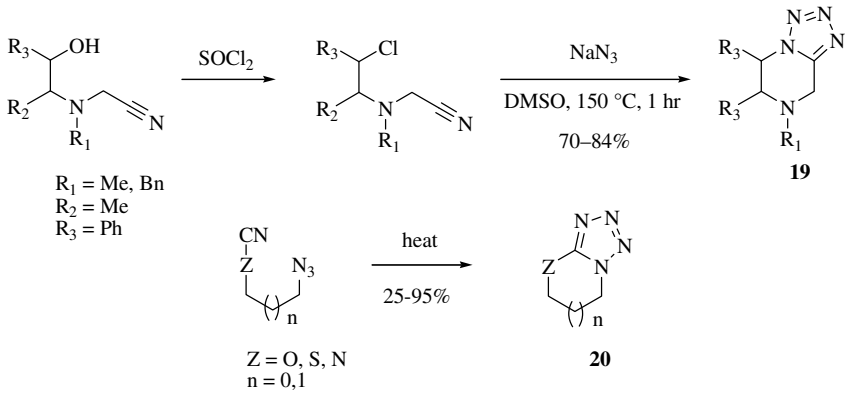
Merck researchers have utilized this methodology under microwave conditions to prepare a small library of tetrazoylpyridines **15**. These compounds were evaluated for their role as dual inhibitors of the serine/threonine kinases Akt1 and Akt2. Using the same protocol, tatrazole analogs of glycyl-L-prolyl-L-glutamic acid have been prepared. Fmoc amino acids were also converted into the corresponding tetrazole compounds where the carboxylic acid group was replaced by the tetrazole ring. Recently, nanocrystalline ZnO was also shown to be an effective heterogeneous catalyst for the [2 + 3] cycloaddition of azides to nitriles to afford 5-substituted-1*H*-tetrazoles in good yields [19].

Palladium-catalyzed three-component coupling reaction of cyano compounds, allyl methyl carbonate and trimethylsilyl azide, under a catalytic amount of $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol%) and tri(2-furyl)phosphine (10 mol%), gives 2-allyltetrazoles **16** in good to excellent yields (Scheme 15.9) [20]. A π-allylpalladium azide complex has been proposed as a key intermediate in this reaction. This methodology has been extended to *N*-cyanoindoles to produce the corresponding indole-fused tetrazoles **17**. Along similar lines, palladium-catalyzed reaction between allene, trimethylsilyl azide and 2-iodo-5-bromobenzene-1-carbonitrile generates tetrazoyltetrahydroisoquinoline **18** [21].



Scheme 15.9 Synthesis of tetrazoles under palladium catalysis [20, 21].

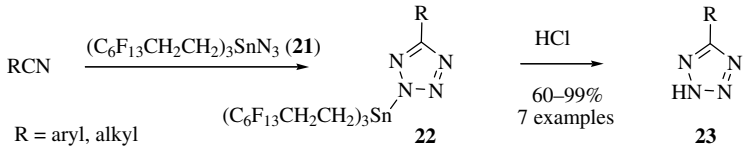
Fused bicyclic tetrazole-piperazines **19** have been obtained in very good yields by reacting *N*-cyanomethyl β-amino chlorides (derived from the corresponding β-amino alcohols) with sodium azide in DMSO at 150 °C (Scheme 15.10) [22]. Fused 5-heterotetrazole ring systems **20** have been obtained in high yields by the intramolecular cycloaddition reaction of organic azides and heteroatom substituted



Scheme 15.10 Synthesis of tetrazoles in a fused ring system [22, 23].

nitriles [23]. Cyanates, thiocyanates and cyanamides are all competent dienophiles for this reaction.

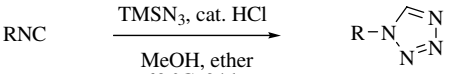
Tetrazoles have also been synthesized using fluorous chemistry (Scheme 15.11) [24]. A fluorous tin azide reagent (**21**) is prepared and reacted with nitriles to produce the corresponding tetrazole compounds **22**. Subsequent cleavage by concentrated hydrochloric acid gives pure tetrazole products **23** and the fluorous tin chloride, which could be reconverted into tin azide. In most cases, a 2–5-fold excess of the fluorous tin reagent is used and good yields of the tetrazole products are obtained.



Scheme 15.11 Synthesis of tetrazoles under fluorous conditions [24].

15.2.4
Isocyanides as Substrates

Isocyanides can also be used to prepare tetrazoles. Hydrazoic acid reacts with isocyanides to produce 1-substituted tetrazoles [25]. This reaction proceeds via the attack of the azide anion on the protonated isocyanide followed by cyclization to give the tetrazole ring. To avoid the use of toxic hydrazoic acid, 1-substituted tetrazoles **24** were synthesized via the [3 + 2] cycloaddition between isocyanides and trimethylsilyl azide in the presence of an acid catalyst and methanol (Scheme 15.12) [26]. Various 1-substituted tetrazoles have been obtained in good to high yields under these conditions. The reaction probably proceeds through the *in situ* formation of hydrazoic acid, followed by a successive [3 + 2] cycloaddition with the isocyanide activated by an acid.



24

R	Yield (%)
p-$MeOC_6H_4$	92
o-$MeOC_6H_4$	85
2,6-$(CH_3)C_6H_3$	87
C_6H_5	67
p-$CO_2MeC_6H_4$	58
p-$NO_2C_6H_4$	77
$CH_3(CH_3)_2$	57
C_6H_{11}	78
t-Bu	92
Me_3SiCH_2	81

Scheme 15.12 Synthesis of tetrazoles form isonitriles [26].

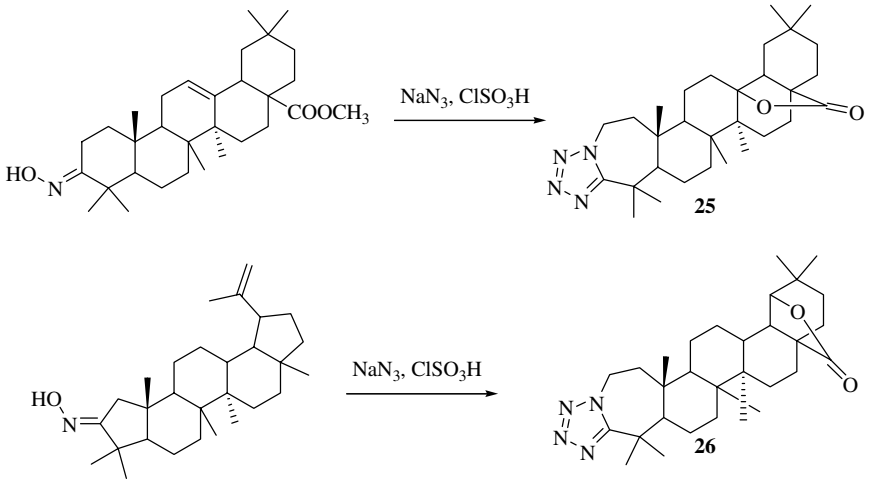
The isocyanide can also be electrophilically activated by iodinium ion or the acylium ion. Thus, if iodine azide is used instead of hydrazoic acid, 1-substituted 5-iodotetrazole can be obtained. Similarly, the reaction of an isocyanide, an acid chloride and sodium azide generates 1-substituted 5-acyltetrazole where the acylium ion activates the isocyanide to the nucleophilic attack by the azide anion. The reaction of isonitriles with azide in the presence of Mannich-type reagent (e.g., formaldehyde and piperidine) provides 1,5-disubstituted tetrazoles. This is a variation of the well-known Ugi reaction and is discussed in more detail later.

15.2.5
Oximes as Substrates

Oximes react with an azide source and reagents like thionyl chloride, chlorosulfonic acid, phenylsulfonyl chloride or phosphorus pentachloride to give 1,5-disubstituted tetrazoles. This transformation occurs via the attack of the azide anion on the nitrilium ion intermediate followed by cyclization to produce the tetrazole ring. Oximes of methyl olenonate and methyl betulonate have been treated with sodium azide in the presence of chlorosulfonic acid to give tetrazoles **25** and **26** respectively (Scheme 15.13) [27].

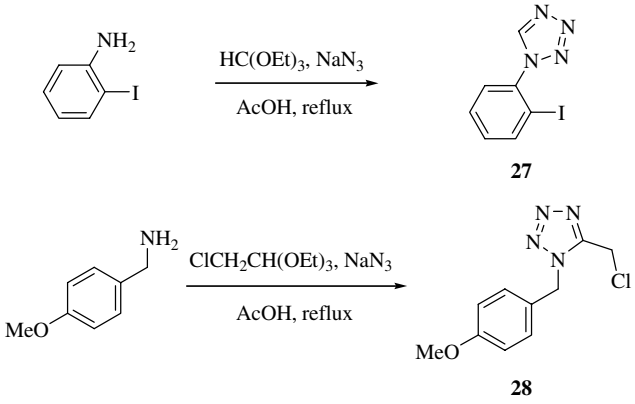
15.2.6
Orthoesters as Substrates

Orthoesters (especially orthoformates) react with sodium azide and amines or anilines to produce tetrazoles. This method can be carried out conveniently with aliphatic, aromatic or heteroaromatic anilines and gives good yields of the corresponding tetrazoles. A synthesis of 1-(2-iodophenyl)-1*H*-tetrazole **27** has been described recently by treating 2-iodoaniline, triethylorthoformate and sodium azide in refluxing acetic acid (Scheme 15.14) [28]. This tetrazole derivative, when used as a ligand in palladium-catalyzed Heck reactions, gives the cross-coupled products in



Scheme 15.13 Synthesis of tetrazoles from oximes [27].

excellent yields. Condensation of *p*-methoxybenzylamine with 2-chloro-1,1,1-triethoxyethane in the presence of sodium azide in acetic acid produces the corresponding tetrazole **28** [29]. Similarly, 2-aminopyridine has been heated with sodium azide and triethylorthoformate in acetic acid to produce 2-tetrazolyl-pyridine [29].



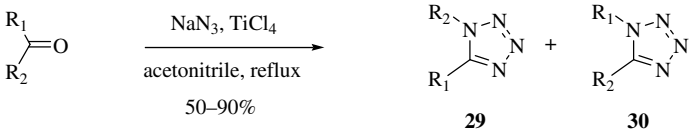
Scheme 15.14 Synthesis of tetrazoles from orthoesters [28, 29].

15.2.7
Ketones as Substrates

Ketones react with an azide source to generate tetrazoles in the Schmidt reaction. Mixtures of 1,5-disubstituted products are generally obtained in this reaction.

Originally, hydrazoic acid was used for this transformation, but now several other reagents are available. A few steroidal ketones have been converted into their corresponding tetrazole derivatives when an excess of hydrazoic acid was used [30]. Undesired side products, like the corresponding amides and lactams, were also formed under these conditions. Boron trifluoride etherate has been used in combination with hydrazoic acid in this type of reaction, but still both tetrazole and lactam products were observed when steroidal ketones were used [31]. In another example, using Pummerer's ketone, 35% of the tetrazole product and 22% of the uncyclized azide product was obtained by the use of hydrazoic acid and boron trifluoride etherate [32].

Other Lewis acids like aluminium trichloride, tin(II) chloride, tin(IV) chloride, titanium tetrachloride, tetrachlorosilane, zinc(II) chloride and trimethylsilyl azide have all been used with success. Typically, an excess of the azide is used in the presence of a Lewis acid and the ketone in this reaction. Mixtures of 1,5-disubstituted 1*H*-tetrazoles **29** and **30** are obtained when aliphatic or aromatic ketones are reacted with excess sodium azide in the presence of titanium chloride in refluxing acetonitrile (Scheme 15.15) [33]. The use of a large excess of sodium azide relative to the amounts of ketone and titanium(IV) chloride (i.e., 8 : 1 : 2) provides the most satisfactory results. Performing the reactions in other solvents like benzene, THF, ether or methylene chloride led to lower yield of the tetrazole products in this study.

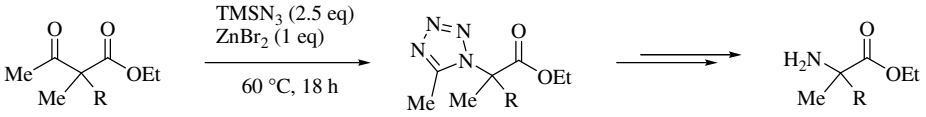


R_1 = Ph, 4-ClPh, 4-OMePh, 4-NO_2Ph
-$(CH_2)_4$-, -$(CH_2)_5$-, Me, PhCH=CH_2

R = Ph, 4-MeOPh

Scheme 15.15 Synthesis of tetrazoles from ketones [33].

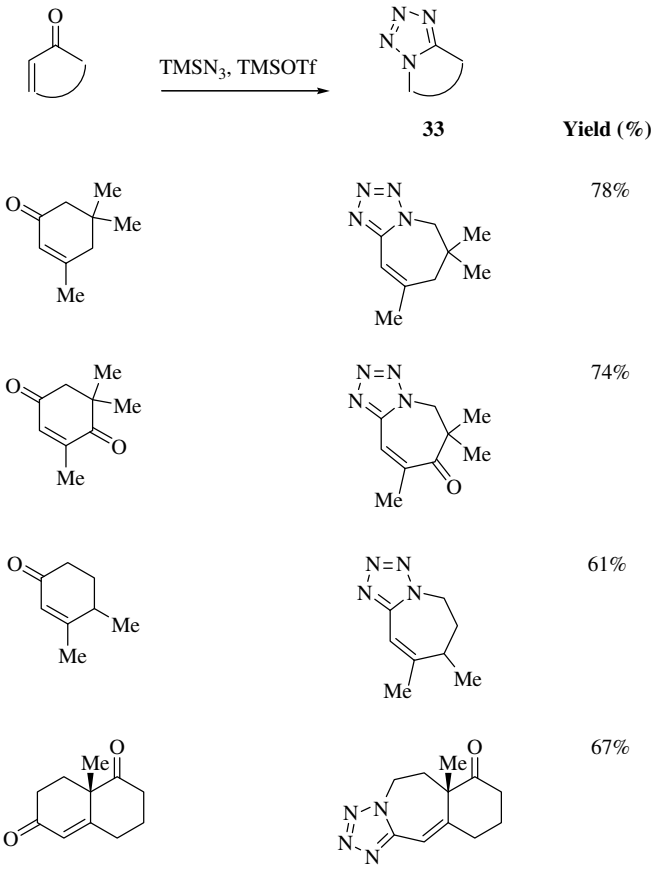
A series of tetrazoles **31** have been prepared by using β-keto esters with trimethylsilyl azide and zinc bromide (Scheme 15.16). These were subsequently transformed into amino acids **32** [34].



R = Et, Bn, *i*Bu, Ph

Scheme 15.16 Synthesis of tetrazoles from β-keto esters [34].

The reactions of a few cyclic α,β-unsaturated ketones with trimethylsilyl azide in the presence of trimethylsilyl triflate produce the corresponding ring-expanded tetrazole derivatives **33** (Scheme 15.17) [35].

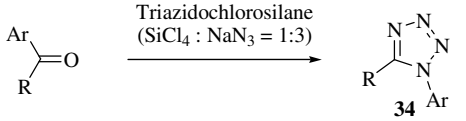


Scheme 15.17 Synthesis of fused tetrazoles from cyclic ketones [35].

Triazidochlorosilane ($ClSiN_3$) is also an excellent reagent for the conversion of ketones and α,β-unsaturated ketones into the corresponding tetrazole derivatives **34** in nearly quantitative yields (Scheme 15.18) [36].

15.2.8
Tetrazoles from Other Substrates

Tetrazoles have also been prepared from amidines, carbodiimides, carbonimidic dichlorides, isocyanates, isothiocyanates, isocyanides, nitrilium salts, oxazolones and thiocyanates; however, these substrates have been utilized on very few occasions in the recent literature and hence are not described here. Moreover, this chemistry is well-documented elsewhere. The syntheses of tetrazole compounds using methods that have rapidly evolved recently and are now being increasingly used in both academia and industry is described next. These include the solid-phase synthesis, microwave synthesis and multicomponent synthesis of tetrazoles.



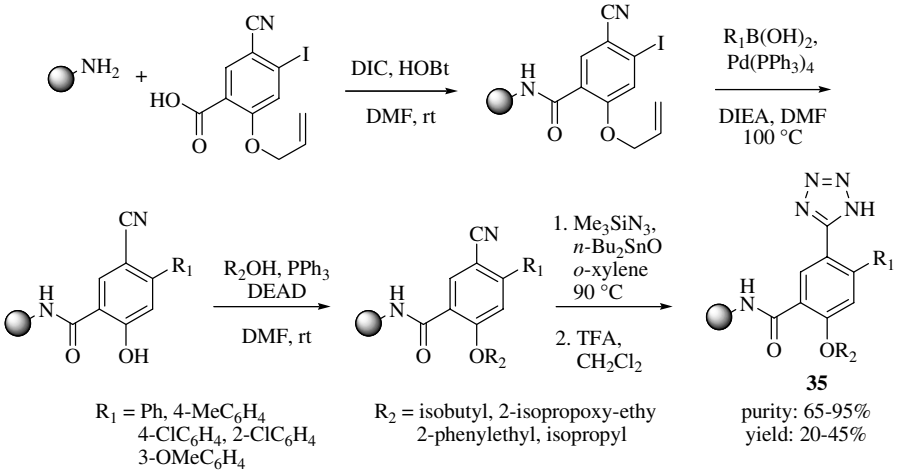
34

Ketone	Yield (%)
Acetophenone	87
4-chloroacetophenone	87
3-nitroacetophenone	60
benzophenone	97
1-indanone	93
benzalacetone	95
benzalacetophenone	94
4-methoxybenzalacetophenone	90
4-chlorobenzalacetophenone	95

Scheme 15.18 Synthesis of tetrazoles from ketones [36].

15.2.9
Solid-Phase Syntheses

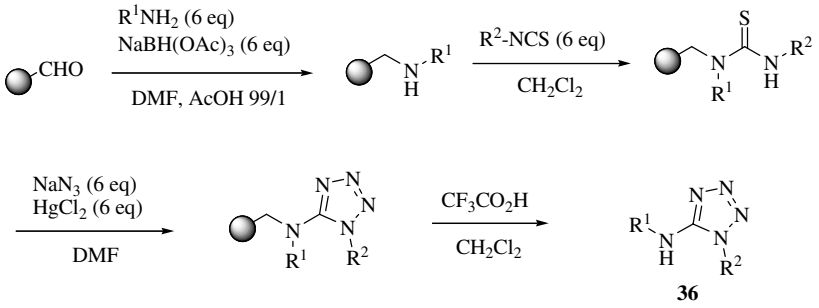
The synthesis of tetrazole derivatives has been reported using solid-phase conditions to produce libraries of compounds – especially in the realm of pharmaceutical research. Rink amide resin has been attached to a suitably substituted benzonitrile that was then reacted with trimethylsilyl azide and a catalytic amount of bis(tributyltin) oxide for 50 h at 90 °C in *o*-xylene to produce the corresponding tetrazole compounds **35** (Scheme 15.19 [37]. This procedure was adapted from the report by Wittenberger that promoted the use of bis(tributyltin) oxide to facilitate the reaction of trimethylsilyl azide with nitriles to produce tetrazoles. The final products were obtained in moderate yields (20–45%) and in reasonably good purity (65–93%).



Scheme 15.19 Synthesis of tetrazoles under solid-phase conditions using a Rink amide resin [37].

The use of trimethylsilyl azide in contrast to azidotrimethyltin or sodium azide makes this process less toxic. In this study, diversity was introduced at two places on the phenyl ring by (i) Suzuki coupling at the iodo atom and (ii) Mitsunobu reaction at the phenolic site.

A dihydropyran carboxylic acid type linker has been attached to tetrazoyl-arylbromide that then underwent Suzuki coupling with two different aryl boronic acids to produce biphenyl-tetrazole products [38]. Parallel solid-phase synthesis of 5-aminotetrazoles **36** was recently achieved by the reaction of resin-bound thioureas with excess mercuric chloride and sodium azide (Scheme 15.20) [39]. The final products were obtained in good yields (60–70%) and good purity (75–85%).



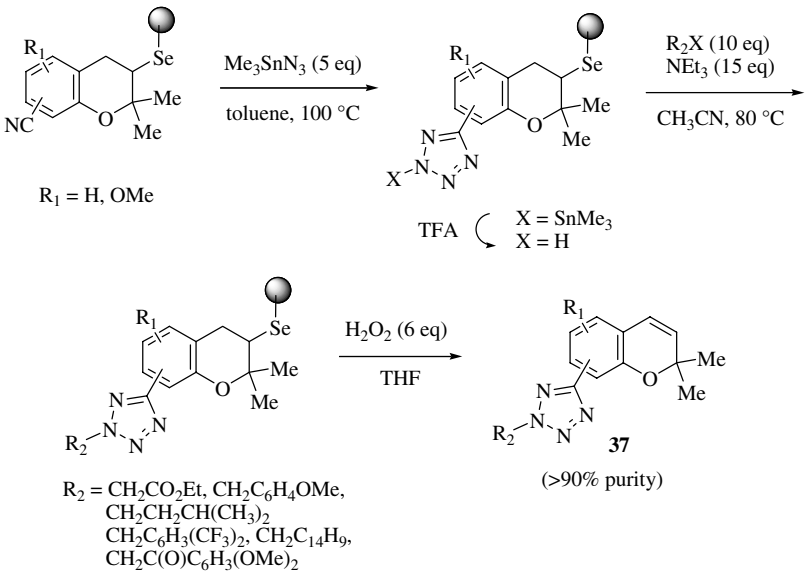
Scheme 15.20 Synthesis of tetrazoles under solid-phase conditions [39].

Tetrazoles have also been incorporated into privileged structures. A series of nitrile-containing benzopyran scaffolds were prepared on selenium-tethered resin and reacted with azidotrimethylstanane to provide the corresponding stannylated tetrazoles (Scheme 15.21) [40]. The trimethylstannyl group was removed using aqueous trifluoroacetic acid (TFA) and the tetrazoles were further alkylated with various alkyl halides. Finally, the resin-bound tetrazoles were cleaved under oxidative conditions to afford the substituted tetrazole products **37**.

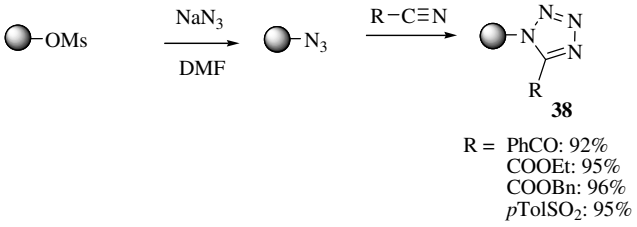
MeOPEG-supported azide has also been utilized as the azide source for the reaction with activated nitriles to produce the corresponding tetrazoles **38** in excellent yields (Scheme 15.22). Subsequent acid hydrolysis provided clean tetrazole products [41].

15.2.10
Microwave Syntheses

The use of microwaves has become an increasingly important component in organic synthesis as more and more types of reactions are successfully performed in their unique environment. The synthesis of tetrazoles often requires high temperatures

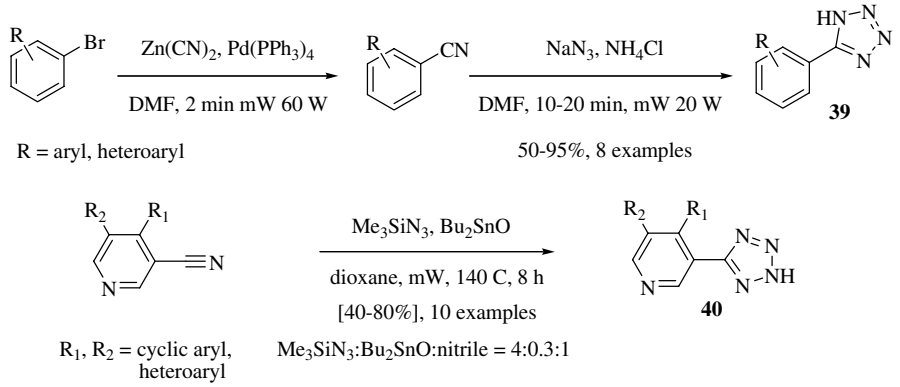


Scheme 15.21 A further example of the synthesis of tetrazoles under solid-phase conditions [40].



Scheme 15.22 Synthesis of tetrazoles using PEG [poly(ethylene glycol)] [41].

and long reactions times under standard conditions. Microwave chemistry promises to improve yields using lower temperatures and very short reaction times. Under microwave conditions, aryl bromides were converted into the corresponding nitriles by using zinc cycanide and $Pd(PPh_3)_4$ in DMF for 2 min at 60 W. These nitriles were then reacted with sodium azide and ammonium chloride in DMF using 20 W power for 15 min to produce the corresponding tetrazoles **39** in good yields (80–95%) (Scheme 15.23) [42]. The same reactions performed using conventional heating took 4–10 h and gave slightly lower yields of the products. The synthesis of hindered tetrazoyl pyridines has recently been described under microwave conditions [43]. Under conventional heating conditions, only one nitrile substrate could be converted into the corresponding tetrazole. Using microwave irradiation at 2450 MHz and 140 °C for 8 h, substituted pyridinyl nitriles were reacted with trimethylsilyl azide and

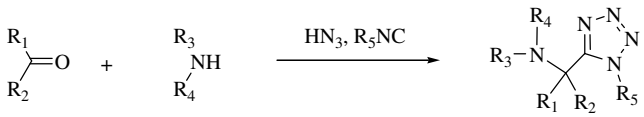


Scheme 15.23 Synthesis of tetrazoles under microwave conditions [42, 43].

bis(tributyltin) oxide in dioxane to generate tetrazole products **40** in decent yields (50–80%). A substantial amount of the unreacted starting nitrile was recovered whenever lower yields of final product were isolated. As microwave instruments become more common in organic laboratories, more examples of its utility in the synthesis of tetrazoles will emerge.

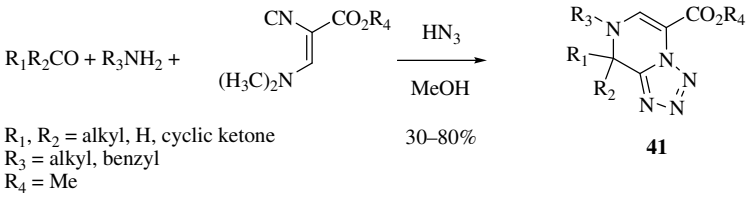
15.2.11
Multicomponent Reactions

It has been known since the 1960s that tetrazoles could be obtained by reacting hydrazoic acid, isonitriles, aldehydes and amines by a variation of the now well-known Ugi reaction (Scheme 15.24) [44].



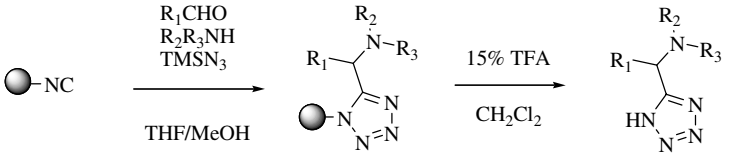
Scheme 15.24 Synthesis of tetrazoles from a modified Ugi reaction.

The Ugi reaction has been increasingly employed to prepare libraries of compounds. It has especially been employed to prepare tetrazole compounds fused to a second ring system. In this regard, a four-component, two-step, one-pot reaction between an aldehyde, a primary amine, methyl-β-(*N*,*N*-dimethylamino)-α-isocyanoacrylate and hydrazoic acid has been used to prepare bicyclic pyrazole compounds **41** in moderate yields (Scheme 15.25) [45]. More recently, a five-centre-four-component Ugi reaction that employed an aldehyde, a primary amine, trimethylsilyl azide and 2-isocyanoethyl tosylate to create tetrazoylpiperazine ring products **42** has been described [46].



Scheme 15.25 Synthesis of fused tetrazoles using multiple components [45, 46].

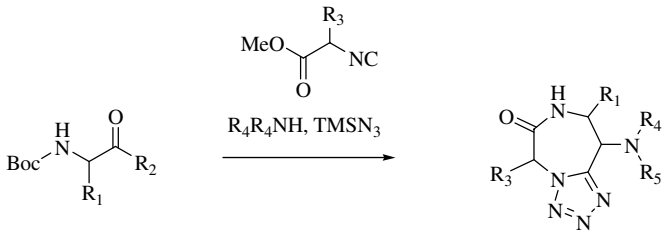
A more recent report demonstrates the synthesis of a series of tetrazoles by a Ugi reaction using the universal Rink-isonitrile resin (Scheme 15.26). The resin-bound nitrile group reacts with aldehydes, secondary amines and trimethylsilylazide to produce the corresponding tetrazoles **43** [47].



R_1	R_2R_3NH	Yield
$PhCH_2CH_2$	piperidine	67%
$PhCH_2Ch_2$	morpholine	76%
Ph	piperidine	89%
Bn	morpholine	25%
4-OCH_3-Ph	morpholine	75%

Scheme 15.26 Solid-phase multi-component synthesis of tetrazoles [47].

In a very interesting variation, a series of fused azepine-tetrazoles **44** have been prepared that utilize the Ugi reaction sequence (Scheme 15.27) [48]. This generated diversity at five positions on the scaffold. Similarly, the reaction of an aldehyde, primary amine, methyl isocyanoacetate and trimethylsilyl azide in methanol at reflux affords bicyclic tetrazole-ketopiperazines **45** in good yield [49]. This efficient one-step protocol creates products with four potential diversity points and has been used to generate arrays of biologically relevant small molecules for general and targeted screening. These examples demonstrate the power of multicomponent reactions to rapidly generate a diverse set of compounds sharing a common core.



Scheme 15.27 Multi-component syntheses of fused tetrazoles [48, 49].

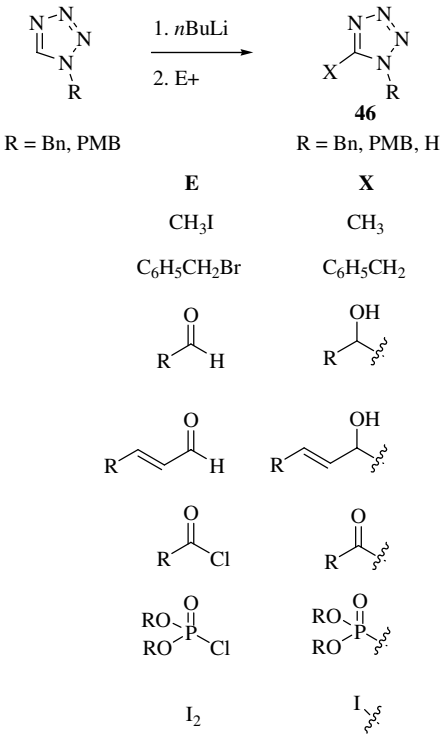
15.3
Reactions of Tetrazoles

The tetrazole ring contains a carbon atom, a pyrrole-type nitrogen atom and three pyridine-type nitrogen atoms. These atoms exhibit their own unique chemical nature and reactivity. The pyrrole-type nitrogen exerts an electron-donating effect (activating the ring) whereas the pyridine-type nitrogens exert an electron-withdrawing effect (deactivating the ring). As mentioned earlier, tetrazoles are nitrogen analogs of carboxylic acids. Tetrazolic acids (R-CN_4H) are easily generated in basic medium as they exhibit a lower pK_a than carboxylic acids. The nature of the R-substituent controls the reactivity – electron-withdrawing groups being more acidic. These tetrazolic acids can react at either the N1 or N2 position and mixtures are often obtained in these types of reactions.

15.3.1
Reactions at C5

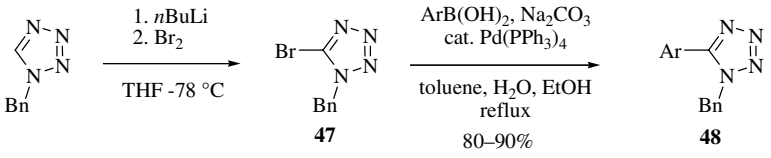
1-Benzyltetrazoles or 1-(*para* methoxybenzyl)tetrazoles have been regioselectively lithiated at the 5-position using *n*BuLi in TMEDA/THF at −98 °C (Scheme 15.28) [50]. These conditions were necessary to obtain regioselectivity consistently. Subsequent addition of electrophiles (aldehydes, ketones, α,β-unsaturated ketones, Weinreb amides, iodine and diethylchlorophosphate) furnishes the corresponding adducts **46**. The benzyl or *para* methoxybenzyl groups can be cleaved under acidic or hydrogenation conditions to produce 5-substituted tetrazoles in good yields.

N1-protected tetrazoles can be brominated using a strong base like *n*BuLi and bromine to produce the C5-bromo products. These activated products can then be



Scheme 15.28 Electrophilic addition to tetrazoles [50].

utilized to prepare various heterocyclic compounds. 1-Benzyl-5-bromotetrazole (**47**) has been conveniently prepared by lithiation of 1-benzyltetrazole with *n*BuLi in THF at −78 °C followed by treatment with bromine (Scheme 15.29) [51]. It was then coupled with various aryl boronic acids to produce the corresponding 5-aryl derivatives **48** under standard Suzuki reaction conditions.

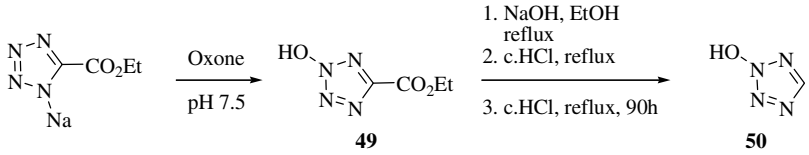


Scheme 15.29 Suzuki coupling on tetrazoles [51].

15.3.2
Reactions at N1 and N2

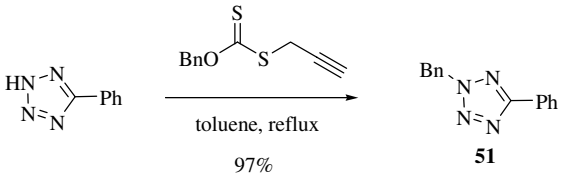
The 2-position of the tetrazole ring is activated and thus reacts under several different conditions.

Oxidation of the commercially available sodium salt of ethyl-tetrazole-5-carboxylate using oxone in aqueous acetone at pH 7.5 forms, exclusively, *N*-2-hydroxytetrazole-5-carboxylate (**49**) (Scheme 15.30) [52]. Subsequent standard basic hydrolysis gives the corresponding acid that can be further decarboxylated to generate 2-hydroxytetrazole (**50**).



Scheme 15.30 Oxidation of tetrazoles [52].

5-Phenyltetrazole can be selectively benzylated by using *O*-benzyl-S-propargyl xanthate in refluxing toluene to give exclusively 2-benzyl-5-phenyltetrazole (**51**) (Scheme 15.31) [53]. In contrast, the use of benzyl bromide generates both 1- and 2-benzyltetrazoles. *O*-benzyl-S-propargyl xanthate is prepared by the reaction of the xanthate salt derived from benzyl alcohol with propargyl bromide.

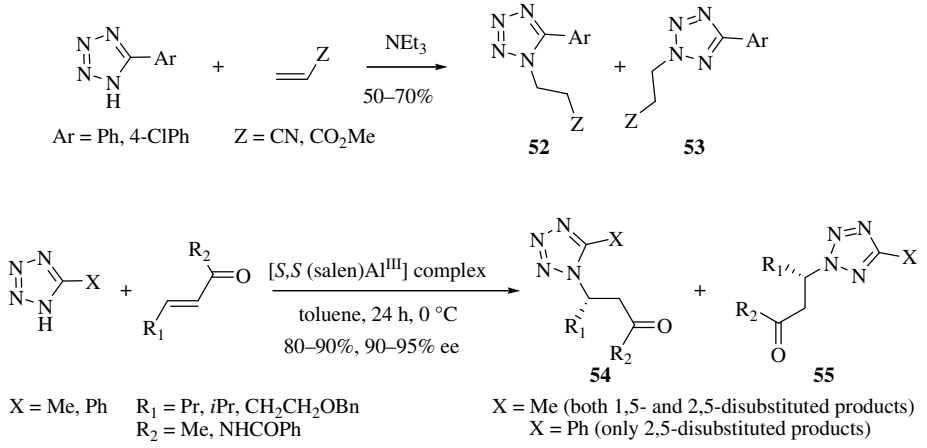


Scheme 15.31 Benzylation of tetrazoles [53].

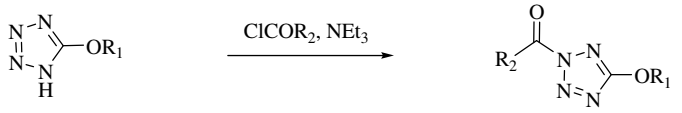
5-Substituted tetrazoles react with Michael acceptors having electron-withdrawing groups to produce 1,5-disubstituted and 2,5-disubstituted products **52** and **53** (Scheme 15.32) [54]. These reactions are also applicable to 1-substituted-tetrazolin-5-ones and 5-substituted-1-hydroxy tetrazoles. An asymmetric version of this reaction has recently been disclosed where 5-methyltetrazole and 5-phenyltetrazole undergo highly enantioselective catalytic conjugate addition to α,β-unsaturated ketones and imides in the presence of chiral[(salen)Al(III)] complexes [55]. Mixtures of 1,5- and 2,5-disubstituted products **54** and **55** were obtained when 5-methyltetrazole was used but 2,5-disubstituted products **55** were exclusively obtained when 5-phenyl tetrazole was used. Tetrazole itself fails to react under these conditions.

Tetrazoles with the C5 substituted as an aryl ether can be conveniently acylated at N2 using the corresponding acyl chlorides and triethylamine to produce products **56** (Scheme 15.33) [56].

C-Arylated tetrazoles react with tetrafluoroborate aryliodinium salts using either copper or palladium catalysts to produce the corresponding C,2N-diaryl



Scheme 15.32 Michael addition reactions of tetrazoles [54, 55].



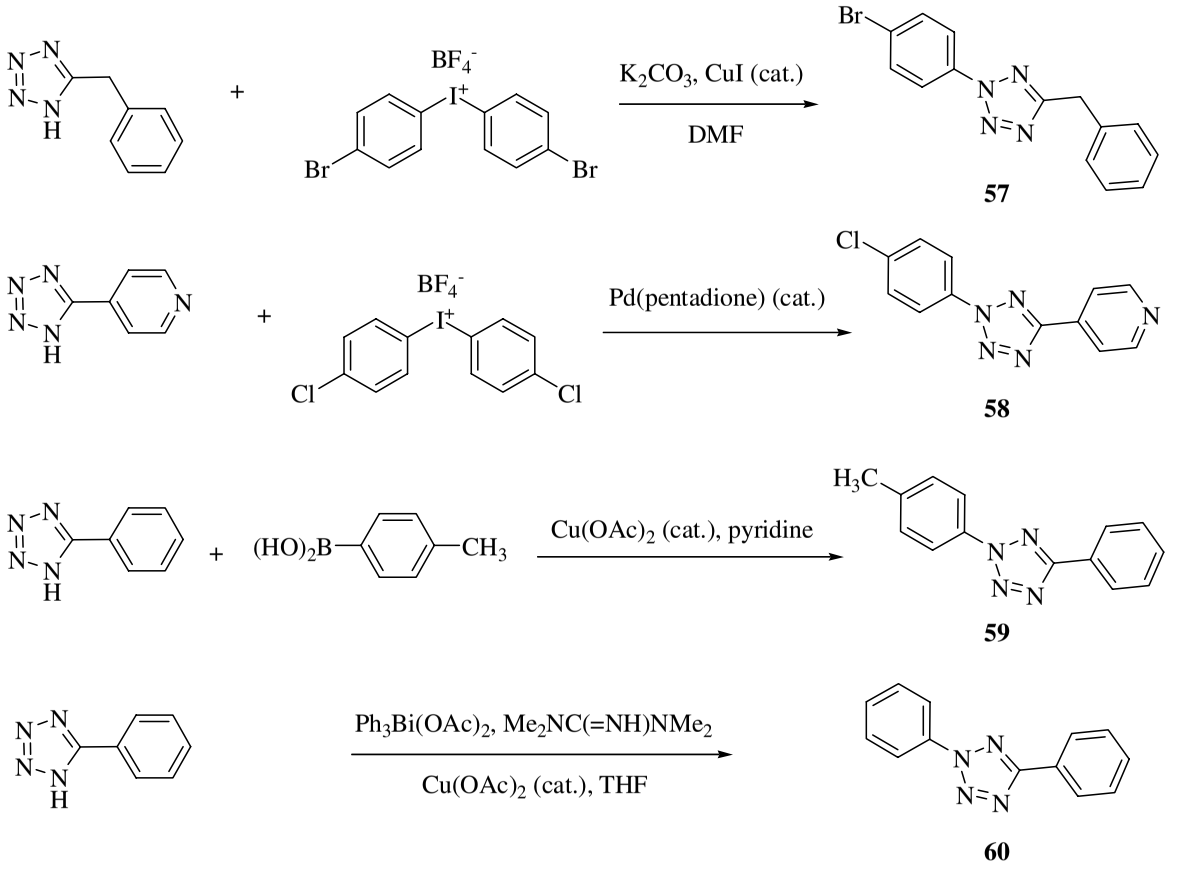
R_1	R_2	Yield
Ph	Me	55%
Ph	Et	57%
2,4,6-Me_3Ph	Me	70%
2,4,6-Me_3Ph	Et	65%
4-NO_2Ph	Me	72%
4-NHAcPh	Me	92%
4-BrPh	Me	94%
4-ClPh	Me	80%
4-MePh	Me	52%

Scheme 15.33 Acylation reactions of tetrazoles [56].

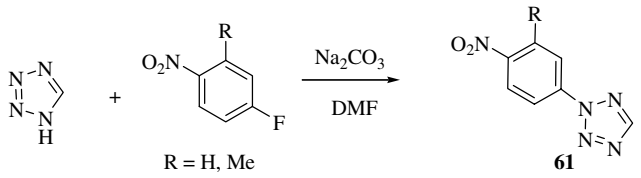
products **57** and **58** (Scheme 15.34) [57]. Phenyl boronic acids and aryl bismuth salts can also be used with copper catalysts to produce C,2N-diaryl tetrazoles **59** and **60**, respectively, from C-arylated tetrazoles [58].

Tetrazole can displace fluorine from 4-nitrofluorobenzenes to produce *N*-(4-nitrobenzene) derivatives **61** (Scheme 15.35) [59].

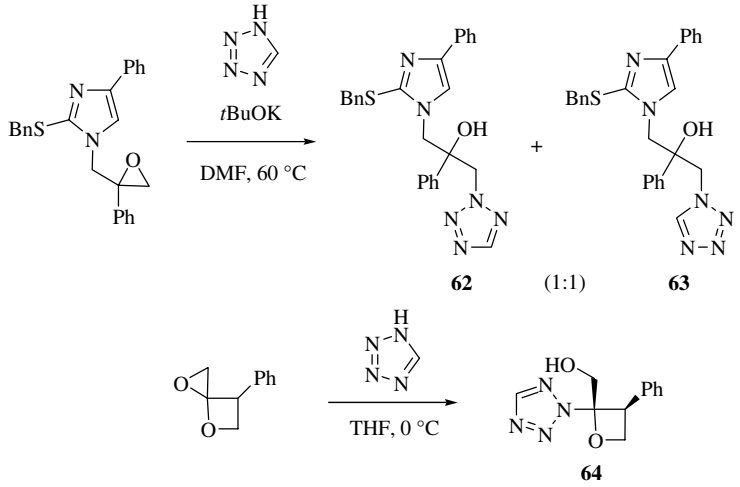
Tetrazoles react with epoxides readily to produce both N1 and N2 substituted adducts depending on the conditions used. When a base like potassium *t*-butoxide is used to deprotonate the tetrazole, both N2 and N1 adducts **62** and **63**, respectively, are obtained (Scheme 15.36) [60]. In contrast, when tetrazole is reacted directly, albeit on a *strained* epoxide, only N2 adduct **64** is obtained [61].



Scheme 15.34 Arylation of tetrazoles [57, 58].



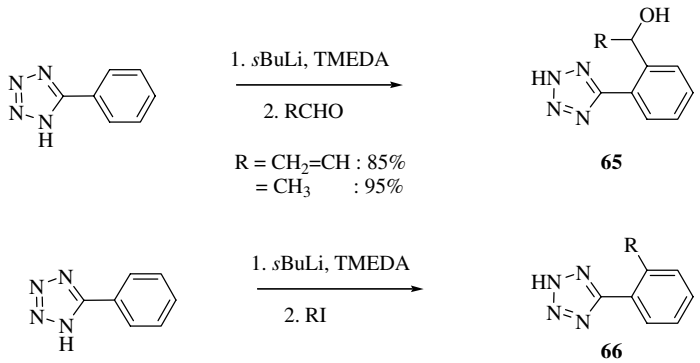
Scheme 15.35 Nucleophilic addition on activated fluorobenzenes [59].



Scheme 15.36 Reactions of tetrazoles with epoxides [60, 61].

15.3.3
Miscellaneous Reactions

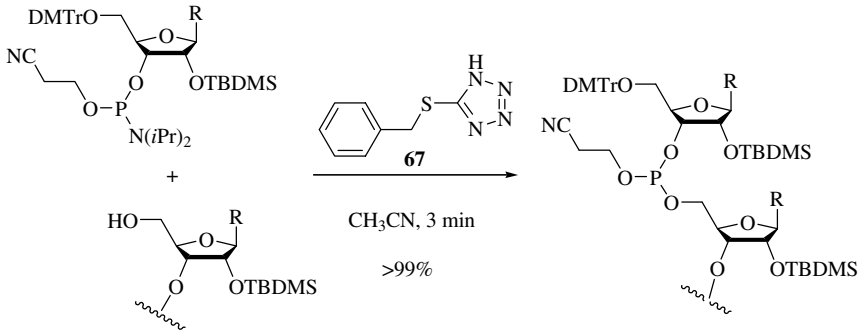
C-Phenyltetrazoles can be lithiated at the ortho position of the phenyl ring – hence the tetrazole ring is seen as an ortho-directing substituent (Scheme 15.37) [62]. These



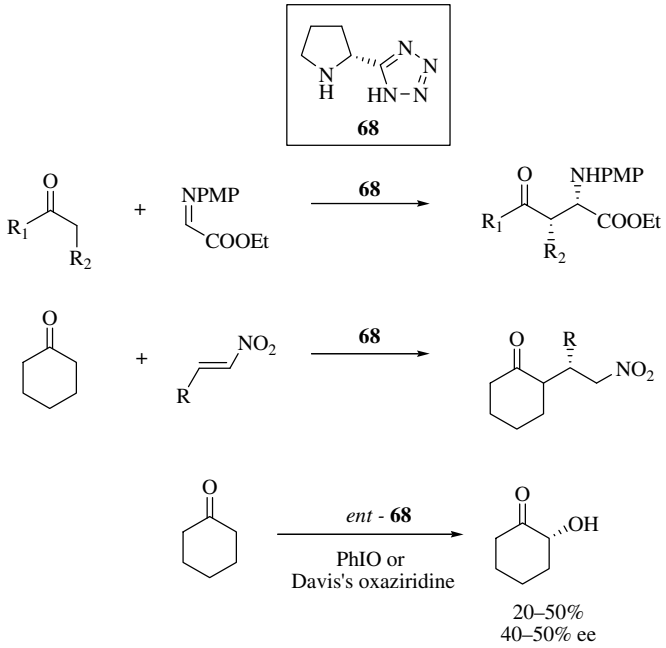
Scheme 15.37 Tetrazole ring as an ortho-directing group [62, 63].

lithiated species can be quenched with various electrophiles to produce the corresponding adducts **65** and **66** [63].

Tetrazole compounds are also used as catalysts in various reactions. They have been extensively used in nucleotide chemistry to couple individual phosphoramidite nucleotides to form long chain RNA molecules. 1*H*-Tetrazole itself has been prominent in this chemistry. More recently, 5-(benzylmercapto)-1*H*-tetrazole (**67**) has been shown to be an excellent activator for RNA synthesis (Scheme 15.38) [64]. Compared to routinely used 1*H*-tetrazole, application of a 0.25 M solution of **67** in acetonitrile allows higher coupling yields (>99%), lower coupling times (3 min) and



Scheme 15.38 Tetrazole derivative used in nucleotide coupling [64].



Scheme 15.39 Reactions using tetrazole compounds as catalysts [65–67].

reduced excess of phosphoramidites in solution over the solid-phase nucleotides (eight-fold). It has been synthesized by reacting benzylthiocyanate with sodium azide and ammonium chloride in a dioxane/water mixture.

The chiral tetrazole compound **68**, derived from proline, has been utilized in asymmetric Mannich, nitro-aldol and nitro-Michael reactions (Scheme 15.39) [65]. It has also been successfully used in asymmetric oxidation recently [66]. Its enantiomer has been utilized in aldol, nitroso-addition and α-fluorination reactions [67].

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16
Six-Membered Heterocycles: Pyridines

Concepción González-Bello and Luis Castedo

16.1
Introduction

Pyridine is the simplest six-membered heterocyclic aromatic compound that is structurally related to benzene with one CH group in the six-membered ring replaced by a nitrogen atom. It is a liquid, with a fish-like, putrid and sour odor, that is obtained from crude coal tar or is synthesized from acetaldehyde and ammonia. Pyridine, widely used as a solvent and reagent in organic chemistry, is a harmful substance by inhalation, ingestion or absorption through skin and it can produce cancer and reduce male fertility.

Pyridine derivatives are named as pyridines, indicating the positions of the substituents as **α**, β or γ or by numbers 2-, 3-, 4-. The radical is named as pyridyl. Some examples are shown in Figure 16.1.

Some alkylpyridines are known by trivial names. For instance, methylpyridines are known as picolines, dimethylpyridines as lutidines, and trimethylpyridines as collidines (Figure 16.2).

16.1.1
Relevant Pyridine Derivatives

16.1.1.1 Natural

Pyridines are rarely found in nature, being exemplified by some vitamins, cofactors and alkaloids (Figure 16.3). For example, niacin is a water-soluble vitamin that assists in the functioning of the digestive system, skin and nerves, and is also related with food metabolism. In addition, pyridoxine (vitamin B6) is an important contributor of protein metabolism. In contrast, the redox-active part of nicotinamide adenine dinucleotide (NAD^+) or nicotinamide adenine dinucleotide phosphate ($NADP^+$), important cofactors for enzymatic redox processes, is a nicotinamide heterocyclic ring.

Few alkaloids contain monocyclic pyridine derivatives, with the notable exceptions being the *tobacco alkaloids*. Of particular importance is nicotine, which is present in

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Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.

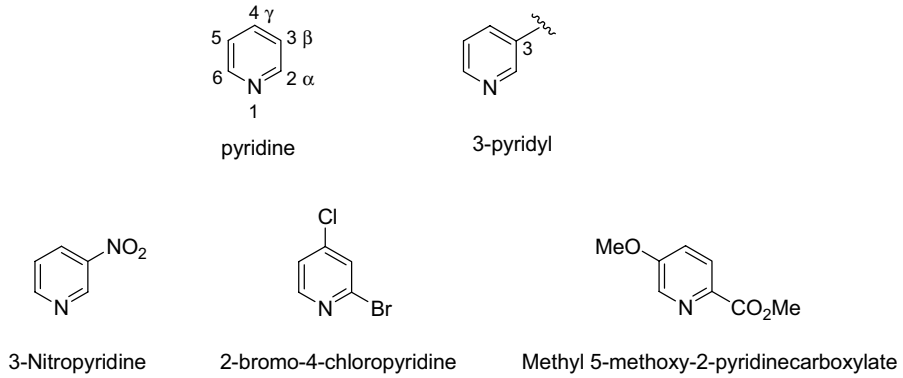


Figure 16.1 Examples of pyridine nomenclature.

dried tobacco leaves and is the active ingredient in cigarettes and other tobacco products. Nicotine produces stimulant and depressant phases of action on all autonomic ganglia and is found in many insecticides. In addition, nicotyrine and anabasine are also important pyridine derivatives of tobacco alkaloids.

16.1.1.2 **Unnatural**

Over the last 50 years interest in pyridine derivatives has risen sharply with the discovery of many bioactive compounds containing a pyridine ring. The development of different pyridine drugs has been especially interesting for the pharmaceutical industry, as the existence of over 7000 drugs with a pyridine ring demonstrates (Figure 16.4) [1, 2]. For instance, isoniazide is an antibiotic used to treat tuberculosis; sulphapyridine is used to help control dermatitis herpetiformis; ABT-594 is a powerful analgesic many times more potent than morphine, without the serious side effects; niaprazine is an antihistamine, bronchodilator and sedative; piroxicam is a non-steroidal anti-inflammatory drug used to relieve the pain, tenderness inflammation and stiffness caused by arthritis; niflumic acid is used as an antirheumatic

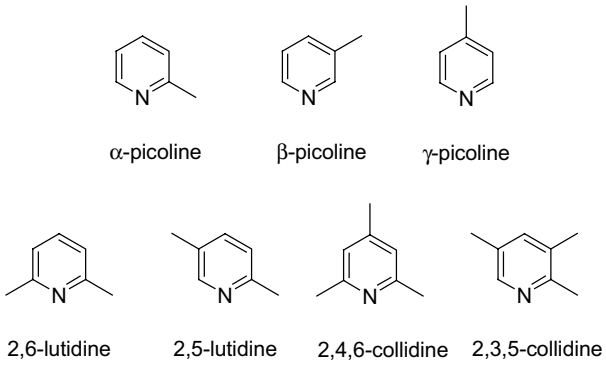
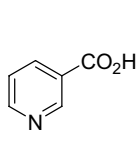
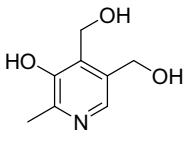


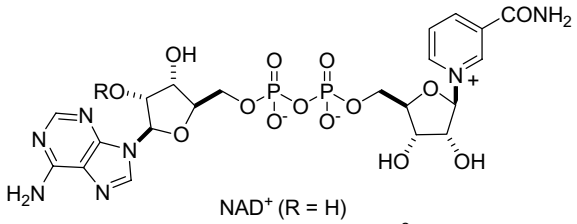
Figure 16.2 Nomenclature of some methylpyridines.



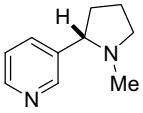
Niacin



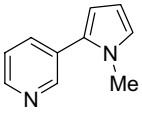
Pyridoxine



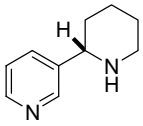
NAD^+ (R = H)
$NADP^+$ (R = OPO_3^{-2})



Nicotine

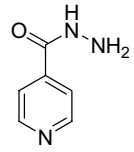


Nicotyrine

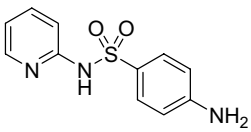


Anabasine

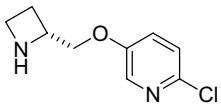
Figure 16.3 Relevant natural pyridine compounds.



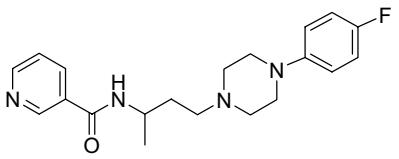
Isoniazide



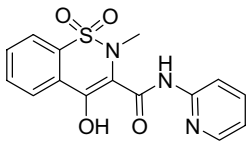
Sulphapyridine



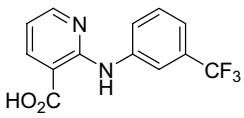
ABT-594



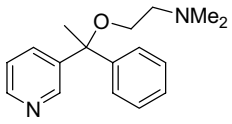
Niaprazine



Piroxicam



Niflumic acid



Doxylamine

Figure 16.4 Relevant pyridine drugs.

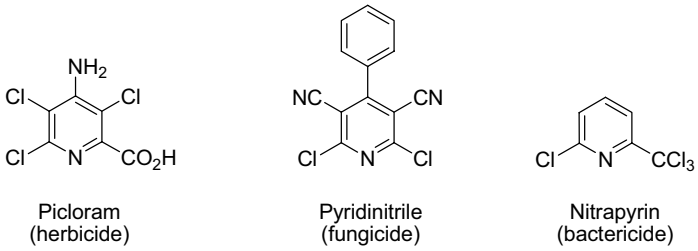


Figure 16.5 Examples of agrochemical pyridine derivatives and their applications.

and analgesic; doxylamine is an antihistamine used for short-term treatment of insomnia and also to treat symptom soft allergy, colds and upper respiratory infections.

Pyridine derivatives are also very important compounds for the agrochemical industry due to their applications as herbicides, fungicides or bactericides (Figure 16.5) [3–5].

16.1.2 Spectroscopic Data

16.1.2.1 NMR Data

The presence of the nitrogen atom in the aromatic ring produces a strong deshielding influence of the ring **α**-hydrogen and **α**-carbon atoms, and a similar but smaller effect on the ring γ-hydrogen and γ-carbon atoms. Typical ^{1}H NMR and ^{13}C NMR chemical shifts are indicated in Figure 16.6. The coupling constants of the pyridine aromatic protons are usually similar to benzenes, except in the case of the H2 proton whose coupling constant is reduced from 7–8 to 4–6 Hz. Substituent effects follow the same general trend as in substituted benzenes.

The ^{15}N NMR signal for pyridine-type nitrogen appears at comparatively low field (57 ppm in CCl_4). Substituent effects are often considerable, particularly when electron-donating groups are present in the aromatic ring and, consequently, downfield shifts are observed. For instance, the chemical shift of N1 in 4-methoxypyridine, 4-aminopyridine and 4-nitropyridine is 90, 105 and 35 ppm (in acetone), respectively (Figure 16.7).

The nitrogen chemical shift of pyridine increases up to 100 ppm when the lone electron pair is protonated. For instance, the nitrogen signal of pyridinium hydrochloride appears at 181 ppm (in water). N-Oxidation of the nitrogen also shifts the signal downfield, but only between 10 and 30 ppm. Hydrogen bonding to the nitrogen lone pair leads to a downfield shift that depends on the strength of the bonding. Shifts of approximately of 20 ppm are usually found.

16.1.2.2 UV Data

Pyridine shows two absorption maxima, at 195 and 250 nm (in CCl_4). The UV spectra varies with pH because of quaternary salt formation. For example, 4-*tert*-butylpyridine

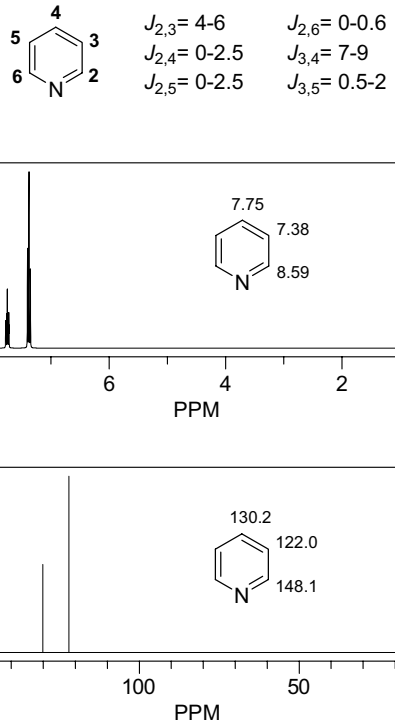


Figure 16.6 Proton coupling constants (Hz) and ^{1}H and ^{13}C NMR spectra of pyridine.

has an absorption maximum at 262 or 255 nm in 0.1 M HCl or 0.1 M NaOH, respectively.

16.1.2.3 **IR Data**

The pyridine IR spectrum is quite similar to the corresponding vibrations of benzene. Pyridine has C–H stretching frequencies in the range 3020–3070 cm^{-1} as well as C=C and C=N stretching frequencies at 1590–1660 cm^{-1} and near 1500 cm^{-1}.

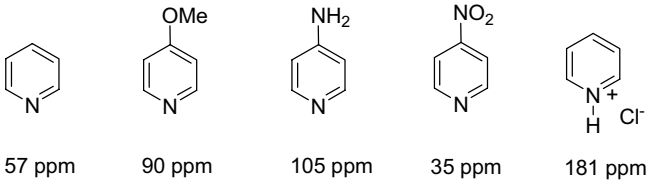


Figure 16.7 Examples of effect of substituents on the nitrogen chemical shift.

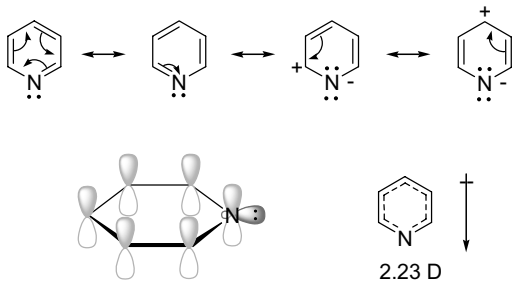


Figure 16.8 Pyridine resonance forms. The ring nitrogen atom has a negative charge.

16.1.3 General Reactivity

Pyridine can be considered a benzene derivative in which an sp^2-hybridized nitrogen atom replaces a CH unit. The pyridine ring is aromatic and several resonance structures may be drawn (Figure 16.8). The aromatic ring electronic structure is strongly modified by the presence of the electronegative nitrogen atom, which has a lone pair of electrons in one of the sp^2 hybrid orbitals orthogonal to the π-system. Consequently, this excess electron density is localized on the ring nitrogen atom and it is not delocalized around the ring. On the other hand, the ring nitrogen atom pulls charge from the ring because the nitrogen atom is more electronegative than carbon and, therefore, pyridine is more polar than benzene, as its dipole moment (2.23 D) shows.

Pyridine reactivity is based on the charge distribution within the ring, the electronic effects of ring substituents and to a lesser extent on steric effects. Pyridines are electron-deficient heterocycles that have many analogies in reactivity with nitrobenzene due to their electron distribution. In both molecules, the positive charge is located at positions 2 and 4 of the ring, and the negative charge is placed in the ring nitrogen atom for pyridines or in the C1 carbon atom for nitrobenzene (Figure 16.9).

The ring nitrogen atom of pyridines is a reasonable nucleophile to react with electrophiles such as alkyl and acyl halides, leading to stable quaternary salts (Scheme 16.1). In addition, pyridines are weak bases compared with the corresponding piperidines; they react with Brønsted acids such as HCl, HNO_3, H_2SO_4 and so on, to form pyridinium ions, and with Lewis acids such as $AlCl_3$, $SnCl_4$, and so on to afford stable pyridinium complexes.

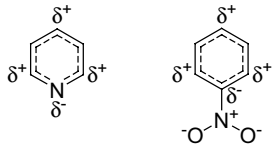
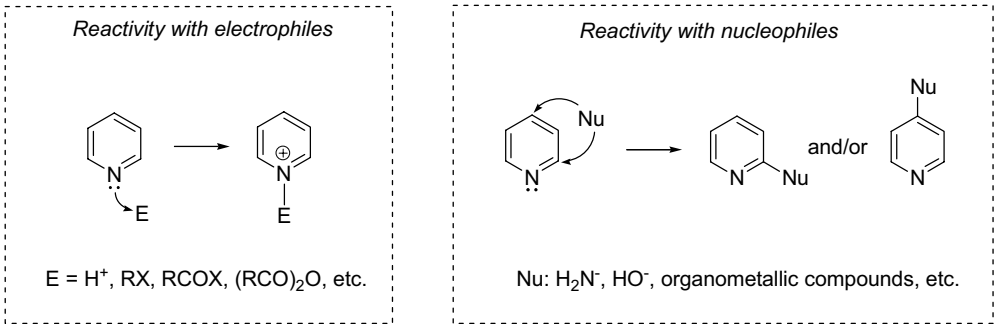


Figure 16.9 Pyridine and nitrobenzene charge distributions.



Scheme 16.1

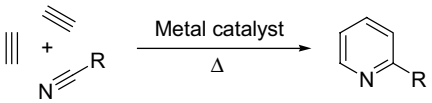
The electron-deficient nature of the pyridine ring allows nucleophiles to react with pyridines by a nucleophilic aromatic substitution mainly at the **α**- and γ-positions. A wide range of nucleophiles can be employed, such as amide anions, hydroxyl groups, organometallic compounds, and so on, allowing the selective functionalization of the **α**- and γ-positions of the pyridine ring with a large variety of functional groups. Pyridine electrophilicity is enhanced in the presence of electron-withdrawing groups in the ring.

16.2
Synthesis of Pyridines

16.2.1
Synthesis by Cycloaddition Reactions

16.2.1.1 [2 + 2 + 2] Cycloadditions

One of the most convenient synthetic approaches to pyridines is the [2 + 2 + 2] cycloaddition of alkynes to nitriles catalyzed by transition-metals (Scheme 16.2) [6–10]. It is an atom-economical and extraordinarily effective method to prepare substituted pyridines. Although in principle thermal [2 + 2 + 2] cycloadditions are symmetry allowed, entropic barriers associated with the approximation of the three components and enthalpic activation energy contributions disfavor the pericyclic process [11–13]. In fact, reports of purely thermal [2 + 2 + 2] cycloadditions are rare in literature. However, these energetic barriers can be circumvented by the use of metals that coordinate to the reaction partners in a step-wise process.



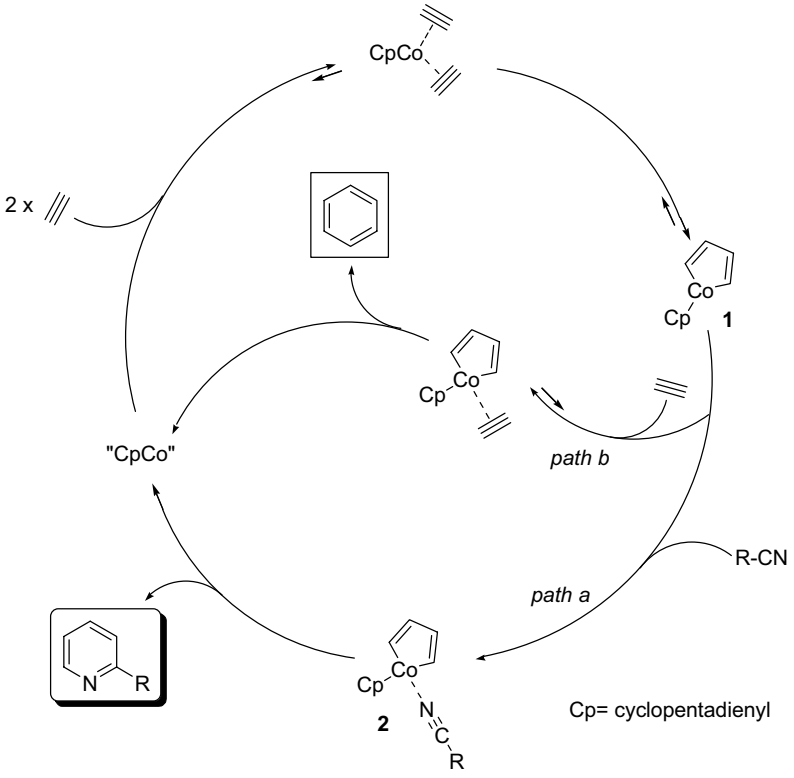
R = alkyl, vinyl, aryl

Scheme 16.2

Until recently, most reported examples of co-cyclization reactions of alkynes to nitriles focused on cobalt-based catalysts. For example, Wakatsuki and Yamazaki [14, 15] reported in 1973 the first synthesis of pyridines using stoichiometric and, later on, catalytic cobaltacyclopentadienes.

The mechanistic and synthetic studies reported by Bönnemann were crucial for the development of this reaction [16–20]. The proposed mechanism is shown in Scheme 16.3. Thus, two alkyne moieties coordinate to the metal, and then oxidative coupling proceeds to give the Co(III)-metallacycle **1**. Because nitriles are generally better σ-donors than alkynes and, therefore, are better ligands for Co(III), the nitrile addition (path a) is more favored than the addition of a third alkyne (path b). Coordination of a nitrile to the metallacycle **1** takes place initially through the nitrogen to afford Co complex **2**, which finally evolves by insertion of the nitrile to the metallacycle followed by reductive elimination to yield the pyridine derivative with concomitant regeneration of the CpCo catalyst.

Whereas the nitriles undergo practically exclusive conversion into pyridine derivatives, the alkyne component always undergoes some degree of conversion into benzene derivatives. The ratio of pyridines to benzene products can be directed in favor of pyridines by using an excess of the nitrile. If catalysis is conducted in the



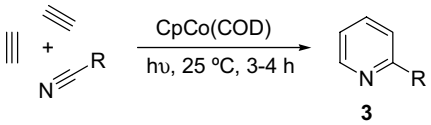
Scheme 16.3

presence of a permanent excess of nitrile and a stoichiometric amount of alkyne, pyridines can be obtained in yields up to 90%.

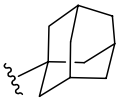
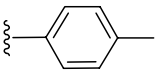
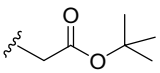
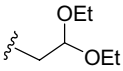
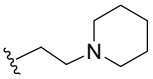
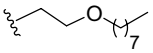
The photochemical variant of the reaction provides a valuable extension of the existing methods, avoiding the harsh reaction conditions of the thermally initiated method. By irradiation of the reaction mixture with UV-Vis light (350–500 nm), or, alternatively, with sunlight as the energy source for catalyst activation [21, 22], the reaction could be carried out at ambient temperature and pressure and even permits the use of water as solvent. Besides improved operational safety with respect to the thermally initiated variant, the photochemical cycloaddition bears the opportunity to improve chemoselectivity by avoiding the homocyclotrimerization of the alkyne moieties [23, 24]. For instance, a series of 2-pyridines **3** have been synthesized at 25 °C in 3–4 hours by the photocatalyzed [2 + 2 + 2] cycloaddition of various nitriles with acetylene (Table 16.1) [25].

The co-cyclization of monosubstituted alkynes **4** to nitriles **5** usually gives a mixture of 2,4,6- (**6**) and 2,3,6-trisubstituted pyridines (**7**), with the former products being predominant (Table 16.2). The regioselectivity of the reaction is related to the electron density on the metal. Co complexes containing electron-withdrawing

Table 16.1 Examples of [2 + 2 + 2] cycloaddition of acetylene with nitriles[a].



3

R	Solvent	Yield (%)
	Hexane	90
	Toluene	80
	Hexane	81
	Water + 2% (v/v) toluene	85
	Toluene	79
	Toluene	80

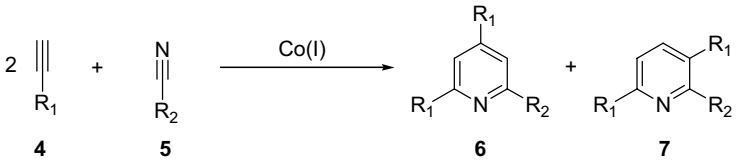
a) COD = cyclooctadiene.

ligands, for instance (C_5H_4COMe)Co(COD) [18, 26] (COD=cyclooctadiene) or ($C_5H_4CO_2Me$)Co(COT) [27], (COT=cyclooctatetraene), give high yields but low regioselectivities (1.5 : 1), whereas Co complexes containing electron-rich ligands, for instance (C_5Me_5)Co(COD), afford higher regioselectivities (3.5 : 1) but low yields. Table 16.2 shows the effect of the type of Co catalyst on the reaction regioselectivity.

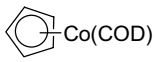
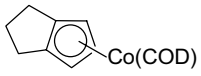
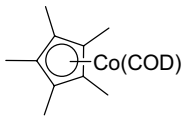
The low regioselectivity of the [2 + 2 + 2] cycloaddition reactions can be circumvented by tethering two of the three reaction components. Two approaches have been employed, either reaction of dialkynes and nitriles (Scheme 16.4a) or alkynenitriles and alkynes (Scheme 16.4b).

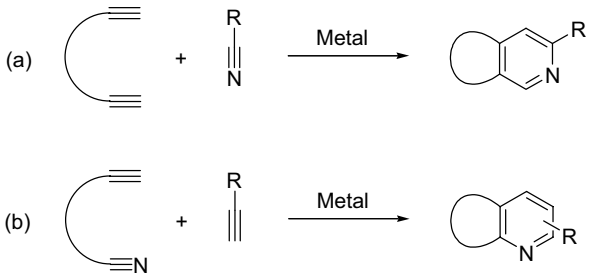
(a) Co-oligomerization of dialkynes with nitriles affords chemo- and regioselective formation of oligoheterocyclic systems in a single step. For instance, the co-oligomerization of diyne **8** with various substituted nitriles **9** gives pyridines **10** in good yields and high selectivities (Scheme 16.5) [29]. Pronounced regioselectivity has been observed in the reaction of 1,7-decadiyne (**11**) with valeronitrile (**12**), affording tetrahydroisoquinoline **13** as the major regioisomer (Scheme 16.5) [29].

Table 16.2 Reaction temperature and regioselectivity for 65% propyne conversion.

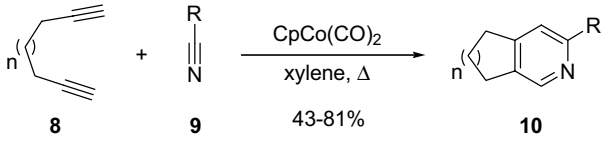


4 **5** **6** **7**

Co complex	*T* (°C)	Ratio **6** : **7** (R_1 = Me; R_2 = Et) [18, 26, 28]
	119	1.22 : 1
	123	1.46 : 1
	144	1.67 : 1
	140	1.73 : 1
	147	1.71 : 1
	180	2.50 : 1
	220	3.51 : 1



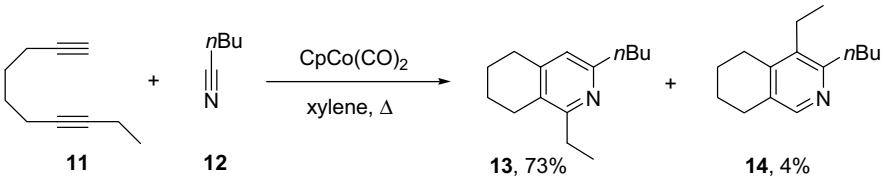
Scheme 16.4



8 **9** **10**

n= 1, 2, 3

R = alkyl, aryl, CH_2OMe, CH_2CO_2Et

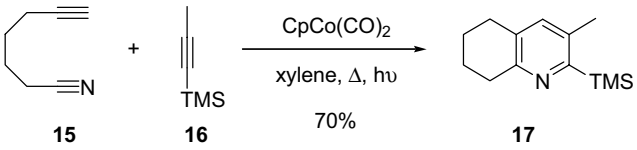


11 **12** **13**, 73% **14**, 4%

Scheme 16.5

(b) **α**,ω-Alkynenitriles **15** are catalytically co-cyclized with alkynes **16** in the presence of $CpCo(CO)_2$ to furnish chemo- and regioselective [*b*]annulated pyridines **17** (Scheme 16.6) [30].

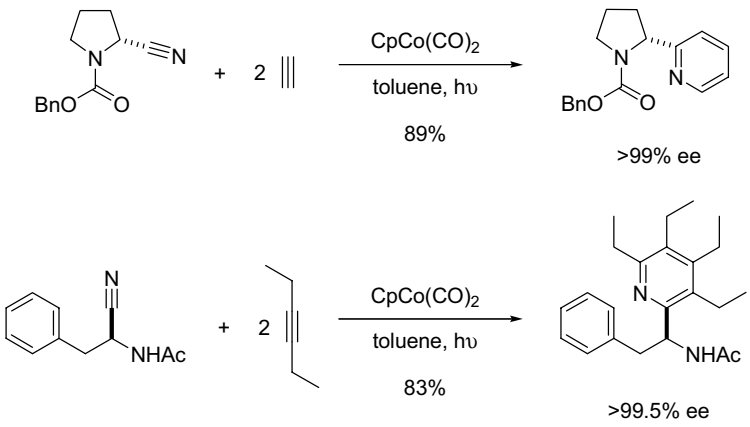
Chiral pyridine derivatives can be obtained by metal-catalyzed cycloaddition of optically pure nitriles and alkynes. Under thermal conditions, the enantiomeric excess of the product decreases in many cases by 2–10%, which is attributed to the high reaction temperatures (>100 °C) necessary to initiate the catalysis [31–39]. However, using the photochemical version of the reaction, this problem is



15 **16** **17**

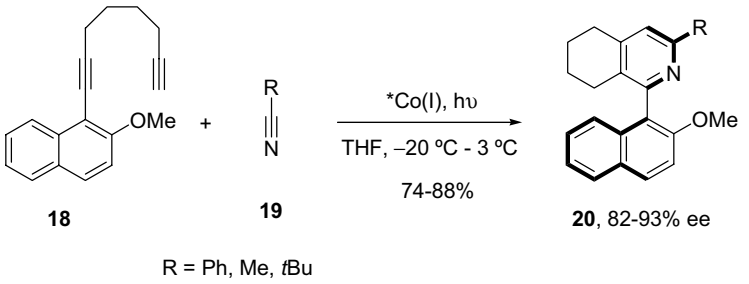
Scheme 16.6

circumvented, affording optically pure pyridine derivatives without detectable loss of enantiomeric purity (Scheme 16.7) [40].



Scheme 16.7

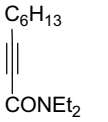
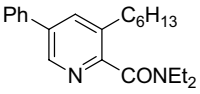
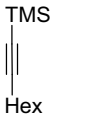
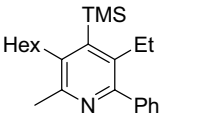
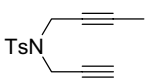
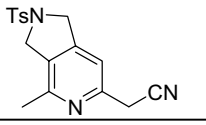
Recently, it has been shown that by using modified chiral Co(I) complexes of the type CpCo(COD) homochiral 1-aryl tetrahydroisoquinolines **20** are obtained in 82–93% ee by co-oligomerization of diyne **18** and various nitriles **19** (Scheme 16.8) [41].



Scheme 16.8

Although many examples of Co-catalyzed [2 + 2 + 2] cycloaddition of nitriles to alkynes have been reported, the regioselective assembly of two different unsymmetrical alkynes and a nitrile, leading to a single pyridine derivative, still remains unsolved. In a few cases, a single pyridine has been obtained with the assistance of a functional group such as an ester group [42]. However, in most cases a mixture of regioisomers is obtained. This can be attributed to the two possible orientations of the nitrile during the formation of the cobaltacyclopentadiene. Therefore, the regioselectivity of the reaction is completely dependent on the substitution of the alkynes. This selectivity problem has been greatly improved with the use of other

Table 16.3 Examples of [2 + 2 + 2] cycloaddition of nitriles to alkynes mediated by diverse transition-metal complexes.

Alkynes	Nitrile	Metal complex	Product	Yield (%)	Reference
		$Ti(OiPr)_4/iPrMgCl$		70	[43]
		Cp_2ZrBu_2 $NiCl_2(PPh_3)_2$		59	[44]
		$Cp^*Ru(COD)Cl$[a]		95	[45]

a) Cp^* = pentamethylcyclopentadienyl.

transition-metal complexes such as Fe, Rh, Ni, Ti, Ta, Ru, Zr/Ni and Zr/Cu [6]. Table 16.3 shows some examples.

16.2.1.2 [4 + 2] Cycloadditions

Pyridine derivatives can be efficiently synthesized by the [4 + 2] cycloaddition (hetero-Diels–Alder) of an azadiene and a dienophile (Figure 16.10a and b) or a diene and an azadienophile (Figure 16.10c). Careful selection of the appropriate azadiene/diene and the complementary dienophile/azadienophile and well-defined reaction conditions can result in a good approach to substituted pyridines.

In selecting an appropriate diene and dienophile it is important to understand that the Diels–Alder reactions can be classified as three types: (i) normal Diels–Alder

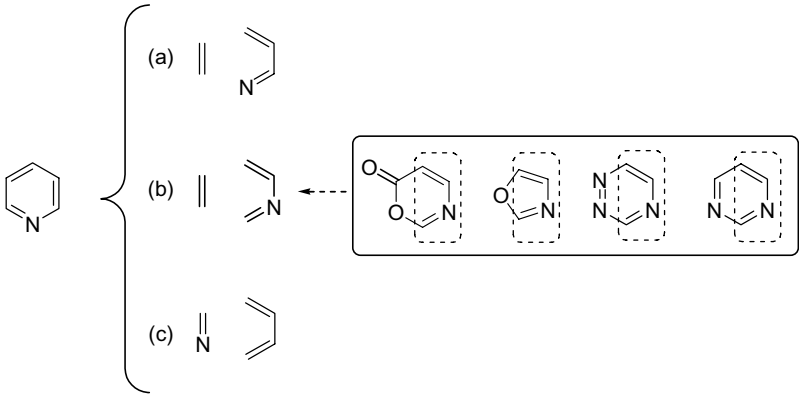


Figure 16.10 Hetero-Diels–Alder approaches to pyridine.

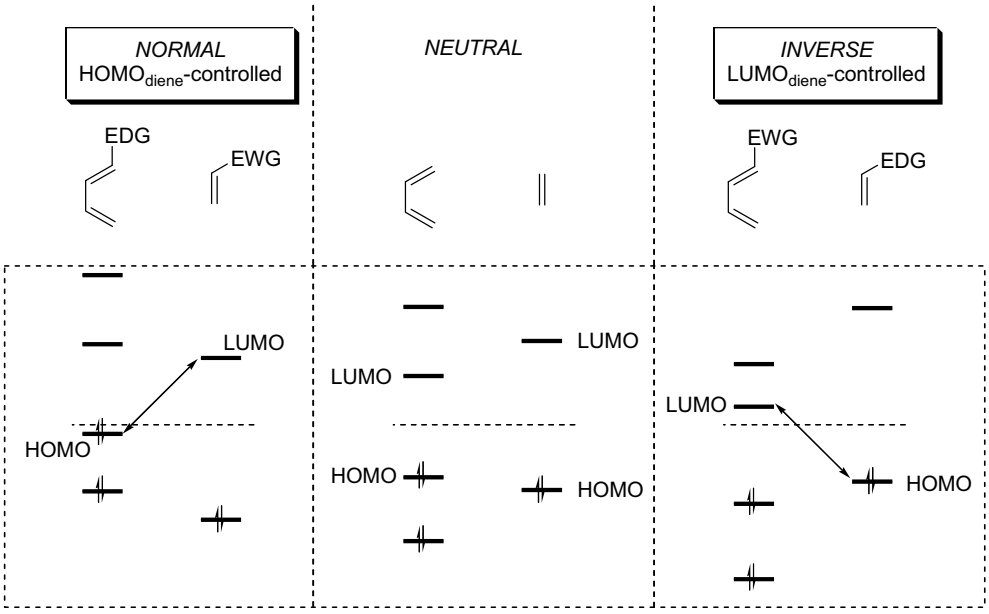
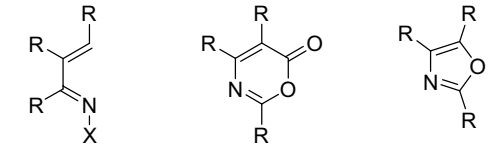


Figure 16.11 Classification of the Diels–Alder reactions.

($HOMO_{diene}$-controlled), customarily employing an electron-rich diene (increased $HOMO_{diene}$) and electron-deficient dienophile (decreased $LUMO_{dienophile}$); (ii) inverse electron demand Diels–Alder ($LUMO_{diene}$-controlled), which is favored by employing an electron-deficient diene (decreased $LUMO_{diene}$) and electron-rich dienophile (increased $HOMO_{dienophile}$); and (iii) neutral Diels–Alder (Figure 16.11) [46–48].

16.2.1.2.1 **Diels–Alder Reaction of Azadienes and Dienophiles** Azadienes as electron-deficient dienes are ideally suited for participation in inverse electron demand Diels–Alder reactions [49–51]. Electron-withdrawing groups in the azadiene accentuate its electron-deficiency and permit the use of electron-rich, strained and even simple alkenes as dienophiles. Strong electron-donating groups in the azadiene reverse its electron-deficient nature and permit the use of conventional dienophiles for normal Diels–Alder reactions. The most commonly used azadienes are azabutadienes, oxazoles, 1,3-diazines, 1,2,4-triazines, and so on (Figure 16.12).

Aza-1,3-butadienes Several examples of hetero-Diels–Alder pyridine synthesis using aza-1,3-butadienes have been reported. For example, Boger and coworkers [52, 53] recently published the total synthesis of Piericidin A1 and B1, in which the pyridine core was synthesized by an inverse electron demand Diels–Alder reaction between *N*-sulfonyl-1-aza-1,3-butadiene **22** and tetramethoxyethene (**23**) followed by Lewis acid-promoted aromatization to give pyridine **24** in good yield (Scheme 16.9).



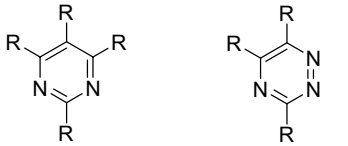
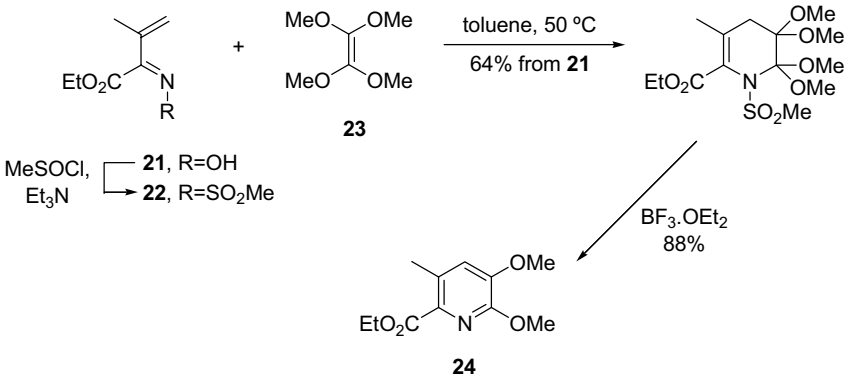
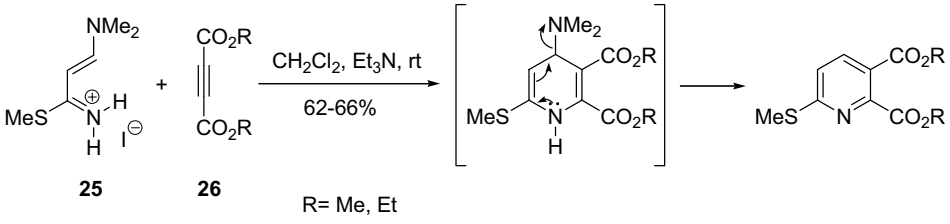


Figure 16.12 Examples of azadienes employed in the Diels–Alder reaction.



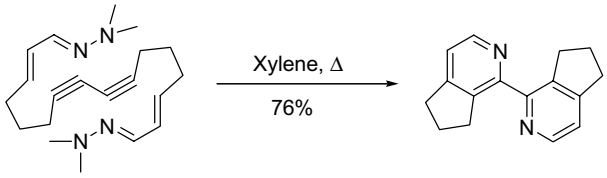
Scheme 16.9

In addition, cationic aza-1,3-butadiene **25** reacts with dialkyl acetylenedicarboxylate **26** by a tandem [4 + 2] cycloaddition/deamination reaction in the presence of triethylamine to give the product pyridines in satisfactory yields (Scheme 16.10) [54].



Scheme 16.10

Heating 1,3-diynyl bis(α,β-unsaturated hydrazone) **27** results in double intramolecular Diels–Alder reaction to give, after aromatization by loss of dimethylamine, 2,2′-bipyridine **28** (Scheme 16.11) [55].

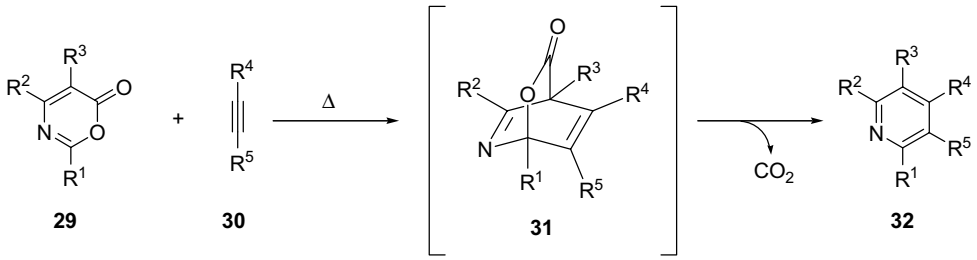


27 **28**

Scheme 16.11

1,3-Oxazin-6-ones 1,3-Oxazin-6-ones react with a large variety of alkynes to afford highly substituted pyridines. Table 16.4 shows some examples of this hetero-Diels–Alder reaction. The initial [4 + 2] cycloadduct **31** undergoes a retro-Diels–Alder reaction with loss of carbon dioxide providing regioselectively pyridine derivatives **32** in good to high yields. Alternatively, these cycloaddition reactions can also be performed with electron-rich alkenes such as 1-ethoxy-1-(dimethylamino) ethylene (Scheme 16.12).

Table 16.4 Hetero-Diels–Alder reaction of 1,3-oxazin-6-ones **29** and alkynes **30**.



29 **30** **31** **32**

Oxazinone substituents			Alkyne substituents			
R^1	R^2	R^3	R^4	R^5	Yield of **32** (%)	Reference
Ph	CF_3	H	H	CO_2Et	96	[56]
Piperidine	CF_3	H	H	CO_2Et	54	[56]
Pyrrolidine	CF_3	H	CO_2Me	CO_2Me	82	[56]
NMe_2	CF_3	H	CO_2Me	CO_2Me	85	[56]
CO_2Et	Ph	H	TMS	H	81	[57]
CO_2Et	Ph	H	TMS	TMS	88	[57]
H	Ph	H	TMS	TMS	71	[57]
*n*Pr	Me	H	NBn_2	Me	69	[58]
*n*Pr	Me	H	NEt_2	Me	83	[58]

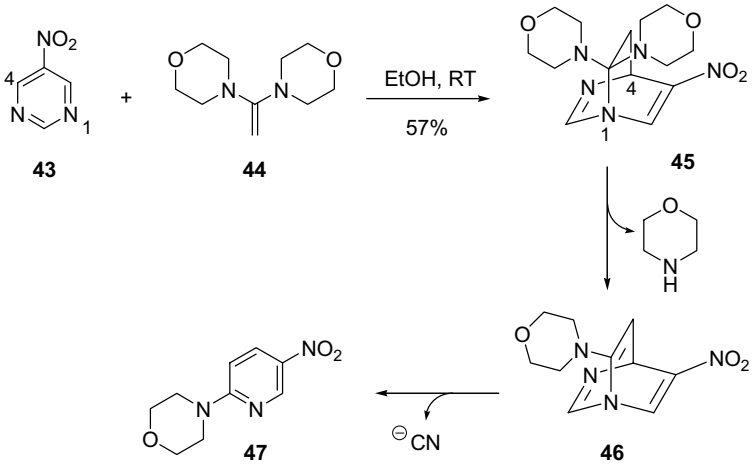
R = *i*Pr, *i*Bu, *t*Bu, CF_3

Scheme 16.12

Oxazoles Oxazoles have been used extensively as azadiene in the hetero-Diels–Alder synthesis of pyridine derivatives [50, 51]. The initial cycloadduct **35** is usually very stable, and even isolable in many cases, and can provide, depending of the reaction conditions, pyridines **36** (dehydratation/aromatization) or 3-hydroxypyridines **37** (elimination/aromatization) (Table 16.5).

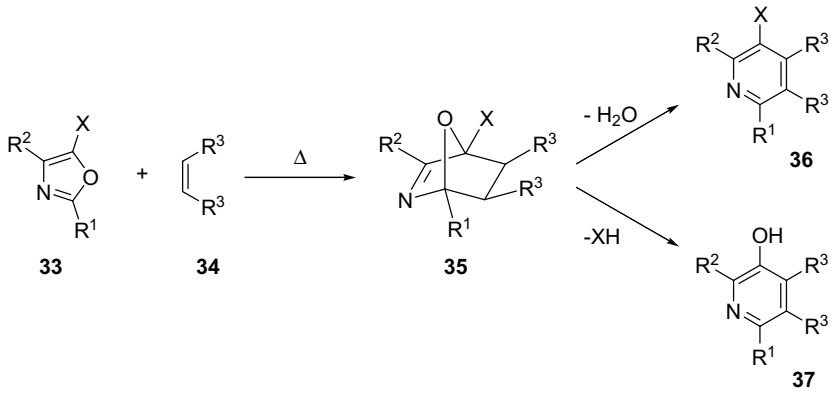
1,3-Diazines 1,3-Diazines can undergo [4 + 2] cycloaddition reactions across positions C2/C5 or N1/C4. The regioselectivity of the reaction depends on the dienophile employed as well as the substituents present in the diazine nucleus. For example, diazine **38** reacts with *N,N*-diethyl-1-propynylamine (**39**) by an inverse electron demand Diels–Alder reaction across position C2/C5 (Table 16.6) [64]. Diazines **38a** and **38b** react via the cycloadduct **40**, affording exclusively regioisomers **41** in excellent yield. However, the opposite regioselectivity is obtained with diazine **38c**, which gives pyridine **42** in 81% yield.

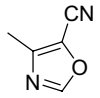
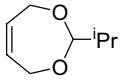
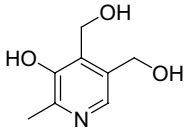
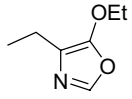
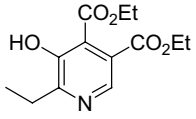
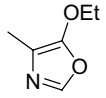
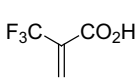
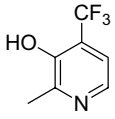
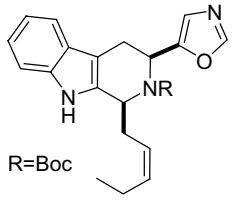
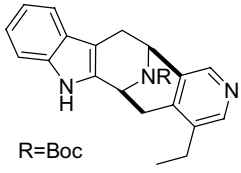
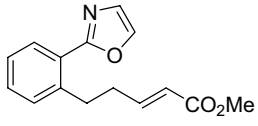
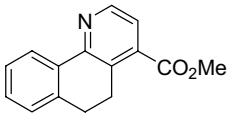
A [4 + 2] cycloaddition reaction across N1/C4 occurs in the reaction of diazine **43** with enamine **44** to give 2-morpholino-5-nitropyridine **47** in 57% yield (Scheme 16.13) [65]. Its formation can be explained via intermediates **45** and **46**.



Scheme 16.13

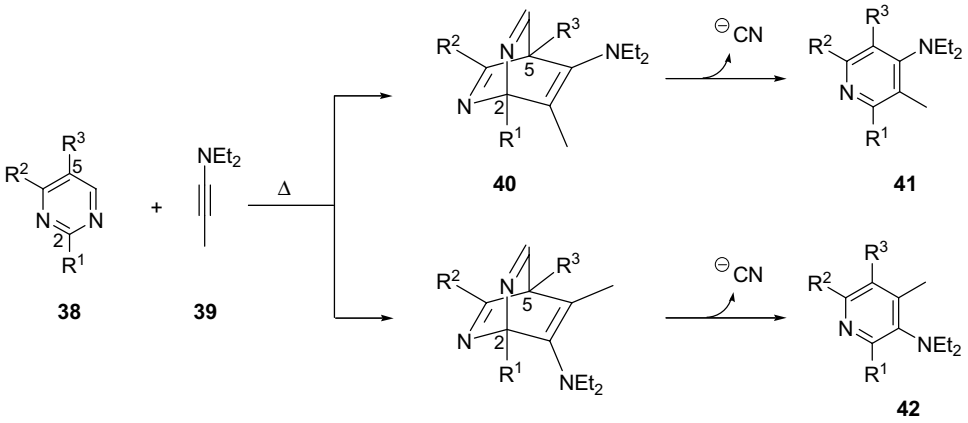
Table 16.5 Examples of hetero-Diels–Alder synthesis of pyridines using oxazoles as azadienes.



Dienophile 33	Diene 34	Conditions	Product	Yield (%)	Reference
		(1) MW, 120 °C (2) H^+		80	[59]
		(1) 115 °C (2) HCl, EtOH		51	[60]
		120 °C		56	[61]
		DBN[a], Δ		69	[62]
		DBN[a], Δ		76	[63]

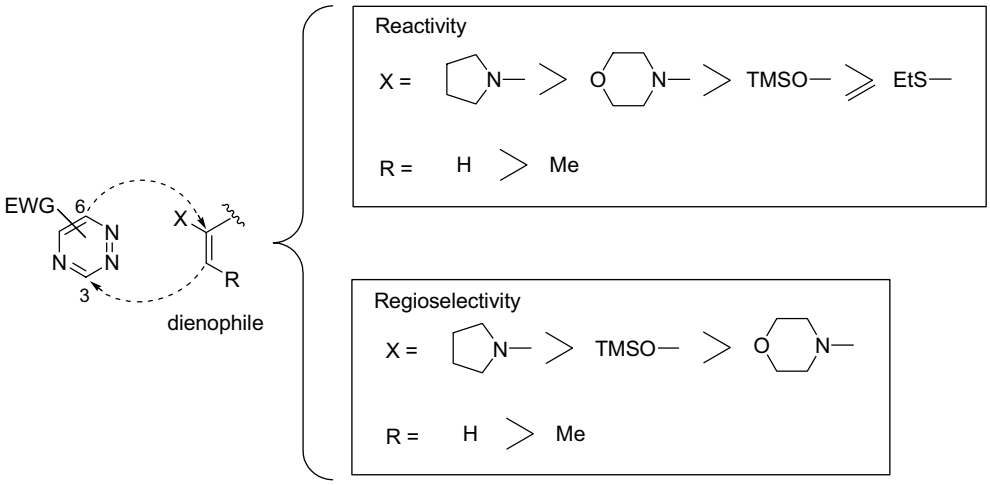
a) DBN = 1,5-diazabicyclo[4.3.0]non-5-ene.

Table 16.6 Hetero-Diels–Alder reaction of *N*,*N*-diethyl-1-propynylamine **(39)** with diverse diazines.



	R^1	R^2	R^3	**41**	**42** (% yield)
38a	H	H	CO_2Me	90	0
38b	H	CO_2Me	CO_2Me	80	0
38c	CO_2Me	CO_2Me	H	0	81

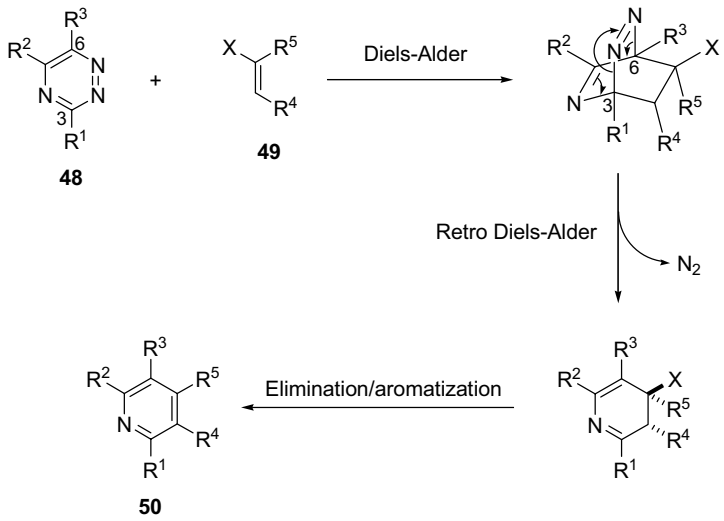
1,2,4-Triazines Aside from oxazoles, substituted 1,2,4-triazines constitute the most thoroughly investigated heteroaromatic azadienes in hetero-Diels–Alder reactions. Two potential modes of [4 + 2] cycloaddition reaction can occur, across positions C3/C6 or C5/N2 of the 1,2,4-triazine nucleus (Scheme 16.14). Regioselective inverse



Scheme 16.14

electron demand Diels–Alder reactions across positions C3/C6 can be achieved with 1,2,4-triazines substituted with electron-withdrawing groups and dienophiles substituted with electron-donating groups. Typical dienophiles are enamines, enol ethers and reactive or strained alkenes. Although the regioselectivity of the C3/C6 cycloaddition is controlled by several factors, such as the electronic and steric properties of the triazine and the dienophile [66] and the reaction conditions, it is the strong preference for the nucleophilic carbon of the dienophile to attack the C3 position of the 1,2,4-triazine nucleus that determines the regioselection outcome.

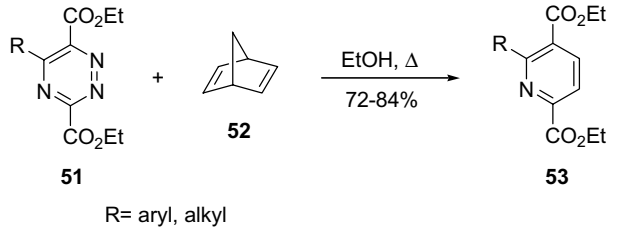
Scheme 16.15 shows the established mechanism for the reaction of 1,2,4-triazines **48** and EDG-dienophiles **49**, in which the first step is the inverse electron-demand Diels–Alder reaction, followed by *in situ* loss of nitrogen and subsequent elimination/aromatization to give pyridine derivative **50**. For instance, 1,2,4-triazines **51** and **54** react with bicyclic alkene **52** and trimethoxyethene **55** to afford pyridines **53** [67] and **56** [68], respectively, in high yields (Scheme 16.16).



Scheme 16.15

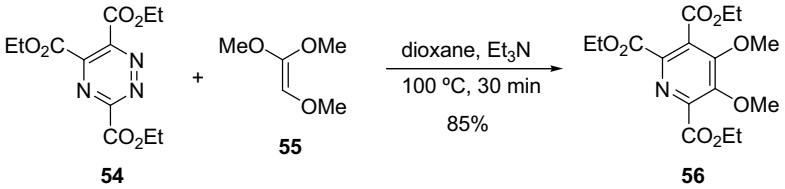
Enamines have been widely used as dienophiles in the [4 + 2] cycloaddition synthesis of highly substituted pyridines [69–71]. For instance, diverse fused bicyclic pyridines **59** have been prepared from 1,2,4-triazines **57** and enamine **58** (Scheme 16.17). Using enamine **61** the reaction takes place with an entirely different regiochemistry, depending on the triazine substitution (Table 16.7).

This approach had two main limitations: the requirement of preformed enamine and the unusual stability of the cycloadduct intermediate. Boger and coworkers [72] circumvented these difficulties by the addition of 4 Å molecular sieves, which allowed enamine formation to catalyze the elimination step (Scheme 16.18). Recently, Taylor and coworkers [73] reported an improved version of this method using a microwave



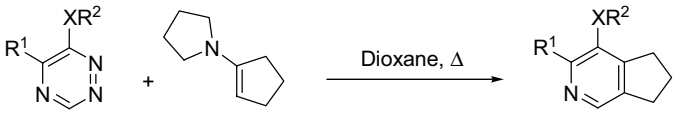
51 53

R= aryl, alkyl



54 56

Scheme 16.16



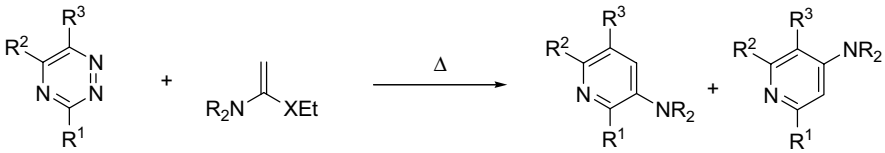
57 58 59

X = S, SO, SO_2
R^1= Me, Ph, $CH(Me)_2$
R^2= Me, Bn

X = S, 91-98%
X = SO, 68-92%
X = SO_2, 46-88%

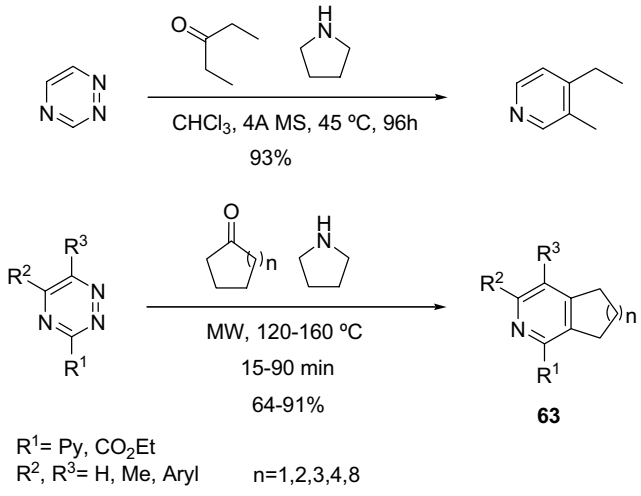
Scheme 16.17

Table 16.7 [4 + 2] cycloaddition of 1,2,4-triazines **60** and enamine **61**.



60 61 62a 62b

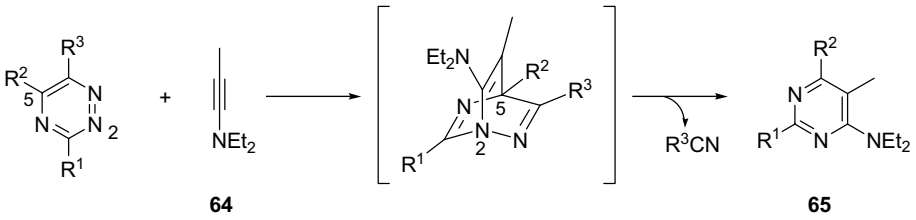
Triazine 60			Enamine 61		Product (% yield)	
R^1	R^2	R^3	X	R	62a	62b
Me	H	H	O	Me	—	60
Ph	H	H	O	Me	81	—
H	Ph	H	O	Me	8	58
Me	H	Ph	O	Me	—	83
CO_2Me	H	H	S	Et	82	—



Scheme 16.18

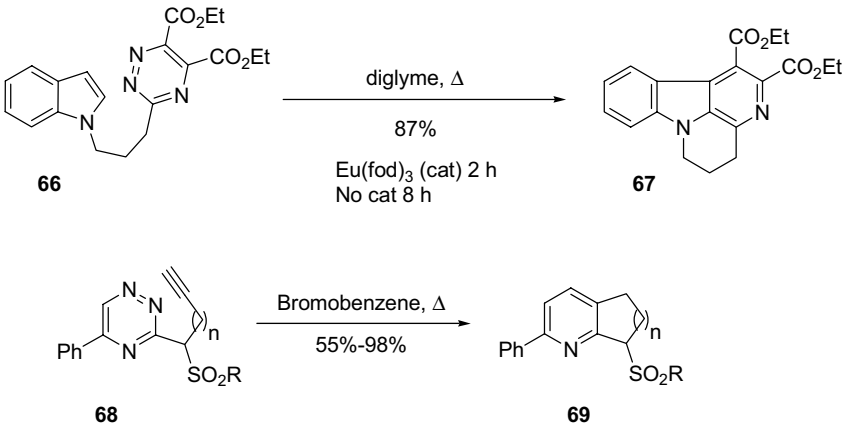
(MW)-promoted procedure. Under these conditions tri-, tetra- and penta-substituted pyridines **63** can be synthesized in good yields with relatively short reaction times.

Although, addition across C3/C6 of the 1,2,4-triazine nucleus is nearly always favored, ynamines **64** react exceptionally across C5/N2 with subsequent loss of nitrile by a retro-Diels–Alder reaction to form pyrimidines **65** (Scheme 16.19) [74–78].



Scheme 16.19

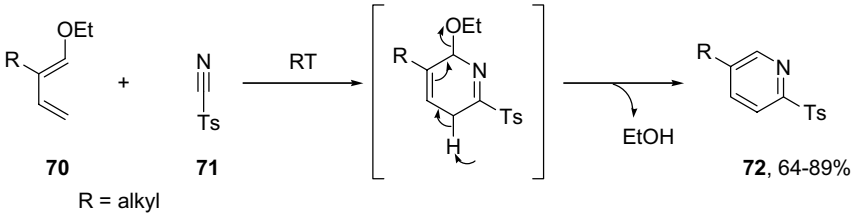
In addition, 1,2,4-triazines undergo intramolecular inverse electron demand Diels–Alder cycloadditions to produce bicyclic pyridines. For instance, 1,2,4-triazine-5,6-dicarboxylate **66** in refluxing diglyme afforded **67** in 8 h (Scheme 16.20) [79–81]. Addition of $Eu(fod)_3$ [europium tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate)] enabled completion of the reaction in only



Scheme 16.20

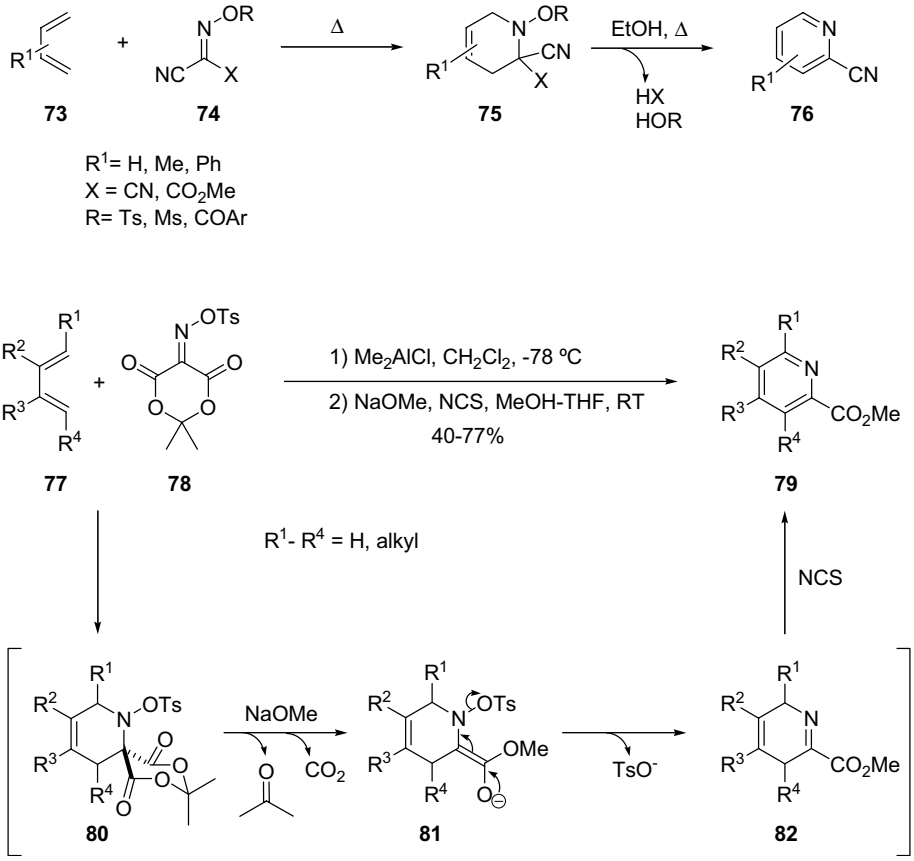
2 h. Also, several quinoline derivatives **69** have been synthesized from acetylenic 1,2,4-triazines **68** [82].

16.2.1.2.2 **Diels–Alder Reaction of Dienes and Azadienophiles** Pyridines can be also synthesized by Diels–Alder cycloaddition of azadienophiles, such as nitriles or imines, and dienes [83, 84]. Usually, imine dienophiles need to be activated by Lewis acids such as $Yb(OTf)_3$, $Sc(OTf)_3$, $In(OTf)_3$, $ZnCl_2$, $SnCl_4$, $TiCl_4$, Et_2AlCl, and so on. For instance, 5-alkyl-2(*p*-tolylsulfonyl)pyridines **72** are obtained in good yields at room temperature by [4 + 2] cycloaddition of 2-alkyl-1-ethoxy-1,3-butadienes **70** to *p*-toluenesulfonyl cyanide (**71**), followed by aromatization of the dihydropyridine intermediate via 1,4-elimination of ethanol (Scheme 16.21) [85].



Scheme 16.21

Oximino derivatives **74** undergo Diels–Alder cycloadditions with dienes **73** to afford adducts **75**, which can be converted into pyridines **76** in refluxing ethanol or by base-promoted elimination (Scheme 16.22) [86–89]. Alternatively, oximinosulfonates derived from Meldrum's acid **78** undergo Diels–Alder cycloaddition reaction with dienes **77** in the presence of dimethylaluminium chloride [90]. The [4 + 2]



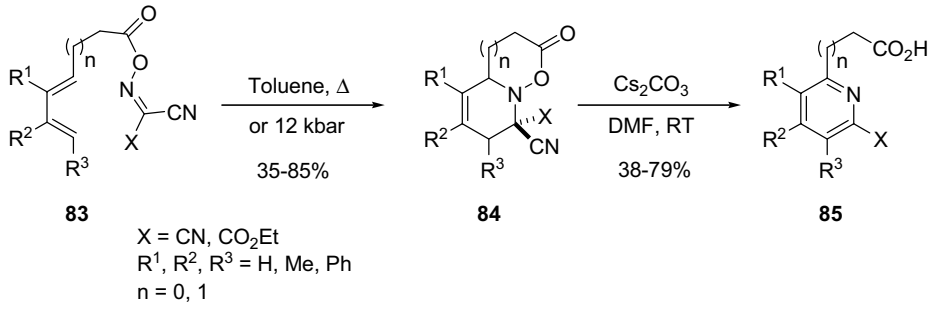
Scheme 16.22

cycloadducts **80** can be transformed by the simultaneous action of a nucleophilic alkoxide and suitable oxidizing agent into the corresponding pyridines **79** under treatment with NaOMe and *N*-chlorosuccinimide (NCS). The mechanism of this multistage reaction probably involves initial cleavage of the dioxandione ring by methoxide with concomitant elimination of acetone and carbon dioxide. β-Elimination of tosylate from the resulting ester enolate **81** then generates a dihydropyridine **82**, which by subsequent chlorination with NCS and elimination of HCl provides pyridines **79**.

In addition, heating acyl oximes **83** under high dilution conditions leads to the corresponding cycloadducts **84**, which by a double elimination reaction under treatment with caesium carbonate give pyridines **85** (Scheme 16.23) [91]. These cycloaddition reactions can also be promoted by high pressure in similar yields.

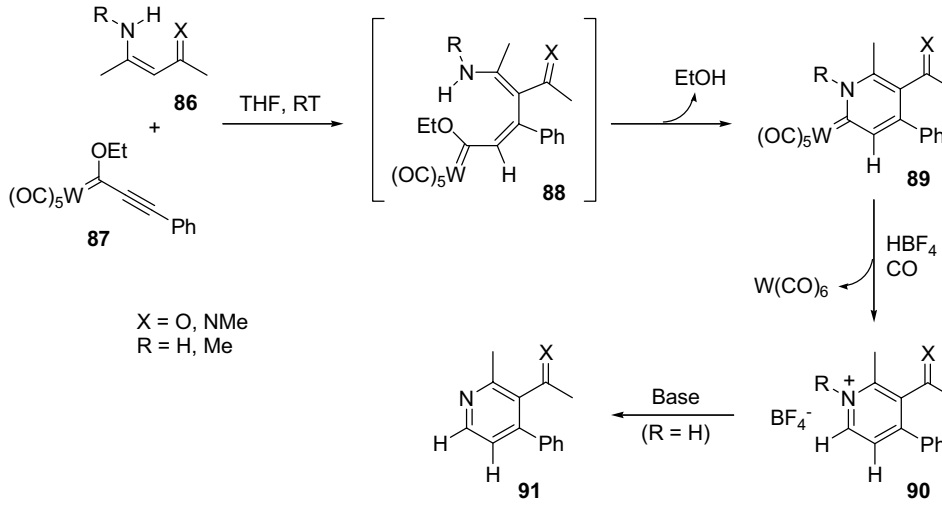
16.2.1.3 Formal Cycloaddition Reactions with Organometallic Derivatives

Aumann and coworkers [92] have shown that pyridinium salts **90** and pyridines **91** can be synthesized by a formal [3 + 3] cycloaddition reaction of alkylnylcarbene



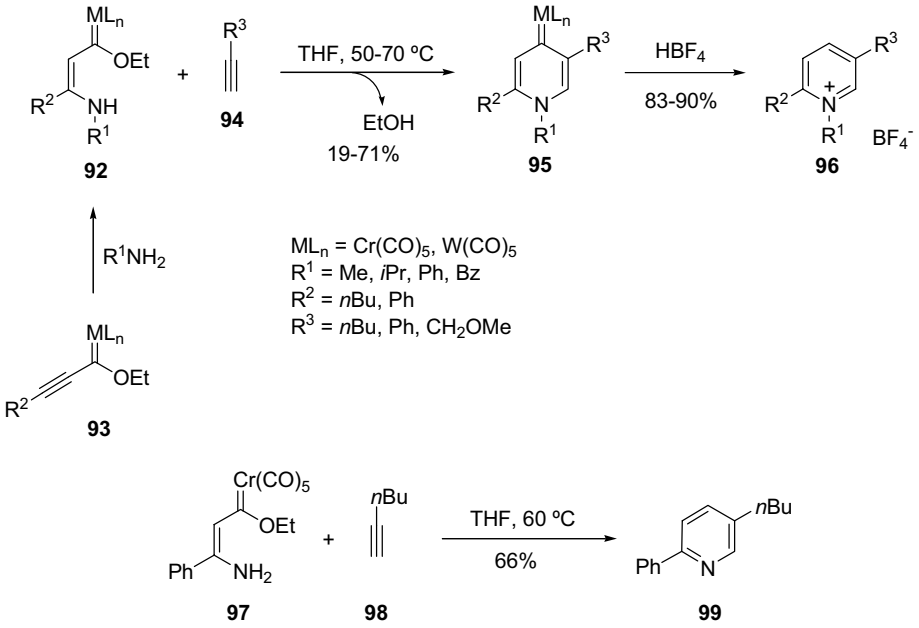
Scheme 16.23

complexes **87** [93] and enaminoketones or enaminoimines **86** (Scheme 16.24). The reaction involves the Michael addition of the enamino derivatives **86** to the alkynylcarbene complex **87** to give 1,3,5-trienes **88** (characterized by NMR spectroscopy), which in turn spontaneously cyclize to form 1,2-dihydropyridin-2-ylidene complexes **89**. Protonation of **89** takes place at the metal–carbon bond, affording the pyridinium salt **90** and the recovery of the metal complex. Treatment of the pyridinium salt **90** (R=H) with base affords the corresponding pyridine derivative **91**. Under these conditions pyridine **91** (X=O) has been obtained in 75% yield.



Scheme 16.24

Pyridines and pyridinium salts can also be obtained from (amino)vinyl carbene complexes and alkynes by a formal [4 + 2] cycloaddition. The reaction of [*(Z)*-β-(monoalkylamino)vinyl] carbene complexes **92**, readily prepared by addition of primary amines to alkynylcarbene complex **93**, with alkynes **94** involves the highly regioselective formation of 4(1*H*)-pyridinylidene complexes **95** (Scheme 16.25) [94].



Scheme 16.25

Protonation of **95** with HBF_4 leads to pyridinium salts **96**. On the other hand, heating [*(Z)*-β-aminovinyl]chromium complex **97** and 1-hexyne (**98**) gives pyridine **99** in 66% yield.

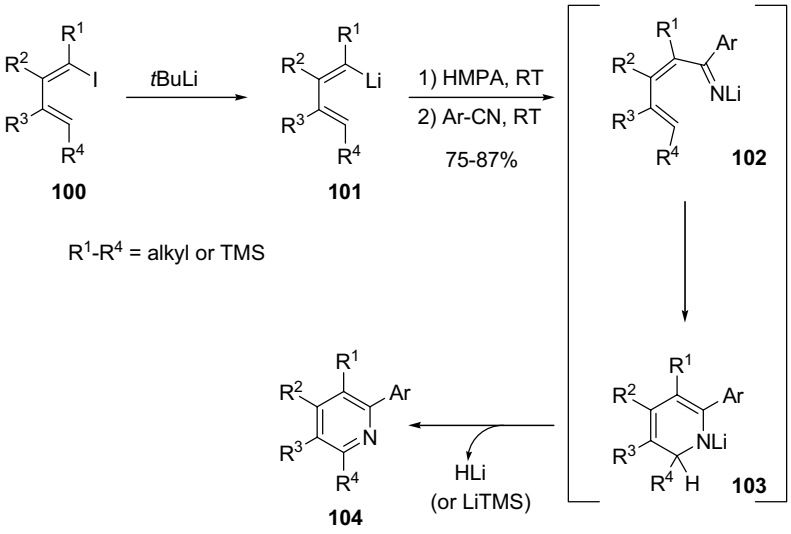
In addition, organolithium derivatives **101** of 1,3-dienes, generated *in situ* by lithiation of their corresponding 1-iodo-1,3-dienes **100**, react with arylnitriles to give *N*-lithioketimines **102** as the first intermediates, which undergo an intramolecular cyclization to produce **103**, which after elimination of LiH or LiTMS (R^4=TMS), generate pyridine derivatives **104** in good yields (Scheme 16.26) [95–97].

16.2.2
Synthesis by Cyclocondensation Reactions

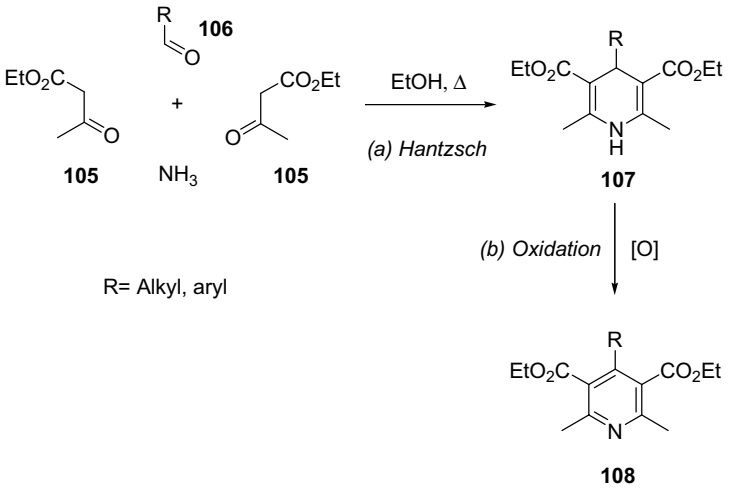
Pyridine ring have also been synthesized successfully by cyclocondensation reactions, of which the most important is the Hantzsch synthesis.

16.2.2.1 Hantzsch Cyclocondensation

The original Hantzsch synthesis consists of a four-component reaction between two molecules of ethyl acetoacetate (**105**), an aldehyde **106** and ammonia to afford 1,4-dihydropyridines (**107**), which by further oxidation afford the corresponding symmetrical pyridine derivatives **108** (Scheme 16.27). The reaction is usually carried out by warming the reagents in ethanol, and has been widely used for the preparation of diverse 1,4-dihydropyridines **107**, where R could be an alkyl or an aryl group [98].

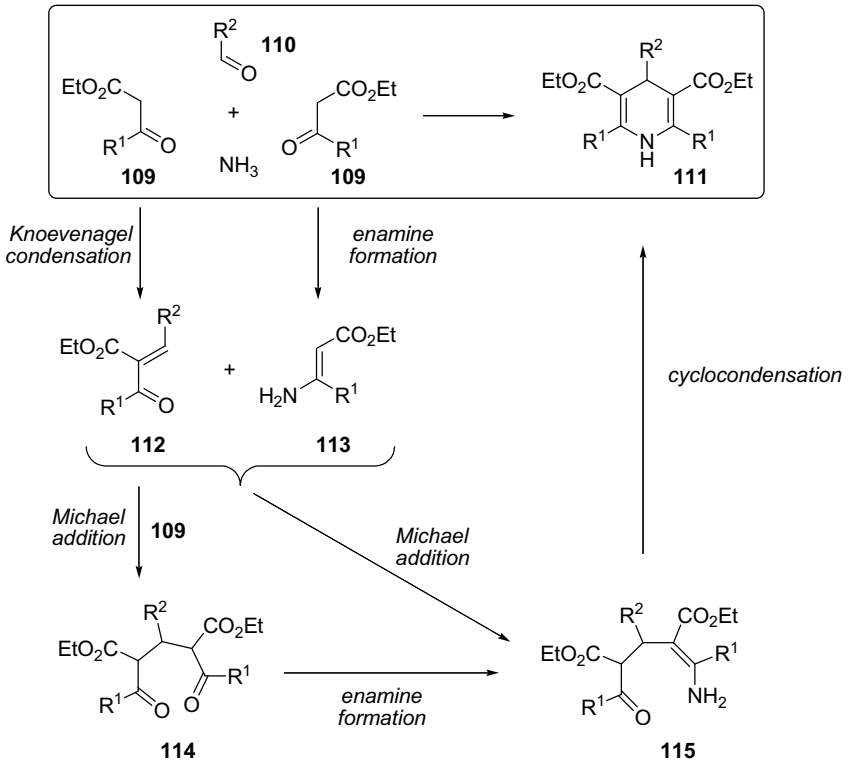


Scheme 16.26



Scheme 16.27

The formation of the 1,4-dihydropyridine derivatives **111** can occur by two pathways (Scheme 16.28) [99]. The first consists of the Knoevenagel condensation of one β-ketoester molecule **109** and the aldehyde **110** to afford **α**,β-unsaturated ketone **112**, which undergoes a Michael addition reaction with the other β-ketoester molecule to give the 1,5-dicarbonyl derivative **114**. Finally, enamine formation followed by cyclocondensation affords the 1,4-dihydropyridine nucleus **111**. Alternatively, 1,4-dihydropyridine derivatives **111** can be formed by reaction first of ammonia and one



Scheme 16.28 Proposed mechanism for the Hantzsch synthesis of 1,4-dihydropyridines.

β-ketoester **109** molecule to afford β-enaminoester **113**, which undergoes Michael addition with **α**,β-unsaturated ketone **112** to give also, as the first pathway, enaminone **115**.

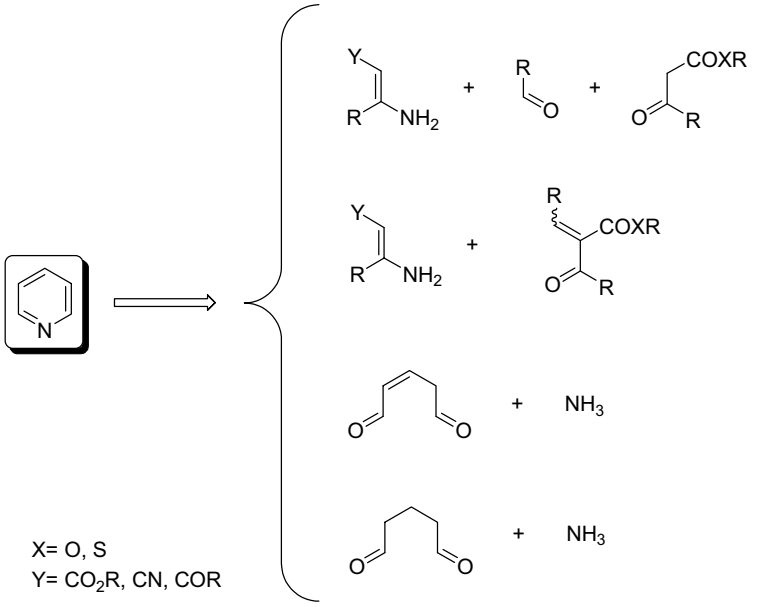
1,4-Dihydropyridines can be oxidized using diverse oxidants, such as HNO_3 [100], $KMnO_4$ [101], quinones [102], cerium(IV) ammonium nitrate (CAN) [103], $NaNO_2$ [104], $Cu(NO_3)_2$ [105], $Mn(OAc)_3$ [106], $Zr(NO_3)_4$ [107], $Pb(OAc)_4$ [108], and so on Recently, more efficient and environmentally benign methods have been developed, such as electrochemical oxidations [109], and catalytic aerobic oxidations by using $RuCl_3$ [110], Pd-C [111], activated carbon [112], $Fe(ClO_4)_3$ [113] or *N*-hydroxyphthalimide [114].

Remarkable improvement of the reaction conditions has been reported, including the promotion by microwave [115], TMSCl, ionic liquid [116], Bu_4NHSO_4 [117] and supported reagents [118].

16.2.2.2 Variants of the Hantzsch Cyclocondensation

Although the Hantzsch 1,4-dihydropyridines synthesis was discovered in 1882, it was not fully developed until 1980 with the discovery that 1,4-dihydropyridines prepared from aromatic aldehydes are calcium channel blocking agents and, therefore,

valuable drugs for heart disease with useful effects on angina and hypertension. Since its discovery, more effective and versatile variants of the original reaction have been developed, including (Scheme 16.29):



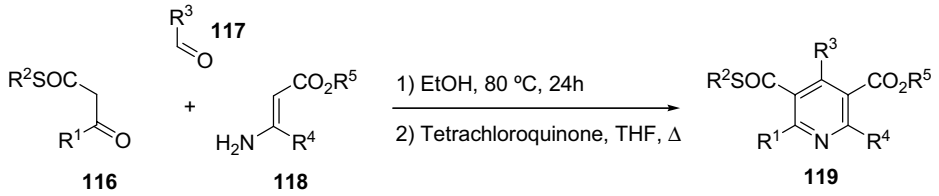
Scheme 16.29

1) Replacement of ammonia and a molecule of β-ketoester by β-enaminoesters, β-enaminonitriles or β-enaminoketones.
2) Utilization of **α**,β-unsaturated ketones instead of an aldehyde and the β-ketoesters.
3) The use of 1,5-dicarbonyl derivatives.

16.2.2.3 **From Enamines**

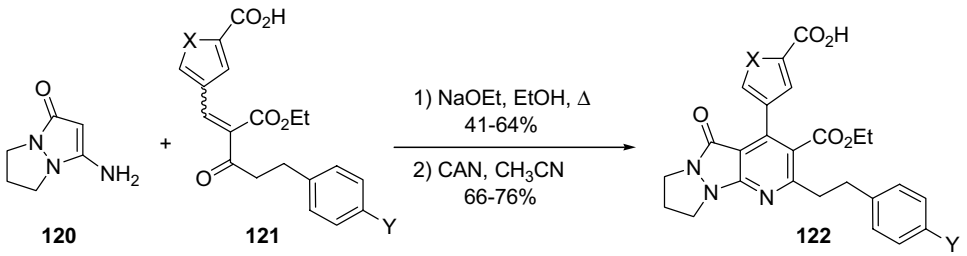
Enamines have been widely used in the cyclocondensation synthesis of highly substituted pyridines. For example, Jacobson and coworkers [119] have reported the synthesis of pyridines **119** by condensation of β-ketoester **116**, aldehyde **117** and β-enaminoester **118** and subsequent oxidation of the resulting 1,4-dihydropyridines with tetrachloroquinone (Scheme 16.30).

Alternatively, cyclocondensation of enamines and **α**,β-unsaturated carbonyl derivatives has also been achieved. For example, Wolfe and coworkers [120] have recently described the use of bicycloenamine **120** and **α**,β-unsaturated ketones **121** in the synthesis of pyrazolopyridines **122** (Scheme 16.31). Treatment of **α**,β-unsaturated ketones **121** with enamine **120**, generated from 1-cyanoacetylpyrazolidine hydrochloride, followed by oxidation of the corresponding dihydropyridines afforded pyridines **122** in good yields.



R^1 = Alkyl, Fluoroalkyl, hydroxyalkyl, thioacetylalkyl
R^2 = Alkyl, Fluoroalkyl, hydroxyalkyl
R^3 = Alkyl, Fluoroalkyl, hydroxyalkyl, aminoalkyl, thioacetylalkyl
R^4 = Aryl
R^5 = Alkyl, Fluoroalkyl

Scheme 16.30



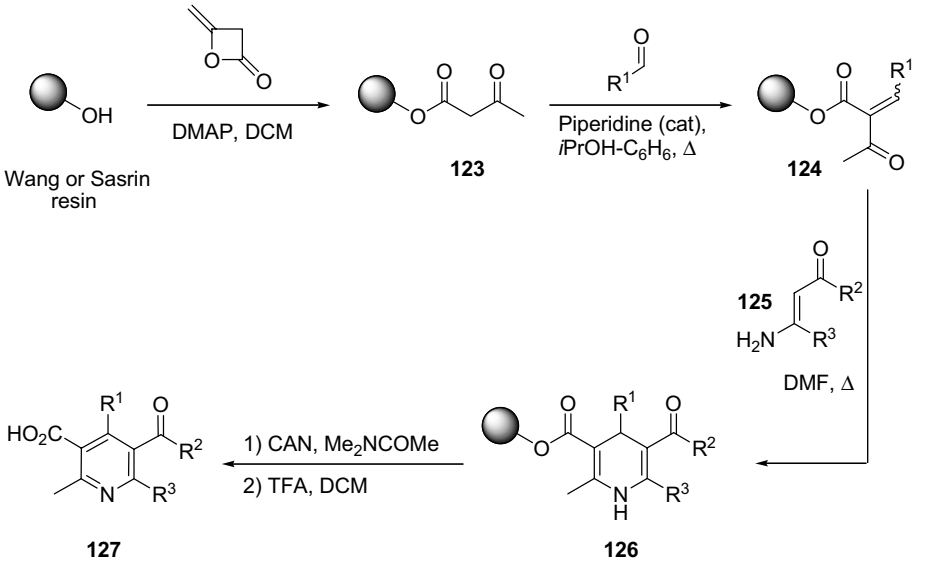
X = S, O, CH=CH
Y = F, CF_3

Scheme 16.31

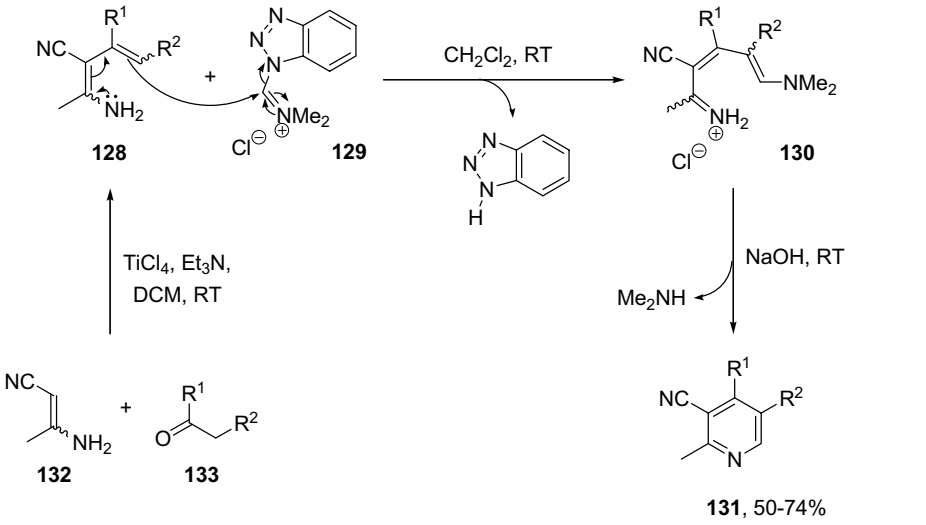
In addition, Gordeev and coworkers [121] have exploited the enamine/**α**,β-unsaturated carbonyl approach to the efficient solid-phase synthesis of diverse pyridines **127** (Scheme 16.32). Treatment of O-immobilized ketoester **123** with diverse aldehydes afforded Knoevenagel derivatives **124**, which by condensation with diverse β-enaminoketones **125** gave 1,4-dihydropyridines **126**. Finally, oxidation and cleavage from resin yielded pyridines **127**.

On the other hand, Katritzky and coworkers [122] have developed a mild and highly regioselective route to diverse nicotinonitriles **131** from β-enaminonitriles **128** with a Vilsmeier-type reagent **129** (Scheme 16.33). The reaction proceeds via intermediate **130** (identified by NMR spectroscopy), which upon treatment with base induced a spontaneous electrocyclization–elimination process to furnish the pyridine core. The β-enaminonitriles **128** were synthesized by a tandem addition–elimination process from β-aminocrotonitrile **132** and ketone **133**.

Alternatively, malononitriles have been employed as enamine synthons in the enamine/**α**,β-unsaturated carbonyl cycloaddition approach. For example, **α**,β-unsaturated ketones **135** were condensed with malononitrile (**134**) in the presence of NaOEt or NaOMe to yield the corresponding cyanopyridines **136** (Scheme 16.34) [123].

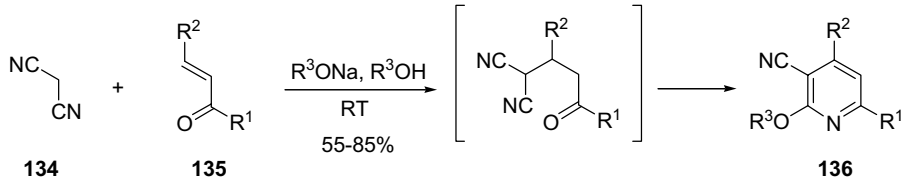


Scheme 16.32



Scheme 16.33

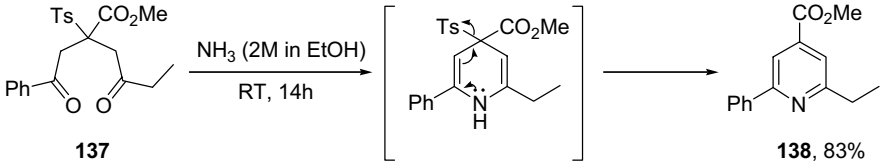
16.2.2.3.1 **From 1,5-Dicarbonyl Derivatives** A good approach to pyridine ring synthesis is the cycloaddition of 1,5-dicarbonyl derivatives and ammonia. For example, pyridine **138** has been synthesized from 1,5-diketone **137** by treatment at room temperature with ethanolic ammonia (Scheme 16.35) [124].



134 135 136

R^1, R^2 = Aryl; R^3= Me, Et

Scheme 16.34



137 **138**, 83%

Scheme 16.35

The 1,5-dicarbonyl/ammonia approach has been successfully applied to a solid-phase synthesis of 2,4,6-trisubstituted pyridines **142** from hydroxyacetophenones **139** (Scheme 16.36) [125]. The strategy includes a Claisen–Schmidt reaction to form **α**,β-unsaturated ketones **140**, a Michael reaction with trimethylsilyl enol ethers to form a 1,5-pentanediones **141**, and cyclization with ammonium acetate to yield, after acid cleavage from resin, pyridine derivatives **142**.

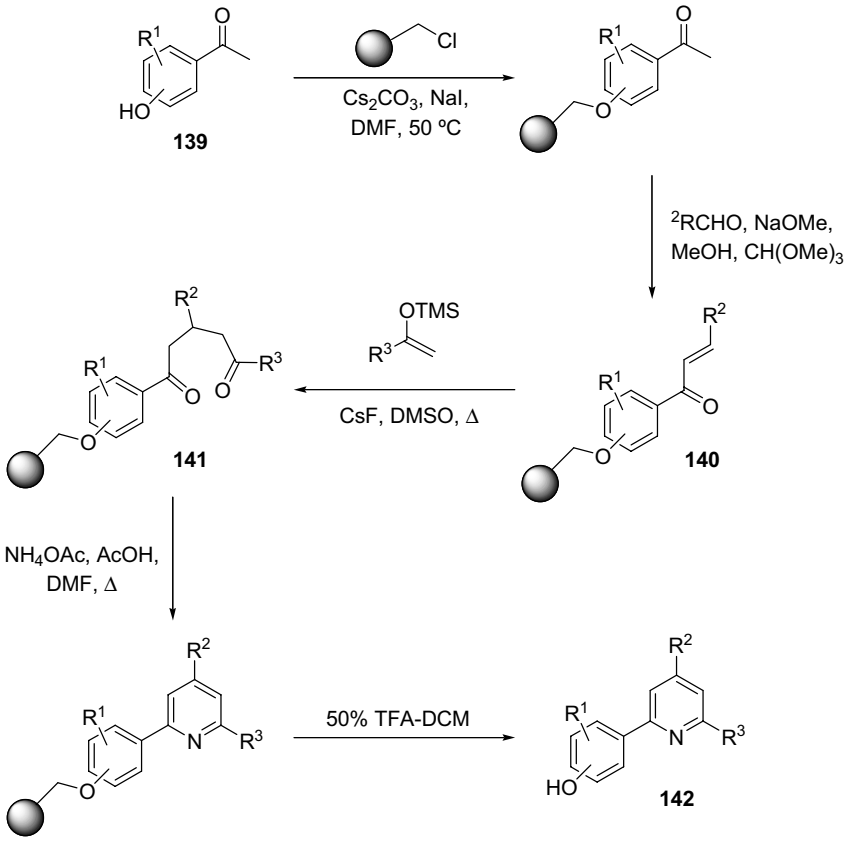
16.2.2.4 **Bohlmann–Rahtz Heteroannulation**

The synthesis of trisubstituted pyridines from β-aminocrotonates and ethynyl ketones was first reported by Bohlmann and Rahtz in 1957 [126]. Originally, the reaction consisted of a two-step process, involving the initial conjugate addition of enamine **143** to alkynone **144** at 50 °C in ethanol to generate an aminopentadienone intermediate **146**, which is isolated and subsequently cyclodehydrated by heating the residue at 120–160 °C under reduced pressure to afford trisubstituted pyridines **145** (Scheme 16.37). Since its discovery, remarkable improvements have been reported, most notably a single synthetic step using either acetic acid, Amberlyst 15 ion exchange resin or Lewis acid catalysts, such as $ZnBr_2$ or $Yb(OTf)_3$ [127–129].

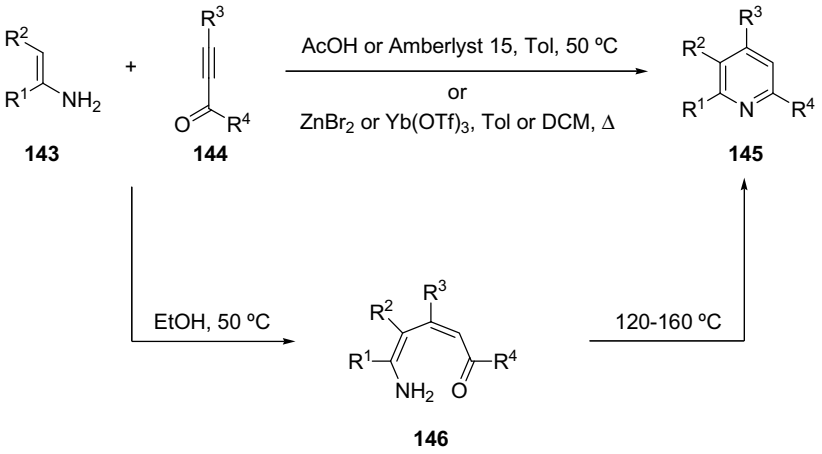
The Bohlmann–Rahtz heteroannulation reaction has also been successfully applied to the combinatorial synthesis of tri- and tetrasubstituted pyridines in solution [130]. Lewis acid-catalyzed methods provided the best overall yields, product ratios and library purity.

16.2.3
Synthesis by Aza-Electrocyclization Reactions

Pyridine rings can also be synthesized by aza-6π-electrocyclic reactions, which result in the formation of just one new σ bond across the ends of a single conjugated



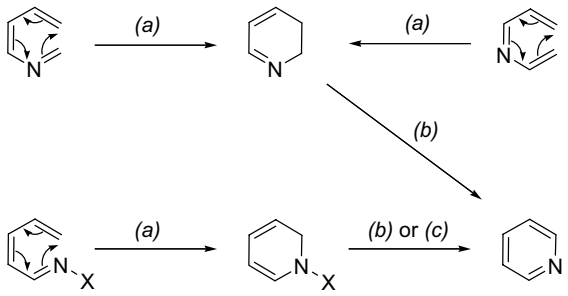
Scheme 16.36



R^1= alkyl, aryl; R^2= CN, CO_2R; R^3= Me, CO_2Et; R^4= H, alkyl, aryl, TMS

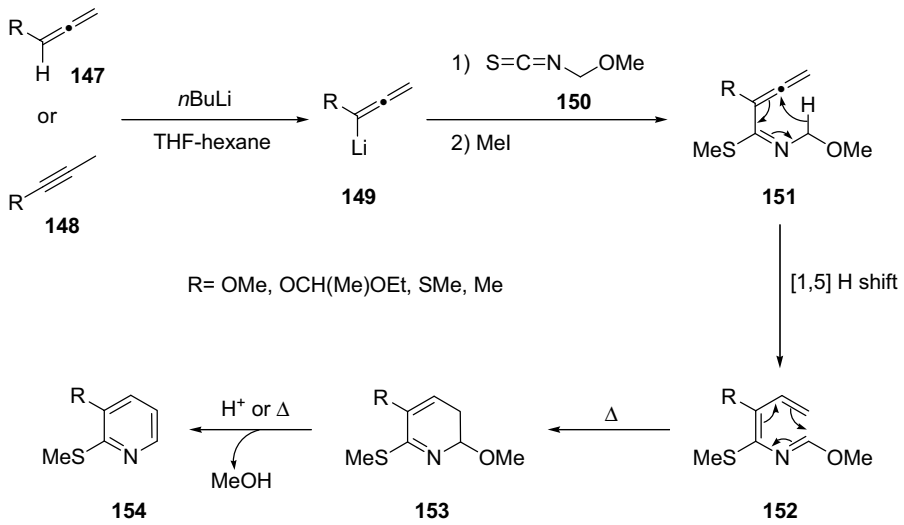
Scheme 16.37

π-system (Scheme 16.38). A good example of this approach has also been reported by Brandsma and coworkers [131, 132] in the synthesis of pyridine derivatives **154** (Scheme 16.39). Reaction of lithiated allene **149**, obtained from allenes **147** or methylacetylenes **148**, with alkylthioisocyanate **150** and subsequent alkylation affords adduct **151**, which isomerizes via [1,5]-hydrogen shift, quantitatively, under mild reaction conditions to generate 1,3-butadienyliminoformates **152**. Electrocyclization of **152** gives 2,3-dihydropyridines **153** in good to excellent yields which under acidic conditions or by heating at high temperatures eliminate methanol to produce 3-substituted 2-methylthiopyridines **154**.



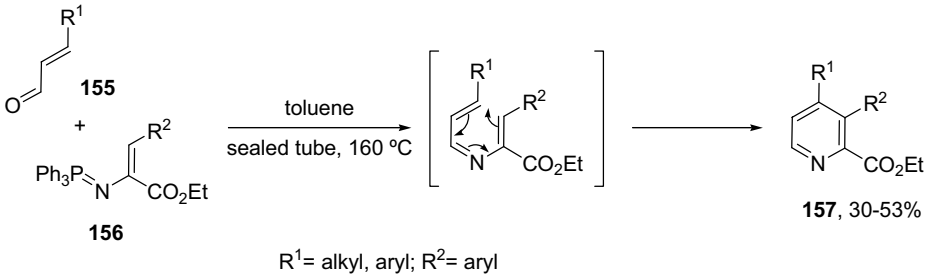
(a) aza-electrocyclization; (b) oxidation; (c) elimination

Scheme 16.38



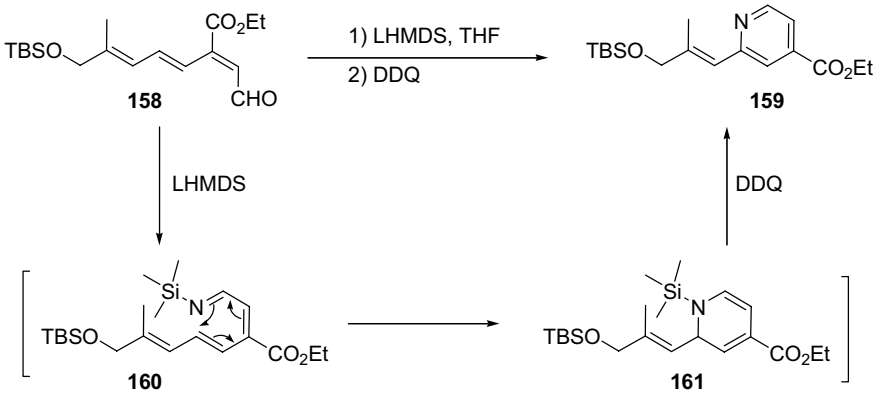
Scheme 16.39

In addition, β-arylvinyliminophosphoranes **156** react with **α**,β-unsaturated aldehydes **155** to give regiospecifically 3-arylpyridines **157** (Scheme 16.40) [133].



Scheme 16.40

Also, intramolecular approaches have been successful. A good example is the synthesis of pyridine **159** reported by Tanaka and Katsumura [134]. It consists of the treatment of the (*E*)-carbonyltrienal **158** with excess of lithium bis(trimethylsilyl) amide (LHMDS), which produces, via intermediate **160**, an aza-electrocyclization reaction to afford the corresponding unstable 1,2-dihydropyridine derivative **161**, which upon oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) leads to pyridine derivative **159** (Scheme 16.41).

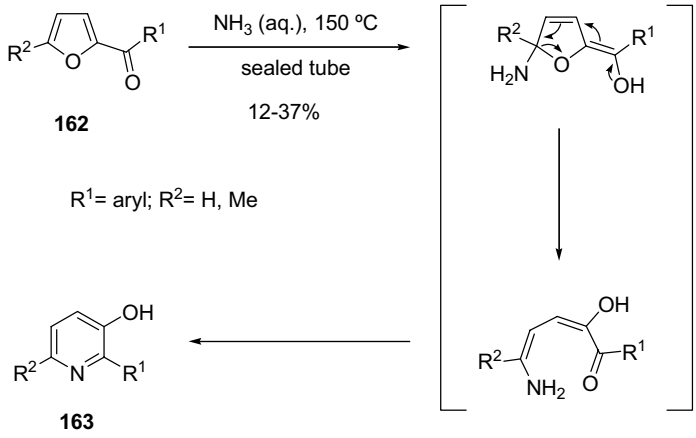


Scheme 16.41

16.2.4
Synthesis via Ring Transformation of Other Heterocycles

16.2.4.1 From Five-Membered Rings

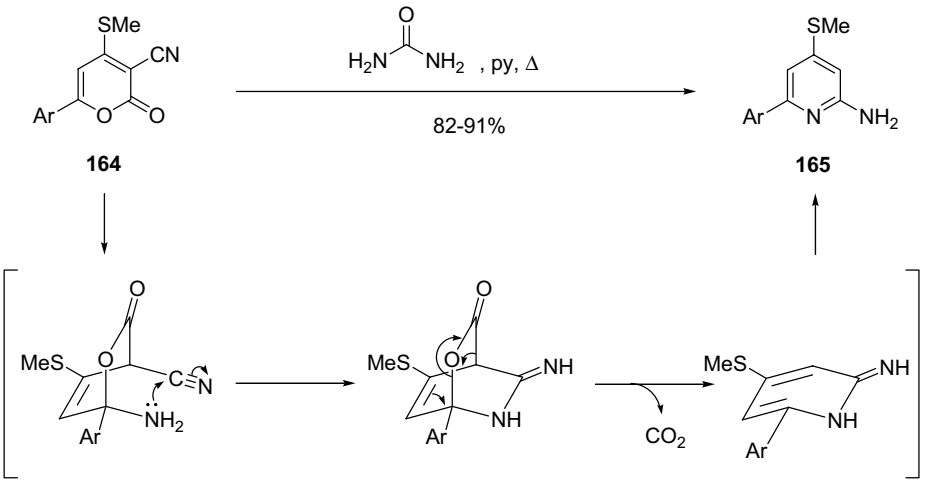
Furan derivatives **162** substituted with an acyl- or carboxylic acid functionality in the 2-position are transformed, in low to moderate yields, into 2-substituted 3-hydroxy pyridines **163** by treatment with ammonia at 150 °C in a sealed tube (Scheme 16.42) [135].



Scheme 16.42

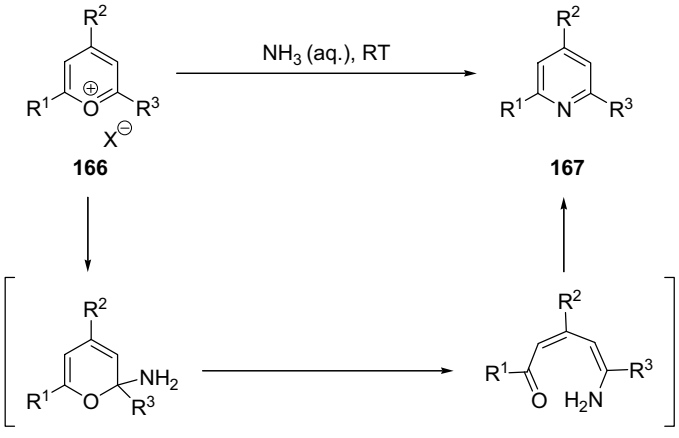
16.2.4.2 From Six-Membered Rings

Pyrones and pyrylium salts are six-membered heterocycles that have been successfully used as templates in pyridine synthesis. For example, 2-aminopyridines **165** have been synthesized regioselectively through nucleophilic-induced ring transformation reaction of 2*H*-pyran-2-ones **164** with urea (Scheme 16.43) [136].



Scheme 16.43

In addition, pyrylium salts **166** upon reaction with ammonia undergo ring-opening/ring-closing reaction sequences to afford excellent yields of the corresponding pyridine derivatives **167** (Scheme 16.44) [137–140]. If primary amines are used pyridinium salts are obtained.

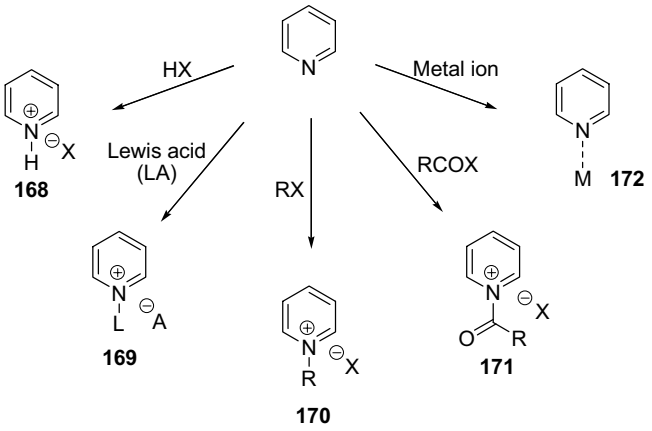


Scheme 16.44

16.3 Reactivity

16.3.1 Reactions with Electrophilic Reagents

Pyridines react easily at the nitrogen atom with a wide range of electrophiles such as, protic acids, Lewis acids, reactive alkyl and acyl halides and transition metal ions to form tertiary salts **168**, complexes **169**, quaternary salts **170** and **171** and coordination compounds **172**, respectively (Scheme 16.45).



Scheme 16.45

16.3.1.1 Reactions with Acids

Pyridines form stable salts with Brønsted acids such as HCl, HNO_3, H_2SO_4, and so on. Pyridine itself, with a pK_a of 5.2 in water, is a much weaker base than saturated aliphatic amines, which have pK_a values mostly between 9 and 11. In general, electron-donating groups in the pyridine ring, especially in the 4-position, increase their basicity. For instance, 2-methyl- and 4-methylpyridine are more basic than pyridine (pK_a 6.0). The opposite effect is produced when electron-withdrawing groups are present in the pyridine ring, especially in the 2-position. For instance 2-nitro- and 2-chloropyridine have a lower pK_as of -2.6 and 0.7, respectively. In the case of substituents such as methoxy or aryl groups, which are resonance donors as well as inductive acceptors, variable effects on pyridine basicity are observed. The position of the substituent in the ring determines which of these effects are predominant. For instance, whereas 2-methoxypyridine (pK_a 3.3) is less basic than pyridine, 4-methoxypyridine (pK_a 6.6) is more basic. Although steric effects are usually unimportant, very hindered pyridines such as 2,6-di-*tert*-butylpyridine (pK_a 3.6), are usually less basic than pyridine.

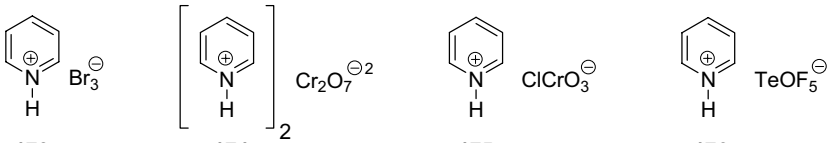
Some pyridinium salts are commercially available reagents that are widely used. This is the case for pyridinium perbromide **173**, which is employed as brominating agent, pyridinium dichromate (**174**, PDC) and pyridinium chlorochromate (**175**, PCC), used as mild and selective oxidizing agents, and pyridinium teflate (**176**), which is utilized as a source of teflic acid, a very weakly coordinating agent (Figure 16.13).

Lewis acids such as $AlCl_3$, $SnCl_4$, BF_3, $SbCl_5$, SO_3, and so on react with pyridines to afford stable pyridinium complexes, some of which are also used as reagents. For instance, sulfur trioxide pyridinium complex ($Py{\cdot}SO_3$) is employed as a mild sulfonating agent.

16.3.1.2 Reactions with Metal Ions

Pyridines can act as monodentate ligands in transition metal complexes. This is the case with simple complexes such as $Ni(Py)_4^{+2}$, $Ag(Py)_2^{+}$, and so on. When **α**-substituents, such as carbonyl groups, imines, metilenamines, heteroaryl groups, and so on, susceptible to coordination are present in the pyridine ring, chelate complexes are formed (Figure 16.14) [141–144].

Based on pyridyl units, many polydentate ligands have been developed in the field of the metallosupramolecular chemistry. A good example is the interaction of two molecules of oligopyridine with various metal ions (Fe^{+2}, Co^{+2}, Cu^{+2}, etc.) to form



173 **174** **175** **176**

Figure 16.13 Examples of commercially available pyridinium salts used as reagents.

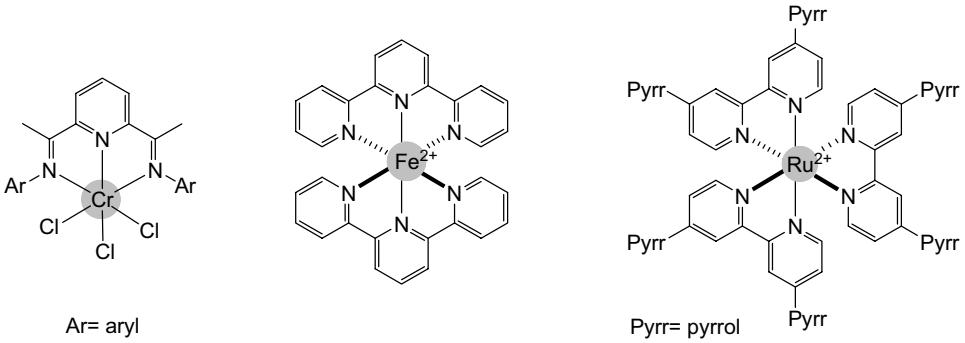
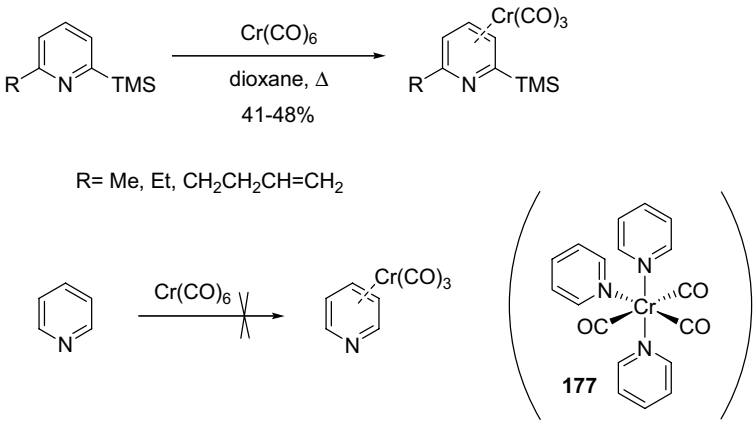


Figure 16.14 Examples of pyridine chelates.

a double-helical complex in which the metal is bonded to a tridentate region from each ligand [145–147].

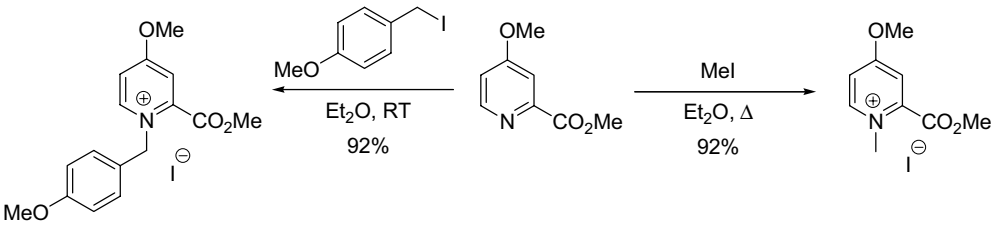
Pyridines can also act as π-ligands to afford η^6-complexes with transition metals such as chromium. Such complexes are usually prepared by thermolysis with hexacarbonyl chromium (Scheme 16.46) [148]. However, pyridine derivatives that lack bulky alkyl groups at the 2- and 6-positions do not afford the corresponding π-complexes. Tricarbonyl(trispyridine)chromium complexes [$Py_3Cr(CO)_3$] (**177**) [149] are obtained instead, in which pyridines are coordinated through their nitrogen lone pairs.



Scheme 16.46

16.3.1.3 **Reactions with Halides and Related Compounds**

Alkyl halides, tosylates, triflates, and so on react readily with pyridines by an S_N2 reaction to give alkylpyridinium salts (Scheme 16.47) [150]. Bulky substituents around the nitrogen ring atom, or tertiary halides or related compounds cause an

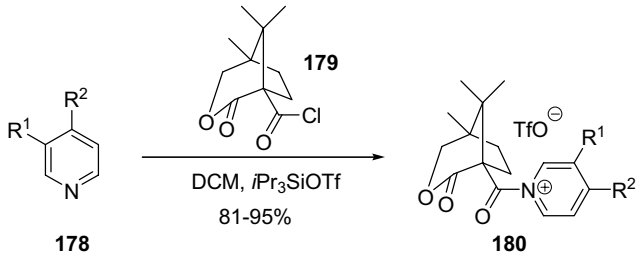


Scheme 16.47

increase in the competing elimination reaction giving rise to the corresponding alkene and tertiary salts. In fact, 2,4,6-collidine is often used as base in elimination reactions.

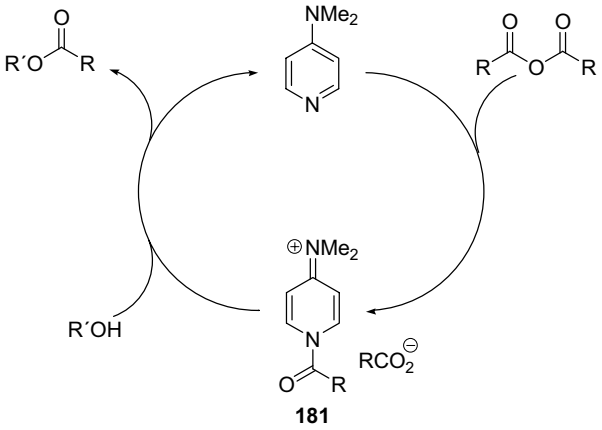
16.3.1.4 Reactions with Acyl Halides and Related Compounds

Acyl and sulfonyl halides and anhydrides react rapidly with pyridines by an addition–elimination reaction to form quaternary salts, which are rarely isolated, since they decompose rapidly on reaction with water, forming salts of the original pyridines. Some acyl pyridinium salts such as **180** can be obtained in good to excellent yields by treatment of pyridines **178** with acid chloride **179** (Scheme 16.48) [151].



Scheme 16.48

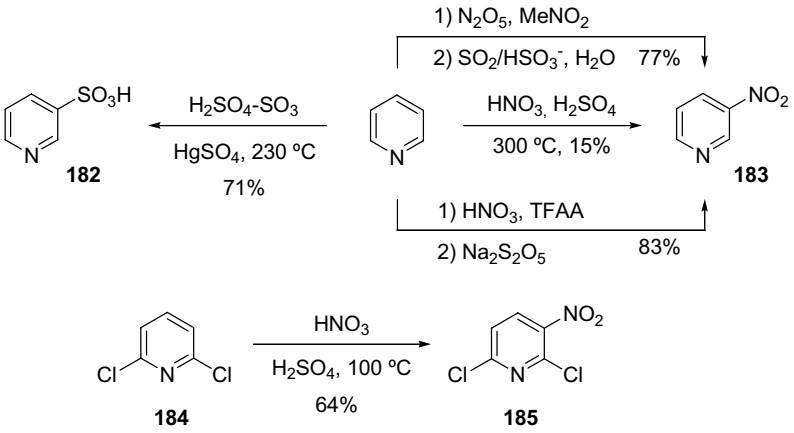
N-Acyl and *N*-sulfonylpyridinium salts are very useful acylating and sulfonating agents. Electron-donor substituted pyridines such as 4-*N,N*-dimethylaminopyridine (DMAP) are commonly used as catalysts in acylation reactions (Scheme 16.49) [152]. The dimethylamino function of DMAP increases both the nucleophilicity and the basicity of the ring nitrogen atom, making intermediate **181** relatively more stable than the corresponding pyridine analogue. These facts lead to a greater concentration of the acylating species **181** and, thus, speed up the reaction. This methodology dramatically enhance yields as well as reaction rates, leading to successful acylations even with the use of tertiary and sterically hindered alcohols.



Scheme 16.49

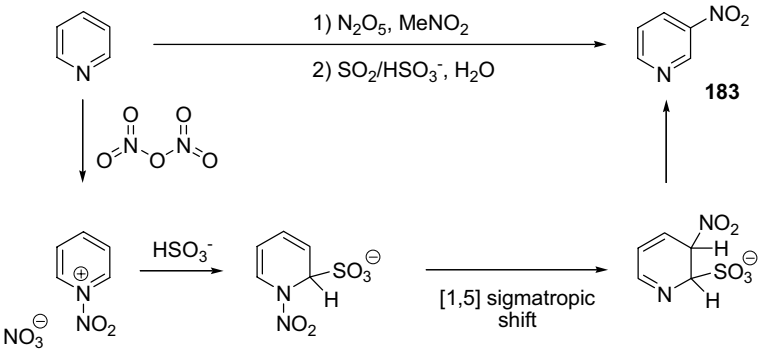
16.3.1.5 **Electrophilic Substitution Reactions**

Pyridines undergo electrophilic substitution reactions (S_EAr) exclusively at the 3-position but much more slowly than benzene, and usually under very drastic reaction conditions. For example, nitration of pyridine with nitric–sulfuric acids mixtures requires 300 °C to afford 3-nitropyridine (**183**) in only 15% yield (Scheme 16.50). In contrast, sulfonation of pyridine affords 3-sulfonic acid **182** in 71% but only at 230 °C and using $HgSO_4$ as a catalyst [153]. The lack of pyridine reactivity in electrophilic substitution derives from protonation of the ring nitrogen. In fact, 2,6-dichloropyridine (**184**), which has two electron-withdrawing groups is significantly less basic than pyridine, and undergoes nitration as the free base to give 2,6-dichloro-3-nitropyridine (**185**) in 64% yield [154].



Scheme 16.50

Bakke and coworkers [155, 156] have overcome the low reactivity of pyridines against common nitrating systems by using dinitrogen pentoxide in an organic solvent, followed by treatment with an aqueous solution of SO_2/HSO_3^- (Scheme 16.51). Under these conditions, an *N*-nitropyridinium ion intermediate is formed that, when reacted with SO_2/HSO_3^- in water, gives 3-nitropyridine (77% yield). It has been suggested that the reaction mechanism implies a [1, 5] sigmatropic shift of the nitro group. Recently, Katrizky and coworkers [157] have developed an improved method that consists of the *in situ* generation of dinitrogen pentoxide from nitric acid and trifluoroacetic anhydride (TFAA) (Scheme 16.50).



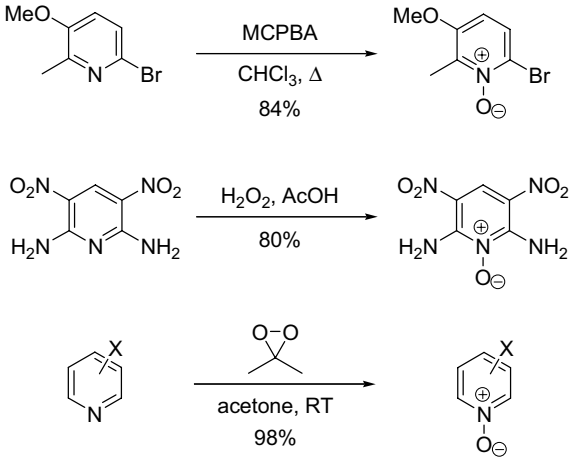
Scheme 16.51

16.3.2
Reactions with Oxidizing Agents

The pyridine ring is remarkably stable towards oxidation. Because of its resistance to oxidation, pyridine can be used as a solvent in oxidation reactions, such as in the Collins oxidation with CrO_3. Only under vigorous conditions, such as neutral aqueous $KMnO_4$ in a sealed tube at 100 °C, can pyridine be oxidized to carbon monoxide, and at about the same rate as benzene. In alkaline media pyridines are oxidized more rapidly than benzenes.

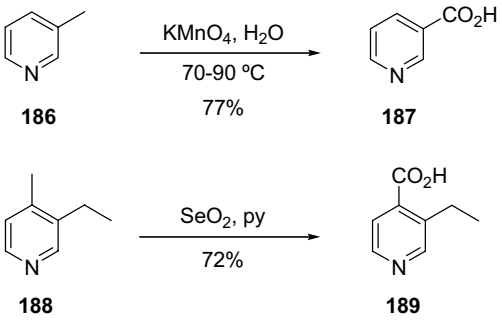
As with other tertiary amines, pyridines react smoothly with diverse oxidizing agents, such as peracids, H_2O_2/AcOH, dimethyldioxirane (DMD), bis(trimethylsilyl)peroxide, oxaziridines, and so on, to give N-oxides (Scheme 16.52) [158–160].

Alkylpyridines can be oxidized at benzylic positions by various oxidizing agents such as $KMnO_4$, O_2, SeO_2, HNO_3, and so on to afford pyridine carboxylic acids (Scheme 16.53). For instance, $KMnO_4$ has been employed in the synthesis of niacin (**187**) from β-picoline (**186**) [161]. Selective oxidation of the methyl group of disubstituted pyridine **188** has been achieved using SeO_2 as the oxidizing agent of choice to give carboxylic acid **189** [162].



X= 4-CN, 4-CF_3, 4-Ph, 4-Me, 4-OMe, H, 3-Br

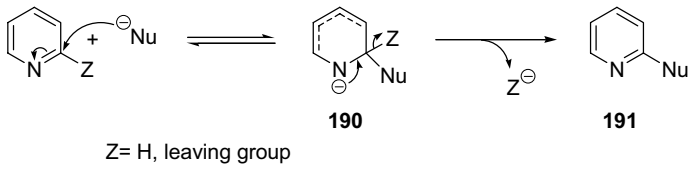
Scheme 16.52



Scheme 16.53

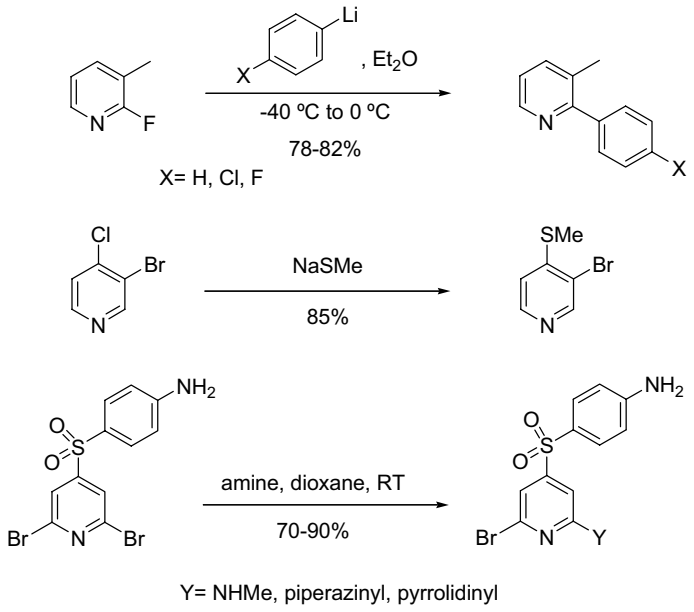
16.3.3
Reactions with Nucleophilic Reagents

The electron-deficient nature of the pyridine ring allows nucleophilic reagents to attack pyridines, preferably at their 2- or 4-ring carbon atoms and less readily in the 3-position. However, only strong nucleophiles such as amide ions, hydroxides or organolithium compounds react. The reaction proceeds by an addition–elimination mechanism, that is, by S_NAr, which involves in the first stage the formation of adduct **190** with concomitant de-aromatization of the pyridine ring and, once formed, loss of hydride occurs to afford pyridine derivative **191** (Scheme 16.54, Z=H). Electron-withdrawing substituents on the pyridine ring, such as nitro or cyano groups, favor the reaction.



Scheme 16.54

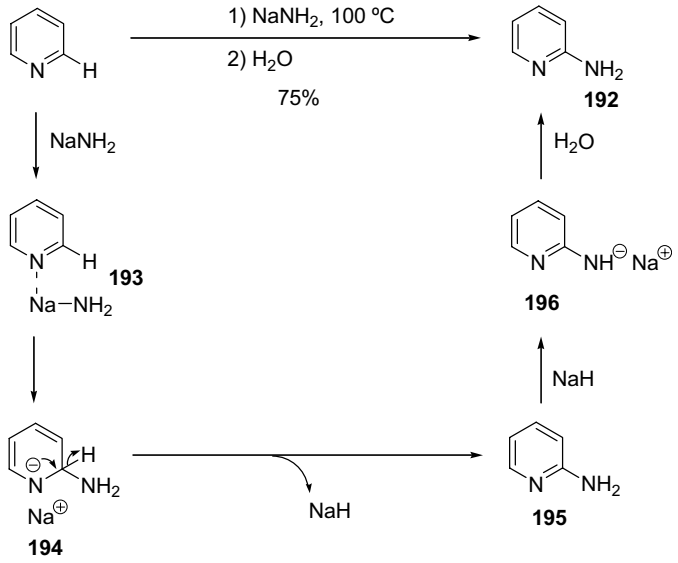
S_NAr reactions with pyridines substituted with halogens or other leaving groups such as alkoxy groups, and so on are most common and proceed much faster than the corresponding unsubstituted rings (Scheme 16.54, Z = leaving group). Usually, the reaction takes place with a wide range of nucleophiles at 2- or 4-positions, but not at 3-positions. Scheme 16.55 shows examples of reactions of this type [163–165].



Scheme 16.55

16.3.3.1 **Reactions with Amide Ions**

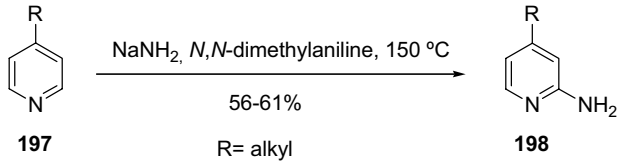
Pyridine reacts with sodium amide in toluene at 100 °C to give, mainly, 2-aminopyridine (**192**) (75%) and a small amount of 4-aminopyridine (Scheme 16.56). At 180 °C, 2,6-diaminopyridine is produced in good yield along with a small amount of 2,4,6-triaminopyridine. This transformation, known as the Chichibabin reaction, is usually carried out at relatively high temperatures in an inert atmosphere or without solvent. It has been suggested that the reaction proceeds via initial formation of an adsorption complex **193** with a weak nitrogen–sodium coordination that increases the electrophilicity of the **α**-carbon ring atom. Subsequently, amide nucleophilic



Scheme 16.56

attack occurs with formation of intermediate **194**, which undergoes a sodium hydride elimination followed by deprotonation to give amide salt **196**. The 2-aminopyridine **192** is finally obtained after a work-up with water.

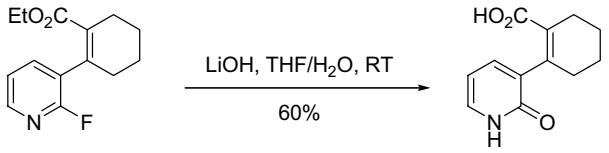
More vigorous conditions are required for the amination of alkylpyridines because proton abstraction from the side-chain by the amide ion occurs preferentially, and therefore ring attack must involve a dianionic intermediate. Nonetheless, 4-alkyl pyridines **197** have been successfully aminated at 150 °C to afford reasonable yields of 2-aminopyridines **198** (Scheme 16.57) [166, 167].



Scheme 16.57

16.3.3.2 **Reactions with Hydroxide Ions**

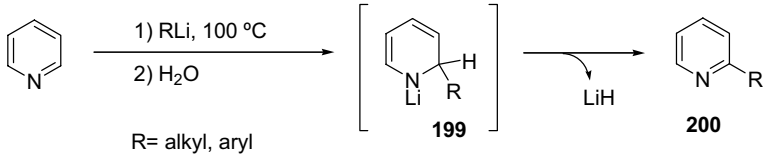
Pyridines react with hydroxide ions under extreme conditions (KOH-air, 300 °C) to give 2-pyridones, the stable tautomers of 2-hydroxypyridines, which are formed by oxidation of the initial adduct. As expected, the reaction is favored by electron-withdrawing substituents on the pyridine ring. The reaction proceeds much faster and under milder conditions with pyridines substituted with halogens or other good leaving groups. For example, even fluoro pyridines can be transformed into pyridones with lithium hydroxide at room temperature (Scheme 16.58) [168].



Scheme 16.58

16.3.3.3 Reactions with Carbon Nucleophiles

Pyridines undergo nucleophilic aromatic substitutions (S_NAr) with carbon nucleophiles such as alkyllithium or aryllithium derivatives, affording 2-alkyl- and 2-arylpyridines, respectively (Scheme 16.59). Grignard reagents give the same reaction products but in lower yields. The reaction requires rather vigorous conditions (e.g., xylene, 100 °C) and proceeds via the dihydropyridine *N*-lithio salts **199**, which are less basic than those formed by reaction of pyridines with sodium or potassium amide and eliminate hydride anions with relative difficulty. The *N*-lithio salts **199** can be detected by NMR spectroscopy and in some cases have been isolated as solids [169–171]. These salts are stable at room temperature for several hours but, on heating, eliminate lithium hydride to give the 2-substituted pyridines **200**.



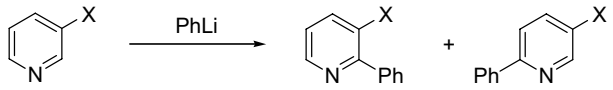
Scheme 16.59

The S_NAr reaction of 3-substituted pyridines **201** with an organolithium compound may lead to the 2,3-isomer **202**, or a mixture of the latter and the 2,5-isomer **203** (Table 16.8). The rate and orientation of such nucleophilic substitution depends on steric and coordination effects. An increase in steric hindrance produces less of the 2,3-isomer **202** (Table 16.8, entry 2 vs. 4), while coordination of the lithium atom with a free electron pair on the substituent favors nucleophilic attack at the 2-position (Table 16.8, entries 6 and 7).

16.3.4 Reactions with Bases

The regiospecific exchange of one aryl hydrogen atom by a metal such as lithium, by treatment with a strong base, usually requires the presence of substituents with lone pairs on heteroatoms (directing metallation groups, DMG), which enable the formation of coordination complexes with the metal, resulting in metallation at sites adjacent to the substituent. This transformation, known as the directed ortho-metallation reaction, in comparison with the same reaction in π-excessive heterocycles, has an extra complication in π-deficient heterocycles such as pyridines,

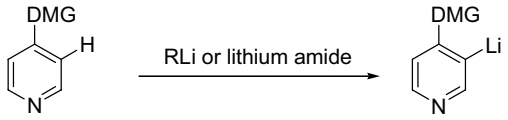
Table 16.8 Reaction of 3-susbstituted pyridines **201** with phenyllithium.



201 **202** **203**

Entry	X	Yield (%)	202	203	Reference
1	H	69	100		[172]
2	Me	42	95	5	[172]
3	Et	39	84	16	[172]
4	*t*Bu	25	4	96	[172]
5		34	50	50	[173]
6	NH_2	25	100	0	[174]
7	OMe	21	100	0	[174]

because the soft alkyllithium reagents (*n*BuLi, PhLi) commonly used can undergo a facile nucleophilic addition to the azomethine (C=N) bond (see Section 16.3.3.3) [175]. However, it is possible to achieve clean metallation reactions with alkyllithium reagents for many DMGs (NHCOR, OR, $OCONR_2$, CONHR, Cl, F) (Scheme 16.60). For pyridines with DMG groups such as $CONR_2$, SOR, I, Br, and so on, which are more reactive towards nucleophilic reactions or halogen–metal exchange, the harder and the less basic lithium diisopropylamine (LDA) or lithium 2,2,6,6-tetramethylpiperidine (LTMP) is normally used.



R= *n*Bu, Ph, *s*Bu
Lithium amide= LDA or LTMP
DMG= NHCOR, OR, $OCONR_2$, CONHR, $CONR_2$, halogen, SOR

Scheme 16.60

The regioselectivity of the reaction is the result of mainly four effects: (i) the strength of the coordination between the DMG-heteroatom and the lithium; (ii) the inductive effect of the DMG; (iii) the electronic repulsion between the carbanion and

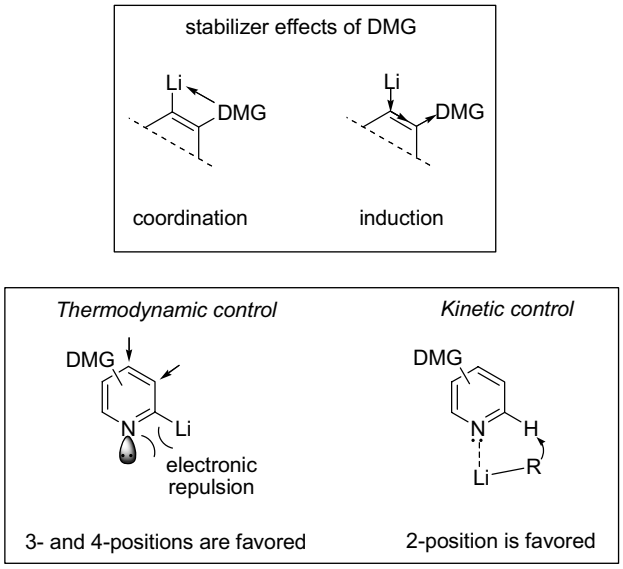
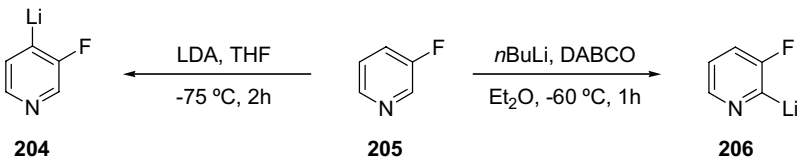


Figure 16.15 Factors affecting the regioselectivity of the reaction.

the lone pair of the nitrogen; and (iv) the complexation of the lithium base with the nitrogen (Figure 16.15). The reaction is usually under thermodynamic control when metal amides such as LDA or LTMP are used, leading to 3- and 4-carbanions. Conversely, alkyllithium reagents proceed under kinetic control. In this case, solvent effects become more important because of the absence of a strong DMG on the ring and because complexation with the nitrogen can occur, in the absence of a chelating solvent such as THF. Therefore, deprotonation takes place at the C2 proton. 3-Fluoropyridine (**205**) is a good example of a metallation substrate in which regioselectivity can be induced by choosing the appropriate base (Scheme 16.61) [176]. LDA abstracts the proton from the 4-position in **205** (thermodynamic) giving lithium derivative **204**, while *n*BuLi in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) affords lithium derivative **206** resulting from proton abstraction at the 2-position in **205** (kinetic).



204 **205** **206**

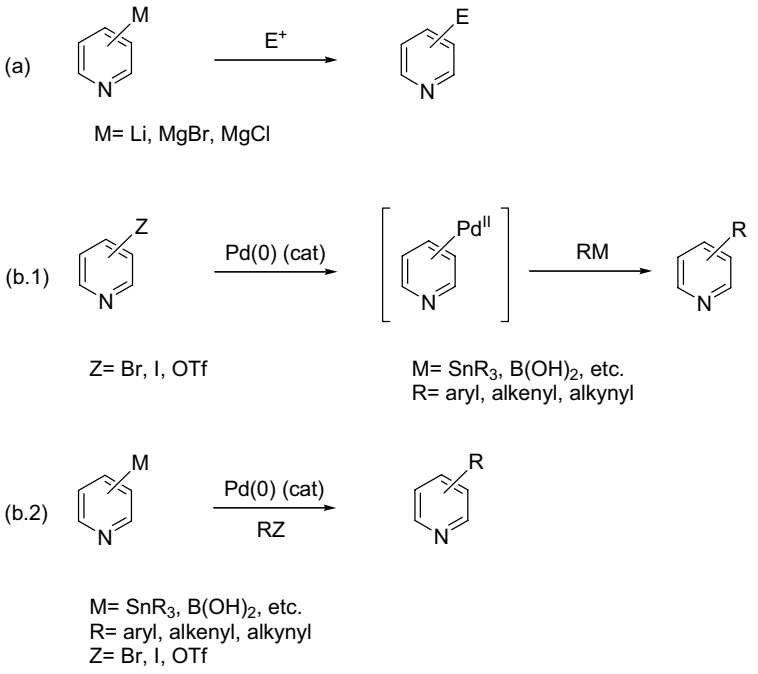
Scheme 16.61

16.3.5
Reactions of C-Metallated Pyridines

Among all possible ways of introducing a pyridine moiety into a more complex structure, the use of C-metallated pyridines is probably one of the most direct. This fact makes C-metallated pyridines one of the most important and widely used pyridyl intermediates, particularly in carbon–carbon bond forming reactions [177].

Basically, they are used in the following type of reactions (Scheme 16.62):

- (a) nucleophilic attack of lithium or Grignard derivatives to electrophiles;
- (b) metal-catalyzed cross-coupling reactions of:
  - –(i) halopyridines or related compounds with organometallic derivatives;
  - –(ii) metal-containing pyridines with halides or related compounds.

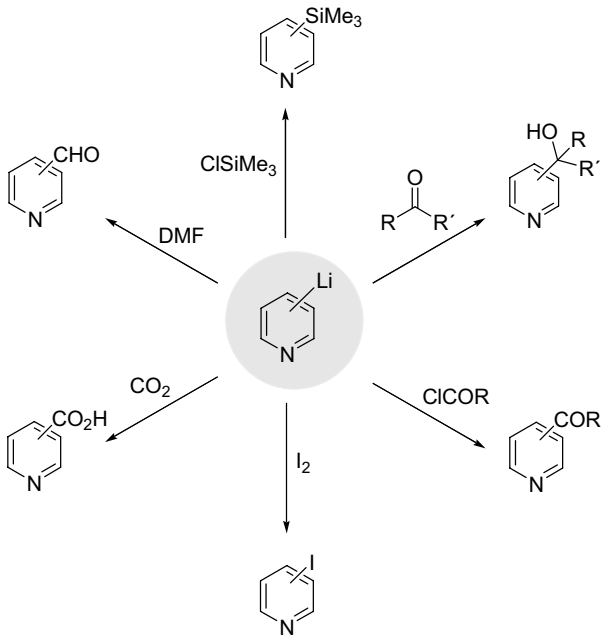


Scheme 16.62

16.3.5.1 **Reactions of Pyridyl Lithium/Grignard Derivatives with Electrophiles**

Pyridines can be readily functionalized upon treatment of either their corresponding organolithium or Grignard derivatives with a large variety of electrophiles. However, the difficulties of preparing pyridine Grignard derivatives have limited their use in synthetic organic chemistry, resulting in their progressive displacement by the more accessible lithium derivatives [177].

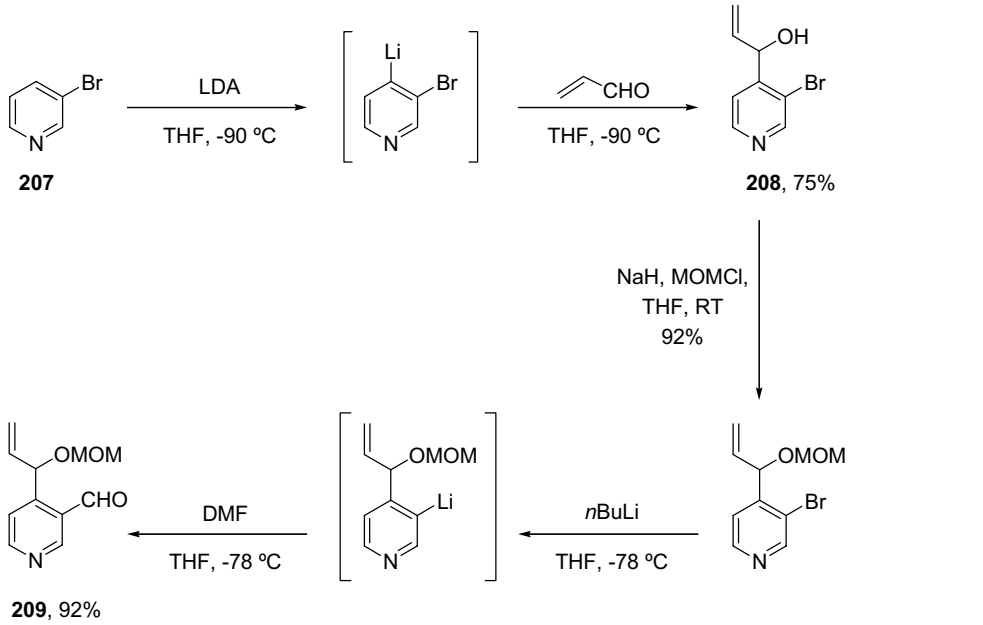
Pyridyl-lithium derivatives are usually prepared either by ortho-metallation using strong bases (Section 16.3.4) or by halogen–metal exchange between halopyridines, mainly bromopyridines, and an organolithium reagent such as *n*BuLi or *t*BuLi or lithium metal. The lithiated species generated by all these methods can react with a wide range of electrophiles such as *N*,*N*-dimethylformamide (DMF), carbon dioxide, iodine, acid chlorides, ketones, trimethylsilyl chloride, and so on, leading to pyridine functionalization with a large variety of functional groups in a single step (Scheme 16.63).



Scheme 16.63

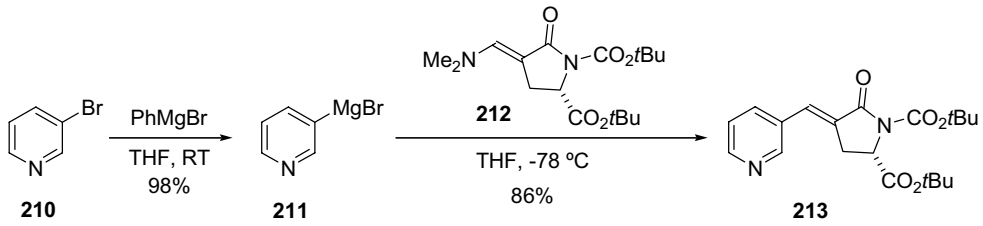
The great synthetic utility of this type of reaction has been demonstrated by Zhai and coworkers [178] in the synthesis of pyridine derivative **209** in three steps starting from simple 3-bromopyridine (**207**) (Scheme 16.64). Ortho-lithiation of **207** with LDA at −90 °C followed by treatment with acrolein at the same temperature gave alcohol **208** in 75% yield. After protection of alcohol **208** as the methoxymethyl ether (MOM), reaction with *n*BuLi produced a bromine–lithium exchange, which was followed by treatment with DMF to afford an excellent yield of aldehyde **209**.

The direct preparation of Grignard derivatives using standard procedures, consisting of the reaction between an haloheterocycle and magnesium, is sometimes rather difficult, mainly due to the basicity of the nitrogen ring atom. In these cases, the usual procedure is the treatment of an halopyridine with commercially available aryl or alkyl Grignard reagents such as PhMgBr, *i*PrMgCl, EtMgBr, and so on. For instance, Madsen and coworkers [179] have employed the Grignard reagent of



Scheme 16.64

3-bromopyridine (**211**), obtained by treatment of **210** with commercially available phenylmagnesium bromide, in the 1,4-addition–elimination reaction with **α**,β-unsaturated carbonyl derivative **212** to furnish pyridine **213** in 86% yield (Scheme 16.65).

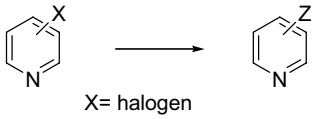


Scheme 16.65

16.3.5.2 **Metal-Catalyzed Cross-Coupling Reactions**

In the last several years, the use of transition metals, particularly palladium, as catalysts for coupling reactions involving metallated species has increased sharply the use of heterocyclic organometallics in all kinds of organic transformations. Metal-catalyzed cross-coupling reactions have remarkably enlarged the toolbox of organic chemistry since their first examples appeared in the late 1960s. A broad variety of substrates, good tolerance of different functional groups, mild reaction conditions,

Table 16.9 Types of metal-catalyzed cross-coupling reactions.



Coupling	Reagents	Z
Stille	$RSn(nBu)_3$	R (alkenyl, alkynyl, aryl)
Suzuki	$RB(OH)_2$/base	R (alkenyl, alkynyl, aryl)
Sonogashira	$R-C\equiv CH$/Cu(I)	$R-C\equiv C$
Heck	$R-CH=CH_2$/base	R−CH=CH
Kumada	RMgX	R (alkyl, alkenyl, alkynyl, aryl)
Negishi	RZnX	R (alkyl, alkenyl, alkynyl, aryl)
Hiyama	$RSiR'_3/F^-$	R (alkenyl, alkynyl, aryl)
Buchwald	R_2NH/base	R_2N

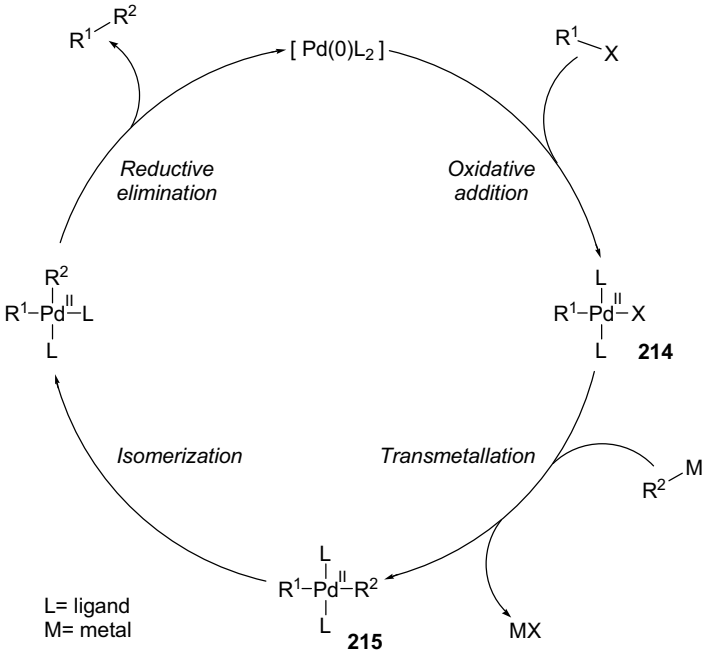
high yields and efficient catalysis make these modern transformations the most widely used reactions for the formation of C−C, C−O, C−N and even C−S bonds.

Nucleophilic attack occurs preferentially at the **α** and γ positions of pyridines. This performance has been attributed to the electronegativity of the ring nitrogen atom, which induces a partial positive charge at these positions of pyridines. A similar trend occurs in the context of metal catalyzed cross-coupling reactions. In fact, **α** and γ-halopyridines are more susceptible to the oxidative addition to Pd(0), relative to simple carbocyclic aryl halides [180]. Even **α**- and γ-chloropyridines are viable electrophilic substrates for Pd-catalyzed reactions under standard conditions [175]. Although nickel, copper and, occasionally, platinum have been used as catalysts for cross-coupling reactions, palladium is the most widely employed catalyst.

Table 16.9 summarizes the most important cross-coupling reactions, indicating the reagents usually employed and the type of group (Z) introduced in the pyridine ring in each case.

Palladium-catalyzed cross-coupling reactions of organohalides or related compounds with organometallic reagents follow a general mechanistic cycle that involves oxidative addition, transmetallation, isomerization and reductive elimination sequences (Scheme 16.66) [181].

A $Pd(0)L_2$ complex (L=ligand, typically a phosphine such as PPh_3) is assumed to be the active catalytic species in the cycle. Sometimes, these Pd(0) species are generated *in situ* by reduction from Pd(II) complexes, such as $Pd(OAc)_2$, in the presence of a suitable ligand such as PPh_3. The first step of the cycle consists in the oxidative addition of R^1–X (X=halogen, OTf, etc.) to form complex **214**, which then undergoes a transmetallation reaction with the organometallic reagent R^2–M to give complex **215**. Both intermediates **214** and **215** have been isolated and/or characterized by different spectroscopic methods. The intermediate **215** undergoes an isomerization reaction followed by a reductive elimination giving rise to a Pd(0) species along with

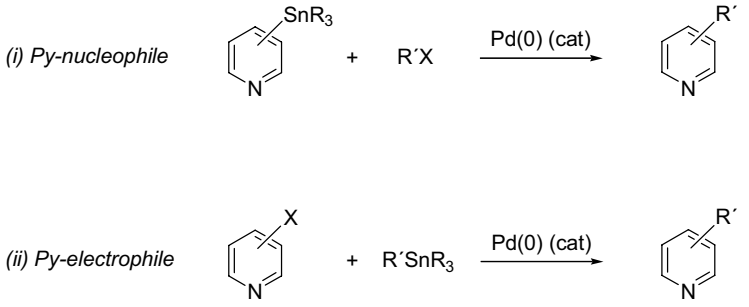


Scheme 16.66

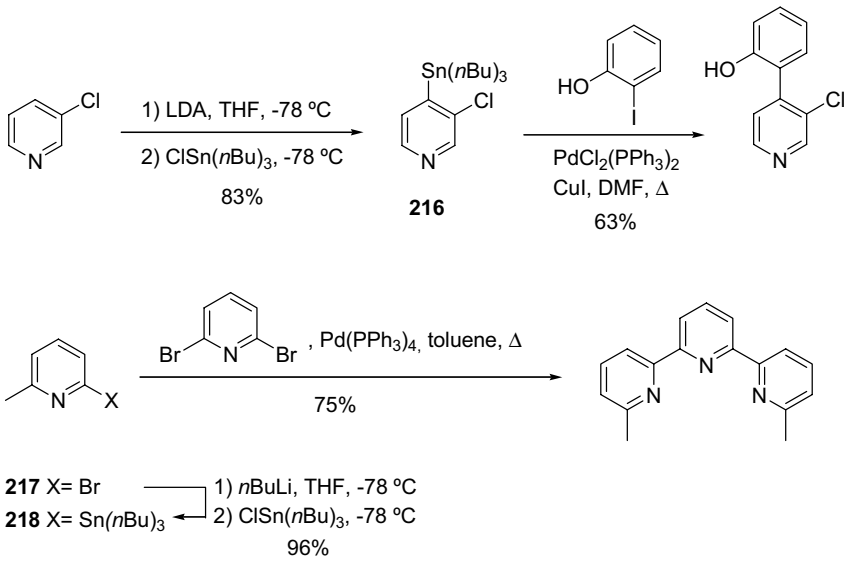
the homocoupling product R^1–R^2. When Pd(0) is regenerated the catalytic cycle starts again. The oxidative addition is often the rate-limiting step and the relative reactivity of R^1–X decreases in the order: I > OTf > Br ≫ Cl.

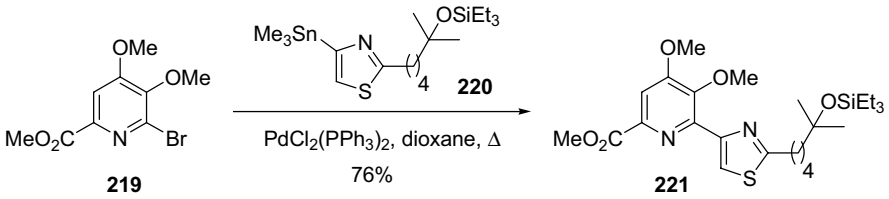
16.3.5.2.1 **Stille Coupling** This type of cross-coupling reaction consists of the Pd-catalyzed reaction between an organostannane and a halide. Typically, the stannane is sp^2 or sp hybridized (aryl, alkenyl, alkynyl) but alkyl-, allyl- and benzylstannanes have also been used. The halides are usually, aryl, vinyl or acyl, bromides, or iodides (and also triflates). In addition, aryl chlorides have also been employed, but they are typically much less reactive.

For a Stille coupling involving a pyridine moiety, the pyridine fragment may be either the nucleophilic or the electrophilic coupling partner (Scheme 16.67). Therefore, two approaches can be employed: the reaction of (i) a pyridyl-stannane (nucleophile) and an halide; or (ii) a halopyridine (electrophile) and an organostannane. In the first case, the pyridyl-stannane is usually prepared either by ortho-metallation or by lithium–halogen exchange followed, in both cases, by treatment with a halide stannane such as $ClSn(nBu)_3$. Procedure (i) is exemplified by derivatives **216** [182] and **218** [183, 184], respectively (Scheme 16.68). A notable example of procedure (ii) appears in the recent literature with the synthesis of the biheteroaryl derivative **221** by Stille cross-coupling using electrophilic pyridine derivative **219** and the stannane **220** [185].



Scheme 16.67

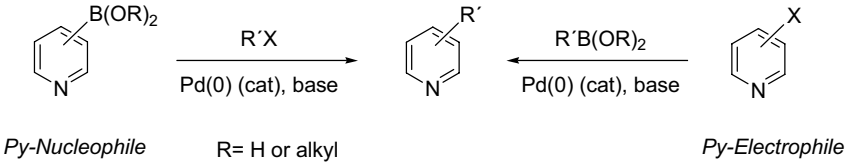




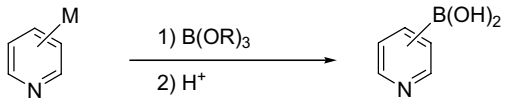
Scheme 16.68

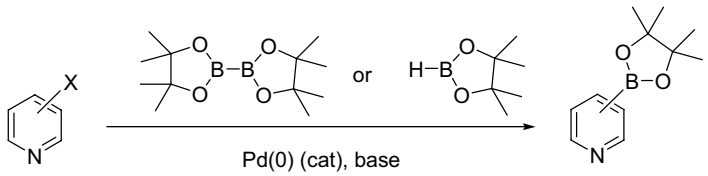
16.3.5.2.2 **Suzuki Coupling** In this reaction, a halide is coupled with an aryl or vinyl boronic acid or boronic ester. The major advantages of the Suzuki reaction are: (i) the stability and rather low toxicity of the boron reagents; (ii) easy access to a broad variety of boronic acids, many of which are commercially available; (iii) tolerance for different functional groups; (iv) straightforward experimental procedures.

Similar to the Stille coupling, two approaches are possible, depending on whether the boron derivative is contained in the pyridine ring or in the reagent (Scheme 16.69). The pyridine boron derivatives are usually prepared by treatment of an organolithium or magnesium pyridine with a trialkylborate (Scheme 16.70). Recently, metal-catalyzed methods have been developed using bis(pinacolato) diboron or pinacolborane as the boron source.



Scheme 16.69





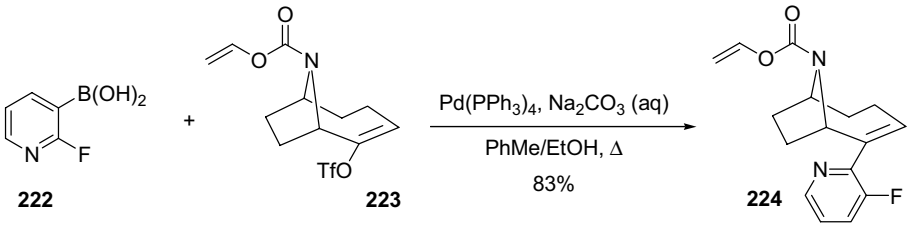
X= Halogen, OTf

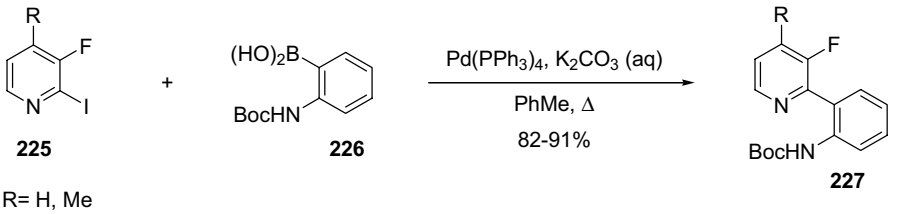
Scheme 16.70

Scheme 16.71 shows examples of Suzuki coupling. The 2-fluoropyridyl group of epibatidine analogue **224** has been introduced by Pd(0)-mediated cross coupling between fluoropyridyl boronic acid **222** and vinyl triflate **223** [186]. In inverse fashion, iodopyridine **225** has been transformed into 2-phenylpyridine **227** using phenylboronic cid **226** [187].

16.3.5.2.3 **Sonogashira Coupling** The Sonogashira reaction is the most direct approach for the synthesis of alkenyl- and arylacetylenes. It consists of the palladium-copper catalyzed coupling of terminal acetylides to arylhalides (Br, I) or triflates to yield alkynylarenes (Scheme 16.72). Chloropyridines can be also used, but these compounds require much higher temperatures.

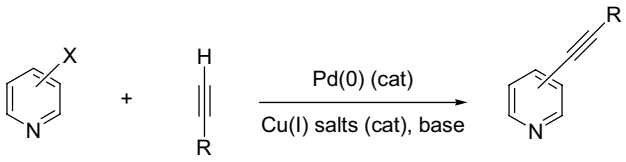
Control of the reaction regioselectivity arises from the difference in electrophilicity at the **α**, β and γ positions of the pyridine ring. For instance, mono-acetylenation of 2,5-dibromopyridine (**228**) with triisopropylsilylacetylene has been achieved under





R= H, Me

Scheme 16.71



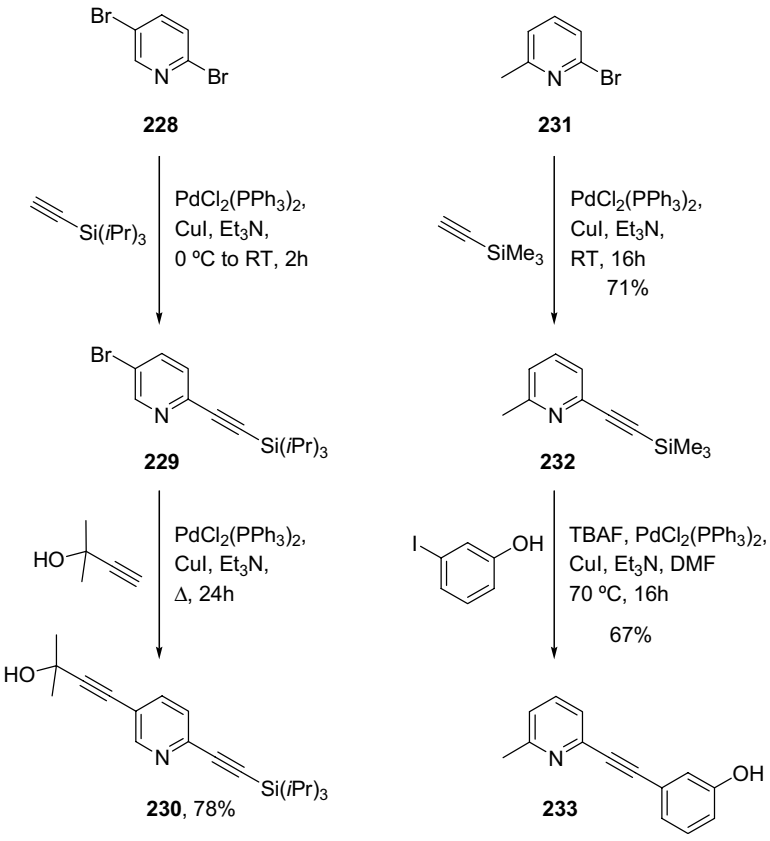
X= Br, I, OTf

Scheme 16.72

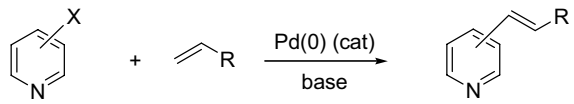
mild conditions (0 °C to room temperature, 2 h) at the more electrophilic **α** position of the pyridine ring to regioselectively afford pyridine **229** (Scheme 16.73) [188]. Further elaboration required much harder reaction conditions (reflux for 24 h) to achieve the second coupling at the less reactive β position of the pyridine ring, which gave pyridine **230** in 78% overall yield.

The use of silylated acetylene avoids the coupling at both positions of the tripe bond and, also, enables a second coupling reaction if the silyl protecting group is removed, leading to unsymmetrical ethynes. For instance, bromopyridine **231** is first coupled with trimethylsilylacetylene to give a good yield of pyridine **232** (Scheme 16.73) [189]. Under similar reaction conditions, but in the presence of tetrabutylammonium fluoride (TBAF) for the *in situ* removal of the silyl protecting group, pyridine **232** undergoes a second Sonogashira coupling with 3-iodophenol to afford bisarylethyne **233** in 67% yield.

16.3.5.2.4 **Heck Reaction** This type of cross-coupling reaction was discovered at the end of the 1960s and consists of the coupling of an alkene with an aryl(or alkenyl) halide (Br, I) or triflate to afford vinylarenes (or dienes) (Scheme 16.74). Terminal



Scheme 16.73

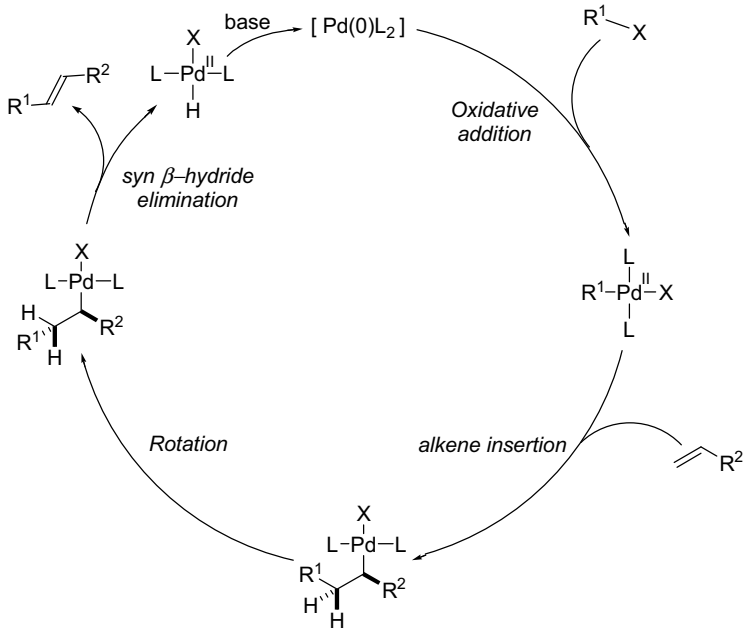


X= Br, I, OTf

Scheme 16.74

alkenes are usually good substrates for the Heck reaction and react at the non-substituted carbon. 1,2-Disubstituted alkenes usually give product mixtures, with a preference for the less sterically hindered carbon.

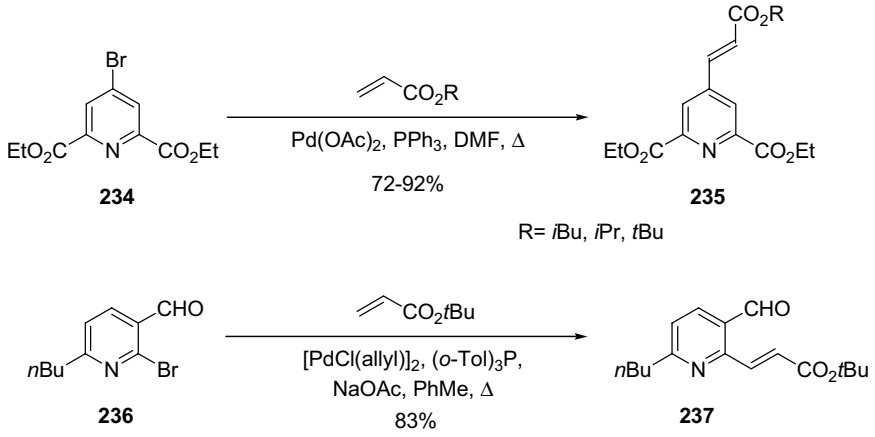
The mechanism of the Heck cross-coupling reaction (Scheme 16.75) differs slightly from the general scheme presented earlier (Scheme 16.66). Although the first steps in both processes are identical, in the Heck reaction there is an absence of the transmetalation step. Alternatively, the C−C bond is formed by an insertion



Scheme 16.75

process, which is followed by a β-hydride elimination to form the substituted alkene product.

Examples of Heck reactions are shown in Scheme 16.76. Bromopyridine **234** can be coupled with inexpensive acrylates to give **α**,β-unsaturated esters **235** in good to excellent yields [190]. The *tert*-butyl acrylate of pyridine **237** is introduced in **236**



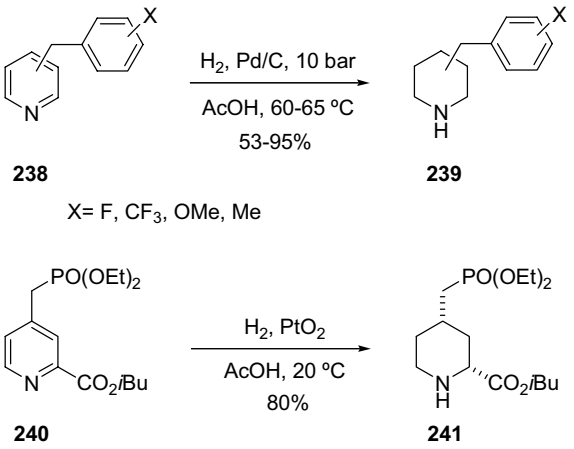
Scheme 16.76

(in 83% yield) by Heck coupling with *tert*-butyl acrylate, using allyl palladium chloride dimer and tri-*o*-tolylphosphine [191].

16.3.6
Reactions with Reducing Agents

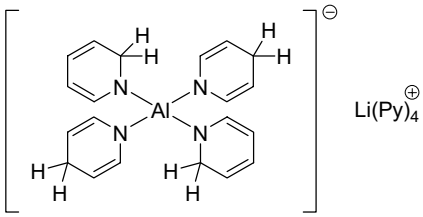
Pyridines can be reduced by catalytic hydrogenation, by metal hydrides or by metals in protic media to piperidines, 1,2- or 1,4-dihydropiperidines, depending on the reducing agents employed and the reaction conditions.

Pyridines are much more easily reduced than benzenes. While the catalytic hydrogenation of benzene requires high pressure and high temperatures, pyridine can be reduced at normal pressure and room temperature to afford piperidine in excellent yield [192]. This fact can be exploited for the selective reduction of pyridines in the presence of phenyl groups. For instance, benzylpyridines **238** have been converted into benzylpiperidines **239** by catalytic hydrogenation (Scheme 16.77) [193]. However, the reaction proceeds smoothly only when piperidines are obtained as ammonium salts, because free bases tend to poison the catalyst. Therefore, hydrogenation of pyridine **240** using PtO_2 as catalyst and in acetic acid gave at room temperature piperidine **241** in 80% yield [194].



Scheme 16.77

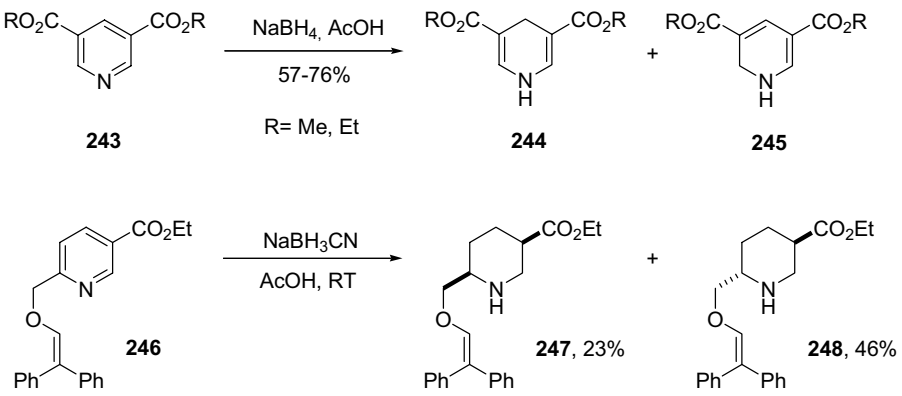
Pyridines can also be reduced with various metal hydrides, but the results depend on the type of hydride. Whereas diisobutylaluminium hydride (DIBALH) or Et_2AlH reduce pyridine slowly, $LiEt_3BH$ (super hydride) efficiently leads to piperidine [195]. In contrast, the reaction of $LiAlH_4$ and pyridine results in the addition of one hydride equivalent to pyridine, yielding the complex **242**, which contains two 1,2- and two 1,4-dihydropyridine units (Figure 16.16) [196–198]. Complex **242**, also known as Lansbury's reagent, has been used as a selective reducing agent of ketones, especially in the presence of carboxylic acids and esters.



242

Figure 16.16 Lansbury's reagent.

Although $NaBH_4$ does not reduce pyridine itself, electron-withdrawing substituted pyridines are effectively reduced to di- or tetrahydropyridines in the presence of $NaBH_4$. For instance, pyridines **243** undergo reduction with $NaBH_4$ to give mixtures of the corresponding 1,4- (**244**) and 1,2-dihydropyridines (**245**) (Scheme 16.78) [199]. Also, the pyridine ring of compound **246** has been fully reduced by treatment with $NaBH_3CN$, leading to a cis-trans diastereomeric mixture of piperidines **247** and **248** [200].



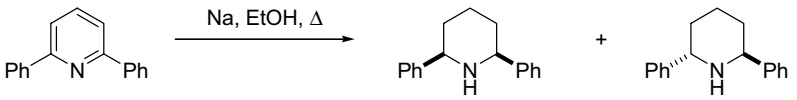
Scheme 16.78

Metals in protic media, typically sodium in ethanol, reduce pyridines to piperidines. This type of reduction is considered to be similar to the Birch reduction of arenes. For instance, reduction of 2,6-diphenylpyridine (**249**) afforded a cis-trans mixture of diastereomers **250** and **251** (Scheme 16.79) [201]. Under aprotic conditions, reduction fails and bipyridines are produced instead (Section 16.3.7).

16.3.7 Reactions with Carbenes, Nitrenes and Radical Reagents

16.3.7.1 Reactions at the Ring Nitrogen Atom: Carbenes and Nitrenes

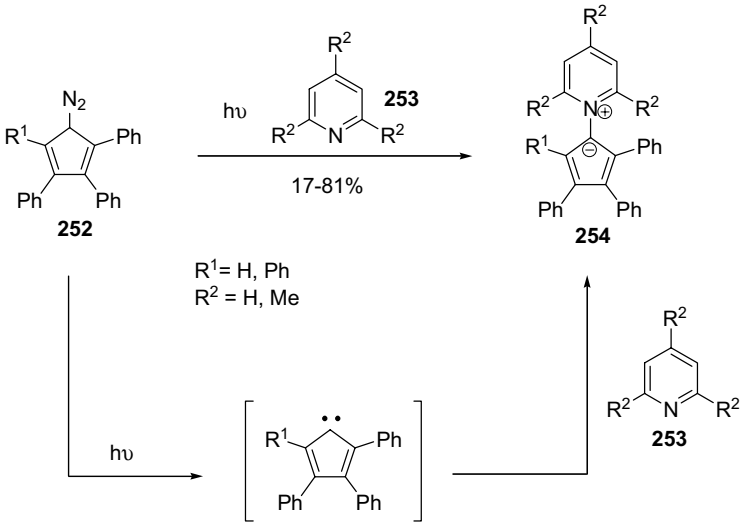
Electrophilic carbenes can react with compounds containing free electron pairs, such as carbonyls, nitriles, ethers, alcohols, and so on to form ylides. In addition, carbenes



249 **250**, 39% **251**, 54%

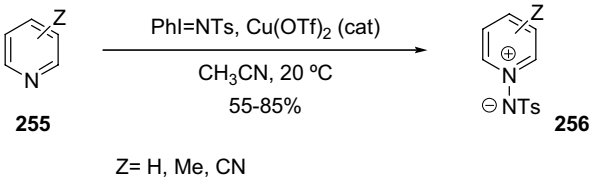
Scheme 16.79

react with pyridines at the ring nitrogen atom to form pyridinium ylides, which have been extensively used as trapped carbenes in studies of carbene reactions by laser flash photolysis. In some cases, pyridinium ylides have been isolated and characterized. For instance, pyridinium cyclopentadienides **254** have been obtained in yields between 17 and 81% by irradiation of diazo derivatives **252** in the presence of pyridines **253** (Scheme 16.80) [202].



Scheme 16.80

Nitrenes give similar results with pyridines to afford pyridinium iminoylides. For instance, treatment of the nitrene precursor PhI = NTs with various pyridines **255** in the presence of a catalytic amount of Cu(II) affords the corresponding *p*-tolylsulfonyliminopyridinium ylides **256** in good yields (Scheme 16.81) [203].



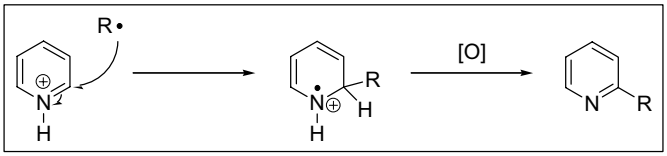
255 **256**

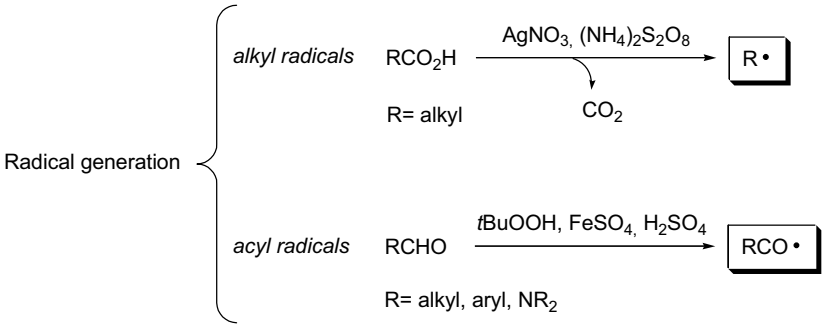
Z= H, Me, CN

Scheme 16.81

16.3.7.2 Reactions at the Ring Carbon Atom: Carbon and Halogen Radicals

16.3.7.2.1 **Carbon Radicals** Free radical substitutions in aromatic systems have long been known, but are used rarely in organic synthesis. Of greater preparative value are the reactions of nucleophilic radicals, such as $HOCH_2^{\cdot}$ and $R_2NCO^{\cdot}$, which can be easily generated under mild conditions. Minisci and coworkers [204] were the first to report that carbon radicals can be used to regioselectively synthesize 2- and 4-alkyl and acylpyridines. These substitutions are carried out on the protonated pyridine, which provides both increased reactivity and selectivity for the 2-position, a transformation that is known as the Minisci reaction (Scheme 16.82) [204]. The radical species are generated either by oxidative silver-catalyzed decarboxylation (alkyl radicals) or by Fenton-type reaction with organic hydroperoxides and Fe(II) or Ti(III) reagents (acyl radicals) [205–207].





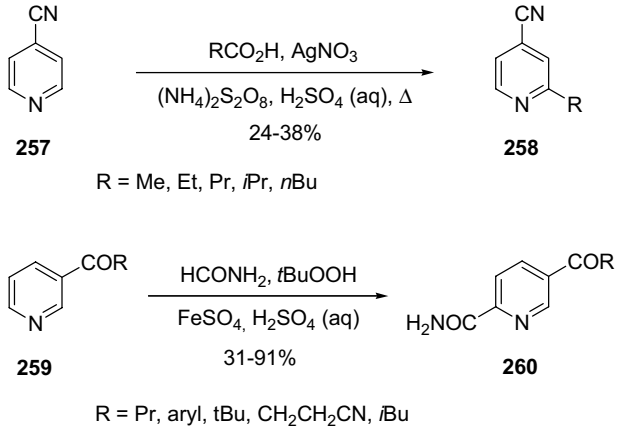
Reactivity: pyridinium cation > neutral pyridine

Selectivity: 2- > 4- >> 3-position

Scheme 16.82

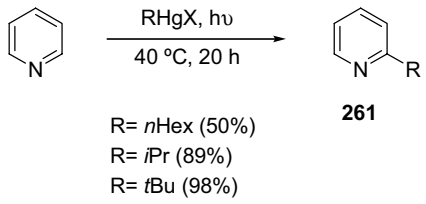
Scheme 16.83 shows examples of reactions of this type. Diverse alkyl radicals generated by oxidative silver-catalyzed decarboxylation of various carboxylic acids have been reacted with 4-cyanopyridine (**257**) to give pyridines **258** with control of regioselectivity [208]. On the other hand, 3-acylpyridines **259** have been regioselectively carbamoylated via the Miscini reaction with $RHNCO^{\cdot}$ radicals generated by treatment of various formamides with *t*-butyl hydroperoxide and Fe(II) to yield pyridines **260** [209].

Alkylmercury halides are also convenient sources of alkyl radicals that react with pyridines, attacking mainly at the **α**-position to give the corresponding 2-alkyl



Scheme 16.83

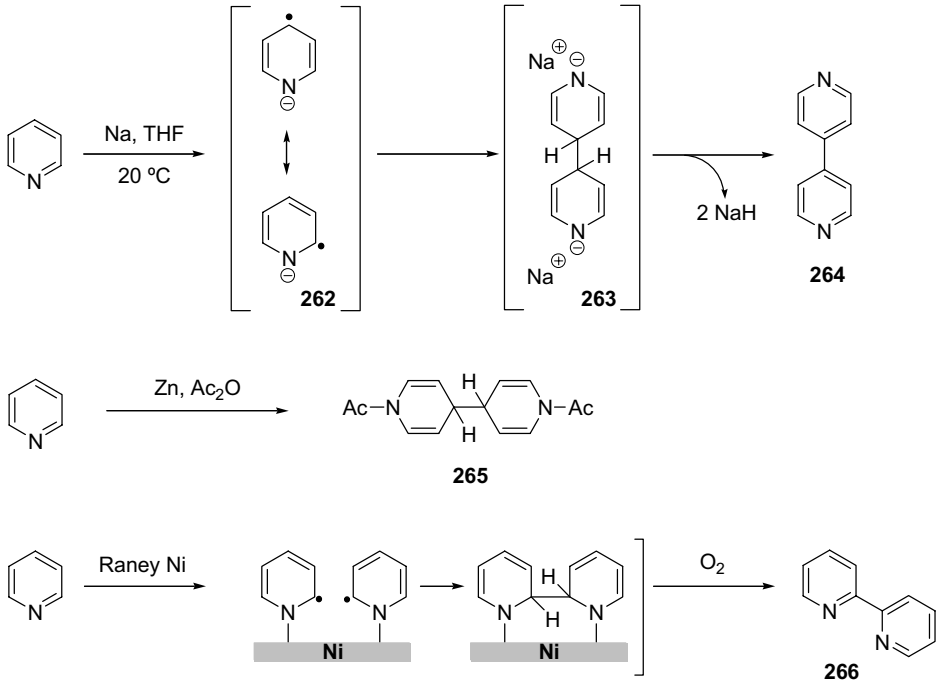
derivatives **261** (Scheme 16.84) [210]. Reaction yields decrease from tertiary, secondary to primary alkyl groups, in accordance with decreasing radical stability.



Scheme 16.84

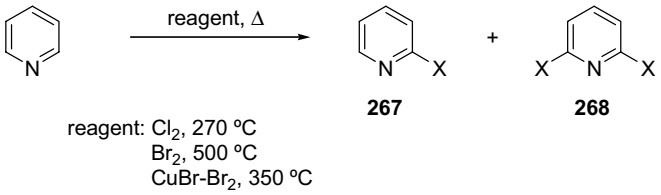
In contrast with alkyl and acyl radicals, aryl radicals generated from $(PhCO)_2O$, PhI $(OCOPh)_2$, and so on give mixtures of 2-, 3- and 4-arylpyridines with low reaction yields.

Certain metals, such as Na, Zn or Ni, under aprotic conditions react with pyridines to form radical anions **262** resulting from an electron-transfer from the metal to the pyridine ring (Scheme 16.85). These radical anions dimerize to give bipyridines in a reaction considered equivalent to the pinacol reduction. At room temperature, pyridine reacts with sodium in tetrahydrofuran (THF) to afford 4,4′-bipyridine (**264**), mainly by coupling through the γ-positions of two pyridine radicals. At higher temperatures, 2,3′-, 3,3′- and 3,4′-bipyridines are also formed. If the reaction is carried out with Zn in the presence of acetic anhydride, the dihydropyridinium intermediate **263** is trapped and 4,4′-bidihydropyridine **265** is obtained [211]. However, pyridines under dimerization conditions using Ni afford 2,2′- (**266**) instead of 4,4′-bipyridine (**264**). This has been attributed to the favored chelation of the radical anion to the metal surface.



Scheme 16.85

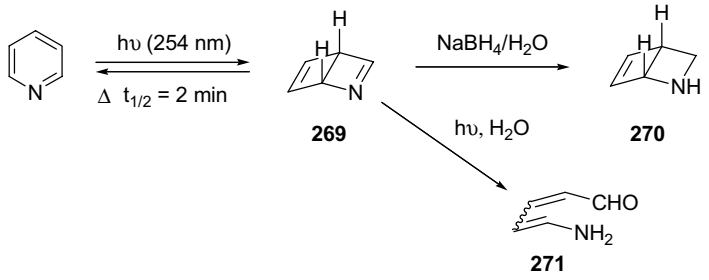
16.3.7.2.2 **Halogen Radicals** Pyridines can be halogenated via radical substitution at high temperatures where chlorine (270 °C) or bromine (500 °C) are appreciably dissociated into their corresponding radicals, affording mixtures of 2-halo **267** and 2,6-dihalopyridines **268** (Scheme 16.86). 2-Fluoropyridines can also be synthesized by reaction with fluorine diluted in an inert gas using polyhalogenated solvents. However, these methods are rarely used in preparative synthesis due to the extreme reaction conditions required, which may be incompatible with other functional groups present in the pyridine nucleus.



Scheme 16.86

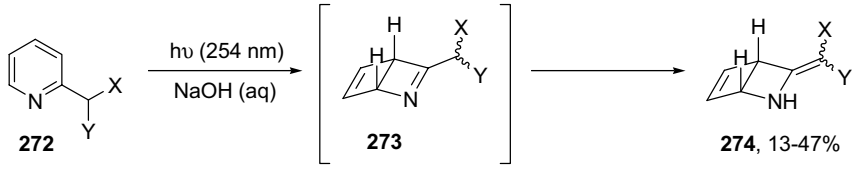
16.3.8
Photochemical Reactions

Pyridines under photochemical irradiation undergo an intramolecular electrocyclic 4π-ring closure to afford highly strained 2-azabicyclo[2.2.0]hexadienes **269**, so-called Dewar pyridines, which contain at least two new stereogenic centers. Complex structures **269** are observable spectroscopically but, usually, are unstable and revert thermally to pyridines or in the presence of water are hydrolyzed to conjugated aminoaldehydes **271** (Scheme 16.87). However, these intermediates can also be trapped by reduction with sodium borohydride to afford amines **270**.



Scheme 16.87

Of particular utility is the photoirradiation of 2-alkylpyridines **272** with electron-withdrawing groups on the alkyl substituent, which under base-catalyzed conditions give stable azabicycles **274** resulting from a proton shift over the initial cycloadduct **273** (Scheme 16.88) [212].

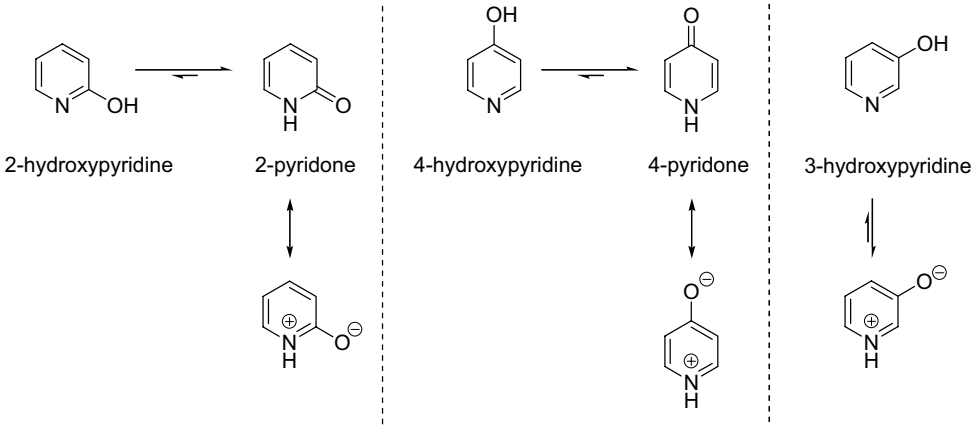


Scheme 16.88

16.4
Pyridine Derivatives

16.4.1
Oxyderivatives

The 2- and 4-hydroxypyridines exist almost entirely in the carbonyl tautomeric forms, known as 2- and 4-pyridones, respectively (Scheme 16.89). Their hydroxyl forms are



Scheme 16.89

detected only in non-polar solvents or in the gas phase. However, 3-hydroxypyridines behave as regular pyridines, which can also be in equilibrium with their zwitterionic forms in a ratio that depends on the type of solvent.

16.4.1.1 Reactions with Electrophilic Reagents

16.4.1.1.1 **Reactions with Acids** According to their structure, pyrones react mainly as unsaturated lactams whereas 3-hydroxypyridines behave as pyridines. As a consequence, 2- and 4-pyridones are protonated on their carbonyl groups (pK_a 0.8 and 3.3, respectively) whereas 3-hydroxypyridines react through their ring nitrogen atom (pK_a 5.2) (Figure 16.17).

16.4.1.1.2 **Reactions with Acid Chlorides and Related Compounds** Acid chlorides react with pyridones and 3-hydroxypyridines through their oxygen atom, affording the corresponding pyridinyl esters. For example, treatment of 4-pyridone and 2-pyridone **277** with benzoyl chlorides **275** and **278** gives, respectively, pyridines **276** [213] and **279** [214] in good yields (Scheme 16.90). Also, the reaction of 2-pyridone **280** with tosyl chloride affords an excellent yield of tosylate **281** [215].

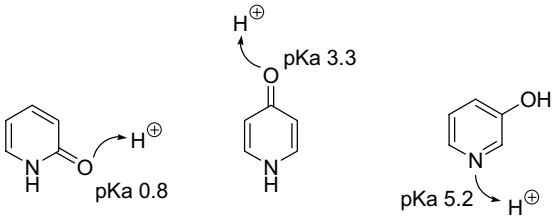
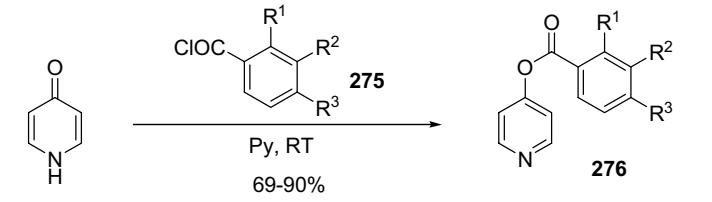
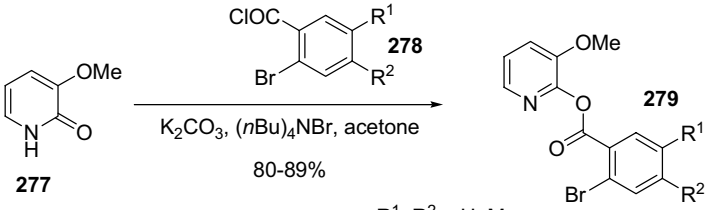


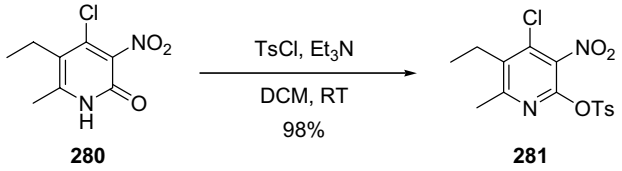
Figure 16.17 The pK_as of pyrones and 3-hydroxypyridine.



R^1, R^2, R^3 = H, Me, Br, Cl, NMe_2, OMe, NO_2



R^1, R^2 = H, Me



Scheme 16.90

16.4.1.1.3 **Electrophilic Substitution Reactions** Pyridones and 3-hydroxypyridines are more reactive to electrophilic substitutions than pyridines and the regioselective preference is to undergo substitution in the ortho and para positions relative to the oxygen functionality (Figure 16.18). These pyridine derivatives can be readily halogenated, nitrated or sulfonated. For example, the nitration of pyridones **282** and **284** affords regioselectively nitropyridones **283** and **285**, respectively (Scheme 16.91) [216, 217].

16.4.1.1.4 **Reactions of Oxypyridine Anions with Electrophiles** Pyridones are weak acids with pK_as of around 11. They form mesomeric anions that readily react with electrophilic reagents at the nitrogen or oxygen atoms depending on the reaction

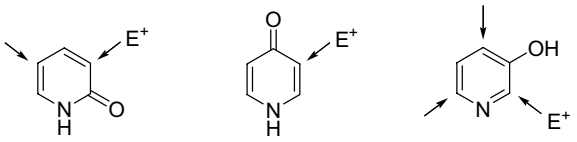
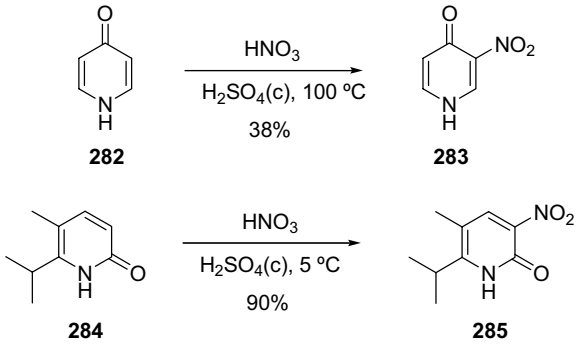
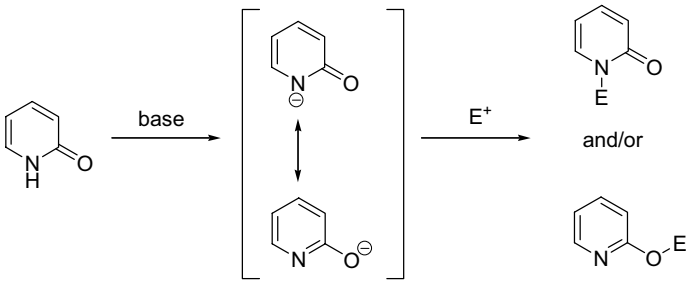


Figure 16.18 Regioselectivity in electrophilic substitutions of pyridones and 3-hydroxypyridine.

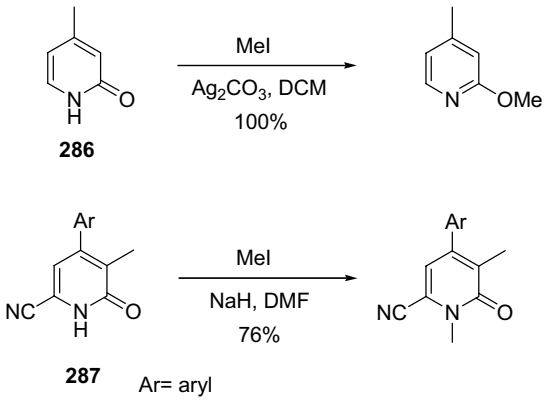


Scheme 16.91

conditions (Scheme 16.92). For example, 2-pyridone **286** [218] is quantitatively *O*-methylated with methyl iodide using silver carbonate as base, whereas 2-pyridone **287** [219] preferentially affords N-methylation using the same alkylating agent but in the presence of sodium hydride (Scheme 16.93).



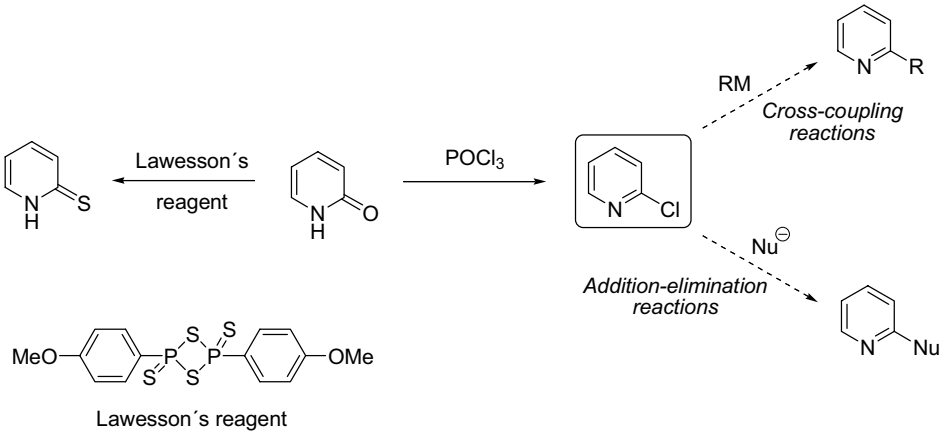
Scheme 16.92



Scheme 16.93

16.4.1.2 **Replacement of Oxygen Function**

The pyridone oxygen can be replaced by other atoms such as chloro or sulfur to afford the corresponding chloropyridines and thiopyridones, respectively. In particular, the conversion of the carbonyl group of pyridones into a good leaving group such as chloride, typically using phosphorus oxychloride, is an important reaction in pyridone chemistry, because chloropyridines are susceptible to cross-coupling reactions with organometallic reagents to form new carbon–carbon bonds or addition–elimination reactions with diverse nucleophiles (amines, cyanide, etc.) (Scheme 16.94). Usually, pyridones are converted into thiopyridones using Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide] [220].



Scheme 16.94

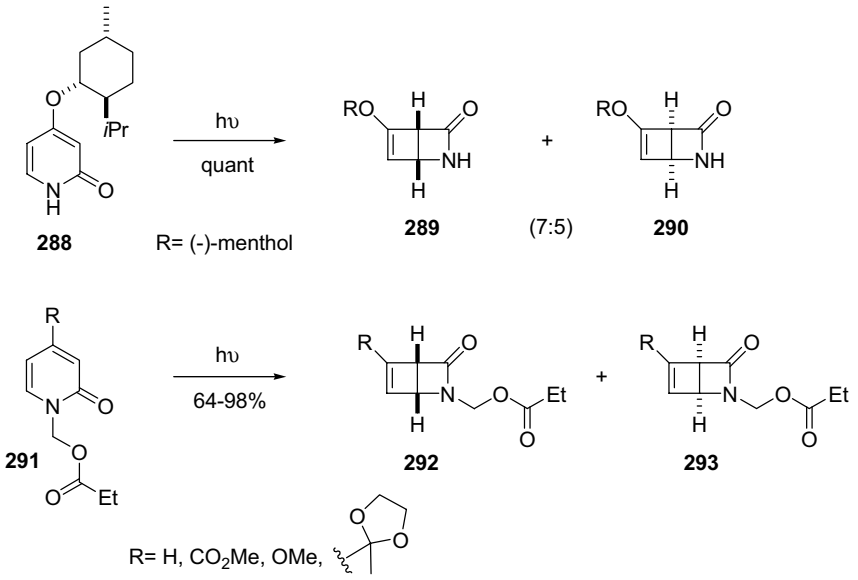
16.4.1.3 **Photochemical Reactions of Pyridones**

Intramolecular electrocyclic 4π-ring closure represents the key photochemical reaction of 2-pyridones. This reaction has been extensively utilized in the synthesis of the carbapenem antibiotics core. Herein, photocyclization of the chiral pyridine **288** leads quantitatively to a mixture of diastereomers **289** and **290** (7 : 5 ratio, respectively) (Scheme 16.95) [221]. Furthermore, *N*-alkylated pyridones **291** undergo this type of reaction, affording diastereomeric bicycles **292** and **293** [222].

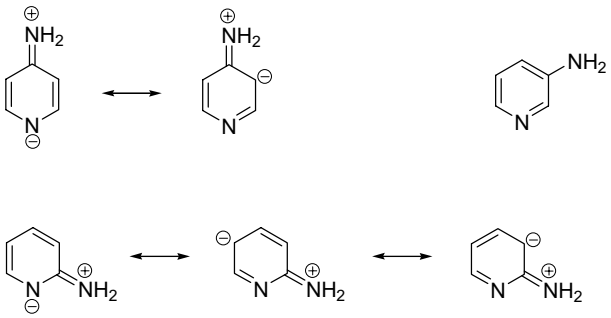
16.4.2
Amino Derivatives

16.4.2.1 **Reactions with Electrophilic Reagents**

Aminopyridines have three possible nucleophilic centers: the ring nitrogen atom, the amino nitrogen and the ring carbon atom (Scheme 16.96). As expected from their resonance forms, aminopyridines react with certain electrophiles such as proton, alkylating and acylating agents preferentially through their ring nitrogen atom.



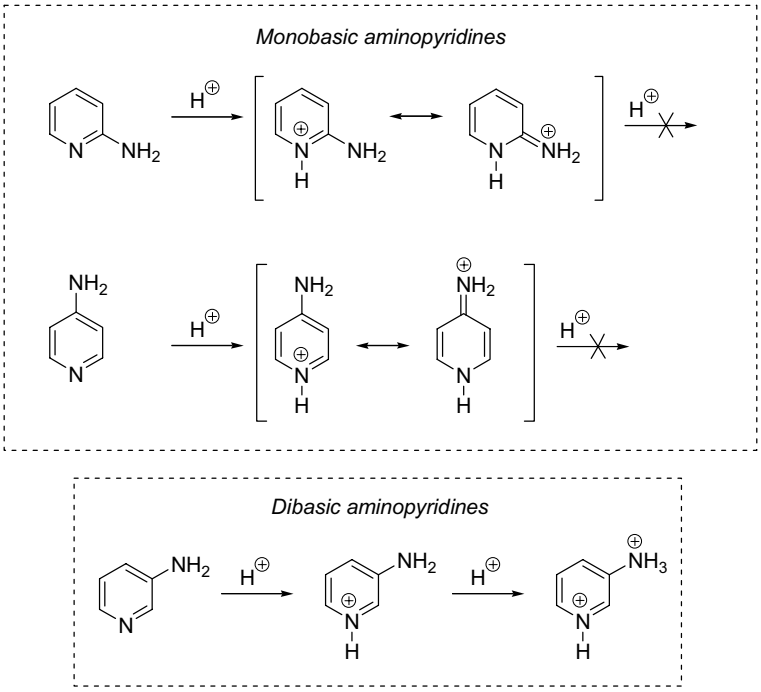
Scheme 16.95



Scheme 16.96

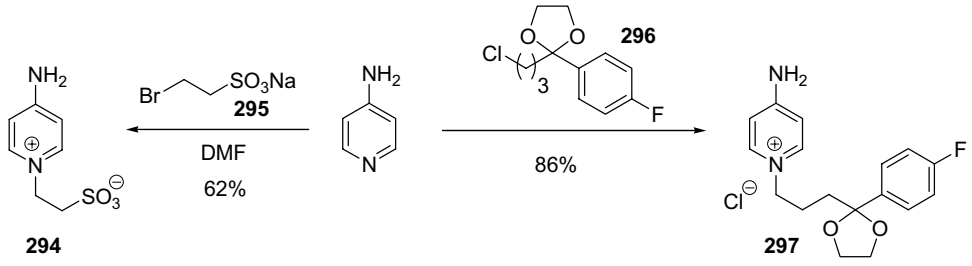
However, other electrophilic reagents react with aminopyridines through their ring carbon atom by an alternative electrophilic substitution pathway. In these cases, the 5- and 3-positions of 2- and 4-aminopyridines, respectively, are favored.

16.4.2.1.1 **Reactions with Acids** The three aminopyridines are all more basic than pyridine itself and form crystalline salts by protonation at the ring nitrogen atom. The **α**- and γ-isomers are monobasic, because the positive charge is delocalized over both nitrogen atoms, which prevents further protonation (Scheme 16.97). This effect is stronger in the γ-isomer than in the **α**-isomer, but it is not possible in the β-isomer. As a consequence β-aminopyridines can be further protonated using strong acids.



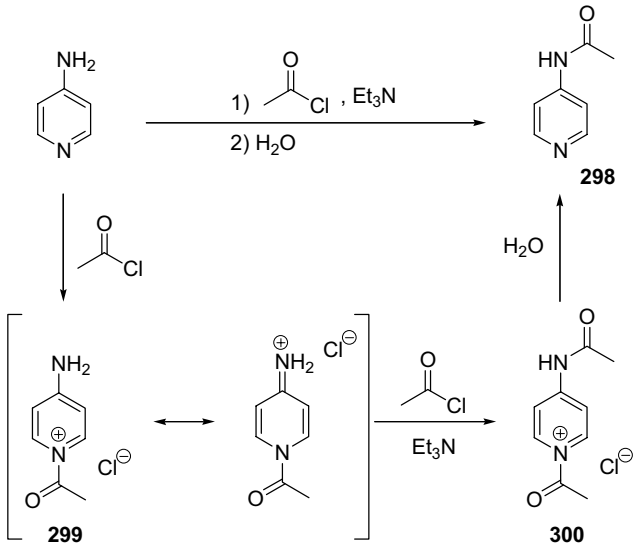
Scheme 16.97

16.4.2.1.2 **Reactions with Alkylating Agents** Aminopyridines react with alkylating agents through the more nucleophilic ring nitrogen atom to afford quaternary ammonium salts. For example, 4-aminopyridine has been alkylated with bromide **295** and chloride **296** to give quaternary pyridinium salts **294** [223] and **297** [224], respectively (Scheme 16.98).



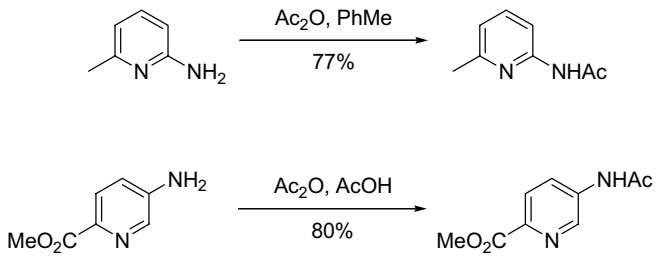
Scheme 16.98

16.4.2.1.3 **Reactions with Acylating Agents** Acid chlorides and related compounds react with aminopyridines through their amino substituent to afford the corresponding amides (Scheme 16.99). The ring nitrogen atom of the aminopyridine reacts first to give *N*-acylpyridinium salts **299**, which then undergo a second acylation reaction



Scheme 16.99

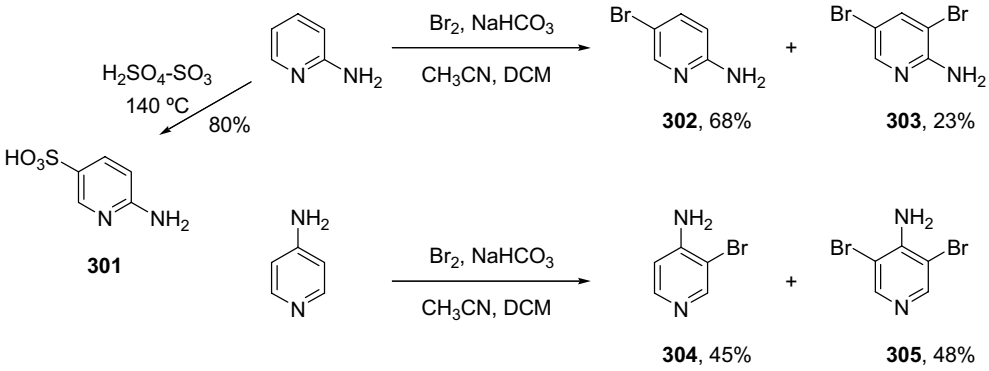
through the amino substituent to yield intermediate **300**. Finally, aqueous work up affords amide **298**. Some examples are shown in Scheme 16.100 [225, 226].



Scheme 16.100

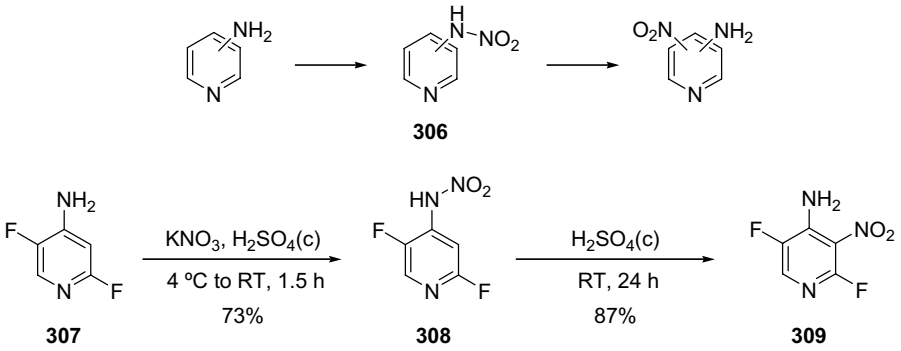
16.4.2.1.4 **Electrophilic Substitution Reactions** Aminopyridines undergo electrophilic substitution under milder conditions than pyridine itself. Usually, the substitution reaction takes place selectively at 5- and 3-positions of 2- and 4-aminopyridines, respectively. For example, 2-aminopyridine has been selectively sulfonated to give pyridine **301** in good yield (Scheme 16.101) [227]. Bromination of 2-aminopyridine afforded mainly 5-brominated pyridine **302**, and also some dibrominated pyridine **303** [228]. In contrast, bromination of 4-aminopyridine gave an almost 1 : 1 mixture of mono- and dibrominated pyridines **304** and **305**, respectively.

The nitration of aminopyridines proceeds via a nitroamino derivative (**306**) resulting from the nitration of the amino substituent, which on further reaction



Scheme 16.101

with concentrated H_2SO_4 gives the corresponding nitropyridine (Scheme 16.102). Nitration of 4-aminopyridine **307** using potasium nitrate in concentrated H_2SO_4 gave first the nitrated amino derivative **308** in 73% yield, which was followed by treatment with concentrated H_2SO_4 to, finally, afford 3-nitropyridine **309** in good yield [229].

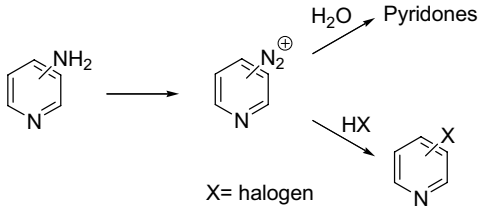


Scheme 16.102

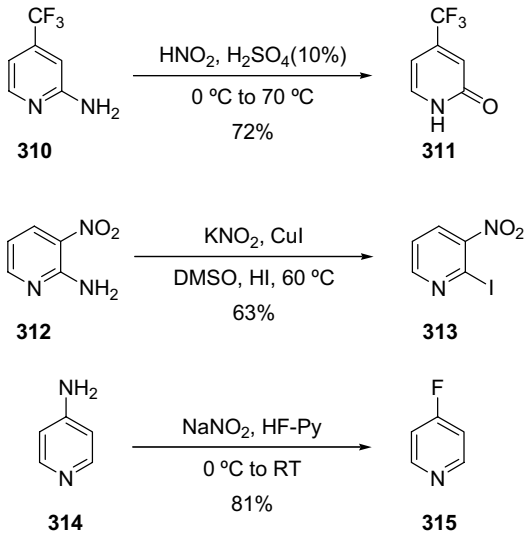
16.4.2.2 **Diazotization of the Amino Group**

Similar to anilines, treatment of aminopyridines with nitrites affords the corresponding diazonium salts, which easily decompose and react with diverse nucleophilic reagents such as HBr, HCl, HF, and so on (Scheme 16.103).

The diazonium salts of 2- and 4-aminopyridines decompose particularly fast and immediately react with the aqueous solvent to give the corresponding 2-and 4-pyridones, respectively. For example, diazotization of 2-aminopyridine **310** in the presence of 10% H_2SO_4 gave 2-pyridone **311** in 72% yield (Scheme 16.104) [220]. However, under controlled conditions, these diazonium salts are susceptible to reaction with diverse nucleophilic reagents. By carrying out the diazotization of aminopyridines **312** and **314** in 50% HI and HF-pyridine solution, respectively, good



Scheme 16.103



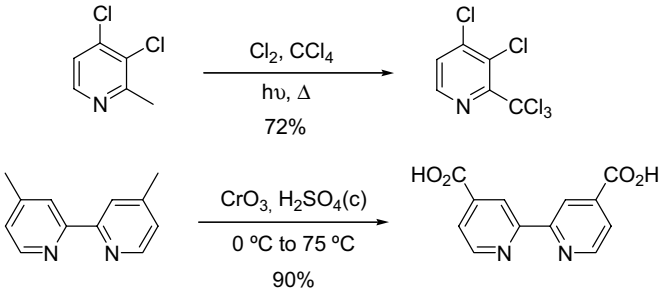
Scheme 16.104

and excellent yields of iodo- **313** [230] and fluoropyridines **315** [231] can be obtained. The diazonium salts of 3-aminopyridines are reasonably stable, affording similar substitution reactions and coupling reactions.

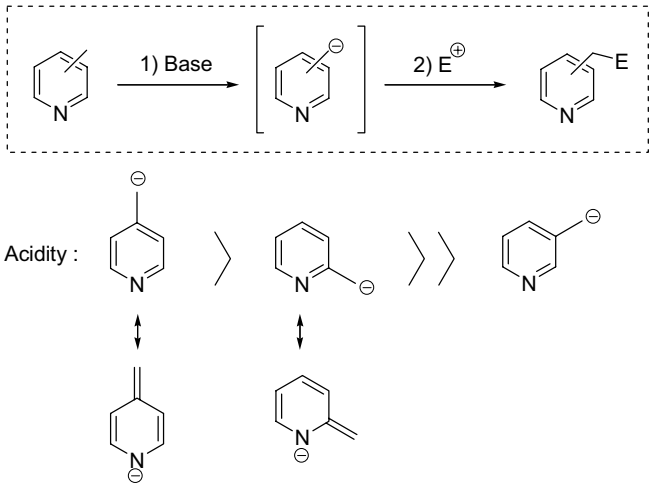
16.4.3 Alkyl Derivatives

Similar to alkylbenzenes, alkylpyridines undergo special reactions at the side-chain such as halogenations and oxidations (Scheme 16.105) [232, 233].

Of particular interest is the deprotonation reaction with strong bases, such as LDA, *n*BuLi, $NaNH_2$, and so on, which occurs 10^5 more rapidly with alkylpyridines than with the corresponding alkylbenzenes (Scheme 16.106). The 2- and 4-isomers are considerably more acidic than the 3-isomer due to the nitrogen stabilization, with the 4-isomer being the most acid. The resulting alkylpyridines anions can react with mild electrophilic reagents to afford a large variety of derivatives. For example,



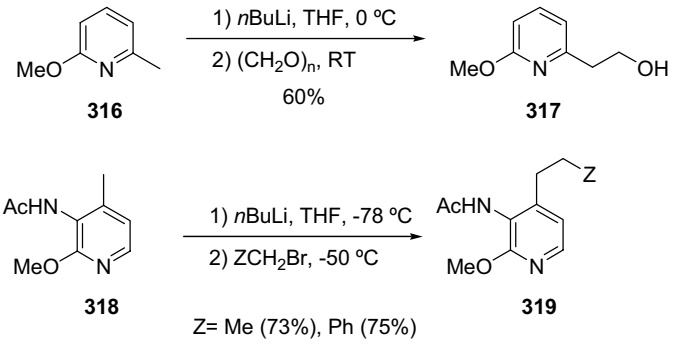
Scheme 16.105



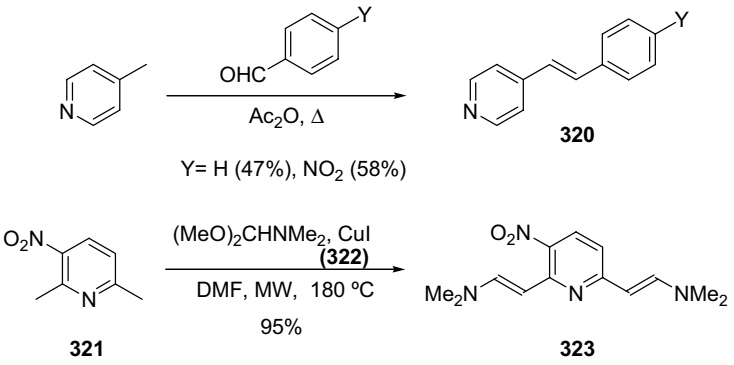
Scheme 16.106

functionalization of the methyl group of pyridines **316** and **318** by proton abstraction of the corresponding methyl groups with *n*BuLi followed, respectively, by reaction with formaldehyde and primary bromide leads to pyridines **317** [218] and **319** [234], respectively (Scheme 16.107). 3-Alkylpyridine also undergoes this type of reaction but the yields are usually lower.

Side-chain hydrogens of alkylpyridines are sufficiently acidic to undergo condensation reactions with aldehydes or acetals. For example, γ-picoline has been condensed with various benzaldehydes to give reasonable yields of hetero-stilbenes **320** (Scheme 16.108) [235]. Furthermore, treatment of dimethylpyridine **321** with dimethylformamide dimethyl acetal (**322**) in the presence of catalytic CuI and microwave acceleration at 180 °C affords an excellent yield of dienamine **323** [236].



Scheme 16.107



Scheme 16.108

16.4.4
Pyridine Aldehydes, Ketones, Carboxylic Acids and Derivatives

In general, these types of compounds behave similarly to the corresponding benzene derivatives. In the case of pyridine carboxylic acids, the presence of the ring nitrogen atom favors the existence of their zwitterionic forms in aqueous solution (Figure 16.19).

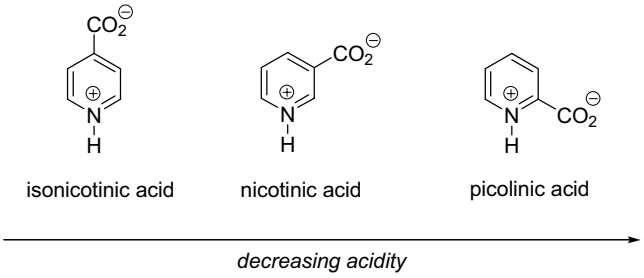
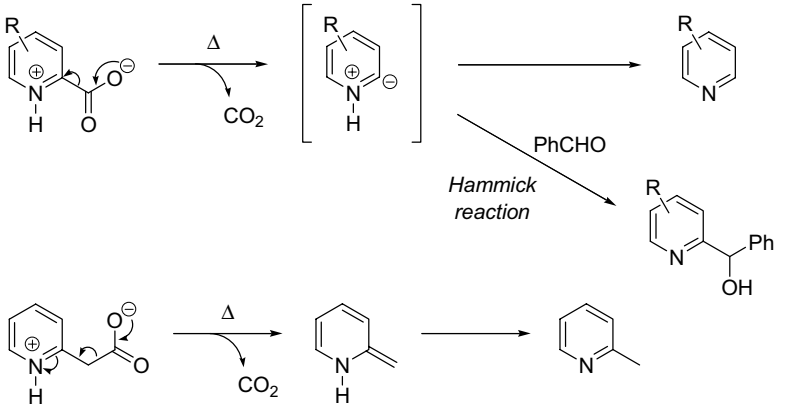


Figure 16.19 Zwitterionic forms of pyridine carboxylic acids in aqueous solution.

All three isomers are more acidic than benzoic acid with the 4-isomer (isonicotinic acid) being the most acidic.

On heating, pyridine carboxylic acids readily undergo decarboxylation to afford the corresponding protonated derivatives. This reaction occurs more easily with pyridine carboxylic acids than with benzoic acids, decreasing in the reactivity order $\alpha > \gamma \gg \beta$ isomer according to the inductive stabilization of the generated carbanions (Scheme 16.109). If the reaction is carried out in the presence of an electrophile such as an aldehyde or a ketone, the resulting carbanion can be trapped to form the corresponding alcohol in a process know as the Hammick reaction [237, 238]. Pyridylacetic acids also undergo a facile β-decarboxylation reaction to afford the corresponding picolines [239, 240].

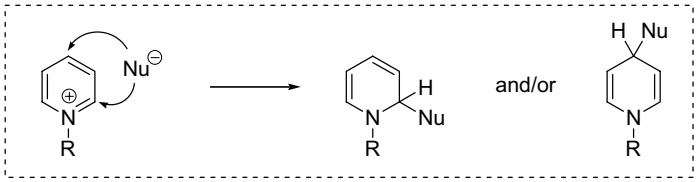


Scheme 16.109

16.4.5 Quaternary Pyridium Salts

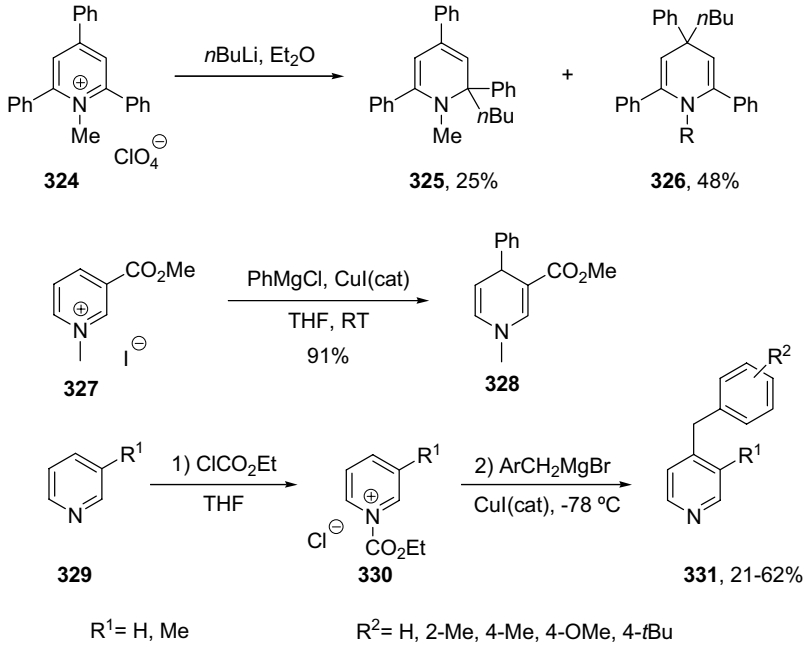
16.4.5.1 Nucleophilic Additions

The reactivity of quaternary pyridinium salts is explained by the increased electrophilicity of α and γ ring carbon atoms, which allows them to react easily with a large variety of nucleophiles (Scheme 16.110).



Scheme 16.110

Usually, organometallic reagents react at both **α** and γ positions; however, selective γ-addition can be achieved using cuprates and also when bulky alkyl groups are present on the ring nitrogen atom. For example, treatment of pyridinium salt **324** with *n*BuLi gave an almost 1 : 2 mixture of 1,2- **325** and 1,4-tetrahydropiperidines **326** (Scheme 16.111) [241]. Selective addition at the 4-position of pyridinium salt **327** was obtained with phenylmagnesium chloride in the presence of catalytic copper(I) iodide to yield 1,4-tetrahydropiperidine **328** in excellent yield [242].



324 **325**, 25% **326**, 48%

327 **328**

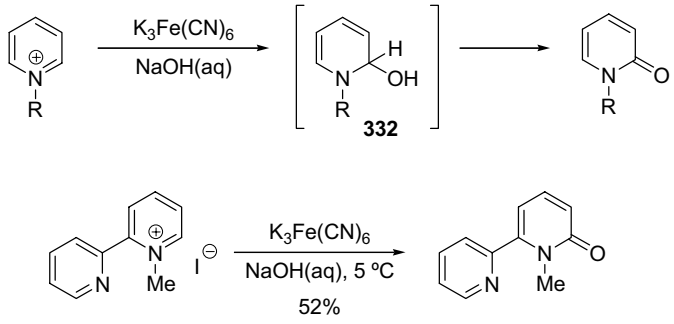
329 **330** **331**, 21-62%

R^1= H, Me R^2= H, 2-Me, 4-Me, 4-OMe, 4-*t*Bu

Scheme 16.111

The stronger reactivity of pyridinium salts compared with pyridines with nucleophiles has been exploited to achieve more effective nucleophilic additions to pyridines by *in situ* generation of pyridinium salts that are hydrolyzed during the workup. For example, formylation at the ring nitrogen atom of pyridines **329** with ethyl chloroformate generates pyridinium salts **330**, which react with Grignard reagents selectively at the 4-position to afford pyridines **331** in good yields [243].

By a related mechanism, pyridinium salts can be oxidized at the **α** position using potassium ferrocyanide in basic media to afford the corresponding *N*-alkyl-2-pyridones (Scheme 16.112). The reaction involves initial **α**-nucleophilic attack of hydroxide to afford hydroxy derivative **332** which is then oxidized by potassium ferrocyanide [244].

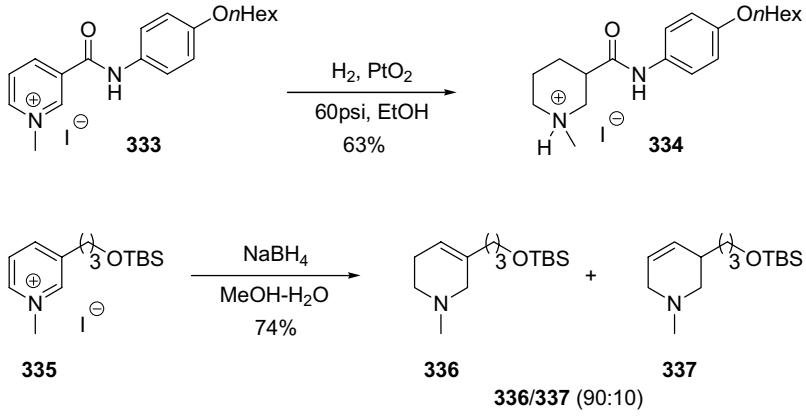


Scheme 16.112

16.4.5.2 **Reductions**

The reduction reactions of pyridinium salts are of particular interest because of their relation to important biological processes, such as the enzymatic NAD^+/NADH or $NADP^+$/NADPH oxidation/reduction reactions.

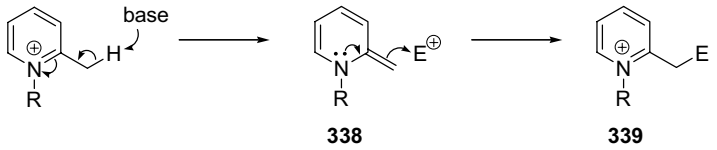
The pyridinium salts are more easily reduced than pyridines to give N-alkyl piperidines, 1,2-dihydropiperidines or 1,2,3,4-dehydropiperidines depending on the reducing agents and the reaction conditions. N-Alkyl piperidines are usually obtained by catalytic hydrogenation whereas metal hydrides and active metals give partially unsaturated piperidines. For example, catalytic hydrogenation of pyridinium iodide **333** affords selective and complete reduction of the pyridinium ring, giving *N*-methylpiperidine hydroiodide **334** in 63% yield (Scheme 16.113) [245]. Conversely, treatment of pyridinium iodide **335** with sodium borohydride gives, mainly, 3,4-dehydropiperidine **336** together with a small amount of 4,5-dehydropiperidine **337** [246].



Scheme 16.113

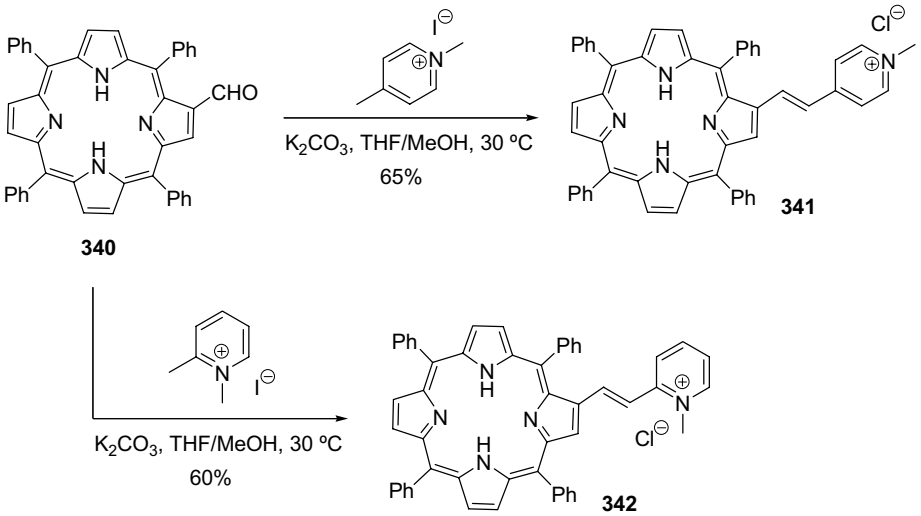
16.4.5.3 Reactions at the Alkyl Side Chain

As with pyridines, **α** and γ-alkyl substituted pyridinium salts can be functionalized at the side chain via the intermediacy of enamine **338**, which is generated by treatment with base. Further reaction of **338** with an electrophile such as an aldehyde or ketone would lead to derivatives **339** (Scheme 16.114).



Scheme 16.114

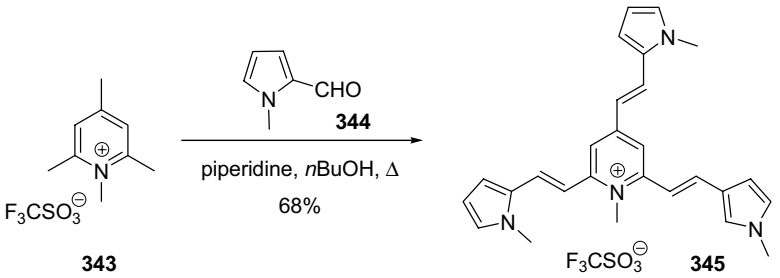
For example, reaction of porphyrin **340** with either 1,4-dimethyl- or 1,2-dimethylpyridinium iodides in the presence of K_2CO_3 gives condensation products **341** and **342**, respectively (Scheme 16.115) [247]. In addition, triple Knoevenagel condensation of collidine salt **343** with aldehyde **344** affords conjugated pyridinium salt **345** (Scheme 16.116) [248].



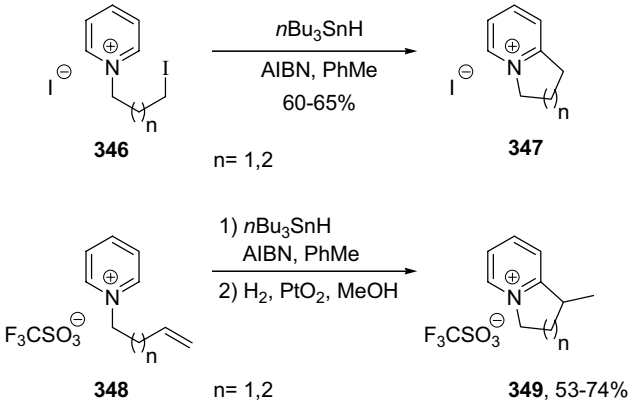
Scheme 16.115

16.4.5.4 α-Cyclizations

Intramolecular free radical substitution of pyridinium salts **346** gives good yields of bicyclic compounds **347** (Scheme 16.117) [249]. Also, compounds **349** have been synthesized by intramolecular cyclization of pyridinium radicals generated from 2-bromo-*N*-alkylpyridinium salts **348** [250].



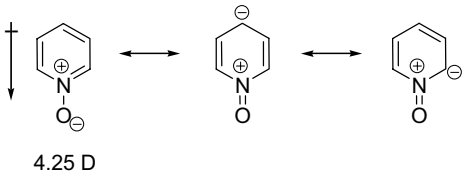
Scheme 16.116



Scheme 16.117

16.4.6
Pyridine N-oxides

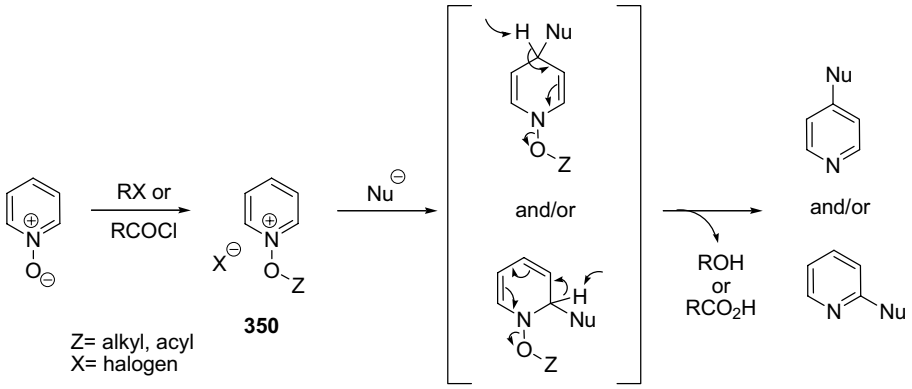
Pyridine N-oxides are stable dipolar species with the oxygen electrons delocalized throughout the pyridine ring (Scheme 16.118). These N-oxides are particularly useful in pyridine synthesis because the usual pyridine reactivity is enhanced by the presence of a positively charged ring nitrogen atom, even more than in quaternary pyridinium salts due to the electron release of the oxygen. This fact is shown in their dipole moment, which is almost twice the value of corresponding pyridines.



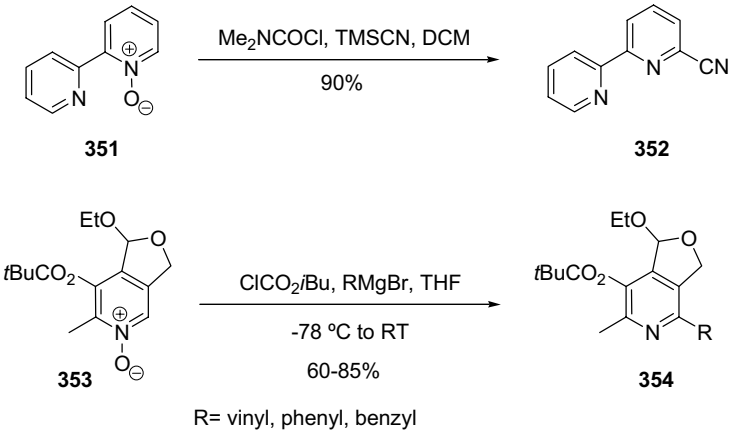
Scheme 16.118

16.4.6.1 Reactions with Electrophilic Reagents

Pyridine N-oxides react with electrophilic reagents through their oxygen atom. Of particular interest is the reaction with alkylating agents such as Me_2SO_4 because it affords *N*-alkyloxypyridinium salts **350**, which are susceptible to further nucleophilic attack at the 2- and 4-positions of the pyridine ring (Scheme 16.119). Subsequent elimination of alcohol ROH gives 2- and 4-substituted pyridines, with the latter usually being the major regioisomer. This transformation has been used for the synthesis of cyanopyridines, the so-called Reissert–Henze reaction, which affords, usually, low reaction yields and mixtures of both 2- and 4-cyanopyridines. However, using an improved method developed by Fife [251], which consists of the use of acid chlorides instead of alkylating agents, permits cyanation exclusively at the 2-position of the pyridine in excellent yields. For example, cyano-derivative **352** has been synthesized from bipyridine *N*-oxide **351** in 90% yield (Scheme 16.120) [252]. Similarly, diverse aryl and alkyl groups have been introduced successfully at the 6-position of protected pyridoxal *N*-oxide **353** to give derivatives **354** [253].

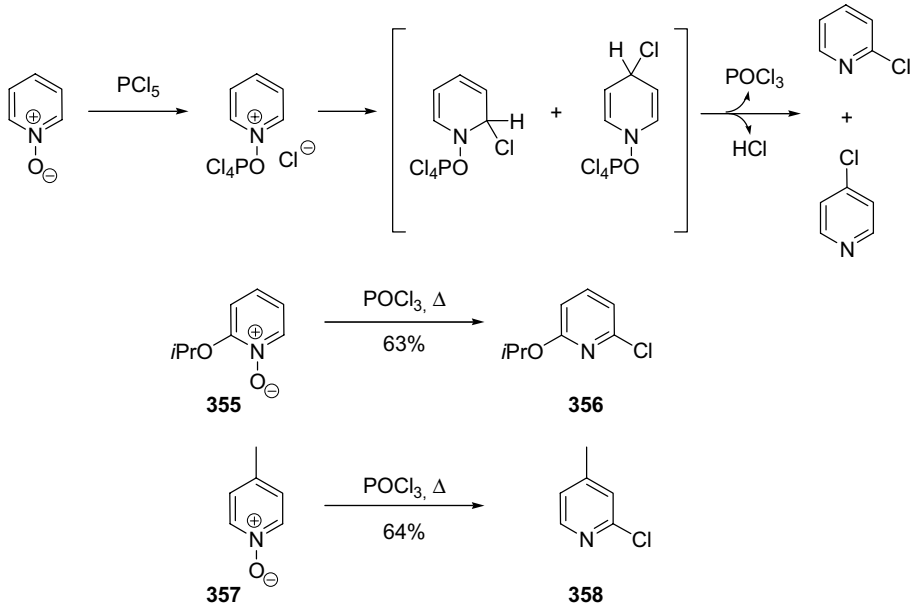


Scheme 16.119



Scheme 16.120

In consistent fashion, chloropyridines can be obtained directly from pyridine *N*-oxides by treatment with PCl_5, $POCl_3$ or $SOCl_2$ (Scheme 16.121). The chlorinating agent (i.e., PCl_5) reacts with the N-oxide through its oxygen atom and the evolved chloride adds to the 2- or 4-position of the pyridine ring. Finally, elimination of $POCl_3$ gives the corresponding chloropyridine. For example, chloropyridines **356** and **358** have been synthesized from N-oxides **355** and **357**, respectively [254].

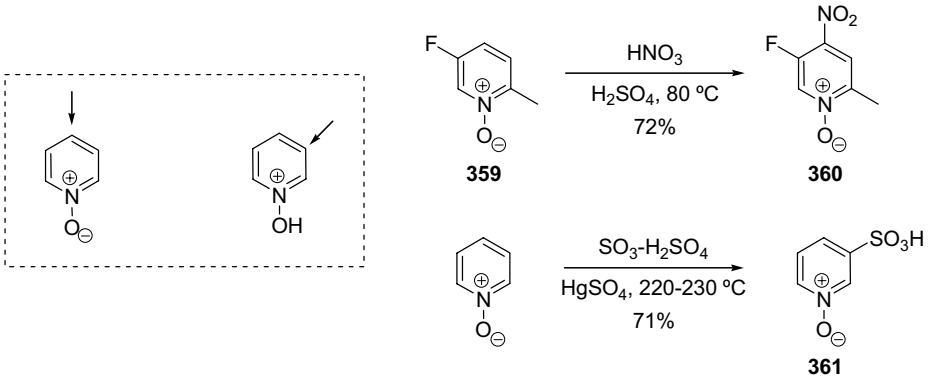


Scheme 16.121

Electrophilic substitutions to the neutral pyridine N-oxides occur selectively at the 4-position; however, if the reaction is carried out through the protonated N-oxides typical pyridinium reactivity is found and 3-substitution is observed (Scheme 16.122). Whereas nitration proceeds by electrophilic addition to the neutral pyridine N-oxide to give 4-nitroderivatives, sulfonation goes through the protonated form and 3-substitution is normally achieved. For example, nitration of pyridine N-oxide **359** affords 4-nitroderivative **360** in good yield [255]. Sulfonation of pyridine N-oxide yields 3-sulfonated derivative **361** [153].

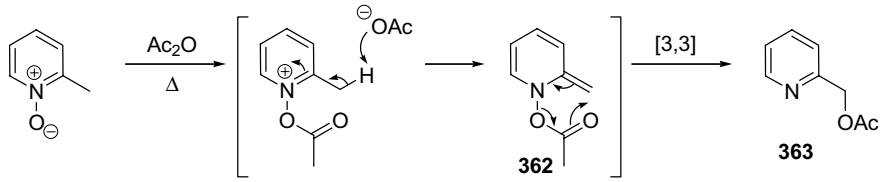
16.4.6.2 **Reactions at the Alkyl Side Chain**

Consistent with the alkylpyridines, **α** and γ alkyl pyridine N-oxides undergo important alkyl side chain reactions such as halogenation, condensation or oxidations. In addition, acyl rearrangement reactions may occur to introduce oxygen functionalities into the side chain, via the so-called Boekelheide reaction. The procedure consists of treatment of pyridine N-oxides with acetic anhydride, which initially produces oxygen



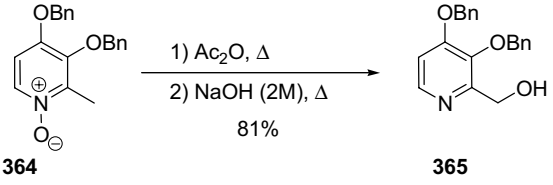
Scheme 16.122

acylation, followed by proton lost from the alkyl side chain to give an uncharged intermediate **362**, which finally undergoes a [3, 3] sigmatropic rearrangement to afford acetate **363** (Scheme 16.123).



Scheme 16.123

Under these conditions, pyridine N-oxide **364** is efficiently transformed into alcohol **365** by a two-step procedure involving an initial Boekelheide reaction followed by basic hydrolysis of the resultant acetyl derivative (Scheme 16.124) [256].

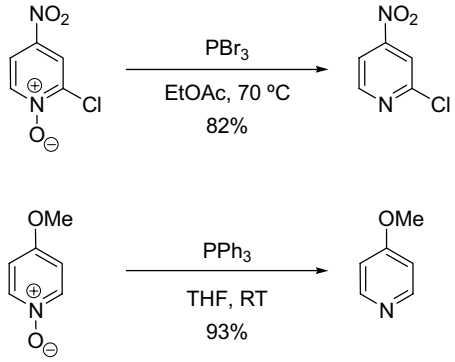


Scheme 16.124

16.4.6.3 **Deoxygenation Reactions**

Several pyridine N-oxide deoxygenation procedures have been developed, including phosphorous trihalides, catalytic hydrogenation over Raney-Ni or Pd-carbon, SmI_2, $NaBH_4/AlCl_3$ or Fe/AcOH. Many of these methods are limited by side reactions such

as substituent reductions. Recently, a milder and highly efficient deoxygenating method has been developed, based on the transfer of oxygen from the N-oxide to PPh_3 catalyzed by Re(V) [257] or Mo(VI) [258] complexes. Scheme 16.125 shows some examples of the deoxygenation reaction [254, 257].



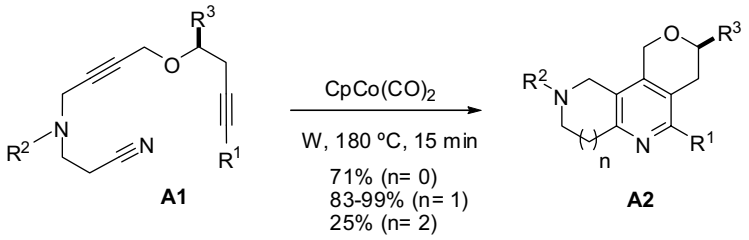
Scheme 16.125

16.5 Appendix

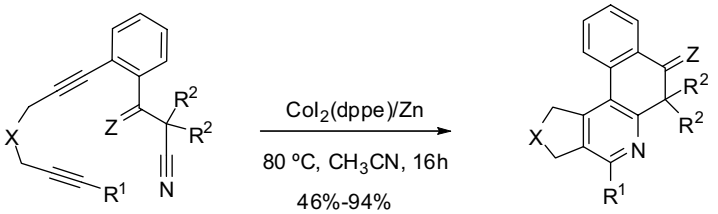
16.5.1 Synthesis of Pyridines by Cycloaddition Reactions

A new review on [2 + 2 + 2] cycloaddition reactions catalyzed by transition metal complexes has appeared [259] that includes recent progress in the synthesis of aromatic and heterocyclic compounds such as pyridines, pyridones, and so on. In this context, two novel variants of the cobalt-catalyzed intramolecular [2 + 2 + 2] cycloadditions have recently been published, allowing the formation of highly functionalized pyridines. Both approaches deal with the co-cyclotrimerization of nitrilediynes. Snyder and coworkers [260] have reported the microwave-promoted cobalt-catalyzed [2 + 2 + 2] cyclization of dialkynylnitriles **A1** to afford tetrahydronaphthyridines **A2** ($n = 1$) and related pyridine derivatives in moderate to excellent yields (Scheme 16.A.1). Alternatively, Cheng and coworkers [261] use the CoI_2(dppe)/Zn system to achieve the efficient synthesis of tetra- and pentacyclic pyridine derivatives **A4** even with highly substituted nitrilediynes **A3** having steric conjunction at the **α** and β positions to the nitrile group and a bulky substituent at the terminal carbon of alkyne (Scheme A.1).

Also important has been the extensive study reported by Yamamoto and coworkers on the scope of the substrate as well as the reaction mechanism of ruthenium-catalyzed [2 + 2 + 2] cycloaddition of 1,6-diynes and nitriles to afford bicyclic pyridines [262].



R^1= H, Me, Et, *n*Bu, Ar, CH_2OPh, CH_2OH, TMS, Ph
R^2= H, Me, *i*Bu, *i*Pr, CH_2CH_2OPh
R^3= Me, $CH_2OC_6H_4OPh$
n= 0, 1, 2

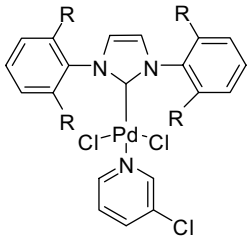


R^1= Ph, Ar, H, TMS, Me
R^2= H, Me; R^2+R^2= $(CH_2)_2$, $(CH_2)_5$
X= O, NTs, CH_2, $(CH_2)_2$
Z= H, O

Scheme 16.A.1

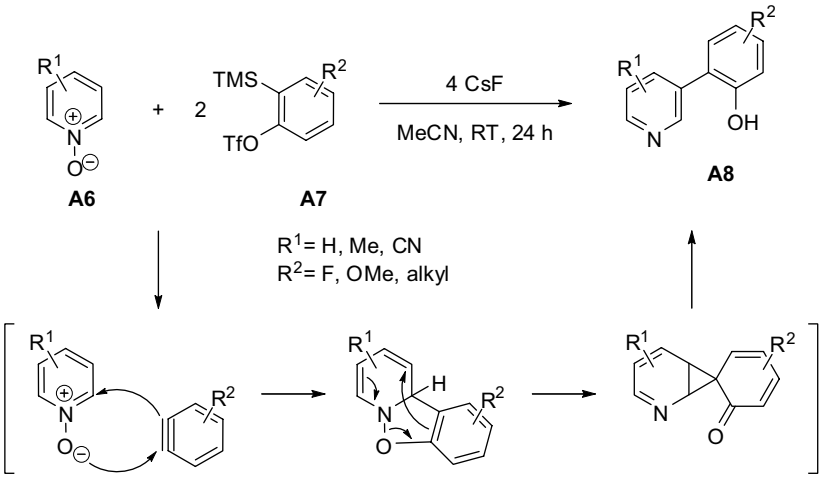
16.5.2
Reactivity of Pyridines

The use of pyridines as monodentate ligands in transition metal complexes has recently been exploited in the development of novel, efficient Pd-NHC complex **A5** (Figure 16.A.1) [263], which is very useful as catalyst in the carbon–carbon



A5 R= ^{i}Pr

Figure 16.A.1 A useful new catalyst in carbon–carbon cross-coupling reactions.



Scheme 16.A.2.

cross-coupling reactions [263–265], particularly in the formation of sp^3-sp^3 carbon–-carbon bonds [263, 264].

16.5.3
Pyridine Derivatives

An interesting application of the reaction of pyridines N-oxides with electrophilic reagents has been reported recently. Various substituted hydroxyphenylpyridines **A8** have regioselectively been prepared in one step by reaction between pyridine N-oxides **A6** and arynes generated from silylaryl triflates **A7** in the presence of caesium fluoride in acetonitrile at room temperature (Scheme 16.A.2) [266]. This transition-metal-free, mild, coupling reaction proceeds in good yield through what appears to be a series of rearrangements.

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17
Six-Membered Heterocycles: Quinoline and Isoquinoline

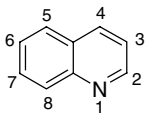
Ramón Alajarín and Carolina Burgos

17.1
Quinoline

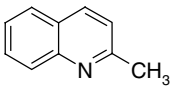
17.1.1
Introduction

Quinoline (**1**) is a benzo-fused pyridine heterocyclic compound and is also known as 1-azanaphthalene, 1-benzazine, or benzo[*b*]pyridine. Formally, quinoline is derived from naphthalene by replacement of one of its α-CH units by nitrogen.

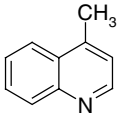
Quinoline (**1**) is a colorless, high-boiling liquid with a sweetish odor. Important derivatives include quinaldine (**2**), lepidine (**3**), 2- and 4-quinolones (**4**, **5**), and the quinolinium cation (**6**). The numbering system of this heterocycle, as treated in this chapter, is shown on structure **1** [1].



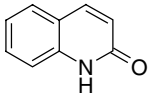
Quinoline **1**

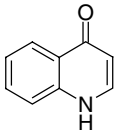


Quinaldine **2**
(2-methylquinoline)

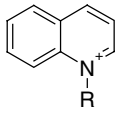


Lepidine **3**
(4-methylquinoline)





2 and 4-quinolones (**4** and **5**) (1*H*-quinolin-2-one and *1H* quinolin-4-one, respectively)



Quinolinium cation **6**

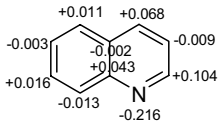
Modern Heterocyclic Chemistry, First Edition.
Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.

17.1.2 General Reactivity

17.1.2.1 Relevant Physicochemical Data, Computational Chemistry, and NMR Data

The presence of nitrogen in this structure produces an irregular distribution of the electron density in both heterocyclic and carbocyclic rings, a situation that alters the physicochemical properties and reactivity. The electronegative nitrogen causes inductive polarization, mainly in the σ-bond framework but also affecting the π-electron system, and also stabilizes those polarized canonical structures in which nitrogen is negatively charged. Consequently, there are fractional positive changes, mainly located on the C2 and C4 pyridine positions, but the local π-deficiency also increases in the benzene ring [2, 3].

The localization energies and total electron densities ($\sigma + \pi$) calculated by extended Hückel theory (EHT) [2] correlate quite conclusively with the experimentally observed data. The values of atomic charges in the quinoline structure are shown here [4].



Quinoline **1**

Additionally, it has been demonstrated that the positional selectivity in electrophilic attack on this heterocyclic molecule can be explained according to the magnitude of the HOMO electron density of each atomic center. The calculated values predict that electrophilic substitution of quinoline will occur at C5 and C8 – in agreement with the experimental data [5]. Other relevant UV and NMR data are compiled in Tables 17.1–17.3

Table 17.1 ^{1}H NMR chemical shifts (ppm) and selected coupling constants (Hz) for quinoline (**1**) [6].

δ (ppm)		$^{3}J_{H-H}$		$^{4}J_{H-H}$	
H2	8.80	H2–H3	4.18	H2–H4	1.78
H3	7.22	H3–H4	8.24	H5–H7	1.44
H4	7.96	H5–H6	8.20	H6–H8	1.23
H5	7.66	H6–H7	6.92		
H6	7.41	H7–H8	8.53		
H7	7.59				
H8	8.10				

^{1}H NMR Spectra recorded at 100 MHz in CCl_4.

Table 17.2 ^{13}C NMR chemical shifts (ppm) for quinoline (**1**) [7].

	δ (ppm)		δ (ppm)
C2	150.2	C7	129.2
C3	120.9	C8	129.4
C4	135.7	C4a	128.2
C5	127.6	C8a	148.3
C6	126.4		

^{13}C NMR spectra recorded at 20 MHz in $CDCl_3$.

17.1.2.2 General Reactivity and Tautomerism

Taking into consideration the physicochemical and structural data outlined above, quinoline, in a similar way to pyridine, undergoes a range of simple electrophilic additions involving donation of the nitrogen lone pair to an electrophile to give "quinolinium salts" **6**. This donation does not destroy the aromatic sextet and the quinolinium salt **6** remains aromatic. Concerning electrophilic substitution on the C-positions, quinoline (**1**) has a benzene ring annelated to the pyridine ring and comparisons with naphthalene chemistry must be considered. For example, S_EAr reactions occur on the carbocyclic ring, preferentially on those of the more activated benzene moiety, and the positional selectivity is C8 > C5 ⋙ other positions. In general, the S_EAr process occurs preferentially via the conjugate acid, that is, the quinolinium ion, which prevents attack on the heterocyclic ring.

The electron-deficiency of the C-heterocycle in quinoline (**1**), in particular on the C2 and C4 positions, makes nucleophilic addition reactions very important in quinoline chemistry. The nucleophilic substitution of quinoline usually proceeds through addition of a nucleophile and then elimination of a negatively charged entity such as H^- or, more favorably, Hal^-. The S_NAr process proceeds more rapidly in quinoline than pyridine because the fused benzene ring stabilizes the addition product through conjugation.

Quinolinium salts **6** are highly resistant to electrophilic substitution but are very susceptible to nucleophilic additions.

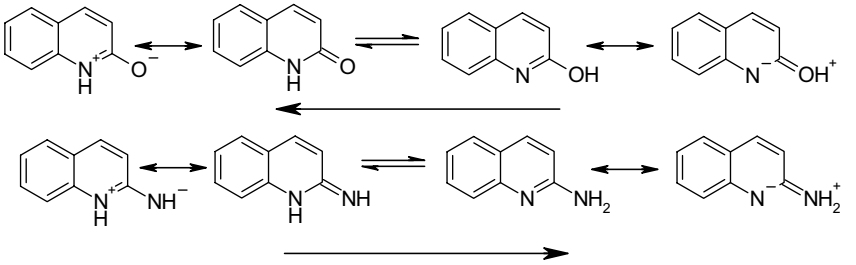
Annular tautomerism does not occur in quinoline (**1**) but this system does have some substituent tautomers. 1*H*-Quinolin-2-one (**4**) and 1*H*-quinolin-4-one (**5**), 2- and 4-quinolones, respectively, could exist in equilibrium with the corresponding

Table 17.3 UV data for quinoline (**1**) in H_2O [8].

UV (H_2O)	
λ (nm)	log ε
226	4.36
275	3.51
299	3.46
312	3.52

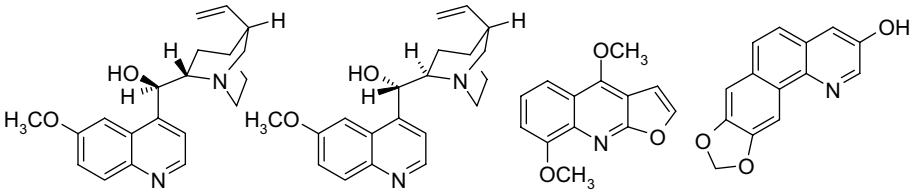
hydroxy derivatives. However, the tautomeric equilibrium lies completely over to the carbonyl tautomeric form [9].

All aminoquinoline derivatives exist predominantly as amino tautomers and their polarized resonance contributions are shown here for the 2-substituted derivatives.



17.1.3
Relevant Natural and/or Useful Compounds

Quinoline (**1**) is mainly used as a building block for other chemical compounds. For example, 8-hydroxyquinoline is a chelating agent and a precursor for pesticides, whereas 2- and 4-alkylquinolines are precursors of cyanine dyes. Quinoline was first extracted from coal tar in 1834 by Friedlieb Ferdinand Runge. Several years later, this compound was also observed as a pyrolytic degradation product of cinchonamine, a *Cinchona* alkaloid closely related to quinine (**7**). The name "quinoline" comes from the term "quinine," an antimalarial agent isolated from cinchona tree bark by Pelletier in 1820 [10].



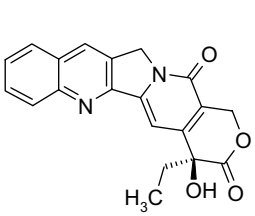
(-) Quinine **7** (+) Quinidine **8** γ-Fagarine **9** Toddaquinoline **10**

In contrast to isoquinoline, there are comparatively few naturally occurring quinolines. In addition to *Cinchona* alkaloids [11] – pairs of diastereomeric compounds such as quinine–quinidine (**7** and **8**), dihydroquinine–dihydroquinidine, as well as cinchonidine–cinchonine – some remarkable members of these families are the biologically relevant quinoline alkaloids from rutaceous plants, such as γ-fagarine (**9**), which was isolated from stems of *Glycosmis arborea*. This compound showed inhibitory activity toward the induction of Epstein–Barr virus early antigen (EBV-EA) in Raji cells by the tumor promoter 12-*O*-tetradecanoylphorbol 13-acetate, and is thus potentially useful as a chemoprotective agent in chemical carcinogenesis [12]. Additionally, **9** showed useful cytotoxicity towards the murine leukemia P-288 cell line [13]. γ-Fagarine (**9**) and related furoquinolines also inhibited human phospho-

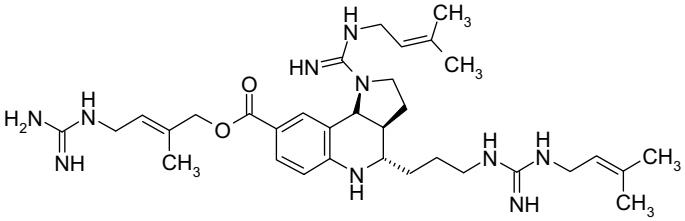
diesterase 5 (hPDE5A), a hydrolytic enzyme that regulates the intracellular levels of cGMP and influences vascular smooth muscle tone [14].

In 1993 Chen and coworkers [15] reported the isolation of toddaquinoline (**10**), a benzo[*h*]quinoline alkaloid that is a constituent of many Asian folk medicines. The alkaloid was extracted from the root bark of Formosan *Toddalia asiatica* – another rutaceous plant [16].

Pyrroloquinoline-based alkaloids have attracted significant interest due to their intriguing structures and biological activity. The best known example is camptothecin (**11**), a novel alkaloid isolated from the stem wood of the Chinese tree *Camptotheca acuminate*, and its analogues. These compounds are collectively known as captothecins and they have potent antitumor activity. Since the isolation of camptothecin (**11**) in 1966 and the elucidation of its structure by Wall and coworkers [17] this compound has been the subject of numerous syntheses [18]. Recently, camptothecin has also shown potent anti-retroviral activity at dose levels that are well tolerated by cells. This compound may therefore represent a new direction in AIDS chemotherapy. Derivatives of camptothecin have a unique mechanism of action: they kill cells by binding to and stabilizing a complex of DNA and the enzyme topoisomerase I [19].

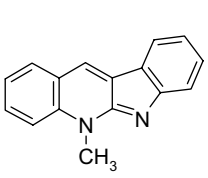


Camptothecin **11**

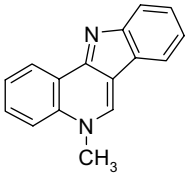


Martinelline **12**

In 1995 Witherup *et al.* [20] reported the isolation of martinelline (**12**) from an extract of *Martinella iquitosensis* roots. This new alkaloid was found to possess antibacterial activity as well as affinity for adrenergic, muscarinic, and bradykinin receptors. The structure of martinelline has attracted considerable attention and several research groups have reported approaches for the preparation of this compound [21].

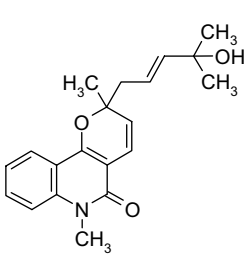


Cryptotackieine **13**

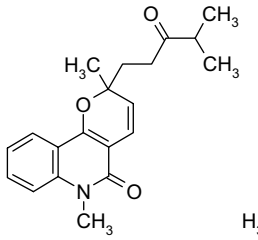


Cryptosanguinolentine **14**

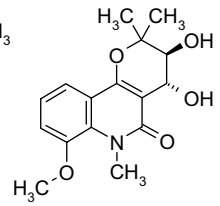
In 1996 two groups [22] independently reported the isolation of cryptotackieine (**13**) and cryptosanguinolentine (**14**), two new alkaloids extracted from *Cryptolepis sanguinolenta*, a shrub indigenous to tropical West Africa. Cryptotackieine **13** displays a strong antiplasmodial activity against *Plasmodium falciparum* chloroquine-resistant strains, and both compounds display various interesting biological properties [23].



Simulenoline **15**



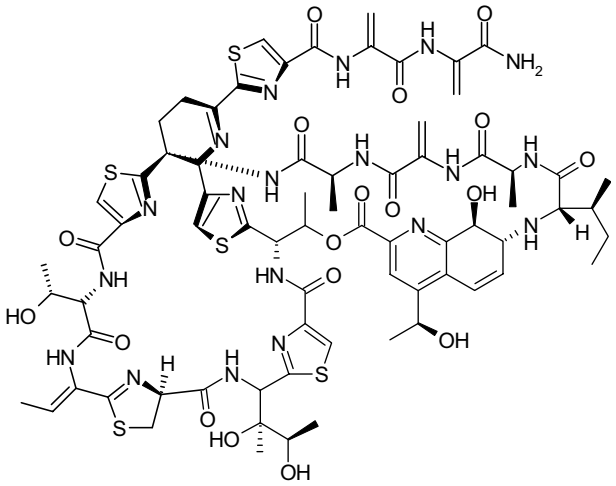
Huajiaosimuline **16**



Zanthodioline **17**

Pyranoquinoline alkaloids are another important group of quinoline derivatives. Simulenoline (**15**), huajiaosimuline (**16**), and zanthodioline (**17**) are representative examples of these natural products isolated from root bark of *Zanthoxylum simulans*, a shrub found in Taiwan and mainland China. These novel monoterpenoid pyranoquinolines are potent inhibitors of platelet aggregation. While simulenoline (**15**) and zanthodioline (**17**) are not cytotoxic, huajiaosimuline (**16**) is toxic toward several human culture cell lines, especially the estrogen receptor-positive breast cancer cells [24].

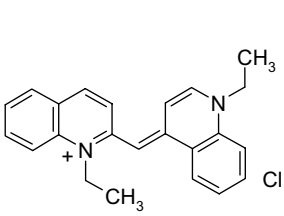
An important group of quinoline derivatives are those obtained from fungal and microbial sources. The prototypical example is thiostrepton (**18**), a thiopeptide antibiotic that contains a 7,8-dihydroquinoline core [25].



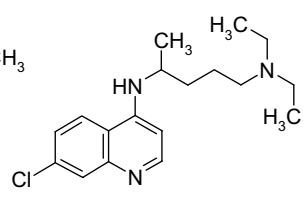
Thiostrepton **18**

As far as synthetic quinoline derivatives are concerned, there are a large group of heterocyclic compounds that display interesting medicinal, agricultural, or some other industrial utility. Quinoline derivatives provided the first photographic film sensitizer: the cyanine dye ethyl red (**19**) [26]. However, some of the most important examples are the pharmacologically active compounds, including several antimalarial drugs based on the quinine parent, for example, chloroquine (**20**) [27]

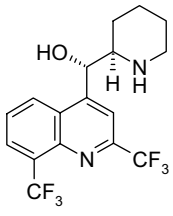
and mefloquine (**21**) [28], and some antibacterial fluoroquinolones such as ciprofloxacin (**22**) [29].



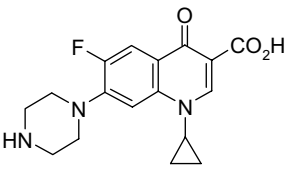
Ethyl red **19**



Chloroquine **20**



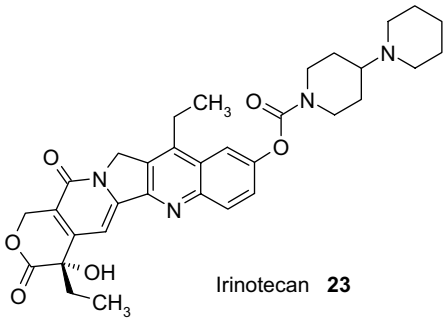
Mefloquine **21**



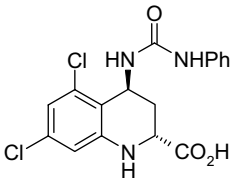
Ciprofloxacin **22**

In recent years some quinoline derivatives have attracted considerable interest for various pharmacological targets. For example, irinotecan (**23**) is an anticancer drug marketed by Pfizer [30], whereas L-689,560 (**24**) is a strong NMDA receptor antagonist identified by the Merck group. Overactivation of the NMDA subtype of excitatory amino acid receptors is implicated in several neurodegenerative disorders, including epilepsy, stroke, and Alzheimer's disease [31].

In conclusion, a great number of biological, pharmacological, and biocidal activities have been fully described in the reviews and monographs published on the compounds treated in this chapter.



Irinotecan **23**



L-689,560 **24**

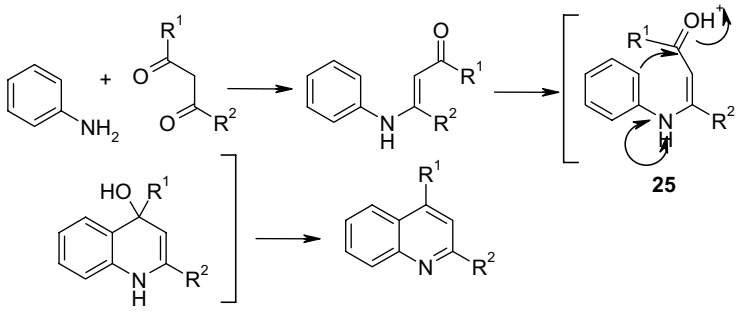
17.1.4 Ring Synthesis of Quinolines

17.1.4.1 Classical Syntheses

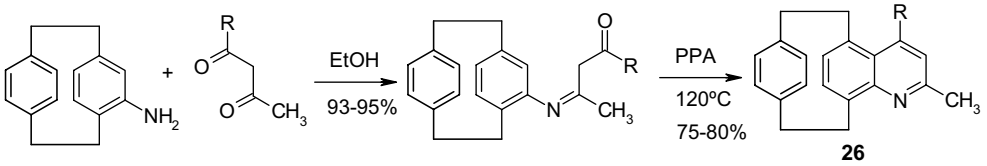
17.1.4.1.1 Anilines Plus 1,3-Dielectrophiles

Combes Synthesis Condensation of a 1,3-dielectrophile, in the simplest case a 1,3-dicarbonyl derivative, with an aniline furnishes a β-aminoenone, which can evolve to an aromatic derivative by treatment with concentrated acid [32]. The cyclization step can be viewed as an electrophilic substitution by the aniline derivative on the *O*-protonated aminoenone **25** (Scheme 17.1).

Quinolinophanes **26** (Scheme 17.2) have been prepared using this method, starting from the appropriate aniline and the 1,3-dicarbonyl derivative [33].



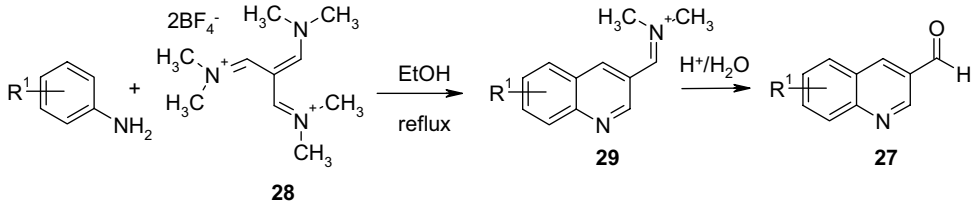
Scheme 17.1



Scheme 17.2

3-Cyanoquinolines are prepared by condensation of anilines with 3,3-dimethoxy-2-formylpropanenitrile [34].

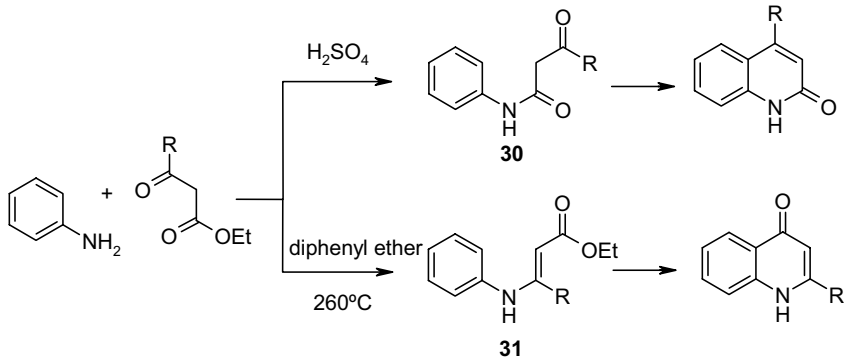
In an unconventional approach to the classical Combes reaction, Tom and Ruel [35] have reported an efficient synthesis of functionalized 3-formylquinolines **27** from substituted anilines and vinamidium salts **28**. The cyclization was followed by hydrolysis of the masked aldehydes **29** to provide the desired products (Scheme 17.3).



Scheme 17.3

Conrad–Limpach–Knorr Synthesis Primary arylamines and β-ketoesters condense in the presence of strong acids to form 2-quinolones (Knorr synthesis) via the corresponding β-ketoanilides (e.g., **30**, Scheme 17.4), whereas a thermal reaction involving β-anilinoacrylic esters (e.g., **31**, Scheme 17.4) yields 4-quinolones (Conrad–Limpach synthesis).

The formation of the 2-quinolone is due to an S_EAr process, analogous to a Combes synthesis, whereas formation of the 4-quinolone, especially in cases where



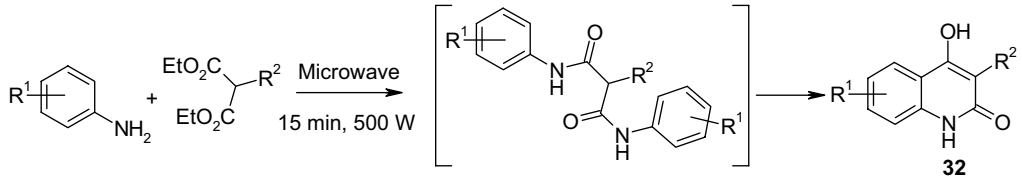
Scheme 17.4

the benzene ring carries an electron-withdrawing group, is probably due to an electrocyclic cyclization [36].

4,2-Trifluoromethyl-substituted 2- or 4-quinolinones have been prepared by condensation of anilines with ethyl trifluoroacetate under different reaction conditions [37].

Recently, Zewge *et al.* [38] discovered that Eaton's reagent (7.7/92.3 wt.% P_2O_5/$MeSO_3H$) could be used to promote the cyclization of aniline derivatives to give substituted 4-quinolones.

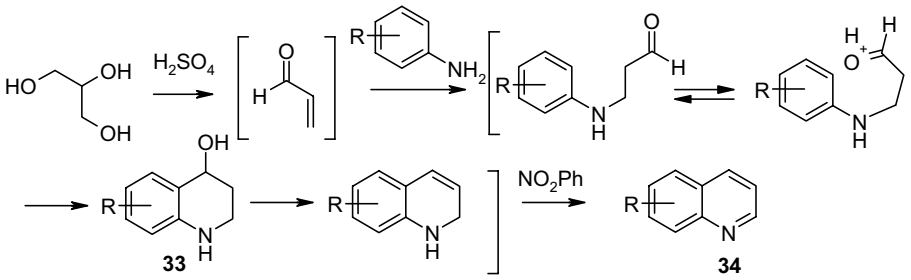
The use of microwave technology in this kind of synthesis continues to gain in popularity. A microwave synthesis of 4-hydroxy-2-quinolinones **32** (Scheme 17.5) under solvent-free conditions has been developed. The quinolinones are easily obtained in a one-pot procedure as a result of the formal amidation of a malonic ester derivative with an aniline and subsequent cyclization of the intermediate malondianilide [39].



Scheme 17.5

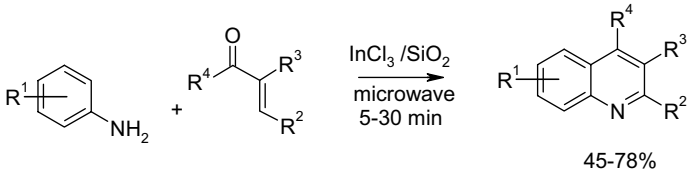
Skraup and Doebner–Miller Syntheses [40] Construction of the quinoline system by the Skraup [41] and Doebner–Miller [42] methods is based on the reaction of an aromatic amine, containing at least one free *ortho* position, with a reagent that is the source of a three-carbon fragment. In the classical Skraup method, the aromatic amine, in the simplest case aniline, is heated with glycerol, sulfuric acid (which catalyzes the dehydration of glycerol to acrolein), and an oxidizing agent, such as nitrobenzene, which transforms the initially formed 1,2-dihydroquinoline into the

fully aromatic heterocycle. The Doebner–Miller synthesis was originally limited to the reaction with crotonaldehyde to give quinaldines, but this name is increasingly used as a generic term for this type of reaction. The sequence of this reaction was established by different methods; the first step being the Michael addition of the amine to the enal system, to supply the β-aminocarbonyl derivative. These systems cyclize, via the protonated carbonyl derivative, to give **33**. Subsequent dehydration and dehydrogenation affords quinoline **34** (Scheme 17.6).



Scheme 17.6

A modification of the Skraup synthesis, using $InCl_3$ on silica gel and microwave irradiation under solvent-free conditions, has been reported by Ranu *et al.* [43] starting from anilines and alkyl vinyl ketones (Scheme 17.7).



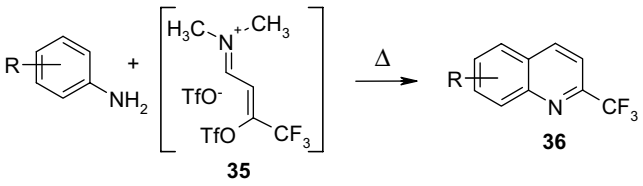
Scheme 17.7

Furthermore, 2,2,4-trisubstituted 1,2-dihydroquinolines have been prepared by a Skraup synthesis in the presence of a lanthanide catalyst and microwave irradiation [44].

The vapor phase synthesis of quinoline from aniline and glycerol in a single step has been investigated over $ZnO\text{-}Cr_2O_3$, $CuO\text{-}ZnO/Al_2O_3$, $MoO_3\text{-}V_2O_5/Al_2O_3$, and $NiO\text{-}MoO_3/Al_2O_3$ catalysts in the presence of air at 623–723 K at atmospheric pressure. Among the catalysts investigated, the $CuO\text{-}ZnO/Al_2O_3$ combination effectively performed this reaction with high activity and selectivity [45].

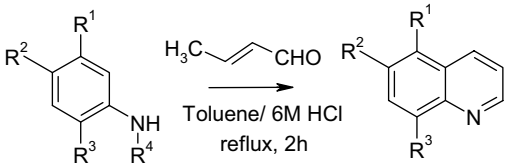
A related process is the reaction of anilines with the iminium triflate **35** to yield trifluoromethylquinolines **36** (Scheme 17.8) [46].

Matsugi *et al.* [47] have reported an improved version of the Doebner–Miller cyclization. The reaction was carried out in a two-phase solvent system. The method



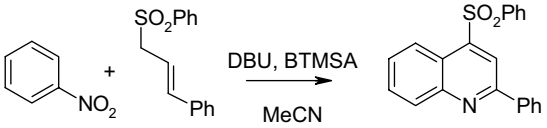
Scheme 17.8

proved to be advantageous in terms of the yield and ease of the work-up process (Scheme 17.9).



Scheme 17.9

The double condensation of nitroarenes with substituted cinnamyl phenyl sulfones in the presence of DBU/silane or DBU/Lewis acid is a procedure that exploits the opposite polarity used in the Skraup reaction (Scheme 17.10) [48].

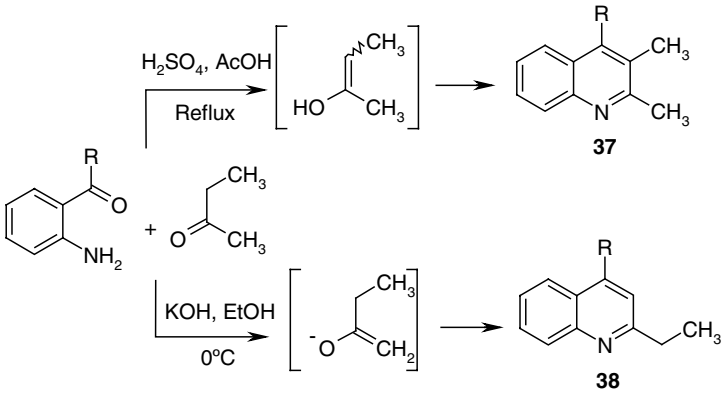


Scheme 17.10

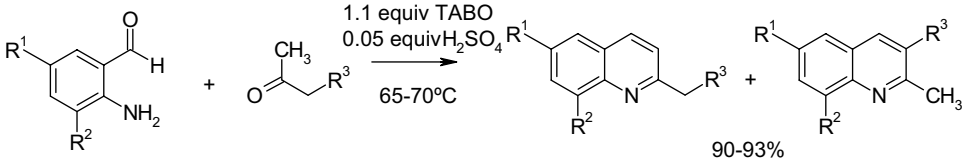
17.1.4.1.2 *o*-Acylanilines Plus Carbonyl Compounds

Friedlander Synthesis and Related Processes *o*-Acylanilines condense with enolizable carbonyl compounds through a base- or acid-catalyzed process to give quinolines. The outcome of the condensation was found to be dependent on the type of catalyst used, with acid catalysis leading predominantly to formation of the thermodynamic product **37** and base catalysis giving mostly the kinetic derivative **38** (Scheme 17.11) [49].

One of the more common ways to synthesize quinolines is through the Friedlander synthesis and, as a result, several variations and improvements have been published for this reaction. For example, in the Friedlander synthesis of quinolines the use of bases such as 1,3,3-trimethyl-6-azabicyclo[3.2.1]octane (TABO) can lead to an increase in the overall yield and the regioselectivity of process. The reaction has been carried out using *o*-aminobenzaldehydes and unactivated methyl ketones to furnish the corresponding substituted quinolines in excellent yields and ratios (6 : 1) (Scheme 17.12) [50].



Scheme 17.11



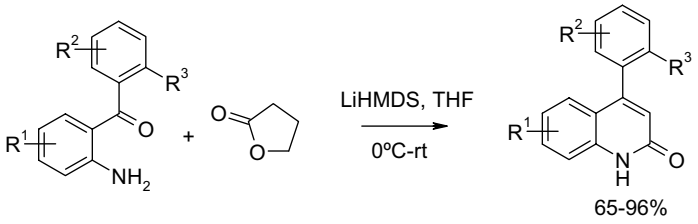
R^1= Cl, Br
R^2= H, Br
R^3= *n*-Pr, CH_2CO_2Et

Scheme 17.12

In the same way, the use of 2-aminobenzophenones and lactones has enabled a mild and scalable synthesis of 4-aryl-quinolin-2-ones (Scheme 17.13) [51].

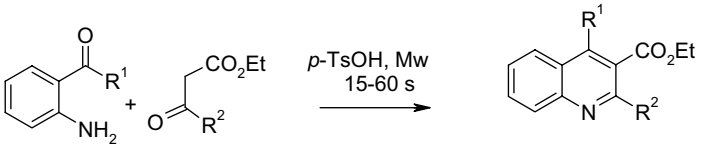
Additionally, other Friedlander variations and improvements have been published for the synthesis of quinoline analogues that were regiospecifically functionalized on both the pyridine and benzo-fused rings [52, 53].

A new methodology has been described that employs ionic liquids as "green" solvents and involves *o*-acyl anilines and various ketones to produce the desired quinolines in high yields and under very mild conditions [54].



Scheme 17.13

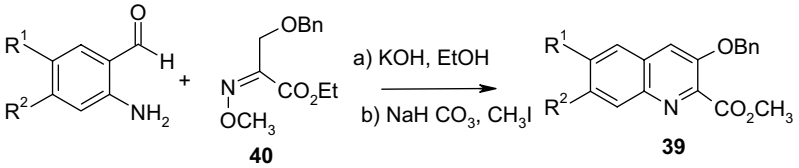
Wang *et al*. have reported a solvent-free method for the Friedlander quinoline synthesis; this involved the reaction of *o*-acyl anilines with various β-ketoesters, using *p*-TsOH and microwave conditions (Scheme 17.14) [55].



Scheme 17.14

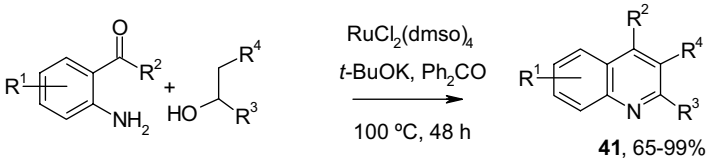
In addition to this work, the same authors reported a water-mediated Friedlander quinoline synthesis, in this case using hydrochloric acid and conventional heating [56].

A direct preparation of selectively protected derivatives of 3-hydroxyquinoline-2-carboxylates **39** was discovered in a modified version of this process, which employed the readily accessible *O*-methyloxime **40** (Scheme 17.15) [57].



Scheme 17.15

Yus *et al*. [58] have reported a Friedlander synthesis of polysubstituted quinolines **41** under solvent-free conditions, using in this case $RuCl_2(dmso)_4$ (Scheme 17.16).

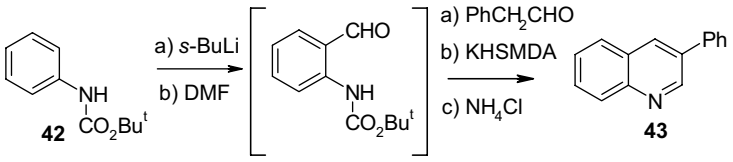


Scheme 17.16

Various other environmentally friendly strategies or methods that utilize mild conditions for the preparation of quinoline derivatives by Friedlander synthesis have also been reported [59–63].

A modification of the Friedlander synthesis of quinolines has been published for the conversion of *o*-nitrobenzaldehydes into quinolines in the presence of ketones or aldehydes. This process occurs through a concomitant nitro reduction in the presence of $SnCl_2/ZnCl_2$ [64] or, alternatively, in the presence of iron and a catalytic amount of HCl [65].

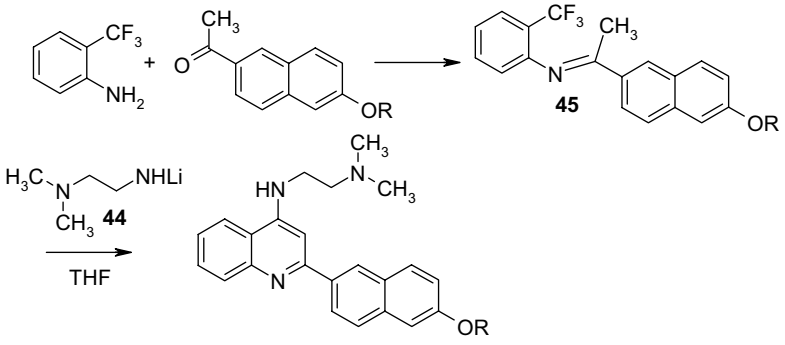
A modified version of this strategy has been reported in which the formyl group is introduced *in situ* by directed *ortho*-metallation onto a *N*-*tert*-butoxycarbonylanilide **42** (Scheme 17.17) in the presence of *s*-BuLi and DMF. The addition of an enolizable carbonyl compound furnished the corresponding substituted quinoline derivative **43** [66].



Scheme 17.17

The use of organometallic reagents has also been successful in a modified version of this approach. Thus, 2-aminobenzyl alcohol was oxidatively cyclized with various ketones in the presence of several Ru catalysts to afford 2-substituted quinolines in good yields [67].

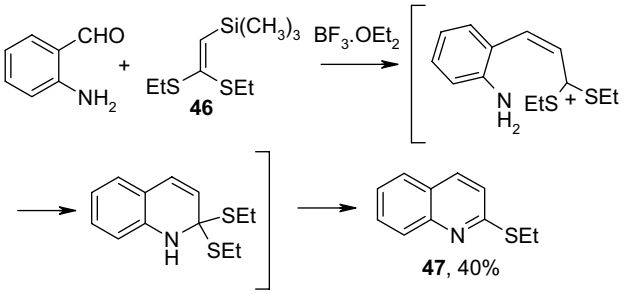
Other variations of the process related to the Friedlander synthesis have also been reported. For example, cyclization of Schiff base **45**, derived from 2-(trifluoromethyl) aniline and a methyl naphthone, mediated by lithium 2-(dimethylamino)-ethylamide **44** (Scheme 17.18), furnished a series of substituted 2-(2-naphthyl)quinolines designed to target triplex DNA [68].



Scheme 17.18

The reaction of α-aroylketene dithioacetals with esters of *o*-aminobenzoic acid under different conditions afforded quinoline and quinolone derivatives [69], whereas silylketene dithioacetal **46** (Scheme 17.19) reacted with 2-aminobenzaldehyde in the presence of a Lewis acid to produce quinoline **47** [70].

A one-pot quinoline synthesis has also been described from 2-aminobenzyl alcohol and carbonyl derivatives, using ruthenium-grafted hydrotalcite as the heterogeneous catalyst. In this approach molecular oxygen was used for the oxidation of the ruthenium species [71]. In a project devoted to the α-alkylation of ketones by alcohols

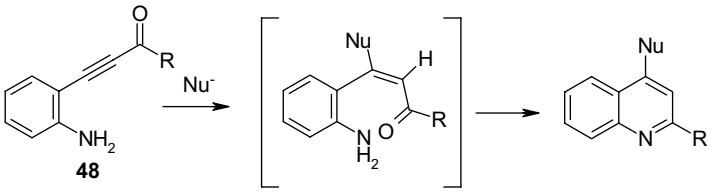


Scheme 17.19

in the presence of $[Ru(dmso)_4]Cl_2$, Yus *et al.* found that the reaction between 2-aminobenzyl alcohol and aryl alkyl ketones gave 2,3-disubstituted quinoline derivatives in good yields [72].

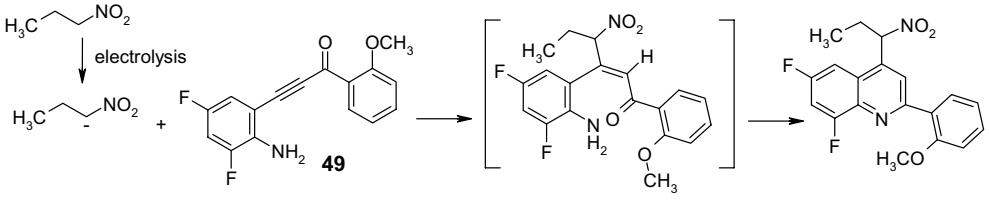
17.1.4.2 Other Processes

17.1.4.2.1 **From Ynones, Enones, and Related Substrates: Formation of Bond 1–2** Ynones and related substrates are frequently used as starting materials for quinoline compounds. For example, α,β-ynone derivatives **48** (Scheme 17.20) can be converted into 2,4-disubstituted quinolines through tandem nucleophilic addition–annulation reactions [73].



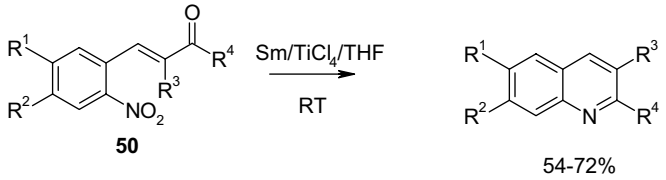
Scheme 17.20

In a related study, the synthesis of functionalized 4-alkylquinolines was developed using electrogenerated carbanions derived from nitroalkanes. In this approach, the desired 4-alkylquinolines were prepared through a sequential alkylation/heterocyclization of α,β-ynone derivatives **49** (Scheme 17.21). This method avoids the use of metal and base catalysts and is performed under solvent-free conditions [74].



Scheme 17.21

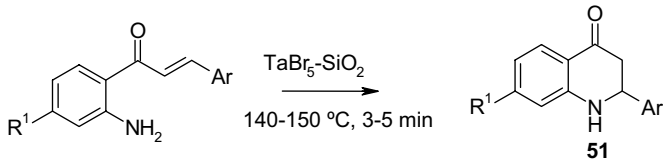
When the *o*-nitrochalcones **50** (Scheme 17.22) were treated with low-valent titanium (prepared from $TiCl_4$ and Sm powder in THF), the intramolecular reductive coupling products were obtained in moderate yields [75]. Similar results were obtained starting from substituted *o*-nitroacrylonitriles [76].



Scheme 17.22

Comparable results have been obtained by Barros and Silva [77] in the preparation of 2-(2-hydroxyaryl)quinolines from 2′-hydroxy-2-nitrochalcones induced by stannous chloride in an acidic medium or ammonium formate/Pd–C in methanol.

The development of environmentally friendly methods that exploit these approaches has attracted considerable attention. For example, Ahmed and van Lier have prepared 2,3-dihydroquinolin-4-ones **51** (Scheme 17.23) under solvent-free and thermal conditions starting from 2-aminochalcones supported on silica gel and $TaBr_5$ as a catalyst [78]. A similar process has been reported by Kumar and Perumal [79] on using microwaves irradiation.



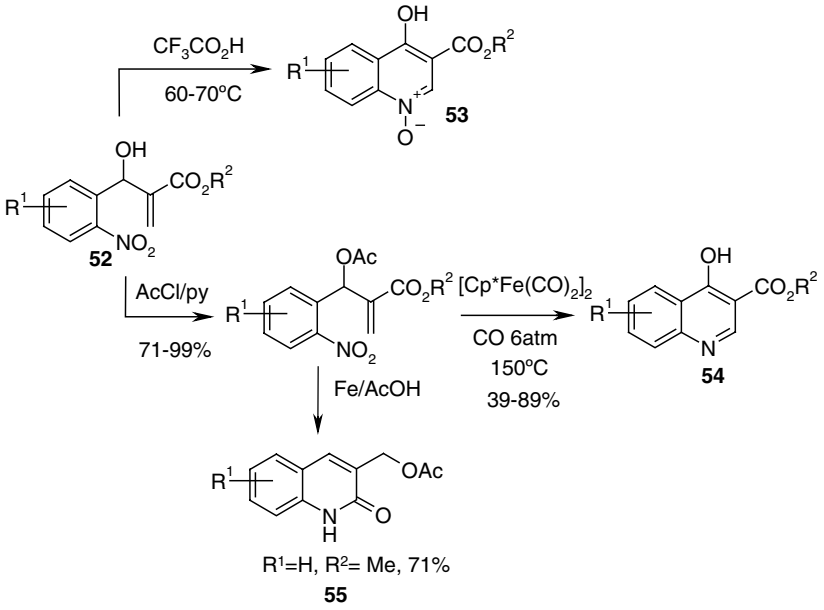
Scheme 17.23

Baker's yeast reduction of *o*-nitrocinnamaldehydes affords quinolines directly [80]. Similarly, other *o*-nitrocinnamic derivatives undergo reduction of the aromatic nitro group followed by cyclization with Zn in near-critical water at 250 °C [81].

The reaction of the Baylis–Hillman adducts of *o*-nitrobenzaldehydes **52** and trifluoroacetic acid at 60–70 °C gave unexpected cyclization products **53**, 3-ethoxycarbonyl-4-hydroxyquinoline *N*-oxide derivatives, in good to moderate yields [82]. However, compounds **52** furnished 3-carboalkoxyquinolines **54** by acylation with AcCl and cyclization by carbon monoxide, catalyzed by $[Cp^*Fe(CO)_2]_2$ [83], or 2-quinolones **55** by treatment with iron in acetic acid (Scheme 17.24) [84].

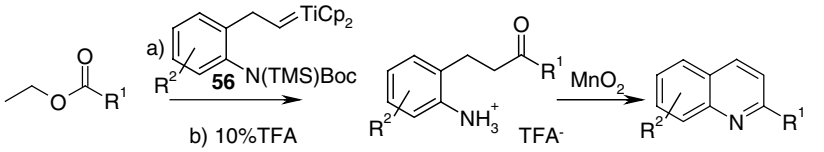
In a related study, reported by Batra *et al.* [85], the synthesis of highly functionalized quinolines, derived from Baylis–Hillman adducts, was accomplished using $SnCl_2$ to mediate tandem reactions.

As part of ongoing efforts to develop methods for the generation of quinoline libraries, titanium alkylidene reagents **56** have been treated with resin-bound esters



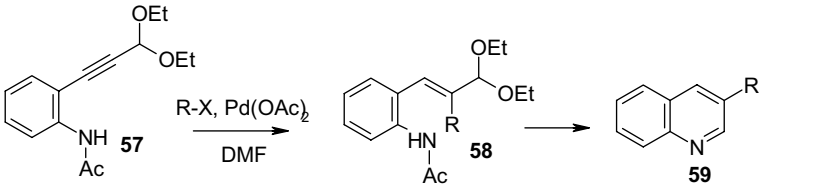
Scheme 17.24

followed by acid-mediated cleavage to give arylammonium salts (Scheme 17.25). Oxidation with MnO_2 gave quinolines of high purity and in moderate yields [86].



Scheme 17.25

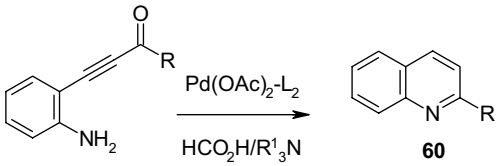
The synthesis of quinoline derivatives using metal-catalyzed, and particularly palladium-catalyzed, chemistry has become of interest for this type of approach. For example, acetylenic acetals (e.g., **57**, Scheme 17.26) or ketals have been reacted with various aryl or vinyl halides in a palladium-catalyzed process to afford alkenes **58**



Scheme 17.26

in good yield. Cyclization to quinolines **59** was performed in the presence of TsOH/EtOH [87].

A related process has been reported in which a palladium-catalyzed hydrogenation/heterocyclization gave the quinoline derivative **60** (Scheme 17.27) [88].

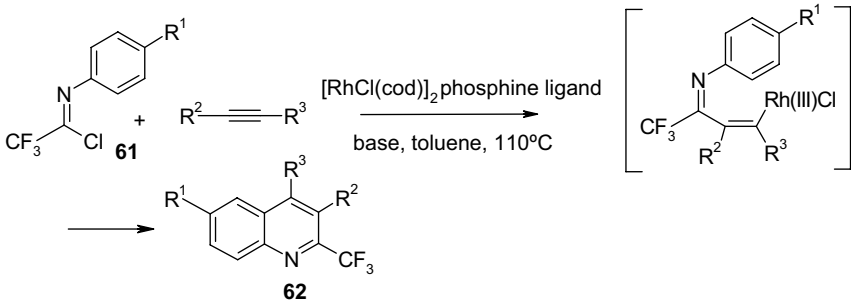


Scheme 17.27

In a similar way, *o*-iodoanilides reacted with terminal acetylenic carbinols in a palladium-catalyzed process to yield *o*-substituted anilides, the starting materials for the synthesis of quinoline or 4-quinolone derivatives [89].

In another metal-catalyzed quinoline synthesis $NiBr_2$(dppe) was used to catalyze the reaction of *o*-iodoanilines with aroylalkynes in acetonitrile to give 2,4-disubstituted quinolines in good yields [90].

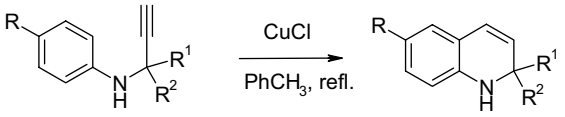
17.1.4.2.2 **From Alkynes, Propargyl Amines, and Related Systems: Formation of Bond 4–4a** Internal and terminal alkynes have been coupled and cyclized to *N*-aryl trifluoroacetimidoyl chlorides **61** (Scheme 17.28) in the presence of catalytic Rh(I) complexes to afford 2-trifluoromethylated quinolines **62**. Various alkynes were applied to this cyclization coupling and high levels of regioselectivity were achieved [91].



Scheme 17.28

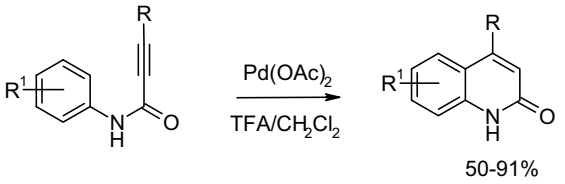
N-(1,1-Disubstituted propargyl)anilines can be cyclized to 2,2-disubstituted 1,2-dihydroquinolines by heating under reflux in toluene containing CuCl (Scheme 17.29) [92].

A new and general method has been developed for the preparation of 2-quinolinones by intramolecular hydroarylation of alkynes. Various aryl alkynanilides undergo rapid intramolecular reaction at room temperature in the presence of a



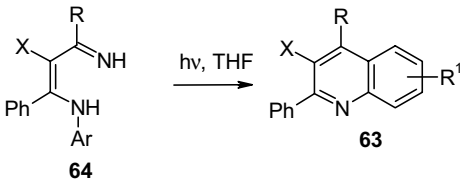
Scheme 17.29

catalytic amount of $Pd(OAc)_2$ in a mixed solvent containing trifluoroacetic acid. This process affords 2-quinolinones in moderate to excellent yields with turnover numbers (TONs) of more than 1000 with respect to Pd (Scheme 17.30) [93].



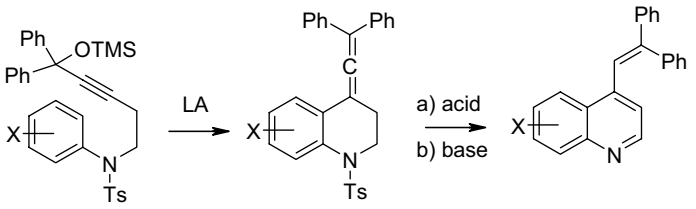
Scheme 17.30

Campos *et al*. have reported the synthesis of 3-haloquinolines **63** by irradiation of amino haloalkenimines **64** (Scheme 17.31) [94].



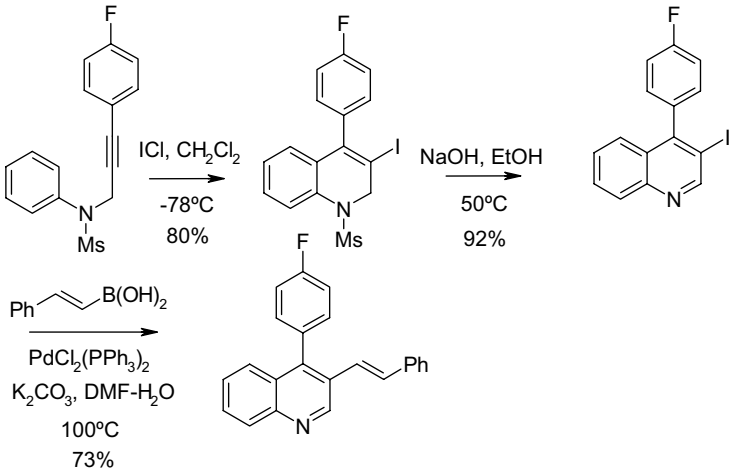
Scheme 17.31

Variations of the Friedel–Crafts reaction are also of interest for the synthesis of quinolines. For example, Saito *et al*. [95] have described a novel method to synthesize a quinoline backbone by incorporating allenyl cations into a catalytic intramolecular Friedel–Crafts reaction. The initial products were isomerized and aromatized upon treatment with acid and base, respectively, to give quinoline derivatives (Scheme 17.32).



Scheme 17.32

Quinolines substituted in the 3-position by an iodo- or phenylseleno-group are readily prepared by an electrophilic cyclization from propargylic anilines with appropriate electrophiles under mild reaction conditions. This method can be followed by palladium-catalyzed substitution reactions to provide further elaboration of the 3-position of the quinoline core (Scheme 17.33) [96].



Scheme 17.33

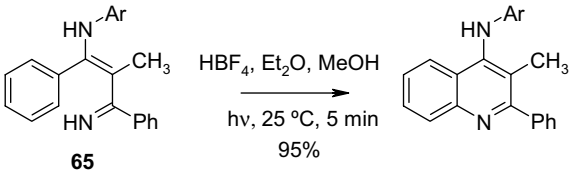
In a similar way, Hajra *et al.* have prepared a series of tetrahydroquinoline derivatives from allyl anilines using a Lewis acid-catalyzed halocyclization [97].

17.1.4.2.3 **From Oximes, Azadienes, and Related Derivatives: Formation of Bond 1–8a** Oxime derivatives are also suitable intermediates for the synthesis of quinolines. Several papers concerning intramolecular cyclization involving some classes of oximes and oxime derivatives have been published [98–103]. Scheme 17.34 shows an example of this methodology.

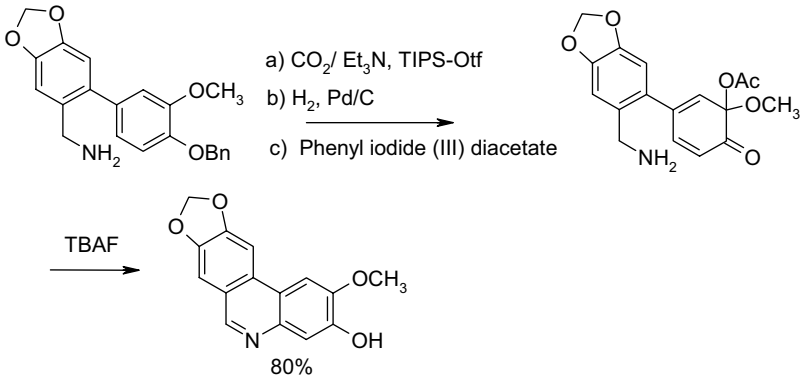
Scheme 17.34

Campos *et al.* [104] have reported that the irradiation of azadiene **65** in the presence of HBF_4 furnishes 4-aminoquinoline derivatives in excellent yields (Scheme 17.35).

Quinoline derivatives have been prepared by Quideau *et al.* [105] from nitrogen-tethered 2-methoxyphenols. Oxidative acetoxylation in the presence of phenyl iodide (III) diacetate, followed by an intramolecular Michael addition, gave the desired quinoline derivatives (Scheme 17.36).

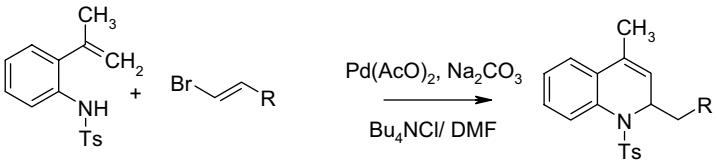


Scheme 17.35



Scheme 17.36

17.1.4.2.4 **Other Processes Involving Metal-Catalyzed Methods** Palladium-catalyzed coupling of *o*-allyl or *o*-isopropenyl-*N*-tosylanilides with vinyl halides or triflates produces dihydroquinolines (Scheme 17.37) [106–110].

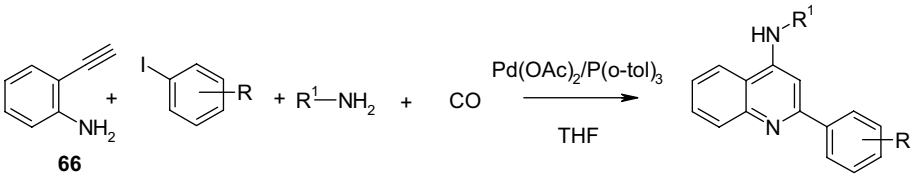


Scheme 17.37

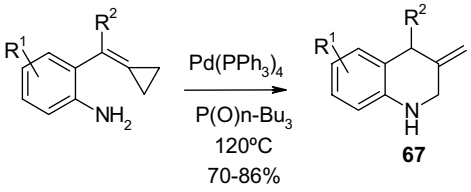
A palladium-mediated multicomponent domino reaction involving ethynylarylamines **66**, aryl iodides, primary amines, and carbon monoxide has been reported to give various substituted quinolines (Scheme 17.38) [111].

Intramolecular addition of anilines to methylenecyclopropanes proceeds smoothly in the presence of catalytic amounts of $Pd(PPh_3)_4$ to afford the corresponding hydroamination products, which ultimately gave quinoline derivatives **67** (Scheme 17.39) [112].

The Buchwald–Hartwig palladium-catalyzed aryl-amino coupling reaction has also been applied successfully to the synthesis of functionalized *N*-phenyl 2-quinolinones [113]. Additionally, aryl–N-bond formation can be used to prepare quinoline



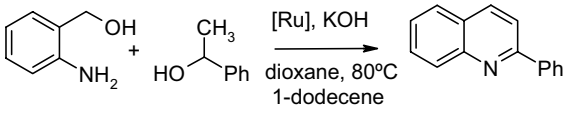
Scheme 17.38



Scheme 17.39

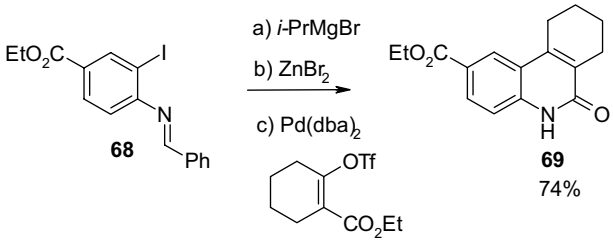
derivatives by intramolecular coupling of amines or amides with an aryl bromide [114].

A successful ruthenium-catalyzed oxidative coupling and subsequent cyclization has been reported between 2-aminobenzyl alcohol and secondary alcohols in the presence of KOH and 1-dodecene to give 2-substituted quinolines (Scheme 17.40) [115].



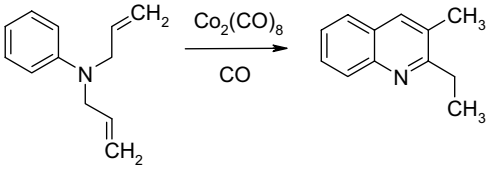
Scheme 17.40

Functionalized zinc reagents – derived from readily available *o*-iodoaniline derivatives and obtained by a straightforward iodine–magnesium exchange followed by transmetalation with zinc bromide – can be used to prepare a wide range of nitrogen heterocycles. For example, treatment of the benzylimine-protected iodoaniline **68** in the presence of a Grignard reagent and subsequent Negishi cross-coupling leads to the quinoline derivative **69** (Scheme 17.41) [116].



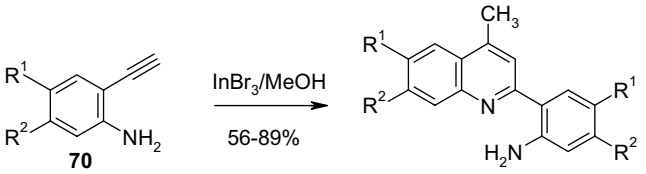
Scheme 17.41

Various diallylanilines have been shown to undergo cobalt-carbonyl-catalyzed rearrangement to quinolines, with the diallylaniline acting as a source of the allyl group in these transformations (Scheme 17.42) [117].



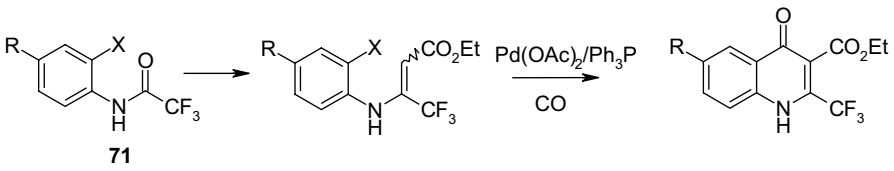
Scheme 17.42

$InBr_3$ promotes the dimerization of 2-ethynylaniline derivatives **70** to give polysubstituted quinolines in good yields (Scheme 17.43) [118].



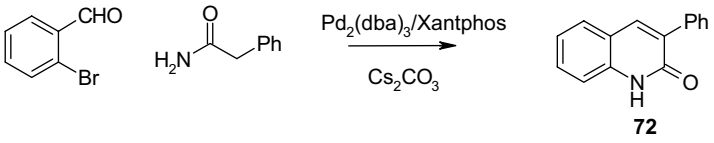
Scheme 17.43

o-Halo-*N*-trifluoroacetylanilines **71** (Scheme 17.44) undergo sequential Wittig and Pd reaction under a CO atmosphere to supply 4-quinolone derivatives [119, 120].



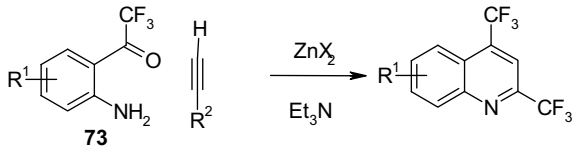
Scheme 17.44

3-Aryl 2-quinolinones have been prepared by a convergent one-pot cascade sequence involving palladium-catalyzed cross-coupling reactions of 2-bromobenzaldehydes with phenylacetamides in the presence of caesium carbonate and xantphos (Scheme 17.45). Final products **72** were obtained by cyclization of the resulting amide intermediate [121].



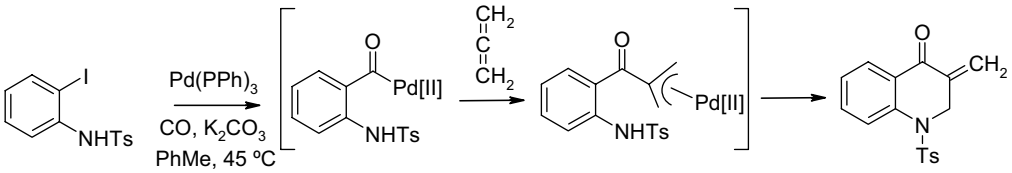
Scheme 17.45

A novel and efficient route to 4-trifluoromethyl-substituted quinoline derivatives through the Zn(II)-mediated alkynylation/cyclization of *o*-trifluoroacetylanilines **73** has been described by Jiang *et al.* (Scheme 17.46) [122].



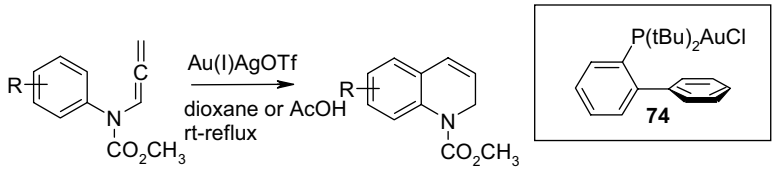
Scheme 17.46

Palladium(0)-catalyzed termolecular queuing processes involving oxidative addition to *o*-iodoanilides followed by low-pressure carbonylation, allene insertion, and capture of the resulting π-allyl palladium(II) species by the internal *N*-nucleophile affords 3-methylene quinolones in good yields (Scheme 17.47) [123].



Scheme 17.47

Gold-catalyzed intramolecular hydroarylation of allenic anilines offers an efficient route to dihydroquinoline derivatives under mild reaction conditions. The reaction has been carried out in the presence of [2-(di-*tert*-butylphosphino)-1,1′-biphenyl]gold (I) chloride (**74**) and silver(I) triflate (Scheme 17.48) [124].



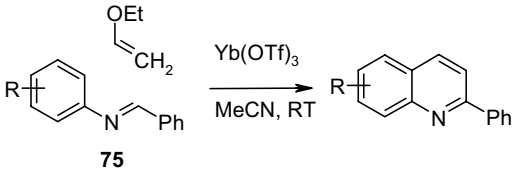
Scheme 17.48

In the same way, Che and coworkers have devised an efficient method to prepare substituted 1,2-dihydroquinolines and quinolines by Au(I)-catalyzed tandem hydroamination–hydroarylation under microwave irradiation [125].

The first enantioselective synthesis has been reported of the martinelline core, a new alkaloid (**12**) that shows antibacterial activity as well as an affinity for adrenergic, muscarinic, and bradykinin receptors, [21c]. The synthesis proceeded in seven steps and gave 23% overall yield through a modification of the palladium-catalyzed carbonylative cyclization procedure reported by Negishi.

17.1.4.2.5 **Cycloaddition Processes**

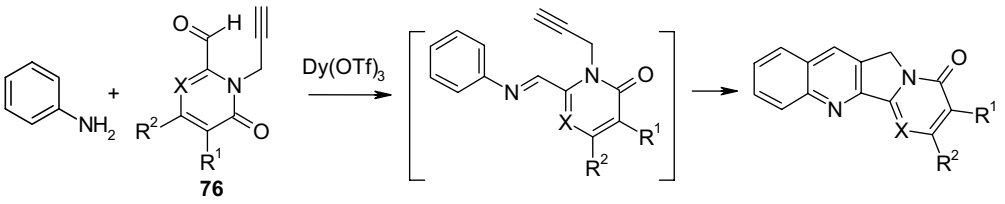
Diels–Alder and Aza-Diels–Alder (Povarov) Reactions The preparation of quinoline derivatives by cycloaddition processes is an important method for the synthesis of this class of compounds. Several cyclization/elimination reactions that formally correspond to Diels–Alder or hetero-Diels–Alder cycloaddition could proceed by a S_EAr mechanism and are usually catalyzed by Lewis acids. For example, the [4 + 2] cycloaddition reaction of *N*-arylaldimines **75** is effectively catalyzed by ytterbium(III) triflate to give quinoline derivatives (Scheme 17.49) [126].



75

Scheme 17.49

Pyrrolo[3,4-*b*]quinolines can be formed through the coupling of anilines with *N*-propargylic-substituted heterocyclic aldehydes in the presence of mild Lewis acid catalysts. The coupling proceeds through sequential imine formation and a formal intramolecular aza-Diels–Alder (Povarov) reaction. This approach has been applied in a total synthesis of luotonin A and a formal synthesis of camptothecin (Scheme 17.50) [19a].



76

Scheme 17.50

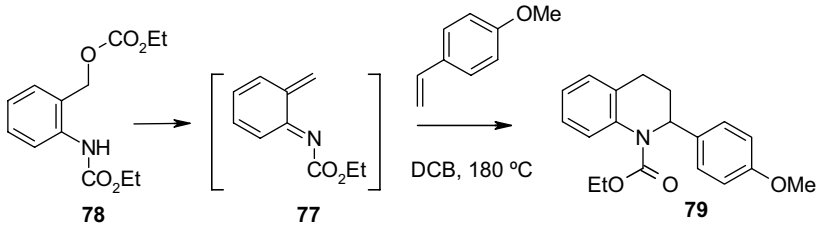
Menendez and colleagues [127] have reported another aza-Diels–Alder reaction between aromatic imines and methacrolein dimethyl hydrazone in the presence of $InCl_3$.

The treatment of azadiene **77**, obtained *in situ* from the carbonate **78**, in the presence of dienophiles produced tetrahydroquinolines **79** (Scheme 17.51) [128].

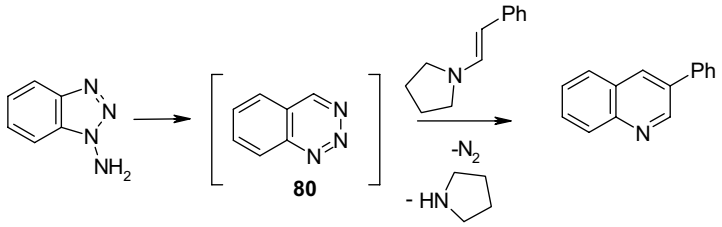
Reaction of the same azadiene with C_{60} gave a quinoline-fused fullerene [129].

Hetero-Diels–Alder reaction of 1,2,3-benzotriazine in the presence of dienophiles produces quinoline derivatives after extrusion of N_2. 1,2,3-Benzotriazine intermediate **80** can be obtained by oxidative rearrangement of 1-aminobenzotriazole (Scheme 17.52) [130].

Liu and coworkers [131] have developed an efficient synthetic method for the preparation of 4-functionalized-quinoline derivatives **81**. Ethynyl ketene-*S*,*S*-acetals **82** can react in a one-pot procedure with various arylamines and aldehydes under

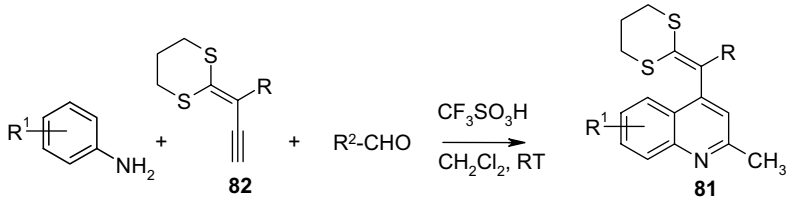


Scheme 17.51



Scheme 17.52

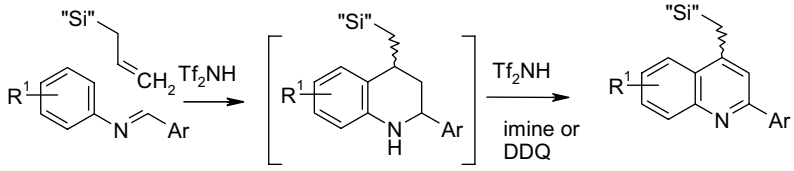
mild conditions through consecutive arylimine formation, regiospecific aza-Diels–Alder (Povarov) reaction, and reductive amination (Scheme 17.53).



Scheme 17.53

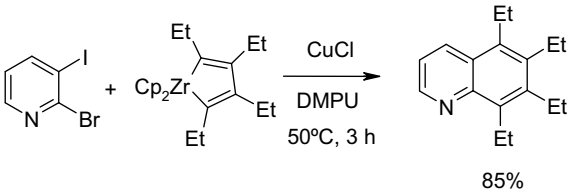
Takasu and coworkers [132], using cascade and one-pot reactions, have carried out an inverse electron demand hetero-Diels–Alder reaction and oxidative aromatization to synthesize substituted quinolines starting from aryl aldimines and allylsilanes (Scheme 17.54).

The construction of hetero-polycyclic aromatic compounds has been addressed by intermolecular cycloaddition reaction of a dihalogenated heteroarene with zircona-



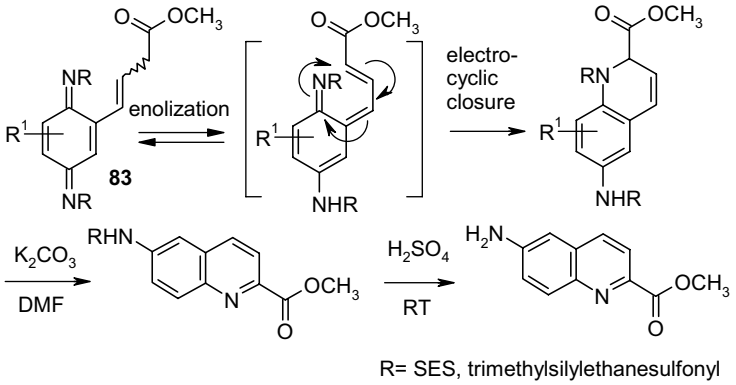
Scheme 17.54

cyclopentadiene. For instance, 2-bromo-3-iodopyridine was reacted in the presence of a zirconacyclopentadiene, CuCl, and 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone (DMPU) to give the corresponding quinoline in 85% yield (Scheme 17.55) [133].



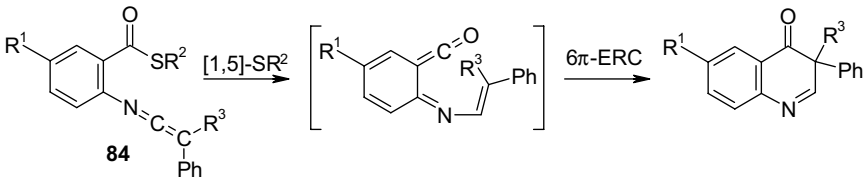
Scheme 17.55

Other Pericyclic Processes Enolizable vinyl quinone mono- and diimide substrates **83** (Scheme 17.56) yield protected 6-aminodihydroquinolines by thermal 6π-electrocyclization. Aromatization provides the corresponding quinolines in quantitative yields [134].



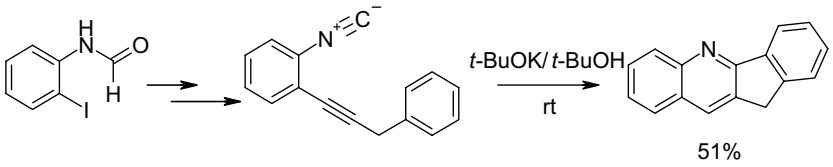
Scheme 17.56

A series of substituted 3*H*-quinolin-4-ones have been synthesized from *N*-{[2-(alkyl- or arylthio)carbonyl]phenyl}ketenimines **84** by means of a [1,5]-sigmatropic migration followed by 6π-electrocyclic ring closure (Scheme 17.57) [135].



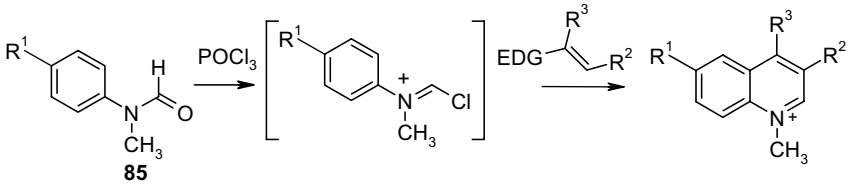
Scheme 17.57

Indenoquinoline has been obtained by a formal [4 + 1] cycloaddition process from *o*-phenylprop-1-ynyl benzoisonitrile in the presence of *t*-BuOK/*t*-BuOH. The starting material was prepared in two steps from *o*-iodoformanilide. However, only poor yields were obtained when the method was applied to other related systems (Scheme 17.58) [136].



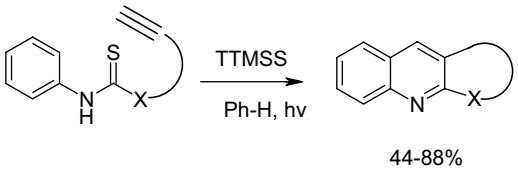
Scheme 17.58

N-Methylformanilides **85** reacted with various electron-rich alkenes in $POCl_3$ solution to supply *N*-methylquinolinium salts in good yields. The mechanism of the cyclization was elucidated and was shown to involve an electrocyclic π_6s process (Scheme 17.59) [137].



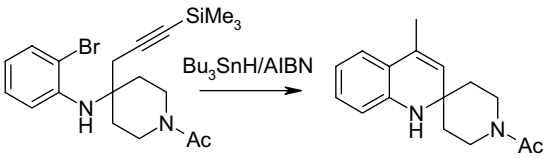
Scheme 17.59

17.1.4.2.6 **Radical Reactions** As far as radical chemistry is concerned, a series of annulated quinolines are readily available from thioamides, thiocarbamates, or thioureas in the presence of tris(trimethylsilyl)silane (TTMSS) and *hν* irradiation (Scheme 17.60) [138].



Scheme 17.60

The intramolecular 6-*endo-dig* cyclization of an aryl bromide onto a silylated acetylene using Bu_3SnH/AIBN provides dihydroquinoline derivatives (Scheme 17.61) [108].



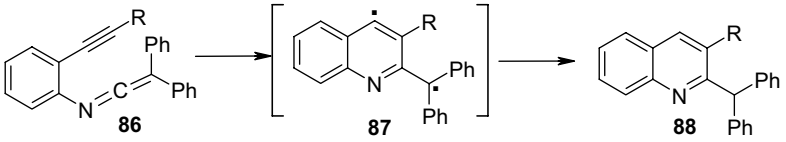
Scheme 17.61

Similarly, the cyclization of an aryl radical onto a pyrrole allows the synthesis of either the spiropyrrolidinyloxindole or the pyrrolo[3,2-*c*]quinoline skeleton, depending on the nature of the protecting group at the N-pyrrole atom [139].

Toddaquinoline (**10**) has been obtained by Harrowven and coworkers by a radical cyclization onto a pyridine ring [16a] and by a cobalt-mediated radical addition to a pyridine derivative [16b].

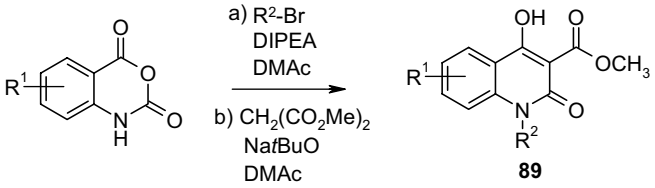
Free radical cyclization reactions of alkylsulfonyl- and alkylthio-substituted aromatic amide derivatives have been described. These radicals undergo either six- or five-membered ring cyclization onto the aromatic ring and provide synthetically useful methods for the preparation of quinolinones among other heterocyclic derivatives [140].

A formal synthesis of martinelline (**12**) has been accomplished by Naito and coworkers using two types of radical reactions as the key steps [141]. Schmittel *et al*. have reported that the thermolysis of enyne carbodiimides **86** (Scheme 17.62) produces the biradical intermediates **87**, which can evolve to quinoline derivatives **88** [142, 143].



Scheme 17.62

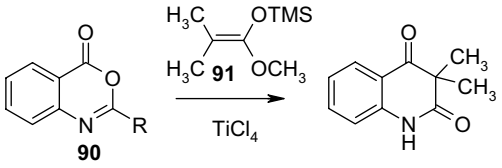
17.1.4.2.7 **Ring Transformations of Heterocycles Leading to Quinolines** An efficient and practical method for the preparation of 4-hydroxyquinolinone esters and amides has been developed by Beutner and coworkers. Compounds **89** were synthesized in good yields and on a kilogram scale from substituted isatoic anhydrides (Scheme 17.63) [144].



Scheme 17.63

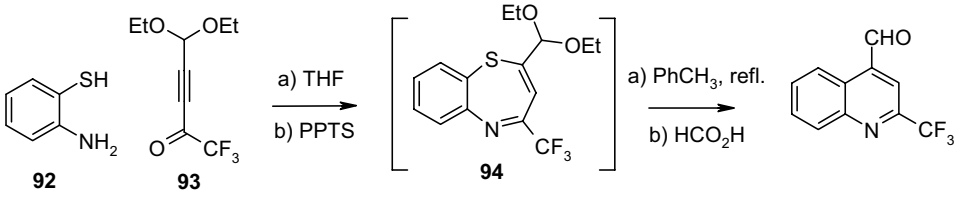
Previously, in a related study, Igglessi-Markopoulou *et al.* [145] described an efficient route to 3-aryl-4-hydroxyquinolin-2-ones through cyclization of the β-ketoesters produced by reaction of arylacetic ester enolates with 2-alkoxy-3,1-benzoxazin-4-ones.

A new one-step methodology has been introduced for the synthesis of quinoline 2,4-diones. The reaction is based on a modification of the Mukaiyama aldol condensation and makes use of the high reactivity of benzoxazin-4-ones **90** in the presence of ketene silyl acetals **91** (Scheme 17.64) [146].



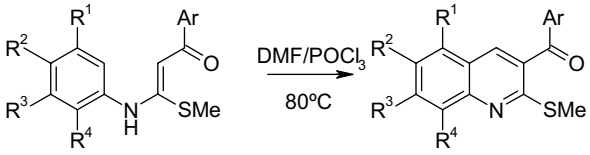
Scheme 17.64

Substituted 2,4-quinolines can be obtained by a novel synthesis that involves cyclization and thermal extrusion of sulfur. The method starts from *ortho*-thioaniline (**92**) and acetylenic ketones **93** and proceeds through the benzo[*b*][1,4]thiazepine **94** (Scheme 17.65) [147]. The same methodology was applied for the preparation of enantiomerically pure 2,4-disubstituted quinoline derivatives [148].



Scheme 17.65

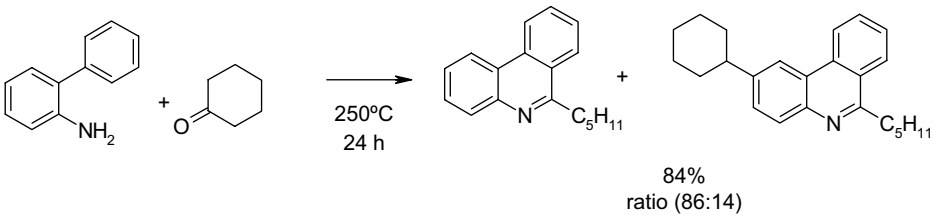
17.1.4.2.8 **Other Notable Methods** A convenient method for the preparation of highly functionalized quinolines in the presence of Vilsmeier's reagent has been reported (Scheme 17.66) [149].



Scheme 17.66

A microwave preparation of 2-quinolinone derivatives obtained by cyclization of the corresponding *o*-vinyl-substituted isocyanate has been described. The method provides access to cryptotackieine (**13**) and cryptosanguinolentine (**14**) [23].

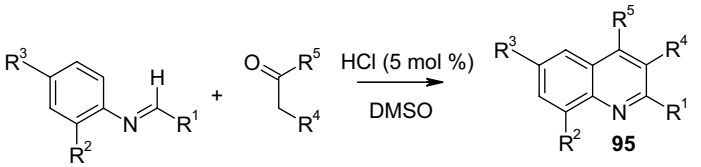
A new method for the synthesis of phenanthridine and related compounds has been developed using the condensation of *o*-phenylaniline and its homologues with cyclic ketones under hydrothermal conditions (Scheme 17.67). The method has been extended to the reaction of 2-isopropenylaniline·HCl to obtain quinoline derivatives.



Scheme 17.67

The product yields and side product distributions were found to be strongly dependent on the reaction temperature [150].

A novel *metal free* approach for the synthesis of substituted quinolines has been reported from imines and enolizable carbonyl compounds under aerobic conditions (Scheme 17.68). A catalytic amount of HCl in DMSO activated the carbonyl compounds, which reacted with benzylidenanilines to supply quinolines **95** [151]. This simple and practical method is applicable on a large scale. Other related metal-free conditions in the presence of iodine have also been communicated [152].

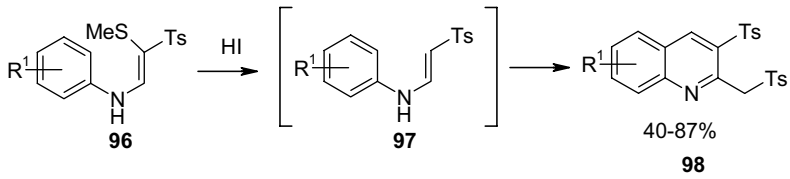


Scheme 17.68

Cyclohexanones have been converted into 8-chloroquinolines and other quinoline or dihydroquinoline derivatives through a series of reactions involving imination, α-alkylation with *N,N*-disilyl-protected ω-bromoamines, transimination, α-chlorination of the resulting bicyclic imines, dehydrochlorination, and/or dehydrogenation [153].

A versatile alternative approach to the synthesis of 2-quinolones has been developed by Arcadi and coworkers that involves galvanoplastic electrolysis and subsequent intramolecular cyclization of alkynes and malonyl moieties [154].

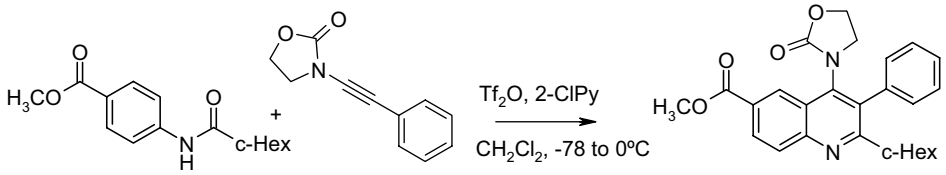
Ogura and coworkers found that the reaction of 2-(arylamino)-1-(methylthio)-1-tosylethenes **96** (Scheme 17.69) with hydrogen iodide in refluxing toluene gave 3-tosyl-2-(tosylmethyl)quinoline derivatives **98** in good yields. In this reaction,



Scheme 17.69

hydrogen iodide not only reductively removes the methylthio group but also serves as a protic catalyst for the subsequent dimeric cyclization of **97** to give the quinoline derivatives **98** [155].

Movassaghi *et al.* [156] have described a flexible procedure for the synthesis of polysubstituted quinolines by direct condensation of aryl amides and π-nucleophiles (Scheme 17.70).



Scheme 17.70

Finally, several examples of intramolecular Schmidt reactions of azides and carbocations have been reported for the synthesis of quinoline and other heterocyclic derivatives. In this way, gephyrotoxin, a naturally occurring substance isolated from the secretions of the poison-dart frog *Dendrobates histrionicus*, was prepared [157].

17.1.5
General Reactivity: Useful Reactions

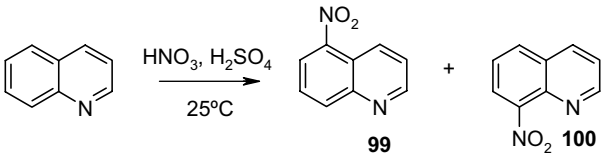
17.1.5.1 Addition to Nitrogen

As in pyridine, the nitrogen in quinoline undergoes protonation, alkylation, acylation, *N*-amination [158], and with peroxyacids or in the presence of other oxidative systems, such as O_2/2-methylpropanal [159], oxidation to the N-oxide. These reactions involve donation of the nitrogen lone pair to electrophiles. The pK_a for *N*-quinoline is 4.94, which shows a similar basicity to pyridine.

17.1.5.2 Reactions with Electrophilic Reagents at Carbon

17.1.5.2.1 Nitration In contrast to pyridine, and according to the above comments, S_EAr reactions occur on the carbocyclic ring, preferentially on the more activated positions of the benzene ring, with a positional selectivity in the order C8 > C5 ⋙ other positions. In general, the S_EAr process occurs preferentially through the conjugate acid, that is, quinolinium ion, which prevents attack on the heterocyclic

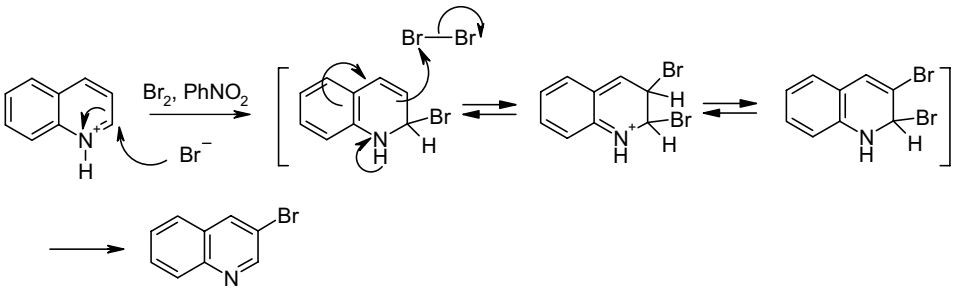
ring. Nitration takes place in the presence of a nitrating agent under mild conditions: mononitrations occur exclusively at the C5 and C8 positions to furnish compounds **99** and **100**, respectively (Scheme 17.71).



Scheme 17.71

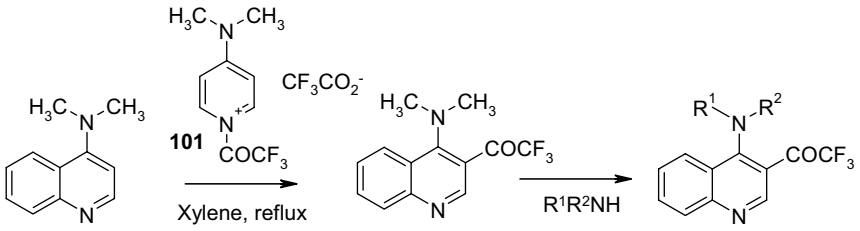
17.1.5.2.2 **Sulfonation** Sulfonation of quinoline produces different products depending on the reaction temperature. At 90 °C the 8-sulfonic acid is formed predominantly; raising the temperature increases the proportion of 5-sulfonic acid [1]. Reactions at higher temperatures produce other isomers under thermodynamic control.

17.1.5.2.3 **Halogenation** As expected, quinoline in the presence of Br_2 in H_2SO_4 yields 5- and 8-monosubstituted products by attack of the halogen on the corresponding salt. However, the introduction of a halogen atom onto the heterocyclic ring occurs through a non-electrophilic process, by reaction of quinoline hydrochloride with excess Br_2 and catalytic Br^- in $PhNO_2$, to supply the 3-bromo derivative (Scheme 17.72) [160].



Scheme 17.72

17.1.5.2.4 **Substitution in Quinolines Bearing Activating Nitrogen and Oxygen Substituents** Electrophilic substitution at carbon on the heterocyclic ring can be effected more readily on oxy- and aminoquinolines than in quinoline itself, and this reaction generally occurs *ortho* and *para* to the activating functionality. For example, acylation of 4-dimethylaminoquinoline with 1-trifluoroacetyl-4-dimethylaminopyridinium trifluoroacetate (**101**) proceeded cleanly to give 3-trifluoroacetyl-4-dimethylaminoquinoline, which can undergo N–N exchange with various amines to furnish 3-trifluoroacetyl-4-aminoquinolines in excellent yields (Scheme 17.73) [161].

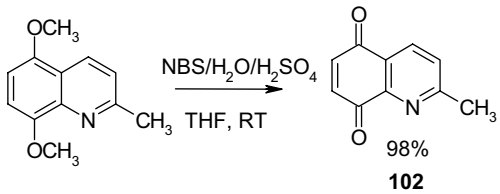


Scheme 17.73

17.1.5.3 Reactions with Oxidizing Reagents

Oxidation of the quinoline system can affect the pyridine ring, the carbocyclic ring, or both. As a result, oxidation can supply the quinoid derivative or the dihydrodiol. In addition, alkyl derivatives can be converted into the corresponding carboxylic acids. Degradation of the benzene ring to generate pyridine dicarboxylic acids, in an alkaline potassium permanganate medium, can be considered the most common oxidative reaction [162]. A series of quinoline-bearing substituents on the pyridine ring have been oxidized electrolytically in sulfuric acids to the corresponding quinolinic acids [163]. Oxidation of 2- and 3-haloquinolines in the presence of either ozone/H_2O_2 or catalytic ruthenium tetroxide gave the corresponding 5- and 6-halopyridine, 2,3-dicarboxylic acids [164].

The conditions have been developed to oxidize 5,8-dimethoxy-2-methylquinoline to 2-methylquinoline-5,8-dione (**102**) using NBS, H_2O, and H_2SO_4 without bromination (Scheme 17.74) [165].



Scheme 17.74

The pyridine ring can be oxidized enzymatically to give various oxygenated derivatives. As part of an earlier study on the bacterial metabolism of bicyclic azaarenes using *Pseudomonas putida*, *cis*-dihydroxylation of quinoline was observed to occur at the carbocyclic ring to yield *cis*-dihydrodiols along with 3-hydroxyquinoline and anthranilic acid [166].

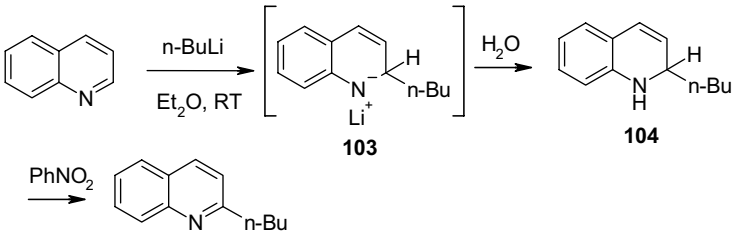
In contrast, hypervalent iodine reagents have also been used in the oxidative transformation of tetrahydro-derivatives into full aromatic quinoline derivatives [167]. In addition, tetrahydroquinolines undergo anodic oxidation with the incorporation of cyanide in the 2-position to supply 2-cyanoquinolines [168].

17.1.5.4 Nucleophilic Substitution Reactions

As expected, nucleophilic substitution of quinoline occurs in the heterocyclic ring at the C2 and C4 positions. In general, S_NAr reactions proceed more rapidly in quinoline than in pyridine because the fused benzene ring stabilizes the reaction intermediate.

17.1.5.4.1 Nucleophilic Substitution with Hydride Transfer

Arylation and Alkylation Reactions These processes occur almost exclusively at the C2 position. In these cases the nucleophilic reagent is an aryl- or alkyllithium or a Grignard reagent. The reaction seems to proceed in two steps: Addition at the C2 position, to give a dihydroquinoline *N*-lithio **103** or *N*-magnesium salt, which can be hydrolyzed to furnish a 2-substituted-1,2-dihydroquinoline **104**. This derivative can be handled and spectroscopically characterized but can also be oxidized in the presence of an oxidant to afford the full aromatic heterocycle (Scheme 17.75).



Scheme 17.75

Chichibabin Amination In a similar way to pyridine, the Chichibabin amination on quinoline proceeds with alkali metal amides in liquid ammonia. Quinoline first reacts with the amide to give the 2-amino-1,2-dihydroquinolinide ion (kinetic product), which subsequently rearranges to the more stable 4-amino-1,4-dihydroquinolinide ion (thermodynamic product) at higher temperatures. Thus, oxidative trapping of the quinoline adducts at different temperatures provides 2- or 4-aminoquinoline [169].

Hydroxylation In contrast to pyridine, quinoline can be hydroxylated directly with potassium hydroxide at high temperature. The formation of 2-quinolone can be regarded as a S_NAr process that proceeds with the evolution of hydrogen [170].

17.1.5.4.2 Nucleophilic Substitution with Displacement of Good Leaving Groups

The S_NAr reactions of quinoline take place in the presence of leaving groups such as halogen when located at the C2 or C4 positions. The reaction works well with a wide range of charged or neutral nucleophiles.

A novel synthesis of 4-quinolyl isothiocyanates from 4-chloroquinoline in the presence of silver thiocyanate in refluxing anhydrous toluene has been reported [171]. The method did not seem to proceed through a classical S_NAr process but rather through a radical pathway.

17.1.5.5 Reactions with Bases

C-Deprotonation of quinoline usually requires bases such as *n*-BuLi and this is not a preparative method. Simple lithioquinolines are generally prepared by metal–halogen exchange. However, the presence of *ortho*-directing substituents, such as chloro, fluoro, methoxy, methylthio, and various carboxamides, makes the process straightforward and such derivatives have been widely used [172].

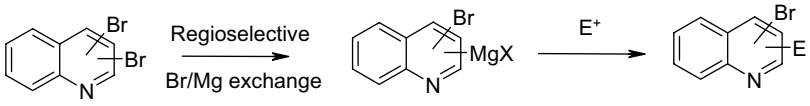
17.1.5.6 Reactions of C-Metallated Heterocycles

Although Li–halogen exchange reactions are important methods for the preparation of lithioquinolines, the competitive nucleophilic addition at activated positions could constitute an additional problem. Consequently, in recent years several groups have devoted some of their effort to the development of selective methods for the preparation of lithioquinolines. For example, Queguiner and coworkers have reported methods for the selective exchange of lithium for bromide followed by electrophile quenching in the preparation of substituted quinolines at benzene ring positions [173]. Comins *et al.* [174] have reported a regioselective lithium–halogen exchange in 2,4-dibromoquinolines to furnish 2-bromo-4-substituted derivatives.

Additionally, Marull and Schlosser [175] have studied the functionalization of polyhalogenated quinolines through organolithium intermediates and used trimethylsilyl entities and iodo-substituents as the sole auxiliary substituents. In these cases, the organolithium intermediates could be generated and the protective groups removed without impairing the bromo-substituent present in the starting materials.

A study of the direct lithiation of unprotected quinoline-carboxylic acids with lithium 2,2,6,6-tetramethylpiperidide (LTMP) has also been reported [176].

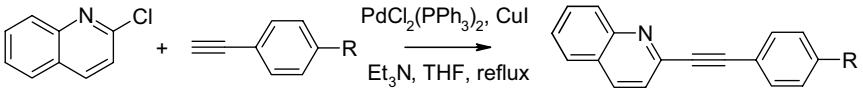
As far as magnesium derivatives are concerned, Knochel and coworkers [177] used halogen–metal exchange reactions to prepare a wide range of polyfunctionalized quinolines by regioselective magnesiation reactions using appropriate Mg reagents (Scheme 17.76).



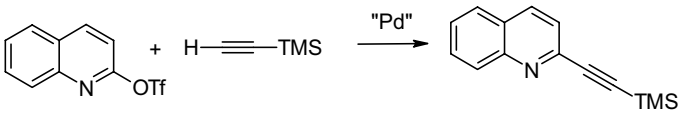
Scheme 17.76

The application of Pd, Zn, Cu, or Ni-mediated coupling reactions was shown to be particularly effective in most examples with quinoline derivatives. Several reports concern cross-coupling reactions and substitution reactions of halo-substituted quinolines. For example, Sonogashira conditions have been applied to 2-chloroquinoline and *para*-substituted phenylethynes to supply fluorescent compounds as blue–green emitters (Scheme 17.77) [178].

Alkynylation of 2-quinoline triflate with TMS-acetylene by Pd-catalyzed cross-coupling methods, and their application for a dynemicin A model, has been reported (Scheme 17.78) [179].

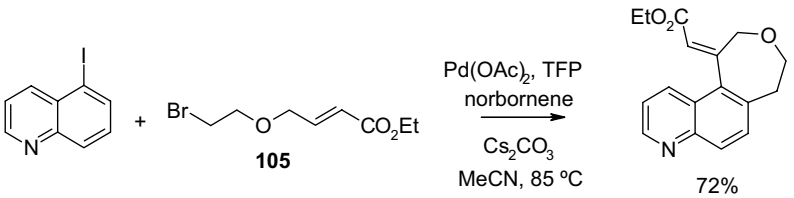


Scheme 17.77



Scheme 17.78

Treatment of 5-iodoquinoline with bromoenoate **105** in the presence of $Pd(OAc)_2$, *tri*-2-furylphosphine, norbornene, and Cs_2CO_3 provided benzoxepine derivatives. This methodology is based on a palladium-catalyzed aromatic substitution followed by an intramolecular Heck sequence (Scheme 17.79) [180].



Scheme 17.79

Strategies for controlling the regiochemistry of the addition reaction between organozinc reagents and 2,4-dichloroquinoline have been developed [181]. Similarly, the palladium-catalyzed carbonylation of quinolyl bromides and triflates has been described [182]. In the same way, the regiochemistry of the palladium-catalyzed carbonylation of 4,7-dichloroquinoline was evaluated [183]. Kappe *et al.* [184] have developed two general microwave methods for the synthesis of symmetrical heterobiaryls from 4-chloroquinolin-2-one in the presence of either Pd(0) or Ni(0).

Buchwald *et al.* [185] have communicated a general and efficient copper-catalyzed method for the amidation of 3-bromoquinoline using copper iodide, a diamine ligand, and K_2CO_3.

Margolis and coworkers [186] have reported a convenient alternative to the S_NAr process for the formation of the C–N bond in 4-aminoquinolines, an approach that involves a Pd-catalyzed methodology starting from 4-haloquinolines.

17.1.5.7 **Reaction with Reducing Agents**

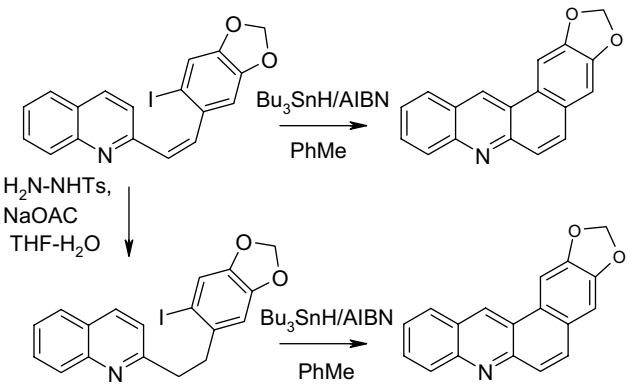
Quinolines are reduced to 1,2,3,4-tetrahydroquinolines with zinc borohydride and dimethylaniline under sonication conditions [187] or with indium metal in

ethanol [188], $NiCl_2 \cdot 2H_2O$–lithium arene [189], $NiCl_2$–$NaBH_4$ [190], lithium *N,N*-dialkylaminoborohydrides [191], in the presence of an Ir catalyst [192–197], and Hantzsch DHP and an organophosphate derivative [198]. Hydrogenations of quinolines to tetrahydroquinolines or decahydroquinolines have also been described [199, 200]. A method to prepare amino-substituted 5,6,7,8-tetrahydroquinolines by catalytic hydrogenation – in the presence of PtO_2 – of the corresponding acetamido-substituted quinolines followed by acetamide hydrolysis has been described [201]. Some of these derivatives were synthesized in an enantioselective manner.

17.1.5.8 **Reaction with Radical Reagents**

Concerning intermolecular processes, quinoline derivatives have been substituted by nucleosides in radical substitution reactions [202]. Russell and coworkers have reported the homolytic radical aromatic *tert*-butylation of quinolinium salts and quinoline *N*-oxides [203].

Harrowven *et al.* [204] have studied the intramolecular radical additions of aryl radicals to C2, C3, and C4 quinoline positions. In each case the formation of heteroaromatic products, rather than dihydroquinolines, was observed (Scheme 17.80).

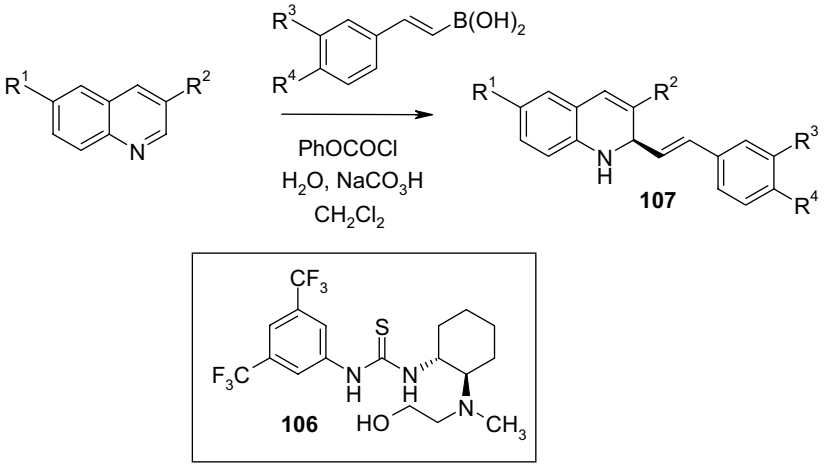


Scheme 17.80

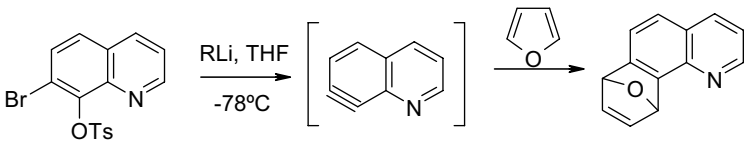
17.1.5.9 **Other Reactions**

A metal-free method involving the use of a new thiourea catalyst (**106**) has been reported for the preparation of 1,2-dihydroquinolines **107**. The catalyst **106** activates organoboronic acids to facilitate the enantioselective Petasis transformation of quinolines to give substituted 1,2-dihydroquinolines **107** with a high degree of stereocontrol (Scheme 17.81) [205].

Collis and coworkers [206] have reported the transient existence of the hetaryne 7,8-quinolyne and its reaction with furan through a Diels–Alder process (Scheme 17.82).



Scheme 17.81



Scheme 17.82

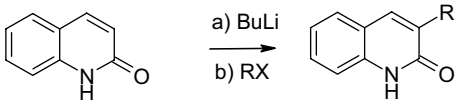
17.1.6 Some Quinoline Derivatives

17.1.6.1 Reactions of Quinolones

N-Unsubstituted quinolones are acidic derivatives and can be deprotonated using the appropriate base. These ambident anions can react with different electrophiles and the selectivity is strongly dependent on the solvent, cation, and alkylating agent. The N- versus O-alkylation of quinolinone derivatives has been investigated extensively [207]. In addition, the reaction of 4-hydroxy-2-quinolones with alkyl halides in the presence of Ag_2CO_3 afforded 2,4-dialkoxyquinolines in moderate to excellent yields [208].

Electrophilic substitution at carbon in 2- and 4-quinolones can be effected more readily than in quinoline itself, and this reaction generally occurs *ortho* and *para* to the activating functionality. However, experimental conditions play an important role and the process is highly dependent upon pH [209]. Several research groups have studied alternative methods of carrying out this type of process. The *ortho*-directing effect of the amide function in the regioselective lithiation of 2-quinolinone was studied by Avendano and coworkers. Subsequent electrophilic substitution can furnish 3-substituted derivatives in good yields (Scheme 17.83) [210].

A series of 3-(*N*-substituted)-aminoquinolin-2-ones have been synthesized by palladium-catalyzed C–N coupling reactions starting from 3-bromoquinolin-2-ones.

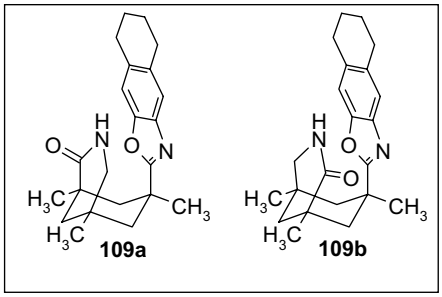


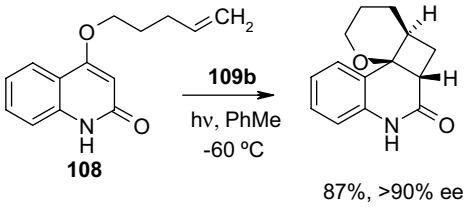
Scheme 17.83

Various nucleophiles, including amines, amides, sulfonamides, carbamates, and ureas, have been used successfully [211].

Some examples of cycloaddition reactions have been reported for the quinolone system. For example, phenanthridone derivatives were prepared by Diels–Alder reactions from 2-quinolones and butadiene compounds [212]. On the other hand, the first total syntheses of the novel pyranoquinoline alkaloids simulenoline (**15**), huajiaosimuline (**16**), and (±)-7-demethoxyzanthodioline have been described. The key feature of these concise total syntheses is the formal [3 + 3] cycloaddition reaction using α,β-unsaturated iminiums and 4-hydroxy-2-quinolones [24a].

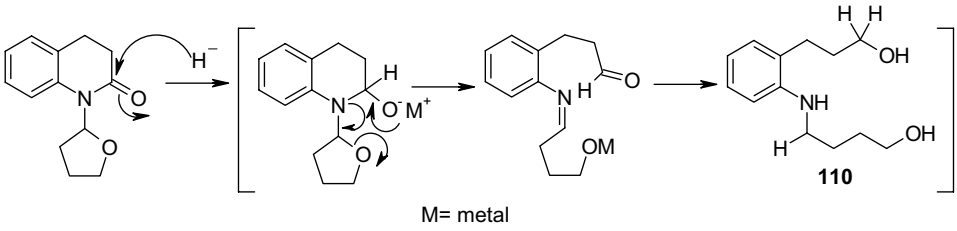
Intermolecular [2 + 2] photocycloaddition of 4-alkoxy-2-quinolones such as **108** (Scheme 17.84), in the presence of chiral lactams such as **109a** or **109b**, proceeds with excellent enantioselectivity (81–98% ee) and gave high yields (61–89%) [213].





Scheme 17.84

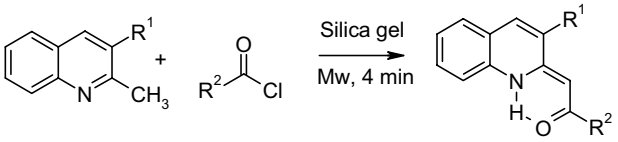
The 3-*aza*-Grob fragmentation of THF-protected 3,4-dihydro-2-quinolinone analogues in the presence of hydride reagents gave products **110** and demonstrates that various hydride reagents can reduce this class of aromatic lactam (Scheme 17.85) [214].



Scheme 17.85

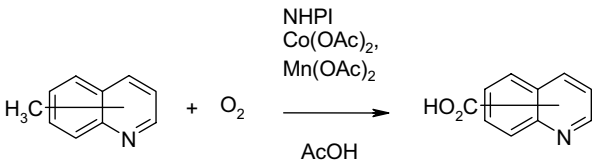
17.1.6.2 **Reactions of Alkylquinolines**

Protons on alkyl groups at the 2- and 4-positions of quinoline are sufficiently acidic for deprotonation by strong bases and are more acidic than alkyl groups at other positions. The main feature of the reactivity of alkylquinolines is deprotonation of such alkyl moieties and reaction with electrophiles [215]. In this context, several 2-ketomethylquinolines have been synthesized by heating 2-methylquinolines with acyl chlorides in a conventional microwave oven and in the presence of silica gel (Scheme 17.86) [216].



Scheme 17.86

On the other hand, the aerobic oxidation of methylquinolines to carboxylic acids has been achieved by using *N*-hydroxyphthalimide (NHPI)/$Co(OAc)_2$/$Mn(OAc)_2$ as a catalyst in the presence of small amounts of nitrogen dioxide as an initiator (Scheme 17.87) [217].

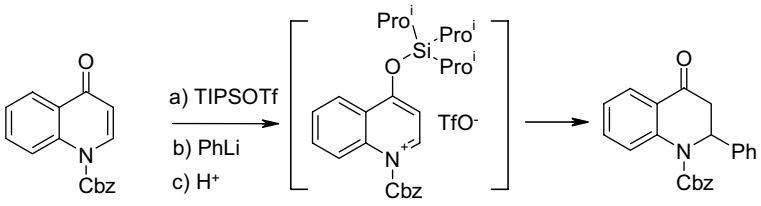


Scheme 17.87

17.1.6.3 **Reactions of Quinolinium Salts**

17.1.6.3.1 **Nucleophilic Additions and Related Processes** Nucleophilic additions to quinoline occur readily after quaternization of the nitrogen and are often the key step in preparatively useful reactions. For example, *N*-protected quinolin-4-ones

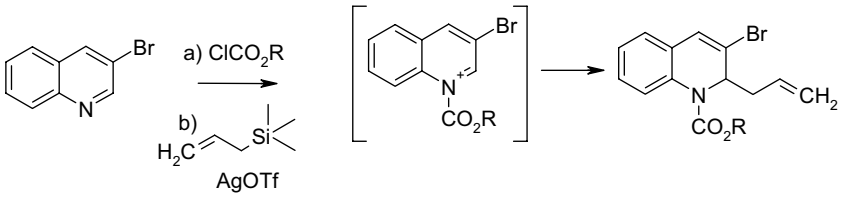
undergo 1,4-addition of organolithium or Grignard reagents by conversion into the 4-silyloxyquinolinium triflate (Scheme 17.88) [218].



Scheme 17.88

Other related studies into this type of process include the use of arylzinc reagents in the presence of chlorotrimethylsilane and rhodium-catalysis, as reported by Hayashi *et al.* [219]. In this case the reaction is conducted in an enantioselective fashion.

Addition of allylsilane to the 2-position of quinolinium salts acylated by chloroformate derivatives can be accomplished in the presence of AgOTf (Scheme 17.89) [220, 221].



Scheme 17.89

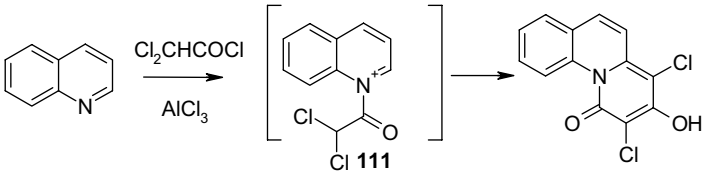
A similar Ir-catalyzed addition of ethynyl(trimethyl)silane to the 2-position of quinoline was also reported [222].

Other examples of functionalization of the quinoline at the 2-position to yield 2-substituted 1,2-dihydroquinolines, by activation with ethyl chloroformate or diethyl pyrocarbonate, have also been reported [223–225].

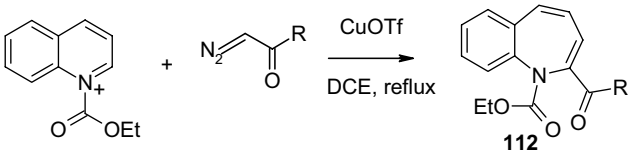
A regioselective route to cyanomethyl-1,2-dihydro-*N*-methylquinolines has been published and this process starts from methylquinolinium iodide and tris(trimethylsilyl)acetonitrile in the presence of fluoride [226].

A novel one-step synthesis of pyridoquinolines from quinolinium salt derivatives **111** (Scheme 17.90) under Friedel–Crafts conditions has been described [227].

17.1.6.3.2 **Cycloadditions of Quinolinium Salts and Related Processes** Concerning the ring expansion of *N*-acyl derivatives, Yadav *et al.* [228] have reported a new process to give easy access to benzoazepine derivatives **112** (Scheme 17.91). Treatment of a quinoline *N*-acyl derivative with α-diazoketones in the presence of catalytic CuOTf in 1,2-dichloroethane (DCE) under reflux gave the target compounds in excellent yields.



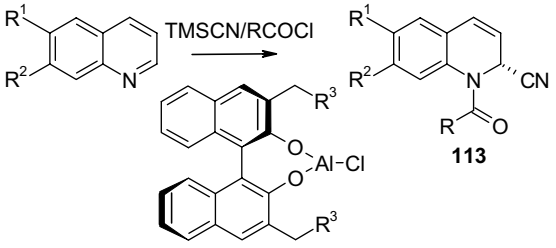
Scheme 17.90



Scheme 17.91

Quinolinium salts, obtained from the corresponding 1-substituted-4-quinolones, have been used in cycloaddition reactions with silyloxy-1,3-butadienes to give acridine compounds [229].

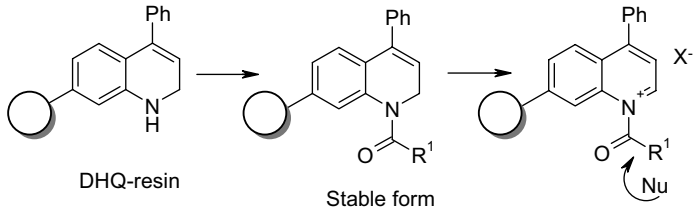
17.1.6.3.3 **Reissert Reaction** Takamura *et al.* [230] have reported an enantioselective version for quinoline derivatives of the Reissert-type reaction with trimethylsilyl cyanide and acyl chlorides in the presence of binaphthols and diethylaluminium chloride. Chiral dihydroquinoline carbonitriles **113** (Scheme 17.92) were obtained with up to 91% ee.



Scheme 17.92

The same authors have published the development and application of this method to the synthesis of the potent NMDA receptor antagonist (−)-L-689,560 (**24**) [31].

A new safety-catch linker for solid phase organic synthesis that is based on a quinoline moiety has been developed. Cleavage from the resin proceeds in two steps: oxidative aromatization leading to an activated quinolinium derivative and nucleophilic displacement of the quinoline resin (Scheme 17.93) [231].



Scheme 17.93

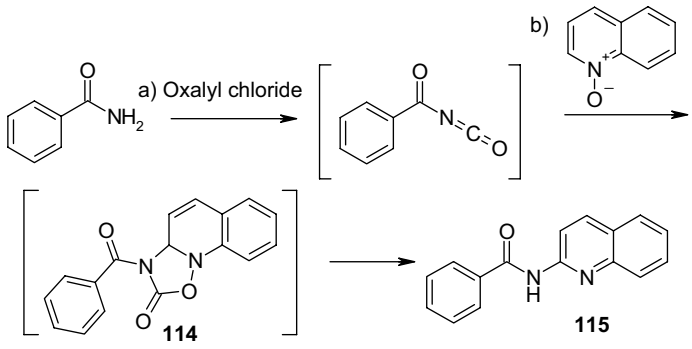
17.1.6.4 Reactions of Quinoline *N*-Oxides

Quinoline reacts with peracids to give the *N*-oxide. In a similar way to pyridine, the presence of the *N*-oxide serves to facilitate both electrophilic and nucleophilic additions to the C2 and C4 positions. In some cases, electrophilic substitution is dependent on the experimental conditions. For instance, nitration of quinoline *N*-oxide in mixed acids takes place at the C5 position, via the O-protonated species, but with a lower acid strength the reaction occurs at C4 [232].

Numerous methods are available for the reduction of the N–O bond in *N*-oxides. In this context, baker's yeast is also a useful reagent for the reduction of *N*-oxides to the respective quinoline [233].

Rearrangements are important processes in the case of quinoline *N*-oxides. For example, 2,3-dichloroquinoline has been prepared in three steps from 3-bromoquinoline through *N*-oxide formation and subsequent rearrangement [234]. More recently, a simple and novel approach for the direct conversion of quinoline *N*-oxides into 2-amidoquinolines has been described [235]. The treatment of primary amides with oxalyl chloride yielded an acyl isocyanate, which reacted in the presence of quinoline *N*-oxide, via intermediate **114**, to give 2-amidoquinolines **115** in good yield (Scheme 17.94).

This methodology is complementary to the Abramovich reaction, which is limited to the introduction of secondary amides via imidoyl chlorides [236].

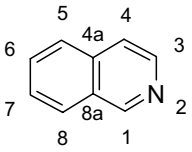


Scheme 17.94

17.2 Isoquinoline

17.2.1 Introduction

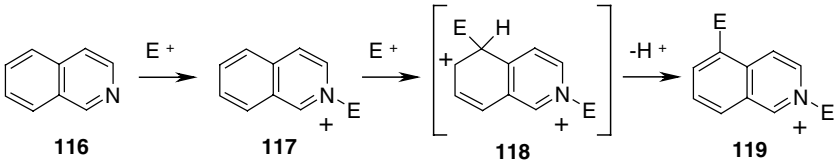
Isoquinoline (**116**) (β-quinoline, 2-azanaphthalene, benzo[*c*]pyridine), a structural isomer of quinoline, is a low-melting solid with a penetrating smell. It was first isolated from coal tar in 1885 by Hoogewerff and van Drop by fractional crystallization of the acid sulfate [237]. This compound was also isolated from the same source in 1914 by Weissgerber through selective extraction [238]. The structure, properties, reactivity, synthesis, and applications of isoquinoline have been reviewed extensively [1, 3, 5, 239–242].



116

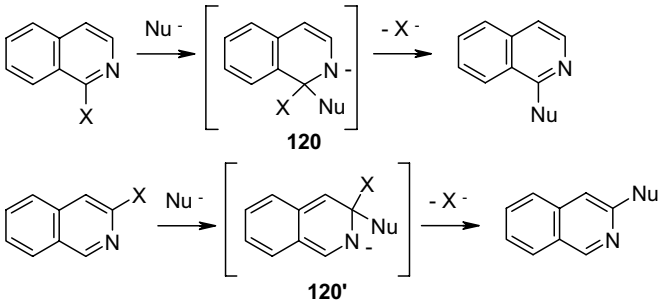
17.2.2 General Reactivity

The presence of the nitrogen sp^2 lone pair makes **116** basic and it will react with protons, or other electrophilic species, at nitrogen by electrophilic addition to give isoquinolinium salts **117**, which in many instances are isolable [243, 244]. Protonation, alkylation, acylation, and oxidation with peroxy acids take place on the nitrogen. The basicity and N-nucleophilicity are enhanced by electron-releasing substituents and diminished by electron-withdrawing groups. Moreover, steric interference of substituents at either or both C1 and C3 positions will slow the rate of N-alkylation [245]. Isoquinoline is a π-deficient heterocycle as a consequence of conjugation of the π-electron pair on the nitrogen. Hence, aromatic electrophilic substitution will take place at a slower rate than in naphthalene [246]. Another major difference is that S_EAr reactions occur through **117**, a more π-deficient heterocycle, which reacts on the benzene ring rather than the electron-poorer pyridine ring, through a high-energy doubly charged Wheland-type intermediate **118**, to give the 5-substituted derivative **119** as the major product [247].

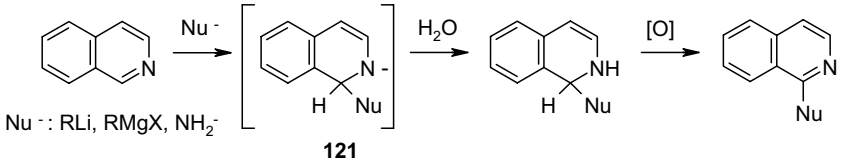


116 **117** **118** **119**

Aromatic nucleophilic substitution is a very important process for π-deficient heterocycles such as **116** [248–250]. This process involves a two-step sequence: addition of a nucleophile species to give a Meisenheimer complex (**120**) is followed by elimination of a good leaving group (usually halide or nitrite). The reaction takes place when the leaving group is located at C1, since the negative charge resides largely on the nitrogen, and at a much slower rate when it is located at C3, due to the higher-energy intermediate **120′**. Thus, the S_NAr reaction of 1- and 3-chloroisoquinolines with ethoxide is about 10^4 times faster in the former [251]. Quaternization greatly increases the rate of nucleophilic substitution [252].



Another important feature in the reactivity of **116**, with no counterpart in the chemistry of aromatic carbocycles, is nucleophilic substitution with hydride transfer by means of strong nucleophilic reagents such as organolithiums, Grignard reagents, or sodium amide to give stable intermediate addition products **121**, which can be characterized as such. These intermediates can be oxidized to afford the substitution products. In this case, only attack at C1 has been observed [253–255].



17.2.2.1 **Relevant Physicochemical Data, Computational Chemistry, and NMR Data**
Isoquinoline is a hygroscopic solid that crystallizes as platelets that have low solubility in water but dissolve in common organic solvents. This compound is as basic (pK_a 5.4) as pyridine and quinoline (pK_a 5.2 and 4.95, respectively) and **116** is also soluble in dilute acids (Table 17.4).

Table 17.4 Physical properties of **116**.

Mp (°C)	Bp (°C/Torr)	Density (g cm^{-3})	pK_a	μ (D)
24.25	242.5/760	1.096	5.4	2.52

Table 17.5 ^{1}H and ^{13}C NMR chemical shifts (ppm) of **116** (in $CDCl_3$).

	δ1	δ3	δ4	δ4a	δ5	δ6	δ7	δ8	δ8a
^{1}H	9.15	8.45	7.50	—	7.71	7.57	7.50	7.87	—
^{13}C	152.5	143.1	120.4	135.7	126.5	130.6	127.2	127.5	128.8

Isoquinoline shows structural and spectroscopic similarities to pyridine and naphthalene. Both the proton and carbon chemical shifts (Table 17.5) are related to the electron density, at a given position, as a result of the mesomeric and inductive electron-withdrawing effects of the nitrogen. As a result, the H1/H3 and C1/C3 signals are shifted to lower field than the other signals in the heterocycle or than the corresponding signals in naphthalene (δ_{H1}: 7.8, δ_{H2}: 7.5, δ_{C1}: 128, δ_{C2}: 126 ppm).

The UV spectrum of **116** (Table 17.6) resembles that of naphthalene [λ_{max} (nm)/log ε: 311/2.39, 275/3.75, and 219/5.10]. The spectrum contains three long wavelength bands that correspond to the $\pi \rightarrow \pi^*$ transitions. However, as the heteroatom has a lone pair, $n \rightarrow \pi^*$ transitions are possible but they are overlapped by the much more intense former bands.

Molecular mechanics have been used by Allinger and coworkers, through their MM3 force field program, but they were unable to estimate the vibrational spectra for **116** with accuracy. However, they did reach a good match for the heat of formation (calculated 49.94 kcal mol^{-1}; experimental 48.2 kcal mol^{-1}) and the dipole moment (calc. 2.30 D; expt. 2.53–2.75 D), with the resonance energy also estimated (25.68 kcal mol^{-1}) [256]. The observed and calculated vibrational spectra were in good agreement when density functional theory (DFT) calculations were performed with the B3LYP functional and 6-31G* basis set [257]. Bond orders were calculated at the Hartree–Fock and the second-order Møller–Plesset (MP2) levels for **116** and other heteroatomic rings [258]. The π-electron charge distribution was calculated by the LCAO method and gave good agreement with experimental data [259]. Aromaticity shows a significant collinearity with magnetic susceptibility, as calculated at the (DFT) B3LYP level with the 6-31G* basis set [260]. Polarizability was calculated using accurate *ab initio* studies at the HF/6-311++G(3d,2d) and BLPY/6-311++G(3d,2p) levels of theory [261].

As regards other physicochemical parameters estimated by computational chemistry methods, the proton affinity of **116** calculated at the 3-21G and 3-21+G *ab initio* levels and at the MNDO and AM1 semiempirical levels gave, after inclusion of diffuse functions, good agreement with experimental data [262]. The extended Hückel theory (EHT) was applied to localization energies and total electron densities ($\sigma + \pi$), which correlate quite conclusively with the experimentally observed site of predominant nucleophilic attack by an amine ion in the Chichibabin reaction (Table 17.7) [2].

Table 17.6 Ultraviolet data ($\pi \rightarrow \pi^*$ transitions) for **116** (in hexane).

λ_{max} (nm)	Log ε	λ_{max} (nm)	Log ε	λ_{max} (nm)	Log ε
317	3.49	266	3.61	217	4.57

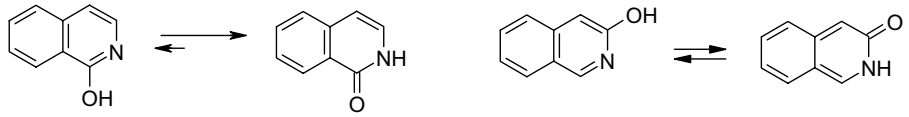
Table 17.7 Electron densities (*Q*) in **116** obtained using extended Hückel theory (EHT).

Position	1	2	3	4	4a	5	6	7	8	8a
π	0.78	1.45	0.91	1.03	0.90	1.02	0.96	1.01	0.97	0.97
σ	2.87	4.49	2.86	3.12	2.98	3.12	3.11	3.11	3.11	2.99
σ + π	3.65	5.94	3.77	4.15	3.88	4.14	4.07	4.12	4.08	3.96

Calculation of the proton and carbon chemical shifts relative to tetramethylsilane, with accuracies of about ±2.62 ppm (^{13}C) and ±0.32 ppm (^{1}H) can be performed using a linear regression formula that converts magnetic shielding constants calculated at common *ab initio* and DFT levels [263].

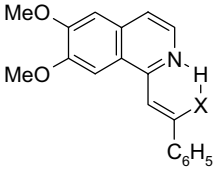
17.2.2.2 **Tautomerism**

In a similar way to oxypyridines, oxyisoquinolines also show tautomerism. The benzo-fusion to the pyridine ring involved in tautomerism has the effect of shifting the equilibrium towards the tautomer that retains full aromaticity of the benzene ring. Thus, isoquinolin-1-ol (**122**) completely tautomerizes to 2*H*-isoquinolin-1-one (**123**) whereas isoquinolin-3-ol (**124**) remains in the equilibrium with 2*H*-isoquinolin-3-one (**125**) in a proportion significantly greater than in the corresponding unfused heterocycle.



122 **123** **124** **125**

Tautomerism also arises in the case of 1-phenacylisoquinolines **126** (X = O) and their corresponding ketenimines **126** (X = NH). The enol and the enamine are reported to exist as a single tautomer due to intramolecular hydrogen bonding [264].

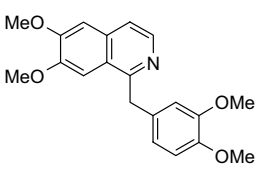


126 (X = O, NH)

17.2.3 **Relevant Natural and/or Useful Compounds**

Isoquinoline plays an important role as a secondary metabolite in a large number of alkaloids that have different biogenetic origins. Many isoquinoline alkaloids occur as 1,2,3,4-tetrahydroderivatives, which can be considered as being derived from

β-phenylethylamines [265]. The synthesis, reactions, and biological activities of isoquinoline natural products have been reviewed extensively [266]. The asymmetric synthesis of these alkaloids has been the focus of significant efforts by both academic and industrial research groups seeking stereochemically modified traditional methods and new advances using the C1-Cα connectivity approach [267], and the use of α-amino acids as excellent chiral building blocks [268]. Diverse biological activities have been reported for isoquinoline natural products and these include anti-inflammatory [269], cardiovascular [270], and antimalarial [271] among others. Isoquinoline marine compounds are also of interest [272]. Some examples of isoquinoline alkaloids are given below and include papaverine (**127**), an opium poppy alkaloid, berberine (**128**), an isoquinolinium alkaloid found in several Korean and Chinese medicinal plants, mimosamycin (**129**), one of the simplest isoquinoline quinones of marine origin, and maritidine (**130**) a chiral tetrahydroisoquinoline alkaloid.



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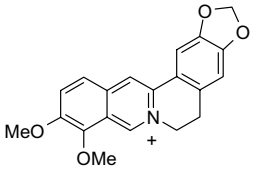

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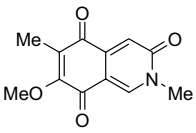

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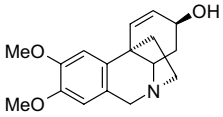

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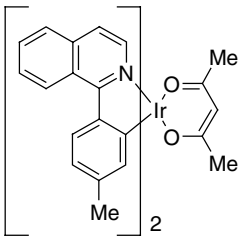
In recent years, several reports have been published on new isoquinoline-based materials with interesting properties. Recently, some studies have highlighted iridium(III) complexes bearing isoquinoline-derived ligands as chemiluminescent materials [273, 274], and some of these can be applied as red or white OLEDs (e.g., **131**) [275, 276]. On the other hand, a new type of donor–spacer–acceptor based on bis(isoquinoline-*N*-oxide) (e.g., **132**) has proved to be an efficient dual channel fluorosensor that acts as a pincer for lithium, magnesium, and calcium cations [277].



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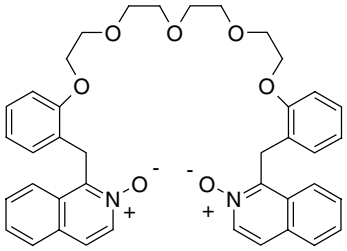


132

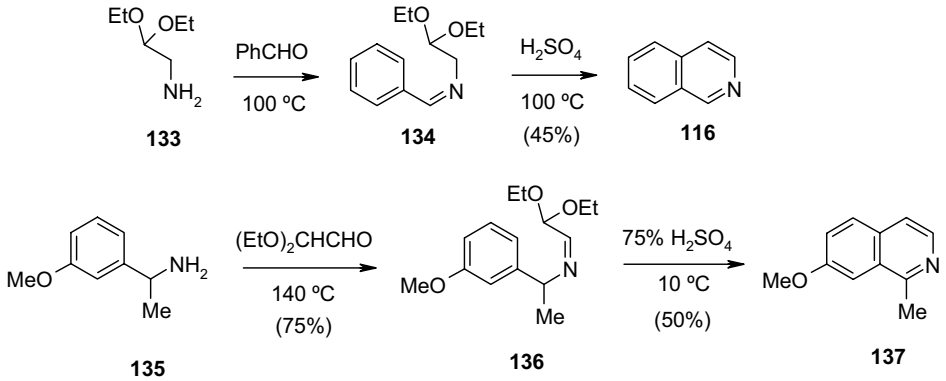
17.2.4
Synthesis of Isoquinolines

Synthetic methods for the isoquinoline skeleton are constantly being updated. Starting from conveniently substituted benzenes, these methods can be classified into two major categories: those that create the fully aromatic heterocyclic ring, which

are covered in this chapter, and those that build the fully or partially reduced pyridine ring [278, 279], which will not be considered here, but are important for the preparation of many isoquinoline natural products [267], such as the classical Bischler–Napieralski and Pictet–Spengler syntheses.

17.2.4.1 Classical Methods

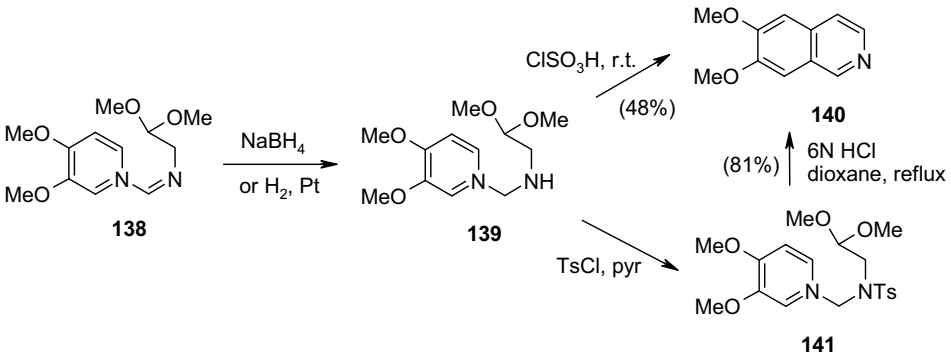
17.2.4.1.1 **Pomeranz–Fristsch Synthesis** This two-step method involves the initial condensation of an aryl aldehyde with a 2-aminoaldehyde acetal [280] or, conversely, a benzylamine with glyoxal diethyl acetal – if C1-substituted isoquinolines are desired [281] – to give an aldimine. The second step involves the cyclization of the aldimine by treatment with a strong acid. For example, **116** has been prepared by condensation of aminoacetal **133** with benzaldehyde to give imine **134**, which was cyclized with sulfuric acid. For C1-substituted isoquinolines, benzylamine **135** was condensed with glyoxal diethyl acetal to give imine **136**, which then cyclizes to **137** (Scheme 17.95).



Scheme 17.95

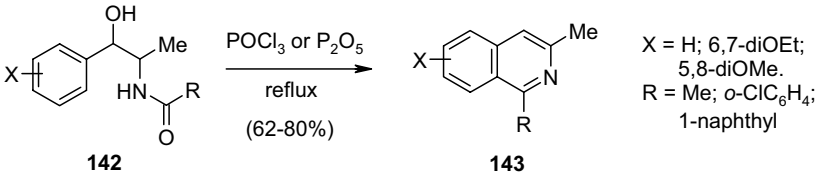
This synthesis works well when the aryl component bears electron-donating groups, preferably *para* to the position of ring closure. However, the overall yield is limited by imine hydrolysis during the cyclization. Two solutions have been developed to overcome this drawback: (i) the use of trifluoroacetic acid/boron trifluoride [282] and (ii) carrying out the cyclization at the amine level instead of the imine. For example, imine **138** was reduced to amine **139**, which can be cyclized directly with chlorosulfonic acid to give **140** [283] or tosylated to give **141** before treatment with HCl (Scheme 17.96) [284]. Tosylamides can be prepared by benzylating the sodium salt of 2-tosylaminoethanal acetal [285], or by Mitsunobu reaction of a benzylic alcohol with *N*-sulfonyl-aminoacetals [286, 287].

17.2.4.1.2 **Pictet–Gams Modification of the Bischler–Napieralski Synthesis** Although the Bischler–Napieralski synthesis provides access to 3,4-dihydroisoquinolines or



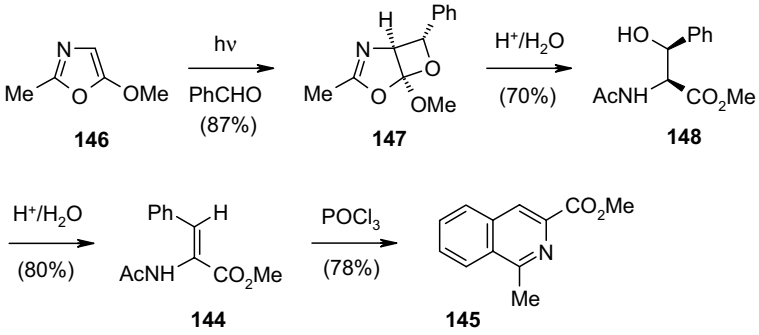
Scheme 17.96

3,4-dihydroisoquinolin-1-ones, the Pictet–Gams modification allows the preparation of fully aromatic isoquinolines starting with unsaturated or potentially unsaturated arylethanamines. Thus, amides from 2-aryl-2-hydroxyethanamines **142** led to isoquinolines **143** when treated with phosphoryl chloride or phosphorus pentoxide (Scheme 17.97) [288–291].



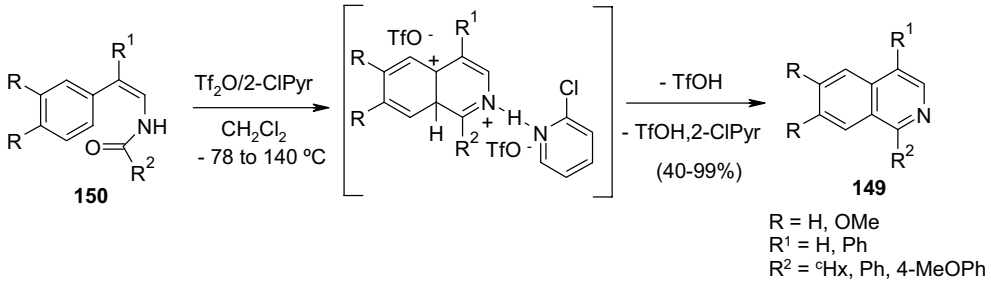
Scheme 17.97

In addition, cinnamic esters substituted with an acetamido group at the C2-position can be converted into isoquinolines. In this way **144** was cyclized to isoquinoline carboxylate **145**. The cinnamic ester derivative was prepared by photocycloaddition of 5-methoxy-2-methyloxazole (**146**) with benzaldehyde to give the oxetane **147**, which under acidic conditions gave first **148** and then **144** (Scheme 17.98) [292].



Scheme 17.98

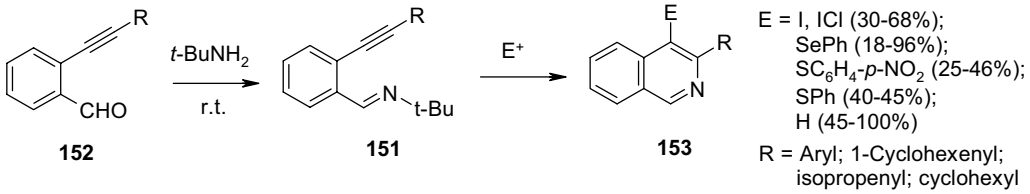
Milder conditions with trifluoromethanesulfonic anhydride in the presence of 2-chloropyridine have been described for the synthesis of isoquinoline and β-carboline derivatives through electrophilic amide activation [293]. Isoquinolines **149** were prepared from sensitive (*Z*)-*N*-vinylamides **150** in good to excellent yields (Scheme 17.99). Moreover, condensation reaction conditions proved to be far more efficient than phosphoryl chloride, oxalyl chloride/$FeCl_3$, or Tf_2O/DMAP.



Scheme 17.99

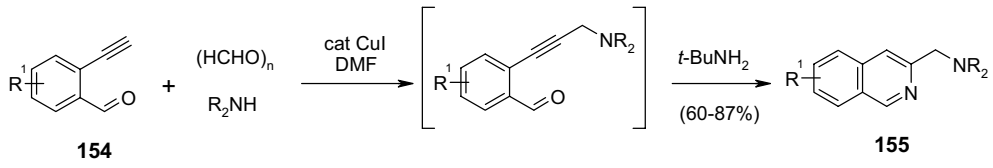
17.2.4.2 Modern Methods

17.2.4.2.1 **Electrophilic Cyclization-Based Methods** Methods based on electrophilic cyclization reactions have been developed using different starting materials. Iminoalkynes **151** prepared by reaction of *tert*-butylamine with *o*-(1-alkynyl)benzaldehydes **152** have been cyclized in the presence of electrophiles such as I_2, ICl, PhSeCl, PhSCl, and p-$O_2NC_6H_4SCl$ to give the corresponding halogen-, selenium-, and sulfur-containing isoquinolines **153** at the C4-position in moderate to excellent yields (Scheme 17.100). Furthermore, silver-catalyzed ring-closure of **151** provides an entry to C4-unsubstituted isoquinolines **153** [294, 295].



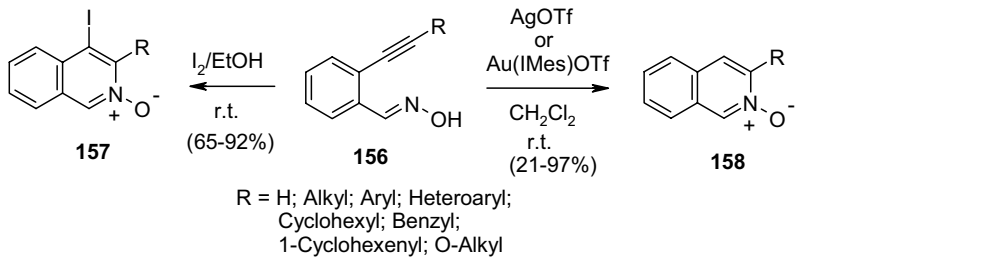
Scheme 17.100

A copper(I)-catalyzed domino four-component coupling–cyclization method using 2-ethynylbenzaldehydes **154**, paraformaldehyde, a secondary amine, and *tert*-butylamine has been reported to give 3-(aminomethyl)isoquinolines **155** in high yields (Scheme 17.101) [296]. This method is efficient when either electron-donating or electron-withdrawing substituents are present in the benzene ring.



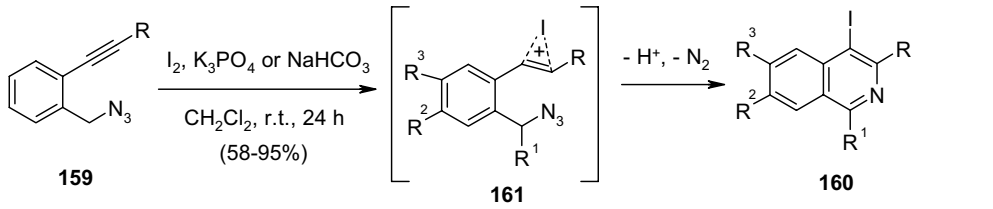
Scheme 17.101

Related to the former method, 2-alkynylbenzaldoximes **156** give C3-substituted-4-iodoisoquinoline-*N*-oxides **157** in good to excellent yields when treated with iodine [297]. Silver(I)- and gold(I)-catalyzed procedures have also been reported to afford C4-unsubstituted-*N*-oxides **158** (Scheme 17.102) [298].



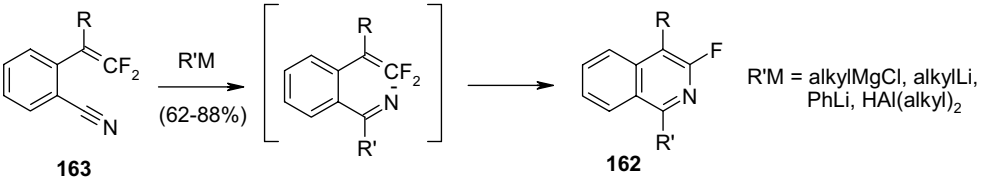
Scheme 17.102

Iodine-mediated electrophilic cyclization of 2-alkynyl-1-azidomethyl benzenes leads to highly substituted isoquinolines [299]. Azides **159** react with iodine, Py_2BF_4–HBF_4 (Barluenga reagent) or NIS as iodium donors to give iodoisoquinolines **160**, via a cyclic iodonium ion **161** followed by nucleophilic cyclization of the azide and subsequent elimination of nitrogen (Scheme 17.103). Electron-neutral or electron-donating substituents at the alkyne terminus are favored. This methodology was applied to the synthesis of norchelerythrine.



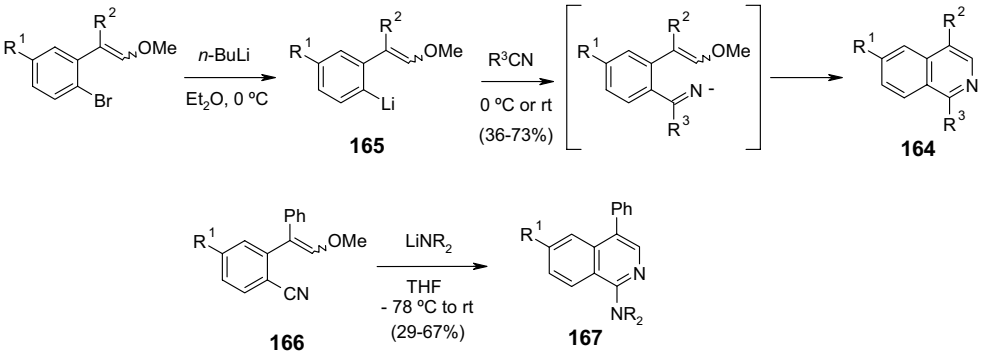
Scheme 17.103

17.2.4.2.2 **Nucleophilic Cyclization-Based Methods** Ring-fluorinated isoquinolines **162** have been prepared by means of nucleophilic intramolecular cyclization of *o*-isocyano-β,β-difluorostyrenes **163** with organometallic reagents via intramolecular sp^2 nucleophiles, which cyclize by substitution of the vinylic fluoride (Scheme 17.104) [300].



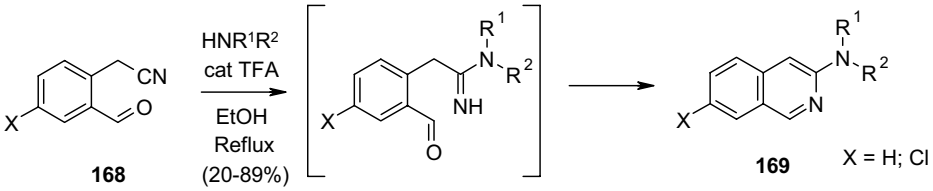
Scheme 17.104

In a similar way, 1,4-disubstituted isoquinolines **164** were obtained by reaction of α-substituted 2-lithio-β-methoxystyrenes **165** with nitriles (Scheme 17.105) [301]. This process has also been carried out starting from *o*-cyano-β-methoxystyrenes **166** [302]. When lithium dialkylamides were used as nucleophiles, 1-dialkylamino-substituted isoquinolines **167** were obtained.



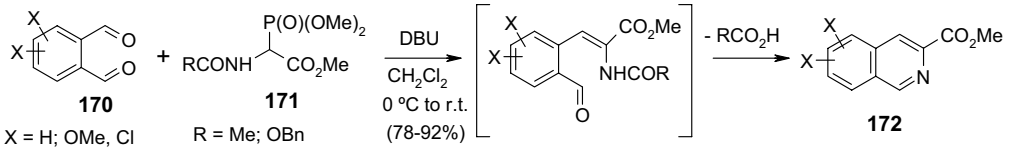
Scheme 17.105

17.2.4.2.3 **Condensation Reaction-Based Methods** The heteroaromatic ring in isoquinoline can also be obtained by ring closure through a condensation reaction on appropriate *ortho*-substituted benzenes. Reaction of nitriles **168** with ammonia, or primary or secondary amines, in the presence of catalytic amounts of TFA leads to 3-aminosoquinolines **169** [303]. Primary amines, as opposed to ammonia or secondary amines, give the aldimine and this slowly dissociates to add to the cyano group (Scheme 17.106). In a similar fashion, 2-acylphenylacetonitriles react with primary amines by acid-catalyzed condensation to give 1-substituted-3-aminoisoquinolines [304].



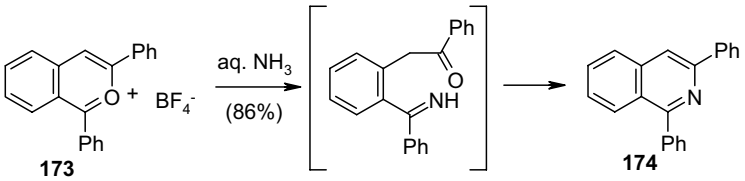
Scheme 17.106

Aromatic 1,2-dialdehydes **170** react with protected phosphonoglycine **171** derivatives using DBU as base to give methyl isoquinoline-3-carboxylates **172** in good to high yields (Scheme 17.107) [305]. This method allows the preparation of isoquinolines bearing electron-withdrawing groups.



Scheme 17.107

2-Benzopyrilium salts **173**, prepared by Friedel–Crafts acylation of benzyl ketones, are converted into isoquinolines **174** by treatment with aqueous ammonia through a Schiff base intermediate (Scheme 17.108) [306].

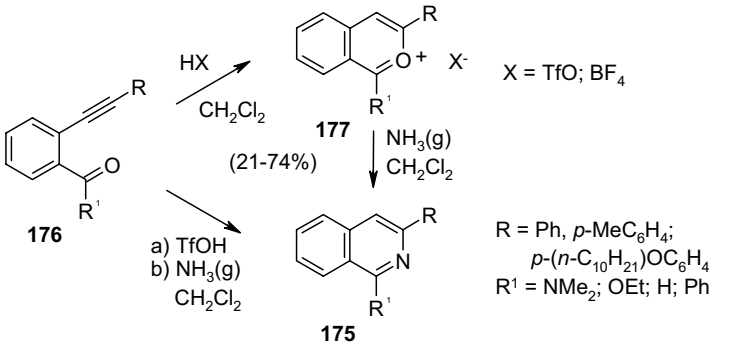


Scheme 17.108

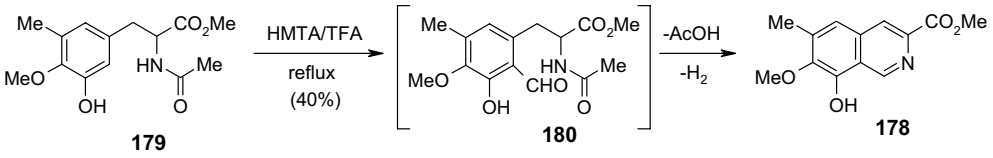
More recently, isoquinolines **175** have been prepared by a one-pot procedure from *o*-alkynyl-benzamides, -benzoates, -benzaldehydes, or -benzophenones **176**. The two-step procedure, which proceeds via the 2-benzopyrilium salt **177**, proved to be equally efficient (Scheme 17.109) [307].

Unexpectedly, isoquinoline-3-carboxylate **178** was obtained when the *N*-acetyl-phenylalanine methyl ester derivative **179** was treated with HMTA/TFA. This process occurred through the formyl intermediate **180**, which then cyclizes and dehydrogenates to give **178** (Scheme 17.110) [308].

17.2.4.2.4 **Metal-Catalyzed Ring Closing Methods** Larock's group has reported a series of isoquinoline syntheses based on palladium-catalyzed annulation processes. The reaction of *tert*-butylimines of *o*-iodobenzaldehydes **181** with internal acetylenes

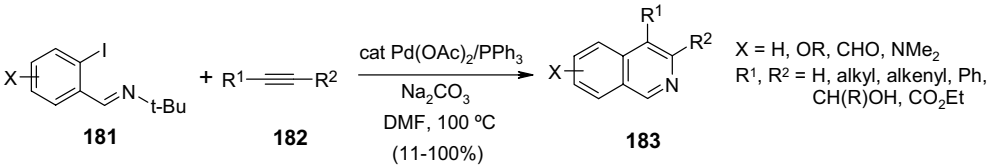


Scheme 17.109



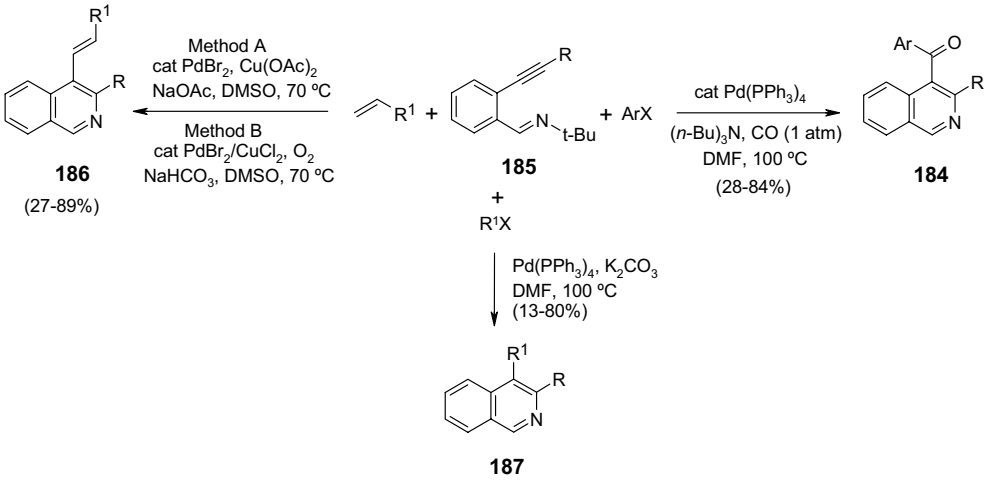
Scheme 17.110

182 in the presence of catalytic $Pd(OAc)_2$ gave various 3,4-disubstituted isoquinolines **183** in moderate to excellent yields (Scheme 17.111) [309, 310]. When a relatively unhindered diyne and enyne, or an electron-rich imine, are employed mixtures of stereoisomers are obtained with high selectivity. The use of trimethylsilyl-containing acetylenes produced 3-substituted isoquinolines. These compounds were also available using terminal acetylenes as substrates and the methodology has been applied to the total synthesis of decumbenine B [311]. A nickel(II) catalyst proved to be efficient to give 3,4-disubstituted isoquinolines by this method in a highly regioselective manner [312]. In addition, 3-substituted 4-fluoroalkylated isoquinolines were prepared using a Pd(0) catalyst [313].



Scheme 17.111

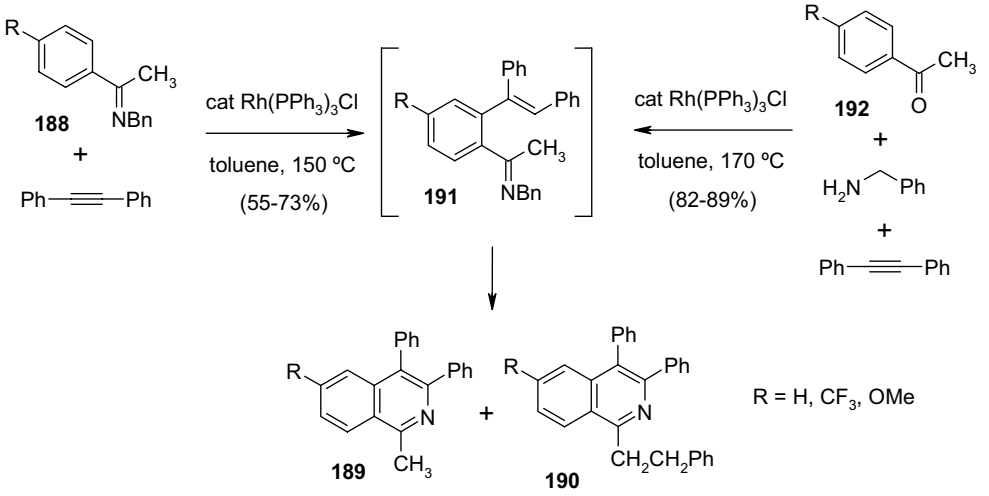
The former methodology was subsequently expanded to the synthesis of 3-substituted-4-aroylisoquinolines **184** by palladium-catalyzed carbonylative cyclization of 2-(1-alkynyl)benzaldimines **185** and aryl halides (Scheme 17.112) [314, 315]. The reaction is useful for both electron-rich and electron-poor aryl halides. Benzaldimines **185** are also versatile starting materials for the synthesis of isoquinolines



Scheme 17.112

186, by palladium-catalyzed cyclization followed by a Heck reaction with olefins [316, 317], or isoquinolines **187** by cross-coupling with aryl, vinyl, alkynyl, allyl, or benzyl halides [318, 319].

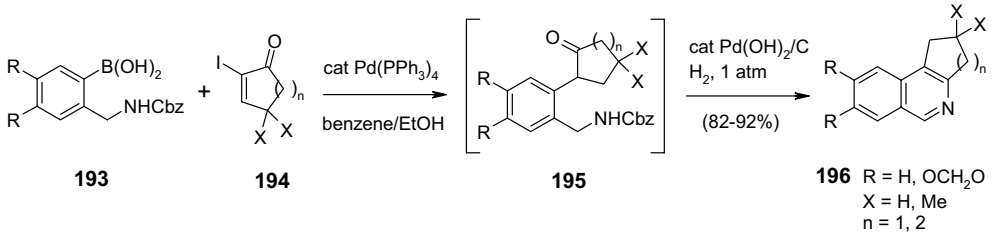
Rhodium(I)-catalyzed tandem *ortho*-alkenylation–cyclization of aromatic *N*-benzylketenimines **188** with alkynes has been applied to the synthesis of mixtures of isoquinolines **189** and **190** [320]. The 1-phenethyl substituted compound **190** is postulated to be formed by the intermolecular migration of the benzyl group in the vinylated ketenimine intermediate **191**. The one-pot tandem process from aromatic ketones **192** was also performed more efficiently (Scheme 17.113). The reaction



Scheme 17.113

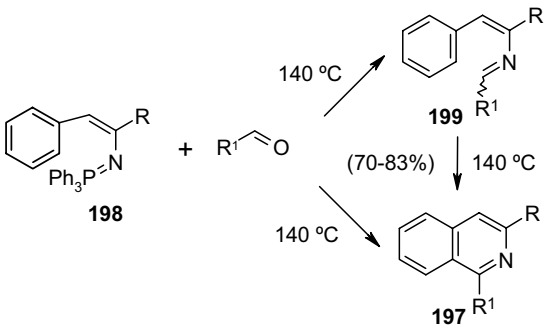
works well when either electron-donating or electron-withdrawing groups are present in the benzene ring.

A Suzuki cross-coupling/reductive debenzyloxycarbonylation sequence has been reported for the synthesis of [*c*]annulated isoquinolines [321]. The reaction of boronic acid **193** with cyclic iodoenones **194** catalyzed by palladium(0) gave intermediates **195** that then cyclized to isoquinolines **196** under reductive conditions (Scheme 17.114). This method has been applied to the synthesis of pancratistatin-like isoquinolines.



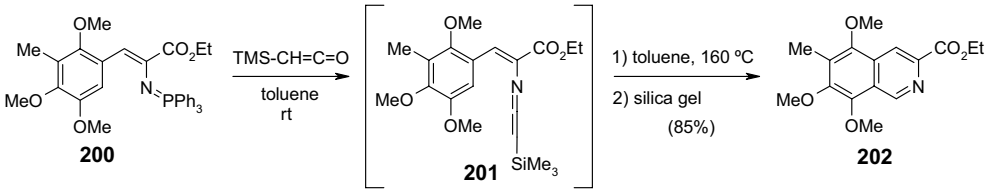
Scheme 17.114

17.2.4.2.5 **Electrocyclic Ring Closing Methods** Hetero-Diels–Alder processes have been widely used to build nitrogen-containing six-membered rings from azadienes. 1,3-Disubstituted isoquinolines **197** can be prepared by electrocyclic ring-closure when aldehydes react with *N*-vinylic phosphazenes **198** through a [4 + 2] cycloaddition [322]. Phosphazenes **198** are obtained by an aza-Wittig [2 + 2] process between phosphoranes and nitriles (Scheme 17.115). The reaction can be performed with isolation of the aza-diene **199** or in a one-pot procedure.



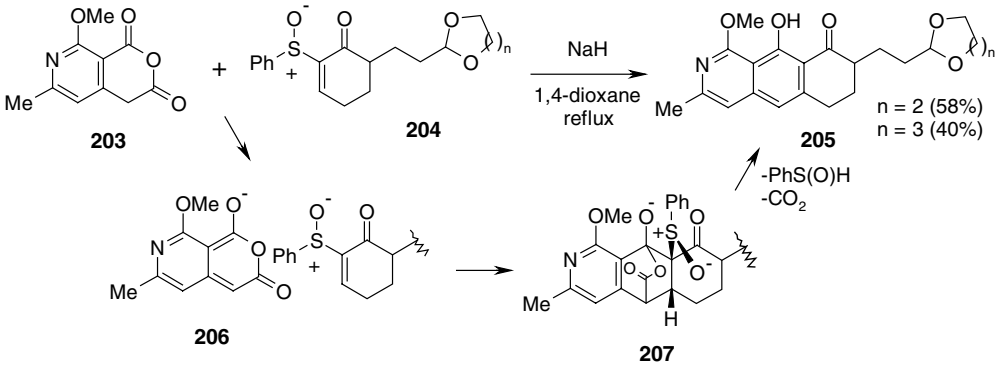
Scheme 17.115

This methodology has been used in the synthesis of a derivative of the marine alkaloid renierol [323]. Thus, phosphacene **200** was reacted with trimethylsilylketene to give the ketenimine **201**, which was then converted into the isoquinoline **202** (Scheme 17.116).



Scheme 17.116

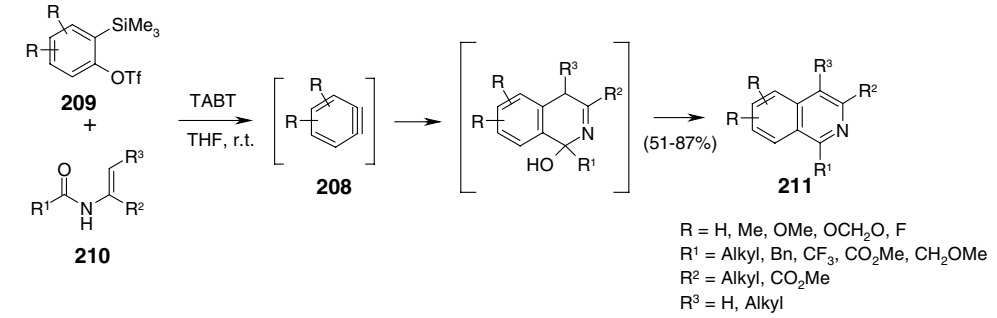
Interestingly, a strong-base-induced [4 + 2] cycloaddition of homophthalic anhydrides, such as **203**, with enolizable enones **204** has been reported to build a key isoquinoline intermediate (**205**) of the antitumor antibiotic fredericamycin A (Scheme 17.117) [324]. Notably, as opposed to the main strategy in the syntheses of isoquinolines, that is, the building of the pyridine ring, in this case it is the benzene ring that is created. The reaction is accelerated in the presence of base to give diene **206**, which cyclizes to the proposed cycloadduct **207** followed by elimination of phenylsulfinic acid and carbon dioxide.

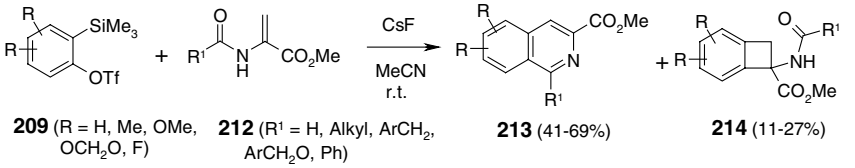


Scheme 17.117

Aryne [4 + 2] cycloaddition reactions have been expanded to the synthesis of isoquinolines. Thus, when aryne **208**, prepared from a silyl aryl triflate (**209**), is reacted with an enamide (**210**), a [4 + 2] addition reaction takes place followed by a dehydrative aromatization to give diversely substituted isoquinolines **211** (Scheme 17.118) [325]. Similarly, the reaction of 2-amidoacrylate esters **212** with silyl aryl triflates **209** using CsF as a fluorine source yields mixtures of isoquinoline-3-carboxylates **213** and benzocyclobutanes **214** (Scheme 17.118) [326].

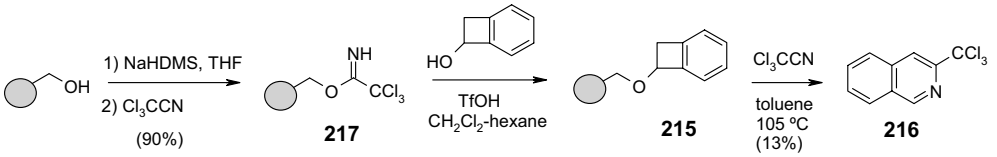
17.2.4.2.6 **Ring Expansion- and Ring Contraction-Based Methods** *o*-Quinodimethanes are highly reactive diene systems in Diels–Alder reactions. In view of this, a traceless solid-phase synthesis based on a benzocyclobutanyl ether resin **215**, a precursor of solid-supported *o*-quinodimethane, has been reported for the hetero-Diels–Alder reaction with trichloroacetonitrile to give isoquinoline **216** in low





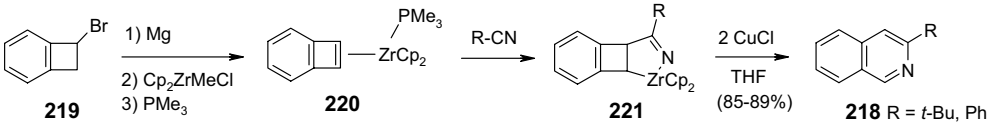
Scheme 17.118

yield [327]. Resin **215** was prepared from a hydroxymethyl resin via the trichloroacetimidate **217** (Scheme 17.119).



Scheme 17.119

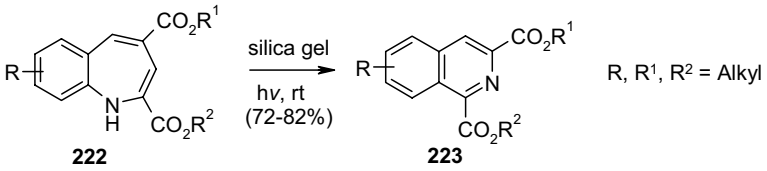
Related to the above method, 3-substituted isoquinolines **218** have been obtained through zirconocene/copper-mediated coupling of benzocyclobutadiene with nitriles (Scheme 17.120) [328]. 1-Bromobenzocyclobutene (**219**) was used as a synthon and was readily converted into $Cp_2Zr(\eta^2$-benzocyclobutadiene)(PMe_3) (**220**), which couples with nitriles to give five-membered-zirconacycles **221**. Subsequent treatment with CuCl gave isoquinolines **218** in high yields.



Scheme 17.120

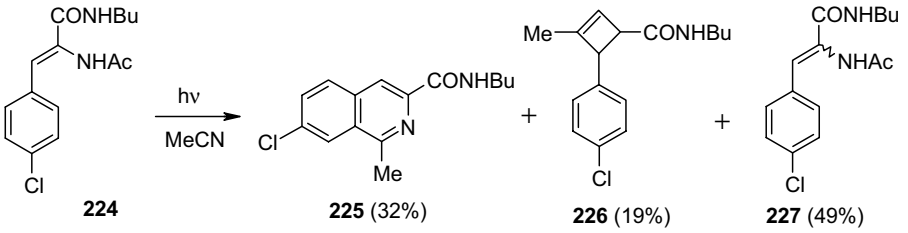
An unprecedented rearrangement of a 1*H*-benzazepine (**222**) to 1,3-disubstituted isoquinolines **223** has been reported to occur in good yields by treatment with silica

gel under normal or UV light, but the mechanism of this process has not been disclosed (Scheme 17.121) [329].



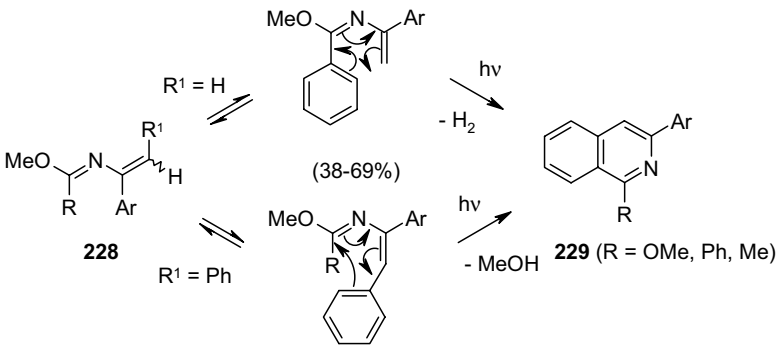
Scheme 17.121

17.2.4.2.7 **Photochemical Methods** Irradiation of substituted α-dehydrophenylalanine **224** in acetonitrile with Pyrex-filtered light has been found to give a mixture of isoquinoline **225**, azetine **226**, and *(E)*- and *(Z)*-**227** in low yields (Scheme 17.122) [330]. Compound **225** was proposed to occur through a 1,5-acetyl migration from *(Z)*-**227**, and **226** by a 1,3-acetyl shift from *(E)*-**227**.



Scheme 17.122

Photocyclization of 2-azadienes **228** in a neutral medium using Pyrex-filtered light has been reported to give 1,3-disubstituted isoquinolines **229** (Scheme 17.123) [331]. When **228** bears a phenyl group at the 4-position this group was involved in the cyclization.

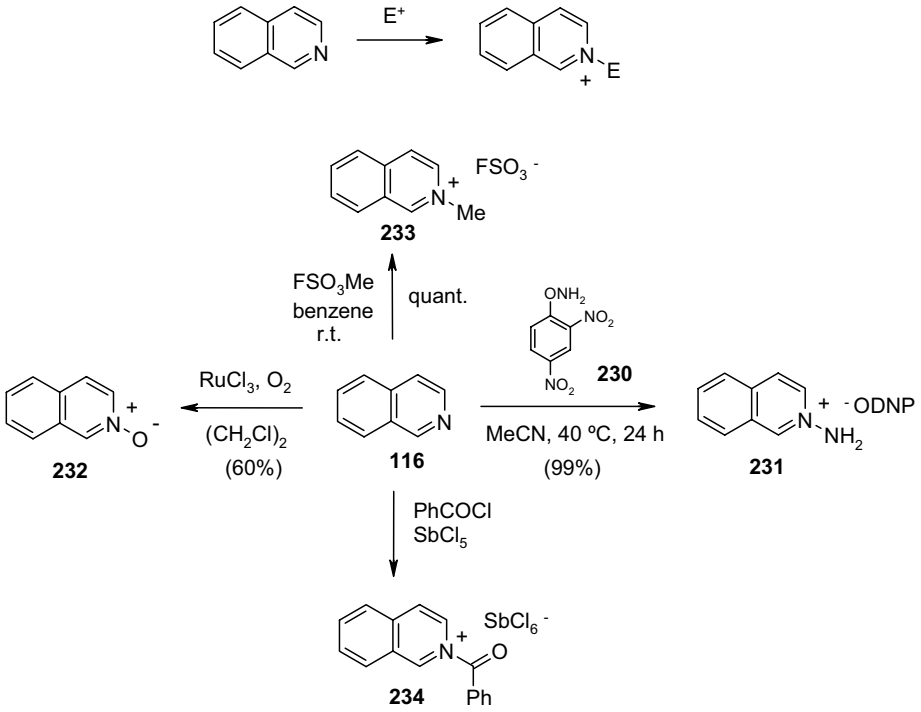


Scheme 17.123

17.2.5 Reactivity of Isoquinolines

17.2.5.1 Reactions with Electrophilic Reagents

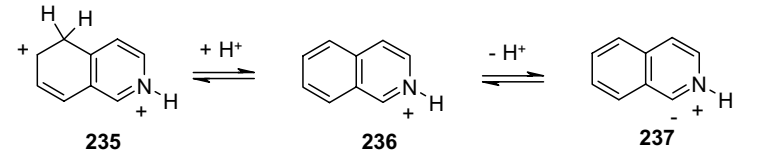
17.2.5.1.1 **Addition to Nitrogen** Like pyridine, isoquinoline reacts as a base ($pK_a = 5.4$) by protonation or as a nucleophile by quaternization through the electron lone pair on the ring nitrogen to form an aromatic isoquinolinium cation (Scheme 17.124). For instance, *O*-(2,4-dinitrophenyl)hydroxylamine (**230**) has proven to be a more efficient aminating reagent than hydroxylamine-*O*-sulfonic acids like HOSA or MSH to give **231** [332]. Nitrogen atom oxidation, as for pyridine, can be performed with peracids to afford isoquinoline-*N*-oxides. Other mild procedures to prepare **232** have been reported and these involve the use of oxygen in the presence of ruthenium trichloride [333], or hydrogen peroxide in the presence of molecular sieves as a catalyst [334]. *N*-Alkylisoquinolinium salts like **233** are obtained using alkyl halides, sulfonates [335], or methyl salicylate [336]. Stable salts of *N*-acylisoquinolinium cations such as **234** can be prepared in the presence of $SbCl_5$ [337]. On the other hand, a large number of transition metal complexes bearing isoquinoline units as ligand have been prepared. Isoquinoline usually links to the metal center through the nitrogen lone pair, except when this is hindered, in which case π-bonded complexes are obtained [338].



Scheme 17.124

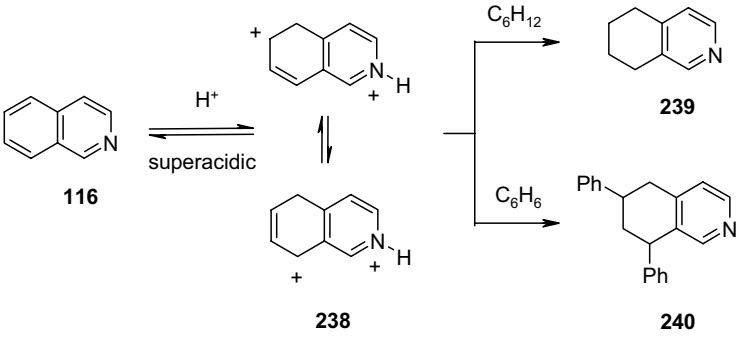
17.2.5.1.2 **Substitution at Carbon**

Protonation N-Protonated isoquinoline gives facile protonation of the carbocyclic ring, as observed in the kinetic study of its reaction with deuteriosulfuric acid at high temperatures [339]. The protonation occurs at positions C5 (**235**) > C8 > C7, but at lower acid strength the isoquinolinium cation **236** exchanges α to the nitrogen at C1 to give the zwitterion **237** (Scheme 17.125).



Scheme 17.125

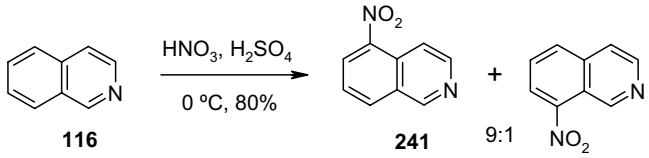
Energies of the LUMO (E_{LUMO}), the square of the coefficients on carbon atoms at the LUMO, NBO charges on CH groups, and total and relative energies of dications have been calculated by the DFT method. The results predict **238** to be the most favorable dication and C6 and C8 to be the electrophilic reaction centers for this dication. Thus, when isoquinoline was activated under superacidic conditions (CF_3SO_3H-SbF_5, HBr-$AlBr_3$-CH_2Br_2, or HBr-$AlBr_3$) and then reacted with cyclohexane or benzene, ionic hydrogenation and electrophilic substitution were observed to give **239** and **240**, respectively (Scheme 17.126) [340].



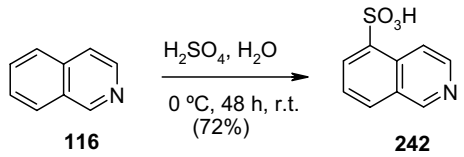
Scheme 17.126

Nitration Nitration of **116** with fuming nitric acid and concentrated sulfuric acid gives 5-nitroisoquinoline (**241**) with high regioselectivity (Scheme 17.127) [341]. Nitration using dinitrogen pentoxide in liquid SO_2 yields **241** regioselectively in low yield [342].

Sulfonation Isoquinoline (**116**) has been sulfonated using 50% oleum under ice-cold conditions to afford isoquinoline-5-sulfonic acid (**242**) (Scheme 17.128) [343].

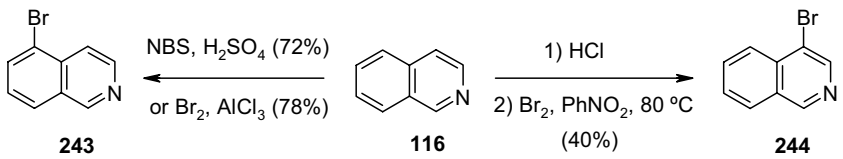


Scheme 17.127



Scheme 17.128

Halogenation Isoquinoline (**116**) has been brominated using bromine in the presence of aluminum chloride [344], or *N*-bromosuccinimide in sulfuric acid, to give **243** (Scheme 17.129) [345, 346]. Halogenation at the pyridine ring to yield **244** occurs at C4 through a different mechanism, which involves the following steps: (i) protonation at nitrogen to give the isoquinolinium cation, (ii) nucleophilic addition of bromide at C1 to yield an enamine; (iii) electrophilic addition of bromine at C4 to produce a β-brominated enamine, and (iv) aromatization through HBr elimination [160].



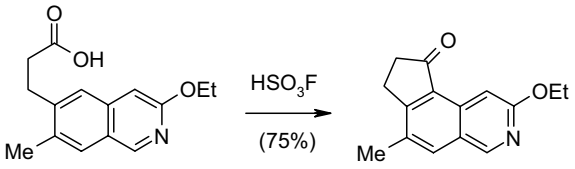
Scheme 17.129

Friedel–Crafts chlorination gives polychloroisoquinolines [347, 348]. Chlorination of 6-aminoisoquinoline with NCS affords 6-amino-5-chloroisoquinoline [349].

Acylation Friedel–Crafts acylation or alkylation reactions on isoquinoline are not possible due to the nucleophilic nitrogen, which rapidly forms the corresponding *N*-acyl or *N*-alkylisoquinolinium salts. However, a few examples of intramolecular Friedel–Crafts acylation have been reported, such as the preparation of cyclopenta[*f*] isoquinoline derivatives **245** (Scheme 17.130) [350] and the synthesis of dinapsoline [351].

17.2.5.2 Reactions with Oxidizing Reagents

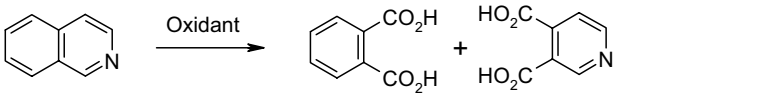
Although isoquinoline is rather stable to oxidative conditions – except for peracids, which cause N-oxidation to give isoquinoline *N*-oxide – both benzene and pyridine



245

Scheme 17.130

rings can be degraded by ozonolysis followed by oxidative cleavage [352], treatment with alkaline potassium permanganate [353], or fuming nitric acid [354] to give a mixture of phthalic acid (**246**) and cinchomeronic acid (**247**) (Scheme 17.131). During the oxidation of **116** in neutral media the benzene ring is not affected and phthalimide is formed [237, 355].



116 **246** **247** ([O] = O_3; 44%) ([O] = HNO_3; 69%)

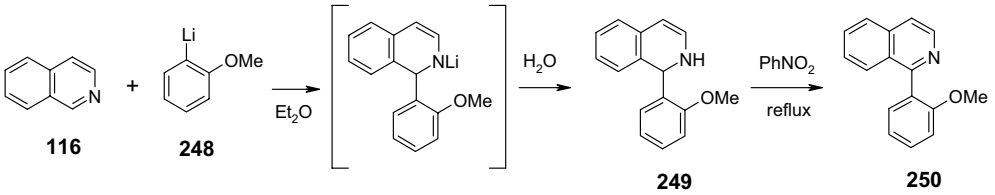
Scheme 17.131

17.2.5.3 Reactions with Nucleophilic Reagents

17.2.5.3.1 **Nucleophilic Substitution with Hydride Transfer** These reactions take place faster at C1.

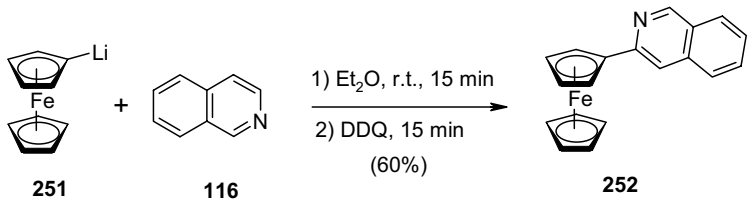
Alkylation and Arylation Isoquinoline selectively undergoes addition of organolithium reagents at C1 to give 1,2-dihydroderivatives [356]. The addition product can be aromatized using an oxidant. Thus, **116** was treated with **248** to give, after quenching with H_2O, 1,2-dihydroisoquinoline **249** which was rearomatized to **250** by oxidation in refluxing nitrobenzene (Scheme 17.132) [253].

Direct C–C coupling of ferrocenyllithium (**251**) with **116** by nucleophilic substitution of hydrogen, using DDQ as an oxidant in the aromatization step, has been performed [357]. Interestingly, coupling was reported to take place at C3 to give 1-(isoquinolin-3-yl)ferrocene (**252**) (Scheme 17.133).



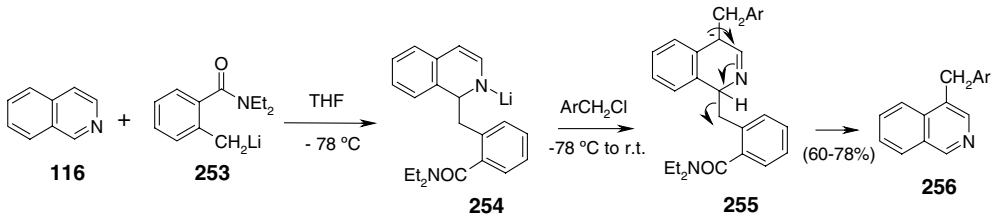
116 **248** **249** **250**

Scheme 17.132



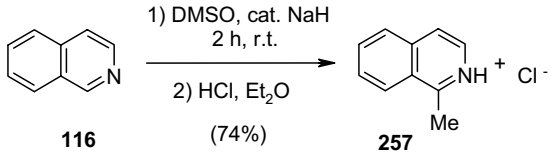
Scheme 17.133

Indirect benzylation at C4 has been carried out by addition of **116** to lithiated *N,N*-diethyl-*o*-toluamide **253** to give the adduct **254**, which was then treated with benzyl chlorides to afford, in the basic reaction conditions, anion **255**. This ion further eliminates anion **253** to give the 4-benzylisoquinolines **256** (Scheme 17.134) [358].



Scheme 17.134

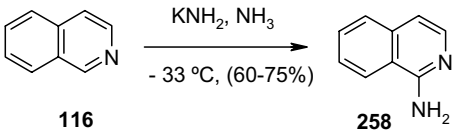
1-Methylisoquinoline, isolated as its hydrochloride **257**, can be easily prepared from **116** with a catalytic amount of sodium hydride in dimethyl sulfoxide and ultrasound activation (Scheme 17.135) [359].



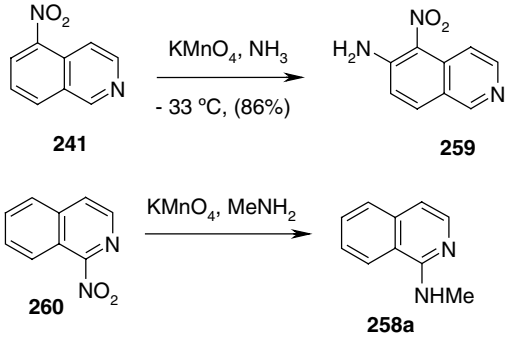
Scheme 17.135

Amination and Nitration Isoquinoline reacts with potassium amide in NH_3 to give, after hydrolysis, 1-aminoisoquinoline (**258**) (Scheme 17.136) [254]. A lower yield was obtained for **258** (20%) when **116** was treated with sodium amide in liquid ammonia under modified Oppenauer oxidation conditions using 9-fluorenone as the hydrogen acceptor [360].

In cases where the isoquinoline ring bears a nitro group, the reaction, in the presence of potassium permanganate, takes a different course. For example, 5-nitroisoquinoline (**241**) was aminated to give the 6-amino derivative **259** (Scheme 17.137) [361]. In contrast, when 1-nitroisoquinoline (**260**) was aminated



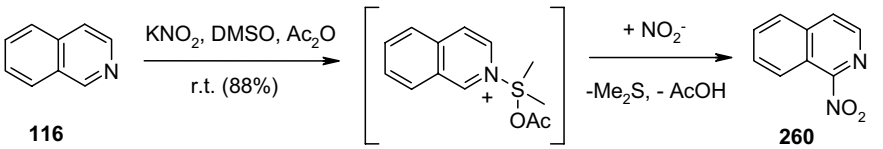
Scheme 17.136



Scheme 17.137

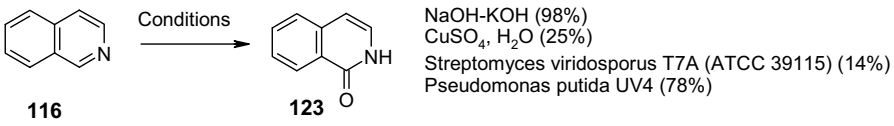
with a liquid methylamine solution of potassium permanganate, displacement of the nitro group occurred to give **258a** (Scheme 17.137) [362].

1-Nitroisoquinoline (**260**) can be easily prepared from **116** using potassium nitrite, dimethyl sulfoxide, and acetic anhydride [363]. In this case, attack of the nucleophile takes place on an intermediate isoquinolinium cation (Scheme 17.138).



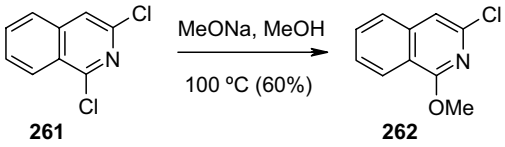
Scheme 17.138

Hydroxylation Hydroxylation of **116** to give **123** can be performed directly at high temperature by potassium hydroxide [170], or cupric sulfate [364], or at room temperature by biotransformations (Scheme 17.139) [365, 366].



Scheme 17.139

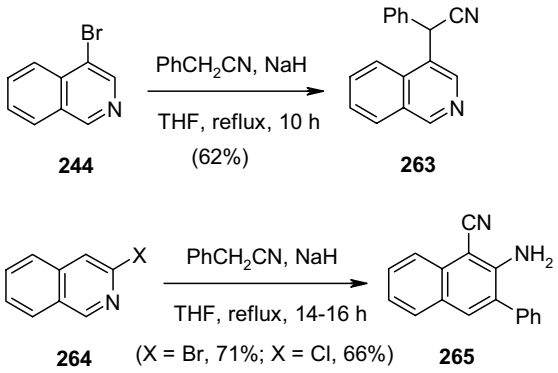
17.2.5.3.2 **Nucleophilic Substitution with Displacement of Halide** Halogens on the pyridine ring are only prone to nucleophilic displacement when the halogen atom is located at C1 or C3, with the halogen at C1 being far more reactive. Halogens on the benzene ring are inert and behave in the same way as halobenzenes. Thus, 1,3-dichloroisoquinoline (**261**) reacts with sodium methoxide to give the monosubstitution product **262** (Scheme 17.140) [367]. Several nucleophiles can displace the halogen atom. For example, reactions on 1-chloro or 1-bromo-substituted isoquinolines with water [368], sodium hydroxide [368], alkoxides [369–371], thioalkoxides [372], trimethylsilanolate [373], ammonia [374], amides [375], amines [376], potassium cyanide [377], and phosphorus ylides [378] have been reported.



261 **262**

Scheme 17.140

Phenylacetonitrile, unlike other active methylene compounds, reacts with 4-bromoisoquinoline (**244**) by halogen displacement, in the presence of sodium hydride, to afford **263**, whereas 3-haloisoquinolines **264** react at C1 to give naphthalene derivative **265** (Scheme 17.141) [379].

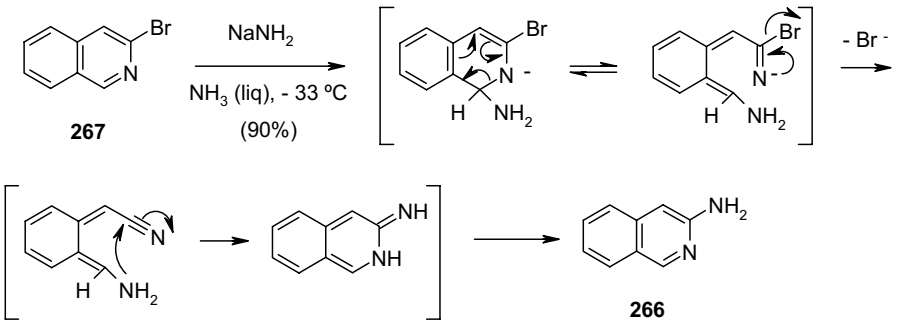


244 **263**

264 **265**

Scheme 17.141

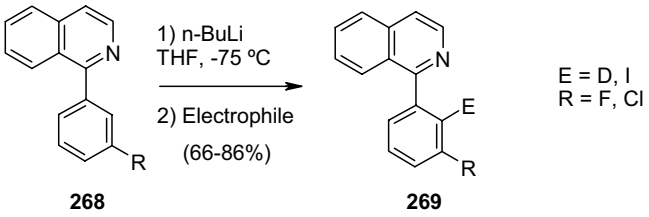
Although 3-haloisoquinolines react slowly, their reactions with sodium amide are unusual and do not follow S_NA but, rather, an ANRORC (addition of nucleophile, ring opening and ring closure) mechanism [380]. By means of this mechanism, the endocyclic nitrogen in the reaction product **266** comes from the nucleophile and the exocyclic nitrogen comes from the starting isoquinoline **267** (Scheme 17.142).



Scheme 17.142

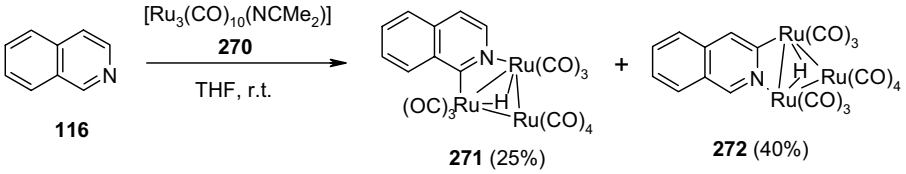
17.2.5.4 Reactions with Bases

17.2.5.4.1 **Direct Metallation** Isoquinoline cannot be directly lithiated with organolithium reagents since they are strong nucleophiles. Interestingly, 1-(halophenyl) isoquinolines **268** are lithiated by *n*-butyllithium, in the position *ortho* to the halogen, under kinetic control, to give **269** without nucleophilic addition on the isoquinoline ring (Scheme 17.143) [381].



Scheme 17.143

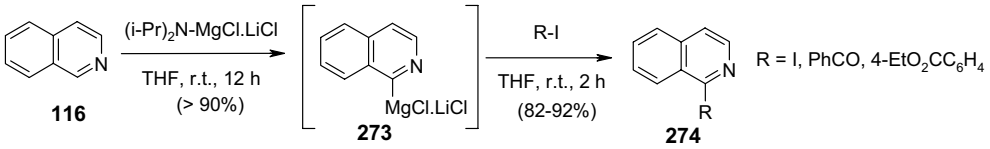
Direct metallation with a less active metal has also been carried out by reaction of the complex $[Ru_3(CO)_{10}(NCMe)_2]$ (**270**) with **116** in tetrahydrofurane. In this way the isomeric *ortho*-metalated complexes $[HRu_3(CO)_{10}(C_9H_6N)]$ **271** and **271** have been prepared (Scheme 17.144) [382].



Scheme 17.144

Isoquinoline magnesium derivatives **273** have been prepared with high regioselectivity using mixed Mg/Li amides of the type $R_2NMgCl{\cdot}LiCl$ as bases

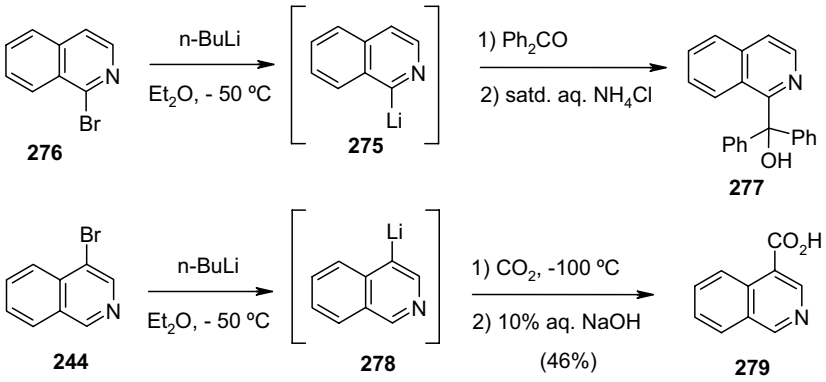
(Scheme 17.145) [383]. Subsequent reactions with electrophiles such as iodine, benzoyl chloride, or iodobenzenes give 1-substituted isoquinolines **274**.



Scheme 17.145

17.2.5.5 Reactions of C-Metallated Isoquinolines

17.2.5.5.1 **Lithium Derivatives** Metal–halogen exchange at low temperature is the method of choice to prepare lithioisoquinolines while avoiding competing nucleophilic addition. Thus, 1-isoquinolyllithium (**275**), prepared from 1-bromoisoquinoline (**276**), was reacted with benzophenone to give alcohol **277**. Furthermore, 4-isoquinolyllithium (**278**), obtained from **244**, reacted with dry ice to give 4-isoquinaldic acid (**279**) (Scheme 17.146) [384]. These types of metallation at C1 [385] and C4 [386, 387] have recently been used as intermediate steps in the preparation of bovine amine oxidase and B-Raf kinase inhibitors [388, 389].

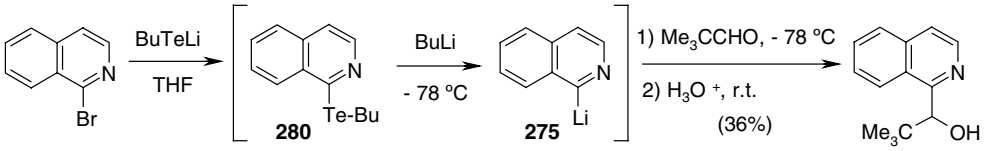


Scheme 17.146

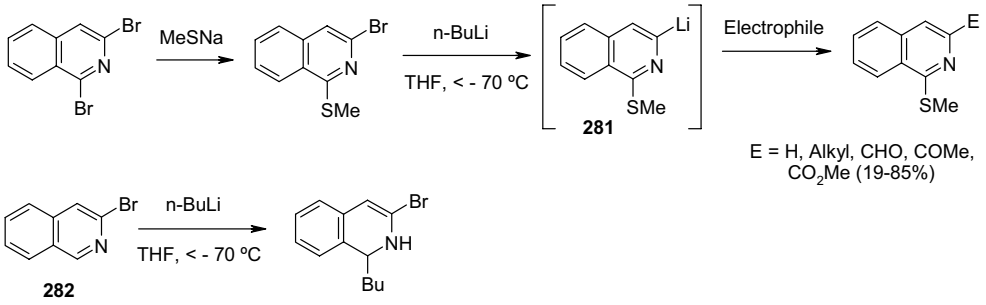
On the other hand, the tellurium–lithium exchange reaction on 1-isoquinolyl telluride **280** has proven useful in the preparation of 1-isoquinolyllithium (**275**) (Scheme 17.147) [390].

Only one example of an isoquinoline derivative lithiated at C3 (**281**) has been reported [391]. C1 must be substituted, otherwise nucleophilic addition takes place as in 3-bromoisoquinoline (**282**) (Scheme 17.148).

17.2.5.5.2 **Zinc Derivatives** 1-Isoquinolylzinc salt **283** has been efficiently prepared by direct insertion of zinc into **284**, a process that is mediated by the addition of

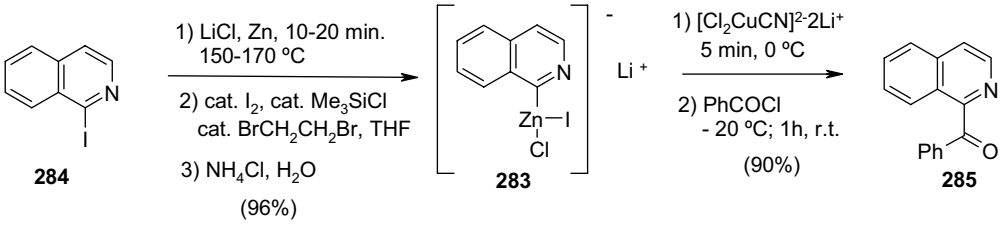


Scheme 17.147



Scheme 17.148

lithium chloride [392]. Subsequent reaction with benzoyl chloride in the presence of Cu(II) yields **285** (Scheme 17.149).

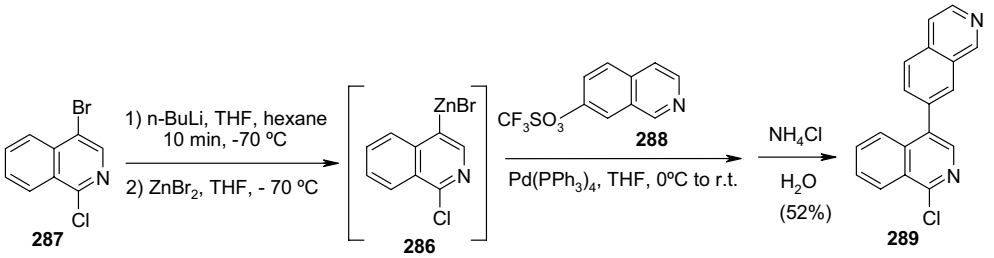


Scheme 17.149

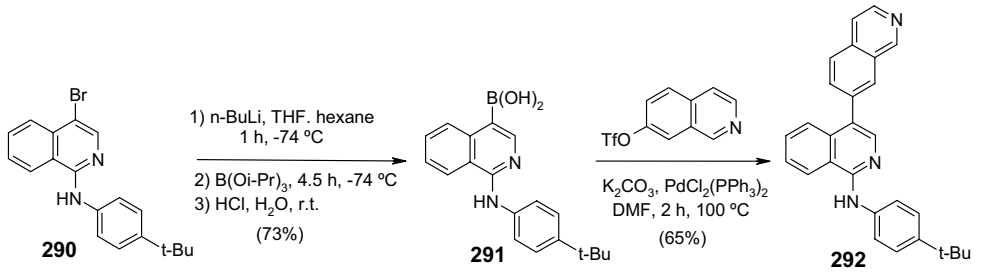
4-Isoquinolylzinc bromide **286**, prepared *in situ* from dihaloisoquinoline **287**, provides the substrate for a palladium-catalyzed Negishi coupling step with 7-isoquinolyl triflate **288** to give the key intermediate **289** in the synthesis of B-kinase inhibitors (Scheme 17.150) [389].

17.2.5.5.3 **Boron Derivatives** 1-Isoquinolyl and 4-isoquinolyl boronic acid derivatives have been prepared from the corresponding halides. Thus, 4-isoquinolylboronic acid derivative **291** was obtained from 4-bromoisoquinoline derivative **290** and reacted under Suzuki conditions to give the kinase inhibitor **292** (Scheme 17.151) [389, 393].

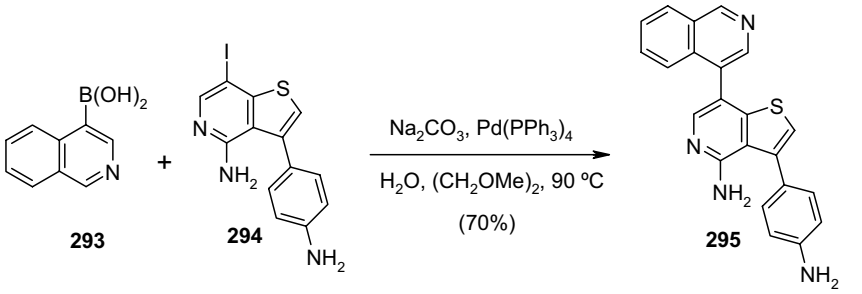
4-Isoquinolylboronic acid (**293**) is also a nucleophilic substrate in palladium-catalyzed Suzuki–Miyaura reactions [394–396]. Reaction of **293** with iodo derivative **294** gives the KDR kinase inhibitor **295** (Scheme 17.152).



Scheme 17.150



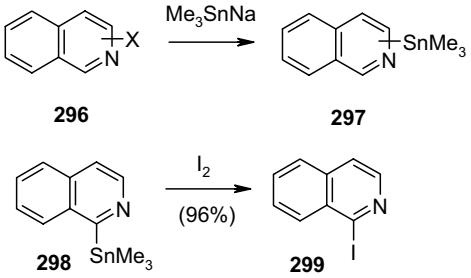
Scheme 17.151



Scheme 17.152

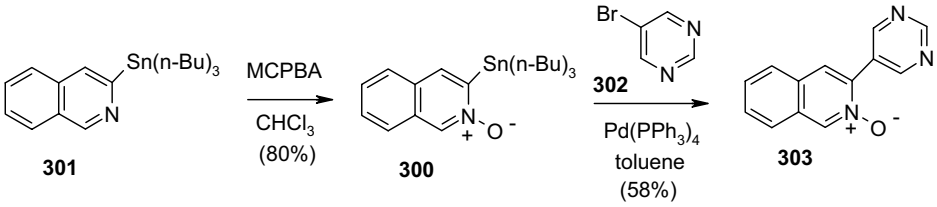
17.2.5.5.4 **Tin Derivatives** Trialkylstannylisoquinoline derivatives at the C1, C3, and C4 positions have been prepared and reacted with electrophiles in both non-catalyzed and palladium-catalyzed processes. The reaction of chloro- or bromoisoquinolines **296** with trimethylstannylsodium – generated *in situ* from chlorotrimethylstannane and sodium – provides stannylisoquinolines **297**. Acylation, alkoxycarbonylation, and iodination reactions were subsequently performed on **297** [397–399]. For example, 1-trimethylstannylisoquinoline (**298**) reacts with iodine to give **299** (Scheme 17.153).

The palladium-catalyzed Stille reaction has been carried out on both 3-stannylisoquinoline *N*-oxide **300** [400] and 4-stannylisoquinoline [401]. N-Oxide **300** was



Scheme 17.153

prepared from 3-tri-*n*-butylstannylisoquinoline (**301**) and *m*-chloroperbenzoic acid (MCPBA). The Stille reaction of **300** with 5-bromopyrimidine (**302**) yields **303** (Scheme 17.154).

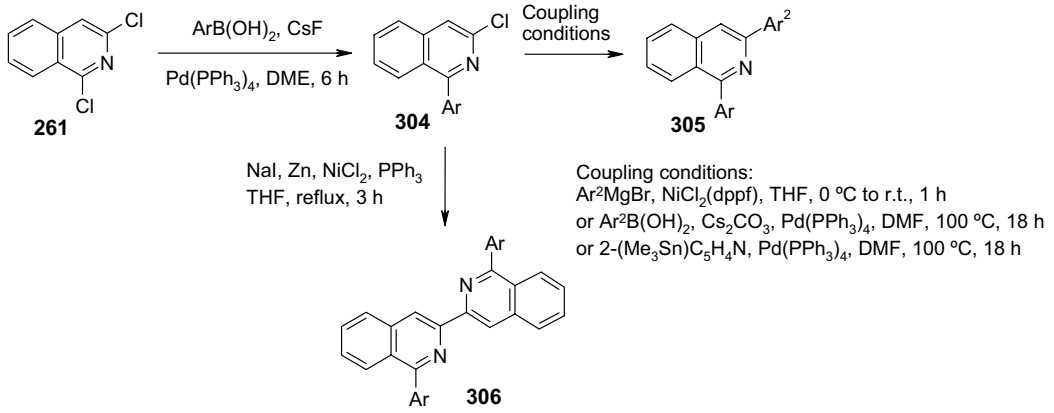


Scheme 17.154

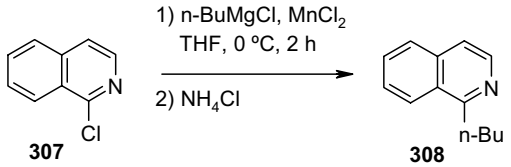
17.2.5.5.5 **Palladium-, Nickel-, and Manganese-Catalyzed Reactions** Numerous metal-catalyzed reactions on haloisoquinolines have been reported. Both Suzuki–Miyaura and Stille reactions provide high yields of coupling products on diversely substituted boronic acids [402–404] and stannanes [375, 404, 405]. Nickel-catalyzed processes using both Grignard reagents [404, 406, 407] or lithium borides [404] have been performed and also lead to interesting homocoupling products [408, 409]. Based on the differential reactivity of the carbon–chlorine bonds in **261**, several carbon–carbon bond forming cross-coupling reactions have been exploited (Scheme 17.155) [404]. Under palladium catalysis, arylboronic acids regioselectively couple at C1 to give 1-aryl-3-chloroisoquinoline derivatives **304**. Further coupling with aryl boronic acids, 2-trimethylstannylpyridine (palladium catalyzed) or arylmagnesium bromides (nickel-catalyzed) gives 1,3-diarylisoquinolines **305**. Furthermore, **304** furnishes 3,3′-bis-isoquinolines **306** under nickel-catalyzed zinc-based Colon reaction conditions.

Recently, a manganese-catalyzed cross-coupling reaction of heterocyclic chlorides with aryl- and alkylmagnesium halides has been developed [410]. Thus, 1-chloroisoquinoline (**307**) yields 1-*n*-butylisoquinoline (**308**) under these conditions (Scheme 17.156).

Heck and Sonogashira couplings have also been performed on haloisoquinolines. 4-Bromoisoquinoline (**244**) couples to 1,5-hexadiene under solid-phase conditions to

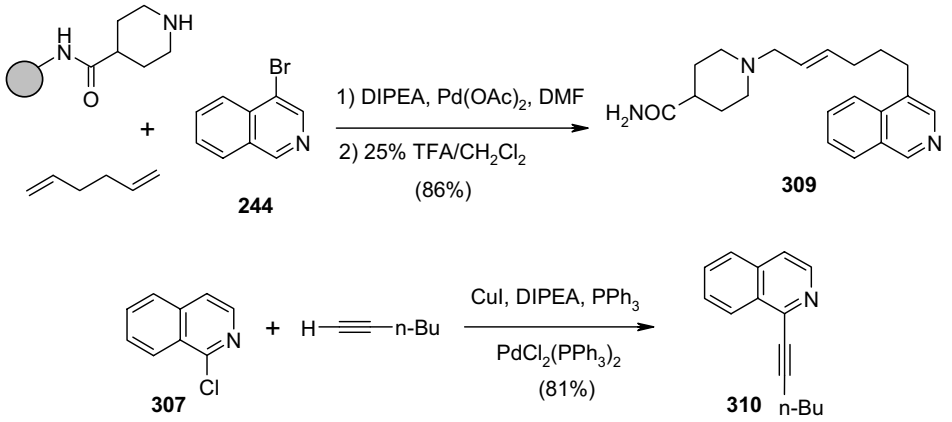


Scheme 17.155



Scheme 17.156

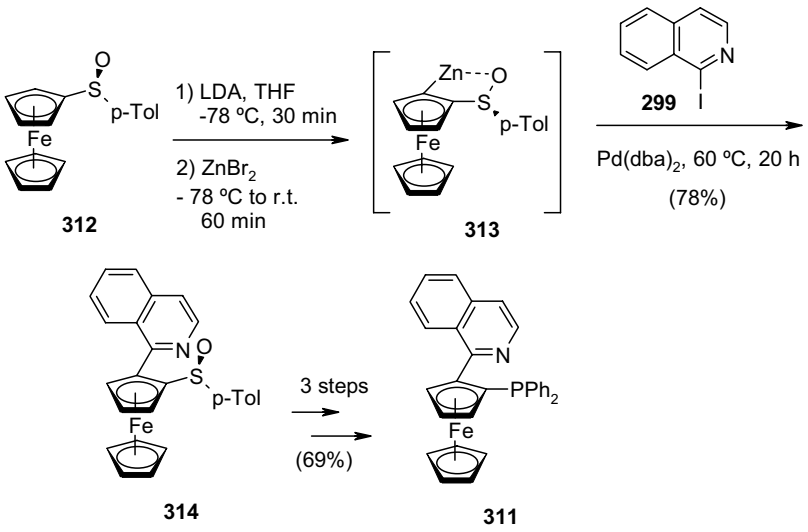
give **309** as result of a three-component process (Scheme 17.157) [411]. 1-Chloroisoquinoline (**307**) couples to 1-hexyne to yield **310** (Scheme 17.157) [412].



Scheme 17.157

Negishi couplings have been performed in the synthesis of ferrocenyl-QUINAP (**311**), a planar P,N-ligand for palladium-catalyzed allylic substitution reactions. Directed *ortho*-lithiation of chiral ferrocenyl sulfoxide **312** with LDA and subsequent

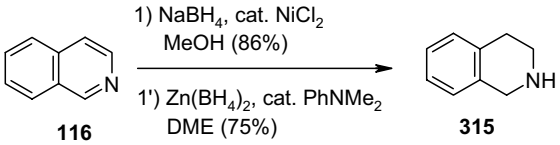
addition of zinc(II) bromide yields organozinc **313**, which is treated with 1-iodoisoquinoline (**299**) under Negishi conditions to give chiral complex **314**. This compound was then converted into **311** in three steps (Scheme 17.158) [413].



Scheme 17.158

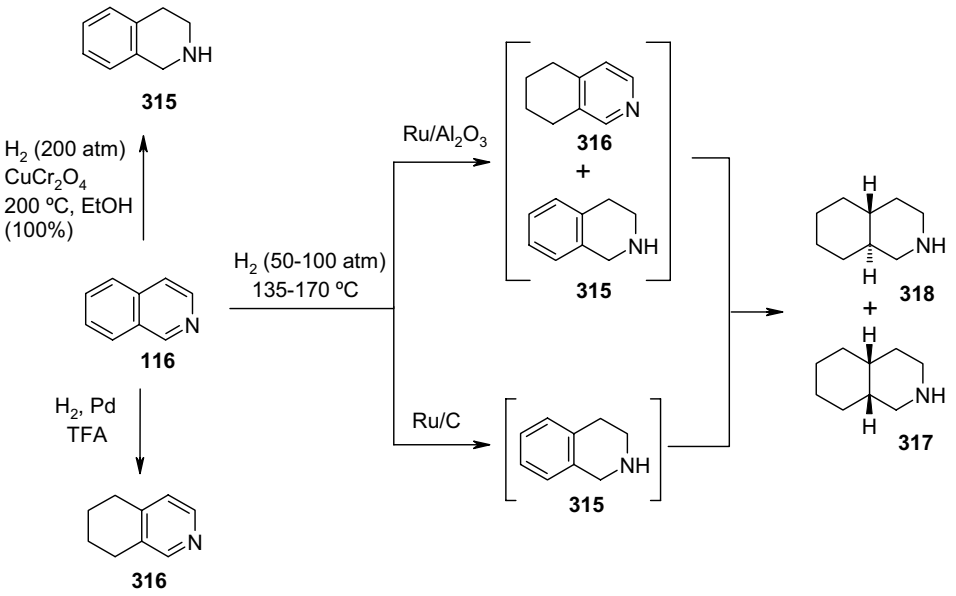
17.2.5.6 **Reactions with Reducing Reagents**

Selective reduction of the pyridine ring in **116** to the tetrahydroisoquinoline **315** can be achieved with sodium cyanoborohydride in acid solution [414], sodium borohydride in the presence of nickel(II) chloride [415], or zinc borohydride (Scheme 17.159) [187]. The dihydride ruthenium complex $RuH_2(PPh_3)_2$ yields **315** with low conversion [416], while hydrosilylation of **116** catalyzed by $[Rh(cod)(PPh_3)_2]PF_6$ afford **315** in high yield [417].



Scheme 17.159

Catalytic hydrogenation reduces the pyridine ring in **116** to give **315** when performed on cupric chromite [418], Raney nickel [419], platinum oxide [420], platinum [421], rhodium [422], or palladium [423]. The benzene ring can be hydrogenated in trifluoroacetic acid solution to provide **316** (Scheme 17.160) [424]. This product can also be obtained by ionic hydrogenation with cyclohexane through superacidic activation, as mentioned in Section 7.2.5.1.2) (Protonation) [340].



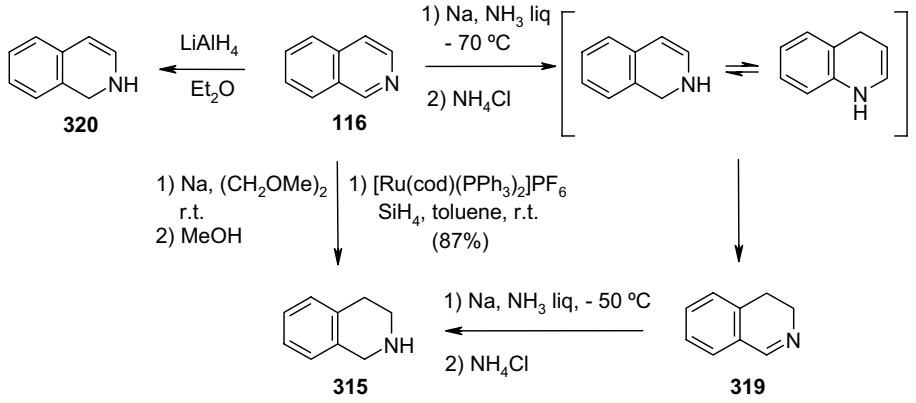
Scheme 17.160

Full hydrogenation using ruthenium leads to *cis*- and *trans*-decahydroisoquinolines **317** and **318**. When the catalyst is supported on carbon the hydrogenation proceeds via **315**. If ruthenium is supported on alumina there is competition between the two tetrahydro intermediates **315** and **316** [425]. The metal hydride complex $Mo(PMe_3)H_4$ can also be used to perform the catalytic hydrogenation of **116** to **315** [426].

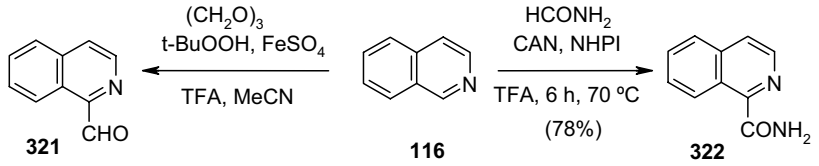
Dihydroisoquinolines can be produced using either sodium in liquid ammonia (3,4-dihydro, **319**) [427] or lithium aluminum hydride (1,2-dihydro, **320**) [427–429]. The dihydroisoquinolines can be oxidized back to **116** with chloranil or disproportionate in acid solution to give a mixture of 1,2,3,4-tetrahydroisoquinoline (**315**) and **116**. Tetrahydroisoquinoline **315** can be obtained directly from **116** by reduction with sodium in a non-protic solvent or from **319** using sodium in liquid ammonia (Scheme 17.161).

17.2.5.7 Reactions with Radical Reagents

The replacement of hydrogen at C1 through homolytic processes is also possible in **116**, with the Minisci reaction being by far the most important approach [430]. Since **116** is a π-deficient heterocycle, nucleophilic free radicals such as hydroxymethyl, alkyl, and acyl give better results. Moreover, acidic conditions are essential to promote N-protonation because this makes C1 more reactive towards the nucleophilic radical [431]. Formylation [432] and carbamoylation [433] reactions have been performed on **116** to give **321** and **322**, respectively, in a selective manner (Scheme 17.162). *tert*-Butyl peroxide, hydrogen peroxide, or *N*-hydroxyphthalimide were used as free radical promoters. Acetylation gives mixtures of acetylated and methylated products [434].

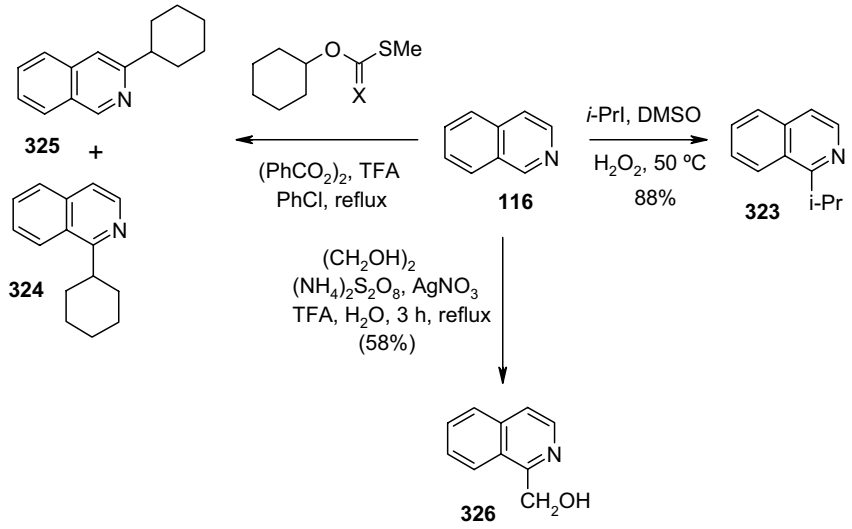


Scheme 17.161



Scheme 17.162

Alkylation of **116** has been carried out with alkyl iodides [435, 436] or alkyl xanthates to give **323** selectively or a mixture of **324** and **325** (Scheme 17.163) [437].



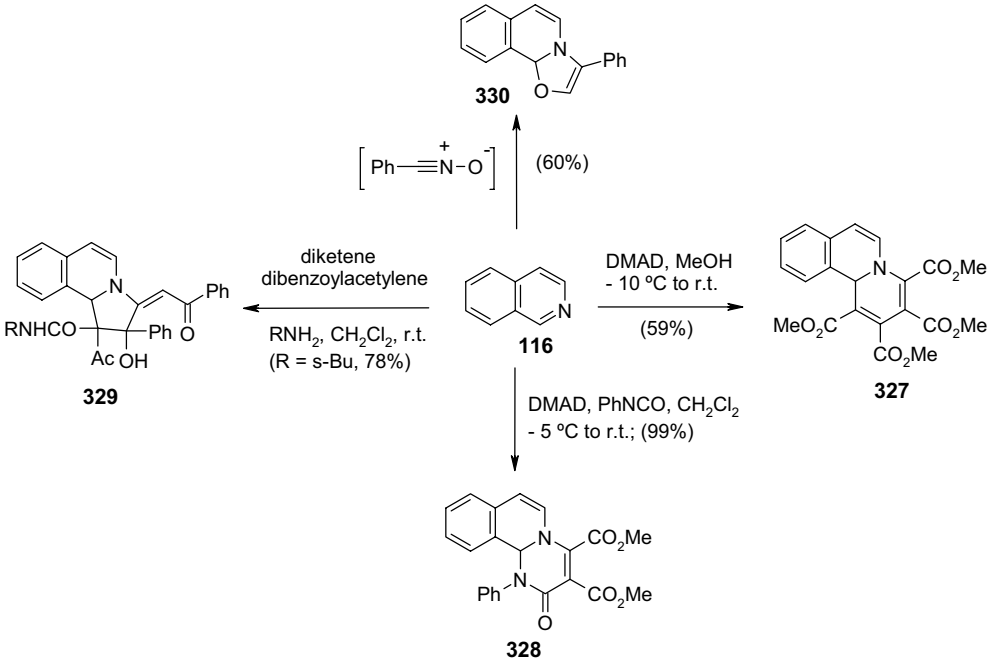
Scheme 17.163

Hydroxymethylation carried out by persulfate oxidation of ethylene glycol can be performed regioselectively to give **326** [438].

17.2.5.8 Electrocyclic and Photochemical Reactions

The greater tendency of isoquinolinium salts towards nucleophilic addition at C1 in comparison to isoquinoline is demonstrated by the number of cycloaddition reactions reported to date. Isoquinoline itself does not undergo cycloaddition processes and this reaction always occurs through an isoquinolinium intermediate. Nevertheless, a theoretical G3(MP2) study regarding the concerted cycloaddition reaction between ethylene and **116** has been published and concluded that 1,4-cycloaddition is the most favorable in terms of both transition state energy barrier and NBO atom charges [439].

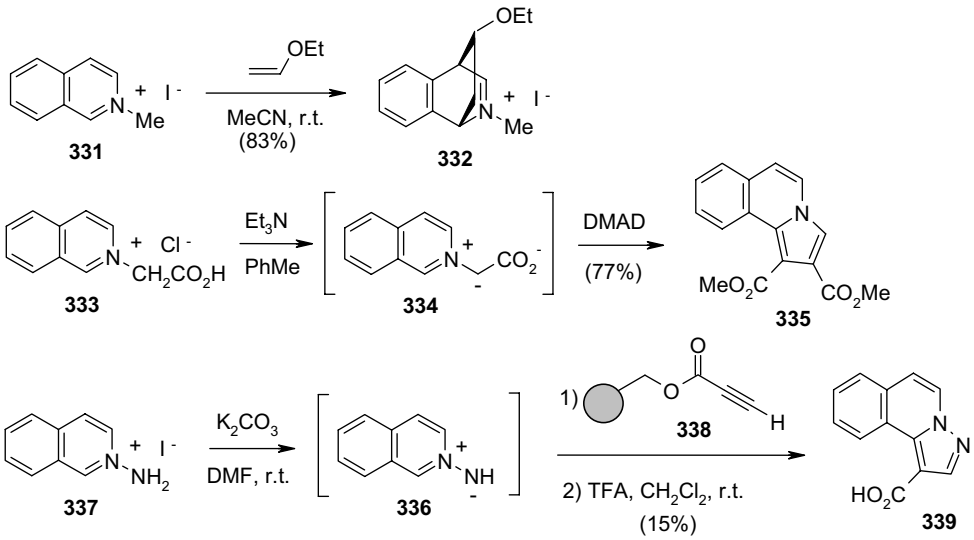
Isoquinoline reacts with dimethyl acetylenedicarboxylate to give quinolizine-tetracarboxylate **327** [440]. When isocyanate is present in the reaction mixture, pyrimidoisoquinoline **328** is obtained [441]. A four-component reaction with dibenzoylacetylene, diketene, and amines to give pyrroloisoquinolines **329** [442], or water to give 1,2-dihydroisoquinolines [443], has been reported. Isoquinoline also gives the cycloadduct **330** with benzonitrile oxide (Scheme 17.164) [444].



Scheme 17.164

Stable isoquinolinium salts and ylides give cycloadditions with several dienophiles. Thus, both *N*-alkyl- [445] and *N*-arylisoquinolinium [446] salts react with electron-rich

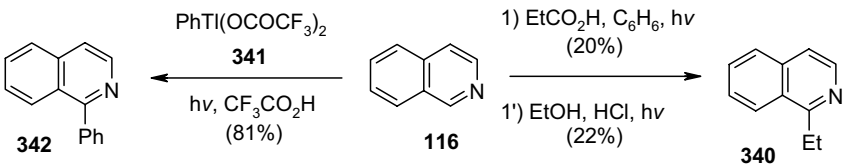
dienophiles such as vinyl sulfides or ethers through the Bradsher cycloaddition reaction. *N*-Methylisoquinolinium iodide (**331**) and ethyl vinyl ether give adduct **332** (Scheme 17.165). Isoquinolinium methylides bearing one or two electron-



Scheme 17.165

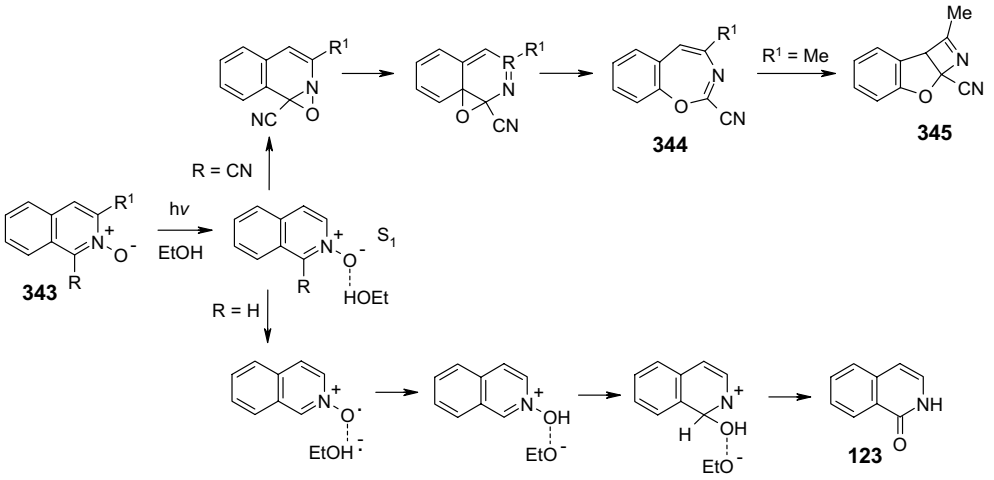
withdrawing substituents at the ylide undergo cycloadditions with aryl- and alkyl-substituted electron-rich olefins [447] or dimethyl acetylenedicarboxylate [448, 449]. This reaction has been exploited in the synthesis of pyrrolo-isoquinolines related to the lamellarins [450]. The reaction of the salt **333** with DMAD in the presence of triethylamine occurs via methylide **334** to yield pyrroloisoquinoline **335**. Quaternary isoquinolinium ylides such as isoquinoline azomethine imine **336**, generated *in situ* from 2-aminoisoquinolinium iodide (**337**), react with polymer-bound alkyne **338** to give pyrazoloisoquinolines **339** after cleavage from the resin [451].

There is very little literature concerning photochemical reactions for isoquinolines when compared with electrocyclic methods. Photochemical free-radical alkylation [452, 453] and phenylation [454] reactions have been reported on **116**. Ethanol or propanoic acid can act as the source of ethyl radicals under light irradiation to give **340**. Phenylthallium bis-trifluoroacetate (**341**) allows selective substitution at C1 under acidic conditions to afford **342** (Scheme 17.166).



Scheme 17.166

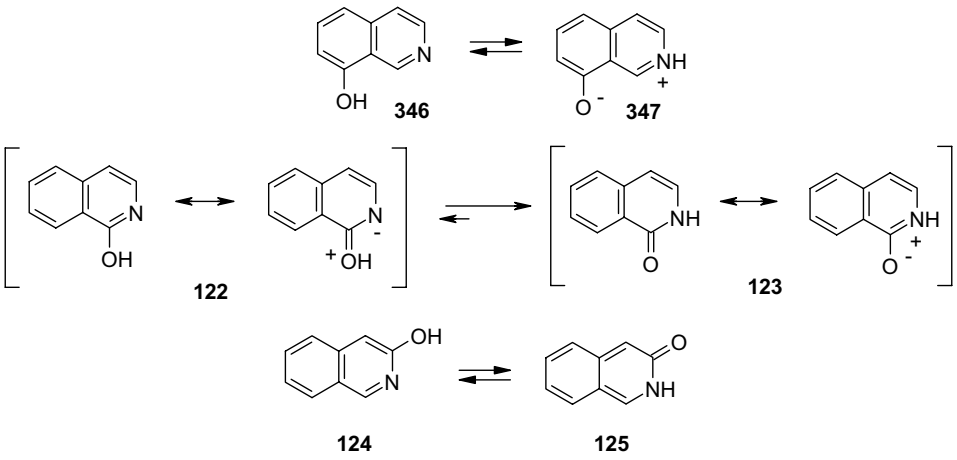
Photolysis of isoquinoline *N*-oxides leads to different products depending upon the reaction conditions and the substitution pattern on the heterocycle. Irradiation of **343** (R, $R^1 = H$) furnished isoquinolone (**123**) via the S_1 state through a radical–ion-pair mechanism, as concluded from magnetic-field effect experiments [455]. However, irradiation of the 1-cyano derivative **343** ($R = CN$; $R^1 = H$) affords 1,3-oxazepine **344** ($R^1 = H$), via the S_1 state, through oxaziridine intermediates (Scheme 17.167) [455, 456]. 1-Cyanoisoquinoline *N*-oxides substituted at C3 can give two consecutive photochemical reactions, resulting first in oxazepine **344** ($R^1 = Me$) and then in benzofuroazete **345** (Scheme 17.167) [457].



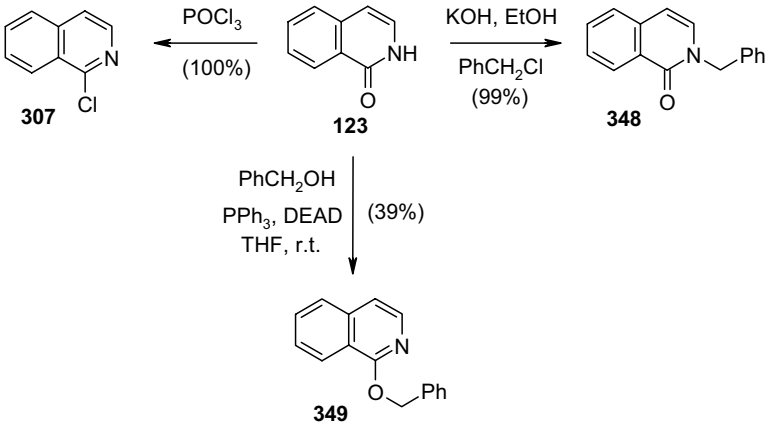
Scheme 17.167

17.2.5.9 **Isoquinoline Derivatives**

17.2.5.9.1 **Oxyisoquinolines** The main feature of hydroxy-substituted isoquinolines is the tautomerism shown by some members of this family. With the exception of 1-hydroxy- and 3-hydroxy-substituted isoquinolines, the others are true phenols; they are in equilibrium with their zwitterions such as, for instance, **346** and **347**, and they behave as naphthols [458–461]. In contrast, isoquinolin-1-ol (**122**) completely tautomerizes to **123** (1-isoquinolone, 2*H*-isoquinolin-1-one) since the hydroxyl tautomer **122** lacks a stable polarized resonance contribution, in contrast to **123** [462]. Isoquinolin-3-ol (**124**) remains in an intermediate situation since **125** (3-isoquinolone, 2*H*-isoquinolin-3-one) is of comparable stability. The less polar tautomer **124** (colorless) predominates in low polarity solvents such as diethyl ether, whereas the more polar **125** (yellow) dominates in water or ethanol [463, 464]. The similar stability of these two systems is due to two opposite factors. In **124** the stability relies on the complete benzene ring, whereas in **125** the amide unit is the major contributor to stability.

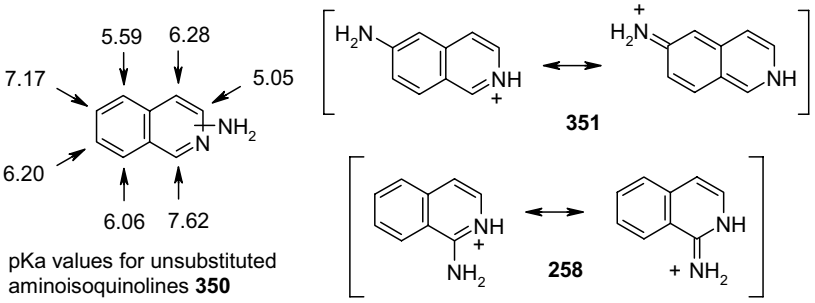


Classical reactions of isoquinolin-1-ones are N- and O-alkylation. Deprotonation of **123** with base and reaction of the resulting bidentate anion with alkyl halides or tosylates are reported to result in alkylation exclusively at nitrogen to give products like **348** (Scheme 17.168) [465], although traces of the corresponding O-alkylated products are also obtained [466]. Harder electrophiles, such as triflic anhydride and silylating agents, react at the exocyclic oxygen, although the nucleophile may be the neutral molecule in these cases [467, 468]. These O-substituted products have also been prepared by displacement of halides from 1-halo-substituted isoquinolines by alkoxides, but harsh conditions are necessary for this to occur. Regioselective O-alkylation to give **349** can be achieved using the Mitsunobu reaction with benzylic electrophiles under mild conditions (Scheme 17.168) [469]. A classical reaction of isoquinolones is their conversion into haloisoquinolines with phosphorus halides. For example, **123** reacts with phosphoryl chloride to give **307** (Scheme 17.168) [470].



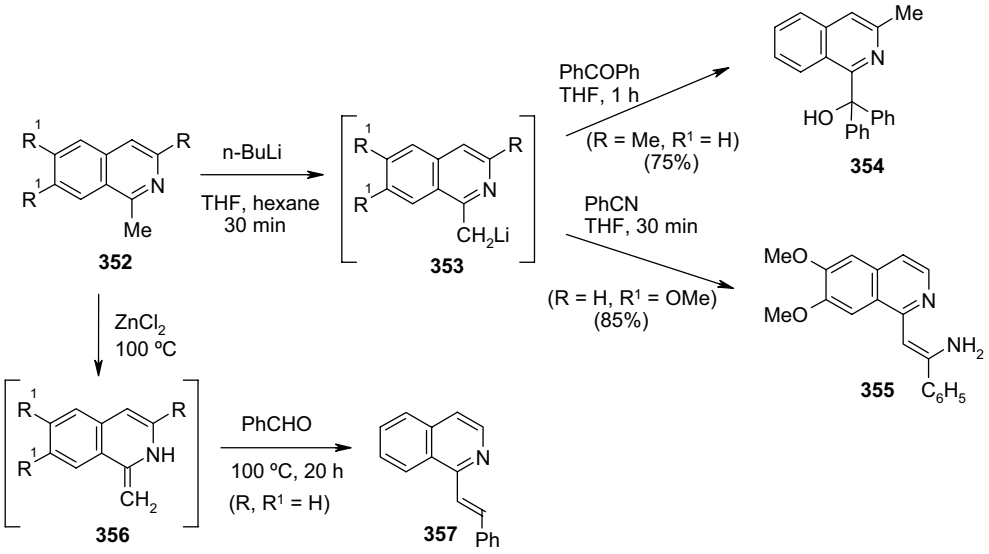
Scheme 17.168

17.2.5.9.2 **Aminoisoquinolines** The whole family of aminoisoquinolines, in contrast to hydroxyisoquinolines, exists only as amino tautomers and all are protonated on the ring nitrogen. Dissociation constants for aminoisoquinolines **350** have been determined by potentiometric titration [471] or spectrophotometry [472]. The most basic aminoisoquinoline bearing the amino group on the benzene ring is the 6-isomer **351**; the high basicity is due to its most stable resonance contribution, that is, a *para*-quinoid structure. When the amino group is located on the pyridine ring, the most basic isomer is 1-aminoisoquinoline (**258**) since this is the only system that retains the aromaticity of the benzene ring in its most stable resonance contribution. The basicity of aminoisoquinoline derivatives has been studied and it was found that the steric effects of bulky substituents neighboring the protonated ring nitrogen atom influence electron transfer in such arrangements [473].

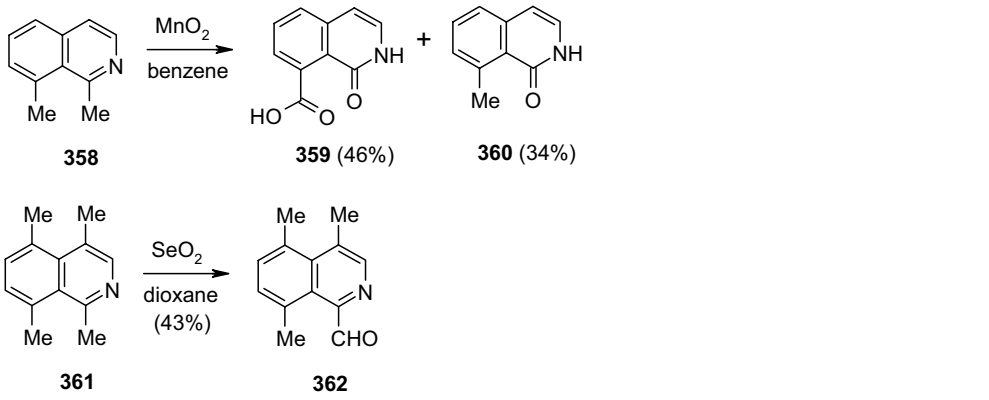


17.2.5.9.3 **Alkylisoquinolines** Heterobenzylic hydrogen atoms of the side chain in the 1-position of isoquinoline are acidic. These protons may be abstracted with strong bases such as *n*-butyllithium, lithium diisopropylamide, or sodium amide to give metalated intermediates that can condense with various electrophiles. Heterobenzylic hydrogens at the 3-position are much less acidic and thus regioselective deprotonation in 1,3-dialkylisoquinolines is possible [264, 474]. Condensation products can also be prepared in acidic media, where the nucleophilic species is an enamine and the acidity of the heterobenzylic hydrogens is enhanced by the prior formation of an isoquinolinium cation [475]. Treatment of 1,3-dialkylisoquinoline **352** ($R = Me$, $R^1 = H$) with *n*-butyllithium regioselectively gives the 1-isoquinolylmethyllithium derivative **353** ($R = Me$, $R^1 = H$). Heterobenzyllithiums derivatives **353** react with benzophenone or benzenenitrile to afford **354** and **355**, respectively (Scheme 17.169). When **352** ($R = R^1 = H$) is heated with benzaldehyde in the presence of a Lewis acid such as zinc chloride, the reaction proceeds via the enamine **356** to afford 1-styrylisoquinoline (**357**) (Scheme 17.169).

It is possible to oxidize alkyl side-chains while leaving the ring intact [476]. The oxidation of **358** with manganese dioxide affords mainly a mixture of **359** and **360**. Selective oxidation of 1-methyl groups, as in **361**, can be achieved with selenium dioxide, in the presence of other methyl groups in both the benzene and pyridine rings, to give **362** (Scheme 17.170).



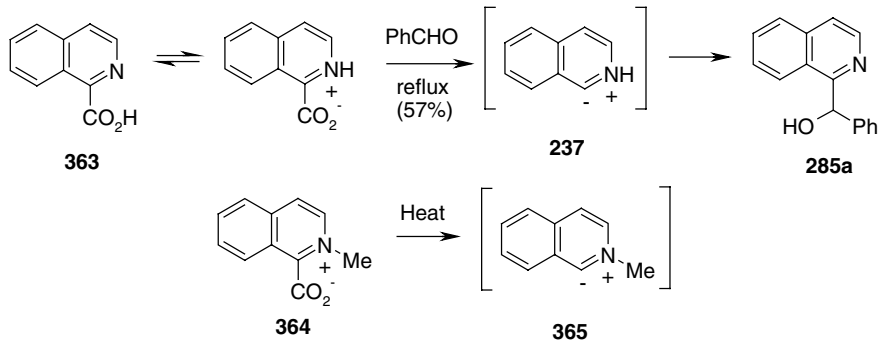
Scheme 17.169



Scheme 17.170

17.2.5.9.4 **Isoquinoline Carboxylic Acids** These derivatives behave as typical aromatic acids. The main difference arises in isoquinoline- and *N*-alkylisoquinolinium-1-carboxylic acids, which can decarboxylate via an ylide intermediate that can be trapped by electrophiles such as aldehydes, diazo compounds, or diazonium ions [477, 478]. Isoquinoline-1-carboxylic acid (**363**) affords **285a** when heated under reflux with benzaldehyde. Betaine **364** yields the corresponding ylide **365** when heated (Scheme 17.171).

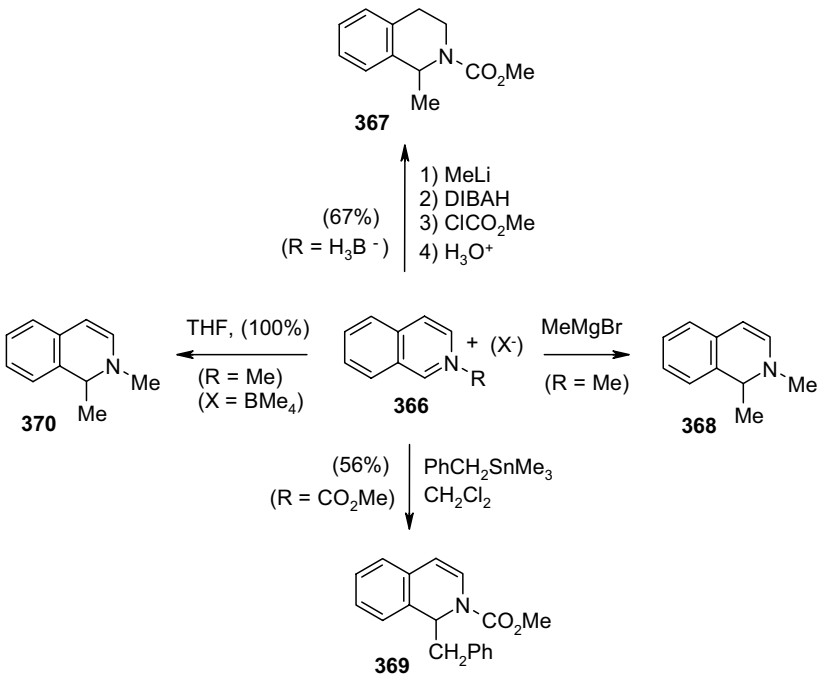
17.2.5.9.5 **Quaternary Isoquinolinium Salts** Although some reactions in this chapter are performed by means of a quaternary isoquinolinium salt, here the high



363 237 285a 364 365

Scheme 17.171

versatility of these compounds will be discussed in more detail. One of the most characteristic features of these compounds is their ease of nucleophilic addition at the 1-position, as compared with isoquinolines, to give relatively stable neutral 1,2-dihydroisoquinolines, which in some cases may disproportionate or be oxidized. Nucleophiles such as organometallics add to different isoquinolinium salts. Organolithiums, for instance, react with isoquinoline-*N*-borane (**366**, R = H_3B^-) as precursors of substituted tetrahydroisoquinolines **367** [479]. Grignard reagents give 1,2-dialkyl-1,2-dihydroisoquinolines (**368**) when reacted with *N*-alkylisoquinolinium salts (**366**, R = Me) [480]. *N*-Acylisoquinolinium salts (**366**; R = CO_2Me) add benzylstannanes to yield dihydroisoquinoline **369** (Scheme 17.172) [481]. Both stannanes

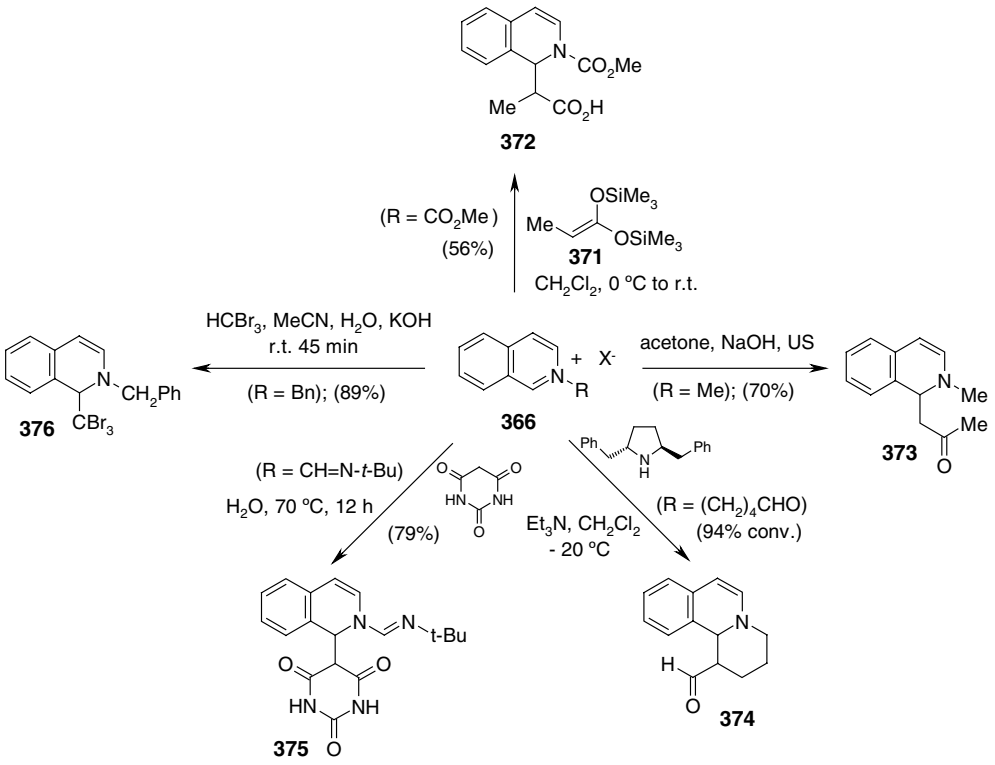


367 370 366 368 369

Scheme 17.172

and Grignard reagents add to chiral isoquinolinium salts in a diastereoselective manner [482, 483]. In addition, Zincke's salt of isoquinoline [**366**; R = 2,4-$(NO_2)_2C_6H_3$] may be transformed into chiral isoquinolinium salts [484] by reaction with chiral amines and the products are then reacted with Grignard reagents to afford 1,2-dihydroisoquinolines diastereoselectively [485]. *N*-Alkylisoquinolinium tetraalkylborates (**366**; R = Me, X = BMe_4) transfer alkyl groups efficiently under thermal or photochemical activation to give **370** (Scheme 17.172) [486]. On the other hand, the enantioselective addition of chiral allylsilanes activated by silver salts to an *N*-acylisoquinolinium cation has been reported to give 1-allyl-1,2-dihydroisoquinolines [487]. These compounds may also be prepared using allyl bromides in the presence of indium [488].

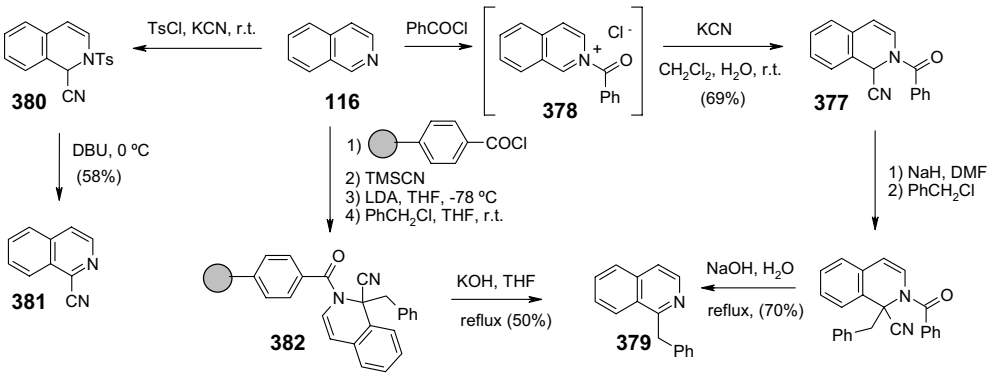
Softer nucleophiles also add to isoquinolinium cations (Scheme 17.173). Silyl enol ethers **371** react with isoquinolinium salts (**366**, R = CO_2Me) to give dihydroisoquinolines **372** [489]. A diastereoselective version of this approach has been applied to the synthesis of (–)-homolaudanosine [490]. *N*-Methylisoquinolinium salts (**366**, R = Me) undergo oxoalkylation with ketone enolates under ultrasound (US) activation to give **373** [491]. When the *N*-alkyl chain bears an aldehyde, as in **366** [R = $(CH_2)_4CHO$], an organocatalytic cyclic oxoalkylation reaction has been performed to give **374** in a high diastereomeric ratio [492]. Active methylene compounds react with



Scheme 17.173

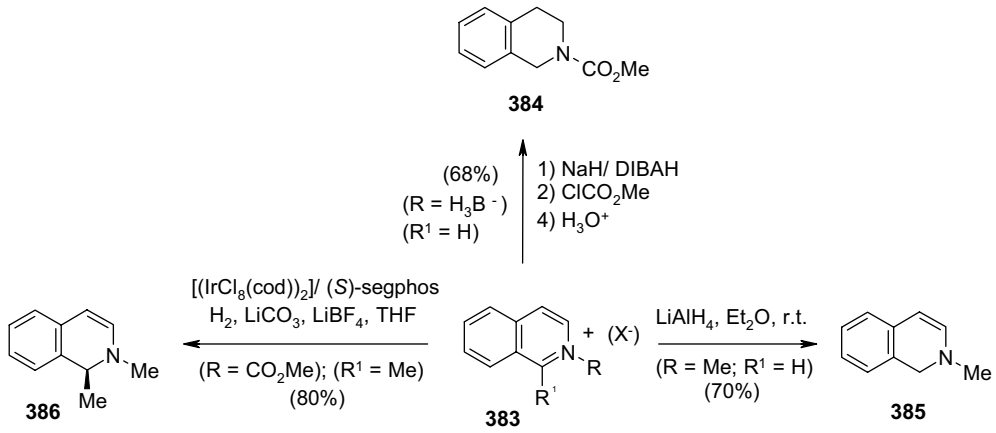
intermediate *N*-formylisoquinolinium imines (**366**, R = CH = N-*tert*-butyl), produced by reaction of isocyanides with isoquinoline, to yield dihydro derivatives **375** through a three-component one-pot reaction [493]. *N*-Benzylisoquinolinium salt **366** (R = Bn) reacts with tribromomethylsodium (generated *in situ* from bromoform) to give the addition product **376** (Scheme 17.173) [494].

The cyanide anion also adds to *N*-acylisoquinolinium salts to give so-called Reissert compounds such as **377** (Scheme 17.174). These compounds can be prepared using conventional phase-transfer catalysis [495], or accelerated with ultrasound [496], as well as crown ether catalysis [497]. Thus, **116** reacts with benzoyl chloride to give the intermediate *N*-benzoylisoquinolinium salt **378**, which in the presence of potassium cyanide affords the dihydroisoquinoline **377** under phase-transfer catalysis conditions. Reissert compounds are useful materials in preparing 1-alkyl- and 1-cyanoisoquinolines. Deprotonation of **377** with NaH followed by alkylation and further removal of the acyl and cyanide groups gives rise to **379** [498]. Furthermore, the *N*-sulfonyl analogues, such as **380**, are prone to eliminate an arylsulfinate to yield **381** [499]. The solid-phase Reissert reaction has also been performed using benzoyl chloride resin through solid-supported intermediate **382** [500]. A highly enantioselective version of the Reissert reaction has been reported using a chiral substituted BINOL catalyst [501].



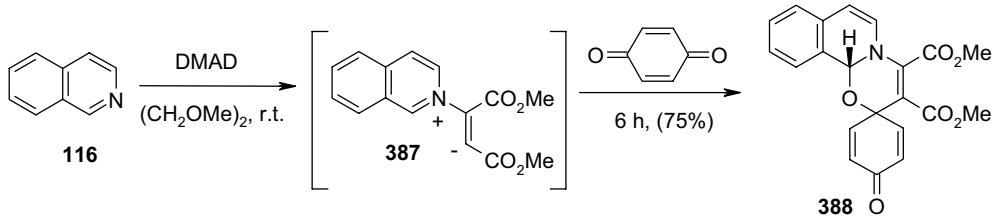
Scheme 17.174

Reduction of quaternary isoquinolinium salts gives stable *N*-substituted 1,2-dihydro- or tetrahydroisoquinolines. Hydrides such as sodium hydride or lithium tetrahydroaluminate react under mild conditions. Isoquinoline-*N*-borane **383** (R = H_3B^-; R^1 = H) adds NaH to give a dihydroisoquinoline that is further transformed into tetrahydroisoquinoline **384** [479]. Lithium tetrahydroaluminate reacts with *N*-alkylisoquinolinium salts **383** (R = Me; R^1 = H) to give the corresponding dihydroderivatives such as **385** [480, 502]. On the other hand, hydrogenation of isoquinolinium salts can also be performed. The iridium-catalyzed asymmetric hydrogenation of **383** (R = CO_2Me; R^1 = Me) affords **386** (Scheme 17.175). This procedure has been applied to the synthesis of naturally occurring alkaloids [194].



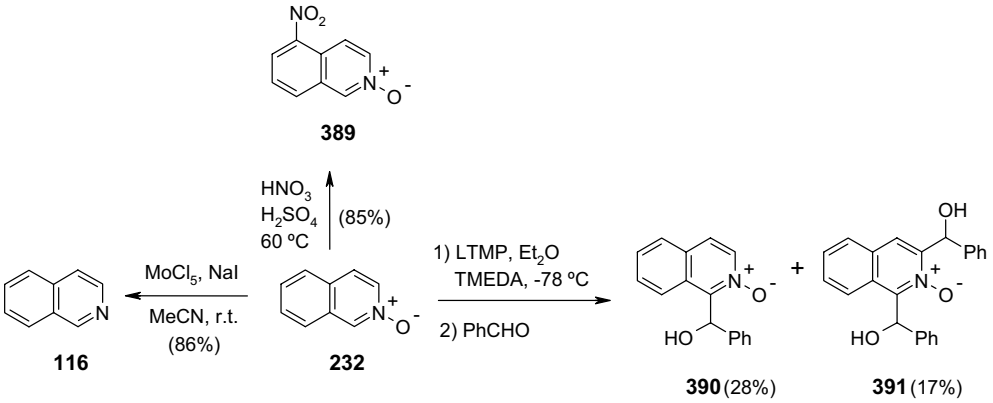
Scheme 17.175

As mentioned earlier in this chapter, isoquinoline gives electrocyclic reactions through isoquinolinium intermediates. Thus, **116** reacts with dimethyl acetylenedicarboxylate (DMAD) through a Huisgen process [503] to give the 1,4-dipolar intermediate **387**, which can be trapped by benzoquinones or activated alkenes to give highly functionalized polycyclic adducts [504, 505]. For example, adduct **388** has been obtained using *p*-benzoquinone (Scheme 17.176).



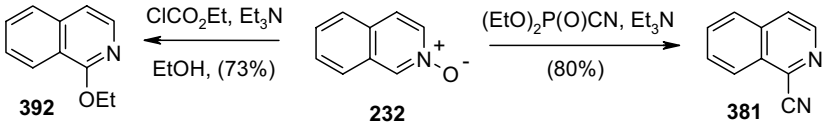
Scheme 17.176

17.2.5.9.6 **Isoquinoline *N*-Oxides** The chemistry of isoquinoline *N*-oxide (**232**) differs from that of pyridine through the ability to undergo electrophilic substitution at the C5-position of the benzene ring. For example, **389** is prepared by nitration of **232** with mixed acid (Scheme 17.177) [506]. Compound **232** has been shown to be less reactive than the corresponding pyridine- and quinoline *N*-oxide towards electrophilic substitution through base-induced deprotonation [507]. Treatment of **232** with lithium 2,2,6,6-tetramethylpiperidide (LTMP) and subsequent reaction with benzaldehyde affords a mixture of mono- and disubstituted *N*-oxides **390** and **391**. Although there are several deoxygenation methods by which to convert **232** into **116**, recently the molybdenum pentachloride/sodium iodide system has proven to be a mild and efficient process [508].



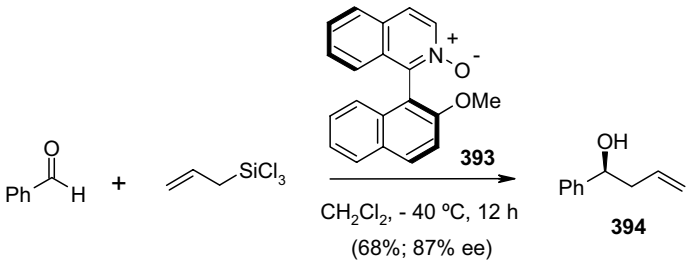
Scheme 17.177

Some reactions performed on N-oxides, such as deoxygenation with phosphorus pentahalides, take place with both Cα-substitution and elimination of an oxygen atom as part of a good leaving group. A base is usually necessary to promote the elimination. As an example, the reaction of **232** with ethyl chloroformate and ethanol leads to **392** [509]. Similarly, treatment of **232** with diethyl cyanophosphonate or trimethylsilyl cyanide gives 1-cyanoisoquinoline (**381**) (Scheme 17.178) [510, 511].



Scheme 17.178

Isoquinoline *N*-oxide compounds can also be interesting catalysts and reagents. QUINOX (**393**), a chiral isoquinoline *N*-oxide, performs asymmetric allylation of aldehydes to give allylic alcohols **394** in good enantiomeric excess (Scheme 17.179) [512].



Scheme 17.179

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18
Six-Membered Rings with One Oxygen: Pyrylium Ion, Related Systems and Benzo-Derivatives

Javier Santamaría and Carlos Valdés

18.1
Introduction

Six-membered oxacycles are a family of compounds that are widely present in natural products as well as in pharmaceuticals and other useful compounds and materials. The parent member of the family is the pyrylium cation **1**, which is the oxa-analog of benzene. Other important unsaturated derivatives are 2*H*-pyran (**2**) and 4*H*-pyran (**3**), which can be seen as the result of the addition of a hydride to the pyrylium cation. Carbonyl-containing pyran-2-one (**4**) and pyran-4-one (**5**) are prominent derivatives of pyrans. Moreover, the benzo derivatives of all these structures also constitute important types of heterocycles. Some of the more common structures, including their usual names are presented in Figure 18.1.

Owing to the structural variety of pyrylium and pyran derivatives, this chapter will concentrate mostly on the parent pyrylium salt, as well as on the important oxa derivatives pyranones and benzopyranones.

18.2
Pyrylium Cation and Benzo-Derivatives

18.2.1
Pyrylium Salts: General Considerations

The pyrylium cation (**1**) is the ring system in which a CH of benzene is replaced by an oxygen atom. It is a cationic and highly perturbed aromatic ring, as a result of the high electronegativity of the oxygen atom. The aromaticity of pyrylium salts is supported by the physical properties of these cations, such as magnetic properties, vibrational spectra, and electronic absorption spectra, and also by their structural parameters [1]. Nevertheless, some of the more common aromaticity indexes indicate that pyrylium salts are less aromatic than most of other aromatic six-membered rings [2]. Figure 18.2 presents the structural parameters of the equilibrium geometry of the pyrylium cation obtained from calculations at different levels of theory [3].

Modern Heterocyclic Chemistry, First Edition.
Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.

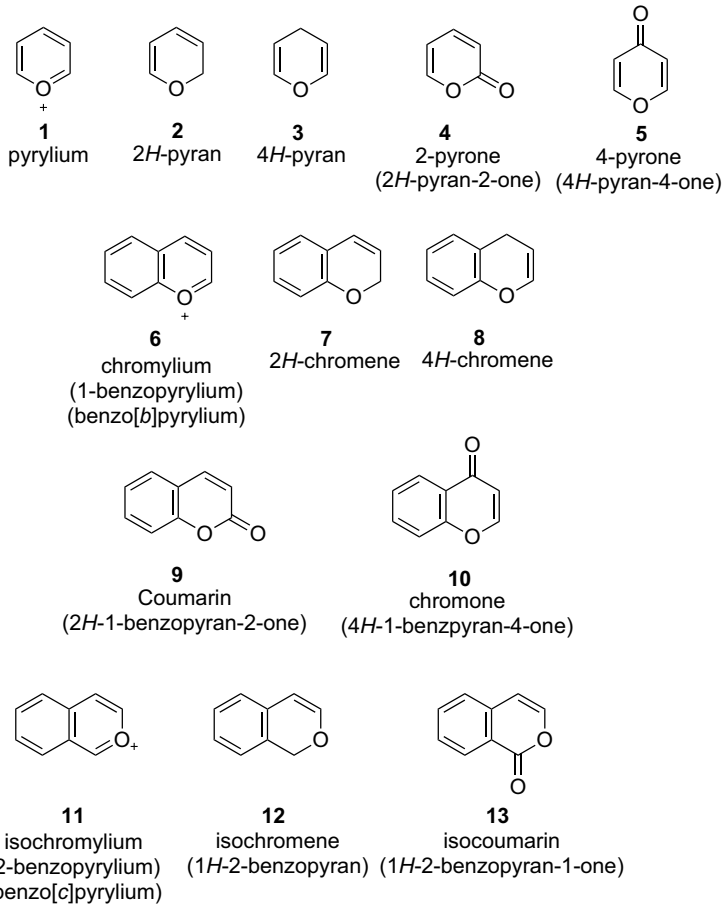


Figure 18.1 Most common six-membered ring oxacycles.

Pyrylium salts are stable but highly reactive species. The nature of the counterion of pyrylium salts depends on the method of preparation, and the most common salts are derived from multi-atomic anions, typically perchlorates, tetrafluoroborates, and hexafluorophosphates. Owing to their easy accessibility and high reactivity,

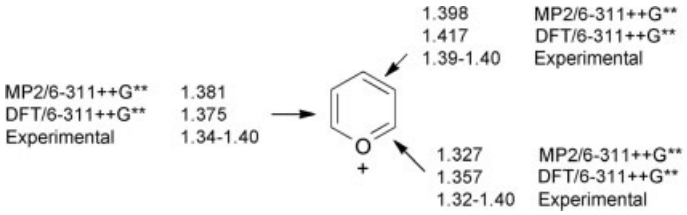
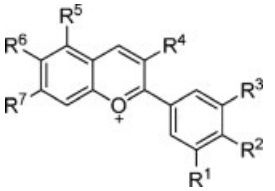


Figure 18.2 Calculated structural parameters of the pyrylium cation.

Table 18.1 Selected anthocyanidines.



	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Color
Cyanidine	OH	OH	H	OH	OH	H	OH	Magenta
Delphinidin	OH	OH	OH	OH	OH	H	OH	Purple, blue
Pelargonidin	H	OH	H	OH	OH	H	OH	Orange, salmon
Malvidin	OCH_3	OH	OCH_3	OH	OH	H	OH	Purple
Peonidin	OCH_3	OH	H	OH	OH	H	OH	Magenta
Petunidin	OH	OH	OCH_3	OH	OH	H	OH	Purple

pyryliums have found widespread applications as synthetic intermediates, mainly for the synthesis of other heterocycles or carbocycles through attack by nucleophile–ring opening–ring closure (ANRORC) sequences. An early review on the synthesis and applications of pyryliums salts is recommended [4]. Moreover, pyrylium compounds are constituents of materials with various interesting applications such as photographic materials, photosensitizers in electrophotography, laser dyes, optical recording material, fluorescent probes, anticorrosion agents, and polymerization initiators.

A particularly important type of pyrylium salts is the flavylium salts (2-phenyl-1-benzopyrylium salts), which constitute the aglycon part of anthocyanines, a family of natural pigments present in flowers, fruits, and leaves. The sugar-free part of anthocyanines, which are called anthocyanidines, are polyhydroxylated flavylium salts, which are used as food additives [5]. Table 18.1 presents some common anthocyanidines.

18.2.2
Synthesis of the Pyrylium Ring

The main strategies for the synthesis of pyrylium salts are based on intramolecular condensations of 1,5-dicarbonyl compounds, according with the scheme presented in Figure 18.3. The cyclocondensation of a penten-1,5-dione **14** gives directly the pyrylium salt. On the other hand, if the reaction involves the condensation of a pentane-1,5-dione (**15**), after the formation of 4*H*-pyran **16** a hydride abstraction step is required. The different variations of these methodologies differ in the way in which the 1,5-dicarbonyl compounds are accessed.

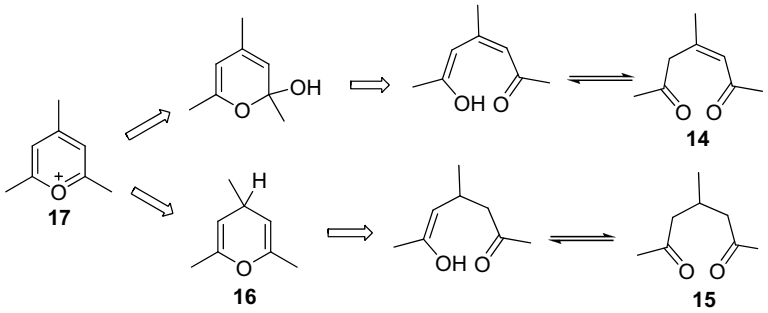
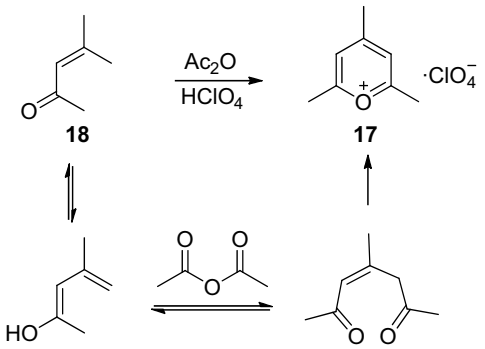


Figure 18.3 Retrosynthetic analysis of the pyrylium cation.

A classical example is the preparation of 2,4,6-trimethylpyrylium perchlorate (**17**) by acylation of pentenone **18** by an anhydride or an acid chloride under strong acidic conditions (Scheme 18.1) [6].



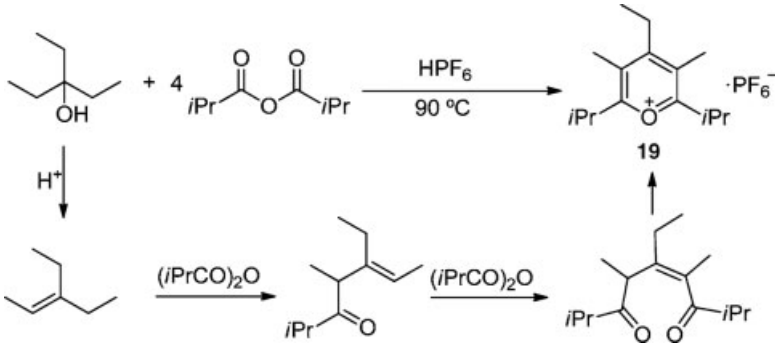
Scheme 18.1 Synthesis of pyrylium salts by acylation of pentenone **18**.

Closely related with this reaction is a very versatile methodology, namely, the classical Balaban synthesis, which involves the diacylation of an alkene. Usually, the alkene is generated *in situ* from the corresponding halide or alcohol [7]. Scheme 18.2 provides a recent application of this methodology leading to the pentasubstituted pyrylium salt **19**.

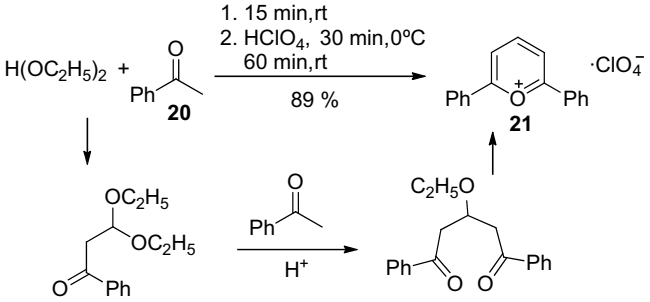
2,6-Diaryl substituted pyrylium salts **21** can be efficiently synthesized by another variation of this method, which consists of the reaction of methyl ketones **20** with triethyl orthoformate in the presence of perchloric acid (Scheme 18.3) [8].

A synthesis of pyrylium salts **24** through the pentenone intermediate includes the reaction of enolizable ketones **22** with 1,3-dicarbonyl compounds **23** under strong acidic conditions (Scheme 18.4) [9].

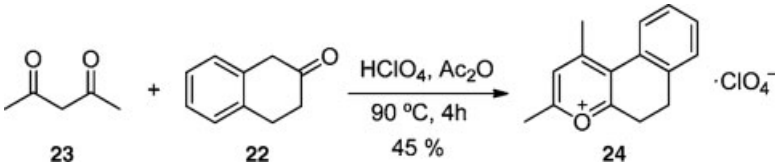
A recent variation of this procedure involves the synthesis of trisubstituted pyrylium salts **29** by reaction of acetophenones **25** with benzoic acids or benzoyl esters **26**. The reaction proceeds through the addition of the enol of the acetophenone



Scheme 18.2 Classic Balaban synthesis of pyrylium salts.



Scheme 18.3 Synthesis of 2,6-diphenylpyrylium salt from acetophenone and an orthoformate.

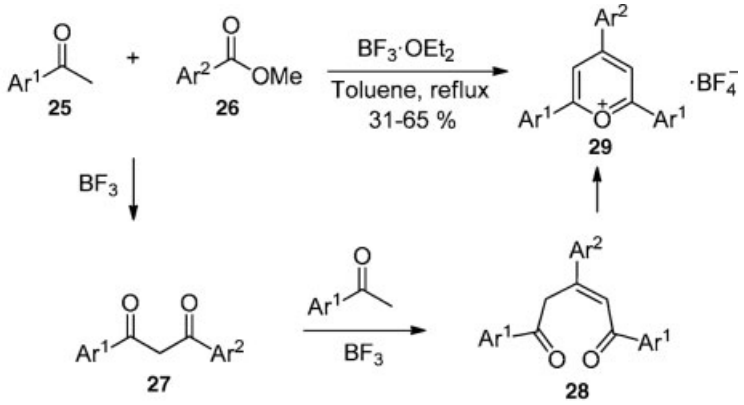


Scheme 18.4 Synthesis of pyrylium salts from 1,3-dicarbonyl compounds and enolizable ketones.

to the ester, to give dicarbonyl compound **27**, followed by aldol condensation of another molecule of acetophenone with the dicarbonyl to give pentenedione **28**, and final cyclization to provide the pyrylium salt **29** (Scheme 18.5) [10].

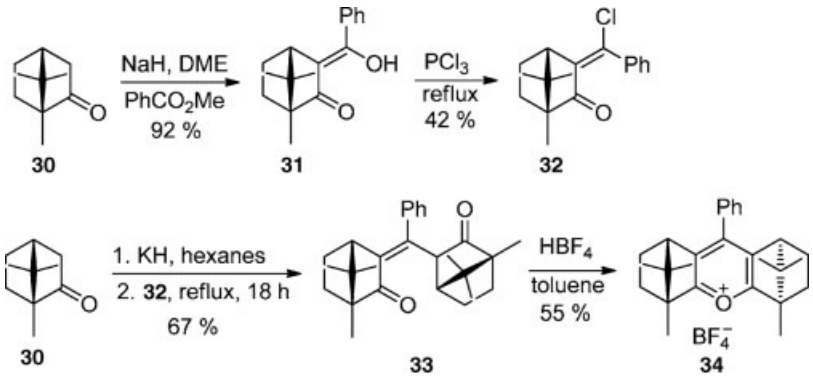
A similar synthetic route, although in a multistep procedure, has been employed to prepare the chiral C_2-symmetric bis-camphorpyrylium salt **34**, taking camphor **30** as starting material (Scheme 18.6) [11]. In this case, the key pentenedione **33** is prepared by Michael addition of the enolate of camphor to chloropentenone **32**, which was obtained by condensation of camphor with methyl benzoate.

Regarding the reactions that consist of the cyclization of saturated diones, one of the most popular strategies is the reaction between a chalcone (**35**) and a methyl



Ar^1: *p*-Br-C_6H_4; Ar^2: *p*-MeO-C_6H_4, Ph, *p*-O_2N-C_6H_4, *p*-Br-C_6H_4

Scheme 18.5 Synthesis of pyrylium salts from acetophenones and benzoyl esters.

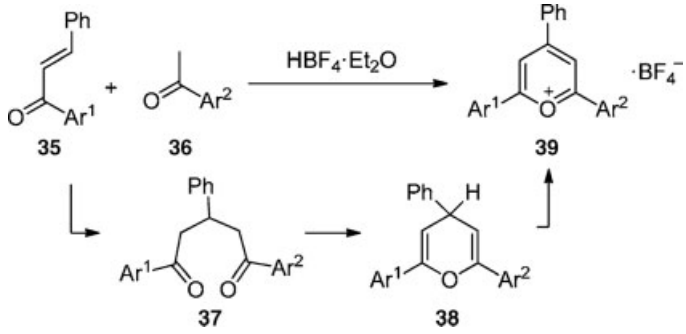


Scheme 18.6 Synthesis of chiral pyrylium salts **34** from camphor.

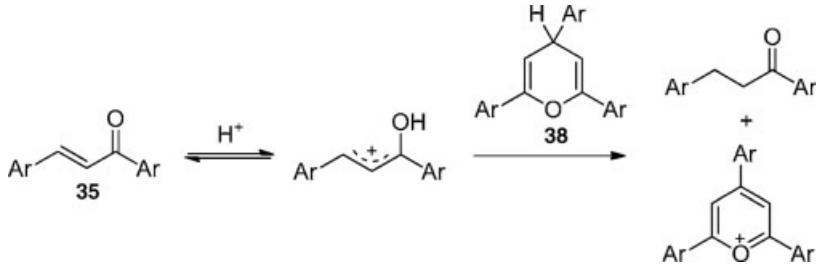
ketone (**36**) (Scheme 18.7) [12]. The reaction must be carried out with two equivalents of chalcone **35**. It has been proposed that the second equivalent serves as hydride abstractor to generate the pyrylium salt from the 4*H*-pyran **38** (Scheme 18.8). This modular approach allows for the synthesis of pyrylium salts **39** with three different aryl substituents [13].

An extension of this strategy consists of a one-pot reaction in which the chalcone is generated from acetophenones and an aromatic aldehyde. In this case the reaction is restricted to symmetrical pyrylium salts such as **41** (Scheme 18.9). Nevertheless, taking into account that the reaction is compatible with several functionalities and the starting materials are very easily available, this reaction is one of the most often employed methods for the preparation of pyrylium salts [14].

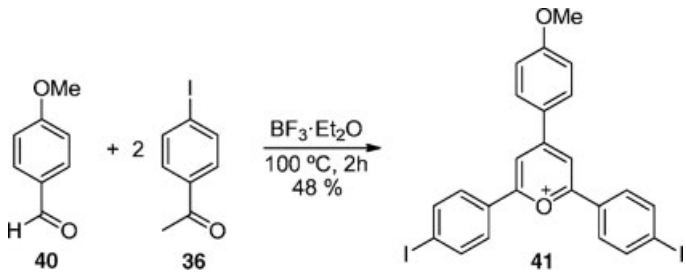
Pyrylium salts can also be prepared by the oxidation of cyclopentadienes with silver salts [15] or by the action molecular oxygen in the presence of perchloric acid [16]. In the



Scheme 18.7 Synthesis of pyrylium salts from chalcones.



Scheme 18.8 Mechanism of the synthesis of pyrylium salts from chalcones.

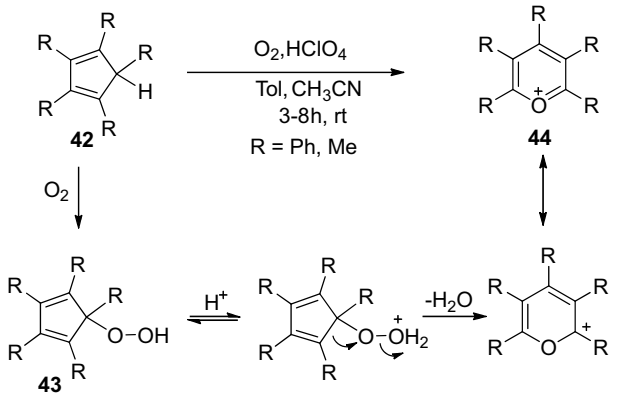


Scheme 18.9 One-pot synthesis of pyrylium salts from aromatic aldehydes and methyl ketones.

latter case, presented in Scheme 18.10, the oxygen insertion on the cyclopentadiene **42** can be explained by a mechanism that implies auto-oxidation to give **43**, followed by an acid-promoted rearrangement that leads directly to the pyrylium salt **44**.

18.2.3
Synthesis of the 1-Benzopyrylium Ring

The synthesis of 1-benzopyrylium salts **45** is closely related to the procedures for the synthesis of pyryliums. As presented in Figure 18.4, most of the methodologies rely



Scheme 18.10 Pyrylium salts by oxidation of cyclopentadienes.

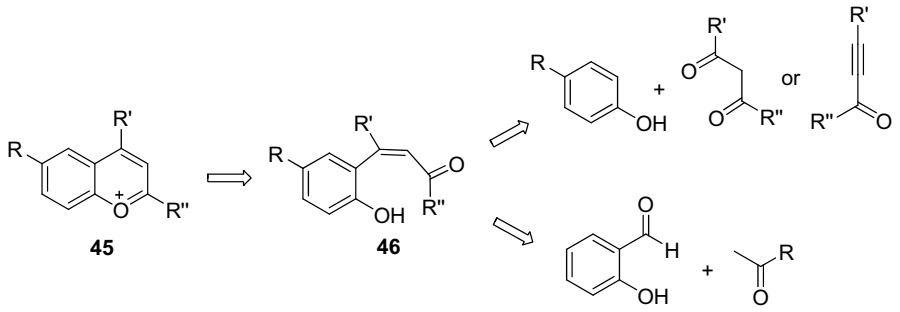
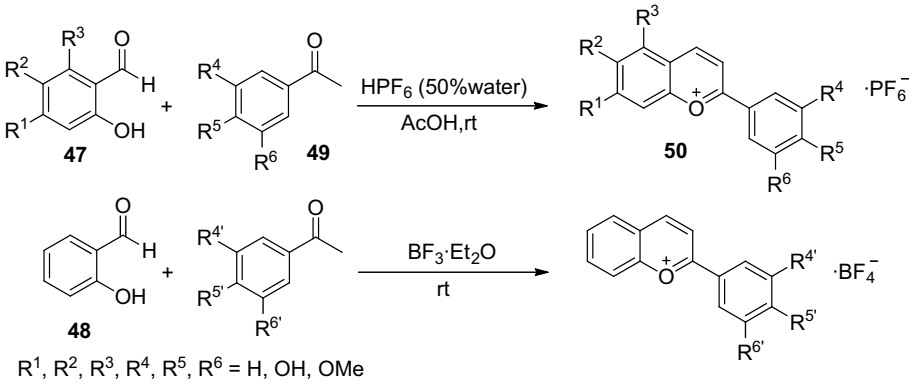


Figure 18.4 General strategies for the preparation of 1-benzopyrylium salts **45**.

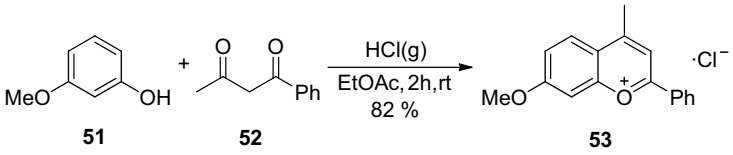
on the intramolecular cyclizations of properly substituted phenols **46**. These cyclization precursors can be prepared by the reactions of phenols with 1,3-bidentate electrophiles, such as 1,3-dicarbonyl compounds or α,β-unsaturated carbonyl compounds. Alternatively, the intermediate phenol **46** can be generated by reaction of salicyl aldehydes or *o*-hydroxyketones with enolizable ketones.

One of the most classical synthesis of flavyliums **50** (2-aryl-1-benzopyryliums) is the Robinson condensation of salicylaldehydes **47** or **48** with acetophenones **49** [17]. Scheme 18.11 presents a recent application of this methodology oriented to the preparation of ligands to brain GABA-A receptors [18].

Flavylium ions such as **53** (Scheme 18.12) are also efficiently prepared by the condensation of activated phenols with 1,3-dicarbonyl compounds. The presence of additional activating groups in the aromatic ring is essential to facilitate the initial electrophilic aromatic substitution reaction. Scheme 18.12 presents a recent example of the reaction of *m*-methoxyphenol (**51**) with benzoylacetone (**52**) catalyzed by gaseous HCl [19].



Scheme 18.11 Classical synthesis of flavyliums from salicyl aldehydes and methyl ketones.



Scheme 18.12 Synthesis of 1-benzopyryliums from 1,3-dicarbonyl compounds and phenols.

18.2.4

Synthesis of the 2-Benzopyrylium Ring

Figure 18.5 presents the main retrosynthetic routes to the 2-benzopyrylium cation **54**. The classical strategy involves the cyclization of dicarbonyl compounds **55** [20]. The most general approach to the dicarbonyl intermediate is the Friedel –Crafts acylation of the benzylic carbonyl compound. Another alternative, which has gained in popularity in recent years, is the electrophilic cyclization of *o*-alkynylbenzaldehydes **56**, which are readily available through Pd-catalyzed cross-couplings.

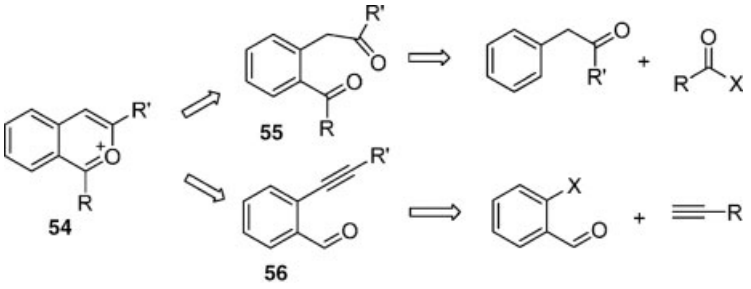
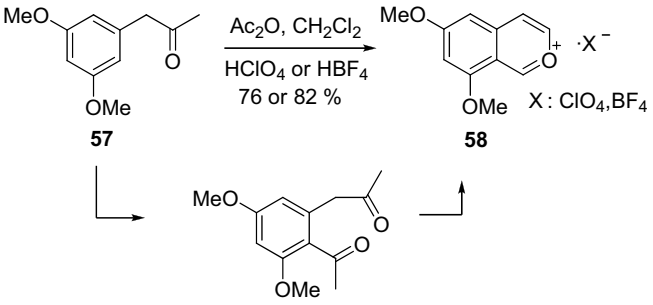


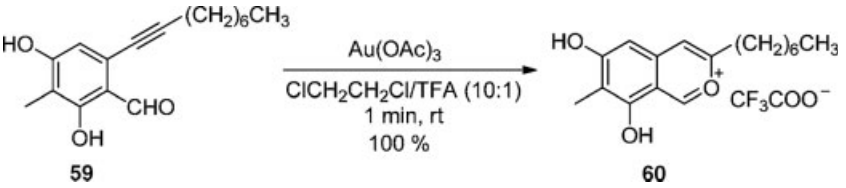
Figure 18.5 General strategies for the preparation of 2-benzopyrylium salts **54**.

Many examples have been disclosed over the years of the first route. For instance, acylation of ketone **57** with acetic anhydride in acidic media gives directly the corresponding pyrylium salt **58** (Scheme 18.13). Nevertheless, this particular reaction is generally restricted to carbonyls that bear activating substituents in the aromatic ring, to facilitate the Friedel–Crafts acylation [21].



Scheme 18.13 Synthesis of 2-benzopyryliums.

As noted, the cycloisomerization of *o*-alkynylbenzaldehydes has emerged recently as an alternative for the preparation of 2-benzopyryliums. The reaction can be promoted by different electrophilic reagents [22], but gold salts have been found to be the best catalysts to promote this type of transformation [23]. For instance, *o*-alkynyl aldehyde **59** is quantitatively converted into benzopyrylium salt **60** in just 1 min (Scheme 18.14) [24].



Scheme 18.14 Cycloisomerization of *o*-alkynylbenzaldehydes.

18.2.5
Reactivity of Pyrylium Salts

Pyrylium cations are extremely π-deficient heterocycles, and therefore they are highly reactive towards nucleophilic systems. Moreover, pyrylium salts are totally unreactive towards electrophiles. The chemical behavior of pyrylium cations towards nucleophiles can be rationalized by considering the resonance forms depicted in Figure 18.6. Addition and substitution reactions can take place at the electron-deficient positions 2, 4, and 6. The particular type of reaction and the regioselectivity depend on the nature of the nucleophile and the substituents of the pyrylium ring.

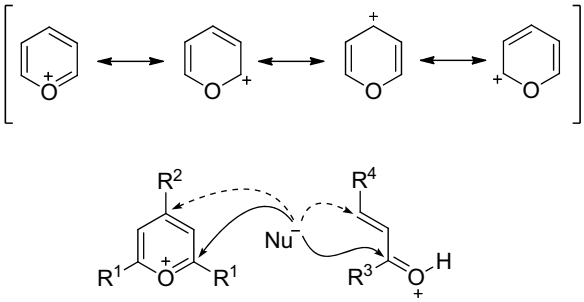


Figure 18.6 General reactivity of pyrylium cations.

18.2.5.1 **Reactions with Nucleophiles**

The reactivity of the pyrylium ion is similar to that of a protonated carbonyl compound. Therefore, nucleophiles attack preferentially position 2. In 4-unsubstituted pyryliums, the addition of the nucleophile can take place regioselectively at position 4 (Figure 18.6).

The reaction with hydroxides (Figure 18.7) serves as a model of a nucleophilic addition on the pyran ring. Attack at position 2 gives hemiketal **61**, which can evolve through ring opening to the pent-2-en-1,5-dione **62**. The equilibrium can be shifted back to the pyrylium under acidic conditions. When the pyrylium salt features an enolizable alkyl group at position 2, a phenol (**63**) can be formed through an intramolecular aldol condensation. These two reactivity patterns can be extended to C, N, S, and P nucleophiles and offer numerous opportunities in the synthesis of heterocyclic and carbocyclic systems through ANRORC cascades, as will be shown below.

18.2.5.1.1 **Synthesis of Other Heterocyclic Systems** Following a similar mechanism, different heterocyclic systems **64** can be prepared from pyrylium salts, employing N, P, S, and other heteroatom-based nucleophiles. Indeed this is a very powerful transformation for the synthesis of certain classes of heterocycles (Figure 18.8).

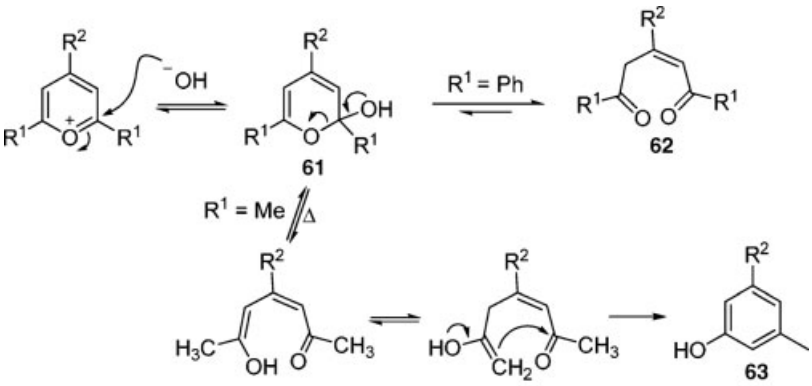


Figure 18.7 Reactivity of pyrylium cation with nucleophiles.

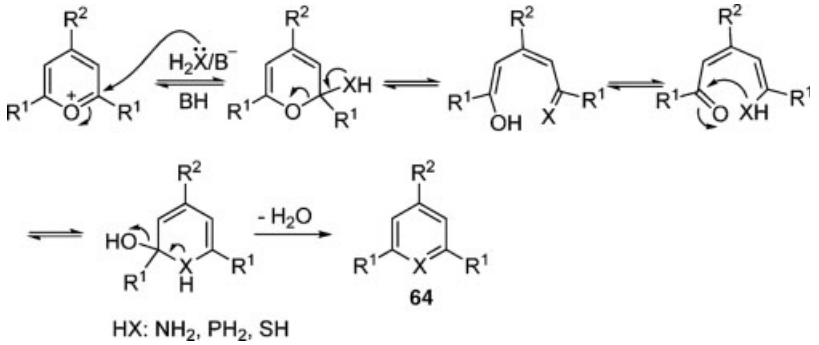
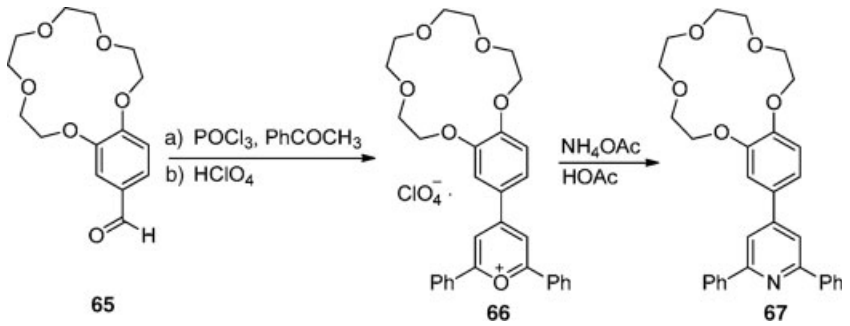


Figure 18.8 General strategy for the synthesis of other heterocycles from pyryliums.

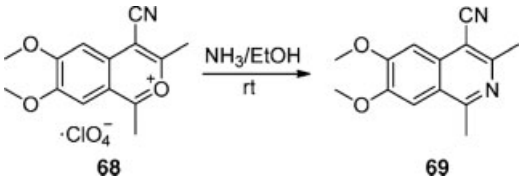
Pyryliums can be transformed into pyridines by treatment with NH_4OAc. This method is an alternative for the preparation of pyridines with some particular substitution patterns. In the example presented in Scheme 18.15 a pyridine carrying a benzo-15-crown-5 (**67**), which is a fluorescent sensor for Mg(II), is prepared through a straightforward two step sequence that involves: (i) formation of the pyrylium perchlorate **66** by the classical reaction of an aromatic aldehyde (**65**) with acetophenone and (ii) treatment with ammonium acetate to give the desired pyridine **67** (Scheme 18.15) [25].



Scheme 18.15 Synthesis of pyridine **67** from the corresponding pyrylium salt.

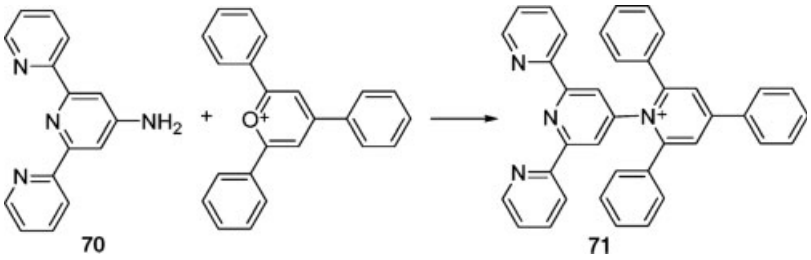
The same reaction can be applied to 2-benzopyryliums, to provide isoquinolines. In the example of Scheme 18.16, the presence of an electron-withdrawing group in the pyrylium nucleus of **68** enables the transformation into isoquinoline **69** under milder conditions [26].

The reactions of pyrylium cations with primary amines give rise to pyridinium cations [27]. This transformation is continuously employed to build molecular structures with interesting properties that are inaccessible through other methodologies. One example application of this methodology is the synthesis of **71**, a molecule that features a tridentate ligand domain and the pyridinium substructure,



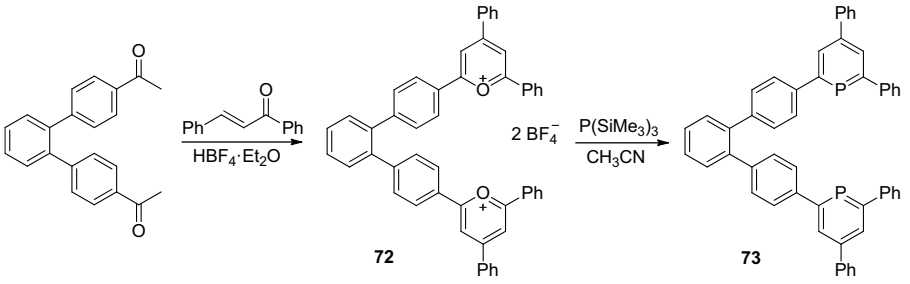
Scheme 18.16 Synthesis of isoquinoline **69** from 2-benzopyrylium salt **68**.

and is the monomer of a photosensitized supramolecular assembly, by condensation of triphenylpyrylium salt with 4-aminopyridine (**70**) (Scheme 18.17) [28]. Other recent examples include the synthesis fluorescent probes for hydrogen abstraction [29], molecular wires based on oligomeric pyridinium chains [30], calixarene-based tricyclic assemblies [31], and the preparation of pyridinium based lipophilic oligomers for gene delivery [32]. Moreover, the reaction can be also applied to 2-benzopyrylium salts to obtain isoquinolinium salts [33].



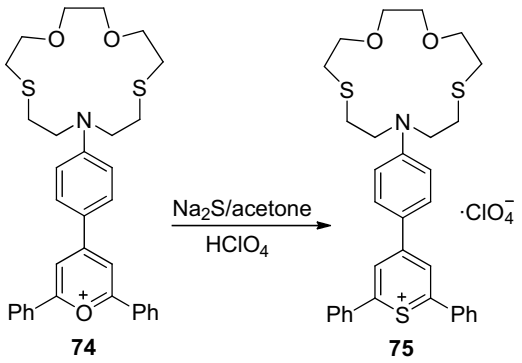
Scheme 18.17 Synthesis of a pyridinium salt from a pyrylium salt.

Pyrylium salts are the simplest source of phosphinines, the phospha analogs of benzene. The O^+–P exchange can be carried out employing $P(CH_2CH_2OH)_3$ or $P[Si(CH_3)]_3$. This reaction has been utilized recently in the preparation of phosphinines with some particular substitutions, to be used as ligands in transition metal catalyzed reactions [34]. As an example, the wide bite-angle diphosphinine **73** has been prepared by this methodology (Scheme 18.18) [35]. The bis-pyrylium derivative **72** is prepared by employing the typical condensation of chalcones with acetophenones.



Scheme 18.18 Synthesis of phosphinine **73** from pyrylium salt **72**.

Analogously, thiopyrylium salts are synthesized by reaction of the corresponding pyrylium salts with Na_2S in acidic media. To illustrate this transformation, Scheme 18.19 shows the synthesis of the thiopyrylium Hg^{2+} and Cu^{2+} sensor **75** from the corresponding pyrylium salt **74** [36].



Scheme 18.19 Synthesis of thiopyrylium **75** from pyrylium salt **74**.

18.2.5.1.2 **Synthesis of Carbocycles** The reactions of pyryliums with certain nucleophiles can lead to a ring opening/ring closure sequence that gives rise to the formation of benzene derivatives. For this type of process to occur it is necessary that the acyclic intermediate **76** (Figure 18.9), which is formed upon addition of the nucleophile, has active hydrogens to permit the C–C bond forming cyclization. There are several variations of this reaction depending on the nature of both the pyrylium salt and the nucleophiles.

For instance, the reaction of secondary amines with trialkylpyrylium salts gives rise to *N*,*N*-dialkylanilines **78** through the formation of an intermediate enamine (**77**) (Scheme 18.20) [37].

Nevertheless, most of the reactions of synthesis of carbocycles from pyrylium salts rely on the second equation presented in Figure 18.9 and employ of C-nucleophiles.

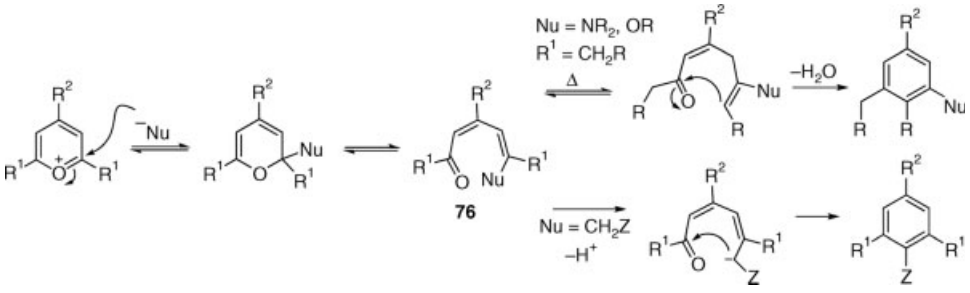
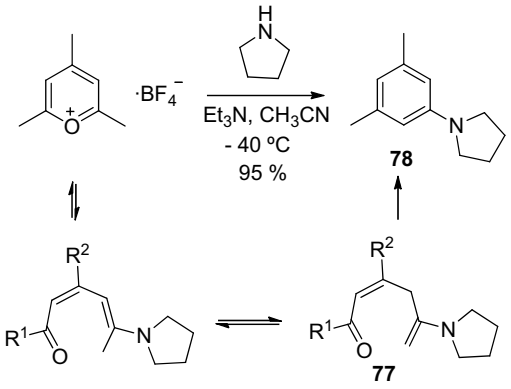
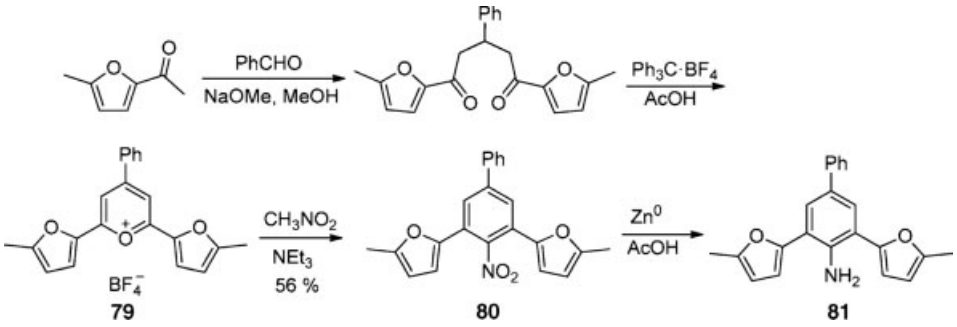


Figure 18.9 General strategy for the synthesis of carbocycles from pyryliums.



Scheme 18.20 Synthesis of anilines from pyryliums.

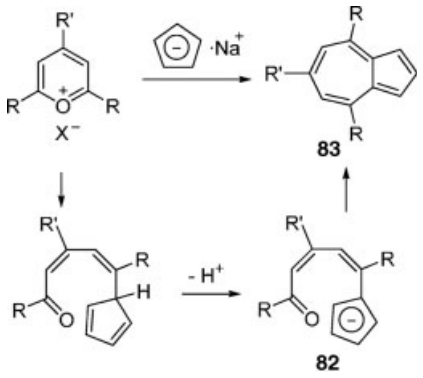
Classical examples are the reactions of pyrylium salts with nitroalkanes in the presence of mild bases, which lead to the corresponding nitroaromatic derivatives [38]. Scheme 18.21 shows a recent application of this reaction. Treatment of pyrylium salt **79** with nitromethane gives trisubstituted nitrobenzene **80**, which has been employed in the preparation of 2,4,6-trisubstituted aniline **81** [39].



Scheme 18.21 Synthesis of carbocycles from pyryliums and nitromethane.

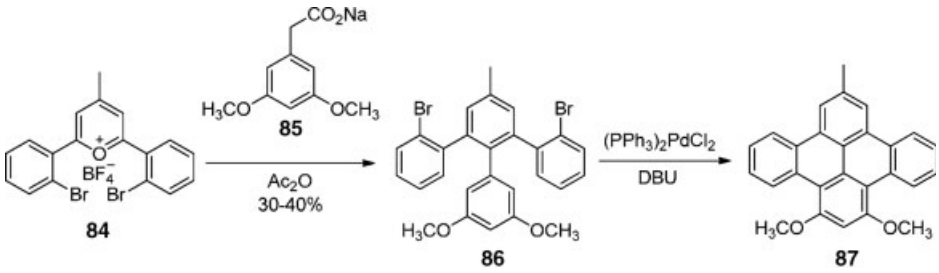
Another interesting synthetic application is the annulation of sodium cyclopentanedienide with pyrylium salts [40]. In this case, the intermediate cyclopentadienyl anion **82** undergoes intramolecular cyclization to produce azulene derivatives **83** (Scheme 18.22).

Pyrylium salts can also react under specific conditions with species that feature weak C–H acids such as anhydrides, esters, or ketones [41]. From a synthetic point of view, an important transformation in this context is the reaction of pyrylium salts with phenylacetates to give *o,o*-disubstituted biaryl systems [42]. Modern applications of this reaction take advantage of the availability of the starting pyrylium salts, and the possibility to include halogens in the aromatic rings, to build complex polyaromatic molecules combining pyrylium chemistry and Pd-catalyzed cross-coupling



Scheme 18.22 Synthesis of azulenes **82** from pyryliums and cyclopentadiene.

reactions [43]. In the example of Scheme 18.23 the pyrylium salt **84** is the starting material to the preparation of dibenzo[*fg,op*]naphthacenes **87** [44]. The key step of the synthesis is the formation of the aromatic dibromide **86** by reaction of pyrylium salt **84** with the corresponding sodium arylacetate **85**.

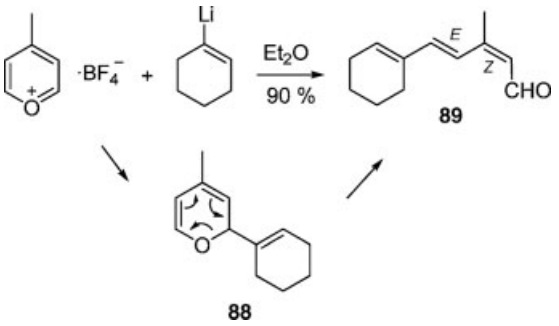


Scheme 18.23 Pyrylium salt **84** as staring material for the synthesis of naphthacene **87**.

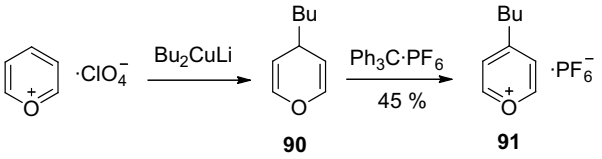
18.2.5.1.3 **Reactions with Organometallic Reagents** Addition of organometallic reagents can take place at positions 2 or 4 depending on the substitution of the pyrylium salt. Organolithium and Grignard reagents add to the 2 position, giving rise to an intermediate 2*H*-pyran **88**, which undergoes an electrocyclic ring opening to give dienones or dienals **89** with retention of the configuration of the double bonds (Scheme 18.24). This reaction has found widespread applicability for the stereocontrolled synthesis of polyenes in natural products synthesis [45, 46].

On the other hand, organocuprates add to 4-position of pyrylium salts, leading to 4-substituted-4*H*-pyrans **90**, which can be subsequently converted into the corresponding 4-substituted pyrylium salts **91** by oxidation with trityl hexafluorophosphate (Scheme 18.25) [47].

An alternative to the preparation of 4-substituted pyrylium salts is the benzotriazole-mediated reaction developed by Katritzky. In a first step, the 4-unsubstituted

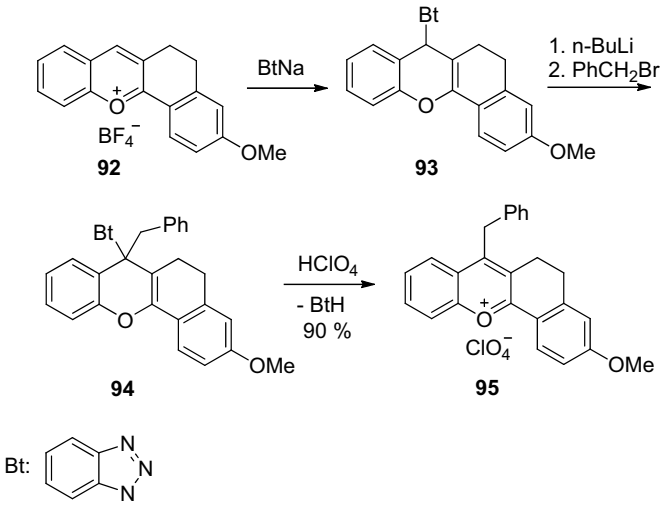


Scheme 18.24 Stereocontrolled synthesis of dienals from pyrylium salts.



Scheme 18.25 Synthesis of 4-substituted-4*H*-pyrans by addition of organocuprates to pyrylium salts.

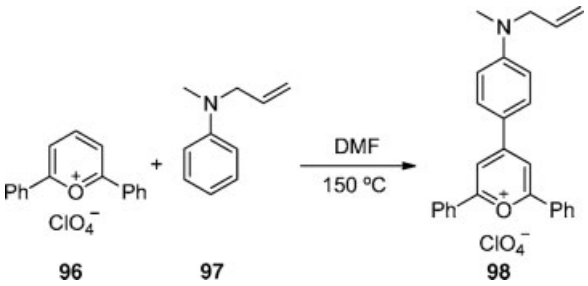
pyrylium salt **92** undergoes addition of benzotriazole to the 4-position to give 4*H*-pyran **93**. Then, deprotonation by treatment with *n*-BuLi produces an 8π-electron heterocyclic anion that can be trapped with an electrophile to give intermediate **94**, which is not isolated and releases the benzotriazole unit upon treatment with a mineral acid to produce the 4-substituted pyrylium salt **95** (Scheme 18.26). The



Scheme 18.26 Benzotriazole mediated substitution in the pyrylium ring.

overall transformation can be envisioned as an indirect electrophilic aromatic substitution in the pyrylium ring. The reaction can be applied to pyrylium and 1-benzopyrylium salts [48].

Pyrylium salts can also react as electrophiles in Friedel–Crafts-like electrophilic aromatic substitutions on electron-rich aromatic rings. For instance, 2,6-diphenylpyrylium perchlorate (**96**) reacts with anilines **97** to furnish the corresponding 4-substituted pyrylium salts **98** (Scheme 18.27) [49].

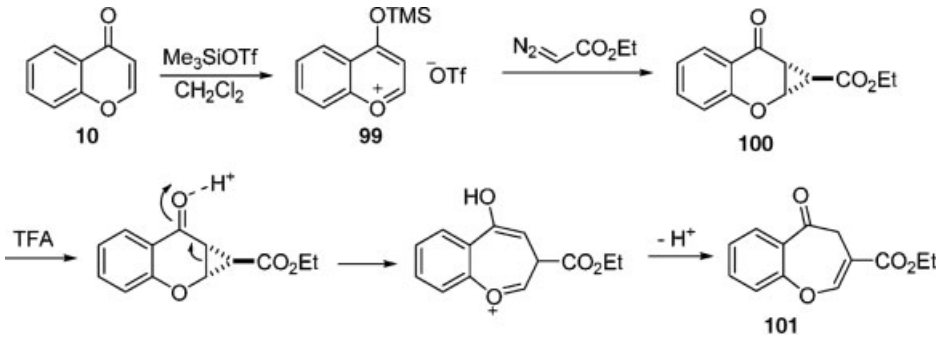


Scheme 18.27 Pyrylium salts as electrophiles in Friedel–Crafts reactions.

18.2.5.2 **Cycloaddition Reactions**

Pyrylium and benzopyrylium salts can participate in several types of cycloaddition reactions.

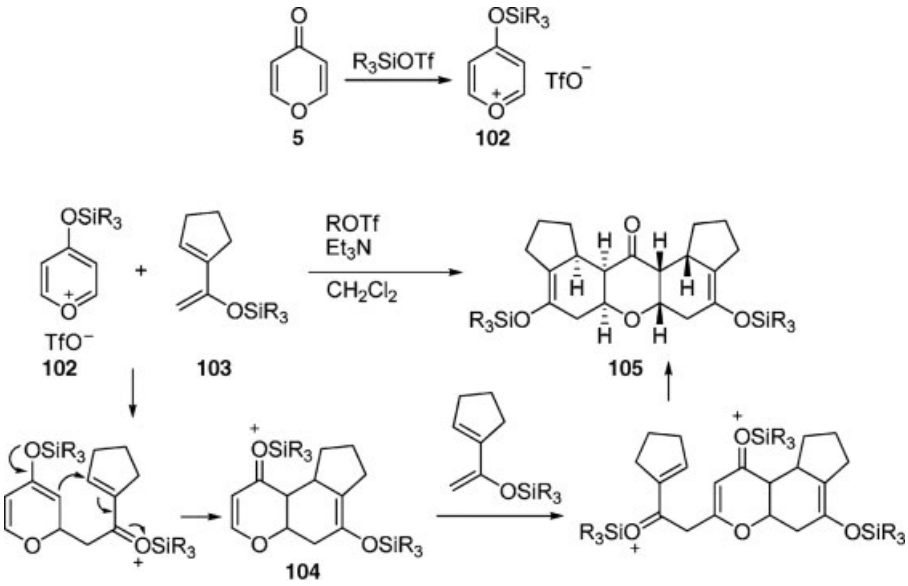
18.2.5.2.1 **[2 + 1] Cycloadditions** Benzopyrylium salt **99**, generated *in situ* from chromone (**10**), undergoes cyclopropanation with ethyl diazoacetate to give the cyclopropanation adduct **100**, which leads ultimately, after acid-promoted ring opening, to the corresponding benzoxepine **101** (Scheme 18.28) [50].



Scheme 18.28 Synthesis of benzoxepine **101** by a cyclopropanation/ring expansion sequence on a pyrylium salt.

18.2.5.2.2 **Dienophiles in [4 + 2] Cycloadditions** 4-Silyloxypyrylium triflate **102**, which is readily prepared from 4-pyrone (**5**), reacts in a domino sequence with

2-silyloxydienes **103** to give polyfunctionalized pyran derivatives **105**. The reactions are triggered by a stepwise [4 + 2] cycloaddition between the electron-rich diene and the C2–C3 bond of the pyrylium salt. Upon formation of intermediate **104**, the attack of a second molecule of silyloxydiene produces polycyclic structure **105** with total diastereoselectivity (Scheme 18.29) [51].

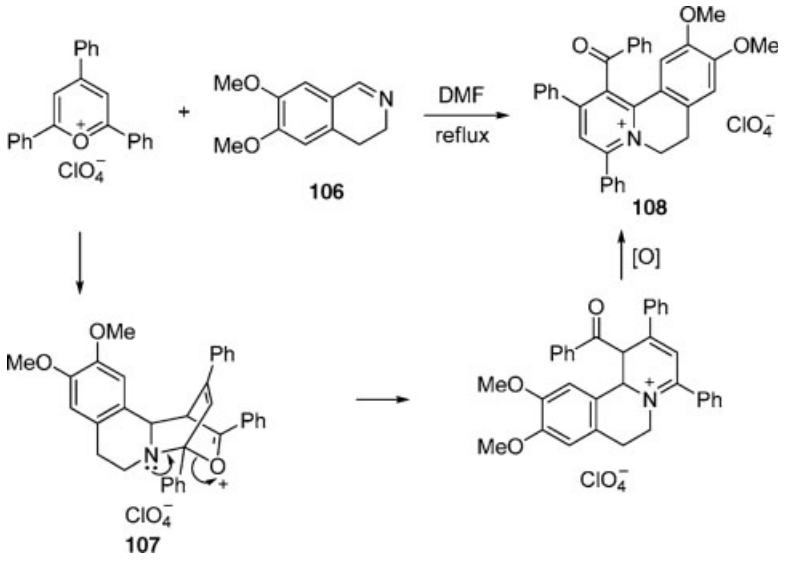


Scheme 18.29 Example of a pyrylium salt as dienophile in a [4 + 2] cycloaddition.

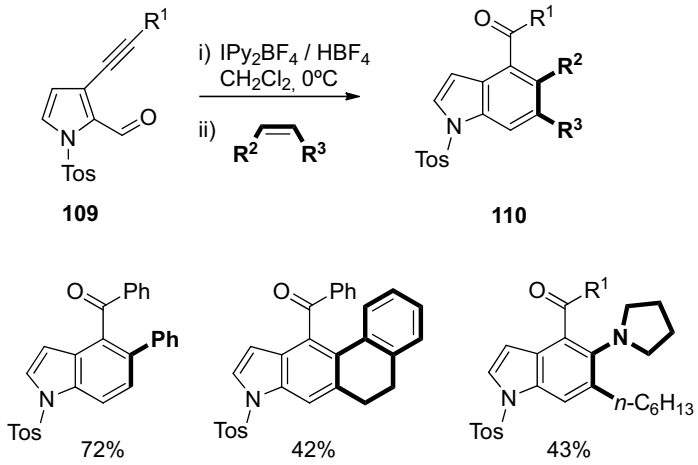
18.2.5.2.3 **Dienes in [4 + 2] Cycloadditions** Pyrylium and benzopyrylium salts can also react as the 4π-component in [4 + 2] cycloadditions. Scheme 18.30 presents the synthesis of pyridinium salt **108** by reaction between triphenylpyrylium perchlorate and dihydroisoquinoline **106**. The mechanism proposed involves a [4 + 2] cycloaddition between the pyrylium salt and the iminic C=N bond, which gives intermediate adduct **107** and provides pyridinium salt **108** after subsequent ring opening and expontaneous oxidation. A similar reaction has been observed with 2-benzopyrylium derivatives [52].

Of particular interest are processes in which the pyrylium salts are generated *in situ* during the annulation of alkynyl aldehydes. For instance, the benzannulation reaction of 3-alkynylpyrrole-2-carboxaldehydes **109** with alkenes, promoted by iodonium ions, yields indoles **110** with a high level of substitution and functionalization in the benzene ring (Scheme 18.31) [53].

Scheme 18.32 shows the mechanism proposed for this unusual transformation. Interaction of the iodonium ion with the triple bond of **109** would promote the formation of 4-iodopyrylium salt **111**. Nucleophilic attack of the alkene to the



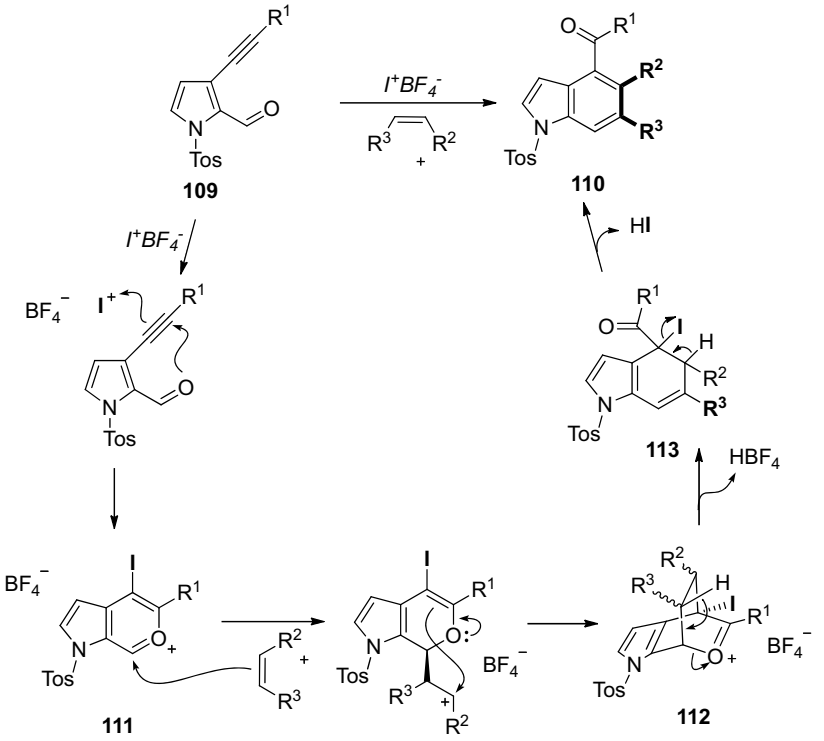
Scheme 18.30 A pyrylium cation as diene in a [4 + 2] cycloaddition.



Scheme 18.31 Synthesis of indoles **110** from *in situ* generated pyrylium cations.

electrophilic carbon of **111**, followed by intramolecular cyclization, would provide **112**. The simple loss of a proton to give a conjugated double bond yields **113**. Finally, aromatization by elimination of HI gives the indoles **110**. This proposal is supported by detailed mechanistic and spectroscopic studies that allowed the isolation of analogues of the cationic intermediates **111** and **112** [54].

Related reactions have been reported in which the formation of the intermediate pyrylium salt is mediated by transition metal catalysts such as Cu and Au [55].

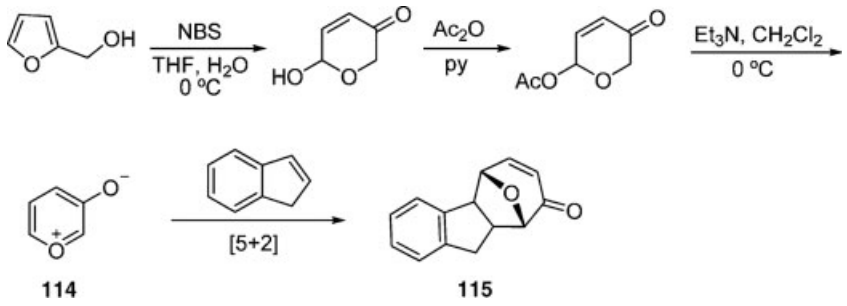


Scheme 18.32 Mechanism proposed for the formation of indoles **110**.

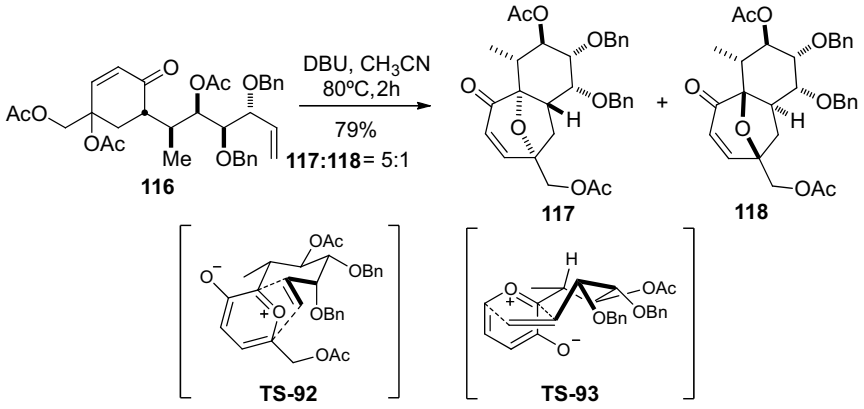
Moreover, Pt-bound pyrylium ions generated *in situ* through the benzannulation of alkynylaldehydes react as dipoles in intramolecular [3 + 2] cycloadditions [56].

18.2.5.2.4 **[5 + 2] Cycloadditions** A particularly interesting derivative is the 3-oxidopyrylium betaine **114** that can participate in [5 + 2] dipolar cycloadditions with the proper dipolarophiles. This reaction has found wide applicability in organic synthesis and a recent review is available [57]. An intermolecular example is the cycloaddition with indene to give polycycle **115** (Scheme 18.33) [58]. Moreover, higher order [6 + 3] reactions with pentafulvenes have also been reported [59].

This methodology is particularly useful in the intramolecular version, and has been extensively employed in the total synthesis of natural products. The interested reader is encouraged to revise the abundant literature cited in Reference [60]. In the example presented in Scheme 18.34, the intramolecular [5 + 2] cycloaddition on the betaine generated from **116** is the key step towards the synthesis of daphnetoxins. This reaction highlights the synthetic power of this cycloaddition reaction in the preparation of structurally complex molecules with a high level of stereocontrol. The structures TS-92 and TS-93 correspond to the proposed transition states for the formation of each diastereoisomer.



Scheme 18.33 [5 + 2] dipolar cycloaddition with 3-oxidopyrylium betaine (**114**).



Scheme 18.34 Intramolecular dipolar cycloaddition with a 3-oxidopyrylium betaine.

Related reactions employing *in situ* generated 2-benzopyrylium-4-olates have also been described, including catalytic asymmetric versions [61].

18.2.5.3 **Side Chain Reactions**

Alkyl substituted pyrylium salts feature relatively acidic hydrogens and, in turn, can react with electrophiles in a similar way to enolizable carbonyl compounds. Therefore, homologous to aldol condensations, Mannich additions and Michael additions can be carried out employing pyrylium salts. In contrast to the reactions with nucleophiles, substituents at C4 react in preference to substituents at C2 (Figure 18.10).

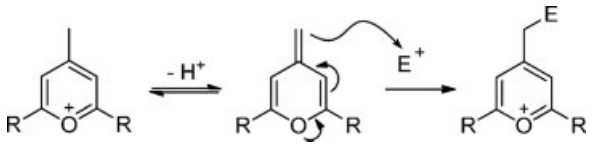
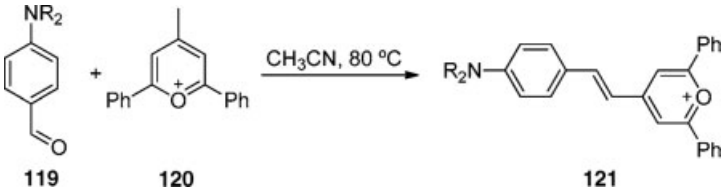


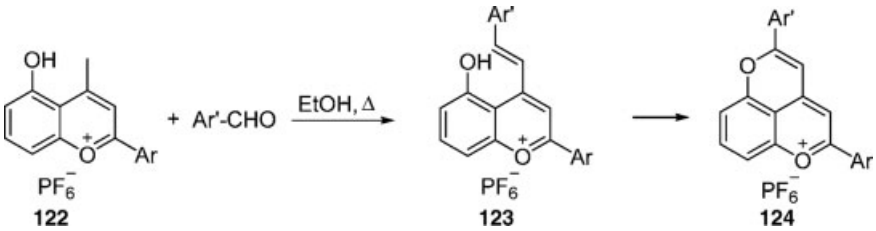
Figure 18.10 General reactivity of the side chain of pyrylium salts.

Thus, alkylpyrylium salt **120** reacts with aromatic aldehydes **119** to give the new polyconjugated pyrylium salts **121**. This reaction finds application in the synthesis of pyrylium dyes (Scheme 18.35) [62].



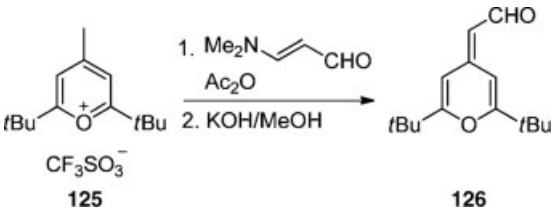
Scheme 18.35 Aldol-like condensation of a pyrylium salt.

Similar reactions can be carried out with benzopyrylium salts, such as in the reaction of 5-hydroxy-4-methylflavilium salts **122**. In this case, subsequent intramolecular cyclization of the initial adduct **123** gives rise to the pyranoflavylium derivative **124** (Scheme 18.36). A charge-transfer complex has been proposed as initiator of this reaction [63].



Scheme 18.36 Synthesis of a pyranoflavylium through the condensation of a flavylium with an aldehyde.

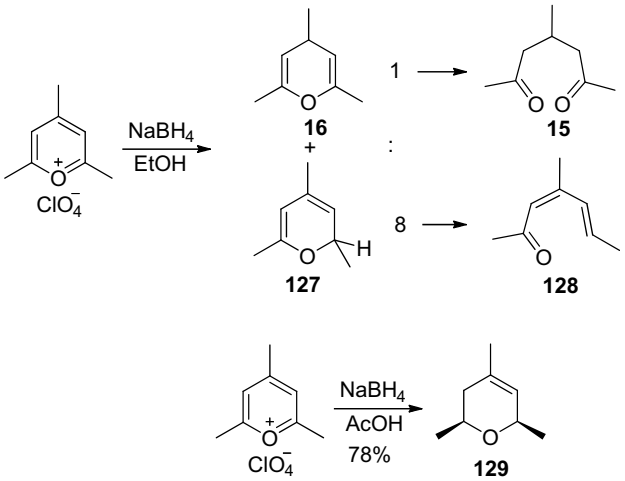
An interesting application of a Michel-type addition is the reaction of 4-methylpyrylium salt **125** with 3-dimethylaminoacrolein to furnish 4*H*-pyranylidene **126**, which has nonlinear optical properties (Scheme 18.37) [64].



Scheme 18.37 Michael-type addition with a pyrylium salt.

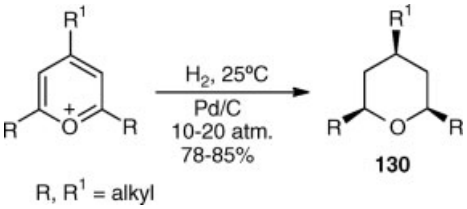
18.2.5.4 Reactions with Reducing Agents

The addition of metal hydride complexes such as $NaBH_4$ to pyrylium salts takes place preferentially at C2, giving rise to 2*H*-pyrans **127**, which undergo ring opening under the reaction conditions to produce dienones **128** (Scheme 18.38). Under more intensive reaction conditions ($NaBH_4$/AcOH) further reduction takes place and Δ^3-dihydropyran derivatives **129** can be isolated. Nevertheless, the regiochemistry of the hydride addition is strongly dependent on the substitution of the pyrylium ring [65].



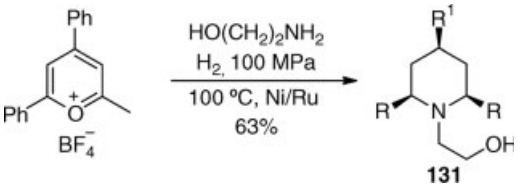
Scheme 18.38 Reduction of pyrylium salts with $NaBH_4$ under different reaction conditions.

Catalytic hydrogenation of alkyl substituted pyryliums leads to the saturated pyran derivatives **130** (Scheme 18.39) [66]. Depending on the reaction conditions and the particular substrates, different types of ring-open compounds can be isolated from pyrylium salts. A review on this subject is available [67].



Scheme 18.39 Catalytic hydrogenation of pyrylium salts.

On the other hand, catalytic hydrogenation in the presence of a primary amine leads to piperidine derivatives such as **131** (Scheme 18.40), in a reaction that could be considered a reductive amination of the pyrylium salt [68].



Scheme 18.40 Reductive amination of pyrylium salts leading to piperidines.

18.3
2*H*-Pyrans and 4*H*-Pyrans

The most relevant compounds featuring the 2*H*-pyran and 4*H*-pyran structures are the corresponding carbonyl systems, 2*H*-pyran-2-one and 4*H*-pyran-4-one, respectively. Each family of compounds is discussed in a separate section. A brief commentary is dedicated here to the ring synthesis of 2*H*-pyrans and 4*H*-pyrans.

18.3.1
2*H*-Pyran Ring Synthesis

The most characteristic property of 2*H*-pyran derivatives is their ability to undergo reversible electrocyclic ring opening to the oxatriene (Figure 18.11). The equilibrium distribution between 2*H*-pyrans and 1-oxatrienes is greatly influenced by the substituents on the ring [69]. Therefore, the main strategies for the preparation of 2*H*-pyran derivatives are directed to the synthesis of the acyclic precursors.

The most classical approach is the Knoevenagel condensation of 1,3-diketones with α,β-unsaturated aldehydes [70]. The reaction between 5-methyl-1,3-cyclohexanedione (**132**) and aldehyde **133** gives rise to pyran **136** (Scheme 18.41) [71]. The reaction proceeds more efficiently in the presence of a secondary amine, through the formation of an iminium salt **134**, which reacts readily with the 1,3-dicarbonyl compound to provide the oxatriene **135**. Electrocyclic ring closure then leads to the pyran **136**.

Several approaches have been devised for the preparation of the oxatriene precursor, such as the oxidation of dienols [72] or Wittig olefination [73]. In a recent approach, monocyclic functionalized 2*H*-pyrans **140** can be synthesized from propargyl vinyl ethers **137** (Scheme 18.42). The cascade process involves a metal-catalyzed Claisen rearrangement to give allene **138**, base-promoted isomerization to oxatriene **139**, and finally the 6π-electrocyclization [74].

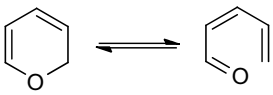
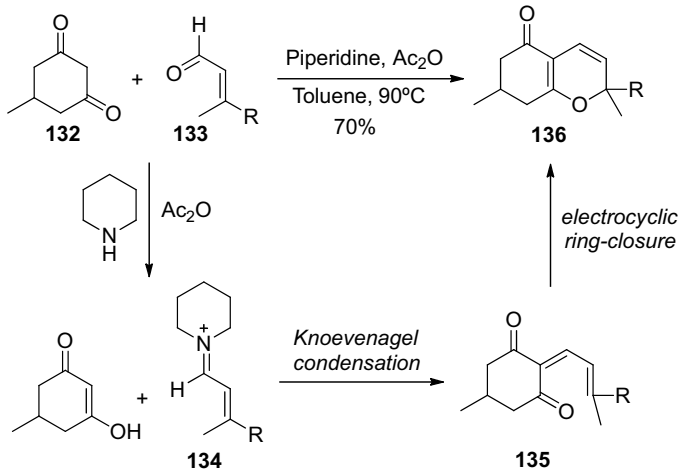
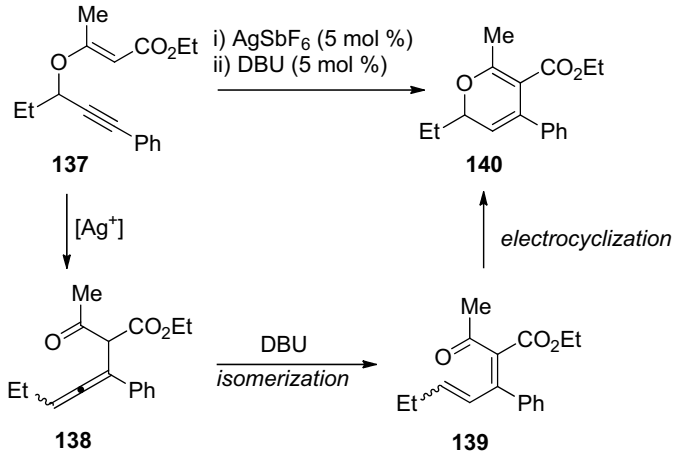


Figure 18.11 Equilibrium 2*H*-pyran↔oxatriene.



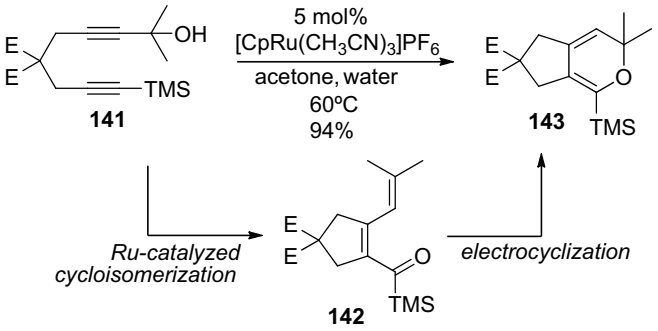
Scheme 18.41 Synthesis of 2*H*-pyrans by Knoevenagel condensation.



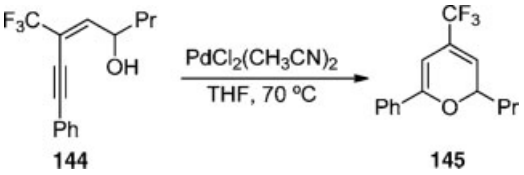
Scheme 18.42 Synthesis of 2*H*-pyrans by metal-catalyzed isomerization of propargyl vinyl ethers.

Bicyclic 2*H*-pyrans **143** have been prepared by a ruthenium-catalyzed cycloisomerization of diyneols **141**, which gives rise to oxatrienes **142** that undergo subsequent electrocyclization (Scheme 18.43) [75].

Another unconventional synthesis is the Pd-catalyzed cycloisomerization of enynols **144** through a 6-*endo*-dig cyclization that leads to 2*H*-pyran **145** (Scheme 18.44). The presence of the electron-withdrawing CF_3 substituent is essential. Otherwise, the formation of a furan, through a more favorable 5-*exo*-dig cyclization, occurs [76].



Scheme 18.43 Synthesis of 2*H*-pyrans by metal-catalyzed cycloisomerization of diyneols.



Scheme 18.44 Synthesis of 2*H*-pyrans by Pd-catalyzed 6-*endo*-dig cyclization of enynols.

18.3.2
4*H*-Pyran Ring Synthesis

The main approach for the preparation of the 4*H*-pyran ring is the intramolecular condensation of 1,5-dicarbonyl compounds (Figure 18.12). The cyclization proceeds in the presence of either protic or Lewis acids. A review that covers the different variations of this reaction is available [77].

In many cases, the dicarbonyl compound is prepared *in situ* by Michael addition of an active methylene or an enolate to an α,β-unsaturated carbonyl compound [78].

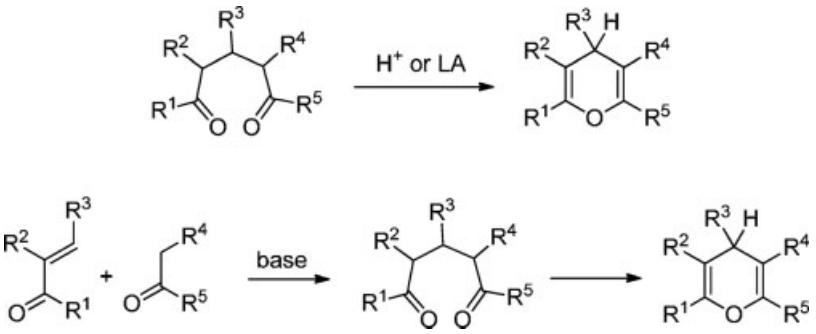
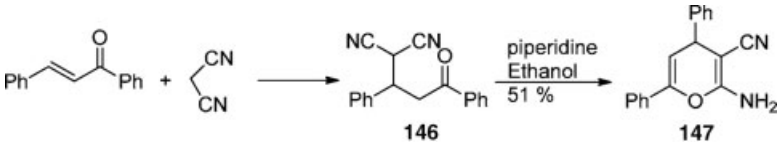


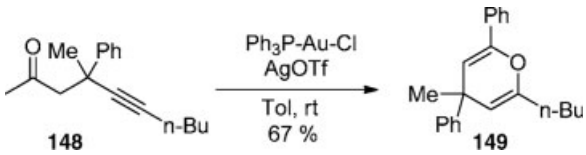
Figure 18.12 General strategies for the synthesis of 4*H*-pyrans.

If the methylene group is activated by the presence of a nitrile, such as malononitrile, intramolecular cyclization of the intermediate adduct **146** takes place at the CN group, giving rise to 2-amino-4*H*-pyrans **147** (Scheme 18.45) [79].



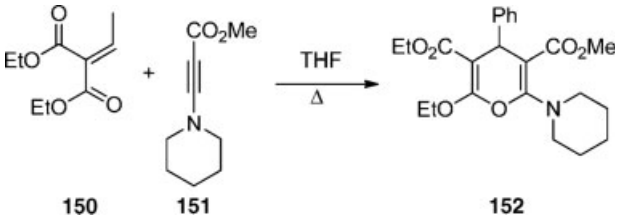
Scheme 18.45 Synthesis of 2-amino-4*H*-pyrans.

Gold-catalyzed cyclization of alk-4-yn-1-ones affords different oxygen heterocycles depending on their structure. Alkynones with one substituent at C3 undergo a 5-*exo*-dig cycloisomerization to substituted furans. However, a 6-*endo*-dig cyclization to 4*H*-pyrans **149** is observed with alkynones **148** bearing two substituents at C3 (Scheme 18.46) [80].



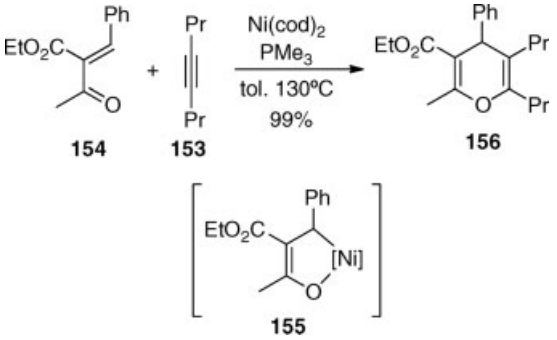
Scheme 18.46 Synthesis of 4*H*-pyrans by gold-catalyzed 6-*endo*-dig cyclization of enynones.

The hetero-Diels–Alder cycloaddition of alkynes with α,β-unsaturated compounds is also a methodology that has been widely employed in the synthesis of 4*H*-pyrans. Owing to the low reactivity of alkynes, highly electron-rich alkynes, typically ynamines, are generally required. Scheme 18.47 presents the reaction between ethylidenemalonate **150** and ynamine **151** to produce polysubstituted pyran **152** [81].



Scheme 18.47 Synthesis of 4*H*-pyrans by inverse-electron-demand [4 + 2] cycloaddition.

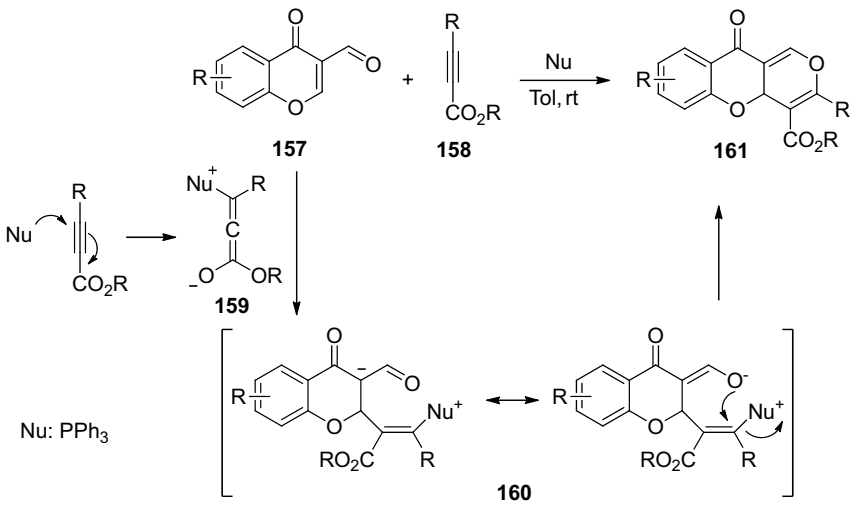
Some of the limitations of this disconnection for the synthesis of 4*H*-pyrans have been overcome recently by the development of a Ni-catalyzed process [82]. Under these conditions, neutral alkynes **153** can be employed in formal [4 + 2] cycloadditions with α,β-unsaturated compounds **154** to give pentasubstituted 4*H*-pyrans **156** (Scheme 18.48). It has been proposed that the reaction proceeds through initial the



Scheme 18.48 Synthesis of 4*H*-pyrans by a Ni-catalyzed formal [4 + 2] cycloaddition.

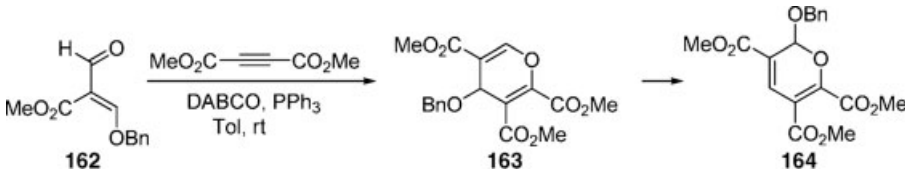
formation of an oxa-nickelacycle **155**, which enables the cycloaddition with the alkyne.

An organocatalyzed [4 + 2] annulation between 3-formylchromones **157** and electron-poor alkynes **158** gives rise to 4*H*-pyrans (Scheme 18.49). The reaction takes place under catalysis by phosphines or tertiary amines [83]. The mechanism involves addition of the nucleophile to the alkyne to give an intermediate zwitterion **159** that adds to the formylchromone through a conjugate addition to afford the intermediate adduct **160**. Ring closure with release of the nucleophile gives the final pyran **161**.



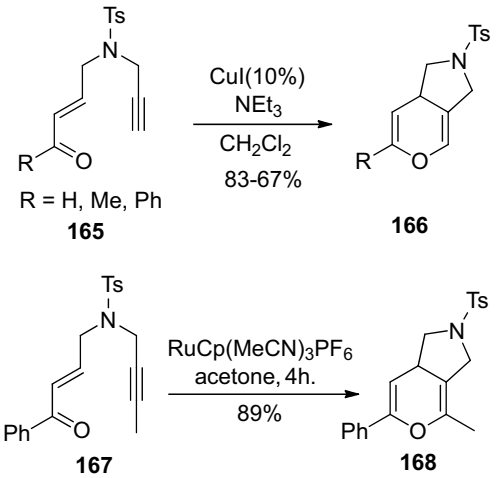
Scheme 18.49 Synthesis of 4*H*-pyrans by an organocatalyzed formal [4 + 2] cycloaddition.

The reaction also proceeds with acyclic oxadienes **162;** however, the 4*H*-pyran cycloadduct **163** undergoes a Claisen rearrangement to give 2*H*-pyran **164** (Scheme 18.50).



Scheme 18.50 Synthesis of 2*H*-pyrans by an organocatalyzed formal [4 + 2] cycloaddition.

The intramolecular version of the [4 + 2] cycloaddition can be performed with neutral alkynes in the presence of transition metal catalysts. For example, the bicyclic 4*H*-pyran **166** is obtained from readily available precursor **165** in a copper-catalyzed intramolecular cycloaddition (Scheme 18.51) [84]. It has been postulated that the reaction proceeds through the formation of a Cu-acetylide, and therefore is limited to terminal alkynes. Analogous adducts **168**, derived from internal alkynes **167**, can be obtained by a Ru-catalyzed reaction that operates through a totally different mechanism [85].



Scheme 18.51 Synthesis of bicyclic 4*H*-pyrans by metal-catalyzed intramolecular [4 + 2] cycloadditions.

18.4
Pyrones, Coumarins, and Chromones

This section is dedicated to the family of oxygenated six-membered rings with the structure of unsaturated lactones. The properties, synthesis, and reactivity of 2*H*-pyran-2-ones (α-pyrones) (**4**), 4*H*-pyran-4-ones (γ-pyrones) (**5**), and the corresponding benzofused analogues such as coumarins (2*H*-1-benzopyran-2-ones) (**9**) and chromones (4*H*-1-benzopyran-4-ones) (**10**) are compiled (Figure 18.13).

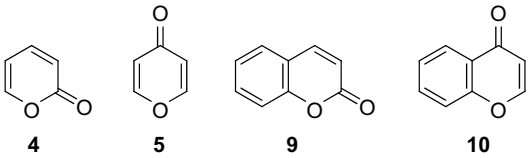


Figure 18.13 Structure of α-pyrone (**4**), γ-pyrone (**5**), coumarin (**9**) and chromone (**10**).

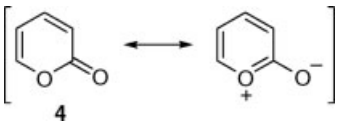


Figure 18.14 Resonance structures for 2*H*-pyran-2-one.

18.4.1
α-Pyrones (2*H*-Pyran-2-ones)

The structure of 2*H*-pyran-2-ones can be presented as a resonance hybrid between two structures: an enol-lactone and a zwitterionic aromatic structure (Figure 18.14).

However, α-pyrones present an absorption frequency in their infrared spectra at around 1730 cm^{-1} [86], which is characteristic of a ketone function. This value indicates low participation of the zwitterionic structure and, as the result, low aromaticity [87].

On the other hand, NMR spectra indicate the location of positive charges at positions 4 and 6 – as a downfield shift in proton [88] and carbon [89] spectra – relative to positions 3 and 5.

As an indication of the interest of these compounds it is worth noting that the α-pyranone structure can be found in several natural compounds [90], some of which exhibit biological properties. As an example, compounds of the family of gibepyrones (6-substitued-3-methyl-2-pyrones) (**169**, **170**) (Figure 18.15) have demonstrated inhibitory activity against some types of bacteria [91].

In addition, while several other examples have been reported related to the properties of α-pyrones, their benzofused derivatives (coumarins) have found greater applicability. These compounds are analyzed in Section 18.4.2.

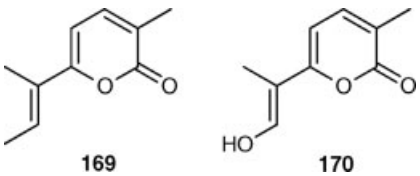


Figure 18.15 Compounds of the family of gibepyrones.

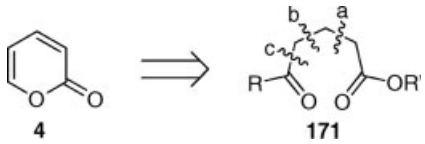


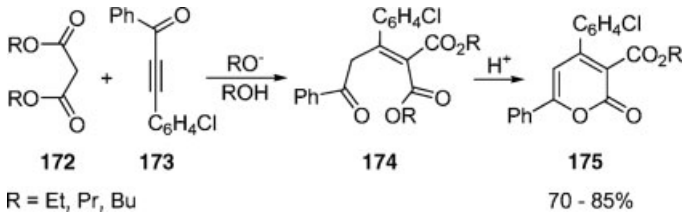
Figure 18.16 Retrosynthetic analysis for the formation of 2*H*-pyran-2-one (**4**) from 5-ketoacid derivative **171**.

18.4.1.1 Synthesis of α-Pyrones

The most common methodology for the formation of 2*H*-pyran-2-ones involves ring closure from isolated, or *in situ* synthesized, 1,5-ketoacid derivatives. This procedure has been followed by many authors and can be achieved by three different approaches:

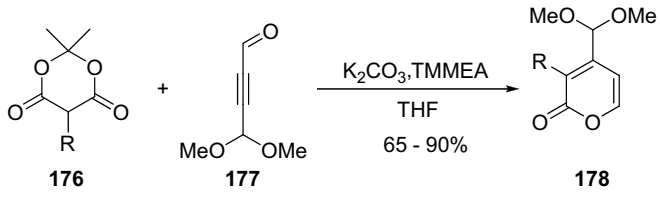
(a) from ester enolates,
(b) from ketone enolates,
(c) through acylation of ester dienolates (Figure 18.16).

The use of malonates or β-ketoesters is a classic procedure for the first approach. In this sense, Scheme 18.52 shows an example following this methodology by using dialkyl malonate **172** and an α,β-unsaturated ketone **173** [92]. The procedure involves the formation of the 5-ketoester **174**, which is transformed, through an ester exchange under acidic treatment, into pyranone **175**.



Scheme 18.52 Synthesis of α-pyrone **175** from malonate **172**.

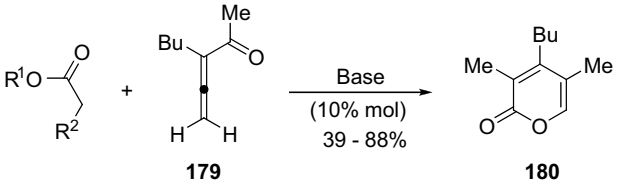
This methodology, starting from malonates, is still described in numerous publications. As an example, Scheme 18.53 shows an α-pyrone formation from a cyclic malonate ester (**176**) and a propionaldehyde (**177**) [93]. After the initial attack,



Scheme 18.53 Synthesis of α-pyrone **178** from cyclic malonate **176**.

the reaction evolves towards the formation of the pyranone **178** through a diol deprotection and ester decarboxylation.

Among the numerous electrophiles that follow this methodology, allenyl ketones have also been reported. Thus, Scheme 18.54 describes the synthesis of polysubstituted 2*H*-pyran-2-one **180** from the reaction of substituted allenyl ketone **179** and malonic ester or other activated methylene groups [94]. The reaction takes place in the presence of a catalytic amount of base and involves a double bond isomerization to form the corresponding 5-ketoester, which suffers an *in situ* cyclization to the pyranone **180**.

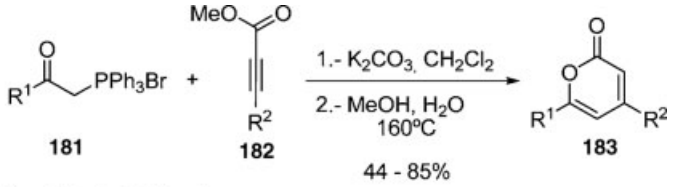


179 **180**

R^1 = Me, Et
R^2 = CO_2Me, CN

Scheme 18.54 From allenyl ketone **179** to α-pyranone **180**.

On the other hand, several approaches to 2*H*-pyran-2-ones from 5-ketoesters have been reported following route (b) (Figure 18.16). This methodology can be considered as the complementary to that of route (a). As an example, Scheme 18.55 shows a procedure that involves a Michael-type addition of the enolate of ketone **181** to the propionic ester **182** [95].

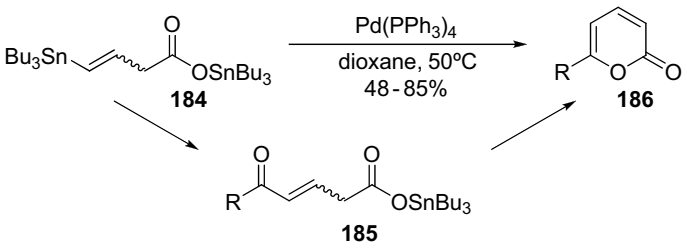


181 **182** **183**

R^1 = 2-Furyl, 2-Thienyl
R^2 = CF_3, *n*-C_2F_5, *n*-C_3F_7

Scheme 18.55 Synthesis of 2*H*-pyran-2-ones **183** through via route (b) in Figure 18.16.

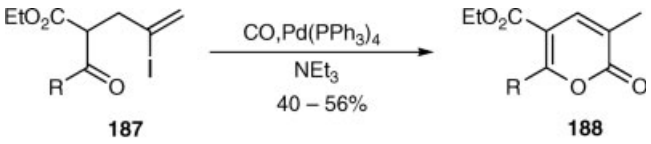
Finally, route (c) (Figure 18.16) implies the acylation of an ester enolate to form the corresponding 5-ketoacid derivative that can be isolated, or *in situ* cyclized, to the corresponding α-pyrones. Thus, Stille coupling of vinyltin **184** affords the 5-ketoester intermediate **185**. This intermediate suffers *in situ* transformation into the corresponding 2*H*-pyran -2-one **186** (Scheme 18.56) [96].



R = Ph, 4-MeO-C_6H_4, 2-Br-C_6H_4, (*Z*)-CH=CHMe, CMe=CH_2,CH=CMe_2, (*Z*)-CH=CHPr (*Z*)-CH=CHPh, *i*-Pr, *i*-Bu, $(CH_2)_3$-Cl, Bn

Scheme 18.56 Synthesis of 2*H*-pyran-2-ones **186** though via route (c) in Figure 18.16.

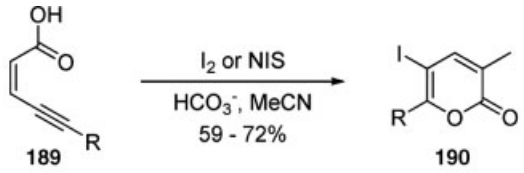
In a similar approach, carbonylation of the alkenyl ketone **187**, under palladium catalysis, followed by O-enolate cyclization affords pyranone **188** (Scheme 18.57) [97].



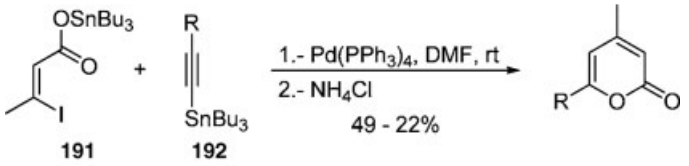
R = Me, CH_2CO_2Et

Scheme 18.57 Synthesis of α-pyrones **188** via carbonylation–cyclization.

In addition to synthesis through the formation of 5-ketoacid derivatives, many alternative methodologies for synthesis of 2*H*-pyran-2-ones have also been reported. Among of them, several examples of lactonization of *(Z)*-2-en-4-ynoate derivatives can be found. Scheme 18.58 describes two examples: an iodolactonization and an



R = Me, *n*-Bu, *n*-C_5H_{11}, *n*-C_6H_{13}, (*E*)-CH=CHC_3H_7



R = *n*-C_5H_{11}, *n*-C_6H_{13}, CH_2OTMS

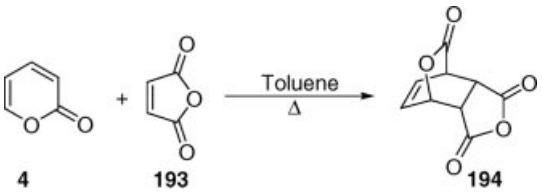
Scheme 18.58 Lactonizations for the synthesis of 2-pyranones.

intermolecular Stille coupling, followed by the corresponding lactonization. Thus, iodine or *N*-iodosuccinimide (NIS) addition to the *(Z)*-2-en-4-ynoic acid **189**, in a basic media, induces its cyclization to the α-pyrone **190** [98]. On the other hand, the *(Z)*-2-en-4-ynoic derivative is *in situ* generated from an alkynyltin **192** and a 3-iodoacrylate **191** to undergo further cyclization [99].

18.4.1.2 Reactivity of α-Pyrones

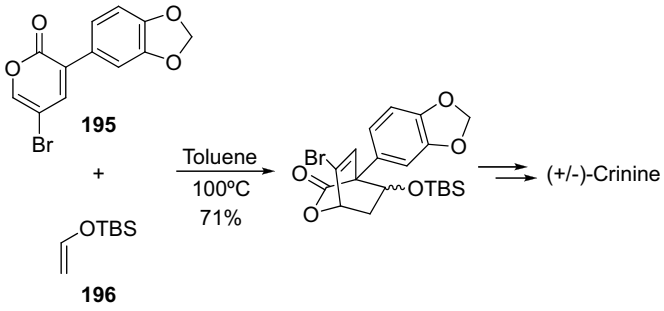
As already mentioned, α-pyrones can be described as hybrids between two resonance structures: an aromatic pyrylium salt and a lactone (Figure 18.14). Although, some reactions can be associated to the aromaticity, most of the reactive patterns are related to a 1,3-diene or a lactone structure.

Participation of α-pyrones as 1,3-dienes in Diels–Alder reactions was described as early as 1931 [100]. In this sense, pyran-2-one (**4**) reacts with maleic anhydride (**193**) to give the corresponding adduct **194** (Scheme 18.59).



Scheme 18.59 Diels–Alder cycloaddition of α-pyranone (**4**).

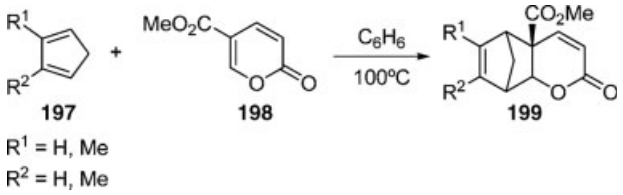
This reactivity pattern has also found application in the modern organic synthesis as several structures have been accessed starting from α-pyrones and dienophiles. Scheme 18.60 describes the Diels–Alder reaction of α-pyrone **195** and vinyl ether **196** in the route to biologically active compounds [101]. Examples of enantioselective Diels–Alder reactions with 2*H*-pyran-2-one have also been reported [102].



Scheme 18.60 Diels–Alder reaction of pyranone **195** in the synthesis of (±)-crinine.

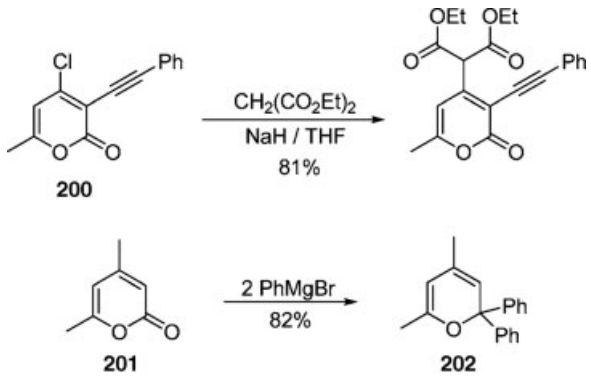
Interestingly, α-pyrones also participate in Diels–Alder reactions as dienophiles. Thus, reaction of the pyran 2-one **198** and cyclopentadiene **197** produces the bicyclic

lactone **199** (Scheme 18.61) [103]. This dienophilic capability of pyranone **198** is facilitated by the presence of an electron-withdrawing group.



Scheme 18.61 α-Pyrone **198** reacting as a dienophile.

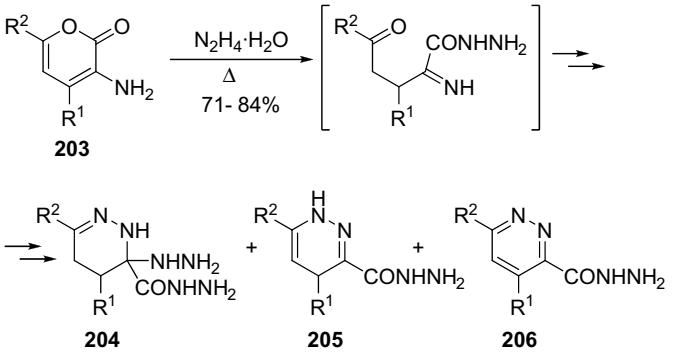
Taking account of their dienone structure, 2*H*-pyran-2-ones are also reactive towards nucleophiles [104]. This reaction can occur at three different electrophilic sites: C4, C6, and the carbonylic carbon C2. Scheme 18.62 shows two examples of nucleophilic attacks to C4 and C2 positions, respectively. In the first example, nucleophilic substitution of the halogen atom has been achieved at the C4 carbon of the pyran-2-one **200** [105]. In the second example, addition of two equivalents of a Grignard reagent to pyranone **201** furnishes 2,2-disubstituted pyrans **202** [106].



Scheme 18.62 Nucleophilic attacks on α-pyrones at C4 and C2.

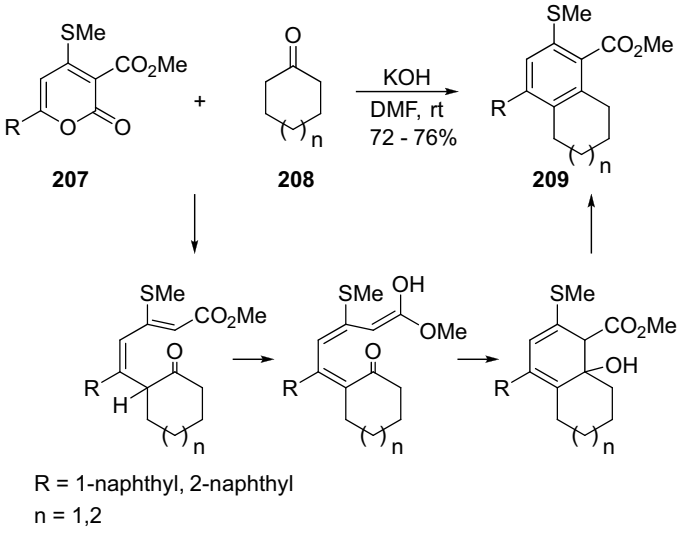
Transformation of 2-pyranones into other heterocycles through nucleophilic additions at C2 is also possible. Scheme 18.63 shows the transformation of 3-amino-2-pyranone **203** into pyridazines **204–206** [107], initiated by a nucleophilic attack of hydrazine on the carbonylic carbon followed by a ring closure. This reaction yields tetrahydropyridazine **204** along with different amounts of dihydropyridazine **205** and pyridazine **206**. Further transformations allow the formation of **206** as the sole product.

C6-attack is also very common, and the reaction usually evolves to the formation of aromatic structures. These reactions begin by a nucleophilic attack, followed by an



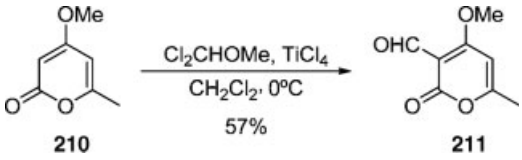
Scheme 18.63 Transformation of 2-pyranone **203** into pyridazine derivatives.

intramolecular cyclization and decarboxylation. Scheme 18.64 reports one such example in which the bicyclic aromatic derivative **209** is formed. This reaction is initiated by the nucleophilic attack of the enolate of ketone **208** on the C6 position of α-pyrone **207** followed by ring opening, decarboxylation, and recyclization [108].



Scheme 18.64 Transformation of α-pyrone **207** into arene **209**.

In a less general approach, α-pyrones also react with electrophiles through the C3 position. In this sense, 2*H*-pyran-2-ones bearing a hydroxy or alkoxy group at C4 have been described as useful intermediates for accessing natural compounds with the skeleton of 4-hydroxy-3-substituted-2-pyranones [109]. Scheme 18.65 shows the



Scheme 18.65 α-Formylation of pyranone **210**.

reaction of the 4-methoxy-2-pyranone (**210**) with an electrophile, in the presence of titanium tetrachloride, to give the 3-formylpyranone **211** [110].

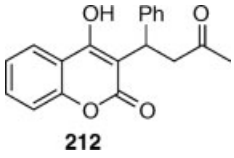
Finally, other reactions such as photochemical reactions [111], hydrogenations [112], and palladium-catalyzed couplings [113] can also take place at the α-pyranone structure.

18.4.2
Coumarins (2*H*-Chromen-2-ones or 2*H*-1-Benzopyran-2-ones)

Coumarins (2*H*-benzopyran-2-ones) are nearly planar compounds and are also considered as enol-lactone systems in a similar way to the corresponding α-pyrones.

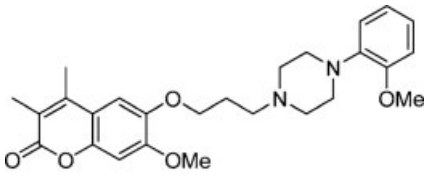
As noted above, coumarins (1,2-benzopyrones) have been widely reported in the scientific literature in respect of their important applications. Pharmacological properties are good examples of this, such as warfarin (**212**, Figure 18.17), a coumarin derivative that has found application as anticoagulant for preventing thrombosis [114]. Owing to its anticoagulant activity it has also found application as pesticide to eradicate rats and mice plagues [115].

Figure 18.18 shows the structure of ensaculin (**213**), another interesting coumarin. It is a 3,4-dimethylcoumarin, with a tethered piperazine moiety, that has demonstrated potential activity against dementia [116].



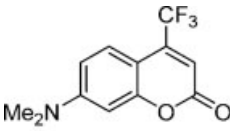
212

Figure 18.17 Structure of warfarin.



213

Figure 18.18 Structure of ensaculin.

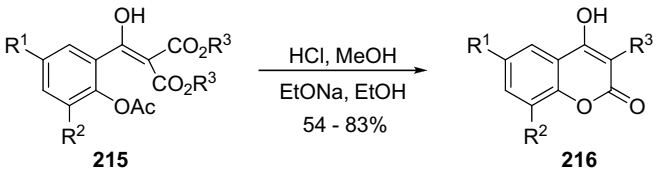


214

Figure 18.19 Fluorescent coumarin **214** is used in laser devices.

In addition to their use in pharmacology, coumarins can also be found in other fields such as material science. For instance, coumarin **214** has found applicability as part of laser devices, due to its fluorescent properties (Figure 18.19) [117].

Perhaps one of the easiest ways to access to the coumarin structure consists in an intramolecular lactonization, as several examples of the synthesis of coumarins following this methodology have been reported. In the reaction shown in Scheme 18.66, coumarin **216** has been synthesized through an acidic and basic deprotection/transesterification sequence from the acetoxy compound **215** [118].

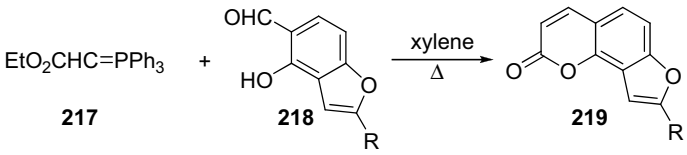


215 **216**

R^1 = H, Me, Cl
R^2 = H, Me, OMe
R^3 = Me, Et

Scheme 18.66 Synthesis of coumarin **216** through an intramolecular lactonization.

Salicylaldehydes are often used as staring materials for the intramolecular lactonization. These compounds can be transformed, following simple procedures such as Wittig [119] or Knoevenagel reactions [120], into intermediates that *in situ* cyclize to the corresponding coumarins. Scheme 18.67 describes the Wittig reaction of phosphorane **217** with salicylaldehyde derivative **218** to form an α,β-unsaturated ester that lactonizes *in situ* to give furanocoumarin **219** [121].

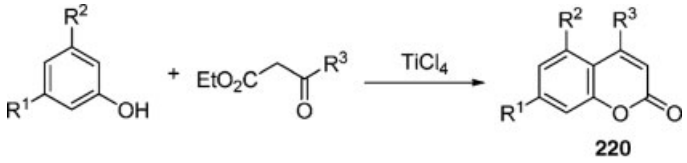


217 **218** **219**

Scheme 18.67 Synthesis of the furanocoumarin **219**.

One of the most extended procedures for coumarin synthesis consists of a Pechmann condensation, an acid-catalyzed condensation of phenol with a β-ketoester. The reaction mechanism is initiated by an electrophilic aromatic substitution

and involves a final step of lactonization. Among the different reaction conditions reported, Scheme 18.68 describes a coumarin synthesis, in the absence of solvent, through a Pechmann condensation catalyzed by titanium tetrachloride [122].



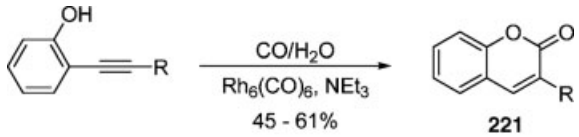
220

R^1 = H, Me, OH, OMe, OCH_2CO_2Et, OCH_2COPh, OCHMeCOMe
R^2 = H, Me, OH
R^3 = Me, CF_3, CH_2Cl

Scheme 18.68 Pechmann condensation for the synthesis of coumarin **220**.

Propionic acids [123] or propionic esters [124] are also used as 1,3-dicarbonyl synthetic equivalents for this reaction. Other intramolecular reactions such as condensations [125], ring closing metathesis [126], or transition metal catalyzed arylation of aryl alkynoates [127] have also been reported.

Finally, it is worth noting an interesting procedure that involves a transition metal catalyzed carbonylation. Thus, Scheme 18.69 describes a coumarin synthesis from *ortho*-alkynylphenols [128]. Rhodium-catalyzed carbonylation followed by lactonization furnishes coumarin **221**, along with certain amount of a benzofuranone.



221

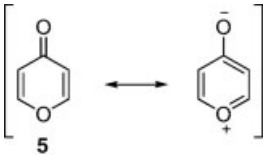
R = Me, *n*-Bu, *t*-Bu, Ph, 4-MeO-C_6H_4, 4-CN-C_6H_4

Scheme 18.69 Synthesis of coumarin **221**, involving a carbonylation step.

Related to their reactivity, coumarins follow similar reaction patterns to those described for α-pyrones. In this sense, reactions with nucleophiles [129], electrophiles [130], and also Diels–Alder cycloadditions [131], with the participation of the lactone ring, are common examples. Only a few procedures involving the benzene fused ring, such as selective nitration of the aromatic ring [132], differ from the reactivity of α-pyrones.

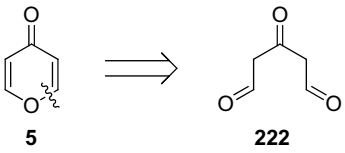
18.4.3
γ-Pyrones (4*H*-Pyran-4-ones)

4*H*-Pyran-4-ones, similarly to 2*H*-pyran-2-ones, can be presented as resonance hybrids between a cross-conjugated cycloenone and a zwitterionic aromatic structure (Figure 18.20).



5

Figure 18.20 Mesomeric structures for 4*H*-pyran-4-one.



5 222

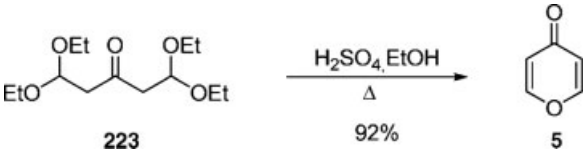
Figure 18.21 Retrosynthetic approach to γ-pyrones.

Taking account of the absorptions in the infrared spectra, γ-pyrones are also mainly considered as lactones instead of aromatic compounds. To support this theory an absorption at the IR spectra around 1660 cm^{-1} is observed [133], similarly to the C=O stretching seen in cyclohexadienones. However, this value is slightly lower than the absorption observed for α-pyrones. These values, in addition to their higher basicity compared to enones, indicate a greater contribution from the aromatic structure [134].

18.4.3.1 Synthesis of γ-Pyrones

The most commonly accepted methodology for the synthesis of 4*H*-pyran-4-ones (**5**) lies in the cyclocondensation of 1,3,5-tricarbonylcompounds (**222**), usually performed under acidic conditions (Figure 18.21) [135].

As an example of this approach, Scheme 18.70 shows a high yield, multi-gram scale (10 g) synthesis of γ-pyrone (**5**) from diketalic bis-aldehyde **223** [136].

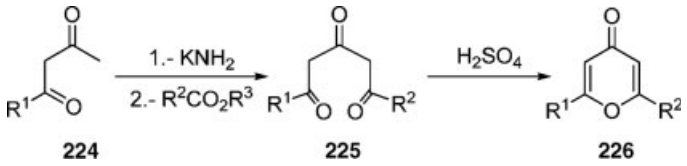


223 5

Scheme 18.70 Large-scale synthesis of γ-pyranone (**5**).

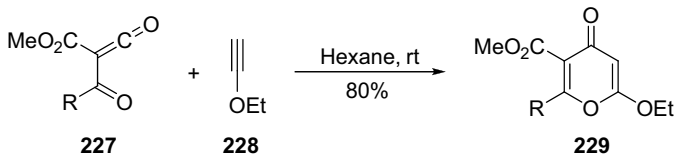
The main differences in the reported methodologies for the synthesis of γ-pyrones usually occur in the procedures involved for accessing the 1,3,5-tricarbonyl compound or analogues. Thus, use of the enolate of diketone **224**, in the reaction with carboxylic esters, yields triketones **225** that cyclize under acidic conditions to give 2,6-disubstituted γ-pyrones **226** (Scheme 18.71) [137].

As another example of this approach, γ-pyrones can also be obtained from α-pyrones. Thus, α-pyrones, after acidic treatment, are cleaved and transformed into a 1,3,5-triketone that *in situ* undergoes recyclization to the corresponding γ-pyrone [138].



Scheme 18.71 4-Pyranone **226** from diketone **224**.

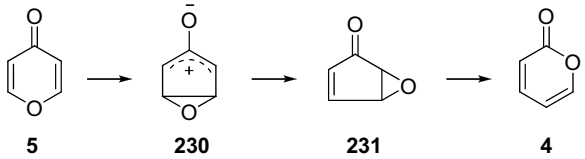
The synthesis of 4*H*-pyran-4-ones has also been reported involving a totally different approach. As an example, Scheme 18.72 describes a hetero-Diels–Alder reaction between the ethoxyethyne (**228**) and ketoketene **227** to form the corresponding substituted γ-pyrone **229** [139]. In a similar way, the use of enol-esters gives rise to 6-unsubstituded pyranones, after elimination of ethanol.



Scheme 18.72 Hetero-Diels–Alder cycloaddition to form γ-pyrone **229**.

18.4.3.2 **Reactivity of γ-Pyrones**

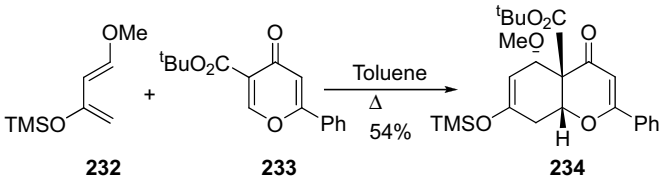
γ-Pyrones can be easily transformed into α-pyrones upon irradiation. This evolution is proposed to involve an initial step of electrocyclization to form the intermediate **230**, which can evolve to the formation of the epoxycyclopentenone **231**. Finally, oxygen migration followed by ring expansion leads to the 2*H*-pyran-2-one (**4**) (Scheme 18.73) [140].



Scheme 18.73 Photochemical transformation of γ-pyrone (**5**) into α-pyrone (**4**).

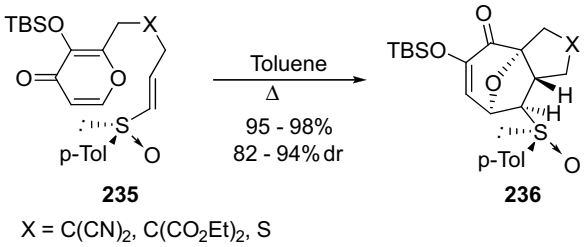
The reactivity of 4*H*-pyran-4-ones shows great similarity to that of 2*H*-pyran-2-ones. Thus, cycloadditions with the participation of one or both pyranone double bonds are good indications of the low aromaticity of γ-pyrones. Scheme 18.74 shows the participation of γ-pyrone **233** as a dienophile in a Diels–Alder reaction with Danishefsky's diene (**232**) to form the bicyclic pyranone **234** [141].

On the other hand, γ-pyrones can be transformed into medium-sized rings through cycloadditions that involve the participation of both unsaturations. In this sense, several intermolecular [5 + 2] cycloadditions have been reported [142].



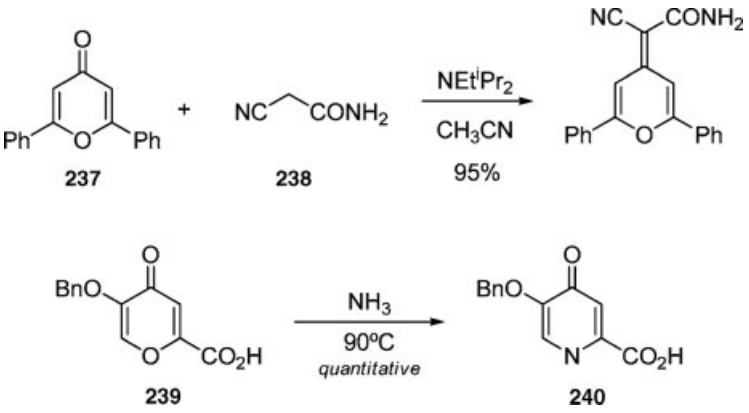
Scheme 18.74 γ-Pyrone **233** as a dienophile.

Among of them, the optically active 8-oxabicyclic[3.2.1]octane **236** has been produced from optically active β-silyloxy-γ-pyrone **235** (Scheme 18.75) [143].

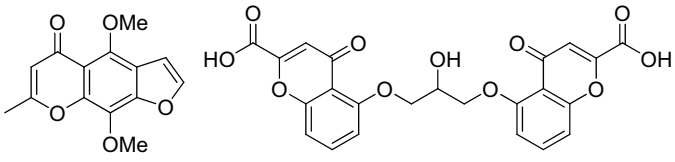


Scheme 18.75 Intramolecular [5 + 2] cycloaddition of γ-pyrone **235**.

4*H*-Pyran-4-ones, similarly to 2*H*-pyran-2-ones, react with nucleophiles, involving an opening–reclosing of the six-membered ring. Nucleophilic attack on γ-pyrones can occur in two different ways: 1,2-addition at the carbonyl group and 1,4-conjugated additions. Scheme 18.76 shows two representative examples that describe this regioselectivity. Thus, 1,2-addition followed by double bond formation is observed in the reaction of the reactive methylene group of the cyanoacetamide (**238**) and γ-pyrone **237** [144]. On the other hand, γ-pyrone **239** has been transformed into the



Scheme 18.76 Nucleophilic attacks on 4-pyranones.



241 **242**

Figure 18.22 Structures of khellin (**241**) and cromoglicic acid (**242**).

pyridone **240** by a nucleophilic 1,4-addition upon ammonium hydroxide treatment [145].

18.4.4
Chromones (4*H*-Chromen-4-ones or 4*H*-1-Benzopyran-4-ones)

As described above for coumarins, several examples of natural occurring compounds with the structure of chromones (4*H*-1-benzopyran-4-ones) have been described.

As an example, khellin (**241**) is a natural biologically active chromone that has been widely used in traditional Egyptian medicine for the treatment of renal colic and it is known that it can also act as a vasodilatator (Figure 18.22) [146]. However, due to the important secondary effects of khellin, resulting headaches or intestinal disorders, other synthetic analogues such as cromoglicic acid (**242**) have been developed. The sodium salt of **242** has found application in the treatment of allergic rhinitis or asthma [147].

Flavones (2-phenylchromones) are also natural occurring compounds, widely found, usually as glycoside derivatives, as pigments in plants. Compounds of this type are luteolin (**243**), which is present in celery, green pepper, and camomile tea, which shows antioxidant properties [148], and apigenin (**244**), a component of parsley and celery with important potential biological [149] and industrial properties as a dye for wool (Figure 18.23). In addition, 3-hydroxyflavones, also known as flavonols, form

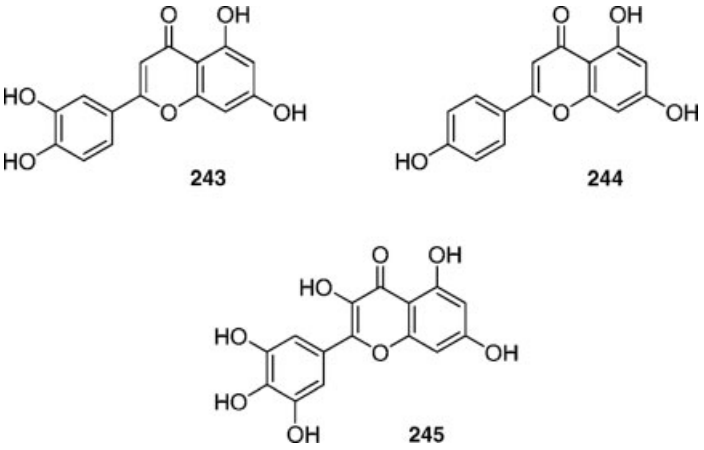
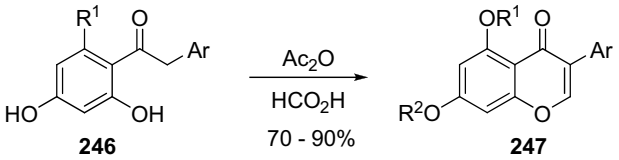


Figure 18.23 Structures of luteolin (**243**), apigenin (**244**), and myricetin (**245**).

another interesting family of biologically active chromones. As an example, myricetin (**245**), found in grapes and other plants, has demonstrated antitumor activity [150].

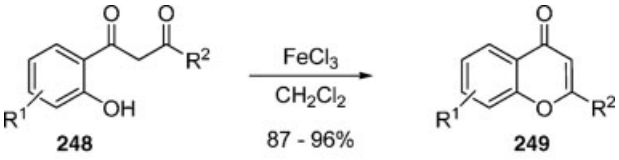
The most extensive methodology for the synthesis of 4*H*-1-benzopyran-4-ones (chromones) involves the formation of the pyranone ring starting from *ortho*-hydroxyarylketones or related compounds. As a general example, Scheme 18.77 shows the synthesis of isoflavone **247** through the treatment of *ortho*-hydroxyphenone **246** with a mixed anhydride (of acetic and formic acids) and further dehydration [151].



R^1 = H,OH
R^2 = H,HCO
Ar = 4-NO_2-C_6H_4

Scheme 18.77 Formation of chromone **247** from *o*-hydroxyarylketone **246**.

The intramolecular cyclization followed by dehydration of *o*-hydroxyacetophenones can be achieved using different experimental conditions. Scheme 18.78 shows a procedure promoted by iron trichloride [152]. The phenols **248** also cyclize under copper treatment and microwave irradiation [153] to form chromones **249**.

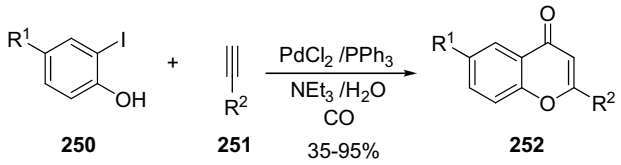


R^1 = H, 5-OH, 5-Me
R^2 = Ph, 2-Cl-C_6H_4, 3-MeO-C_6H_4, 4-Cl-C_6H_4, 4-BnO-C_6H_4
4-MeO-C_6H_4, 4-NO_2-C_6H_4, 3,4-$(MeO)_2$-C_6H_4
3,4,5-$(MeO)_3$-C_6H_4

Scheme 18.78 Iron-promoted formation of chromone **249**.

The synthesis of chromones starting from *o*-hydroxyketones or related compounds has also been reported through an intramolecular cyclization of aryl ethynylketones [154] or 2-acetoxy- [155], benzyloxy- [156], or hydroxychalcones [157], followed by oxidation.

In addition to the procedures reported here, it is worth mentioning an interesting example involving a carbonylation step. This reaction is described in Scheme 18.79: chromone **252** is synthesized through a palladium-catalyzed carbonylation of *o*-iodophenol **250**, in the presence of a terminal alkyne (**251**) [158].



250 **251** **252**

R^1 = H, Me, *t*-Bu, Ph, Cl, CO_2 Et

R^2 = *n*-Bu, *t*-Bu, *n*-C_6H_{13},TMS

Scheme 18.79 Synthesis of chromone **252** through a palladium-catalyzed carbonylation.

Finally, chromones can also be synthesized starting from other heterocycles. Scheme 18.80 shows the transformation of benzofuran **253** into chromone **254** upon treatment with osmium tetroxide followed by hydrolysis [159]. The reaction involves a double bond oxidation followed by opening of the furan ring and a final recyclization to form a six-membered ring.

253 **254**

Scheme 18.80 Transformation of benzofuran **253** into chromone **254**.

Finally, no section is specifically dedicated to compiling reported examples of the reactivity of chromones because, in addition to the typical aromatic substitution at the arene ring and similar behavior to coumarins, their reactivity follows a similar pattern to the non-benzofused compounds, the γ-pyrones.

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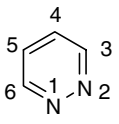
19
Six-Membered Heterocycles: 1,2-, 1,3-, and 1,4-Diazines and Related Systems

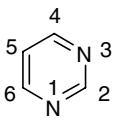
María-Paz Cabal

19.1
Introduction

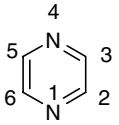
Diazines are aromatic six-membered heterocycles that contain two sp^2-hybridized nitrogen atoms in the ring. The three diazine isomers are pyridazine (1,2-diazine) [1–3] (**1**), pyrimidine (1,3-diazine) [4] (**2**), and pyrazine (1,4-diazine) [5] (**3**). They are stable, colorless compounds that are soluble in water. Being rather expensive, and not readily available, these parent compounds are rarely used as starting materials for the synthesis of their derivatives.



Pyridazine
1

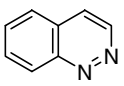


Pyrimidine
2

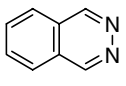


Pyrazine
3

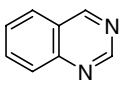
Four types of bicyclic variants in which a benzene ring is fused onto the diazine include cinnoline (benzo[*c*]pyridazine) (**4**), phthalazine (benzo[*d*]pyridazine) (**5**), quinazoline (benzo[*d*]pyrimidine) (**6**), and quinoxaline (benzo[*e*]pyrazine) (**7**). In addition, pteridine (**8**) and the diazanaphthalene system phenazine (dibenzopyrazine) (**9**) are also important derivatives.



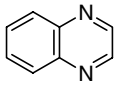
Cinnoline
4



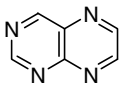
Phthalazine
5



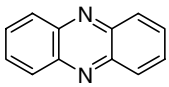
Quinazoline
6



Quinoxaline
7



Pteridine
8



Phenazine
9

Modern Heterocyclic Chemistry, First Edition.
Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.

19.2
General Reactivity

19.2.1
Physical and Spectroscopic Properties [6]

As 6π-electron heteroaromatic compounds diazines are electron-deficient due to the inductive effects of the nitrogen atoms that induce a partially positive charge on the carbon atoms. The calculated π-electron density [7] distributions for each ring, compared to pyridine (Figure 19.1), are consistent with the observed reactivities towards electrophiles, which are notably lower than those towards nucleophiles.

Pyridazine and pyrimidine have a planar, slightly distorted hexagonal geometry, while pyrazine is planar with D_{2h} symmetry. Each of these heterocycles can be regarded as aromatic in character, and, consequently, the bond lengths and internal bond angles (Figure 19.2) are also very similar to those in benzene (1.39 Å), based on X-ray diffraction, gas-phase electron diffraction and microwave spectroscopy studies [8].

However, the resonance energies of pyrimidine (110 kJ mol^{-1}) and pyrazine (100 kJ mol^{-1}) are significantly lower than those of benzene (150 kJ mol^{-1}) or pyridine (117 kJ mol^{-1}), which means that these compounds are less aromatic. Another way to measure the degree of aromaticity is by the structural index of aromaticity that is calculated based on the bond lengths; in such set of values the aromaticity is expressed as a percentage of that of benzene (Table 19.1).

The N−N bond in pyridazine has significant single bond character, supporting theoretical calculations suggesting that canonical form **1a**, having double bonds

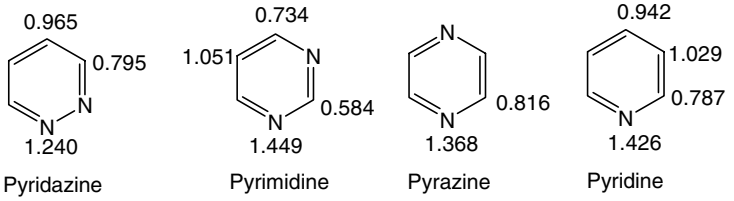


Figure 19.1 Calculated π-electron density distributions for each ring, compared to pyridine.

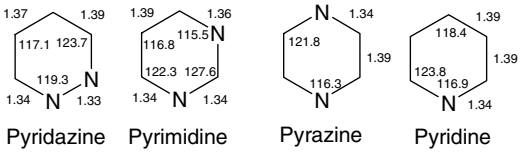


Figure 19.2 Bond lengths (Å) and internal bond angles (°) of pyridazine, pyrimidine, pyrazine, and pyridine.

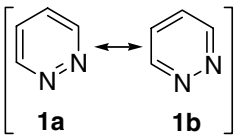
Table 19.1 Aromaticity index (%).

Benzene	100
Pyridine	82
Pyridazine	65
Pyrimidine	67
Pyrazine	75

Table 19.2 ^{1}H NMR chemical shifts (ppm) of diazines compared with pyridine.

Compound	H2	H3	H4	H5	H6	C2	C3	C4	C5	C6	Solvent
Pyridazine	—	9.17	7.52	7.52	9.17	—	153.0	130.0	130.3	153.0	$CDCl_3$
Pyrimidine	9.26	—	8.78	7.36	8.78	158.4	—	156.9	121.9	156.9	$CDCl_3$
Pyrazine	8.60	8.60	—	8.60	8.60	145.9	145.9	—	145.9	145.9	$CDCl_3$
Pyridine	8.52	7.16	7.55	7.16	8.52	149.5	125.6	138.7	125.6	149.5	$CDCl_3$

between the nitrogens, contributes less to the resonance hybrid than the N−N single bond structure **1b**.



The ^{1}H and ^{13}C NMR spectra of the diazines show close similarities with pyridine (Table 19.2). The additional nitrogen atom in the ring is responsible for a greater downfield shift of the ring protons and C-atoms at the 3- and 6-positions in pyridazine, the 2-, 4-, and 6-positions in pyrimidine, and in all the carbons in pyrazine. The symmetrical 1,4-diazines structure, of course, is reflected in the ^{1}H and ^{13}C NMR spectra, showing one signal for the four ring protons and C-atoms.

The vicinal coupling constants of ortho protons on the rings vary considerably, depending on the type of heterocycle, and are typically smaller for those protons located closer to the heteroatoms (Figure 19.3). The magnitude of the coupling constants in effect reflects the degree of double bond character in the particular C−C bond. ^{15}N NMR spectroscopy has also been used to estimate the hybridization of the nitrogen atoms [9].

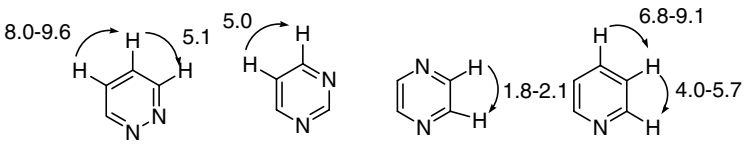


Figure 19.3 Vicinal coupling constants (Hz) of ortho protons.

Table 19.3 UV absorption bands of the diazines versus pyridine.

Compound	$\pi \rightarrow \pi^*$	Log ε	$n \rightarrow \pi^*$	Log ε	Solvent
Pyridazine	241	3.02	340	2.56	Hexane
	251	3.15			
Pyrimidine	238	3.48	272	2.62	H_2O
	243	3.50			
Pyrazine	261	3.81	301	2.88	H_2O
	267	3.72			
Pyridine	195	2.65	270	3.87	Hexane
	251	3.30			

Table 19.3 lists the principal bands in the UV spectra of the three monocyclic systems. The six-membered aza-aromatic compounds possess the 6π-electron system of benzene, and have non-bonding electron pairs on the nitrogen atoms. These electron pairs are responsible for $n \rightarrow \pi^*$ electronic transitions at longer wavelengths. These absorptions are weak in comparison to the $\pi \rightarrow \pi^*$ transition of the ring electrons and are frequently difficult to locate in spectra except when the two nitrogen atoms are adjacent. Thus, the $n \rightarrow \pi^*$ bands are more obvious features of the UV spectra of compounds such as pyridazine (**1**) and cinnoline (**4**).

The introduction of a nitrogen atom into a benzene ring tends to make a derivative more crystalline and less volatile; this effect is even greater for the diazines, especially pyridazine and pyrazine. Pyridazine, in contrast, is a colorless liquid, soluble in water and alcohols but insoluble in hydrocarbons. The high boiling point of pyridazine, 80–90 °C – higher than the other two diazines (Table 19.4) – is attributed to the polarizability of the N–N unit, which results in extensive dipolar association in the liquid state. Alkyl groups attached to ring carbon atoms usually increase the boiling points by 20–60 °C, while hydrogen bonding groups such as carboxylic acids, amides, amino, and hydroxy substituents afford solids. Methoxy, methylthio, and dimethylamino derivatives are often liquids, while chloro compounds have boiling points similar to those of the corresponding ethyl derivatives, and approximately 25 °C lower than their bromo analogues.

Table 19.4 Physical properties of pyridazine, pyrimidine, and pyrazine versus pyridine.

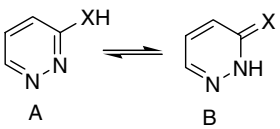
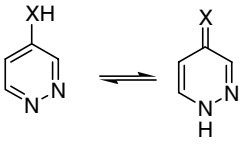
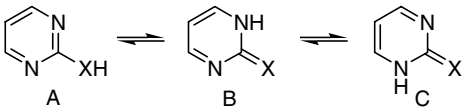
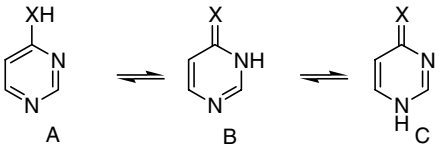
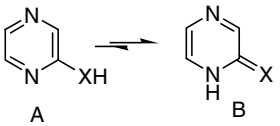
Property	Pyridazine	Pyrimidine	Pyrazine	Pyridine
Mp (°C)	−8	22.5	57	−42
Bp (°C/760 mmHg)	208	124	116	115
pK_a	2.3	1.3	0.4	5.2
Dipole moment (μ, D)	4.22	2.33	0	2.22
$\Delta H°$ (kJ mol^{-1})	4397.8	4480.2	4480.6	

The basicities of the diazines are sharply reduced from that of pyridine and, consequently, they are more difficult to protonate on the nitrogen centers. This is reflected by the significantly lower pK_a values the protonated species have compared to pyridinium cation (pK_a 5.2): 2.3 for protonated pyridazine, 1.3 for protonated pyrimidine, and 0.4 for protonated pyrazine. The dipolar moment of pyridazine is higher than that of pyrimidine, while pyrazine is symmetrical and has no dipole moment. The calculated enthalpies of formation for the diazines show that pyridazine is 83 kJ mol^{-1} more stable than pyrimidine and pyrazine.

19.2.2
Tautomerism

Table 19.5 summarizes the tautomeric features of hydroxy-, mercapto-, and amino-substituted azines for dilute solutions in water at 20 °C. For systems having X = O or S, the non-aromatic tautomer form(s) in general is favored over the aromatic species,

Table 19.5 Tautomeric equilibria of some monofunctional azines.

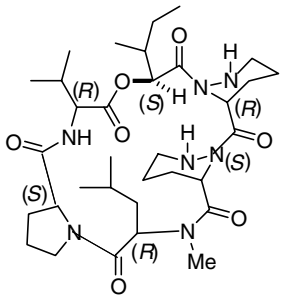
Entry	Compounds	X = O	X = S	X = N
1		B > A	B > A	A > B
2		B > A	B > A	A > B
3		B/C > A	B/C > A	A > B/C
4		B/C > A	B/C > A	A > B/C
5		B > A	B > A	A > B

although in the vapor phase the thiol predominates over the thione. For 4-hydroxypyrimidine (entry 4), which can exist as three different tautomers, the general tendency favors amide B over the vinylogous amide C. For X = N, the aromatic structure is consistently favored over the other tautomers B and C.

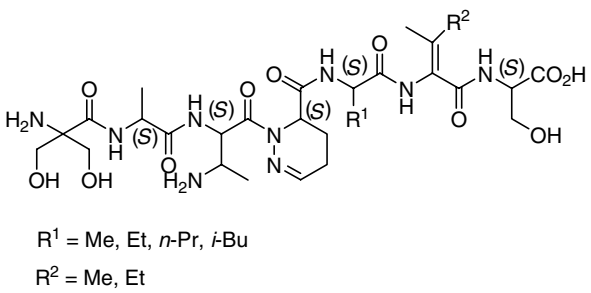
19.3 Relevant Natural/Biological Compounds

19.3.1 Pyridazines (1,2-Diazines)

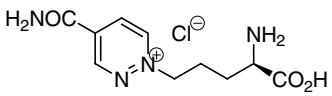
Unlike other heterocycles found in many important natural products, pyridazines were discovered only after 1970, and relatively few pyridazines have thus far been isolated from natural sources. The first representative examples include some fungal metabolites from *Streptomyces* species. These are now a big group of over 15 related compounds. Monomycin X [10] (**10**, from *Streptomyces jamaicensis*) is just one example of cyclohexadepsipeptide antibiotics. Antrimycins [11] (**11**, from *Streptomyces xanthocidiens*) are tuberculostatic peptides that also contain nonribosomal amino acids. The quaternary salt pyridazinomycin [12] (**12**, from *Streptomyces violaceoniger*) is an antifungal antibiotic whose amino acid side chain can be viewed as L-ornithine with its terminal nitrogen atom as part of the pyridazine ring.



10 Monomycin X



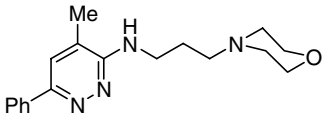
11 Antrimycins



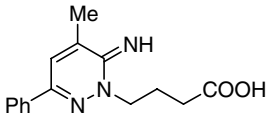
12 Pyridazinomycin

As synthetic compounds, pyridazines constitute an important pharmacophoric moiety present in many drugs acting on various pharmacological targets. Minaprine (**13**) [13] is a synthetically-derived aminopyridazine possessing dopaminergic, serotoninergic, cholinergic, and GABA-ergic activities, while SR 95103 (**14**) [14], an

analog of γ-aminobutyric acid (GABA), serves as a powerful inhibitor of monoamine oxidase and acetylcholine esterase [15, 16].

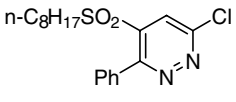


13 Minaprine

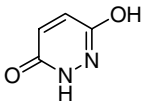


14 SR 95103

Several pyridazines are selective plant growth regulators and are used as herbicides. Pyridate, **15**, and 3-hydroxy-6(*1H*)-pyrazinone, **16**, are two examples currently used in commercial lawn weed killers.



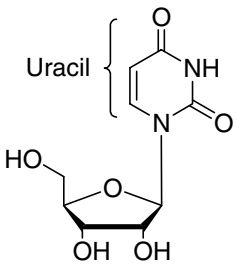
15 Pyridate



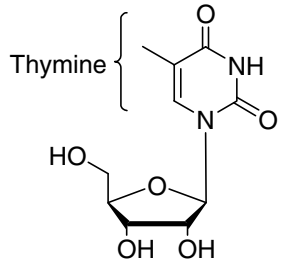
16 3-Hydroxy-6(1H)-pyrazinone

19.3.2
Pyrimidines (1,3-Diazines)

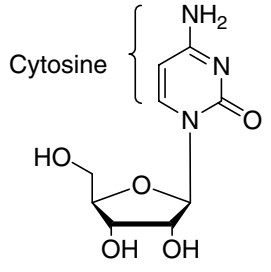
The most important naturally occurring diazines are the pyrimidine bases uracil, thymine, and cytosine, which comprise the fundamental nucleoside building blocks in deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) [17]. These compounds exist as tautomers in which the hydroxypyrimidines adopt the lactam form [uridine (**17**) and thymidine (**18**)] whereas aminopyrimidines prefer the enamine structure (cytidine, **19**).



17 Uridine



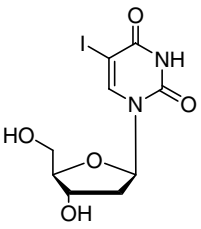
18 Thymidine



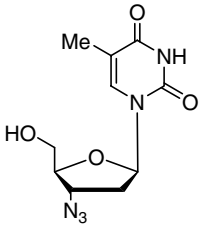
19 Cytidine

In addition, several pyrimidine nucleoside analogues have been developed as antiviral agents [18]. Idoxuridine, **20**, is used in the treatment of herpes infections of

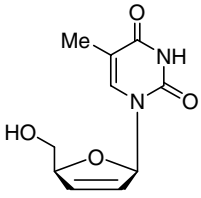
the eye; AZT (**21**) is the most widely used anti-AIDS drug; stavudine, **22**, is effective in the treatment of HIV infections and AIDS, and lamivudine, **23**, is used to treat both hepatitis B and AIDS.



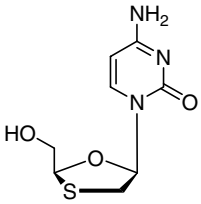
20 Idoxuridine



21 AZT

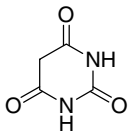


22 Stavudine

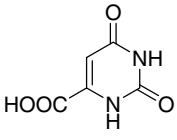


23 Lamivudine

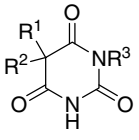
Barbituric acid, **24**, and orotic acid, **25**, a key compound in the biosynthesis of naturally occurring pyrimidine derivatives, are also important pyrimidine derivatives. 5,5-Diethylbarbituric acid was the first therapeutic barbiturate (E. Fischer 1903, veronal or barbital, **26**), and other derivatives are still used as sedatives, antiepileptic drugs, and anesthetics. Sedative barbiturates have toxicity and dependency problems and have now been replaced by other drugs.



24 Barbituric acid

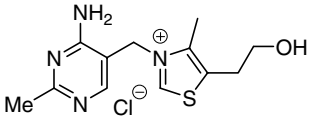


25 Orotic acid



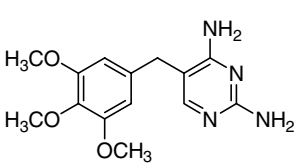
26 Veronal (Barbital)
$R^1 = R^2 = Et$
$R^3 = H$

Vitamin B_1 (thiamine), **27**, occurs in yeast, rice husk, and various cereals, and represents another well-known naturally-occurring pyrimidine essential in our daily lives. A deficiency of vitamin B_1 causes beriberi and damage to the nervous system (polyneuritis).

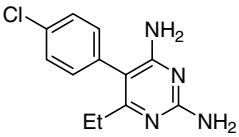


27 Vitamin B1

Several pyrimidine-containing antibiotics, especially those isolated from *Streptomyces,* possess potent antitumor properties, such as the structurally complex bleomycins. Trimethoprim, **28**, an antibacterial agent widely used in combination with sulfamethoxazole, and the antimalarial pyrimethamine, **29**, are examples of synthetic 2-amino-substituted pyrimidines in the pharmaceutical area.

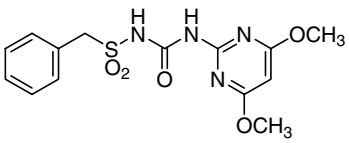


28 Trimethoprim

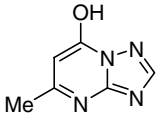


29 Pyrimethamine

Bensulfuronmethyl, **30**, a sulfonylurea derived from 4,6-dimethoxy-2-aminopyrimidine, acts as a powerful plant growth regulator and is an active herbicide. 7-Hydroxy-5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine, **31**, serves as an emulsion stabilizer in various photographic materials.



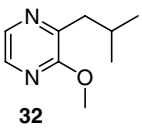
30 Bensulfuronmethyl



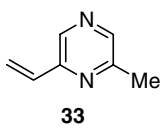
31

19.3.3
Pyrazines (1,4-Diazines)

Alkylpyrazines occur frequently as constituents in foodstuffs and are responsible for their flavor and strong aroma. Although being present in very small amounts, they are highly odiferous and can be detected at extremely low concentrations (10^{-5} ppm). 3-Isobutyl-2-methoxypyrazine, **32**, is a simple natural derivative isolated from green peas and wine, and 2-methyl-6-vinylpyrazine, **33**, is an aromatic component of coffee. Several polyalkylpyrazines such as 2-ethyl-3,5-dimethylpyrazine, **34**, also act as alarm pheromones in ants. Several pyrazin-2(1*H*)-ones and 1-hydroxypyrazin-2(1*H*)-ones (**35**) have antibiotic properties.

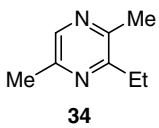


32



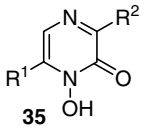
33

Food aroma components



34

pheromone



35

antibiotic

19.4
Synthesis of Pyridazines (1,2-Diazines)

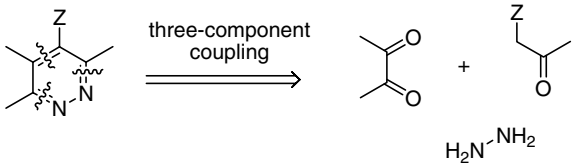
The first pyridazines were first synthesized as early as 1886 by Fischer [19], but their chemistry has only been explored since the 1950s. This is likely because pyridazines do not occur as natural products despite having a nitrogen–nitrogen linkage that

could conceivably be obtainable from biochemical transformation of dinitrogen. However, since many pyridazines possess potential therapeutic or plant growth inhibitory effects, a wide variety of new syntheses have been developed more recently.

19.4.1 Synthesis by Ring-Closure Reactions

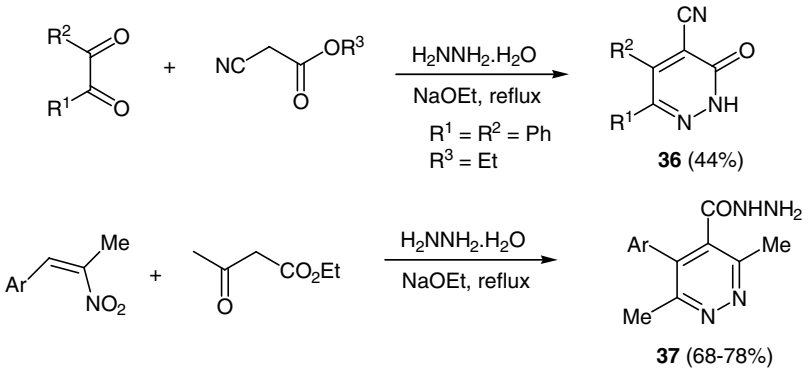
19.4.1.1 Three-Component Couplings

Although the assembly of pyridazines from three discrete coupling units is relatively uncommon, three-component reactions do represent a useful method for the preparation of 1,2-diazines (Scheme 19.1).



Scheme 19.1

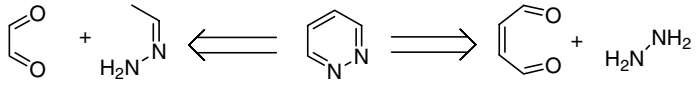
As an example (Scheme 19.2), a 1,2-diketone, a cyanoacetate, and hydrazine combine under basic alcoholic conditions to afford 5,6-disubstituted pyridazine-3 (2*H*)-ones **36** bearing a nitrile group at position 4 [20], a versatile precursor to fused pyridazines [21, 22]. Similarly, the reaction of 1-aryl-2-nitroprop-1-enes with an acetoacetate ester and hydrazine offers 3,6-dimethylpyridazines **37** bearing an aryl group at position 5 and a carbohydrazide at position 4 [23, 24].



Scheme 19.2

19.4.1.2 Two-Component Couplings

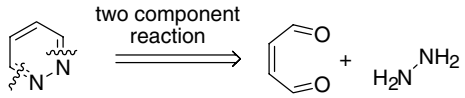
Two different strategies can be considered for the assembly of pyridazines by a two-component coupling (Scheme 19.3).



Scheme 19.3

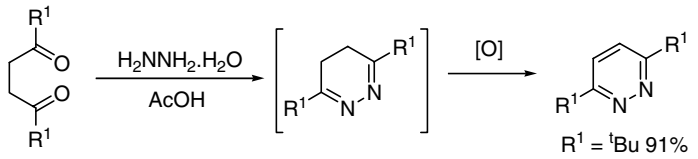
A more common route to 1,2-diazines involves a coupling of formal [4 + 2] cyclocondensation precursors to create the six-membered ring in one step. Examples are illustrated below.

19.4.1.2.1 **[C-C-C-C] + [N-N]** The condensation of hydrazine or substituted hydrazines with appropriate four-carbon synthons represents one of the most widely used approaches to pyridazines and pyridazinones (Scheme 19.4) [25a]. Carbons 1 and 4 of these building blocks must bear functional groups that are susceptible to nucleophilic attack by a hydrazine nitrogen atom (usually followed by elimination of a small molecule like water, an alcohol, etc.). Depending on the degree of saturation of the C2–C3 bond, fully aromatic or partially saturated pyridazines are obtained, in which case various methods for oxidation/aromatization are available (Br_2/AcOH; $CuCl_2$/CH_3CN, etc.).



Scheme 19.4

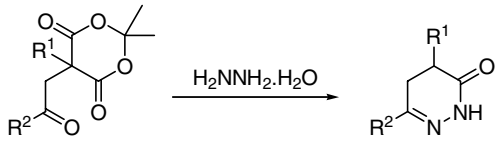
A long-established method to prepare 3,6-disubstituted pyridazines is the condensation of saturated 1,4-dicarbonyl compounds with hydrazine, semicarbazide, or similar hydrazine derivatives (Scheme 19.5). The fully aromatic pyridazines can often be obtained by spontaneous oxidation of the dihydro intermediates [25b]. When saturated 1,4-diketones are used, the reaction is carried out in the presence of mineral acids to prevent the competing formation of *N*-aminopyrroles.



Scheme 19.5

One interesting alternative is the use of Meldrum's acid derivatives **38**, which are easily available and readily cyclize with hydrazine at room temperature, with subsequent decarboxylation, to provide the 4,5-dihydropyridazin-3(2*H*)-ones **39** (Scheme 19.6) [26].

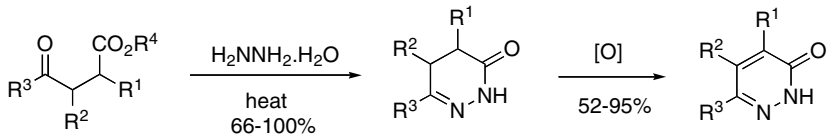
4-Oxoalkanoic acids where R^3 = alkyl/aryl/heteroaryl residues, with or without further substituents R^1 and R^2, have been employed for condensation reactions with



38 39

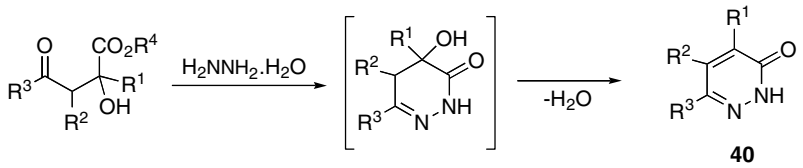
Scheme 19.6

hydrazine (Scheme 19.7) [27]. Whereas in most cases the free carboxylic acids ($R^4 = H$) are employed, esters are also frequently used [28]. For the latter case, a protocol suitable for high-throughput organic synthesis has been developed that is based on construction of the oxo ester precursor by silver(I)-catalyzed addition of zirconocenes to epoxy esters [29].



Scheme 19.7

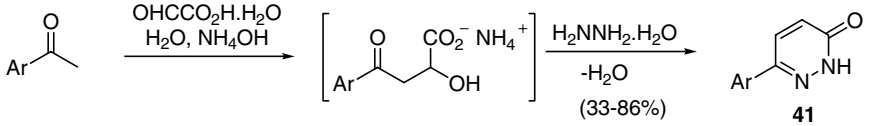
When 4-oxoalkanoic acids with a 2-hydroxy group are employed for cyclization with hydrazine spontaneous dehydration of the initial intermediate occurs to give pyridazine-3(2*H*)-ones **40** (Scheme 19.8). In some cases, the 4-hydroxydiazinone intermediate can be isolated [30].



40

Scheme 19.8

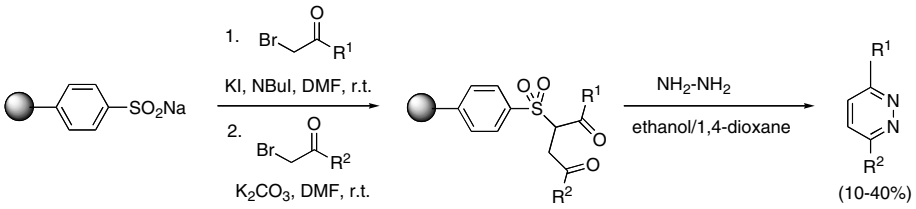
A useful one-pot protocol based on this route has been developed by Coates (Scheme 19.9) [31] that employs substituted acetophenones with glyoxylic acid monohydrate in the presence of ammonium hydroxide, in which the initial aldol adduct is converted into the pyridazin-3(2*H*)-one **41** with hydrazine. The reported yields are, however, highly variable.



41

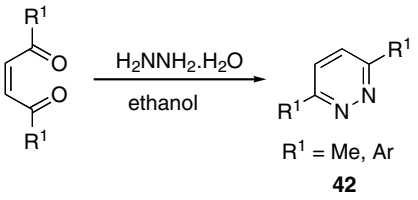
Scheme 19.9

Lam and Lee have devised a solid-phase procedure for the synthesis of various 3,6-disubstituted pyridazines (Scheme 19.10) [32]. Sodium benzenesulfinate resin was treated sequentially with α-bromoketones in two steps to give immobilized diketo sulfones, from which a library of substituted pyridazines could be prepared by condensation with hydrazine. Release of the adducts from the resin occurs by spontaneous elimination driven by ring aromatization.



Scheme 19.10

Unsaturated 1,4-dicarbonyls likewise undergo cyclization with hydrazine to afford directly the pyridazine product **42** (Scheme 19.11) [33]. While *(Z)*-alkenyl diketones react readily with ethanolic hydrazine hydrate at room temperature, cyclization of the corresponding *(E)*-isomer also occurs but requires higher reaction temperatures [34].

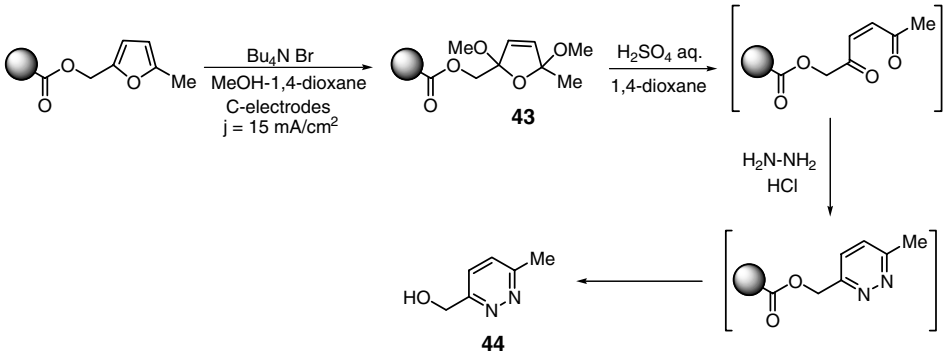


Scheme 19.11

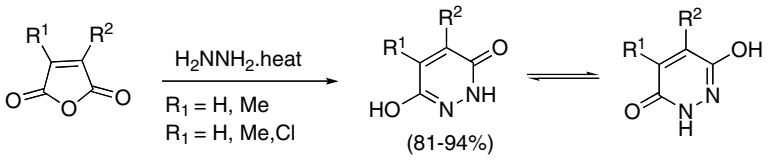
The unsaturated 1,4-dicarbonyl compound can be generated electrolytically from polymer-bound furans [35]. The initial oxidation product **43** can be hydrolyzed in aqueous acid and, through condensation with hydrazine and concomitant hydrazinolysis of the ester linkage, pyridazines **44** are obtained in 50–65% overall yield (Scheme 19.12).

The use of maleic acid derivatives with substituted hydrazines is a general method for the preparation of 6-hydroxypyridazin-3(2*H*)-ones **45**, bearing various substituents at the 2, 4, or 5 positions (Scheme 19.13). These serve as versatile intermediates to other pyridazines since the oxo/hydroxyl groups at C3 and C6 can be easily converted into chloro substituents for nucleophilic replacement [36].

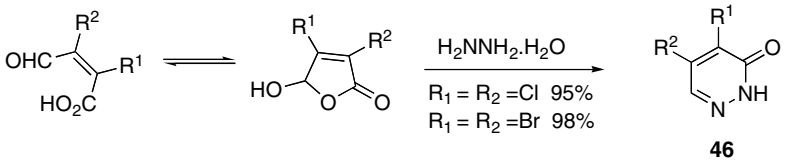
3-Formylpropenoic acids and their hydroxylactone tautomers react with hydrazine to afford pyridazin-3(2*H*)-ones **46** in a single step (Scheme 19.14). Thus, the



Scheme 19.12



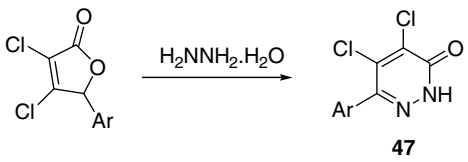
Scheme 19.13



Scheme 19.14

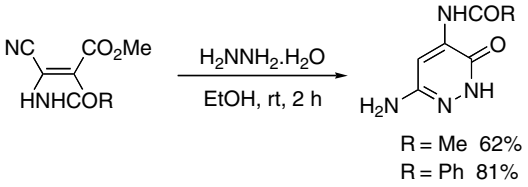
condensation of 2,3-dichloro-4-oxobut-2-enoic acid (mucochloric acid, R^1 and R^2 = Cl) or its bromo congener with hydrazine gives the corresponding 4,5-dihalopyridazin-3(2*H*)-ones [37].

The same precursors have been used for the preparation of 6-aryl-4,5-dihalopyridazin-3(2*H*)-ones **47**, via an intermediate lactone resulting from the Friedel–Crafts reaction of an arene with the 3-formyl acid (Scheme 19.15) [38].



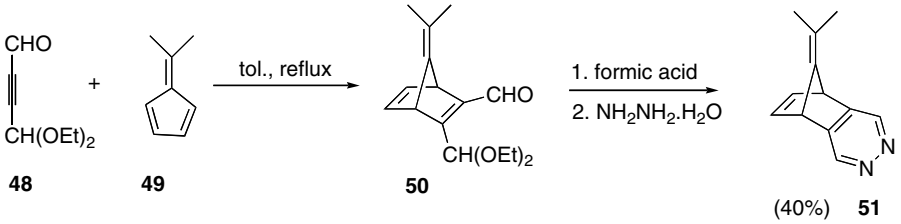
Scheme 19.15

α-Amino-γ-cyanopropenoate esters can be used to obtain the corresponding 3,5-diaminopyridazines (Scheme 19.16) [39].



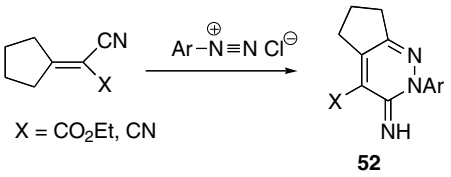
Scheme 19.16

An interesting variation of this reaction has been described by Ohta and coworkers in the synthesis of the pyridazine-fused isopropylidene norbornadiene **51** (Scheme 19.17). The cyclization was carried out by hydrolysis of diethyl acetal **50** with formic acid followed by condensation with hydrazine hydrate [40]. Compound **50** was prepared by the Diels–Alder cycloaddition of propargylic aldehyde **48** with dimethylfulvene **49**.



Scheme 19.17

As an alternative to hydrazine-based cyclizations, Elassar has reported a Japp–Klingemann type reaction of aryldiazonium salts to produce pyridazines **52** (Scheme 19.18) [41].

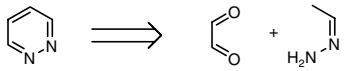


Scheme 19.18

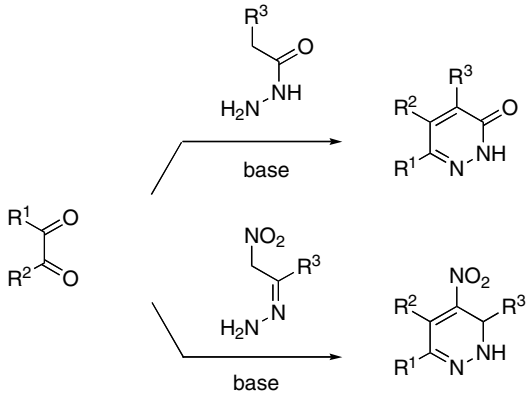
19.4.1.2.2 **[N-N-C-C] + [C-C]**

Reaction of Methylene-Activated Hydrazides with 1,2-Dicarbonyl Compounds The two-component reaction of 1,2-dicarbonyl compounds with hydrazides possessing an active methylene group, such as cyanoacetohydrazide [20], heteroaryl-substituted

acetohydrazides [42], or similar derivatives of 2-nitroacetic acid [43, 44], gives pyridazin-3(2*H*)-ones in fairly good yields (Schemes 19.19 and 19.20). Glyoxal, α-keto aldehydes, and α-diketones can all be employed as 1,2-dicarbonyl units for these cyclizations, thereby affording a wide range of substituted pyridazines.

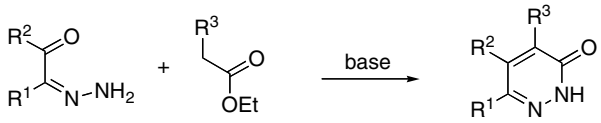


Scheme 19.19



Scheme 19.20

Reaction of 1,2-Dicarbonyl Monohydrazones with Methylene-Activated Compounds An alternative method for the construction of pyridazin-3(2*H*)-ones **53** is the use of monohydrazones of 1,2-dicarbonyl compounds in combination with esters or nitriles possessing reactive α-methylene groups (Scheme 19.21) [45–47]. As for the above method, an assortment of substitution patterns can be introduced through selection of suitably substituted starting materials.

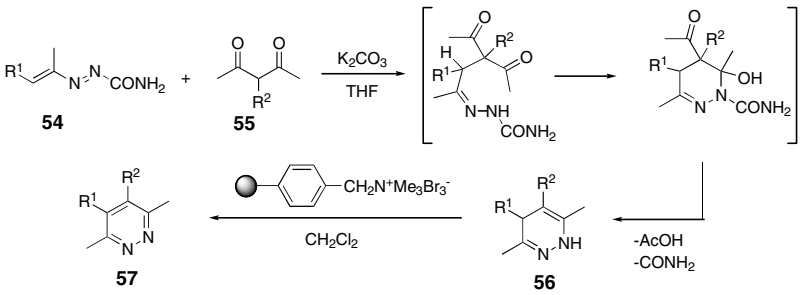


53

Scheme 19.21

Reactions of 1,2-Diaza-1,3-Dienes with Alkyl 2-Acetylacetoacetate Derivatives In addition to their use as dienes in hetero-Diels–Alder reactions, 1,2-diaza-1,3-dienes **54** with an electron-withdrawing group at N1 can be coupled with acetyl acetoacetates **55**

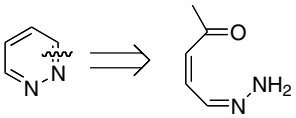
under mildly basic conditions to give pyridazine products **57** (Scheme 19.22). Mechanistically, this sequence involves a 1,4-addition of the carbanion generated from the acetyl acetoacetate, followed by attack of the NH nitrogen atom on the oxo function and subsequent elimination of acetic acid and loss of the carbamoyl residue [48, 49]. These N-unsubstituted-1,4-dihydropyridazines **56** can be aromatized to pyridazines using, for example, a solid-phase supported brominating agent [50].



Scheme 19.22

19.4.1.3 One-Component Couplings

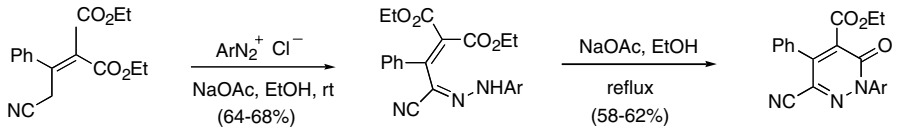
19.4.1.3.1 **[N-N-C-C-C-C]** The conceptually simplest route to pyridazines is the cyclization reaction of a hydrazone onto a suitably positioned carbonyl functionality (Scheme 19.23).



Scheme 19.23

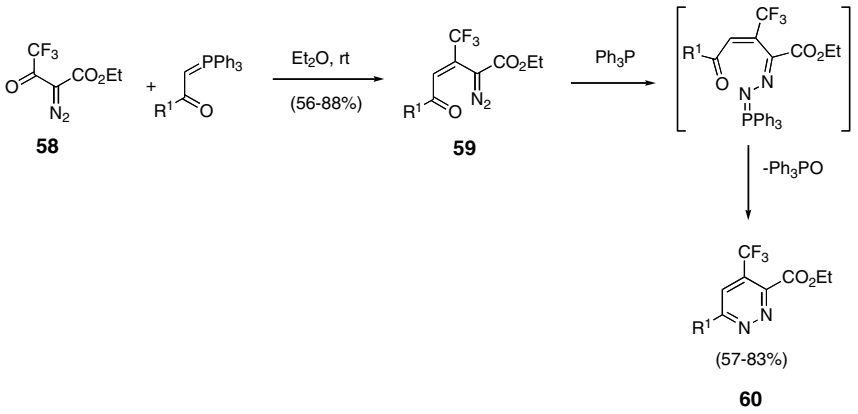
There are two different strategies for the synthesis of pyridazines using a one-component reaction for the ring closure.

Cyclization of Hydrazones of 4-Oxoalkenoic Acid Derivatives The intramolecular ring-closure reactions of the hydrazones of 4-oxoalkenoic acid derivatives, such as esters or nitriles, occur under various reaction conditions to afford pyridazinones or iminopyridazines (Scheme 19.24) [51]. In most cases, arylhydrazones [52] have been used as the cyclization substrates, being conveniently available by electrophilic substitution of methylene-activated precursors with arenediazonium salts [53].



Scheme 19.24

Reductive Cyclization of Diazo(vinyl)methanes Bearing a Carbonyl Group 4-(Trifluoromethyl)pyridazine-3-carboxylate esters **60** bearing an alkyl or alkoxy group at C6 can be prepared in two steps from the trifluoroacetyl-substituted diazo esters **58** (Scheme 19.25). First, the ketone is olefinated with stabilized Wittig reagents to afford the *(E)*-configured alkoxycarbonylvinyl diazomethane **59**, which undergoes ring closure under very mild conditions by treatment with triphenylphosphine. Mechanistically, a "diaza-Wittig" reaction of an intermediate phosphazine has been suggested [54].



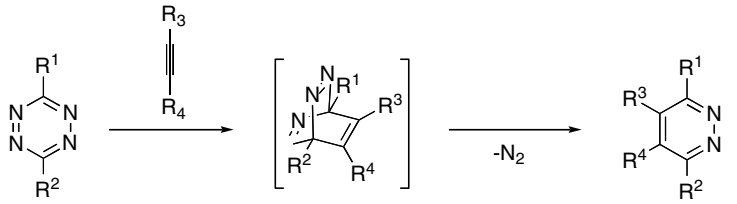
Scheme 19.25

19.4.2 Cycloaddition Reactions

One of the most versatile methods for synthesizing functionalized pyridazines lies in the use of cycloaddition reactions between suitable dienes and dienophiles.

19.4.2.1 [4 + 2]-Cycloaddition Reactions of 1,2,4,5-Tetrazines

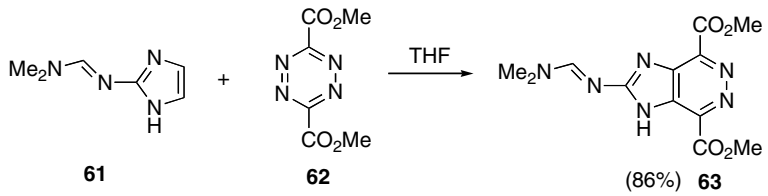
A reaction that has been used extensively for the synthesis of a wide variety of substituted pyridazines is the inverse-electron-demand (LUMO diene-controlled) Diels–Alder reactions of 1,2,4,5-tetrazines with alkene- or alkyne-type dienophiles, followed by elimination of dinitrogen to give the 1,2-pyrizadine (Scheme 19.26) [55]. This process works best when the tetrazine has electron-withdrawing substituents



Scheme 19.26

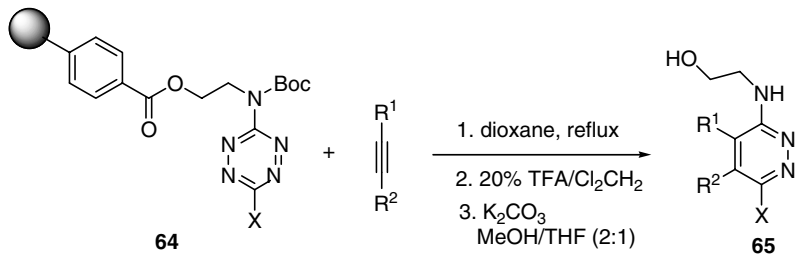
and the dienophile is electron-rich, thereby decreasing the energy gap between the respective frontier molecular orbitals ($LUMO_{diene}$–$HOMO_{dienophile}$) [56]. Commonly used dienophiles are mono- and disubstituted alkynes such as ynamines, but also a wide range of substituents, including nitro, trimethylsilyl and trimethyltin, can be incorporated onto the acetylene. Alternatively, electron-rich alkenes such as enamines, enol ethers, and ketene acetals can be employed to provide routes to substituted pyridazines not easily available by other methods [57].

Wan and Snyder have applied this strategy to the inverse-electron demand cycloadditions of 2-substituted imidazoles **61** with 1,2,4,5-tetrazine-3,6-dicarboxylate, **62**, to afford imidazo[4,5-d]pyridazines **63** in high yields (Scheme 19.27) [58].



Scheme 19.27

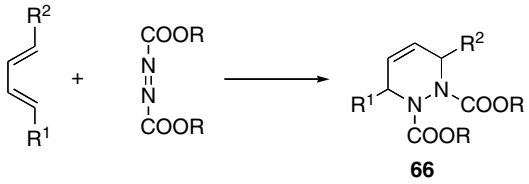
This methodology has been extended to solid-phase synthesis for the rapid assembly of pyridazine compound libraries (Scheme 19.28). A resin-bound aminotetrazine with a functional group at the C6 position (**64**) has been used in combination with a wide range of electron-rich dienophiles to give pyridazines **65** after cleavage from the solid support [59].



Scheme 19.28

19.4.2.2 [4 + 2]-Cycloaddition Reactions of Azodicarboxylic Esters

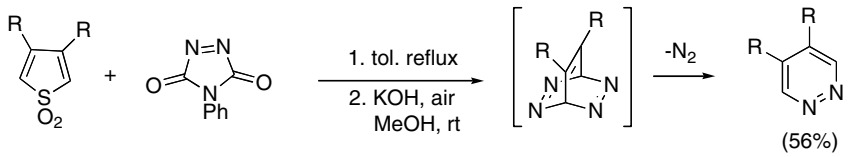
Tetrahydropyridazines **66** can alternatively be produced by a Diels–Alder reaction of substituted 1,3-butadienes with azodicarboxylic esters (Scheme 19.29). The usual stereochemical and substituent effects of these reactions follow according to Woodward–Hoffmann considerations.



Scheme 19.29

19.4.2.3 Cycloaddition Reactions with N-Phenyltriazolinedione

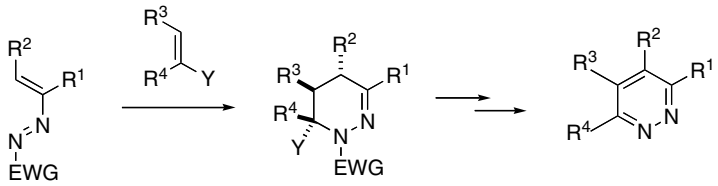
Thiophene S,S-dioxides with bulky 3,4-disubstitution (R = adamant-1-yl) react with *N*-phenyltriazolinedione by a Diels–Alder reaction to give 1:2 adducts, followed by hydrolysis to afford 4,5-disubstituted pyridazines (Scheme 19.30) [60].



Scheme 19.30

19.4.2.4 Hetero-Diels–Alder with Electron-Rich Alkenes

A convenient method for the preparation of various pyridazines is the inverse-electron-demand hetero-Diels–Alder reaction of 1,2-diaza-1,3-dienes bearing at least one acceptor group with electron-rich alkenes such as enol ethers or enamines [61]. These [4 + 2]-cycloaddition reactions show a high degree of regio- and stereochemical control [62, 63]. The primary reaction products are tetrahydropyridazines but they can be oxidatively transformed into the fully aromatic compounds (Scheme 19.31) [64].

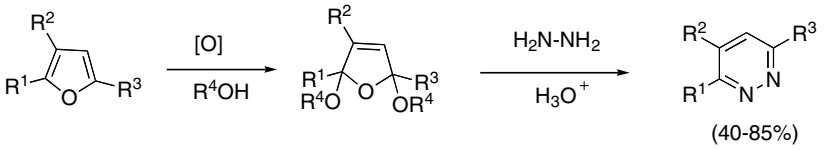


Scheme 19.31

19.4.3
Synthesis by Ring Enlargement

19.4.3.1 From Furan Derivatives

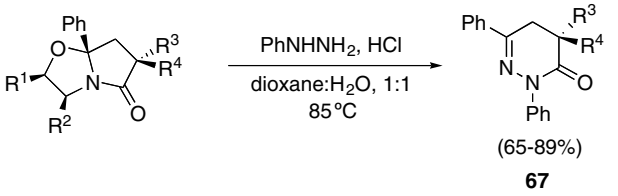
Several examples of this reaction have been shown already (Section 19.4.1.2.1). Aromatic furans have been reported to undergo synthetically useful ring transformation into pyridazines in two steps [65]. First, the furan is converted into 2,5-dialkoxy-2,5-dihydrofuran by oxidative addition of two moles of an alcohol, followed by an acid-promoted ring expansion in the presence of hydrazine (Scheme 19.32) [66].



Scheme 19.32

19.4.3.2 From γ-Bicyclic Lactams

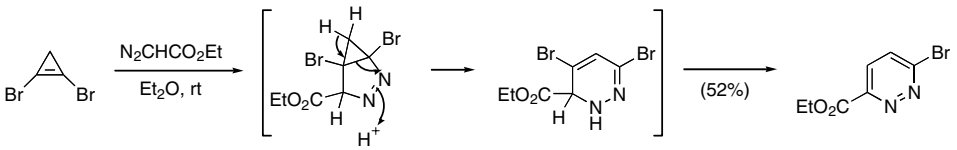
Bicyclic lactams have been used as precursors for the synthesis of chiral 4,5-dihydro-2*H*-pyridazin-3-ones **67** through thermal ring expansion reaction with hydrazines (Scheme 19.33) [67].



Scheme 19.33

19.4.3.3 From Bromocyclopropenes

Under mild conditions α-diazoesters undergo 1,3-dipolar cycloadditions with di, tri-, and tetrahalocyclopropenes, leading to unstable cyclopropane-fused pyrazolines, which readily rearrange to pyridazines with loss of hydrogen halide (Scheme 19.34) [68].

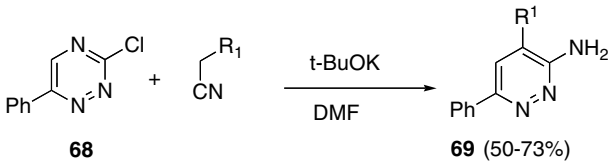


Scheme 19.34

19.4.4
Synthesis by Ring Atom Exchange

19.4.4.1 Rearrangement of 1,2,4-Triazines

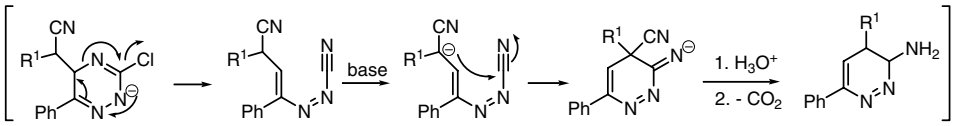
This elegant method is based on ring transformation of an appropriate 6-aryl-3-chloro-1,2,4-triazine, **68**, to give 3-amino-6-arylpyridazines **69** with an electron-withdrawing substituent (R^1 = cyano, aryl, phenylsulfonyl or ester) at C4 (Scheme 19.35) [69].



68 **69** (50-73%)

Scheme 19.35

In the mechanism, a nucleophile [phenylacetonitrile, ethyl cyanoacetate, malonitrile, or (phenylsulfonyl)acetonitrile anions] attacks the C5 position of the 1,2,4-triazine, inducing a ring-opening, ring-closing process that leads to the diazine (Scheme 19.36).

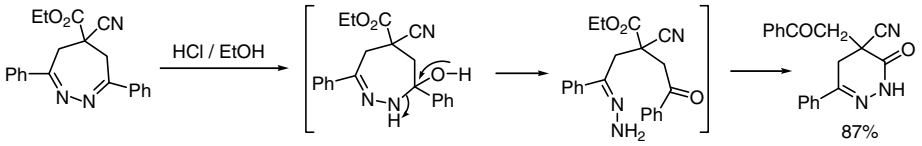


Scheme 19.36

19.4.5
Synthesis by Ring Contraction

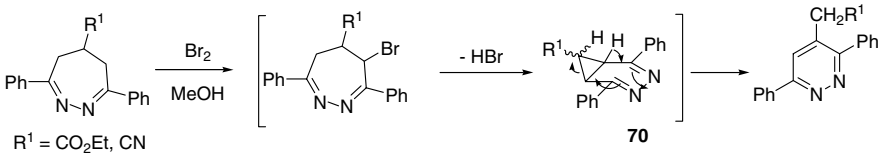
19.4.5.1 From 1,2-Diazepines

Pyridazines can be synthesized by contraction of 1,2-diazepines by two different mechanisms. Acid hydrolysis of 5-carboalkoxydihydroazepines with hydrochloric acid in ethanol affords pyridazinones in high yields (Scheme 19.37) [70].



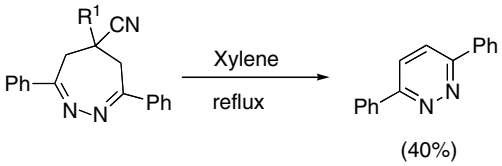
Scheme 19.37

Using a second strategy, the C5 carbon can be extruded by halogenation of the dihydroazepine through a diazanorcaradiene **70** intermediate (Scheme 19.38). The products in these reactions were found to be strongly dependent upon the nature of C5 substituents as well as the reaction conditions [71].



Scheme 19.38

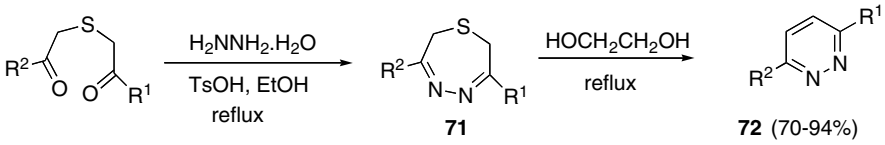
On the other hand, 1,2-diazepines, consisting of a seven-membered, ring can undergo ring contraction through loss of one of the ring atoms as a stable entity upon thermolysis. As an example, 3,7-diphenyl-5,6-dihydro-4*H*-1,2-diazepines bearing strong electron-withdrawing substituents at C5 (CN, CO_2Et) have been reported to be unstable and undergo thermal ring contraction at the temperature of boiling xylene, to afford the 3,6-diphenylpyridazine (Scheme 19.39) [72]. No mechanism has been suggested for this reaction.



Scheme 19.39

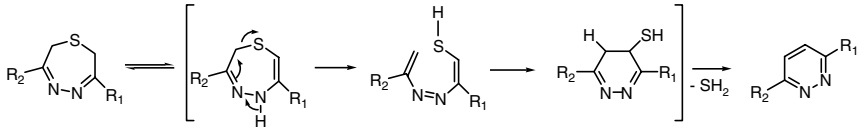
19.4.5.2 **From Hetero-1,2-Diazepines**

Similarly to the above transformation, 1,2-diazepines containing an additional heteroatom at the C5 position (**71**) undergo ring contraction to afford pyridazines **72** (Scheme 19.40). The heteroatom unit can be nitrogen [73], sulfur [74], or selenium [75]. The reaction conditions involve either halogenation or heating in an inert solvent.



Scheme 19.40

The mechanism suggested for this process presumes a thermal tautomerization to an enamine, followed by ring opening and electrocyclic ring closure with loss of hydrogen sulfide (Scheme 19.41).



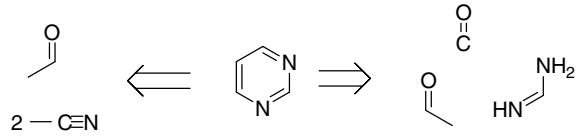
Scheme 19.41

19.5 Synthesis of Pyrimidines (1,3-Diazines)

19.5.1 Synthesis by Ring-Closure Reactions

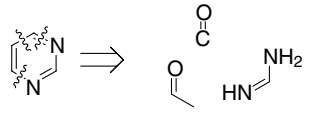
19.5.1.1 Three-Component Couplings

There are two main strategies for the synthesis of pyrimidines by a three-component coupling (Scheme 19.42).

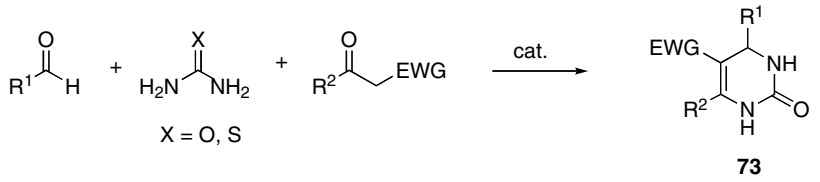


Scheme 19.42

19.5.1.1.1 **[C-C] + [C] + [N-C-N]** The Biginelli reaction, a three-component condensation reaction between an aldehyde, a urea or thiourea, and an easily enolizable carbonyl compound, was originally described by the Italian chemist Pietro Biginelli in 1893 [76]. This multi-component reaction provides a straightforward approach to functionalized 3,4-dihydropyrimidine-2-(1*H*)-ones **73** (Schemes 19.43 and 19.44) [77].

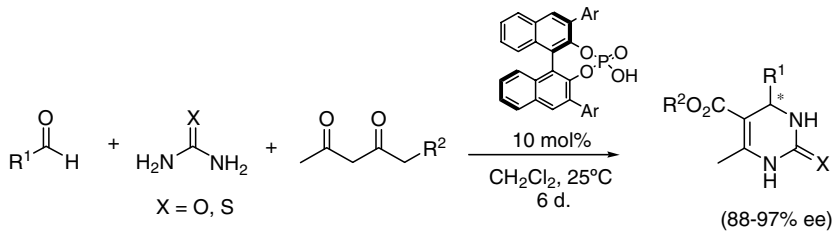


Scheme 19.43



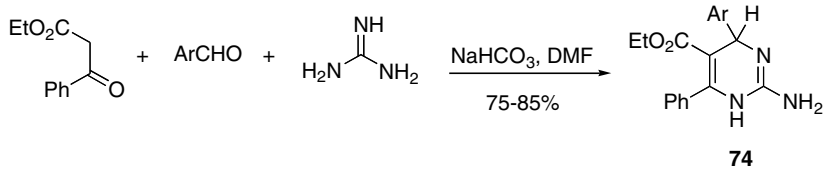
Scheme 19.44

In recent decades, many efforts have focused on the preparation of optically active 3,4-dihydropyrimidine-2-(1*H*)-ones. In this context, the enantioselective version of the Biginelli reaction was achieved using chiral phosphoric acids as catalysts (Scheme 19.45) [78].



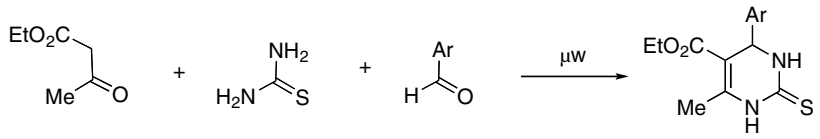
Scheme 19.45

Eynde and coworkers [79] have reported a three-component [80] coupling of a β-keto ester, aryl aldehyde, and guanidine to obtain 1,4-dihydropyrimidines **74** in good yields (Scheme 19.46).



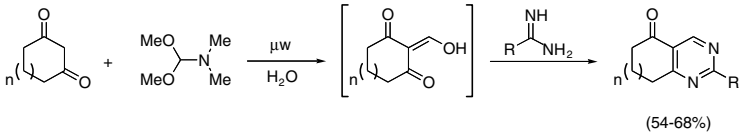
Scheme 19.46

Typically, this tandem Michael addition–elimination–cyclodehydration requires refluxing in a high-boiling solvent under acid catalysis. In this same manner, microwave irradiation proves to be an effective alternative in giving excellent yields of pyrimidine-thiones [81] without the need for a solvent or long heating periods (Scheme 19.47).



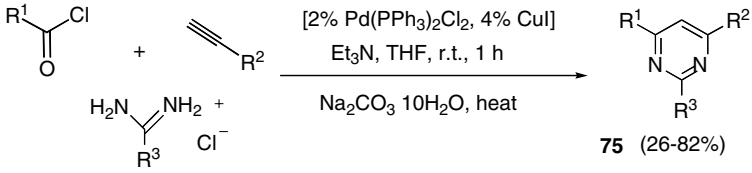
Scheme 19.47

Molteni and coworkers [82] likewise have reported that microwave irradiation promotes the conversion of enaminoketones, formed *in situ* from formamide acetals and active β-diketones in water, into pyrimidines by reaction with amidines (Scheme 19.48). The method offers short reaction times and facile purification by precipitation of the product in aqueous media.



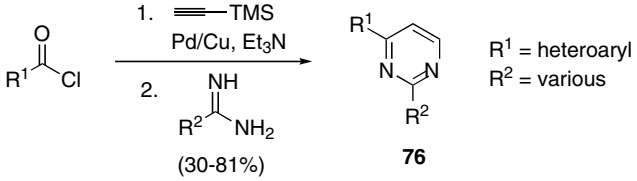
Scheme 19.48

Müller has reported the three-component coupling of acid chlorides with terminal alkynes under Sonogashira conditions, with trapping of the intermediate alkynyl ketone with an amidine, as a one-pot procedure for synthesizing 2,4-di- and 2,4,6-trisubstituted pyrimidines **75** (Scheme 19.49) [83].



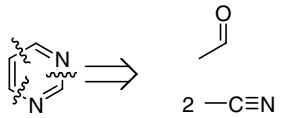
Scheme 19.49

The same author [84] has used the methodology for the one-pot, three-component synthesis of 2,4-disubstituted pyrimidines **76** (Scheme 19.50), using TMS-acetylenes in the Sonogashira coupling.

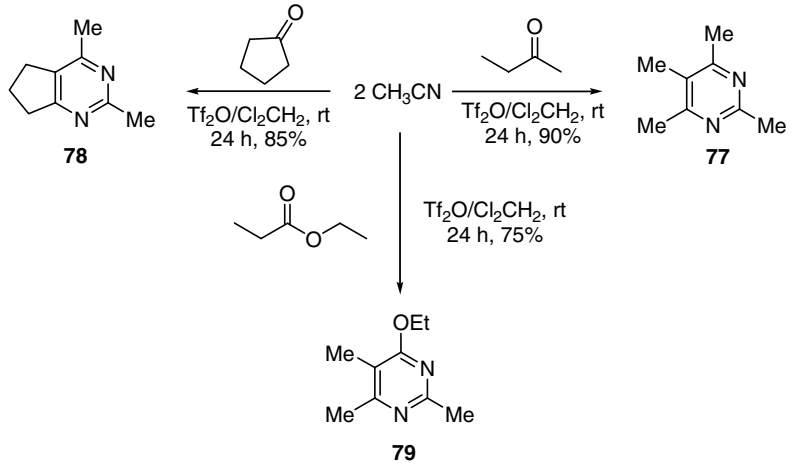


Scheme 19.50

19.5.1.1.2 **[C-C] + [C-N] + [C-N]** The reaction of aliphatic and alicyclic ketones with triflic anhydride (Tf_2O) under mild conditions in the presence of a nucleophile such as an aliphatic or aromatic nitrile leads to the formation of pyrimidines **77** and condensed pyrimidines **78** [85] where the substituents at C2 and C4 of the ring are identical (Schemes 19.51 and 19.52). As an extension, Fernández and coworkers have



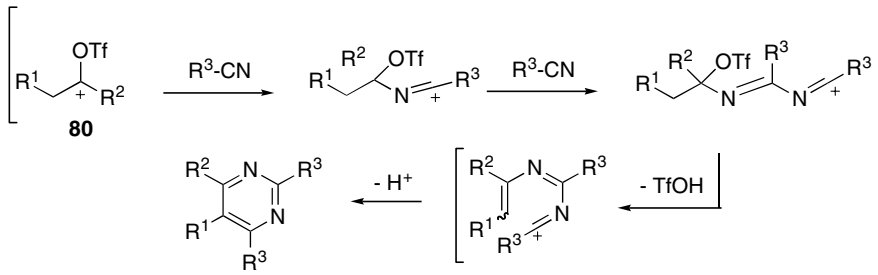
Scheme 19.51



Scheme 19.52

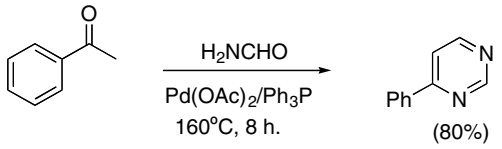
reported the preparation of biologically interesting 4-alkoxypyrimidines **79** by the condensation and cyclization of readily available aliphatic esters [86].

The reaction is postulated to take place via a (triflyloxy)carbenium intermediate **80** [87], which in the presence of another molecule of the nitrile is trapped to give sequential resonance-stabilized nitrilium intermediates before cyclizing to the pyrimidine (Scheme 19.53).



Scheme 19.53

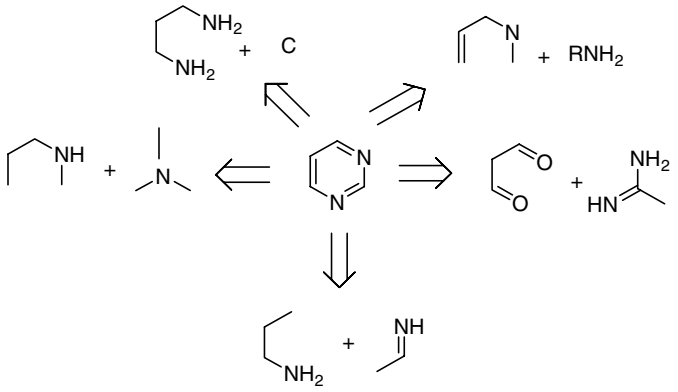
Lejon and coworkers have optimized the production of 4-substituted pyrimidines using Pd(0) or Pd(II) catalysts in the Leuckart reaction between formamide and α-methyl or α-methylene ketones (Scheme 19.54) [88].



Scheme 19.54

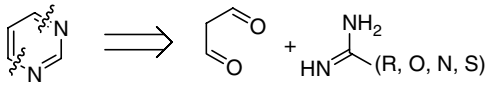
19.5.1.2 **Two-Component Couplings**

There are several two-component strategies for the synthesis of pyrimidines (Scheme 19.55).



Scheme 19.55

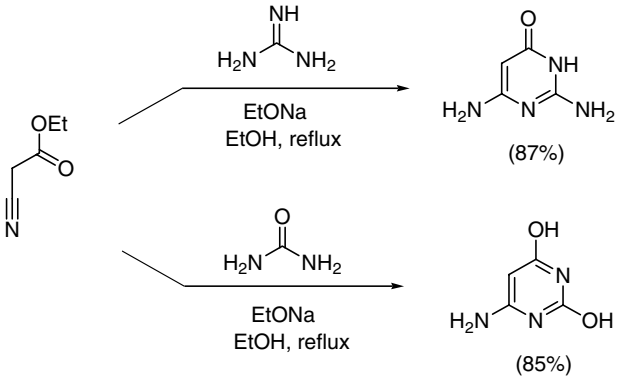
19.5.1.2.1 **[C-C-C] + [N-C-N]** The most general pyrimidine ring synthesis involves the combination of a 1,3-dicarbonyl component with an amidine as source of the requisite [N-C-N] unit (Scheme 19.56). The [N-C-N] component can also be formamide or an orthoester in the presence of ammonia, a guanidine, a urea, or thiourea, affording pyrimidines with different substitution at C2.



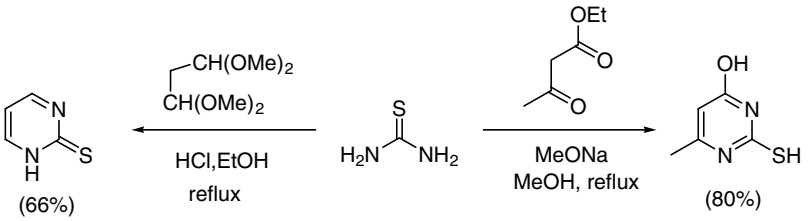
Scheme 19.56

The following modifications are noteworthy: the amidine can be replace by guanidine [89], or urea [90], affording to 2-amino- or 2-hydroxypyrimidines, respectively. Replacement of one of the carbonyls by a cyano group leads to 4-aminopyrimidines (Scheme 19.57).

When thiourea used instead of an amidine [91], 2-thiopyridazines are obtained. In this case, 1,1,3,3-tetramethoxypropane can be also used as a synthon for the dicarbonyl unit (Scheme 19.58) [92].

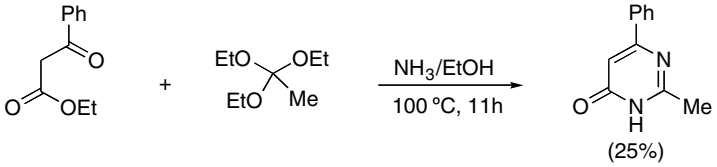


Scheme 19.57



Scheme 19.58

In addition, an orthoester in the presence of ammonia can be used as an *in situ* amidine source, although the yield is low (Scheme 19.59) [93].

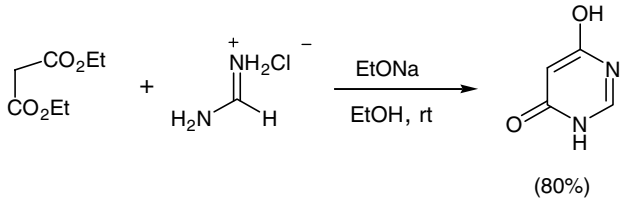


Scheme 19.59

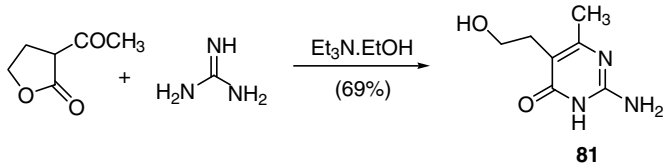
If one or both of the carbonyl groups in the 1,3-dicarbonyl is replaced with a carboxylic ester, 4-pyrimidinones and 6-hydroxy-4-pyrimidinones are formed (Scheme 19.60) [94].

The widespread use of pyrimidine-containing compounds as anticancer drugs has led to the development of numerous pyrimidine preparations using this basic approach. One of these is illustrated here, involving the opening of butyrolactone esters with guanidine to give pyrimidinone **81** (Scheme 19.61) [95].

Use of an α,β-unsaturated carbonyl compound as the addend gives a dihydropyrimidine framework, which can be oxidized to the saturated heterocycle

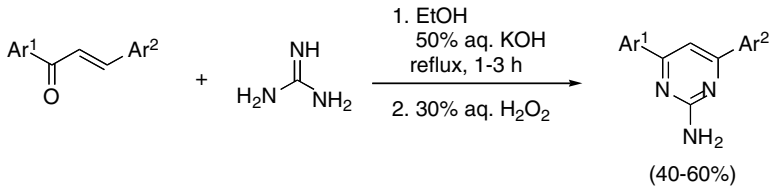


Scheme 19.60



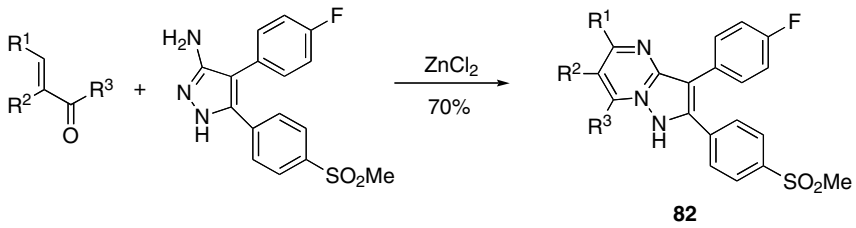
Scheme 19.61

(Scheme 19.62). This methodology has been developed into a solution-phase parallel synthesis of 4,6-diarylpyrimidine-2-ylamines with polymer release being executed via a rearrangement reaction [96].



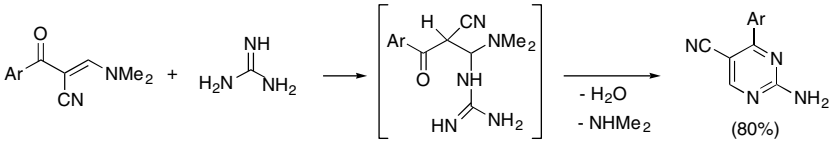
Scheme 19.62

The same protocol has been used by Almansa and coworkers, in the search for COX-2-selective inhibitors, who synthesized various pyrazolo[1,5-*a*]pyrimidines **82** (Scheme 19.63) by condensing 3-aminopyrazoles and various enones in the presence of zinc chloride [97].



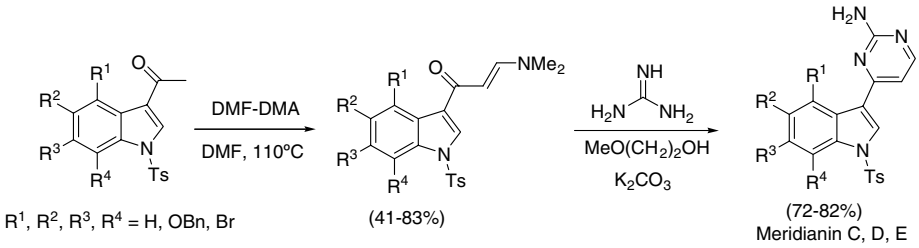
Scheme 19.63

Enaminones (vinylogous amides) also react with guanidines to produce 2-aminopyrimidines by a conjugated addition followed by ring closure and aromatization (Scheme 19.64) [98].



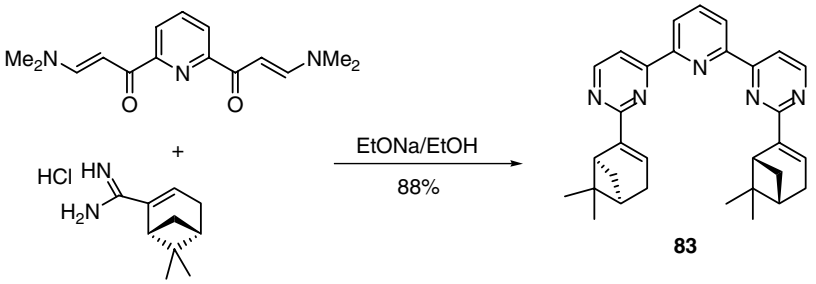
Scheme 19.64

Molina and coworkers have used this reaction in their synthesis of the biologically active marine natural products meridianins C, D, and E (Scheme 19.65) [99].



Scheme 19.65

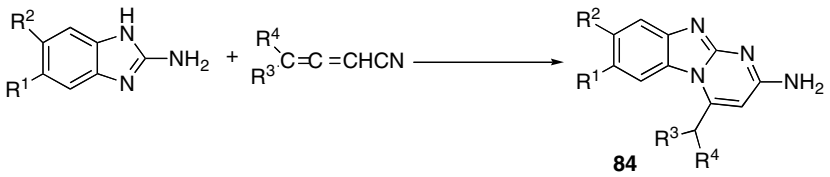
This methodology has been used to prepare several new chiral ligands that contain pyrimidine rings (**83**), through the bis-condensation of a chiral amidine with α,β-unsaturated carbonyl compounds, in high yield (Scheme 19.66) [100].



Scheme 19.66

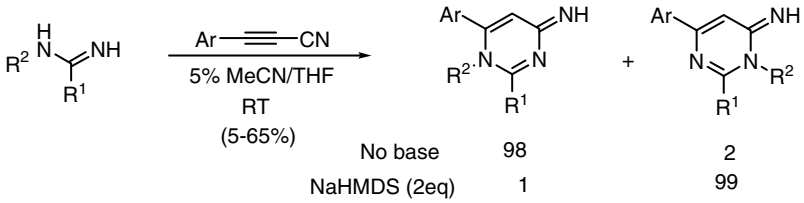
Other dicarbonyl synthons can be used as well, such as 1,1,3,3-tetramethoxypropane [92] (for malonodialdehyde), nitriles, and tosyl isocyanates [101], to prepare pyrimidine derivatives in good yields. Fomum and coworkers have reported a novel

synthesis of biologically active pyrimido[1,2-*a*]benzimidazole **84** by the cycloaddition of different aminobenzimidazoles with allenic nitriles (Scheme 19.67) [102].



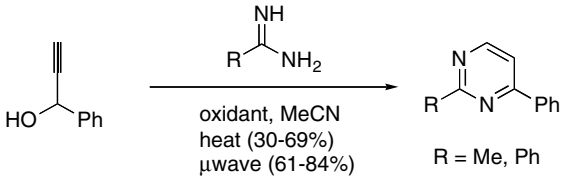
Scheme 19.67

Certain alkynes can be also be implemented as dicarbonyl synthons for these cyclizations. In this context, conjugated addition of amidines to cyanoalkynes followed by subsequent ring closure of the resulting amidate nitrogen onto the pendant nitrile affords 4-iminopyrimidines with nearly complete regioselectivity [103]. Moreover, product regioselectivity can be reversed by the use of sodium hexamethyldisilazide (NaHMDS) as a base (Scheme 19.68).



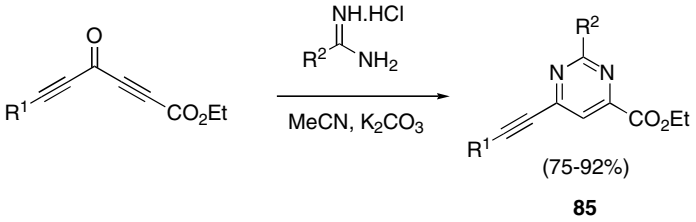
Scheme 19.68

One-pot syntheses of pyrimidines continue to be developed as efficient routes to pyrimidines. For example, pyrimidines can be prepared in a single step from propargylic alcohols by *in situ* oxidation to the aldehyde with *o*-iodoxybenzoic acid (IBX) or manganese dioxide, which reacts with amidines to yield the pyrimidines (Scheme 19.69) [104]. The heteroannulation can be executed under either thermal or microwave-assisted conditions, although the latter affords higher yields.



Scheme 19.69

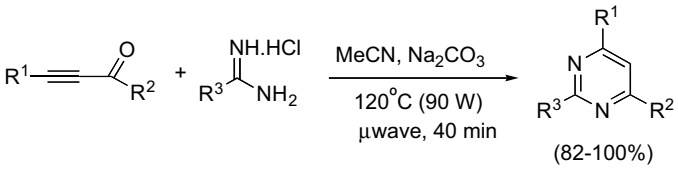
Highly reactive diacetylenic ketones react smoothly with amidines to yield a range of alkynyl-substituted pyrimidines **85** in high yields (Scheme 19.70) [105]. Notably,



Scheme 19.70

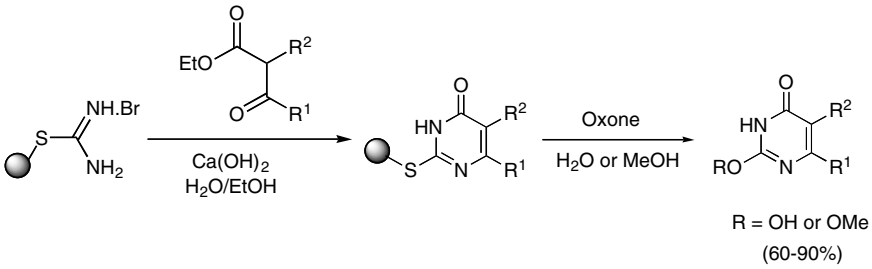
the pyrimidine compounds were obtained as single regioisomers, which is attributed to the acetylenic carbon bearing the ester group being the most electron deficient, making this the preferential site for nucleophilic attack of the amidine.

Microwave irradiation is now an established tool in organic synthesis, and its use in pyrimidine syntheses is particularly valuable. In this context, a microwave-assisted synthesis of 2,4-disubstituted and 2,4,6-trisubstituted pyrimidines in high yield has been reported from amidines and a range of readily available alkynones described (Scheme 19.71) [106].



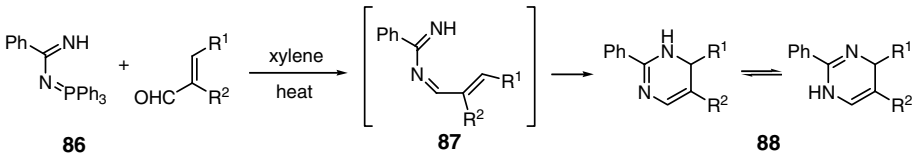
Scheme 19.71

Solid-phase syntheses of pyrimidines continue to appear at a rapid pace. A versatile solid-phase approach for the synthesis of a series of pyrimidinone derivatives has been described (Scheme 19.72) [107]. In the key step, a polymer-bound thiouronium salt is condensed with different β-ketoesters by adding an excess of $Ca(OH)_2$ in aqueous ethanol solution.



Scheme 19.72

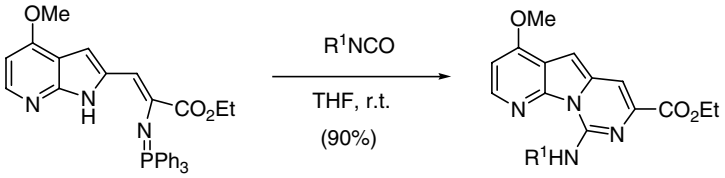
The use of iminophosphoranes has been emerging as a valuable tool for the construction of nitrogen-containing heterocycles [108]. The aza-Wittig reaction of iminophosphorane **86** with acyclic α,β-unsaturated aldehydes has been reported by Rossi and coworkers as a means to produce 1,6(1,4)-dihydropyrimidines **88** through electrocyclic ring closure of 1,3-diaza-1,3,5-triene intermediate **87** (Scheme 19.73) [109].



86 **87** **88**

Scheme 19.73

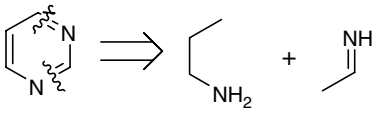
Molina has used this methodology in the last step of his synthesis of the tricyclic ring system **90**, which is present in the marine natural products variolins (Scheme 19.74) [99]. In this case the aza-Wittig reaction takes place between the iminophosphorane **89** with several aromatic isocyanates in dry THF at room temperature to give directly the desired pyrimido annelation products in high yields.



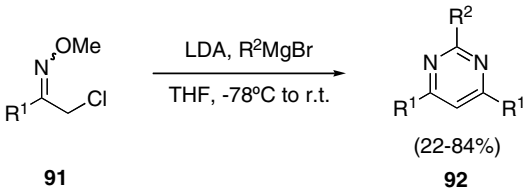
89 **90**

Scheme 19.74

19.5.1.2.2 **[C-C-N] + [C-C-N]** 2,4,6-Trisubstituted pyrimidines **92** can be obtained from an interesting reaction of α-chloro oxime ethers **91** with Grignard reagents (Schemes 19.75 and 19.76). This methodology presents the advantage that alkyl and aryl groups can be easily introduced at the 2-position of the pyrimidine core [110].



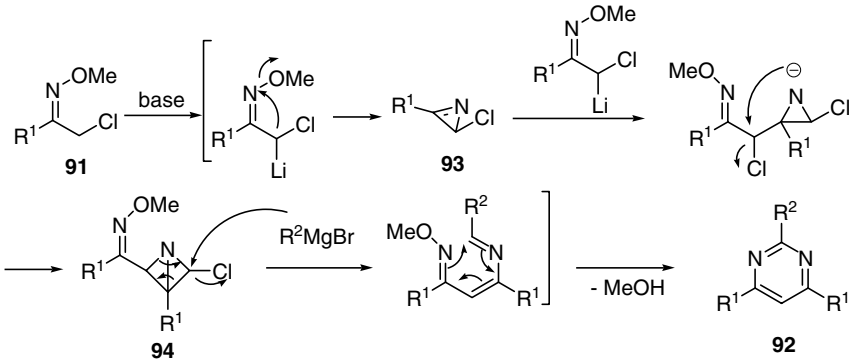
Scheme 19.75



91 **92**

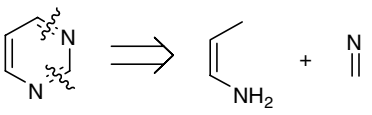
Scheme 19.76

The authors propose a plausible mechanism (Scheme 19.77) involving deprotonation of α-chloro oxime ether **91** to generate a carbenoid species, which then undergoes Neber-type cyclization [111] to provide a reactive chloroazirine **93**. Nucleophilic addition of a second molecule of the oxime to the azirine intermediate, and subsequent intramolecular cyclization, is believed to yield 2-chloro-1-azabicyclo [1.1.0]butane **94**. Halide displacement by the Grignard alkyl group triggers ring opening to an imino oxime, which undergoes electrocyclization and methanol elimination to the pyrimidine **92**.

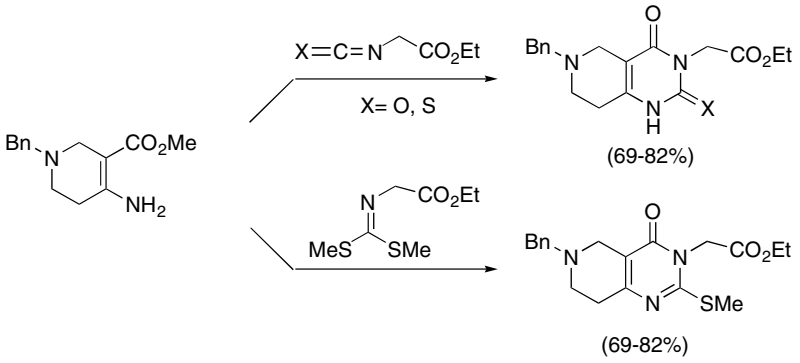


Scheme 19.77

19.5.1.2.3 **[C-C-C-N] + [C-N]** Fused pyrimidones can be synthesized from the cyclization of vinylogous carbamates with isocyanates, isothiocyanates, or thiomethyleneglycinates in acetic acid (Schemes 19.78 and 19.79) [112].

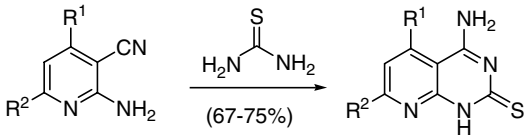


Scheme 19.78



Scheme 19.79

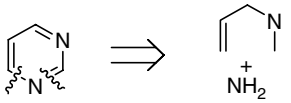
In related fashion, Kumar and coworkers [113] have reported the conversion of 2-amino-3-cyanopyridines into aminopyrimidinethiones **95** in good yield by cyclization with thiourea (Scheme 19.80).



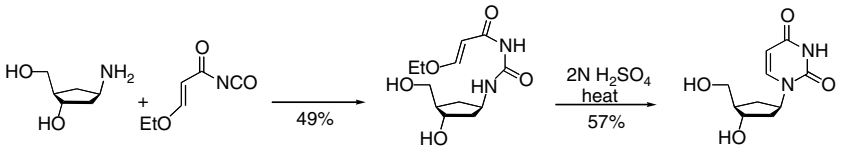
95

Scheme 19.80

19.5.1.2.4 **[C-C-C-N-C] + [-N-]** Uracil derivatives can be prepared by addition of primary amines to 3-ethoxyacryloylisocyanate [114], methoxyacryloylisothiocyanate [115], or acryloylcarbamates [116] by addition and intramolecular displacement of the vinylic alkoxy group (Schemes 19.81 and 19.82). This method is suitable for complex amines and has found applications in recent years in the synthesis of nucleoside analogues as potential anti-viral agents [117].

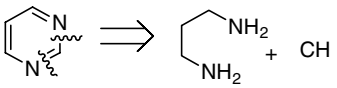


Scheme 19.81

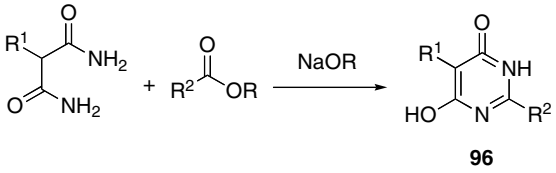


Scheme 19.82

19.5.1.2.5 **[N-C-C-C-N] + [-C]** The Remfry–Hull synthesis based on cyclocondensations of 1,3-diaminopropene or 1,3-diaminopropanes with carboxylic esters has been adapted to the use of malonamides to afford 6-hydroxypyrimidin-4(3*H*)-ones **96** (Schemes 19.83 and 19.84).



Scheme 19.83

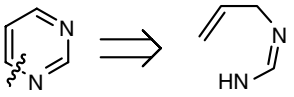


Scheme 19.84

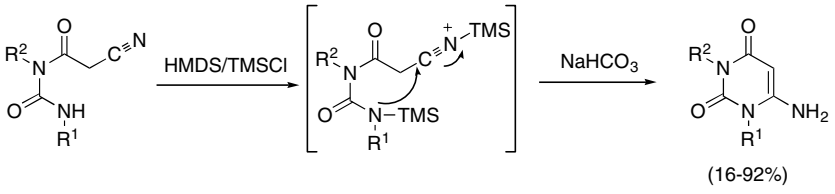
19.5.1.3 One-Component Couplings

19.5.1.3.1 [N-C-N-C-C-C]

From Cyanoacetylureas Condensation of an N-substituted urea with cyanoacetic acid yields cyanoacetylureas, which when heated in the presence of HMDS/TMSCl (hexamethyldisilazane/trimethylchlorosilane) affords 6-aminouracil derivatives. The reported mechanism (Schemes 19.85 and 19.86) involves activation of the cyano functionality with TMSCl, which triggers the cyclization [118]



Scheme 19.85

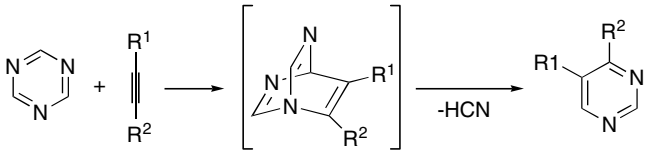


Scheme 19.86

19.5.2 Cycloaddition Reactions

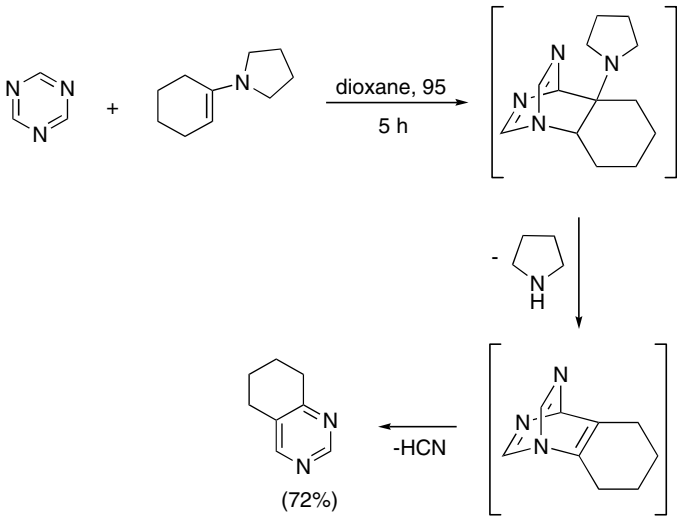
19.5.2.1 [4 + 2]-Cycloaddition Reactions of 1,3,5-Triazines

Boger [119] has described a simple pyrimidine annulation process based on the regiospecific, inverse electron demand cycloaddition of 1,3,5-triazine with an alkyne. This reaction presumably proceeds via formation and retro-cyclization of a bridged cycloadduct with loss of hydrogen cyanide (Scheme 19.87).



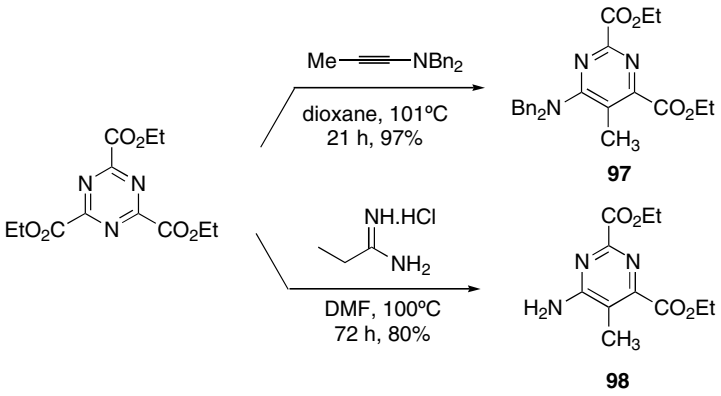
Scheme 19.87

This process can also utilize various acetylene synthons such as pyrrolidine enamines (Scheme 19.88), wherein the initial [4 + 2]-cycloadduct loses pyrrolidine, which enables rearomatization through expulsion of HCN [120].



Scheme 19.88

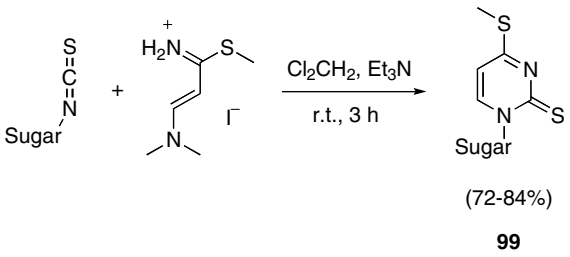
Highly electron-deficient triazines such as 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine react with ynamines or amidines (via the α-aminoenamine) to afford excellent yields of amino-substituted 1,3-pyrimidines **97** and **98** respectively (Scheme 19.89) [121].



Scheme 19.89

19.5.2.2 Other [4 + 2] Cycloaddition Reactions

Pyrimidine nucleosides **99** have been prepared by [4 + 2]-cycloadditions of glycosyl isothiocyanates with diazadienium iodide as a cationic heterodyne (Scheme 19.90) [122]. The advantages of this methodology are the ready availability of starting materials, good yields in the cycloaddition, high diastereo- and regioselectivity, and experimental simplicity of the procedure. These types of N-nucleosides have important applications as antiviral and antitumor drugs.



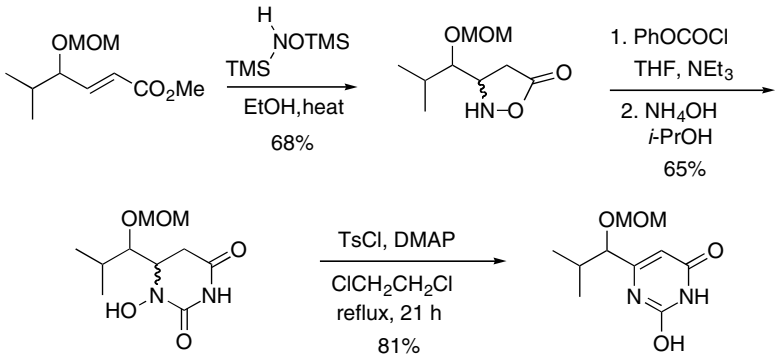
Scheme 19.90

19.5.3 Synthesis by Ring Enlargement

19.5.3.1 From Isoxazolidin-5-ones

Besides well-established strategies for the preparation of pyrimidines, some new pathways have been developed. Weinreb and Keen [123] have reported a novel route to pyrimidones from an isoxazolidin-5-one by treatment with phenyl chloroformate to

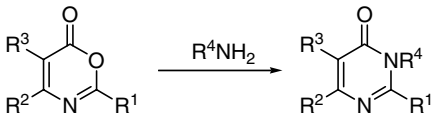
give the *N*-acylation product. Ammonolysis and aromatization give the pyrimidone product. Isoxazolidin-5-one can be obtained as a 1:1 mixture of diastereoisomers, from the reaction of α,β-unsaturated ester and *N,O*-bis-(trimethylsilyl)hydroxylamine (a convenient source of hydroxylamine) (Scheme 19.91).



Scheme 19.91

19.5.4
Synthesis by Ring Atom Exchange

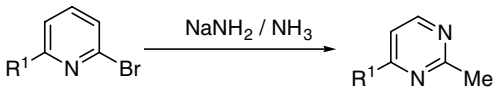
Similarly to the rearrangement of 1,2,4-triazines in the presence of a nucleophile to afford 3-aminopyridazines (Section 19.4.4.1) [69], 1,3-oxazin-6-ones are converted by amines into 4-pyrimidinones **100** (Scheme 19.92). The reaction occurs via a nucelophilic cleavage of the ester followed by cyclocondensation to close the ring.



100

Scheme 19.92

The same methodology can be applied to prepare pyrimidines from 2-bromopyridines (Scheme 19.93).



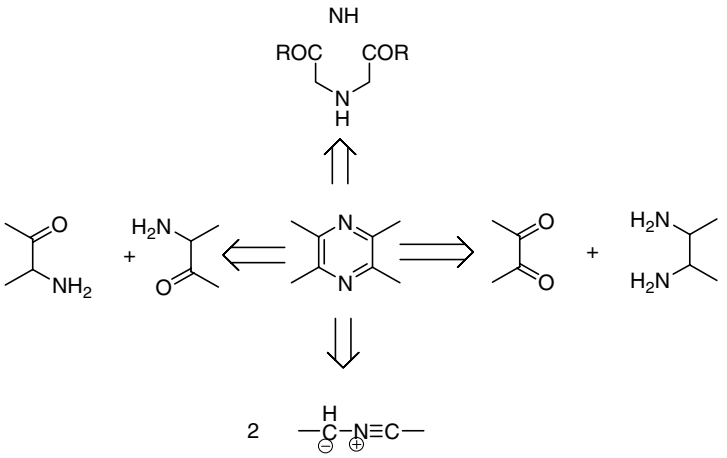
Scheme 19.93

19.6
Synthesis of Pyrazines (1,4-Diazines)

19.6.1
Synthesis by Ring-Closure Reactions

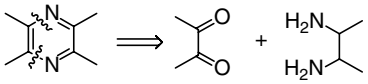
19.6.1.1 Two-Component Couplings

Four strategies have been devised for the synthesis of pyrazines by two-component couplings (Scheme 19.94).

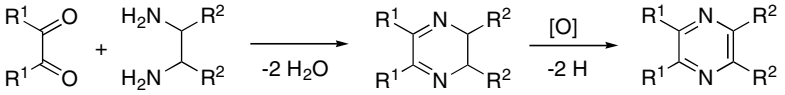


Scheme 19.94

19.6.1.1.1 **[C-C] + [N-C-C-N]** The most common way to construct the pyrazine ring is the cyclocondensation of 1,2-dicarbonyl compounds with 1,2-diaminoethanes (with double imine formation) to afford 2,3-dihydropyrazines, which are conveniently oxidized to pyrazines by CuO or MnO_2 in KOH/ethanol (Schemes 19.95 and 19.96). Symmetrical starting compounds yield the best results using this straightforward approach [124].

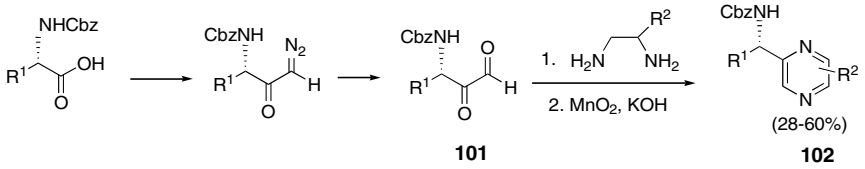


Scheme 19.95



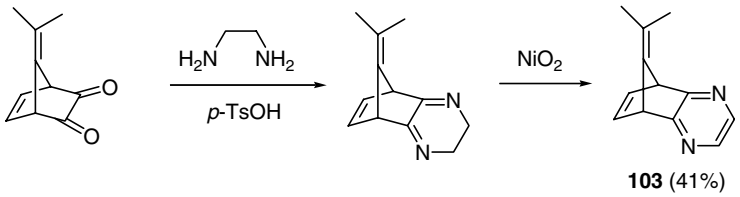
Scheme 19.96

McKervey and coworkers [125] have used N-protected α-amino glyoxals from diazoketones **101**, as 1,2-dicarbonyl components, to condense with simple 1,2-diamines to form dihydropyrazines (Scheme 19.97). These adducts can be dehydrogenated to pyrazines **102** by treatment with manganese dioxide in the presence of potassium hydroxide.



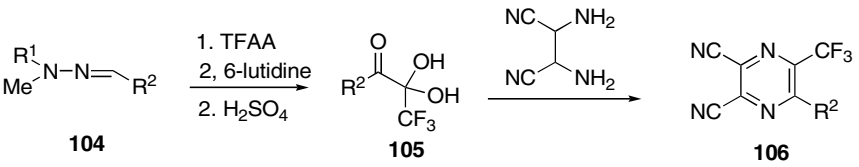
Scheme 19.97

Similarly, the pyrazine moiety of pyrazine-fused-isopropylidene norbornadiene **103** has been prepared by condensation of a 1,2-diketone and ethylenediamine, followed by dehydrogenation in the presence of nickel peroxide (Scheme 19.98) [40].



Scheme 19.98

Using this methodology, Kamitori has reported a new procedure to synthesize fluorinated pyrazines **106** (Scheme 19.99). Dialkylhydrazones **104** were treated with trifluoroacetic anhydride (TFAA) followed by hydrolysis with H_2SO_4 to afford α-diketohydrates **105**, which react readily with diamines such as diamino succinonitrile to afford pyrazines **106** in good yields [126].

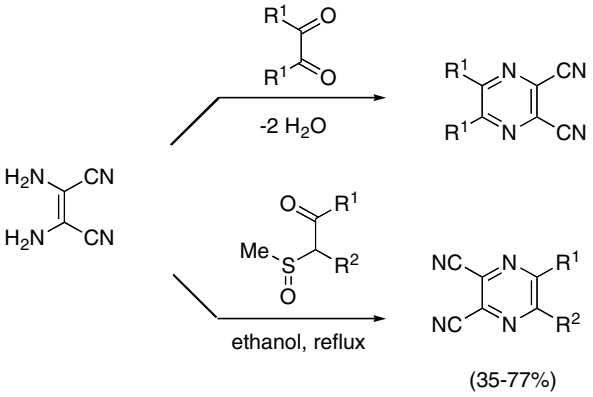


104 **105** **106**

Scheme 19.99

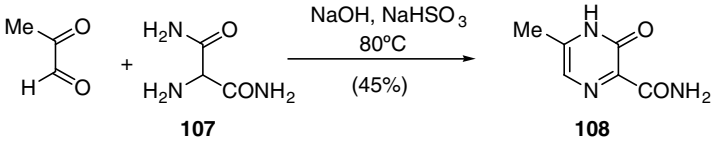
Direct synthesis of aromatic pyrazines requires a 1,2-diaminoalkene but simple examples of such compounds are rare; however, diaminomalononitrile can condense

with 1,2-diketones [127] or β-keto sulfoxides [128] to yield 2,3-dicyanopyrazines (Scheme 19.100).



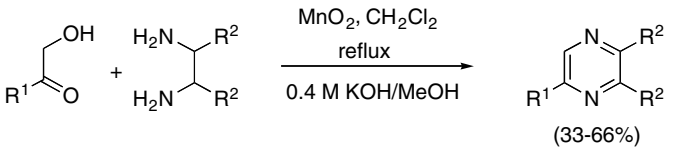
Scheme 19.100

α-Amino malonamides **107** are also unsaturated diamine synthons from which pyrazinones **108** can be formed (Scheme 19.101) [129].



Scheme 19.101

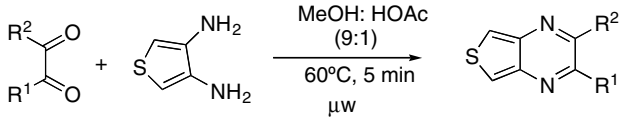
To avoid the need to isolate the highly reactive 1,2-dicarbonyl intermediates, Taylor has developed a novel methodology for the conversion of α-hydroxyketones into pyrazines in fair to good yields, via a tandem oxidation procedure with *in situ* trapping using 1,2-diamines (Scheme 19.102) [130].



Scheme 19.102

Functionalized pyrazines have been prepared in excellent yields (69–99%) from common 1,2-diketones and 1,2-diamines under microwave irradiation, which

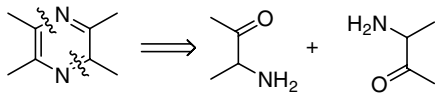
suppresses the formation of the polymeric by-products characteristic of conventional thermal heating (Scheme 19.103) [131].



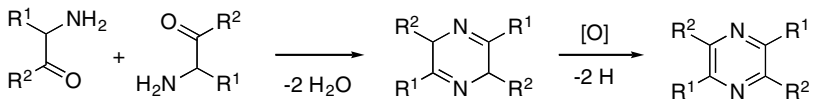
Scheme 19.103

19.6.1.1.2 [C-C-N] + [C-C-N]

Cyclodimerization of α-Amino Carbonyl Compounds An important preparation of pyrazines involves the self-condensation of α-amino ketones to give 2,5-dihydropyrazines that subsequently oxidize to the corresponding pyrazines (Schemes 19.104 and 19.105). The required α-amino aldehydes or ketones are usually prepared *in situ* because of their instability, and can be obtained from α-hydroxycarbonyl compounds and ammonium acetate or by catalytic reduction of α-oximino- or α-azidocarbonyl compounds.

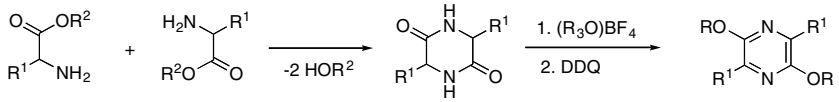


Scheme 19.104



Scheme 19.105

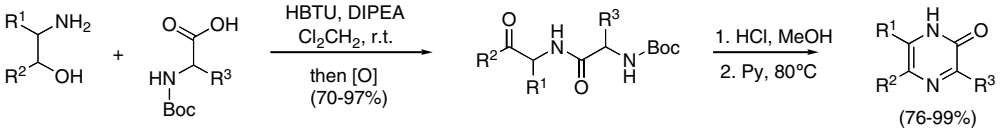
Cyclodimerization of α-Amino Acids Correspondingly, cyclodimerization of α-amino acids or their esters gives 2,5-dioxopiperazines **109** (Scheme 19.106), which by treatment with trialkyloxonium salts followed by oxidation with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) provides 3,6-dialkoxypyridazines **110** [132].



109 **110**

Scheme 19.106

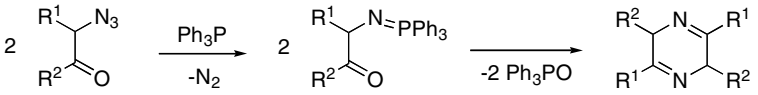
Meier has described a new and efficient synthesis of trisubstituted 1*H*-pyrazin-2-ones **111** and tetrasubstituted pyrazines by coupling Boc-protected amino acids with α-amino ketones or with α-amino alcohols and subsequent oxidation (Scheme 19.107). These syntheses afford the advantage of the use of readily available starting materials yielding various products in high yield [133].



111

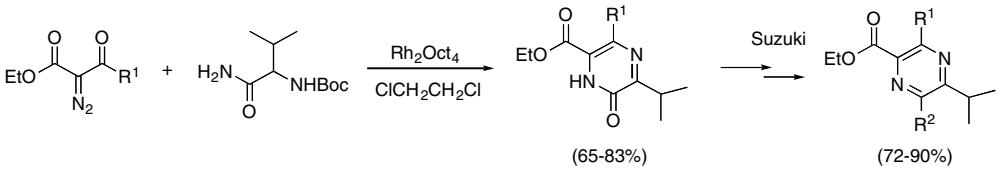
Scheme 19.107

Cyclodimerization of α-Phosphazinyl Ketones An alternative synthesis of pyrazines utilizes an aza-Wittig cyclization of α-phosphazinyl ketones, which are accessible from α-azido ketones and triphenylphosphine (Scheme 19.108).



Scheme 19.108

Metal-Assisted Reactions A series of α-diazo-β-ketoesters have been reacted with Boc-protected α-amino amides in the presence of rhodium octanoate catalyst, and the resulting N-H insertion products were treated with acid to provide pyrazine-6-ones **112** after air oxidation of the intermediate 1,4-dihydropyrazines. These products were further derivatized to tetrasubstituted pyrazines **113** by N-alkylation or by conversion into the arylpyrazines using sequential bromination and Suzuki coupling reactions (Scheme 19.109) [134]. The authors have shown that this methodology is amenable to the synthesis of compound libraries using solid-phase procedures.

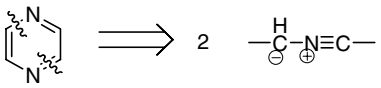


112 **113**

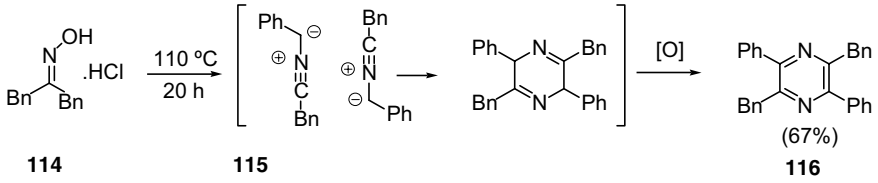
Scheme 19.109

19.6.1.1.3 **[C-N-C] + [C-N-C]**

Cyclodimerization of Nitrile Ylides In an interesting approach, Chandrasekhar has used a thermal Beckmann rearrangement to construct fully substituted pyrazines from dimerization of oximes (Schemes 19.110 and 19.111). The starting oxime hydrochloride **114** was thermally dehydrated and deprotonated to the nitrile ylide **115**, which dimerizes to form, after air oxidation, the corresponding tetrasubstituted pyrazines **116** [135].



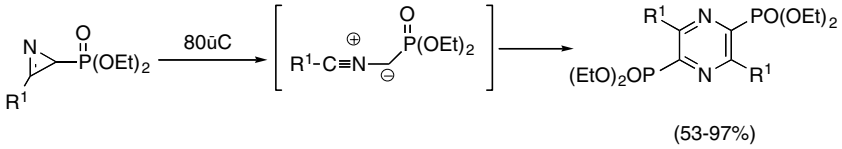
Scheme 19.110



114 **115** **116**

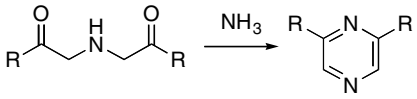
Scheme 19.111

Similar methodology was used for the synthesis of tetrasubstituted pyrazines containing two phosphonate groups by the thermal treatment of 2*H*-azirine-2-phosphonate (Scheme 19.112) [136].



Scheme 19.112

19.6.1.1.4 **[C-C-N-C-C] + [N]** Pyrazines are obtained by oxidative ring closure of bis (acylmethyl)amines with ammonia (Scheme 19.113).

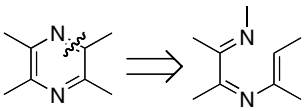


Scheme 19.113

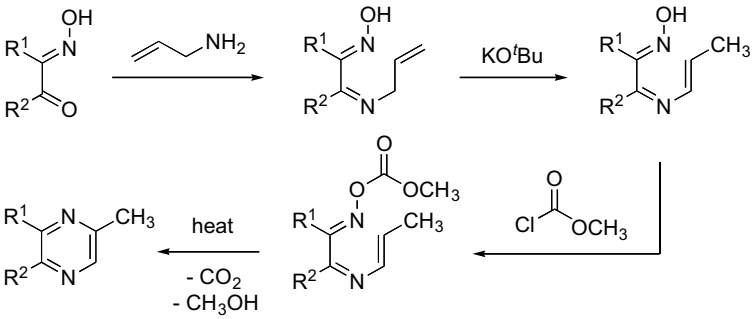
19.6.1.2 One-Component Couplings

19.6.1.2.1 [N-C-C-N-C-C]

Electrocyclic Ring Closure Alkylpyrazines are obtained regioselectively from α-hydroxyimino ketones that condense with allylamines followed by olefin isomerization, O-acylation, and electrocyclization with loss of CO_2 and CH_3OH (Schemes 19.114 and 19.115) [137].



Scheme 19.114

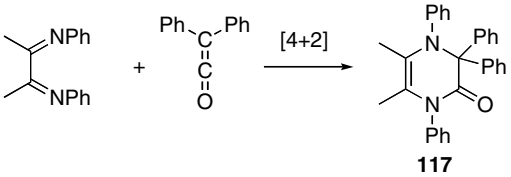


Scheme 19.115

19.6.2 Cycloaddition Reactions

19.6.2.1 [4 + 2]-Cycloaddition Reactions of α-Diimines

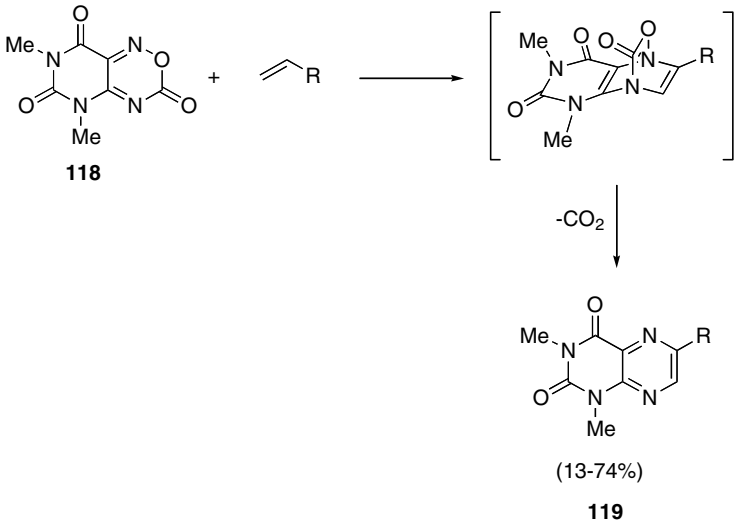
The cycloaddition reaction of α-diimines and ketenes yields tetrahydropyrazinones **117** (Scheme 19.116).



117

Scheme 19.116

Another pyrazine preparation is the [4 + 2]-cycloaddition of electron-rich dienophiles with 1,4-diaza-3-oxa-2-ones **118** to produce lumazines **119** (Scheme 19.117) [138], which are of the same class of compounds as many natural pteridines of biological importance.

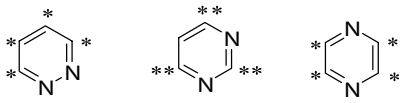


Scheme 19.117

19.7 Reactivity of Diazines

The reaction chemistry of diazines has very little in common with that of benzene and its derivatives. The notable reactivity differences already existing between benzene and its nitrogen variant, pyridine, are further accentuated by having a second nitrogen atom in the ring. Some of the general features of diazine chemistry can be summarized as follows.

1) Owing to the presence of the two nitrogen atoms in the ring, the energies of the π-molecular orbitals are lowered, particularly those with large coefficients on nitrogen. As a result, this makes electrophilic attack on the ring carbon atoms rather difficult while facilitating nucleophilic addition onto the ring.
2) All the ring carbon atoms in the diazines, with the exception of C5 of pyrimidine, are *ortho* or *para* to at least one ring nitrogen atom. Intermediates formed by nucleophilic attack onto the ring, or by deprotonation at these positions, are well stabilized. This provides selective activation of specific positions in each of the three diazine ring systems as shown below (a * indicates a propensity for nucleophilic attack, while ** reflects an even greater degree of reactivity).



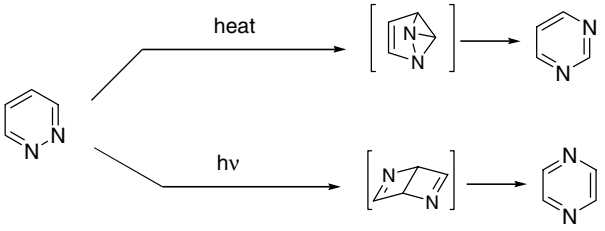
3) The availability of nitrogen lone pair(s) is also reduced, making each of the diazines less basic that pyridine. Cations derived from these heterocycles by electrophilic attack on nitrogen are less stabilized due to the electron-withdraw-

ing influence of the second nitrogen, thereby making the heterocycles more difficult to N-alkylate or N-oxidize.

19.7.1 Thermal and Photochemical Reactions

19.7.1.1 Pyridazines (1,2-Diazines)

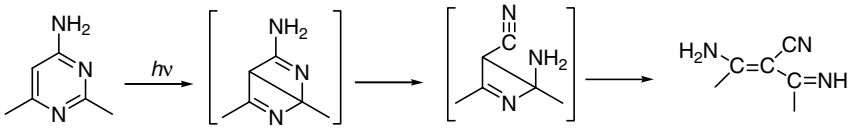
Pyridazine can be regarded as a cyclic bis-hydrazone and the mutual proximity of the nitrogen atoms is reflected in different physical properties and reactions compared to those of pyrimidine and pyrazine. The reactivity of 1,2-diazines under thermal and photochemical conditions are particularly noteworthy (Scheme 19.118). Pyridazine (1,2-diazine) is converted into pyrimidine (1,3-diazine) upon heating to 300 °C, most likely via a diazabenzvalene intermediate. Conversely, photolysis yields mainly pyrazine (1,4-diazine), where, presumably, a transient intermediate similar to Dewar benzene is involved in the process [139]. Thus, in this way, pyridazine can undergo isomerization to either of its other two diazine forms.



Scheme 19.118

19.7.1.2 Pyrimidines (1,3-Diazines)

Pyrimidines experience a similar fate under photochemical conditions, reverting to a Dewar pyrimidine species [140]. In the case of 4-amino-2,6-dimethylpirimidine, photoisomerization yields an acyclic aminoimine by ring-opening of the Dewar pyrimidine intermediate (Scheme 19.119).

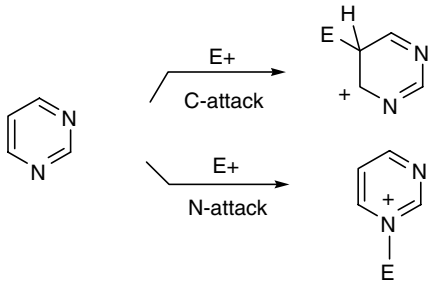


Scheme 19.119

19.7.2 Reactions with Electrophilic Reagents

Owing to the electronegativity of the two nitrogen atoms, all of the diazines are electron-deficient heterocycles that fail to react with most electrophiles. Electrophilic

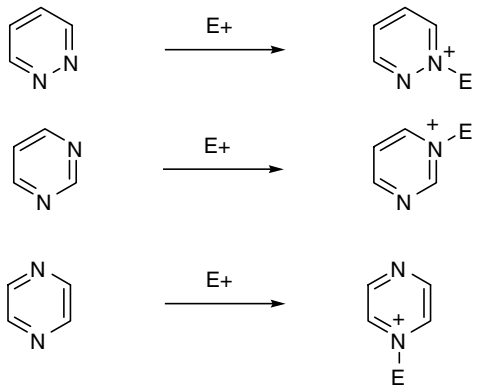
substitution at one of the carbon centers of the ring must first break the aromaticity of the π-system, giving an intermediate that is further deactivated by the two electronegative nitrogen atoms. This is exemplified in Scheme 19.120 by the case of pyrimidine (top pathway). The electrophilic susceptibility of pyrimidine is comparable to that of 1,3-dinitrobenzene or 3-nitropyridine. Consequently, the kinetically preferred pathway for electrophilic addition is at nitrogen (bottom pathway). Activation of the diazine ring by attachment of one or more electron-donating substituents promotes electrophilic substitution on the ring, as will be illustrated in examples below.



Scheme 19.120

19.7.2.1 Electrophilic Addition at Nitrogen

Diazines behave as tertiary amines in their reactions with a wide range of electrophiles (Scheme 19.121): protic acids (to give salts), Lewis acids (to form coordination compounds), transition metal ions (to form complex ions), alkyl halides (to give quaternary salts), halogens (to form halo adducts), and oxidizing agents (to yield amine oxides) [141]. The facility of these reactions depends on two major factors: the nucleophilicity of the nitrogen atom and the degree of steric hindrance. Although the pK_a of a protonated nitrogen is a convenient measure of thermodynamic basicity of the free amine, it is not a reliable indicator of



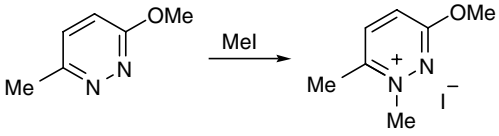
Scheme 19.121

kinetic nucleophilicity where steric effects of nearby substituents on the ring (particularly at the α-carbon) are likely.

19.7.2.1.1 **Protonation** Pyridazines (pK_a 2.3 for protonated form) are much weaker bases than pyridine (pK_a 5.2 for pyridinium cation) due to inductive withdrawal by the second ring nitrogen. The α-effect of the two nitrogen electron pairs is not sufficiently strong to overcome the electron-withdrawing effect of the N−N bond. N,N′-Diprotonation has only been observed in very strong acidic media ($pK_{a(2)}$ −7.1 for the dicationic species). Predictably, electron-donating substituents on the ring enhance the nitrogen's basicity, with protonation of 3-substituted pyridazines occurring on N2. In 4-substituted pyridazines, where steric and inductive effects are less important factors, protonation occurs at N1 for electron donor groups, and at N2 for electron acceptor substituents. In 3,6-disubstituted pyridazines, protonation occurs α to the less bulky and more powerful electron-donating substituent.

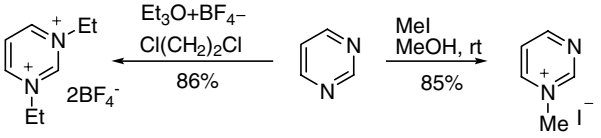
19.7.2.1.2 **Metal Ions** As a monodentate ligand in transition metal complexes, pyridazine forms tetrahedral and octahedral structures [e.g., Co(II) salts], and as a bidentate ligand it gives polymeric complexes. Pyrazine can replace three of the carbonyl groups in group VI metal hexacarbonyls to form compounds of the type $Cr(CO)_3Py_3$. The other diazines are known to also form metal complexes.

19.7.2.1.3 **Alkylation** Diazines react with activated alkyl halides by S_N2 displacement to give the anticipated mono-quaternary salts. Unsymmetrically-substituted diazines can give rise to two isomeric quaternary salts. Pyridazines are the most reactive of the diazines towards alkylation due to the α-effect. Substituents influence the orientation mainly by steric and inductive effects, rather than mesomeric effects. For example, methylation of 3-methoxy-6-methylpyridazine takes place adjacent to the methyl substituent, at N1, although mesomeric release would have been expected to favor attack at N2 (Scheme 19.122) [142].



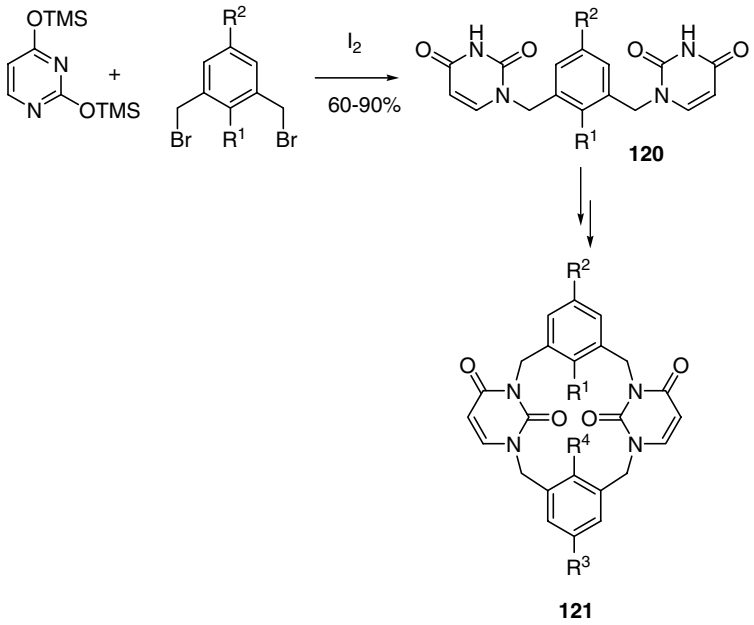
Scheme 19.122

Pyrimidines react with alkyl halides to give mono-quaternary salts. Dialkylation can be achieved with trialkyloxonium tetrafluoroborate (Scheme 19.123) [143].



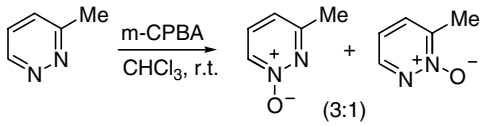
Scheme 19.123

2,4-Disubstituted pyrimidines undergo selective alkylation at the less sterically hindered N1. Kumar and coworkers have reported the coupling of 2,4-bis(silyloxy) pyrimidine with benzyl bromides in the presence of iodine to yield one regioisomeric bis-adduct (**120**) (Scheme 19.124) [144]. This was a key intermediate in their synthesis of heterocalixarenes **121**, which were use in subsequent biological cation binding studies.



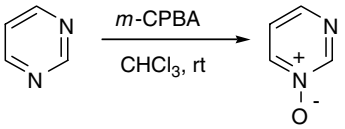
Scheme 19.124

19.7.2.1.4 **Oxidation** Pyridazines react with peracids to give *N*-monoxides [145]. For substituted diazines, the regiochemistry of N-oxidation is governed by the same factors as alkylation, thus 3-aminopyridazine gives mainly 2-oxides, but 3-methylpyridazine provides the 1-oxide as the main (3:1) product (Scheme 19.125) [146]. The acidity of the medium can also influence the regiochemistry of oxidation; for example, 3-cyanopyridazine reacts at N1 with peracetic acid, but under strongly acidic conditions oxidation occurs at N2, presumably due to the heterocycle existing as its N1-protonic salt [147].



Scheme 19.125

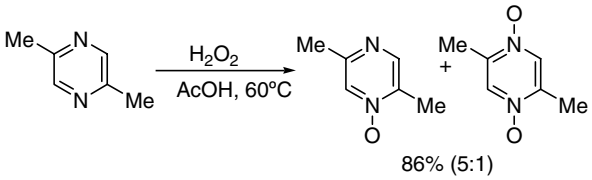
Pyrimidine and its simple alkyl derivatives can be converted into N-oxides **122**, although the yields are usually low due to the relative instability of the products under the acidic conditions (Scheme 19.126) [148].



122

Scheme 19.126

Pyrazine and its benzo derivatives are easily converted into both the mono-N-oxide (major) and di-*N*-oxides (minor) (Scheme 19.127) [145], although di-*N*-oxides have also been reported for pyridazines and pyrimidines.



Scheme 19.127

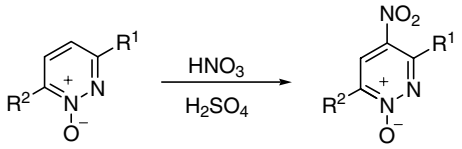
19.7.2.2 **Electrophilic Substitution at Carbon**

The S_EAr reaction at the ring C-atoms of diazines is difficult to carry out due to deactivation by the second nitrogen. Nitration or sulfonation of a diazine or alkyldiazine has been reported to take place only in the presence of multiple strong electron-donating substituents [149]. In addition, it should be noted that N-oxidation facilitates the substitution in some cases [150].

19.7.2.2.1 **Nitration**

Pyridazines (1,2-Diazines) 4-Amino-3,6-dimethoxypyridazine undergoes nitration to afford the 5-nitro compound. However, the less highly activated 3-methoxy-5-methylpyridazine requires more vigorous conditions, yielding a complex mixture of 4-nitro, 6-nitro, and 4,6-dinitro derivatives [151]. Pyridazine 1-oxide and many of its substituted derivatives undergo nitration with nitric and sulfuric acid to form the corresponding 4-nitropyridazine-1-oxide **123** (Scheme 19.128) [152]. If the 4-position is occupied nitration can occur at the 6-position.

Pyrimidines (1,3-Diazines) Notably, C5 in pyrimidine is the only position, in all three diazines, that is not in a α- or γ-relationship to a ring nitrogen, and in effect is equivalent to a β-position in pyridine, which is susceptible to electrophilic substitution. Nevertheless, electrophilic substitution at carbon is not observed in the parent compound. Electron-donating substituents (OH, NH_2) increase the S_EAr reactivity in

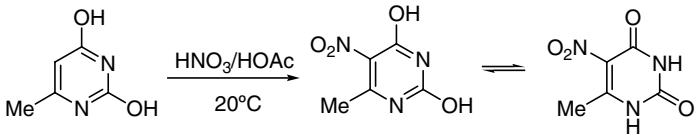


R^1, R^2 = H, alkyl, alkoxy, chloro

123

Scheme 19.128

the pyrimidine system and thus enable nitration, nitrosation, aminomethylation, and azo-coupling to take place at the 5-position [153]. Two or more electron-releasing substituents make nitration of pyrimidines relatively easy; 2,4-dihydroxy-6-methylpyrimidine, for instance, yields the 5-nitro compound **124** (Scheme 19.129).

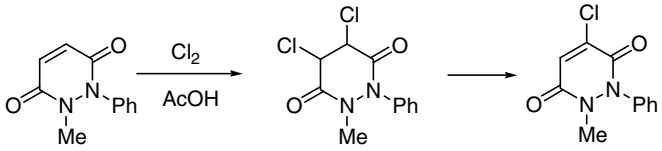


124

Scheme 19.129

19.7.2.2.2 Halogenation

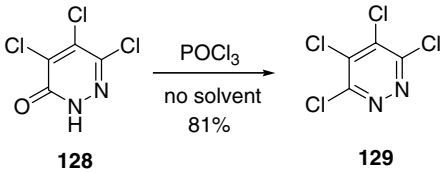
Pyridazines (1,2-Diazines) Pyridazines undergo electrophilic substitution only with difficulty, and thus direct halogenation is not expected to be a method of wide application. Nevertheless, dehydrochlorinations of pyridazines are known. 3,6-Dichloropyridazine can be converted by means of PCl_5 into 3,4,5,6-tetrachloropyridazine [152]. Simultaneous introduction of chlorine (or bromine) followed by dehydrohalogenation and substitution of the potential hydroxyl with chlorine has been performed with several 3(2*H*)-pyridazinones using a mixture of $POCl_3$ and PCl_5. The halogen atom always enters at the C4 position. Thus, 1-methyl-2-phenyl-3,6-pyridazinedione (**125**) adds bromine or chlorine to give the 4,5-dihalo adduct **126**, which is stable in neutral media, but dehydrohalogenation occurs in the presence of base to give solely the 4-halogenated product **127** (Scheme 19.130) [154].



125 **126** **127**

Scheme 19.130

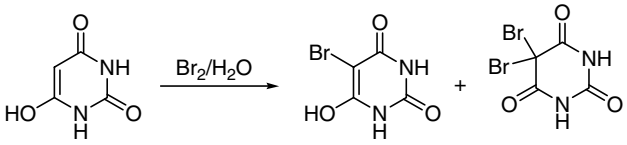
Perchlorinated pyridazines **129** (Scheme 19.131) can be prepared in good yields via chlorination of pyridazone **128** using phosphorus oxychloride [155].



128 **129**

Scheme 19.131

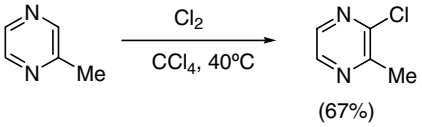
Pyrimidines (1,3-Diazines) As with nitration, pyrimidine undergoes halogenation under vigorous conditions to give the 5-substituted product; bromination occurs at 230 °C. When the diazine has one or more activating groups the reaction proceeds much more easily (Br_2 or Cl_2 in H_2O, AcOH, or $CHCl_3$, 20–100 °C). Sometimes 5,5-dihalo products are formed, however (Scheme 19.132).



Scheme 19.132

As strong donor substituents, amino groups activate the heteroarene towards *ortho*- and *para*-substitution. However, other substituents may alter the substitution pattern.

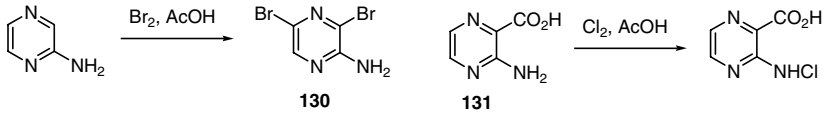
Pyrazines (1,4-Diazines) Chlorination of 2-methylpyrazine occurs under such mild conditions that it is almost certain that an addition/elimination sequence is involved, rather than a classical electrophilic aromatic substitution (Scheme 19.133) [156].



(67%)

Scheme 19.133

Also in this case, the halogenation reaction depends on the presence of other substituents on the diazine ring (Scheme 19.134). For instance, 2-aminopyrazine readily undergoes ring halogenation to give 3,5-dibromo-2-aminopyrazine **130**, but 3-aminopyrazine-2-carboxylic acid **131** is too electronically-deactivated on the heterocycle and, instead, the amino group is halogenated [153].



Scheme 19.134

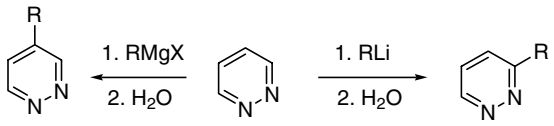
19.7.3 Reactions with Nucleophilic Reagents

Diazines are considerably more reactive toward nucleophilic addition than are pyridines due to the presence of an extra nitrogen atom. There are still only a few synthetic approaches to inducing substitution on this electron-deficient ring and, therefore, more diverse methods for functionalization of these heterocycles continues to be of interest.

19.7.3.1 With Replacement of Hydrogen

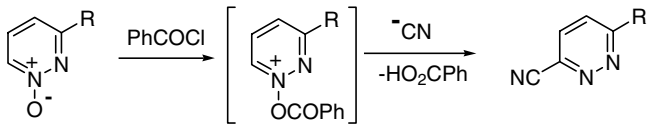
19.7.3.1.1 **Alkylation and Arylation** The diazines readily add alkyl and aryllithiums and Grignard reagents to give dihydro-adducts that can be rearomatized by oxidation with reagents such as potassium permanganate or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

Pyridazines (1,2-Diazines) Reactions with carbon nucleophiles occur at the C4 center (Grignard reagents) [157] or at C3 (organolithium compounds) (Scheme 19.135).



Scheme 19.135

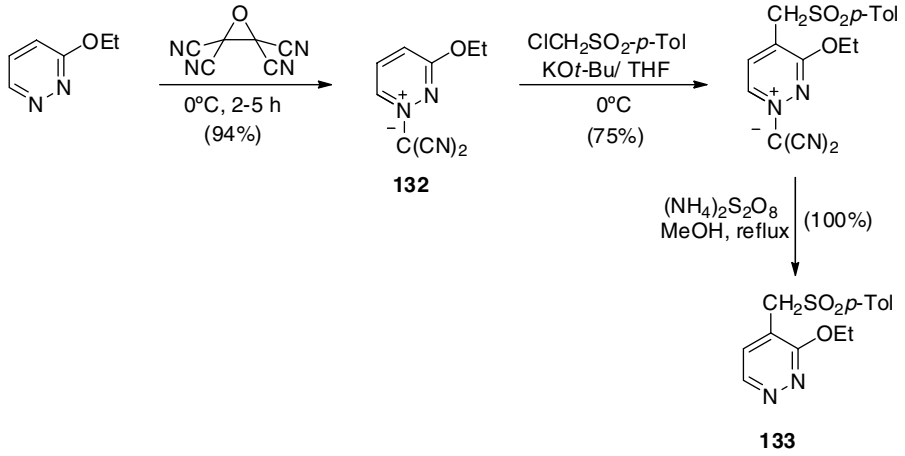
Alternatively, O-acylation of 3-substituted pyridazine 1-oxides gives a cationic species that reacts with nucleophiles such as cyanide by analogy to a Reissert reaction, functionalizing the C6 position (Scheme 19.136).



Scheme 19.136

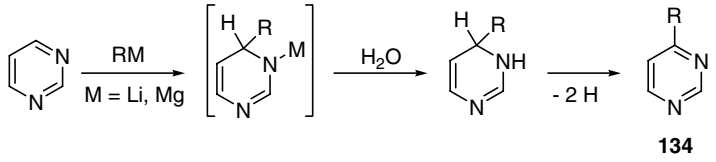
Ohsawa has reported a three-step procedure to regioselectively introduce an alkyl sulfone substituent (and thus potentially other groups) to position C4 of 3-substituted pyridazines (Scheme 19.137) [158]. First, pyridazine is reacted with tetracyanoethy-

lene oxide to form a dicyanomethylide zwitterion **132** (with subsequent loss of hexafluoroacetone), in which the existing C3 substituent blocks formation of the ylide at N2 in favor of N1. This species then undergoes base-promoted alkylation by an α-halosulfone, which the authors propose as occurring by a vicarious nucleophilic substitution (VNS) process, and cleavage of the dicyanomethylene group to afford exclusively the 4-alkylated pyridazine **133**.



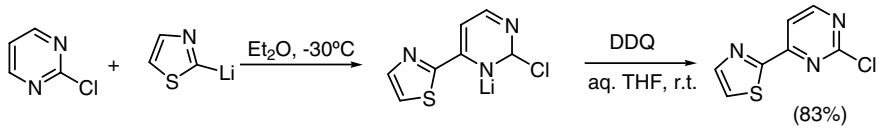
Scheme 19.137

Pyrimidines (1,3-Diazines) Nucleophilic attack on pyrimidine may occur at the 2-, 4-, or 6-position; although only a few such examples are known for pyrimidine itself, the addition of organometallic compounds gives the 4-alkylated pyrimidine **134** upon air oxidation of the dihydro adduct (Scheme 19.138).



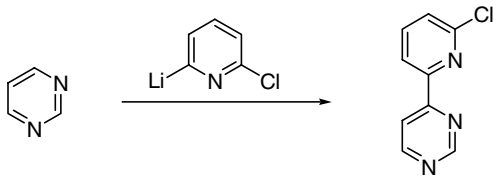
Scheme 19.138

Interestingly, 2-chloropyrimidine does not undergo nucleophilic substitution at the halogenated carbon, but instead gives the halogen-retained product with the new substituent at C4 (Scheme 19.139) [159].



Scheme 19.139

Another example of the regioselective addition of a nucleophile to an unsubstituted position on the pyrimidine ring, with C4 typically being the site of addition, has been reported by Fort and coworkers (Scheme 19.140); addition of 2-chloro-6-lithiopyridine to pyrimidine forms the coupled adduct **135** after rearomatization, albeit in low yield [160].

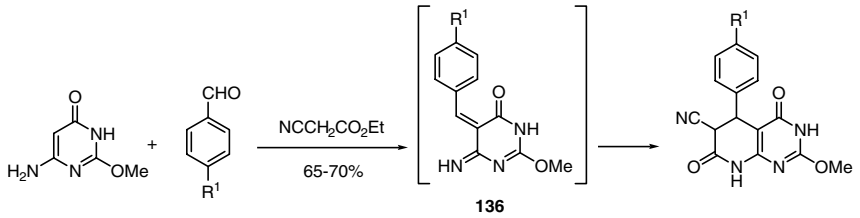


(25%)

135

Scheme 19.140

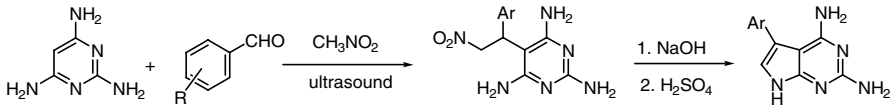
Electron-donating substituents enhance the nucleophilicity of pyrimidines and thus increase the effectiveness of electrophilic attack on the ring. As an example, the reaction of ethyl cyanoacetate with an aryl aldehyde produces a three-component coupling adduct **136**, by the conjugated addition of stabilized cyanoacetate carbanion to the initial Knoevenagel condensation adduct (Scheme 19.141) [161].



136

Scheme 19.141

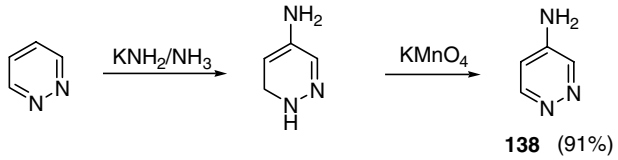
The process shown in Scheme 19.142 is thought to proceed by an analogous mechanism [162]. The authors noted that this tandem Nef reaction/Michael addition produced the final product **137** in a single step with sonication.



137

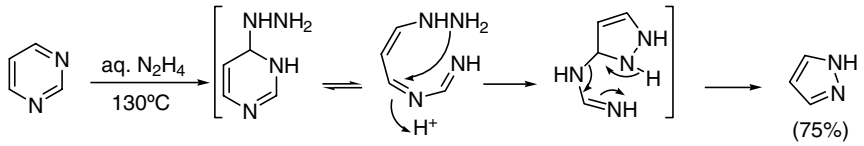
Scheme 19.142

19.7.3.1.2 **Amination** The Chichibabin reaction of diazines is less general than that for pyridines due to the diminished aromaticity of the diazine π-system. However, the initial addition is quite easy, while the subsequent loss of hydride (rearomatization) is difficult, but high yields of 4-aminopyridazine **138** (Scheme 19.143), 4-aminopyrimidine, and 2-aminopyrazine can be obtained by *in situ* oxidation of the dihydro-adduct with potassium permanganate [163].



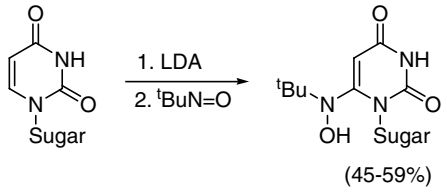
Scheme 19.143

Pyrimidines (1,3-Diazines) Pyrimidine is converted into pyrazole when heated with aqueous hydrazine by a process that involves nucleophilic addition as a first step, which triggers ring opening and subsequent reclosure to the five-membered aromatic ring (Scheme 19.144).



Scheme 19.144

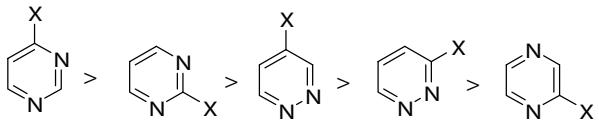
Amination can be achieved by direct lithiation of pyrimidine derivatives with LDA, or *sec*-BuLi, and *in situ* quenching with nitroso electrophiles (Scheme 19.145) [164].



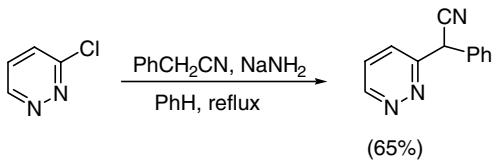
Scheme 19.145

19.7.3.2 **With Replacement of Good Leaving Groups**

All the halodiazines, except 5-halopyrimidines, react readily with nucleophiles (amines, thiolates, malonate anions) with substitution of the halide. The relative reactivity is summarized here.

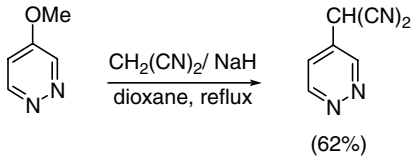


19.7.3.2.1 **Pyridazines (1,2-Diazines)** Nucleophilic aromatic substitution (S_NAr) reactions with an assortment of anionic nucleophiles proceed smoothly with pyridazines having a halogen leaving group at C3 (Scheme 19.146).



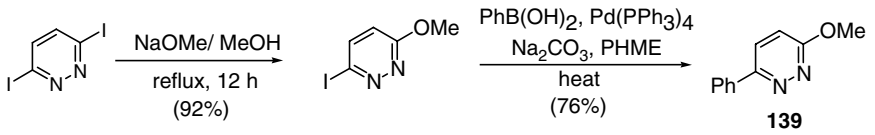
Scheme 19.146

Methoxy groups can also serve as leaving groups that can be exchanged by carbanions via an addition/elimination process (Scheme 19.147) [165].



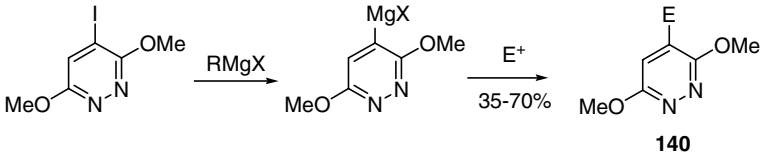
Scheme 19.147

Unsymmetrical 3,6-disubstituted pyridazines **139** can be prepared in a mild, efficient manner from commercially available 3,6-halopyridazines through stepwise nucleophilic mono-substitution followed by palladium-catalyzed coupling with an arylboronic acid (Scheme 19.148) [166].



Scheme 19.148

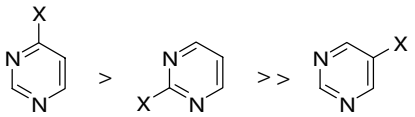
Grignard reagents can be prepared efficiently from halopyridazines followed by quenching with electrophiles such as acetaldehyde, ethyl cyanoformate, DMF, or phenyl sulfide to give **140** in acceptable yields (Scheme 19.149) [167].



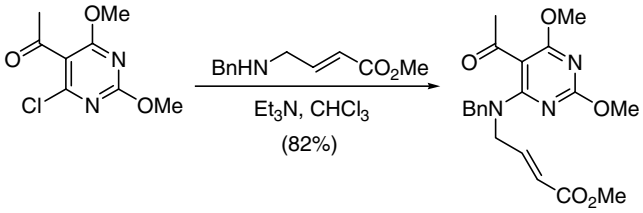
140

Scheme 19.149

19.7.3.2.2 **Pyrimidines (1,3-Diazines)** Remarkable differences in reactivity with nucleophiles exist for halopyrimidines and triflate derivatives, which depend on the location of the leaving group on the ring. Leaving groups at the C4 and C6 positions are much more prone to S_NAr processes than the C2 center due to the stabilizing effect of the nitrogen centers. The facility of S_NAr displacement for halopyrimidines follows a predictable order, as shown here.



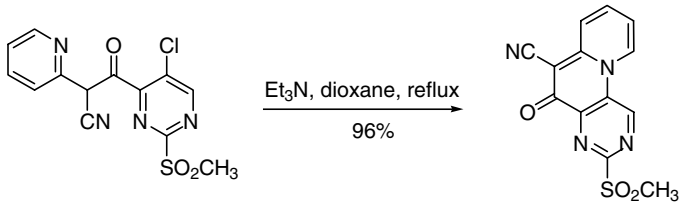
Nucleophilic aromatic substitution reactions have also been commonly applied to the transformation of pyrimidines into introduce a wide variety of new hetero and carbon ring substituents, as illustrated in Scheme 19.150 [168].



Scheme 19.150

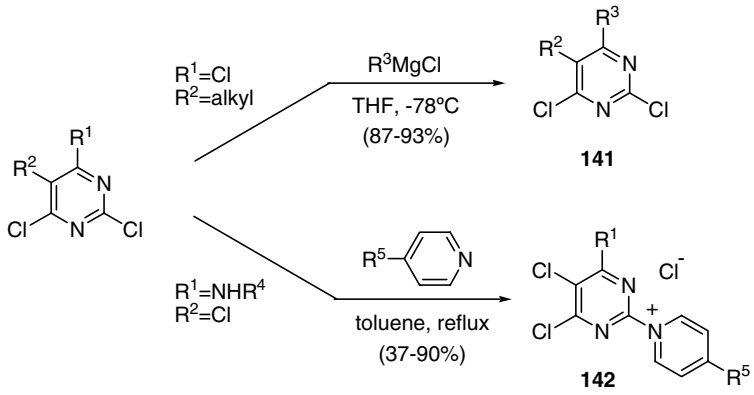
An intramolecular version of this reaction has been reported by Volovenko, where pyridine or other nitrogen-containing heterocycles can nucleophilically cycloadd to chloropyrimidines to produce various condensed pyrimidines (Scheme 19.151) [169].

The following reaction exemplifies the difference in reactivity of polychloropyrimidines with aliphatic nucleophiles (Grignard reagents, organolithiums, organo-



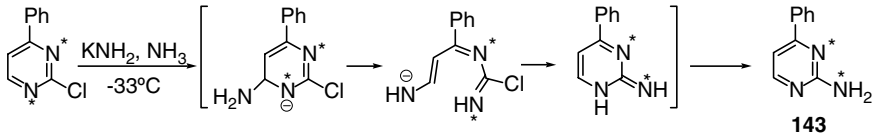
Scheme 19.151

sodiums, and thiolates) (Scheme 19.152), which predominantly yield 4-substituted pyrimidines **141** [170], versus heteroaromatic nucleophiles, which afford the 2-substituted pyrimidines **142** [171].



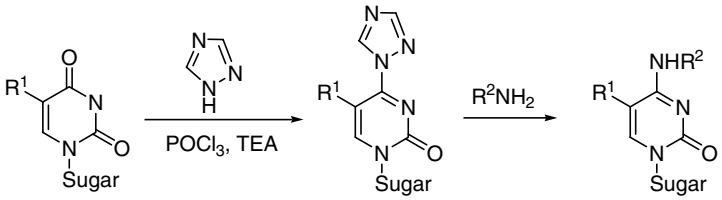
Scheme 19.152

Generally, all nucleophilic substitution reactions on halodiazines go by a conventional addition–elimination pathway. However, some transformations are not as straightforward, such as the reaction of 2-chloro-4-phenylpyrimidine with potassium amide in liquid ammonia, which gives 2-amino-4-phenylpyrimidine **143** (Scheme 19.153). Although this process appears to be an addition–elimination, radiolabeling experiments have revealed that a nucleophilic ring opening–ring closure mechanism is involved [172].



Scheme 19.153

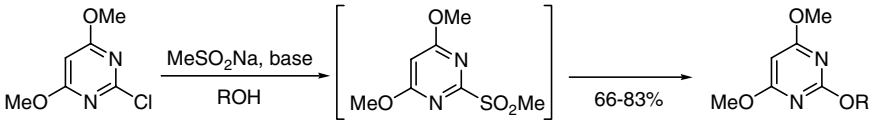
When the corresponding chloride fails to provide the desired substitution compound, triazoles are also often used as leaving groups in C–N bond formation. This procedure has been utilized by Leumann in the synthesis of deoxynucleosides **144** (Scheme 19.154) [173]. Other leaving groups, such as sulfonate, have also been reported for the introduction of N-substituents onto pyrimidines [174].



144

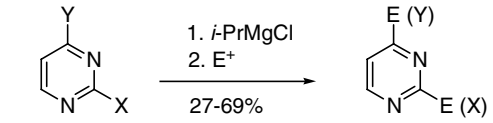
Scheme 19.154

2-Chloropyrimidine can be displaced by alcohols through the use of sodium methylsulfinate as a catalyst (Scheme 19.155). Significant rate enhancements as well as improved yields have been reported with this method [175].



Scheme 19.155

Iodopyrimidines could be converted into their Grignard derivatives by the action of *i*-PrMgCl, which then react with various electrophiles [167]. Quéguiner and coworkers have reported the synthesis of pyrimidines **145** bearing alcohols, aldehydes, and esters through this methodology (Scheme 19.156).



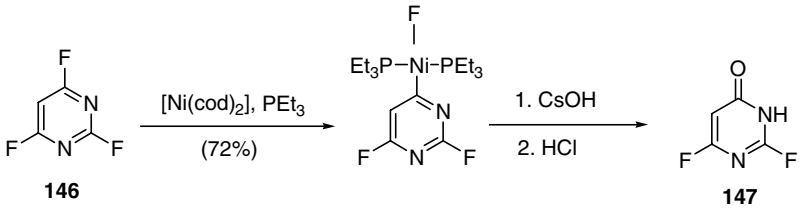
X = I, Y = OCH_3
X = SCH_3, Y = I

145

Scheme 19.156

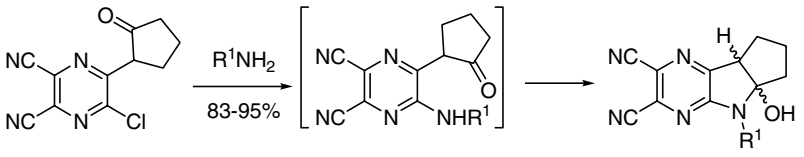
Fluorinated pyrimidones **147** are also of general interest as building blocks in agrochemicals and because of their antitumor activity. The selective substitution of the 4-fluoro substituent of 2,4,6-trifluoropyrimidine **146** by a hydroxyl group was

realized by the reaction with [Ni(cod)$_2$] in the presence of triethylphosphine followed by caesium hydroxide oxidation of the aryl nickel intermediate (Scheme 19.157) [176].



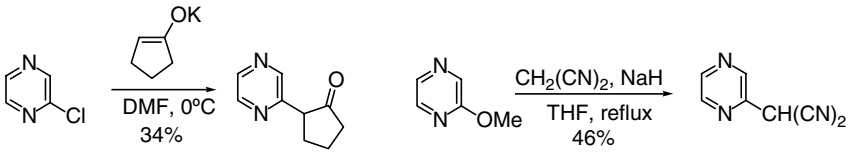
Scheme 19.157

19.7.3.2.3 **Pyrazines (1,4-Diazines)** Pyrazine is more reactive than pyridine towards nucleophilic attack. The Chichibabin amination of pyrazine itself is unsatisfactory, but substitution of the halogen in 2-halopyrazine occurs readily using ammonia, amines, amides, cyanide, alkoxide, and thiolate anion. In the example shown in Scheme 19.158, primary amines react with pyridazine to first yield the corresponding 3-amino derivatives, which subsequently added to the carbonyl group to give the ring-closed aminal [177]. The products prepared are all of interest as potential pesticides.



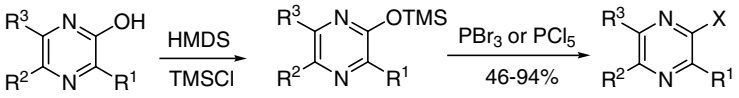
Scheme 19.158

Halo- and methoxy-substituted pyrazines (Scheme 19.159) can likewise be displaced by various carbon and hetero-nucleophiles [148].



Scheme 19.159

Sato and Narita have provided an improved synthesis of halopyrazines **149** in which hydroxypyrazines **148** were activated with TMSCl to give silyl ethers [178]. Subsequent treatment with the appropriate phosphorus-based halogen source provided halopyrazines in 46–94% overall yield (Scheme 19.160). This two-step



148 **149**

Scheme 19.160

process was accomplished without isolation of the siloxyl intermediate and provides a milder, more convenient approach than the traditional heating of hydroxypyrazines with PX_n directly.

Pyrazines undergo Grignard formation from halopyrazines and subsequently react with certain electrophiles to produce pyrazine derivatives **150** (Scheme 19.161) [167].

150 (11-59%)

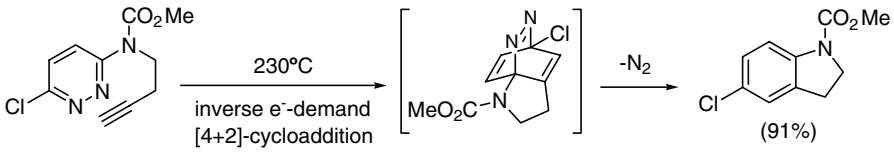
Scheme 19.161

19.7.4 Cycloaddition Reactions

All the diazines with electron-withdrawing substituents undergo inverse-electron demand Diels–Alder additions with electron-rich dienophiles [179].

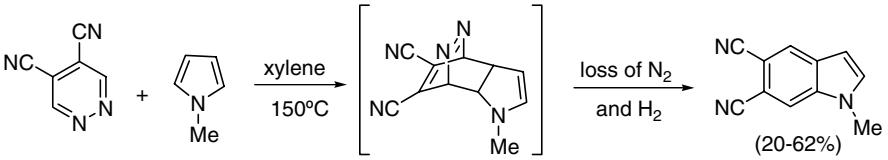
19.7.4.1 Pyridazines (1,2-Diazines)

The inverse electron demand Diels–Alder of pyridazines continues to be a commonly explored topic. The adjacent nitrogen atoms of pyridazines not only help create an electron-deficient heteroatomic diene but the N=N bond also functions as a good leaving group in a subsequent retro-Diels–Alder reaction. Intramolecular reactions of this type occur very rapidly, without even the presence of activating substituents. The immediate products of the initial [4 + 2]-cycloaddition usually lose dinitrogen (N_2) through rearomatization to generate benzene products (Scheme 19.162) [180].



Scheme 19.162

Intermolecular variants of this cycloadditive route to functionalized fused benzene derivatives are also readily executed, as shown for 4,5-dicyanopyridazine **151** with *N*-methylpyrrole (Scheme 19.163). The reaction occurs thermally at 150 °C to give a Diels–Alder adduct (**152**), which goes on to provide the indole heterocycle **153** upon expulsion of H_2 and N_2 [181]. Numerous examples of both the intramolecular and intermolecular processes similar to these have been described in the literature and applied to natural products total synthesis.

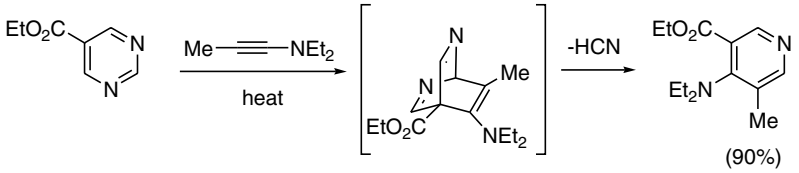


151 **152** **153**

Scheme 19.163

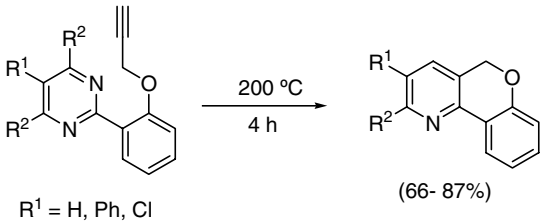
19.7.4.2 Pyrimidines (1,3-Diazines)

The corresponding [4 + 2]-cycloadditions of pyrimidines with electron-rich alkynes takes place to give regioselective substituted pyridine products, through loss of hydrogen cyanide (Scheme 19.164) [182].



Scheme 19.164

Intramolecular inverse-electron demand Diels–Alder reactions of pyrimidines with a dienophilic side chain have received considerable attention during the last few years. The broad scope and relatively mild conditions of these reactions make them fruitful. (Scheme 19.165) [183].

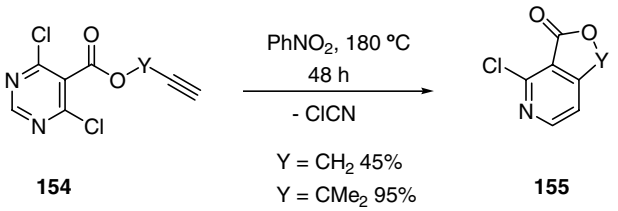


R^1 = H, Ph, Cl

R^2 = H, Me

Scheme 19.165

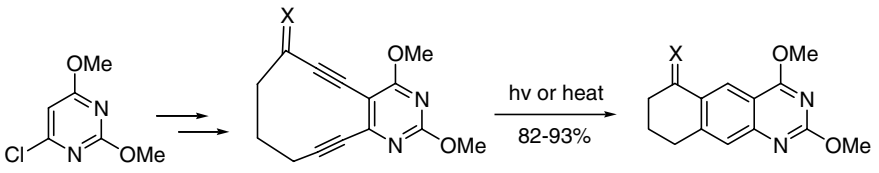
Following the earlier studies by van der Plas, Dehacen and coworkers have illustrated how the electron-deficient pyrimidine ring **154** can be exploited in the intramolecular inverse electron demand Diels–Alder reactions to obtain 2-chloropyridines **155** under thermal conditions (Scheme 19.166) [184].



154 **155**

Scheme 19.166

In a novel application, pyrimidine enediynes **156** have been prepared and subjected to Bergman cyclization to give tricyclic pyrimidines **157** (Scheme 19.167), which were shown to cleave dsDNA [185].



156
X = H, OH
X = O

157

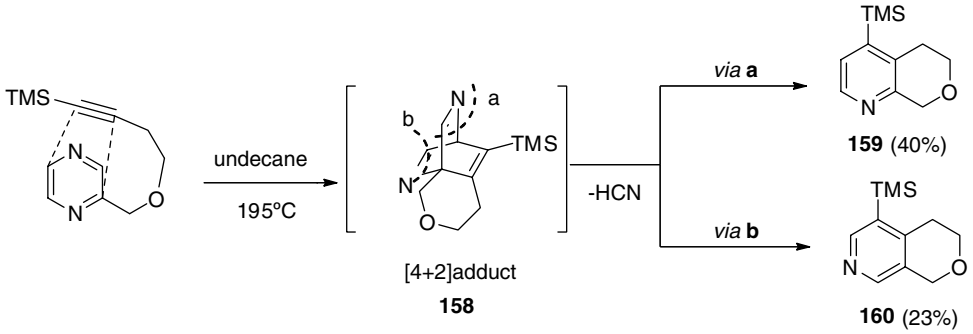
Scheme 19.167

19.7.4.3 **Pyrazines (1,4-Diazines)**

Likewise, pyrazines can be employed as electron-deficient dienes to prepare substituted pyridines, as shown in the following example [186]. A mixture of 8*H*-5,6-dihydropyrano[3,4-*b*]pyridine **159** and 1*H*-3,4-dihydropyrano[3,4-*c*]pyridine **160** are obtained (Scheme 19.168). In the formation of the intermediate cycloadduct **158** considerable steric hindrance develops between the trimethylsilyl group and the C = N bridge, and the fact that product **159** is favored over **160** implies that loss of hydrogen cyanide from cycloadduct **158** indicated by route a is faster than of that indicated by route b.

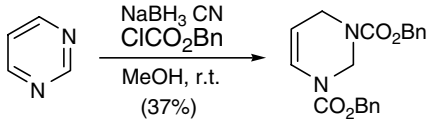
19.7.5
Reactions with Reducing Agents

Owing to the lower degree of aromaticity, diazines are more easily reduced than are pyridines. All the diazines can be reduced to tetrahydro derivatives with *in situ*



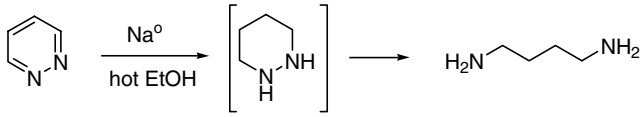
Scheme 19.168

carbamation on nitrogen, which aids in stabilization and thus allows isolation [187]. Yields, however, are generally not very high (Scheme 19.169).



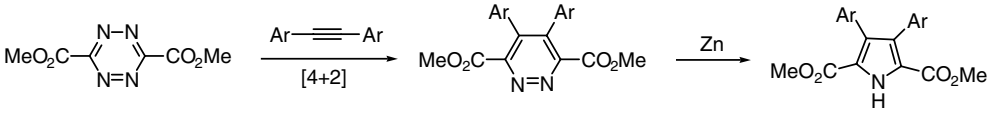
Scheme 19.169

Caution must be exercised in carrying out these conversions for pyridazines, however, since over-reduction to the hexahydro derivative may lead to subsequent cleavage of the N−N bond. As an example, reduction of pyridazine with sodium metal in hot ethanol affords tetramethylenediamine (via N−N bond cleavage) as well as partially hydrogenated ring products (Scheme 19.170). Under these conditions pyrimidines and pyrazines are normally reduced to hexahydro derivatives [6].



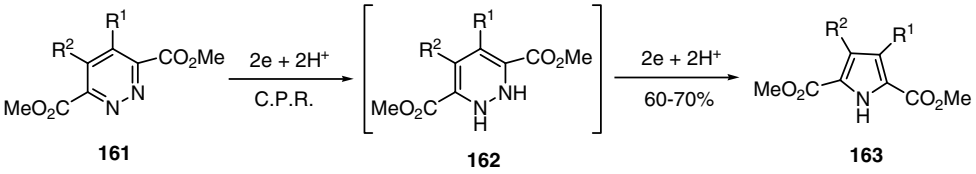
Scheme 19.170

Reductive ring contraction of pyridazines is an efficient methodology to produce densely functionalized pyrrole derivative, capitalizing on the versatility of the azadiene Diels–Alder cycloaddition route to 1,2-diazines (Scheme 19.171) [188].



Scheme 19.171

In this sense, activated pyridazines **161** have been converted into the corresponding functionalized pyrroles **163** by nitrogen extrusion by electrochemical reduction process, proceeding through 1,2-dihydro intermediate **162** (Scheme 19.172) [189].

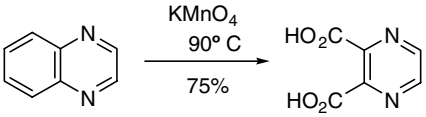


161 **162** **163**

Scheme 19.172

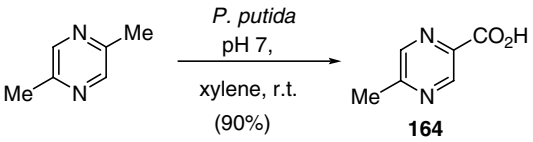
19.7.6
Reactions with Oxidizing Agents

Diazines are generally resistant to oxidative attack at the ring carbons, although alkaline oxidizing agents (H_2N-NH_2, heat) can afford degradation via intermediates produced by initial nucleophilic addition (Section 19.7.3.1.2). Alkyl substituents and fused aromatic rings [190] can be oxidized to carboxylic acid residues without affecting the heterocyclic ring (Scheme 19.173).



Scheme 19.173

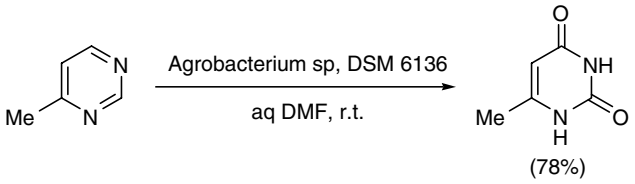
Some bacteria such as *Pseudomonas putida* (ATCC 33 015) can be used as biocatalysts for the selective oxidation of a methyl group in the 2,5-dimethylpyrazine to the corresponding mono-carboxylic acid **164** (Scheme 19.174) [191].



164

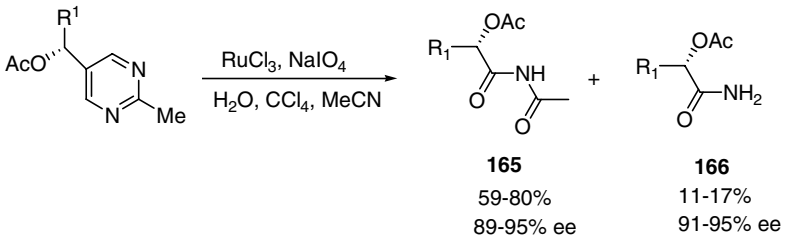
Scheme 19.174

Similarly, other bacteria such as *Agrobacterium* can selectively *C*-hydroxylate unsubstituted C2 and/or C4 positions of pyrimidines without altering side chains on the ring (Scheme 19.175) [192].



Scheme 19.175

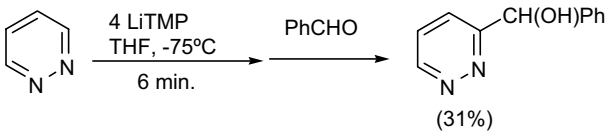
The first oxidative cleavage of the pyrimidine ring has been reported by Soai and coworkers [193]; thus RuO_4 (prepared *in situ* from $RuCl_3$ and $NaIO_4$),provides a new route for the transformation of acetates of chiral pyrimidylalkanols into chiral α-acetoxy-*N*-acetylamides **165** and α-acetoxyamides **166**, which are synthetic equivalents of chiral α-hydroxy carboxylic acids, without racemization (Scheme 19.176).



Scheme 19.176

19.7.7
Reactions of Metallated Pyridazines

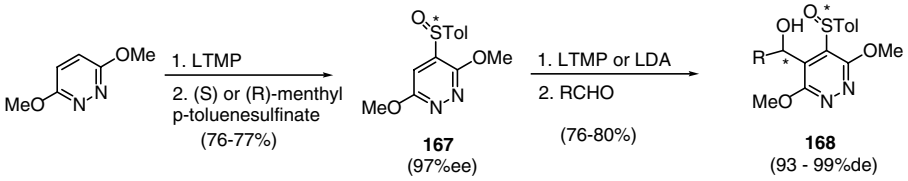
Quéguiner and coworkers have reviewed the directed deprotonation (*ortho*- metalation) of azines and diazines [194]. In general, diazines are more difficult to *ortho*-metalate than are pyridines, due to having sufficiently lower LUMO energies, which makes them prone to nucleophilic additions and electron-transfer processes. For this reason, non-nucleophilic lithium 2,2,6,6-tetramethylpiperidide (LiTMP) is a more efficient *ortho*-metalating agent than are alkyllithiums, but the resulting heteroaryllithium species are very unstable and can easily dimerize. These by-products can often be avoided by using very short lithiation times or by *in situ* trapping with a compatible electrophile (Scheme 19.177) [195].



Scheme 19.177

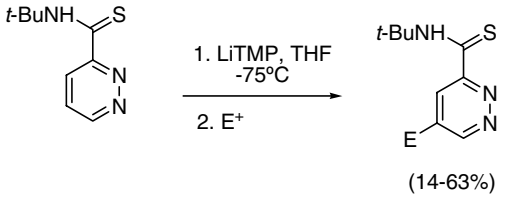
19.7.7.1 Pyridazines (1,2-Diazines)

Queguiner and coworkers [196] have reported the *ortho*-lithiation of pyridazine with subsequent trapping with chiral sulfinate esters, affording chiral sulfoxides **167** with high enantiomeric excesses (% ee) (Scheme 19.178). These sulfoxide adducts can then be subjected to a second *ortho*-lithiation-electrophile trapping sequence with aldehydes to provide fully-substituted pyridazines **168** with high diastereoselectivities (% de).



Scheme 19.178

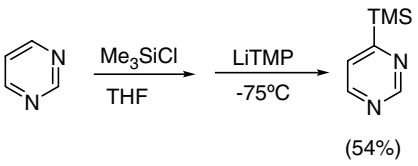
A surprising result is obtained for pyridazine thiocarboxamides (Scheme 19.179), which undergo metalation–electrophilic attack regioselectively *meta* to the thiocarboxamide group [197].



Scheme 19.179

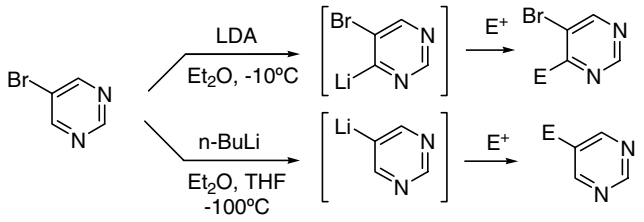
19.7.7.2 Pyrimidines (1,3-Diazines)

For pyrimidines, *ortho*-lithiation occurs selectively at C4, not at C2, despite the enhanced electronegativity of C2 due to its two electron-withdrawing nitrogens (Scheme 19.180).



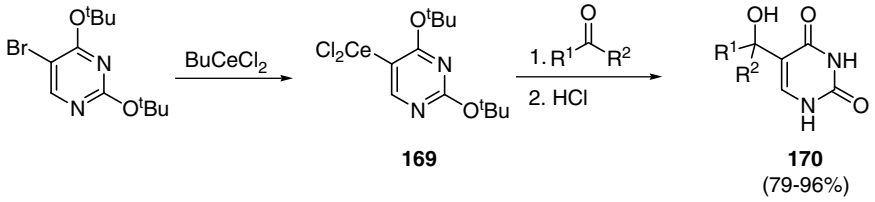
Scheme 19.180

Metalation of diazines bearing directing groups (chloro, fluoro, methoxy, methylthio, and carboxamides) has been widely reported [198]. Interestingly, pyrimidines can be lithiated either by deprotonation or by halogen exchange (Scheme 19.181). Deprotonation is favored at higher temperature (−10 °C) using lithium diisopropylamide (LDA), while lithium–halogen exchange occurs at low temperature (−100 °C) with *n*-BuLi. The presence of ring substituents at the C2 and/or C4 centers help to stabilize the resulting lithiated pyrimidines [199].



Scheme 19.181

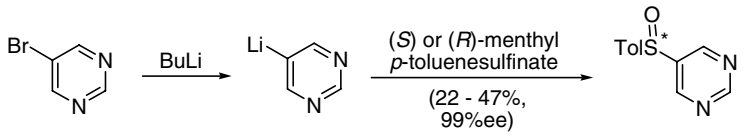
5-(Pyrimidinyl)magnesium chloride and 5-(pyrimidinyl)cerium dichloride reagents **169**, prepared from bromopyrimidines via metal–halogen exchange, react with aldehydes and ketones to give high yields of alcohols **170** (Scheme 19.182) [200].



169 **170** (79-96%)

Scheme 19.182

Similarly, lithiation of 5-bromopyrimidine and reaction with enantiomerically-pure chiral sulfinate esters gives chiral sulfoxides **171** with high enantioselectivities (Scheme 19.183) [196].

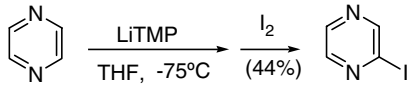


171

Scheme 19.183

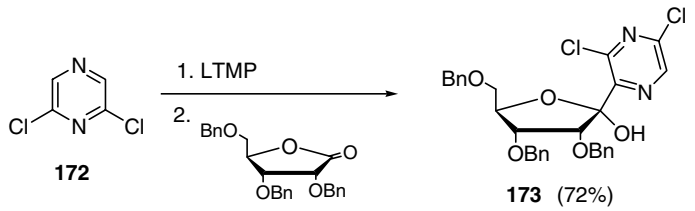
19.7.7.3 **Pyrazines (1,4-Diazines)**

Directed metalation of pyrazines has been reported as well, and can be used to prepare ortho-halogenated derivatives (Scheme 19.184).



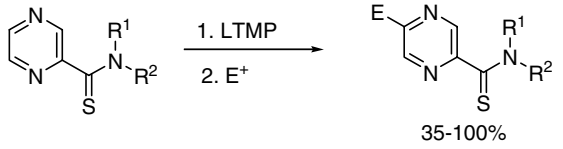
Scheme 19.184

Ortho-metalation of 2,6-dichloropyrazine **172** with lithium 2,2,6,6-tetramethylpiperidide (LTMP) followed by quenching with a lactone produces the *C*-heteroaryl glycoside **173** (Scheme 19.185) [194].



Scheme 19.185

It is reported that pyrazine thiocarboxamides undergo lithiation at the *para* position (Scheme 19.186), although the *ortho* product could be selectively generated under certain conditions [201].



Scheme 19.186

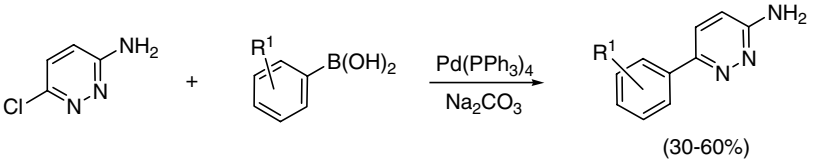
19.7.8 Palladium-Catalyzed Reactions

Organopalladium chemistry is a rapidly growing field with wide application to heterocyclic synthesis [202]. This section shows representative types of palladium-mediated transformations of diazine derivatives.

19.7.8.1 Coupling Reactions

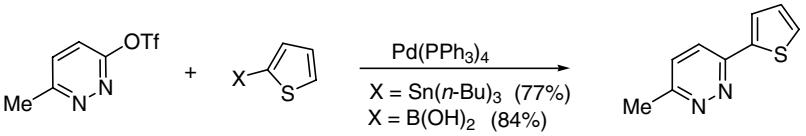
19.7.8.1.1 **Pyridazines (1,2-Diazines)** New developments in the field of palladium-catalyzed cross-coupling reactions have included halodiazines and diazene triflates.

Rival and coworkers reported what is described as being the first Suzuki cross-coupling for the synthesis of 3-amino-6-arylpyridazines [203]. Electron-donating substituents on the arylboronic acid provided optimal yields (Scheme 19.187).



Scheme 19.187

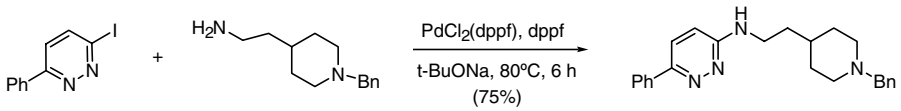
Aldous and coworkers have reported similar studies on palladium-catalyzed Stille and Suzuki coupling reactions of pyridazinyl triflates **174** with electron-rich arylstannanes and aryl boronates, respectively (Scheme 19.188). In general, Suzuki couplings were found to be more efficient than the corresponding Stille couplings [204].



174

Scheme 19.188

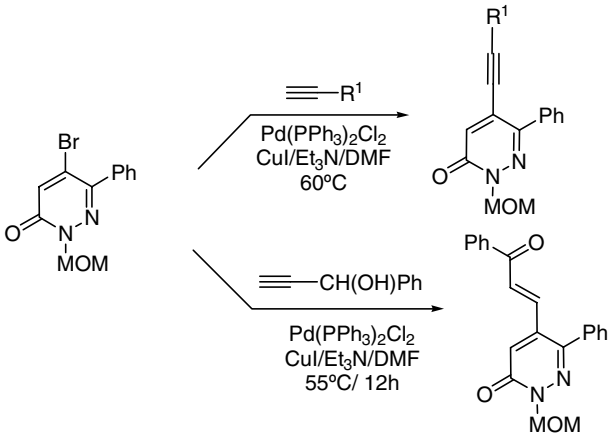
In the absence of palladium catalysts, the direct amination of 3-chloropyridazines with primary amines requires drastic conditions with difficult work up procedures, giving poor yields of the desired product and low reproducibility. For this reason the formation of a carbon–nitrogen bond via palladium cross-coupling reactions represents a powerful synthetic tool. Hibert [205] has developed an operationally simple and efficient palladium-assisted procedure for the amination of 3-iodo-6-arylpyridazines **175** (Scheme 19.189).



175

Scheme 19.189

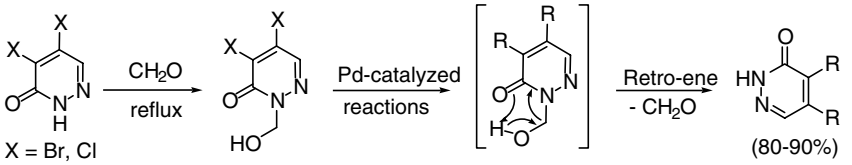
Palladium-catalyzed alkynylations have also been studied with pyridazines. As an illustration, several 6-phenyl-3(2*H*)-pyridazinones (Scheme 19.190) bearing different alkynyl groups at position 5 have been prepared by Sonogashira cross-coupling [206].



Scheme 19.190

When 1-phenyl-2-propyn-1-ol was used, the *(E)*-chalcone adduct was isolated in excellent yield.

An efficient one-pot bis-functionalization of the 4,5-positions of the 3-pyridazinone ring has been performed using Suzuki, Sonogashira, and Stille cross-coupling reactions assisted by a retro-ene fragmentation (Scheme 19.191) [207]. This route allows quick access to several pharmacologically useful novel 3(2*H*)-pyridazinone-based antiplatelet agents [208].

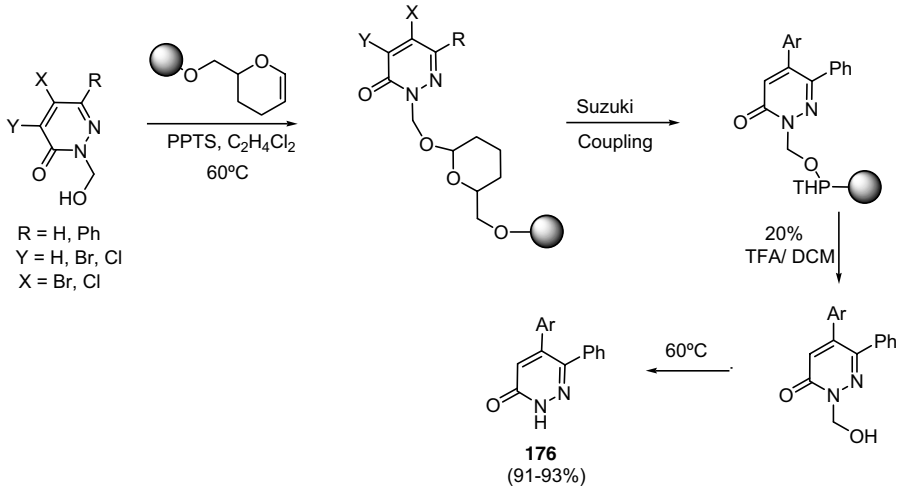


Scheme 19.191

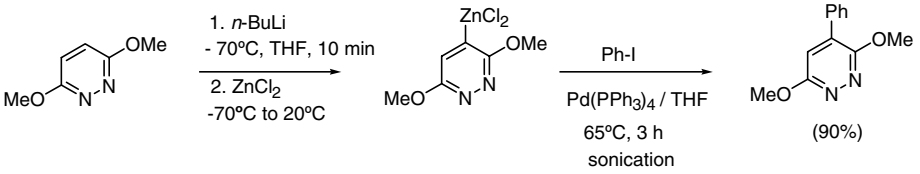
This same methodology has been applied to a "traceless" solid-phase synthesis of 3(2*H*)-pyridazinones **176**, employing a dihydropyran-functionalized resin and cleavage conditions that promoted a retro-ene fragmentation (Scheme 19.192) [209].

In the case of 1,2-diazines, the lithiopyridazines prepared by *ortho*-lithiation have been converted by reaction with zinc chloride into the more stable zinc compounds for use in palladium-catalyzed cross-coupling reactions [210]. The use of sonication, for the first time in a Negishi reaction, lowered the reactions times significantly and improved the yields (Scheme 19.193).

19.7.8.1.2 **Pyrimidines (1,3-Diazines)** Palladium-catalyzed cross-coupling reactions have also been reported for pyrimidines. The increased stability of organozinc reagents compared to lithium or magnesium organometallics allows the Negishi reactions to be carried out at high temperature. In this way, *ortho*-lithiation of

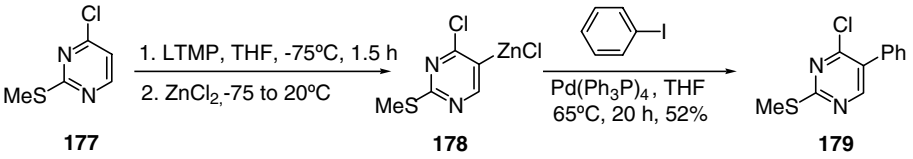


Scheme 19.192



Scheme 19.193

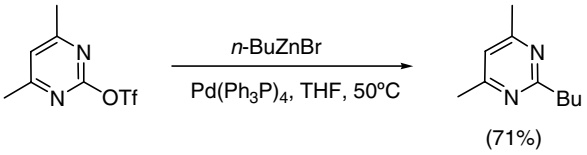
4-chloro-2-methylthiopyrimidine **177** using LTMP and subsequent treatment with $ZnCl_2$ led to organozinc reagent **178**, which was then cross-coupled with iodobenzene to furnish the 5-arylpyrimidine **179** (Scheme 19.194) [210].



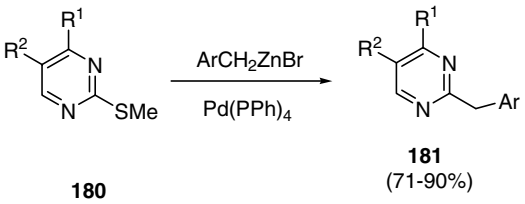
Scheme 19.194

Although alkyl halide substrates are prone to β-hydride elimination in these reactions, alkylzinc or alkylboron reagents can take part in Negishi or Suzuki coupling without detectable β-hydride elimination to produce alkylpyrimidines (Scheme 19.195) [211].

The cross-coupling reaction of methylthiopyrimidines **180** with organozinc compounds in the presence of palladium was found to produce substituted pyrimidines **181** in good to excellent yields (Scheme 19.196) [212].

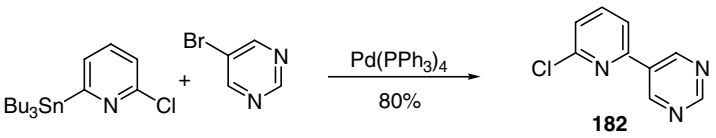


Scheme 19.195



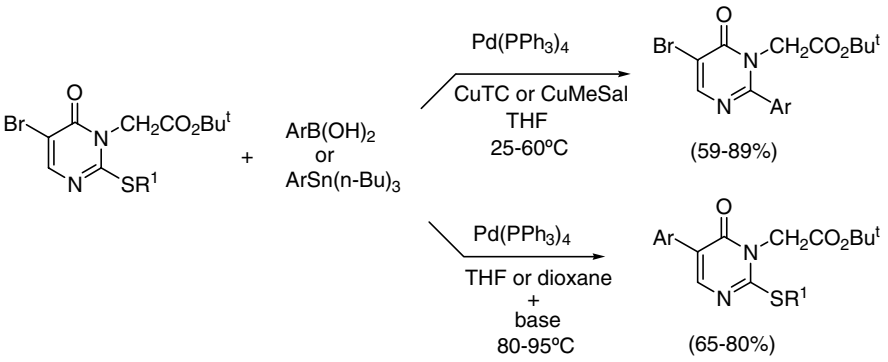
Scheme 19.196

The traditional Stille-type cross coupling of stannanes with bromopyrimidines has been reported to provide chlorobiaryls **182** in good yields (Scheme 19.197) [160].



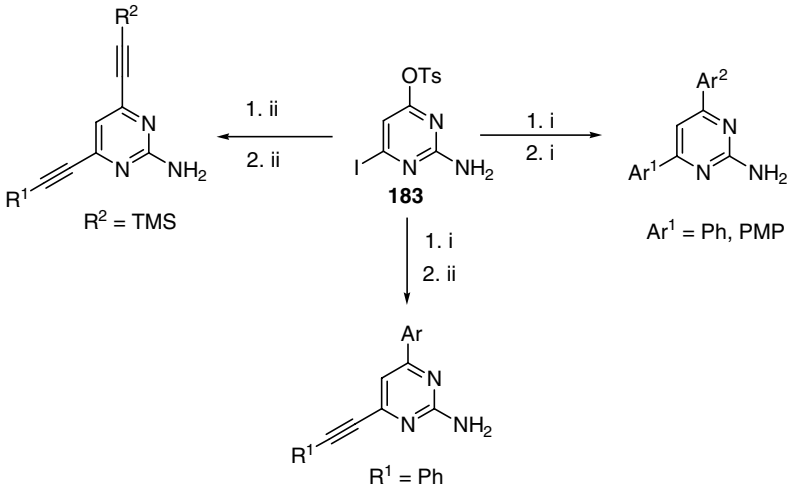
Scheme 19.197

A modular synthesis of functionalized pyrimidinones via a selective sulfide versus halide cross-coupling protocol has been reported (Scheme 19.198) [213]. The exchanges are complementary and depend solely on the experimental conditions.



Scheme 19.198

In the same way, 2-amino-6-iodo-4-tosyloxypyrimidine (**183**, which is easily prepared from commercially available material, is a key intermediate for the preparation of differentially substituted 2-aminopyrimidines by means of sequenced Suzuki and/or Sonogashira reactions (Scheme 19.199) [214].

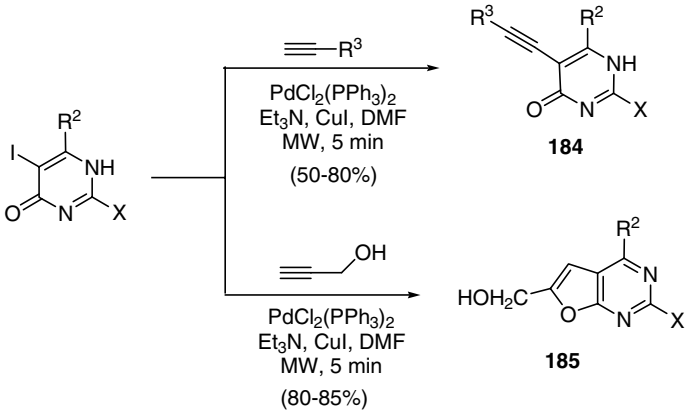


Scheme 19.199

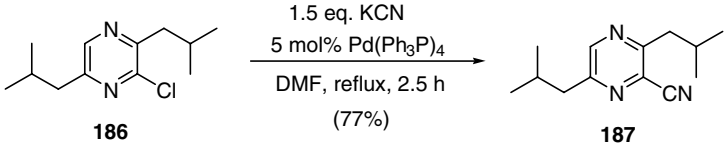
Microwave activation is becoming a very popular and useful technique in organic chemistry. The combination of solvent-free reaction conditions and microwave irradiation leads to significantly reduced reaction times, enhanced conversions, and, sometimes, higher selectivity, with the advantage of an eco-friendly approach (green chemistry). In this context, Botta has described a microwave-assisted Sonogashira coupling of pyrimidinones with alkynes to give the corresponding 5-alkynyl derivatives **184**, or furano-fused pyrimidines **185** when using propargyl alcohol (Scheme 19.200) [215].

19.7.8.1.3 **Pyrazines (1,4-Diazines)** Chloropyrazines and their N-oxides both undergo a wide range of palladium-catalyzed carbon–carbon bond-forming reactions. The oxidative addition of chloroarene to Pd(0) occurs using sterically hindered, electron-rich phosphine ligands, as reported by Reetz [216], Fu [217], and Buchwald [218]. In 1981, Otha *et al.* [219] introduced a cyano group by refluxing chloropyrazine **186** with KCN in DMF in the presence of a catalytic amount of $Pd(Ph_3P)_4$ to give cyanopyrazine **187** (Scheme 19.201).

Palladium-catalyzed coupling reactions between chloropyrazines and organometallic reagents without β-sp^3-hydrogens are straightforward and generally proceed in

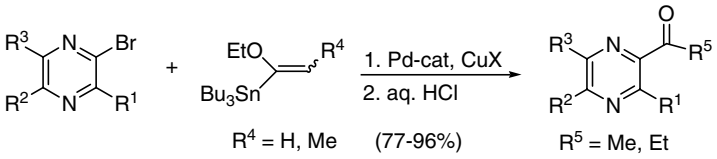


Scheme 19.200



Scheme 19.201

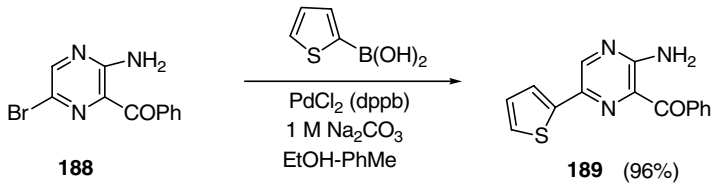
good yields. Stille coupling of chloropyrazines and their N-oxides has been carried out with tetraphenyltin [220] and aryl-, heteroaryl-, allyl-, and alkylstannanes [221]. Acylation of pyridazines by Stille reactions of bromopyrazines with 1-ethoxyvinylstannanes (Scheme 19.202) has been accomplished by Sato *et al.*, using a copper cocatalyst [222]. They found that the copper additive increased the yields from 31% to 93%. The Cu-induced acceleration was most prominent for electron-deficient pyrazines, which are more reactive in Pd-catalyzed reactions.



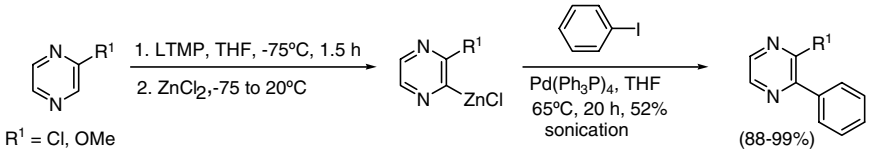
Scheme 19.202

Suzuki couplings have likewise been conducted using halopyrazines and boronic acids. In this way (Scheme 19.203), bromopyrazine **188** and 2-thiopheneboronic acid have been coupled to deliver the desired thienylpyrazine **189** [223].

In addition, some pyrazine derivatives can be coupled with aryl halides through a Negishi reaction (*ortho*-lithiation and transmetalation with $ZnCl_2$) [210]. In this case, sonication has a great influence on the yield and reaction time (Scheme 19.204).

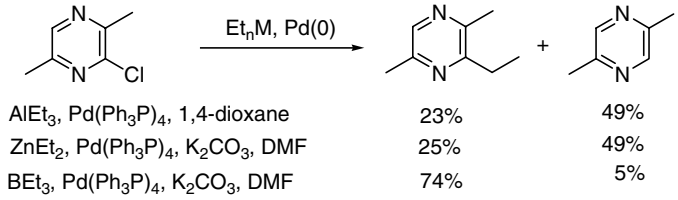


Scheme 19.203



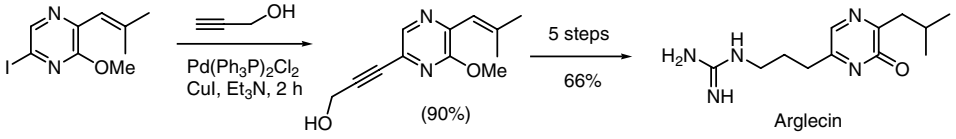
Scheme 19.204

Palladium-catalyzed alkylation reactions of chloropyrazines with alkyl organometallic reagents bearing β-sp^3-hydrogens have sometimes proven to be difficult [224]. In addition to coupling, dehalogenation may also take place. In comparison, when trialkylaluminium or dialkylzinc reagents are used low yields of the alkylated product are obtained, while trialkylboranes give the best results (Scheme 19.205).



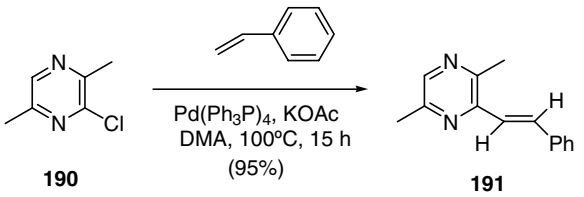
Scheme 19.205

Akita and Otha disclosed one of the earliest Sonogashira reactions of chloropyrazines and their N-oxides [225]. Under standard cross-coupling reaction conditions [$Pd(Ph_3P)_2Cl_2$, CuI, Et_2NH], many alkynylpyrazines have been synthesized [226], among them being some natural products (Scheme 19.206) [227].



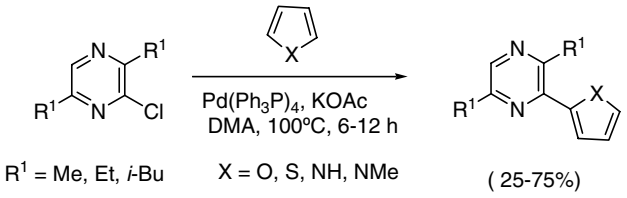
Scheme 19.206

Heck reactions of 2-chloro-3,6-dimethylpyrazine **190** with styrene in the presence of $Pd(Ph_3P)_4$ and KOAc provides a convenient route to vinylpyrazine derivatives **191** (Scheme 19.207) [228]. This methodology was also extended to 2-chloropyrazines *N*-oxides, although the yields were considerably lower (28–38%) [229].



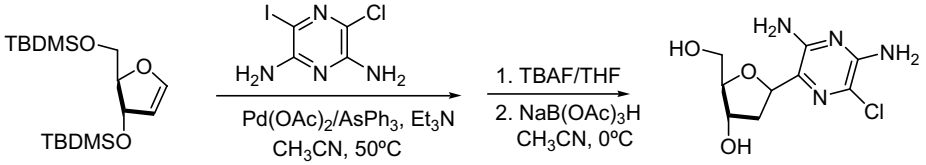
Scheme 19.207

Ohta's group has advanced this methodology to Heck reactions of halopyrazines with both π-electron-rich and π-electron-deficient heteroarenes (Scheme 19.208) [230].



Scheme 19.208

A stereospecific Heck-cross-coupling reaction of an iodo-substituted diaminopyrazine has been reported by Townsend in which a glycal serves as the acceptor, giving exclusively the β-configuration of the C-glycosidic bond [231]. It was not necessary to protect the two amino groups of the pyrazine due to the relatively weak basicity of the amino nitrogens on the electron-deficient pyrazine ring (Scheme 19.209).



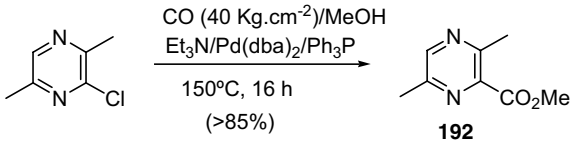
Scheme 19.209

19.7.8.2 **Carbonylation Reactions**

Alkoxycarbonylation reactions of halo-substituted diazines can be carried out with carbon monoxide and palladium acetate in an alcohol solvent, providing an effective route to pyrimidine esters (Scheme 19.210) [232].

Scheme 19.210

Similarly, pyrazine-carboxylic esters **192** and pyrazine carboxamides can be synthesized in excellent yield from chloropyrazines by Pd-catalyzed carbonylation in the presence of either an alcohol or dialkylamine (Scheme 19.211) [233].

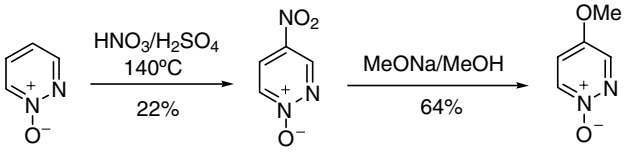


Scheme 19.211

19.8 Important Derivatives

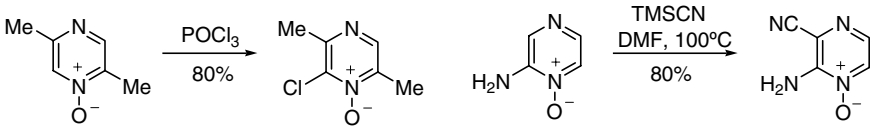
19.8.1 Diazines *N*-Oxides

Pyridazine *N*-oxides and pyrazine *N*-oxides can be prepared by selective N-oxidation of the parent heterocycles, but pyrimidine *N*-oxides are more difficult to obtain in this way and are best prepared by ring synthesis [234, 235]. Pyridazine *N*-oxides and pyrazine *N*-oxides give electrophilic aryl substitution and nucleophilic displacement (Scheme 19.212). Interestingly, the nitro group can be removed readily either at the β- or γ-position to the N-oxide function.



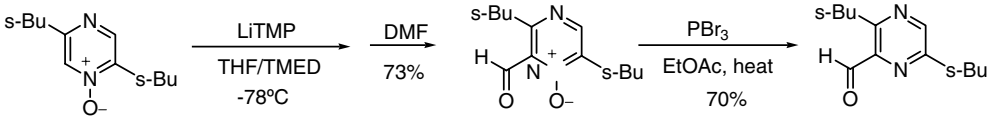
Scheme 19.212

All three diazene N-oxide systems are prone to nucleophilic substitution by halide, cyanide, enamines, or acetate with loss of the oxide function [236]. Depending on the types of substituents present on the ring, the site of introduction of the nucleophile is not always α to the N-oxide as would be predicted by analogy with pyridine chemistry (Scheme 19.213).



Scheme 19.213

The N-oxide group can also serve as an activating substituent to allow regioselective metalation (*ortho*-lithiation) and further reaction with electrophiles, as shown in Scheme 19.214. The N-oxide can be removed with phosphorus tribromide [237].

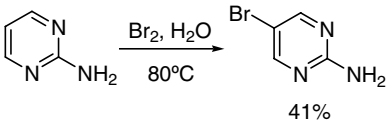


Scheme 19.214

19.8.2 Aminodiazines

Aminodiazines exist in the fully aromatized amino form but significant anionic charge character is built up on the ring nitrogen by resonance (a shown below), making protonation occur on the anionically-enriched ring nitrogen. The order of preference for protonation of a ring nitrogen is $\gamma > \alpha > \beta$ to the amino group.

The presence of an amino group facilitates electrophilic substitution, as illustrated for halogenation (Scheme 19.215). Predictably, two amino groups further activate the ring to enable attack by weaker electrophiles.



Scheme 19.215

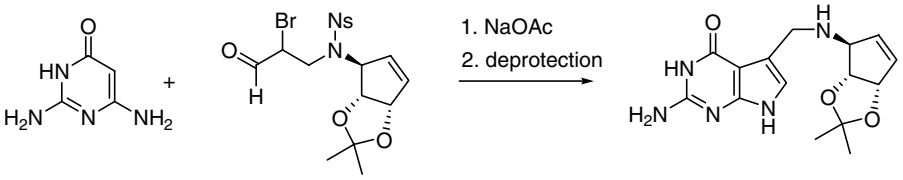
Often, it is difficult to regioselectively alkylate 2-aminopyrimidines without producing a mixture of endo- and exocyclic *N*-alkylation products. Alvarez-Builla and coworkers [238] have reported methodology for selectively preparing 2-alkylaminopyrimidines **194** with high regioselectivity, after reductive removal of the pyridine moiety from the N-alkylated product (Scheme 19.216). The reaction is

193 194

Scheme 19.216

thought to proceed through formation of an intramolecular hydrogen bond between the pyridine and pyrazine rings, which prevents alkylation of the ring nitrogens. Similar methodology can be applied to 2-aminopyrazines.

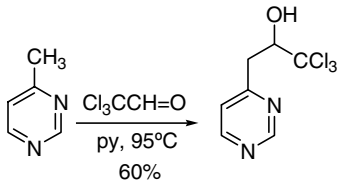
Various biologically important natural products contain the 2-aminopyrimidine moiety in their structure, and various reactions involving these substituted heterocycles have been reported (condensation with aldehydes and ketones [239], Michael additions [240]). For example, Grubb has employed the cyclocondensation of an α-bromoaldehyde with diaminopyrimidone in a total synthesis of quinine (Q Base), found in tRNA (Scheme 19.217) [241].



Scheme 19.217

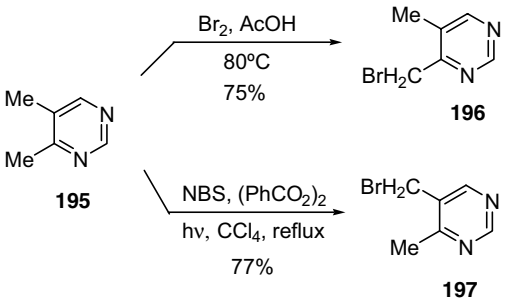
19.8.3
Alkyldiazines [242]

Alkyldiazines undergo condensations that involve deprotonation of the pendent alkyl group. The intermediate anions are stabilized by mesomerism involving one or both nitrogens. Thus, pyrimidines system shows side-chain reactivity; CH_3 groups at the C2, C4, or C6 undergo aldol or Claisen condensations with marked preference at C4 (Scheme 19.218).



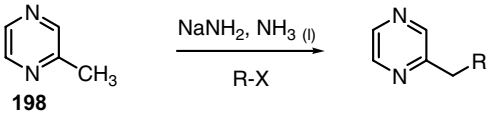
Scheme 19.218

The regioselectivity of the side chain reactions on disubstituted pyrimidine can be controlled by adjusting the reaction conditions (Scheme 19.219). Thus, in the bromination of 4,5-dimethylpyrimidine (**195**) under ionic conditions (Br_2, HOAc) substitution at the C4 methyl group **196** is favored, but under radical conditions (NBS, CCl_4) the halogenation occurs at the C5 methyl group (**197**) [243].



Scheme 19.219

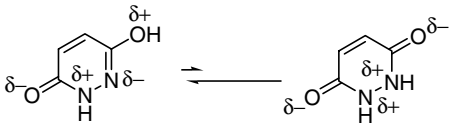
Like the other diazines, alkylpyrazine can undergo base catalyzed C–C bond-forming reactions of the CH groups adjacent to the heteroatom. Thus, 2-methylpyrazine (**198**), after deprotonation with $NaNH_2$ in liquid NH_3, can be alkylated, acylated, and nitrosated (Scheme 19.220).



Scheme 19.220

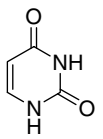
19.8.4 Hydroxydiazines

All the mono-oxygenated diazines, except 5-hydroxypyrimidine, exist predominantly as carbonyl tautomers and are thus categorized as diazinones. The dioxydiazines do not obey a straightforward rule, for where both oxygens are α or γ to a nitrogen both are expected to exist in carbonyl form but one remains in the hydroxyl form, as seen in the case of maleic hydrazide. The preference for the mono-oxo tautomer is likely due to the favorable interaction between two adjacent, oppositely charged nitrogen atoms as opposed to dual cationic nitrogens in the di-oxo form (Scheme 19.221).



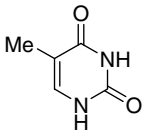
Scheme 19.221

On the other hand, uracil, **199**, thymine, **200**, and cytosine, **201**, all exist in the dione form and most of their reactions can be interpreted on this basis [244]. Similarly, barbituric acid, **24**, prefers the tricarbonyl tautomer.



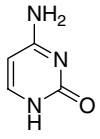
Uracil

199



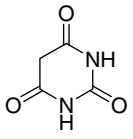
Thymine

200



Cytosine

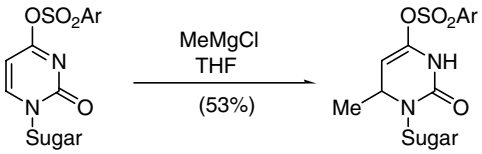
201



Barbituric Acid

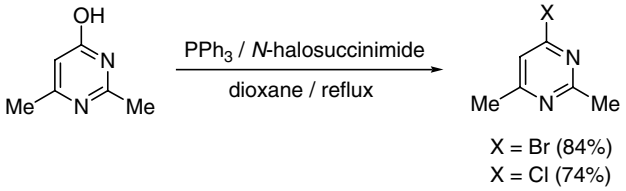
24

Diazinones are highly susceptible to nucleophilic attack, generally via Michael-type addition rather than by direct attack at a carbonyl center (Scheme 19.222). There are, of course, exceptions to this general trend. Grignard reagents add to the ring to give dihydro-compounds and good leaving groups can be displaced [245].



Scheme 19.222

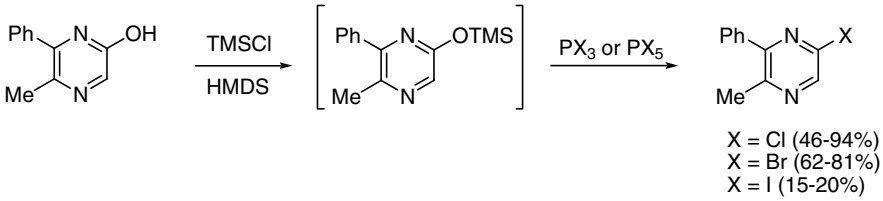
For certain synthetic transformations it is often convenient to use halo- or alkoxy-substituted diazines to enhance solution solubility, or product yield, compared to the underivatized compound. Oxydiazines with the oxygen α to nitrogen can be converted into halo- and thio-compounds using the same reagents used for 2- and 4-pyridones, including *N*-bromosuccinimide with triphenylphosphine or phosphorus oxyhalide (Scheme 19.223) [246].



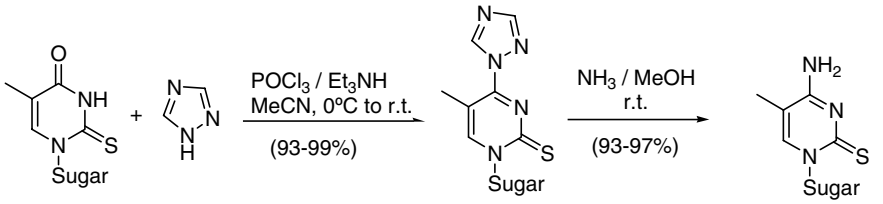
Scheme 19.223

This same transformation can be effected via generation of the O-silylated pyrazinones with phosphorus(III) halide or phosphorus(V) chloride under mild conditions and without the need for isolation of the silyl intermediate (Scheme 19.224) [247]. The iodo adducts were obtained in low yield.

Diazinones **202** can be converted into aminodiazines **204** by various processes, including the use of 1,2,4-triazole intermediate **203** (Scheme 19.225) [248].



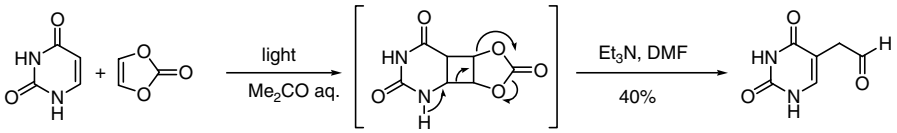
Scheme 19.224



202 **203** **204**

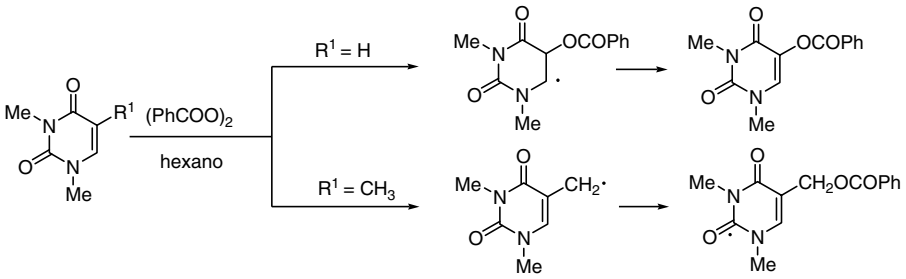
Scheme 19.225

Owing to the importance of light-induced mutagenesis, photochemical transformations of the double bond in oxypyrimidines have been investigated in depth. From this comes useful [2 + 2] cycloaddition methodology, as illustrated in the reaction of uracil with vinylene carbonate to prepare a 5-alkylated derivative (Scheme 19.226) [249].



Scheme 19.226

Uracils also undergo radical additions (Scheme 19.227), which are of possible relevance to mutagenesis mechanisms [250].



Scheme 19.227

19.8.5
Halodiazines

Most of the chemistry concerning halodiazines derivatives has been discussed above in the context of various nucleophilic sing substitutions (Sections 19.7.3.2 and 19.7.8).

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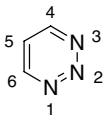
20
Six-Membered Heterocycles: Triazines, Tetrazines and Other Polyaza Systems

Cristina Gómez de la Oliva, Pilar Goya Laza, and Carmen Ochoa de Ocariz

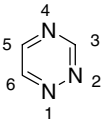
20.1
Introduction

Triazines and tetrazines have been the subject of previous surveys. Reference textbooks include *Comprehensive Heterocyclic Chemistry I* [1–4], *Comprehensive Heterocyclic Chemistry II* [5–9] and *The Chemistry of Heterocyclic Compounds* [10]. In addition, *Progress in Heterocyclic Chemistry* [11] which appears annually and always includes a chapter with these ring systems. In other heterocyclic series, such as *Advances in Heterocyclic Chemistry,* several chapters have dealt with 1,2,3-triazines [12], dihydrotriazines [13, 14], reaction of triazines with nucleophiles [15–17] and 1,2,4-triazine-N-oxides [18]. Some of the references cited therein have been considered in the present chapter and the reader is referred to them for additional details.

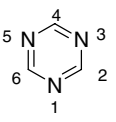
Among the three triazine isomers the 1,2,3-triazines (**1**) are the least studied in comparison with their 1,3,5- (**3**) and 1,2,4- (**2**) isomers, because of the well known fragility of chains and rings with contiguous nitrogen atoms [19].



1



2

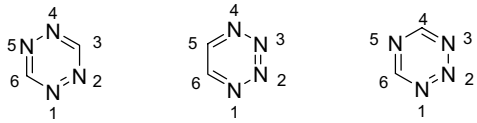


3

Several reviews on the chemistry of 1,2,3-triazine, also called ν-triazine, have been published [12, 20–26]. Study of the reactivity and stability of the unsubstituted ring systems has been possible only since 1981 when the first synthesis of the parent compound **1** was reported [27].

1,2,4-Triazines, also called α-triazine or *as*-triazine, are well-known compounds and a wide variety of synthetic methods for the preparation of substituted derivatives are available. Compounds containing the 1,2,4-triazine moiety are found in natural materials and some of them show biological activity. Several reviews dealing with 1,2,4-triazines have appeared, particularly on account of their biochemical properties [16, 18, 24, 26, 28–32]. The parent compound **2** was prepared for the first time by Paulder and Barton in 1966 [33].

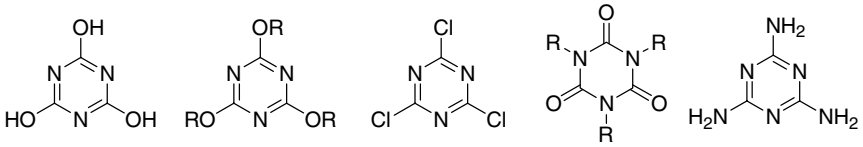
Modern Heterocyclic Chemistry, First Edition.
Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.



9 **10** **11**

Figure 20.1 Numbering of the three possible isomers of tetrazine.

1,3,5-Triazines have been known for almost 200 years. Originally, they were called the symmetric triazines, usually abbreviated to *sym*-triazine. Like many heterocyclic compounds, 1,3,5-triazines are often referred to by trivial names such as cyanuric acid (**4**), cyanurates (**5**), cyanuryl chloride (**6**), isocyanurates (**7**) and melamines (**8**).



4 **5** **6** **7** **8**

There have been many studies dealing with the chemistry of 1,3,5-triazine [26, 34–41]. Triazine **3** was first isolated in 1895 by Nef [42]. An incorrect molecular weight determination led Nef to assign a wrong structure. This incorrect assignment was accepted by other workers, but in 1954 a correct cryoscopic molecular weight determination established the structure of **3** [43].

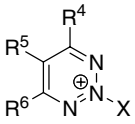
Tetrazines have been less studied than triazines since there are fewer known examples [44]. The three possible isomers of tetrazine are known and numbered as indicated in Figure 20.1. There are more examples of 1,2,4,5-tetrazines (**9**), also named *s*-tetrazines and *sym*-tetrazines, than of the other two isomers. 1,2,3,4-Tetrazine (**10**) is also known as ν-tetrazine. 1,2,3,5-Tetrazines (**11**), also named *as*-tetrazines, are the least studied class. The parent compound of the 1,2,4,5-tetrazine series (**9**) was first synthesized by Hantzsch and Lehman in 1900 [45].

20.2
1,2,3-Triazines

20.2.1
Relevant Computational Chemistry, Physicochemical and Spectroscopic Data

Few monocyclic 1,2,3-triazines are known, so knowledge of the structure of these compounds is poor. 4,5,6-Tris(4-methoxyphenyl)-1,2,3-triazine was the first monocyclic triazine to be studied by X-ray crystallographic analysis [46]. This work showed the planarity of the triazine ring, as expected for a molecule with some degree of electron delocalization. The X-ray analysis of the parent compound **1** has been performed and the results fully agree with the planar and aromatic nature of the ring system [47–49]. X-Ray crystallographic analyses with alkyl and aryl substituents of

1,2,3-triazines **12** [50], **13** [50], **14** [51] and triazinium salts **15** [50], **16** [50], **17** [50] and **18** [52] have been described.



12 R^4 = Ph, R^5 = H, R^6 = Me; **13** R^4 = Ph, $R^5 = R^6 = (CH_2)_4$
14 $R^4 = R^6$ = Ph, $R^5 = NEt_2$
15 R^4 = Ph, R^5 = H, R^6 = Me, X = O^-; **16** $R^4 = R^6$ = Me, R^5 = H, X = O^-
17 $R^4 = R^5 = R^6$ = Me, X = NH^-; **18** $R^4 = R^6$ = Ph, R^5 = H, X = CH_3

In 2004, Fabian and Lewars described a computational study of the stability, homodesmotic stabilization energy, electron distribution and magnetic ring current of triazines [53]. The proton affinity of **1** has been calculated [54]. The results suggest that 1,2,3-triazine has almost the same basicity as pyrazine and 1,2,4-triazine, but it is more basic than 1,3,5-triazine [54]. The electronic absorption spectrum of 1,2,3-triazine has been obtained [55, 56]. In addition, the excited state geometries and vibrational spectra of **1** have been calculated using different levels of *ab initio* theory, with the results being in agreement with experimental studies [55, 57]. Harmonic [58] and anharmonic [58, 59] frequencies have also been calculated. Solvent effects on the lowest excitation of 1,2,3-triazine have been studied using a method developed for estimating solvent shifts of triazines that have strong specific interactions with the solvent [60]. The heat of formation has been calculated for 1,2,3-triazine [61].

Most known 1,2,3-triazines are stable at room temperature. The parent compound **1** can be obtained as colorless plates from ether and it undergoes slow thermal decomposition at room temperature, but is stable for several months when stored under *vacuum* at −20 °C. Table 20.1 gives the melting points, ^{1}H and ^{13}C NMR data of various 1,2,3-triazines. The relatively high melting point of **1** suggests the tight stacking of the unsubstituted triazine ring, which was shown in X-ray data [48]. The low-field chemical shifts of the ring protons are consistent with deshielding by a ring current of π-electrons; thus the triazine ring is aromatic. The ^{13}C NMR data show the aromatic nature of the triazine ring.

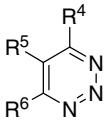
Figure 20.2 shows the ^{15}N-signals of 1,2,3-triazines **1** [48], **19** and **20** [72] and those obtained recently for **21** and **27–29** [67]. ^{15}N NMR spectra of 1,2,3-triazines derivatives have been recorded in $CDCl_3$ solution, using nitromethane as internal standard. In salts all nitrogen signals are shifted to higher field compared to the corresponding 1,2,3-triazines.

Mass spectrometry of 1,2,3-triazine affords a characteristic fragmentation. The general fragmentation pattern of monocyclic 1,2,3-triazines shows peaks for [M^+-N_2], and for an acetylene and a nitrile, which is in accordance with the results of thermolysis and photolysis. The mass spectrum of the parent triazine **1** shows peaks at 81 (M^+, 47%), 53 (M^+–N_2, 69%), 27 (HCN, 13%), 26 (C_2H_2, 100%) [62]. The presence of alkyl and/or aryl substituents diminishes the molecular ion peak [67].

20.2.2
Relevant Natural and Useful Compounds

To date, no compound containing the 1,2,3-triazine system has been isolated from natural sources. Derivatives of 1,2,3-triazine are an important class of heterocyclic

Table 20.1 Melting point and ^{1}H and ^{13}C NMR data of 1,2,3-triazines.



1 R^4 = H, R^5 = H, R^6 = H; **14** R^4 = R^6 = Ph, R^5 = NEt_2
19 R^4 = Me, R^5 = R^6 = H; **20** R^4 = R^6 = Me, R^5 = H
21 R^4 = R^6 = H, R^5 = Ph; **22** R^4 = R^6 = H, R^5 = Me
23 R^4 = R^6 = Me, R^5 = CH_2COPh; **24** R^4 = Ph, R^5 = OH, R^6 = Me
25 R^4 = R^6 = Me, R^5 = $CONH_2$; **26** R^4 = R^6 = Me, R^5 = CH_2SO_2Ph

	mp (°C)	^{1}H NMR ($CDCl_3$) δ (ppm)	^{13}C NMR ($CDCl_3$) δ (ppm)
1	70	9.06 (2H, d, $J = 6.0$ Hz), 7.45 (1H, t, $J = 6.0$ Hz) [62]	149.7, 117.9 [62]
14	216	7.20–8.00 (10H, m), 2.68 (4H, q, $J = 7.0$ Hz), 0.90 (6H, t, $J = 7.0$ Hz) [63]	153.0, 137.0, 129.4, 128.7, 128.4, 46.1, 12.8 [63]
19	30	8.92 (1H, d, $J = 6.0$ Hz), 7.33 (1H, t, $J = 6.0$ Hz), 2.70 (3H, s) [64]	159.7, 148.8, 117.8, 21.4 [65]
20	87	7.11 (1H, s), 2.68 (6H, s) [66]	158.8, 117.6, 21.1 [65]
21	145	9.95 (2H, s), 7.69–7.63 (2H, m), 7.57–7.51 (3H, m) [67]	147.4, 131.4, 131.1, 130.1, 127.3 [67]
22	67	8.93 (2H, s), 2.40 (3H, s) [64]	146.9, 137.4, 123.5, 17.4 [65]
23	130	8.08–8.06 (2H, m), 7.72–7.68 (3H, m), 7.55–7.59 (2H, m), 2.44 (2H, s), 2.59 (6H, s) [68]	193.1, 158.8, 135.7, 134.3, 129.1, 128.2, 124.9, 37.2, 19.6 [68]
24	182	8.12–8.25 (2H, m), 7.31–7.41 (3H, m), 2.41 (3H, s), 2.17 (1H, bs) [69]	164.1, 156.4, 147.7, 132.3, 129.5, 127.9, 127.7, 15.5 [69]
25	210	6.60 (2H, bs), 2.72 (6H, s) [70]	166.1, 154.8, 126.5, 17.5 [70]
26	136	7.36–7.92 (5H, m), 4.44 (2H, s), 2.52 (6H, s) [71]	159.6, 138.2, 134.9, 129.9, 128.2, 118.8, 54.9 [71]

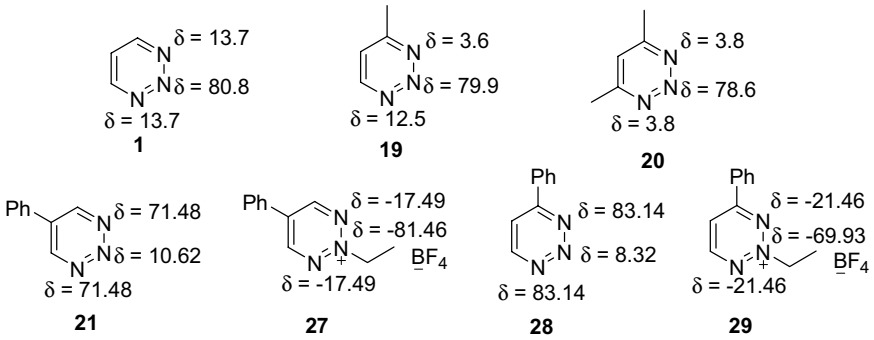


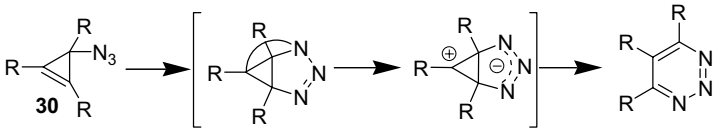
Figure 20.2 ^{15}N NMR data of some 1,2,3-triazines.

compounds that are useful in organic synthesis, their importance being due to the fact that they can react as diene in inverse-demand Diels–Alder cycloadditions with electron-rich dienophiles. The use of 1-*t*-butyl-3-ethyl-2-methylhexahydro-1,2,3-triazine as a corrosion inhibitor for steel is mentioned in the literature [73]. For several other compounds containing the 1,2,3-triazine system, claims for biochemical or technical applications have been made, but these seem to have been mostly for the purposes of obtaining patents on the compounds involved, and it appears that no significant uses are yet known. Reports on the medicinal chemistry of 1,2,3-triazine have appeared [74–82].

20.2.3 Synthesis

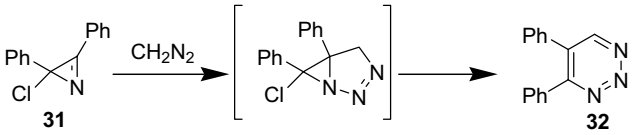
20.2.3.1 From Tricycles

The rearrangement of cyclopropenyl azides **30** (Scheme 20.1) is a method used for the synthesis of monocyclic 1,2,3-triazines [83–90]. This method is limited to the synthesis of trisubstituted triazines, because only trisubstituted cyclopropenyl azides have been rearranged.



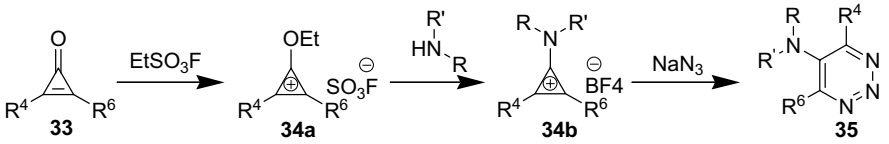
Scheme 20.1

Diphenylchloroazine **31** and diazomethane yield 4,5-diphenyl-1,2,3-triazine **32** (Scheme 20.2) [91].



Scheme 20.2

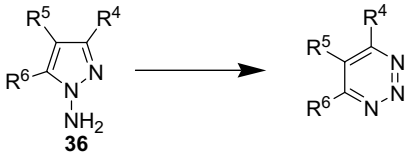
Matsumoto *et al.* have reported the preparation of 5-amino-4,6-dialkyl-1,2,3-triazines **35** from the corresponding dialkylcyclopropenones **33** [63, 92, 93] (Scheme 20.3).



Scheme 20.3

20.2.3.2 From Pentacycles

The more general synthetic method to obtain various mono-, di- and tri-substituted alkyl- and aryl-triazines, besides the parent triazine **1**, is by oxidation of *N*-aminopyrazoles **36** with lead(IV) acetate (LTA; $Pb(C_2H_3O_2)_4$), nickel peroxide or sodium perchlorate [27, 48, 64, 66, 94, 95] (Scheme 20.4). The amino nitrogen is incorporated into the triazine ring as the central nitrogen N2, probably via insertion of the nitrene moiety to the N−N bond of the pyrazole ring [72].

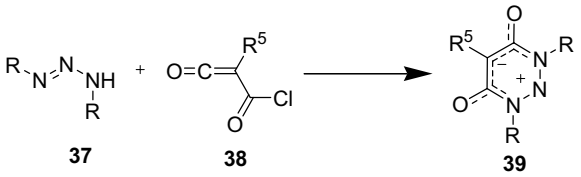


Scheme 20.4

Butler *et al.* have reported that 2,5-dihydro-1,2,3-triazine derivatives are obtained by the 1,3-dipolar cycloaddition of 1,2,3-triazole N-oxide and dimethylacetylene dicarboxylate (DMAD) [96, 97]. The same group have reported another synthesis in which pyrrolo[2,3-*d*]-1,2,3-triazoles thermally rearrange to 2,5-dihydro derivatives [98].

20.2.3.3 Cycloaddition of [3 + 3] Fragments

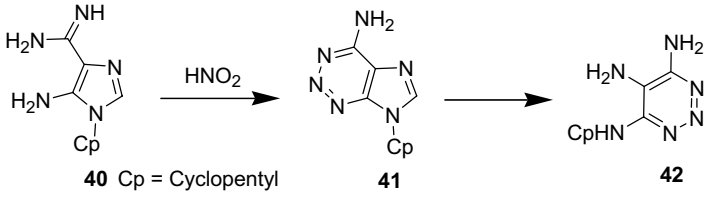
Another 1,2,3-triazine system (**39**) has been obtained by the reaction of triazenes **37** with chloroformylketones **38** (Scheme 20.5) [99].



Scheme 20.5

20.2.3.4 Cycloaddition of [5 + 1] Fragments

The cycloaddition of [5 + 1] fragments has also been used indirectly for the synthesis of one monocyclic 1,2,3-triazine. Compound **40** (Scheme 20.6) is cyclized with



Scheme 20.6

nitrous acid to give 4-aminoimidazo[4,5-*d*][1,2,3]triazine **41**, which affords 4,5-diamino-6-cyclopentylamino-1,2,3-triazine **42** [100].

20.2.3.5 Cycloaddition of [6 + 0] Fragments

Cyclization of triazenes **43** affords 1,3-disubstitued-3,4,5,6-tetrahydro-1,2,3-triazinium salts **44** [101] (Scheme 20.7).

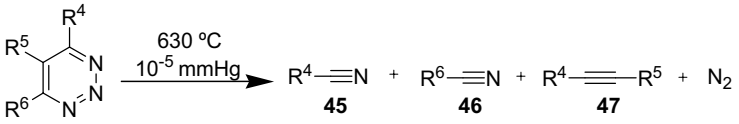
43 **44**

Scheme 20.7

20.2.4 Reactivity

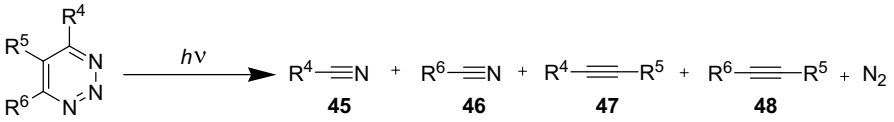
20.2.4.1 Thermal and Photochemical Reactions

Flash vacuum thermolysis (FVT) of 1,2,3-triazines affords nitriles **45** and **46**, alkyne **47** and nitrogen (Scheme 20.8). With unsymmetrically substituted triazines, fragmentation proceeds selectively. The results indicate that a bulky substituent at C4(6) makes the adjacent C−N bond break more easily than the opposite C−N bond. The photolysis of triazines (Scheme 20.9) gives the fragments nitriles **45** and **46**, alkyne **47** and nitrogen, as under FVT conditions [83, 85, 102–104]. In contrast to the FVT, unsymmetrical triazines also give the other possible alkyne **48**.



45 **46** **47**

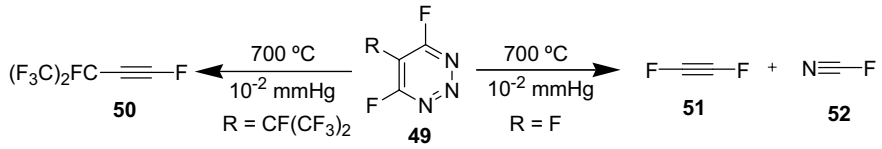
Scheme 20.8



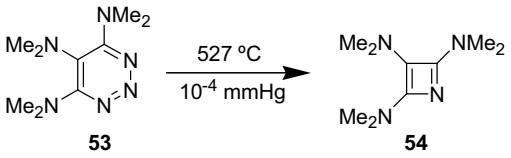
45 **46** **47** **48**

Scheme 20.9

FVT has been applied to the synthesis of fluorinated alkynes, such as perfluoro-3-methyl-1-butyne (**50**) and difluoroethyne (**51**) [105, 106] (Scheme 20.10). Seybold *et al.* have obtained the first isolable unfused azete **54** by FVT of tris(dimethylamino) triazine (**53**) [87] (Scheme 20.11).



Scheme 20.10



Scheme 20.11

20.2.4.2 **Reactions with Electrophilic Reagents**

Electrophilic reaction on ring carbon C5 of 1,2,3-triazines cannot proceed because of the intensive π-electron deficiency of the ring system.

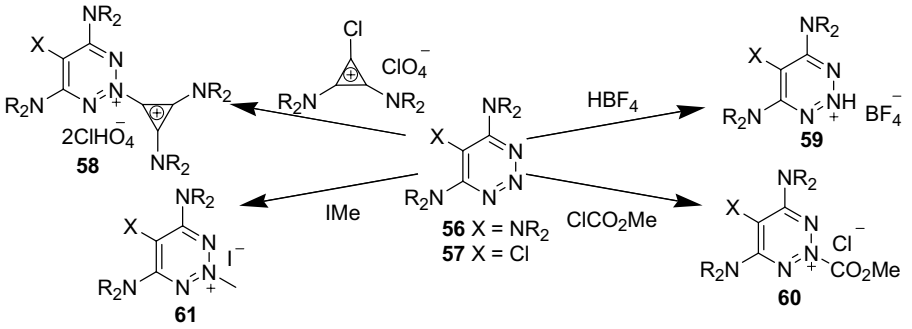
Protonation of alkyl and/or aryl substituted 1,2,3-triazines is difficult due to the low basicity of the ring nitrogen, and only when 4-phenyl (**28**) and 5-phenyl-1,2,3-triazines (**21**) are treated with tetrafluoroboric acid is the isolation of protonated 1,2,3-triazinium salts **55** possible [67]. The N2 substituted isomer is the most stable (Scheme 20.12).

21 R^4 = H, R^5 = Ph
28 R^4 = Ph, R^5 = H

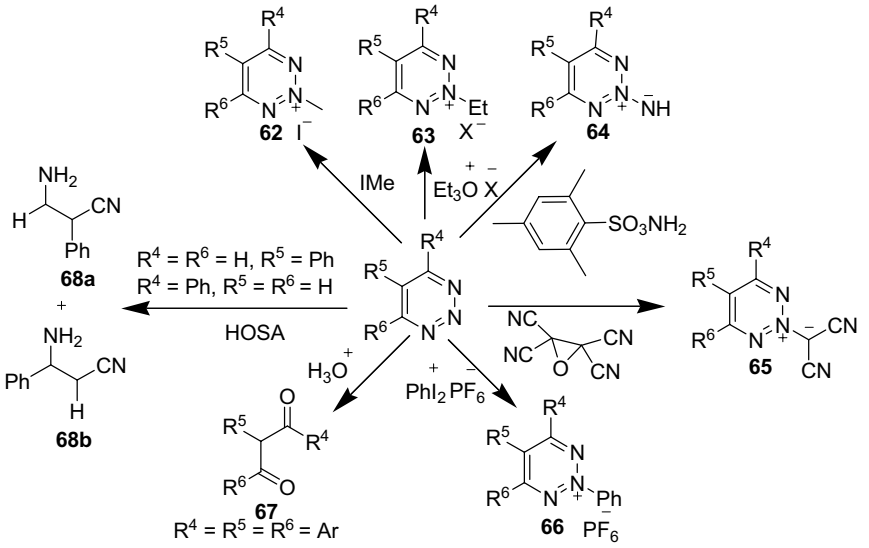
Scheme 20.12

However, 4,6-diamino-1,2,3-triazines have relatively high nucleophilicity at N2 and undergo various kinds of reactions with electrophiles [107] (Scheme 20.13).

Other electrophilic reactions proceed on the ring nitrogen of substituted 1,2,3-triazines (Scheme 20.14). The reaction with methyl iodide takes place easily to give 2-methyl derivatives **62** [63, 68, 92, 108]. Ethylation of substituted 1,2,3-triazines occurs when these compounds are treated with triethyloxonium, and so derivatives **63** have been obtained [67, 109]. Both N-amination and N-dicyanomethylidation of triazines also occurs and the corresponding 2-substituted isomers **64** [70] and **65** [109] are obtained in good yields. The N-phenylated 1,2,3-triazinium **66** has been obtained from copper-catalyzed reaction between 1,2,3-triazines and diphenyliodonium hexafluorophosphate [67]. Treatment of triaryl-1,2,3-triazines with aqueous hydrochloric



Scheme 20.13



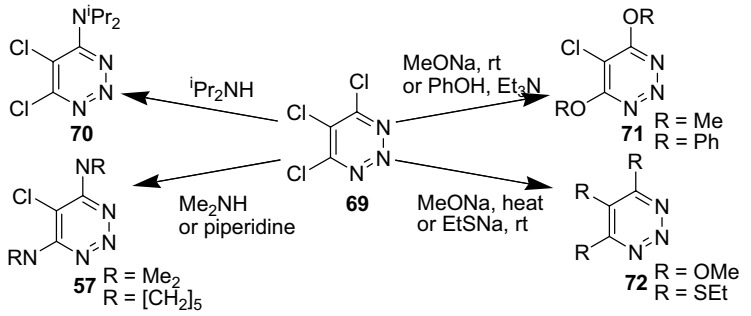
Scheme 20.14

acid at higher temperatures leads to hydrolysis of the ring and formation of 1,3-dicarbonyl compounds **67** [83]. The reaction of monosubstituted 1,2,3-triazines with hydroxylamine-*O*-sulfonic acid gives 3-amino-2(3)-phenylacrylonitriles **68a,b** [109].

20.2.4.3 Reactions with Nucleophilic Reagents

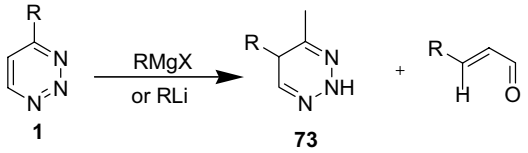
1,2,3-Triazines are highly π-electron deficient and are readily attacked by nucleophiles. The reaction site is almost exclusively at the C4 position, even in the presence of a substituent at C4 [69, 110, 111].

Gompper *et al.* [107] have reported that 4,5,6-trichlorotriazine undergoes substitution reactions with amines and alcohols. The first reaction site was the C4 position, and successive displacement(s) occur, depending on the nature of the nucleophile (Scheme 20.15).



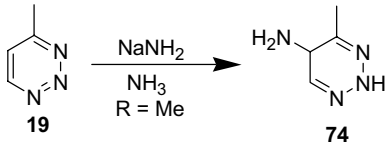
Scheme 20.15

Therefore, the 1,2,3-triazine ring system has been shown to have insufficient stability for direct introduction of substituents. For example, the parent triazine slowly decomposes in methanol at room temperature, which suggests that nucleophilic attack of methanol occurs in the solution. Also, softer nucleophiles undergo a redox reaction with triazine (**1**) to give 2,5-dihydro derivatives **73** without ring substitution [112] (Scheme 20.16).



Scheme 20.16

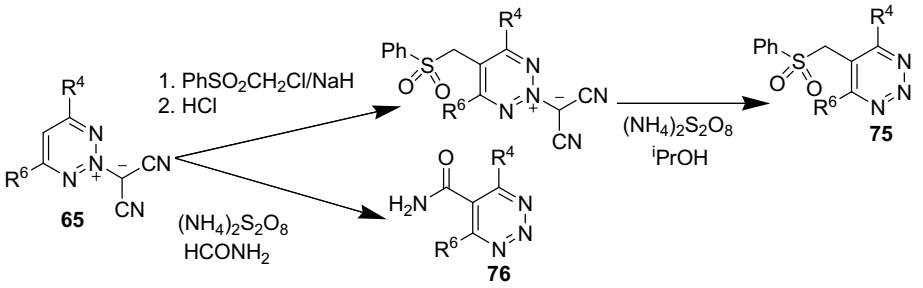
On the other hand, 4-methyl-1,2,3-triazine (**19**) reacts with sodium amide in ammonia to give 5-amino-4-methyl-2,5-dihydro-1,2,3-triazine (**74**) [48] (Scheme 20.17).



Scheme 20.17

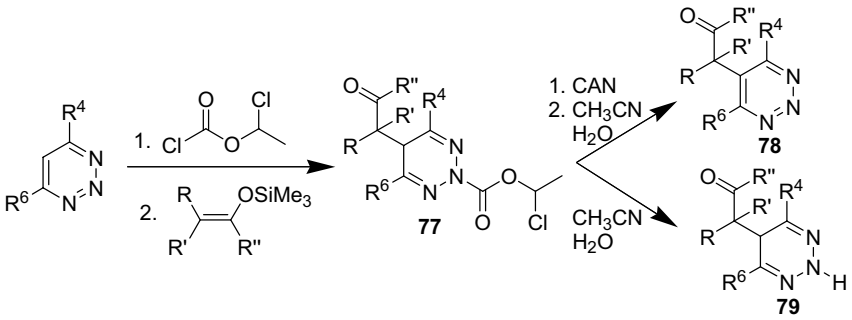
The introduction of nucleophiles at the C5 position of 1,2,3-triazine has been carried out for ring activation of N2, that is, addition of nucleophiles was successful when 1,2,3-triazinium salts were used as substrate. The dicyanomethylene group is a good activator, whose removal was simultaneously effected under the reaction conditions. Makosza [113] has developed a method named vicarious nucleophilic substitution of hydrogen to transform 1,2,3-triazinium 2-dicyanomethylylides **65**

into 5-benzenesulfonylmethyltriazines **75** [71, 114] by a radical reaction (Scheme 20.18). Radical nucleophilic carbamoylation, which was developed by Minisci [115], has been applied to triazinium dicyanomethylides to form 5-carbamoyl-1,2,3-triazines **76** [70, 116].



Scheme 20.18

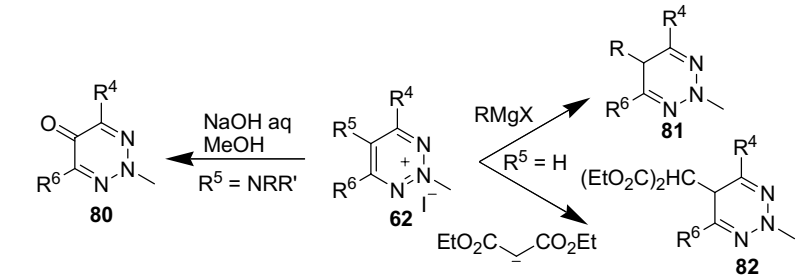
However, this procedure was limited to these two reactions because of the instability of the dicyanomethylene group toward other nucleophiles. Ohsawa *et al*. [68, 117] have found an alternative method for ring activation – ketene silyl acetals or silyl enol ether react with 1,2,3-triazine in the presence of 1-chloroethyl chloroformate to give 2,5-dihydro adducts **77**, which upon aromatization with ceric ammonium nitrate (CAN) give the corresponding 5-substituted triazines **78**. 2,5-Dihydro-1,2,3-triazine **79** has been obtained by hydrolysis in acetonitrile/water under reflux (Scheme 20.19).



Scheme 20.19

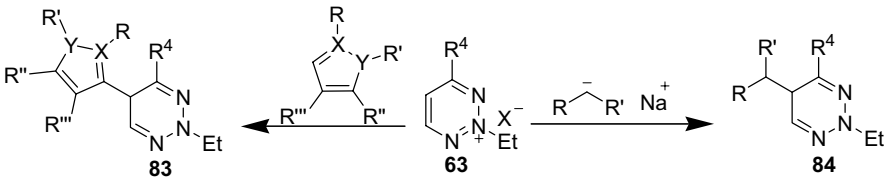
Hydrolysis of 5-amino-1,2,3-triazinium salt **62** with aqueous sodium hydroxide affords 1,2,3-triazin-5-ones **80** [63, 92, 93] (Scheme 20.20). 2-Methyltriazinium quaternary salts are highly reactive to nucleophiles; the reactive site is the 5-position, giving 2,5-dihydro derivatives **81** and **82** [118].

When 2-ethyl-1,2,3-triazinium salts are allowed to react with C-nucleophiles the expected attack occurs in the case of the 4-alkyl triazinium salt to obtain **83**



Scheme 20.20

(Scheme 20.21); however, 5-alkyl-1,2,3-triazinium salts did not react [67]. Reactions with these C-nucleophiles suffer from poor yields due to the weak nucleophilicity. Reaction of **63** with compounds with acidic protons allows one to obtain **84** in good yields.



Scheme 20.21

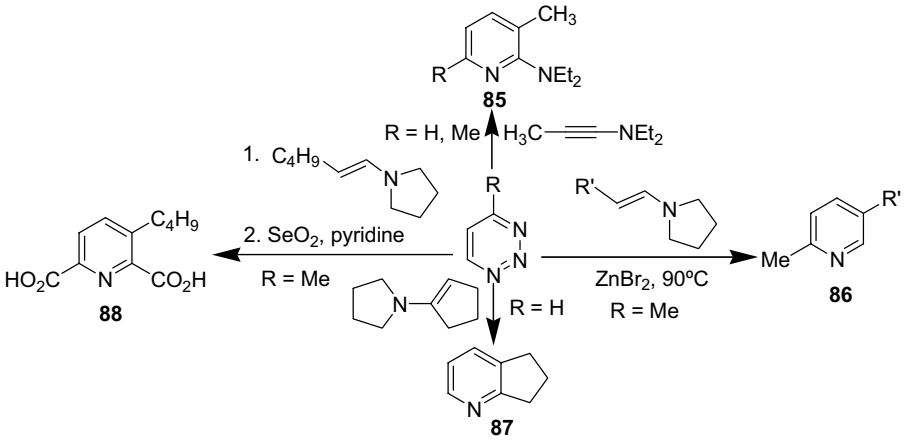
In addition, other nucleophiles can react with 1,2,3-triazines while keeping the aromaticity of the ring. Consequently, reaction between 4,6-dimethyl-1,2,3-triazine with halogenating reagents yields 5-halotriazine [119]. The use of interhalogen reagents affords 5-halotriazines derived completely or mainly from the more electronegative halogen.

Monocyclic 1,2,3-triazine 2-oxides are quite stable and unreactive toward reagents such as Grignard reagents, alkyl- and aryllithiums and other organometallic compounds. This fact suggests that the N-oxide moiety back-donates electrons to the triazine ring, thus making the α- and γ-positions less reactive toward nucleophiles.

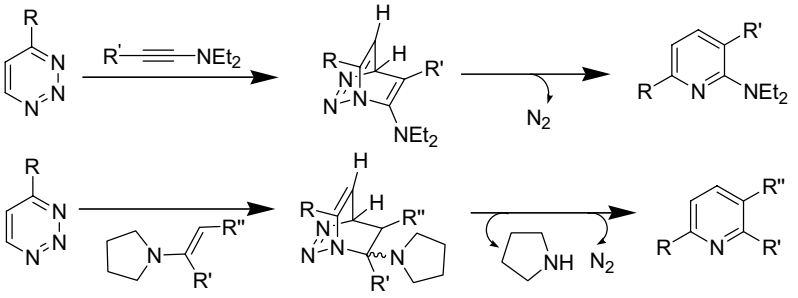
20.2.4.4 Cycloaddition Reactions

1,2,3-Triazines are useful compounds that participate in cycloaddition reactions [120]. These compounds behave as π-deficient dienes and undergo inverse-demand Diels–Alder cycloadditions with electron-rich dienophiles [121]. Several reactions of 1,2,3-triazines with ynamine or enamine have been reported to afford pyridines **85** [48, 122] or **86** [94, 123] respectively (Scheme 20.22). This approach has been successfully employed for the total synthesis of pyridine alkaloids [124, 125], such as fabianine (**87**) [48, 126] and fusaric acid (**88**) [127, 128].

The mechanisms proposed for these reactions are described in Scheme 20.23.

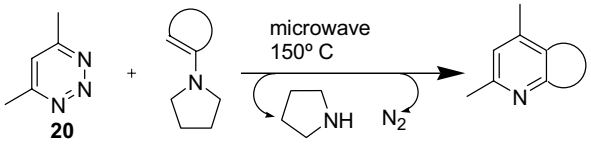


Scheme 20.22



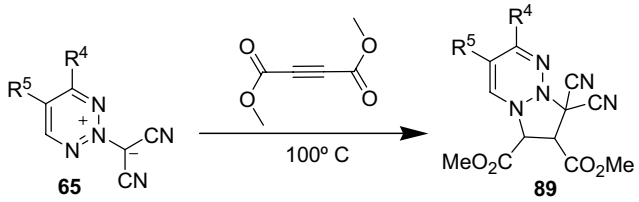
Scheme 20.23

4,6-Dimethyl-1,2,3-triazine (**20**) also reacts as diene with enamines under microwave irradiation [129, 130] (Scheme 20.24). The presence of alkyl substituents in the triazine ring diminishes the electron deficiency of the ring and increases the steric hindrance experienced in the cycloaddition. For these reasons, cycloaddition reactions are scarce and reaction conditions are very energetic, therefore microwave irradiation in solvent-free conditions is used. To date, Diels–Alder reactions of 4,5,6-trimethyl-1,2,3-triazine have not been reported.



Scheme 20.24

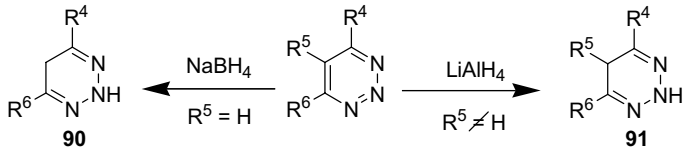
In 2004 [109] the first report was made of a 1,3-dipolar cycloaddition reaction between 1,2,3-triazonium *N*-ylides **65** and electron-deficient dipolarophiles, affording a new class of bicyclic heterocycles (**89**) (Scheme 20.25).



Scheme 20.25

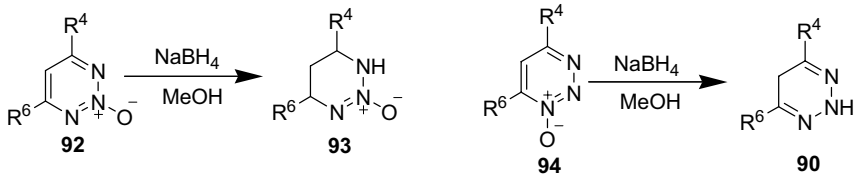
20.2.4.5 **Reactions with Reducing Reagents**

Sodium borohydride reduction of 4,6-disubstituted triazines in methanol afforded 2,5-dihydrotriazines **90** in good yields [66]. 4,5,6-Triaryltriazines have been reduced with $LiAlH_4$ to give also the corresponding 2,5-dihydro compounds **91** in moderate yields [48] (Scheme 20.26).



Scheme 20.26

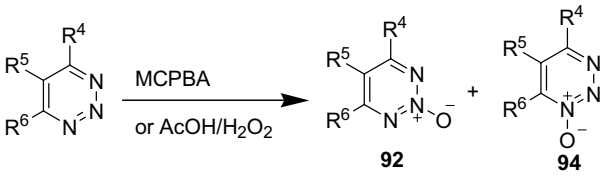
Reduction of the 2-oxide **92** with $NaBH_4$ gives tetrahydro derivatives **93** (Scheme 20.27) in good yields [131]. Reduction of the triazine 1-oxide **94** affords 2,5-dihydrotriazines **90**.



Scheme 20.27

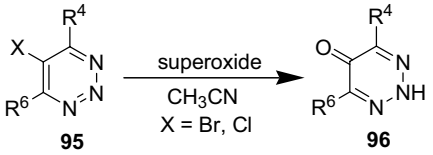
20.2.4.6 **Reactions with Oxidizing Reagents**

2-Oxides **92** and/or 1-oxides **94** have been obtained by treatment of monocyclic 1,2,3-triazines with MCPBA or $AcOH/H_2O_2$ (Scheme 20.28). Triazines with bulky aryl groups on C4 and C6 give predominantly 2-oxides **92**, while with alkyl groups on C4 and/or C6 it is possible to obtain 1-oxides **94** [48]. There are no reported 1(3)-oxides without substituent on the adjacent carbon.



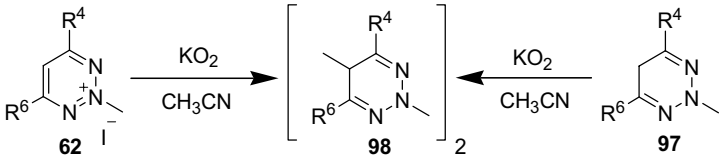
Scheme 20.28

5-Halo-1,2,3-triazines **95** react with superoxide to give 1,2,3-triazin-5(2*H*)-ones **96** [69, 111] (Scheme 20.29). The 5-oxo forms are predominant rather than the 5-hydroxy tautomers.



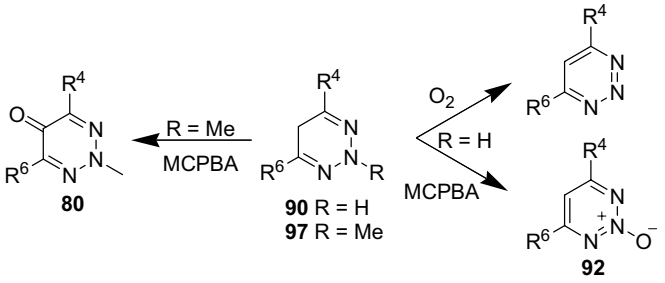
Scheme 20.29

The reactions of triazinium salts **62** [111, 118] and 2,5-dihydrotriazines **97** [132] with superoxide give 5,5′-bi(2-methyl-2,5-dihydrotriazinyls) **98**, which are formed by one-electron reduction with superoxide followed by dimerization (Scheme 20.30).



Scheme 20.30

2,5-Dihidrotriazines **90** slowly oxidize in air to give the corresponding triazines (Scheme 20.31), whereas oxidation with MCPBA affords 2-oxides exclusively **92**; *N*-

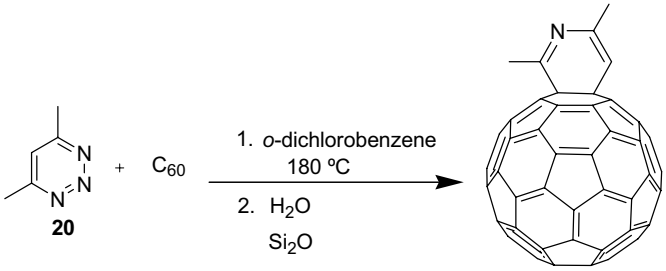


Scheme 20.31

methyl derivatives **97** are oxidized with MCPBA to afford 5-oxo-2,5-dihydrotriazines **80** [133].

20.2.4.7 **Relevant Examples**

Direct Diels–Alder reactions of 1,2,3-triazine with fullerene C_{60} should be unfavorable because 1,2,3-triazines behave as π-deficient dienes with inverse-electron demand and the 6-6 junction double bond of C_{60} acts as an electron-deficient dienophile. However, the reaction took place to give an azacyclohexadiene fused derivative such as **99** by extrusion of N_2 [134, 135] (Scheme 20.32)



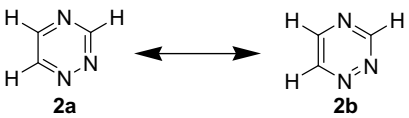
20 **99**

Scheme 20.32

20.3 1,2,4-Triazines

20.3.1 Relevant Computational Chemistry, Physicochemical and Spectroscopic Data

Much detailed data on the structure of 1,2,4-triazine have been published. Two Kekulé structures can be drawn for this molecule (**2a** and **2b**,Scheme 20.33). Theoretical calculations suggest that structure **2a** gives a higher contribution to the ground state of the molecule. This is supported by X-ray crystallographic structure determinations. It is explained by the fact that structures with a formal N=N double bond are energetically unfavorable; they are destabilized and so tend not to be formed [136].



2a **2b**

Scheme 20.33

Several theoretical methods have been used to study 1,2,4-triazines. Thus, the Hückel method was used to calculate the π-electron energies [137, 138], the electronic excitation energies and intensities were calculated by the RPAC molar properties program [139], the electronic state of 1,2,4-triazines were obtained [140] and the ionization energies were calculated by the outler valence Green function technique (OVGF) [141]. The CNDO/2 method has been used to calculate the sites of protonation and alkylation [142]. The acidities and basicities of **2** have been calculated by the MOSP method [143]. The proton affinities have been calculated by the 3-21 + G, 3-21G, MNDO, and AM1 methods [54], the tautomeric equilibrium by the AM1 and MNDO-PM3 methods [144] and the lithium-triazine binding energies by the 6-31G* method [145].

A computational study of the stability, homodesmotic stabilization energy, electron distribution and magnetic ring current of 1,2,4-triazines has been conducted [53]. The geometry and vibration spectra of 1,2,4-triazine have been obtained [57]. Harmonic [58] and anharmonic [58, 59] frequencies have also been calculated. The heat of formation of 1,2,4-triazine have been reported [61, 146].

Investigations employing the semi-empirical AM1, MNDO and MINDO/3 in the program package AMPAC to calculate both electronic charge distribution and structure optimization on compounds containing a 1,2,4-triazine ring demonstrate that these methods are not useful in studying heteroaromatic compounds containing nitrogen–nitrogen ring bonds [147].

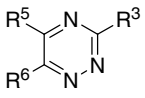
The relative stability of the nine possible dihydro-1,2,4-triazines and three dihydrotriazinium cations has been studied at HF, MP2, generalized gradient approximation DFT and CBS-4 levels of theory. The quantum chemical calculations support that the most stable isomer is the 2,5-dihydro-1,2,4-triazine [148].

Most 1,2,4-triazines are crystalline compounds, the melting points depending on the structure and the substituents present. Alkyl-substituted 1,2,4-triazines are yellow and melt at low temperatures, or a few cases are liquid at room temperature and they are reasonably stable. Aryl-substituted 1,2,4-triazines have melting points around 100 °C, while all heterosubstituted 1,2,4-triazines have melting points in the 200 °C region – these compounds are thermally very stable.

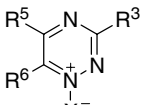
Several X-ray crystallographic studies have been reported for 1,2,4-triazines derivatives [149–161]. The X-ray studies on two Lamotrigine analogs, 3,5-diamino-6-(2-fluorophenyl)-1,2,4-triazine methanol solvate and 3,5-diamino-6-(2-methylphenyl)-1,2,4-triazine monohydrate, show that these compounds contain two conformers of the triazine molecule, each conformer with significant, distinct dihedral angles between their respective phenyl and triazine rings [162, 163]. The reader is referred to the *Cambridge Structural Database* for further structure determinations.

NMR spectra of 1,2,4-triazines are well documented. The parent compound **2** shows three signals in the ^{1}H NMR spectrum: δ = 9.88 (1H, d, H3), 8.84 (1H, d, H5), 9.48 (1H, dd, H-6) ppm [33]; coupling between H3 and H5 is never observed in simple 1,2,4-triazines. The ^{13}C and ^{15}N NMR data of 1,2,4-triazine and some derivatives are gathered in Table 20.2. ^{15}N NMR data for **101** and **102** have only been measured with the addition of $Cr(acac)_3$.

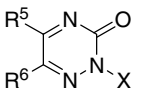
Table 20.2 ^{13}C and ^{15}N NMR [164] data of 1,2,4-triazines.



2, 100



101



102

Substituent	^{13}C NMR (DMSO-d_6) (δ, ppm)	^{15}N NMR (DMSO-d_6)[a] (δ, ppm)		
		δ (N1)	δ (N2)	δ (N3)
$R^3 = R^5 = R^6 = H$ (**2**)	158.3, 150.7, 149.2 [165]	39.24	−4.89	−80.34
$R^3 = SCH_3$, $R^5 = OCH_3$, $R^6 = H$ (**100a**)	170.9, 161.1, 138.6, 54.1, 13.1 [164]	33.3	−56.1	−140.0
$R^3 = OCH_3$, $R^5 = SCH_3$, $R^6 = H$ (**100b**)	167.8, 163.8, 143.4, 55.1, 11.3 [164]	27.1	−79.0	−129.4
$R^3 = SCH_3$, $R^5 = SCH_3$, $R^6 = H$ (**100c**)	171.1, 165.1, 144.3, 13.0, 11.3 [164]	23.0	−50.0	−108.5
$R^3 = SCH_3$, $R^5 = SCH_3$, $R^6 = CH_3$ (**100d**)	168.7, 164.4, 151.5, 18.0, 13.1, 11.7 [164]	14.6	−52.3	−108.2
$R^3 = SCH_3$, $R^5 = OCH_3$, $R^6 = CH_3$ (**100e**)	168.8, 160.3, 146.5, 54.8, 16.1, 13.1 [164]	23.0	−58.3	−141.3
$R^3 = OCH_3$, $R^5 = CH_3$, $R^6 = H$, X = O (**101a**)	168.1, 166.3, 135.7, 49.8, 54.1 [164]	−140.5	−123.3	−153.7
$R^3 = SCH_3$, $R^5 = CH_3$, $R^6 = H$, X = O (**101b**)	174.6, 163.5, 136.5, 49.7, 12.6 [164]	−122.6[b]	−123.1	−125.1
$R^5 = OCH_3$, $R^6 = CH_3$, X = CH_3 (**102**)	163.8, 153.6, 134.8, 39.3, 54.5, 15.5 [164]	−28.61	−142.4	−142.4

a) Nitromethane as reference.
b) Assignment of nitrogen ascertained by HMBC exponent.

Palmer has determined the 1,2,4-triazine ^{14}N quadrupole coupling constants from a joint study by microwave spectroscopy and *ab initio* calculations [166].

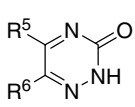
The mass spectra of 1,2,4-triazines have been extensively studied since they can be used for structure determination. The fragmentation pattern depends on the structure of the 1,2,4-triazine system (**2**) and on the substituents [2, 6]. Detailed studies on 1,2,4-triazines substituted with oxygen or sulfur in the 3- and 5-position have shown that five distinct fragmentation patterns can be observed upon electron impact, but none involve initial loss of nitrogen [167].

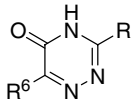
Information on the IR spectra of 1,2,4-triazines can be found [168–171]. UV spectra have been used to determine tautomeric structures in 1,2,4-triazin-3-ones [172–174], 1,2,4-triazin-5-ones [175, 176], 1,2,4-triazin-6-ones [177], 1,2,4-triazinethiones [178] and amino-1,2,4 triazines [179]. Unsubstituted 1,2,4-triazine [180] **2** has two absorption bands in methanol, at 374 (ε = 400) and 247.8 nm (ε = 3020). The UV spectra of the different 1,2,4-triazines have been reviewed [168].

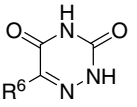
For many 1,2,4-triazines of varied structure the pK_a values have been determined and, depending on their structure, they range from 1.5 to 10.3 [181–186].

20.3.2
Tautomerism

As mentioned already, UV spectra have been used to determine the predominant tautomeric forms of 1,2,4-triazinones, 1,2,4-triazinethiones, and amino-1,2,4-triazines. In most cases, 1,2,4-triazines with oxygen or sulfur substituents exist predominantly in the oxo form (**103** [172, 173], **104** [168, 175], **105** [187], **106** [178]) or thioxo form (**106** [178], **107**, and **108**), while 1,2,4-triazines with a nitrogen substituent occur predominantly as the amino tautomer (**109** [179], **110**).


103


104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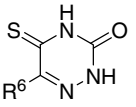
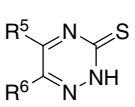

106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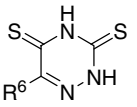
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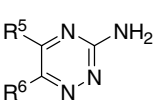
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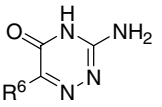
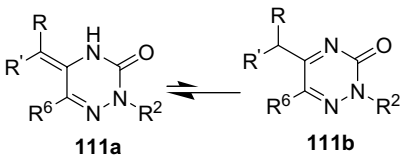
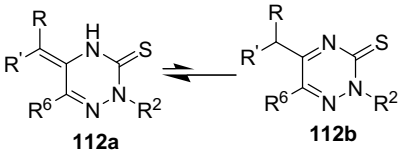

110

On the other hand, ^{1}H NMR spectroscopy shows that 5-alkyl-1,2,4-triazine-3-ones **111** [173] and 5-alkyl-1,2,4-triazine-3-thiones **112** [188] (Scheme 20.34) with a proton at C1 of the alkyl group can occur in two tautomeric forms, the alkylidene group (**111a** or **112a**) and the structure with an alkyl form (**111b** or **112b**). The ratio of the two tautomers depends on the solvent.


111a **111b**

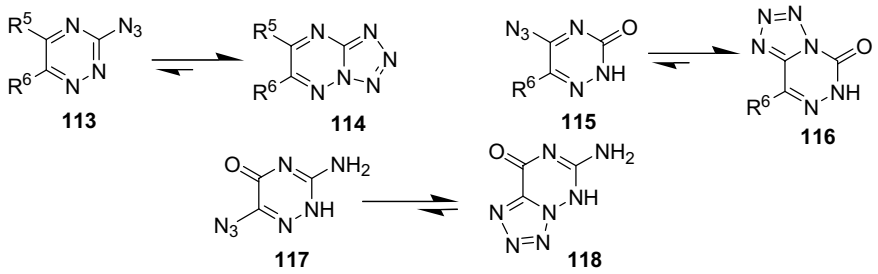

112a **112b**

Scheme 20.34

Azido-1,2,4-triazines may exist also as tetrazolo-fused tautomers. 3-Azido-1,2,4-triazines **113** spontaneously cyclize to give the tetrazolo[1,5-*b*][1,2,4]triazines **114** (Scheme 20.35), if cyclization to N2 is possible; no cyclization to N4 has been observed [189, 190]. 5-Azido-*2H*-1,2,4-triazin-3-ones **115** also cyclize to give **116** [191, 192]. In contrast, when the 6-azido tautomer **117** is stirred for a few minutes in a polar solvent it is quantitatively transformed into the tetrazole tautomer **118** [193].

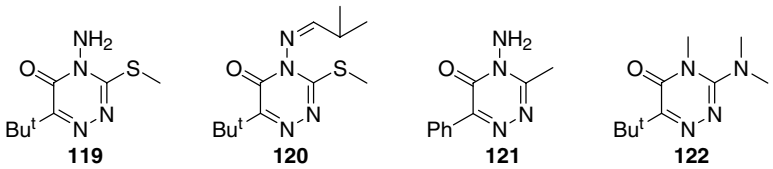
20.3.3
Relevant Natural and Useful Compounds

1,2,4-Triazines are biologically very active compounds. Many have been tested for use in agrochemistry or medicine. Amino-1,2,4-triazin-5-ones are, biochemically, highly



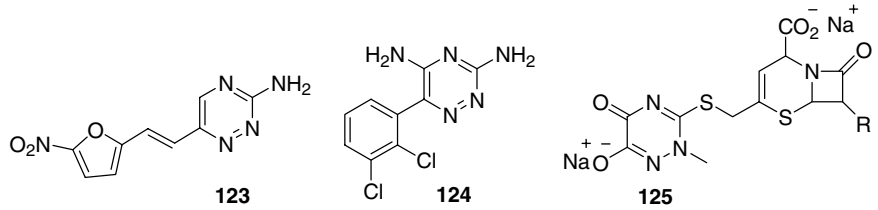
Scheme 20.35

active substances and are used as herbicides [168]. Some potent herbicides are 4-amino-6-*tert*-butyl-4,5,-dihydro-3-methylthio-1,2,4-triazin-5-one (**119**) (Metribuzin, Sencor, Lexone), 6-*tert*-butyl-4,5,-dihydro-4-isobutylideneamino-3-methylthio-1,2,4-triazin-5-one (**120**) (Isomethiozin), 4-amino-4,5,-dihydro-3-methyl-6-phenyl-1,2,4-triazin-5-one (**121**) (Metamitron, Goltix) and 6-*tert*-butyl-4,5,-dihydro-3-dimethylamino-4-methyl-1,2,4-triazin-5-one (**122**) (Amibuzin).



Two reviews on the role of uncondensed 1,2,4-triazine derivatives as biocide plant protection and therapeutic agents appeared in 2001 [194, 195].

Several 1,2,4-triazines show pharmacological properties (**123–125**). Compound **123** has been tested for its antibacterial and tuberculostatic activity [168]. 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (**124**) (Lamotrigine), a sodium channel blocker, is the active component of Lamictal and is in clinical use as an anticonvulsant therapy. Cefriaxome (**125**) [196, 197], a semi-synthetic parenteral cephalosporin, is a leading injectable antibiotic in hospital use.



Several 1,2,4-triazines have been tested as analgesic and anti-inflammatory agents [198–202]. Significant activity towards leukemia, ovarian cancer and anti-HIV were observed *in vitro* for some 3,5,6-trisubstituted-1,2,4-triazines [203–208]. 1,2,4-Triazine-*N*-oxide derivatives have been studied as potential hypoxic cytoxins [209–211]. Recently, the pyrrolotriazine nucleus has been identified as a potent and selective inhibitor of the tyrosine kinase [212–214].

Dihydro-1,2,4-triazine derivatives have been described as antimalarials due to their ability to inhibit multiple mutants of *Plasmodium falciparum* dihydrofolate reductase [215].

Many 1,2,4-triazines form complexes with metal ions and can be used for their determination [168, 216–219]. Other metallic complexes of 1,2,4-triazine have been also reported [220–224].

20.3.4 Synthesis

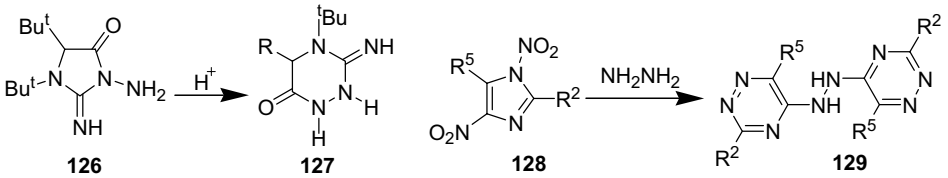
The 1,2,4-triazine ring can be synthesized by cycloaddition reactions of several different fragments – [3 + 3], [4 + 2], [5 + 1] – or by cyclization of a chain containing the necessary six carbon and nitrogen atoms. However, in many cases, reaction occurs in more than one step starting from smaller fragments. Other examples, starting from different heterocycles, have also been described.

A review dealing with the synthesis of 1,2,4-triazine mono-*N*-oxide appeared in 2002 [18].

20.3.4.1 From Other Heterocycles

There are some examples of preparation of 1,2,4-triazines by transformation of different heterocycles. For example, treatment of diaziridinone with α-metallated isocyanides yields 5-substituted 1,2-dihydro-6-hydroxy-1,2,4-triazines [225]; the reaction of 3-benzoyl-1,2,4-oxadiazoles with hydrazine furnishes the *(Z)*-oxime of 1,4-dihydro-6-phenyl-1,2,4-triazin-5-ones [226]; cyclization of 2,6-difluorphenylpyruvic acid with 2-aryl-5,5-dimethyltriazolidinine under acidic conditions affords the 6-(2,6-difluorbenzyl)-2-aryl-1,2,4-triazine-3,5-dione [227]; the reaction of arenediazonium salts with 5-methyl- and 5-ethylpyrimidine-4,6-diones yields 2,4-dihydro-6-alkyl-2-aryl-1,2,4-triazin-5-ones [228].

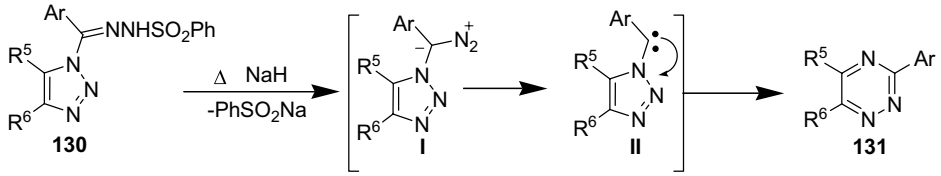
N-Aminoimidazolidinone **126** undergoes acid-catalyzed rearrangement to yield 1,2,4-triazinone **127** (Scheme 20.36). This product is also formed by reacting the aziridinone with hydrazine followed by cyanogen bromide [229]. On the other hand, 1,4-dinitroimidazole **128** reacts with hydrazine to give the product of imidazole ring expansion **129** [230].



Scheme 20.36

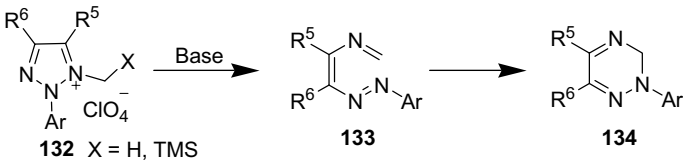
The transformation of 1-benzohydrazonoyl-1,2,3-triazoles **130** into 1,2,4-triazines **131** by heating with a slight excess of sodium hydride in dry benzene has been

described recently [231]. This process can be considered to proceed via the formation and decomposition of aryl(1,2,3-triazol-1-yl)diazomethanes **I** by a Bamford–Stevens reaction, followed by the ring enlargement of the resulting carbenes **II** as shown in Scheme 20.37 [231].



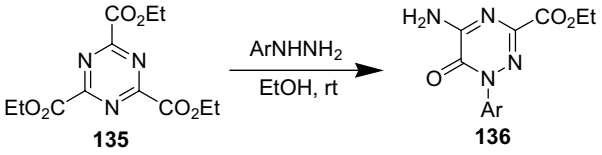
Scheme 20.37

The transformation of 1,2,3-triazolium salts **132** to yield substituted 2,3-dihydro-1,2,4-triazines **134** has been achieved on treating **132** with different bases via 1,2,5-triazahexa-1,3,5-trienes **133** [232–234] (Scheme 20.38).



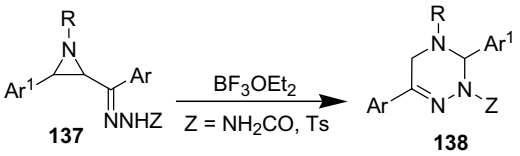
Scheme 20.38

Some examples of the preparation of 1,2,4-triazines by transformation of 1,2,4,5-tetrazines are considered in Section 20.5.4.2. Treatment of 1,3,5-triazine-2,4,6-tricarboxylic acid triethyl ester **135** with arylhydrazines provides 5-amino-6-oxo-1,6-dihydro-1,2,4-triazine-3-carboxylic acid ethyl esters **136**, after intramolecular rearrangement, in moderate to good yields [235–237] (Scheme 20.39).



Scheme 20.39

In 1996 Morioka reported the reaction of **137** with diethyl ether-boron trifluoride (1/1) to give 1,2,5,6-tetrahydro-1,2,3-triazine derivatives [238, 239]. Nevertheless, in 1998 X-ray crystallography analysis demonstrated the uncorrected assignment of this structure. The product obtained was established as 2,3,4,5-tetrahydro-1,2,4-triazine **138** [240] (Scheme 20.40).



Scheme 20.40

20.3.4.2 Cycloaddition of [3 + 3] Fragments

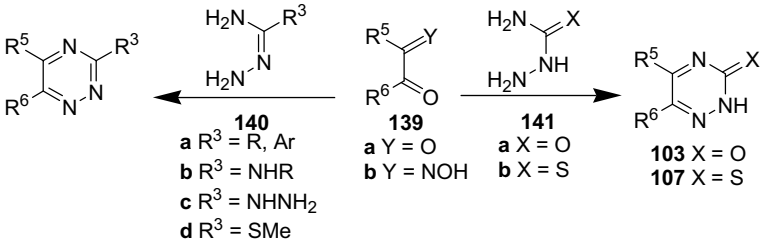
Few examples have been reported of this method. Among them, the reaction of α-amino ketones with thiosemicarbazides affords 3-amino-4,5-dihydro-1,2,4-triazines and dihydrotriazine-3-thiones [241]; and the cyclocondensation of nitrilimines with α-amino esters gives 1,4-dihydro-1,2,4-triazin-6-ones [242].

20.3.4.3 Cycloaddition of [4 + 2] Fragments

As for other six-membered rings, cycloadditions of [4 + 2] fragments are the most frequently used methods to obtain 1,2,4-triazines. Several examples of combinations of [4 + 2] atom fragments are known [243]. Of all possible [4 + 2] fragment combinations, [N(1)N(2)C(3)N(4) + C(5)C(6)] (A), [C(3)N(4)C(5)C(6) + N(1)N(2)] (B), [N(4)C(5)C(6)N(1) + N(2)C(3) (C), [C(5)C(6)N(1)N(2) + C(3)N(4)] (D), C(6)N(1)N(2)C(3) + N(4)C(5)] (E) and [N(2)C(3)N(4)C(5) + C(6)N(1)] (F), many examples have been reported save for combination (F) which is unknown to date.

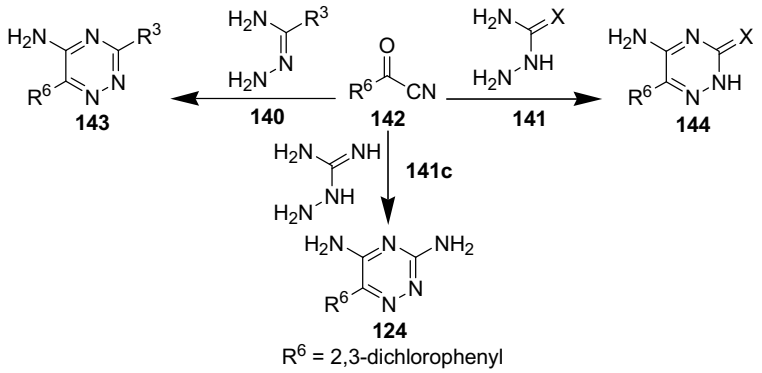
The following examples of the more frequent combination (A) are now considered.

The reaction of symmetrical 1,2-dicarbonyl compounds **139a** with derivatives **140** is the method most suitable to synthesize trisubstituted 1,2,4-triazines [180, 244, 245] (Scheme 20.41). Thus, this procedure has been used to obtain the parent 1,2,4-triazine and for the synthesis of compounds containing more than one 1,2,4-triazine nucleus [246]. When dione **139a** is an asymmetrical compound the reaction often leads to a mixture of regioisomeric triazines. Also, reactions of semicarbazide **141a** or thiosemicarbazide **141b** with **139a** afford the corresponding 1,2,4-triazin-3-ones **103** or 3-thiones **107** [247] (Scheme 20.41). Furthermore, the reaction of compounds **141** with monosubstituted glyoxal oxime **139b** ($R^5 = H$) is a suitable method to obtain 6-substituted-1,2,4-triazin-3-ones **103** ($R^5 = H$) and 3-thiones **107** ($R^5 = H$) [248]. However, reaction of monosubstituted glyoxal **139a** ($R^6 = H$) with semicarbazide (**141a**) affords mainly 5-substituted-1,2,4-triazin-3-ones **103** ($R^6 = H$) [248].



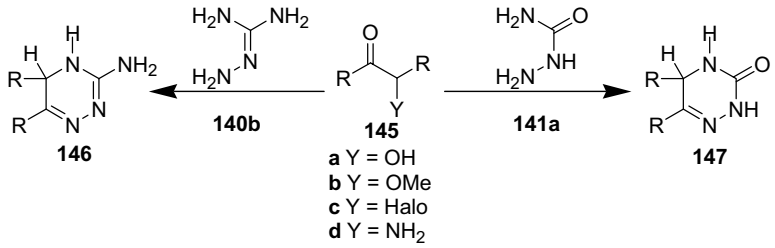
Scheme 20.41

Substitution of 1,2-dicarbonyl compounds by acylcyanides **142** affords 5-amino-1,2,4-triazines **143** and **144** [249] (Scheme 20.42). The condensation/cyclization of aminoguanidine (**141c**) with the acylnitrile **142** leads to Lamotrigne (**124**) (Scheme 20.42).



Scheme 20.42

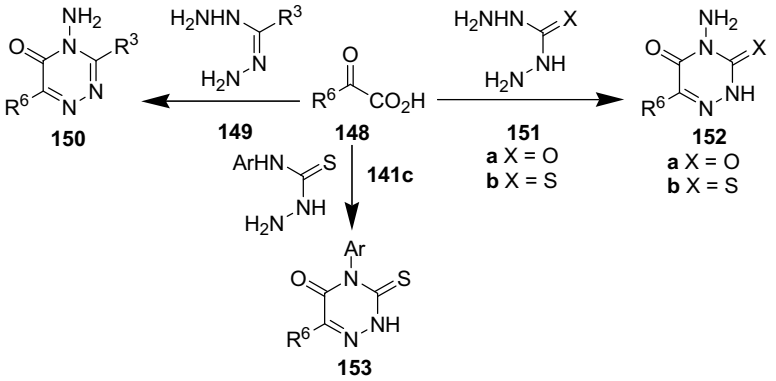
3-Amino-4,5-dihydro-1,2,4-triazine **146** can be synthesized by the reaction of α-haloketones **145c** and **140b** (Scheme 20.43), whilst reaction of α-hydroxy **145a**, α-methoxy **145b**, α-halo **145c** or α-amino ketones **145d** with semicarbazide (**141a**) affords 4,5-dihydro-1,2,4-triazin-3(2*H*)-ones **147** [250] (Scheme 20.43).



Scheme 20.43

Reaction of **149** with α-ketocarboxylic acids **148** is a suitable way to obtain 4-amino-1,2,4-triazin-5-ones **150** [251] (Scheme 20.44). On the other hand, carbonohydrazide (**151a**) or thiocarbonohydrazide (**151b**) yields the 4-amino-3,5-diones **152a** and 4-amino-3-thioxo-1,2,4-triazin-5-ones **152b** respectively. Cyclization of **148** with *N*-aryl thiosemicarbazide **141c** affords the 3-thioxo-1,2,4-triazin-5-one **153** [227] (Scheme 20.44).

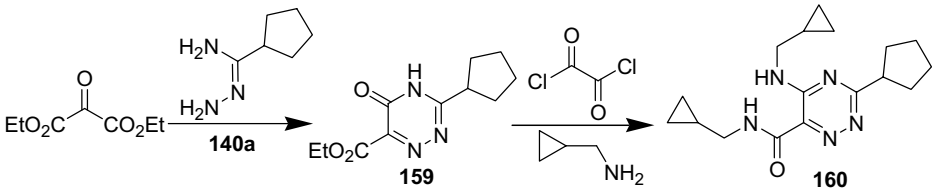
Another literature method for obtaining 1,2,4-triazin-5-one involves the cyclization of α-ketoamide **154** with **140d** to give 3-methylthio-1,2,4-triazin-5-one **155** [252]; similarly, **156** can react with 2-methylsemicarbazide (**157**) to afford 6-hydroxy-2-methyl-3-thioxo-1,2,4-triazin-5-one (**158**) [196] (Scheme 20.45).



Scheme 20.44

Scheme 20.45

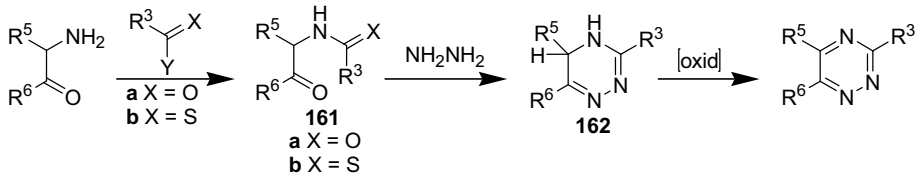
A recent example of the reaction between an α-ketocarboxylic acid and derivatives **140a** has been developed to obtain a ring-open isofervenulin analog **160** through triazine **159** [253] (Scheme 20.46).



Scheme 20.46

The combination [C(3)N(4)C(5)C(6) + N(1)N(2)] – listed as (B) above – is also a much used method to prepare 1,2,4-triazines. In this method, hydrazine, its derivatives or different diazo compounds are used as starting materials. Thus, α-acylamino **161a** and α-thioacylamino ketones **161b** react with hydrazine to yield 4,5-dihydro-1,2,4-triazines **162**, which can be oxidized to 1,2,4-triazines [254] (Scheme 20.47). Since, compounds **161** can be obtained by acylation of α-amino-ketones or thioketones, this procedure can also be considered as a [3 + 1 + 2] combination method.

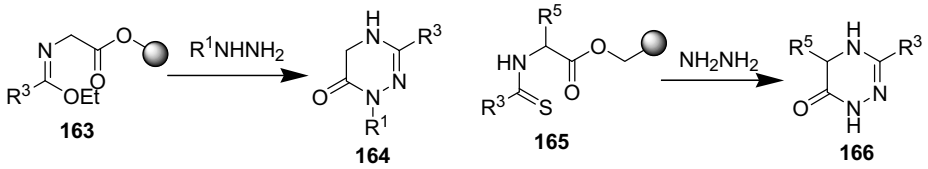
Similarly, hydrazine or substituted hydrazines react with *N*-alkyl(*N*-acyl) α-aminoester [255], malonamide [256], α-imidoyl esters [177], α-isocyano esters [257], and



Scheme 20.47

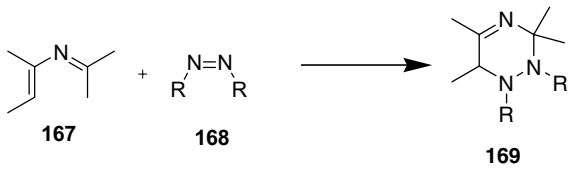
N-(cyanomethyl)-imidates [258, 259] to give 1,2,4-triazin-ones, diones, thioxo and amino derivatives. Another method to introduce the [N(1)N(2)] fragment is the reaction of diazonium salts or other diazo compounds with activated methylene groups to obtain 1,2,4-triazin-3,5-dione [260].

The reaction of imidate ester **163** with substituted hydrazines is a known reaction for the preparation of 1-substituted 4,5-dihydro-1,2,4-triazin-6(1*H*)-one **164** [177, 261, 262]. This synthesis has also been studied in the solid phase [263] (Scheme 20.48). Another procedure for the solid-phase synthesis of functionalized 4,5-dihydro-1,2,4-triazin-6(1*H*)-ones **166** has been developed from thioamide **165** and hydrazine [264, 265] (Scheme 20.48).



Scheme 20.48

Cycloaddition of 2-azabutadienes **167** with azo compounds **168** affords 1,2,3,6-tetrahydro-1,2,4-triazines **169** [259, 266–268] (Scheme 20.49).

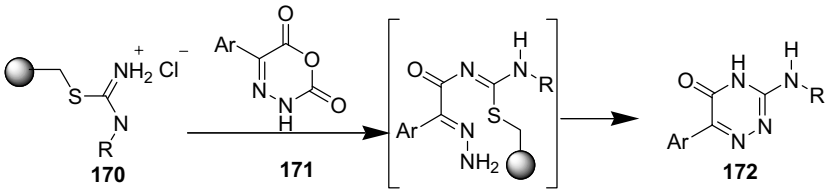


Scheme 20.49

Frequently, five-membered heterocyclic systems have provided the [C(3)N(4)C(5)C(6)] fragment used in this method, as mentioned in Section 20.3.4.1.

The combination [N(4)C(5)C(6)N(1) + N(2)C(3) – listed as (C) above – has been used in the synthesis of 1,2,4-benzotriazines but for monocyclic 1,2,4-triazines there are no examples.

An interesting case of the combination [C(5)C(6)N(1)N(2) + C(3)N(4)] – listed as (D) above – has appeared in the literature in which the first solid-phase synthesis of 3-amino-1,2,4-triazin-5-ones are described. The polymer-bound isothiourea **170**, which supports the C(3)N(4) fragment, reacts with a stoichiometric amount of 2,3-diaza-3-pentenoic anhydride **171**, the C(5)C(6)N(1)N(2) fragment, to give 3-amino-1,2,4-triazin-5(4*H*)-ones **172** [269] (Scheme 20.50).



Scheme 20.50

Another reported combination (D) involves the reaction of aryl bromomethyl ketone phenylsulfonylhydrazones with benzylideneaniline to give 6-aryl-3,4-diphenyl-2-phenylsulfonyl-2,3,4,5-tetrahydro1,2,4-triazine [270].

1,2,4,5-Tetrazines are the main starting material to use combination (E), C(6)N(1)N(2)C(3) + N(4)C(5), since they are reactive dienes in Diels–Alder reactions with inverse electron demand and can react with both C−C and C−N multiple bonds (Section 20.5.4.2).

20.3.4.4 Cycloaddition of [5 + 1] Fragments

Many of the methods discussed in this section can be considered as a combination of more than two fragments, since the fragment with five atoms usually is obtained previously from shorter chains.

Only C(3) and N(4) atom-fragments are found in the literature for the synthesis of 1,2,4-triazine derivatives using cycloadditions of [5 + 1] fragments.

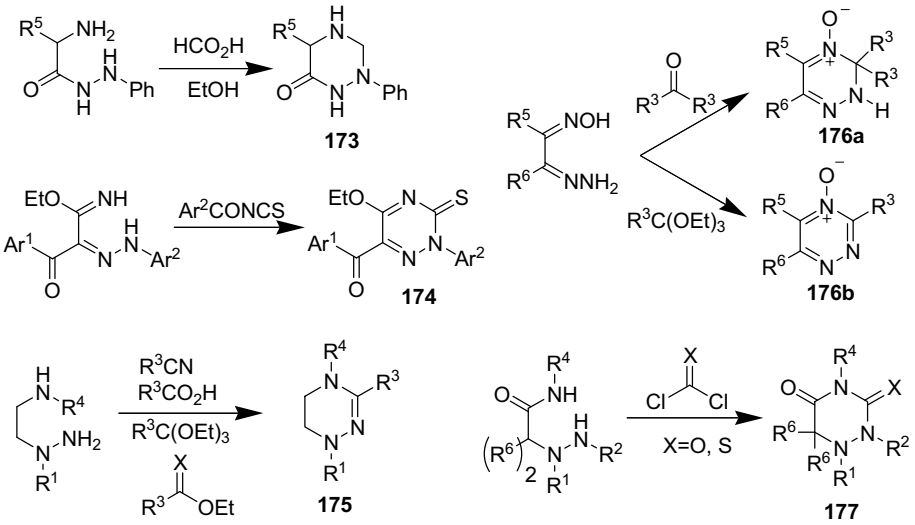
Compounds that provide the C(3) include aldehydes [271–274], isothiocyanates [275], nitriles [276], imidates [276, 277], thioimidates [276], ketones, orthoesters [278–281], carbon disulfide, phosgene, and thiophosgene [282]. Some examples are shown in Scheme 20.51.

The reaction of hydrazono-2-oximinoethane **178** with pyridine-2,6-dicarboxaldehyde led to **179** [283], however, in the presence of Pb_3O_4 yields 4-oxide-1,2,4-triazines **180** [284] (Scheme 20.52)

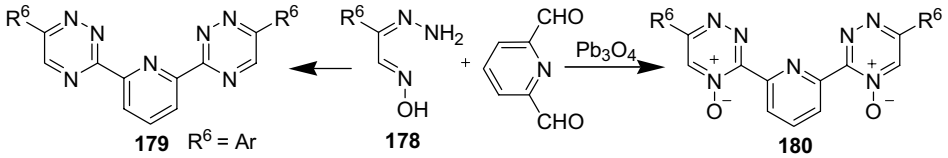
Compounds reported to date that provide N(4) are ammonia or its derivatives [285–289] (Scheme 20.53).

20.3.4.5 Cycloaddition of [6 + 0] Fragments

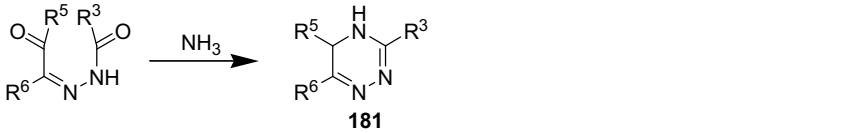
Most reactions dealing with the cyclization of a six-membered chain can also be considered as a synthesis of 1,2,4-triazines from more than one fragment since, usually, the chain is obtained from two or more fragments. Several of these cyclizations occur by photochemical or thermal processes, the latter carried out in many cases in basic or acid conditions.



Scheme 20.51

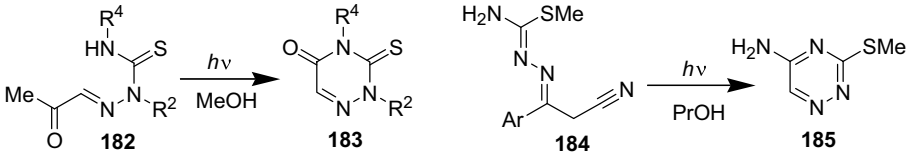


Scheme 20.52



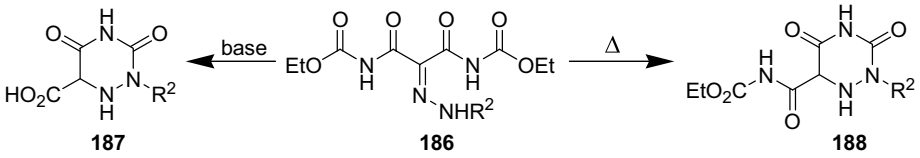
Scheme 20.53

Photolysis of 1,6-diazido-2,5-diphenyl-3,5-diaza-2,4-hexadiene afforded 3,6-diphenyl-1,2,4-triazine [290], photochemical cyclization of thiosemicarbazones **182** yields 3-thioxo-1,2,4-triazin-5-ones **183** [291] and photolytic cyclization of **184** gives 5-amino-1,2,4-triazine **185** [252] (Scheme 20.54).



Scheme 20.54

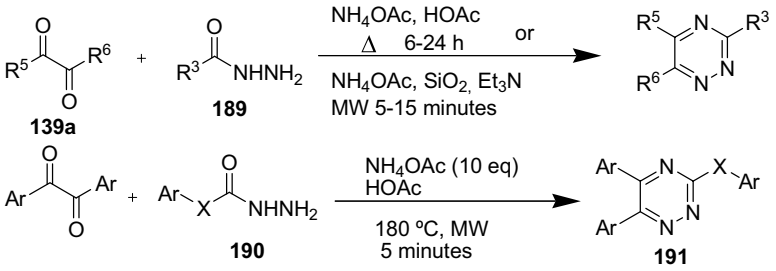
Basic cyclization of hydrazonomalonic diamides **186** yields 3,5-dioxo-1,2,4-triazine-6-carboxylic acids **187** while their thermal cyclization gives carboxamides **188** [292] (Scheme 20.55).



Scheme 20.55

20.3.4.6 Synthesis from More than Two Fragments

Many of the above-mentioned examples could be considered under this section. The synthesis of 1,2,4-triazines, via the condensation of 1,2-diketones **139a** with acyl hydrazides **189** and ammonium acetate under traditional thermal [293] and dry media microwave-assisted reaction conditions [294], has been reported (Scheme 20.56). The extension to hetaryl acyl hydrazides **190** and diaryl 1,2-diketones using the microwave assisted-method on a Smith synthesizer has allowed the synthesis of a 48-membered library of 1,2,4-triazines **191** in very high yields [295].



Scheme 20.56

20.3.5 Reactivity

The most reactive position of the 1,2,4-triazine ring is position 5. This position is easily attacked by nucleophilic agents and many times this attack is followed by an electrophilic attack at positions 4 or 2. Most 1,2,4-triazines are less stable toward bases than toward acids.

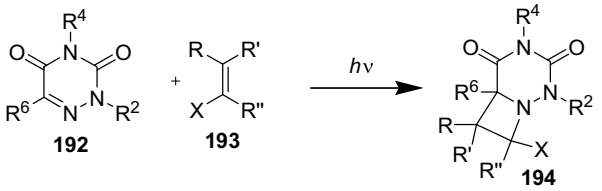
The reactivity of 1,2,4-triazine mono N-oxides was reviewed in 2002 by Chupakhin *et al.* [18].

20.3.5.1 Thermal and Photochemical Reactions

Since most 1,2,4-triazines are thermally very stable, only a few examples of thermal reactions have been described [296–300].

Photochemical hydration of the C(6)−N(1) bond of 1,2,4-triazines has been described for 1,2,4-triazine-3,5-dione and 5-amino-1,2,4-triazin-3-ones to yield 6-hydroxy-1,2,4-triazine-3,5-dione and 5-amino-6-hydroxy-1,2,4-triazin-3-ones, respectively [301]. Chemical and photochemical induced reduction of some dihydro-1,2,4-triazines and aromatic 1,2,4-triazines have been described [302–305].

The [2 + 2] cycloaddition reactions of 1,2,4-triazine-3,5-diones **192** with alkenes **193** involve a photochemical addition of the alkene to the C(6)–N(1) double bond of 1,2,4-triazines to give azeto[2,1-*f*][1,2,4]triazinediones **194** [306–308] (Scheme 20.57).

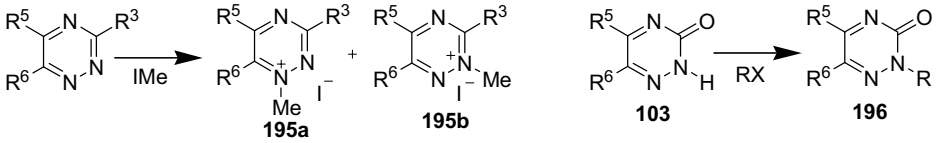


Scheme 20.57

20.3.5.2 **Reactions with Electrophilic Reagents**

The salts of simple 1,2,4-triazines are obtained by addition of dry acids to a solution of the triazine in organic solvents. Addition of concentrated hydrochloric acid to a solution of 5,6-diphenyl-1,2,4-triazine in sulfuric acid leads to the precipitation of the crystalline hydrochloride [309].

Alkylation and acylation of 1,2,4-triazine systems have been extensively studied. Alkylation of 1,2,4-triazines with methyl iodide gives mainly 1-methyl-1,2,4-triazinium iodides **195a** and in few cases the colorless 2-methyl isomers **195b.** The formation of **195a** or **195b** depends on the substituents on the triazine ring [175, 176, 310–312]. Alkylation and acylation of 1,2,4-triazin-3-ones **103** yield 2-alkyl(acyl)-1,2,4-triazin-3-ones **196** [173, 313, 314] (Scheme 20.58).



Scheme 20.58

When 1,2,4-triazin-5-ones are methylated with diazomethane, 2-methyl-, 4-methyl- and 5-methoxy- derivatives are obtained in different ratios depending on the solvent used [311, 312].

Alkylation of 1,2,4-triazine-3,5-diones with methyl iodide affords the N(2)-methyl derivative while dimethyl sulfate or diazomethane yield first the N(4)-methyl derivative. In all cases, the 2,4-dimethyl derivative is obtained on further alkylation [315]. Acylation of 1,2,4-triazine-3,5-diones yields mainly 2-acyl derivatives.

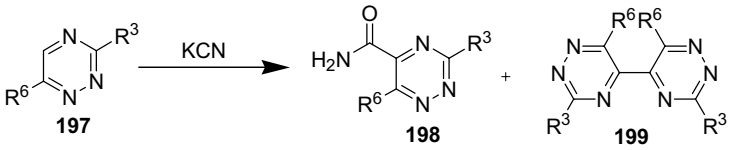
The results of alkylation of 3-amino-1,2,4-triazines depend on the alkylating agent and the nature of the 5- and 6-substituents. Reaction of 3-amino-5,6-diphenyl-1,2,4-triazines with ethyl iodide [316] or halo-acetic acid [317] yields 2-alkyl-3-imino-5,6-diphenyltriazine. However, alkylation with dimethyl sulfate affords 3-amino-1-methyl-1,2,4-triazinium salts and other authors have reported the isolation of a mixture of 1-methyl and 4-methyl-3-amino-1,2,4-triazinium salts on treating 3-amino-1,2,4-triazine with methyl iodide [318].

Direct halogenation of the parent 1,2,4-triazine (**2**) has not been reported, and any electron-donating substituents present will not necessarily counteract the inherent resistance of the ring to electrophilic substitution [319, 320]. An oxo substituent at the 5-position is sufficiently activating to permit the 6-bromination of some 1,2,4-triazin-5-ones and -3,5-diones [183]. Although the presence of an N-oxide function proved insufficient to allow chlorination and bromination, both the 3-amino- and 3-methoxy-1,2,4-triazine 1- or 2-oxides gives 6-halogeno derivatives [321–323].

20.3.5.3 Reactions with Nucleophilic Reagents

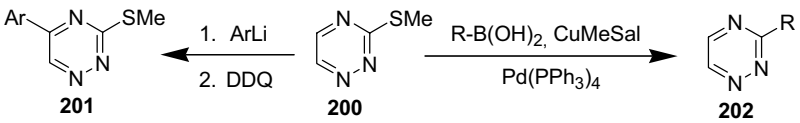
Nucleophilic attack on the carbon atoms of the 1,2,4-triazine ring is well known [324].

1,2,4-Triazines and some of its 3-methoxy, 3-methylthio or 3-aminoderivatives **197** react with potassium cyanide to give two products, the 1,2,4-triazine-5-carboxamide **198** and the bis-1,2,4-triazin-5-yl derivatives **199** [325, 326] (Scheme 20.59).



Scheme 20.59

Guillaumet has studied the control of relative positions 3, 5 and 6 of the 1,2,4-triazine ring with Grignard reagents. Indeed, the most active position is C5 and the least active is C3 [327]. As expected, the addition of aryllithium to 3-thiomethyl-1,2,4-triazine **200** led to 5-substituted compounds and a further oxidation step gave 5-aryl-1,2,4-triazine **201** [327] (Scheme 20.60). However, when palladium-catalyzed the reaction of **200** with different organoboron compounds in the presence of copper(I) 3-methylsalicilate affords the corresponding 3-substituted 1,2,4-triazines **202** in good yields [328]. Addition of arylmagnesium bromide to **201** occurs at the 6-position [327].



Scheme 20.60

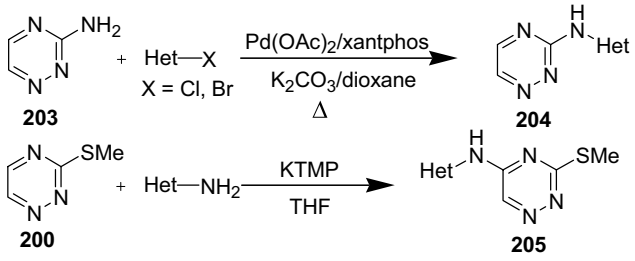
Most leaving groups in the 3-, 5-, or 6-positions of 1,2,4-triazines can be substituted by carbon nucleophiles prepared from aldehydes, malonates, acetonitrile, malonodinitrile, and other CH acidic compounds [329–333].

Carbanions bearing leaving groups at the carbanionic centers react with 1,2,4-triazines by replacement of hydrogen atoms in the 5-, 6-, and 3-positions with the carbanionic moiety and loss of the leaving group. Carbanions of nitroalkanes, chloromethyl, phenylsulfones, chloromethane, sulfonomorpholides and acetonitriles and 4-pentenyl iodide have been used in this vicarious nucleophilic substitution [334–339].

There are many examples of exchange of a heterosubstituent in the 3-, 5-, or 6-position by another heterosubstituent. This class of exchange has been widely used for the preparation of 3-, 5-, or 6-alkynyloxy-, alkynylthio- and alkynylamino-1,2,4-triazines [340–344].

1,2,4-triazin-5-ones react with electron-rich heterocycles in acetic anhydride to yield 6-aryl-1,2,4-triazin-5-ones [345].

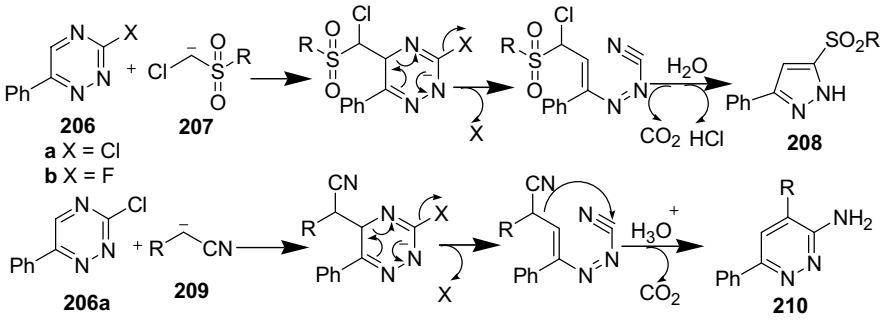
An easy access to 3- or 5-heteroarylamino-1,2,4-triazines by selective nucleophilic substitution of 1,2,4-triazines has been reported recently. In reactions of 3-amino-1,2,4-triazine (**203**) with different halo-heterocycles using palladium acetate as catalyst and xantphos as ligand, an S_NAr process takes place and 3-heteroarylamino-1,2,4-triazines **204** are obtained [346, 347]. In contrast, the use of bases such as 2,2′,6,6′-tetramethylpiperidine/tBuOK/nBuLi (KTMP) in the reaction of 3-methylthio-1,2,3-triazines (**200**) and aminoheterocycles leads regioselectively to 5-substituted 1,2,4-triazines **205** via S_NH substitution [347] (Scheme 20.61).



Scheme 20.61

1,2,4-Triazine is converted in high yield into 5-amino-1,2,4-triazine on treatment with liquid ammonia and potassium permanganate [348]. Similar reactions have been reported for 3- and 6-substituted 1,2,4-triazine. The substitution of chlorine by amino groups using potassium amide in liquid ammonia has been studied by Rykowski and Van der Plas [349–351].

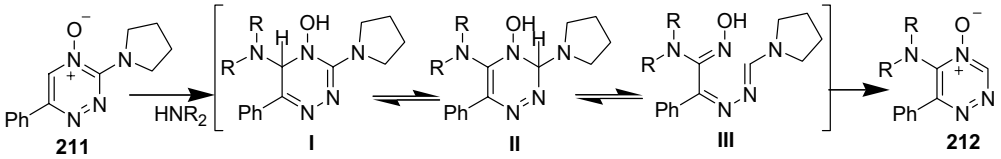
In the reactions of 5-unsubstituted-1,2,4-triazines **206**, with a good leaving group at C3, and α-chlorocarbanions **207**, ring contraction into a pyrazole **208** is preferred to vicarious nucleophilic substitution at C5 and displacement of the C3 substituent [352] (Scheme 20.62). In contrast, the reaction of **206a** with a carbon nucleophiles bearing a cyano substituent yields the corresponding 3-aminopyridazines **210** via an



Scheme 20.62

ANRORC mechanism involving addition of the nucleophiles at position 5, ring opening with cleavage of the N_4-C_5 bond and intramolecular ring closure of the resulting open-chain intermediate [353].

Nucleophilic attack at the 5-position of 1,2,4-triazin-4-oxides is often accompanied by ring-opening reactions [32, 354–356]. However, ammonia addition at the 5-position of 6-aryl-3-pyrrolidin-1,2,4-triazine-4-oxides **211** is followed by a [1,5]sigmatropic hydrogen shift to give intermediate **II** followed by ring-opening with cleavage of the C_3-N_4 bond. In this case, this ring opening is a reversible process that allows the cyclic dihydro intermediates to be aromatized with elimination of the dialkyamino group, to give 5-amino-1,2,4-triazine-4-oxide **212** [357] (Scheme 20.63).



Scheme 20.63

Nevertheless, reaction of 6-aryl-3-dimethylamino-1,2,4-triazine-4-oxide with the cyanide anion causes a similar [1,5]sigmatropic hydrogen shift-ring-opening, followed by recyclization into 3-amino-4-nitrosopyrazoles (according to the ANRORC mechanism) [358].

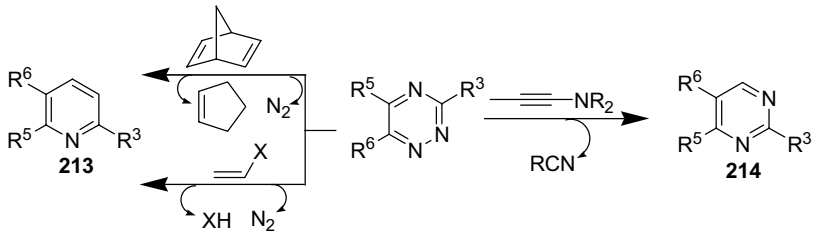
Reaction of hydroxylamine at the 3-position of 6-aryl-5-amino-1,2,4-triazine-4-oxide leads to 6-aryl-5-hydroxylamino-1,2,4-triazines [359]. Cyanation of 3,6-disubstituted-1,2,4-triazine-4-oxide has been achieved with acetone cyanhidrine in the presence of triethylamine to afford 3,6-disubstituted-5-cyano-1,2,4-triazine [284]. 1,2,4-Triazine 4-oxides can be hydrolyzed by bases, affording 2-acylhydrazono oximes. [354] In this case, initial attack occurs at the 3-position.

20.3.5.4 **Cycloaddition Reactions**

Diels–Alder reaction with inverse-electron demand is the most extensively studied reaction of 1,2,4-triazines. Triazines behave as reactive electron-deficient dienes and

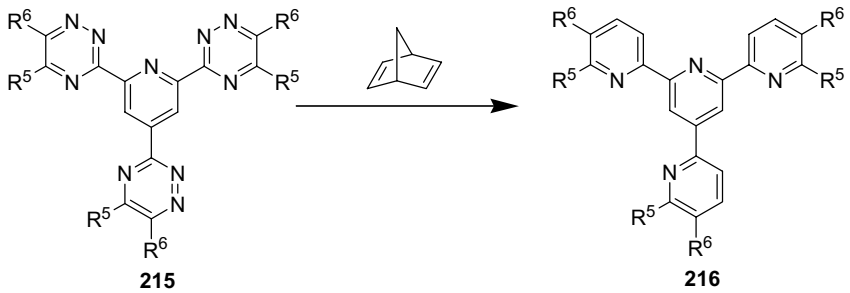
so are able to react with dienophiles such as electron-rich alkenes and acetylenes among others. Some reviews on inter- and intramolecular Diels–Alder reactions have appeared [30, 120, 360, 361].

1,2,4-Triazines participate as electron-poor dienes in inverse type Diels–Alder reactions with electron-rich dienophiles such as dienes [120, 244], enamines [362–372] or methoxyethylene [373] to yield pyridine derivatives **213** (Scheme 20.64). Cycloaddition of 1,2,4-triazines with ynamines to yield pyrimidines **214** [374–376] has also been studied. It has been demonstrated that this type of reaction is a [4 + 2] cycloaddition to N2 and C5 and not a [2 + 2] cycloaddition to the N(4)-C(5) bond [377]. If the 5-position is substituted, dienophile attack occurs at the 3-position [375, 377, 378]. A tethered imine-enamine methodology has been developed for the direct conversion of 1,2,4-triazines into highly substituted pyridines [379].



Scheme 20.64

Several examples of a new and simple "LEGO" system to obtain 2,6-oligopyridines **216** [244, 246, 283, 284, 380–385] from 1,2,4-triazines have been described (Scheme 20.65).

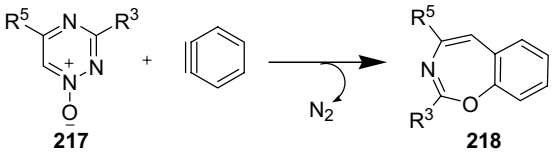


Scheme 20.65

Ethynyltributyltin cycloadds to 3,5-disubstituted-1,2,4-triazine to furnish mainly 2,4-disubstituted-4-tributylstannylpyridine [386, 387]. A Diels–Alder reaction has been employed to obtain 4,5-dihydroazocines from 3-(ethoxycarbonyl)-5-phenyl-1,2,4-triazines, cyclobutanone and secondary amines [388].

In addition, the intermolecular Diels–Alder reaction has been studied and used to obtain condensed pyrimidines, pyridines [339, 370, 389, 390] and β-carbolines [391], tetrahydro-1,5-naphthyridines and related heterocycles [392].

Reaction of the unsubstituted 1,2,4-triazine 1-oxides **217** with benzyne gives the 1,3-benzoxazepidines **218** via 1,3-dipolar cycloadducts [393] (Scheme 20.66).



Scheme 20.66

20.3.5.5 Reactions with Reducing Reagents

Treatment of 1,2,4-triazines and their 3-oxo derivatives with reducing agents such as Raney nickel, sodium borohydride, titanium(III) chloride, hydrogen and palladium catalyst, or electrochemical reduction affords dihydro and further tetrahydro-1,2,4-tetrazine derivatives [290, 310, 394, 395]. In the case of oxo derivatives reduction occurs in the triazine ring, affording dihydrotriazinones that can further yield tetrahydotriazinones or imidazoles [395, 396].

1-Methyl-3,5,6-triphenyl-1,2,4-triazinium iodide reacts with zinc in acetic acid to yield 2,4,5-triphenylimidazole and methylamine, probably through 1,2-dihydro-triazine [310].

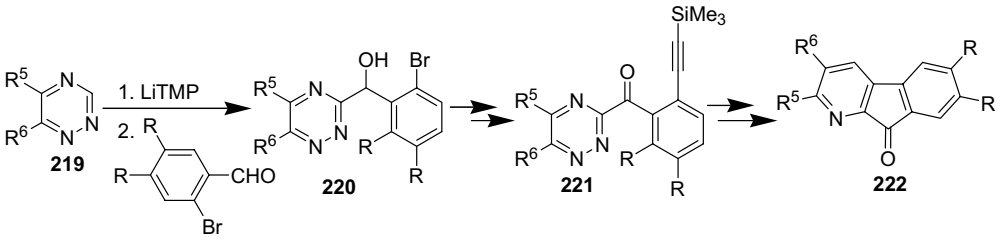
Deoxygenative versus vicarious nucleophilic substitution of hydrogen in reactions of 1,2,4-triazine-4-oxide with α-halocarbanions has been described [397].

20.3.5.6 Reactions with Oxidizing Reagents

Oxidation of 1,2,4-triazines can follow different ways, yielding several derivatives. Thus, oxidation at nitrogens of the heterocyclic ring affords mainly 1- or 2-N-oxide derivatives, whereas oxidation at the triazine ring occurs first at the 5-position and then at 6-position, affording 5-oxo or 5,6-dioxo derivatives. Dihydro-1,2,4-triazines can be oxidized to the corresponding aromatic derivatives; *p*-benzoquinone is one of the best reagents for this purpose.

20.3.5.7 Relevant Examples

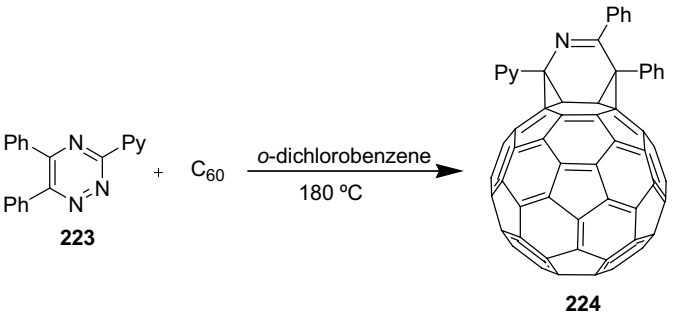
A metallation and intramolecular inverse Diels–Alder strategy may open up a short pathway for the synthesis of various fluorenones; in this way, 1,2,4-triazine **219** (Scheme 20.67) reacts with LiTMP, followed by addition of several 2-bromobenzal-



Scheme 20.67

dehydes to give **220**. Several transformations led to **221**, which upon intramolecular Diels–Alder reactions in triisopropylbenzene and desilylation under TBAF-conditions resulted in 1-azafluorenones **222** [398].

A Diels–Alder reaction takes place when 3-(2-pyridyl)-5,6-diphenyl-1,2,4-triazine (**223**) reacts in a thermal liquid-phase with fullerene C_{60} to afford aza open-cage fullerene derivative **224**, which has an eight-membered-ring orifice in the fullerene cage [399] (Scheme 20.68).



Scheme 20.68

20.4 1,3,5-Triazines

20.4.1 Relevant Computational Chemistry, Physicochemical and Spectroscopic Data

1,3,5-Triazines have been studied extensively both theoretically and experimentally. The 1,3,5-triazine ring is known as an important conjugated heterocycle whose electronic properties are expected to show subtle differences from those of benzene due to the alternate replacement of CH groups by nitrogen atoms.

The IR and Raman spectra of 1,3,5-triazine have been determined [400–407]. Likewise, different approaches for the calculation of a force field for this molecule have been accomplished [407–412]. The analysis gave: C−N bond length = 1.338 Å, C−H = 1.106 Å, CNC bond angle = 113.9°, NCN = 126.1°, HCN = 116.9°. The geometries of **3** and its protonated form have been fully optimized at STO-3G, 3-21G levels [413]. *Ab initio* calculations of the electronic spectra of 1,3,5-triazine have been determined via the complete active space method (CASSCF). This method describes the major features in the electronic structure of the excited state of **3** [414]. More recently, the molecular structure of 1,3,5-triazine ($^{12}C_3{}^{14}N_3H_3$) and its isotopomers ($^{12}C_3{}^{15}N_3H_3$, $^{13}C_3{}^{14}N_3H_3$, $^{13}C_3{}^{15}N_3H_3$ and $^{12}C_3{}^{14}N_3D_3$) in gas, solution and crystal phases and by *ab initio* calculations (6-31G*, 6-311G**) has been studied. By combining gas- and solution-phase data in a single analysis a very precise structure has been obtained, with final parameters values ($r_\alpha{}^\circ$) of r(C−N) 133.68(1) pm,

r(C−H) 108.9(2) pm, and <(CNC) 113.82(9)° [415]. The photodissociation of *sym*-triazine has been widely studied [416–424].

A computational study of the stability, homodesmotic stabilization energy, electron distribution and magnetic ring current of 1,3,5-triazines has been described [53]. Recently, density functional theory has been used to study the geometries, electronic structure, harmonic vibrational frequencies and high energy density material properties of 1,3,5-triazines [425]. The heat of formation of 1,3,5-triazine has been calculated [61, 146]. The calculated energies for the addition of one equivalent of hydrogen suggest that 1,3,5-triazine has lower resonance energy than benzene, pyridine, pyrazine and pyrimidine, which have essentially the same resonance energy [426]. Photoelectron spectra of 1,3,5-triazines have been recorded [427] and the parent compound **3** shows five major bands [428].

Creuzet and Langlet have employed *ab initio* and semi-empirical calculations in a comparative study of the structural parameters for 1,3,5-triazine and amino derivatives [429]. The results showed that the introduction of amino groups at the 2- and 4-positions did not distort the ring, AM1 revealed that 2- and 4-amino-substituents affect the bond lengths but the bond angle remains unchanged. *Ab initio* computations of bond dissociation energies of hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) [430] and an *ab initio* study of RDX decomposition mechanisms [431, 432] have been described. Theoretical predictions for 2,4,6-trinitro-1,3,5-triazine have been carried out [433].

Most 1,3,5-triazines are solids at room temperature. Cyanuric acid (**4**), thiocyanuric acid and melamine (**8**) melt above 300 °C due to strong intermolecular hydrogen bonding. 1,3,5-Triazines decompose to hydrogen cyanide under thermal ($T > 600$ °C) and photochemical conditions.

X-Ray crystallographic studies have been used to obtain the molecular dimensions of 1,3,5-triazines. The C−N bond length has been reported as 1.319 Å with CNC and NCN bond angles of 113.2° and 126.8°, respectively. The presence of substituents has little effect on the bond lengths or bond angles [434].

Cyanuric acid (**4**) has C−N, C−O and N−H bond lengths of 1.37, 1.22 and 0.9 Å respectively. The CNC and NCN bond angles have been reported to be, respectively, 124.6° and 115.4°. An X-ray analysis confirms the predominance of the triketo form. The molecule is hydrogen bonded and the bond lengths are 2.77–2.80 Å [435]. 2,4,6-Trihydrazino-1,3,5-triazine molecules are hydrogen bonded; the shortest hydrogen bond is particularly close, 2.83 Å [436].

An X-ray crystal structure determination of 2,4-diphenyl-6-(2-hydroxyphenyl-4-methoxyphenyl)-1,3,5-triazine has been carried, out together with absorption and emission spectra and ^{1}H and ^{13}C NMR studies, as this compound can be employed to inhibit the photodegradation of polymers. These studies have established the intramolecular hydrogen bond in this type of 1,3,5-triazines for the solid state [437].

The reader is referred to the *Cambridge Structural Database* for further structure determinations of 1,3,5-triazines.

The ^{1}H NMR spectra of 1,3,5-triazines are quite simple, as expected [438–444]. The chemical shifts of the ring protons are 1 to 2 ppm downfield from benzene protons, due to the effect of the ring nitrogens. The presence of electron-releasing substituents

leads to slight upfield shifts. The parent compound **3** shows one signal in the ^{1}H NMR spectrum at 9.25 ppm [438].

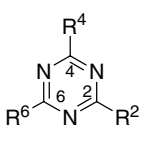
^{1}H NMR of dihydrotriazines has been used to examine the position of the NH protons [445]. Structural determination and a study of the dynamic behavior of 2-chloro-4,6-bis(pyrazolylamino)-1,3,5-triazines have been carried out by means of ^{1}H and ^{13}C NMR dynamic studies [446].

The ^{13}C chemical shifts of ring carbon atoms of some 1,3,5-triazine derivatives are gathered in Table 20.3.

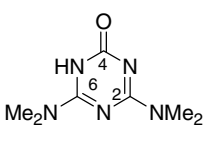
The ^{13}C NMR spectrum of **3** shows a peak at 166.1 ppm. The introduction of a methyl group at position 2 results in a deshielding of 10 ppm. The ^{13}C NMR spectrum of cyanuric acid (**4**) shows only one signal whilst the spectrum of **230** shows two broad signals at 165.32 ppm and 157.19 ppm with a sharp peak at 160.09. This indicates a keto-enol tautomeric exchange process [442]. The room temperature proton decoupled spectrum of **227** displays three distinct signals for the triazine ring, indicating non-equivalence of C(2) and C(4) due to the hindered rotation of the C(6)–NHEt bond at room temperature [447].

The ^{15}N NMR spectrum of the parent compound **3** shows a unique signal at 98.5 ppm (relative to nitromethane) [454, 455], which reflects the high π-electron density at the nitrogens. This chemical shift ranges from 95.3 to 106.1 ppm, depending on the solvent used [456]. Table 20.4 shows ^{15}N chemical shifts of some 1,3,5-triazine derivatives.

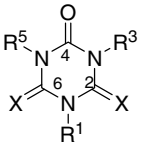
Table 20.3 ^{13}C NMR data of 1,3,5-triazines ($CDCl_3$).



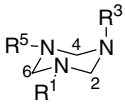
A



B



C



D

	Compound	C2 (δ, ppm)	C4 (δ, ppm)	C6 (δ, ppm)
A	$R^2 = R^4 = R^6 = H$ (**3** [446])	166.1	166.1	166.1
A	$R^2 = R^4 = R^6 = OH$ (**4** [442])	149.8	149.8	149.8
A	$R^2 = R^4 = R^6 = Cl$ (**6** [442])	172.5	172.5	172.5
A	$R^2 = Me$, $R^4 = R^6 = H$ (**225** [446])	176.7	165.8	165.8
A	$R^2 = Ph$, $R^4 = R^6 = H$ (**226** [446])	171.2	166.3	166.3
A	$R^2 = R^4 = Cl$, $R^6 = NHEt$ (**227** [447])	169.2	170.8	165.4
A	$R^2 = R^4 = CF_3$, $R^6 = CCl_3$ (**228** [448])	161.6	161.6	164.0
A	$R^2 = R^4 = CF_3$, $R^6 = NH_2$ (**229** [449])	166.6	166.6	168.9
B	(**230** [440])	160.1	157.2	165.3
C	$R^1 = Me$, $R^3 = R^5 = H$, X = O (**231** [450])	149.0	148.3	149.0
C	$R^1 = Ph$, $R^3 = R^5 = H$, X = S (**232** [451])	177.8	143.0	177.8
D	$R^1 = {}^{t}Bu$, $R^3 = R^5 = Me$, (**233** [452])	70.2	77.8	70.2
D	$R^1 = R^3 = R^5 = {}^{i}Pr$, (**234** [453])	74.7	74.7	74.7

Table 20.4 ^{15}N NMR data for 1,3,5-triazines[a)].

	Compound	N(1) N(2) N(3) (δ, ppm)
A[b)]	$R^2 = R^4 = R^6 = H$ (**3** [455])	98.5[c)]
A	$R^2 = R^4 = R^6 = Cl$ (**6** [457])	110.6[c)]
A	$R^2 = R^4 = R^6 = F$ (**235** [457])	168.8[c)]
A	$R^2 = R^4 = R^6 =$ 1-pirazolyl (**236** [458])	173.9[d)]
A	$R^2 = R^4 = R^6 =$ 1-imidazolyl (**237** [458])	158.2[d)]
A	$R^2 = R^4 = R^6 =$ 1-triazolyl (**238** [458])	160.3[d)]
A	$R^2 = R^4 = R^6 =$ 1-benzaimidazolyl (**239** [458])	157.0[d)]

a) Referenced to NO_2CH_3.
b) See Table 20.3 for structure.
c) $CDCl_3$ as solvent.
d) CF_3CO_2H as solvent.

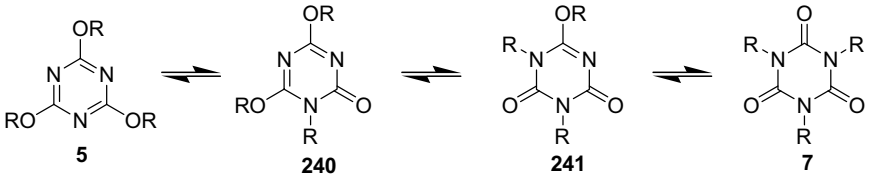
^{15}N NMR spectroscopy has been used to study internal rotation and structural information in the solid state of 2,4,6-tris(amino)-1,3,5-triazines [459], thione-thiol tautomerization in the solid state and acetone solution of 6-[(4-vinylbenzyl)propylamino]-1,3,5-triazine-2,4-dithione (VBATDT) [460] and ^{15}N–^{1}H couplings in natural abundance in the nematic phase [461]. Some ^{35}Cl NMR [462] and ^{19}F NMR [463] studies in halogen derivatives of 1,3,5-triazine have been carried out.

Mass spectra of 1,3,5-triazine (**3**) show the molecular ion (*m/z* 81) as base peak. The major fragments (*m/z* 54 and 27) are formed by the stepwise loss of two molecules of hydrogen cyanide. Aryl-1,3,5-triazines show molecular ions with base peaks of the aryl cyanide ions [464, 465]. The spectra of cyanuric chloride (**6**) and other chloro-1,3,5-triazines are characterized by either loss of a chlorine atom or ring cleavage with elimination of cyanogen chloride [466].

The UV spectrum of 1,3,5-triazines has been reported in a review [37]. The UV absorption of the parent **3** shows two bands, at 272 and 222 nm, assigned as n-π^* and π–π^* transitions, respectively. The UV spectra of 1,3,5-triazine derivatives that contain π-electron donors have also been studied [467]. The presence of substituents that can conjugate with the triazine ring results in the expected bathochromic shift and the band may be very intense [468].

20.4.2 Tautomerism

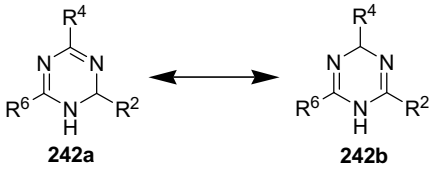
The tautomerism of 1,3,5-triazines has been reviewed [469]. ^{1}H NMR, IR, UV, and X-ray studies have shown that cyanuric acid exists in the trioxo form. Although the cyanurates **5** and isocyanurates **7** are the two major derivatives, compounds with both types of functional groups present in the same molecule are possible (Scheme 20.69). In general, triazine derivatives bearing oxygen or sulfur atoms at 2-, 4-, and/or 6-positions exist in the oxo/thioxo instead of the OH/SH form. In contrast melamine (**8**) exists mainly in the triamino form.



Scheme 20.69

The hydroxy tautomer of 2,4,-diamino-6-hydroxy-1,3,5-triazine predominates in the gas phase. *Ab initio* calculations found the hydroxyl tautomer to be 4.82 kcal mol^{-1} lower in energy than the carbonyl one [470].

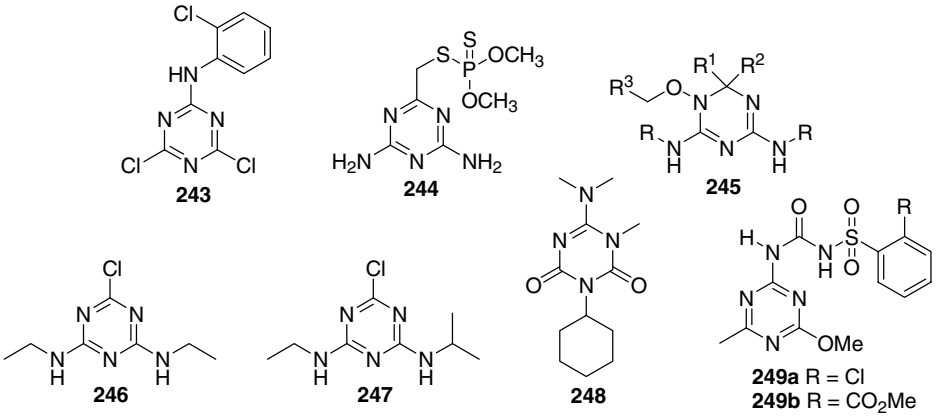
Prototropic tautomerism of dihydro-1,3,5-triazines has been studied by means of ^{1}H NMR, UV, and IR techniques [445]. The existence of the two possible tautomers, 1,2-dihydro (**242a**) and 1,4-dihydro (**242b**) (Scheme 20.70), in an equilibrium mixture of both tautomers, with a ratio of 2 : 1 in favor of the 1,2-dihydro form, has been confirmed by ^{1}H NMR spectroscopy.



Scheme 20.70

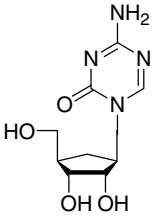
20.4.3
Relevant Natural and Useful Compounds

One of the most important applications of 1,3,5-triazines is in the agricultural field as fungicides, insecticides and herbicides. Some representative examples include Anilazine (**243**) as fungicide, Menazon (**244**) [471] and *N*-oxydihydrotriazines (**245**) [472] as insecticides and Simazine (**246**), Atrazine (**247**), Hexacinone (**248**), Chlorsulfuron (**249a**), Metsulfuron (**249b**) [473], Dipropetryn, Prometon, Prometryn, Propazine, Simetryn, Thifensulfuron-methy, Trietazine and Cyanazine as herbicides.

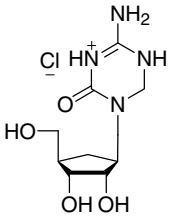


1,3,5-Triazines are also important as pharmaceuticals [474–477] and are claimed as antibacterial (5-Azacytidine, Sulfasymazine), antimalarial (Cycloguanil), antiprotozoal (Melarsoprol), antispasmodic (Hydramitrazine), antitrypanosomal (Antiprotozoal), antiulcerative agents (Irsogladine), antineoplastic (Triethylenemelamine; Altretamine) and to possess diuretic properties (Amanozine, Chlorazanil).

5-Azacytidine (**250a**) exhibits cancerostatic, bacteriostatic and mutagenic properties. It is incorporated into both RNA and DNA, and it disrupts protein synthesis, probably through its incorporation into RNA [478]. It has proved particularly effective against myelogeneous leukemia [479, 480] but the full clinical use of the drug has been limited by its facile hydrolysis. The dihydro derivative **250b** is more stable and shows potential as an antitumor drug [481].

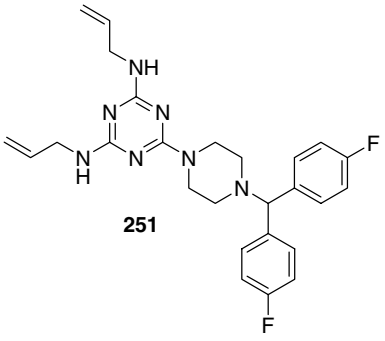


250a



250b

Almitrine (**251**), which is useful in respiratory problems, served as the lead compound to develop triazine derivatives as potent modulators of multidrug resistance in cancer therapy [482]. On the other hand, Melarsoprol (**252**) (Mel B, Arsobal, Aventis), another derivative of melamine, is one of the drugs licensed for the treatment of sleeping sickness [483]. An extensive range of 1-aryl substituted 2,4-diamino-1,6-dihydro-6,6-dimethyl-1,3,5-triazines have shown potent antimalarial activity, such as Cycloguanil (**253**) [484]. Triazinetriones are an important class of molecules with pharmaceutical [485–487] and agricultural utility [488–490]. An example of such biologically interesting derivatives is toltrazuril (**254**). Compound **255** (TPT) is a new and mild esterification agent for the preparation of penicillin and cephalosporin ester [491]. This esterification procedure has been successfully applied to the industrial production of diphenylmethyl 6β-(4-toluamido)penicillate, an important intermediate for the production of Shionogi β-lactam antibiotics Lactamoxef, Flomoxef and Ceftibuten. The use of **255** is safer and more economical on a large scale with a better product yield than other known esterification procedures. 1,3,5-Triazine-2,4-dithione derivative **256** (VBATDT) is an important dental material [460].



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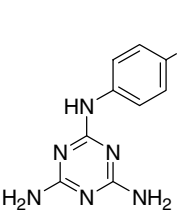

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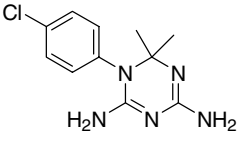

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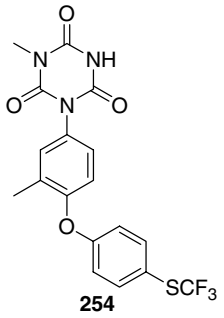
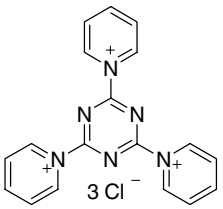
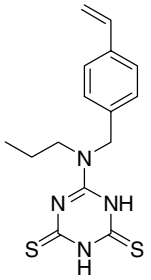


254



255 (TPT)

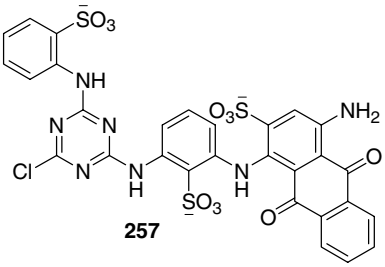


256 VBATDT

1,3,5-triazine derivatives are important reagents for the synthesis of peptides [492–495]. High-loading resins functionalized with 1,3,5-triazine dendrimers can be used as scavenger resins for combinatorial chemistry [496, 497]. 1,3,5-Triazines have been used to form new classes of star-shaped discotic liquid crystals (LC) for potential nonlinear optical applications [498–502]. Substituted 1,3,5-triazines have been used as chiral solvating agents for chiral discrimination [503–506]. For the separation of (+) and (−) isomers of amino acids by HPLC, bis[carbamoyl](alkyl)methylamino]-6-chloro-1,3,5-triazine derivative can be used as stationary phase [507]. Transition metal complexes of 2,4,6-trimercapto-1,3,5-triazine (TMT) can be used as precursors of nanoparticulate metal sulfides [508].

Melamines are an important class of organic compounds since they have shown a wide range of biological activities such as anti-angiogenesis [509], anti-tumor activity for breast [510, 511] and ovarian [475] cancer treatment, effective treatments for menopausal symptoms and postmenopausal osteoporosis [512, 513] and anti-metastatic activities [514]. Melamine and its polymers have application in many industrial fields. The major uses of the resins are in the formation of high-pressure laminates for home furniture, as moldings for crockery and in finishing textiles, to improve crease resistance, and as coatings for wet strength paper. Polymer gels containing melamine derivatives are stable catalytic systems [515]. Melamine derivatives bearing a guanidinium ion can recognize nucleotides through hydrogen bondings [516]. Melamine derivatives bearing thiourea and thiouronium ions have been prepared as flavin receptors [517]. Trichloromelamine is a useful reagent for the selective oxidation of alcohols to the corresponding carbonyl compounds [518].

Cyanuric chloride (**6**) is the precursor of many fiber-reactive dyes [519, 520]. The fiber-reactive dyes are prepared by nucleophilic displacement of one or two chlorines with a dye or dyes, then the product is bound on to the textile by displacement of the third chlorine with the hydroxyl group in cellulose fiber or with amino functions in polyamide, silk and wool. Cibacron blue 3GA (**257**) and Procion scarlet MXG (**258**) are typical examples of reactive dyes.



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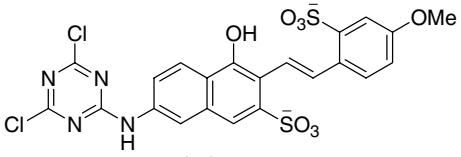


258

Cyanuric chloride has been loaded on different types of NH_2-functionalized resins [521, 522]. This reagent has been used for the solution-phase synthesis of different amides [521, 522] and dipeptides [522, 523]. Cyanuric chloride is used as a coupling reagent in the formation of macrocyclic lactones [524] and β-lactams [525, 526]. In addition, it has been employed as condensing agent in several reactions to utilize mild conditions such as Beckmann transformation of ketoxime into amides and aldoximes into nitriles [527]; the transformation of carboxylic acids to alcohols [528], to Weinreb amides [529] or to diazoketones [530]; the oxidation of alcohols to carbonyl compounds [531, 532]; the selective conversion of primary alcohols into the corresponding esters [533]; and the preparation of sulfonyl chlorides from sulfonic acids [534] or to prepare pyrazoles from ketones [535].

2,4-Dichloro-6-methoxy-1,3,5-triazines have been used to prepare affinity chromatography adsorbents; these compounds are valuable for the purification of enzymes [536]. 2-Chloro-4,6-dimethoxy-1,3,5-triazine has been used as reagent for the synthesis of aldehydes [537], esters [538], amides [539, 540] or oxazolines [541] from carboxylic acids; as coupling agents for cephalosporin derivatives [542]; and to separate an enantiomeric mixture of amides or dipeptides [543].

4-(4,5-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride has been employed as condensing agent for the preparation of amides or esters by coupling between carboxylic acids and amines [544–546] or alcohols [547].

Triallyl cyanurate is used as a minor comonomer with a range of monomers and performed polymers, imparting heat resistance, solvent resistance, adhesion and strength to the polymers. It is particularly valuable for the preparation of high temperature electrical insulation components. It is also used in curing fluoro polymers such as Vinton. Triallyl isocyanurates may be used similarly. 1,3,5-Trichloroisocyanurate is used as a disinfectant of swimming pools.

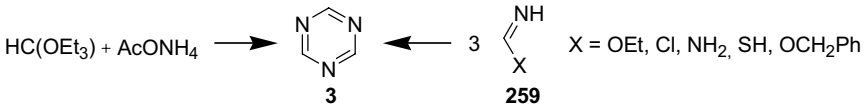
Substituted perhydro-1,3,5-triazines have shown utility as corrosion inhibitors [548], biocides [549], crosslinking agents for the manufacture of polyurethanes [550, 551], stabilizers for natural rubber latex foam and scavengers for the removal of sulfide gases from petroleum fuels.

20.4.4
Synthesis

This section is divided according to the nature of the compounds to be synthesized and not to the class of reactions used.

20.4.4.1 Synthesis of 1,3,5-Triazines and Mono-, Di- and Tri- 2-, 4-, 6-Substituted Derivatives

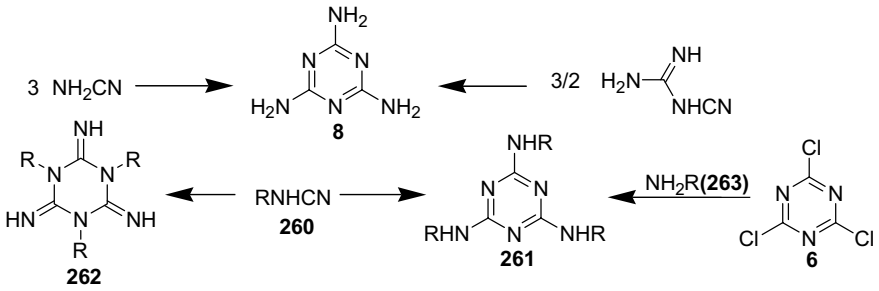
The best method to obtain the parent compound 1,3,5-triazine (**3**) is the reaction of ammonium acetate and triethyl orthoformate described by Maier and Bredereck in 1979 [552] (Scheme 20.71). Various imino derivatives **259** have been used in the synthesis of 1,3,5-triazine (**3**) via a cyclotrimerization reaction.



3 **259**

Scheme 20.71

Melamine (**8**) is synthesized from cyanimide on heating above its melting point or by fusing dicyanamide [553] (Scheme 20.72). Substituted cyanamides **260** react to afford either the expected 1,3,5-triazine derivative **261** [554, 555] or their imino isomers **262** [554]. On the other hand, nucleophilic displacement of chlorine atoms of cyanuric chloride is the most useful method to obtain symmetrical 2,4,6-trisubstituded-1,3,5-triazines. Thus treatment of **6** with different amines [556–558] or arylamine **263** [558–561] affords 2,4,6-trisubstituded-1,3,5-triazines **261**.



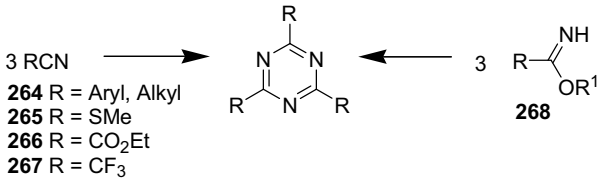
8 **262** **261** **6**

Scheme 20.72

Trimerization of cyanogen chloride in the gas phase on activated charcoal is probably the most useful industrial route to obtain cyanuric chloride (**6**) [562]. Trimerization of isocyanates, isothiocyanates and carbodiimides lead to isocyanurates (**7**), isothiocyanurates and =NR derivatives of compound **262**, respectively [563].

Cyanuric acid (**4**), cyanurates (**5**) and thiocyanuric acid can be synthesized by treatment of cyanuric chloride (**6**) with acetic acid, alcohols in basic medium or sodium sulfide, respectively. The reaction of cyanuric chloride with hydroxyaryl(alkyl) compounds affords 2,4,6-triaryl(alkyl)oxy-1,3,5-triazines (**5**) [557, 564, 565].

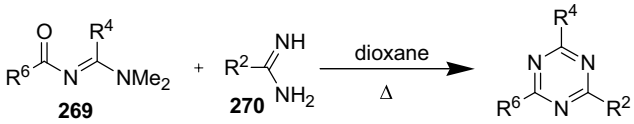
Cyclotrimerization of aryl [555, 566, 567] or alkyl [555, 557] nitriles **264**, thiocyanates [555] **265**, ethyl cyanoformate [237] **266**, trifluoroacetonitrile **267** [568], or imidates **268** [569] yields symmetrical 2,4,6-trisubstituted-1,3,5-triazines (Scheme 20.73).



Scheme 20.73

The use of solvent-free reactions is an alternative in organic synthesis to eliminate substances hazardous to human health and environment [570]. In the literature, methods of synthesis of tris(aryl)-1,3,5-triazines by cyclotrimerization of aromatic nitriles in solvent-free conditions have been described [566, 571].

Unsymmetrical 2,4,6-substituted 1,3,5-triazines are formed in different ways. The condensation of imidates or acylamidines with amidines proved an excellent route to obtain 6-substituted 2,4-dialkyl-1,3,5-triazines. 2,4,6-Substituted 1,3,5-triazines are synthesized conveniently by the reaction of acylamidines **269** with amidines **270** [572] (Scheme 20.74).

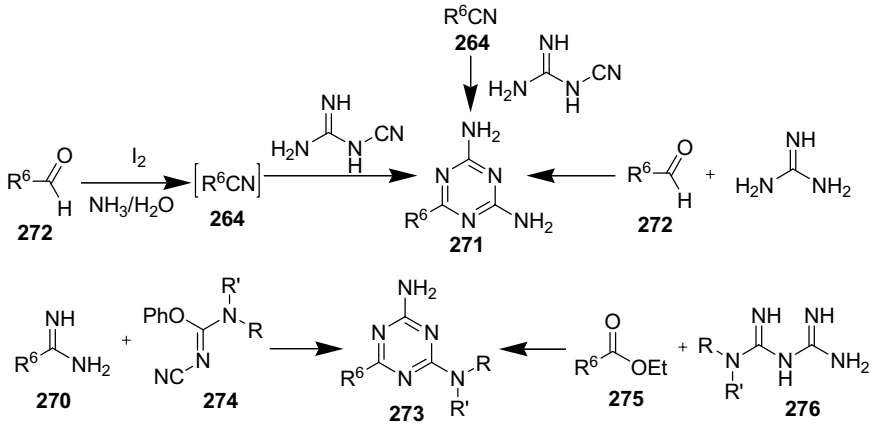


Scheme 20.74

In general, the best routes available to obtain trisubstituted 1,3,5-triazines are substitution reactions of chlorine atoms of cyanuric chloride with different nucleophiles [207, 497, 522, 556, 565, 573–583]; it is possible to substitute one, two or three selectively (Section 20.4.5.3).

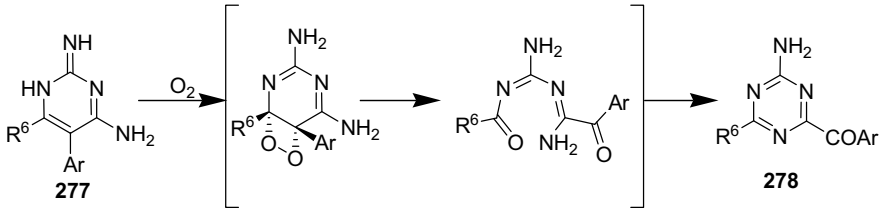
2-Amino-1,3,5-triazines can be obtained by treatment of 1,3,5-triazine (**3**) with 1-amidinopyrazole. However, they are best prepared by reaction of triformamidomethane with formyl guanidine [38]. 2-Amino-4,6-bis(disubstituted-amino)-1,3,5-triazines can be obtained in one pot from disubstituted cyanamindes and formamides [584].

6-Substituted 2,4-diamino-1,3,5-triazines **271** have been prepared by reaction of dicyandiamide with nitriles **264** under microwave irradiation [585–587]. This method can be considered as a green procedure due to the reduction in the use of solvents during synthesis and purification (Scheme 20.75). Various aldehydes **272** reacted with iodine in ammonia/water to give the nitrile intermediates **264**, which have been trapped by addition of dicyandiamide to produce **271** [588]. Aldehyde **272** also reacts with guanidine to give diaminotriazine **271** [589]; this method was employed to protect aldehydes. Diamino-1,3,5-triazines **273** have been synthesized from amidines **270**, which are readily prepared from the corresponding phenylacetonitriles, and isoureas **274** [577] or from carboxylic acid ester **275** with biguanidine **276** [444, 590, 591] (Scheme 20.75).



Scheme 20.75

There are several ways of obtaining unsymmetrical trisubstituted 1,3,5-triazines from other heterocycles, with pyrimidines being the most used starting material. Photosensitized oxygenation of 5-aryl 2,4-diaminopyrimidines **277** in protic solvents affords 4-amino-1,3,5-triazin-2-yl ketones **278** [592] (Scheme 20.76).



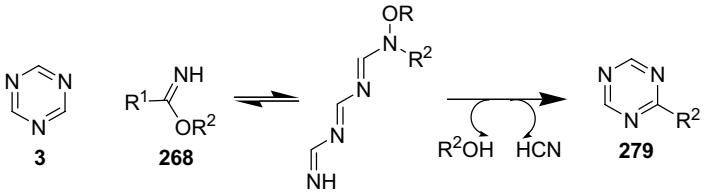
Scheme 20.76

The reaction of chloroacetamidine and phosgene followed by treatment of $POCl_3$ and then H_2/Pd has been used to obtain 2,4-dimethyl-1,3,5-triazine [593]. Muchowski has reported a specific way to prepare 2-dimethylamino-4-trichloromethyl-1,3,5-triazine from trichloroacetonitrile and 4-dimethylamino-4-trichloromethyl-1,3-diaza-1,3-butadiene [594].

Phenyl-1,3,5-triazine [595] and triphenyl-1,3,5-triazine [596] have been obtained by irradiation or electroreduction of 5-phenyl-1,2,4-thiadiazole and 3,4-diphenyl-1,2,5-thiadiazole respectively.

With respect to monosubstituted 1,3,5-triazines, 2-alkyl(aryl) derivatives **279** are prepared by the reaction between 1,3,5-triazine (**3**) and imidates **268** [597, 598] (Scheme 20.77).

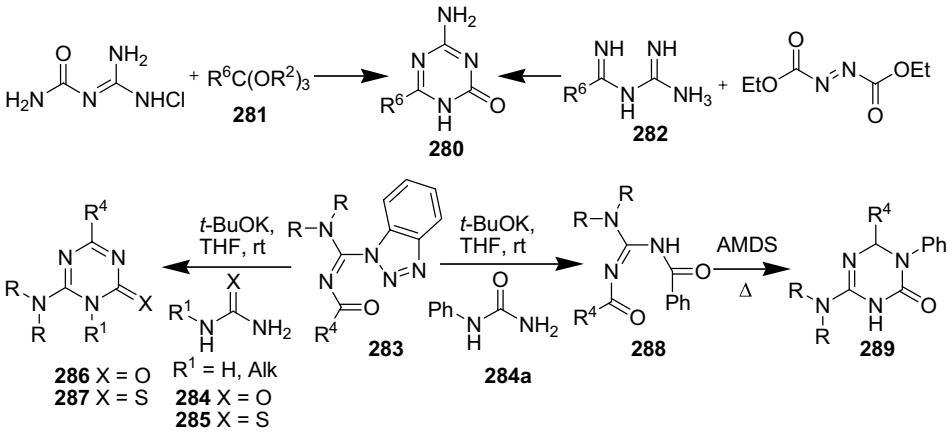
Triazine has elicited considerable interest as an ideal combinatorial library scaffold due to its ease of manipulation and the low price of the starting material, resulting in the publication of several triazine libraries [575, 578, 599–605]. All of the reported library synthesis procedures utilize the reactivity differences of the three reaction sites.



Scheme 20.77

20.4.4.2 Synthesis of 1,3,5-Triazinones and 1,3,5-Triazinthiones

Known synthesis of 4(6)-amino-1,3,5-triazin-2-ones include: cyclocondensation of *N*-carbamoylguanidine hydrochloride with orthoesters **281** [606] (Scheme 20.78); reactions of biguanidines **282** with diethyl azodicarboxylate [607]; reactions of cyanoguanidines with carboxylic acid [608, 609], cyclizations of *N*-acyl-*N*-cyanoguanidines [610], cyclization of isobiurets with ethyl orthoformate [610, 611], reactions of guanylureas with dimethylformamides dimethylacetal [610] and sequential displacements of two chlorine atoms followed by hydrolysis of the third chlorine in cyanuric chloride [556]. More recently, Katritzky and coworkers have described a new method to prepare 4(6)-amino-1,3,5-triazin-2-ones **286** and **289** and 2-thiones **287**, consisting in the reaction of 1-acyl derivatives of 1*H*-benzotriazole-1-carboxamides **283** with ureas **284** or thioureas **285** in the presence of potassium *tert*-butoxide [612] (Scheme 20.78).

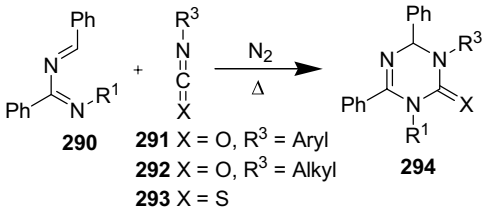


Scheme 20.78

Triazapentadienium iodides react with arylisocyanates or isothiocyanates to give 1,3,5-triazinones and triazinethiones [613]. Cyclization of *N*-acyl-*N*'-carbamoyl-*S*-methylisothioureas affords 1,3,5-triazin-2-ones [572].

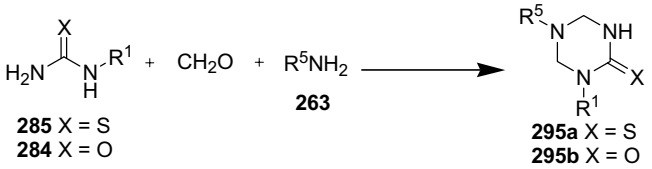
Cycloaddition reactions of 2,4-diphenyl-1,3-diazabuta-1,3-dienes **290** with aryl isocyanates **291**, alkyl isocyanates **292** and isothiocyanates **293**, in a sealed tube

under nitrogen atmosphere without solvent, afford various 1,3,5-triazin-2-one and 2-thione derivatives **294** [614] (Scheme 20.79).



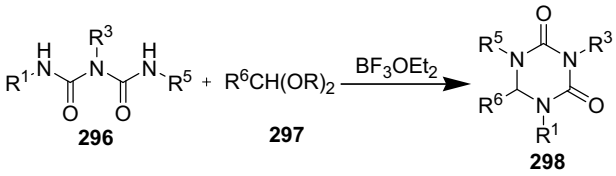
Scheme 20.79

Hexahydro 1,3,5-triazin-2-thione **295a** can be prepared by aminomethylation of thioureas **285** with formaldehyde and aromatic/heterocyclic amines **263** [615] (Scheme 20.80). This reaction can be performed under microwave irradiation [616]. 1,3,5-Triazin-2-ones **295b** can be obtained by a multi-component condensation of substituted ureas **284**, aqueous formaldehyde and substituted amines **263** under microwave irradiation [616, 617] (Scheme 20.80).



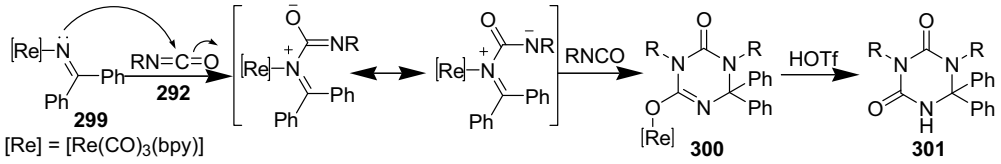
Scheme 20.80

In general, hexahydro 1,3,5-triazine-2,4-dione derivatives **298** are obtained by cyclocondensation of biurets **296** with aldehyde acetals **297** in the presence of boron trifluoride etherate [618] (Scheme 20.81). The reaction of carbomethoxy *O*-methyl-isoureas with isocyanates is another general way to obtain 1,3,5-triazinediones [619].



Scheme 20.81

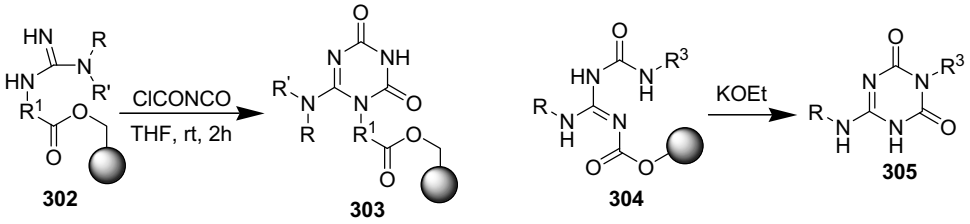
Metal complex **299** reacts with two equivalents of alkyl isocyanates **292** to yield complex **300**. Reaction of **300** with triflic acid (HOTf) cleanly gives demetallated 1,3,5-triazine-2,4-diones **301** [620] (Scheme 20.82)



Scheme 20.82

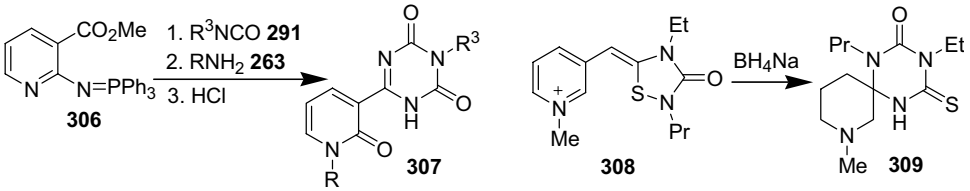
A novel route to synthesize 1,3,5-triazin-2,4-diones consists in the desulfurization of thiocarboamides, such as 1,3-disubstituted 2-thioureas, trisubstituted thioureas and N-substituted thioamides, by silver cyanate [621]. A new synthetic method to afford 6-aryl-1,3,5-triazine-2,4-diones lies in the reaction of *N-t*-butylbenzamidines with diphenyl imidodicarboxylate [622].

Several papers have described the solid-phase synthesis of 6-amino-1,3,5-triazine-2,4-diones. Scheme 20.83 shows two approaches to employ the resin–bound guanidine, **302** and **304**. 6-Amino-1,3,5-triazine-2,4-dione **303** was synthesized utilizing chlorocarbonyl isocyanates [623] while **305** was synthesized via intramolecular cyclization of guanidine **304** with potassium ethoxide [624].



Scheme 20.83

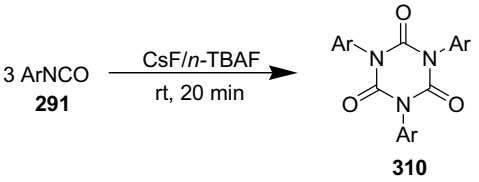
1,3,5-Triazine-2,4-diones **307** have been obtained unexpectedly by intramolecular aza-Wittig reaction of **306** with aryl isocyanate **291** followed by attempted heterocyclization by use of primary amines **263** [625] (Scheme 20.84). Another unexpected reaction was found in the reduction of the methylpyridinium salt **308**, which afforded the piperidine spiro 6-thioxo-1,3,5-triazin-2-one derivative **309** [626].



Scheme 20.84

1,3,5-Triazine-2,4,6-triones can be prepared by cyclotrimerization of isocyanates with several catalysts, such as Lewis bases [627], anions [628] and metallic

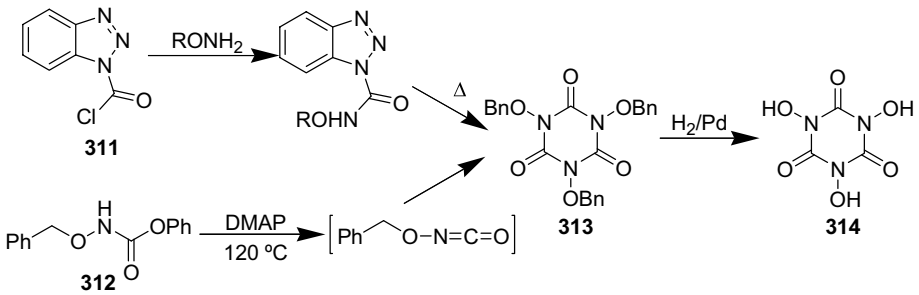
compounds [629, 630]. However, the best catalysts are CsF or tetrabutylammonium fluoride (TBAF). Trimerization of aryl isocyanates **291** with CsF or TBAF as catalyst at room temperature yields triazinetrione **310** [628] (Scheme 20.85). Phenyl isocyanate trimerized in the reaction with $(C_5Me_5)_2Nb(=O)H$ [631]. Zirconacyclopentanes react with *p*-chlorophenyl isocyanate to give the trimerization product [632].



Scheme 20.85

The electrochemical approach of Carelli *et al*. is also a useful procedure to obtain 1,3,5-triazinetriones [633]. This method consists of the cyclotrimerization of aryl isocyanates in the presence of the anionic species generated *in situ* by electrochemical reduction of catalytic amounts of α-bromoesters in dipolar aprotic solvents.

1,3,5-Trihydroxycyanuric acid **314** (THICA) and its alkoxy derivatives can be prepared by several methods [634–637]. Butula and Takac [638] have reported an alternative synthesis of THIC in three steps using 1-benzotriazolecarboxylic acid **311** as a key compound (Scheme 20.86). Recently, a new synthetic route to THICA using benzyloxycarbamic acid phenyl ester **312**, synthesized from *O*-benzylhydroxyamine and phenyl chloroformate, has been developed [639].

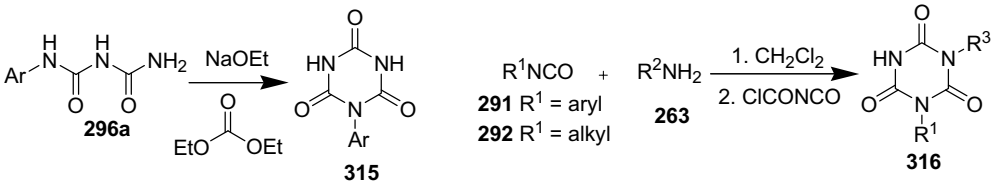


Scheme 20.86

Symmetrical 1,3-disubstituted triazinetriones can be prepared by condensation of two molecules of isocyanates with a metal isocyanate in a dipolar aprotic solvent [640].

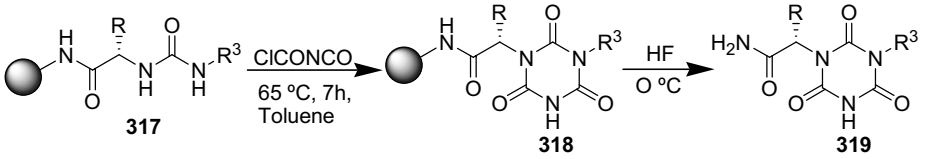
There are few literature reports on the synthesis of asymmetric triazinetriones with two or three different substituents. Kappe and coworkers have synthesized 1-(benzimidazol-2-yl-methyl)-3-phenyl-*s*-triazine-2,4,6-trione from the corresponding urea and *N*-ethoxycarbonyl isocyanate [641]. Biouret **296a** cyclized with NaOEt in EtOH with diethyl carbonate to give 1-aryl-1,3,5-triazine-2,4,6-trione **315** [642]

(Scheme 20.87). Recently, a one-pot synthesis of asymmetric 1,3,5-triazine-2,4,6-triones **316** was developed by loss of an equimolar amount of isocyanate **291**/**292** and primary amine **263** in dichloromethane, followed by addition of *N*-chlorocarbonyl isocyanate [643].



Scheme 20.87

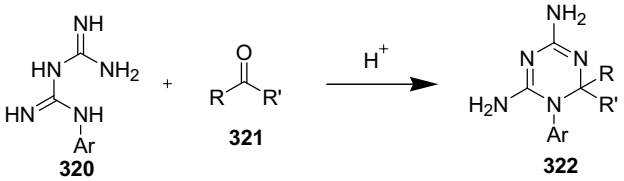
An efficient parallel solid-phase synthesis of 1,3,5-trisubstituded 1,3,5-triazine-2,4,6-triones **319** from chlorocarbonyl isocyanate with resin-bound urea **317** has been reported [644]. Triazinetrione **318** was cleaved from the resin using HF (Scheme 20.88).



Scheme 20.88

20.4.4.3 **Synthesis of Hydro-1,3,5-Triazines**

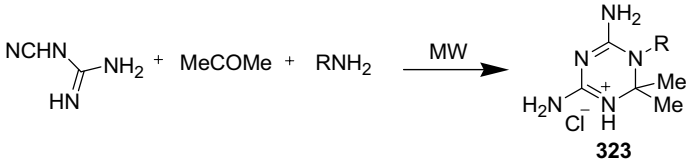
Acid-catalyzed reaction between the corresponding biguanidine and carbonyl compounds is an effective route to obtain 4,6-diamino-1,2-dihydro-1,3,5-triazine [645]. This method has been used to synthesize a solution-phase combinatorial library of 1-aryl-4,6-diamino-1,2-dihydro-1,3,5-triazines **322** from a set of carbonyl compounds **321** and arylbiguanidines **320** (Scheme 20.89) [646, 647].



Scheme 20.89

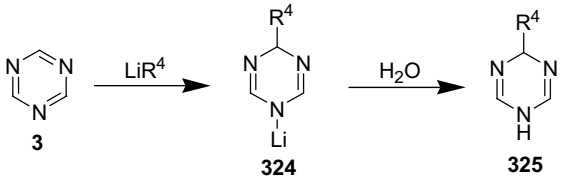
Microwave assisted parallel synthesis of a library of 20 aryl dihydrotriazines **323** was successfully achieved from dicyandiamide, acetone and primary amines [648]

(Scheme 20.90). This reaction can be considered as a cycloaddition of [4 + 1 + 1] fragments. This method decreased the reaction time from an average of 22 h to 35 min in comparison to conventional parallel synthesis.



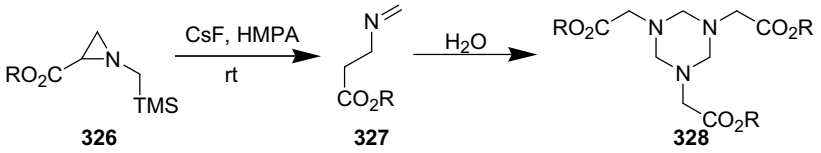
Scheme 20.90

Wakefield and coworkers have described the formation of triphenyl dihydrotriazines by the reaction of 2,4,6-triphenyl-1,3,5-triazine with lithium reagents [649]. Lappert and coworkers have reported the facile synthesis of monosubstituted dihydrotriazines **325** from parent triazine (**3**) and alkyllithium reagent and subsequent protonolysis of the presumed lithio(alkyl)triazines **324** [650, 651] (Scheme 20.91).



Scheme 20.91

Reaction of aziridines **326** with cesium fluoride and HMPA, followed by treatment of intermediate **327** with water, yields triazines **328** [652] (Scheme 20.92).

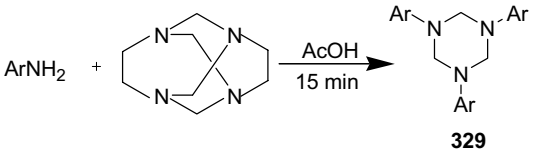


Scheme 20.92

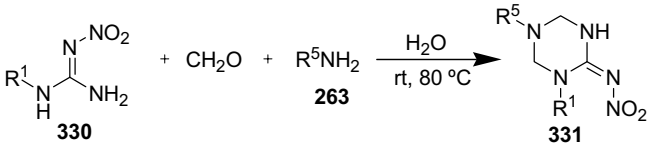
The reaction of aniline derivatives with 1,3,6,8-tetrazatricyclo[4.4.1.1^{3,8}]dodecane affords 1,3,5-triaryl-hexahydro-1,3,5-triazines **329** [653] (Scheme 20.93).

Nitroimino-1,3,5-triazine derivatives **331** are formed via Mannich condensation of nitroguanidine **330**, formaldehyde and the appropriate primary amine **263** [654, 655] (Scheme 20.94).

A general way to obtain 1,3,5-triazinetriimines is the co-trimerization of amines with cyanogen bromide [656, 657].



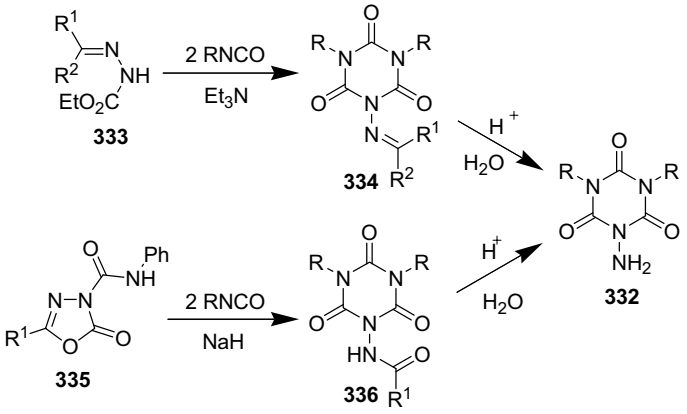
Scheme 20.93



Scheme 20.94

20.4.4.4 Synthesis of N-Amino and N-Oxide 1,3,5-Triazines

N-Amino-1,3,5-triazine derivatives **332** have been synthesized from ethoxycarbonylhydrazones **333** and two equivalents of aryl or methyl isocyanates followed by hydrolysis of intermediate triazine **334** [658] or by transformation of sodium salts of 1,3,4-oxadiazol-2-ones **335** with two equivalents of aryl or ethyl isocyanates and hydrolysis of intermediate **336** [659] (Scheme 20.95).



Scheme 20.95

With respect to the preparation of N-oxide derivatives of 1,3,5-triazines, Shaw has described the oxidation of triazines with peracetic acid and the preparation of 2,6-diamino-4-methyl-1,3,5-triazine *N*-oxides from potassium dicyanoacetamide and hydroxylamine [660]. Formation of triazine *N*-oxides by reaction of amidooxime with ethyl orthoacetate gives poor yields [661].

20.4.5 Reactivity

The reactivity of 1,3,5-triazine (**3**) has been thoroughly reviewed [26, 39, 41, 474, 662] and the chemistry of melamine, cyanuric acid and cyanuric halides has also been reviewed [34, 35, 120, 663]. In general, many of the reactions of 1,3,5-triazines reflect the chemistry of the ring substituents.

20.4.5.1 Thermal and Photochemical Reactions

The parent compound **3** decomposes to form three molecules of hydrogen cyanide on heating above 600 °C. The thermal decomposition of hexahydro-1,3,5-trinitro-1,3,5-triazine has been studied [664]. Thermal isomerization of cyanurates and thiocyanurates to isocyanurates and thioisocyanurates, respectively, is also known [665, 666].

A novel reversible thermal electrocyclic reaction of chiral 1,2-dihydro-1,3,5-triazines has been described [667].

Photodissociation of 1,3,5-triazine to yield hydrogen cyanide is also known [419, 421, 422]. Photolysis of 2-azido-4,6-dichloro-1,3,5-triazine, in a low temperature argon matrix, yields a cyclic carbodiimide containing four nitrogen atoms in a seven-membered ring [668]. Consecutive photolysis of triazido-1,3,5-triazine, in a low temperature nitrogen matrix, has been studied [669, 670]. 2,2,4,6-Tetraphenyldihydro-1,3,5-triazine undergoes photochemical reactions to yield a mixture of six products, among which 2,4,5-triphenylimidazole and 2,4,6-triphenyl-1,3,5-triazine could be identified [671, 672]. The S-chlorination reaction of isothiocyanuric acid under UV-irradiation at −45 °C affords 1,3,5-triazine-2,4,6-trisulfenyltrichloride [673].

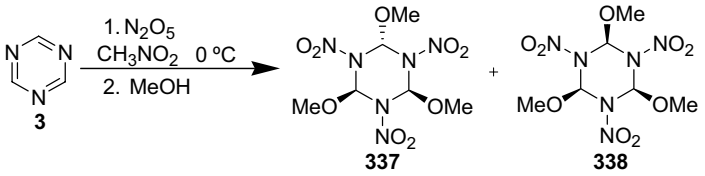
20.4.5.2 Reactions with Electrophilic Reagents

Chlorination and bromination of 1,3,5-triazine occur only under vigorous conditions, bromination being rather more successful. The reactions are probably not electrophilic [35, 39, 43, 320, 674]. Treatment of 1,3,5-triazine with chlorine or bromine at room temperature gives rise to perhalides [43]. Melamine has been halogenated to form products containing one to six halogens, depending on the reaction conditions [35]. Sulfonation or nitration preferentially leads to the ring hydrolysis [39]. Alkyl side chains of 1,3,5-triazine are quite readily α-halogenated by what are believed to be ionic mechanisms [675].

Some examples on the preparation of nitro derivatives of 1,3,5-triazine are found in the literature. Thus, when 1,3,5-triazine is allowed to react with dinitrogen pentoxide, at 0 °C, and quenched with methanol the cis and trans isomers of 2,4,6-trimethoxy-1,3,5-trinitrohexahydro-1,3,5-triazine **337** and **338** can be isolated in equimolar ratio [676] (Scheme 20.96).

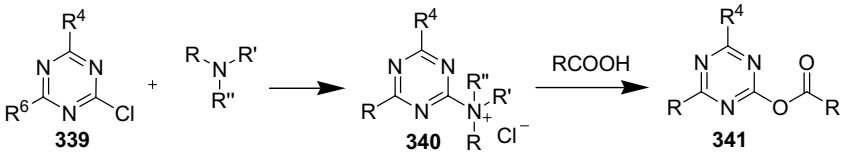
Alkylation of thiocyanuric has been described [565]. Phase-transfer has been employed to catalyze polycondensation of 6-dialkylamino-1,3,5-triazine-2,4-dithiols with 1,10-dibromodecane [677].

Carboxylic acids have been condensed with 1,3,5-triazine by activation of the triazine ring. Thus, chlorotriazine **339** is activated with amine, to give the salt **340** that



Scheme 20.96

reacts with a carboxylic acid to generate the ester **341** [522, 539, 543, 544] (Scheme 20.97).

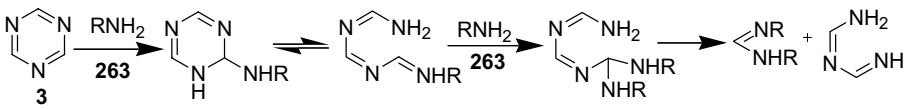


Scheme 20.97

N-Alkylation of 1,3-disubstituted 1,3,5-triazine-2,4,6-triones is well documented [643, 644]. Silylation of the amino groups of melamine and 2,4-diamino-6-substituted-1,3,5-triazines is achieved by reaction with chlorotrimethylsilane and triethylamine in refluxing acetonitrile to give the monosilylated amino derivatives [678].

20.4.5.3 **Reactions with Nucleophilic Reagents**

1,3,5-Triazines are extremely sensitive to nucleophilic substitution, particularly hydrolysis in the presence of even trace atmospheric water [35]. Nucleophilic attack at the aromatic 1,3,5-triazines results in ring cleavage in most cases. The reaction of 1,3,5-triazine **3** with a primary amine is an example of this fact [39] (Scheme 20.98).

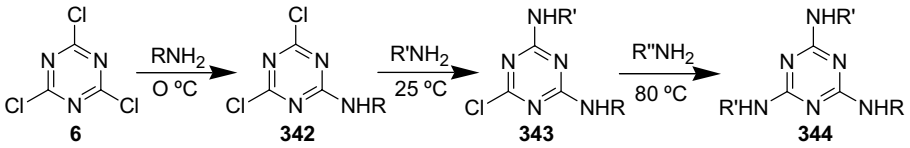


Scheme 20.98

In the Gattermann aldehyde synthesis, 1,3,5-triazine can be used as a substitute for hydrogen cyanide [679]. On treatment of triazine (**3**) with aryl Grignard reagents the corresponding aryl aldehyde is obtained.

Several nucleophilic substitutions of halogen derivatives of 1,3,5-triazines can be found in the literature. The more common method is displacement of chlorine atoms of cyanuric chloride with different nucleophiles. It is possible to obtain mono-, di- or tri-substituted-1,3,5-triazine by controlling the nature of the nucleophiles or the reaction temperature. Thus, 2-amino-1,3,5-triazine **342**, 2,4-diamino-1,3,5-triazine

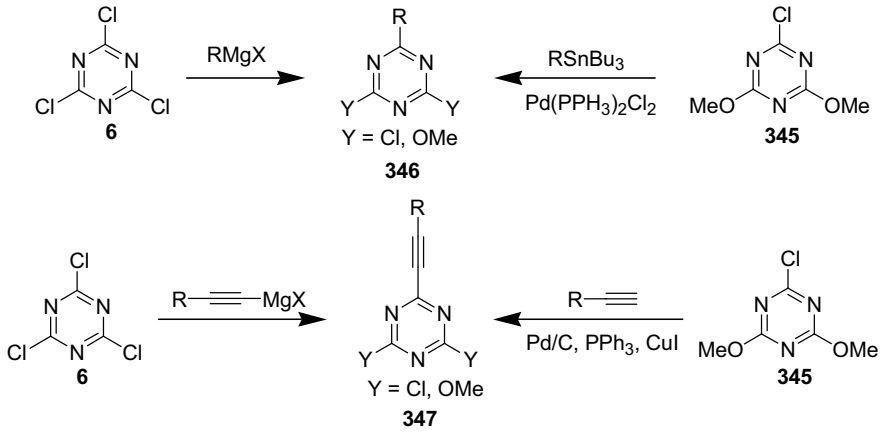
343, or 2,4,6-triamino-1,3,5-triazine **344** can be obtained by sequential addition of amines [497, 558, 577, 578, 580–582, 680, 681] (Scheme 20.99). 2,4-Diamino-1-alkoxy-1,3,5-triazine [565, 578, 579], 2-amino-4-alkoxy-1,3,5-triazine [576, 577], 2-amino-4,6-dialkoxy-1,3,5-triazine [207, 544, 682], 2,4-dialkoxy-1,3,5-triazine [573, 574], and 2,4,6-triaryloxy-1,3,5-triazines [564] have also been described.



Scheme 20.99

Reaction of cyanuric chloride with 1-benzylpyrazole under solvent-free conditions and microwave irradiation yielded, within 10 min, tris-2,4,6-(pyrazol-1-yl)-1,3,5-triazine by a quaternization–dequaternization procedure [683]. This compound has been employed as a 5-connecting building-block for infinite nets [684].

Organometallic alkylations of cyanuric acid (**6**) [577] or 2-chloro-4,6-dimethoxy-1,3,5-triazine (**345**) [685] have been described to afford alkyl-1,3,5-triazines **346** (Scheme 20.100). Alkynyl-1,3,5-triazines **347** have been synthesized by reaction of cyanuric chloride **6** with Grignard reagents [583] or by Pd-catalyzed cross-coupling between alkynes and **345** [686, 687].



Scheme 20.100

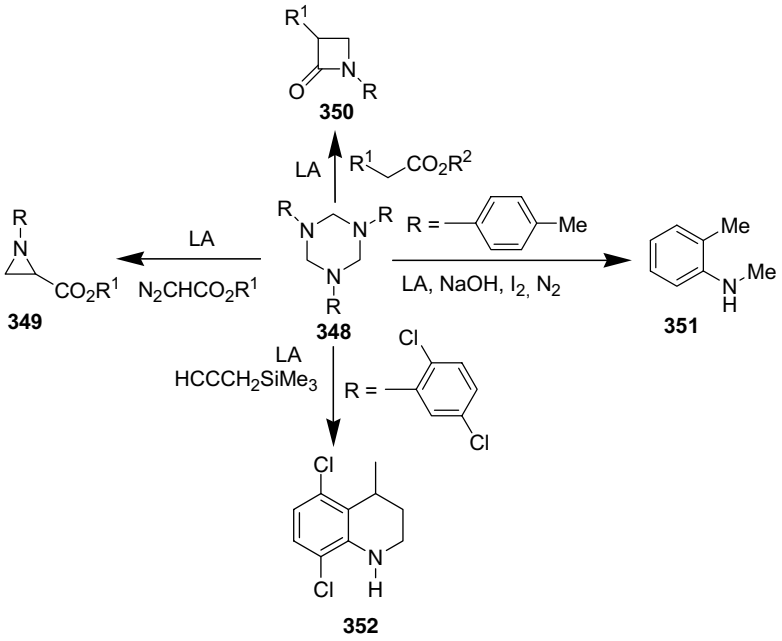
A new synthetic route, via the Suzuki cross-coupling of resin-bound 2,4-diamine-6-chlorotriazines, using various arylboronic acids and palladium catalysts has been developed to prepare a 2,4-diamine-6-aryl-1,3,5-triazine library [604].

Reaction of 2,4,6-trifluoro-1,3,5-triazine and hexafluoropropene yields perfluoro-(isopropyl)-1,3,5-triazines, which react with a range of oxygen nucleophiles [688].

There are other similar reactions to obtain 2,4,6-tris(perfluoroalkyl)- and perfluoroalkylether-1,3,5-triazines from 2,4,6-trihalotriazines [689].

Other substituents than halogen at 2-, 4- and 6-positions may be displaced by nucleophilic reagents. Thus, reactions of 2,4,6-tris[di(*t*-butoxycarbonyl)nitromethyl]-1,3,5-triazine with nucleophiles have been reported [690]. Substitution of an OMe group by a hydrazino group in a methoxyribosyltriazinone has been accomplished [691].

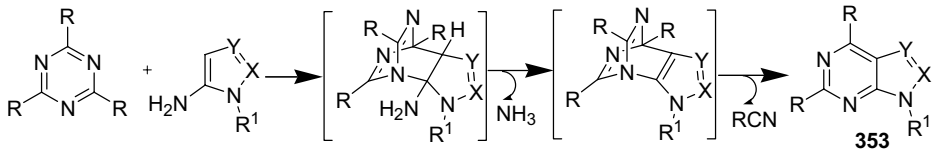
N-Methyleneamine equivalents can be generated *in situ* from hexahydro-1,3,5-triazines **348** (Scheme 20.101) in the presence of a Lewis acid (LA) and reacted with various nucleophiles for the synthesis of aziridine **349** [692, 693], azetidin-2-ones **350** [694, 695], anilines **351** [696, 697], tetrahydroquinolines **352** [697], 5-aminomethyl-dihydrofuran-2-ones [698], and anilinomethylazides [699]. Synthetic applications of N-methyleneamine equivalents were reviewed in 2002 [700].



Scheme 20.101

20.4.5.4 **Cycloaddition Reactions**

1,3,5-Triazines may also undergo inverse electron demand cycloaddition reactions, although in to minor extent compared with 1,2,4-triazines, to yield heterocyclic compounds such as substituted [120] or condensed [701–707] pyrimidines. Theoretical studies [708, 709] of an inverse-electron demand Diels–Alder reaction between amino-substituted heterocycles and 1,3,5-triazines have been described. Scheme 20.102 show the mechanism proposed for this reaction.



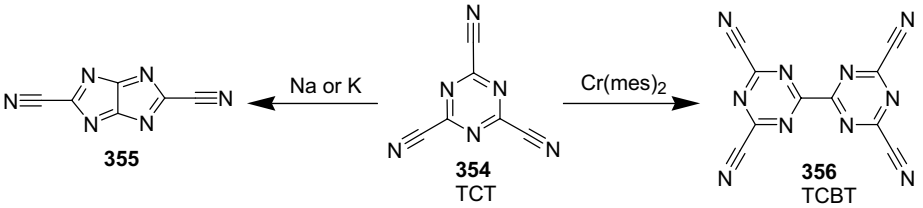
Scheme 20.102

An isocyanurate-containing fullerene has been obtained by [3 + 2]-cycloaddition of 5-[5′-azidopentyl)]-1,3-diallyl-1,3,5-triazine-2,4,6-trione to C_{60} [710].

20.4.5.5 Reactions with Reducing Reagents

A few examples of reduction reactions of 1,3,5-triazines can be found in the literature.

2,4,6-Tricyano-1,3,5-triazine **354** (TCT) undergoes an irreversible one-electron reduction with Na or K to form **355** [711] (Scheme 20.103). Chemical reduction of TCT with strong reducing agents, such as bis(mesitylene)chromium(0), affords the dimerized compound **356** (TCBT) [712, 713] (Scheme 20.103)

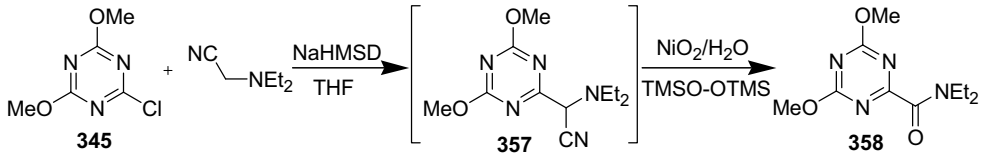


Scheme 20.103

20.4.5.6 Reactions with Oxidizing Reagents

There are few oxidation reactions on the ring of 1,3,5-triazines. Study of the kinetics and energies of one-electron oxidation of 1,3,5-triazines has been published [714].

Oxidation of a substituent cyano group to the corresponding amide has been described recently. One-pot preparation of triazinyl amide **358** via a sequential S_NAr substitution and oxidation has been achieved using diethylaminoacetonitrile as amide synthon. An important advantage of this process is that the oxidation of the intermediate **357** occurs under mild conditions using NiO_2–H_2O in THF at room temperature [715] (Scheme 20.104).



Scheme 20.104

Reactions of substituted 1,3,5- triazines with peroxides [716] and peracids [717] afford the corresponding oxygenated substituents.

Dihydro-1,3,5-triazines are aromatized to triazines on oxidation with potassium permanganate [718].

20.4.5.7 Reactions of Metallated 1,3,5-Triazines

Metallated triazines react with electrophiles to give different substituted derivatives. Chloro-1,3,5-triazines are lithiated using lithium powder and naphthalene in the presence of various electrophiles such as aldehydes and ketones to give, after hydrolysis, the expected substituted triazines. The reaction presumably takes place through the organolithium intermediate [719].

1,3,5-Triazine reacts with lithium alkyl to give 1,4-adducts, which on hydrolysis yielded the first simple 4-substituted 1,4-dihydrotriazines [650]. The reaction of 1,3,5-triazines and lithium amidinate, alkyl- or 1-azaallyllithium affords substituted 1,3,5-triazines [651].

20.5 Tetrazines

Tetrazine chemistry has been extensively reviewed in *Comprehensive Heterocyclic Chemistry I* [4] and *Comprehensive Heterocyclic Chemistry II* [9]. A whole chapter is devoted to 1,2,4,5-tetrazine in *Comprehensive Heterocyclic Chemistry II* [8]. The chemistry of 1,2,3,4-tetrazines has recently been updated in *Chemical Reviews* [44].

Therefore, only the most important relevant data that have appeared since these publications is considered here.

20.5.1 Relevant Computational Chemistry, Physicochemical and Spectroscopic Data

Theoretical calculations of the 1,2,3,4-tetrazine [53] and 1,2,3,5-tetrazines [53, 720] system have been published.

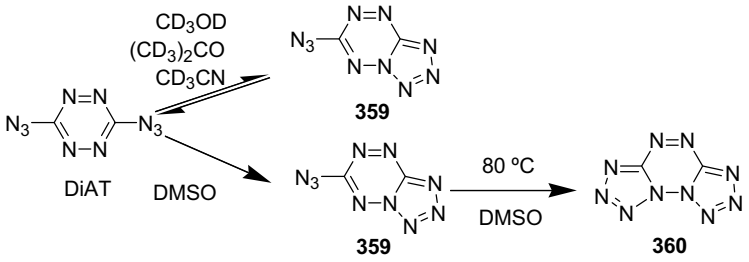
The 1,2,4,5-tetrazine system is the only stable isomer of the three possible tetrazines. Most theoretical studies have dealt with the 1,2,4,5-tetrazine isomer. Fabian and Lewars have described a computational study of the stability, homodesmotic stabilization energy, electron distribution and magnetic ring current of tetrazines [53]. Harmonic [58] and anharmonic [58, 59] frequencies have also been calculated. The electronic spectrum [721–725] and density functional calculations [57, 726–728] have been published. Heats of formation of tetrazines have been calculated [61]. The coordination chemistry of 1,2,4,5-tetrazines and its 3,5-disubstituted derivatives has been described [729].

The X-ray crystallographic analysis of 1,2,4,5-tetrazines derivatives recently reported include: *trans*-3,6-dibenzyl-1,2,4,5-tetrazine 3,6-diphenyl-1,2,4,5-tetrazine [730]; diphenyl 3,6-bis(4-chlorophenyl)-1,2-dihydro-1,2,4,5-tetrazine-1,2-dicarboxylate [731]; 3,6-diphenyl-1,4-bis(*p*-tolylsulfonyl)-1,4-dihydro-1,2,4,5-tetra-

zine [732]; dipropyl 3,6-diphenyl-1,2-dihydro-1,2,4,5-tetrazine-1,2-dicarboxylate [733]; 1-acetyl-3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine [734]; ethyl 3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine-1-carboxylate [735]; 1-acyl-3,6-disubstituted phenyl-1,4-dihydro-1,2,4,5-tetrazines [736]; 3,6-bis(2-chlorophenyl)-1,4-dihydro-1,2,4,5-tetrazine [737]; 3,6-bis(2-pyridinio-1,2,4,5-tetrazine) diperchlorate [738]; 3,6-bis(2-pyridinyl)-1,2,4,5-tetrazine [739]; hexahydro-1,2,4,5-tetrazines [740]; and 1,5-dimethyl-1,2,4,5-tetrazinane-3,6-dione [741].

20.5.2
Tautomerism

Unexpected azido-tetrazolo tautomerizations and irreversible tetrazolo transformation have been studied in a report dealing with 3,6-diazido-1,2,4,5-tetrazine (DiAT), for which an improved synthetic pathway is also provided [742]. DiAT undergoes azido-tetrazolo equilibria in CD_3OD, $(CD_3)_2CO$ and CD_3CN and transforms into tetrazolo isomer **359** in DMSO (Scheme 20.105). The transformation from **359** into **360** only occurs when the temperature is at least 80 °C.



Scheme 20.105

20.5.3
Relevant Natural and Useful Compounds

Recent reports have dealt with the antitumor activity of the 1,2,4,5-tetrazine skeleton [736, 743–751]. On the other hand, 1,2,4,5-tetrazines have demonstrated powerful synthetic utility through their ability to participate in inverse electron demand Diels–Alder reactions, providing access to a wide range of other heterocycles and natural products [30, 752] (Section 20.5.4.2).

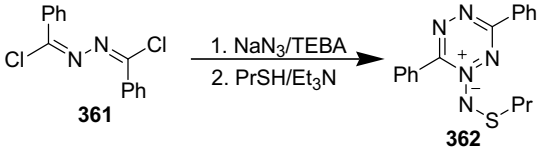
The 1,2,4,5-tetrazine ring system displays unique material properties as well. This electroactive, colored ring system typically exhibits high electron affinity, low lying π^* orbitals and n-π^* transitions in the visible light region – attractive properties for optical and electroactive materials applications [753]. Furthermore, tetrazines also posses high positive heats of formation and crystal densities, properties important in energetic material applications [754, 755].

3,6-Diethyl-1,2,4,5-tetrazine has been employed as unique solvatochromic probe in the Solvent Acidity Scale [756]. 3,6-Diazido-1,2,4,5-tetrazine has been synthesized for the preparation of carbon nanospheres and nitrogen-rich carbon nitrides [757].

20.5.4
Synthesis of 1,2,4,5-Tetrazines

Only recent synthetic methods of tetrazines are commented on here.

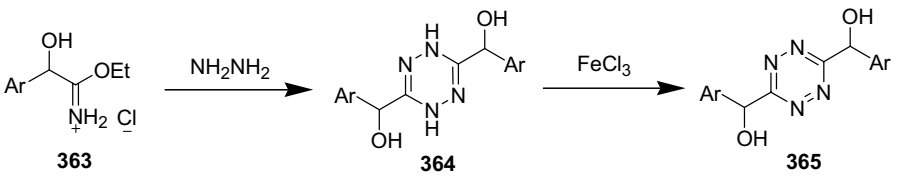
Kaszynski has developed an alternative route to obtain 3,6-diphenyl-1,2,4,5-thiatriazine **362** in a one-pot reaction from a nucleophilic double substitution on dichloride **361** [758] (Scheme 20.106).



Scheme 20.106

3,6-Bis(phenanthrolin-2-yl)-1,2,4,5-tetrazine has been synthesized from the reaction of 2-cyanophenanthroline with hydrazine followed by oxidation with nitric acid in acid acetic [759]. Hydrazine reacts with 4-hydroxybenzimidic acid methyl ester followed by oxidation with sodium nitrite to give 3,6-bis(4-hydroxyphenyl)-1,2,4,5-tetrazine [760]. Aryl nitriles react with hydrazine to form 1,2-dihydro-3,6-diaryltetrazines [761], which are oxidized to 3,6-diaryl-1,2,4,5-tetrazines [753].

Imidate **363** reacts with hydrazine hydrate to afford 1,4-dihydrotetrazine **364**. Deliberate oxidation of **364** has been accomplished by treatment with ferric chloride to provide tetrazine **365** [762] (Scheme 20.107).

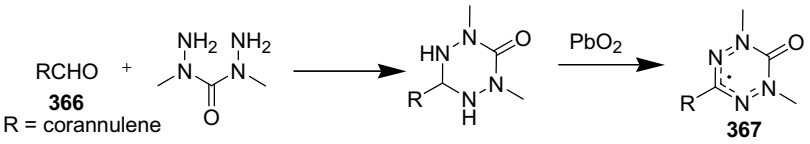


Scheme 20.107

New 1,2,4,5-tetrazines derivatives has been synthesized from substituted nitrilimines and different hydrazines [763–765] or hydrazones [765, 766].

A new neutral oxoverdazyl radical conjugated with the corannulene system has been designed and synthesized for the first time as a stable solid in air [767]. The radical **367** was synthesized by the condensation of aldehyde **366** with

2,4,-dimethylcarbonohydrazide at room temperature followed by treatment with PbO_2 (Scheme 20.108).



Scheme 20.108

The synthesis of 1,5-diisopropyl substituted 6-oxo-verdazyls has been accomplished starting from 2,4-diisopropylcarbonohydrazide bis-hydrochloride. The introduction of isopropyl groups results in free radicals more stable and soluble than their methyl counterparts [768]. 6-(4-Substituted-phenyl)-2,4-diphenylverdazylium salts have been prepared by the reaction of 3-(4-substituted-phenyl)-1,5-diphenylformazans with formaldehyde and different organic and inorganic acids in a two-phase chloroform/water medium by brief and gentle heating [769].

20.5.5 Reactivity of 1,2,4,5-Tetrazines

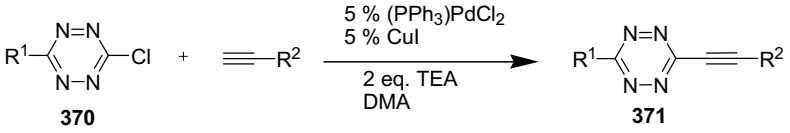
Some examples of the reactivity of 1,2,4,5-tetrazines published since 1995 are described here.

20.5.5.1 Reactions with Nucleophilic Reagents

The electron-deficient aromatic ring of tetrazine and its reactivity towards nucleophiles have been utilized in the preparation of non-symmetrically substituted tetrazines by substitution of leaving groups, such as chloro [770, 771], methylthio [770, 772–775] or dimethylpyridazolyl [755, 757, 776, 777] with nitrogen, oxygen or sulfur nucleophiles. The use of carbon nucleophiles, such as organolithium or Grignard reagents, with 3,6-disubstituted 1,2,4,5-tetrazines **368** led to the addition of an organic group onto a ring nitrogen atom to afford 1,4-dihydrotetrazines **369** [778] (Scheme 20.109).

Scheme 20.109

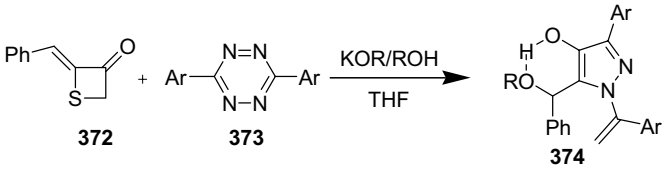
The first cross-coupling reactions in tetrazines have been described: a series of substituted chlorotetrazines **370** were reacted with different terminal alkynes under Sonogashira or Negishi coupling conditions to furnish alkynyl-tetrazines **371** [779] (Scheme 20.110).



Scheme 20.110

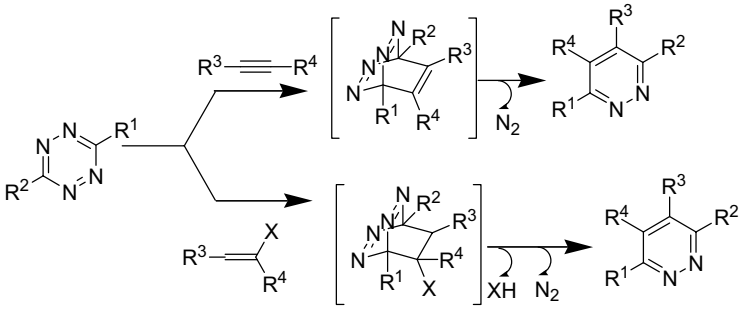
20.5.5.2 **Cycloaddition Reactions**

A simple, yet non-obvious method for the construction of pyrazol-4-ols **374** by a consecutive series of condensation–fragmentation–cyclization extrusion reactions of thietanone **372** with 1,2,4,5-tetrazine **373** has been described [780] (Scheme 20.111).



Scheme 20.111

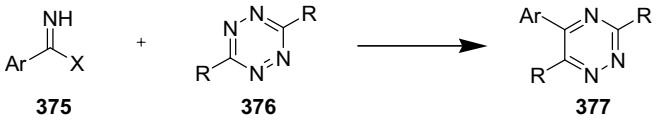
Inverse electron demand Diels–Alder reaction of 1,2,4,5-tetrazines are well known in the literature. Cycloadditions with electron-rich alkynes [759, 762, 774, 776, 781–788] or alkenes [602, 762, 772, 773, 781, 784, 789–792] afford the expected donor-substituted pyridazines (Scheme 20.112). Fused pyridazines have also been obtained [269, 770, 775, 784, 793–802].



Scheme 20.112

1,2,4-Tetrazine **377** can be obtained the from reaction of thioimidate **375** with 1,2,4,5-tetrazine **376** [762] (Scheme 20.113).

Zhou *et al.* have described an alternative Diels–Alder route to the well-known C,C cycloaddition (Carboni–Lindsey reaction). Quantum mechanical calculations showed that N,N cycloaddition of alkenes and alkynes to *s*-tetrazines is possible.



375 **376** **377**

Scheme 20.113

The formation of 1,2,4-triazole derivatives (formal product of N,N cycloaddition) along with the pyrazole (formal product of C,C cycloaddition) corroborates this theoretical prediction [803].

Thermal Diels–Alder reactions between C_{60} and electron-deficient 3,6-diaryl-1,2,4,5-tetrazines yielded monoadducts possessing a diaryldihydropyridazine function nested atop the fullerene [804]. However, when 3,6-diaryl-1,2,4,5-tetrazines and C_{60} react upon irradiation with visible light, the four membered ring-containing C_{62} derivatives were obtained [805].

20.5.5.3 Reactions with Oxidizing Reagents

1,4-Dihydrotetrazines have been aromatized to tetrazines by exposure to nitrous gases [784]. 1,2,4,5-Tetrazines have been oxidized by DBU to obtain a novel azepine derivative [806]. In contrast, 1,2,4,5-tetrazines have been oxidized by methyl(trifluoromethyl)dioxirane to form the *N*(1)-oxide isomer [807].

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21
Seven-Membered Heterocycles: Azepines, Benzo Derivatives and Related Systems

Juan J. Vaquero, Ana M. Cuadro, and Bernardo Herradón

21.1
Introduction

The replacement of a carbon atom by a heteroatom in a seven-membered carbocycle leads to the corresponding seven-membered heterocyclic ring system. Different types of heterocycles can be formed depending on the nature of the carbocycle. In a cycloheptatriene the replacement can involve any of the six sp^2 hybridized carbons or the sp^3 carbon atom, whereas in cycloheptane all carbon atoms are equivalent and replacement affords exclusively the fully saturated heterocyclic systems. Partially saturated seven-membered heterocycles can be viewed as derivatives or related systems of these two main seven-membered heterocyclic units arising from carbon replacement in cycloheptatriene and in cycloheptane.

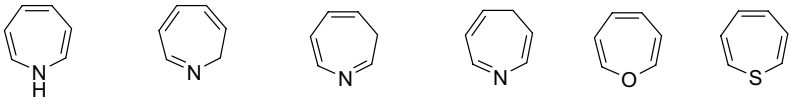
Replacement of the sp^3 hybridized carbon atom in cycloheptatriene by a nitrogen leads to an azacycloheptatriene known as 1*H*-azepine (**1**) and the corresponding 2*H*-, 3*H*-, and 4*H*-azepines (**2–4**) are the tautomeric forms generated by the replacement of the sp^2 carbons. 1*H*-Azepine is an unstable red oil that is prone to rearrange to the also unstable 3*H*-azepine in the presence of acids and bases. However, this tautomer seems to be more stable than both 4*H*- and 2*H*-azepine.

The structures related to 1*H*-azepine that bear an oxygen or sulfur atom are known as oxepine (**5**) and thiepine (**6**) (thiepin is favored by Chemical Abstracts Service). Oxepine is much more stable than thiepine and has been synthesized, isolated, and characterized at room temperature while thiepine has not been detected to date. Stable monocyclic thiepines were prepared and characterized in the 1980s. Azepines, oxepines, and thiepines that are constrained to planar or almost planar conformations should be antiaromatic molecules with negative resonance energy and, as a consequence, these compounds are unknown.

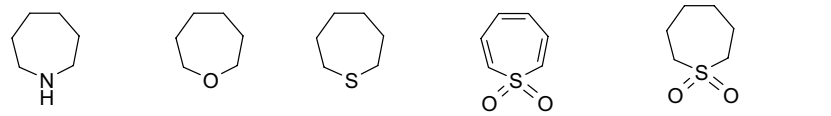
The fully saturated seven-membered heterocycle containing one nitrogen is azepane (**7**) (hexahydroazepine or perhydroazepine); the oxygen and sulfur analogues are known as oxepane (**8**) and thiepane (**9**). All of these compounds are stable and show typical behavior of secondary amine, ether and thioether, respectively. Two

Modern Heterocyclic Chemistry, First Edition.
Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.

other interesting systems are the sulfur-oxidized forms of **6** and **9**, which are known as thiepine 1,1-dioxide (**10**) and thiepane 1,1-dioxide (**11**), respectively.

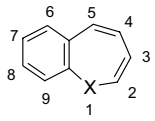


1*H*-Azepine **1** | 2*H*-Azepine **2** | 3*H*-Azepine **3** | 4*H*-Azepine **4** | Oxepine **5** | Thiepine **6**

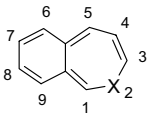


Azepane **7** | Oxepane **8** | Thiepane **9** | Thiepine 1,1-dioxide **10** | Thiepane 1,1-dioxide **11**

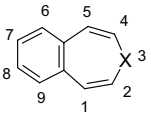
Annelation of all these seven-membered heterocycles to aromatic and heteroaromatic rings leads to a great variety of heterocyclic systems. The most widely studied are those generated by fusion of one or two benzene rings to the fully unsaturated nuclei. There are three possible ways for this annulation of a benzene ring to heterocycles **1–11** and four isomeric possibilities result from the fusion with two benzene rings (**12–32**). In general, the resulting benzo derivatives and dibenzo derivatives are more stable than the parent monocyclic systems.



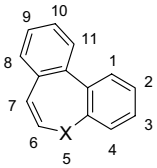
12: X = NH: 1*H*-1-Benzazepine
13: X = O: 1-Benzoxepine
14: X = S: 1-Benzothiepine



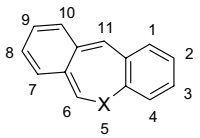
15: X = NH: 2*H*-2-Benzazepine
16: X = O: 2-Benzoxepine
17: X = S: 2-Benzothiepine



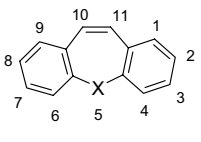
18: X = NH: 3*H*-3-Benzazepine
19: X = O: 3-Benzoxepine
20: X = S: 3-Benzothiepine



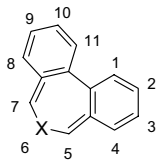
21: X = NH: 5*H*-Dibenz[*b,d*]azepine
22: X = O: Dibenz[*b,d*]oxepine
23: X = S: Dibenz[*b,d*]thiepine



24: X = NH: 5*H*-Dibenz[*b,e*]azepine
25: X = O: Dibenz[*b,e*]oxepine
26: X = S: Dibenz[*b,e*]thiepine



27: X = NH: 5*H*-Dibenz[*b,f*]azepine
28: X = O: Dibenz[*b,f*]oxepine
29: X = S: Dibenz[*b,f*]thiepine



30: X = NH: 5*H*-Dibenz[*c,e*]azepine
31: X = O: Dibenz[*c,e*]oxepine
32: X = S: Dibenz[*c,e*]thiepine

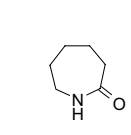
The chemistry and properties of most common seven-membered heterocycles have been reviewed in previous surveys, mainly in *Comprehensive Heterocyclic Chemistry I* [1, 2], *Comprehensive Heterocyclic Chemistry II* [3–5] and *Comprehensive Heterocyclic Chemistry III* [6–8]. Other reviews on azepines have been published [9–11] and benzazepines have been covered in a reference series [12]. The synthesis of oxepines and oxepanes has been reviewed elsewhere [13–16], as have the synthesis and applications of some dibenzoxepines [17]. Earlier studies on the chemistry of thiepines and thiepanes have been reviewed [18, 19] and, more recently, these heterocycles have been described in Houben-Weyl's *Science of Synthesis* [20]. A review of dibenzo[*b*,*f*]thiepine has also been published [21]. In addition to these general surveys, annual accounts on seven-membered heterocyclic ring systems are given in *Progress in Heterocyclic Chemistry* [22].

21.2
Relevant Natural and Useful Compounds

The seven-membered lactam **33** (ε-caprolactam or hexahydroazepin-2-one) is probably the most relevant azepine derivative to date. This compound has been isolated from natural sources and has biological properties such as growth-inhibiting activity [23] and allelopathy [24]. However, its most relevant use is as an intermediate in the synthesis of nylon 6 through a polymerization process [25, 26]. The structural fragment of ε-lactam is incorporated into various naturally occurring products such as the bacterial translocase 1 inhibitor **34** isolated from *Streptomyces griseus* SANK 50 196 [27] and the azepinone bengamides Z (**35**) and Q (**36**) isolated from a *Jaspis* species [28]. Muscaflavin (**37**) has been isolated from the poisonous mushroom *Amanita muscaria* and is one of the few examples of simple monocyclic azepine derivatives found in nature [29].

The most useful compounds based on the azepine system are fused-ring derivatives that exhibit a wide range of pharmacological activities. Examples of benzazepine derivatives with pharmacological interest are the 1*H*-2-benzazepine derivative **38**, which is an inhibitor of acetylcholinesterase [30], and the potential anti-HIV agent **39** [31]. Examples of dibenzazepines include imipramine (**40**) and clomipramine (**41**), two 10,11-dihydrodibenz[*b*,*f*]azepine alkaloids that have been used for the treatment of depressive disorders [32], perlapine (**42**), a dibenzo[*b*,*e*]azepine with antipsychotic and sedative activities [33], and azapetine (**43**), an antiadrenergic dibenzo[*c*,*e*]azepine [34].

The instability of most monocyclic oxepines precludes any significant commercial application, although they do play a remarkable role as intermediates in the biosynthesis and metabolism of natural products and xenobiotics [35]. It has been assumed that oxepines such as **44** and **45** are involved in the biosynthesis of tyrosine [36] and gliotoxin [37] and that the formation as intermediates of oxepines **46** and **47** occurs in the conversion of cinnamic acid into *ortho*- and *para*-coumaric acid, respectively [38]. Methyl-substituted oxepines **48** have also been postulated as intermediates in the metabolism of arenes by liver enzymatic systems [39]. Some



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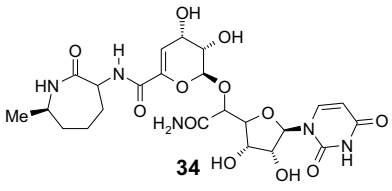

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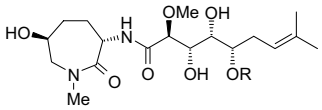
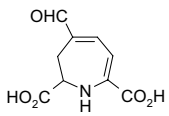


35: R = H
36: R = $CO(CH_2)_{12}Me$



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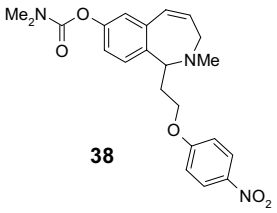
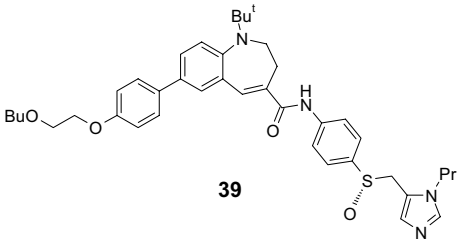
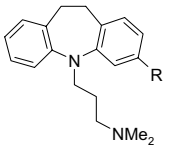


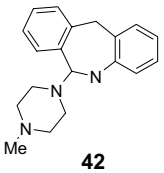
38



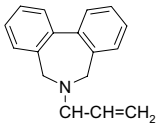
39



40: R = H
41: R = Cl



42

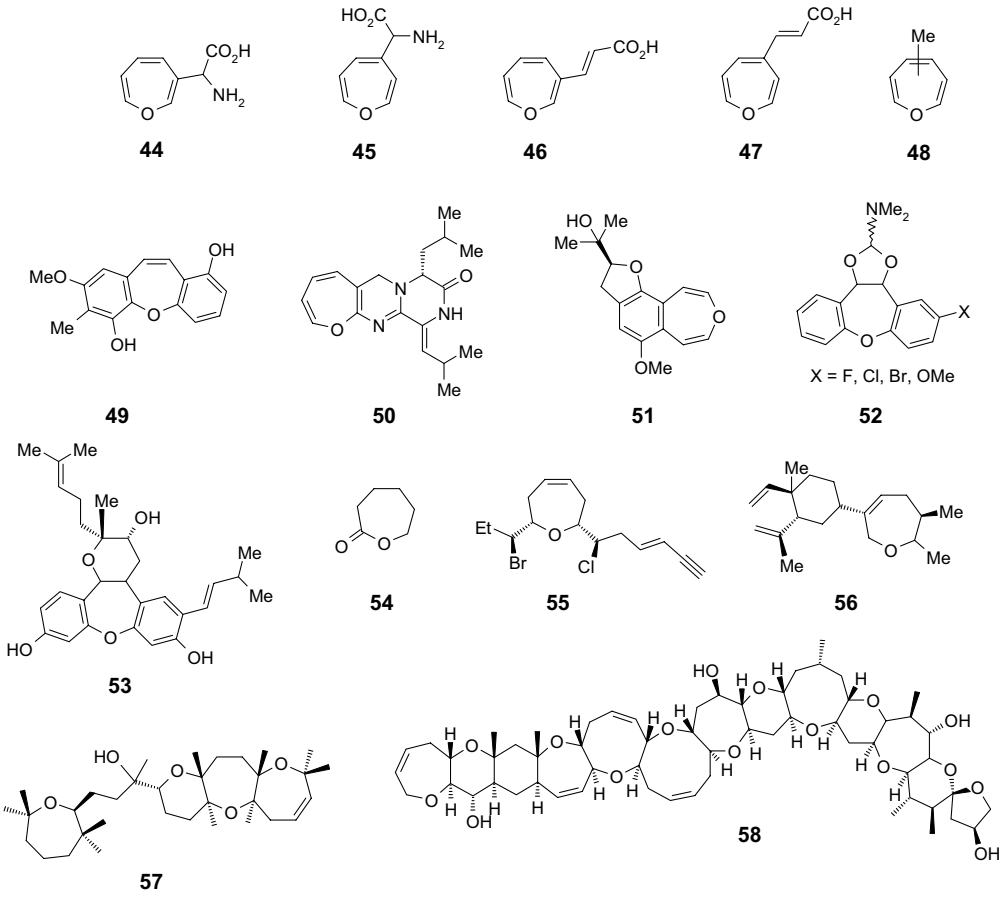


43

annelated oxepines are found in nature and these include bauhiniastatin (**49**) [40], janoxepin (**50**) [41], and perillosin (**51**) [42], and some relevant pharmacological activities have been described for some dibenzoxepine derivatives *inter alia* anxiolytic activity for **52** [43] and anti-inflammatory action for artocarpol (**53**), a natural product isolated from the root bark of *Artocarpus rigida* [44].

Oxepanes and partially reduced oxepines are of considerable interest, with oxepan-2-one (**54**) (ε-caprolactone) being an important monomer used in the synthesis of poly-ε-caprolactone, a polymer with a wide range of relevant applications [45]. A remarkable number of natural marine products contain oxepane or a reduced oxepine in their structure [46]. Representative examples are isolaurepinnacin (**55**) [47] and lobatrienetriol (**56**) [48], both of which are structurally based on a monocyclic tetrahydrooxepine, armatol A (**57**) [49], with two oxepane and one tetrahydrooxepine rings, and ciguatoxin 3C (**58**), which is one of the most powerful polyether neurotoxins [50].

Significant applications of simple monocyclic thiepines and thiepanes and their monobenzo derivatives have not been reported to date. On the other hand, interesting biological activities have been described for some dibenzo derivatives – especially those belonging the dibenzo[*b,f*]thiepine and dibenzo[*b,e*]thiepine series. Dibenzo[*b,f*] thiepine derivatives of the general structure **59** display a wide range of pharmacological activities, including antischizophrenic, anti-inflammatory, antidepressant, antihistaminic, anti-bradykinin, neuroleptic, and as 5-$HT_{2A/2C}$ inhibitors [51, 52].

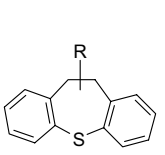


The activity of dibenzo[*b*,*e*]thiepines is represented by **60**, which has antidepressant activity [53], tiopinac (**61**), an anti-inflammatory agent [54], and **62**, a calcium antagonist [55].

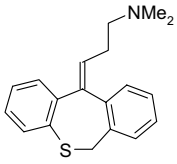
Apart from these applications, liquid crystals based on the dibenzo[*c*,*e*]thiepine scaffold have been reported and the enantiomerically pure compound **63** shows axial chirality [56].

21.3
Relevant Computational Chemistry, Physicochemical, and Spectroscopic Data

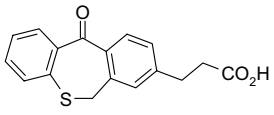
1*H*-Azepine (**1**) was first obtained in 1963 [57] by hydrolysis and decarboxylation of ethyl 1*H*-azepine-*N*-carboxylate, but it was not characterized until 1980 [58]. This azepine isomer is stable for only a few hours in solution even at −78 °C [it polymerizes and tautomerizes to the 3*H*-tautomer (**3**)]. 3*H*-Azepine (**3**) is less



59



60



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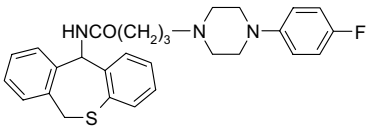
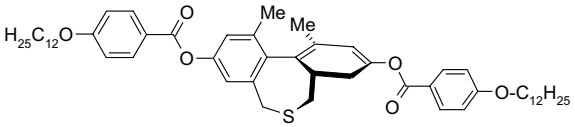


62

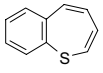


63

prone to polymerization than **1** and it can be distilled under vacuum. N-Substituted 1*H*-azepines are oils or stable solids with well-defined melting points. Azepane (**7**) was first obtained in 1963 and is a typical secondary amine with a pK_a of 11.29 [59].

Oxepine (**5**) is a heterocyclic compound that at room temperature is in equilibrium with its valence bond isomer, the benzene oxide, but it has been synthesized, isolated, and characterized. Thiepine (**6**) is a highly unstable structure and this compound remains unknown. Oxidation of the sulfur atom to form the thiepine 1,1-dioxide (**10**) stabilizes the thiepine ring system. Table 21.1 gives the bond lengths for some of these seven-membered heterocycles.

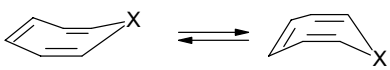
Table 21.1 Bond lengths (Å) for some representative seven-membered heterocycles.

Heterocycle	Het–C1	C1–C2	C2–C3	C3–C4	Method	Reference
 **1**	1.420	1.347	1.466	1.350	SCF-MO	[60]
 **5**	1.434	1.284	1.444	1332	*Ab initio*	[61]
 **6**	1.791	1.347	1.466	1.450	HMO	[62]
 **10**	1.723	1.344	1.429	1.333	X-ray	[63]
 **14**	1.781	1.321	1.448	1.308	X-ray	[64]

Het = Heteroatom.

The conformation of these fully unsaturated seven-membered heterocycles has made them the focus of enormous interest since a planar structure would involve an overlap of the nitrogen lone pair with the cyclic triene system, leading in turn to the formation of an antiaromatic 8π electronic system [60, 65].

Theoretical calculations carried out on 1*H*-azepine (**1**) have demonstrated that this tautomer is not a planar molecule; instead the results suggest that this heterocycle has a boat conformation with a significant contribution (22%) of the chair conformation. Consequently, this out-of-plane conformation allows the destabilizing overlap of the nitrogen lone pair to be avoided and the π-delocalization of the cyclic triene is at a similar level to that found in a linear polyene (Scheme 21.1). Comparative molecular-orbital-based molecular mechanics (MOMM) calculations carried out on 1*H*- and 3*H*-azepine (**3**) show that the π-electronic system is highly localized in both systems and the geometry of 1*H*-azepine is better represented for a defined boat conformation. Similarly, a boat conformation is the preferred geometry for 3*H*-azepine, which is predicted to be 4.7 kcal mol^{-1} more stable than the planar conformation and 17 kcal mol^{-1} more stable than 1*H*-azepine [66]. Recent studies [67] using DFT methods (B3LYP6-31G* and B3LYP/6-311 + + G**) and MP2/6-311 + + G** calculations show that destroying the antiaromaticity of **1** results in a reward of 10.8 kcal mol^{-1}.



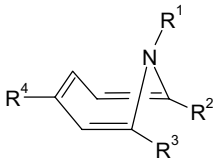
X = NH, O, S

Scheme 21.1

Extensive ^{1}H NMR studies have been carried out to establish the energy barriers for the ring inversion between the two stable boat conformations of the azepine ring. The barrier for boat-to-boat inversion depends on the number and nature of the substituents and the azepine tautomer. For simple substituted azepines it has been established that the barrier is below 5 kcal mol^{-1}.

Semiempirical and *ab initio* studies have shown that both oxepine (**5**) and thiepine (**6**) also adopt a boat-type conformation similar to that found in 1*H*-azepines, with four carbons (C2, C3, C6, and C7) arranged in the same plane and the heteroatom and the remaining two carbons (C4 and C5) out of the main plane (Scheme 21.1). Barriers for the ring inversion of thiepine have been obtained at different levels of theory [68] and range from 5.8 to 11.4 kcal mol^{-1}. From nucleus-independent chemical shift (NICS) values the planar structure is antiaromatic and the boat-like conformation appeared to be nonaromatic.

Experimental evidence for the boat-like conformation in azepines [69], oxepines [70], and thiepines [71] has been obtained by X-ray crystallography. These studies confirmed the boat-like conformation for the seven-membered rings of derivatives **64**–**66**, with bond lengths for C2−C3, C4−C5, and C6−C7 very close to those of the C(sp^2)−C(sp^2) single bond and the C−heteroatom lengths very similar to the distance of a single bond.



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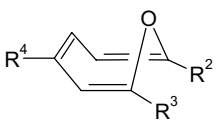

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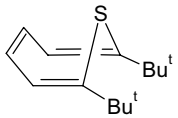
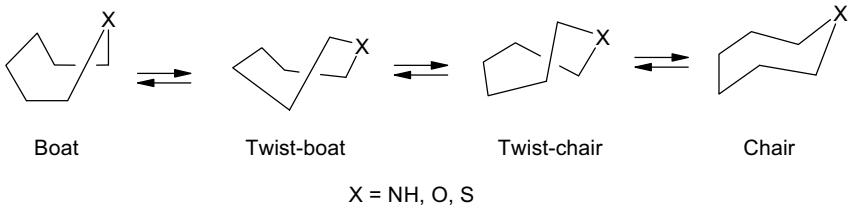


66

Conformational analyses of azepane (**7**) [72], oxepane (**8**) [73] and thiepane (**9**) [74] using different force fields have been described. Such compounds show a complex pseudorotational equilibrium between the chair, twist-chair, boat, and twist-boat forms, with the twist-chair conformations generally the most abundant conformers (Scheme 21.2). When a double bond is introduced into the ring, the number of conformations present in the pseudorotational equilibrium is reduced and the twist-boat or chair forms are usually stabilized.



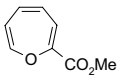
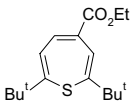
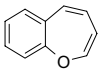
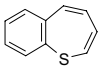
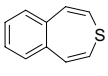
Scheme 21.2

The potential structural diversity of benzo and dibenzo fused seven-membered heterocycles and the lack of systematic conformational studies make it difficult to establish general conclusions for the preferred conformations of these systems. It is clear that the annelation of a benzene ring results in an increase in the barriers to ring inversion and that chair conformations appear to be preferred in benzo derivatives of the fully saturated systems **7**–**9** [75]. However, analysis of the benzoannelated system involving the fully unsaturated heterocycles **1**–**6** is much more complex because of the potential whole range of aromatic, antiaromatic, and nonaromatic situations and valence tautomerism (detailed below) that can be found.

NMR data for azepines, oxepines, and thiepines have also been very valuable in establishing their preferred conformations and provide detailed information about the ring inversion energies of these ring systems. The nonplanar character of the seven-membered nuclei results in the chemical shifts of the protons and carbons lying in the polyene region of the spectra. Tables 21.2 and 21.3 give ^{1}H NMR and ^{13}C NMR data for some representative compounds.

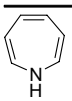
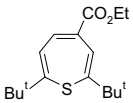
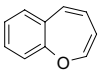
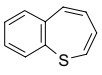
^{1}H and ^{13}C NMR data for monocyclic thiepines also provide relevant structural information. In the ^{1}H NMR spectra the ring proton signals clearly appear in the alkene region, with coupling constants consistent with a nonplanar seven-membered triene structure. This finding confirms the nonaromatic character of the nucleus. Chemical shifts in the ^{13}C NMR spectra are also consistent with the triene structure.

Table 21.2 ^{1}H NMR data (ppm) for some representative seven-membered heterocycles.

Heterocycle	H1	H2	H3	H4	H5	H6	H7	H8	H9	Reference
 **1**	—	5.22	4.69	5.57	5.57	4.69	5.22	—	—	[58]
 **2**	—	3.61	5.69	6.35	6.74	6.60	7.84	—	—	[76]
 **3**	—	6.2–6.7	2.42	5.35	6.2–6.7	6.2–6.7	7.55	—	—	[58]
 **5**	—	5.7	5.7	6.3	6.3	5.7	5.7	—	—	[77]
	—	5.62	4.47	2.32	2.32	4.47	5.62	—	—	[78]
	—	—	6.9	6.4	6.5	5.8	5.9	—	—	[79]
	—	—	6.76		7.43	6.40		—	—	[80]
 **13**	—	6.21	5.45	6.01	6.63	6.89–7.22				[81]
 **14**	—	5.86	6.40	6.40	7.06	7.16–7.28				[81b,82]
 **20**	6.72	5.89	—	5.89	6.72	7.10–7.18				[82]

MS, IR, and UV spectroscopic methods seem to be considered less significant for the structural elucidation of seven-membered heterocycles except for some isolated cases and systematic studies have not been reported. The UV data for some stable monocyclic derivatives have been used to confirm the nonplanar structure of the trienic ring. The UV spectra of 1*H*-azepine derivatives show three bands at 210–215, 240–247 and 285–330 nm, with the latter being the strongest absorption band [84]. The simplest stable compound 2,7-di-*tert*-butylthiepine shows three bands at 226, 252 and 362 nm with log ε values of 4.02, 3.35 and 2.51, respectively [85]. Notably, the mass spectrum of 2,7-di-*tert*-butylthiepine does not show ions generated by the loss of sulfur, an observation that is unexpected.

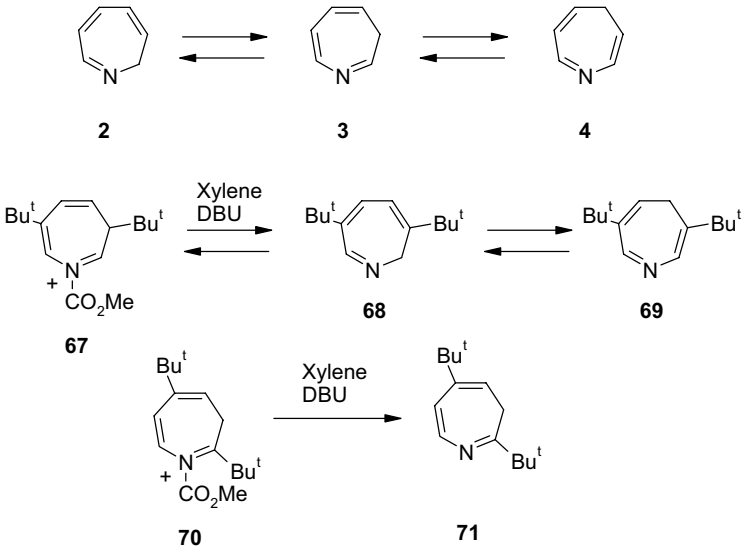
Table 21.3 ^{13}C NMR data (ppm) for some representative seven-membered heterocycles..

Heterocycle	C2	C3	C4	C5	C6	C7	C8	C9	Reference
 **1**	138.0	113.0	132.3	132.2	113.0	138.0	—	—	[58, 83]
 **2**	50.9	126.7	129.3	136.7	130.8	158.5	—	—	[76, 83]
 **3**	136.4	34.3	113.3	127.3	117.5	141.0	—	—	[58, 83]
 **5**	141.8	117.6	130.8	130.8	117.6	141.8	—	—	[77b]
	126.0	127.0	134.0	140.0	151.0	158.2	—	—	[80]
 **13**	146.74	115.09	126.68	132.55	121.01	24.61, 128.97		130.10	[81b]
 **14**	124.5	130.5, 133.9		136.9	127.9, 128.7, 130.1, 132.0				[81b,84]

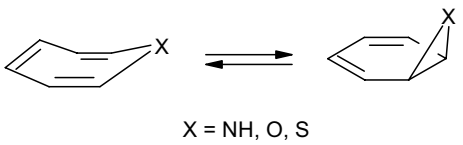
Tautomerism in azepines via an allowed 1,5-hydrogen shift has been studied for different azepine isomers and it was found that the ratio of azepine tautomers is related to their relative thermal stabilities [69d, 86]. For instance, when heated in toluene both 2*H*- and 3*H*-azepines **2** and **3** are converted into mixtures containing the 2*H*-, 3*H*-, and 4*H*-azepine tautomers in similar ratio (about 10: 50: 1). A similar result has been found in the demethoxycarbonylation of the 3*H*-azepine derivative **67**, which upon heating in toluene in the presence of DBU affords a mixture of **67** and the 2*H*- and 4*H*-tautomers **68** and **69**, respectively. However, under the same conditions the methyl 2,5-di-*tert*-butyl-3*H*-azepine-1-carboxylate **70** gave only the 3*H*-tautomer **71** (Scheme 21.3).

21.4
Valence Tautomerism in Seven-Membered Heterocycles

An interesting structural feature of fully unsaturated seven-membered heterocyclic systems is the possibility of valence tautomerism [87]. Early studies based on X-ray analysis discarded the azepine–benzeneimine equilibrium (Scheme 21.4) for simple 1*H*-azepines in the solid state, and ^1H NMR data obtained at different temperatures were also consistent with the azepine structure [58]. However, other NMR studies [88]



Scheme 21.3

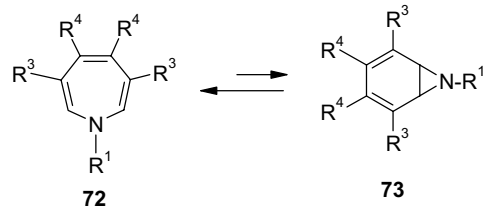


Scheme 21.4

demonstrated the existence of the azepine–benzeneimine equilibrium in densely substituted 1*H*-azepines such as **72**, where the bicyclic isomer **73** is present at a level of 3–10% in the equilibrium mixture (Scheme 21.5). Further theoretical studies (MINDO/3) showed that the benzeneimine is a nonplanar bicycle in which the aziridine ring is 72.6° out of the plane of the six-membered ring. Moreover, the stability of the tautomers was calculated from their heats of formation, which showed that 1*H*-azepine **73** is much more stable than the benzeneimine form (43.10 versus $-8.50\,\text{kcal mol}^{-1}$) [61].

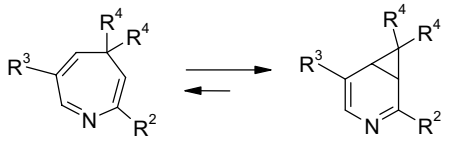
Valence tautomerism studies on 4*H*-azepines proved that 4*H*-azepine can also be in equilibrium with its bicyclic tautomer, the 3-azanorcaradiene. Early studies showed that 4*H*-azepine was the most stable isomer [89]. However, in some substituted derivatives such as **74** the equilibrium is displaced towards the bicyclic isomer **75** and it is necessary to heat the sample to 178 °C to detect the 4*H*-azepine form in the ^{1}H NMR spectrum [90].

With regard to 3*H*-azepines, it was found that acid treatment of some 7-amino-3-trityl-3*H*-azepines (**76**) led to the stable azanorcaradiene salts **77**, which reverted to **76** when treated with potassium carbonate (Scheme 21.5) [91]. Moreover, the selective formation and isolation of 2-methoxy-2*H*-azepine **79** from 3,6-di-*tert*-butyl-3*H*-azepine (**78**) – probably via an azatropylium cation – has been reported. The isolated compound **79** did not revert into its valence isomer at room temperature [92].



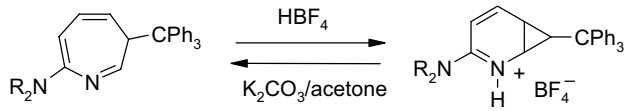
72 **73**

R^1 = *p*-Ts, Ac, CO_2Me; R^3 = H; R^4 = CO_2Me

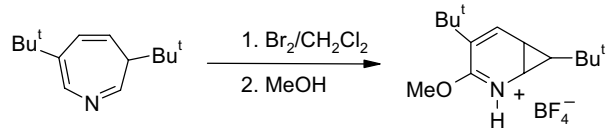


74 **75**

R^2 = CO_2Me; R^3 = Ph; R^4 = Me



76 **77**

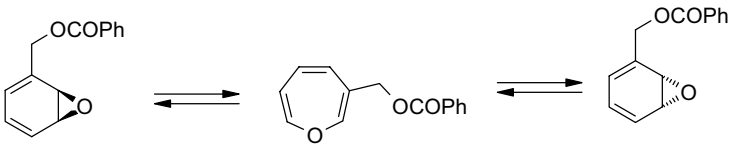


78 **79**

Scheme 21.5

The parent oxepine (**5**) is in spontaneous equilibrium with the valence isomer benzene oxide at room temperature (a thermal disrotatory electrocyclic reaction according to Woodward–Hoffmann rules). Different NMR and UV studies have been carried out to investigate this equilibrium. At room temperature the ^{1}H NMR spectrum of **5** contains three multiplets at δ 5.20, 5.65, and 6.10 ppm, which correspond to H4, H3, and H2, respectively, involved in a fast exchange process. At lower temperatures (−134 °C) both the oxepine and the benzene oxide are distinguishable in the ^{1}H and ^{13}C NMR spectra [77b]. UV spectroscopy has also proven to be very valuable in detecting both isomers since the oxepine tautomer shows an absorption band at 305 nm while benzene oxide absorbs at 271 nm (ε = 900 and 1430, respectively).

Studies on monosubstituted oxepines **80** also support the existence of two enantiomers in equilibrium with the oxepine (Scheme 21.6) [93]. The oxepine–benzene oxide ratio depends on temperature, solvent, and substitution of the oxepine ring. The oxepine form seems to be favored in less polar solvents [94] while at low

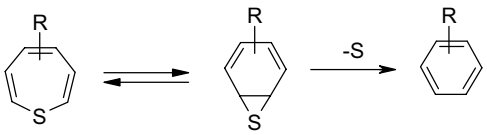


80

Scheme 21.6

temperatures the benzene oxide is the preferred form. As a general remark, substituents at the C3 position favor the benzene oxide tautomer and substitution at C2 and C4 the oxepine form. Recent theoretical studies (*ab initio*) have also being carried out on the tautomerization oxepine benzene-oxide of substituted oxepines [95].

Theoretical studies at a high level of theory dealing with the stability of thiepine and its valence tautomer have shown a significant preference for the valence tautomer benzene sulfide, which was estimated to be 7.02 kcal mol^{-1} more stable than the parent thiepine [96]. A remarkable difference with azepines or oxepines is that valence isomers in simple thiepines are prone to extrude the sulfur atom in an irreversible process (Scheme 21.7). It is assumed this loss of sulfur precluded the isolation of the parent thiepine (**6**). Monocyclic thiepines can be stabilized by steric effects. For example, the presence of bulky substituents at C2 and C7 produces derivatives that are very stable at high temperatures (130 °C) with long half-lives (>250 h) [85]. Recent theoretical studies show how steric effects can favor thiepines over their benzene sulfide tautomers [97].

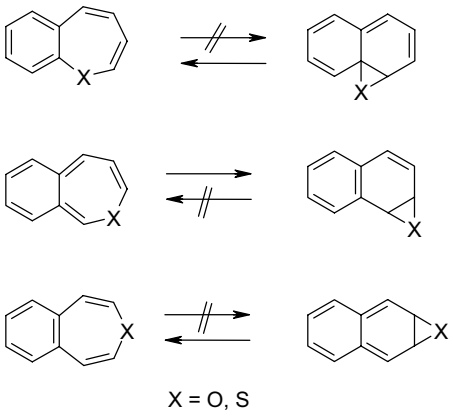


Scheme 21.7

Azepines, oxepines, and thiepines fused with benzene rings are stabilized by electronic effects and may also be in equilibrium with their corresponding valence isomers. Resonance energies have been calculated for the three possible isomeric benzoxepines **13**, **16**, and **19** as 19.55, 1.15, and 18.77 kcal mol^{-1}, respectively [98]. These data support experimental evidence that benzo derivatives **13** and **19** are relatively stable compounds while the formation of **16** from the 1,2-naphthalene oxide would involve a significant loss of resonance energy since one of the benzene nuclei in this valence tautomer retains aromatic character [99].

Aromatic ring annelation of thiepine (**6**) can lead to quite stable derivatives [100]. Resonance energy calculations for benzothiepines **14** ($+6.14$ kcal mol^{-1}), **17** (-5.90 kcal mol^{-1}), and **20** ($+7.13$ kcal mol^{-1}) have been used to predict that **14** and **20** should have nonaromatic character whereas **17** should be a highly unstable molecule [101]. As was the case with the oxepine–arene oxide equilibrium, electronic

effects could also strongly affect the thiepine–episulfide equilibrium of naphthalene. Benzothiepine **14** only exists in the thiepine form and has been characterized by X-ray analysis [64]. The higher stability of the valence tautomer of **17** explains why this thiepine has not been isolated (Scheme 21.8).



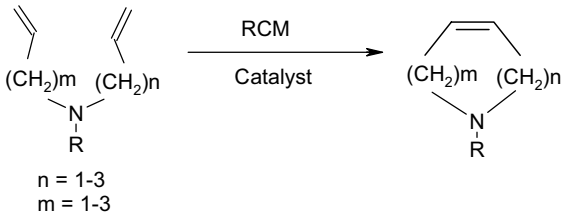
Scheme 21.8

21.5 Synthesis

21.5.1 Synthesis of Azepines

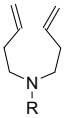
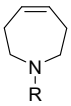
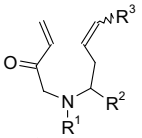
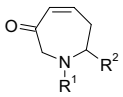
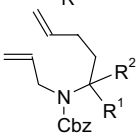
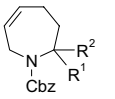
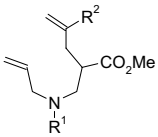
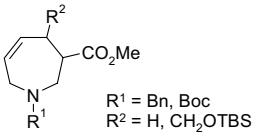
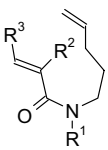
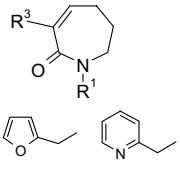
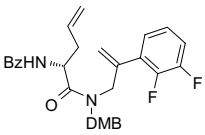
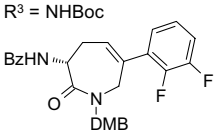
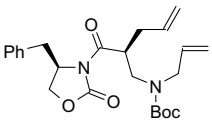
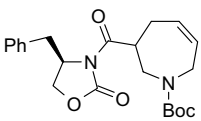
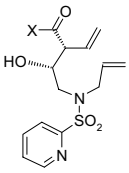
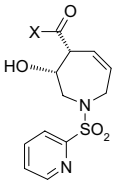
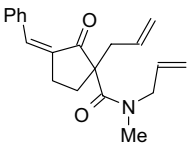
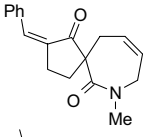
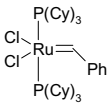
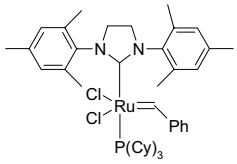
21.5.1.1 From Acyclic Compounds

The formation of the seven-membered ring of an azepine from an appropriate acyclic compound through a cyclization reaction has been extensively used for the synthesis of azepine fused-ring derivatives but had rarely been used for monocyclic azepine derivatives until the advent of the metathesis reaction [102]. The power and utility of the ring-closing metathesis (RCM) reaction (Scheme 21.9) for the preparation of different tetrahydroazepines using Grubbs I and Grubbs II catalysts is exemplified in Table 21.4.

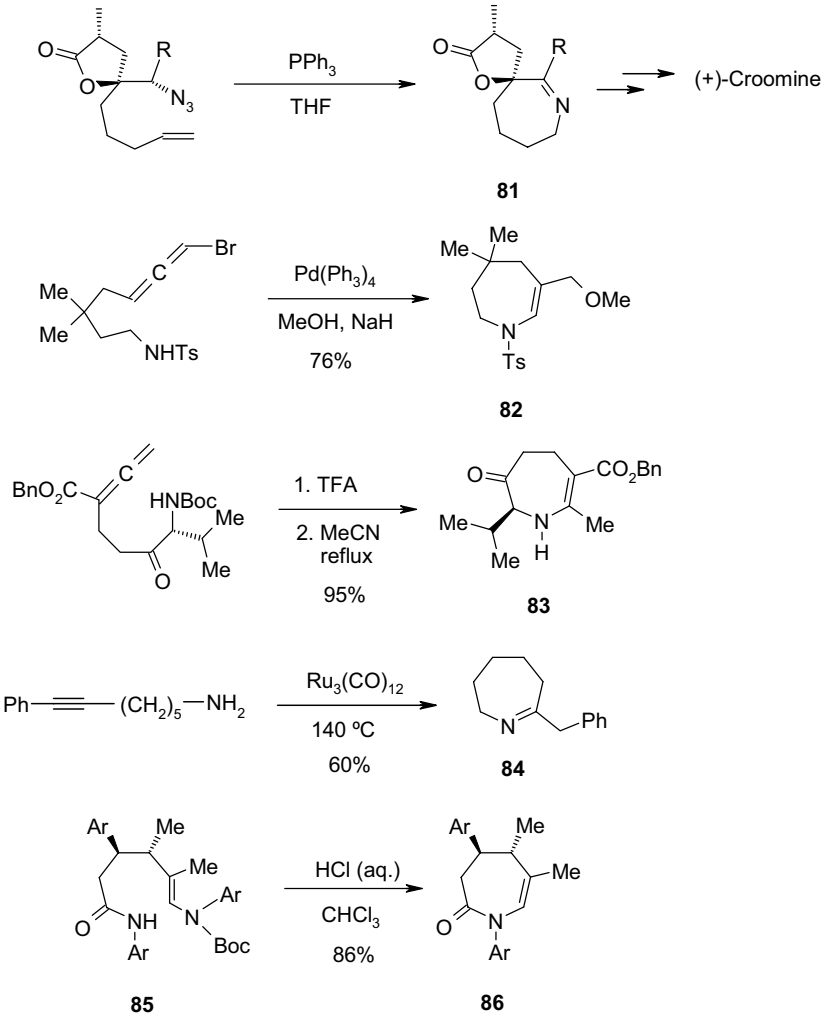


Scheme 21.9

Table 21.4 Synthesis of tetrahydroazepines by ring-closing metathesis (RCM) reactions.

Diene	Conditions	Azepine	Yield (%)	Reference
	CH_2Cl_2, 40–50 °C	 R = Ts, SO_2CH_2Br	100	[103]
	CH_2Cl_2, heat	 R^1 = Boc, CBz, (2-Py)SO_2 R^2 = H, Me	90–99	[104]
	$ClCH_2CH_2Cl$, reflux	 R^1 = H, Me R^2 = Ph, Me	75–89	[105]
	CH_2Cl_2	 R^1 = Bn, Boc R^2 = H, CH_2OTBS	82–90	[106]
	CH_2Cl_2 or $ClCH_2CH_2Cl$, r.t./40 °C/90 °C	 R^1 = Bn R^3 = NHBoc	88–92	[107]
	CH_2Cl_2, 10 °C		58	[108]
	CH_2Cl_2, reflux		97	[106b]
	CH_2Cl_2, reflux		75	[109]
	C_6H_6, reflux		87	[110]
Grubbs I 		 Grubbs II		

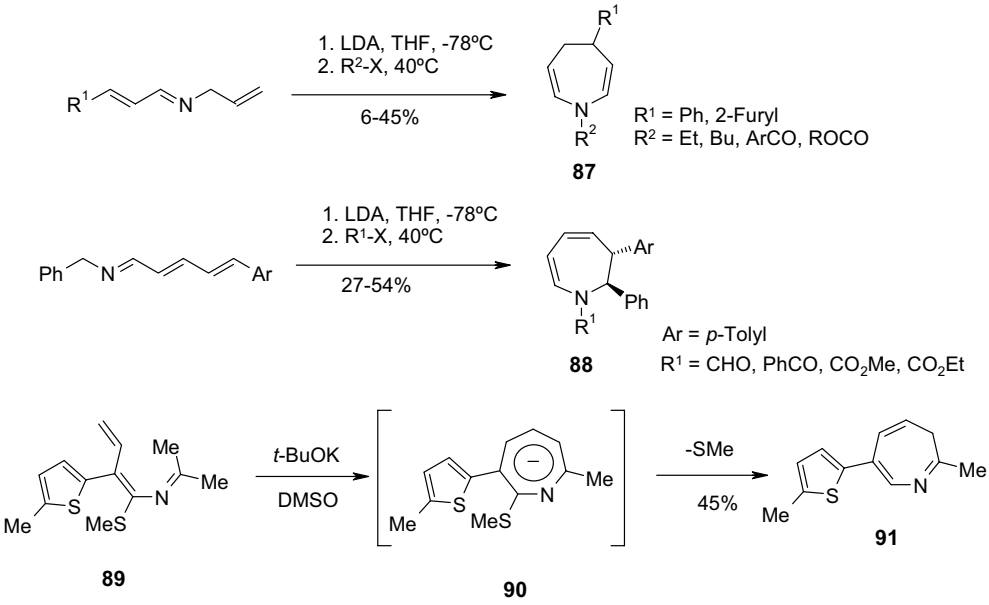
Other alternatives to the ring-closing metathesis reaction to access tetrahydroazepine derivatives through cyclization include the different approaches shown in Scheme 21.10. The intramolecular insertion of nitrenes by thermolysis of the corresponding azides (the Staudinger reaction) [111] is an efficient route to cyclic imines [112] that has been applied to the synthesis of the tetrahydroazepine derivative **81**, an intermediate in the synthesis of (+)-croomine [113]. The reaction of a bromoallene in the presence of $Pd(Ph_3)_4$ afforded the tetrahydroazepine derivative **82** in good yield [114]. Azepinones can also be obtained from substituted allenes, which on deprotection followed by reflux in acetonitrile gave the azepinone derivative **83** in excellent yield [115]. Simple substituted azepine derivatives **84** have been obtained by ruthenium-catalyzed intramolecular hydroamination of an aminoalk-



Scheme 21.10

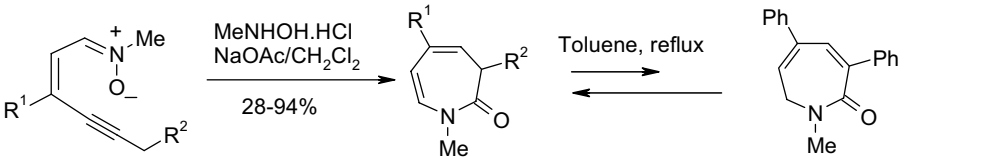
yne [116]. A more classical cyclization leading to azepine derivatives is exemplified by the formation of azepinone **86** by acid treatment of **85** [117].

N-Substituted dihydroazepines **87** and **88** can be obtained by lithium-promoted electrocyclization of imine-dienes followed by *N*-alkylation or *N*-acylation. Yields are poor to moderate depending on the R^1 substituent [118]. A carbanion-promoted 1,7-electrocyclization of **89** led to the antiaromatic azepine anion **90**, which loses methylthiolate to generate the thienyl-substituted 3*H*-azepine **91** (Scheme 21.11) [119].



Scheme 21.11

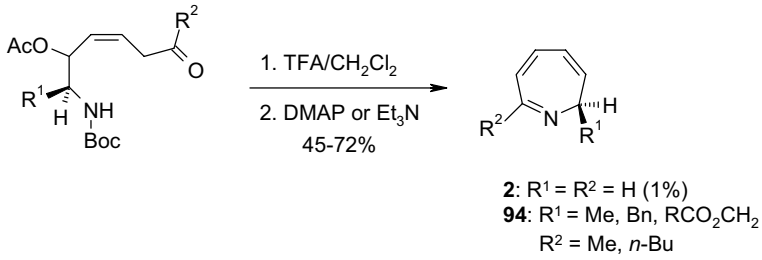
A novel synthesis of azepinone derivatives **92** has been reported and a key step in this process is an intramolecular cycloaddition of a nitrone followed by rearrangement through N−O homolysis and subsequent electrocyclic recyclization. On heating **92a** ($R^1 = R^2 = Ph$) in toluene an isomerization was observed to the azepinone isomer **93a,** although the latter is present in the equilibrium at a level of only 3% (Scheme 21.12) [120].



92a: $R^1 = R^2 = Ph$ (94%)
92b: $R^1 = Me$; $R^2 = H$ (28%)

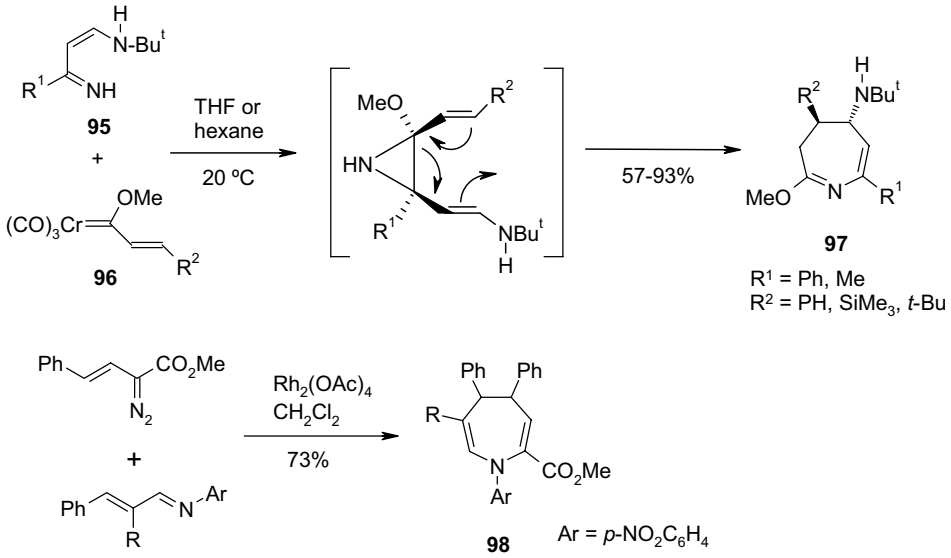
Scheme 21.12

The parent 2*H*-azepine (**2**) and the enantiomerically pure derivatives **94** were obtained for the first time by cyclization of an *N*-protected ε-amino aldehyde or ketone [76]. The ring formation involves deprotection with TFA followed by treatment with a base (Scheme 21.13). Although the yield of **2** was only 1%, this isomer was stable enough at 25 °C to allow its characterization. 2*H*-Azepines **94** were obtained in yields in the range 45–72% but are prone to isomerize to the more stable 3*H*-isomers [121].



Scheme 21.13

The formation of the azepine nucleus by processes involving the formation of two bonds is exemplified by a few cases such as the [4 + 3] annulations of Fischer chromium carbene complexes with azadienes [122]. Thus, the reaction of **95** and **96** affords the dihydroazepine **97** through the formation of an aziridine followed by an aza-Cope rearrangement and 1,3-proton shift (Scheme 21.14). The dihydroazepine derivatives **98** have been obtained by reaction of ylides generated *in situ* from styryldiazoacetates and imines [123] (Scheme 21.14).

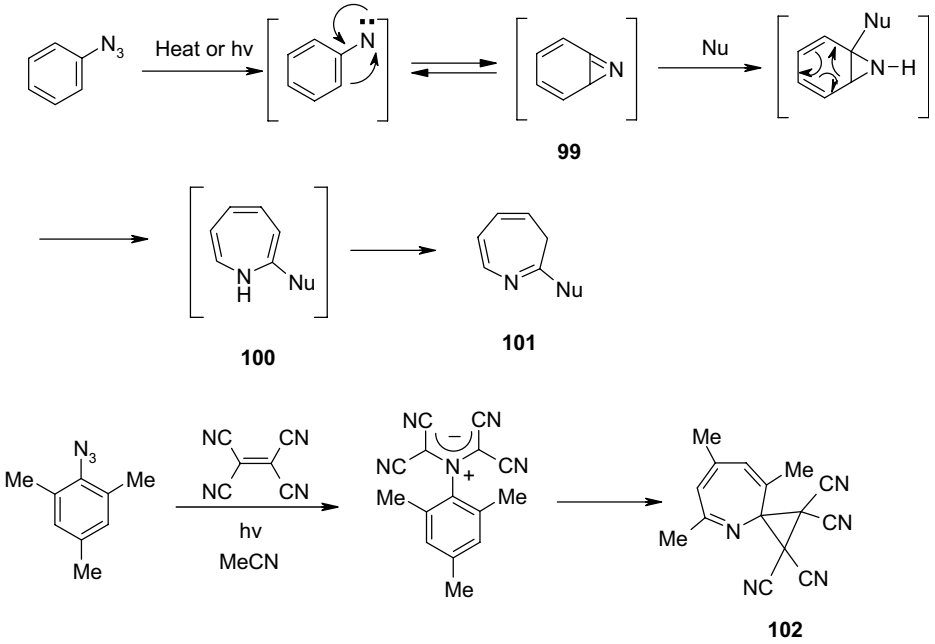


Scheme 21.14

21.5.1.2 From Cyclic Compounds

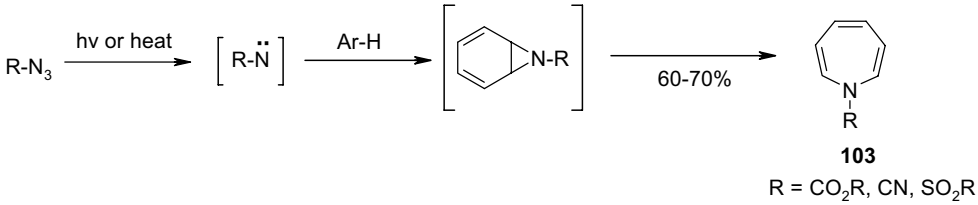
21.5.1.2.1 **From Carbocycles** The first approach to fully unsaturated azepines was reported by Wolff in 1912 and involves the thermal decomposition of a phenylazide in aniline, although it was Huisgen in 1955 who assigned the structure of 7-anilino-2*H*-azepine to the reaction product, which had remained unknown. On the basis of ^{1}H NMR data, this initial structure assignment subsequently had to be modified in favor of the 3*H* tautomer **101**. This procedure is considered to be the most useful method for the synthesis of 3*H*-aminoazepines [124] and some related compounds since nucleophiles other than amines have been successfully used [125]. The mechanism of the formation of the 3*H*-azepines is shown in Scheme 21.15 and involves the intermediacy of a benzazirine (**99**) *via* the initial generation of a nitrene. The attack of the nucleophile on the azirine ring promotes an electrocyclic ring opening to give the 1*H*-azepine **100**, which rearranges to the more stable 3*H*-tautomer. Nitroso and nitroarenes have also been used as alternatives to azides as the source of nitrenes. In this case the nitrene is generated by treatment with phosphines or phosphites. The aryl nitrene generated by photochemical decomposition of the corresponding azide is trapped with tetracyanoethylene and this leads to the formation of spiroazepine **102** (Scheme 21.15) [126].

Based on this approach to the azepine system, Hafner [57] and Lwowski [127] reported independently the most synthetically useful procedure for the synthesis of 1*H*-azepines. They discovered that some nitrenes were able to react with arenes to afford azanorcaradienes (the valence isomers of azepines), which rearrange to give stable azepines (Scheme 21.16). The nitrene is usually generated by thermal or photolytic decomposition and, in general, the reaction is more appropriate for



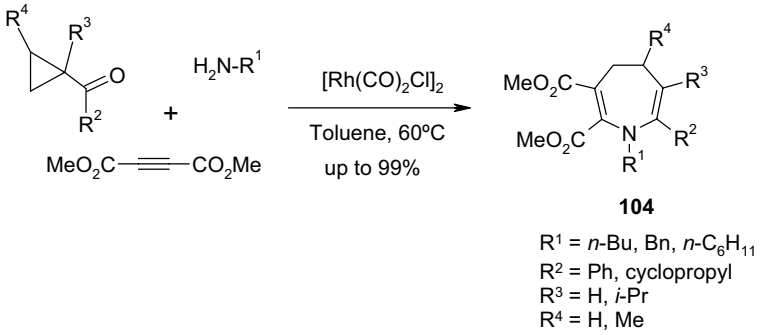
Scheme 21.15

N-substituted azepines **103** bearing electron-withdrawing substituents. The reaction of the nitrene with substituted benzenes usually has poor regioselectivity and mixtures of 1*H*-azepines are formed, a fact that limits the scope of this method (Scheme 21.16) [128].



Scheme 21.16

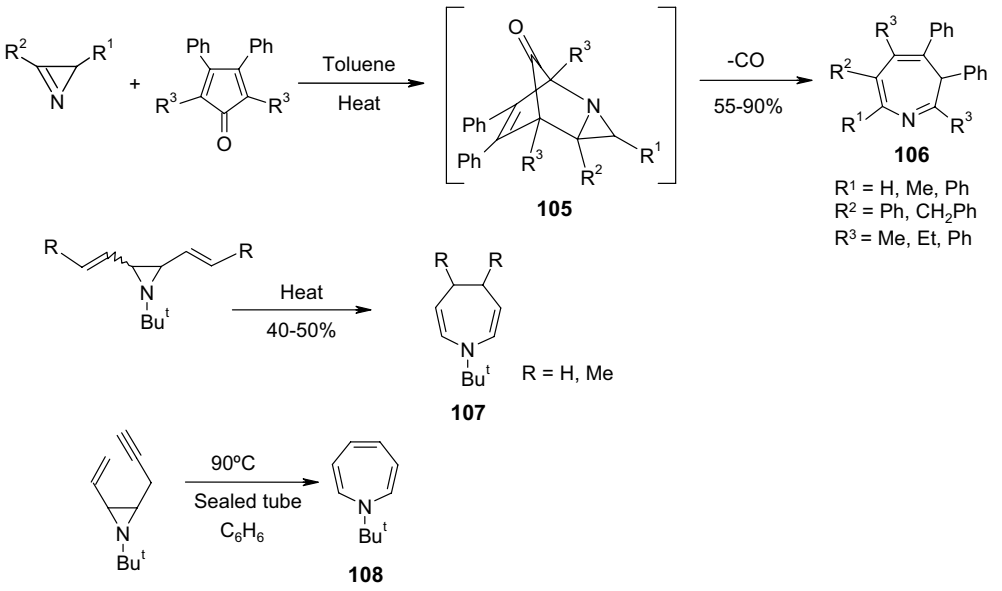
4,5-Dihydroazepines have been synthesized using cyclopropane derivatives in a multicomponent reaction that also involves primary amines and dimethyl acetylenedicarboxylate (DMAD). Initial formation of the corresponding cyclopropylimines followed by a rhodium-mediated [5 + 2] cycloaddition afforded substituted 4,5-dihydroazepines **104** in good yields (Scheme 21.17) [129].



Scheme 21.17

21.5.1.2.2 **From Heterocycles** 2*H*-Azirines react with cyclopentadienones in a [4 + 2] cycloaddition reaction to give polysubstituted 3*H*-azepines **106** by loss of carbon monoxide from the *endo* adduct **105** [130]. Aziridines have also been transformed into dihydroazepine or azepine derivatives **107** [78, 131] and **108** [132] by a Cope-type rearrangement on warming or at room temperature. Studies on these rearrangements show that the *trans* isomers are less prone to cyclization than *cis* isomers and higher temperatures are needed to produce the rearrangement (Scheme 21.18).

Five-membered heterocyclic rings can also be converted into azepine systems by cycloaddition and rearrangement reactions. One example of the first process is the 1,3-dipolar cycloaddition of heterobetainic compounds with cyclobutenes to yield the 4,5-dihydro-1*H*-azepines **109** through the loss of carbon dioxide from the initially formed cycloadduct (Scheme 21.19) [133]. Rearrangements leading to azepines from five-membered rings are illustrated by the examples shown in Scheme 21.19. In the first case



Scheme 21.18

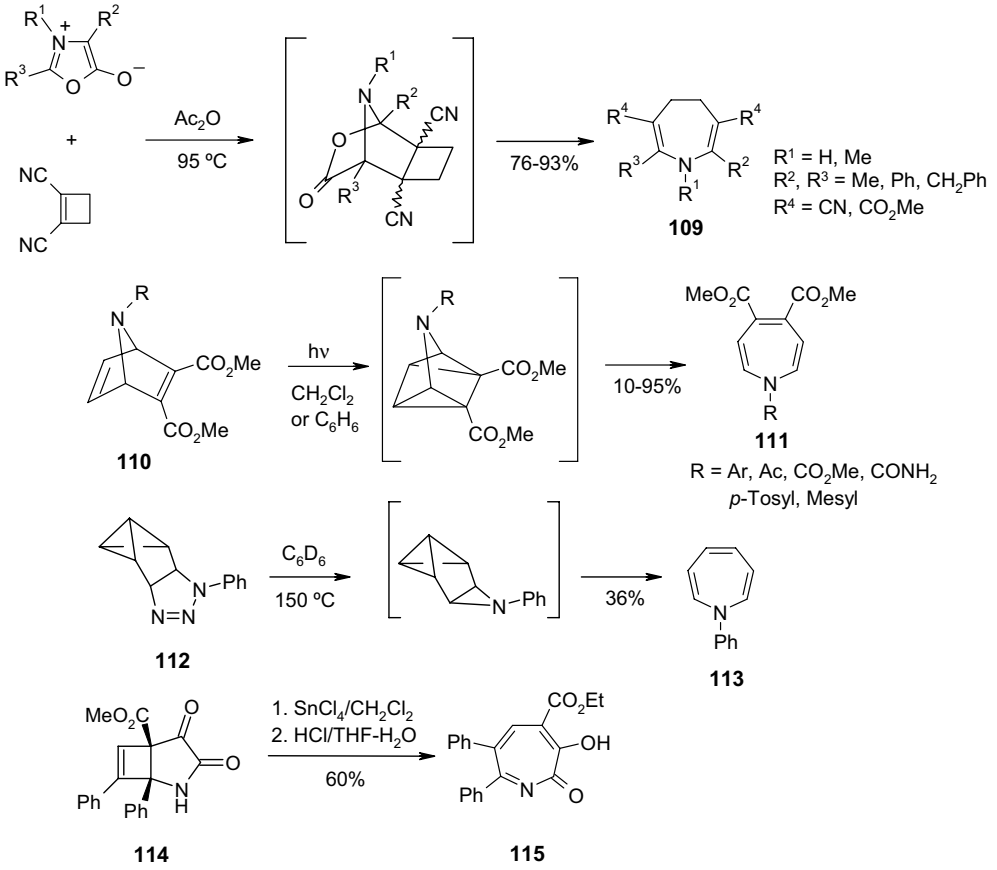
cycloadducts **110**, obtained from DMAD and pyrroles, are photochemically converted into thermally unstable azaquadricyclanes, which rearrange to the substituted 1*H*-azepine derivatives **111** [134]. The other two examples concern the synthesis of the 1-phenyl-1*H*-azepine **113** by thermal decomposition of the triazole derivative **112** [135] and the preparation of azepinones **115** by ring expansion of the dioxopyrrole derivatives **114** [136].

The ring expansion of six-membered heterocycles is one of the main strategies for the formation of 4*H*-azepines. 4-Chloromethyl-1,4-dihydropyridines can be transformed into the 4*H*-azepine derivatives **116** in the presence of various nucleophiles, including alkoxides, amines, cyanide, thiolates, and enolates [137]. On the other hand, the 4*H*-azepine derivatives **117** are obtained by sequential Diels–Alder reaction of 1,2,4-triazines and cyclopropenes [138] followed by N_2 extrusion and ring enlargement (Scheme 21.20). In both cases the isolated 4*H*-azepines are prone to isomerization to the more stable 3*H*-isomers. A substituted 2-pyridone has also been transformed into the 3*H*-azepinone **118** by treatment with LDA (Scheme 21.20) [139].

21.5.2 Synthesis of Oxepines

21.5.2.1 From Acyclic Compounds

As with azepines, ring-closing metathesis (RCM) has become the main strategy for the synthesis of dihydro- and tetrahydrooxepines through a C=C bond forming reaction as this approach is simple and allows the easy identification of the target acyclic precursor of the desired oxepine. Although most of the RCM strategies have been applied to benzo and other fused azepine derivatives, one of the first examples of the application of the RCM to simple oxepines was reported by Nicolaou during the

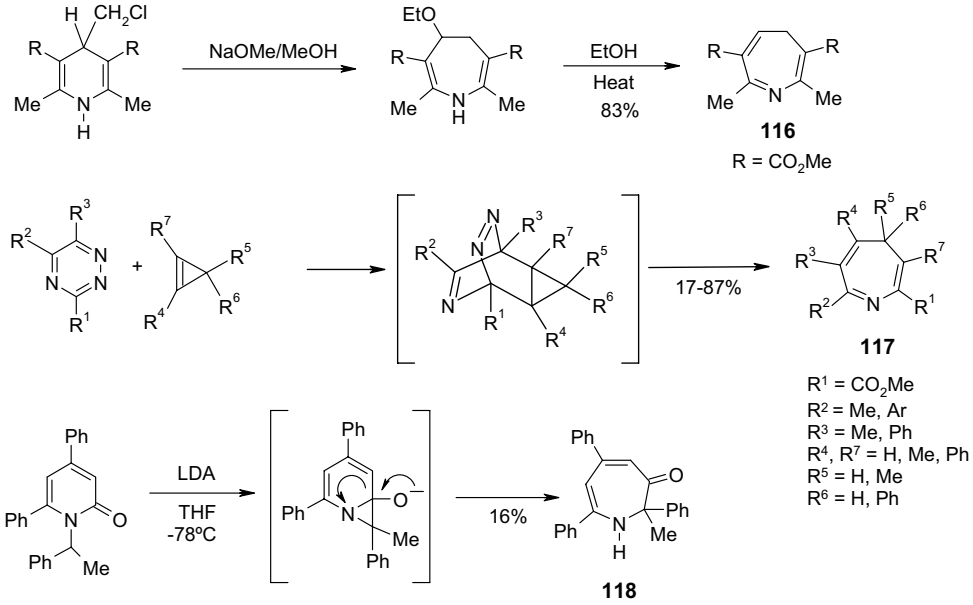


Scheme 21.19

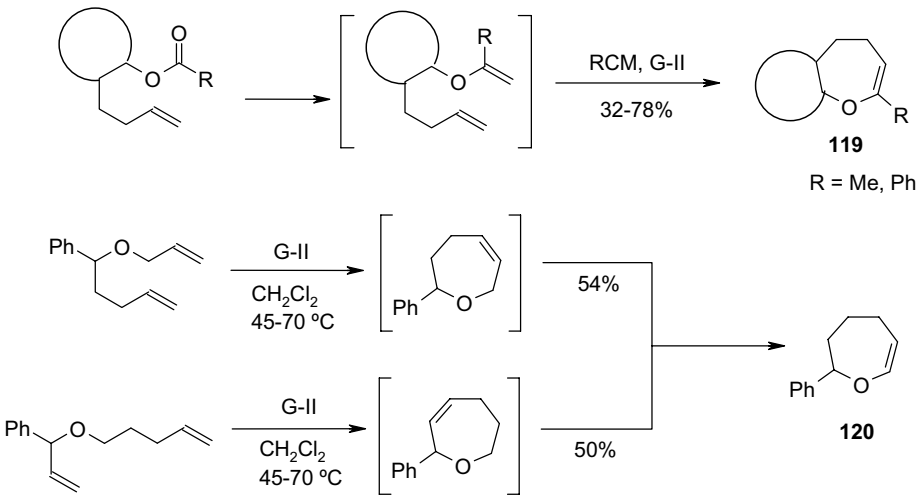
total synthesis of the complex polyethers ciguatoxin and brevetoxin. Different 4,5,6,7-tetrahydroazepine derivatives **119** were obtained in a tandem reaction involving the metathesis of an alkene and a vinyl ether promoted by a titanium catalyst [140]. An alternative approach to tetrahydroazepine **120** involved RCM reactions of two alkenes (Scheme 21.21) [141]. The reaction was carried out in the presence of Grubbs' second-generation catalyst (G-II) and H_2 (5%) to facilitate the double bond migration through the formation of a ruthenium hydride species.

The 2,5,6,7-tetrahydroazepine **122** has been reported by van Boom and was synthesized by RCM of **121** in 68% yield using Grubbs' first-generation catalyst (G-I) [142]. This catalyst was also employed successfully in the synthesis of the more complex 2,3,6,7-tetrahydroazepine derivative **124**, which was obtained in 95% yield from **123** [143] (Scheme 21.22). In an example of a double RCM reaction, the bis-tetrahydrooxepine **126** has been obtained from the tetraene derivative **125** [144].

An ene-allene carbocyclization reaction mediated by rhodium(I) has been reported to give 2,3,4,5-tetrahydrooxepines **127** in moderate yields (Scheme 21.23) [145]. Complete decomposition of the same substrates was observed depending upon their substitution pattern.

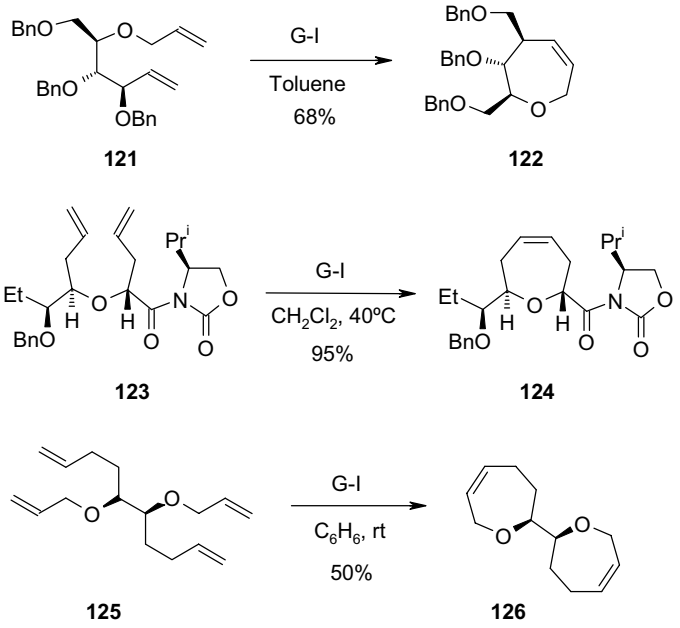


Scheme 21.20

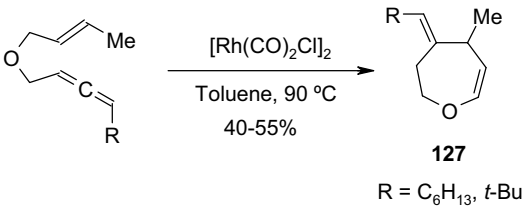


Scheme 21.21

Formation of the oxepine ring through C—O bond formation has been achieved by exploiting the nucleophilicity of the oxygen towards an appropriate electrophilic carbon. Several different strategies leading to tetrahydrooxepine derivatives based on this bond formation have been described. The cyclization of 1,6-diols is one of the classical approaches to oxepane and oxepane derivatives. It was also found that hexane-1,6-diol cyclizes to give 4,5,6,7-tetrahydrooxepine (**128**) in the presence of



Scheme 21.22

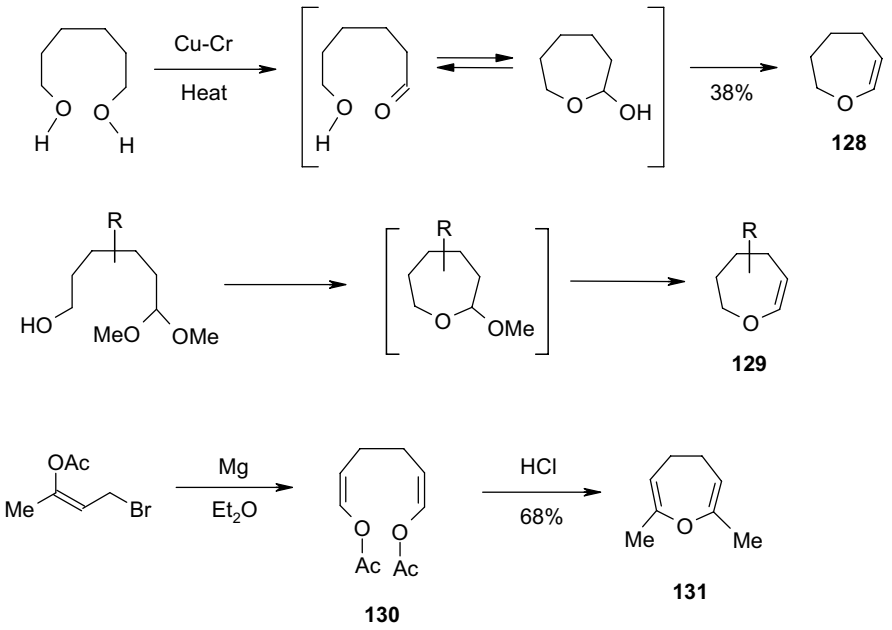


Scheme 21.23

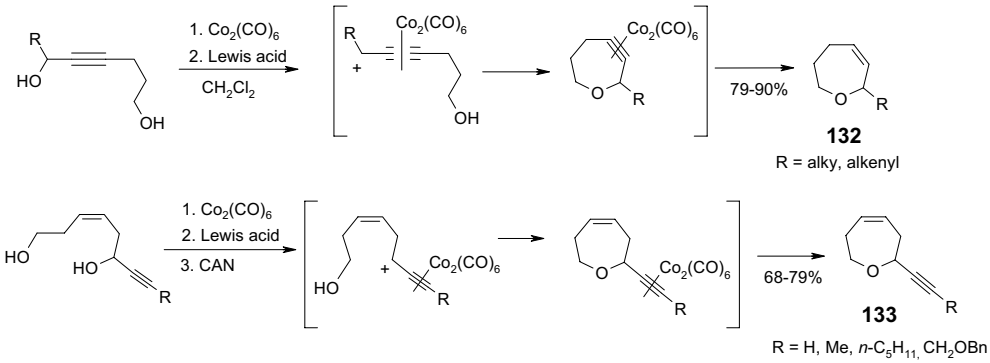
Cu-Cr catalyst at high temperature (250 °C) [146]. Substituted derivatives **129** are obtained from acyclic hydroxy-acetals (Scheme 21.24) [147]. 2,7-Dimethyl-4,5-dihydrooxepine (**131**) has been synthesized by the cyclization of diester **130** upon treatment with hydrochloric acid [148].

The intramolecular version of the Nicholas reaction [149] has been employed to obtain oxepine derivatives by attack of the oxygen of an alcohol to propargylic carbocations, which are stabilized by alkynyl-dicobalt complexes. The decomplexation is carried out under reducing conditions or with cerium ammonium nitrate (CAN). Two different arrangements of the carbocation and the oxygen, leading to the 2,5,6,7-tetrahydrooxepine and 2,3,6,7-tetrahydrooxepine derivatives **132** and **133**, respectively, are shown in Scheme 21.25. The first approach has been used in the synthesis of ciguatoxin [150] and the second one in the preparation of 2,7-disubstituted oxepines similar to isolaurepinnacin [151].

The transition metal-mediated cycloisomerization of alkynols, which is extensively used for five- and six-membered rings, has also been expanded to the synthesis of



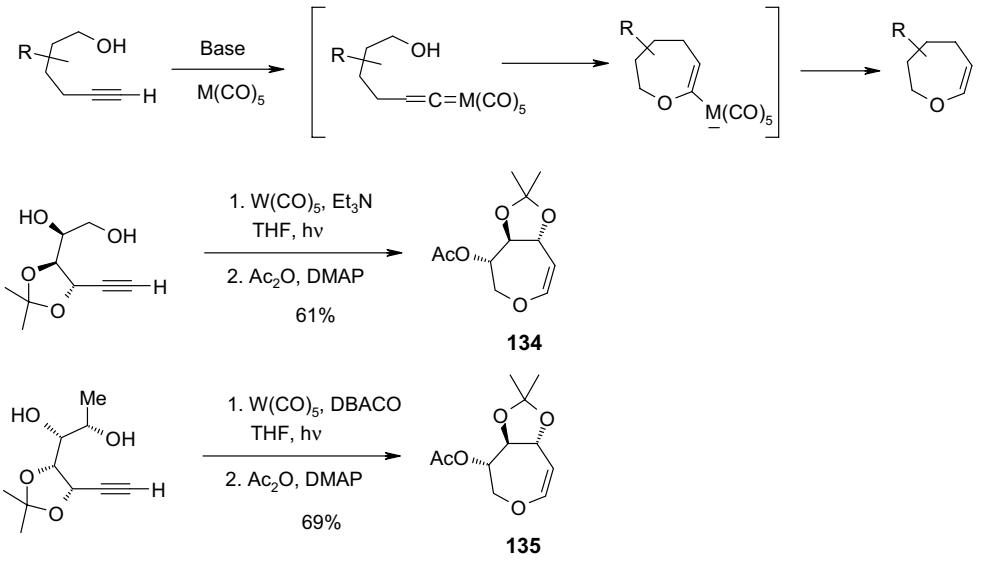
Scheme 21.24



Scheme 21.25

some 4,5,6,7-tetrahydrooxepines such as **134** and **135** from furanose-derived alkynols (Scheme 21.26) [152]. The cycloisomerization to the corresponding seven-membered cyclic enol ethers under tungsten carbonyl catalysis proceeds with good yields and virtually complete regioselectivity for all diastereomers, favoring the product resulting from *endo*-mode cyclization. The unexpected regioselectivity may be dependent on the presence of the dioxolane structure tethering the terminal alkyne and diol functional groups.

Palladium-mediated C−O bond formation via a cationic π-allylic palladium complex has proven its utility in the cyclization reaction of bromoallenes through intramolecular attack of an oxygen nucleophile. Appropriate allenes can



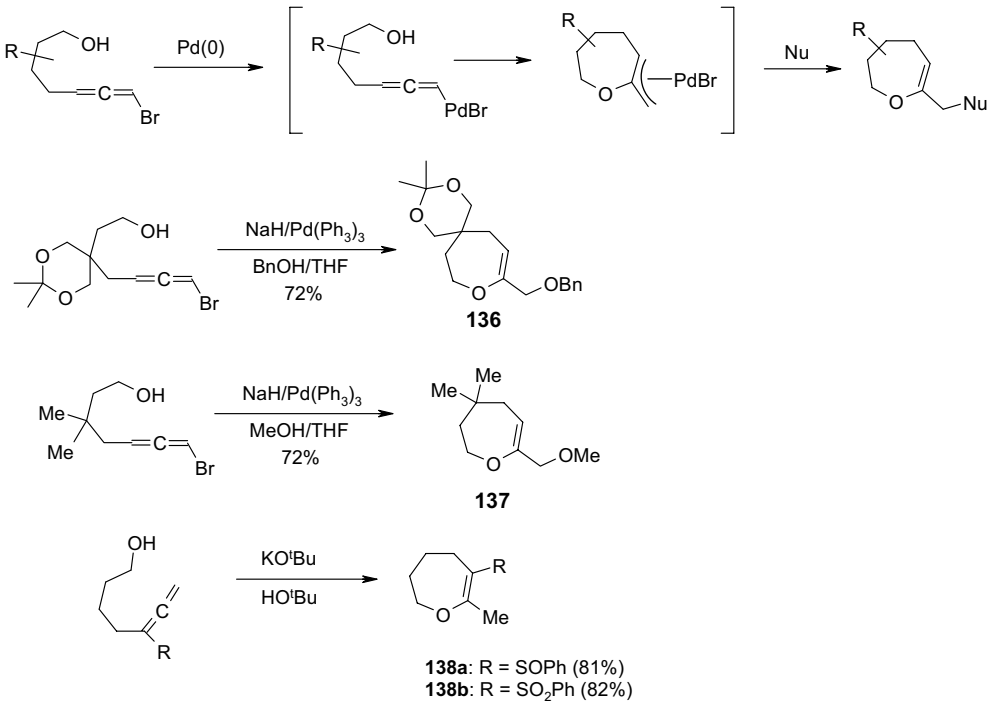
Scheme 21.26

lead to seven-membered rings that, in the presence of a second nucleophile, afford substituted 3,4,5,6-tetrahydrooxepines [153] **136** and **137** (Scheme 21.27). A mechanistically related reaction is the cyclization of allenyl sulfoxides and sulfones, which under basic conditions afford the corresponding 1-methyl-2-sulfinyl- and 1-methyl-2-sulfonyl-tetrahydro-oxepines **138a** and **138b** in goods yields [154].

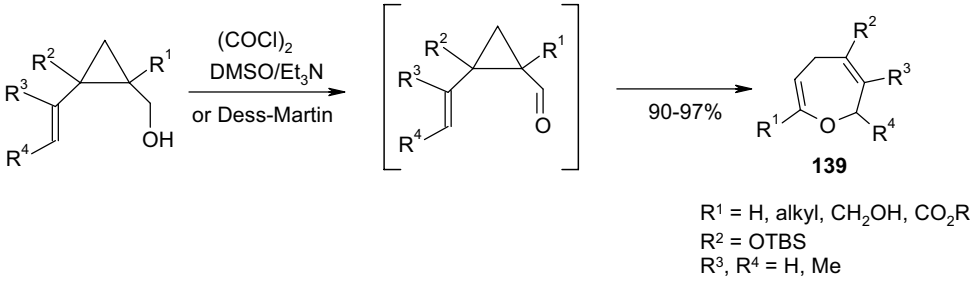
21.5.2.2 From Cyclic Compounds

21.5.2.2.1 **From Carbocycles** Three-, four-, and seven-membered carbocycles have been employed as starting materials for the construction of the oxepine ring system, although the most synthetically useful procedures involve cyclopropanes and cyclohexenes as starting carbocycles. The most efficient method for the synthesis of dihydro- and tetrahydrooxepines involves the ring expansion of alkenylcyclopropylcarbinols. These cyclopropane derivatives are transformed into the corresponding aldehydes under controlled oxidation conditions (Swern or Dess–Martin periodinane). Subsequent hetero-Cope rearrangement affords substituted 2,5-dihydrooxepines **139** (Scheme 21.28) [155]. MP2/6-31G* studies on vinylcyclopropane carbaldehyde as a model show that the aldehyde and the oxepine are almost isoenergetic and the activation energy is about 25 kcal mol^{-1} [156].

The ring expansion of a four-membered ring is illustrated by the formation in low yield of oxepine (**5**) from bicyclo[2.2.0]hexa-2,5-diene (Scheme 21.29). The method involves epoxidation of the bicyclobutene ring followed by rearrangement of the resulting tricycle [157]. The method has also been applied to the formation in low yield of perfluorinated dihydrooxepines **140** from perfluorobicyclo[2.2.0] hexanes [158].

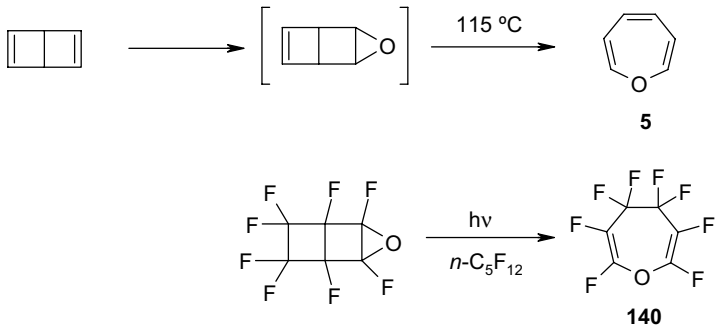


Scheme 21.27

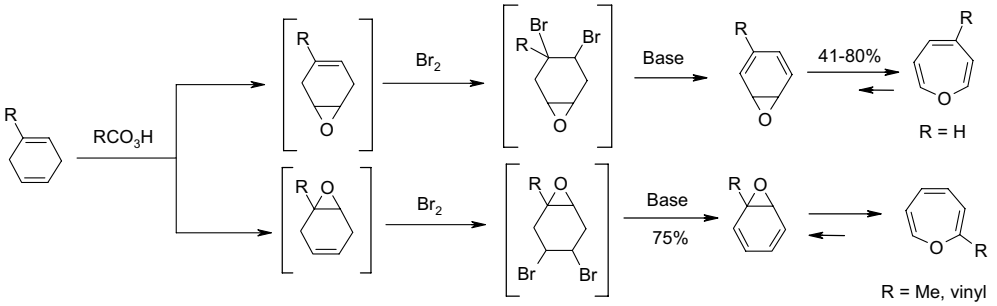


Scheme 21.28

The formation of the oxepine ring from six-membered carbocycles is one of the most useful routes to monocyclic oxepines. The method is based on the epoxidation and bromination of 1,4-cyclohexadienes. The dibromoepoxides, when subjected to dehydrohalogenation conditions, afford the corresponding oxepine–benzene oxides and these tautomerize to oxepines (Scheme 21.30). The electronic nature of the substituents in the cyclohexadiene ring determines which of the two possible substituted azepines is formed and this depends on which of the two double bonds are initially involved in the epoxidation or bromination reactions [159]. 2-Vinylox-



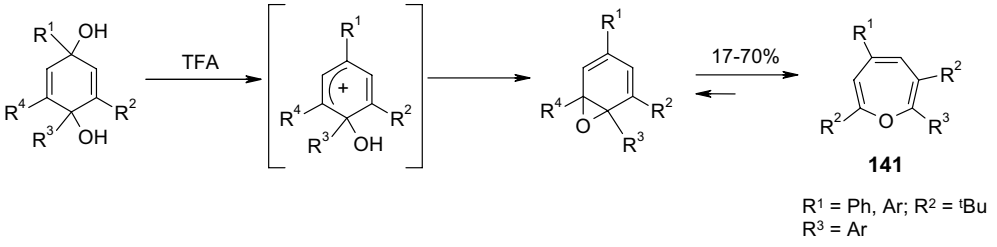
Scheme 21.29



Scheme 21.30

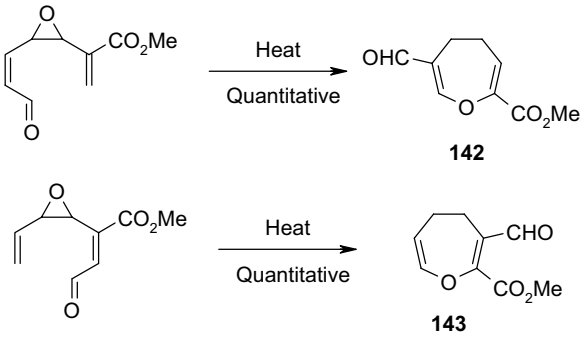
epine, one of the less stable oxepines, has been synthesized using this approach [160], which has also been used for the synthesis of disubstituted oxepines such as 2,7-diphenyloxepine [70a].

Arene oxides can also be formed by the acid-catalyzed dehydration of some substituted cyclohexene-1,4-diols. The subsequent ring expansion produces relatively stable polysubstituted oxepines **141** (Scheme 21.31) [161].



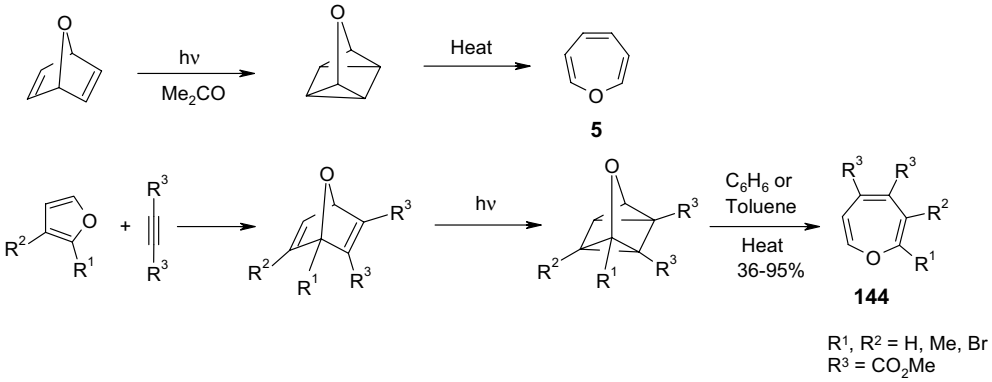
Scheme 21.31

21.5.2.2.2 **From Heterocycles** Oxiranes have been used as extensively starting heterocyclic compounds in the preparation of oxepanes. Some oxirane derivatives have also been employed in the synthesis of oxepine derivatives. The two examples shown in Scheme 21.32 lead to 2,6- and 2,3-disubstituted-4,5-dihydrooxepines **142** and **143**, respectively [162].



Scheme 21.32

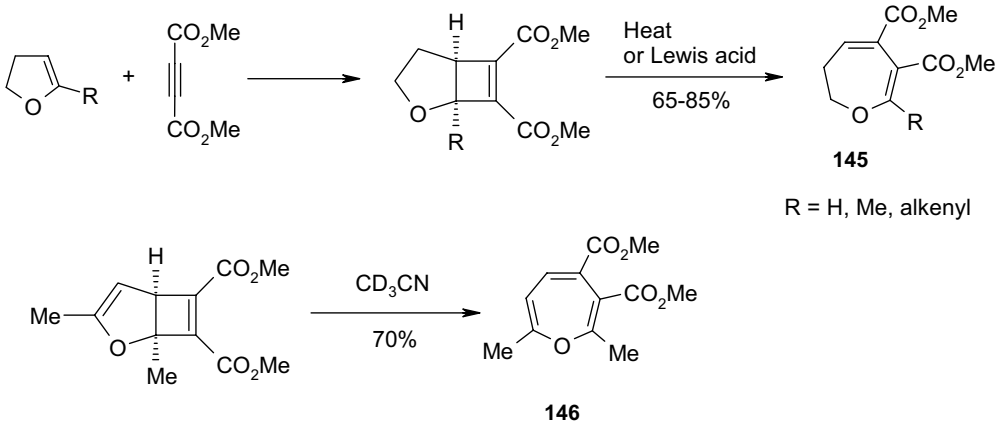
The parent oxepine (**5**) can be prepared by a short and efficient route starting from 7-oxanorbornadiene as the five-membered heterocycle. Isomerization of this bicyclic compound into the monocyclic oxepine is promoted photochemically and this is followed by thermal rearrangement [163]. Several di-, tri-, and tetrasubstituted oxepines **144** have been prepared using the same approach, which is based on a Diels–Alder reaction of substituted furans with alkynes to give the corresponding 7-oxonorbornadienes (Scheme 21.33) [164].



Scheme 21.33

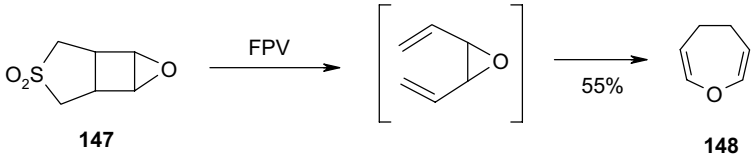
A 2,3-dihydrofuran is the starting material in a [2 + 2] cycloaddition reaction with alkynyl or alkenyl compounds to give bicyclic adducts, which in turn give 2,3-dihydrooxepines **145** by thermolysis or acid Lewis catalysis (Scheme 21.34) [165].

In a similar approach the substituted oxepine **146** can be obtained from a bicyclic furan derivative under thermolysis conditions [166].



Scheme 21.34

An alternative procedure for the synthesis of 4,5-dihydrooxepine (**148**) involved the use of the fused sulfolane **147**. This tricyclic system under flash vacuum pyrolysis produces the *cis*-2,3-divinyloxirane, which by a Cope rearrangement affords **148** in 55% yield (Scheme 21.35) [167].

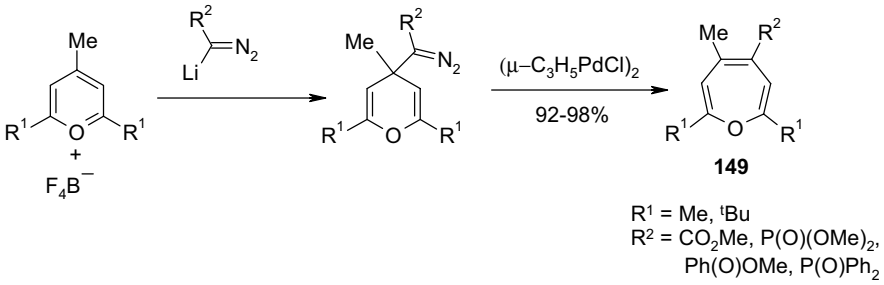


Scheme 21.35

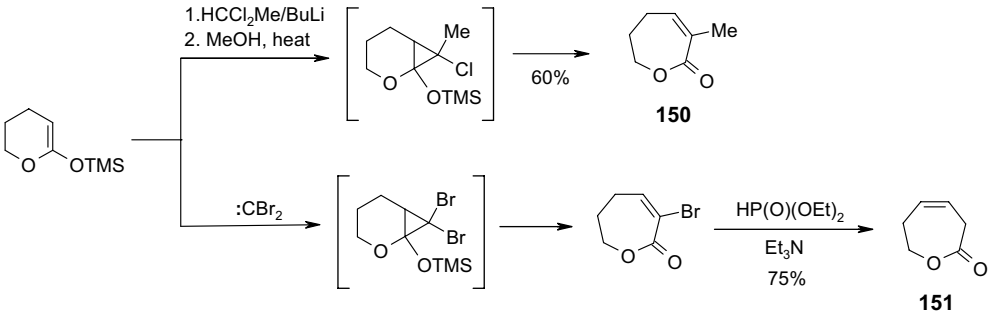
Six-membered O-heterocycles have also been used as starting materials in different approaches to oxepines. One of the most efficient routes starts with pyrilium salts, which are converted into the 4-diazomethyl-4*H*-pyrans. A ring enlargement promoted by allylpalladium chloride as a catalyst affords the corresponding substituted oxepines **149** in almost quantitative yield (Scheme 21.36) [168].

Another route to dihydrooxepinones involves the reaction of 2,3-dihydropyran derivatives with carbenes. The intermediate bicycles undergo a similar ring expansion process to that shown in Scheme 21.37, giving the corresponding tetrahydrooxepinones **150** [169] and **151** [170].

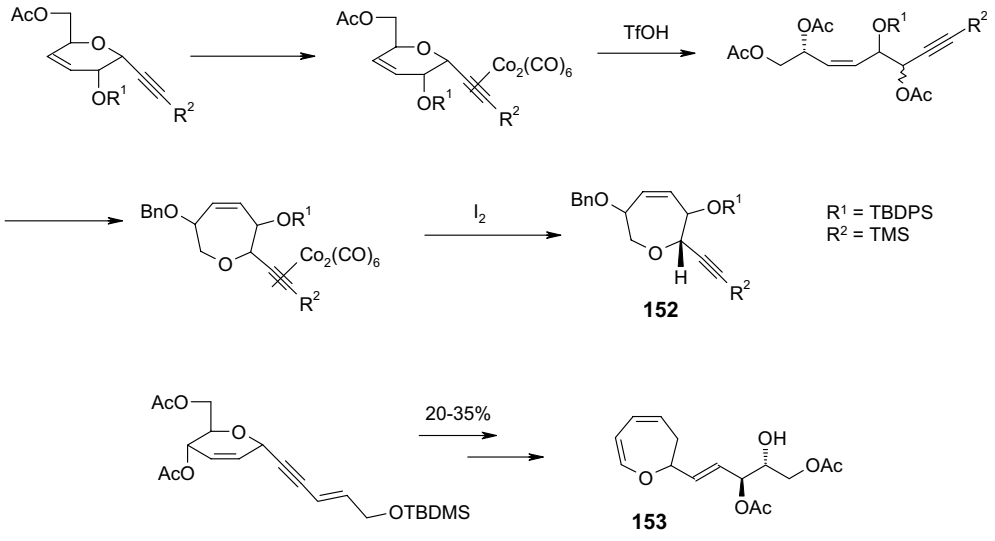
Alkynylpyranosides have also been used as starting heterocyclic compounds for the synthesis of oxepines. Examples of this strategy are shown in Scheme 21.38 for the synthesis of tetrahydrooxepines **152** and dihydrooxepine **153**. The synthetic route starts with the formation of the cobalt complexes and this is followed by a



Scheme 21.36



Scheme 21.37



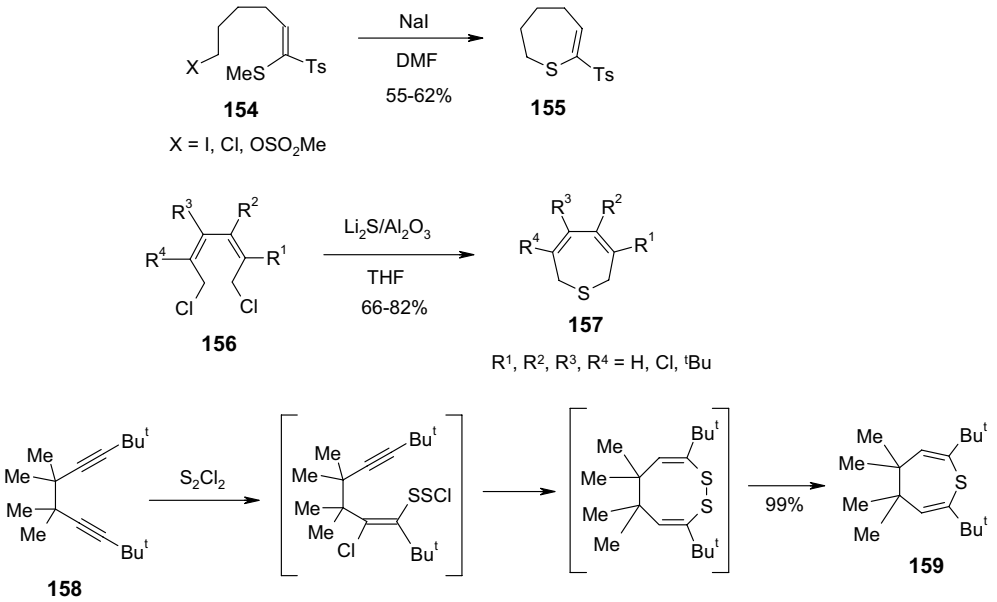
Scheme 21.38

ring-opening reaction catalyzed by TfOH. Recyclization of the resulting ring-opening products followed by decomplexation affords the corresponding oxepine derivatives [171].

21.5.3 Synthesis of Thiepines

21.5.3.1 From Acyclic Compounds

Although cyclization reactions have been used extensively for the synthesis of thiepane derivatives, the use of acyclic compounds as starting materials in thiepine synthesis is very limited. One of the few examples was reported in 2001 for the synthesis of the 2-tosyl-4,5,6,7-tetrahydrothiepine (**155**), which was obtained by cyclization of the hexane derivatives **154** in the presence of sodium iodide in DMF (Scheme 21.39) [172]. It was suggested that cyclization of the chloride and methanesulfonate takes place via the iodo derivative.

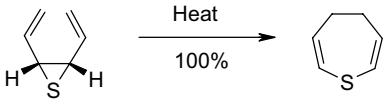


Scheme 21.39

Based on a reported method for the synthesis of the parent thiepane by a double nucleophilic substitution, the reaction of the dienic dichlorides **156** with Li_2S gave the corresponding 2,7-dihydrothiepines **157** in moderate or good yields (Scheme 21.39) [173]. An excellent yield has been reported for the reaction of decadiyne **158** with S_2Cl_2 to afford the 4,5-dihydrothiepine **159** [174] through the mechanism shown in Scheme 21.39.

21.5.3.2 From Cyclic Compounds

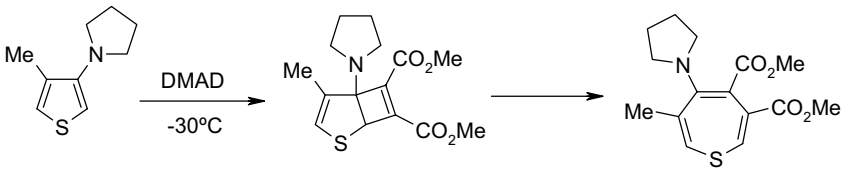
21.5.3.2.1 **From Heterocycles** A similar thermal rearrangement to that used for the synthesis of 4,5-dihydrooxepine from divinyloxirane has been reported for the preparation of the corresponding 4,5-dihydrothiepine **160** from *cis*-1,2-divinylthiirane (Scheme 21.40) [175].



160

Scheme 21.40

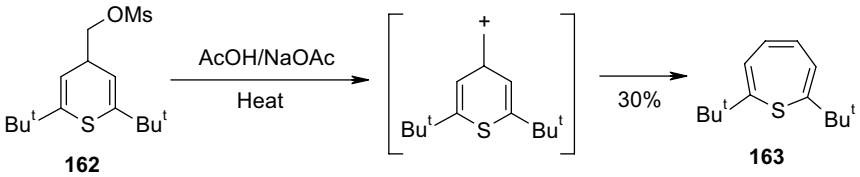
Stable monocyclic thiepines have been obtained from thiophene derivatives, which react with DMAD in a cycloaddition reaction to afford the corresponding bicyclic adduct. Subsequent thermal isomerization gave the first monocyclic thiepine **161**, which has been fully characterized (Scheme 21.41) [176].



161

Scheme 21.41

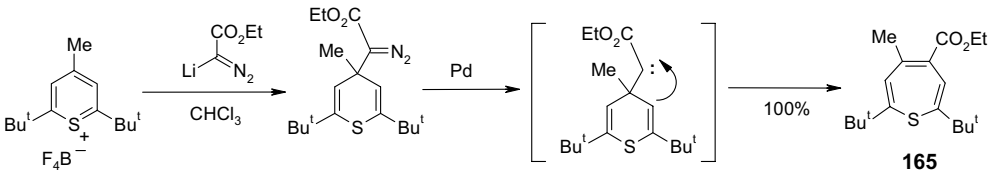
The ring expansion of thiopyrans has been used as the main strategy to synthesize monocyclic thiepines, although moderate or low yields have usually been obtained. For example, one of the most widely studied thiepines, 2,7-di-*tert*-butylthiepine **163**, was obtained in 30% yield from the thiopyran derivative **162** by treatment with acetic acid in the presence of sodium acetate and acetic anhydride at 90 °C. The formation of the seven-membered ring is assumed to take place via the carbenium ion intermediate under the solvolysis conditions (Scheme 21.42) [71].



162 **163**

Scheme 21.42

Six-membered thiopyrylium salts have also been used as starting heterocycles in the synthesis of other stable monocyclic thiepines. For example, salts **164** react with ethyl lithiodiazoacetate to give the corresponding thiopyrans, which in the presence of palladium or under acidic conditions are able to generate the corresponding substituted thiepines **165** via a carbene intermediate (Scheme 21.43) [177].



Scheme 21.43

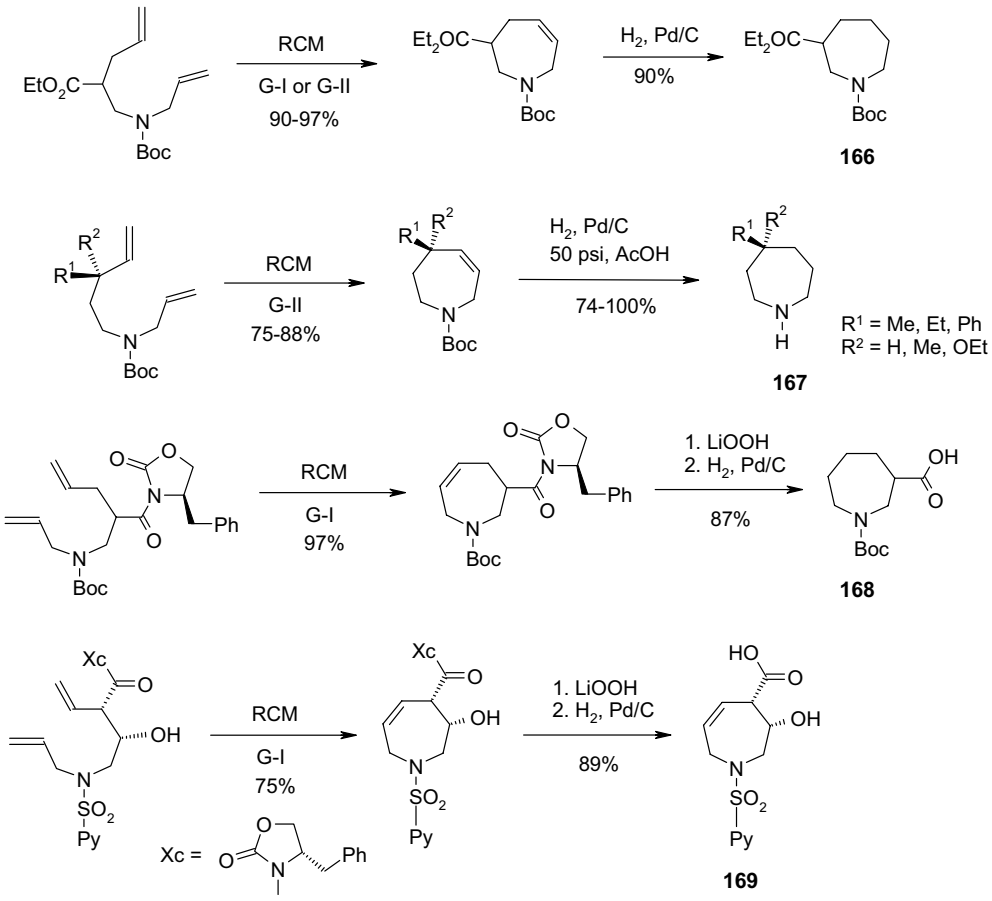
21.5.4
Synthesis of Azepanes, Oxepanes, and Thiepanes

Most of the synthetic methodologies based on cyclization reactions used for the preparation of monocyclic azepine, oxepine, and thiepine derivatives can also be applied to the synthesis of fully unsaturated seven-membered systems **7–9**, especially given that hydrogenation of dihydro-, tetrahydro-, or even fully unsaturated seven-membered heterocyclic rings is an easy process that can be carried out under very mild conditions. A RCM reaction followed by hydrogenation of the resulting dihydro derivative is one of the most successful approaches to azepane systems. Several examples of this strategy are represented in Scheme 21.44 [109, 178].

Several densely functionalized chiral azepanes have been prepared by multistep sequences starting from carbohydrates. In a typical example, an appropriate carbohydrate is transformed into a suitable amine or azide, such as **170** [179] or **172** [180], and this is cyclized to the corresponding azepane derivatives **171** and **173** under the conditions shown in Scheme 21.45.

Two classical synthetic approaches are useful in the synthesis of azepin-2-ones and these include the industrial synthesis of hexahydro-1*H*-azepin-2-one (**33**) (ε-caprolactam). One is the Beckmann rearrangement of oximes generated from cyclohexanones [181] and the other is the Schmidt reaction applied to cyclohexanones [182]. The main problem associated with these reactions as synthetic strategies for some azepinone derivatives is that unsymmetrically substituted cyclohexanones can give two isomeric products (Scheme 21.46).

In a similar strategy to that used for the synthesis of azepane, dihydro- and tetrahydrooxepines have been transformed into oxepane (**8**) by catalytic hydrogenation under standard conditions, such as those used on the conversion of 2,3-tetrahydrooxepine into oxepane (Scheme 21.47) [183].

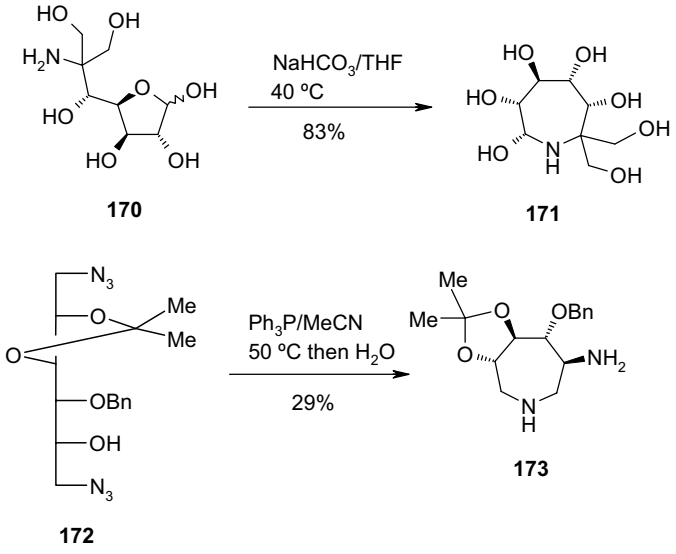


Scheme 21.44

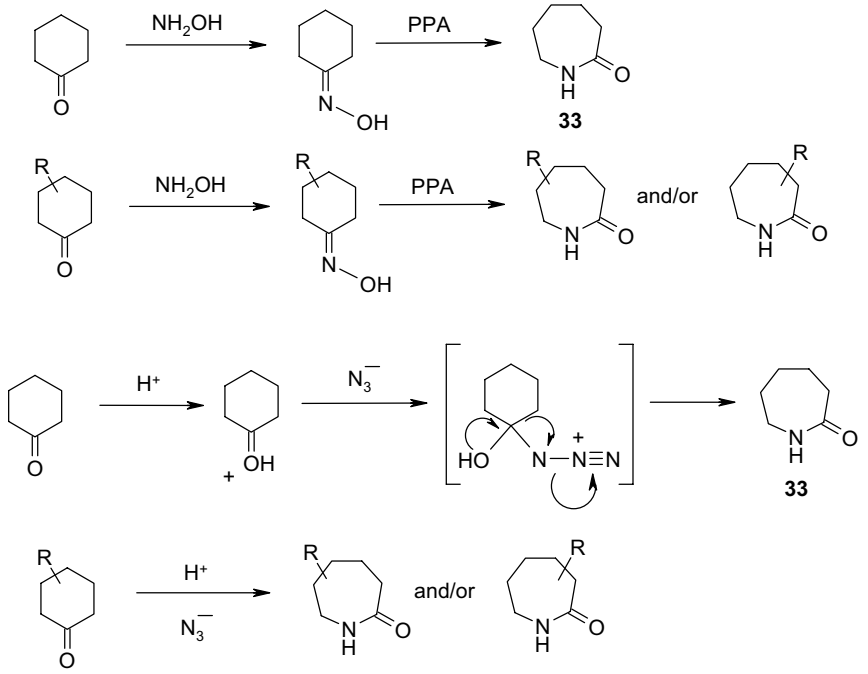
Another of the most widely used approaches to oxepane (**8**) and oxepane derivatives such as **174** is the intramolecular cyclization of 1,6-hexanediols using various dehydrating agents (Scheme 21.48) [184].

Other similar cyclization reactions of 1,6-disubstituted hexanes involving different leaving groups in the presence of various catalysts have also been employed in the synthesis of oxepane derivatives (Scheme 21.49) [185]. One of the most interesting versions of this cyclization is the regioselective intramolecular ring-opening reaction of epoxyalcohols catalyzed by acidic or basic conditions, a strategy that has been successfully used in the total synthesis of polyethers [16, 186]. Careful control of the ring-opening process is necessary to avoid the formation of the tetrahydropyran derivative.

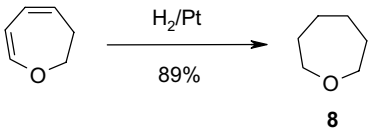
The Baeyer–Villiger oxidation [187], a typical transformation of cyclic ketones into lactones, has been used in the synthesis of seven-membered lactones (ε-caprolactones) from cyclohexanone derivatives in the presence of typical peracids



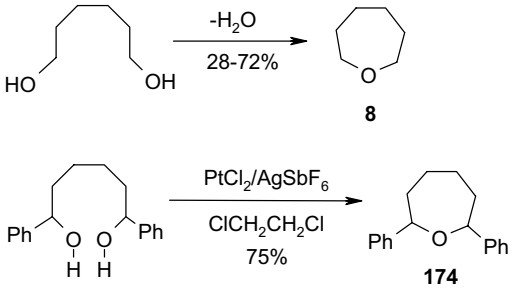
Scheme 21.45



Scheme 21.46



Scheme 21.47



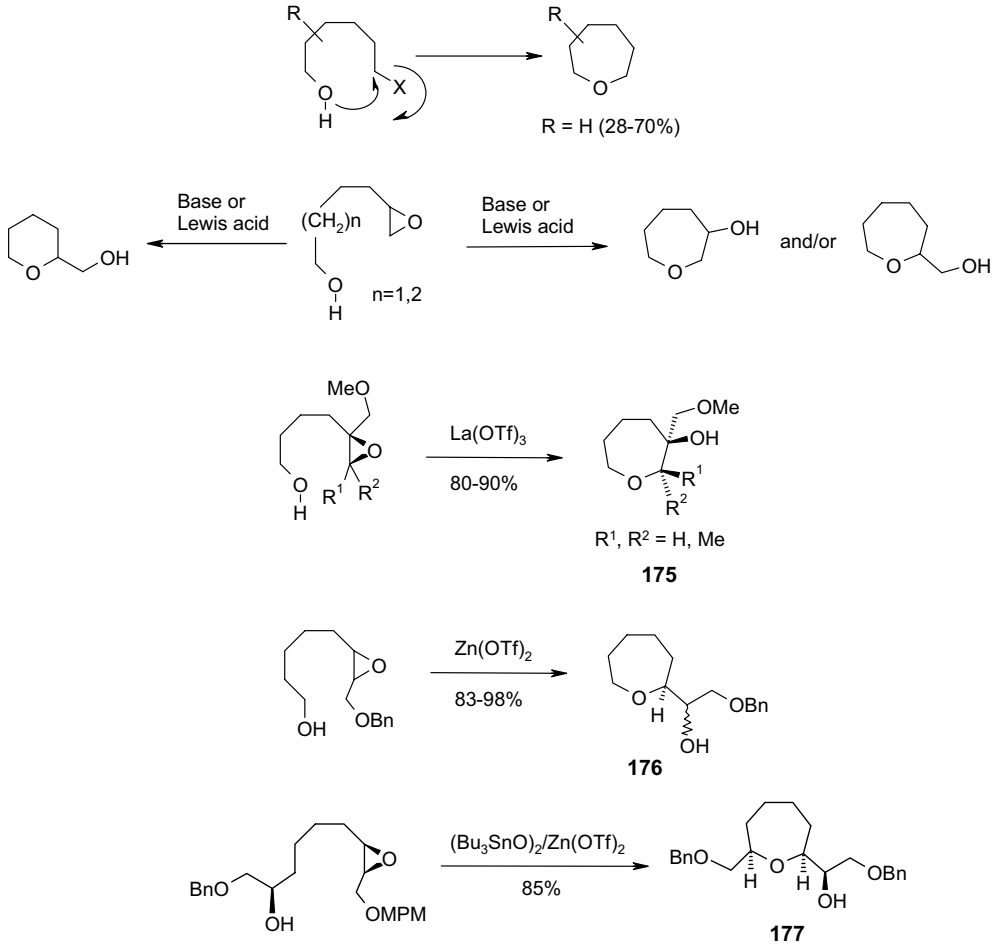
Scheme 21.48

(Scheme 21.50). Some recent developments include oxidation by urea/hydrogen peroxide and trifluoroacetic anhydride [188], and aqueous hydrogen peroxide with diaryl diselenides [189] or tin zeolite [190]. Additionally, some biocatalytically driven methods include monooxygenase [191] and genetically modified yeasts [192] as well as the combination of hydrogen peroxide and myristic acid catalyzed by lipases [193]. The use of oxygen as an oxidant catalyzed by mixtures of Fe(II) and Ni(II) or with MnO_2 or RuO_2 in the presence of benzaldehyde has also been reported [194]. The use of chiral metallic complexes gave lactones in high ee yields [195]. Some representative examples of these oxidations are shown in Scheme 21.50 for lactones **179–181**.

Thiepane (**9**) was first obtained by a radical cyclization reaction of 5-hexenethiol under photolysis conditions (Scheme 21.51) [196]. It has also been prepared by a double nucleophilic substitution from 1,6-dibromohexane either using sodium sulfide (59%) [197] or, better still, by *in situ* generated lithium sulfide (from hexamethyldisilathiane and methyllithium in a polar aprotic solvent) (Scheme 21.51) [198].

Chiral thiepane derivatives such as **182** and **183** have been synthesized by a thio-heterocyclization method involving bis-epoxides and a sulfide salt [199]. This approach is based on an initial regioselective ring opening of one of the epoxides followed by attack of the resulting thiolate to the other epoxide to form the seven-membered thiepane ring (Scheme 21.52).

Thiepan-2-one (**184**) has been prepared by a similar strategy to that employed for **9** by cyclization of 6-bromohexanoic acid chloride using lithium sulfide generated *in situ* (Scheme 21.53) [200]. The synthesis of thiepan-3-one (**185**) was described initially by a Dieckmann-type cyclization [201] and later by reaction of the thiacyclohexan-3-one with diazomethane [202], a procedure also employed for the preparation of the thiepan-4-one (**186**) [203] (Scheme 21.53).



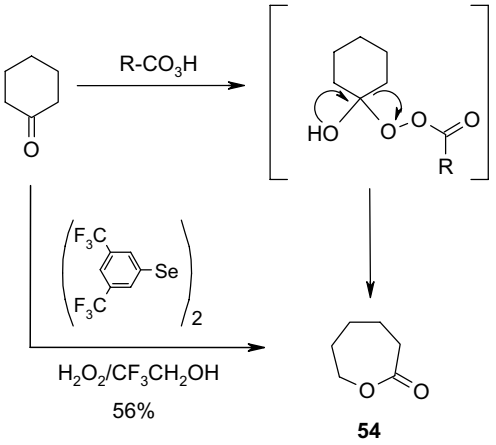
Scheme 21.49

21.5.5 Synthesis of Benzo Derivatives

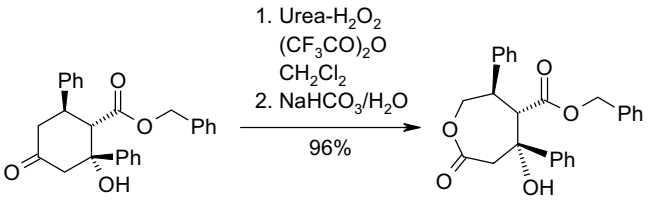
21.5.5.1 Synthesis of Benzazepines

The three isomeric parent benzazepines are not known, although stable derivatives of **12**, **15**, and **18** have been prepared using many of the synthetic strategies employed in the preparation of monocyclic azepines.

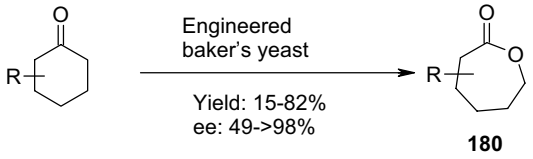
1*H*-1-Benzazepine derivatives **187** have been obtained by cyclization reactions [204, 205]. An unusual ring expansion of quinolinium salts also afforded *N*-substituted derivatives **188** in good yields [206], and the ring-closing metathesis reaction is an important method for the preparation of stable dihydro derivatives [207] (Scheme 21.54).



54

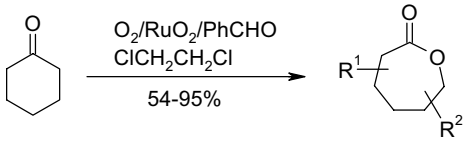


178 **179**



180

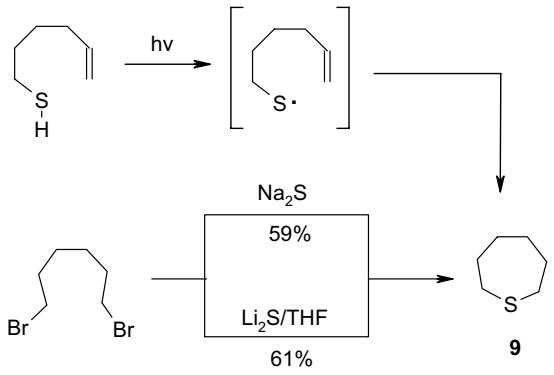
R = Me, Et, *n*-Pr, *i*-Pr, allyl, *n*-Bu



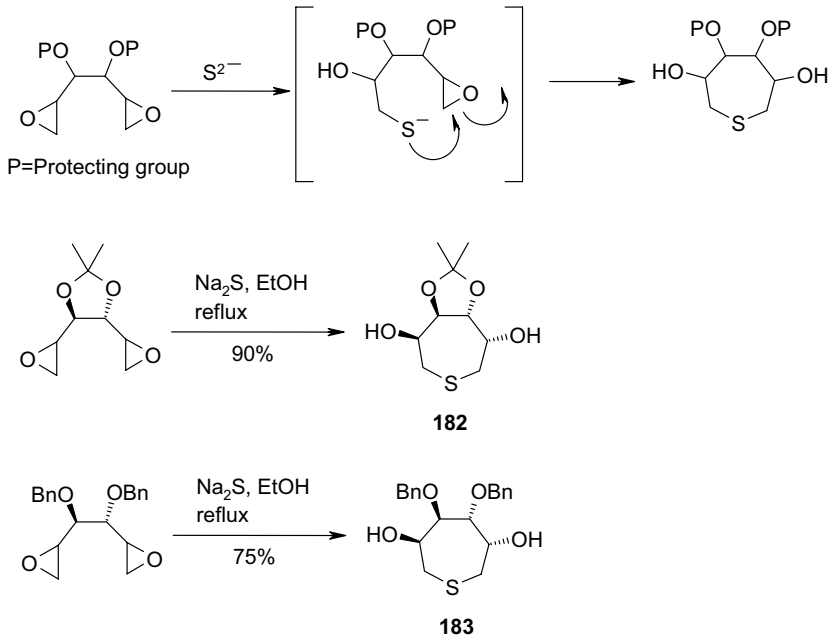
181

R^1 = H, Me
R^2 = H, Me, $(CH_2)_6Me$, *i*-Pr, *t*-Bu, CH_2CH_2COMe

Scheme 21.50



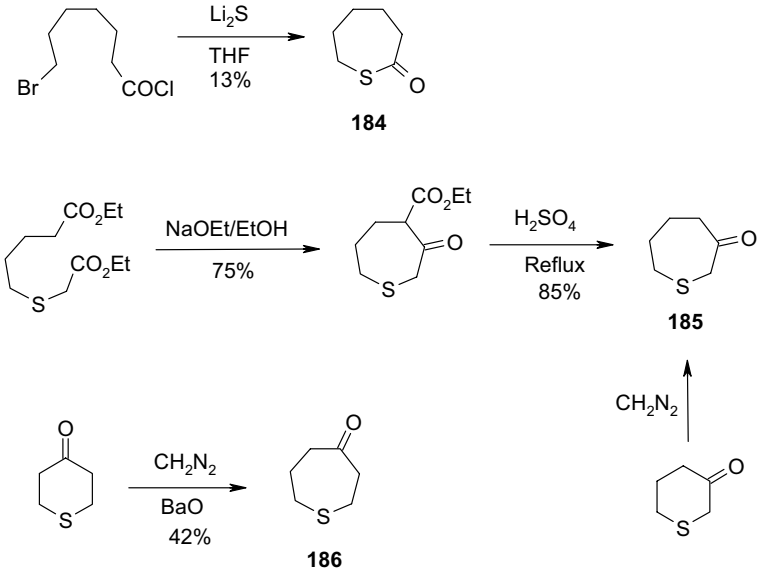
Scheme 21.51



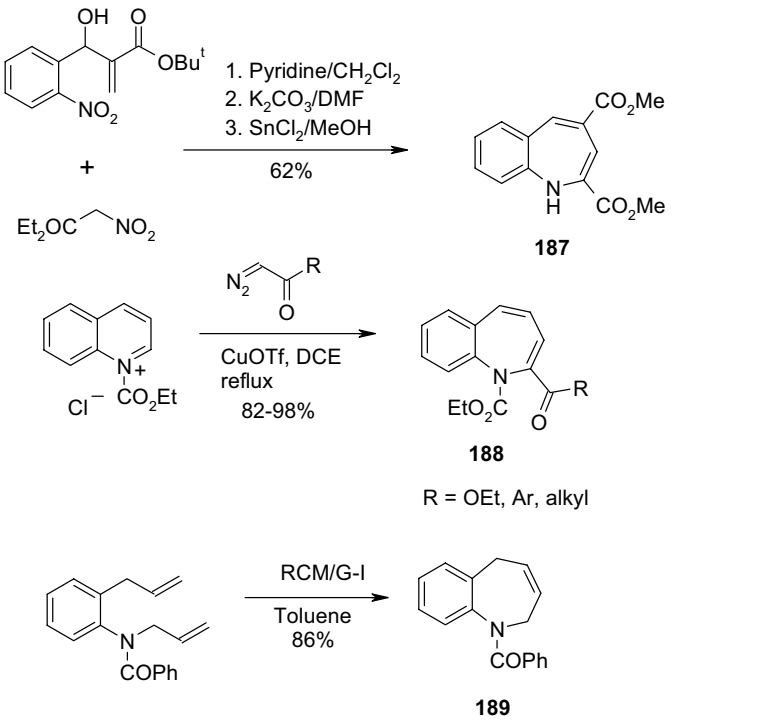
Scheme 21.52

2*H*-2-Benzazepine (**15**) is unknown and only a few 1*H*-, 3*H*-, and 5*H*-derivatives have been prepared. The examples shown in Scheme 21.55 include a ring expansion of dihydroisoquinolines **190** [208], the ring-closing metathesis reaction of diene **193** [209], the acid-catalyzed cyclization of phenylsulfanylacrylamides **195** [210], and the transformation of nitrones **197** into the 1*H*-2-benzazepin-3-ones **198** by a complex mechanism [211].

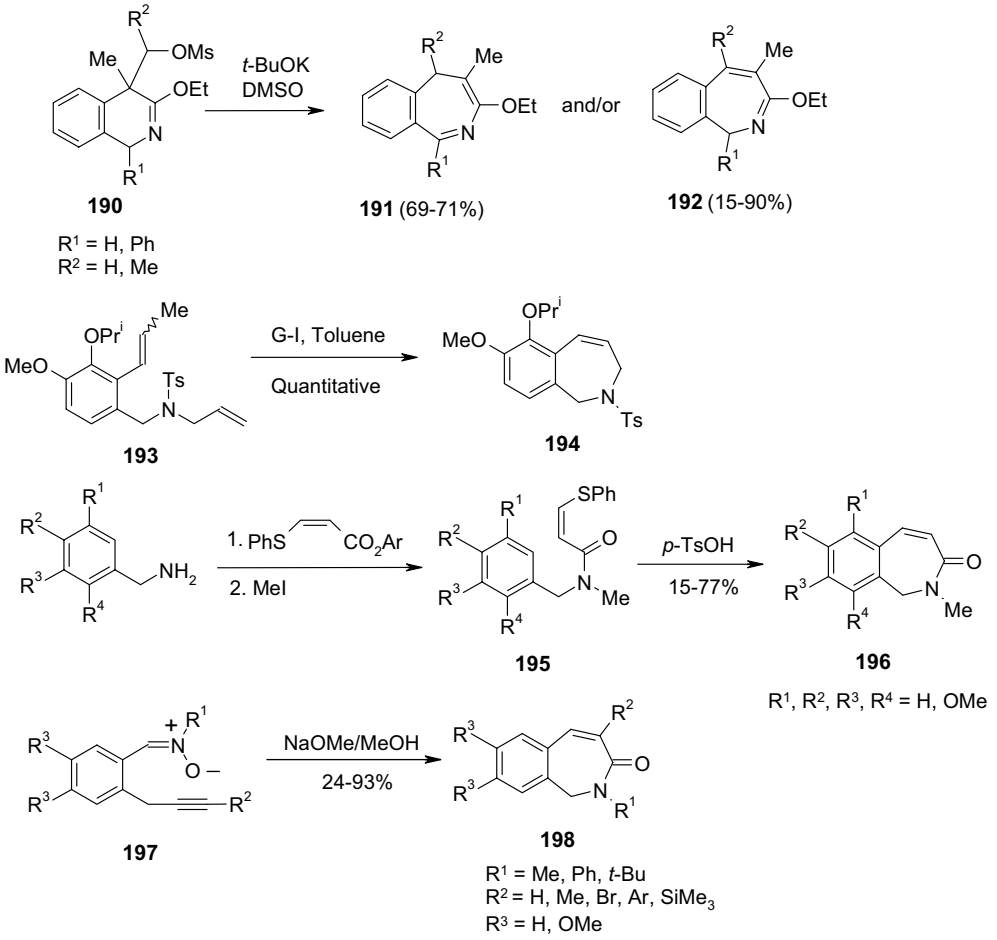
3*H*-3-Benzazepines are known as 1*H*-tautomers or *N*-substituted derivatives but the parent compound **18** remains unknown. As is the case for 2*H*-2-benzazepines,



Scheme 21.53



Scheme 21.54

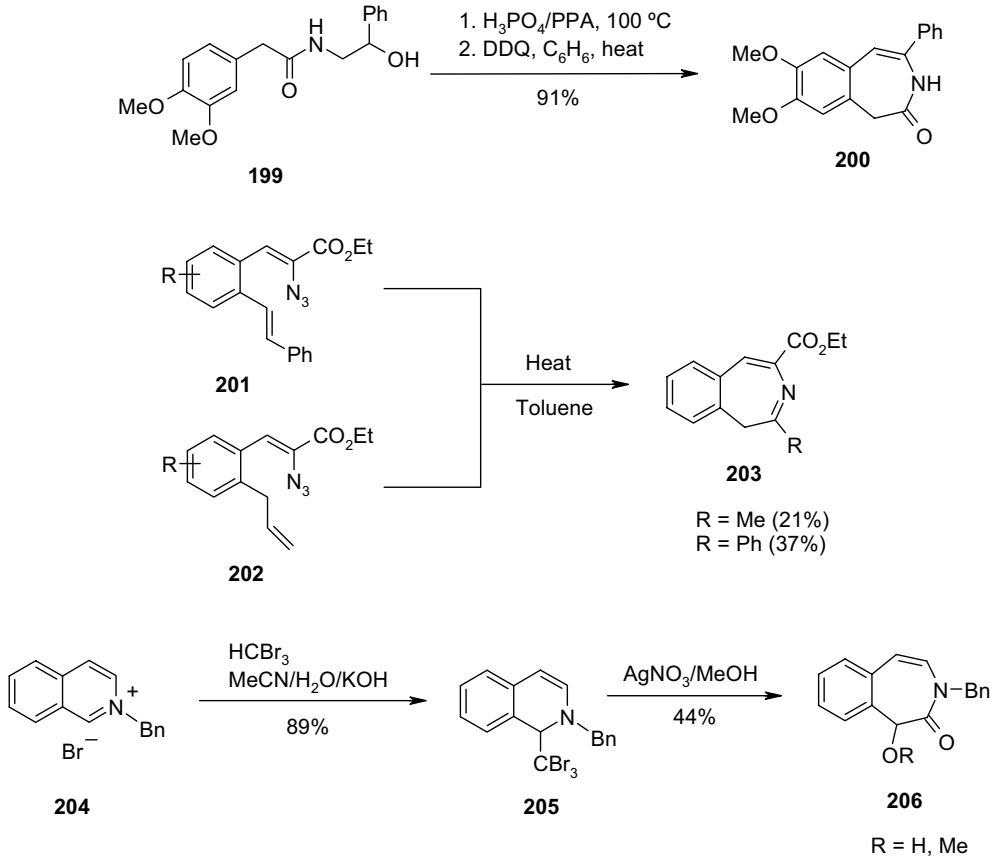


Scheme 21.55

the number of known derivatives is limited and only a few procedures are synthetically useful for the preparation of such compounds. These methods include the synthesis of derivatives **200** from **199** [212], the insertion of nitrenes generated *in situ* from thermolysis of azidocinnamates such as **201** and **202** [213], and the ring expansion of isoquinolinium salts **204** [214] (Scheme 21.56).

21.5.5.2 **Synthesis of Benzoxepines**

The parent 1-benzoxepine (**13**) was first obtained from a tetrabromoepoxide precursor (**207**), which under basic conditions is transformed into the corresponding arene oxide **208**. The valence tautomerization of **208** yields a mixture of **13** and the bicyclic oxepine **209** [215]. The reaction of pyridazine *N*-oxide with benzyne produced **13** (and some derivatives from pyridazines) in moderate yield, via a 1,3-cycloadduct [81b]. An intramolecular Wittig reaction on **210** also afforded **13** in 25% yield



Scheme 21.56

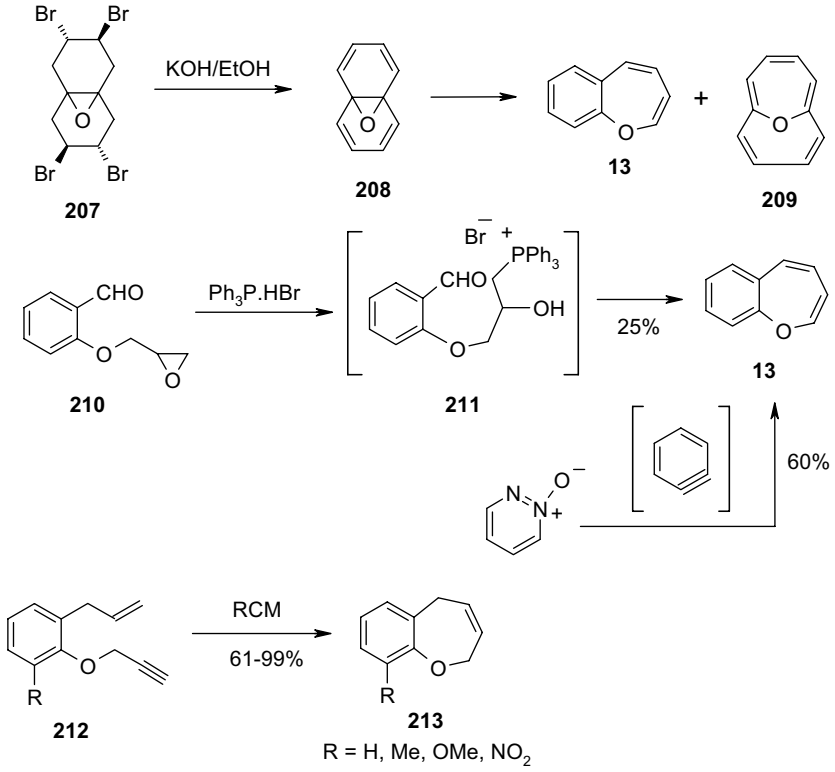
(Scheme 21.57) [216]. The RCM reaction of enynes **212** has also been used in the synthesis of dihydro-1-benzoxepines **213** with yields ranging from 61% to 99% depending on the reaction conditions [217].

2-Benzoxepine (**16**) has not been prepared to date and only a few derivatives are available. For example, the dihydro derivatives **214** have been obtained by the cyclization of allene ethers in the presence of palladium catalysts [218]. 2-Benzoxepin-5-ones **215** have been prepared in a multistep synthesis from phthalides (Scheme 21.58) [219].

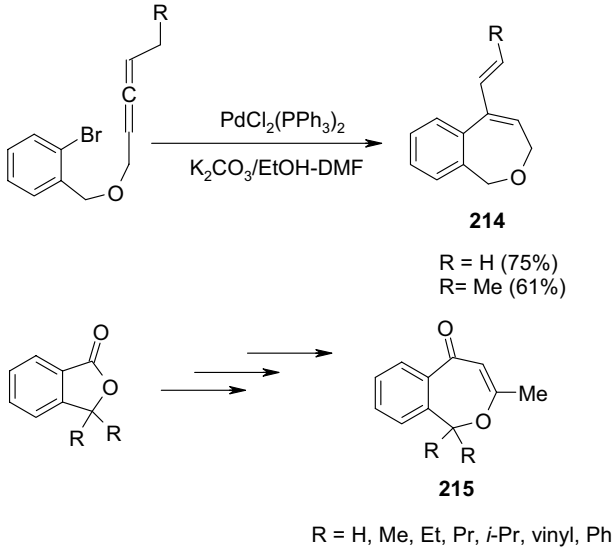
3-Benzoxepine (**19**) has been prepared in 55% yield from phthalaldehyde and an appropriate bis-phosphonium salt by a double Wittig reaction (Scheme 21.59) [220].

21.5.5.3 **Synthesis of Benzothiepines**

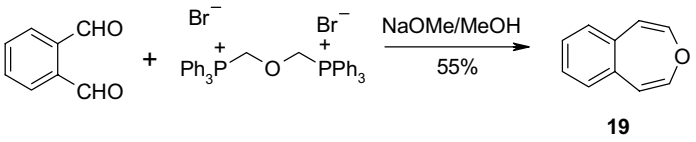
The parent 1-benzothiepine (**14**) and various substituted 1-benzothiepines **218** have been obtained from 2*H*-1-benzothiopyrans **216**. This precursor reacts with *n*-BuLi/CH_2Cl_2 and the intermediate anions formed by quenching with electrophiles afford



Scheme 21.57



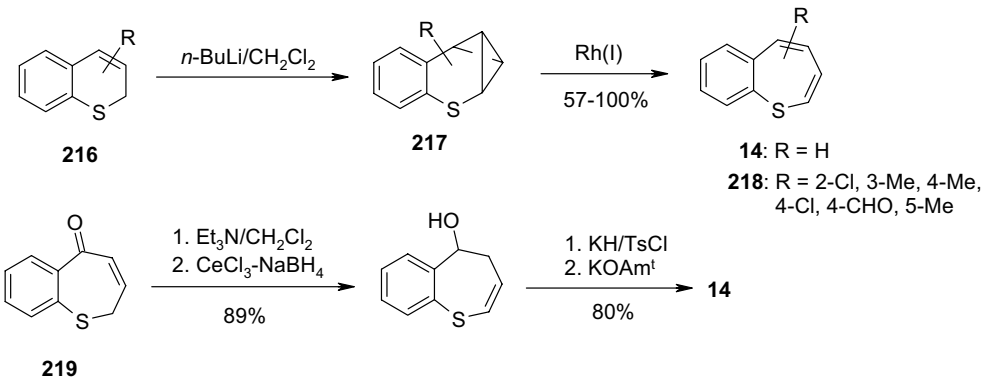
Scheme 21.58



19

Scheme 21.59

the tetracyclic compounds **217**, which under mild conditions in the presence of a Rh (I) catalyst isomerize to the corresponding 1-benzothiepines (Scheme 21.60) [221]. An alternative route to **14** has been described from the 1-benzothiepinone **219** in a four-step sequence that involves isomerization of the double bond in the presence of Et_3N, reduction of the ketone with $CeCl_3/NaBH_4$, formation of the tosylate, and elimination with potassium *tert*-amylate [81b] (Scheme 21.60).



216 **217**

14: R = H

218: R = 2-Cl, 3-Me, 4-Me, 4-Cl, 4-CHO, 5-Me

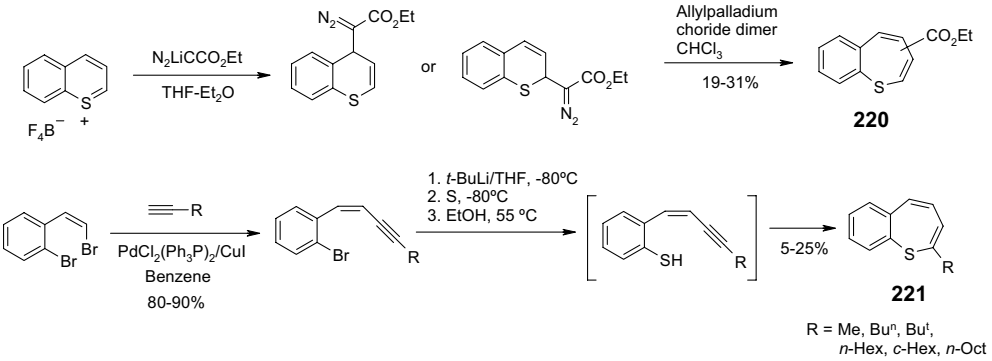
219

Scheme 21.60

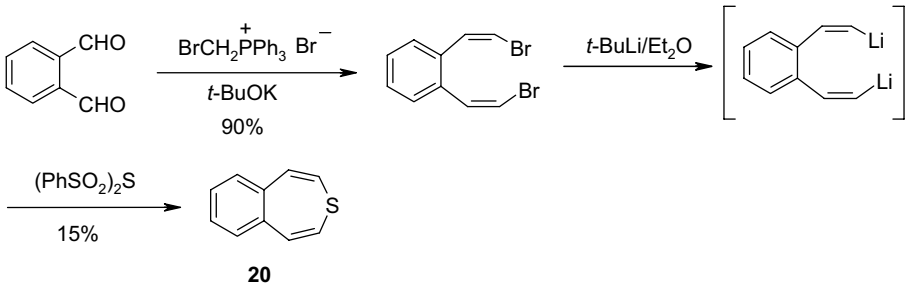
The ring expansion method shown in Scheme 21.43 for the preparation of monocyclic thiepines has also been employed in the synthesis of ethoxycarbonyl-substituted 1-benzothiepines **220** from benzo-1-thiopyrilium tetrafluoroborate [222]. The reaction of dibromostyrene with alkynes in the presence of a palladium catalyst leads to the formation of the corresponding enynes in good yields. These enynes can be transformed into 2-alkyl-1-benzothiepines **221** in moderate or low yields by metalation with *tert*-butyllithium followed by reaction with sulfur and ethanol (Scheme 21.61) [223].

Although 2-benzothiepane and some derivatives have been described, the parent 2-benzothiepine (**17**) and stable simple derivatives remain unknown. However, 3-benzothiepine (**20**) has been prepared from phthalaldehyde [224] under the conditions shown in Scheme 21.62.

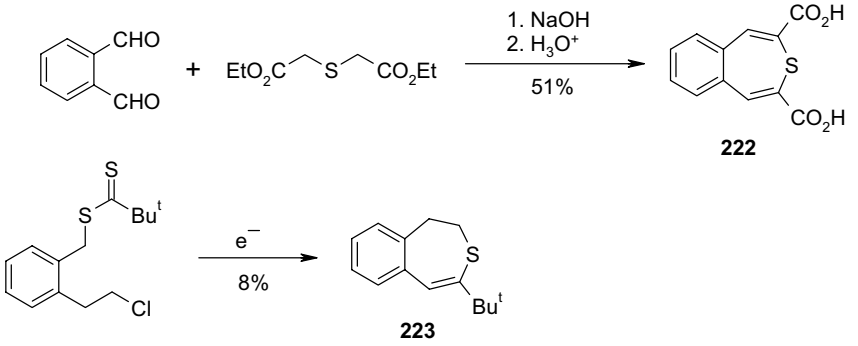
Among the few simple 3-benzothiepine derivatives known, the dicarboxylic acid was the first 3-benzothiepine derivative obtained from phthalaldehyde by a double Knoevenagel condensation (Scheme 21.63) [225]. The 2-*tert*-butyl-4,5-dihydrobenzothiepine (**223**) is reported to be obtained by cathodic reduction [226].



Scheme 21.61



Scheme 21.62

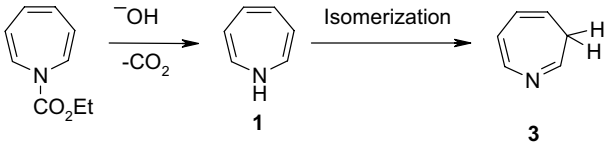


Scheme 21.63

21.6
Reactivity of Azepines

21.6.1
Reactivity of Azepines and Benzofused Derivatives

As stated above, the azepine systems occur in four tautomeric forms, and the derivatives of the 1*H*- and 3*H*-tautomers are the most widely studied. The parent heterocycle 1*H*-azepine (**1**) is a red oil that rearranges in the presence of acid or base to the more stable 3*H*-azepine (Scheme 21.64). The 1*H*-azepine tautomer is unstable [83, 227] and, as a consequence, only *N*-substituted derivatives of 1*H*-azepine exist in the 1*H*-tautomeric form. The 4*H*-azepine can be isolated and stored but in basic solution also isomerizes to the 3*H*-azepine.



Scheme 21.64

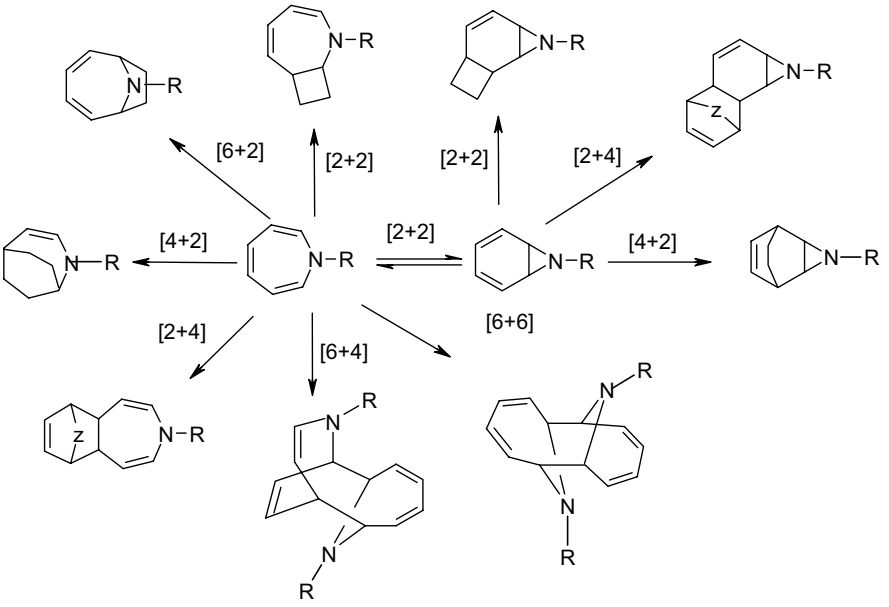
The stability of the 1*H*-azepine is enhanced by the presence of electron-withdrawing substituents, particularly at the 1-position, because they decrease the electron density in the 8π antiaromatic ring system. Consequently, reduced and partially reduced azepines are particularly common, together with the benzo derivatives.

The increase in ring size constrains these compounds and they are nonplanar so as to decrease the ring strain. The lack of planarity, however, affects aromaticity, and so the reactivity of unsaturated azepines is similar to that of cyclic polyenes. In general, the reactions of these compounds involve neutral molecules. Although stable as anions, the cations or radicals derived from azepines are less common, but some processes have been described as occurring through these species, particularly for partially saturated systems. Thus, anions derived from 1*H*-, 3*H*-, and 4*H*-azepines are difficult to obtain because they would lead to the formation of antiaromatic 8π species; however, annulation increases the stability and in 2004 the generation of the first azepinium ion reported [228]. Recently, attention has been drawn to the role of azepinium ions as intermediates in different reactions.

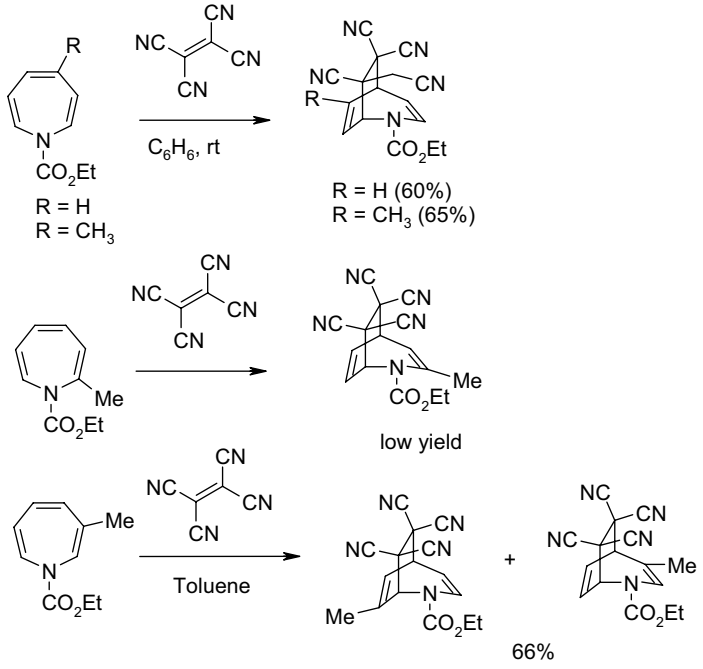
21.6.1.1 Cycloaddition Reactions

The polyenic structure of an azepine and its bicyclic tautomer both determine its reactivity in cycloaddition reactions [9]. Thus, azepines can participate in cycloaddition reactions as 2π, 4π, or 6π components (Scheme 21.65).

Cycloaddition reactions of N-substituted azepines with various dienophiles have been studied. For example, 1-alkoxycarbonyl-1*H*-azepines undergo [4 + 2] π Diels–Alder reactions with most dienophiles at the C2−C5 positions, as exemplified in Scheme 21.66 with tetracyanoethylene (TCNE) [229]. On the other hand, asymmet-



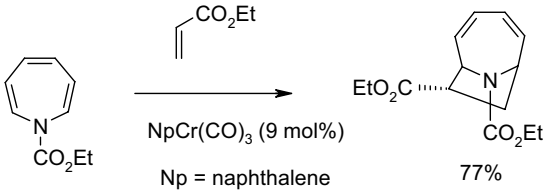
Scheme 21.65



Scheme 21.66

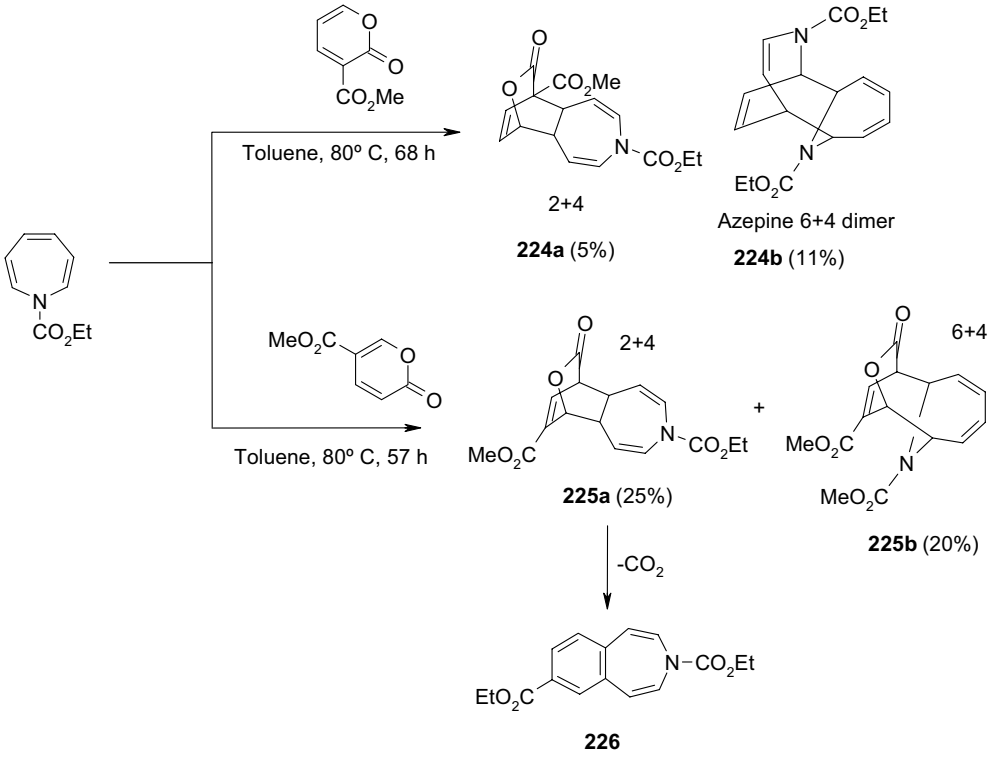
rically substituted 1*H*-azepines can undergo addition at C4−C7 or a mixture of isomers can result from C2−C5 and C4−C7 addition [230].

However, the presence of sterically bulky substituents at C3 and C6 makes the azepine function as a triene-[6 + 2] π-system; this is the case even with unsubstituted azepines when the reaction is performed in the presence of tricarbonylchromium(0) to produce the homotropane as a single diastereomer in 77% yield (Scheme 21.67) [231].



Scheme 21.67

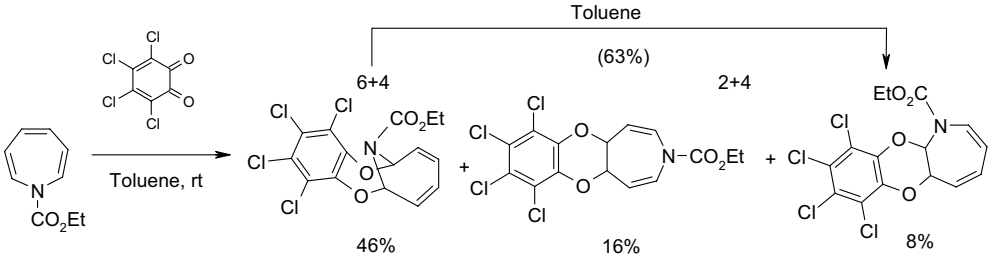
The ability of alkyl-1*H*-azepine-1-carboxylate to participate simultaneously as a diene and dienophile in cycloaddition reactions can be exemplified by the reaction of methylpyrone-3-carboxylate (Scheme 21.68) and the 5-isomer [232]. The 3-substi-



Scheme 21.68

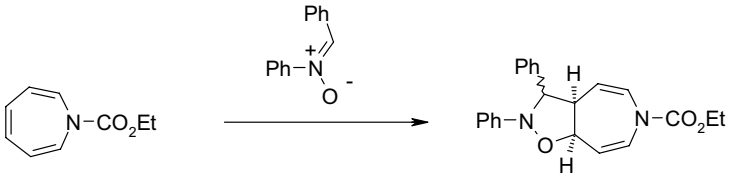
tuted pyrone adducts **224a** and [6 + 4]-type dimer **224b** were obtained in low yield. Under similar reaction conditions, 5-substituted pyrone gave adducts **225a** and **225b.** The former, on prolonged heating, lost carbon dioxide to form benzo[*d*]azepine **226**.

The reaction of 1-ethoxycarbonyl-1*H*-azepine with 3,4,5,6-tetrachloro-1,2-benzoquinone [233] acting as a heterodiene gave a [6π + 4π] and two regioisomeric [2π + 4π] adducts. This behavior is representative of the dual character of azepine in cycloaddition reactions. Furthermore, interestingly, the [6π + 4π] adduct rearranges to the [2π + 4π] isomer on heating in toluene (Scheme 21.69).



Scheme 21.69

The reported examples of 1,3-dipolar cycloaddition to azepines are limited to diazomethane and *N*,α-diphenylnitrone. Thus, the reaction of 1-ethoxycarbonyl-1*H*-azepine with *N*,α-diphenylnitrone afforded *exo*- and *endo*-cycloadducts in similar distributions through a concerted process (Scheme 21.70) [234].

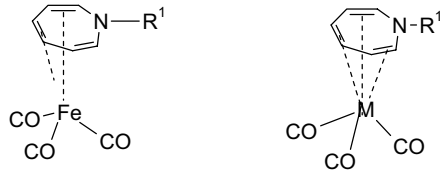


Scheme 21.70

21.6.1.2 **Reaction with Metal Carbonyl Complexes**

In contrast to cycloheptatriene, the metal complex chemistry of azepine has received rather limited attention. In 1965 Fisher and Rühle [235] reported the formation of iron carbonyl complexes of several azepines, including the parent system 1*H*-azepine. The isolated azepine is very unstable and was generated in the complexed state from the *N*-ethoxycarbonyl derivative.

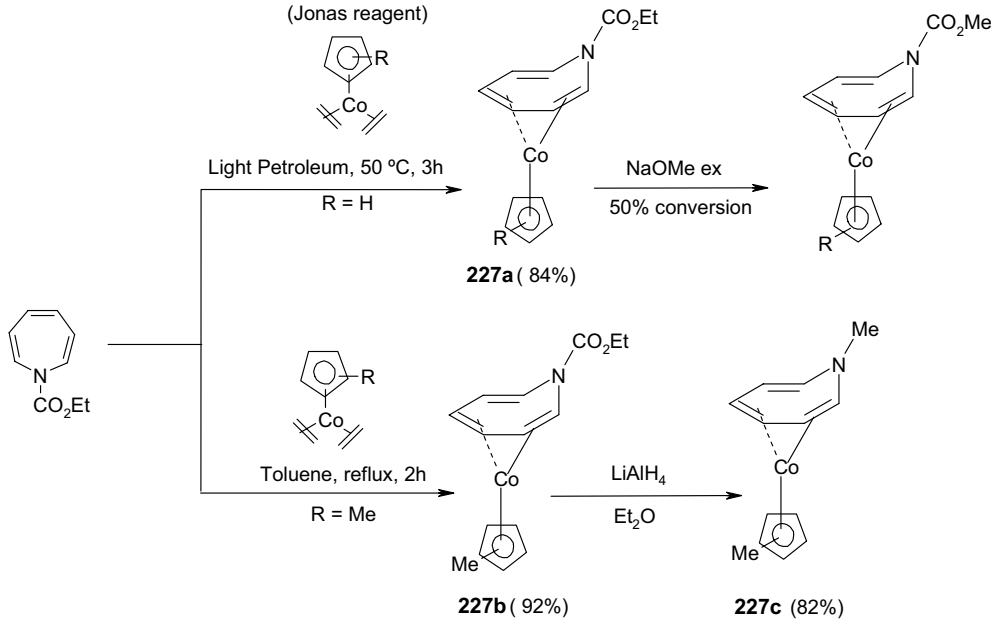
The tricarbonyl chromium, molybdenum, and tungsten complexes of azepine 1-carboxylate have also been prepared by treating the azepine 1-carboxylate with the metal tricarbonyl tris-acetonitrile complex in THF solution. The tricarbonylruthenium complex has also been reported (Scheme 21.71) and this undergoes interesting cycloaddition reactions with electron-deficient alkenes and ketones.



R^1 = H, CO_2Et M = Cr, Mo,

Scheme 21.71

The synthesis, structure, and dynamic behavior of some cyclopentadienyl- and pentamethylcyclopentadienyl-cobalt complexes of *N*-methoxy- and *N*-ethoxycarbonylazepines or *N*-methylazepine have been carried out by Wadepohl [236]. Cyclopentadienylcobalt complexes of *N*-ethoxy- and *N*-methoxy compounds were obtained by treatment of the 1-ethoxycarbonyl-1*H*-azepine with Jonas reagent [$(CpCo(C_2H_4)_2$]. Subsequent reaction with excess NaOMe in methanol gave approximately 50% conversion to the *N*-methoxy derivative, although these compounds could not be separated by column chromatography (Scheme 21.72).

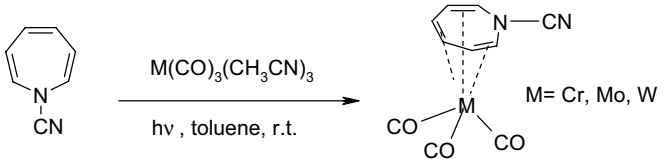


Scheme 21.72

The complexes undergo a degenerate valence tautomerization, which is more facile in pentamethylcyclopentadienylcobalt[2-5-η-(*N*-methyl)azepine] (**227c**) than in cyclopentadienylcobalt[2-5-η-*N*-ethoxycarbonyl)azepine] (**227a**) and pentamethylcyclopentadienylcobalt[2-5-η-(*N*-ethoxycarbonyl)azepine] (**227b**). At low temperatures,

compound **227a** has restricted rotation around the amide bond, which leads to the presence of two diastereomers.

Tricarbonyl(*N*-cyanoazepine)metal(0) complexes of chromium (**228a**), molybdenum (**228b**), and tungsten (**228c**) are formed when tricarbonyl-tris(acetonitrile)chromium(0), -molybdenum(0) and -tungsten(0), respectively, are treated photochemically with *N*-cyanoazepine at room temperature in toluene (Scheme 21.73) [237]. The resulting complexes take part in [6 + 2] cycloadditions with alkynes (see next section).

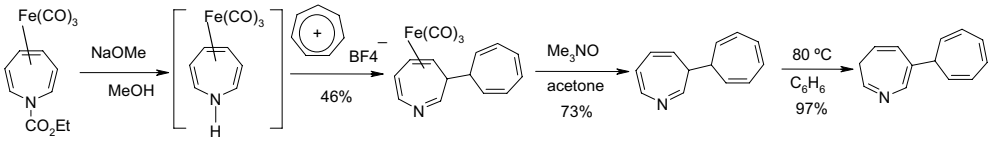


228a, M = Cr (84%)
228b, M = Mo (74%)
228c, M = W (60%)

Scheme 21.73

21.6.1.3 Reactions through Metal Carbonyl Complexes

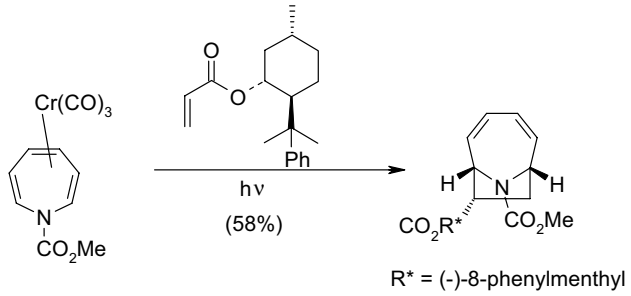
The ease with which 1*H*-azepines form transition metal carbonyl complexes has led to interesting reactions. For example, tricarbonyl(2-5-η-1*H*-azepine)iron, which is unstable, reacts with the tropylium cation and several electrophiles to give derivatives that, after decomplexation with trimethylamine oxide, afforded 3-(2,4,6-cycloheptatrienyl)-3*H*-azepine. This compound is stable but undergoes a facile 1,5-hydrogen migration in benzene to give 6-(2,4,6-cycloheptatrienyl)-3*H*-azepine in 97% yield after purification [238] (Scheme 21.74).



Scheme 21.74

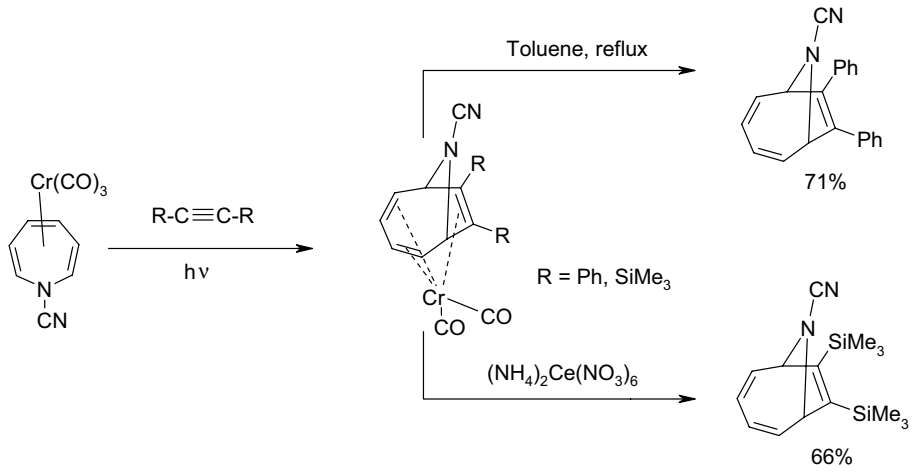
Chromium(0)-mediated higher-order cycloaddition reactions have emerged as an important method for the rapid assembly of structurally elaborate polycyclic systems. Rigby's group have been particularly active in this area, using both thermally and photochemically activated cycloadditions of chromium(0) complexes of azepines with alkenes and alkynes. A successful route to the tropane alkaloid (+)-ferruginine by reaction between tricarbonyl *N*-(methoxycarbony1)azepinechromium(0) and (−)-8-phenylmenthyl acrylate provided the desired diastereomerically homogeneous homotropane *endo* adduct as the major product with high diastereomeric excess

(Scheme 21.75) [239]. Furthermore, [6π + 2π] cycloaddition reactions mediated by solid-supported Cr(0) [240] have also been described for azepines with yields comparable to those obtained in photochemical and thermal versions.



Scheme 21.75

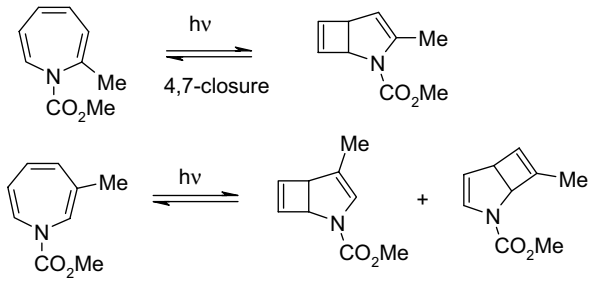
Other examples of [6π + 2π] cycloadditions with alkynes through the Cr(0) complex have been reported. The decomplexation can be performed either thermally or oxidatively, depending on the nature of the substituent (Scheme 21.76).



Scheme 21.76

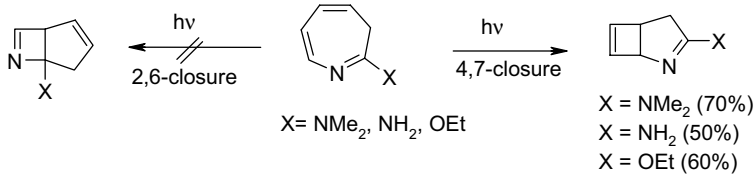
21.6.1.4 **Pericyclic Reactions**

The nonplanar polyene nature of azepines allows them to take part in a wide variety of intra- and intermolecular pericyclic processes. Irradiation of 2-methyl-1*H*-azepine selectively gives a 4,7-ring closure product due to the steric interaction between the methyl group and the N-substituent. In contrast, the 3-methyl and 4-methyl derivatives give two four-membered products in a 1 : 1 ratio (Scheme 21.77) [221].



Scheme 21.77

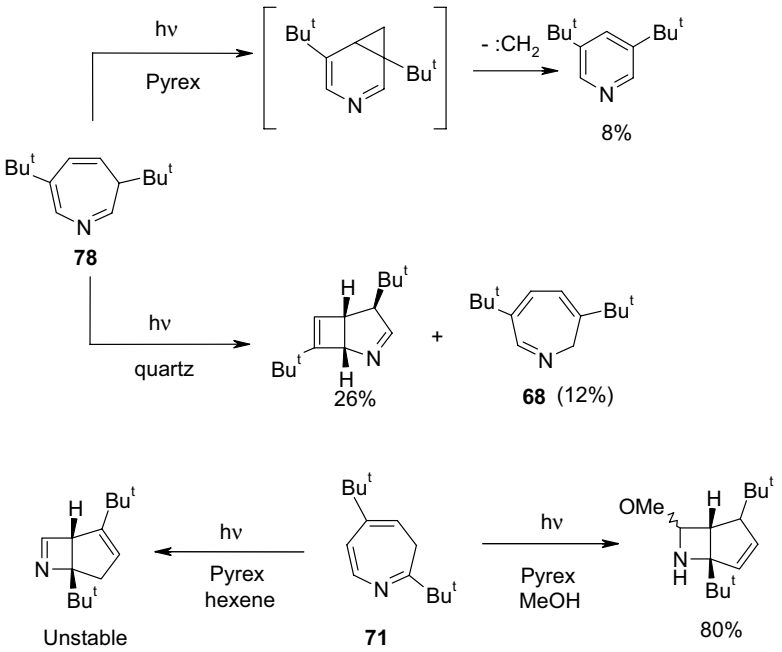
The orbital symmetry-allowed disrotatory processes of 2-substituted 3*H*-azepines could yield both 3-substituted- and 5-substituted 6-azabicyclo[3.2.0]hept-2,6-dienes. However, the reaction is selective and gives only the 3-substituted derivative through a 4,7-closure rather than a 2,6-closure (Scheme 21.78) [241].



Scheme 21.78

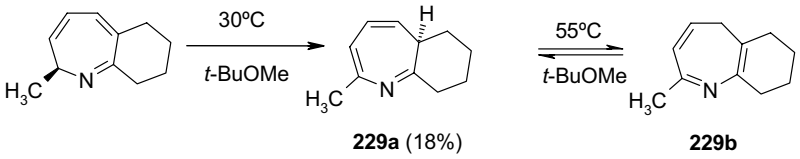
Different photochemical behavior for 3,6-di-*tert*-butyl-3*H* azepines and 2,5-di-*tert*-butyl-3*H*-azepines has been observed [242]. For example, photoisomers were not detected upon photoirradiation of the 3,6-isomer in hexane through a Pyrex filter. In contrast, irradiation through a quartz filter in hexane gave the 4,7-di-*tert*-butyl-2-azabicyclo[3.2.0]hepta-2,6-diene along with the azepine **68** (Scheme 21.79). Irradiation of 2,5-di-*tert*-butyl-3*H*-azepine (**71)** through a Pyrex filter gave the 2,5-di-*tert*-butyl-6-aza-bicyclo[3.2.0]hepta-2,6-diene through a 2,6-closure, as confirmed by formation of the methanol addition product (Scheme 21.79). These results indicate that the regioselectivity for photoelectrocyclization is not exclusively caused by the steric hindrance of the product.

It is known that the four tautomeric monocyclic azepines are interchangeable to the more stable derivative by 1,5-sigmatropic hydrogen shift, and the accepted order of stability of the azepines is $3H > 4H > 2H > 1H$. The 1*H*-azepine isomerizes under thermal catalytic (acid/base) and non-catalytic conditions and 2*H*-azepines isomerize easily to the thermodynamically more stable 3*H* derivatives by 1,5-sigmatropic hydrogen shift [121, 238, 243]. This rearrangement occurs on standing in organic solvents at room temperature or on warming. Thus, (*S*)-2-methyl-6,7,8,9-tetrahydro-2*H*-l-benzazepine undergoes a thermally allowed suprafacial [1,5]-sigmatropic H-shift (Scheme 21.80) in *tert*-butyl methyl ether at 30 °C to give the optically active 3*H*-azepine derivative **229a** in low yield, which exhibits a high optical rotation and supports a stereoselective mechanism for the rearrangement. At elevated



Scheme 21.79

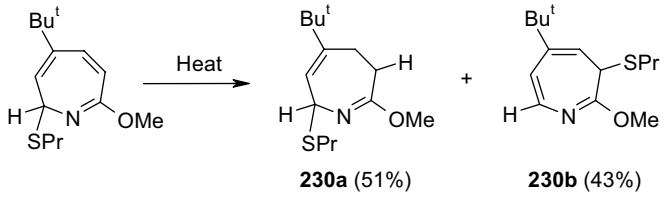
temperatures a second, reversible hydrogen migration occurs and this establishes an equilibrium with the achiral 3*H*-azepine **229b**.



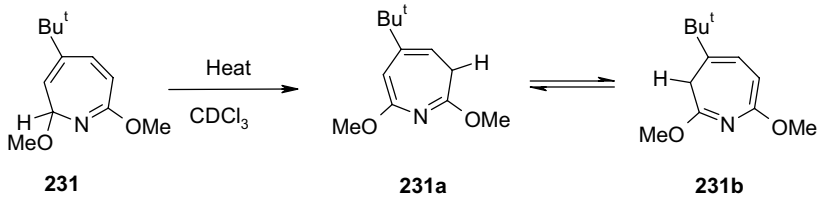
Scheme 21.80

Recently, Satake and co-workers [244] have described an unusual competitive reaction between a [1,5]-sigmatropic alkylthio shift and a [1,5]-sigmatropic hydrogen shift in a 2*H*-azepine ring, to afford 7-propylthio- and 3-propylthio-3*H*-azepines **230a** and **230b**, respectively, in a 1 : 1 ratio (Scheme 21.81). Kinetic measurements revealed that the observed [1,5]-propylthio shift proceeds through a concerted mechanism.

On the other hand, when 2-methoxy-2*H*-azepine **231** was heated in chloroform a hydrogen shift was observed exclusively to give a mixture of 5-*tert*-butyl- (**231a**) and 4-*tert*-butyl-2,7-dimethoxy-3*H*-azepine (**231b**) in a 1 : 8 ratio (Scheme 21.82). The thermal [1,5]-sigmatropic hydrogen shift was studied by ^{1}H NMR spectroscopy and the spectrum of the isomerization of 4-*tert*-butyl-2,7-dimethoxy-2*H*-azepine (**231)** in $CDCl_3$ showed that **231a** and **231b** were formed in a 1 : 8 ratio with a simultaneous decrease in **231**, suggesting that the [1,5]-hydrogen shift from **231a** and **231b** is very



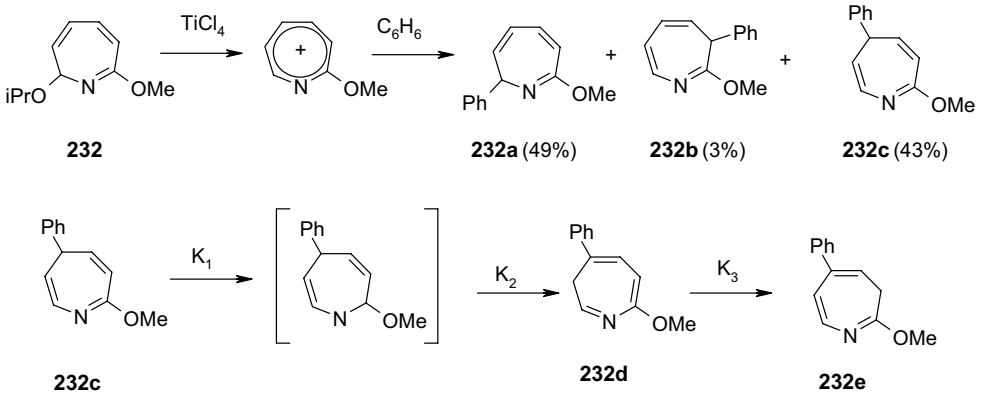
Scheme 21.81



Scheme 21.82

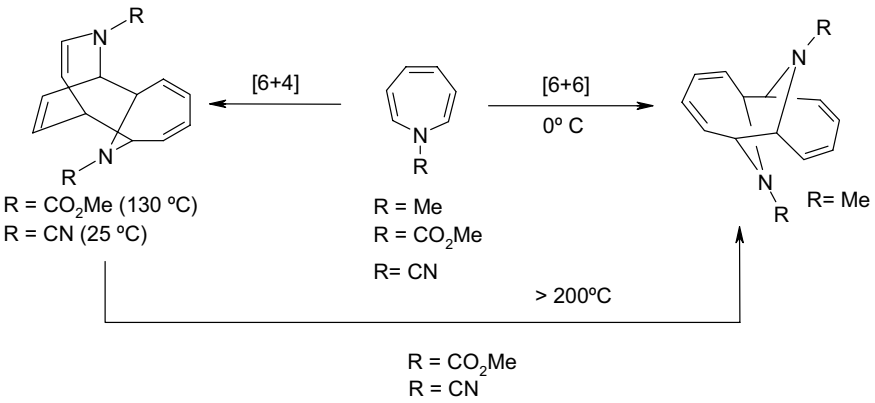
fast. These results indicate that the rapid equilibrium between **231a** and **231b** is reached as soon as the isomerization of **231** occurs. The [1,5]-methoxy shift was not observed in the thermal isomerization of **231**.

The same group has described the formation of 4*H*-azepines (**232c**) for the first time from the 2-methoxyazepiniun ion and its sigmatropic isomerization. This process apparently occurs as a two-step reaction from **232c** to initially give **232d**, which is then converted into the most thermally stable **232e** (Scheme 21.83) [245]. The absence of a substituent at position 5 in the azepinium ring offers a good example of the reactivity and electrophilic character and allows the formation of rare 4*H*-azepines.



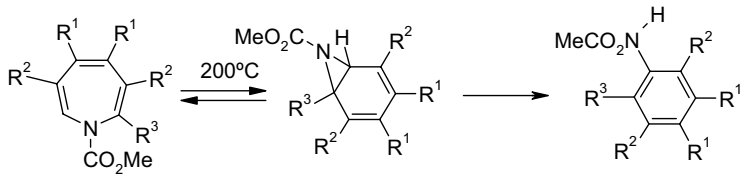
Scheme 21.83

The dimerization of 1*H*-azepines [246] involves a temperature-dependent cycloaddition process, which in turn depends on substitution. *N*-Methylazepine undergoes dimerization at 0 °C to give a [6 + 6] dimer. On the other hand, the *N*-cyano- and *N*-ethoxycarbonyl derivatives dimerize at higher temperature through a [6 + 4] process. The initially formed [6 + 4] adducts rearrange to the [6 + 6] adducts on heating at high temperature (Scheme 21.84).



Scheme 21.84

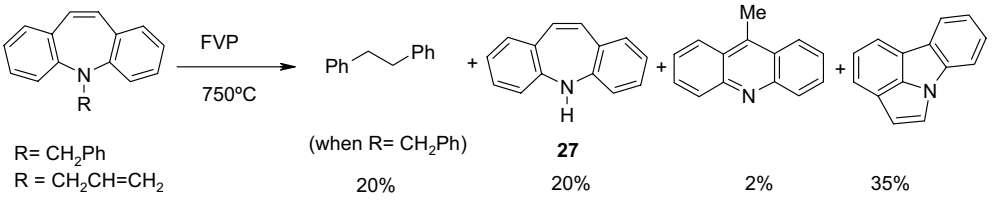
In contrast to *N*-substituted 1*H*-azepines and their 3- and 4-methyl derivatives, which readily undergo dimerization at elevated temperatures, in cases where the positions directly involved in the dimerization process (2-, 4-, and 7- positions) are substituted the dimerization process is hindered and a valence tautomerization reaction takes place [247]. Thus, 2-methyl-, 4,5-dimethyl-, and 3,6-dimethyl derivatives (**233**) at 200 °C were converted into the aromatic carbamates (Scheme 21.85). This behavior is not shared by the 2,7-dimethyl derivative, which is stable even at 250 °C, probably due to steric hindrance.



a: $R^1 = R^2 = H$, $R^3 = CH_3$
b: $R^1 = CH_3$, $R^2 = R^3 = H$
c: $R^1 = R^3 = H$, $R^2 = CH_3$

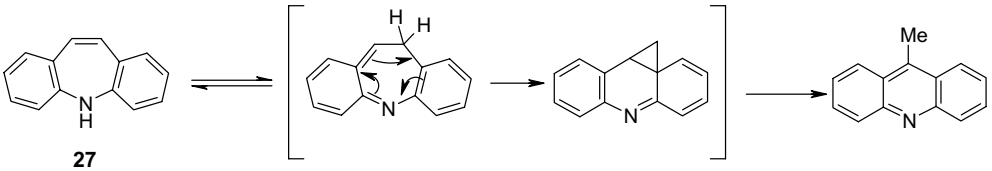
Scheme 21.85

Recently McNab and co-workers [248] have identified a new thermal ring contraction of dibenzo[*b*,*f*]azepines by controlled flash vacuum pyrolysis (FVP) of *N*-allyl- or *N*-benzyldibenzo[*b*,*f*]azepine at temperatures (750–950 °C). When the *N*-benzyl derivative was subjected to FVP at 750 °C, four products were identified from the reaction mixture (Scheme 21.86).



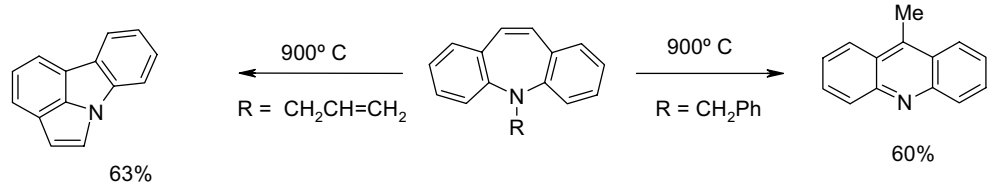
Scheme 21.86

The formation of bibenzyl (20%) provided confirmation that radical generation had been successful. Cleavage of *N*-benzyl or *N*-allyl groups led to recovery of 5*H*-dibenzo[*b*,*f*]azepine (20%) and, in addition, two ring-contraction products were obtained. One of them, 9-methylacridine (2%), is likely to be formed by ring contraction of 5*H*-dibenzo[*b*,*f*]azepines (by the 1,5-shift, electrocyclization, ring cleavage, hydrogen shift sequence mechanism indicated in Scheme 21.87) and the major product is pyrrolo[3,2,1-*jk*]carbazole (35%). However, under more vigorous conditions (950 °C) this process gave 9-methylacridine as the sole product in 60% yield.



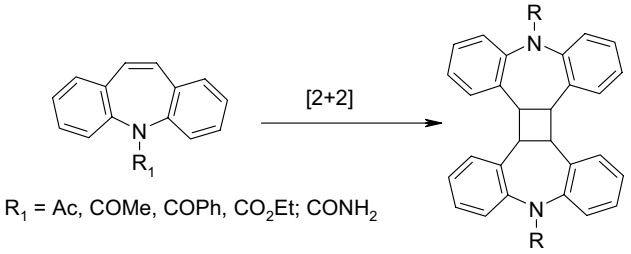
Scheme 21.87

The temperature of the pyrolysis proved to have a dramatic effect on the product distribution, because the *N*-allyl derivative at 950 °C gave 63% yield of pyrrolocarbazole (Scheme 21.88).



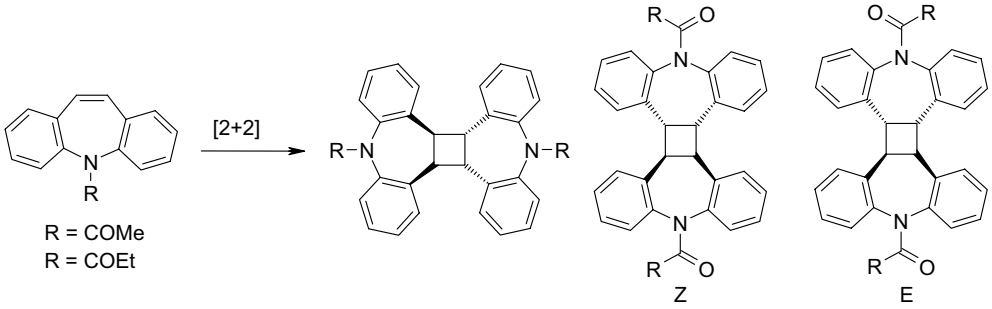
Scheme 21.88

Although several N-substituted derivatives of 5*H*-dibenzo[*b*,*f*]azepines are known to give [2 + 2] cycloadducts photochemically to form a cyclobutane (Scheme 21.89), the parent compound and its N-alkyl derivatives are photochemically inactive [249].



Scheme 21.89

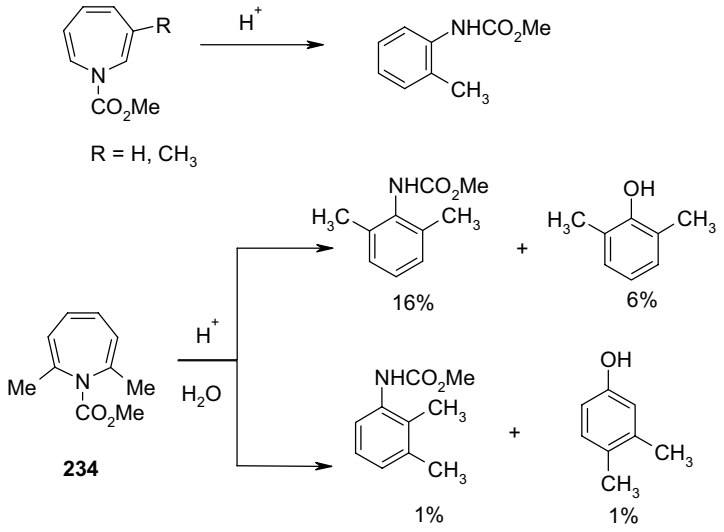
A structural analysis by ^{1}H NMR spectroscopy of the photoproducts of N-acyl derivatives of 5*H*-dibenzo[*b*,*f*]azepines proved the presence of two stereoisomers (Scheme 21.90), probably due to restricted rotation of the amide bond [250].



Scheme 21.90

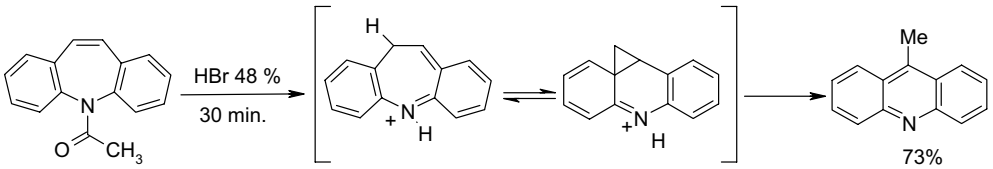
21.6.1.5 **Reactions with Electrophiles**

The conjugated azepines – and their partially unsaturated derivatives – are unstable in acidic media and undergo either rearrangement or ring contraction to an aromatic system. 1*H*-Azepines with N-alkyl substituents are unstable in acidic solutions and afford resinous products. However, *N*-acyl- or *N*-ethoxycarbonyl derivatives lead rapidly to *N*-phenylcarbamate under acidic conditions (Scheme 21.91). For example, the 3,6-dimethyl-1*H*-azepine (**233c**) on standing in 10% sulfuric acid at room temperature for 2 h yields 82% of the corresponding carbamate [247]. Similar treatment of the 2,7-dimethyl derivative for 4 h led only to recovery of unreacted starting material, probably due to steric hindrance. However, when the same mixture was heated under reflux for 1 h, the 2,7-dimethylazepine **234** was completely transformed into a viscous brown oil. The major identifiable component of this oil was the 2,6-dimethyl-*N*-methoxycarbonylaniline (16%) in addition to 3,4- and 2,6-dimethylphenols, with the remainder being polymeric material (Scheme 21.91).



Scheme 21.91

The acid-catalyzed rearrangement of dibenzo[*b,f*]azepines to 9-methylacridines was first described by Schindler and Blattner [251] (Scheme 21.92).

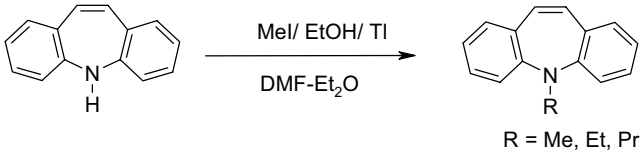


Scheme 21.92

In general, the alkylation of azepines is effected by alkyl halides or tosylates in the presence of base. Quaternization of 2-dialkylamino-3*H*-azepine with methyl iodide takes place at the exocyclic nitrogen and its hydrolysis provides a useful path to 3*H*-azepinones [252].

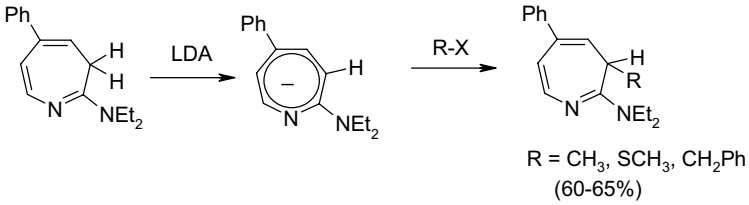
The N-alkylation of some 5*H*-dibenzo[*b,f*]azepines (and 10,11-dihydro derivatives) has been studied extensively under classical conditions and under phase-transfer catalysis (PTC) [253], although the method is less successful with 10,11-dihydro derivatives [254].

The alkylation can be effected with an alkyl chloride, bromide, or tosylate, using a wide range of bases and refluxing in toluene. *N*-Methyl-, *N*-ethyl-, and *N*-propyl derivatives, for example, can be prepared in good yield under mild conditions from the iminostilbene and the corresponding alkyl iodide using thallium ethoxide as base (Scheme 21.93) [255].



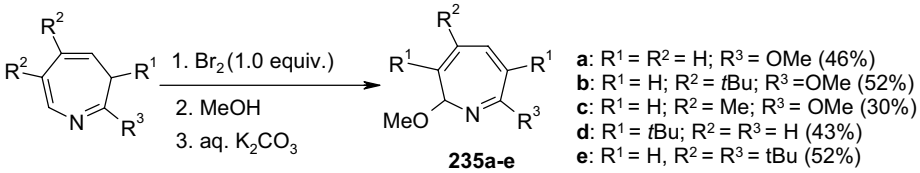
Scheme 21.93

C-Alkylation, described by Streef and van der Plas [256], is achieved through reaction of the anion of 2-diethylamino-5-phenyl-3*H*-azepine with different electrophiles to give azepines substituted at C3 (Scheme 21.94).



Scheme 21.94

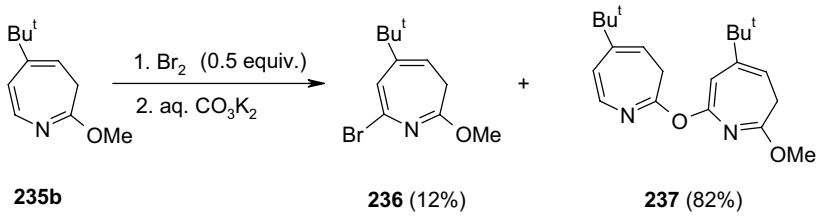
Satake and co-workers reported the specific formation of 2-methoxy-2*H*-azepine derivatives **235a–e** by sequential reaction of 3*H*-azepines with bromine, methanol, and aqueous potassium carbonate (Scheme 21.95). Studies on the mechanism of the reactions of 3*H*-azepines with bromine and NBS [243, 257] suggest the 1,4-addition of an electrophile and subsequent 1,2-dehydrobromination.



Scheme 21.95

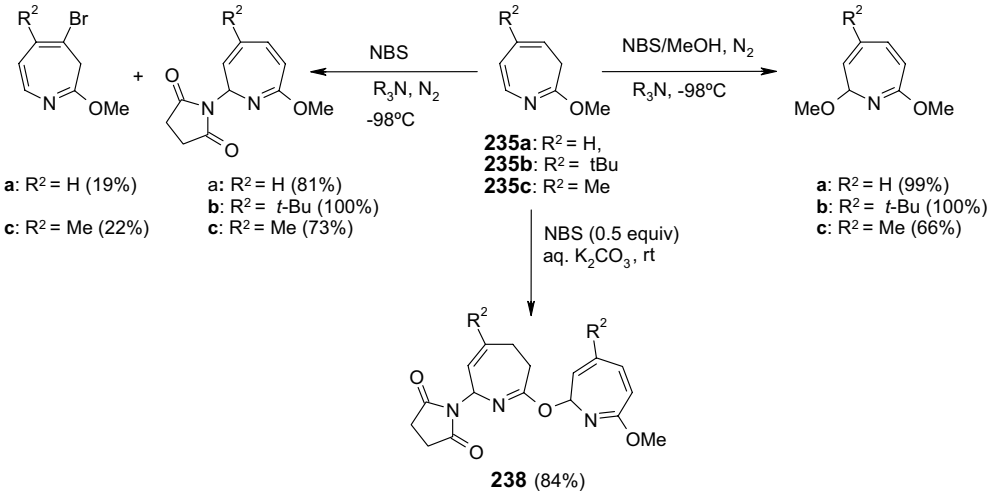
On the other hand, the sequential reaction of **235b** with half an equivalent of bromine and aqueous potassium carbonate (Scheme 21.96) gives the 7-bromo-3*H*-azepine derivative **236** (12% yield) and the ether **237** (82% yield).

An alternative attempt to understand the mechanism of the previously described conversion of 3*H*-azepines into 2*H*-azepines has been carried out by replacing bromine with NBS (Scheme 21.97). In the presence of methanol, quantitative conversion of 3*H*-azepines **235a,b** into 2-methoxy-2*H*-azepines was observed, although the reaction with **235c** produced both 2-methoxy-2*H*-azepine (66% yield) and the 2-succinimido-2*H*-azepine (33% yield). In the absence of methanol the 3*H*-azepines **235a–c** and efficiently gave 2-succinimido-2*H*-azepines in good yields



235b **236** (12%) **237** (82%)

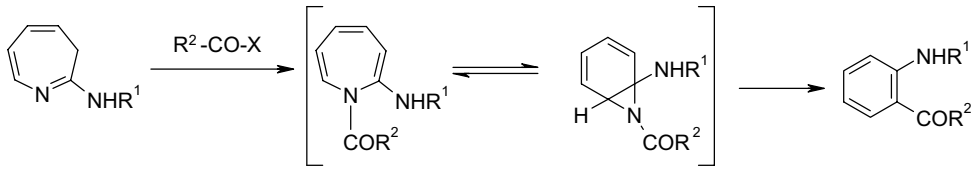
Scheme 21.96



Scheme 21.97

together with the brominated products (19–22%). Replacing bromine by NBS led to improved yields due to the chemoselectivity of the reagent as well as the lower concentration of HBr [258]. Reaction of **235b** and NBS in a 2 : 1 molar ratio at room temperature produced the ether **238** in 84% yield.

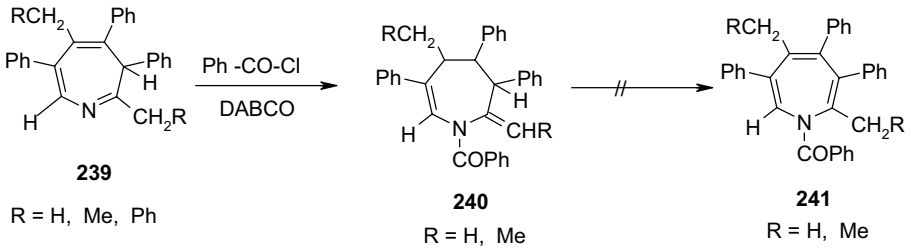
Acylation of 2-amino-3*H*-azepines under Schotten–Baumann conditions did not afford the azepine derivative but the 2-(benzamido)diphenylamine through the intermediacy of an azanorcaradiene [259] (Scheme 21.98). However, benzenesulfonylation proceeds normally at the exocyclic nitrogen.



Scheme 21.98

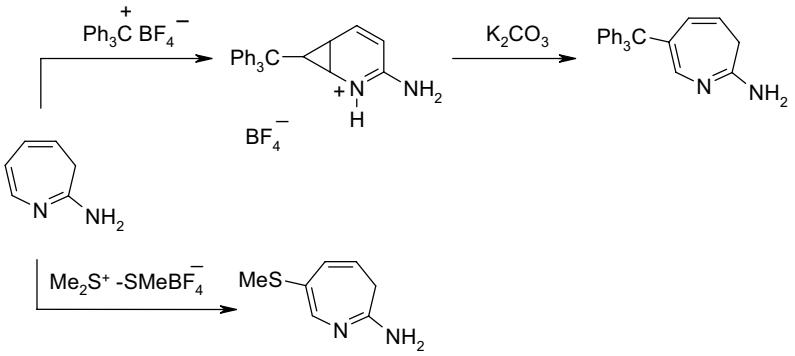
Treatment of the densely substituted 3*H*-azepines **239** with benzoyl chloride in the presence of DABCO gave the 2-methylene-3*H*-azepine derivatives **240**

(Scheme 21.99) [260]. When the 2-methyl group was replaced by a phenyl group, there was no reaction even under forcing conditions. Attempts to isomerize the exo-methylene azepine **240** to the conjugate 1*H*-isomer **241** failed, both by treatment with weak or strong bases. In the latter case the starting 3*H*-azepine was obtained.



Scheme 21.99

The reaction of 2-amino-3*H*-azepine with either trityl tetrafluoroborate or dimethyl (methyl)sulfonium tetrafluoroborate [91] has been reported to give the product substituted at C6 (Scheme 21.100). In the former case, the corresponding azanorcaradiene was isolated.

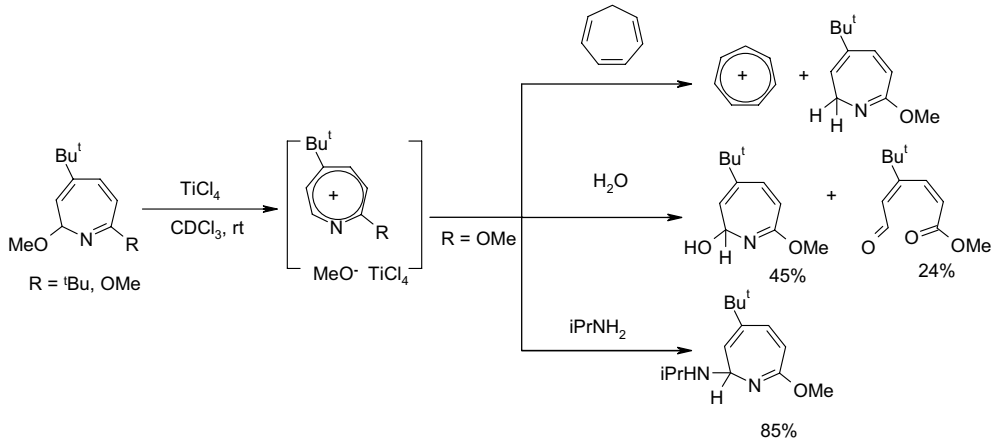


Scheme 21.100

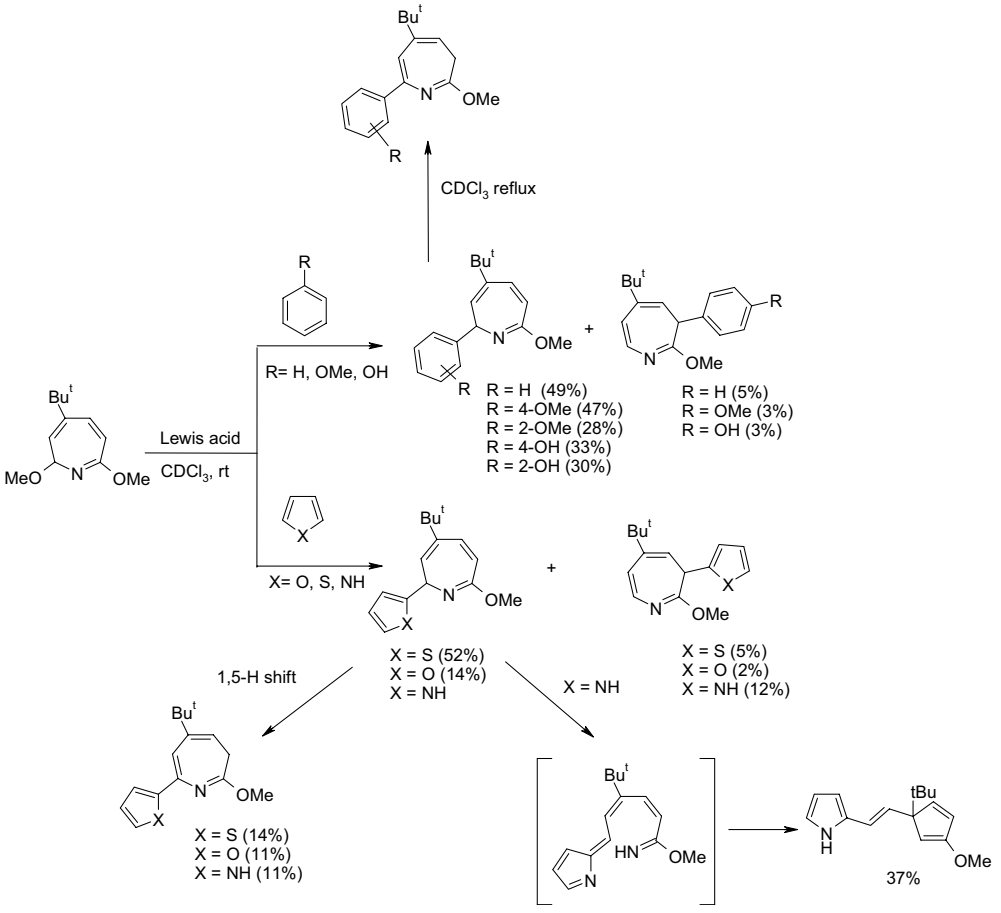
21.6.1.6 **Reactions with Nucleophiles**

Satake and co-workers have reported the formation of the azepinium ion from the reaction of a 2-methoxy-2*H*-azepine derivative and titanium tetrachloride ($TiCl_4$) (Scheme 21.101) [243,257b].

In contrast to analogous tropylium systems, which have poor reactivity [261], the azepinium ions are quite reactive [249, 262] – as shown in Schemes 21.102 and 21.103. The results indicate that the azepinium ion is a strong electrophile. In the reaction with aromatic compounds these systems undergo nucleophilic substitution primarily at position C7 and, less frequently, at position C3. An interesting

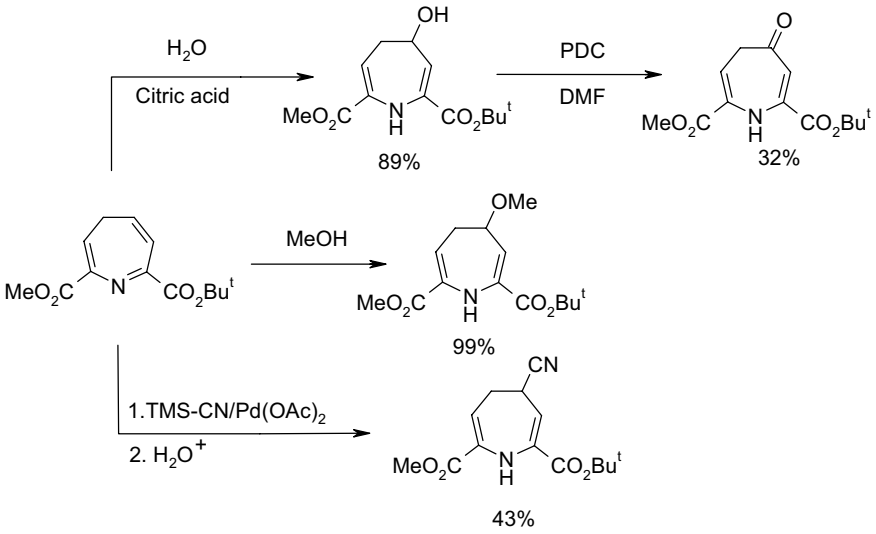


Scheme 21.101



Scheme 21.102

result was obtained in the reaction with pyrrole, which gave a ring-contracted product.



Scheme 21.103

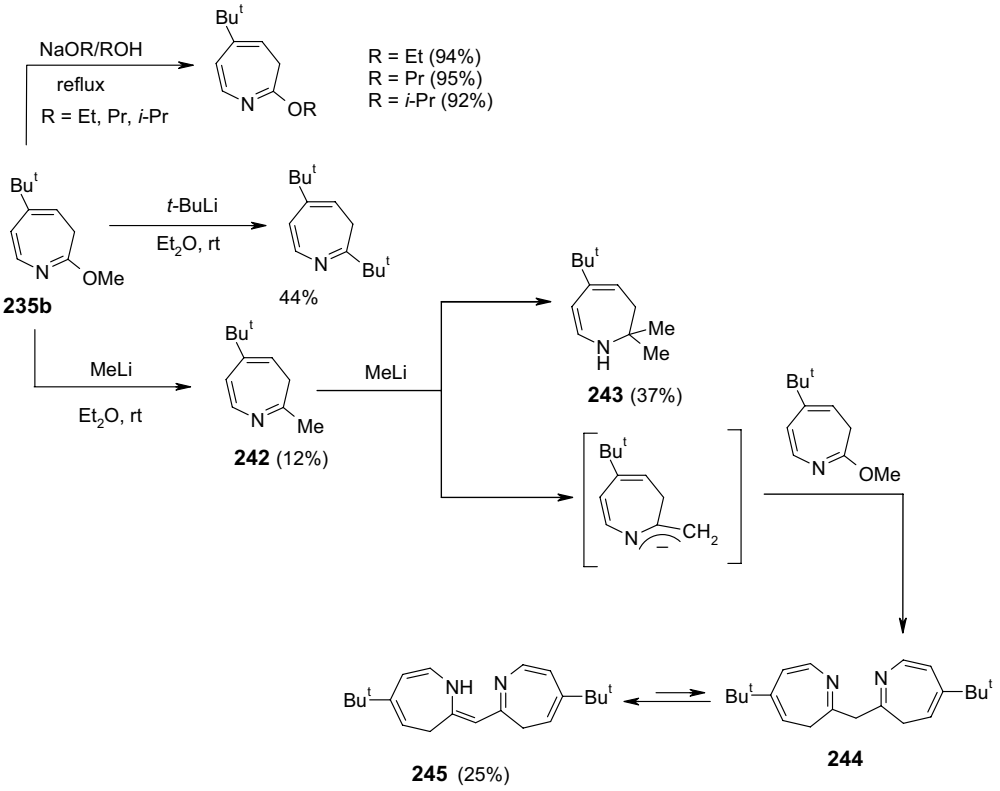
4*H*-Azepine-2,7-dicarboxylic esters undergo 1,4-addition of nucleophiles [263] catalyzed by either acid or Pd(II) (Scheme 21.103).

Although it is known that the alkoxy group of the 2-alkoxy-3*H*-azepine derivative is displaced by alkylamines or carbanions from active methylene compounds, Satake and co-workers have explored the reactivity of 3*H*-azepines having an imidate conjugation with various alkoxy groups at the 2-position (Scheme 21.104). Thus, the nucleophilic reaction of 5-*tert*-butyl-2-methoxy-3*H*-azepine **235b** with an appropriate alkoxide [264] took place effectively at the 2-position of the ring. When a bulky alkyllithium was used as a nucleophile, a similar displacement occurred to give the 2-alkyl-3*H*-azepine derivative as a single product.

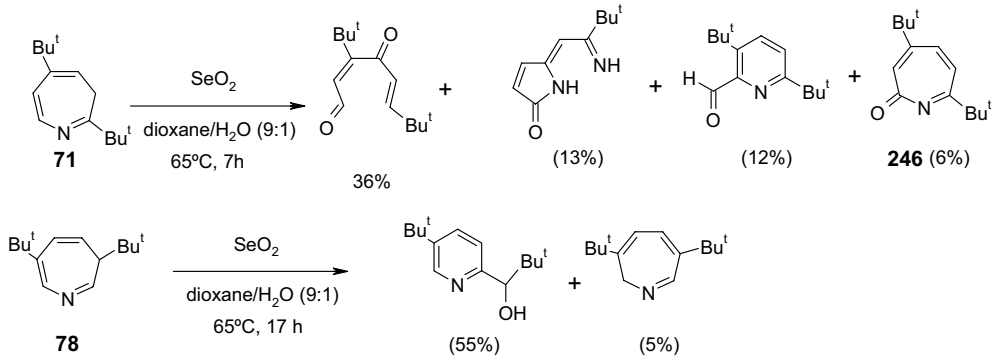
In contrast, the reaction of **235b** with methyllithium gave not only 2-methyl-3*H*-azepine **242**, but also 2,2-dimethyl derivative **243** (37%) and methylenedi-3*H*-azepine **244**, which tautomerized into the thermodynamically more stable vinamidine or 5-*tert*-butyl-2-(5-*tert*-butyl-2,3-dihydro-1*H*-azepin-2-ylidenemethyl)-3*H*-azepine **245** (25%).

21.6.1.7 **Reactions with Oxidants**

To investigate similarities and differences in the chemical behavior of 3*H*-azepines and the isoelectronic 1,3,5-cycloheptatriene, Kimura and co-workers [265] have studied the oxidative ring cleavage of dialkyl-3*H*-azepines on treatment with selenium dioxide. Thus, the oxidation of 2,5-di-*tert*-butyl derivative **71** afforded, *inter alia*, 4-oxo-octa-2,5-dienal by a new ring cleavage along with the 2-azatropone **246**



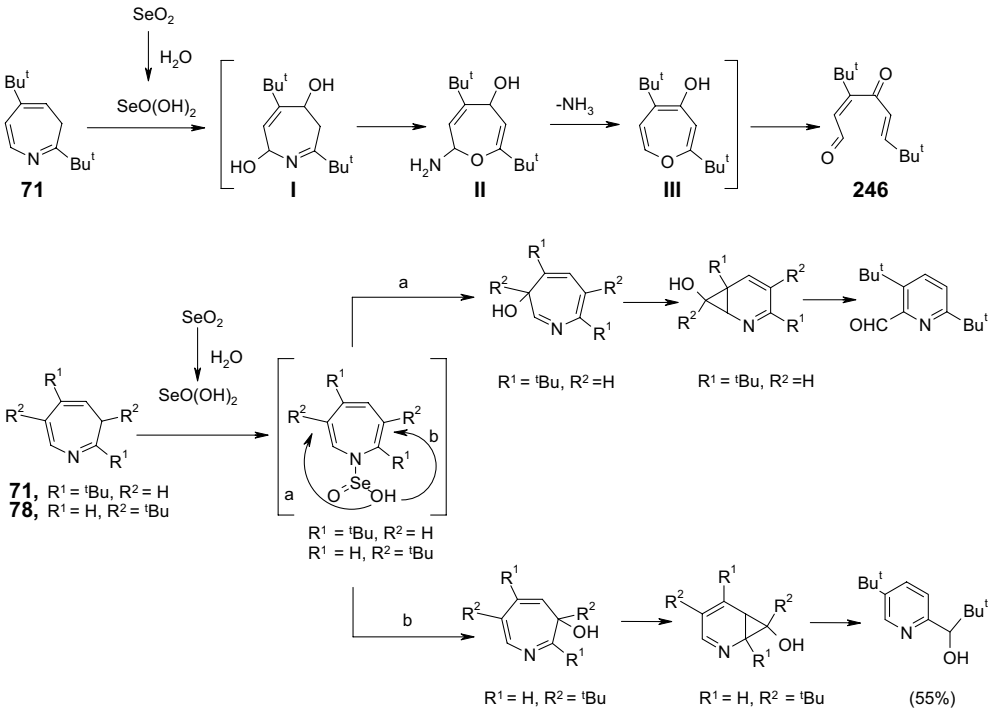
Scheme 21.104



Scheme 21.105

(Scheme 21.105). Under the same conditions the isomeric 3,6-di-*tert*-butyl-3*H*-azepine **78** gave pyridylpropanol as the major product.

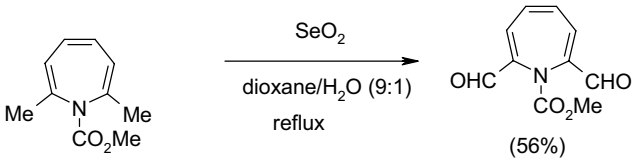
The putative reaction course for the formation of **246** from **71** is indicated in Scheme 21.106. Compound **71** gave the dihydroxy derivative **I**, which rearranged to



Scheme 21.106

the 2-amino-2*H*-oxepine **II**. Subsequent elimination of ammonia was followed by Claisen rearrangement to **246**, On the other hand, the formation of pyridinecarbaldehyde or pyridylpropanol can be explained in terms of electrophilic attack of selenous acid on the C=N double bond in 3*H*-azepine **71** or **78** and subsequent nucleophilic attack by the carbonyl group of selenous acid on the methylene proton in the 3-position (Scheme 21.106). After this attack, the intermediates are formed with an N−Se bond, and this leads to intermediates through a [2,3]-sigmatropic shift. Finally, the intermediates are converted into the 2-azanorcardienes, which ultimately give the final products.

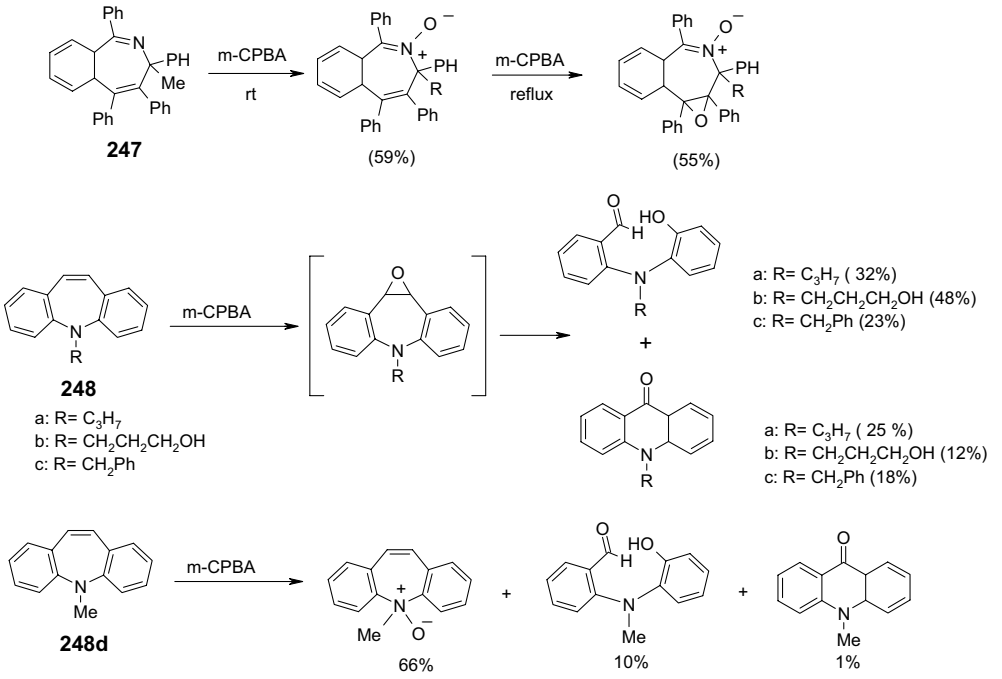
A different type of behavior has been described for *N*-methoxycarbonyl-2,7-dimethyl-1*H*-azepine in dioxane, which by oxidation with SeO_2 gave *N*-methoxycarbonyl-1*H*-azepine-2,7-dicarboxaldehyde (Scheme 21.107) in moderate yield [266].



Scheme 21.107

In this case, as expected, oxidation of the alkyl groups is faster than oxidation of the aromatic ring.

The reaction of benzazepines with *m*-CPBA [267] proceeds through N-oxidation and double bond epoxidation (Scheme 21.108). On the other hand, the oxidative behavior of *N*-substituted dibenzo[*b*,*f*]azepines **248** is complex because several products were obtained depending on the nature of the N-substituents. *N*-Alkyl derivatives, with the exception of *N*-methyl, afford mixtures of diphenylamines and acridones (Scheme 21.108). The *N*-methyl derivative **248d** gave the *N*-oxide along with ring-opening and ring-contracted products (Scheme 21.108). The *N*-acyl deri-



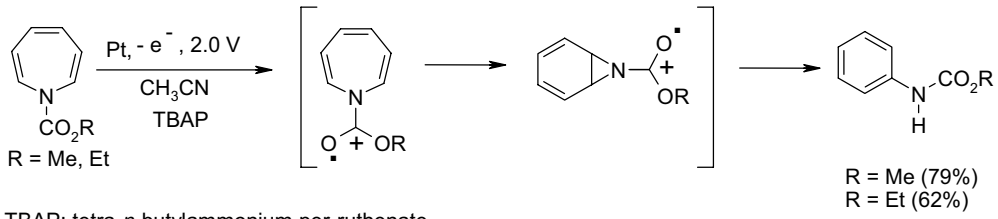
Scheme 21.108

vatives undergo epoxidation of the C10–11 bond and the *N*-aryl derivatives are hydroxylated at the phenyl ring [268].

Electrochemical oxidation [269] by ring contraction of *N*-alkoxycarbonyl-1*H*-azepine leads to *N*-alkoxycarbonylaniline by initial oxidation of the carbamate to give the radical cation, followed by electrocyclic rearrangement and C−N cleavage (Scheme 21.109).

21.6.1.8 **Hydrogenation and Hydrogen Transfer**

Complete reduction of the azepine ring in the monocycles and in their benzo derivatives is readily achieved with hydrogen and the appropriate metal or metal oxide

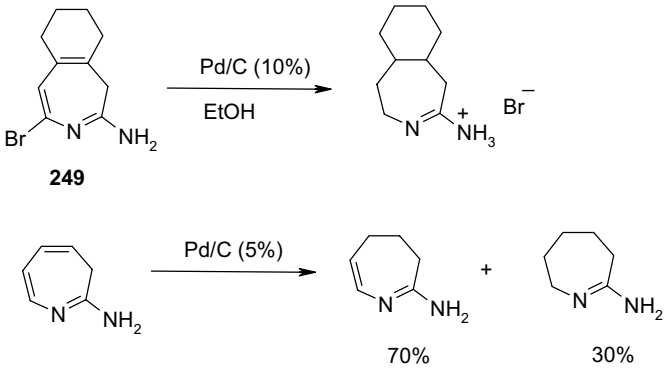


TBAP: tetra-*n*-butylammonium per-ruthenate

Scheme 21.109

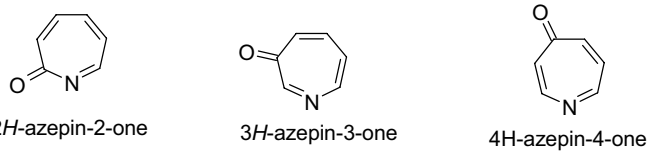
catalyst. Extensive use of Raney nickel, palladium charcoal [270] and platinum oxide [271] has been reported.

With 2-aminobromoazepine **249** [12a, 72], partial reduction is accompanied by hydrodebromination. Initially, the hydrogenation in aqueous dimethylformamide in the presence of potassium bicarbonate or in dioxane containing triethylamine in the presence of a 10% palladium-charcoal catalyst was unsuccessful, but in ethanol, in the absence of a base, reduction occurred rapidly through a hydrogen-transfer reaction. However, only the saturated amidine hydrobromide could be isolated (Scheme 21.110). Partial reduction of 2-dimethylamino-3*H*-azepine can be effected in the presence of 5% Pd/C to give 4,5-dihydro- and 4,5,6,7-tetrahydro-3*H*-azepine derivatives [273].

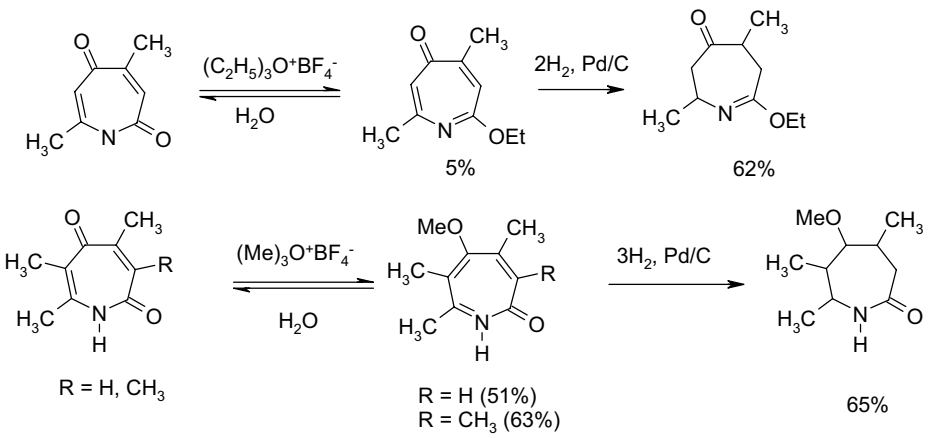


Scheme 21.110

The similarity of keto derivatives of azepines and tropones has prompted some studies on the reactivity of the former systems. As shown here, there are three types of azepinones –aza analogues of tropone – corresponding to the three isomeric parent compounds, 2*H*-azepin-2-one, 3*H*-azepin-3-one, and 4*H*-azepin-4-one.

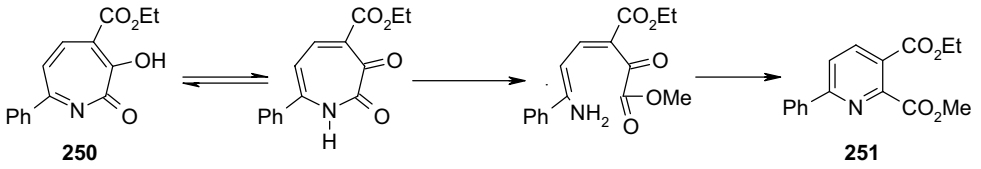


The chemistry of these systems has been reviewed. Examples of all three types have been synthesized, although the parent compounds themselves are unknown. By far the most common are derivatives of 2*H*-azepin-2-one. Among them, 2*H*-azepin-2-one and 4*H*-azepin-2-one have been obtained from azepinediones with trimethyl- or triethyloxonium tetrafluoroborate in acceptable yields [274]. These compounds undergo facile hydrogenation – to the perhydro-derivatives – and acid hydrolysis (Scheme 21.111).



Scheme 21.111

Although these compounds do not exhibit special chemical reactivity, the 3-hydroxy-2*H*-azepin-2-one derivative **250**, described for first time in 1990 by Sano and co-workers [275], is extremely reactive in protic solvents, undergoing a ring contraction to give the pyridine-2-carboxylate **251** (Scheme 21.112). This result demonstrates that the azatropolone nucleus has a strongly electrophilic character.



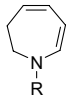
Scheme 21.112

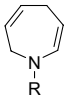
21.6.2 Reactivity of Partially Reduced Azepine Derivatives

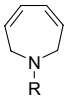
21.6.2.1 Dihydroazepines

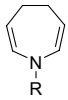
Although there are references on this group of compounds, we have restricted the discussion of reactivity to those cases in which the starting materials are stable or have

similarities with the azepine reactivity considered previously (some examples are given here).


2,3-Dihydro-1*H*-azepine


2,5-Dihydro-1*H*-azepine


2,7-Dihydro-1*H*-azepine


4,5-Dihydro-1*H*-azepine

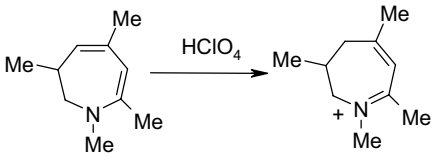

3,6-Dihydro-2*H*-azepine


5,6-Dihydro-2*H*-azepine


4,5-Dihydro-3*H*-azepine


3,4-Dihydro-2*H*-azepine

Among these compounds, the 2,3-dihydro-1*H*-azepines are relatively stable due to the conjugated dienamine structure. Protonation takes place at the C4 position [276]. Thus, Paquette has described the preparation of 6,7-dihydroazepinium **252a** by reaction of **252** with perchloric acid (Scheme 21.113).



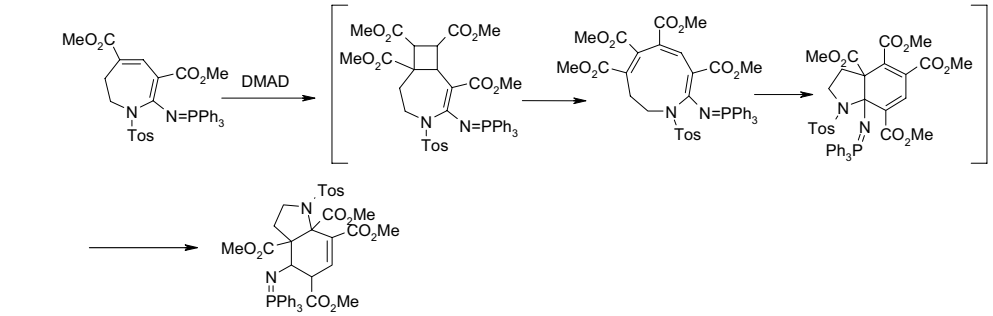
252 **252a**

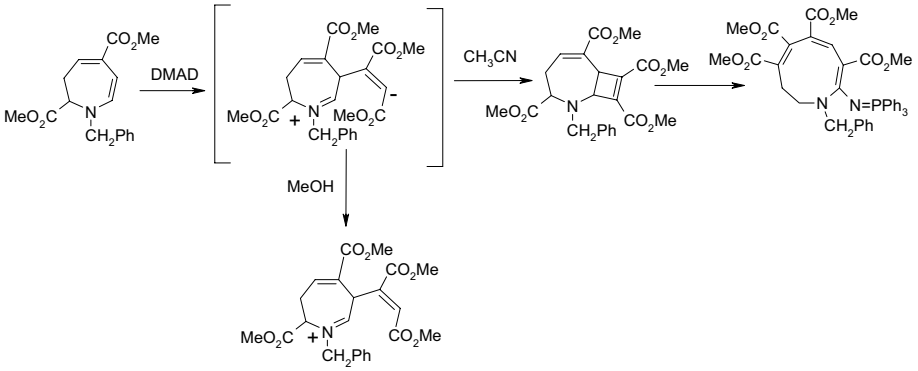
Scheme 21.113

The [4 + 2] cycloaddition reaction occurs readily even with DMAD [277], which ordinarily reacts with enamines in a [2 + 2] manner following a ring expansion process [278]. However, the 6,7-dihydro-1*H*-azepine reacts with DMAD to give the tetrahydroindole derivative **253** [279]. The first step is the formation of a [2 + 2]π adduct, which undergoes ring expansion and subsequent recyclization (Scheme 21.114). Alternatively, the reaction in polar solvents [280] proceeds due to the enamine character of the dihydroazepine, generating a heterobetainic intermediate that, depending on the solvent, affords different products.

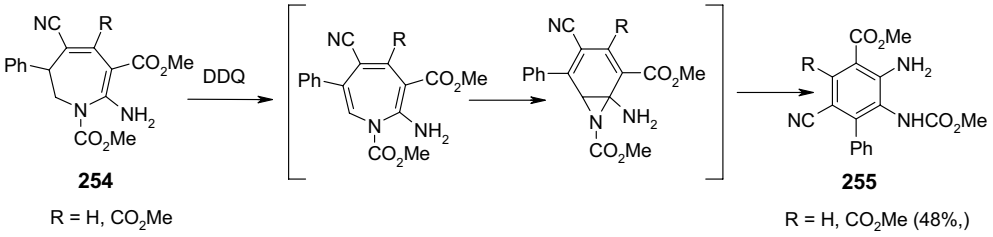
Dihydroazepines and tetrahydroazepines can undergo several rearrangements that generally involve a ring contraction. As an example, oxidation of 6,7-dihydro-1*H*-azepine **254** [281] with DDQ (2,3-dicyano-5,6-dichoro-*para*-benzoquinone) (Scheme 21.115) gives the arylurethane **255**.

4,5-Dihydro-1*H*-azepines are sensitive to many reagents. The *N*-alkyl derivatives of 4,5-dihydro-1*H*-azepines appear to be rather reactive [78,132b,282] because they contain a double enamine moiety, but the N-acyl derivatives are more easily handled. Electron-withdrawing groups at C2, C3, C6, and C7 have an effect on the stability. Catalytic hydrogenation of these materials affords azepanes [283].





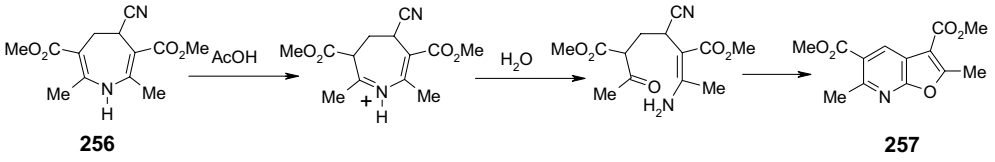
Scheme 21.114



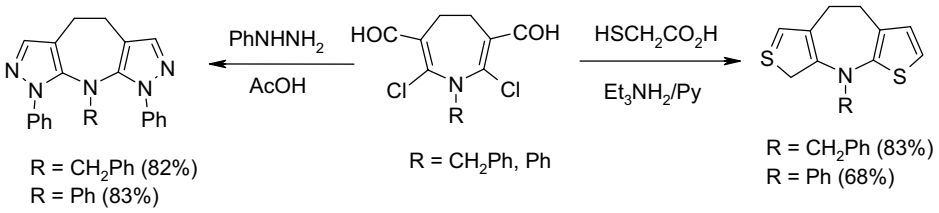
Scheme 21.115

In the case of 2,3-dihydro-1*H*-azepines, protonation occurs at the δ-position and for 4,5-dihydro-*1H*-azepines protonation occurs at the electron-rich β-position. For example, the rearrangement of 5-cyano-4,5-dihydro-*1H*-azepine **256** to the furo[*2,3-b*] pyridine **257** with sodium nitrate in acetic acid in aqueous ethanol proceeds by initial protonation of C3 or C6 (Scheme 21.116) [284].

The synthesis of derivatives of 4,5-dihydro-1*H*-azepines fused with thiophene and pyrazole rings has also been reported [284] from β-chlorovinyl aldehydes with 2-mercaptoacetate or phenylhydrazine, respectively (Scheme 21.117).



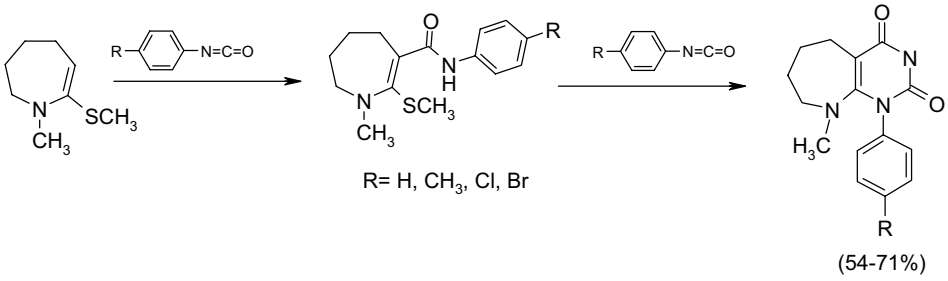
Scheme 21.116



Scheme 21.117

21.6.2.2 **Tetrahydroazepines**

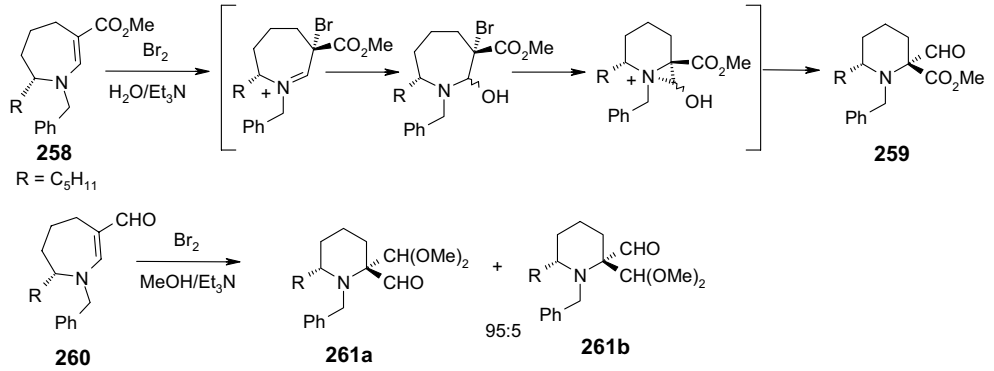
The 2,3,4,5-tetrahydro-1*H*-azepines are enamines and are fairly reactive compounds, particularly those that are unsubstituted on the N atom. Alkylation or acylation on the N atom produces more stable compounds, which react mostly as enamine derivatives (Scheme 21.118) [285].



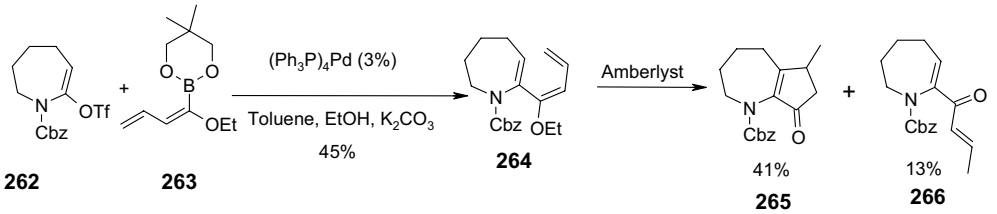
Scheme 21.118

2,3,4,5-Tetrahydro-1*H*-azepines also undergo ring contraction reactions by treatment with bromine followed by water/triethylamine. The enamino ester **258** was converted into the formyl ester **259** in quantitative yield. A similar reaction on the enamino aldehyde **260** gave the aldehyde derivative **261a** as the major product. In this case, the formation of about 5% of the minor isomer **261b** was observed (Scheme 21.119) [286].

Palladium-catalyzed cross-coupling reactions have been carried out by reaction of triflate **262** with alkoxydienylboronates **263** (Scheme 21.120) to afford azepine derivative **264** in 45% yield after chromatography. Subsequent acid-catalyzed



Scheme 21.119



Scheme 21.120

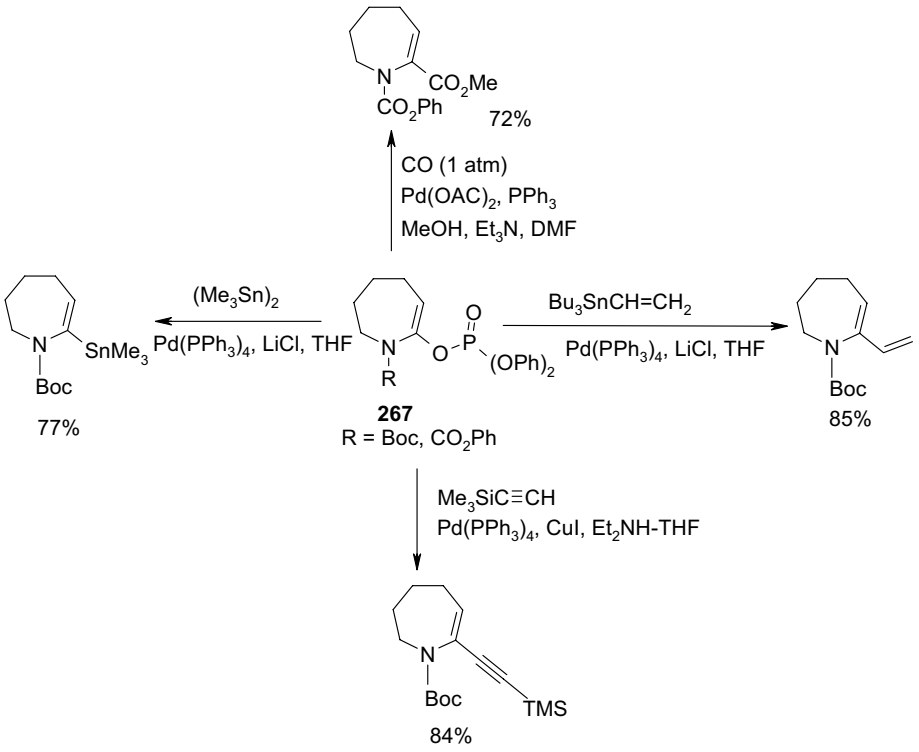
hydrolysis over Amberlyst gave the fused azepines **265** in 41% yield together with a smaller amount of azepine unsaturated ketone **266** (13%) [287].

Although the functionalization of lactams to substituted heterocycles via the corresponding enol triflates has been reported, they are rather unstable and the triflate reagent is expensive. In contrast, lactam-derived phosphate [288] intermediates present remarkable stability. Thus, *N*-Boc or *N*-CO_2Ph protected lactams, via their potassium enolates, gave the diphenyl phosphate derivatives **267** and the reactions with appropriate partners under Stille or Sonogashira coupling conditions and carbonylation (Scheme 21.121) have been tested.

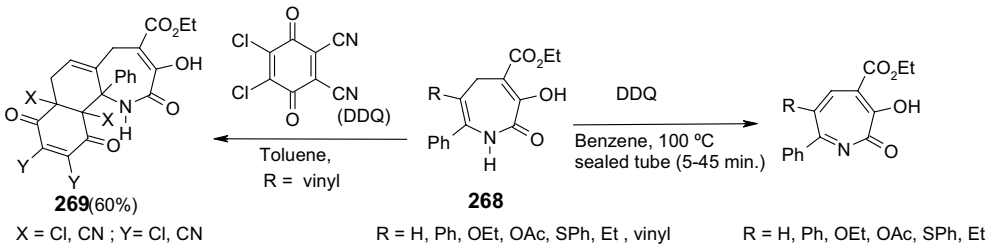
21.6.2.3 **Dihydroazepinones**

This section describes only several relevant examples of all the possible derivatives.

21.6.2.3.1 **Dihydroazepin-2-ones** The most extensive research on 1,5-dihydroazepin-2-ones has been carried out by Sano and co-workers [275]. The chemistry is essentially based on their relationship with azatropolones and azatropones by dehydrogenation. For example, dehydrogenation of **268** with DDQ yielded the corresponding azatropolones, but the reaction is affected by the nature of the substituents. The oxidation of 6-OEt and 6-H derivatives gave the corresponding azatropolones in moderate yields (65% and 50%, respectively) but with the other derivatives the yields were lower (2–17%) (Scheme 21.122).



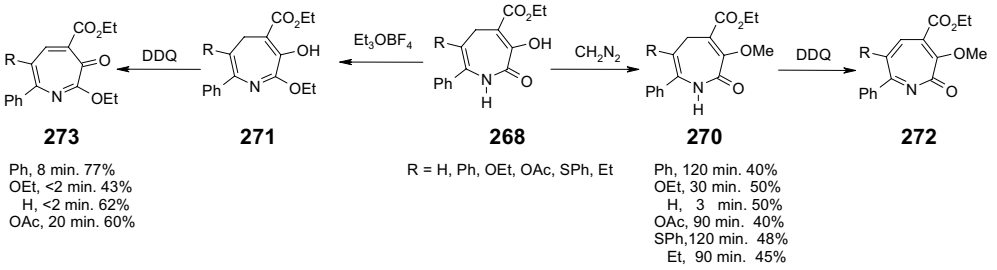
Scheme 21.121



Scheme 21.122

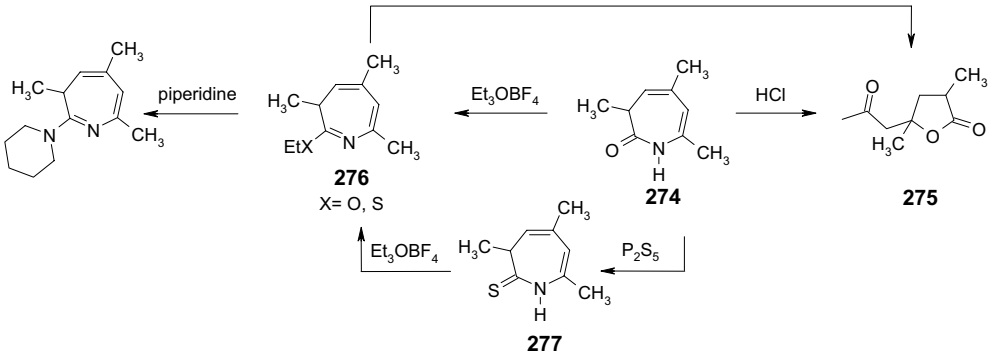
The vinyl derivative of **268**, when heated with DDQ in toluene, underwent a Diels–Alder reaction to give the adduct **269** in 60% yield rather than the dehydrogenation product (Scheme 21.122). Methylation of 1,5-dihydro-2*H*-azepin-2-ones **268** with diazomethane takes place at the enolic 3-OH and gives the corresponding compound **270**, and the reaction with triethyloxonium tetrafluoroborate occurs at the lactam oxygen to afford the azepine **271**. Treatment of the methyl ether **270** with DDQ in benzene at 100–120 °C gave the dehydrogenated product or azatropolone **272** in moderate yield. Dehydrogenation of **271** (R = H) and (R = OEt) occurred in a few

minutes while for the rest of compounds longer reaction times were required (Scheme 21.123). These results indicate that the rate of dehydrogenation is affected by the electronic character and the bulk of the substituent in C6 position.



Scheme 21.123

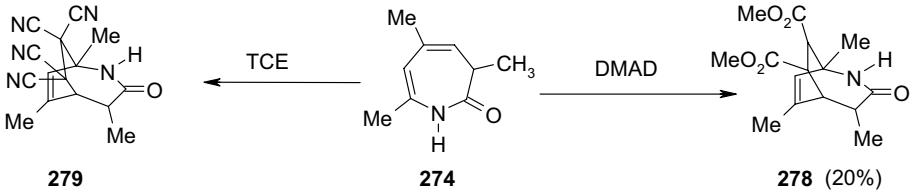
Treatment of 1,3-dihydroazepin-2-ones **274** with HCl yielded the lactone [289] **275**. O-Alkylation is achieved using triethyloxonium tetrafluoroborate and the hydrolysis of **276** (X = O) in dilute acid gives the lactone **275**. Further transformation of dihydroazepinones **274** with P_2S_5 led to the thio analog **277**, which can also react with triethyloxonium tetrafluoroborate to give the corresponding derivative **276** (X = S) (Scheme 21.124).



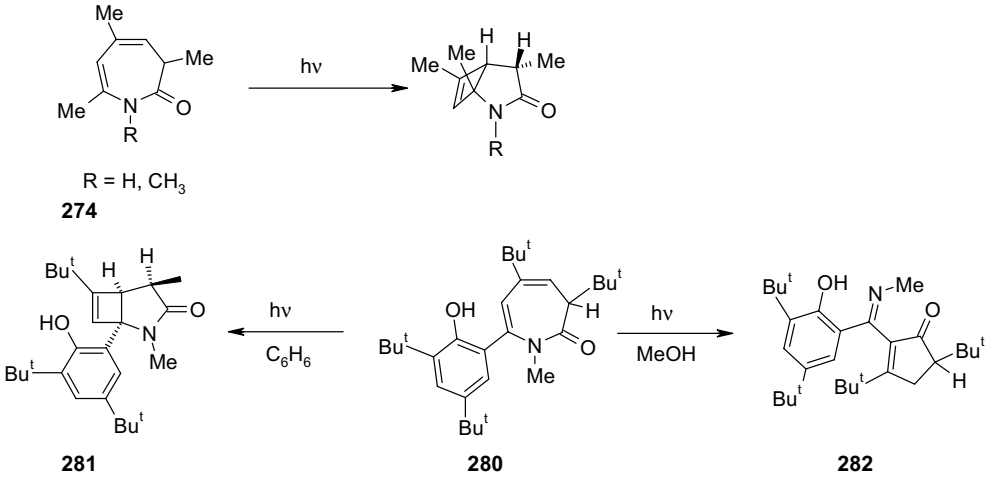
Scheme 21.124

Although treatment of compound **274** [290] with maleic anhydride or *N*-phenylmaleimide failed to produce the corresponding adduct, the Diels–Alder reaction with DMAD did proceed upon heating without solvent at 120–130 °C to give the adduct **278** in a poor yield (20%). In contrast, **274** reacted readily with tetracyanoethylene (TCE) in tetrahydrofuran to afford a quantitative yield of the adduct **279** (Scheme 21.125).

The photochemical behavior of dihydroazepin-2-ones has also been studied. For example, compound **274** (R = H) in THF or methanol and its N-methyl derivative give in each case a single photoisomer in 70% yield (Scheme 21.126) [276b, 291].



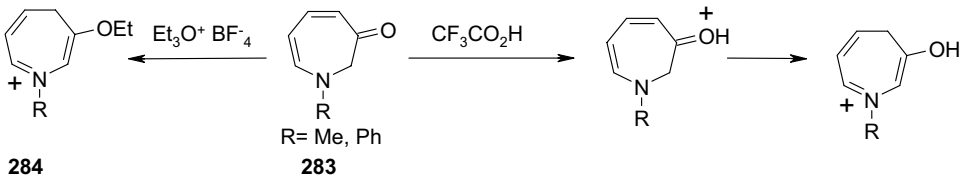
Scheme 21.125



Scheme 21.126

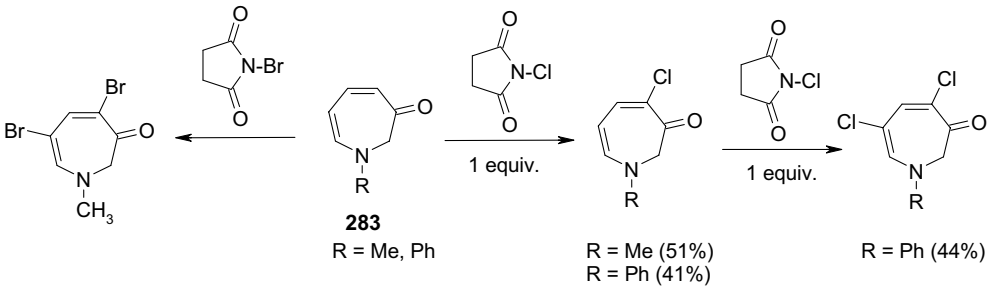
Irradiation of derivatives functionalized in position-7 of dihydroazepin-2-ones (**280**) gave different products depending on the solvent. For example, in ether or benzene the ketoamide-annelated cyclobutene **281** was obtained by intramolecular $2\pi + 2\pi$ cycloaddition. In contrast, irradiation in MeOH gave the cyclopentenone derivative **282** (Scheme 21.126) by a ring contraction (1,3-acyl shift) and subsequent double-bond migration [292].

21.6.2.3.2 **Dihydroazepin-3-ones** A summary of the more important aspects of the reactivity of these compounds is given here [293]. The 1,2-dihydroazepin-3-ones **283** (R = Me, Ph) are smoothly protonated with trifluoroacetic acid and the solutions are stable for several weeks. The azepinium derivative **284** has been obtained by treatment of **283** with triethyloxonium tetrafluoroborate in DCM (dichloromethane) (Scheme 21.127).



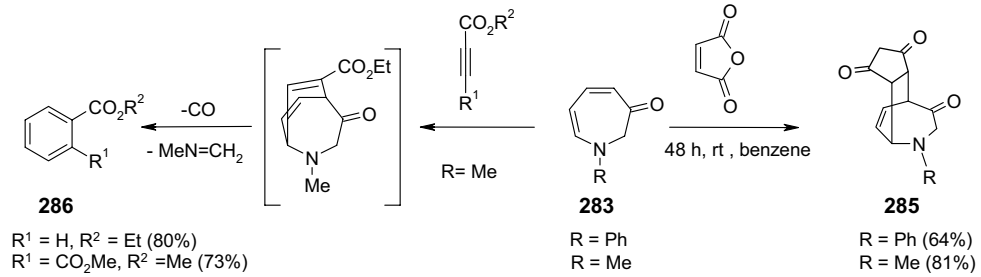
Scheme 21.127

The reaction of **283** (Scheme 21.128) with one equivalent of *N*-chlorosuccinimide in methanol at 0 °C gave the 4-chloroderivatives, which are stable in the solid state but not in solution. Further chlorination led to the 4,6-dichloroderivative. Treatment of 1-methylazepinone with either one or two equivalents of *N*-bromosuccinimide gave the 4,6-dibromo derivative as the only product in 8% and 60% yield, respectively (regardless of the amount of reagent).



Scheme 21.128

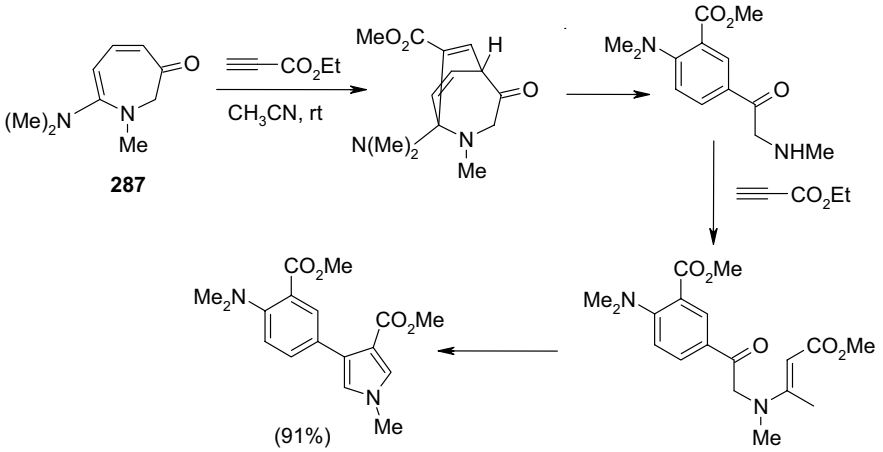
1,2-Dihydroazepin-3-one **283** reacts with dienophiles to give [4 + 2] adducts, many of which are important intermediates in ring transformation products. Cycloaddition of **283** with maleic anhydride at room temperature in benzene gave the adducts **285** in 64% (R = Ph) and 81% (R = Me) yield. However, the cycloaddition with DMAD or ethyl propiolate yielded benzoic acids **286** by a sequential Diels–Alder, retro Mannich, and decarbonylation process (Scheme 21.129) [294].



Scheme 21.129

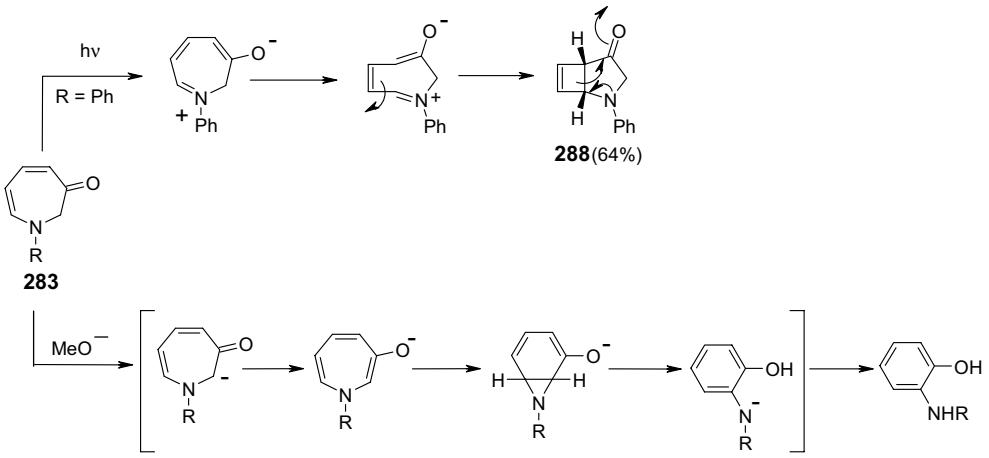
In contrast, the cycloaddition of the more reactive 7-dimethyl derivative **287** with two equivalents of methyl propiolate gave a 1,3,4-trisubstituted pyrrole in 91% yield. The mechanism for this unexpected transformation is shown in Scheme 21.130 [295].

Photolysis of azepinone **283** (R = Ph) by an electrocyclization process gave the expected product **288** in 64% yield. The bicycloheptanone is stable at room temperature or below, but this compound reverts to the starting material on thermolysis in



Scheme 21.130

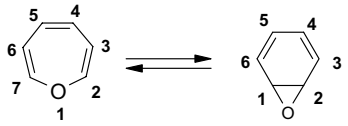
toluene [294]. Treatment of the azepinone **283** with sodium methoxide in methanol led to a ring contraction to give 2-aminophenol (Scheme 21.131) [296].



Scheme 21.131

21.7 Reactivity of Oxepines

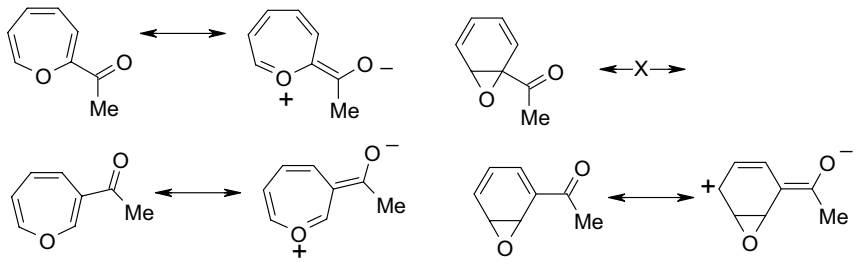
Monocyclic oxepines exist in equilibrium with isomeric benzene oxides and the existence of a rapid oxepine–benzene oxide equilibration does not allow oxepines to be treated as separate entities, thus helping to interpret their reactivity because some reactions can involve the benzene oxide tautomer (Scheme 21.132).



5a/5b

Scheme 21.132

The spontaneous oxepine–benzene oxide isomerization [297] proceeds as a thermally allowed disrotatory process according to the Woodward–Hoffmann rules. Oxepine and substituted derivatives are highly reactive compounds due to ring strain present in the benzene oxide tautomer. Furthermore, the oxepine–benzene oxide equilibrium position depends on the nature and position of the substituent [61, 298]. Generally, substitution at position-2 with electron-acceptor groups favors the oxepine ring while substitution at position-3 favors the benzene oxides. This effect has been explained in terms of the maximum number of alternative resonance contributors. Some examples are shown in Scheme 21.133.



Scheme 21.133

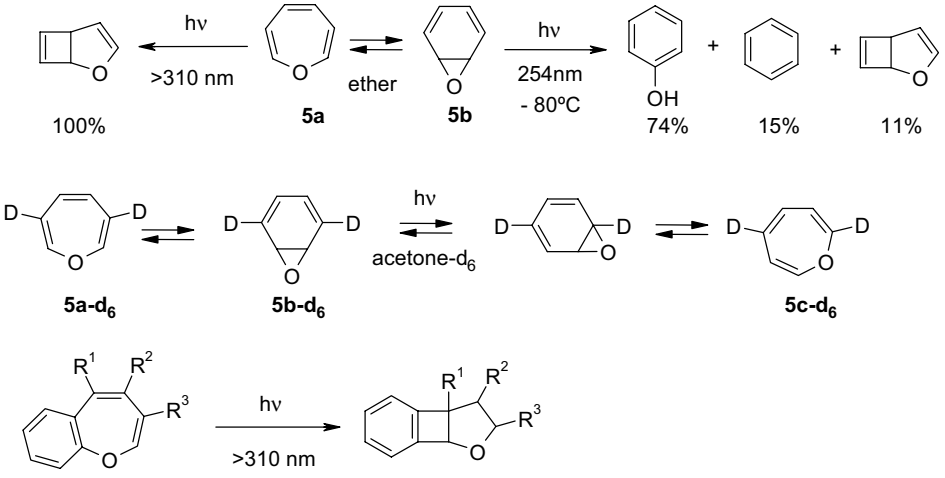
Owing to their structure and functionality, the reactivity of oxepines encompasses those reactions expected for a conjugated cyclic triene or those reactions of vinyl ethers, starting from reactions of annular oxygen. Consequently, two main groups of reactions can be considered in general terms: addition and cycloaddition reactions and the cleavage of the oxepine ring. This reactivity has been covered extensively in *Comprehensive Heterocyclic Chemistry, I, II* and *III* [2, 4, 7] and the present section is intended to provide only a summary and update.

21.7.1 Reactivity of Oxepines and Benzofused Derivatives

21.7.1.1 Thermal and Photochemical Reactions

Thermal ring closure reactions are thermally allowed disrotatory process. An illustrative example is the oxepine–benzene oxide equilibrium in which the oxepine tautomer is favored at high temperatures (Scheme 21.132).

The oxepine–benzene oxide (**5a/5b**) system is also attractive for photochemical studies, because the equilibrium varies with the solvent polarity and, to some extent, with the temperature. The photochemical rearrangement of the system (**5a/5b**) using UV light has been described by Holovka and Gardner [299] and gives the corresponding cyclobutene, via an excited singlet state, when the reaction was carried out in diethyl ether at $\lambda > 310$ nm, which allows only the excitation of **5a.** By contrast, irradiation of (**5a/5b**) at a shorter wavelength (254 nm) at $-80\,^{\circ}C$ produces mainly phenol (triplet), minor amounts of the cyclobutene, and benzene (singlet), indicating that these products come from **5b.** Irradiation at 254 nm in acetone produces phenol (Scheme 21.134).



Scheme 21.134

The photolysis of (**5a/5b**) has been reexamined [300] using isotopically labeled compounds (D at the 3- and 6-positions). Thus, irradiation at 254 nm (acetone-d_6 and room temperature) gave (NMR-analysis) phenol (40%) along with 12% of the isomeric oxepine **5c** through an oxygen-walk or circumambulatory [301] rearrangement of arene oxides.

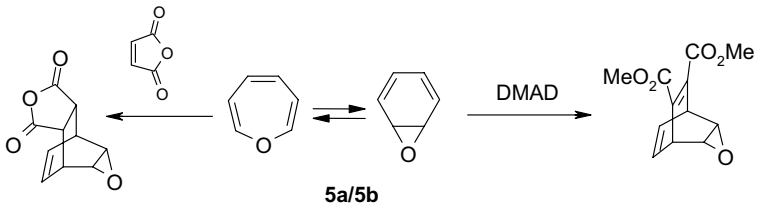
The photoreactions of benzoxepines are analogously dependent on the wavelength and the yields are higher on using wavelengths up to 310 nm (Scheme 21.134) [302].

21.7.1.2 Cycloaddition Reactions

Oxepines undergo cycloaddition reactions with unsaturated molecules due to their cyclic polyenic character. This structure possesses different reaction centers and can behave as an ene, diene, and triene according to the kind of dienophile and considering the oxepine–benzene oxide (**5a/5b**) system.

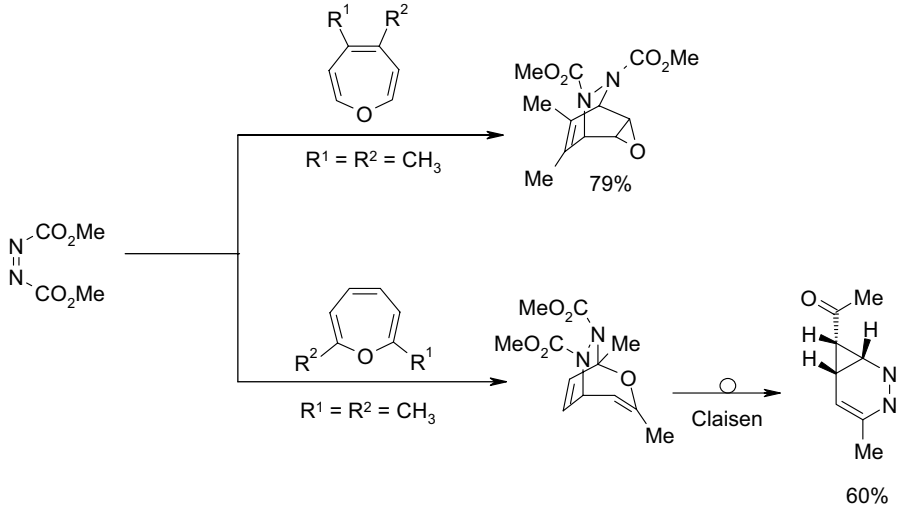
The cycloaddition reaction proceeds more readily on the benzene oxide form (**5a/5b**) in which the diene is closer to planarity. Thus, with dienophiles such as

DMAD or maleic anhydride [88] the [4 + 2] cycloadducts were obtained as indicated in Scheme 21.135.



Scheme 21.135

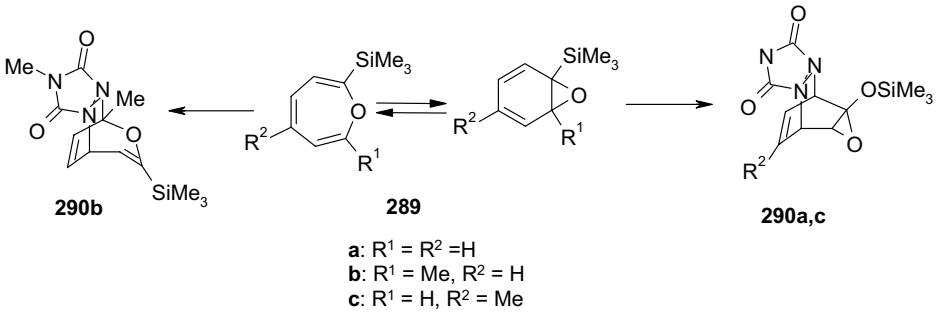
The reaction of 4,5-disubstituted oxepines [303] with azo compounds gives similar adducts to those indicated above (Scheme 21.136), whereas 2,7-disubstituted oxepines afforded an adduct from the oxepine valence isomer that is not stable but undergoes Claisen rearrangement to a cyclopropyl ketone (Scheme 21.136) [304].



Scheme 21.136

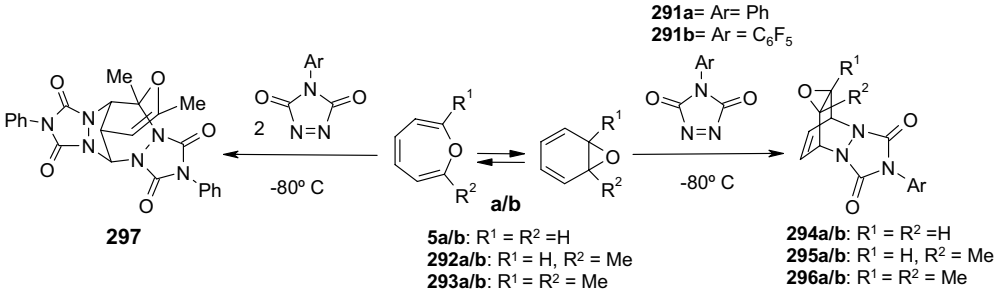
Similar behavior has been described by Boyd and Berchtold [305]. In this case, the reaction of 1-(trimethylsilyl)benzene oxide–oxepines **289** with 4-methyl-1,2,4-triazoline-3,5-dione is also affected by substituents and affords the expected Diels–Alder adducts **290a** and **290c** from the benzene oxide valence isomer, and the adduct **290b** (100%) from reaction of the oxepine valence isomer (Scheme 21.137).

More recently, Golding and co-workers [306] have described the reaction of benzene oxide–oxepine (**5a/b**,**292a/b**) with 4-phenyl-1,2,4-triazoline-3,5-dione (**291a**) in acetone at −80 °C. This gave a single adduct **294b**,**295b**, whose structure



Scheme 21.137

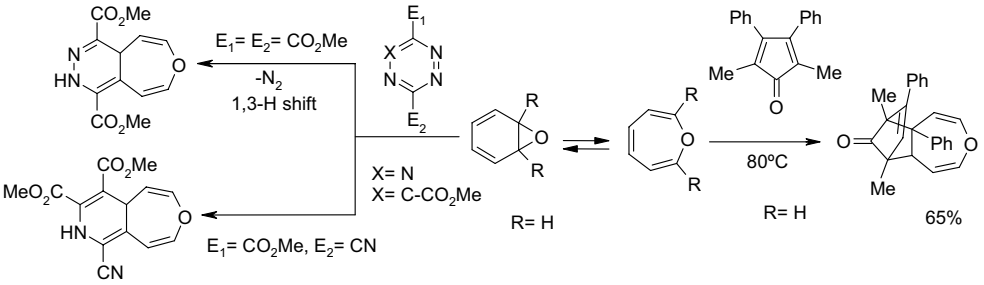
was validated by NMR and X-ray diffraction, showing that the dienophile approaches the diene *anti* to the epoxide moiety of the diene. These data are consistent with the previous adducts of benzene oxide obtained with other dienophiles [307, 308] and with other studies carried out recently by Harper and co-workers [35c]. The reaction of **293a/b** with **291a** gave two adducts, one of which is the expected [1 + 1] adduct **296b** (derived from **293b**) and shows again the preference for *anti* addition (dienophile versus epoxide) and the second adduct arises from two molecules of dienophile **291a** and one molecule of **293a/b** (Scheme 21.138). Formation of **297** requires molecular rearrangement and its structure has been elucidated by NMR and X-ray diffraction analysis.



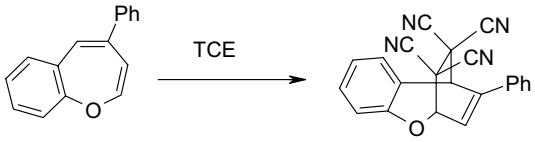
Scheme 21.138

Oxepines also undergo cycloaddition reactions at the C4−C5 bond, where they participate as a dienophile in [2 + 4] cycloaddition with cyclopentadienone [270] and with 1,2,4,5-tetrazine or 1,2,4-triazine derivatives [309] bearing electron-withdrawing groups (Scheme 21.139).

The benzo derivatives also undergo cycloaddition reactions. For example, reaction with tetracyanoethylene (TCE) [82, 310] affords the corresponding adduct **298** (Scheme 21.140).



Scheme 21.139

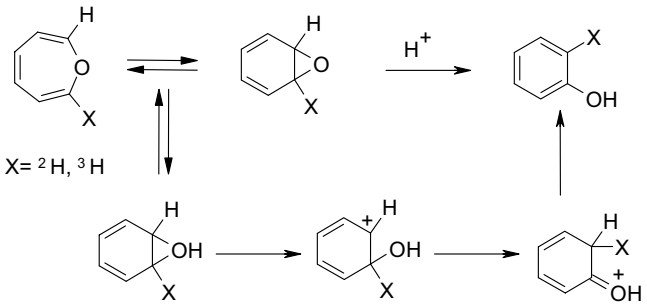


298

Scheme 21.140

21.7.1.3 **Reactions with Electrophiles**

The protonation of oxepine–benzene oxides takes place at the ring oxygen atom and generally results in C−O ring cleavage with the formation of several carbocations before conversion into phenol (Scheme 21.141). The acid-catalyzed isomerization has been studied extensively [311]. Deuterium and tritium labeling experiments have established a sequence that involves a 1,2-shift of the hydrogen isotope (X = ^{2}H, ^{3}H) and an enolization step. This process has been described as the NIH-shift[1)] (Scheme 21.141).

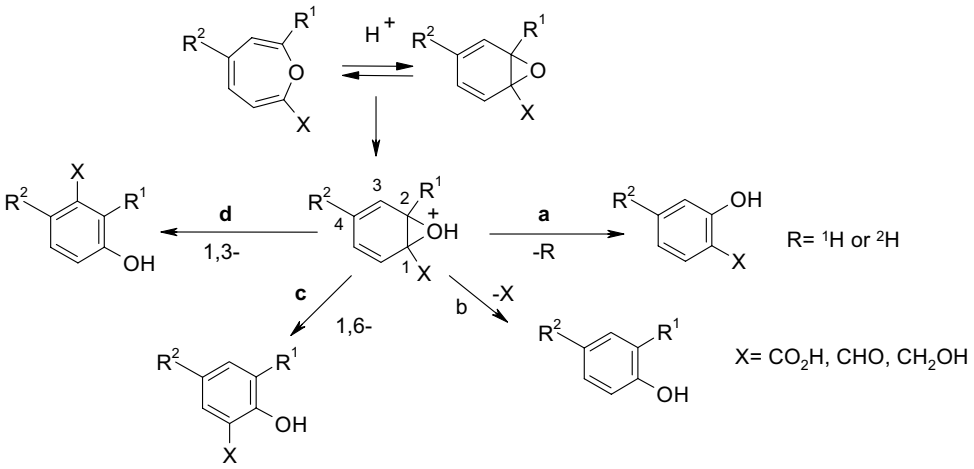


Scheme 21.141

1) The NIH-shift, named after the National Institute of Health, Bethesda, USA, where it was discovered in the context of biosynthetic studies.

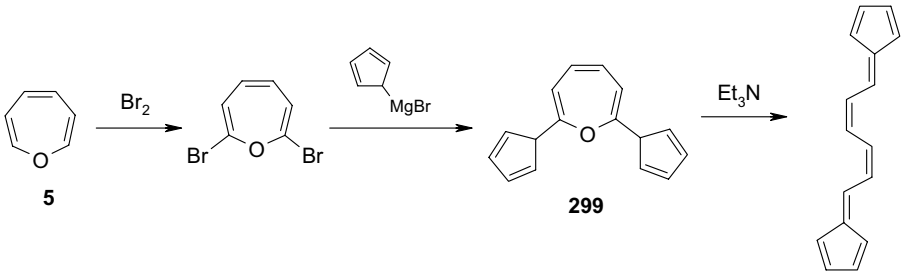
The acid-catalyzed isomerization is dependent on the nature and position of the substituents relative to the ring oxygen atom. The sequence observed in the NIH-shift was also found for Cl, Br, Me, and CO_2R substituents.

Potential reaction pathways are indicated in Scheme 21.142 at C2 in the acid-catalyzed process and these include: (a) loss of R, (b) loss of X, (c) 1,6-migration and retention of X, and (d) 1,3-migration and retention of X.



Scheme 21.142

The parent compound **5** has been halogenated by successive addition of bromine [312] and the resulting compound reacted with cyclopentadienylmagnesium to give **299**, which upon treatment with triethylamine gave fulvalene derivatives (Scheme 21.143).

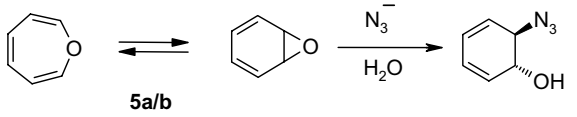


Scheme 21.143

21.7.1.4 **Reactions with Nucleophiles**

The arene oxide valence tautomer of oxepines could react with nucleophiles as a simple epoxide. However, the oxepine–benzene oxide is quite unreactive towards

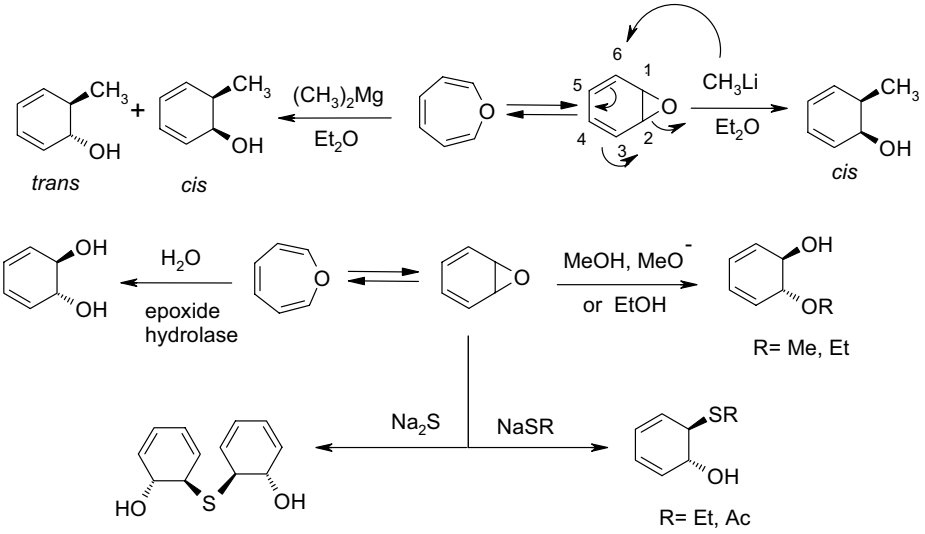
nitrogen nucleophiles such as NH_3, NH_2^-, and RNH_2 although it reacts with the azide anion to give cyclohexadiene derivatives (Scheme 21.144) [313].



Scheme 21.144

The reactivity of benzene oxide–oxepine has also been studied with carbon, oxygen, and sulfur nucleophiles, affording in most instances 1,2-dihydroaromatic products.

The reaction with methyllithium gave only *cis*-6-methylcyclohexa-2,4-dien-1-ol in 67% yield by 1,6-addition (Scheme 21.145). On the other hand, reaction with dimethylmagnesium gave a mixture of alcohols consisting of 37% cis isomer by 1,6-addition and 63% trans isomer by 1,2-addition. The mechanistic rationale was established by reactions with benzene-oxide oxepin-3,6-d_2.

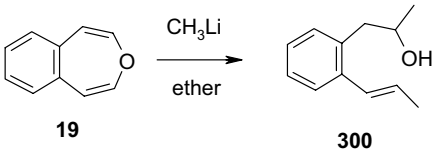


Scheme 21.145

Alcohols add only with difficulty, and the addition of water occurs in the presence of epoxide hydrolase enzyme [314]. Sulfur nucleophiles readily attack the oxepine ring as soft nucleophiles to produce the corresponding trans derivative as a result of direct 1,2-opening (Scheme 21.145).

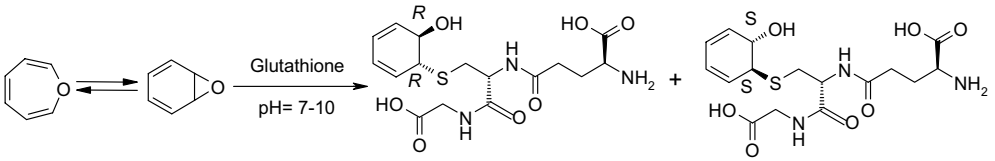
The reaction of the 3-benzoxepine (**19**), which appears to exist exclusively in the oxepine form, with methyllithium was much slower and resulted in ring-opening to give the propenylphenylpropanol **300** (Scheme 21.146).

The reaction of intracellular glutathione with benzene oxide–oxepine gave an initial metabolite of benzene, presumed to give 1-[*S*-glutathionyl]-cyclohexa-3,5-dien-



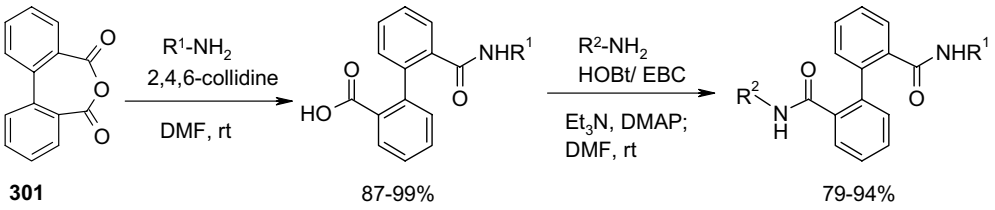
Scheme 21.146

2-ol, which underwent dehydration to *S*-phenylglutathione, the precursor of *S*-phenylmercapturic acid. In an effort to validate the proposed route to *S*-phenylglutathione, reactions of benzene oxide–oxepine with glutathione and other sulfur nucleophiles have been studied by Golding and co-workers [35b]. The data obtained confirm that benzene oxide–oxepine can be captured by glutation to give (1*R*,2*R*) and/or (1*S*,2*S*) products as indicated in Scheme 21.147. Further dehydration leads to the S-phenylglutathione. The process at pH 7 is relatively inefficient but is accelerated at higher pH.



Scheme 21.147

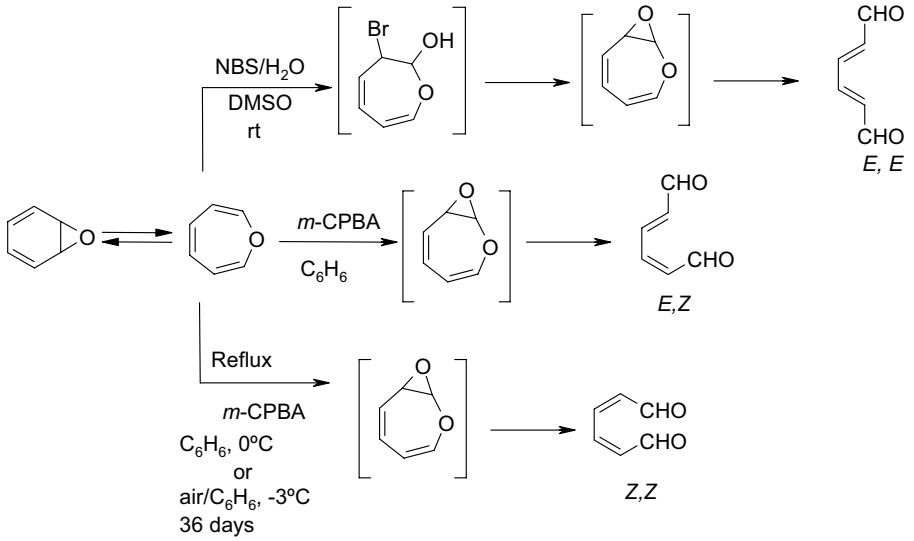
Herradón and co-workers have reported the opening of dibenzo[*c*,*e*]oxepin-5,7-dione (**301**) with amino acid and peptide derivatives to give peptide-biphenyl hybrids that are calpain inhibitors (Scheme 21.148) [315]. The method has also been applied in the solid phase [316].



Scheme 21.148

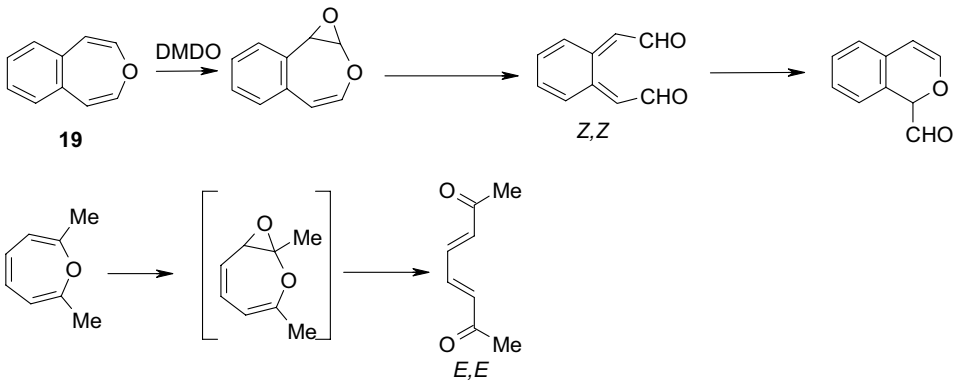
21.7.1.5 **Reactions with Oxidants**

The reactions of oxepine with NBS/H_2O or *m*-CPBA gave only stereoisomers of muconaldehyde (Scheme 21.149) [317]. The epoxides are assumed to be intermediates.



Scheme 21.149

However, in 2004 Nauduri and Greenberg [318] described the first unambiguous observation of an oxepine-2,3-oxide, as determined by ^{1}H-NMR spectroscopy (Scheme 21.150). 3-Benzoxepine (**19**) reacted with deuterated dimethyloxirane (DMDO) at 50 °C in acetone-d_6 to give the corresponding 2,3-oxide, which at 5–10 °C rearranged rapidly to its isomer 1*H*-2-benzopyran-1-carboxaldehyde. In contrast, 2,3-oxides of monocyclic oxepines rearrange to stable ring-opened dialdehydes or diketones as occurs, for example, with 2,7-dimethyloxepine.



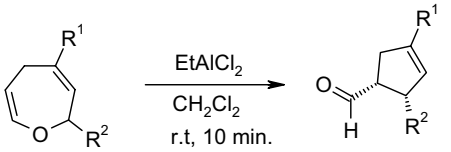
Scheme 21.150

21.7.2 Reactivity of Partially Reduced Oxepines

21.7.2.1 Dihydrooxepines

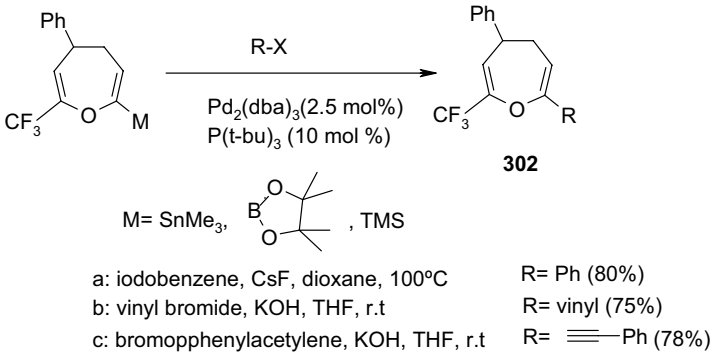
Rovis and Nasveschuk [319] have described an interesting ring contraction reaction from 2,5-dihydrooxepins to cyclopentenes, which involved a diastereoselective 1,3-rearrangement promoted by ethylaluminium dichloride as a Lewis acid. The scope of the 1,3-ring contraction was evaluated with various substituents in different positions.

The reaction provides access to *cis*- and *trans*-cyclopentene carboxaldehydes with good selectivities and can lead to tetrasubstituted cyclopentenes in high enantiomeric excess and with high diastereoselectivity (Scheme 21.151).



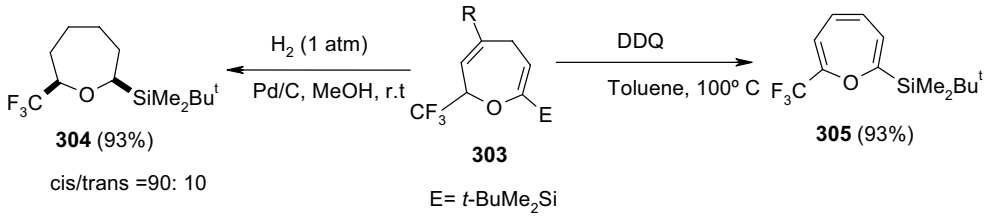
Scheme 21.151

2-Trifluoromethyl-substituted 4,5-dihydrooxepines **302** have been obtained by palladium(0)-mediated cross-coupling reactions from boryl, silyl, and stannyl dihydrooxepines (Scheme 21.152) [320].



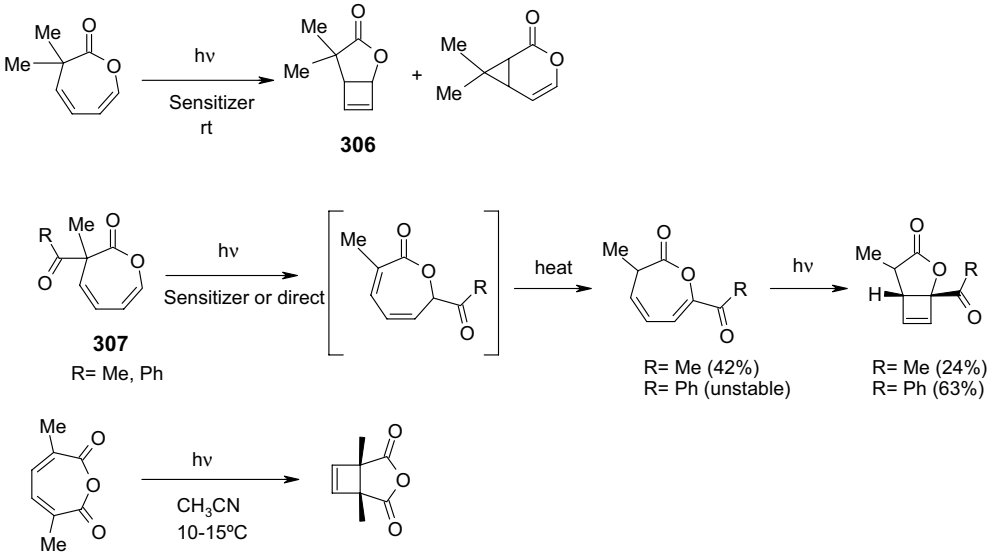
Scheme 21.152

2-Trifluoromethyl-2,5-dihydrooxepine **303** has been hydrogenated to the fully saturated **304** and oxidized to oxepine **305** (Scheme 21.153).



Scheme 21.153

The photochemical behavior of 3,3′-dimethyl-3*H*-oxepin-2-ones has been reported [321]. The method efficiently proceeds through cyclization to give exclusively compound **306**. However, reexamination of this photoreaction also found small amounts of the product arising from a 1,2-acyl shift (2.5–5%). A study of the photochemical process showed that the product distribution is greatly affected by the reaction temperature and that the yield of the 1,2-acyl shift product may be increased up to 28% at 70 °C (Scheme 21.154).

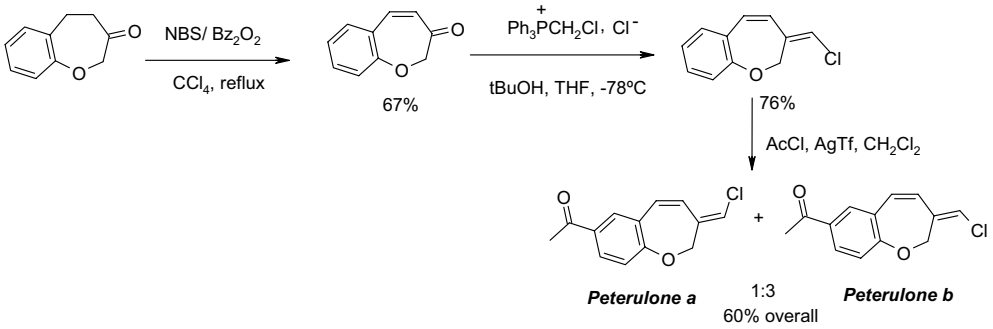


Scheme 21.154

Other photochemistry studies have been carried out on 3-acetyl and 3-benzoyl 3-methyloxepine-2-ones (**307**), which efficiently undergo a 1,5-acetyl or 1,5-benzoyl shift (Scheme 21.154) followed by double bond isomerization [322]. Cyclization of 1,5-products by a second photoreaction to give the bicyclic systems is a common reaction, but this process can be suppressed completely when the photolysis is carried out at −60 °C (6 h, R = Me) and the reaction mixture is allowed to stand at room temperature overnight, yielding only the 1,5-acethyl product in 80%.

Oxepine-2,7-diones [323] also undergo photochemical ring closure to the corresponding bicyclic anhydrides (Scheme 21.154).

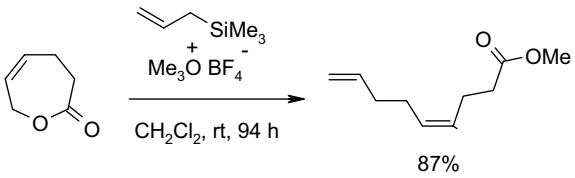
Pterulone a, a chlorinated benzoxepine derivative that has potent antifungal activity, has been synthesized from 4,5-dihydro-2*H*-benzoxepin-3-one in a sequence of three reactions (Scheme 21.155). The first step is an oxidation to generate the double bond and this was carried out by radical bromination with NBS. This was followed by elimination of HBr to give the 3(2*H*)-oxepinone in 67% yield. The keto group was transformed into a chlorovinyl group by a Wittig reaction to afford only the *(Z)*-isomer in 76% yield. Finally, a Friedel–Crafts acetylation with silver triflate and acetyl chloride in DCM yielded a 1: 3 mixture of peterulone a and its *(Z)*-isomer in 60% overall yield [324].



Scheme 21.155

21.7.2.2 **Tetrahydrooxepines**

Several syntheses of acyclic and carbocyclic natural products are based on the use of *(Z)*-4-hexenolide (4,7-dihydro-3*H*-oxepin-2-one) and substituted derivatives. This lactone reacts with allyltrimethylsilane [325] in the presence of trimethyloxonium tetrafluoroborate in a ring-opening process to give methyl 4,8-nonadienoate with exclusive *(Z)*-configuration in 87% yield (Scheme 21.156).



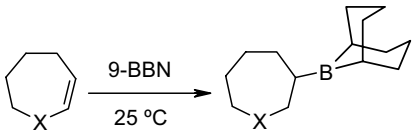
Scheme 21.156

To understand the role of the heteroatom on the rate of hydroboration, Brown and co-workers [326] undertook a study of representative heterocyclic olefins in comparison with the corresponding carbocyclic analogues. The results showed that

Table 21.5 Relative reactivity of olefins towards 9-BBN in THF at 25 °C (1-hexene = 100).

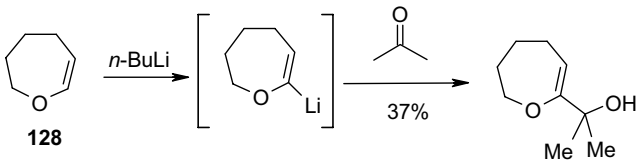
Hetero and related olefins	Relative rates
1-Hexene	100
Cycloheptene	6.9
1-Methyl-1-cyclopentene	1.59
2,5-Dihydrofuran	1.54
2,3,4,5-Tetrahydrooxepin	2.31×10^{-1}

2,3,4,5-tetrahydrooxepine reacts 30 times slower than cycloheptene (Table 21.5), and the hydroboration with 9-borabicyclo[3.3.1]nonane (9-BBN) is exclusively directed to the 3-position, which is probably controlled by a strong mesomeric contribution of the oxygen (Table 21.5, Scheme 21.157).



Scheme 21.157

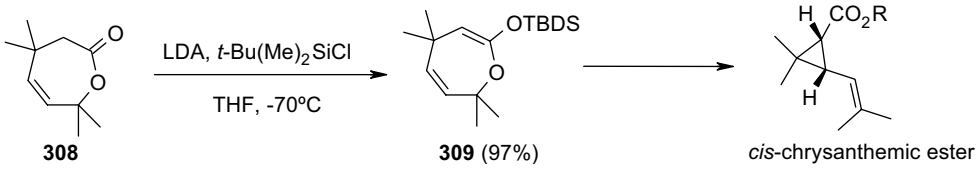
Another type of reactivity that has been studied [327] is the metallation of 2,3,4,5-tetrahydrooxepine with *n*-BuLi or *t*-BuLi to afford 7-lithio-2,3,4,5-tetrahydrooxepine by vinylic deprotonation (Scheme 21.158).



Scheme 21.158

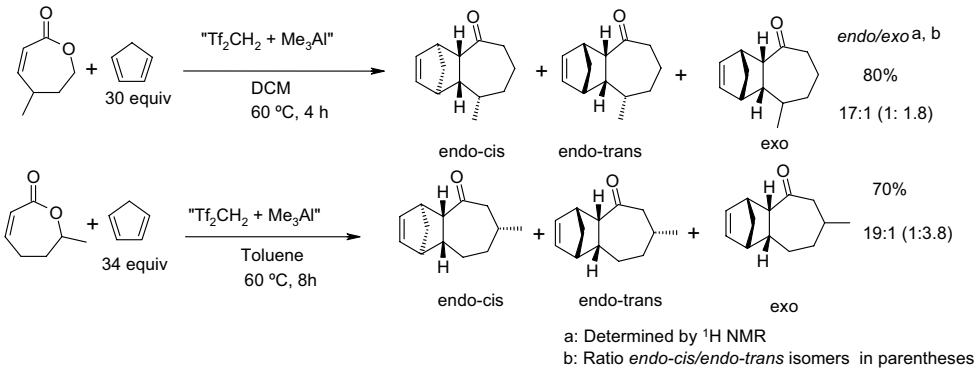
Under standard silylation [328] conditions (LDA, *t*-BuMe$_2$SiCl, THF, −70 °C) lactone **308** gave **309** in 97% yield and this rearranged to give cyclopropane carboxylic acids (e.g., the *cis*-chrysanthemic ester) by Claisen–Ireland rearrangement (Scheme 21.159).

Although seven-membered α,β-unsaturated lactones can be used as dienophiles, they are less reactive than their acyclic counterparts and the Diels–Alder reaction is not a general approach to complex polycyclic systems. In an effort to overcome these synthetic problems, Taguchi and co-workers [329] have developed an efficient Lewis



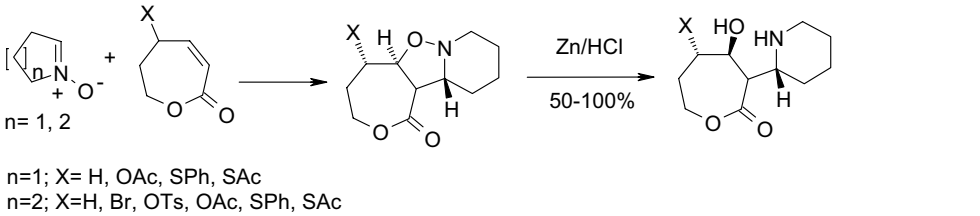
Scheme 21.159

acid by mixing Tf_2CH_2 and Me_3Al for the Diels–Alder reaction with cyclopentadiene (CP), which in the case of γ- or ε-methylated seven-membered lactone derivatives preferentially reacted with CP by the *syn* face (Scheme 21.160).



Scheme 21.160

The 1,3-cycloaddition reaction of nitrones to olefins is an effective tool for the preparation of isoxazolidones. In particular, the adduct from the cycloaddition of cyclic nitrones to α,β-unsaturated lactones [330] such as 6,7-dihydro-5*H*-oxepin-2-one was converted into the corresponding piperidyl (and pyrrolidyl) oxepinone by reduction of the nitrogen–oxygen bond (Scheme 21.161) [331].



Scheme 21.161

21.8
Reactivity of Thiepines

The development of the chemistry of thiepines is linked to their theoretical and biological interest. The theoretical interest concerns the question of whether thiepines with 8π electrons are nonaromatic or antiaromatic. Research in this field has focused on simple derivatives that could provide information to increase our understanding of the nature of thiepines while the biological interest is linked to the pharmacological activity of this system.

Since simple thiepines are generally very reactive, the chemical reactivity has been studied on polycyclic systems. On the other hand, the reactivity of this system can be considered separately from the bicyclic isomer thiirane, which on desulfurization and ring contraction yields arenes (Scheme 21.7). Thiepine thus appears to exist exclusively in this valence isomer. The stability of thiepines is enhanced by the presence of bulky substituents [332] at the C2 and/or C7 positions and electron-donating or -withdrawing groups. Additional stability is achieved in the transformation to S,S-dioxides (sulfones) and thiepinium salts.

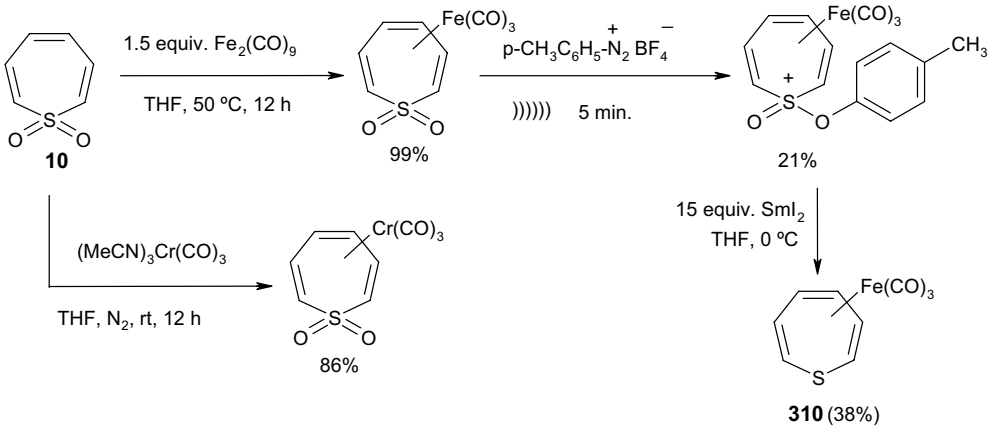
21.8.1
Reactivity of Thiepines and Benzofused Derivatives

As simple thiepines are thermally unstable, the reactivity of these heterocycles has been studied with either monocyclic structures stabilized by *tert*-butyl groups at the 2,7-positions or annulated thiepines, 1,1-dioxide derivatives, or as transition metal derivatives.

21.8.1.1 Reactions with Metal Carbonyl Complexes

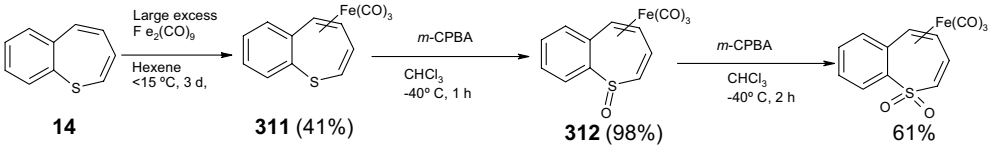
The capacity of transition metals to stabilize labile species by complexation allows the isolation of unstable conjugated molecules such as, for example, norcaradiene [333] among others. In the field of thiepines, the transition metal complexation strategy has been used to synthesize and isolate thermally unstable compounds. Thiepine-1,1-dioxide has been isolated as a stable crystalline compound, but the 1-oxides are considered to be extremely unstable [18]. In relation to the benzo-derivatives, 1-benzothiepine and its 1,1-dioxide are well characterized but the 1-benzothiephine 1-oxides are referred to polysubstituted derivatives. Consequently, efforts have been directed to the unstable 1-benzothiepine-1-oxide and thiepine and its 1-oxide.

The first synthesis and characterization of thiepine-iron tricarbonyl (**310**) was carried out by Nishino and co-workers [177a] from thiepine 1,1-dioxide with $Fe_2(CO)_9$, a process that gave (thiepine 1,1-dioxide)iron tricarbonyl in 99% yield. Subsequent treatment of this complex with *p*-toluenediazonium tetrafluoroborate promoted by ultrasound irradiation led to the corresponding tolyloxysulfoxonium tetrafluoroborate as a mixture of stereoisomers, which were reduced by reaction with samarium diiodide/THF complex without affecting the 6,7-double bond to produce **310** in 38% yield (Scheme 21.162). Other complexes of thiepine 1,1-dioxide with Cr-, Mo-, and W-carbonyls have also been described [334].



Scheme 21.162

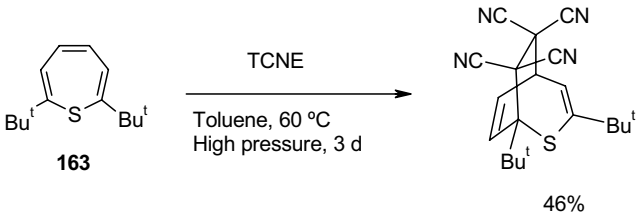
Application of the transition metal strategy to 1-benzothiepine (**14**) gave the complex **311** in 41% yield, which on oxidation with *m*-CPBA was converted into monoxide **312** in 98% yield [335]. This compound, under analogous reaction conditions, gave the 1,1-dioxide complex (Scheme 21.163).



Scheme 21.163

21.8.1.2 **Cycloaddition Reactions**

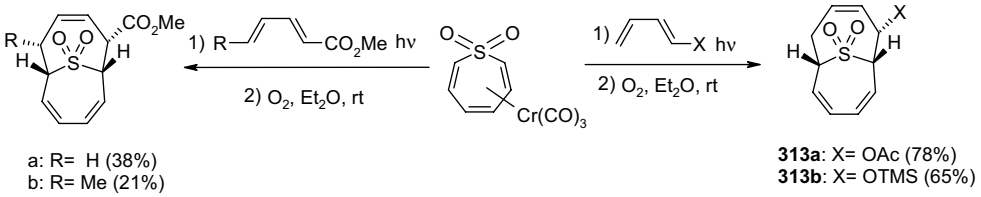
One of the essential characteristics of conjugated polyenes is their capacity to undergo cycloaddition reactions and, as a consequence, this reaction has been studied with different thiepines. For example, the cycloaddition of 2,7-di-*tert*-butylthiepine (**163**) with tetracyanoethylene (TCNE) produced only the [4 + 2] cycloadduct, although the steric repulsion of *tert*-butyl groups could promote a [2 + 2] process (Scheme 21.164) [336]. The reaction in toluene at 60 °C under



Scheme 21.164

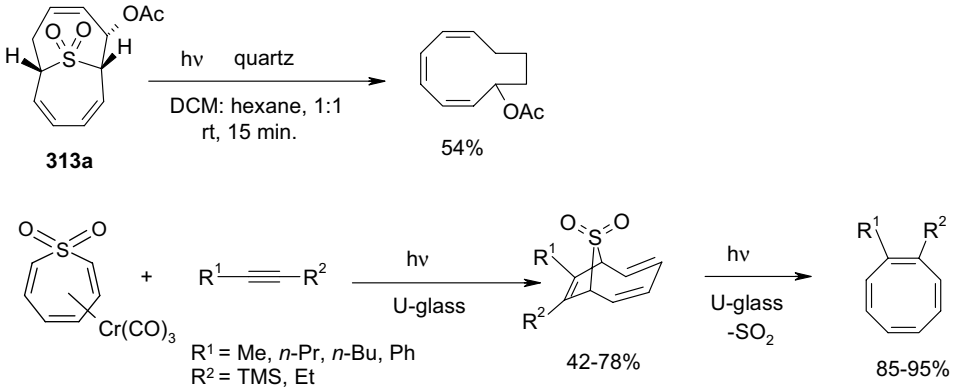
high pressure for 3 days gave the adduct in 46% yield as the major product and the same reaction in acetonitrile at atmospheric pressure over two weeks gave 49% yield.

In an analogous way to azepine derivatives, the higher-order cycloaddition reactions (i.e., $6\pi + 4\pi$, $4\pi + 4\pi$, and $6\pi + 2\pi$) have emerged as a powerful method for the construction of stereochemically and structurally complex polycyclic systems. Rigby's group have been particularly active in this area, using both thermally and photochemically activated cycloadditions of chromium(0) complexes of azepines and thiepines. Scheme 21.165 shows selected examples [337].



Scheme 21.165

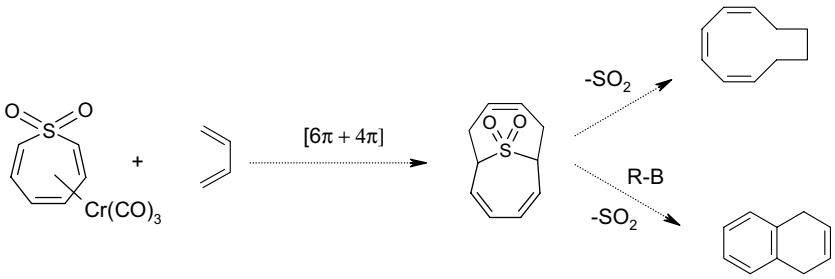
Photolysis of decomplexed cycloadduct **313a** afforded the all-*(Z)* cyclodecatetraene in 54% yield through a chelotropic reaction (Scheme 21.166). Extension of the reaction with alkynes [338] afforded substituted cyclooctatetraenes. The two-step process involves consecutive $[6\pi + 2\pi]$ cycloaddition and the elimination of sulfur dioxide (Scheme 21.166).



Scheme 21.166

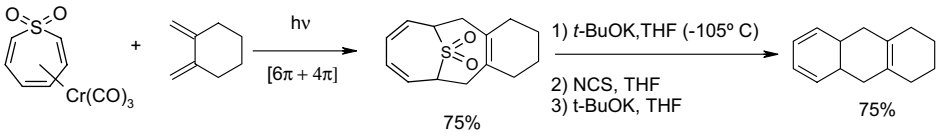
A complementary application of the cycloaddition–chelotropic extrusion sequence is the benzannulation (Scheme 21.167) in which the elimination of SO_2 occurs as part of a Ramberg–Bäcklund (R-B) rearrangement process [339].

This protocol includes the simultaneous formation of two rings. The overall process takes place with a high level of convergency, with all of the carbon atoms comprising the arene substructure introduced in a single step through the thiepine



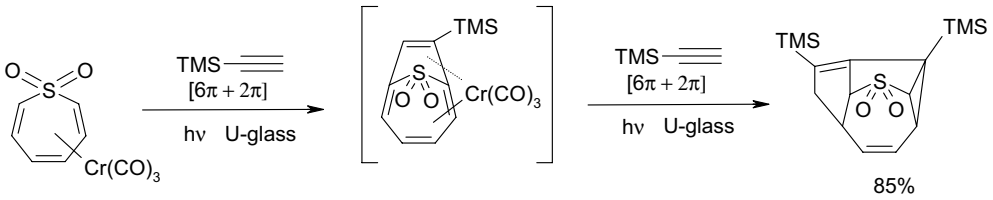
Scheme 21.167

dioxide triene system (a good example of atom economy [340]). Scheme 21.168 shows a typical benzannulation process.



Scheme 21.168

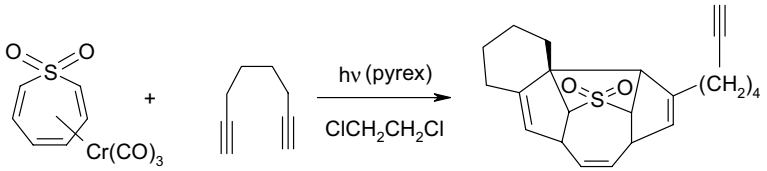
Modifications through a multicomponent reaction [341] have been described that involve three-components, that is, a Cr(0) complex in combination with two terminal alkyne units to give cycloadducts in good yields in a process that can be viewed formally as two consecutive Cr(0)-mediated [6π + 2π] cycloadditions (Scheme 21.169).



Scheme 21.169

An extension of this concept has been applied to four-component chromium(0)-mediated cycloaddition processes involving thiepine 1,1-dioxide/tricarbonylchromium(0) and various tethered diyne reaction partners. In a typical example of this process, photocycloaddition of the complex with excess 1,7-octadiyne in dichloroethane afforded the pentacyclic triene sulfone **314** in 45% yield (Scheme 21.170) [342]. A similar reaction with 1,8-nonadiyne gave the corresponding product in 38% yield. The reaction with 1,6-heptadiyne afforded only the three-component cycloadduct.

The adduct is formally derived from a sequential [6π + 2π]/[6π + 2π]/[2σ + 2π] process. The first two steps involve a similar transformation to the pathway observed



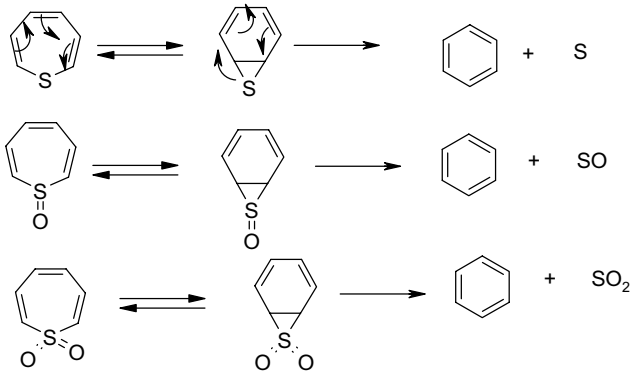
314 (45%)

Scheme 21.170

in the three-component process [6π + 2π]/[6π + 2π] and the third cycloaddition [2σ + 2π] takes place with the cyclopropene unit and the additional alkyne component. The role of chromium(0) in promoting the critical [2σ + 2π] process is not yet clear.

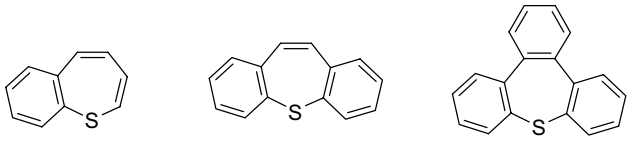
21.8.1.3 Thermal and Photochemical Reactions

The most common thermal reaction of thiepines is the extrusion of a sulfur atom [343]. A similar reaction occurs with thiepine 1-oxide and 1,1-dioxide, which lose sulfur monoxide and sulfur dioxide, respectively (Scheme 21.171).



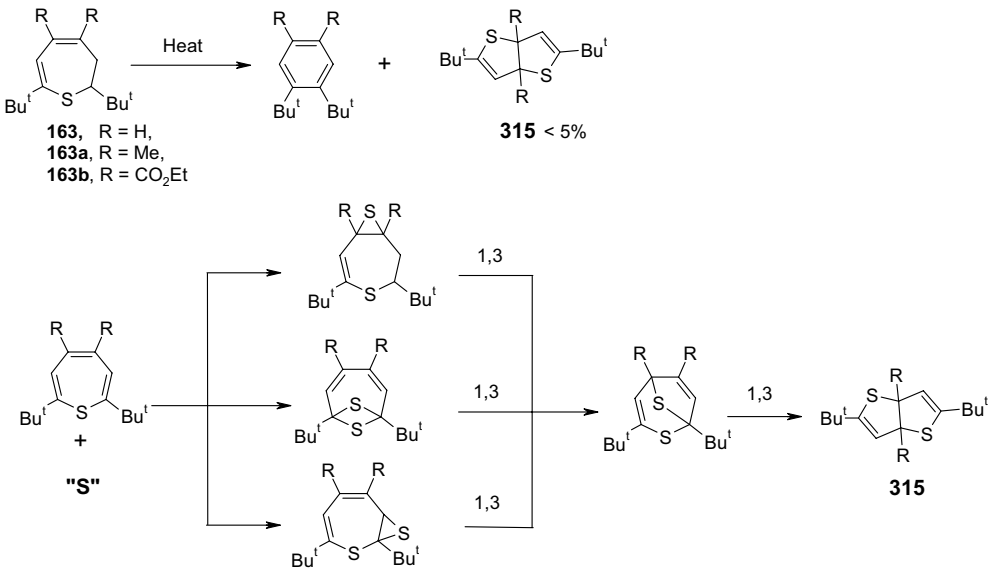
Scheme 21.171

The relative stability of fused benzo derivatives of thiepine [344] is assessed by the temperature at which sulfur extrusion occurs: 47 °C for compound **14**, 250 °C for **29**, and 380 °C for the tribenzo derivative **29b** [345].



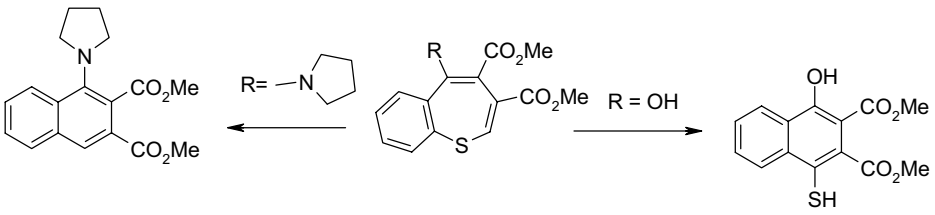
14 **29** **29b**

Thermolysis of stable monocyclic thiepines such as 2,7-di-*tert*-butylthiepines **163** gave the sulfur-extruded benzene derivative as the major product, together with the thienothiophene derivative **315**, the structure of which was confirmed by X-ray diffraction [346]. The formation of **315** can be explained by addition of extruded sulfur, which is in a highly reactive monomeric form, to the thiepine to produce different intermediates that can be transformed into **315** by 1,3-shifts, as indicated in Scheme 21.172.



Scheme 21.172

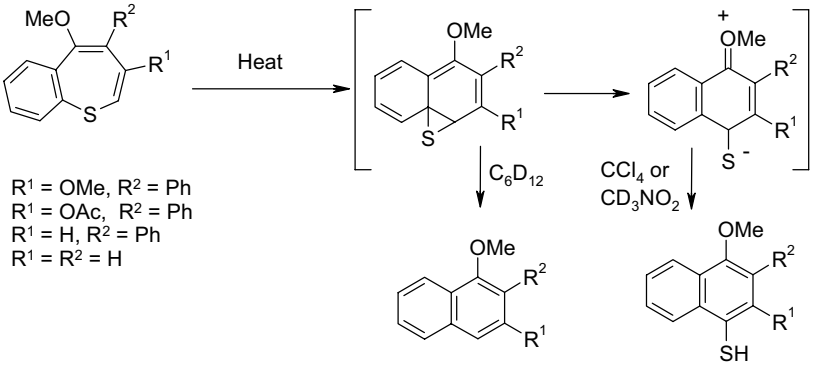
On the other hand, it is worth noting that the reactivity of benzo[*b*]thiepine derivatives depends on the substituent at position-5 and this can occur by either sulfur extrusion or rearrangement to 4-mercapto-1-naphthol (Scheme 21.173), probably via the thianorcaradiene as an intermediate [347].



Scheme 21.173

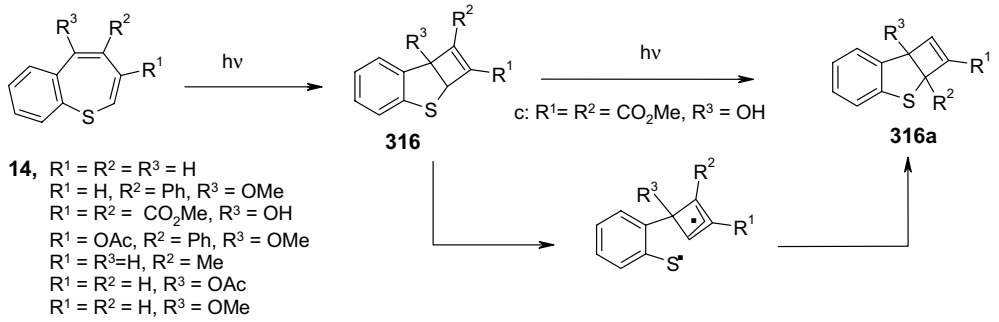
Other benzothiepine derivatives undergo the same transformation, depending on the solvent [348]. Thus, heating in cyclohexene gives the usual desulfuration

products, whereas in carbon tetrachloride or nitromethane the benzothiepine isomerizes to the thionaphthol as indicated in Scheme 21.174.



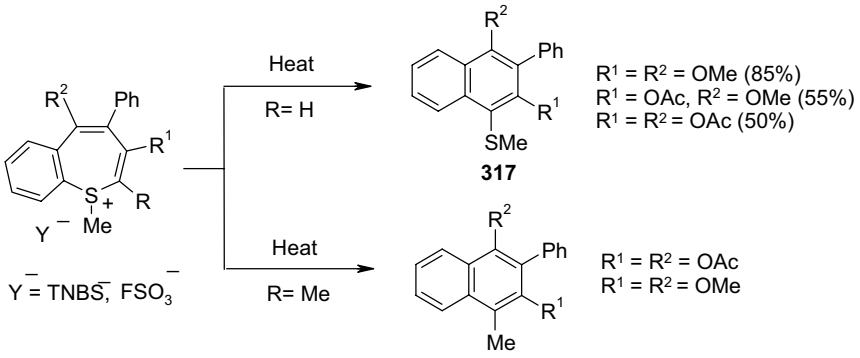
Scheme 21.174

The photochemical reactivity of benzothiepine and substituted benzothiepine derivatives is similar to that found with benzoxepines and the valence tautomeric cyclobutene is formed by a concerted disrotatory ring closure mechanism (Scheme 21.175) [349]. Under prolonged irradiation [221], compound **316** ($R^3 = OH$, $R^1 = R^2 = CO_2Me$) was converted into another isomer (**316a**). This transformation proceeds by rupture of the C−S bond to give a stabilized diradical with subsequent formation of a new C−S bond.



Scheme 21.175

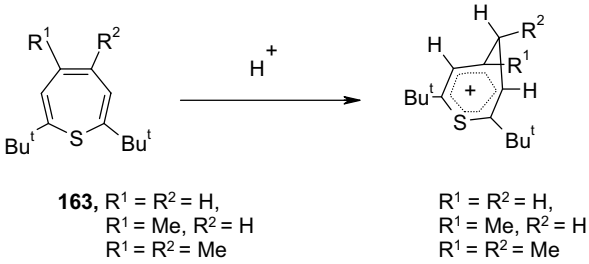
In general, 1-methylbenzothiepinium salts are more stable than the corresponding benzothiepines and the thermolysis of such salts gives the naphthyl thioethers **317** (Scheme 21.176) [350]. However, thermolysis of 1,2-dimethyl-4-phenyl-1-benzothiepinium salts gives sulfur-free reaction products [351].



Scheme 21.176

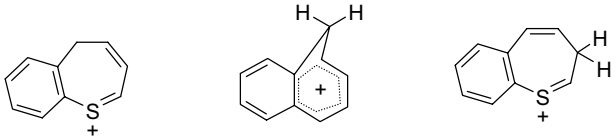
21.8.1.4 **Reactions with Electrophiles**

4*H*-Thiepinium ions have been generated by treatment of thiepines with fluorosulfuric acid ($FSO_3H/CD_2Cl_2/SO_2$) solution at −70 °C or sulfuric acid at room temperature [352]. The ^1H NMR analysis showed that these ions possess a homothiopyrylium structure. Protonation occurs regiospecifically at position-5 in thiepines to give the 4*H*-ions (Scheme 21.177).



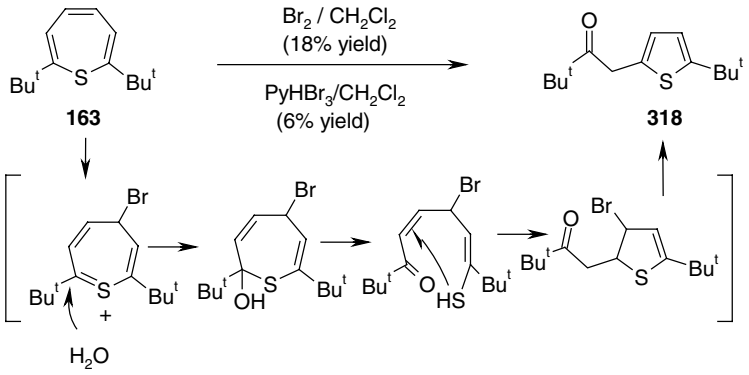
Scheme 21.177

Both 5*H*- and 3*H*-1-benzothiepinium ions have been generated under analogous conditions ($FSO_3H/CD_2Cl_2/SO_2$) and have been characterized by ^1H and ^{13}C NMR spectroscopy. The former ion can be regarded as having a benzohomothiopyrylium ion structure whereas the 3*H*-benzothiepinium has a localized ion structure rather than a delocalized one (as shown here).



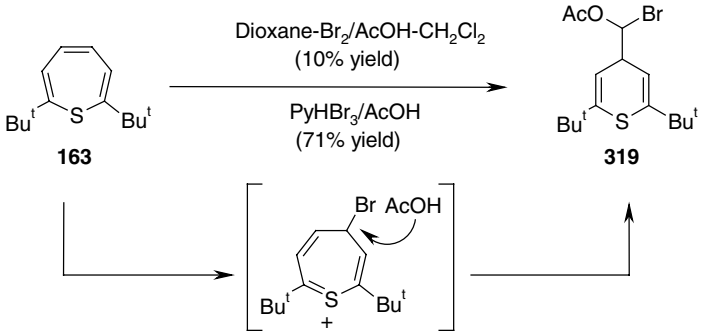
Bromination of 2,7-di-*tert*-butylthiepine [353] (**163**) directly with bromine at −78 °C or with pyridinium hydrotribromide at room temperature in dichloromethane

gave compound **318** in low yield along with several unidentified products (Scheme 21.178).



Scheme 21.178

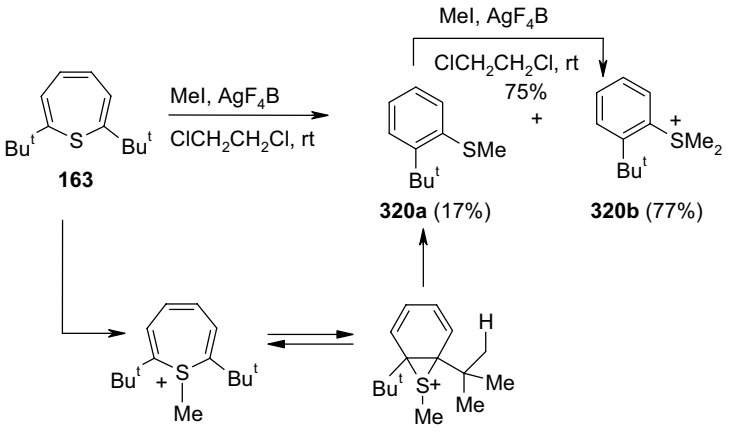
Although reaction of thiepine **163** with a dioxane/bromine complex in CH_2Cl_2 at −70 °C produced a complex mixture in a nucleophilic solvent ($AcOH/CH_2Cl_2$, 3 : 1) at 0 °C, the bromo acetate **319** was obtained in 10% yield. However, when the reaction was carried out with pyridinium hydrotribromide in AcOH at room temperature compound **319** was obtained in 71% yield (Scheme 21.179).



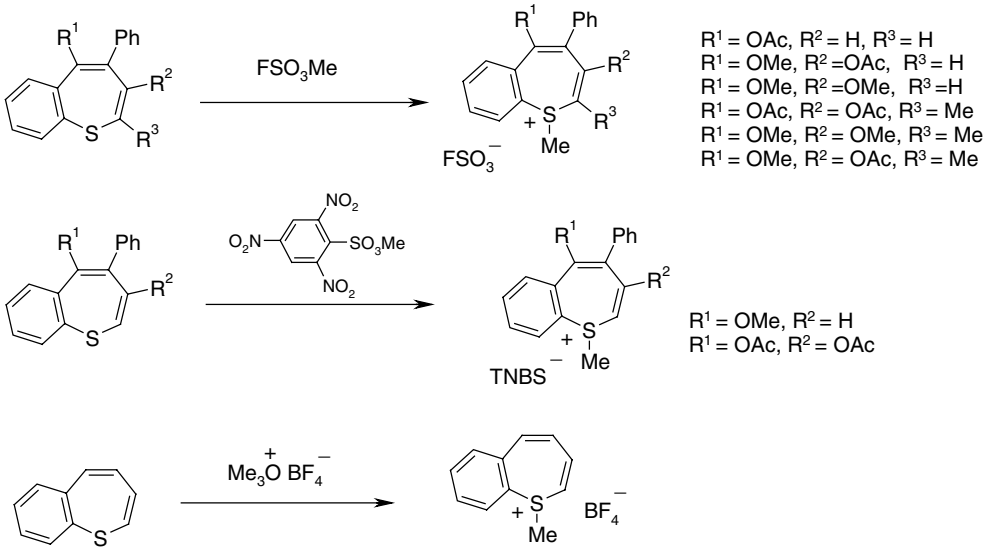
Scheme 21.179

Alkylation of 2,7-di-*tert*-butylthiepine with methyl iodide/silver tetrafluoroborate in CH_2Cl_2 at room temperature did not give the expected 1-methylthiepinium derivative, but the reaction afforded compounds **320a** and **320b** in 17% and 77% yield, respectively; compound **320a** is an intermediate, as demonstrated by the fact that further identical treatment of **320a** gave **320b** in 75% yield (Scheme 21.180).

Methyl fluorosulfonate, methyl 2,4,6-trinitrobenzosulfonate, and trimethyloxonium tetrafluoroborate have been used as methylating agents for the formation of *S*-methylthiobenzothiepinium salts (Scheme 21.181).



Scheme 21.180

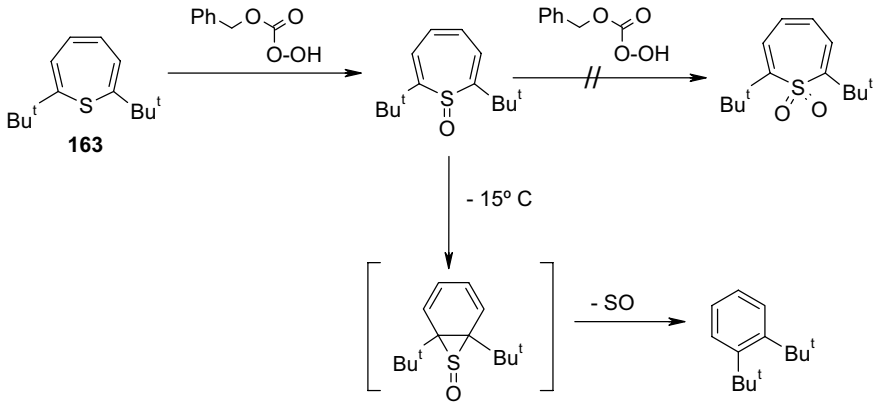


Scheme 21.181

21.8.1.5 **Reactions with Oxidants**

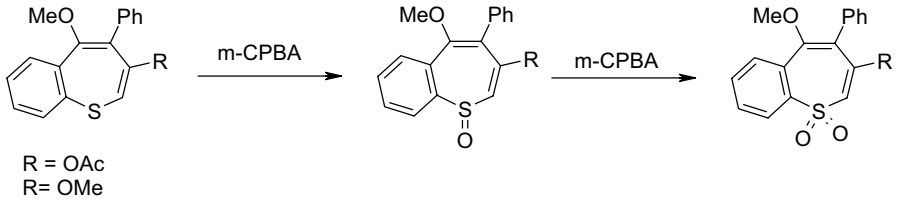
While thiepine 1-oxide has not been prepared, the 1,1-dioxide is a stable crystalline compound. In relation to benzo derivatives, the oxidation of benzothiepine to 1-benzothiepine 1-oxide failed, as indicated previously, but its 1,1-dioxide has been synthesized by direct treatment with two equivalents of *m*-CPBA. On the other hand, oxidation of 2,7-di-*tert*-butylthiepine (**163**) has been tested with *o*-benzylmonoperoxycarbonic acid in an NMR tube. Signals consistent with the structure of

2,7-di-*tert*-butyl-thiepin-1-oxide were observed, but when the mixture was allowed to warm up to −15 °C the compound gradually transformed into *o*-di-*tert*-butylbenzene. The 1-oxide was not further oxidized to the sulfone, probably because the two bulky *tert*-butyl groups sterically hinder the approach of the second equivalent of the peracid (Scheme 21.182).



Scheme 21.182

Oxidation of substituted benzothiepines [354] with *m*-CPBA afforded the corresponding 1-oxides and 1,1-dioxides, respectively (Scheme 21.183).



Scheme 21.183

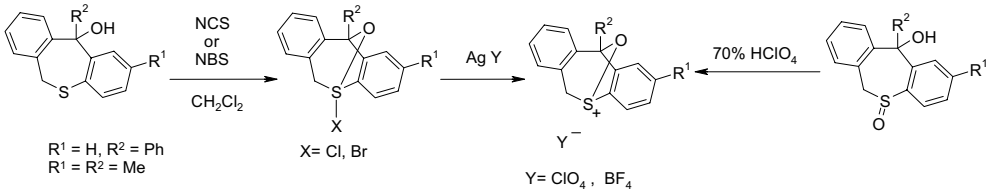
21.8.2
Reactivity of Partially Reduced Thiepine Derivatives

In this section the reactions are classified into several categories: reactions on the sulfur atom, reactions of the substituents on the sulfur atom, reactions that occur in other parts of the molecule that are able to form adducts, at the carbons, or reactions of substituents attached to ring carbon atoms.

21.8.2.1 Dihydrothiepines

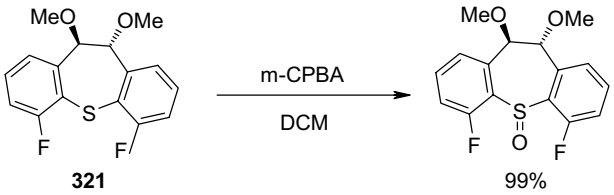
S-Chloro and S-bromo derivatives of dihydrobenzothiepines [355] have been synthesized by treatment with NCS or NBS at room temperature. The chlorosulfuranes

are more thermally stable than bromosulfuranes during the recrystallization process. To investigate the covalent nature of these species, the corresponding thiepinium salts were synthesized (Scheme 21.184) and their physicochemical data compared with those of sulfuranes. Furthermore, the sulfur–halogen bond was studied by ^{1}H NMR spectroscopy, MS, and X-ray diffraction analysis.



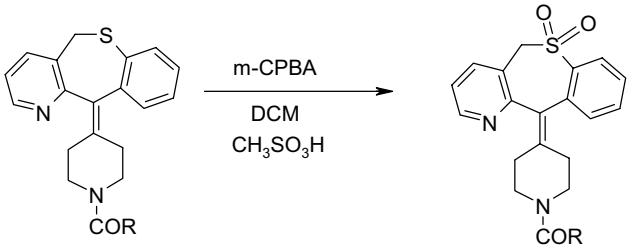
Scheme 21.184

As indicated previously, the oxidation with *m*-CPBA is readily conducted and the dihydrodibenzo[*b*,*f*] thiepine is transformed into the sulfoxide in quantitative yield. This process usually has to be conducted carefully to avoid over-oxidation to the sulfone [356]. However, this was not the case with **321** because it did not react under various oxidizing conditions, probably due to the electron-withdrawing nature of the fluoro-substituents (Scheme 21.185).



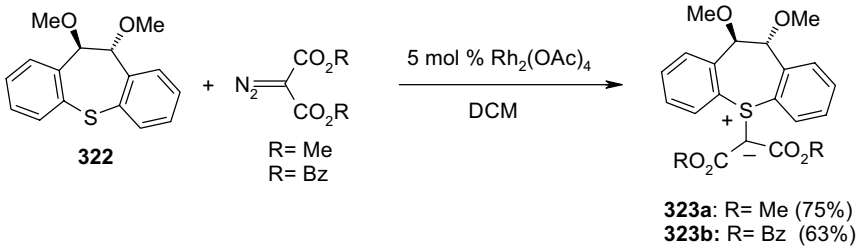
Scheme 21.185

A 1-benzothiepine fused to a pyridine ring has also been oxidized to the corresponding sulfone using *m*-CPBA in DCM containing 3–5 equivalents of methanesulfonic acid to avoid pyridine *N*-oxide formation (Scheme 21.186) [357].



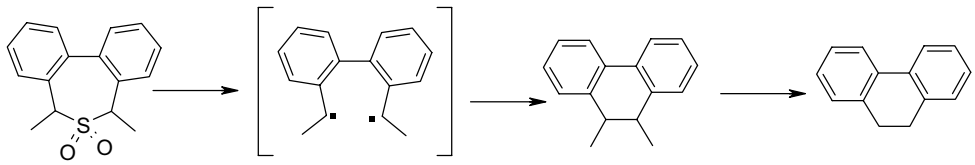
Scheme 21.186

The reaction of sulfides with diazo compounds bearing electron-withdrawing groups to give stabilized sulfonium ylides is a well known process. The reaction of dihydrobenzothiepine **322** with dimethyl diazomalonate and dibenzyl diazomalonate in the presence of 5 mol.% $Rh_2(OAc)_4$ gave the ylides **323a** and **323b** in 75% and 65% yields, respectively (Scheme 21.187) [325].



Scheme 21.187

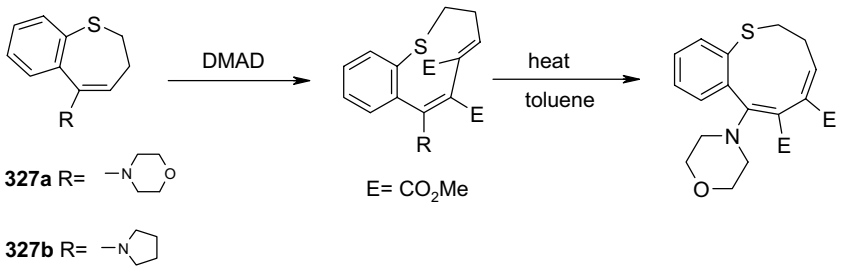
Flash vacuum thermolysis of dihydrobenzothiepine dioxide **324** (550 °C/0.2 mmHg) led to 9,10-dimethyl-9,10-dihydrophenanthrene **325** in 86% yield with loss of SO_2. When the product was subjected to more extreme conditions (730 °C/1 mm Hg) 9,10-dihydrophenanthrene **326** was obtained as the major product. Labeling studies indicate that the mechanism of dihydrophenanthrene formation involves a biradical as an intermediate, which undergoes ring closure to **325** followed by loss of two methyl radicals to give **326** (Scheme 21.188) [358].



Scheme 21.188

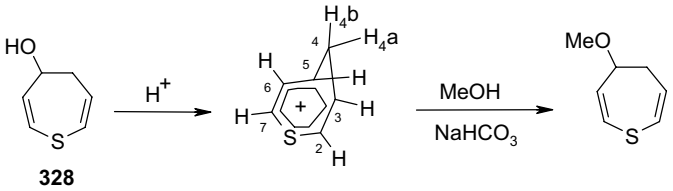
Cycloaddition of dihydro benzothiepines **327a** with DMAD gave the nine-membered ring compound at room temperature through a ring-opening reaction. The initially formed adduct, with a cis,trans configuration of the resulting butadiene, isomerized to the cis,cis-isomer by heating under reflux in toluene for 4 h. The initial cyclobutene adduct was not obtained [359]. However, the reaction of **327b** with DMAD yielded an equilibrium mixture of the cyclobutene and its cis,trans cyclooctadiene valence isomer, which was irreversibly transformed into the cis,cis isomer (Scheme 21.189) [360].

Nucleophilic attack at the carbon can occur on the 4,5-dihydrothiepinium ion, generated by treatment of alcohol **328** with $FSO_3H/CD_2Cl_2/SO_2$ in an NMR tube under nitrogen at −78 °C, by subsequent reaction with methanol in the presence of



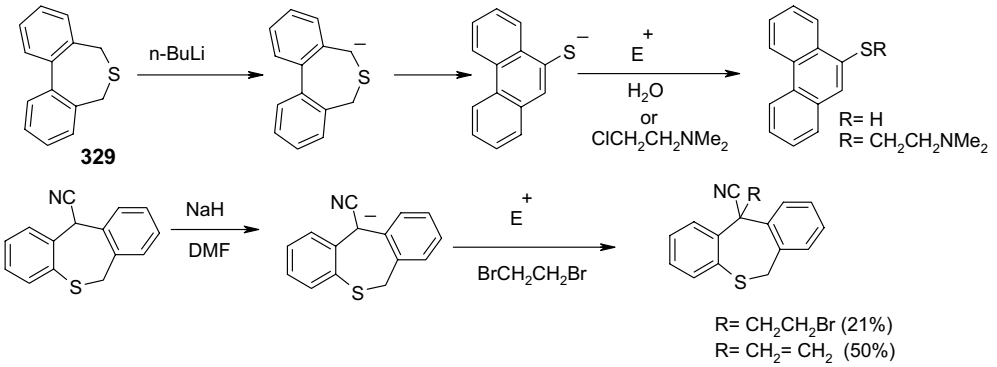
Scheme 21.189

sodium hydrogen carbonate (Scheme 21.190). Delocalization of the charge is indicated by the proton chemical shifts in the homothiopyrylium ion (average $\delta = 7.9$ except for H4a,b), which demonstrates that the C-atoms at 2, 3, 5, 6, and 7 are part of a six-membered ring. Retention of the seven-membered ring was confirmed by quenching the solution of homothiopyrylium with methanol [361].



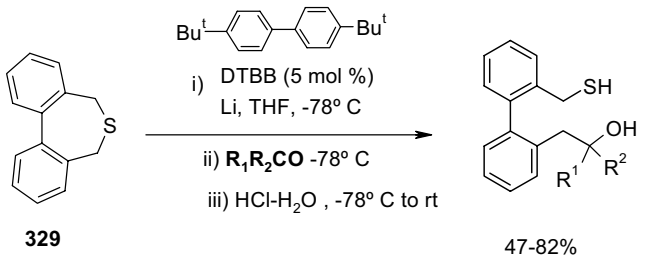
Scheme 21.190

The reactivity of carbanions depends on the capacity of the substituents to stabilize a negative charge. Thus, the reaction of **329** with *n*-butyllithium in hexane/ether generates a carbanion that undergoes a rearrangement to the stable thiolate anion. On the other hand, the carbanion can be generated with sodium hydride in DMF followed by treatment with electrophiles (Scheme 21.191) [362].



Scheme 21.191

Although organolithium compounds can be prepared through a wide range of methodologies [363], the last few years have witnessed their use as reagents for the reductive opening of heterocycles [364]. This method has been applied to the transformation of dihydrobenzothiepines and dihydrodinaphthothiepines [365]. For example, the reaction of 5,7-dihydrodibenzo[*c*,*e*]thiepine (**329**) with excess lithium in the presence of a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB, 5 mol%) in THF at −78 °C followed by treatment with different electrophiles (e..g, with carbonyl compounds) led, after hydrolysis, to the corresponding hydroxymercaptans in 47–82% yield (Scheme 21.192) [366].



329 47-82%

R_1R_2CO = *t*-BuCHO, $Ph(CH_2)_2CHO$, PhCHO, Me_2CO, $(n\text{-}C_5H_{11})_2CO$, $(CH_2)_5CO$, $(CH_2)_7CO$, (-)menthone

Scheme 21.192

An interesting sequential reductive lithiation has been described. The lithium derivative **I** is generated from **329** and reacts with a first electrophile (i.e., a carbonyl compound) to give **II**, which instead of being hydrolyzed was further lithiated to **III** and reacts with a second electrophile to afford **IV.** Scheme 21.193 gives some examples [366].

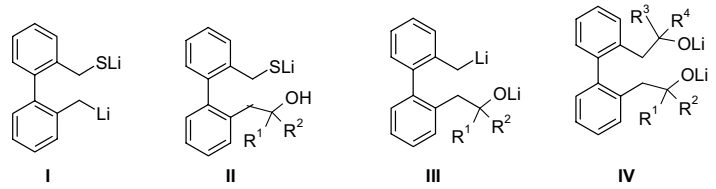
21.8.2.2 Tetrahydrothiepines

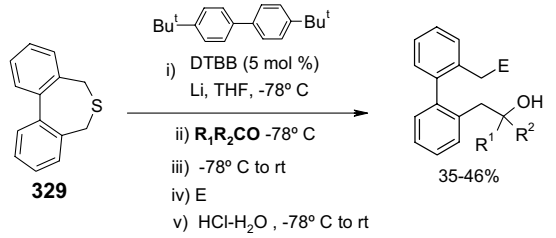
Bridged bicyclic sulfolenes can be easily converted into the corresponding 1,3-dienyl carbocycles in good yield by direct thermolysis (Scheme 21.194) [367] or by treatment with lithium aluminum hydride at room temperature [368].

Tetrahydrothiepines such as **330** are easily oxidized with *m*-CPBA in dichloromethane (Scheme 21.195) or with sodium periodate in methanol [350] to give the corresponding sulfoxide or sulfone. Oxidation with two equivalents of *m*-CPBA yields the sulfone.

Attempts to achieve ring expansion processes [369] by heating a methanolic solution of 5-methylene-2,3,4,5-tetrahydrothiepine **331** and silver nitrate under reflux in the presence of iodine gave a benzothiophene derivative as a consequence of intramolecular attack by sulfur at the initially formed halomethyl group (Scheme 21.196) [370]. No evidence for the formation of ring expansion products was found.

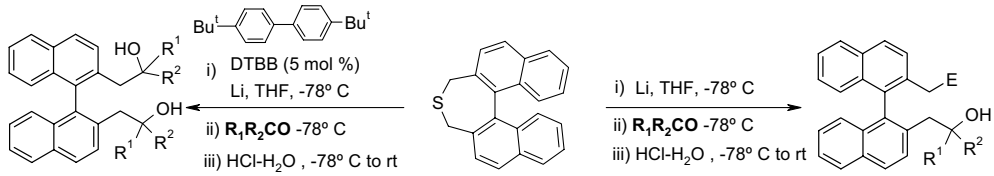
In general, the treatment of sulfoxides that have α-hydrogens with electrophiles such as carboxylic acid anhydrides affords products in which sulfur is reduced and





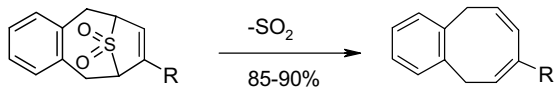
R_1R_2CO = Me_2CO, $(n\text{-}C_5H_{11})_2CO$, $(CH_2)_5CO$, $(CH_2)_7CO$, (-)-menthone

E= Me_2CO, Et_2CO, $(CH_2)_5CO$, $ClCO_2Et$



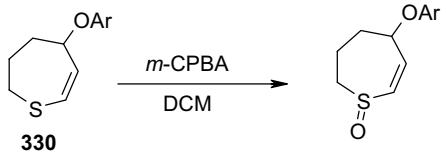
R_1R_2CO = Me_2CO, Et_2CO, $(CH_2)_4CO$, $(CH_2)_5CO$,

Scheme 21.193

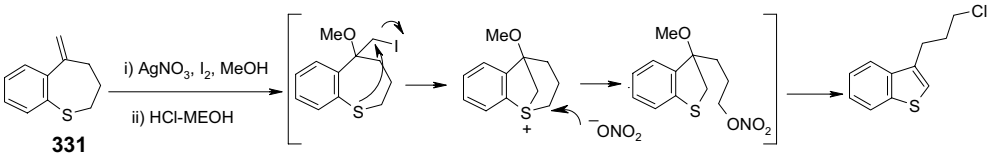


R= Me, Et, *t*-Bu

Scheme 21.194



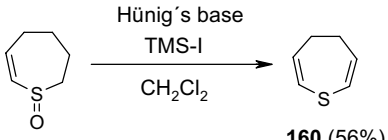
Scheme 21.195



331

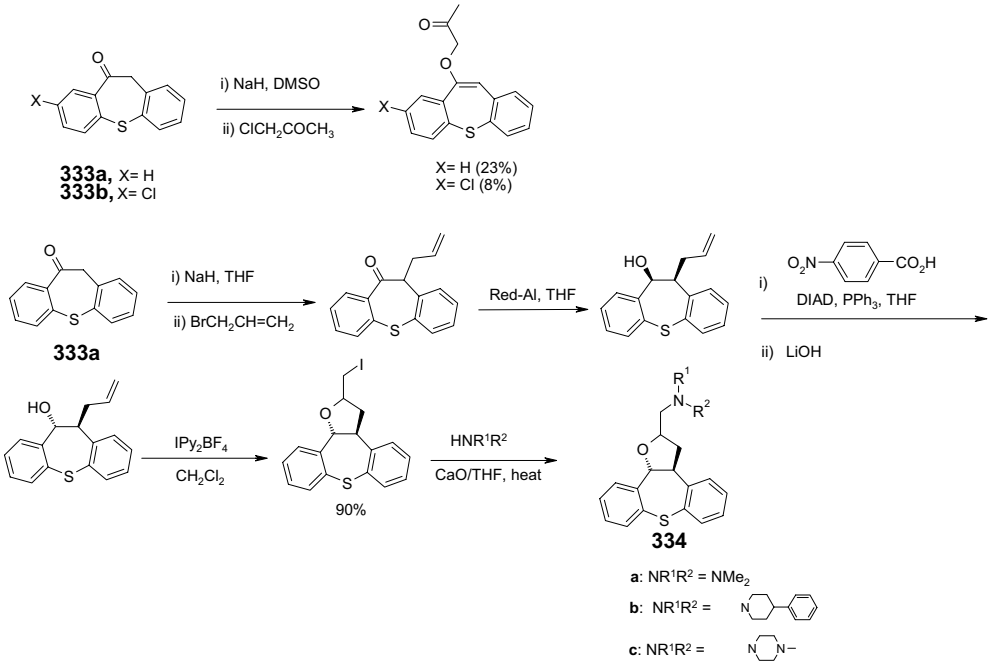
Scheme 21.196

the adjacent carbon is oxidized (Pummerer reaction). This reaction has been applied to the sulfoxide **332** [371], although the conversion was carried out under modified Pummerer conditions using Hünig's base or *N,N*-diisopropylethylamine in DCM and trimethylsilyl iodide under nitrogen (Scheme 21.197).



332 **160** (56%)

Scheme 21.197

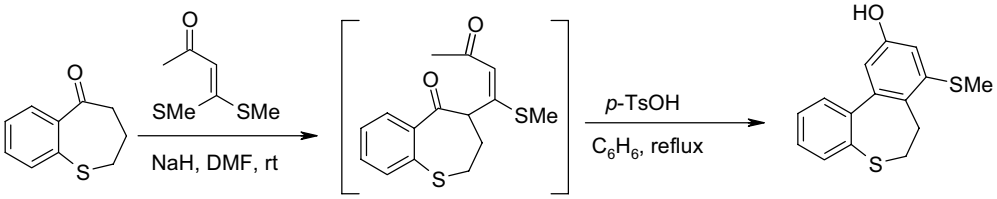


Scheme 21.198

21.8.2.3 **Thiepinones**

Reported examples of the reactivity of thiepinones are typical of cyclic ketones. Some examples are shown in Scheme 21.198 [372]. The transformation of **333a** into the biologically active dibenzo[*b,f*]thiepine **334** involves several transformations of ketone, alcohol, olefin, and iodide.

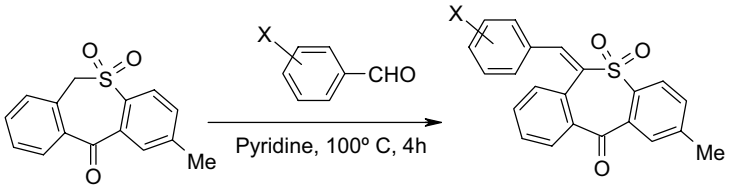
The dibenzo[*b,d*]thiepine **336** has been obtained from the benzo[*b*]thiepinone **335** by sequential conjugate addition/elimination and Claisen-type condensation (Scheme 21.199) [373].



335 **336** (62%)

Scheme 21.199

On the other hand, thiepinone dioxide **337** reacts with aromatic aldehydes to produce the Knoevenagel condensation products **338** in moderate to good yields (Scheme 21.200) [374].



337

338 X= H; 4′-Cl; 4′- NO_2; 4′-NMe_2; 4′- OMe; 3′,4′,5′- $(OMe)_3$; 3′,4′- OCH_2O-; 2′- OH

Scheme 21.200

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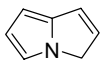
22
Heterocycles Containing a Ring-Junction Nitrogen

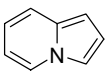
Juan J. Vaquero and Julio Alvarez-Builla

22.1
Introduction

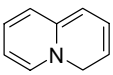
In addition to the biologically important purines and pteridines and the major benzofused heterocycles such as indole, many other aromatic, fused heterocyclic ring systems are known and the most important of these are ones that contain a ring-junction nitrogen, that is, where a nitrogen is common to two rings. The vast majority of these systems do not occur naturally, but they have been the subject of numerous studies from the theoretical viewpoint or in the preparation of potentially biologically active analogues and for other industrial uses. For brevity, only combinations of five- and six-membered rings are considered here, although many other combinations are possible and are known.



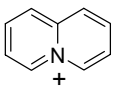
3*H*-Pyrrolizine



Indolizine



4*H*-Quinolizine



Quinolizinium

Of the parent systems that have the ring-junction nitrogen as the only heteroatom, only indolizine (often called "pyrrocoline" in the older literature) has a neutral, fully conjugated ten-electron π-system, consisting of four pairs of electrons from the four double bonds and a pair from nitrogen, much as in indole. Another such system is pyrrolizine, which is already aromatic in being a pyrrole (with a Q-vinyl substituent). Similarly, 4*H*-quinolizine is not aromatic as a saturated atom interrupts the conjugation. However, the cation (quinolizinium) formed by the formal loss of hydride from quinolizine does have an aromatic 10π-electron system. This system is isoelectronic with naphthalene and the positive charge results from the higher nuclear charge of nitrogen versus carbon. Replacement of a carbon atom and its attached hydrogen by heteroatoms either in five- and/or six-membered rings leads to a wide variety of heterocycles. Coverage of these systems is, however, beyond the scope of this book.

Figure 22.1 shows some of the general structures for combinations of five- and six-membered rings.

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Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.

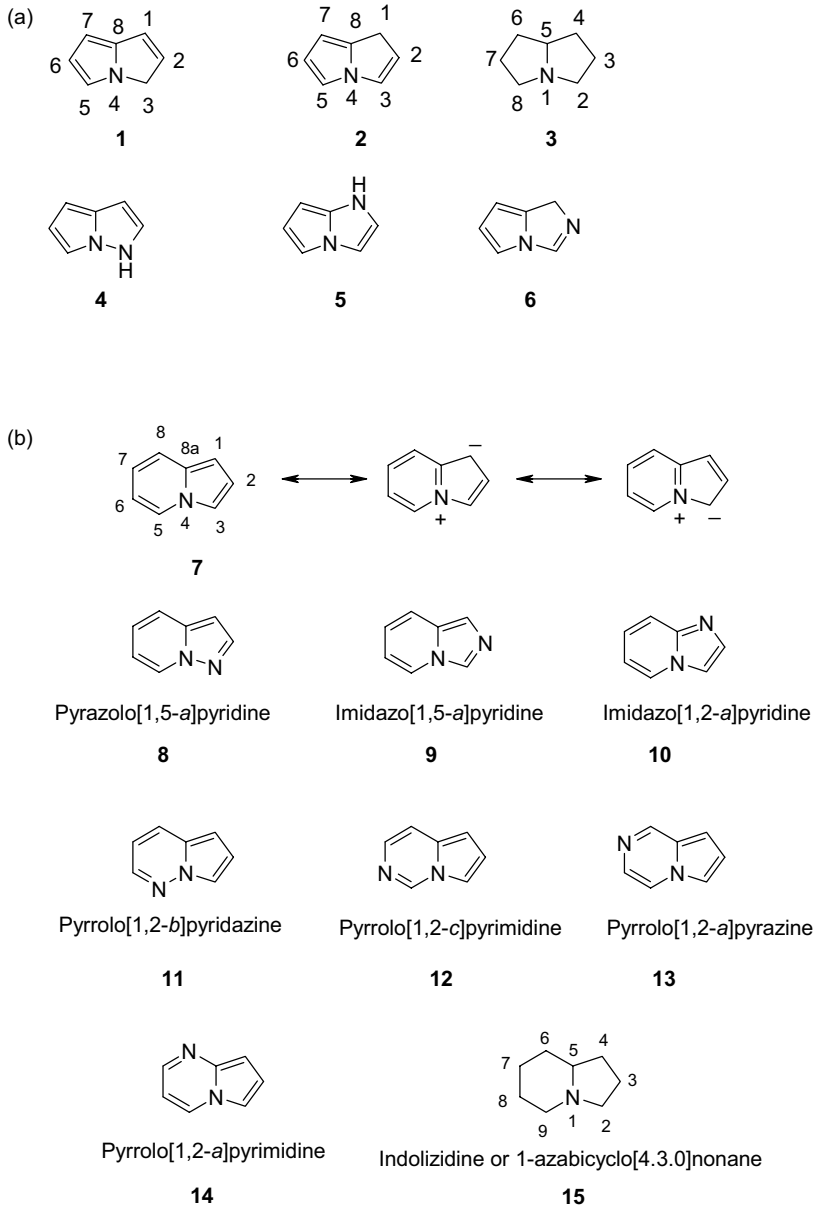


Figure 22.1 General structures for combinations of five- and six-membered rings: (a) pyrrolizines; (b) indolizines; (c) quinolizinium (**16**), quinolizines (**17**–**19**), quinolizidine (**20**) and azaquinolizinium isomers (**21–24**); and (d) benzoquinolizinium salts and related systems.

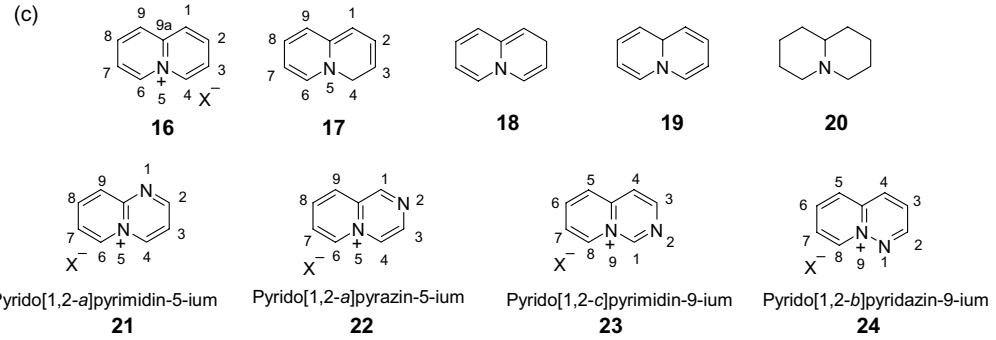


Figure 22.1 (*Continued*)

22.2 Pyrrolizines

22.2.1 General Structure and Reactivity

The trivial name pyrrolizine [1] is applied to the fused C_5-C_5 bicyclic system having a bridgehead nitrogen, which is systematically named as pyrrolo[1,2-*a*]pyrrole. There are two possible tautomeric pyrrolizidines and it has been demonstrated that 3*H*-pyrrolizine (**1**) is more stable than the 1*H*-tautomer (**2**). The partially hydrogenated structure, which retains aromaticity, is considered as a dialkyl pyrrole derivative while hexahydro-1*H*-pyrrolizine is known as pyrrolizidine or 1-azabicyclo[3.3.0]octane (**3**).

The inclusion of a second heteroatom produces a diverse range of structures (18 basic heterocycles) due to the different arrangements that the double bonds can adopt in the bicyclic system. Pyrrolo[1,2-*b*]pyrazole (**4**), pyrrolo[1,2-*a*]imidazole (**5**), and pyrrolo[1,2-*c*]imidazole (**6**) are representative structures with two nitrogen atoms, all of which can exist as four tautomeric systems.

The literature on pyrrolizines is compiled in two reviews [2, 3] and a chapter in the *Comprehensive Heterocyclic Chemistry II,* 1996 [4]. Pyrrolizidines have also been reviewed [5, 6], although their chemistry and that of natural pyrrolizidines is beyond the scope of this book.

22.2.2 Relevant Natural and/or Useful Compounds

Pyrrolizine and pyrrolizidine derivatives occur as natural secondary metabolites in a large number of plants. The alkaloids based on the skeleton of these two heterocycles appear to have a function in protecting the plants from predators and some of these alkaloids are toxic to animals and to humans, causing liver disease and in some cases cancers. However, some of these plants have been used in folk medicine to treat

(d)

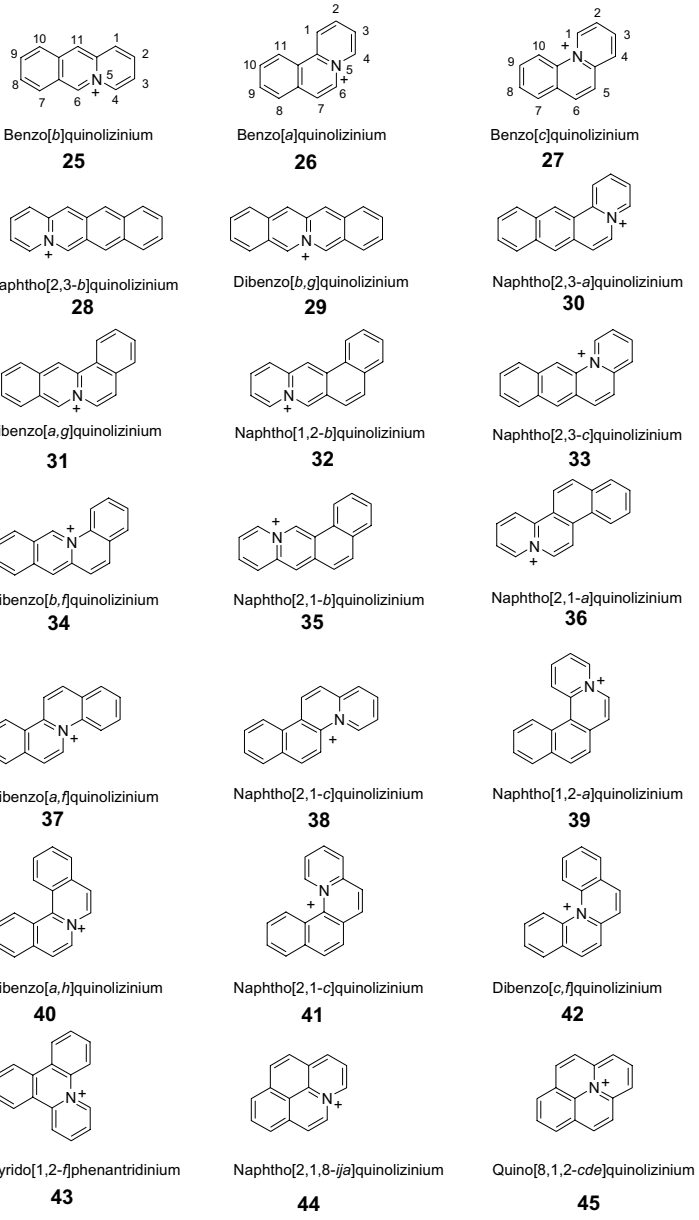
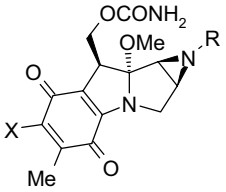


Figure 22.1 (*Continued*)

"tumors" [7], menstrual disorders [8], and as emetic and diuretic compounds [9]. The pyrrolizidine nucleus is widespread in nature in pyrrolizidine alkaloids [10]. Examples of these alkaloids are the family of mitomycins (**46**) [11], which exhibit important antitumor activity, and the family of polyhydroxylated pyrrolizidine

alkaloids represented by alexine (**47**) and casuarine (**48**), which are glycosidase inhibitors [12]. 3,5-Dioxopyrrolizidine (**49**, Rolziracetam) is a cognition activator of the nootropic class [13].



Mitomycins

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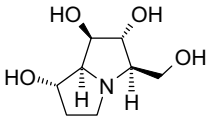

Alexine

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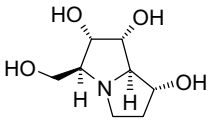
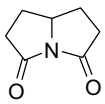


Casuarine

48



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22.2.3
Relevant Computational Chemistry and Physicochemical and Spectroscopic Data

3*H*-Pyrrolizine (**1**) is an oil that has a high boiling point (68–70 °C/15 Torr). The resonance energy (REPE) of **1** has been obtained from HMO calculations and clearly indicates that this tautomer is more stable than **2** (0.0107β versus 0.0153β) [2, 14]. This finding is consistent with the results of ^{1}H NMR studies, which show 3*H*-pyrrolizine (**1**) to be more stable than the 1*H*-tautomer (**2**) – which could not be detected at all.

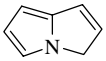
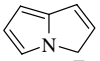
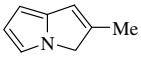
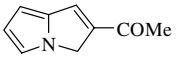
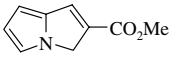
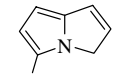
The pK_a of **1** (29) has been estimated by measuring the rate of exchange of the protons with 5 M D_2O in DMF containing triethylamine (1 M). This high value is attributed to the aromaticity of the pyrrolizine anion [15]. However, attempts to explain the acidity of **1** by the HMO theory met with limited success [15].

Table 22.1 shows ^{1}H NMR data for **1**, its anion, and some simple derivatives. It is worth nothing the shielding of H2 and H7 in **1** and the deshielding of H1 and H5. The main coupling constants are $J_{1,2} = 6.2$ Hz and $J_{2,3} = 2.2$ Hz and long-range coupling constants are observed between H1 and H3, H1 and H5, and H3 and H7. H1 and H3 are strongly modified in the spectrum of the anion, with H3 appearing strongly deshielded while H5 and H6 have similar displacements in both compounds.

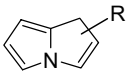
The UV abortion spectra of compound **1** and simple alkyl derivatives show two major bands at 210–220 nm and 285–295 nm of similar intensity and little difference can be observed between the spectrum of **1** and its anion [8]. The IR spectrum of **1** is not particularly characteristic and the common feature of the few published mass spectra of 3*H*-pyrrolizines is a strong M^+ or $(M-1)^+$ peak [2].

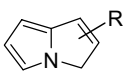
Monosubstituted pyrrolizines can exist as four tautomers (**1a–d**). For simple derivatives, and in the absence of strong substituent influences, 3*H*-isomers **1b** and **1c** are more stable than 1*H*-pyrrolizines **1a** and **1d**. In the parent compound **1** (R = H) the 1*H*-tautomer could not been detected in the ^{1}H NMR spectrum. However, in the attempted preparation of 5-methyl-3*H*-pyrrolizine (R = 5-Me) the formation of a mixture of **1a**, **1c**, and **1d** in a 44 : 66 : 10 ratio was observed [22]. In pyrrolizines substituted in the C2(C6) position, the tautomeric equilibrium

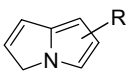
Table 22.1 ^{1}H NMR chemical shifts (ppm) of 3*H*-pyrrolizine (**1**), its anion, and some simple derivatives.

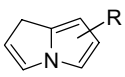
Compound (solvent)	H1	H2	H3	H5	H6	H7	Reference
 **1** (neat)	6.20	5.63	3.75	6.54	6.08	5.77	[16]
 (THF)	4.75	6.03	7.62	6.43	6.03	4.75	[17]
 $CDCl_3$	6.40	—	4.18	6.0	5.92	5.50	[18]
 $CDCl_3$	6.1	—	4.6	7.2	6.9	6.2	[19]
 $CDCl_3$	7.05	—	4.69	7.44	6.24	6.36	[20]
 Acetone-d_6	6.6	6.25	4.26	—	6.4	5.96	[21]

depends on the electronic nature of the substituent. For example, tautomer **1b** is the stable form for 2-methyl- and 2-phenylpyrrolizine [22, 23] whereas when R = 2-COPh or 2-CO_2Me the tautomeric form **1c** is more stable [24].


1a


1b


1c


1d

In terms of reactivity, 3*H*-pyrrolizines are vinylpyrroles and a predominant reactivity towards electrophiles can be expected. However, the instability of pyrrolizines limits the application of electrophilic substitution.

22.2.4
Synthesis of Pyrrolizines

All of the synthetic methodologies reported for the construction of the 3*H*-pyrrolizine system are based on a pyrrole ring, which is used as a template to build up the second

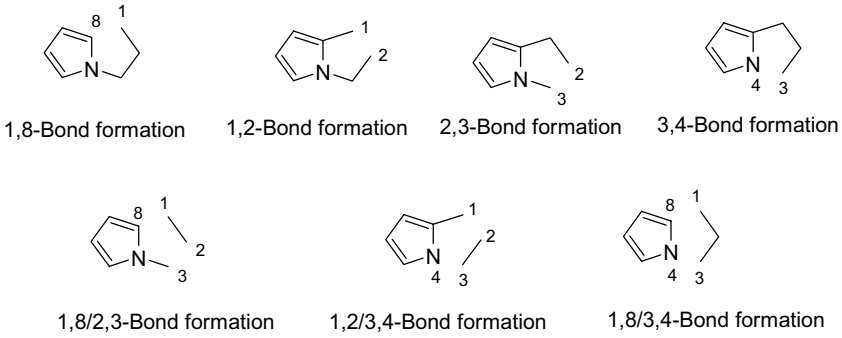


Figure 22.2 Cyclization and [3 + 2] approaches for building up the pyrrolizine nucleus.

pentacyclic ring. Cyclizations and [3 + 2] approaches are the most representative synthetic strategies for building up the pyrrolizine nucleus (Figure 22.2).

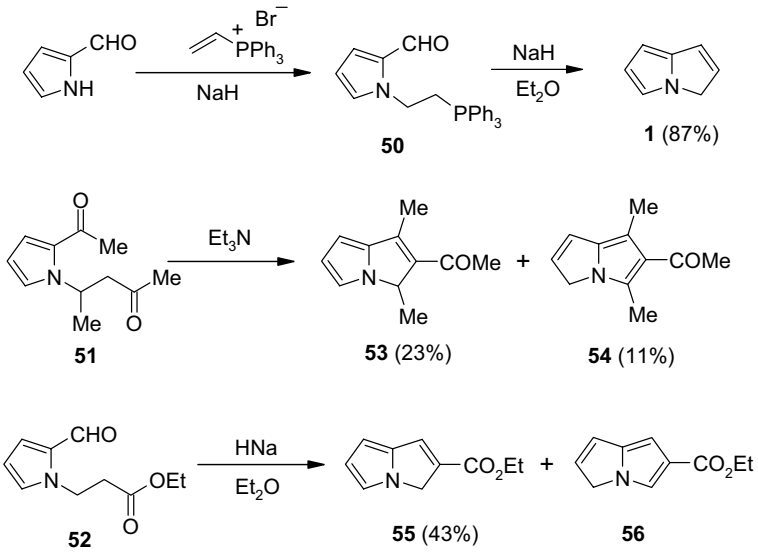
22.2.4.1 By Cyclization Reactions

Formation of the second pentacyclic ring by a cyclization reaction involving 1,2-bond formation has been widely employed for the preparation of pyrrolizine and different derivatives. The synthesis of the parent heterocycle **1** is based on an intramolecular Wittig reaction of the vinylphosphonium salt **50**, which is obtained from formylpyrrole and vinyltriphenylphosphonium bromide in the presence of sodium hydride [25]. Numerous substituted pyrrolizines have been prepared by this strategy from 2-acylated pyrroles [24, 26]. The same 1,2-bond formation to give the bicyclic system is also employed with appropriate 1,6-dicarbonyl compounds to prepare some derivatives. For example, diketone **51** has been used to obtain a mixture of pyrrolizines **53** and **54** under basic conditions [27]. A similar mixture (**55/56**) is obtained from the 2-formylpyrrole derivative **52** (Scheme 22.1) [27].

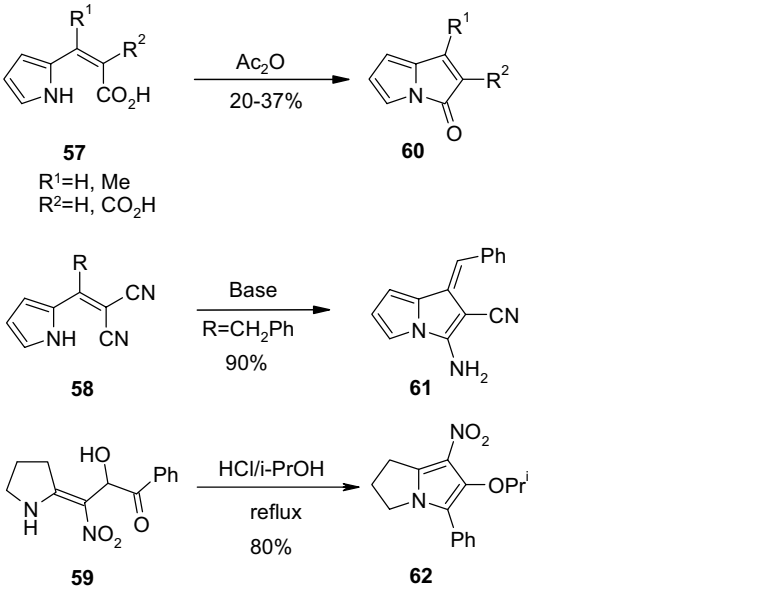
Several derivatives (**60–62**) have been obtained from pyrrolyl carboxylic acids [28], nitriles [29], and nitroenamines [30] under acid or basic conditions through a strategy based on N–C bond formation (3,4-bond). This approach exploits the nucleophilic character of the pyrrole nitrogen, which can be enhanced by deprotonation with appropriate bases (Scheme 22.2).

Cyclizations involving 2,3- and 1,8-bond formation [2] have also been used in the synthesis of various derivatives. Representative examples of 1,8-bond formation include the Houben–Hoesch cyclizations of 1-cyano-β-ethylpyrroles. For example, nitrile **63** in the presence of hydrogen chloride yields the 3*H*-pyrrolizine derivative **64** [31] or 1-oxo-2,3-dihydropyrrolizines (**65**) if the nitrile is hydrolyzed to the corresponding acid prior to reaction. Malonic acid derivative **66** in the presence of phosphorus pentachloride gives pyrrolizin-1-one **67** under very mild conditions [32] (Scheme 22.3).

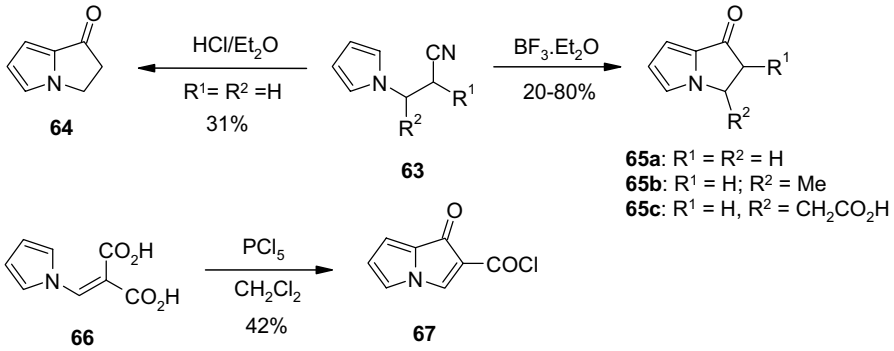
1,2-Diacylated pyrroles have been used as appropriate substrates for the cyclization reaction involving 2,3-bond formation. The synthesis of the 2,3-diphenylpyrrolizin-1-one (**69**) from **68** is the only representative example of this strategy [33] (Scheme 22.4).



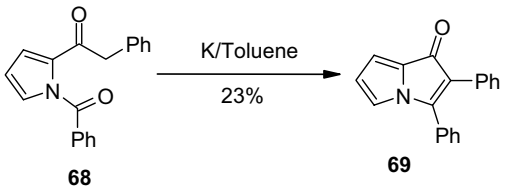
Scheme 22.1



Scheme 22.2



Scheme 22.3



Scheme 22.4

22.2.4.2 By [3 + 2] Approaches

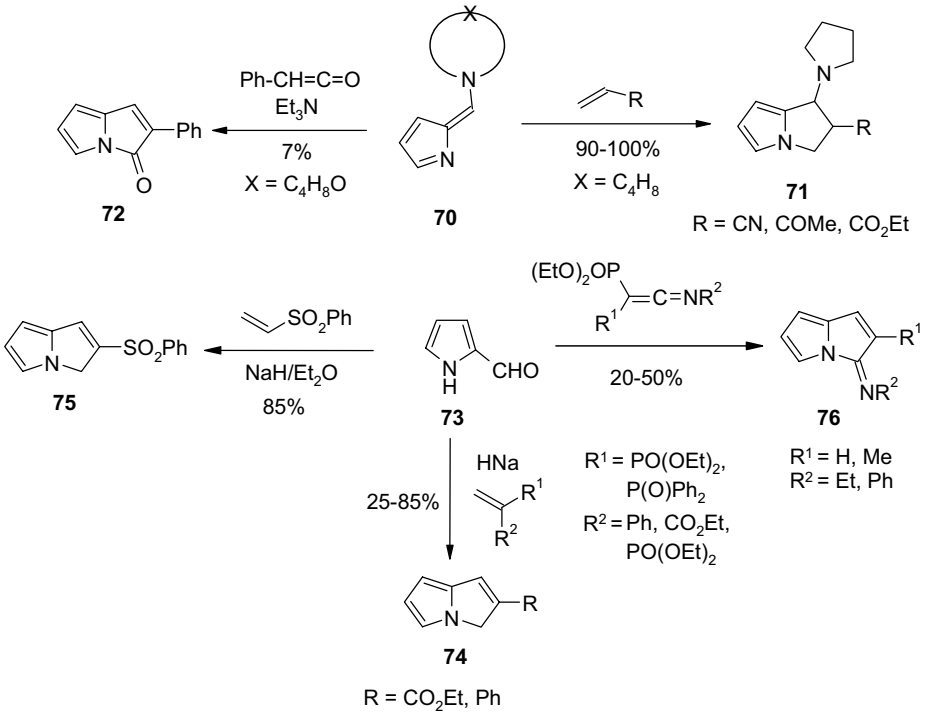
The most useful syntheses based on a [3 + 2] strategy are those involving 1,2/3,4-bond formation, with 1,3-dipolar cycloaddition being one of the representative reactions of this approach. Vilsmeier bases of pyrroles such as **70** react with electron-deficient olefins [34] and ketenes [35] to yield substituted dihydropyrrolizines **71** and the 2-phenylpyrrolizin-3-one (**72**), respectively. Reaction of pyrrole carboxaldehyde **73** with alkenes is also a good example of this type of strategy, which allows the synthesis of 2-substituted derivatives **74** [36]. Vinylsulfones react to give 2-phenylsulfonyl-3*H*-pyrrolizine (**75**). Keteniminophosphoranes react to form 3*H*-pyrrolizin-3-imines (**76**) (Scheme 22.5) [37].

Another example of a [3 + 2] strategy with the formation of 1,8/3,4-bonds is the reaction of pyrrole with malonic acid derivatives to give 1-pyrrolizin-3-ones (**77**) in the presence of phosphorus oxychloride [38] (Scheme 22.6).

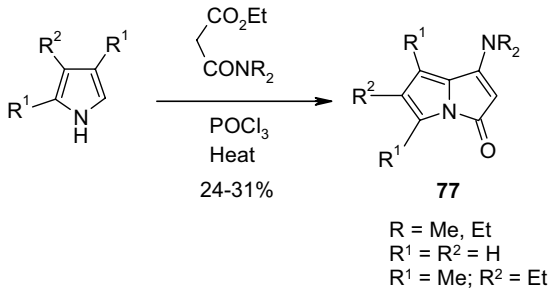
22.2.5 Reactivity of Pyrrolizines

22.2.5.1 Electrophilic Attack

Electrophilic substitution on pyrrolizines is similar to that on 1,2-disubstituted pyrroles in terms of reactivity and orientation of the electrophile. The C5 position



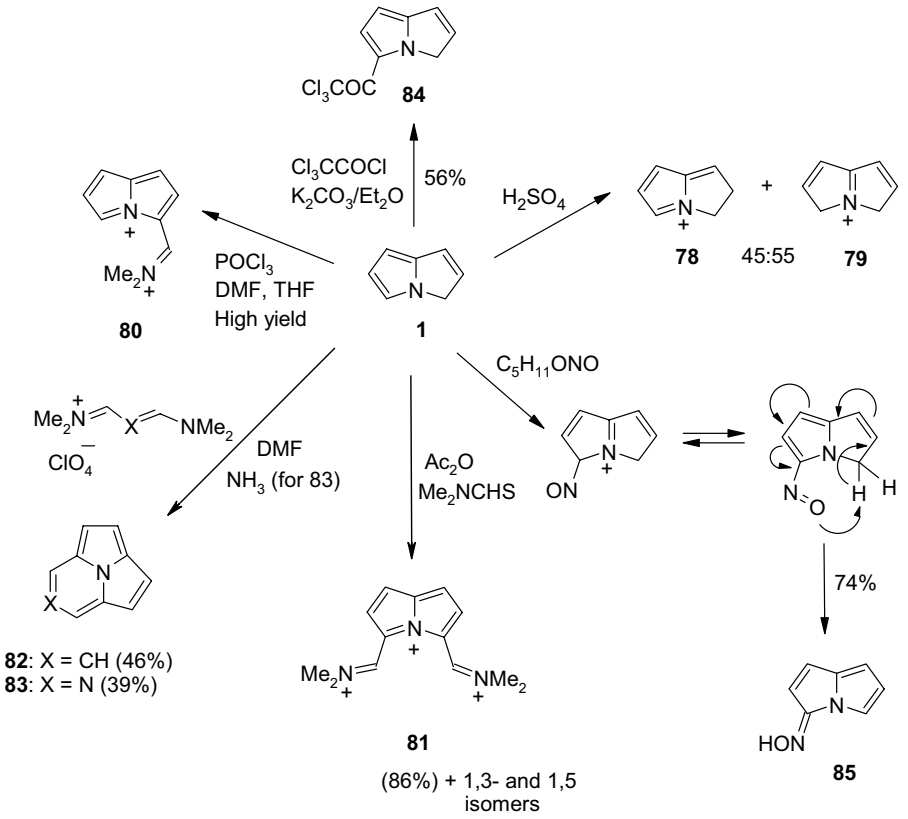
Scheme 22.5



Scheme 22.6

is usually the most reactive, although most electrophilic reactions give mixtures of products on C5 and C6 and/or C7 positions, with the product composition depending on the conditions.

Most pyrrolizines are unstable in dilute acids but pyrrolizine (**1**) is protonated in concentrated sulfuric acid to give stable derivatives **78** and **79** in 45% and 55% yields, respectively (Scheme 22.7) [24]. The Vilsmeier reaction of **1**, by treatment with

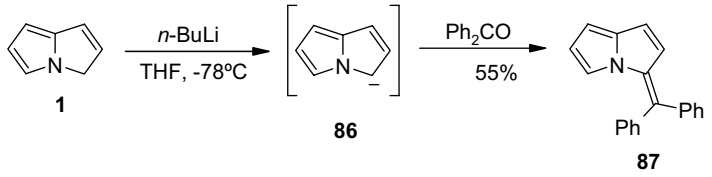


Scheme 22.7

dimethylformamide and phosphoryl chloride at low temperature (−60 °C), affords the Vilsmeier salt **80** while from the reaction with dimethylthioformamide and acetic anhydride derivative **81** was obtained as the main reaction product [39]. The syntheses of cyclazine (**82**) [40] and azacyclazine (**83**) [39] have also been reported from the reaction of **1** with appropriate iminic dienes.

Acyl Derivatives of **1** are formed by a reaction with ketenes. Good yields of acylated derivatives **84** are obtained from the reaction of acyl chlorides in ether in the presence of anhydrous potassium carbonate, although the 2-acetyl derivative can not be obtained from acetyl chloride under these conditions [41]. The reaction with amyl nitrite affords the oxime **85**, which is probably formed by an electrophilic attack [24] according to the mechanism detailed in Scheme 22.7.

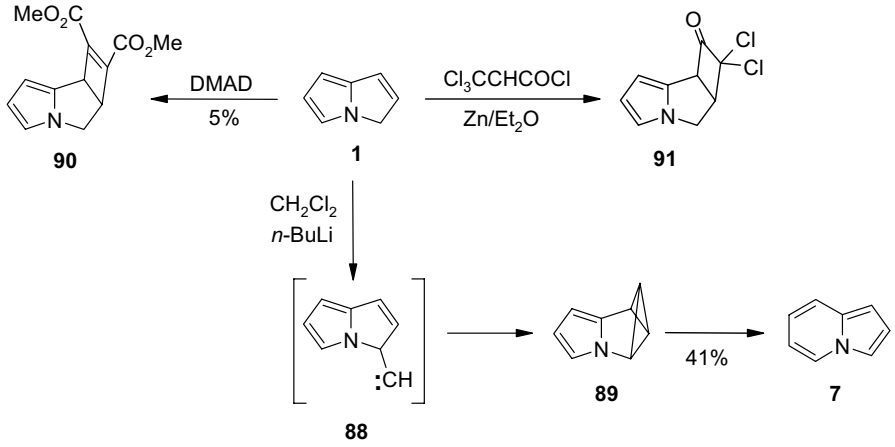
Deprotonation of **1** is an easy process due to its high pK_a and the aromatic character of the pyrrolizine anion **86**. The anion is usually formed with lithium bases and its behavior resembles that of reactive carbanions towards electrophiles such as carbonyl compounds. For example, the reaction with benzophenone gives the fulvene-like product **87** (Scheme 22.8) [42].



Scheme 22.8

22.2.5.2 **Cycloaddition Reactions**

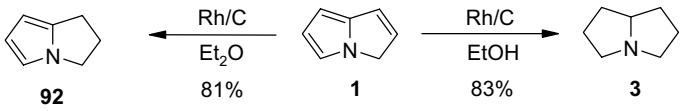
The 1,2-double bond of 3*H*-pyrrolizine can be involved in cycloaddition reactions. An example of such reactivity is the reaction of **1** with the carbene generated from dichloromethane and *n*-butyllithium. The addition of the carbene to 3*H*-pyrrolizine gives a 3-pyrrolizinyl carbene **88** and subsequent addition to the C1–C2 bond affords the tetracyclic pyrrolizine derivative **89**, which evolves to indolizine (**7**) [43] by a ring expansion process (Scheme 22.9). Tricyclic derivatives **90** and **91** are obtained in low yield by [2 + 2] cycloadditions with DMAD and dichloroketene generated from trichloroacteyl chloride and activated zinc in ether, respectively [22, 44].



Scheme 22.9

22.2.5.3 **Reduction Reactions**

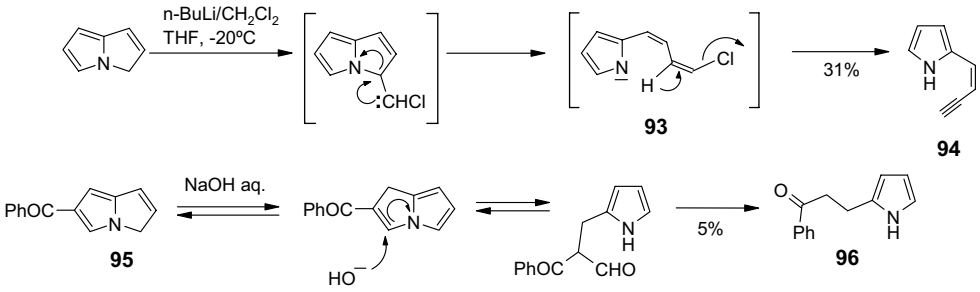
The 1,2-double bond of 3*H*-pyrrolizine is much more easily reduced than the pyrrole ring. Thus, **1** can be reduced to the dihydro derivative **92** with hydrogen at atmospheric pressure and room temperature using a rhodium on carbon catalyst in ether without affecting the pyrrole ring (Scheme 22.10). The same catalyst yields the fully hydrogenated derivative (pyrrolizidine) if the reaction is carried out in ethanol [25a]. The pH of the reaction medium is important for hydrogenation using platinum oxide as catalyst, with acidic conditions promoting the total reduction and neutral media favoring partial hydrogenation [33a].



Scheme 22.10

22.2.5.4 **Ring-Opening Reactions**

Ring-opening reactions are known in pyrrolizine and some related derivatives. Lithium dicarbenoid species react with **1** to give an anionic intermediate **93**, which was converted into indolizine (see Scheme 22.9) and butenyne **94** [45], presumably by the mechanism shown in Scheme 22.11. Benzoylpyrrolizines such as **95** can also be converted into pyrroles **96** by treatment with dilute aqueous sodium hydroxide. Initially, the pyrrolizine isomerizes to the 1*H*-isomer, which after two sequential hydrolysis steps gives the pyrrole derivative **96** (Scheme 22.11) [24].

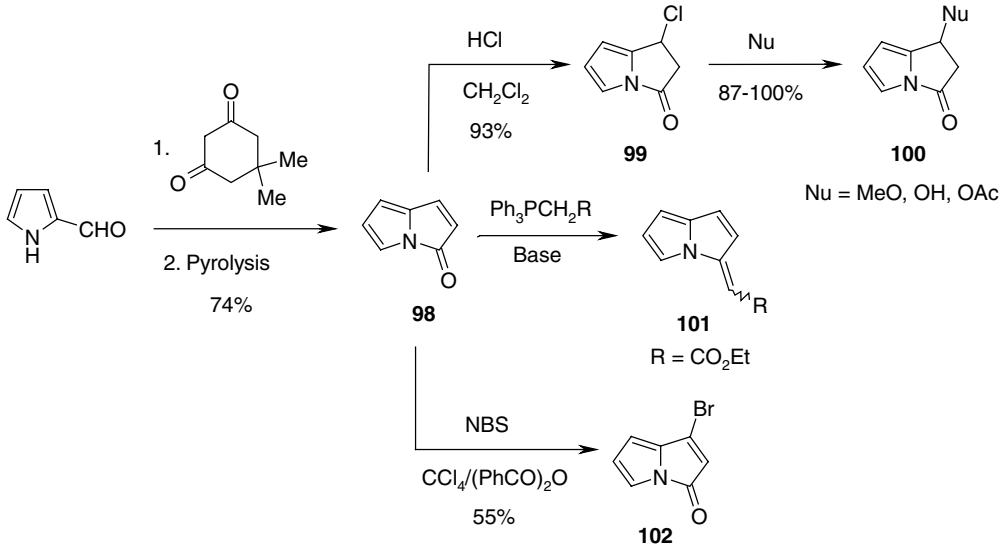


Scheme 22.11

22.2.6 **Derivatives**

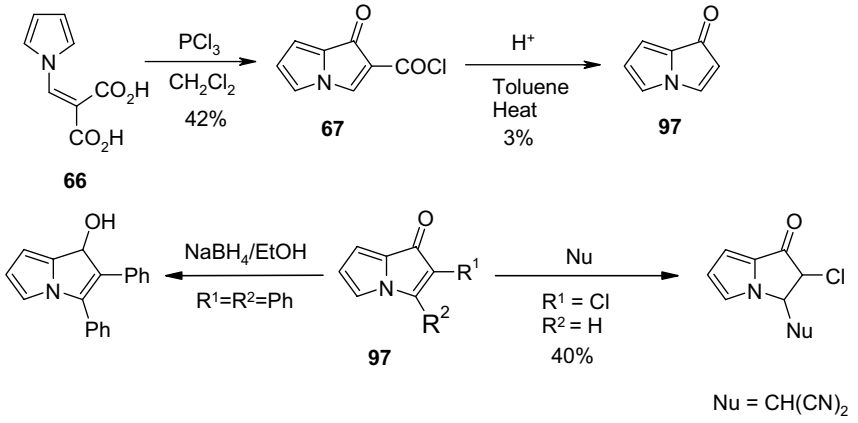
Among the 3*H*-pyrrolizine derivatives only oxo-derivatives warrant further consideration. These derivatives are represented by 1-oxo- and 3-oxopyrrolizinones **97** and **98**, both of which have high resonance energies (REPE = 0.0110β and 0.0155β, respectively) that account for the high stability of these compounds [1].

The natural product pyrrolizin-3-one (**98)** has been synthesized as shown in Scheme 22.12 from 2-pyrrolecarboxaldehyde [46]. Electrophilic additions have been reported for **98** with dry hydrogen chloride to give the 1-chloro-1,2-dihydro derivative **99** [47]. The halogen is readily displaced by O-nucleophiles to give methoxy, hydroxy, or acetoxy derivatives **100** in good yields. Derivative **98** can also be brominated by *N*-bromosuccinimide (NBS) under free radical conditions to give 2-bromopyrrolizin-3-one (**102**) (Scheme 22.12) [47]. Wittig reactions on the parent **98** to give azafulvenes such as **101** are also known [22].



Scheme 22.12

Examples of the above reactions for **98** have not been described for **97**, which has been prepared [32] from **66** as shown in Scheme 22.13. Examples of its reactivity are Michael additions with some derivatives such as the 2-chloro derivative **97** [32] (Scheme 22.13). Examples of reduction with hydride donors such as sodium borohydride have also been described for derivatives of **97** and these reactions afford the corresponding alcohol [48].



Scheme 22.13

22.3
Indolizines

22.3.1
General Structure and Reactivity

Indolizine (**7**) possesses a delocalized 10π-electron system resulting from the combination of a π-excessive (pyrrole-like) and a π-deficient (pyridine-like) ring. The aromatic character of indolizine is expressed by three main mesomeric contributors, two of which incorporate a pyridinium moiety; other forms that incorporate neither a complete pyrrole nor a pyridinium are less important (Figure 22.1b).

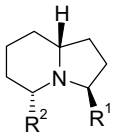
Aza-indolizines of general structure **8–14** are the most representative and interesting C_5-C_6 heterocycles bearing and extra heteroatom (Figure 22.1b). The fully unsaturated heterocyle **15** is known as indolizidine or 1-azabicyclo[4.3.0]nonane. The chemistry of these bicyclic C_5-C_6 systems with one ring junction nitrogen atom has been the subject of previous surveys. Reference textbooks on this subject include *Comprehensive Heterocyclic Chemistry I* [49] and *Comprehensive Heterocyclic Chemistry II* [50]. Heterocyclic series such as *Advances in Heterocyclic Chemistry* have also dealt with indolizines [51] and the other significant heterocycles included in this chapter. Additionally, a review covering the chemistry of pyridines containing a ring-junction nitrogen [52] and the excellent text from Joule and Mills [53] and some of the references cited therein have been considered in this chapter and the reader is referred to them for further coverage of this topic.

22.3.2
Relevant Natural and/or Useful Compounds

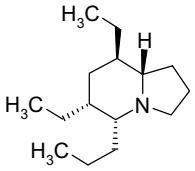
Aromatic indolizines are very rare in nature but the fully reduced (indolizidine) nucleus is widespread, particularly in alkaloids. These compounds belong to two main classes: the amphibian and the polyhydroxy indolizidine alkaloids. The first family belongs to a large class of compounds isolated from the skin of neotropical brightly colored frogs and they have attracted interest in recent years for their numerous biological properties, including neurotoxicity, potentiation of muscle contraction, and immunomodulatory activity [54]. This interest has resulted in the development of numerous total syntheses of these alkaloids and several reviews have been published on the subject [55]. Most of the compounds that contain the perhydroindolizine ring with substituents in positions C3, C5, C6, and C8 belong to the class of gephyrotoxins. The structures of some relevant compounds (**103–107**) are detailed below and relevant references can be obtained for **103a** [56].

The polyhydroxyndolizidine alkaloids (sugar mimetics), the most important examples of which are castanospermine (**108**), lentiginosine (**109**), and swainsonine (**110**), are interesting due to their potent glycosidase inhibitory activity [57]. Glycosidases play a crucial role in many important biological processes, opening up the possibility of these compounds to behave as therapeutic targets for the treatment of diseases like diabetes, cancer, and viral diseases. Therefore, a great deal of interest in

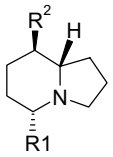
the synthesis of this class of natural compounds has been shown in recent years and relevant references related to their synthesis can be found for **108** [58].



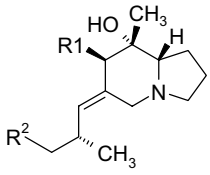
	R^1	R^2
103a	H	*n*-C_3H_7
103b	*n*-C_4H_8OH	*n*-C_4H_9
103c	COOEt	*n*-C_4H_9



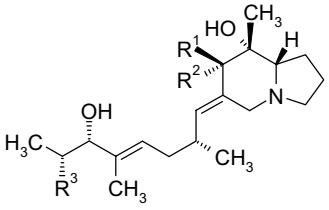
104



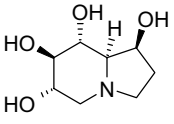
	R^1	R^2
105a	*n*-C_5H_{11}	CH_3
105b	*n*-C_3H_7	*n*-C_3H_7
105c	4-pentenyl	CH_3



	R^1	R^2	
106a	H	n-C_3H_7	(+)-Pumiliotoxin 215D
106b	H	CH_2OH	(+)-Pumiliotoxin 225F
106c	OH	n-C_3H_7	Allopumiliotoxin 267A

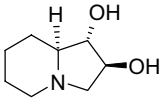


	R^1	R^2	R^3	
107a	H	H	H	(+)-15-(S)-Pumiliotoxin A
107b	H	H	OH	(+)-Pumiliotoxin B
107c	OH	H	OH	(+)-Allopumiliotoxin 339B



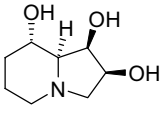
(+)-Castanospermine

108



(+)-Lentiginosine

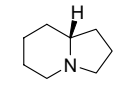
109



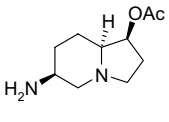
(-)-Swainsonine

110

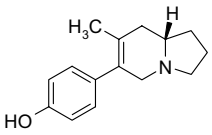
Other natural products bearing the indolizidine nucleus have been isolated. Some representative structures (**111–115**) are shown and relevant references concerning the synthesis of these products can be seen for **111** [59]. Other important compounds include A-289 099 (**116**), an orally active antimitotic agent against various cancer cell lines that acts through inhibition of tubulin polymerization by binding at the colchicine site [60]. A series of indolizidinones of general structure **117** has been designed and synthesized to evaluate their inhibitory effect on Factor VIIA (FVIIa) in comparison to thrombin [61]. The bicyclic 2-pyridone derivative **118** has been described as a 3CP (human rhinovirus 3C protease) inhibitor and exhibited potent antirhinoviral activity in cell cultures when tested against different human rhinovirus (HRV) serotypes [62]. The synthesis and cytotoxicity of septicine (**119**) and several analogues has been reported [63].


(-)-Coniceine

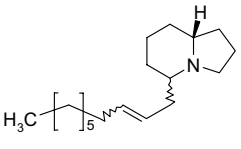
111


(-)-Slaframine

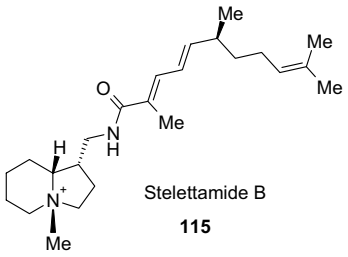
112


(-)-Ipalbidine

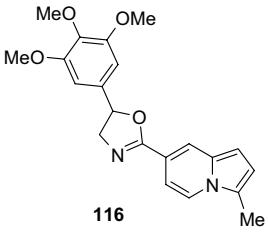
113

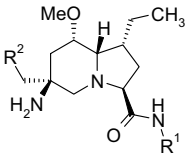

Piclavine

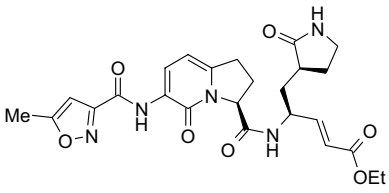
114


Stelettamide B

115


116


117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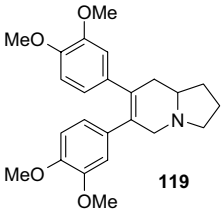
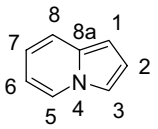

119

22.3.3
Relevant Physicochemical Data, Computational Chemistry, and NMR Data

The reactivity of the system is characterized as outlined above: the five-membered ring undergoes electrophilic substitutions whereas the six-membered ring shows reactivity similar to that of a pyridine ring. Recent density functional theory (DFT) calculations (B3LYP/6-31G*) showed that the pyrrole-like ring has an extended highest occupied molecular orbital (HOMO), whereas the lowest unoccupied molecular orbital (LUMO) is mostly located on the pyridine ring, a distribution that is not appreciably varied by the introduction of an electron-withdrawing group at the C6 position [64]. Moreover, another study performed on substituted indolizines (DFT, B3LYP/6-31G) indicated that C3 is always the carbon atom with the highest electron density and with the largest atomic coefficient in the HOMO and is, therefore, the preferential site of attack by an electrophile [65].

The NMR spectra of indolizidine derivatives have already been extensively described [54]. More recently, the use of mono- and bidimensional ^{1}H and ^{13}C NMR spectra has allowed the structural assignment of natural compounds possessing an indolizidine nucleus [66]. Table 22.2 gives typical ^{1}H and ^{13}C NMR chemical shifts of the indolizine nucleus.

Table 22.2 ^{1}H and ^{13}C NMR chemical shifts for indolizine (**7**).



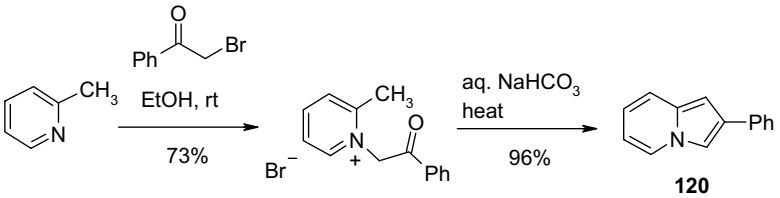
7

Proton chemical shifts (δ, ppm)							Reference
H1	H2	H3	H5	H6	H7	H8	[67]
6.28	6.44	7.14	7.75	6.31	6.50	7.25	
Coupling constants, *J* (Hz)							[68]
1.2	1.3	1.5	2.3	2.7	2.8	3.5	
3.9	1.2	1.0	2.7	0.0	0.0	0.0	
3.8	5.6	5.7	5.8	6.7	6.8	7.8	
0.5	6.8	1.0	1.2	6.4	1.0	8.9	
Carbon-13 chemical shifts (δ, ppm)							[69]
C1	C2	C3	C5	C6	C7	C8	C8a
99.44	114.07	113.01	125.61	110.44	117.16	119.56	133.35

22.3.4 Synthesis of Indolizidines

22.3.4.1 Intramolecular Condensation: Approaches Related to the Chichibabin Synthesis

The most general approach to indolizines is the Chichibabin synthesis (Scheme 22.14) [70]. This route involves quaternization of a 2-alkylpyridine with an α-haloketone followed by base-catalyzed intramolecular cyclization by deprotonation of the pyridinium *o*-methyl group, which is easier when the alkyl group is further activated. A representative process is the synthesis of 2-phenylindolizine (**120**) [71].

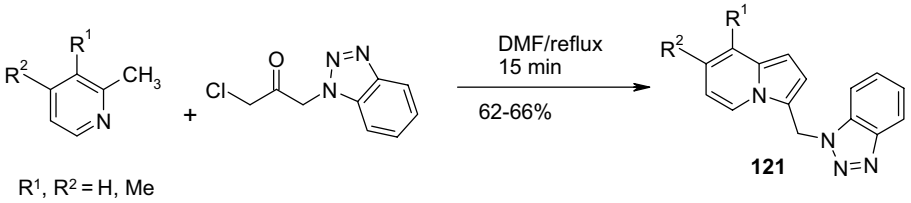


120

Scheme 22.14

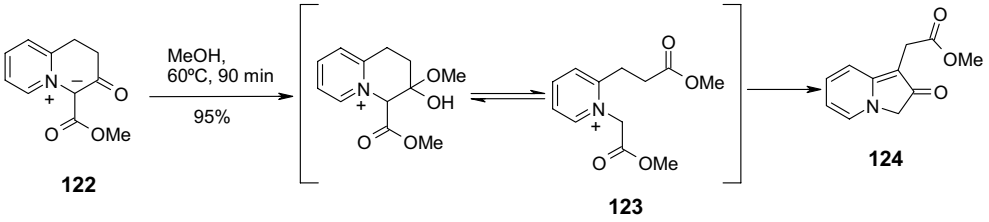
The synthesis of indolizines by the Chichibabin reaction has been revisited and some variations have been proposed. The process can be simplified by using the pyridine as a basic catalyst, thus producing the indolizine in one step. Indolizine **121**

(Scheme 22.15) bears a triazole moiety that has proved useful in the construction of benzo-annulated indolizines [72].



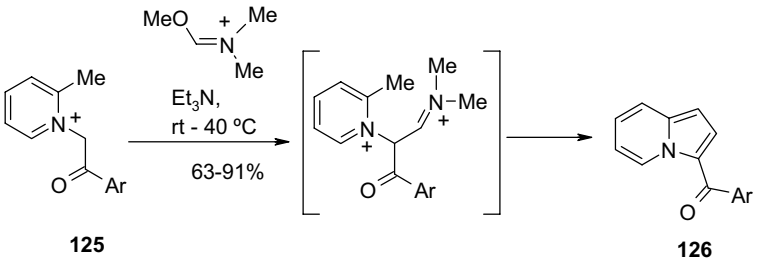
Scheme 22.15

A process related to the Chichibabin approach has been described in which cyclic iminium ylides like **122** can generate, after solvolysis, intermediates **123**, which can afford the corresponding indolizin-2-ones **124** through a Dieckmann process (Scheme 22.16) [73].



Scheme 22.16

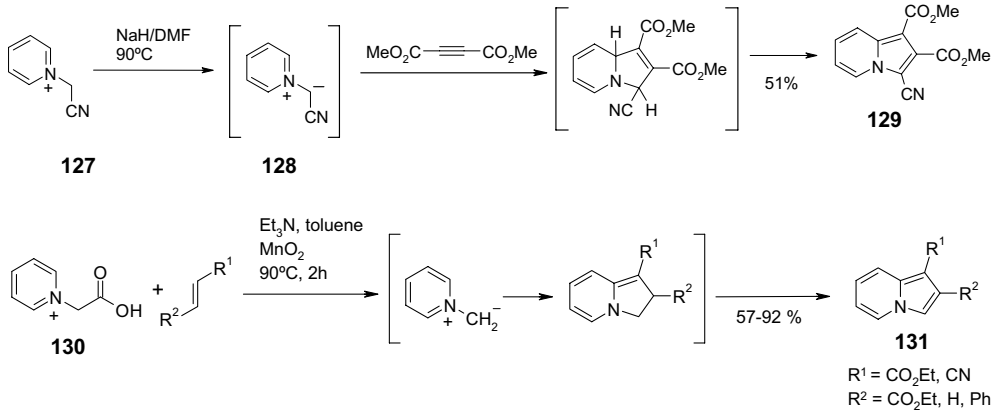
Another related process has been described by Sun and co-workers and involves the preparation of 3-acylated indolizines **126** (Scheme 22.17) from picolinium salts **125** and an iminium salt. This is a straightforward process with short reaction times, low cost, and easy isolation of the products [74].



Scheme 22.17

22.3.4.2 By a [3 + 2] Approach: 1,3-Dipolar Cycloaddition

Another useful method involves the intermediacy of a pyridinium ylide as a 1,3-dipole in a cycloaddition. The 1,3-dipolar cycloaddition of pyridinium ylides such as **128** with



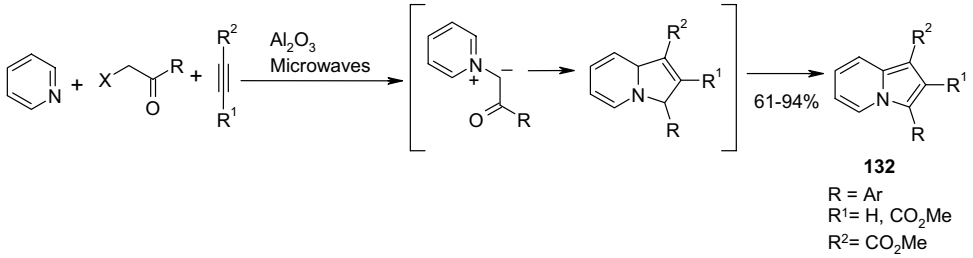
Scheme 22.18

electron-deficient alkenes and alkynes has long been used. Scheme 22.18 shows an example of the synthesis of substituted indolizine derivative **129**. More recently, this reaction has been applied to the synthesis of 3-unsubstituted indolizines **131** using (carboxymethyl)pyridinium halides, which underwent decarboxylation upon cycloaddition [75]. The reaction was performed using electron-deficient alkenes together with a mild oxidant such as MnO_2 to obtain the fully conjugated product (Scheme 22.18).

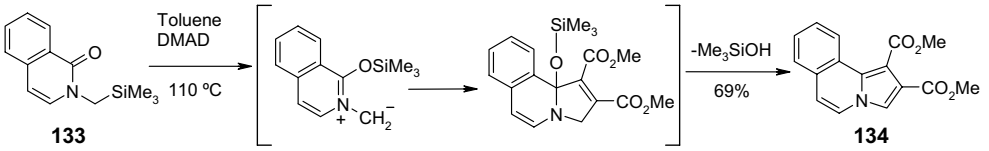
A recent method for the synthesis of the indolizine skeleton is represented by a three-component reaction between α-bromoketones, pyridine, and ethyl propiolate or diethyl acetylenedicarboxylate. These three reagents, under microwave irradiation and catalysis by basic alumina, afford a wide variety of 3-arylindolizines **132** (Scheme 22.19) [76].

Another variation of this procedure is provided by the use of *N*-(silylmethyl)-pyridinone analogues **133**, which through 1,4-silatropy and subsequent 1,3-dipolar cycloaddition afford the corresponding indolizines **134** (Scheme 22.20) [77].

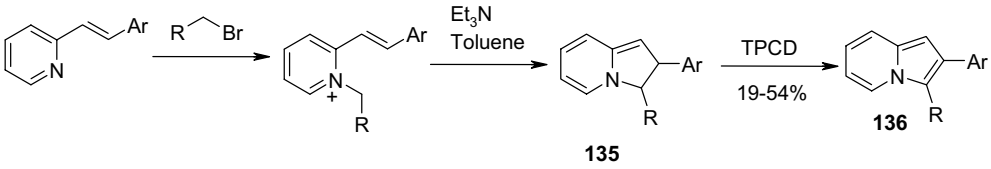
A useful method for the synthesis of 1-unsubstituted 2-arylindolizines **136** is provided by the 1,5-dipolar cyclization of pyridinium ylides in the presence of the oxidant tetrakis(pyridine)cobalt(II) dichromate (TPCD), which oxidizes the intermediate dihydroindolizine **135** (Scheme 22.21). The study demonstrated that the presence of an aryl group on the double bond was necessary for the reaction to occur [78].



Scheme 22.19



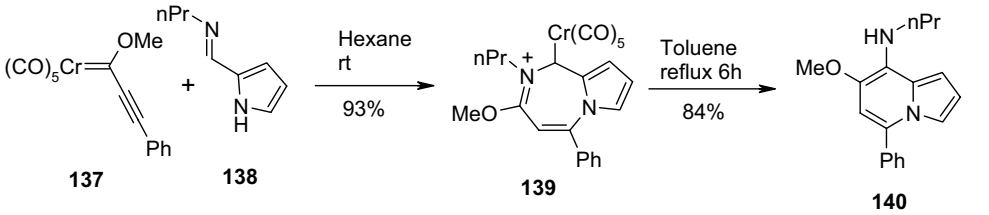
Scheme 22.20



Scheme 22.21

22.3.4.3 **Organometallic Processes**

Alkenyl and alkynyl Fischer carbene complexes **137** react with pyrrole imine **138** to give, through a 1,2- and 1,3-metal migration, respectively, indolizine derivatives **140** at a different level of unsaturation [79] (Scheme 22.22).

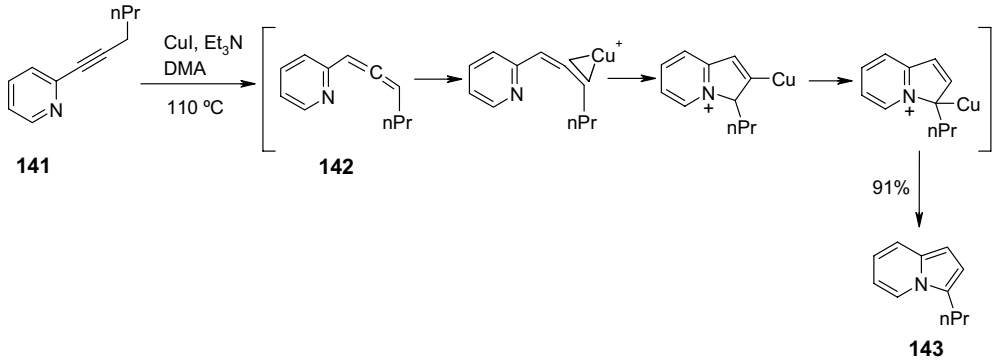


Scheme 22.22

22.3.4.4 **Rearrangement of Acetylenic Derivatives**

Allene-substituted lactams or cyclic imines are useful intermediates in the synthesis of indolizine derivatives. The former are stable and require a Pd(0) catalyst and the presence of phenyl iodide to react [80], whereas the latter are produced *in situ* and react immediately [81]. On the other hand, the substituted pyridine **141** was proposed to undergo a base-induced propargyl allenyl isomerization. Allene **142** underwent the transformation into **143** [81] through the mechanism proposed in Scheme 22.23.

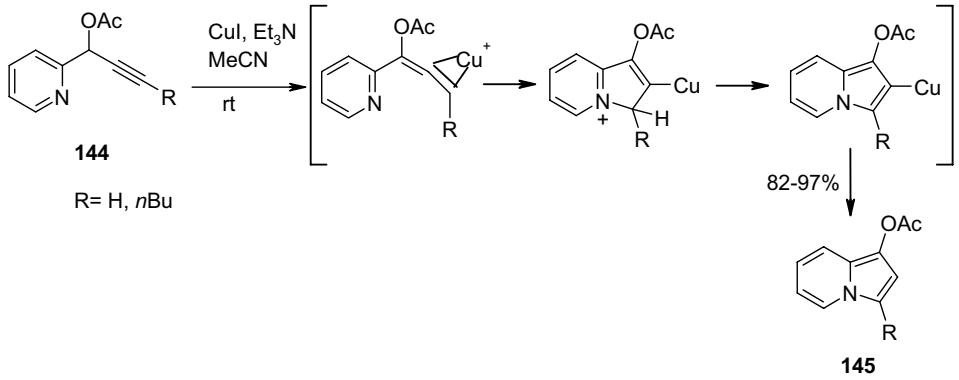
Variations on the above scheme have been studied in recent years. For example, 2-pyridyl-substituted propargylic acetates **144** offer an efficient route to C1 oxygenated indolizines **145** [82] according to mechanism shown in Scheme 22.24. A similar



Scheme 22.23

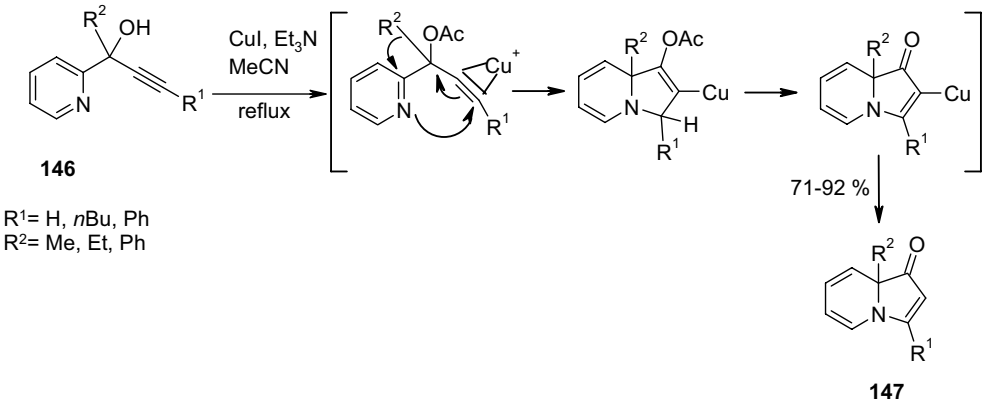
process has been described with the use of iodine in dichloromethane, which produces the corresponding 2-iodoindolizine [83].

Further variations on the strategy described in Scheme 22.24 have allowed the synthesis of indolizin-1-ones **147**, starting from 2-pyridyl-substituted propargyl alcohols **146** (Scheme 22.25) [84]. The same process was simultaneously described [85] with the use of either Pt or $InCl_3$. Furthermore, the same process has also been described without the need for a catalyst by the use of microwaves in ethanol [86].

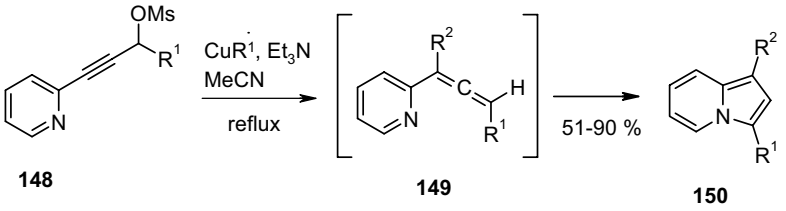


Scheme 22.24

A related process, mediated by organocopper reagents, has been described. In this approach propargyl mesylates **148**, when treated with an organocopper reagent, undergo a cascade involving addition and cyclization to give the indolizine **150** [87] via the allenic intermediate **149** (Scheme 22.26).



Scheme 22.25



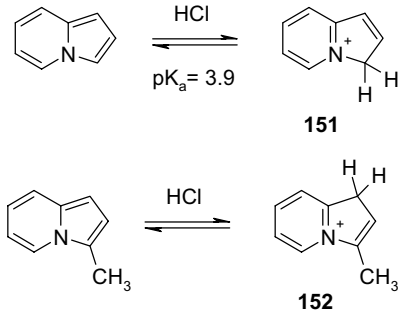
Scheme 22.26

22.3.5 Reactivity of Indolizidines

Indolizine is an electron-rich system and the easiest reactions for this system are mainly electrophilic substitutions, which occur as readily as for indole and preferentially at C3. Indeed, only when this position is blocked does the attacking electrophile enter at C1. Consistent with their similarity to pyrroles, indolizines are not attacked by nucleophiles and there are no examples of nucleophilic displacement of halide.

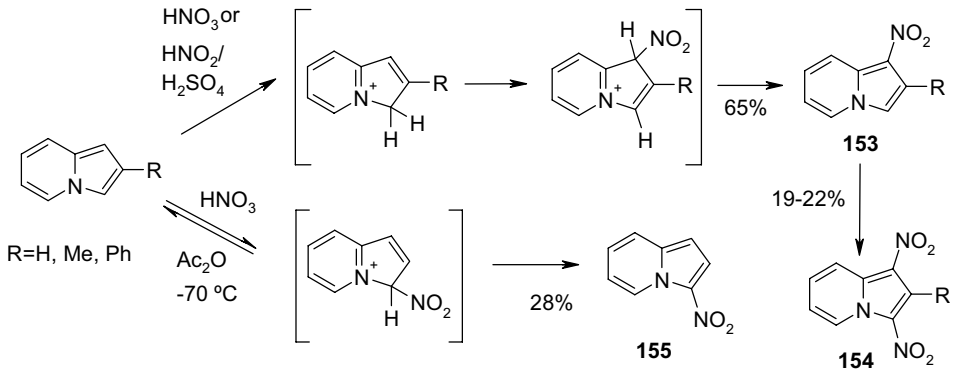
22.3.5.1 Reactions with Electrophilic Reagents

Indolizine (pK_a 3.9) [88] is much more basic than indole (pK_a −3.5) and the implied relative stability of the cation makes it less reactive and thus resistant to acid-catalyzed polymerization. Indolizine protonates at C3, but 3-methylindolizine protonates mainly at C1; other derivatives such as 1,2,3-trimethyl- and 3,5-dimethylindolizines protonate exclusively at C3 (Scheme 22.27).



Scheme 22.27

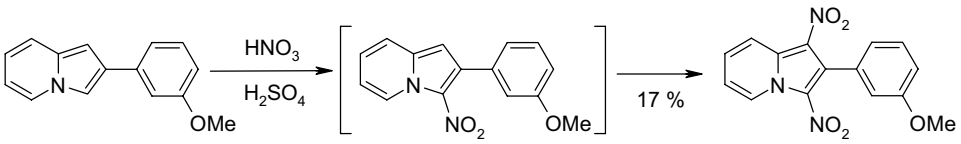
The nitration of indolizines with nitric acid and with nitric and sulfuric acids [89] produced mixtures. The major product was l-nitro-derivative **153** (Scheme 22.28), when the process was performed at 0 °C, and 1,3-dinitroindolizines **154** when higher temperatures were used. Borrows, Holland, and Kenyon have also studied the effect of acetic anhydride and nitric acid on 2-methylindolizine but were unable to isolate any solid product, while Scholtz [90] reported that indolizine cannot be nitrated because of its sensitivity to oxidizing agents. Treatment of indolizine and 2-methylindolizine with nitric acid in excess acetic anhydride at −70 °C gave moderate yields of the corresponding 3-nitroindolizines **155** and other isomers were not detected (Scheme 22.28) [91]. Thus, indolizines fall into the category of aromatic substrates that show a wide variation in the proportion of isomers according to the conditions of nitration. By analogy with other reactive aromatic species, it appears possible that the nitronium ion is the effective electrophile in both instances, whereas the substrate varies with the solvent. In the case of acetic anhydride the substrate is presumably the free indolizine, which is nitrated at C3 – that is, the position commonly susceptible to electrophilic attack. With nitric or sulfuric acid as solvent, however, where 1-nitration predominates, the species that is attacked should be a 3-protonated indolizine. In any



Scheme 22.28

case, the low yields obtained in most of the examples are due to extensive decomposition of the heterocyclic ring associated with oxidation.

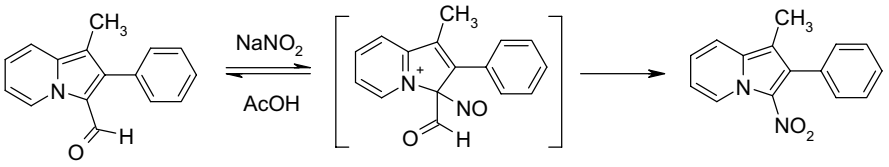
The process based on the use of nitric acid/acetic anhydride at low temperature has been used to nitrate functionalized indolizines such as 8-nitro derivatives [92]. The use of nitric/sulfuric acid to produce 1,3-dinitro derivatives **154**, as indicated in Scheme 22.28, has been described in relation to the development of new antimicrobial agents (Scheme 22.29) [93].



156

Scheme 22.29

Reaction of 1- and 3-substituted indolizines with HNO_2 gave ipso-substituted nitro derivatives **157** (Scheme 22.30). An electron-transfer process has been proposed for the initial step, ultimately yielding nitro derivatives either at the 1- or 3-position [94].



157

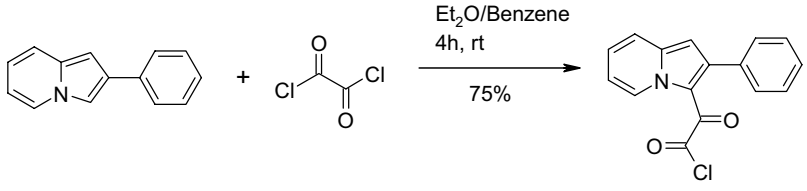
Scheme 22.30

A similar process to obtain 3-nitrosoindolizines, using sodium nitrite and hydrochloric acid, has been described by Hickman and Wibberly [95] along with diazocoupling [96]. These reactions occur at C3 in all cases.

Acylation of indolizines was initially described by Scholtz [90] but the process has been extensively applied by simply heating the substrate with the acyl halide or anhydride in a nonpolar solvent. In certain cases the use of a base improves the final yield. As in other electrophillic substitutions, acylation occurs at C3, but if this position is occupied then C1 is acylated.

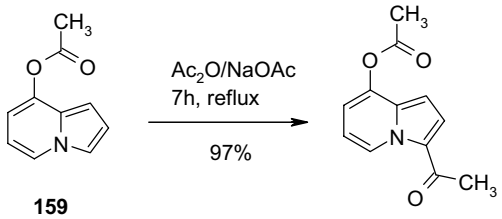
A classical paper describes acylation of 2-phenylindolizine using oxalyl chloride (Scheme 22.31) [97]. Related processes with oxalyl derivatives have been described with essentially the same procedure and results [98]. A similar procedure has been performed using pyridine as a base at $-78\,^{\circ}C$ [98b].

A very simple method has been described for the functionalization of indolizines **159** to afford the acyl derivative **160** [99] in excellent yield (Scheme 22.32). Very



158

Scheme 22.31

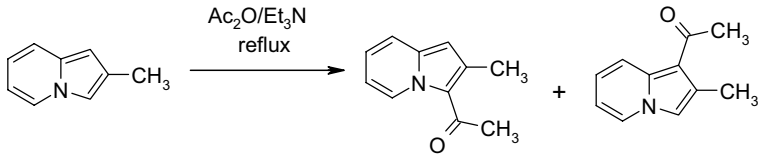


159 160

Scheme 22.32

similar results are described in other papers as part of the synthesis of differently functionalized indolizines [100].

Another representative method has been described by Babaev and Bobrovskii [101], who studied the acylation of indolizines with aliphatic and aromatic halides. Small percentages of the 1-isomer **162** were detected on acylation of 2-methylindolizine (Scheme 22.33).

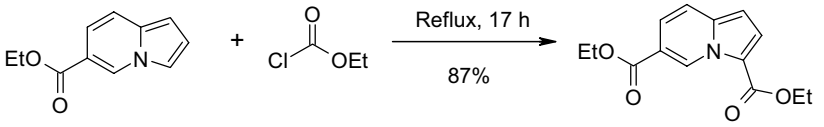


161 (87%) **162** (1.5%)

Scheme 22.33

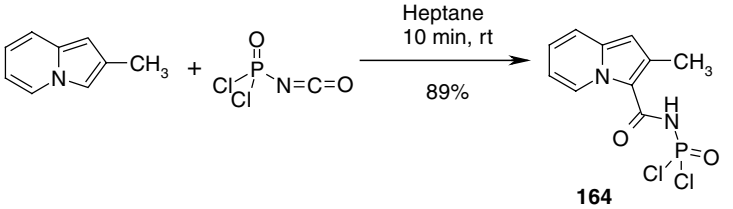
Ethyl chloroformate has recently been used to generate the corresponding diester **163** from 6-ethoxycarbonylindolizine and, as expected, this reaction occurs in the 3-position (Scheme 22.34) [102]. A similar process involving thermal treatment using β-oxoesters as acylating agents has been described [103].

Similarly, acylation has been performed using isocyanatophosphoryl chloride [104] to yield the amide **164**, which can be transformed further (Scheme 22.35).



163

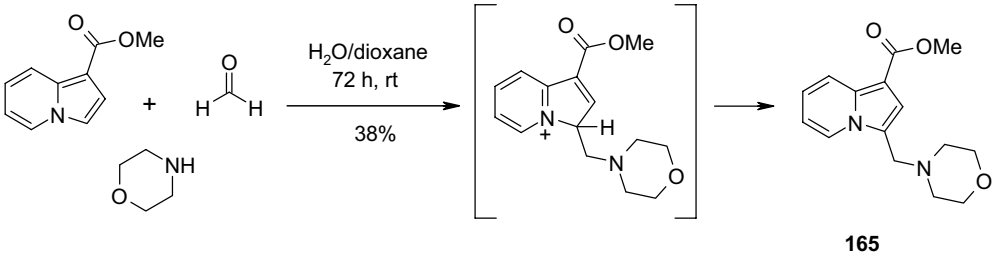
Scheme 22.34



164

Scheme 22.35

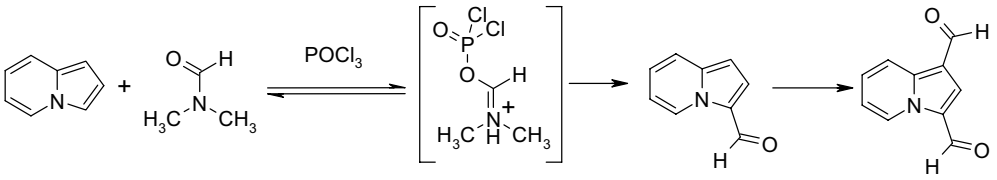
Mannich bases such as **165** have been prepared from indolizine derivatives, following the general pattern of reactivity, with selective attack on C3 [105] as indicated in Scheme 22.36. Other papers have been published concerning different medicinal activities of these compounds [106].



165

Scheme 22.36

Vilsmeier formylation has also been used in the field of indolizines to generate aldehydes, mostly in the 3-position of the ring (Scheme 22.37) [107]. Depending on



166 **167**

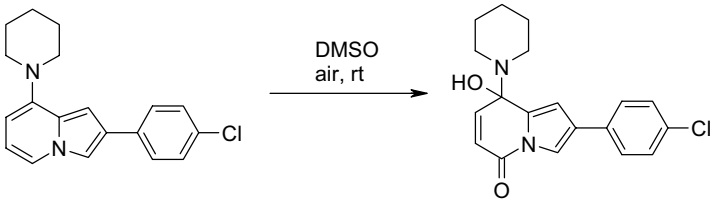
Scheme 22.37

the substrate and the reaction conditions, formylation does not stop at aldehyde **166** but continues to give **167**.

22.3.5.2 Reactions with Oxidizing Agents

Indolizines are special in terms of their electronic structure in that they have a bridgehead nitrogen atom, which causes a large dipole moment in the molecule, making the pyridine electron deficient and the pyrrole electron rich. This structure makes the system and its derivatives sensitive to light and to aerial oxidation, which leads to destruction of the ring system.

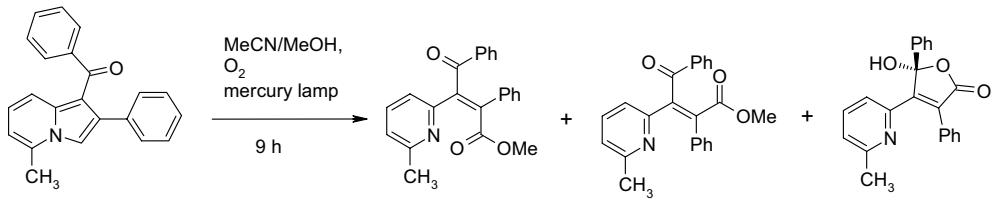
Despite the instability associated with the system, several groups have published processes that involve the use of different oxidants. As a representative example, Tielmann and Hoenke [108] have described the oxidation of 8-aminoindolizine **168** to form, in DMSO solution and in the presence of air, the quinonoid structure **169** (Scheme 22.38).



168 **169**

Scheme 22.38

Similarly, Xu and co-workers [109] have described the photooxygenation of indolizines like **170**, which gives mixtures of products with a pyridine structure through ring-opening reaction of the pyrrole moiety (Scheme 22.39).



170

22% **171**

23% **172**

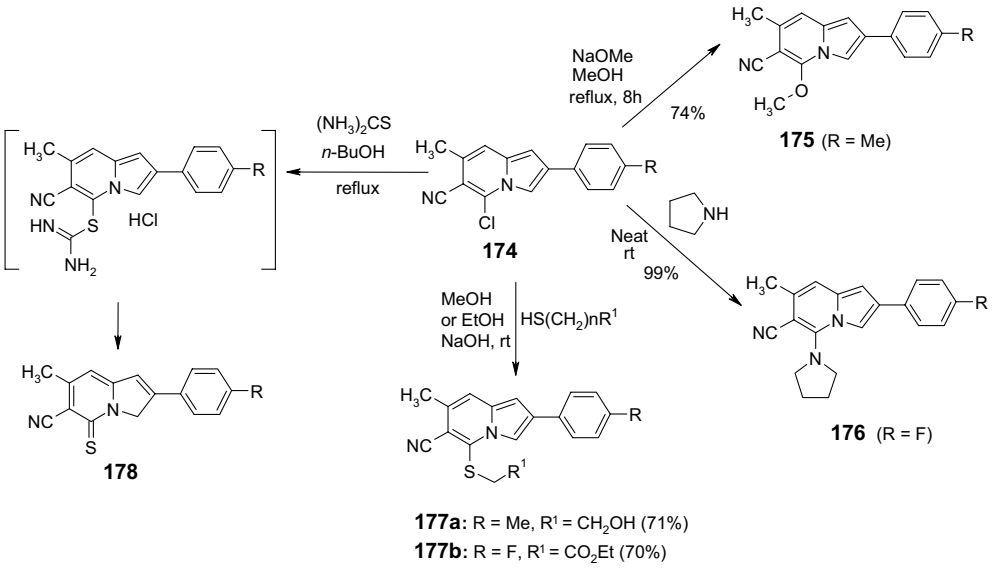
40% **173**

Scheme 22.39

22.3.5.3 Reactions with Nucleophilic Reagents

On considering the structure of indolizine, one would expect that C5 of the system would be the most suitable for nucleophillic attack based on the earliest statements by

Coulson [110] and Fukui [111]. Nucleophillic attack, however, has only been confirmed for indolizines with an additional electron-withdrawing group at the C6 or C8 position. For example, 8-nitroindolizines have been described to undergo amination at position C5 (S_NH substitution) under the action of secondary amines [112]. In addition, substitution of the chloro-substituent in 5-chloro-6-cyanoindolizine derivatives **174** has been studied by Babaev and co-workers [113], who described the process with oxygen, nitrogen, and sulfur nucleophiles to give derivatives **175–178** (Scheme 22.40). The reactivity of simple 5-haloindolizines remains unclear [114].



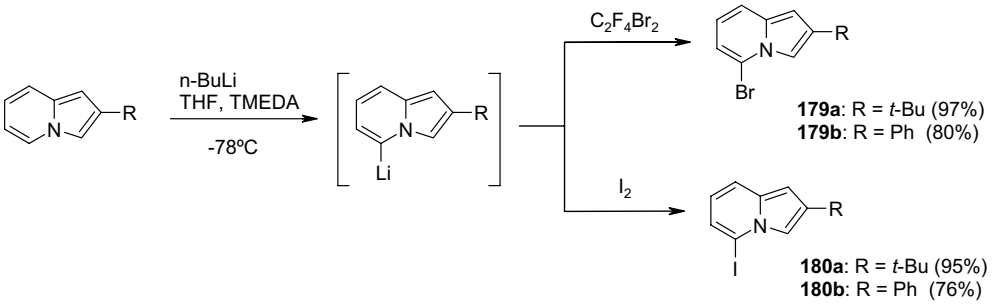
Scheme 22.40

22.3.5.4 Reactions with Bases

2-Phenylindolizine can be lithiated at C5 and the resulting lithium derivative has been reacted with $ClSiMe_3$ and other C-electrophiles [115]. The same process has been optimized by Babaev and co-workers [116], using the lithium derivative to prepare the corresponding 5-iodoindolizine. This group also described the same lithiation to obtain, using parallel chemistry, the corresponding 5-bromo- and iodo derivatives, which were later used as substrates in Pd-catalyzed reactions (Scheme 22.41) [117]. In addition, 5-methylindolizine undergoes lithiation at the methyl group [118].

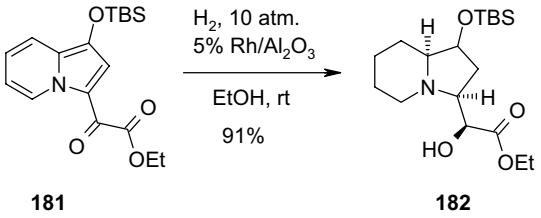
22.3.5.5 Reactions with Reducing Agents

Catalytic reduction in acidic solution of the indolizinium cation in the presence of Pd/C has been described as giving a pyridinium salt [119]. Complete saturation, affording indolizidines, has been achieved with reductions over platinum [120].



Scheme 22.41

The most recent results concern a study into the reduction of substituted pyrroles, with the reduction of indolizine **181** to the corresponding indolizidine **182** [98b] (Scheme 22.42). As indicated by related examples, the carbonyl group is reduced before the indolizine system.

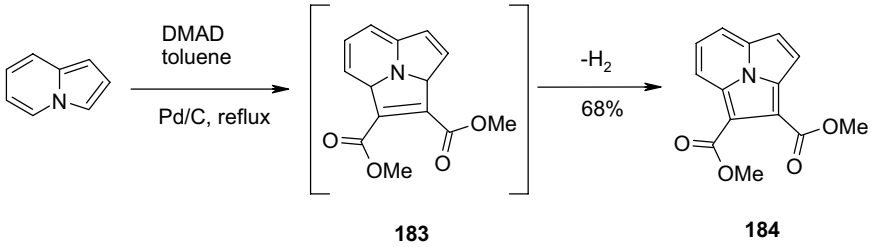


Scheme 22.42

Kim and Gevorgyan [121] have described recently the Birch reduction of indolizine derivatives. As a result, the simpler indolizines yielded 5,6-dihydro derivatives.

22.3.5.6 **Electrocyclic Reactions**

Despite being a ten-electron aromatic π-system, indolizine apparently participates in reactions with activated acetylenes such as DMAD. When the reaction was carried out in the presence of a noble metal catalyst, the initial adduct **183** was converted into an aromatic cyclazine **184** (Scheme 22.43) [122].

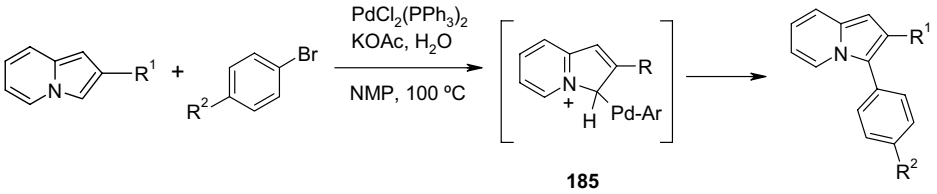


Scheme 22.43

A similar process has been studied by Babaev and co-workers [117] starting from a 5-bromoindolizine derivative. In this case, the dihydro analogue to **183** aromatizes, not by oxidation, as indicated in Scheme 22.43 (so the Pd catalyst is not necessary), but by HBr elimination, which produced higher yields.

22.3.5.7 **Reactions of C-Metallated Indolizines**

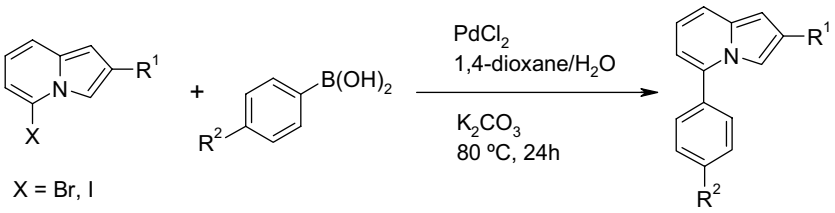
A classical paper from Renard and Gubin concerns the preparation of 5-Li-indolizines and the reactions with different electrophiles [115]. However, the most recent advances in the chemistry of metallated indolizines concern the chemistry of palladium-catalyzed reactions. For example, Gevorgyan and co-workers [123] have described a Heck arylation of indolizines (Scheme 22.44). A combination of kinetic and computational studies indicates an intermediate like **185** in the mechanistic proposal for the formation of **186**.



186a: R^1 = COOEt, R^2=NO_2 (91%)
186b: R^1 = Me, R^2 =OMe (73%)

Scheme 22.44

As indicated above, Babaev and co-workers [117] have described a halogenation method to prepare 5-haloindolizines and a Suzuki arylation performed in parallel to obtain **187** (Scheme 22.45). The use of the iodo analogues as starting materials usually led to higher yields.

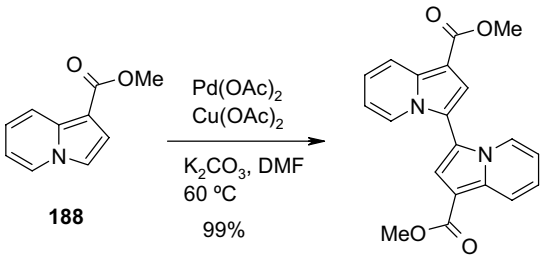


187a: R^1= *t*-Bu, R^2=OMe (70%)
187b: R^1= Ph, R^2=OMe (64%)

Scheme 22.45

The most recent addition to this field has been the dimerization of **188**, which was described by You and co-workers [124], through homocoupling using a combination

of palladium and copper acetates (Scheme 22.46). The synthesis has been carried out on a wide variety of functionalized indolizines and has also been used as a key step in the preparation of a macrocyclic compound.



188 **189**

Scheme 22.46

22.3.6
Derivatives

Only a few functional derivatives of this system are available at present. To give a general view, it is necessary to bear in mind the easy cleavage of carboxyl and acyl groups on heating with aqueous acid and the instability of amino indolizines, which are unstable to oxidation and cannot be diazotized, but which can be converted into stable amides.

22.4
Quinolizinium Salts

22.4.1
General Structure and Reactivity

The C_6-C_6 fused bicyclic ring systems containing a bridgehead nitrogen atom are represented by different heterocycles depending on the oxidation state of the system. The representative heterocycle of the fully aromatized structure is the pyrido[1,2-*a*] pyridinium, which is known as quinolizinium (**16**, Figure 22.1c), an approved name that has the advantage of simplicity but is not consistent with the rules of nomenclature, which assign this name to any of the cations formed by protonation of a quinolizine. The quinolizines themselves (**17**–**19**) are the archetypes of partially unsaturated C_6-C_6 fused bicyclic systems. None of the three possible isomeric quinolizines have been isolated although 4*H*-quinolizine (**17**) is documented as

having a transient existence. Quinolizidine (**20**) is the representative heterocycle of the C_6-C_6 fully saturated system containing a nitrogen ring-junction.

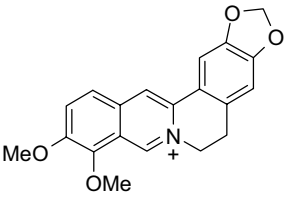
Replacement of a carbon atom and its attached hydrogen by heteroatoms in quinolizines leads to various heterocycles. The aza analogues of **16** are known as azaquinoliziniums, a simple and convenient name that is not used for the rest of these systems, probably because the presence of other heteroatoms may lead to some confusion. Of the four possible azaquinolizinium isomers (**21–24**, Figure 22.1c), the 3-azaquinolizinium system **23** is currently unknown. A detailed discussion of the chemistry and properties of non-aromatic and non-cationic systems is beyond the scope of this chapter. Likewise, an exhaustive discussion of the benzo derivatives of these systems is not undertaken, although a brief survey of the properties and chemistry of tricyclic and polycyclic cations having a bridgehead quaternary nitrogen is included at the end of this chapter.

The first review covering the literature on these polycyclic aromatic nitrogen cation systems appeared in 1961 [125] and in 1965 the chemistry of quinolizinium salts was reviewed by Thyagarajan [126]. Jones [127] published a review covering the chemistry of quinolizinium and its benzo derivatives, and a fourth review is devoted to polycyclic aromatic nitrogen cations [128]. Two more reviews appeared [129, 130] before a chapter in *Comprehensive Heterocyclic Chemistry* in 1984 [131] and another chapter in the updated version in 1996 [132], which provided a comprehensive treatment of these cationic heterocycles. A more recent review has been published by Ihmels [133].

22.4.2
Relevant Natural and/or Useful Compounds

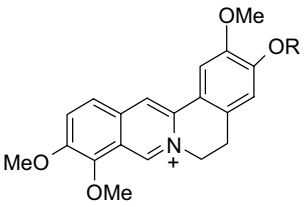
The quinolizinium cation is present in the structure of relevant natural alkaloids such as the berberine family. Berberine (**190**) is one of the most widely distributed of all alkaloids, having been found in plants of the nine botanical families [134, 135]. Berberine and related protoberberine alkaloids such as palmatine (**191**) [136] and jatrorrhizine (**192**) incorporate the dihydro form of the quinolizinium system. Berberine has been used extensively in folk medicine [137] and exhibits a wide range of pharmacological activities [138]. Coralyne (**193**), the first reported compound containing the fully aromatic quinolizinium nucleus was described by Schneider and Shroeter in 1920 [139]; it is another important member of this group of alkaloids and possesses significant antitumor activity [140] and interacts with DNA through intercalation [141].

Many relevant alkaloids are based on a betainic structure (neutral conjugated molecules that can be represented only by dipolar structures in which both the negative and the positive charges are delocalized within the π-electron system) [142]. Quinolizinium ylides are well-known conjugated heterocyclic mesomeric betaines (CMBs) that are present in different families of alkaloids such as those based on the indolo[2,3-*a*]quinolizinium system represented by sempervirine (**194**), flavopereirine (**195**), afrocurarine (**196**), neooxygambirtannine (**197**), and flavocarpine (**198**), among others [143].

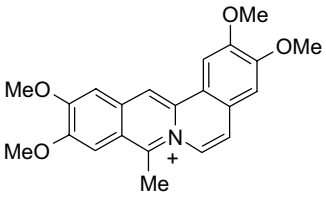


Berberine

190

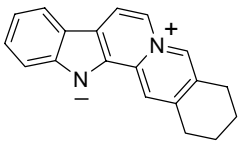


191 Palmitine: R=H
192 Jatrorrhizine: R=Me



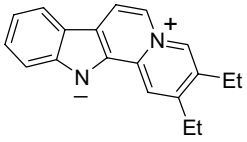
Coralyne

193



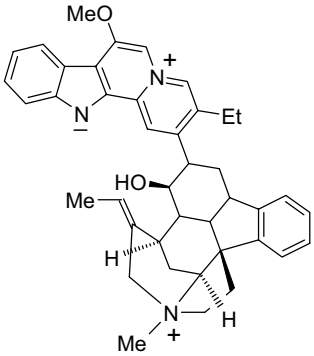
Sempervirine

194



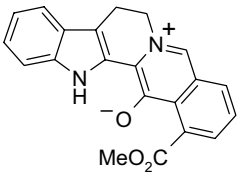
Flavopereirine

195



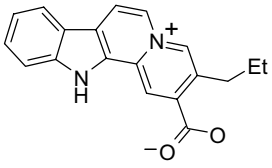
Afrocurarine

196



Neooxygambirtannine

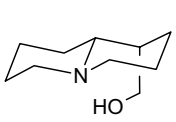
197



Flavocarpine

198

The quinolizidine alkaloids are also widely distributed in nature; nearly 30% of all known alkaloids belong to the quinolizidine-indolizidine family. Some representative members of this group of alkaloids are the structurally simple lupinine (**199**) and nupharidine (**200**). Tetracyclic and tricyclic systems are exemplified by the *Lupinus* alkaloid sparteine (**201**) and the *Lythrceae* alkaloid vertaline respectively (**202**) [144].



Lupinine

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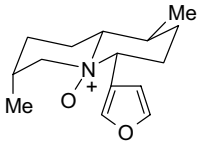
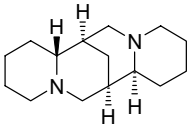


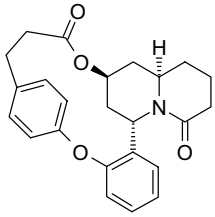
Nupharidine

200



Sparteine

201



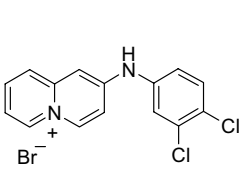
Vertaline

202

Different pharmacological properties have been described for quinolizinium derivatives. For example, 2-aminoquinolizinium compounds are anthelmintic agents [145], nolinium bromide (**203**) possesses antispasmodic and antisecretory

properties [146], 6-hydroxybenzo[*c*]quinolizinium (**204**) is a potent protein kinase CKII inhibitor [147] and the azaquinolizinium derivatives **205** and **206** exhibited DNA intercalating properties and antiproliferative activity [148], acridizinium derivative **207** has been described as a fluorescent probe for DNA and protein detection [149] and the cyanine dyes **208** are based on a benzo[*a*]quinolizinium system [150].

Many quinolizidine derivatives also show pharmacological activities and remarkable affinity towards various receptors. For example, the ortopramides **209** show good gastric prokinetic properties [151]. (+)-Butaclamol (**210**) is a potent neuroleptic agent [152], emetine (**211**) is an antitumor and amoebicidal agent [153], and the quinolizine derivative **212** is an inhibitor of the angiotensin-converting enzyme (ACE) [154].



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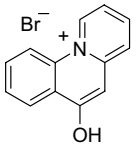

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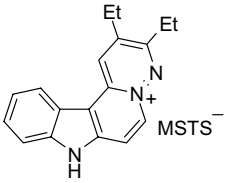

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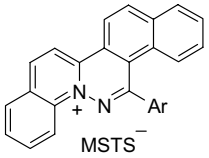

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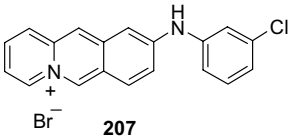

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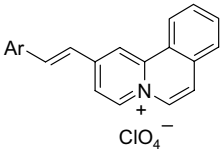

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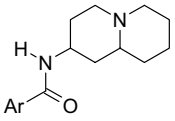

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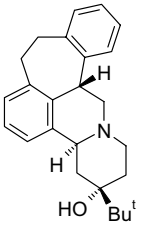

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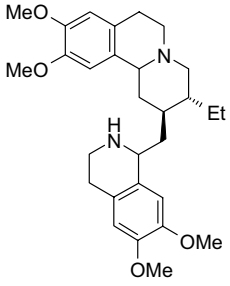

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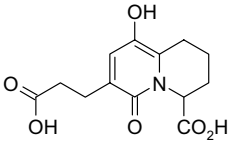

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22.4.3

Relevant Computational Chemistry, and Physicochemical and Spectroscopic Data

The structures of quinolizinium hexafluorophosphate [155] and some benzo[*b*] quinolizinium derivatives [156] have been determined by X-ray diffraction analysis. As expected, the quinolizinium ring is planar; the maximum deviation from the best

plane through the non-H atoms is for atom C1, which deviates by only 0.010(1) Å. The most significant structural differences between this aromatic cation and naphthalene [157] are contractions of the N−C bond lengths in **16**, by 0.04 Å for N5−C9a and by 0.03 Å for N5/C9a−C1.

Quinolizinium and related heterocyles are isoconjugate with the corresponding aromatic hydrocarbons and the delocalization energy or resonance energy of the heteroaromatic cations is nearly the same as for the parent hydrocarbon [142], as shown by the calculated values for quinolizinium and benzoquinolizinium (Table 22.3).

Electronic densities of quinolizinium and benzo derivatives have been calculated using different molecular orbital methods [(Hückel molecular orbital theory (HMO) [142] and the Pariser–Parr–Pople method (PPP) [158]] and results for **16** are summarized in Table 22.4. Perturbation theory supports the idea that the azonia nitrogen gathers electronic density from the carbon atoms of opposite parity.

In the ^{1}H NMR spectrum of quinolizinium bromide [159] the signals due to H2 and H3 appear in the aromatic region at lower frequencies ($\delta = 8.43$ and 8.14 ppm, respectively) than those of H1 and H4 ($\delta = 8.69$ and 9.58 ppm, respectively). The H4 and H6 protons appear to be strongly deshielded by the effect of the positive charge of the nitrogen, an effect that can also be observed in benzo- and naphthoquinolizinium cations. Table 22.5 shows the chemical shifts and coupling constants for quinolizinium and some simple quinolizinium derivatives [160].

Table 22.6 shows the ^{13}C NMR resonances of the quinolizinium cation and some simple derivatives [161]. In quinolizinium the chemical shifts of the C1 and C3 atoms appear at lower frequencies than those of the C2 and C4 atoms, an observation that is consistent with data reported for electron densities and electrophilic reactivity, which is predicted to occur preferentially at the C3 and C7 positions. The $^{13}C^{14}N$ coupling is responsible for the broadening of C4 and C6 signals. The ^{1}J(CH) values for these two carbons are also higher than those for the other carbon atoms. Substitution leads to either shielding or deshielding of the carbon to which the substituent is bonded. This effect is particularly significant in the case of the hydroxy group.

Quinolizinium, azaquinolizinium, and polycyclic cations that have a quaternary bridgehead nitrogen are chromophoric molecules that absorb light by a transition of

Table 22.3 Delocalization energies (DE) for aromatic hydrocarbons and azonia heteroaromatic cations.

Compound	DE
Naphthalene	3.68
Quinolizinium (**16**)	3.89
Anthracene	5.32
Benzo[*b*]quinolizinium (**25**)	5.53
Phenanthrene	5.45
Benzo[*a*]quinolizinium (**26**)	5.66
Benzo[*c*]quinolizinium (**27**)	5.67

Table 22.4 Electron densities of the quinolizinium cation (**16**).

Method	C1	C2	C3	C4	N5	C9a
HMO	1.005	0.916	1.011	0.856	1.550	0.874
PPP	1.010	0.976	1.013	0.940	1.185	0.940

Table 22.5 ^{1}H NMR chemical shifts (ppm) of quinolizinium and some derivatives (in DMSO-d_6).

Substituent	H1	H2	H3	H4	H6	H7	H8	H9
H	8.65	8.42	8.15	9.49	9.49	8.15	8.42	8.65
2-OH	7.68	—	7.62	9.23	9.06	7.63	7.99	8.23
2-Br	9.07	—	8.36	9.42	9.51	8.13	8.41	8.54
3-Me	8.49	8.16	—	9.56	9.50	7.96	8.24	8.53
4-NMe_2	8.26	8.46	7.89	—	9.54	8.12	8.36	8.56
4-Br	8.79	8.59	8.34	—	9.69	8.25	8.52	8.74

the electronic state of the aromatic π-electron system. The absorption spectrum of quinolizinium iodide [162] shows well-defined absorption bands in the near-UV and visible regions at 226 (log ε 4.25), 272 (3.42), 283 (3.47), 310 (4.03), 316.5 (3.98), and 323.5 (4.23) nm. Comparison with naphthalene shows a bathochromic shift due to the presence of the cationic nitrogen.

Noncovalent interactions between these heteroaromatic chromophores and biomolecules such as DNA causes changes in the UV absorption spectra of the chromophore (usually hyperchromic and bathochromic effects), which in turn provide information about whether an interaction takes place. The benzo[*b*]quinolizinium chromophore exhibits pronounced emission properties [163].

Chromophores based on the quinolizinium ion are colored solids that have high melting points, which usually increase with the molecular weight of the compound (Table 22.7). Changes in the counter anions can significantly modify the melting points of these cationic compounds and in some cases these salts can even become hygroscopic. Some derivatives of these polycyclic cations are fluorescent at room temperature.

Table 22.6 ^{13}C NMR chemical shifts (ppm) of quinolizinium and some derivatives (in DMSO-d_6).

Substituent	C1	C2	C3	C4	C6	C7	C8	C9	C9a
H	127.9	138.0	125.0	137.0	137.0	125.0	138.0	127.9	143.0
2-OH	108.9	164.4	117.0	139.2	135.5	120.8	135.9	125.7	145.9
2-Br	130.1	133.2	128.4	137.4	137.4	125.2	139.2	127.1	143.4
3-Me	126.1	139.0	134.6	134.0	135.1	123.6	135.7	126.6	140.5
4-Br	137.8	126.5	131.5	128.0	136.7	129.8	138.7	128.8	146.6

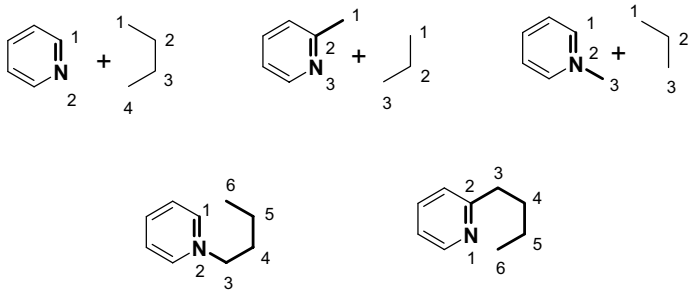
Table 22.7 Physical properties of some quinolizinium cations.

Counterion	Mp (°C)	Solvent	Appearance
Iodide	220–230 (dec)	EtOH/EtOAc	White crystals
Picrate	180–181	EtOH	Yellow needles
Perchlorate	285–288	EtOH	Yellow needles
Bromide	260–261	EtOH	White crystals

The low volatility and thermal degradation of quinolizinium and related cations precludes the gathering of useful information from the mass spectra of these cations using the electron impact ionization (EI) technique. It is necessary to use fast atom bombardment (FAB) and field desorption (FD) techniques to obtain information about molecular ions of the cations.

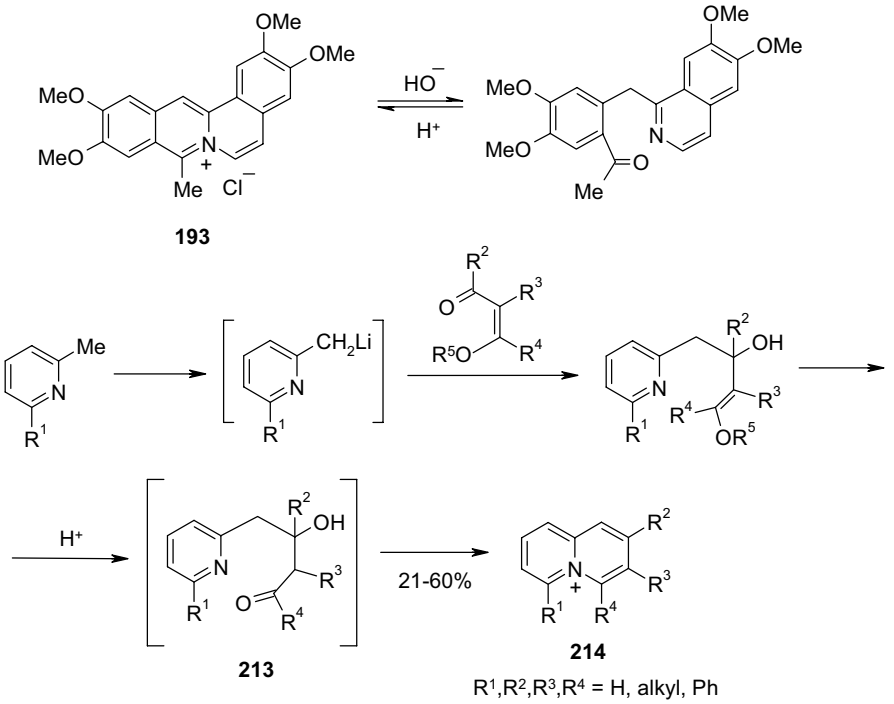
22.4.4
Synthesis of Quinolizinium Salts

All of the synthetic methodologies reported for the construction of the quinolizinum cation are based on a pyridine ring, which is used as a template to build up the second heterocyclic ring. Depending on the number of atoms of the pyridine or pyridine derivative involved in the formation of the bicyclic system, there are different general approaches to the quinolizinium nucleus and the most relevant are summarized here.



22.4.4.1 By [3 + 3] Approaches

In 1920 it was reported that treatment of the natural alkaloid coralyne (**193**) in a strongly alkaline solution led to a new compound that in an acidic medium generated coralyne once more (Scheme 22.47) [139]. It is assumed that this is the first example of cyclization leading to the quinolizinium moiety and this inspired Woodward in his quinolizinium synthesis used in the total synthesis of the methochloride of sempervirine (**194**). The Woodward method is the first [3 + 3] approach to the quinolizinium system [164] involving a 1,3-dicarbonyl equivalent and a 2-methylpyridine (picoline) (Scheme 22.47).

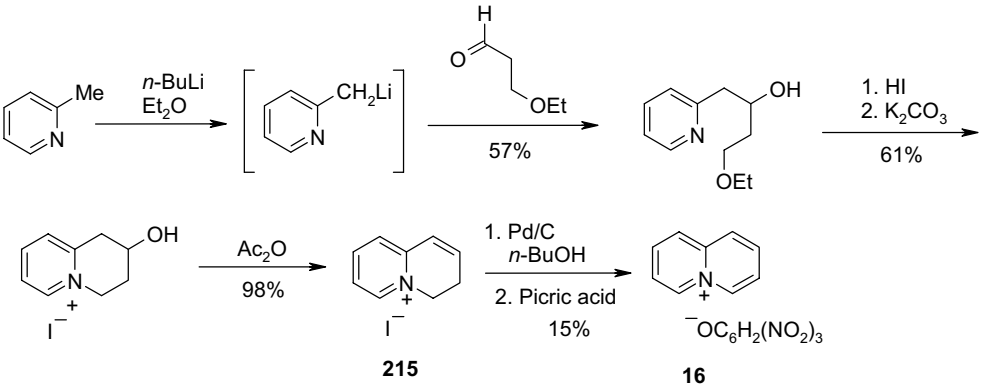


Scheme 22.47

The drawbacks of this method are the limited variety of substituents accessible (only alkyl and phenyl substituents are reported), the low yields obtained in the preparation of most of the substituted quinolizinium compounds (21–60%), and the parent quinolizinium itself, which is reported to be obtained in very poor yield. Moreover, the presence of at least one substituent at the C2 position seems to be critical for the success of this reaction. In a variant of this method the carbonyl group is protected as an acetal or ketal, with compound **213** also being an intermediate. The acidic conditions were achieved with ethanolic picric acid, acetic anhydride with a few drops of sulfuric acid, or dry hydrobromide in acetic anhydride, with the latter being the best conditions [161b, 165].

Boekelheide and Gall described the first synthesis of the parent quinolizinium salt (**16**) using the same [3 + 3] strategy [166]. In this case the reaction of 2-picolyllithium with β-ethoxypropionaldehyde gives the corresponding alcohol, which by consecutive treatment with hydroiodic acid and potassium carbonate is converted into the tetrahydroquinolizinium alcohol. Dehydration followed by dehydrogenation yields **16** in an overall yield close to 5%, although yields obtained in the final dehydrogenation step of the dihydroquinolizinium derivative **215** have thus far been low (Scheme 22.48).

A more useful [3 + 3] approach to **16** and some derivatives involves the reaction between 2-cyanopyridine and 3-ethoxypropylmagnesium bromide [167] to give the



215 **16**

Scheme 22.48

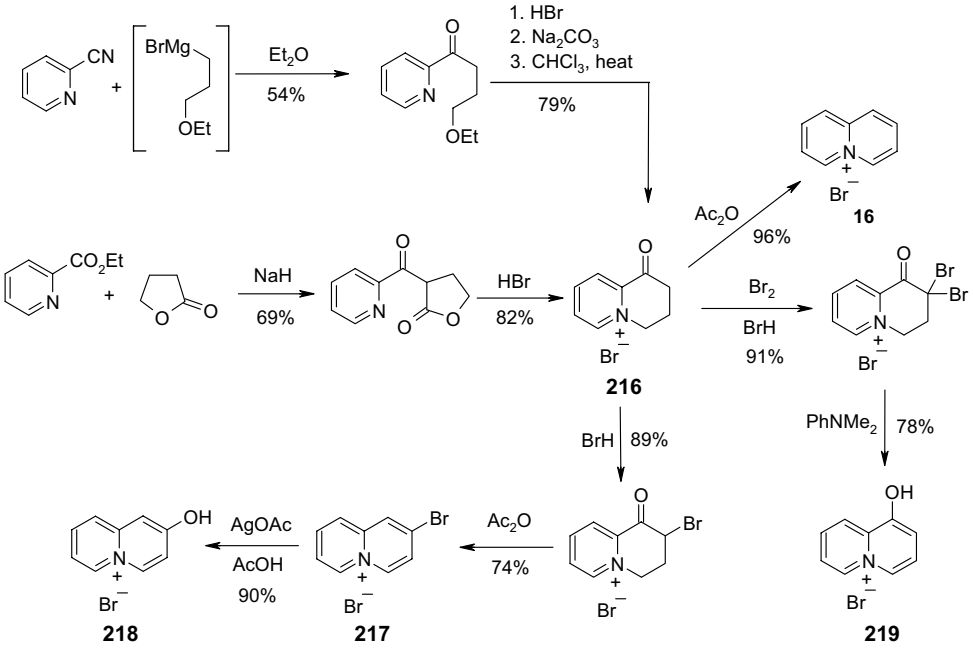
corresponding ketone after hydrolysis of the resulting imine. Cleavage of the ether with hydrobromic acid allows the formation of the bromide, which cyclizes to the bicyclic ketone **216** by heating in chloroform. This ketone is the common intermediate to produce **16** by heating under reflux in acetic anhydride [168] and can also give 1-hydroxy-, 2-hydroxy- and 2-bromoquinolizinium derivatives (**217–219**) using simple reagents [169]. Ketone **216** can be obtained in better yield by reaction of 2-ethoxycarbonylpyridine and γ-butyrolactone in the presence of NaH followed by treatment with hydrobromic acid to produce decarboxylation, bromination, and cyclization (Scheme 22.49) [170].

The mechanism of the aromatization of **216** to **16** is thought to occur via the enol acetate **220**, which rearranges to the 1,4-dihydro derivative **221**. Elimination of acetic acid affords the fully aromatized quinolizinium cation (Scheme 22.50).

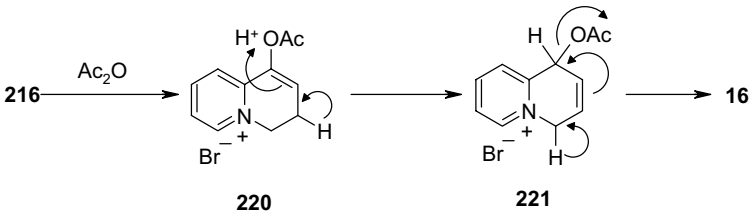
The 3-bromoquinolizinium derivative **222** is obtained by reaction of 5-bromo-2-ethoxycarbonylpyridine and γ-butyrolactone [170]. This method also allows the preparation of the 2-, 3-, and 4-methylquinolizinium salts (**223–225**) by using 3-ethoxypropylmagnesium bromides with the appropriate substitution [168]. 1-Methylquinolizinium picrate (**226**) can be obtained by reaction of 3,3-diethoxypropylmagnesium chloride with 2-acetylpyridine [165c] (Scheme 22.51).

4-Bromo- and 4-hydroxyquinolizinium salts are also prepared by a [3 + 3] approach involving the reaction at 180 °C of ethyl 2-pyridylacetate and diethyl ethoxymethylenemalonate [171]. The quinazolone **227** – initially formed on heating under reflux in hydrochloric acid – yields the 4-hydroxyquinolizinum derivative **228**, which was converted into 4-bromoquinolizinium bromide (**230**) by reaction with phosphorus tribromide (Scheme 22.52) [160b]. NMR studies have shown that 4-quinazolone (**229**) is the main component in the equilibrium of the tautomeric species [172].

Malondialdehyde (and its acetal) and malonic acid derivatives have also been successfully used in the reaction with 2-pyridylacetonitrile to form 1-cyanoquinolizinium derivatives, although the 1-cyanoquinolizinium perchlorate **231a** was only obtained in 8% yield [173] (Scheme 22.53).



Scheme 22.49

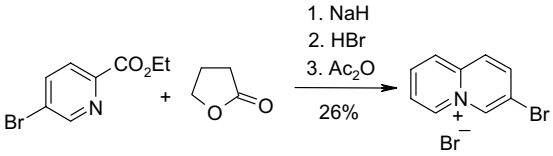


Scheme 22.50

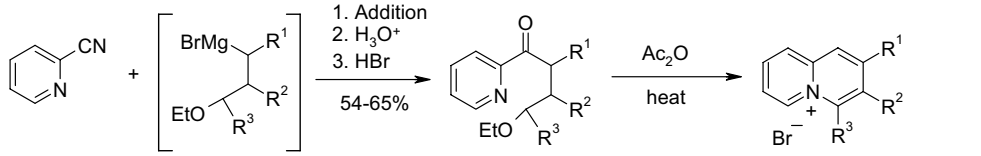
22.4.4.2 **By [4 + 2] Approaches**

The Westphal reaction was described in 1961 [174] and is the representative [4 + 2] approach to a wide variety of substituted quinolizinium salts and some polycyclic cations based on this system. The partners for this synthesis are a pyridinium salt (**232**) bearing active methylenes attached directly to the N1 and C2 positions (1,4-dinucleophile) and a 1,2-dicarbonyl compound (**233**) (1,2-dielectrophile). In the presence of a base (usually a secondary or tertiary amine or $NaHCO_3$) a double condensation reaction occurs to give the quinolizinium system.

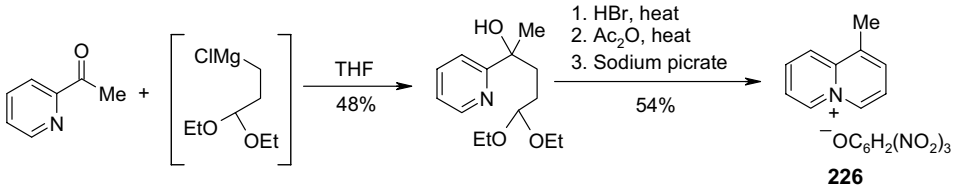
Nowadays, the Westphal condensation can be viewed as a general process involving different types of pyridinium (or azinium) salts, namely, C−C, N−C, N−N, and C−N substrates, and different 1,2-dicarbonyl partners (Scheme 22.54) to afford quinolizinium and aza- and diazaquinolizinium cations [175]. While C−C,



222

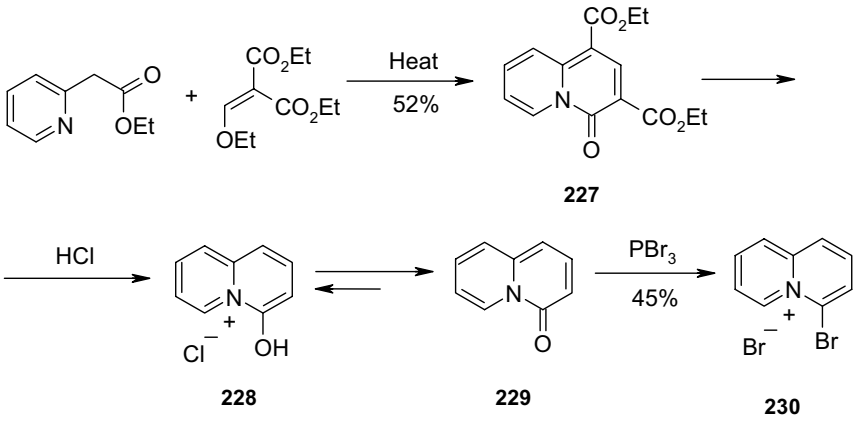


223: R^1 = Me; R^2 = R^3 = H (65%)
224: R^1 = R^3 = H; R^2 = Me (100%)
225: R^1 = R^2 = H; R^3 = Me (65%)



226

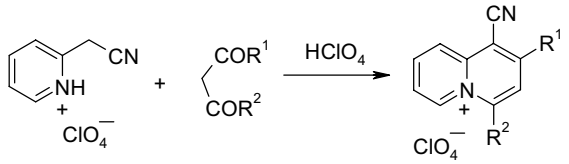
Scheme 22.51



Scheme 22.52

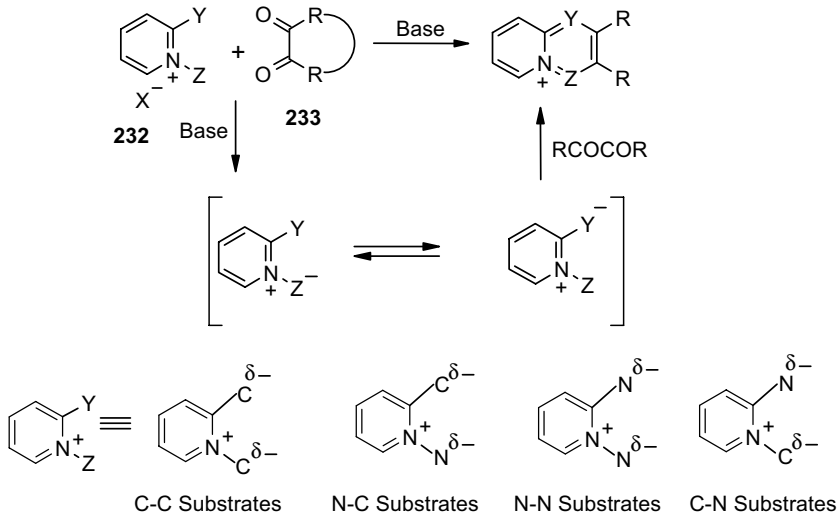
N−C, and N−N substrates are well represented in Westphal-like reactions, attempted condensations involving C−N substrates have been unsuccessful to date.

The first example of this reaction involved the synthesis of various substituted quinolizinium salts **234** by reaction of N-alkyl-substituted 2-picolinium salts and 1,2-diketones in the presence of an organic base (Scheme 22.55) [174]. The reaction was



231a: $R^1 = R^2 = H$ (8%)
231b: $R^1 = R^2 = Me$ (46%)
231c: R^1 = COEt; R^2 = Me (77%)

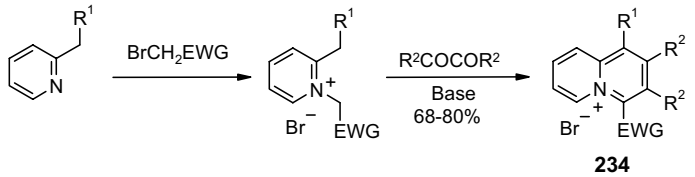
Scheme 22.53



Scheme 22.54

successful with different alkyl- and aryl-diketones and quinones and pyridinium salts bearing electron-withdrawing substituents at N1 to facilitate ylide formation.

The condensation of 1-ethoxycarbonylmethyl-2-hydroxymethylpyridinium and diacetyl and benzyl led to 1-hydroxyquinolizinium derivatives **235a,b** in 5% and

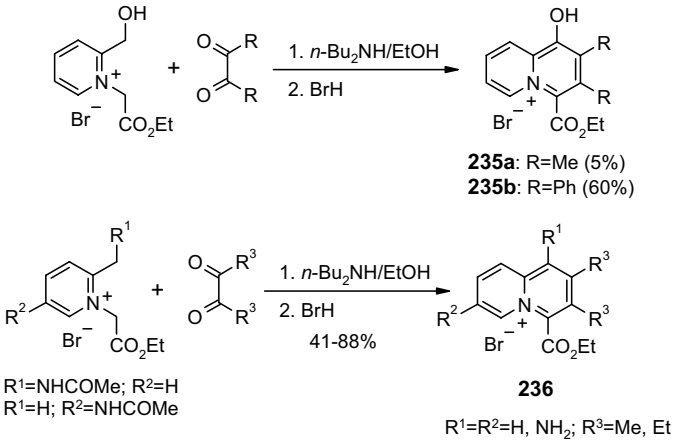


234

R^1=H
R^2=alkyl, aryl
EWG=CN, CO_2R, COR, CONHPh

Scheme 22.55

60% yields, respectively. 1-Amino- and 7-aminoquinolizinium salts **236** were also obtained from appropriate picolinium salts bearing protected amino groups and 2,3-butanedione and 3,4-hexanedione, in ethanol, using di-*n*-butylamine as the base (Scheme 22.56).



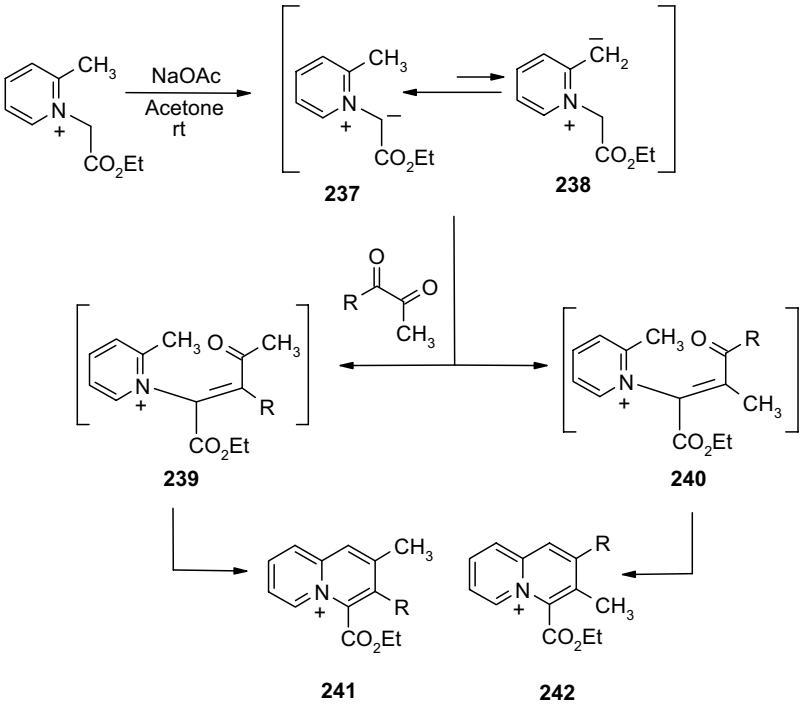
Scheme 22.56

As a result of the large number of studies and applications for this useful reaction [175] the following conclusions have been established:

1) The choice of base, solvent, and reaction conditions play a significant role in the success of the reaction.
2) The reactivity of the 1-methylene is mainly influenced by the nature of the stabilizing group, whereas the reactivity of the α-alkyl substituent strongly depends on the heterocyclic moiety and the presence or absence of further substituents (methyl or alkyl/arylmethyl groups), which could eventually stabilize canonical forms without charge separation (anhydrobases) and these would predominate in the resonance hybrid and make the intermediate less reactive.
3) The presence of a carbonyl moiety in the group attached to the quaternary nitrogen usually results in lower yields of the quinolizinium cation due to the competitive Chichibabin reaction, which involves a cyclization leading to 2-indolizin-2-one derivatives.
4) In the reaction of azinium salts bearing *N*-ethoxymethylcarbonylmethyl substituents and 1,2-diketones the ester group was lost in most of the isolated quinolizinium salts. It was proved that hydrolysis and decarboxylation was an easy process if the resulting quinolizinium salt is partially soluble in the reaction medium, otherwise the ester group remained in the condensation product.

The regioselectivity of this condensation has also been investigated for C−C and N−C substrates with different unsymmetrical 1-aryl-2-propanediones under basic conditions [176]. Deprotonation of the starting salt produces the more stable N-ylide

intermediate **237**. The reaction of this ylide with the diketone should produce the intermediate **239** under kinetic control whereas the more conjugated intermediate **240** should be the thermodynamic control product. The molar ratio of **241**/**242** is highly dependent on the electronic character of the aryl group (phenyl or heteroaryl) in the starting diketone (Scheme 22.57).



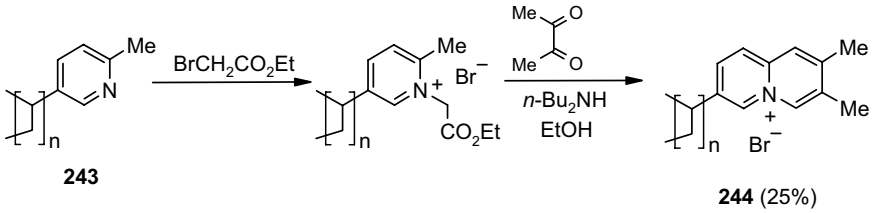
R	Yield (%)	**241/242** Ratio
Et	88	50:50
Ph	67	100:0
	88	40:60
	81	100:0

Scheme 22.57

The results show how kinetic control predominates with 1-(4-pyridyl)- and 1-phenyl-1,2-propanediones, which produce only 2-methyl derivatives **241**. In contrast, π-excessive aromatic systems such as 1-(2-thienyl)-1,2-propanedione produced significant amounts of regioisomer **242** as a consequence of the higher stability of the

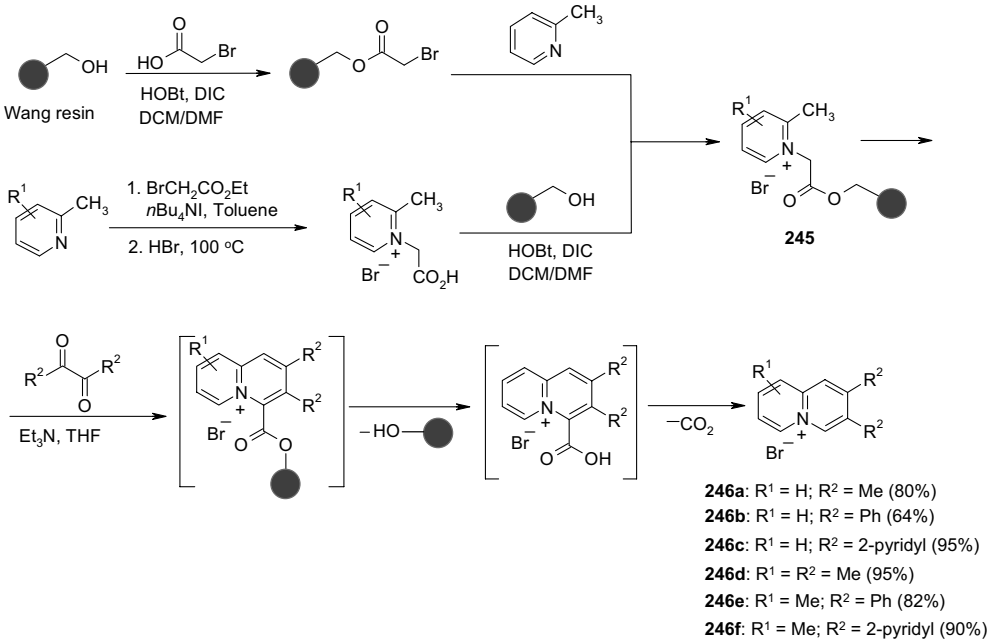
more conjugated intermediate. When 2,3-pentanedione was used as a representative example of a diketone without electronic effects to differentiate between carbonyls, 1 : 1 mixtures of the two regioisomers were formed.

The Westphal process has also been useful for the preparation of resins for ion exchange [177]. The polymeric substrate **243**, bearing 2-methylpyridine, reacted with ethyl 2-bromoacetate to give the corresponding salt, which condensed with 2,3-butanedione in the presence of di-*n*-butylamine to afford the 2,3-dimethylquinolizinium **244** incorporated in the resin (Scheme 22.58).



Scheme 22.58

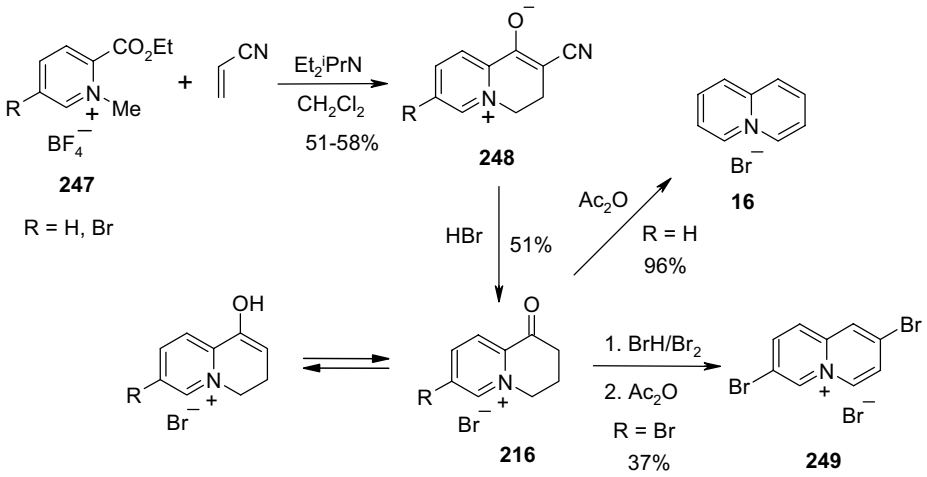
Based on this precedent, the C–C Westphal reaction has been described in the solid phase [178]. The appropriate substrate **245** is prepared in two different ways (Scheme 22.59) using Wang resin as the solid support. A study of the reaction conditions was reported and shows that the optimal yields were obtained



Scheme 22.59

with three equivalents of triethylamine as base in THF at 70 °C. Under these reaction conditions, the initial Westphal condensation product is not stable and spontaneously undergoes hydrolysis of the ester and decarboxylation of the resulting acid. This hydrolysis/decarboxylation sequence has also been observed in the conventional Westphal reaction, as stated earlier. A small library of nitrogen bridgehead azinium and azolium compounds has been synthesized with high yields and purities. Some examples of quinolizinium derivatives (**246a–f**) are shown in Scheme 22.59.

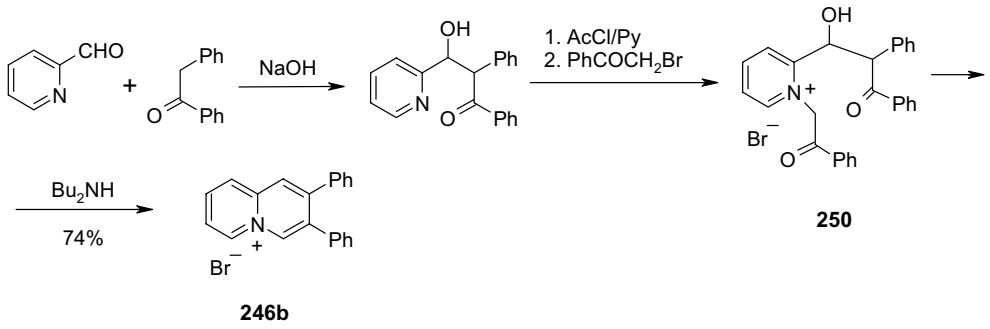
The reaction of 2-ethoxycarbonyl-1-methylpyridium salts with acrylonitrile is also a synthetically useful [4 + 2] approach for building up bicyclic quinolizinium and simple derivatives, although in this procedure the pyridine derivative **247** behaves a nucleophile–electrophile substrate [179]. The initial product of this reaction is the heterobetaine **248**. Removal of the cyano substituent by acid hydrolysis and decarboxylation affords the ketone **216**, which through the same treatment as shown in Scheme 22.49 afforded **16** or 2,7-dibromoquinolizinium bromide **249** [160b] under the conditions shown in Scheme 22.60.



Scheme 22.60

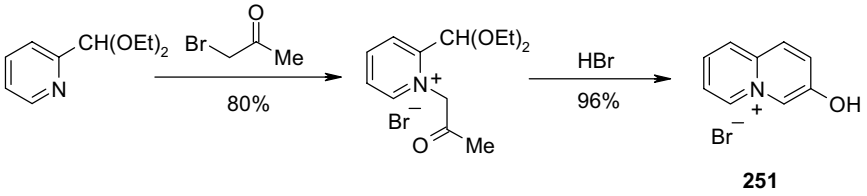
22.4.4.3 **By Cyclization Reactions**

Quinolizinium syntheses based on cyclization methods are represented by a few examples involving different bonds to form the second ring. For example, formation of a bond in the β-position with respect to the heteroatom is represented by the reaction of 2-picolinaldehyde with benzyl phenyl ketone to form the corresponding aldol, which is acetylated and quaternized with phenacyl bromide to afford the pyridinium salt **250** [180]. Treatment with di-*n*-butylamine then generates the quinolizinium derivative, which undergoes debenzoylation to afford 2,3-diphenylquinolizinium bromide (**246b**) (Scheme 22.61).



Scheme 22.61

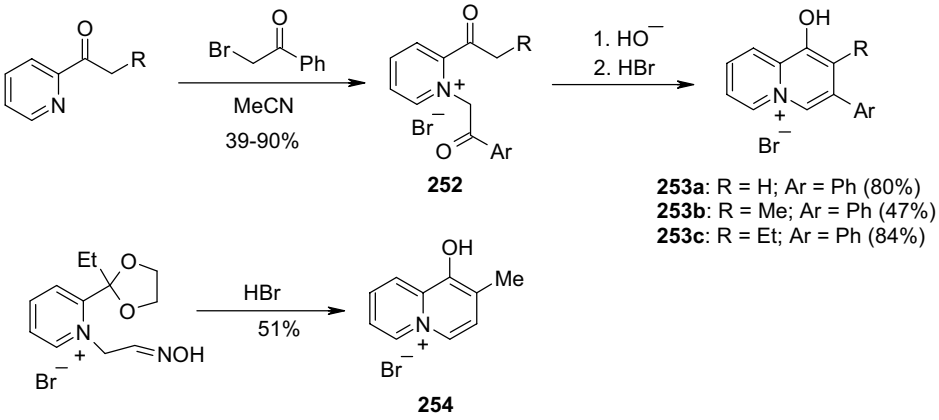
An example involving the formation of a bond δ to the heteroatom represents the most efficient route to prepare 3-hydroxyquinolizinium bromide [181]. This derivative is obtained by reaction of bromoacetone with 2-piconaldehyde acetal followed by acid deprotection and intramolecular condensation to give a 77% overall yield of **251** (Scheme 22.62).



Scheme 22.62

Diketones **252** are obtained by quaternization of 2-acetylpyridines with phenacyl bromides and these are cyclized under basic conditions to the 1-hydroxyquinolizinium hydroxides, which are converted into the salts **253** by treatment with hydrobromic acid. This cyclization involves the formation of a bond γ to the heteroatom and allowed the synthesis of a series of 1-hydroxyquinolizinium bromides with yields ranging from 47% to 84% (Scheme 22.63) [182]. A similar approach starting from an oxime quaternary salt has been used to prepare 1-hydroxy-2-methylquinolizinium salt (**254**) in moderate yield.

Thus far the most general and efficient method for the preparation of the dihydroquinolizinium system by a cyclization strategy is a recently reported procedure based on a ring-closing metathesis (RCM) reaction of 1-butenyl-2-vinylpyrinium salts (**255**) in the presence of a second-generation Grubbs catalyst [183]. In this case the construction of second ring also involves the formation of a δ bond to the nitrogen. These reactions afford various heteroaromatic cations in good overall yield from readily available starting materials (Scheme 22.64). The dihydroquinolizinium salts (**256a–d**) obtained by this method are oxidized to the corresponding quinolizinium salt **16** and quinolizinium derivatives **257b–d** with Pd/C in acetic acid in 67–89%

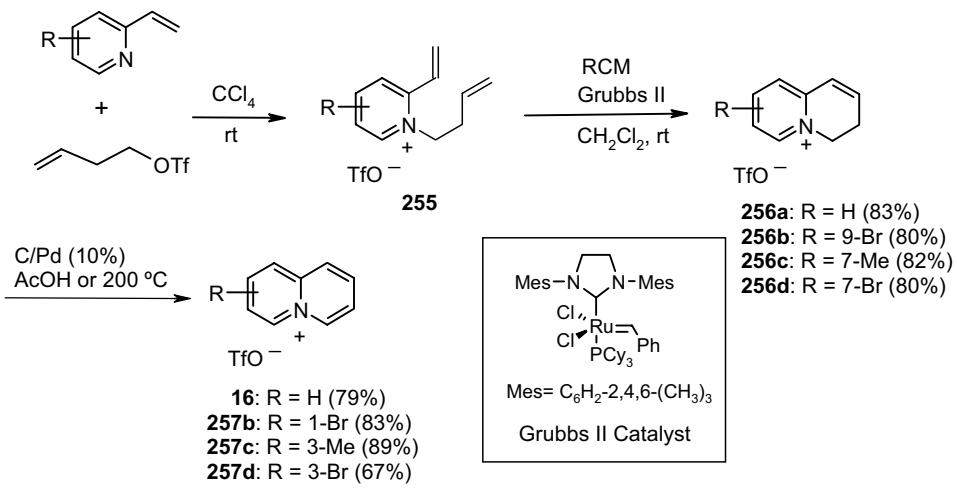


252

253a: R = H; Ar = Ph (80%)
253b: R = Me; Ar = Ph (47%)
253c: R = Et; Ar = Ph (84%)

254

Scheme 22.63



255

256a: R = H (83%)
256b: R = 9-Br (80%)
256c: R = 7-Me (82%)
256d: R = 7-Br (80%)

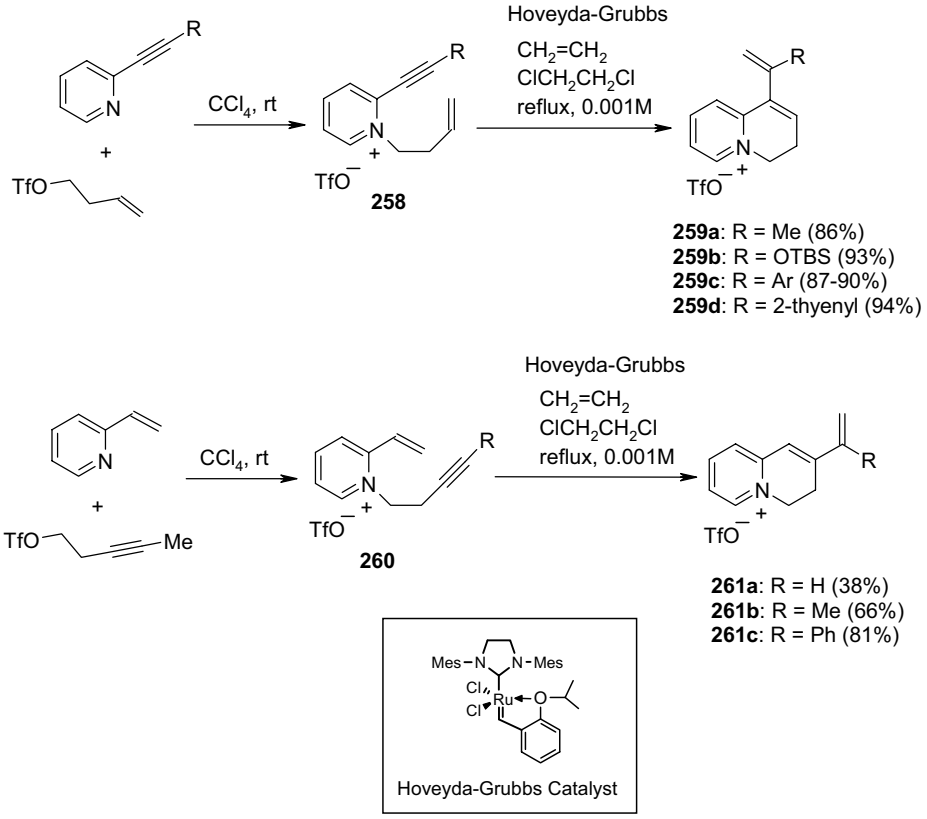
16: R = H (79%)
257b: R = 1-Br (83%)
257c: R = 3-Me (89%)
257d: R = 3-Br (67%)

Scheme 22.64

yield by improving a reported oxidation method [184]. This metathesis reaction leads to various quinolizinium triflates in 10–54% overall yields, thus making this procedure one of the most efficient and general to date to obtain quinolizinium cations.

Pyridinium enynes can also be employed as suitable substrates in this type of metathesis reaction using the Hoveyda–Grubbs catalyst in combination with high dilution and an atmosphere of ethylene to prevent the intermolecular process and/or polymerization of the enyne. Two versions of this enyne RCM reaction allow the synthesis of 1-vinyl- and 2-vinyl-substituted 3,4-dihydroquinolizinium salts in good yields [185]. 1-Vinyl-3,4-dihydro-quinolizinium salts (**259**) were obtained by the RCM of 1-(3-butenyl)-2-ethynylpyridinium salts (**258**) under the optimized conditions

found for this reaction. The substrates **258** for the metathesis reaction are obtained by N-alkylation of 2-ethynylpyridines with 3-butenyl triflate (Scheme 22.65).



Scheme 22.65

2-Vinyl-3,4-dihydroquinolizinium derivatives (**261**) have prepared from 1-(3-butynyl)-2-vinyl-3,4-dihydroquinolizinium substrates (**260**) under the same conditions as used for the synthesis of **259**. In this case the reaction does not seem to be as general because both the enyne and the dihydroquinolizinium derivative are prone to polymerization under the reaction conditions.

Pyridinium substrates bearing substituents in both the ethynyl and ethenyl moieties were also tested but only in one case was the metathesis reaction successful and in this case the 3,4-dihydroquinolizinium compound was obtained in only 19% yield.

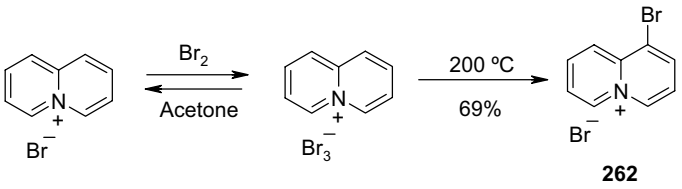
22.4.5 Reactivity of Quinolizinium Salts

The key feature of the quinolizinium ion (**16**) is its aromatic cationic nature along with the partial iminic character of the carbon–nitrogen double bond. For this reason

this heterocycle behaves as an electron-poor aromatic system, lacks reactivity towards typical electrophiles used in electrophilic heterocyclic chemistry, and offers a potential site for the attack of nucleophilic reagents. On the other hand, the high symmetry of the quinolizinium cation only allows the existence of four monosubstituted isomers for any given substituent.

22.4.5.1 Reactions with Electrophilic Reagents

As stated earlier, the most activated positions towards electrophilic substitution in the quinolizinium cation are C3 and C7, but an unequivocal case of electrophilic substitution on the unsubstituted cation has not been reported. Bromine reacts in a reversible process with quinolizinium bromide to form the perbromide salt, which when heated at high temperature (>200 °C) is converted into the 1-bromoquinolizinium bromide (**262**) (Scheme 22.66) [160b, 186]. The high temperature needed for this process is consistent with a radical reaction but an electrophilic mechanism can not be ruled out despite the fact that the C1 position is not the preferred site for the entry of the electrophile.



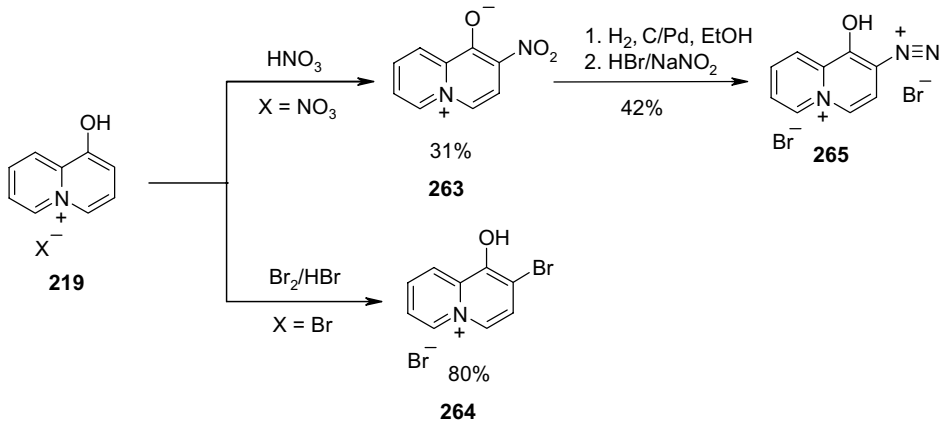
262

Scheme 22.66

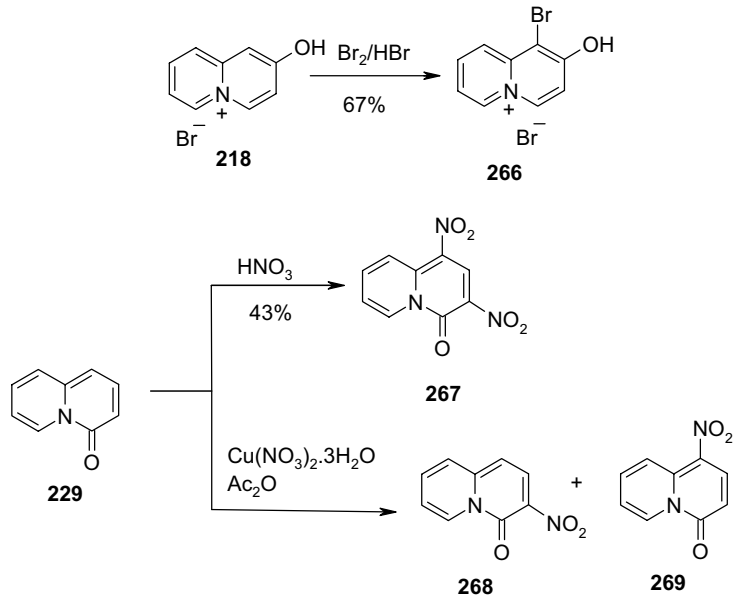
Electrophilic aromatic substitution on the quinolizinium cation requires strongly electron-donating substituents such as hydroxy or amino groups for the success of this reaction [169, 181]. 1-Hydroxyquinolizinium salts (**219**) undergo electrophilic substitution preferentially at the C2 position [187]. Nitration is carried out with nitric acid but this gives a yield of only 31% of the 2-nitrated betaine. In contrast, a much better yield (80%) is obtained with bromonation using bromine and hydrobromic acid (Scheme 22.67).

Under the same conditions of bromination as for **219**, the 2-hydroxyquinolizinium (**218**) gives the 1-bromo derivative **266** in 67% yield. Quinolizin-4-one (**229**) [the most stable tautomeric form of the 4-hydroxyquinolizinium (**228**)] yields the 1,3-dinitro derivative **267** when the nitration is carried out with nitric acid in acetic acid. Mononitration can be achieved using cupric nitrate in acetic anhydride to yield a mixture of the 1- and 3-nitro isomers (Scheme 22.68) [187b].

1-Amino- and 2-aminoquinolizinium salts behave in a similar way to the hydroxy derivatives in promoting electrophilic substitution at the C2 and C1 positions, respectively. In the only reported example of activation by amino groups, substituted 1-amino quinolizinium salts give 2-bromo- or 4-bromo-substituted derivatives **270** and **271** while 8-amino-2,3-dimethylquinolizinium bromide undergoes bromination at the C1 position (Scheme 22.69) [188].



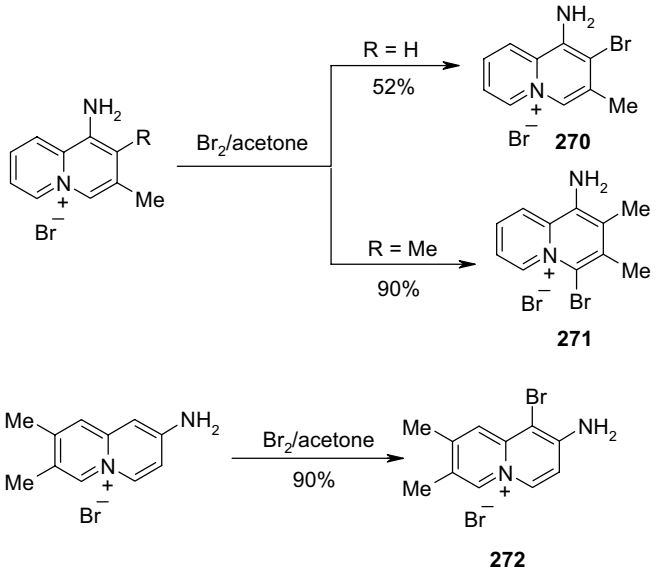
Scheme 22.67



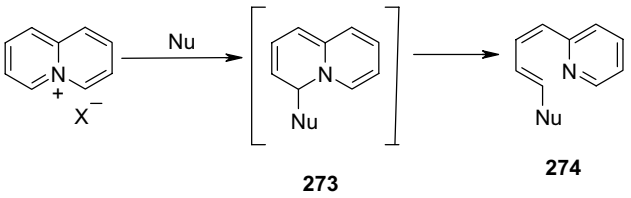
Scheme 22.68

22.4.5.2 **Reactions with Nucleophilic Reagents: Ring-Opening Reactions**

The lability of the quinolizinium cation towards nucleophiles is a key feature of its reactivity, although substitution can modify this reactivity, depending on the nature and position of the substituents. Theoretical calculations predict that the reaction of nucleophiles should take place at C4 although the resulting product (pseudobase) **273** is an intermediate that evolves to the most stable ring-opened compound **274** (Scheme 22.70).

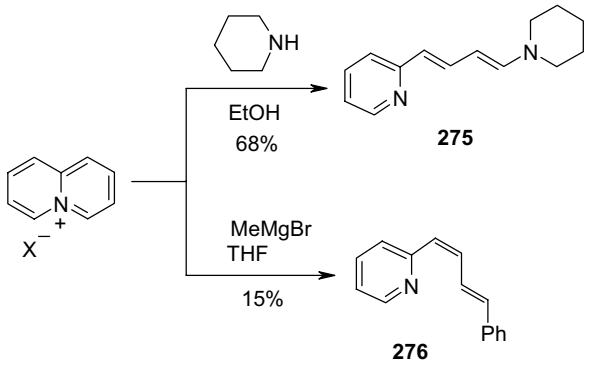


Scheme 22.69



Scheme 22.70

Early in the study of the chemistry of natural alkaloids having a quaternary bridgehead nitrogen it was observed that treatment of tetracyclic coralyne **193** with an alkaline solution gave the corresponding isoquinoline derivative (see Scheme 22.47), which is presumably formed by nucleophilic attack of the hydroxide anion followed by ring opening to form the enol and tautomerization to the most stable ketone [164]. This is the first and only example of the isolation of the carbonyl compound by reaction of the hydroxide ion with a quinolizinium system. Treatment of the parent quinolizinium iodide (**16**) with 10 M NaOH leads to decomposition and both rings lose their aromaticity. When **16** reacts with N-nucleophiles such as aniline a complex mixture of fragmentation products is also formed [189] but good yields of *trans,trans*-1-piperidinyl-4-(2-pyridyl)butadiene (**275**) have been obtained from the reaction of **16** with secondary amines such as piperidine [190]. 1-Methyl-4-(2-pyridyl)-1,3-butadiene (**276**) is also isolated when Grignard reagents are reacted with **16** although in this case the main product is the cis,trans isomer (Scheme 22.71) [191].

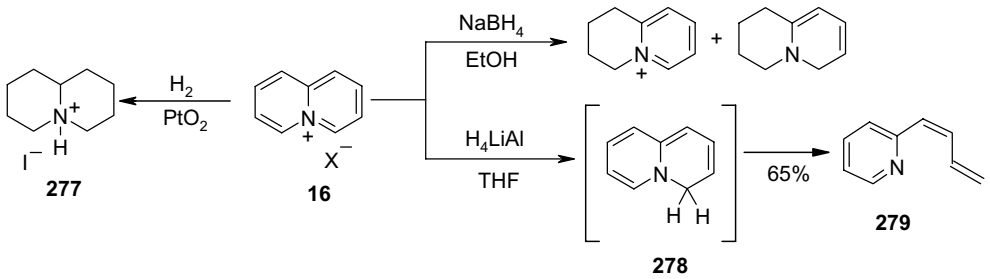


Scheme 22.71

Although the reaction with stabilized carbanions is exemplified with benzoquinolizinium salts, examples with quinolizinium itself have not been reported. Similarly, the reaction with the cyanide anion has not yet been described.

22.4.5.3 **Reactions with Reducing Reagents**

Quinolizinium iodide is fully hydrogenated in the presence of Adams catalyst to give quinozilidine hydroidide (**277**). This reaction with five moles of hydrogen was initially used to prove the structure of the quinolizinium cation [171]. Partial reduction can be accomplished with sodium borohydride in ethanol to give a mixture of the tetrahydro and hexahydro products. However, the attempted reduction with a stronger hydride donor such as lithium aluminum hydride in THF affords 1-(2-pyridyl)-1,3-butadiene (**279**) with *cis* stereochemistry, presumably *via* the 4*H*-quinolizine (**278**) (Scheme 22.72) [192].

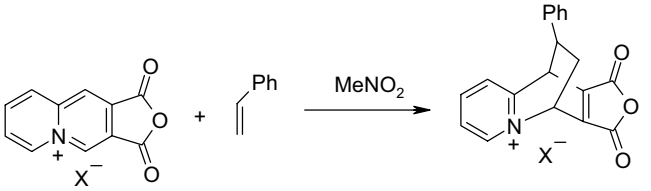


Scheme 22.72

22.4.5.4 **Cycloaddition Reactions**

A common reaction of some benzo[*b*]quinolizinium cations is as dienes in the Diels–Alder cycloaddition. However, neither quinolizinium nor 2,3-dimethylquinolizinium react with typical electron-poor or electron-rich dienophiles such as maleic anhydride or 1,1-diethoxyethylene. The only quinolizinium derivative known to

undergo the Diels–Alder reaction is the anhydride of the quinolizinium 2,3-dicarboxylic acid (**280**), which reacts with styrene to yield the adduct **281** across the C1 and C4 positions (Scheme 22.73) [193].



280 **281**

Scheme 22.73

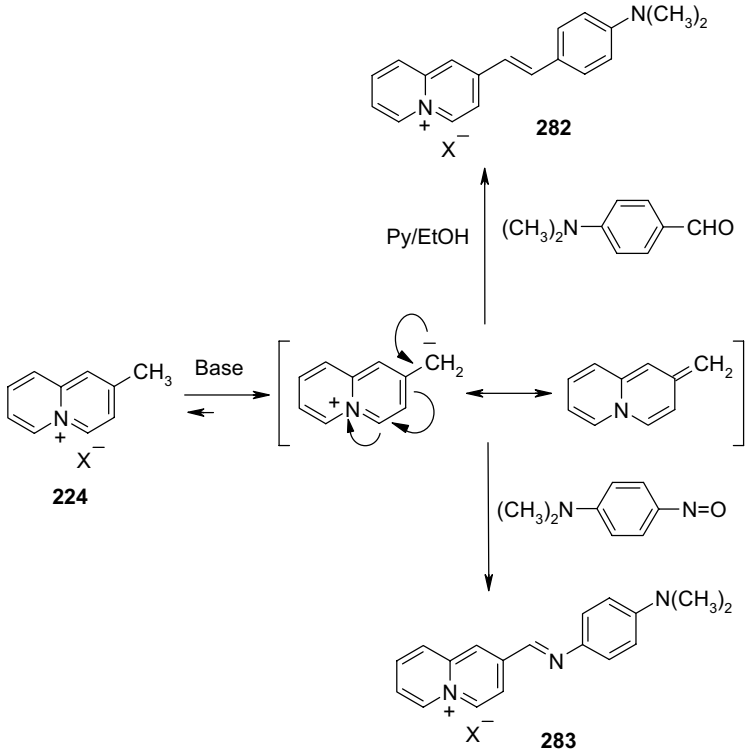
22.4.6 Quinolizinium Derivatives

22.4.6.1 Alkyl Derivatives

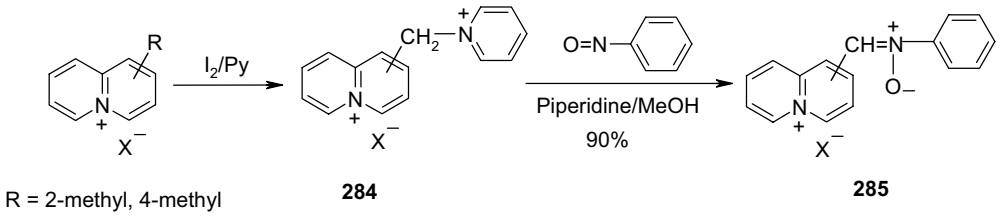
The four most common substituents on the quinolizinium nucleus (methyl, hydroxy, amino, and bromo) usually enhance the reactivity of the substituted quinolizinium cation. Hydrogens of the methyl groups attached to the quinolizinium cation are acidic, particularly those at the C2 and C4 positions. The acidity of the methyl protons can be theoretically estimated on the basis of the resonance stabilization energy. Perturbation theory suggests that this energy is highest for methyl groups in positions C2 and C4. In addition, the values for π energy carbanion formation predict that methyl groups in the α- and γ-positions to the nitrogen are the most reactive in benzoquinolizinium salts. Experimental results are in good agreement with these theoretical expectations [160f,194]. For example, in the presence of a base the methyl groups at C2 are easily deprotonated and the resulting anion behaves as a reactive stabilized carbanion towards different electrophiles such as aldehydes or nitroso compounds to afford styryl and anyl derivatives **282** and **283** in moderate yields (Scheme 22.74) [165b]. The 2,4,6-trimethylquinolizinium salt reacts selectively at the 2-methyl-substituent [165a].

The activation of these methyl groups makes 2-methyl- and 4-methylquinolizinium salts good substrates for the Ortoleva–King reaction, forming dications **284** in the presence of iodine and pyridine. Reaction of these salts with nitrosoarenes produces the expected nitrones **285** (Scheme 22.75) [195].

The electronic effect on these two positions also facilitates the oxidation of alkyl substituents and this can be used to achieve selective oxidation in the presence of other substituents in the C1 and C3 positions. In an example of this behavior the reaction of 1-acetylamino-2,3-dimethylquinolizinium (**286**) with selenium dioxide affords a mixture of the aldehyde **287** and the acid **288** as result of the oxidation of the 2-methyl substituent while the 3-methyl remained unaltered (Scheme 22.76) [196].

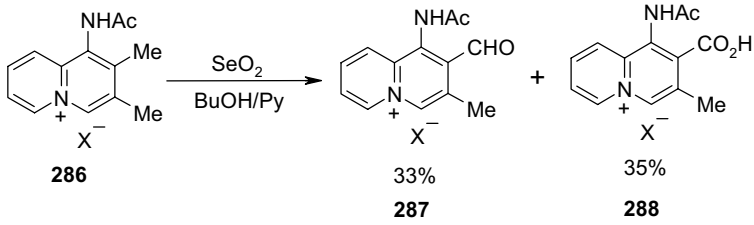


Scheme 22.74



R = 2-methyl, 4-methyl

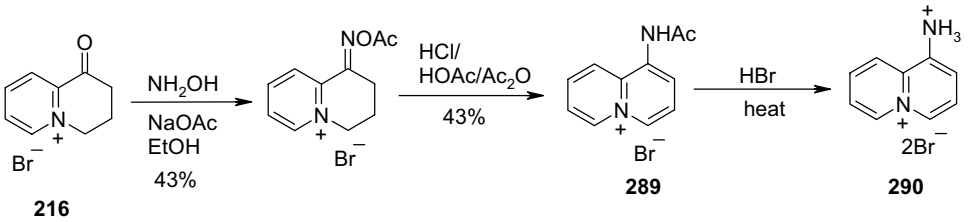
Scheme 22.75



Scheme 22.76

22.4.6.2 Hydroxy and Amino Derivatives

Hydroxy and amino substituents clearly enhance the reactivity of the quinolizinium cation towards electrophiles. In fact, most of the electrophilic substitution reactions on the quinolizinium nucleus are facilitated by the presence of this type of strongly electron-donating substituent. Although substituted 1-, 2-, and 3-aminoquinolizinium derivatives are known, only the parent 1-aminoquinolizinium cation (**290**) has been obtained, from ketone **216** (Scheme 22.77) [197]. Examples of 4-aminoquinolizinium derivatives have not been described.



216 **289** **290**

Scheme 22.77

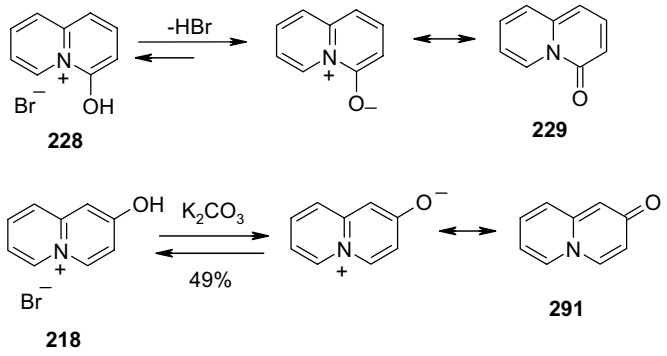
The four isomeric hydroxyquinolizinium derivatives are known and their acidities have been determined by UV spectroscopy and calculated using both a resonance effect and a solvation effect. The calculated pK_a (Table 22.8) largely depend on solvation effects rather than on resonance effects [198] and they are in good agreement with those experimentally determined for hydroxyl groups at the C1 and C3 positions. Calculated values predict that hydroxyl groups in the C1 and C4 positions (δ and α to the nitrogen, respectively) should be more acidic than those in the C2 and C3 positions (γ and β to the nitrogen, respectively) but experimental values show that the most acidic hydroxyls are located at C2 and C4, which is in better agreement with reactivity results.

Notably, all of these hydroxyl derivatives are much more acidic than the corresponding naphthols, and the hydroxyl at C4 is so acidic that this derivative loses HBr very easily to form the uncharged covalent structure 4-quinolizone (**229**). 2-Quinolizone **291** is also obtained from a 2-hydroxyquinolizinium salt in moderate yield by treatment with potassium carbonate (Scheme 22.78).

1-Hydroxy- and 3-hydroxyquinolizinium salts **219** and **251** can also be easily deprotonated to generate the corresponding dipolar structures. In these isomers both the negative and the positive charges can be delocalized within the common π-electron system but, in contrast with the 2- and 4-hydroxyquinolizinium derivatives

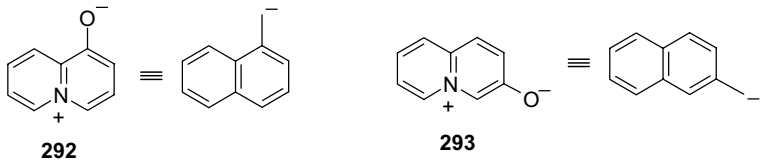
Table 22.8 pK_a values for monohydroxyquinolizinium bromides.

Position	C1	C2	C3	C4
Calculated	4.94	5.76	5.34	3.43
Observed	5.03 ± 0.69	4.14 ± 0.66	5.06 ± 0.47	<2



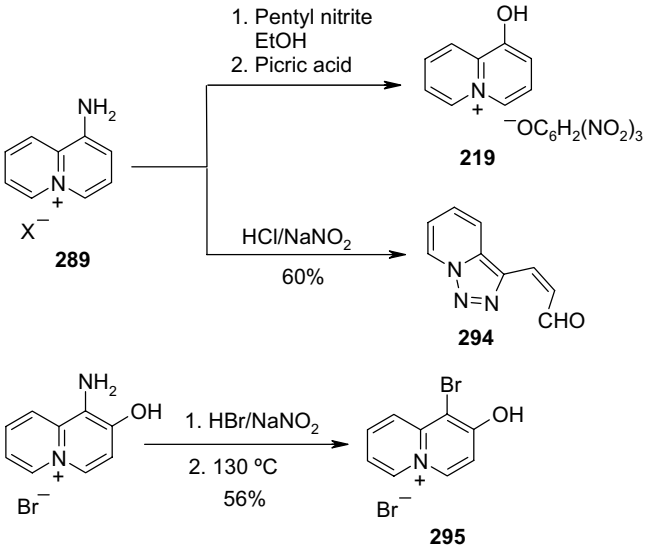
Scheme 22.78

in which at least one uncharged covalent structure can be drawn, **292** and **293** can not be represented by one uncharged covalent structure. As a result, both compounds are classified as conjugated mesomeric betaines that are isoconjugate with the α-naphthylmethyl anion and the β-naphthylmethyl anion, respectively [142].



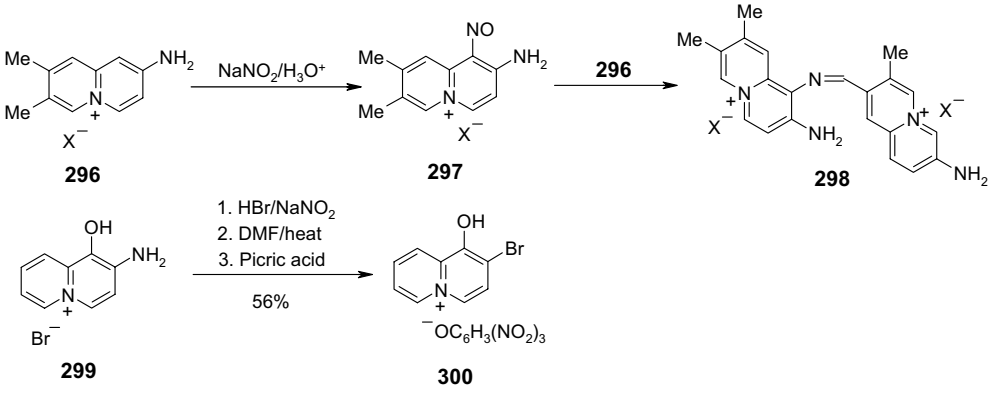
As stated above, electrophilic substitution only occurs in quinolizinium systems bearing electron-donating substituents such as hydroxy and amino groups. Diazotization is a typical reaction of 1-amino- and 3-aminoquinolizinium derivatives and this leads to the hydroxy derivative when carried out with pentyl nitrite in ethanol. However, if diazotization is carried out under classical aqueous conditions (dilute $HCl/NaNO_2$) unexpected compounds can be formed. For example, [1,2,3] triazolo[1,5-*a*]pyridylacrolein (**294**) is isolated as the main reaction product from the diazotization of 1-aminoquinolizinium [199]. It was proposed that the formation of this product involves a ring-opening reaction by attack of water on the C4 position followed by cyclization of the resulting intermediate. This ring-opening reaction is not a general process in the diazotization of all 1-aminoquinolizinium systems in aqueous solution. As an example, 1-amino-2-hydroxyquinolizinium bromide is diazotized ($HBr/NaNO_2$) and affords the diazonium bromide, which decomposes on heating to yield 1-bromo-2-hydroxyquinolizinium bromide (**295**) (Scheme 22.79) [200].

In contrast, the amino groups attached at the C2 and C4 positions are weakly basic due to the delocalization of the nitrogen electrons across the heterocyclic cationic system. As a consequence of this low basicity the attempted diazotization of 2-amino-7,8-dimethylquinolizinium (**296**) with $HCl/NaNO_2$ failed and nitrozation at the C1 position to form **297** was followed by condensation of the nitroso group with the methyl group at C7 of **296**, a process that explains the isolation of **298** as the main



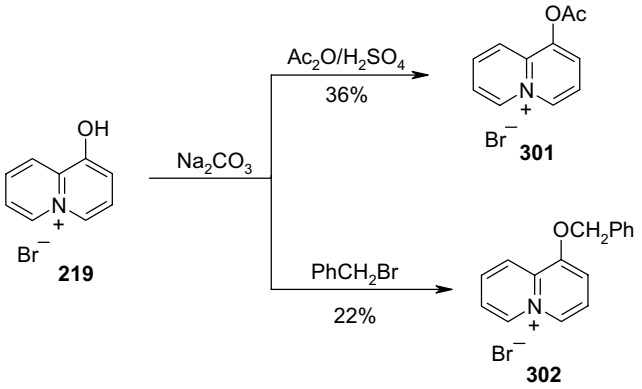
Scheme 22.79

reaction product (Scheme 22.80). An increase in the basicity of the C2 amino group by the presence of other strong electron-donating substituents in the quinolizinium ring can promote the normal diazotization reaction, for example, in the transformation of 2-amino-1-hydroxyquinolizinium bromide (**299**) into the 2-bromo-1-hydroxyquinolizinium picrate (**300**) (Scheme 22.80) [188].



Scheme 22.80

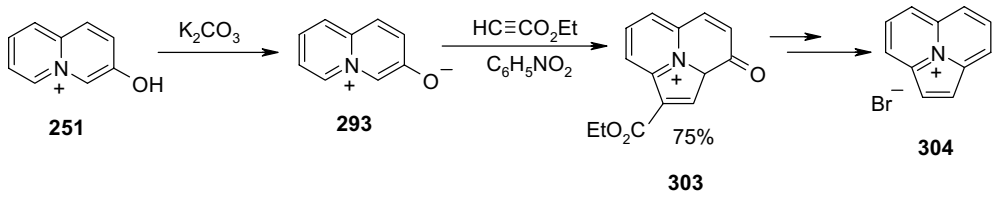
Phenolic-type reactions are produced on 1-hydroxy- and 3-hydroxyquinolizinium salts [169a]. Thus, **219** can be acetylated and alkylated under conventional conditions to yield the corresponding quinolizinium derivatives **301** and **302**, albeit in low yields (Scheme 22.81). An example of a quinone within the quinolizinium system by



Scheme 22.81

oxidation of 1- or 4-hydroxy derivatives has yet to be described, although some examples involving the benzo[*b*]quinolizinium system have been reported [201].

The betainic compound **293** is obtained from 3-hydroxyquinolizinium **251** and reacts with ethyl propiolate in boiling nitrobenzene in a 1,3-cycloaddition reaction to give the tricyclic cycloadduct **303**. This compound has been transformed in a four-step sequence into the azonia derivative of acenaphthylene **304** (Scheme 22.82) [202].

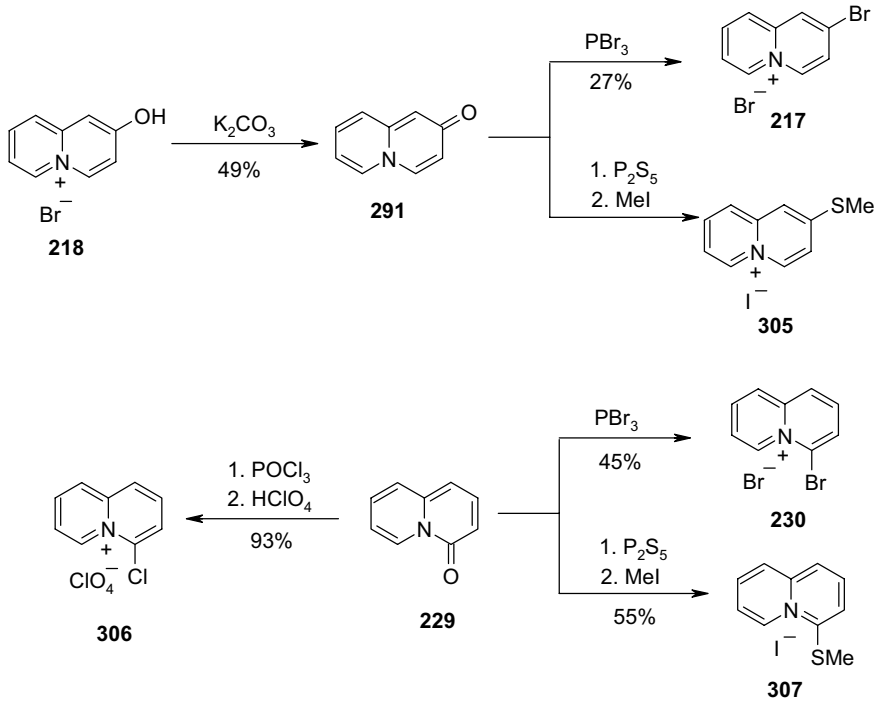


Scheme 22.82

Quinolizin-2-one (**291**) and quinolizin-4-one (**229**) are useful intermediates in the synthesis of some quinolizinium derivatives [169b, 203], as shown in Schemes 22.49, 22.52, and 22.83.

22.4.6.3 Halo Derivatives

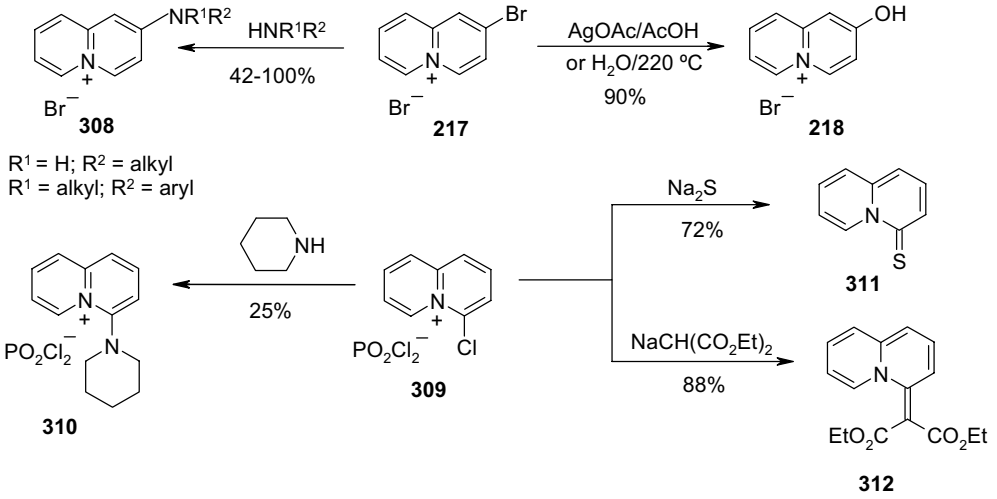
Quinolizinium systems bearing halogens (Br, Cl) in all four possible positions [160b] are prone to react with nucleophiles at the position to which the halogen is attached. However, the reactivity of such compounds has not been studied systematically. Nucleophilic substitutions are common reactions on these types of quinolizinium derivatives. One of the most extensive applications of haloquinoliziniums has been their conversion into aminoquinolizinium salts **308** by reaction with primary or secondary amines [145]. Silver acetate or hot water has been used to obtain the



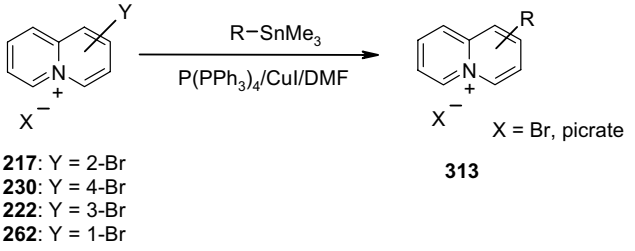
Scheme 22.83

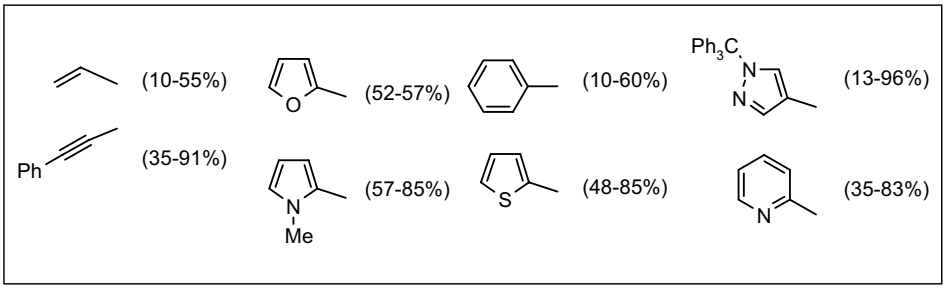
hydroxy analogues [169b]. The 4-chloroquinolizinium **309** also reacts with secondary amines such as piperidine, to give **310**, although less satisfactory results were obtained. Other nucleophiles that have been employed include sodium sulfide and the sodium salt of diethyl malonate, with quinolizine-4-thione **311** and diethylquinolizin-4-ylidene malonate **312** obtained, respectively, in good yields (Scheme 22.84) [204]. Dehalogenations by hydrogenolysis have been achieved with Pd/H_2 but this does not appear to be an efficient process [200].

One of the most recently described applications of bromoquinolizinium derivatives is their use as electrophilic partners in palladium-catalyzed cross-coupling reactions. It has been demonstrated that the four isomers of bromoquinolizinium bromide can be involved in the catalytic cycle of the well-known palladium-promoted C–C bond forming Stille and Suzuki reactions. This palladium methodology provides an easy and efficient procedure for the functionalization of quinolizinium cations [205], which is otherwise very difficult or impossible by classical methods in heterocyclic chemistry. The coupling process of the four bromoquinolizinium salts has been tested with tributylvinyl-, alkenyl-, alkynyl-, phenyl-, and heteroaryl-stannanes and boronic acids. In a comparative study, the Stille reaction proved to be more general than the Suzuki reaction and also gave better yields of derivatives **313** in those cases in which both reactions were used to afford the same coupling products (Scheme 22.85) [206].



Scheme 22.84



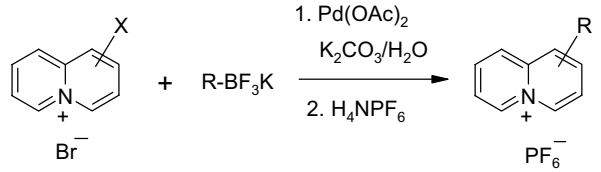


Scheme 22.85

In relation to the reactivity of the different bromo-derivatives and the yields of the coupling products, a correlation was established between the halogenated position of quinolizinium and the efficiency of the Stille process. Thus, with deactivated positions C1 and C3, the transfer of groups with different electrodonicity did not have a large effect on the yield. However, for 2-bromoquinolizinium there was a

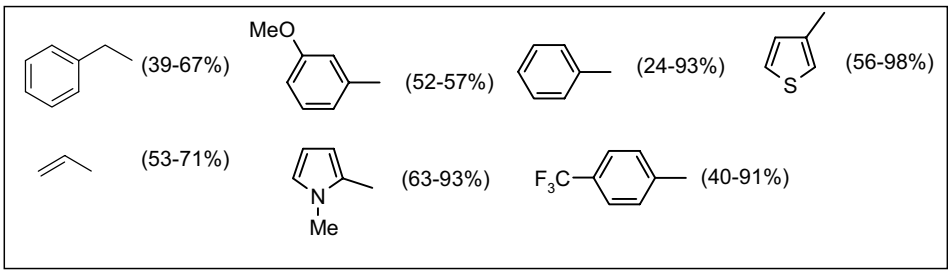
correlation between the electronic effect on the transfer ligands on tin and the electron-deficient position at C2, although this behavior is surprising with electron-deficient stannanes such as 2-tributylstannyl-pyridine in the deficient position at C4. The above methodology, however, failed to transfer alkyl groups on using trialkylbutylstanannes.

More recently it has been demonstrated that organotrifluoroborates can be used as efficient partners for the Suzuki coupling reaction with the four isomeric bromo quinolizinium bromides [207]. This cross-coupling reaction allows the synthesis of new quinolizinium derivatives **313** that were not achieved by the Stille reaction or clearly improves the yields of those previously obtained by this reaction. Moreover, the ease with which these potassium organotrifluoroborates reacted with quinolizinium salts in water (greener procedure) and the fact that the coupling products can be isolated are further advantages of this procedure (Scheme 22.86).



217: X = 2-Br
230: X = 4-Br
222: X = 3-Br
262: X = 1-Br

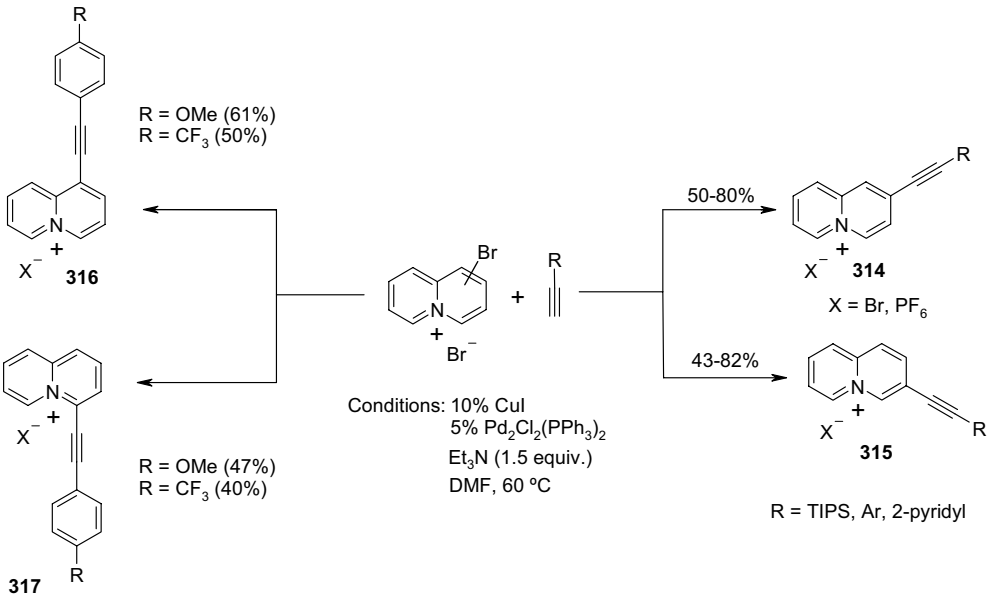
313



Scheme 22.86

The four isomeric bromoquinolizinium bromides also react with various aryl- and heteroarylacetylenes under Sonogashira conditions [208]. The reactions proceed with moderate-to-high yields, particularly at the C2 and C3 positions, to afford aryl- and heteroarylethynyl quinolizinium cations **314** and **315**. The coupling reactions at the C1 and C4 positions give lower yields of **316** and **317** because of the lower stability of these substrates under the reaction conditions (ring-opening products are observed in the reactions of 1-bromo- and 4-bromoquinolizinium salts) (Scheme 22.87).

Another interesting aspect of the bromoquinolizinium salts is their ability to participate in palladium-promoted homocoupling processes to give biquinolizinium dications. The homocoupling reaction was achieved by forming *in situ* the trialk-

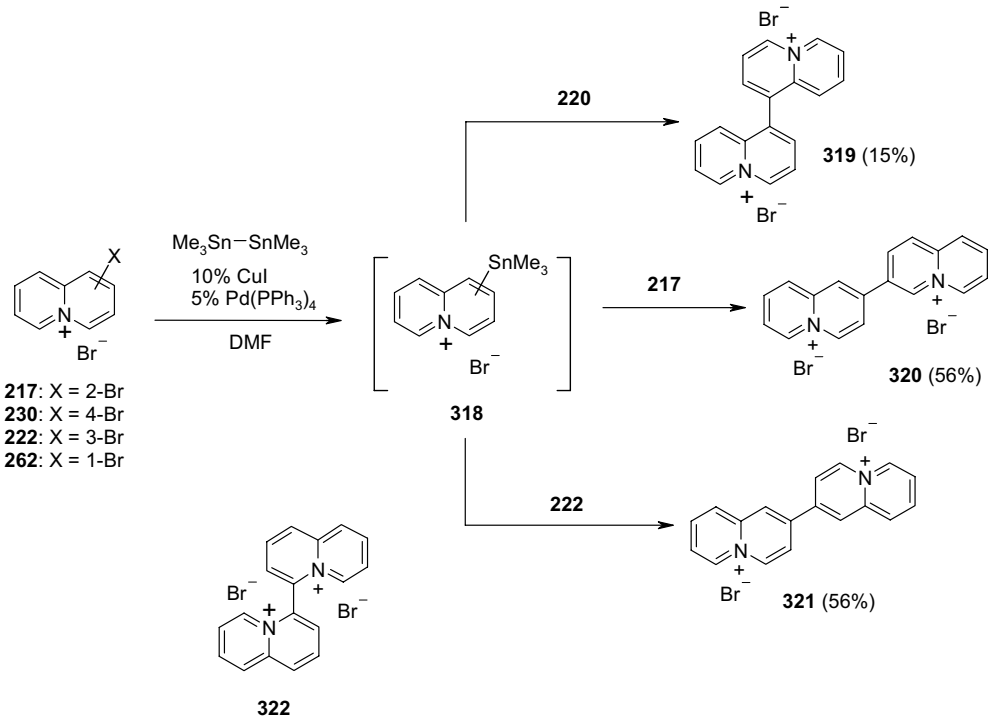


Scheme 22.87

ylquinolizinium stannane **318** from bromoquinolizinium and slow addition of one further equivalent of the bromoquinolizinium. The 1,1′-, 2,2′-, and 3,3′-biquinolizinium cations (**319**–**321**) were formed in low or moderate yields but the reaction failed to give the 4,4′-biquinolizinium (**322**) [209]. The homocoupling from 2-bromo- and 3-bromoquinolizinium, which have different electronic character, gave the same yields; by contrast, the low yield of 1,1′-biquinolizinium, the formation of which involves a position that is electronically similar to C3, is explained by the steric hindrance around the coupling positions. Steric considerations along with a strong charge repulsion are the likely reasons for the failure of the homocoupling of 4-bromoquinolizinium. Theoretical calculations predict a rotational energy barrier of 44 kcal mol^{-1} for the 1,1-carbon bond and as a consequence **319** can adopt two non-convertible conformations at room temperature (atropoisomers) (Scheme 22.88).

22.4.7
Benzoquinolizinium Salts and Related Systems

In a simple way quinolizinium and related cations can be envisaged as polycyclic aromatic hydrocarbons in which the bridgehead carbon (or one of the bridgehead carbons) is replaced by an azonia nitrogen. When the quaternary nitrogen replaces C4a in naphthalene, the resulting heterocycle is quinolizinium. Similarly, replacements in anthracene and phenanthrene lead to benzo[*b*]-, benzo[*a*]-, and benzo[*c*] quinolizinium salts (**25**–**27**) (Figure 22.1d). A total of 18 heteroaromatic cations can be envisaged from the six possible tetracyclic aromatic hydrocarbons and the number

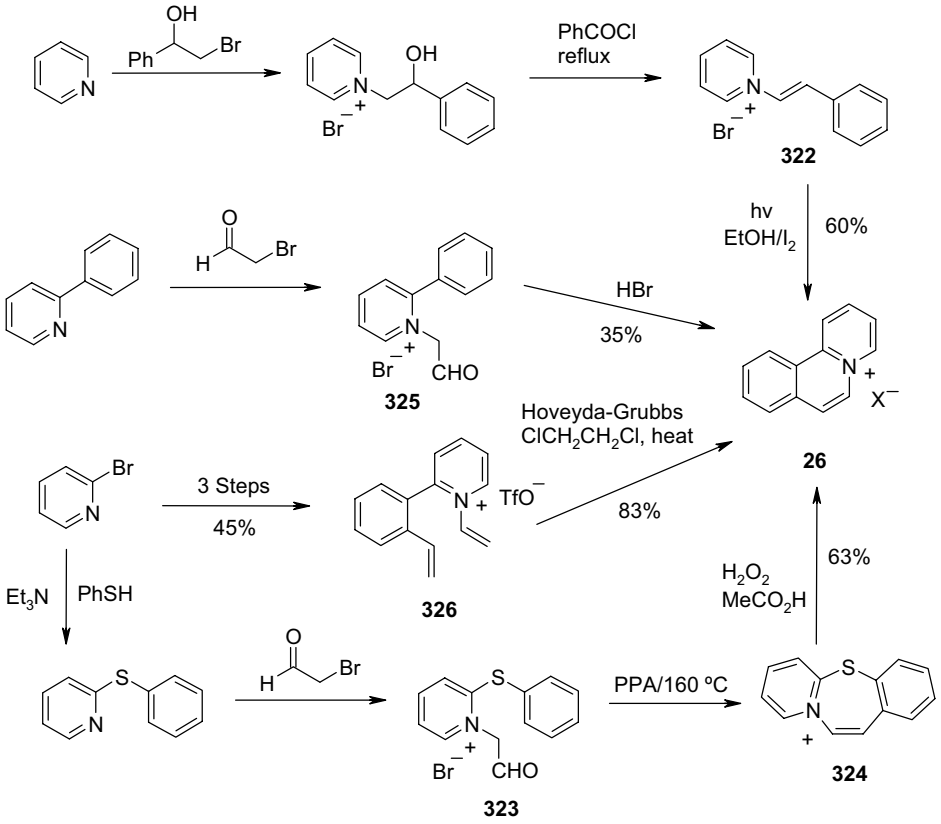


217: X = 2-Br
230: X = 4-Br
222: X = 3-Br
262: X = 1-Br

Scheme 22.88

of azonia cations increases to 83 when the 15 possible pentacyclic hydrocarbons are considered, although only 17 of these pentacyclic cations have been synthesized to date.

Most of the synthetic strategies developed for **16** can be applied to the synthesis of the three benzoquinolizinium cations, their derivatives, and other polycyclic systems containing a bridgehead quaternary nitrogen. However, in some cases these systems have been obtained by procedures specifically developed to build up the tricyclic system. This is the case for the benzo[*a*]quinolizinium cation (**26**) prepared by four different routes based on a cyclization reaction as the key step. In one of these routes **26** is obtained by photocyclization of a styrylpyridinium salt (**322**) in the presence of iodine. It is assumed that under UV irradiation the *trans*-styryl salt is isomerized to the cis configuration, which is the appropriate isomer to produce the cyclization followed by loss of hydrogen [210]. The salt **323**, prepared from 2-phenylthiopyridine and the oxime of bromoacetaldehyde, is cyclized to the thiazepinium salt **324** with PPA or boiling hydrobromic acid (Scheme 22.89). The salt **324**, upon exposure to hydrogen peroxide in acetic acid, is oxidized to the corresponding sulfoxide and this led to ring contraction through loss of sulfur with the formation of **26** [211]. The cyclodehydration method to produce **26** requires quaternization of 2-phenylpyridine with bromoacetaldehyde and acid treatment of the resulting pyridinium salt **325** [130]. The most recent synthetic route – the ring-closing metathesis

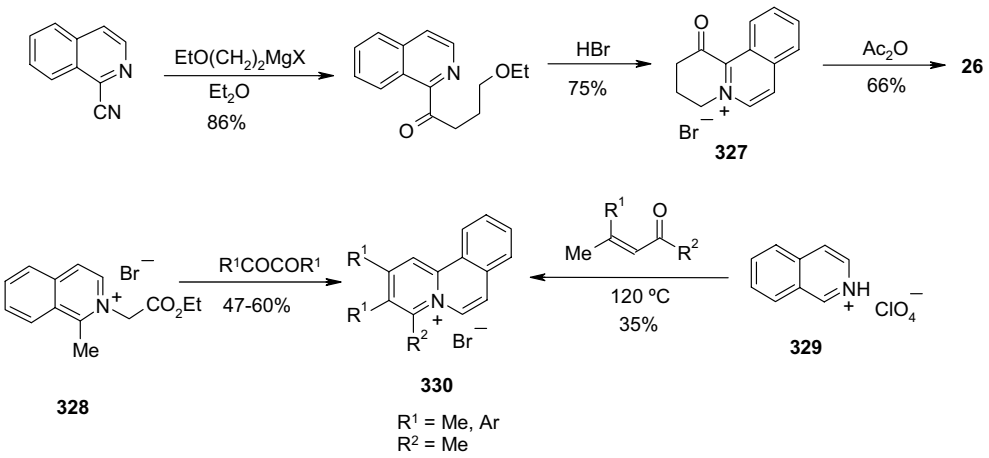


Scheme 22.89

reaction of the pyridinium salt **204** – also allowed the formation of **26** in good yield [212]. These procedures have also been used for the preparation of a large number of derivatives.

There are three other methods for the preparation of benzo[*a*]quinolizinium systems using isoquinoline derivatives as starting materials. Of the three only one of them enabled the isolation of the parent compound **26** while the two other are useful for the synthesis of derivatives. The same strategy used for the synthesis of the ketone **216** (Scheme 22.49) when applied to 1-cyanoisoquinoline, afforded the tricyclic ketone **327**, which under the aromatization conditions gave **26** in 66% yield (Scheme 22.90) [168]. The Westphal reaction between 1,2-diketones and the appropriate isoquinolinium salts **328** yields 9,10-disubstituted derivatives **330** [213] while the 8,10-dimethyl derivative is also obtained by reaction between isoquinoline perchlorate (**329**) and mesityl oxide [214].

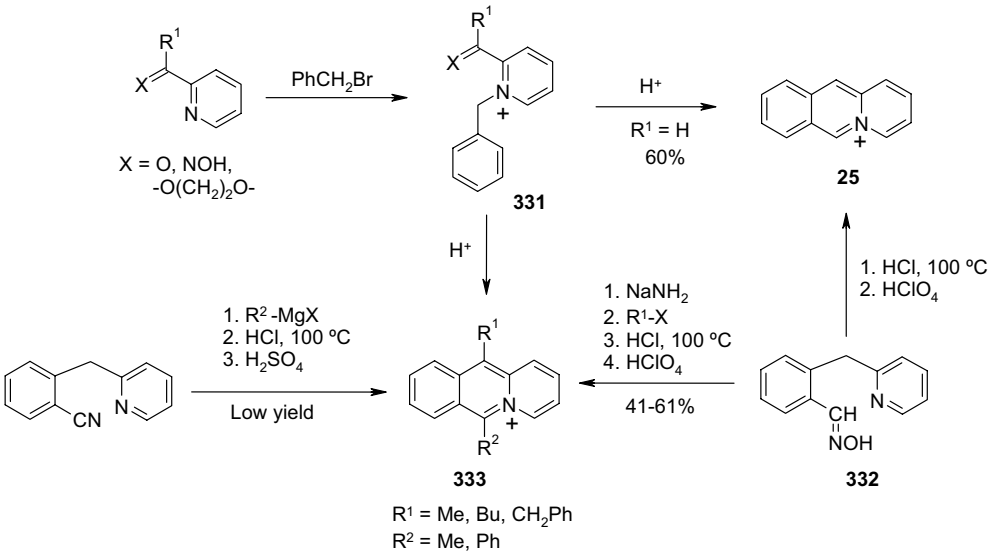
The benzo[*b*]quinolizinium salt **25** is obtained by different classical synthetic methods based on the cyclodehydration of the appropriate 1-benzylpyridinium salt under acidic conditions. The first synthesis of this system gave a 60% yield by reaction of 2-pyridinecarboxaldehyde with benzyl bromide in the presence of hydrobromic



Scheme 22.90

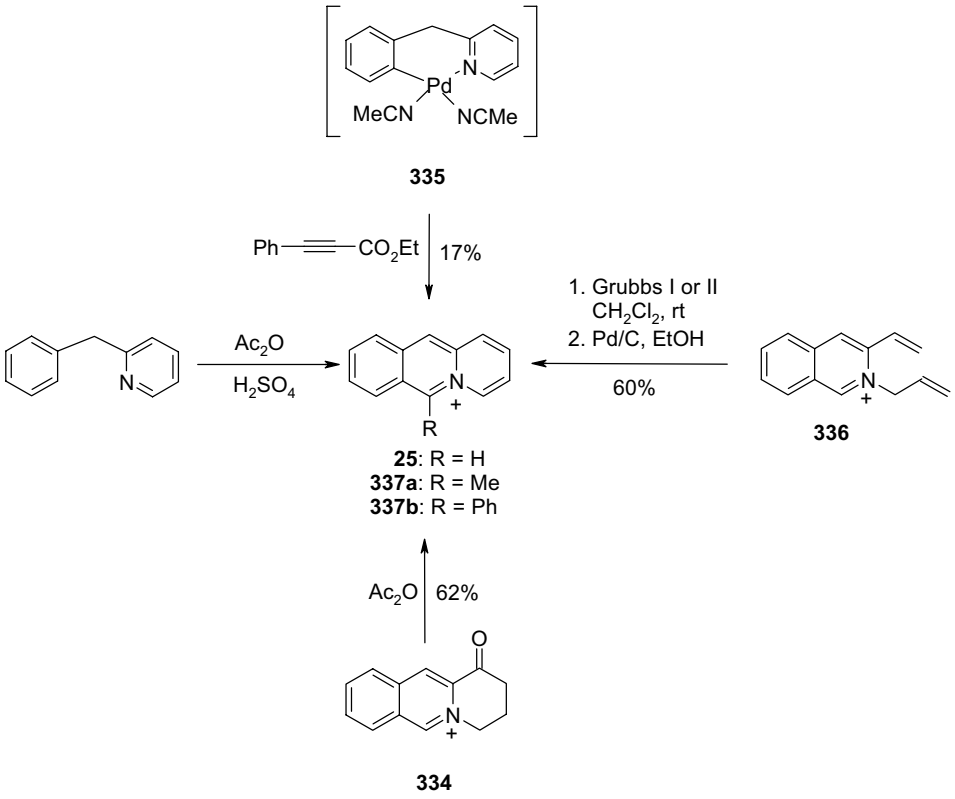
acid (48%) [215]. Modification of this procedure using oximes and acetals instead of the aldehyde allowed the synthesis of benzo[*b*]quinolizinium derivatives (**333**) using different acidic media (PPA, HCl, HF, H_2SO_4) [216]. Alternative methods that produce **25** and alkyl- and phenyl-derivatives **333** in poor yields involve cyclization of 2-(2-picolyl)benzonitrile and 2-(2-picolyl)benzaldoxime (Scheme 22.91) [217].

Treatment of the ketone **334**, obtained in a similar way to **327**, with boiling acetic anhydride also furnished **25** in 62% yield [168] while cyclization of 2-benzylpyridine with acetic acid/sulfuric acid is also a convenient procedure for the preparation of the



Scheme 22.91

6-methyl derivative **337a** (Scheme 22.92) [218]. Two more recent methods have also allowed the synthesis of the 6-phenyl-derivative **337b** and the parent **25** using different strategies. In the first case the use of an organopalladium compound (**335**) that can react with 3-phenylpropiolate afforded the 6-phenylbenzo[*b*]quinolizinium salt, albeit in low yield (17%) [219]. In the last approach to **25** the metathesis reaction developed for the synthesis of the quinolizinium system shown in Scheme 22.64 has been adapted to the preparation of **25** from isoquinolinium substrate **336**. This approach gave good yields under the same conditions employed for the synthesis of **16** [183].

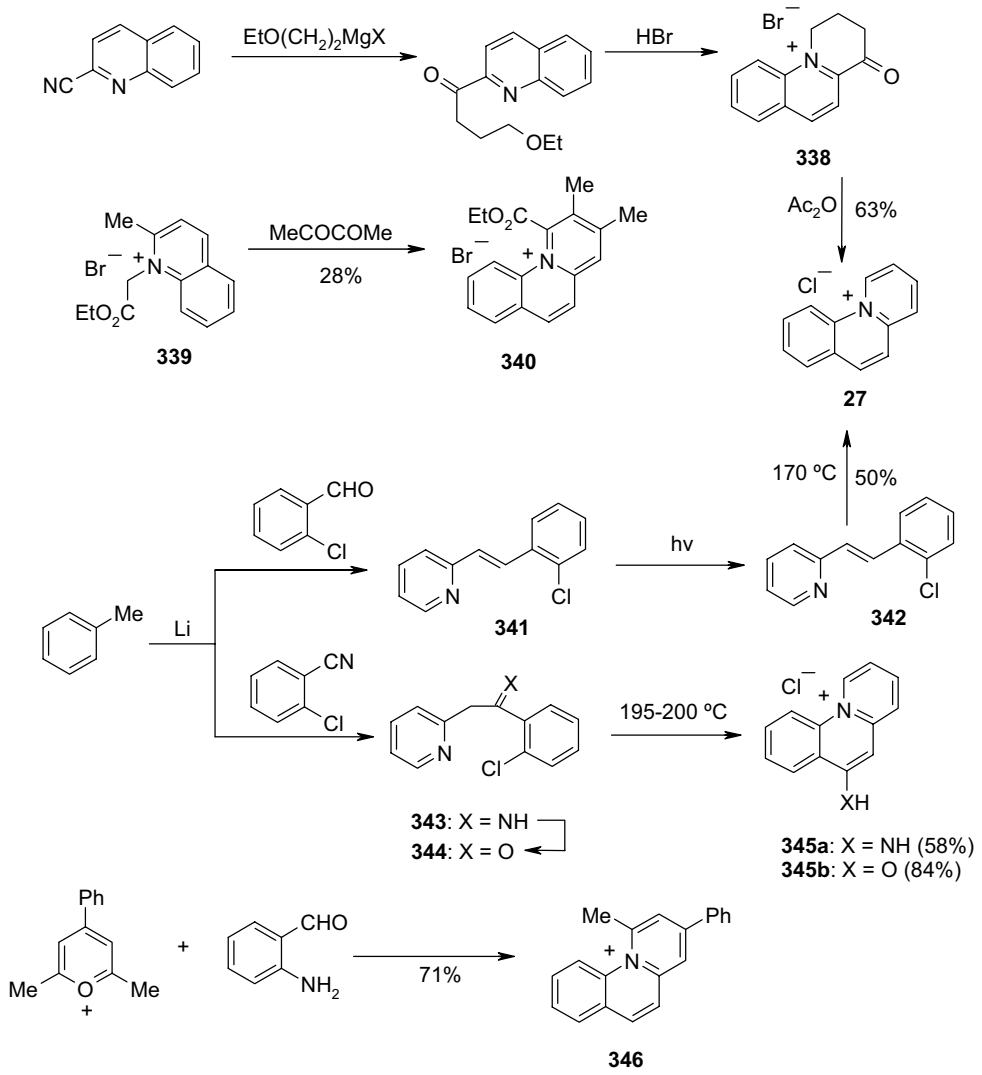


Scheme 22.92

The benzo[*c*]quinolizinium system **27** has been prepared by five different methods and these resemble those employed for the other two benzoquinolizinium cations. Quinoline derivatives are used as starting materials in the synthesis of the precursor ketone **338** [168] and in the Westphal substrate **339** [174]. From methylpyridine two similar approaches have been developed to construct the cationic tricycle by reaction with 2-chlorobenzaldehyde and 2-chlorobenzonitrile. In the first case the reaction product, the *trans*-chlorostilbazole **341**, is isomerized under UV irradiation to the cis

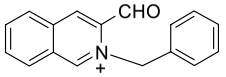
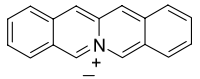
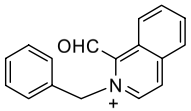
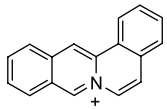
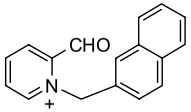
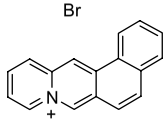
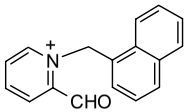
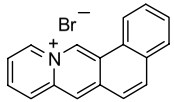
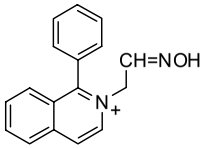
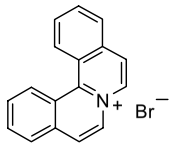
isomer **342**, which cyclizes to **27** on heating [220]. In a closely related cyclization the imine **343** or the ketone **344** (obtained by hydrolysis of **343**) are cyclized by heating to form the corresponding 6-amino- and 6-hydroxybenzo[*c*]quinolizinium chlorides **345a**,**b** [221]. Finally, 1,3-disubstituted derivatives **346** have been synthesized by the reaction of pyrilium salts and 2-aminobenzaldehyde (Scheme 22.93) [222].

Most of the synthetic methods developed for systems **25–27** have been slightly modified for the preparation of currently known polycyclic cations. Table 22.9 gives some representative examples of the synthesis of parent tetracyclic and pentacyclic cations.

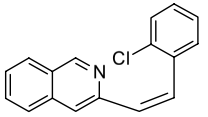
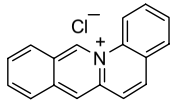
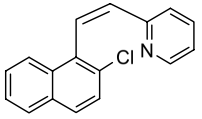
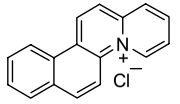
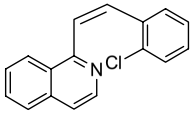
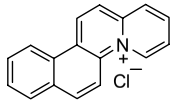
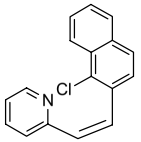
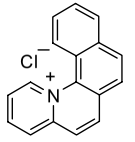


Scheme 22.93

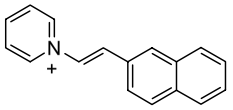
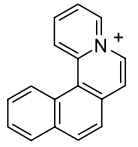
Table 22.9 Representative examples of the synthesis of parent tetracyclic and pentacyclic cations.

Precursor	Conditions	Polycyclic cation	Yield (%)	Reference
Cyclodehydration of azinium salts				
	HBr	 **29**	23	[223]
	HBr	 **31**	52	[224]
	HBr	 **35**	72	[225]
	HBr	 **36**	52	[223]
	HBr	 **40**	74	[226]

Thermal cyclization of arylvinyl azines

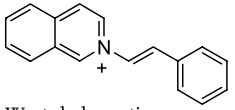
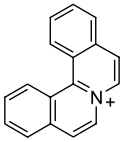
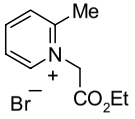
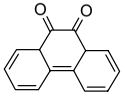
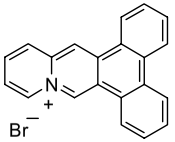
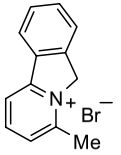
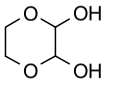
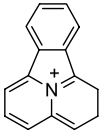
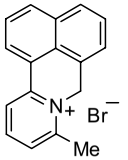
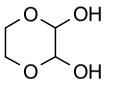
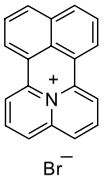
	180 °C	 **34**	[227]
	180 °C	 **38**	75 [227]
	200 °C	 **38**	70 [227]
	180 °C	 **42**	50 [227]

Photocyclization of arylvinyl azinium salts

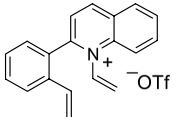
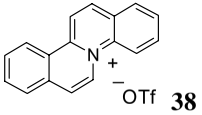
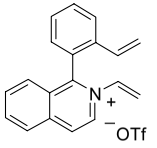
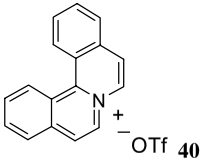
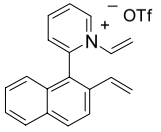
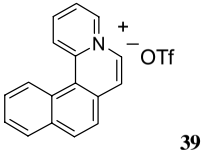
	*hν*	 **39**	45 [228]

(*Continued*)

Table 22.9 (*Continued*)

Precursor	Conditions	Polycyclic cation	Yield (%)	Reference
 Westphal reaction	*hν*	 **40**	24	[228]
	 NaOAc/acetone		75	[174, 213, 229]
	 EtOH/Et_3N		33	[230]
	 EtOH/Et_3N		55	[231]

Ring-closing metathesis (RCM)

	Hoveyda–Grubbs catalyst (5 mol.%), $ClCH_2CH_2Cl$, 83 °C	 **38**	82	[212]
	Hoveyda–Grubbs catalyst (5 mmol.%), $Cl_2CHCHCl_2$, 130 °C.	 **40**	53	[212]
	Hoveyda–Grubbs catalyst (10 mol.%), $ClCH_2CH_2Cl$, 83 °C.	 **39**	68	[212]

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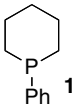
23
Phosphorus Heterocycles

François Mathey

23.1
Introduction

The official start of phosphorus–carbon heterocyclic chemistry took place in 1915 with the description of 1-phenylphosphinane (**1**) [1], but the actual development of the field began only in the 1970s. As with nitrogen, oxygen, and sulfur, the two most significant heterocycles in this category are the fully unsaturated five- and six-membered species, that is, phospholes and phosphinines. The other P-C heterocycles are briefly considered in Section 23.4.



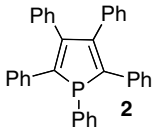
1

23.2
Phospholes

23.2.1
History and Nomenclature

The story of phospholes started in 1959 with the discovery of the pentaphenyl derivative **2** [2]. The unstable parent system was characterized by NMR spectroscopy at low temperature in 1987 [3]. As initially shown by Quin and coworkers [4], phospholes are pyramidal at P. The reason lies in the intrinsically high inversion barrier of trivalent phosphorus, which overcomes the aromatic stabilization of the planar state. As a result, phospholes are poorly aromatic and their chemistry is widely different from that of pyrroles. Several reviews describing phosphole chemistry are available [5].

Modern Heterocyclic Chemistry, First Edition.
Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.



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Three isomers of the phosphole system are known, namely, the 1*H*-, 2*H*-, and 3*H*-phospholes (A, B, C, Figure 23.1) but, in practice, the 2*H* and 3*H* systems incorporating dicoordinate P-centers are unstable except when fully substituted by bulky groups and mainly intervene in the chemistry of phospholes as reactive intermediates. Conversely, the phospholide ion (D), isoelectronic with thiophene, is highly stable and aromatic.

23.2.2
Spectral, Structural and Theoretical Studies

Phospholes have been characterized mainly by ^{1}H, ^{13}C, ^{31}P NMR spectroscopy and X-ray crystal structure analysis and thoroughly studied from a theoretical standpoint. Broadly speaking, the NMR spectra of phospholes do not show any exceptional features, for example, $\delta\ ^{31}P$ (1-methylphosphole) $= -8.7$ ppm [6] (85% H_3PO_4 as external reference, δ positive for downfield shifts). Extensive tabulation of data is available from the reviews of Quin [5]. The data for the simplest species are quoted in Reference [3]. In contrast, whereas phosphide ions resonate around 0 ppm (Ph_2P^- $\delta - 19$ ppm in THF with Na^+ as the counterion [7]), the parent phospholide (Li^+) resonates at $+77.2$ ppm in THF [3], and resonances at much lower fields can be observed according to the substitution scheme (e.g., with 2,5-dibenzoyl-3,4-dimethyl, δ $+209.6$ ppm [8]). This deshielding has been explained by the presence of the in-plane P-lone pair, which is only weakly coupled to the ring and induces a large downfield paramagnetic shift of the ^{31}P resonance [9].

X-Ray structural studies of phospholes show a somewhat flattened P-pyramid and some shortening of the P−C ring bonds. The alternation between single and double CC ring bonds is higher than in the corresponding pyrroles, thiophenes and furans. The structure of 1-benzyphosphole is given as an example [4]: ring P−C, 1.783 Å; C=C, 1.343 Å; C−C, 1.438 Å; internal <C−P−C, 90.7°; $\Sigma <$ C−P−C, 302.7°. These data reflect the low aromaticity of the phosphole ring. Sizeable variations have been observed in the pyramidality of the phosphole phosphorus. Presently, the most pyramidal structure has been recorded for 1-cyano-3,4-dimethylphosphole: $\Sigma <$ C−P−C $= 290.3°$ [10], and the flattest for 1-(2,4,6-tri-*t*-butylphenyl)-3-methylphosphole: $\Sigma <$ C−P−C $= 331.7°$ [11]. As a general trend, the cyclic delocalization increases when the pyramidality decreases but other factors also play a role, as

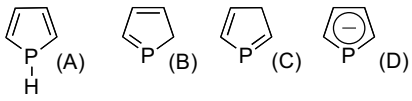


Figure 23.1 The three isomers of the phosphole system (A–C) and the phospholide ion (D).

shown with 1-alcoxyphospholes, which are relatively flat with a negligible delocalization [12]. Contrary to phospholes, the structure of phospholide ions reflects their high aromaticity. For example, the planar 2,3,4,5-tetramethylphospholide with Li(TMEDA)$^+$ as the counterion displays the following parameters [13]: P–C, 1.715 Å; C=C, 1.396 Å; C−C, 1.424 Å; <C−P−C, 90.5°.

Theoretical studies have mainly dealt with two problems, the aromaticity of the ring and the equilibrium between 1*H*-, 2*H*-, and 3*H*-phospholes. It is now well established that the phosphole ring is poorly aromatic, the most recent estimate of its aromatic stabilization energy being 3.2 kcal mol^{-1} for the parent ring [14]. Conversely, the planar transition state is even more aromatic than pyrrole [15]. As a result, the pyramidal inversion barrier of phospholes is quite low, ca. 16–17 kcal mol^{-1}, confirming early NMR measurements [16]. As expected, the aromaticity of the phospholide ion is of the same order of magnitude as that of the cyclopentadienide ion [15]. A recent study has shown that 2*H*-phosphole is more stable than 1*H*-phosphole by 6.0 and 3*H*-phosphole by 3.3 kcal mol^{-1}, thus confirming earlier calculations [17, 18]. The barrier between 1*H*- and 2*H*-phospholes is very low at 19.6 kcal mol^{-1} but much higher between 2*H*- and 3*H*-phosphole at 30.7 kcal mol^{-1}.

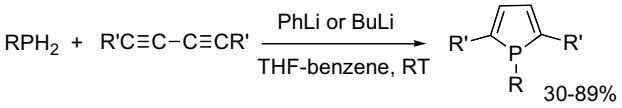
Whereas hydrogen migrates very easily from phosphorus to the α-carbon, the migrating ability varies widely for other groups. Some groups such as alkyl or alkoxy do not migrate under conditions that are compatible with the stability of the phosphole ring, while others migrate under acceptable heating such as aryl, alkynyl, CN, SR, and so on, and others migrate even below room temperature, such as acyl and silyl. These trends have been discussed in a recent review [19]. Another recent study has given an interpretation of the characteristic UV absorption band of alkylphospholes (280–290 nm, ε 3.3–3.9), of their PES spectra and correlated the low basicity of phospholes with their strained cyclic structure [20].

23.2.3 Synthesis

23.2.3.1 Synthesis of Phospholes

There are three main syntheses of the phosphole ring. The first involves the cycloaddition of primary phosphines with substituted 1,3-diynes. The reaction is catalyzed by strong bases (in general BuLi) and provides a convenient access to 1,2,5-trisubstituted phospholes [16, 21]. (Scheme 23.1)

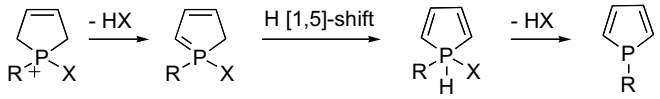
This method has been used to prepare a phosphole with two optically active (−)-menthyl substituents at the 2,5-positions [22]. Another interesting application concerns the synthesis of phospholes bearing bulky substituents (such as *tert*-butyl)



Scheme 23.1

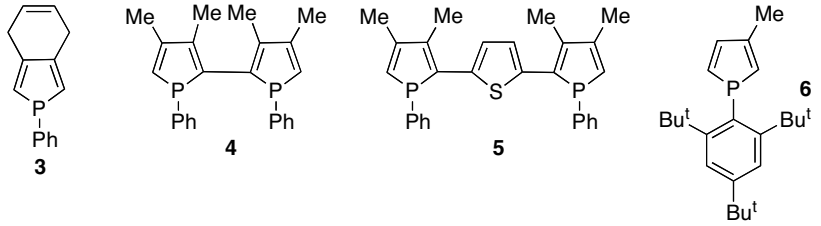
at the α-positions of the ring [23]. These groups stabilize otherwise unstable η^5-phospholyl complexes.

The second method relies on the dehydrohalogenation of diene-dihalophosphine cycloadducts [24]. The postulated mechanism is depicted in Scheme 23.2 [25].

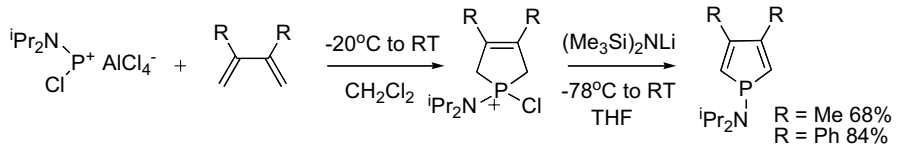


Scheme 23.2

In most cases, the initial cycloadduct is obtained via the well-known McCormack reaction of conjugated dienes with dihalophosphines at, or near, room temperature. Recently, a bicyclic phosphole **3** [26], which can serve as a precursor of η^5-3,4-benzophospholide complexes, has been prepared by this route. Alternatively, it is also possible to use the addition of bromine onto trivalent phosphol-3-enes. This variant has been used to prepare a 2,2′-biphosphole (**4**) [27], 2-aryl- or heteroarylphospholes such as **5** [28] and a flattened phosphole (**6**) with a bulky substituent at P [11].



Generally, the base used in the process is a tertiary amine such as α-picoline. However, recently, the much stronger LiHMDS has been used to prepare 1-aminophospholes (Scheme 23.3) [29].

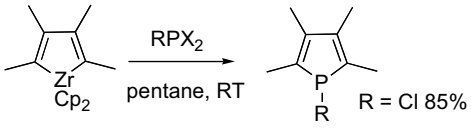


Scheme 23.3

Both the cycloaddition and the dehydrohalogenation reactions proceed much faster than in the usual process.

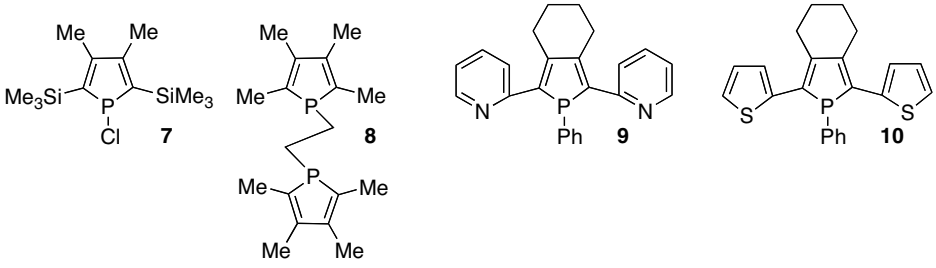
The third method relies on a zirconium to phosphorus exchange upon reaction of dihalophosphines with zirconacyclopentadienes (Scheme 23.4) [30].

The starting zirconacyclopentadienes are prepared by [2 + 2 + 1] cycloaddition between two molecules of alkynes and a zirconocene unit. Numerous persubstituted



Scheme 23.4

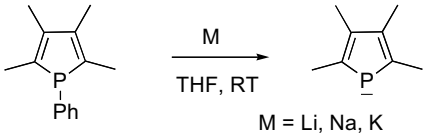
phospholes have been recently prepared by this route, most of them for applications in the field of molecular materials. 1-Halophospholes are also accessible from phosphorus trihalides. Some representative examples are compounds **7**–**10** [31–34].



Several other syntheses of phospholes have been reported in the literature but their applicability seems to be rather limited.

23.2.3.2 Synthesis of Phospholide Ions

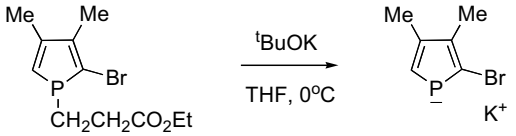
In most cases, phospholide ions are synthesized from preformed phospholes by cleavage of the exocyclic P−R bond by alkali metals (Scheme 23.5). The first report was published by Braye [35].



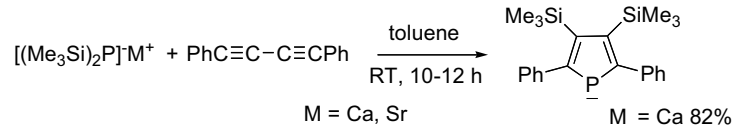
Scheme 23.5

The driving force behind this selective cleavage of the exocyclic P−C bond is, of course, the high aromaticity of the phospholide ion. The reaction involves the initial formation of a radical anion that collapses to give the phospholide ion and a phenyl radical [36]. In some cases, it is advantageous to use a variant relying on the base-induced dealkylation of 1-(β-ethoxycarbonylethyl)phospholes, thus avoiding undesired side-reactions due to the radical process. A striking illustration is provided in Scheme 23.6 [37].

Finally, in one instance, a phospholide ion has been directly synthesized from acyclic precursors by a process similar to the synthesis of phospholes from primary phosphines and diynes (Scheme 23.7) [38].



Scheme 23.6



Scheme 23.7

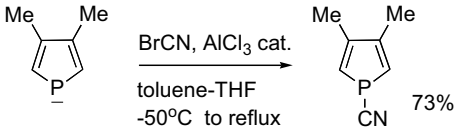
23.2.4 Reactivity

Since phospholes are not aromatic, their chemistry is completely different from that of their nitrogen, oxygen or sulfur analogues. The classical electrophilic substitution reactions are unknown and the ring can behave either as a phosphine or as a cyclopentadiene. It is quite convenient to divide the reactions of phospholes between those taking place at P, at the diene, the [1,5]-sigmatropic shifts, the functionalization reactions, the ring openings and the ring expansions. A few words on the rich and diverse complexation chemistry will close this survey.

23.2.4.1 Reactions at Phosphorus

The reactivity of the phosphole phosphorus is essentially normal although both the basicity and the quaternization ability are somewhat reduced [6] as a result of both the slight delocalization of the P-lone pair and the increase of cyclic strain occurring upon the P(III) into P(IV) conversion. The P-H$^+$ salts are only stable when the counterion (e.g., $TaCl_6^-$) does not display any coordinating ability [39]. Otherwise they evolve to give phospholene oxides via a pentacoordinate intermediate and a [1,5]-shift of H [25]. The oxides tend to dimerize via a [4 + 2] Diels–Alder reaction and display a limited life time at room temperature [40] except when heavily substituted on the ring. The sulfides are more stable as monomeric species, although they also dimerize upon prolonged heating at high temperature. The most specific reaction of phospholes at P is the exocyclic P−C bond cleavage by alkali metals that has been discussed already (Scheme 23.5). All of the chemistry of the resulting phospholides takes place at phosphorus. Among the various electrophiles that have been allowed to react with these ions, one of the most interesting from a practical standpoint is cyanogen bromide (Scheme 23.8) [41].

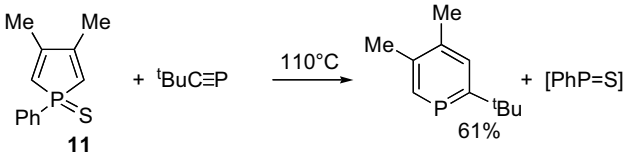
The resulting 1-cyanophospholes display a high electrophilicity at P and provide a convenient access to 1-alkoxy- and 1-amino-phospholes by reaction with the appropriate anions.



Scheme 23.8

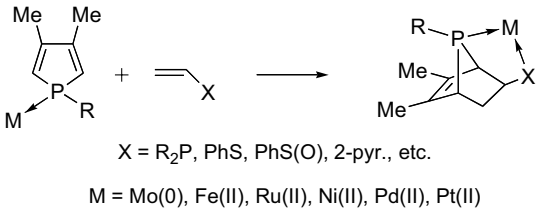
23.2.4.2 **Reactions at the Diene**

The reactivity of the dienic system is somewhat reduced by the cyclic delocalization and several dienophiles such as dimethyl acetylenedicarboxylate tend to react at the P-lone pair. This is the reason why most of the initial studies were performed with phosphole sulfides or phosphole complexes. From this standpoint, the most studied sulfide has been the 1-phenyl-3,4-dimethylphosphole sulfide **11**. This species can behave either as a diene or a dienophile according to the nature of the reaction partner [42]. One of the most spectacular applications of this chemistry is the synthesis of a phosphinine shown in Scheme 23.9 [43].



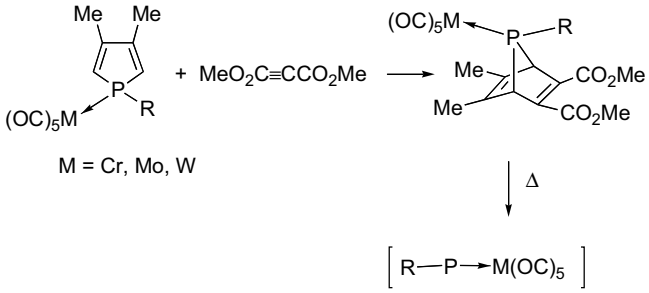
Scheme 23.9

The diene reactivity tends to increase upon complexation of the P-lone pair. If the dienophile also contains a coordinating group, intramolecular [4 + 2] cycloadditions become extremely easy (Scheme 23.10). This kind of chemistry has been developed by the group of Nelson [44].



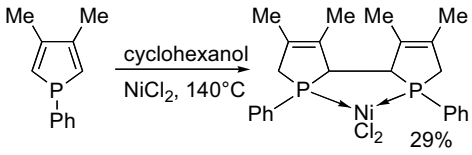
Scheme 23.10

The same general approach has served to prepare a range of optically active chelating ligands [45]. Whereas the adducts of phosphole sulfides with dimethyl acetylenedicarboxylate are unstable, those with selected phosphole complexes are stable and can serve as useful precursors of electrophilic terminal phosphinidene complexes (Scheme 23.11) [46].



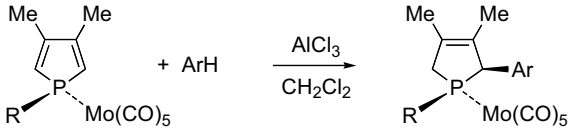
Scheme 23.11

These transient species display a rich carbene-like chemistry that has been the subject of several reviews [47]. Phosphole complexes also undergo reactions other than the Diels–Alder cycloadditions. With nickel derivatives, a reductive C−C coupling is observed in high-boiling alcohols (Scheme 23.12) [48].



Scheme 23.12

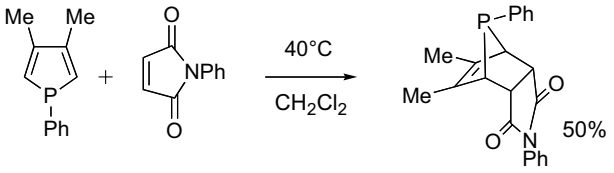
The dienic system of molybdenum carbonyl complexes can be used to perform the electrophilic Friedel–Crafts alkylation of electron-rich arenes or heteroarenes (Scheme 23.13) [49].



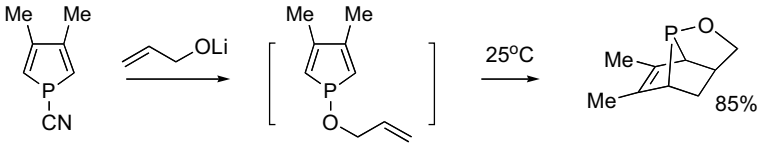
Scheme 23.13

Without activating and protecting groups at phosphorus, tervalent phospholes behave as rather poor dienes. The first clear-cut example of dienic behavior is depicted in Scheme 23.14 [50].

Electronegative substituents at P such as CN or OR enhance the dienic reactivity of phospholes [10]. A spectacular consequence of this fact is the spontaneous intramolecular [4 + 2] cycloaddition taking place within 1-allyloxyphospholes (Scheme 23.15) [51].

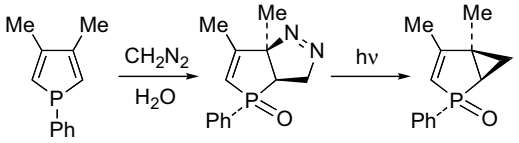


Scheme 23.14



Scheme 23.15

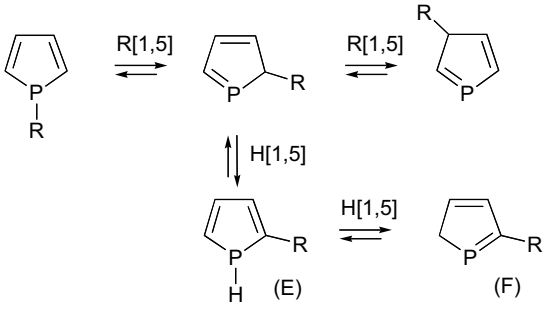
Finally, in another vein, the reaction of phospholes with diazomethane is worth mentioning (Scheme 23.16) [52].



Scheme 23.16

23.2.4.3 **[1,5]-Sigmatropic Shifts**

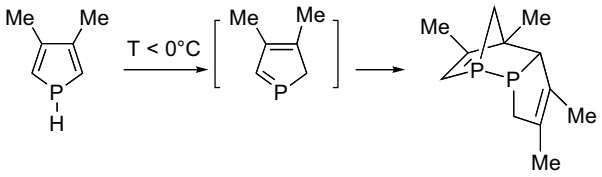
As a result of the pyramidal structure of phospholes, there is a significant overlap between the σ-orbital of the exocyclic P−R bond and the π*-orbitals of the dienic system. This situation favors the [1,5]-sigmatropic shifts of the R-substituent from phosphorus to the α-carbons of the ring. Migrations to the β-carbons are also possible but far more difficult. The overall picture is depicted in Scheme 23.17.



Scheme 23.17

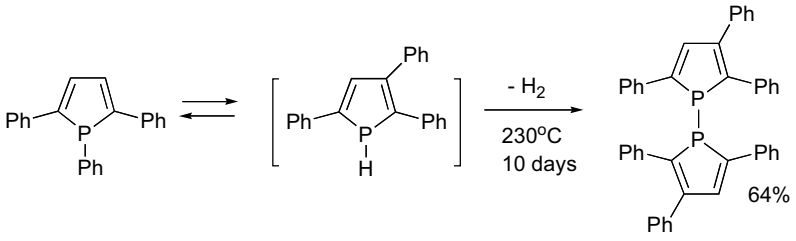
It must be stressed that the P-to-αC migrations in the phosphole ring need, in the general case, far less energy than the corresponding migrations in the cyclopentadiene ring. In practice, the 2*H*-phospholes resulting from these migrations are far more reactive than the starting 1*H*-phospholes, so that the equilibrium mixtures can serve to investigate the chemistry of pure 2*H*-phospholes of type (F). This chemistry has been reviewed recently [53]. Two points must be stressed. The migration ability varies widely according to the nature of R. Some R-substituents migrate below room temperature, such as H, acyl or silyl groups. This explains why the parent phosphole has been so difficult to characterize [3]. Some others migrate upon heating, such as phenyl, thienyl, SR, CN, alkynyl groups. Some others do not migrate, such as alkyl or alkoxy groups. Since these migrations are concerted, the migrating substituent remains attached to the ring by the same atom both before and after the migration. This fact has numerous useful consequences.

When no trapping reagent is added to the equilibrium mixture of Scheme 23.17 and when the reaction takes place around or below room temperature, 2*H*-phosphole (F) evolves to give a [4 + 2] P−P bonded *endo*-dimer. One such dimer has been characterized by X-ray crystal structure analysis (Scheme 23.18) [54]. This dimer equilibrates with its *exo* stereoisomer around 100 °C.



Scheme 23.18

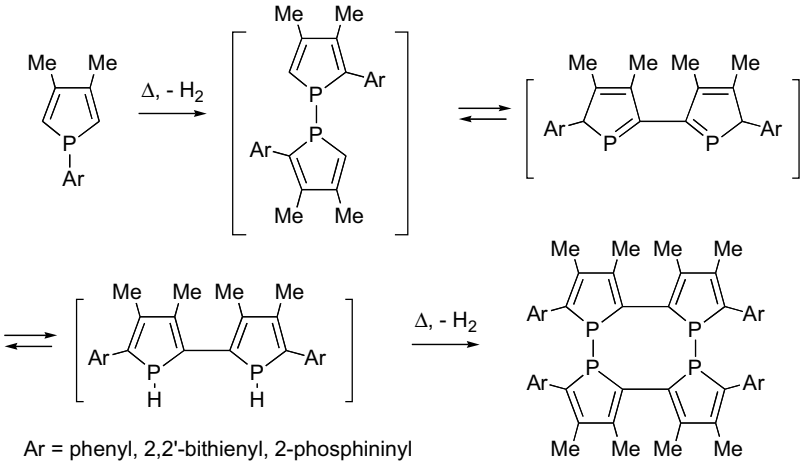
When the equilibrium mixture of Scheme 23.17 stands at around 200 °C, a dehydrogenative dimerization takes place, probably at the expense of phosphole (E), to give a 1,1′-biphosphole (Scheme 23.19) [55].



Scheme 23.19

Upon further heating, if the two α-positions carry hydrogen, the final evolution leads to P−P bonded tetramers (Scheme 23.20) [56].

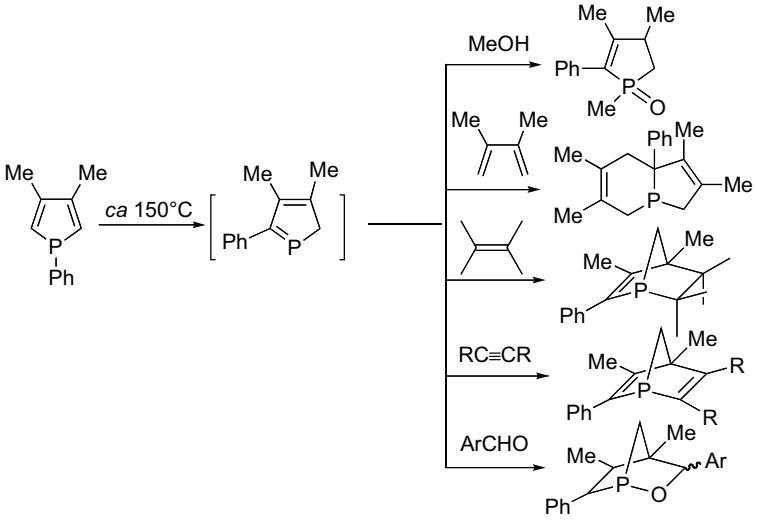
One such tetramer has been characterized by X-ray crystal structure analysis [57].



Scheme 23.20

When a trapping reagent (inert toward phosphorus lone pairs) is added to the equilibrium mixture of Scheme 23.17, then 2*H*-phosphole (F) is efficiently trapped before any further evolution. These reagents include MeOH, non-activated alkynes, conjugated dienes [58], alkenes [59] and aldehydes (Scheme 23.21) [60].

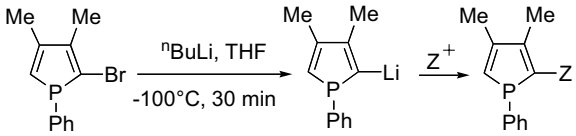
This cycloaddition chemistry is extremely effective. It has served to prepare a new series of efficient bicyclic phosphorus ligands for enantioselective catalysis [61]. All these ligands are characterized by a chiral bridgehead phosphorus that cannot racemize.



Scheme 23.21

23.2.4.4 Functionalization Reactions

Since phospholes are not aromatic, their chemistry is normally devoid of the electrophilic substitution and α-metallation reactions that characterize the chemistry of pyrrole, furan and thiophene and serve to prepare most of their functional derivatives. Electrophilic substitutions become possible to a limited extent with "flattened" phospholes carrying a very bulky group at phosphorus [11]. In practice, only two reliable and versatile methods exist that allow functionalization of a preformed phosphole ring. The first relies on the existence of 2-bromophospholes, which can be prepared from their non-bromo precursors by a classical sequence involving protection, bromination, dehydrobromination and deprotection. These 2-bromophospholes are readily transformed into 2-lithiophospholes at low temperature (Scheme 23.22) [62].

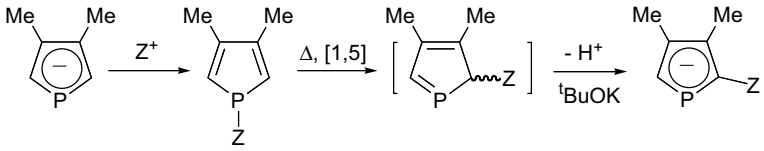


Z = CO_2H,CO_2R,CHO,C(O)Ph,$SiMe_3$, C-C bridge, C≡CR

Scheme 23.22

This chemistry has served to prepare α-alkynyl derivatives [63], an α-connected tetraphosphole [64] and a tetraphosphole macrocycle [65].

The second method relies on the $1H \leftrightarrow 2H$-phosphole equilibrium. The function is first grafted onto P, then the equilibrium is established and the resulting 2-functional-2*H*-phosphole is deprotonated by a base (Scheme 23.23) [66–71].



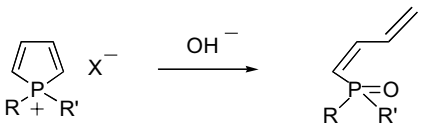
Z = Ph,CO_2H,CO_2R, C(O)R,SiR_3, 2-pyridyl, 2-pyrrolyl, etc.

Scheme 23.23

Two conditions must be met by the functional group: it must be compatible with the base and able to migrate. This last condition excludes alkyl and alkoxy groups. This chemistry has served to prepare the first easily accessible 2,5-difunctional phospholes [Z = CO_2H, CO_2R, C(O)R].

23.2.4.5 Ring Openings and Expansions

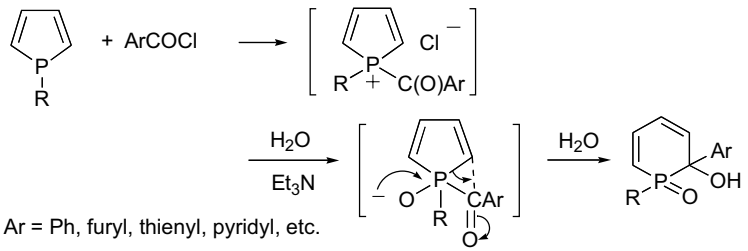
The best documented ring-opening reaction takes place upon hydrolysis of phospholium salts (Scheme 23.24) [72, 73].



Scheme 23.24

In the transient hydroxyphosphorane, the phosphole ring probably occupies a axial–equatorial position, leading to cleavage of the elongated axial P−C bond.

The best documented ring expansion reaction also relies on the hydrolysis of intermediate phospholium salts. It takes place during the reaction of phospholes with aromatic acid chlorides in the presence of water and triethylamine (Scheme 23.25) [74–76].



Scheme 23.25

This reaction is the first step of a route transforming phospholes into 2-arylphosphinines.

23.2.4.6 **Phospholes and Phospholides in Coordination Chemistry**

Phospholes and phospholides give a large range of complexes. The possible structures are shown in Figure 23.2. Several reviews deal with all or some of these complexes [77, 78].

In the first complexes (G in Figure 23.2), phospholes behave as normal phosphine ligands. As we have seen earlier, the reactivity of the diene is enhanced [44–46].

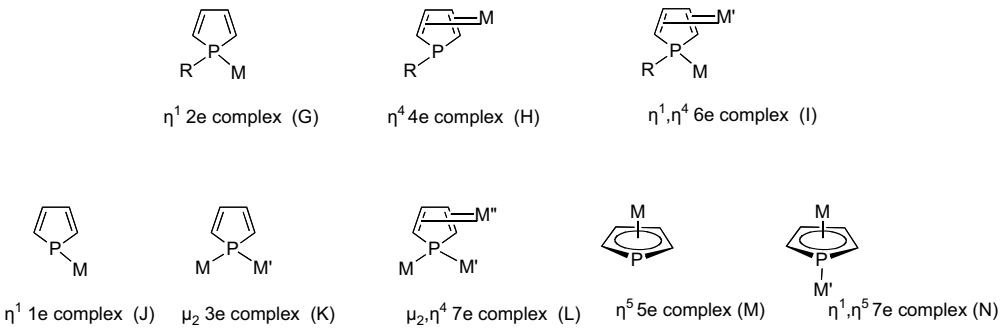


Figure 23.2 Possible structures phospholes and phospholide complexes.

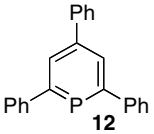
The second type (H) is extremely rare. One η^4-$Fe(CO)_3$ complex has been studied in some depth [79]. The third type (I) is more frequent. The most spectacular example incorporates a chain of four cobalt atoms sandwiched between two phospholes acting as 6e-ligands [80].

The variety of phospholide complexes is even larger. The η^1- complexes (J) can be viewed as organometallic phospholes. Since the transition metal substituent is, in general, rather bulky they tend to be more planar than usual. In a η^1-$W(CO)_3Cp$ complex [81], the sum of the angles around phosphorus has been found to be as high as 319.6°. Otherwise, their chemistry is remarkably similar to that of normal phospholes. The μ_2-complexes (K) are completely devoid of aromaticity. Their dienic system is rather reactive and easily gives π-complexes (L). One of the most spectacular complexes of this type incorporates a heptanuclear Mn_4Pd_3 core surrounded by four phospholyl rings [82]. By far the most important phospholyl complexes are the η^5 species (M). They are known for almost all of the transition metals of the periodic table, including rare earths [83] and uranium [84]. Most of them are 18e species but, recently, a 16e phosphachromocene [85], a 17e phosphaferricinium [86], a 19e phosphacobaltocene [87] and a 20e phosphanickelocene [88] have been described. They are also known for some main group metals such as gallium [89], germanium, tin, and lead [90]. From an organic standpoint, the most interesting chemistry is that of phosphaferrocenes. These species display a complete range of electrophilic substitution reactions (acylation [91], formylation [91] and carboxylation [92]) and thus occupy a unique position among phosphorus heterocycles. Their complexes at phosphorus (N) also play an interesting role in asymmetric catalysis (Section 23.5).

23.3 Phosphinines

23.3.1 History and Nomenclature

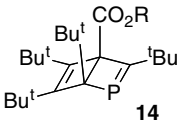
The discovery of 2,4,6-triphenylphosphinine (**12**) by Märkl in 1966 was a landmark of phosphorus chemistry [93]. It proved simultaneously that simple compounds containing dicoordinate phosphorus could be stable and that phosphorus could participate in a cyclic delocalization. The somewhat less stable parent system **13** was characterized five years later by Ashe [94]. Since phosphorus is less, whereas nitrogen is more, electronegative than carbon, the heteroatom is electron-poor in phosphinines and electron-rich in pyridines. Thus, although both systems are highly aromatic, their chemistry is completely different. Several reviews describing phosphinine chemistry are available [95].



12

13

The ring has been called phosphabenzene, phosphorin or phosphinine. The latter, the official (IUPAC) name, is now prevalent. Two Dewar phosphinines, **14** and **15**, stabilized by bulky substituents, have been described [96]. Besides trivalent phosphinines, the so-called λ^5-phosphinines **16**, incorporating a tetracoordinate phosphorus atom, display a distinct chemistry resulting from their delocalized ylidic structure [97].



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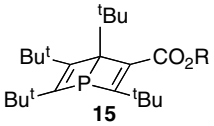


15

16

23.3.2
Spectral, Structural and Theoretical Studies

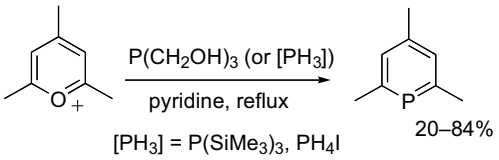
Phosphinines have been extensively characterized by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy. The data for the parent compound **13** are given hereafter [98] (δ in ppm): δ^{31}P +211, $\delta^{13}C_\alpha$ 154.1, ^1J(C-P) = 53 Hz, $\delta^{13}C_\beta$ 133.6, ^2J(C-P) = 14 Hz, $\delta^{13}C_\gamma$ 128.8, ^3J(C-P) = 22 Hz, δH_α 8.61, ^2J(H-P) = 38.0 Hz, δH_β 7.72, ^3J(H-P) = 8.0 Hz, δH_γ 7.38, ^4J(H-P) = 3.6 Hz. Phosphinines display the characteristic low-field shifted ^{31}P resonances of phosphaalkenes. The huge ^{1}J(C-P) coupling is also noteworthy. Conversely, λ^5-phosphinines show more conventional ylid-like resonances. The 1,1-dimethyl derivative **16** (R = Me) displays a ^{31}P resonance around 0 ppm and shows highly shielded H_α and C_α resonances at 3.98 and 67.5 ppm, respectively [99]. High-field shifts are also observed for γ-CH: δH_γ 4.62, $\delta^{13}C_\gamma$ 94.0. These data are in line with the high concentration of negative charge at the α- and γ-positions of **16**.

The structure of parent phosphinine has been established by a combination of electron diffraction and microwave data [100]. The ring is planar, the P−C bonds are short (1.732 Å) and the C−C bond alternation is minimal (1.413 and 1.384 Å). The intracyclic C−P−C angle is relatively acute at 101° (vs. 116.9° for C−N−C in pyridine). All these data are compatible with a high electronic delocalization within the ring.

The theoretical data on phosphinines have been summarized in a review [101]. The most important points are selected hereafter. The computed aromatic stabilization energy lies in a range from 88 to 97% of that of benzene. The NICS(1) value at −10.8 is very close to that of benzene (−11.3). The best computed structures indicate a negligible alternation of the C−C bond lengths (less than 0.01 Å). Also of interest is the order of the occupied orbitals. Whereas the lone pair corresponds to the HOMO in pyridine, it corresponds to the third occupied level in phosphinine. More recently, a careful evaluation of the proton affinity and the pK_a of the protonated form has been carried out [102]. At 195.8 ± 1.0 kcal mol^{-1}, the PA of phosphinine is substantially smaller than that of pyridine (219.4 kcal mol^{-1}). The pK_a of $C_5H_5PH^+$ has been evaluated at −16.1 in water, vs. 5.2 for pyridinium. The drastic differences between the chemistry of pyridines and phosphinines are already quite visible.

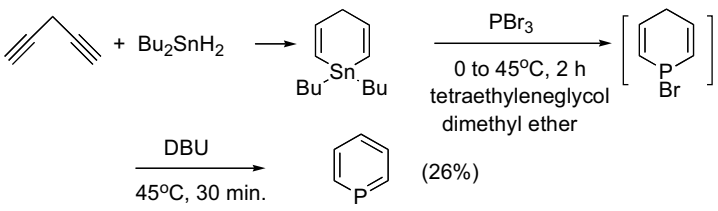
23.3.3
Synthesis

There is a wealth of synthetic methods for making phosphinines and discriminating between those which, ultimately, will prove the most useful is difficult. The initial method of Märkl relying on the O^+ to P exchange in pyrylium salts is still a method of choice due to its simplicity (Scheme 23.26).



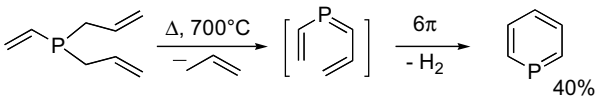
Scheme 23.26

The source of PH_3 can be either $P(CH_2OH)_3$ [93], $P(SiMe_3)_3$ [103] or PH_4I [104]. The synthesis of the parent phosphinine by Ashe [94] relies on a tin to P exchange in a 1,4-dihydro-stannabenzene (Scheme 23.27). A detailed description of the procedure is available [95c].



Scheme 23.27

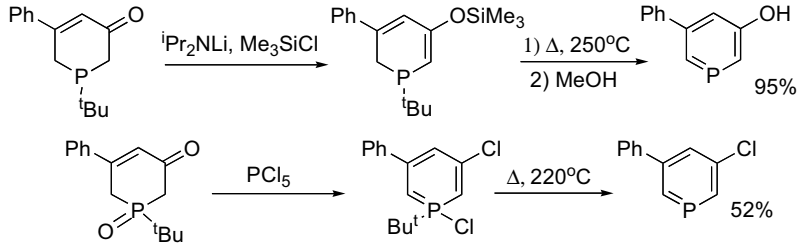
This route has been generalized by Märkl for the preparation of 4-substituted phosphinines [105]. The parent phosphinine is more easily obtained by pyrolysis of vinyldiallylphosphine (Scheme 23.28) [106].



Scheme 23.28

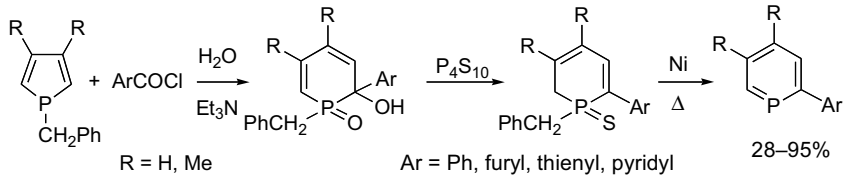
The mechanism of this reaction sequence has been studied recently from a theoretical standpoint [107].

Various specialized routes start from phosphacyclohexenones and end with the thermolysis of 1,2-dihydro- or λ^5-phosphinines. Two examples are given in Scheme 23.29 [108, 109].

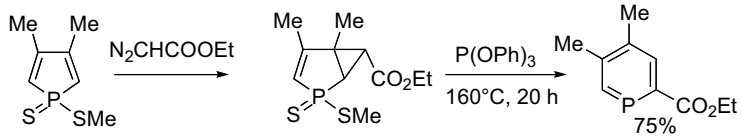


Scheme 23.29

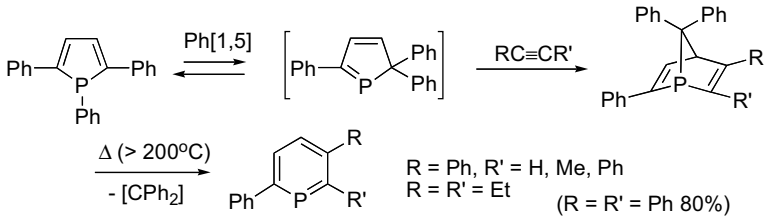
Phospholes are also versatile starting points for the synthesis of phosphinines. Several examples are depicted in Schemes 23.30–23.33 (see also Scheme 23.9) [110–113].



Scheme 23.30

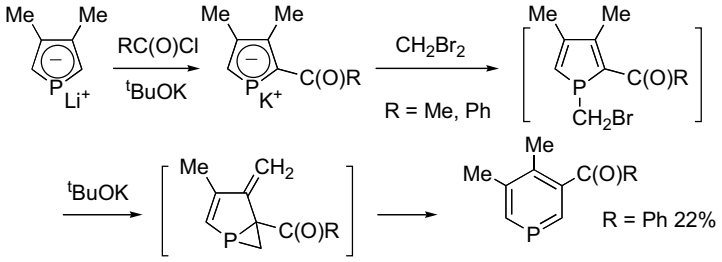


Scheme 23.31

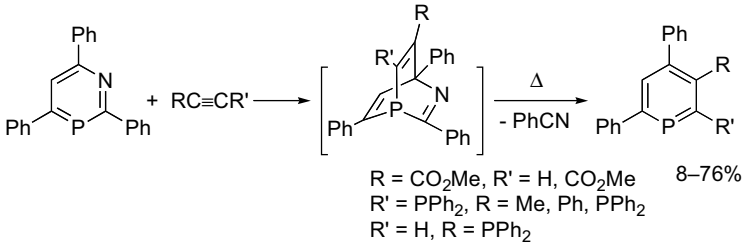


Scheme 23.32

Azaphosphinines constitute another versatile starting point for the synthesis of phosphinines. The first illustration of this approach was described by Märkl [114]. The 1,3-azaphosphinines are first synthesized from 1,3-azapyrylium salts. Then, they are reacted with alkynes (Scheme 23.34).

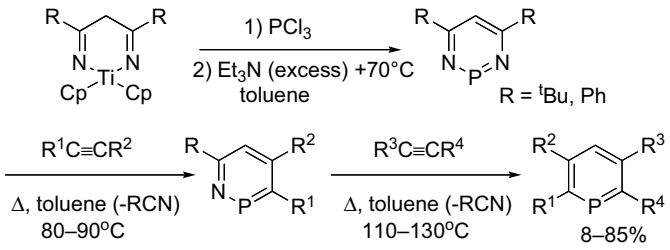


Scheme 23.33



Scheme 23.34

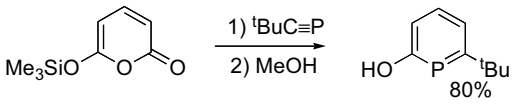
A more versatile approach starts from 1,3,2-diazaphosphinines which are prepared *in situ* from the corresponding titanacycles (Scheme 23.35) [115].



Scheme 23.35

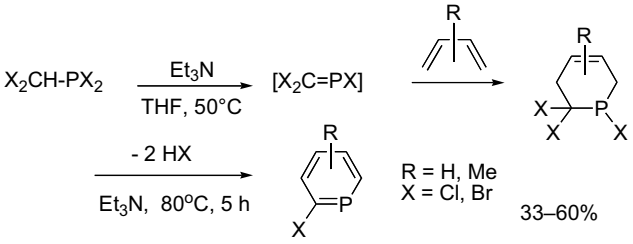
The most spectacular application of this approach is the synthesis of macrocycles incorporating three or four phosphinine units [116].

Another group of methods involve the [4 + 2] cycloaddition of a conjugated diene with a phosphaalkyne or a precursor of phosphaalkyne. An example is given below in Scheme 23.36 [117].



Scheme 23.36

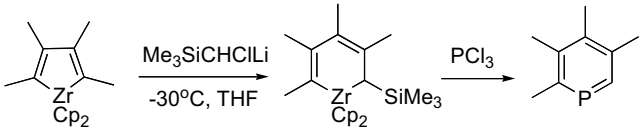
The simplest application of this approach is the one-pot synthesis of 2-halophosphinines from dihalomethyldihalophosphines and conjugated dienes (Scheme 23.37) [118].



Scheme 23.37

The most difficult part of the scheme concerns the preparation of the starting dihalophosphines. A detailed procedure is available [95c].

Finally, a zirconium route has been described recently (Scheme 23.38) [119].



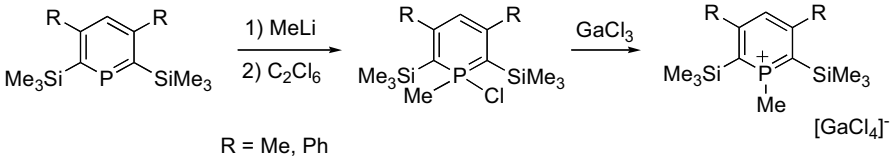
Scheme 23.38

Numerous other approaches have been described but they are either cumbersome or of very limited generality.

23.3.4 Reactivity

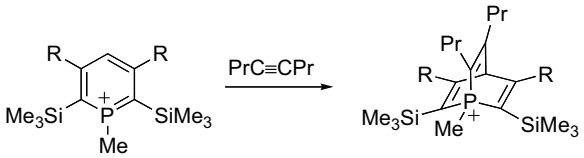
23.3.4.1 Reactions at Phosphorus

As we have already pointed out, the reactivity of the phosphorus lone pair in phosphinines is extremely low. As a result, phosphininium salts remained unknown for a very long time. However, recently, the preparation and full characterization of such species has proved possible (Scheme 23.39) [120].



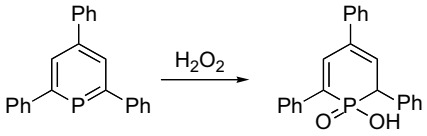
Scheme 23.39

The ^{31}P resonance of the salts occurs at about 160 ppm, that is, about 100 ppm at lower fields by comparison with the λ^5-phosphinine precursors. The C_α and C_γ resonances are similarly shifted to low fields. The structure of the salt for R=Ph shows a very short P–C bond at 1.697 Å and a widened C–P–C angle at 117.7°. The most significant reaction of these salts takes place with alkynes at room temperature to give phosphabarrelene derivatives (Scheme 23.40).



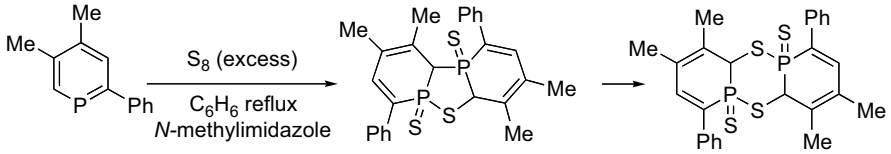
Scheme 23.40

The P-oxides are unstable and immediately add water upon formation (Scheme 23.41) [121].



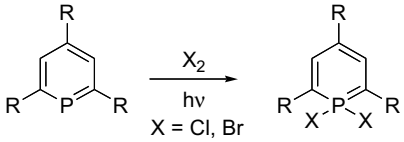
Scheme 23.41

The P-sulfides can be detected in solution by ^{31}P NMR spectroscopy [122], but none has been completely characterized until now [123]. Upon further sulfurization, polycyclic structures are formed (Scheme 23.42) [124].



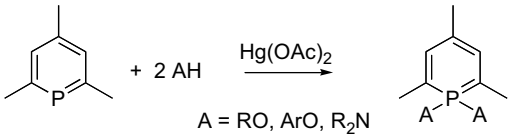
Scheme 23.42

When the α and γ positions are substituted, halogens add onto phosphorus under UV irradiation (Scheme 23.43) [125].



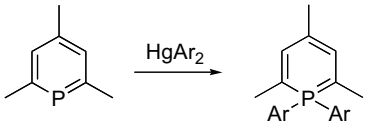
Scheme 23.43

The 1,1-difluoro-λ^5-phosphinines are obtained by metathesis (SbF_3 or $AgBF_4$) from the corresponding chloro or bromo derivatives. Oxidative addition of alcohols, amines, and so on is also possible (Scheme 23.44) [126–128].



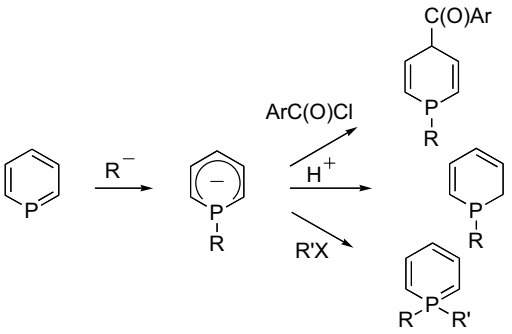
Scheme 23.44

Modified crown ethers have thus been prepared from poly(ethylene glycol)s. Diarylation at P is observed with diarylmercury derivatives (Scheme 23.45) [129].



Scheme 23.45

The reaction of strong nucleophiles such as organolithium or organomagnesium compounds also takes place at phosphorus. A delocalized dihydrophosphinine carbanion is thus formed (Scheme 23.46) [130–132].

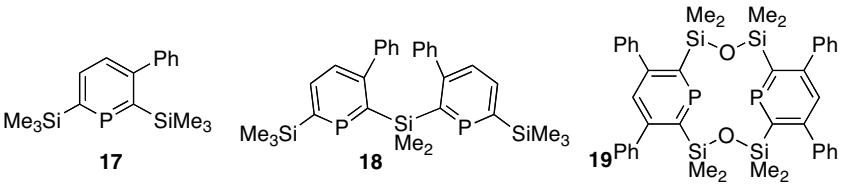


Scheme 23.46

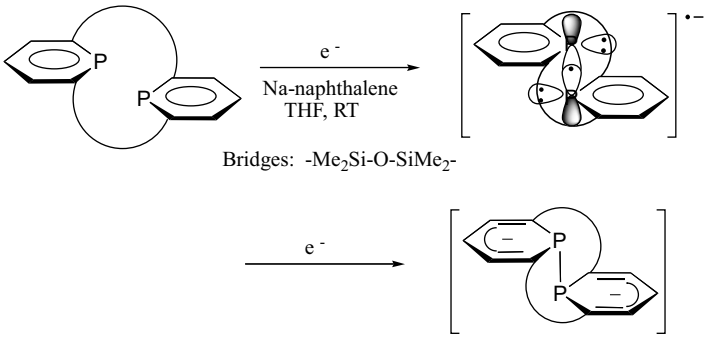
The X-ray crystal structure analysis of several such carbanions has been reported recently [133]. The lithium counterion is η^5-coordinated to the C_5 delocalized unit and DFT calculations indicate a high concentration of negative charge on the α-carbons. These anionic species react with hard electrophiles at the α- or γ-carbons to give dihydrophosphinine derivatives and with soft electrophiles at phosphorus to give λ^5-phosphinines.

Another point of interest concerns the reduction of phosphinines. This study has been carried out using sodium naphthalenide, potassium mirror or electrochemistry

as the reduction techniques and a monophosphinine (**17**), a bis-phosphinine (**18**) and a bis-phosphinine macrocycle (**19**) as substrates. The reduction products have been characterized by EPR, ^{31}P NMR, and X-ray analysis whenever possible. DFT calculations have completed the study [134, 135].



In all cases, the overall scheme appears identical. The monoelectronic reduction product reacts with another neutral phosphinine ring to give a dimeric structure with a one-electron P—P bond. Then, a second reduction takes place to give a dianionic dimeric structure with a normal two-electron P—P bond. The process is shown for the macrocycle in Scheme 23.47. In this case, the one-electron P—P bond has a computed length of 2.763 Å.

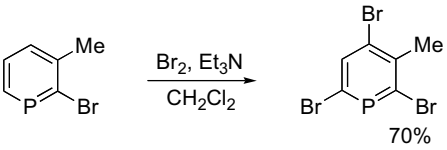


Scheme 23.47

23.3.4.2 **Substitution and Functionalization Reactions**

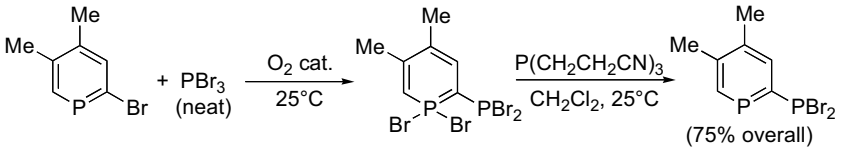
Since most nucleophiles and electrophiles tend to attack at P, only a few substitution and functionalization reactions at the ring carbons are known and it is impossible to develop a classical aromatic chemistry with phosphinines.

Whenever a α or γ position is unsubstituted, it is possible to brominate it via a Br_2-addition-HBr-elimination sequence (Scheme 23.48) [136].



Scheme 23.48

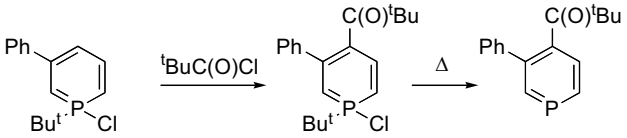
This formal substitution reaction must be compared with the addition reaction depicted in Scheme 23.43. In the same vein, the reaction with PBr_3 ultimately affords the Br_2P-substituted phosphinines (Scheme 23.49) [137].



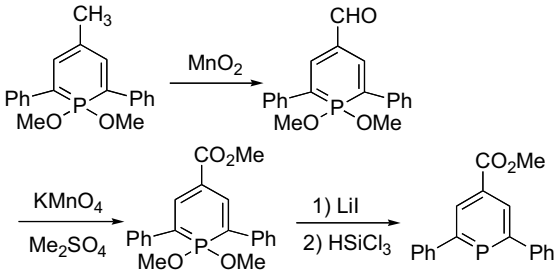
Scheme 23.49

A few nucleophiles react with halophosphinines to give the substituted products. This is the case with lithium amides [138], trimethylstannylsodium [139] and lithium phospholides [140].

Since most of the reagents attack phosphinines at phosphorus, one obvious way to redirect the attacks at the carbons of the ring is to protect phosphorus. This has been done using λ^5-phosphinines or phosphinine complexes. Examples of the two approaches are given hereafter in Schemes 23.50–23.52 [141–143].

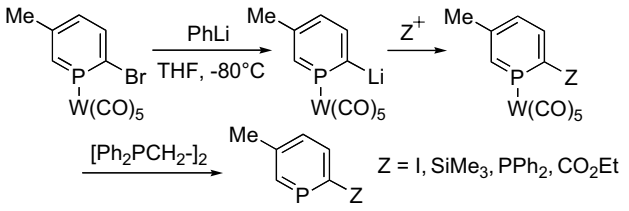


Scheme 23.50

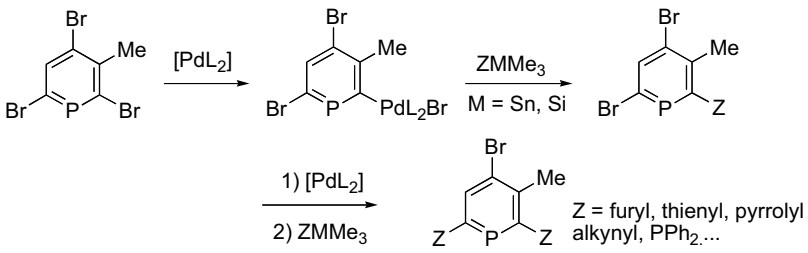


Scheme 23.51

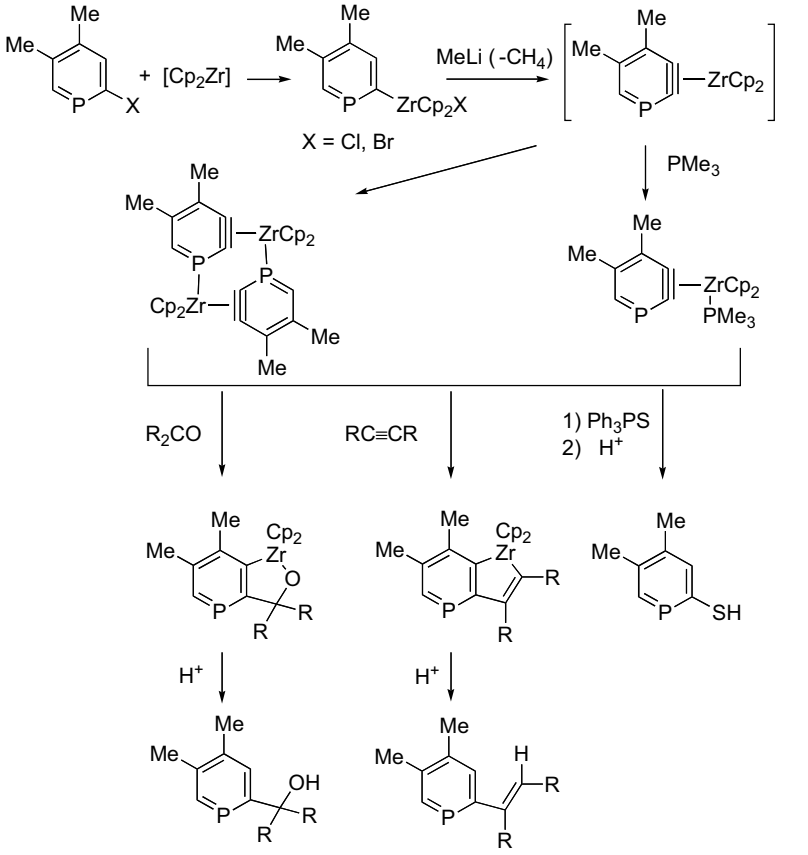
Of course, it is far better to avoid these protection–deprotection steps. Two methods achieve this aim. Both rely on the activation of the C–X bonds of 2-halophosphinines, either by Pd(0) [144, 145] or by zirconocene [146, 147] (Schemes 23.53 and 23.54).



Scheme 23.52

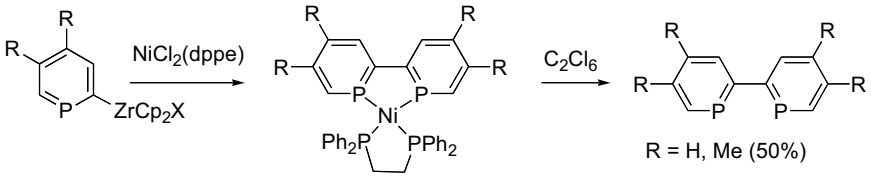


Scheme 23.53



Scheme 23.54

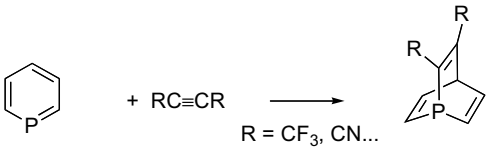
The phosphabenzyne dimeric complex has been characterized by X-ray crystal structure analysis [147]. As expected, the formal C≡C triple bond is rather long at 1.361 Å. This value is similar to those found in benzyne-zirconium complexes. This dimeric complex reacts exclusively via its $C_\alpha-Zr$ bond. An interesting application of this zirconium chemistry is the synthesis of 2,2′-biphosphinines, which are very interesting ligands for transition metals (Scheme 23.55) [148].



Scheme 23.55

23.3.4.3 **Cycloaddition Reactions**

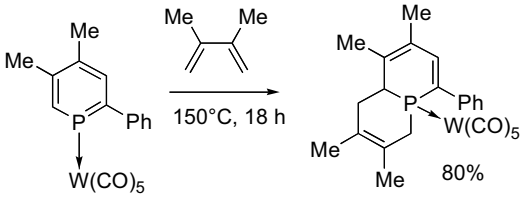
Due to their aromaticity, phosphinines are unreactive as dienophiles and poorly reactive as dienes. In practice, they only react with highly activated (electron-poor) alkynes (Scheme 23.56) [149].



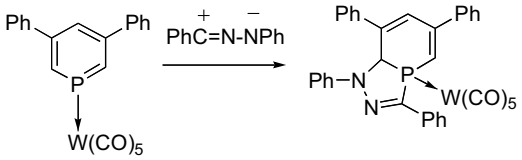
Scheme 23.56

The reactivities as dienes or dienophiles are sharply enhanced upon P-complexation [150–153] or sulfurization [122, 154, 155]. Some examples are depicted in Schemes 23.57–23.59.

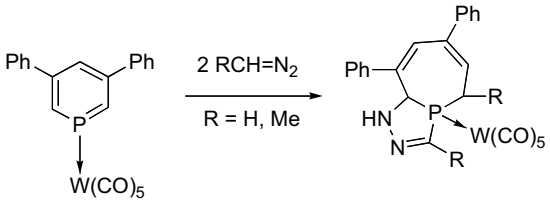
Activation by sulfur has served to devise the first known access to 2,2′-biphosphinines [155].



Scheme 23.57



Scheme 23.58

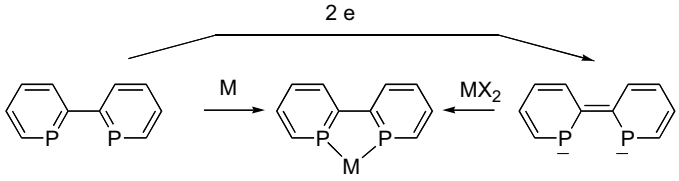


Scheme 23.59

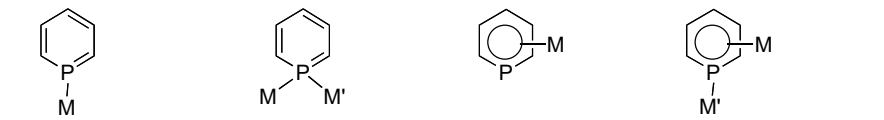
23.3.4.4 **Phosphinines in Coordination Chemistry**

Phosphinines give mainly four types of complexes (O to R in Figure 23.3).

By far the most common are those of type O. Among them, the most noteworthy are a series of homoleptic complexes of the parent phosphinine (**13**) prepared by the group of Elschenbroich, NiL_4, FeL_5, CrL_6 [156–158]. In this type of complexes, phosphinines behave as relatively weak σ-donors and strong π-acceptors, somewhat resembling CO. The ability of phosphinines to stabilize low oxidation states has been spectacularly demonstrated with 2,2′-biphosphinines (P-P). These complexes are either prepared from neutral 2,2′-biphosphinines or from their dianions (Scheme 23.60) [159].



Scheme 23.60



η¹ 2e complex (O) μ² 2e complex (P) η⁶ 6e complex (Q) η⁶,η¹ 8e complex (R)

Figure 23.3 Types of phosphinine complexes.

A series of homoleptic complexes derived from metals in negative oxidation states has thus been prepared, such as $[M(P\text{-}P)_3]^{2-}$ (M=Ti, Zr, Hf) [160]. Another illustration of this phenomenon is the stabilization of a gold(0) complex by a tetraphosphinine macrocycle [161].

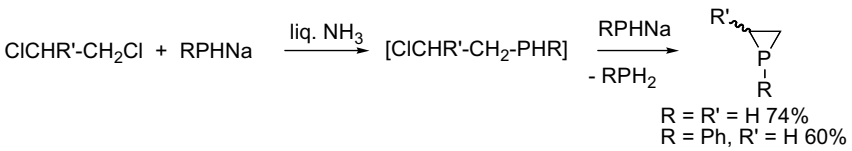
Even though the η^6-coordination mode (Q) is much less common, it has produced some interesting species such as the bis(η^6-phosphinine)vanadium (0) sandwich complex,the structure of which has been established by X-ray analysis [162].

23.4
Other P Heterocycles

The heterocyclic chemistry of phosphorus is now so vast a domain that it is impossible to cover all of its aspects in the limited space available. Two books have been specifically devoted to the subject [163, 164]. This brief survey is restricted to the three-, four-, and five-membered phosphorus–carbon heterocycles containing a single heteroatom. Phospholes and phosphinines are, of course, excluded.

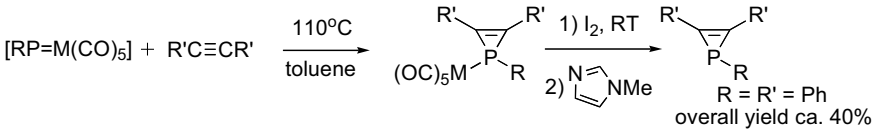
23.4.1
Three-Membered Rings: Phosphiranes and Phosphirenes

A review on this topic is available [165]. The saturated ring (phosphirane) was discovered by Wagner in 1963 (but was not reported in the literature until 1967) [166] and its synthesis is remarkably simple (Scheme 23.61).



Scheme 23.61

The unsaturated ring (phosphirene) was discovered in 1982 via a trickier approach [167] (Scheme 23.62).

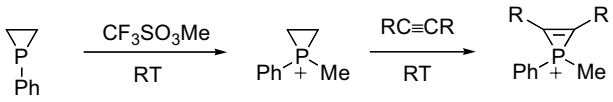


Scheme 23.62

The terminal phosphinidene complexes that are used in this synthesis are generated by cycloreversion from the appropriate 7-phosphanorbornadiene complexes.

As expected, both rings have a very small C–P–C internal angle (phosphirane 47° [168], phosphirene 42° [169]) and display a high ring strain (phosphirane $\Delta E - 22\,\text{kcal mol}^{-1}$) [170]. Their more characteristic spectral feature is their ^{31}P resonances at very high field (parent phosphirane −341 ppm [171], 1,2,3-triphenylphosphirene −190 ppm [169]).

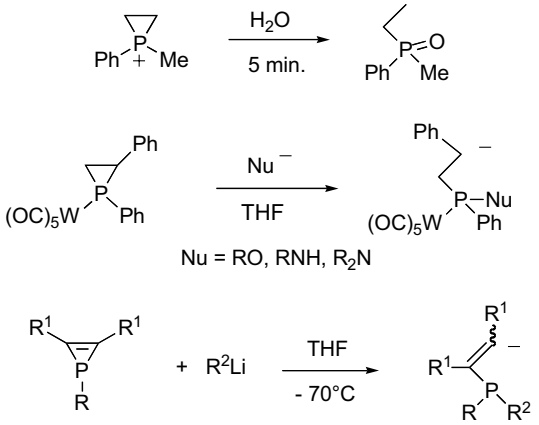
The chemistry of these rings is controlled by their strain. They tend to cleave upon oxidation. The phosphiranium salts are marginally stable and can be used as efficient precursors of phosphenium cations (Scheme 23.63) [172].



Scheme 23.63

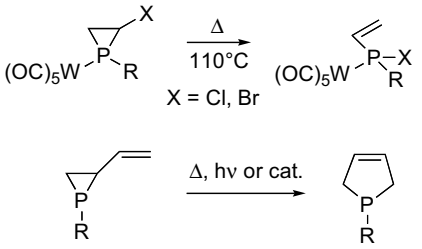
Phosphirenium salts are more stable than their saturated counterparts due to some aromatic stabilization [173]. In the same vein, a highly reactive dicoordinate phosphirenylium cation has been characterized in liquid SO_2 at low temperature [174].

Most of the reactions of these species involve ring opening or ring expansions. A few representative examples are depicted in Schemes 23.64–23.66 [175–180].

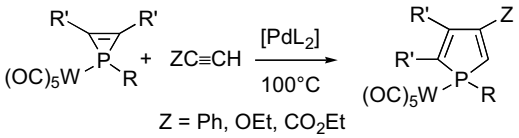


Scheme 23.64

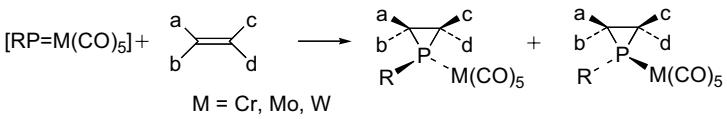
Since both phosphiranes and phosphirenes are heavily stabilized by complexation with $[M(CO)_5]$ (M=Cr, Mo, W), a lot of work concerning these rings has been carried out in the coordination sphere of these transition metals. The phosphirane complexes are directly obtained from the reaction of terminal phosphinidene complexes and alkenes (Scheme 23.67) [181].



Scheme 23.65

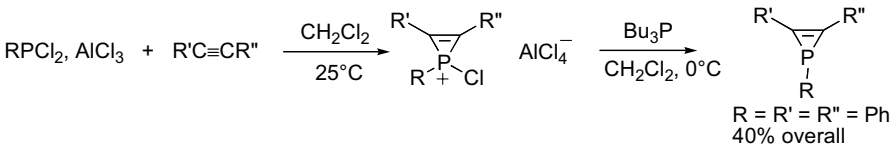


Scheme 23.66



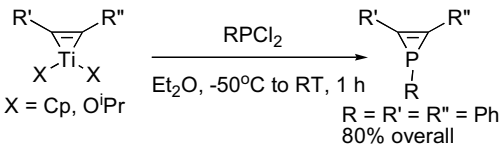
Scheme 23.67

The corresponding work has been summarized in two reviews [182, 183]. A surprisingly simple synthesis of phosphirenes has also been devised (Scheme 23.68) [184, 185].



Scheme 23.68

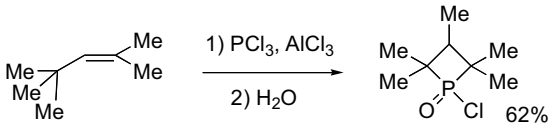
Of interest too is the synthesis of phosphirenes from titanacyclopropenes (Scheme 23.69) [186].



Scheme 23.69

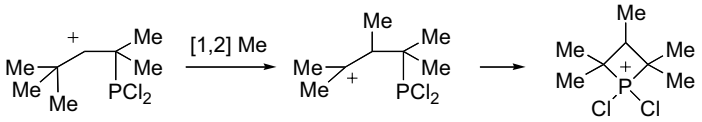
23.4.2
Four-Membered Rings: Phosphetanes, Dihydrophosphetes and Phosphetes

A review on phosphetanes is available [187]. The ring was discovered by McBride in 1962 [188]. Its initial synthesis relied on the condensation of halophosphines with polymethyl-substituted olefins in the presence of $AlCl_3$ (Scheme 23.70).



Scheme 23.70

The mechanism involves a methyl 1,2-migration (Scheme 23.71).



Scheme 23.71

Owing to its simplicity, this route to phosphetanes is still a method of choice today.

The structure of a tervalent phosphetane shows a C−P−C intracyclic angle of 76.9°, with relatively long intracyclic P−C bonds at 1.863–1.887 Å [189]. According to a theoretical study, the ring strain of phosphetane is relatively low at 17.9 kcal mol^{-1} [190].

Apart from a classical chemistry at phosphorus (oxidation, quaternization, complexation, etc.), the phosphetane ring undergoes several ring openings and ring expansions. Some examples are collected in Scheme 23.72 [191–193].

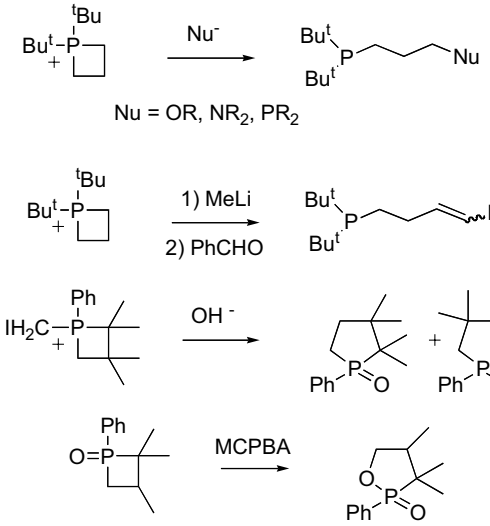
Besides the McBride synthesis, the most convenient access to phosphetanes relies on the reaction of primary phosphines with 1,3-diol derivatives (Scheme 23.73) [194, 195].

The 1,2-dihydrophosphete (phosphetene) ring was unambiguously characterized for the first time in 1985 [196]. A review is available [197]. The intracyclic angle in 1,2,3-triphenylphosphet-2-ene is 74.0°, the P−Csp^2 bond length is normal at 1.821 Å, and the P−Csp^3 bond length is long at 1.886 Å [198].

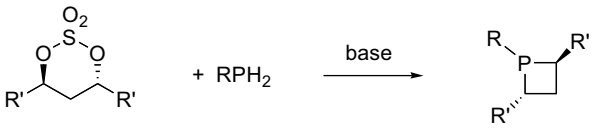
1-Phosphadienes and 1,2-dihydrophosphetes are connected by a cyclization–cycloreversion equilibrium that has been studied from a theoretical standpoint [199]. When appropriately substituted, a phosphetene ring can be used as a masked 1-phosphadiene as shown in the following example (Scheme 23.74) [200].

Two interesting ring expansion reactions have also been described (Schemes 23.75 and 23.76) [201, 202].

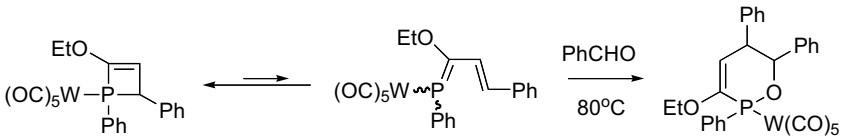
The most straightforward synthesis of phosphetenes relies upon a titanium-phosphorus exchange in titanacyclobutenes (Scheme 23.77) [198].



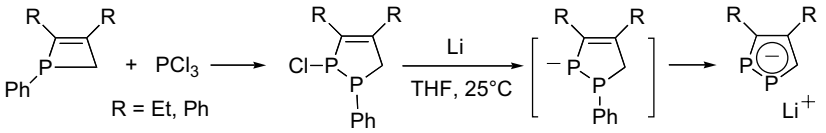
Scheme 23.72



Scheme 23.73

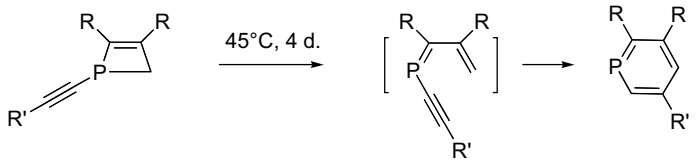


Scheme 23.74

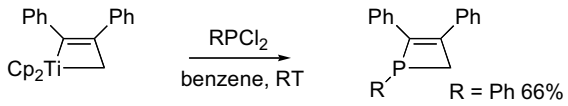


Scheme 23.75

The ring can also be obtained by cyclization of 1-phosphadienes [203, 204] and by [2 + 2] cycloaddition between electron-poor phosphaalkenes and electron-rich alkynes [205].



Scheme 23.76

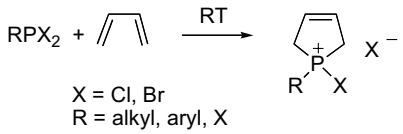


Scheme 23.77

As expected, the phosphete ring is antiaromatic and is only known as stable η^4-transition metal complexes [206].

23.4.3
Five-Membered Rings: Phospholenes

Saturated phospholanes were discovered as early as 1916 [207]. Neither their synthesis nor their chemistry show some specificity by comparison with their acyclic counterparts. Conversely, unsaturated phospholenes, discovered in 1953 by McCormack [208], can be considered as the genuine starting point of phosphorus–carbon heterocyclic chemistry. Their synthesis, via the so-called McCormack reaction, has no equivalent in nitrogen or arsenic chemistry (Scheme 23.78).

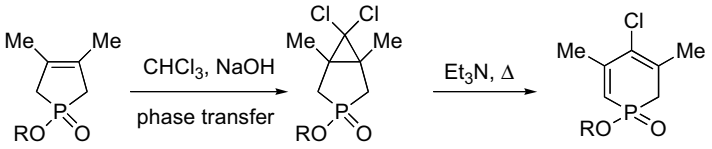


Scheme 23.78

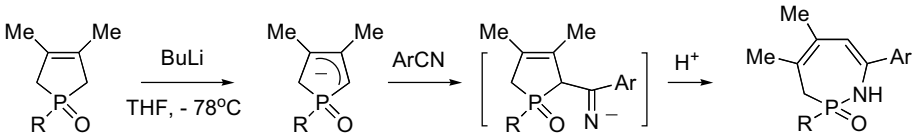
This original cycloaddition reaction and its various applications have been reviewed in some depth in the book of Quin [163]. As a general rule, the reaction takes place slowly at room temperature. Heat cannot be used because the cycloadducts are thermally unstable, but high pressure accelerates the process [209]. Hydrolysis of the adducts gives the phospholene oxides [210], magnesium reduction the tervalent phospholenes [210] and dehydrohalogenation the phospholes [24].

A lot of classical and non-classical chemistry has been performed with phospholene oxides. Ring expansion has been observed upon dichlorocarbene addition (Scheme 23.79) [211].

Another ring expansion occurs upon metallation and reaction with aromatic nitriles (Scheme 23.80) [212].



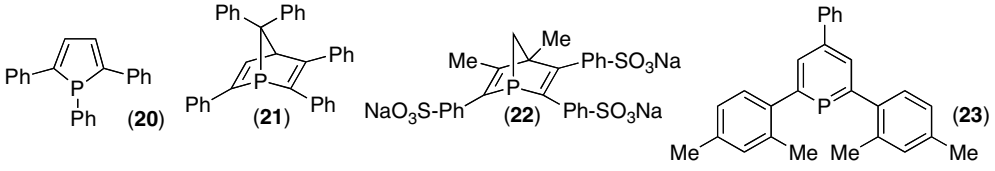
Scheme 23.79



Scheme 23.80

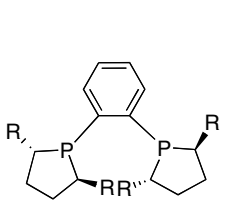
23.5
Applications of Phosphorus Heterocycles

The use of phosphorus–carbon heterocycles as ligands for homogeneous catalysis was considered very early on [213]. It was soon noticed that 1,2,5-triphenylphosphole (**20**) is an excellent ligand, both for the cobalt- and rhodium-catalyzed hydroformylation of olefins. A curious feature of the Rh/(**20**) system is that its catalytic activity does not depend on the Rh/P ratio [214]. The active species appears to be [RhH(CO)(**20**)$_2$] [215]. In the same vein, both the 1-phosphanorbornadiene (**21**) [216] and its water-soluble version (**22**) [217] are efficient ligands for alkene hydroformylation, the second one in the rhodium biphasic Rhône-Poulenc process converting propene into butyraldehyde. More recently, it has been shown that 2,4,6-triarylphosphinine (**23**) is exceptionally efficient for the rhodium-catalyzed hydroformylation of polysubstituted alkenes [218]. The low-lying LUMO of the phosphinine would favor the reductive–elimination steps.

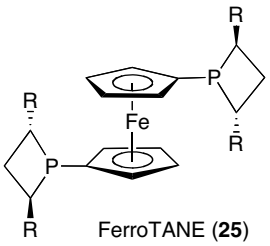


In a different vein, a series of C_2-, C_3-, C_4-bridged bis-(2,3,4,5-teramethylphospholes) have been shown to give remarkably active catalysts for the palladium-promoted copolymerization of ethylene and CO [219]. But the most spectacular applications of heterocyclic phosphines are in the field of enantioselective catalysis. To cite only the best known examples, the phospholane-based DuPHOS (**24**) [220], phosphetane-based FerroTANE (**25**) [221, 222], phosphanorbornane-based PennPhos (**26**) [223] and the phosphanorbornadiene-based BIPNOR (**27**) [224] all display

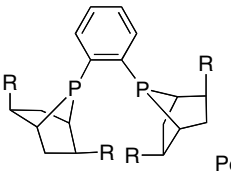
impressive efficiencies in the rhodium- or ruthenium-catalyzed asymmetric hydrogenation of dehydroamino-acids or ketones.



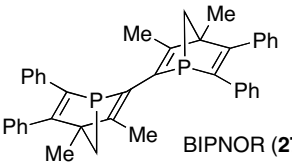
DuPHOS (**24**)



FerroTANE (**25**)

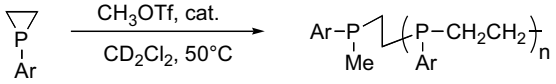


PennPhos (**26**)



BIPNOR (**27**)

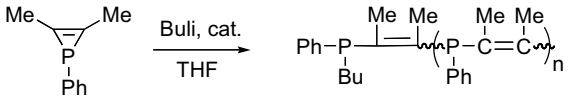
Phosphorus heterocycles are also showing some promise in the field of molecular materials. A low-molecular weight polymer (up to 7800) has been obtained by cationic polymerization of a phosphirane (Scheme 23.81) [225].



Ar = 2,4,6-$^{t}Bu_3C_6H_2$

Scheme 23.81

Based on the chemistry described in Scheme 23.64, the anionic polymerization of a phosphirene has yielded a much higher molecular weight polymer (up to 60 000) (Scheme 23.82) [226].



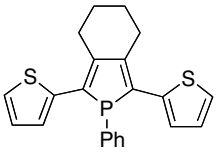
Scheme 23.82

More is certainly to come, since a careful theoretical study has predicted that phosphetanes are better candidates than phosphiranes for radical polymerization [227].

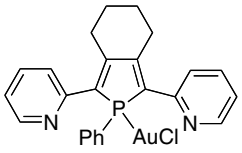
Theoretical studies have shown that α-connected polyphospholes would be better substrates for the preparation of molecular electroconducting materials than the well-known polypyrroles or polythiophenes [228–230]. However, the synthesis of oligophospholes is difficult and only a tetraphosphole is presently known [231].

Interesting results have, nevertheless, been obtained by Réau with mixed thiophene-phosphole and pyridine-phosphole systems. This work has been reviewed [232]. As an illustration, it has been possible to manufacture powerful light-emitting diodes based on phosphole (**28**) [233].

In a completely different vein, a highly potent gold-phosphole inhibitor (**29**) of human glutathione reductase has been described [234].



(**28**)



(**29**)

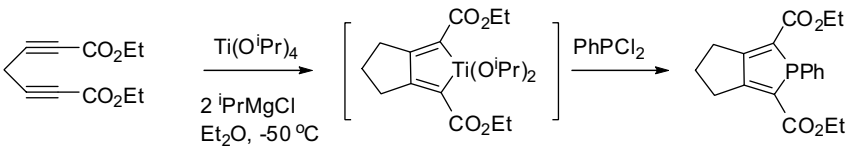
It is, thus, quite clear that phosphorus–carbon heterocyclic chemistry is on the eve of major applications in the fields of homogeneous catalysis, molecular materials and biology.

23.6 Addendum

By far the most significant advances that have taken place in phosphorus heterocyclic chemistry during the last five years (2006–2010) deal with phospholes and phosphinines. Of special interest is the discovery that phospholes are extremely versatile building blocks for the manufacture of optoelectronic materials and that phosphinines display very specific properties as ligands for homogeneous catalysis. These applications are, of course, outside of the scope of this addendum but numerous recent papers and reviews cover these aspects [235–237].

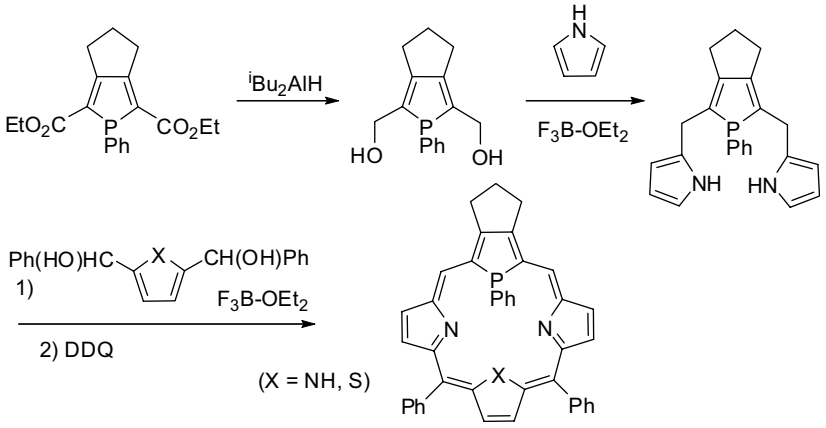
23.6.1 Phospholes

Undoubtedly, the most spectacular results concerning phosphole chemistry have been obtained by the group of Matano while working on the synthesis of phosphaporphyrins. This work has been summarized in a review [238]. A milder variant of the zirconium route to phospholes (Scheme 23.4) using titanium is first used to synthesize phosphole 2,5-diesters (Scheme 23.83) [239].



Scheme 23.83

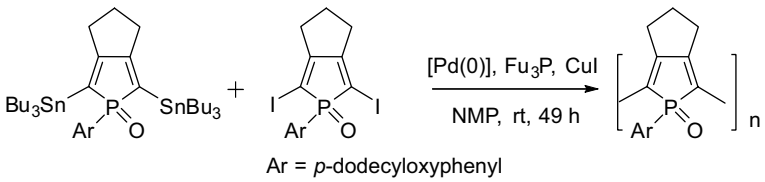
After reduction and acidic condensation with pyrrole, the phosphatripyrrane thus obtained is allowed to react with a heterocyclic 2,5-diol to give the corresponding porphyrinogen, whose oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) affords the heteroporphyrin (Scheme 23.84) [240].



Scheme 23.84

Several variations around this basic scheme lead to phosphole-containing calixpyrroles, calixphyrins, and sapphyrins. The use of a perfluorophenyl substituent at phosphorus enhances the yields and the stability of these rings [241]. Extensive 18π cyclic delocalization in these structures has been demonstrated by NMR and DFT calculations. The coordination chemistry of these new macrocycles has been studied extensively [242–244].

We have previously mentioned the synthesis of a α-connected tetraphosphole [64]. Unfortunately, higher oligomers were not accessible by this route. Very recently, the group of Matano has demonstrated that this impossibility is a consequence of the 3,4-dimethyl substitution preventing the coplanarity of the phosphole rings. Indeed, when using the less demanding cyclopentane annulation, a polyphosphole oxide can be efficiently obtained (Scheme 23.85) [245].

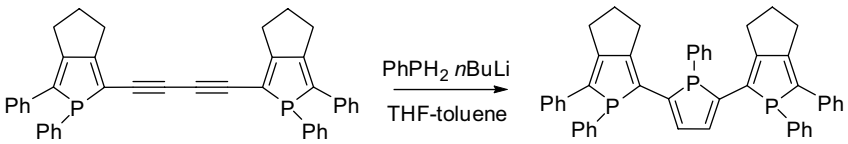


Scheme 23.85

The dodecyloxy substituent is used for solubility. The polymer is obtained as a deep-blue solid in 51% yield with an average molecular weight of 13 000.

The polyphosphole oxide displays a very narrow band gap and an absorption maximum at 655 nm – significantly redshifted by comparison with polythiophene.

Matano has also reinvestigated the synthesis of α-substituted alkynylphospholes using his titanium route [246]. This has led to the synthesis of an original terphosphole (Scheme 23.86).

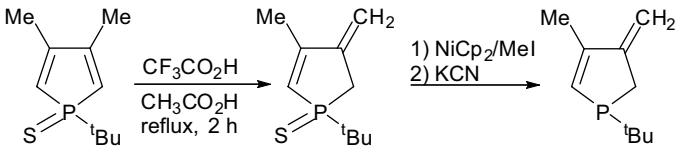


Scheme 23.86

The three phosphole rings are coplanar, contrary to what was previously observed in the quaterphosphole [64].

Finally, the group of Mathey has described the synthesis of phosphole isomers whose nucleophilicity is similar to that of tris(*tert*-butyl)phosphine as a result of the destabilizing overlap between the lone pair and the HOMO of the diene (Scheme 23.87) [247].

These ligands look promising for catalytic applications.

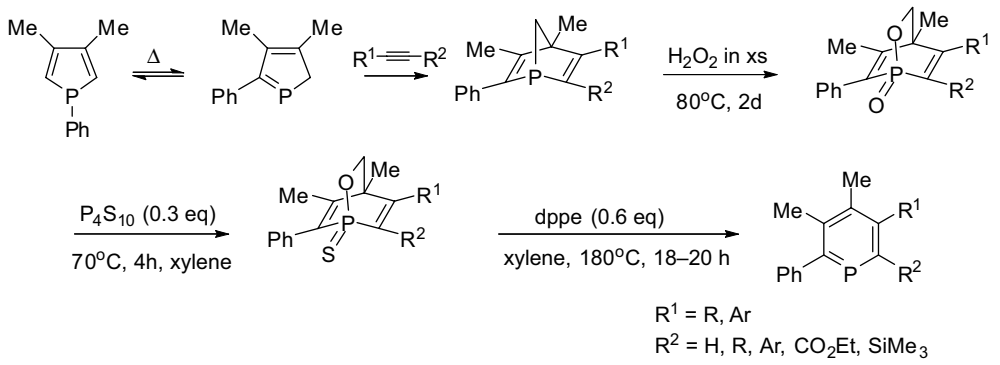


Scheme 23.87

23.6.2 Phosphinines

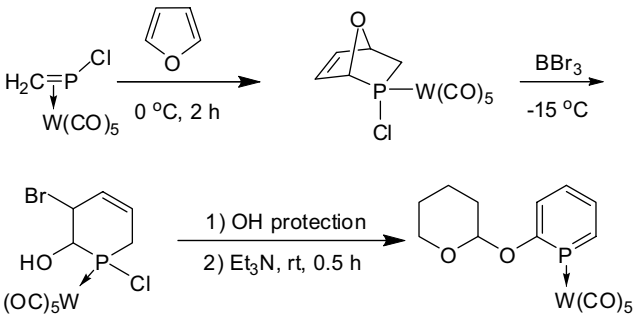
A conversion of phospholes into phosphinines via 1-phosphanorbornadienes has been described in Scheme 23.32. Its drawback is that the extrusion of the carbene bridge works only for the diphenyl-substituted species at high temperature (230 °C). To generalize this potentially useful route, a selective oxidation of the P–C bridge bond has been carried out. The non-concerted extrusion of the triplet diphenylcarbene is replaced by the concerted extrusion of singlet formaldehyde. The aromatization takes place at lower temperature (180 °C) and the reaction is compatible with several functionalities (Scheme 23.88) [248].

A potentially versatile transformation of furans into phosphinines has also been devised. All the steps are performed at or below room temperature. Protection of the



Scheme 23.88

OH group is necessary to avoid a ring expansion into 1,2-oxaphosphepines (Scheme 23.89) [249].



Scheme 23.89

The main advance in the chemistry of phosphinines is the description of the first protonated species. The protonation of 2,4,6-tris(*tert*-butyl)phosphinine at phosphorus is carried out with a carborane superacid $H[CHB_{11}Me_5Cl_6]$ [250]. The resulting salt gives a ^{31}P resonance at 60 ppm with a $^1J_{PH}$ coupling of 625 Hz. The X-ray crystal structure analysis shows a strictly planar ring with short P−C bonds (1.696–1.698 Å). In the same vein, stable phosphinine sulfides have been fully characterized by NMR spectroscopy and X-ray crystal structure analysis. Their electronic structure has been studied by DFT [251].

Finally, another noteworthy result concerns the synthesis of the first enantiopure atropisomeric phosphinines using the original synthesis of Märkl (Scheme 23.26) [252]. The enantiomers are separated by HPLC on a chiral stationary phase. The barrier to racemization has been determined: $\Delta G^{\neq}_{298} = 109.5 \pm 0.5\ \text{kJ mol}^{-1}$.

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24
The Chemistry of 2-Azetidinones (β-Lactams)

Benito Alcaide, Pedro Almendros, and Amparo Luna

24.1
Monocyclic Derivatives

24.1.1
Introduction

The large number of recent reports on β-lactam chemistry demonstrates the increasing interest in this important class of compounds. Monocyclic β-lactams frequently serve as precursors for the synthesis of classical bicyclic β-lactam antibiotics. The cyclic 2-azetidinone skeleton has been extensively used as a template on which to build the heterocyclic structure fused to the four-membered ring, using the chirality and functionalization of the β-lactam nucleus as a stereocontrolling element. The discovery of nonclassical β-lactam antibiotics, such as monobactams and nocardicins, coupled with ever-growing new applications such as enzyme inhibition has triggered a renewed interest in the building of new monocyclic β-lactam derivatives. Besides the utility of β-lactams as biologically active agents, they are used as intermediates in α- and β-amino acid synthesis, as well as building blocks for alkaloids, heterocycles, taxoids and other types of compounds of biological and medicinal interest.

24.1.2
Physicochemical Data

24.1.2.1 Computational Chemistry

Theoretical studies show that β-lactams are weaker bases, in the gas phase, than acyclic amides [1]. The attenuation of basicity upon cyclization is stronger than that found for cyclic ketones of similar size due to the existence of a negative hyperconjugation effect that is present in β-lactams but not in cyclic ketones. *Ab initio* calculations indicate that both β-lactams and acyclic amides are oxygen bases, but the gap between the oxygen and nitrogen intrinsic basicities is much smaller in the former due to the aforementioned cyclization effects. This decrease of the oxygen

Modern Heterocyclic Chemistry, First Edition.
Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.

intrinsic basicity of β-lactams with respect to the aliphatic amides of the same size is a direct consequence of the hybridization changes undergone by the carbonyl carbon and is very well described by a topological analysis of the corresponding electronic charge densities. The topological analysis of bond activations upon protonation reveals that for 2-azetidinones these effects are not dramatic when protonation takes place at the oxygen atom, whereas they are quite significant if protonation takes place at the ring nitrogen.

Model chiral β-lactam molecules, (3*S*)- and (4*R*)-fluoro-2-azetidinone, have been calculated at the B3PW91/aug-cc-pVTZ level to be hydrogen bonded with achiral HX molecules (X = F, Cl, Br) [2]. Two stable structures of the complex are possible: a cyclic or a bent H-bond, in which the HX molecule interacts with the CO group and is either close to NH or CH_2 (CHF) moiety, respectively. The VCD effect of these two forms differs in several respects; however, the main difference is the sign of the VCD rotational strength of the ν(HX) stretching vibrations, revealing the geometry of the hydrogen bond complex. A related report on halogenoazetidinones has considered in the influence of the halogen atom, at the C4 position of the 2-azetidinone ring, on the geometry, IR, Raman and vibrational circular dichroism spectra [3]. The vibrational spectra were calculated for the chiral (4*R*)-X-2-azetidinone (X = F, Cl or Br) molecules at the B3PW91/aug-cc-pVTZ level. It was shown that the geometry of the molecules studied do not change much upon changing the halogen atom. In case of the vibrational spectra, the position and, even more so, the intensities depend strongly on the kind of halogen substituent.

Ab initio MP2/6-31G(d,p) and 6-31 + + G(d,p) calculations have been performed to investigate the intramolecular hydrogen-bonding in two model monocyclic β-lactams: monobactams and nocardicins [4]. It was found that the intramolecular C=O ··· H−O=S− hydrogen bond stabilizes a monobactam, while a nocardicin is destabilized by C=O ··· H−O−C=O− hydrogen bond formation. This observation suggests that monobactams could block themselves by the intramolecular bond and, therefore, could be less active towards a receptor active site than nocardicins.

The effect of an ancillary water molecule on the neutral and alkaline hydrolysis mechanisms of a simple β-lactam molecule (*N*-methylazetidinone) has been studied at the Hartree–Fock and MP2 levels using the 6-31G* and 6-31 + G* basis sets [5]. Solvent effects have been also considered by means of a polarizable continuum model. In neutral hydrolysis, the additional water molecule diminishes the free-energy barriers only when correlation energy is taken into account, Concerted and stepwise mechanisms have been described. The corresponding barriers are close, and the actual mechanism could be conditioned by the molecular environment, solution, protein, and so on. Using the results of a molecular dynamics simulation of *N*-methylazetidinone in aqueous solution, it has been shown that the stepwise process is more likely to occur in such conditions. In alkaline hydrolysis, the first reaction step consists of the formation of a tetrahedral intermediate that requires a desolvation of the hydroxyl anion, which is difficult to reproduce by calculation. Afterward, the hydrolysis reaction proceeds through either concerted or stepwise mechanisms for ring opening and proton transfer. The concerted channel presents a very low energy barrier, and the species involved are dependent on the calculation

level. The stepwise mechanism is virtually the same as that previously reported for the unassisted hydrolysis, the relative energy of all the points along the path being diminished and the energy barriers remaining essentially unaltered.

Kinetic experiments have been performed to characterize the reactivity of aztreonam against amine nucleophiles relative to that of penicillin compounds (6-APA) [6]. The magnitude of the experimentally determined kinetic constants (k_1, k_2 and k_3) shows that aztreonam is slightly more reactive than 6-APA, despite common assumptions that the amide bond should be less activated in monobactams. Interestingly, these kinetic results are consistent with the experimentally determined rate for aztreonam covalent linkage to the ε-amino groups of lysine residues in HSA plasma proteins (70% of the initial aztreonam fixed to HSA after 24 h of reaction), which is higher than that reported for benzylpenicillins (3% after 48 h). Furthermore, the kinetic influence of substitution on the attacking nucleophile was also investigated. Most remarkably, for ethanolamine in reaction with either aztreonam or 6-APA, the corresponding rate law has a kinetic term proportional to $[RNH_2][RNH_3^+]$, in contrast with previous reports on the reaction between benzylpenicillin and ethanolamine. To gain a better understanding of the various effects controlling the rates of the reactions between β-lactams and amines, the molecular details of the reactive processes have been investigated by quantum chemical calculations. The APA and MONO model systems were considered to compute the rate-determining $\Delta G_{solution}$ barriers corresponding to various reaction mechanisms, all involving bifunctional catalysis by water, a second amine molecule or the *N*-sulfonate groups of monobactams. The theoretical results confirm the ability of the water-assisted (k_1) and amine-assisted (k_2) mechanisms to explain experimental data on the aminolysis of β-lactams. Thus, the computed $\Delta G_{solution}$ barriers have moderate values ranging from about 26 to about 34 kcal mol^{-1}. For the aminolysis of monobactams, the previously proposed *N*-SO_3^--assisted mechanism turns out to be 5.2 kcal mol^{-1} less stable than the water-assisted route. Moreover, the theoretical calculations undertaken in this study satisfactorily reproduce several experimentally observed kinetic trends: the prevalence of the amine-assisted mechanism (k_2 term in the rate law) over the water-assisted route (k_1) and the higher reactivity exhibited by the monobactam. Nevertheless, the most interesting prediction made by these calculations is that the kinetic term in the experimental rate law proportional to $[CH_2OHCH_2NH_2]\cdot[CH_2OHCH_2NH_3^+]$ can be interpreted in terms of the bifunctional catalysis performed by the hydroxy group of the protonated amine molecule. Finally, from comparison between experimental and theoretical data, it was concluded that a combination of standard DFT gas-phase calculations with SCRF solvation methodologies can yield relative $\Delta G_{solution}$ barriers with semiquantitative accuracy and give valuable insights into the various factors controlling the rate of chemical processes in the condensed phase.

24.1.2.2 **Experimental Structural Methods**

The analysis of β-lactams by X-ray diffraction indicates that the four-membered ring is planar. Several 2-azetidinone derivatives, for example, β-lactam pseudopeptides [7],

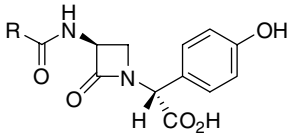
4-aryl-substituted β-lactams [8], 3,3-dichloro-*N*-*p*-methoxyphenyl-4-(2-phenylstyryl)-2-azetidinone [9], 4-(2-oxoethylidene)azetidin-2-ones [10], isoxazolidinyl- and pyrrolidinil-β-lactams [11], 4-(1-hydroxy-3-oxobutyl)-β-lactams [12] and an oxiranyl-β-lactam [13], have been recently studied by X-ray crystallography.

The method most useful for the determination of the relative stereochemistry of β-lactams is ^{1}H NMR spectroscopy. The assignment of the cis-stereochemistry to β-lactams is based on the observed coupling constants of about 5.0 Hz for methine protons H3 and H4, whereas trans-stereochemistry is consistent with methine coupling constants of *about* 2.0 Hz in their ^{1}H NMR spectra [14]. The ^{13}C NMR spectra of 2-azetidinones show the carbonyl resonance between 160 and 167 ppm. Interestingly, the carbonyl resonances of γ- and larger-membered lactams appear between 170 and 180 ppm. The infrared C=O absorption frequency for the monocyclic 2-azetidinone ring is about 1745 cm^{-1}.

24.1.3
Biologically Relevant Monocyclic β-Lactams

The word "antibiotic" refers to a chemical agent that either kills or prevents the growth of microorganisms and is itself derived from a microorganism. Although the term "antimicrobial" is better and more precise because it includes the synthetic agents that have been commonly employed for several decades to treat infections, for ease of use the prevalent term antibiotic will be kept herein.

The minimum structural features believed to be essential for antimicrobial activity in the β-lactam antibiotics have undergone considerable revision. Since in recent years several natural monocyclic β-lactams have been shown to exhibit high antibacterial activity, it now appears that the minimum requirement for biological activity is a suitably substituted monocyclic 2-azetidinone ring. The most representative examples of these monocyclic β-lactams exhibiting antibiotic activities are the naturally occurring nocardicins **1** [15], and monobactams **2** [16].



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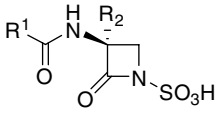

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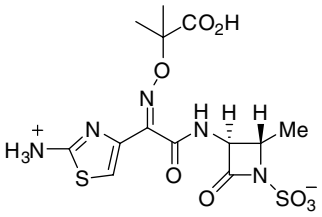
The common structural feature of these monocyclic β-lactams is the absence of substitution at the C4 carbon of the 2-azetidinone ring. The antibiotic activity of this type of β-lactams has stimulated considerable activity in this area. As a consequence, aztreonam (**3**) [17] and carumonam (**4**) [18], both with a monobactam structure but bearing substituents at C4, have been synthesized. The relevant feature of these compounds is the β-lactam nucleus, but the nature as well as the sterical arrangement of the substituents also play an important role in the antibiotic activity.



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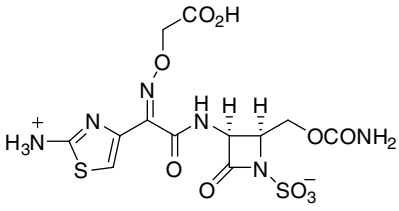
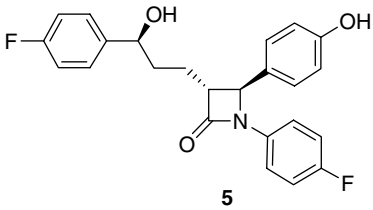


4

Recent discoveries have shown other biological properties of these compounds apart from their antibacterial action. Some of the more notable advances concern the use in gene activation as well as the development of mechanism-based serine protease inhibitors of elastase, cytomegalovirus protease, thrombin, prostate specific antigen, and cell metastasis and as inhibitors of acyl-CoA cholesterol acyl transferase [19]. The cholesterol-lowering agent ezetimibe (**5**) [20], as well as the irreversible inhibitor of glutamine synthetase tabtoxinine-β-lactam (**6**) [21], are representative example of these trends.



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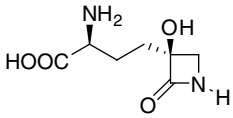

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24.1.4
2-Azetidinone Nucleus Synthesis

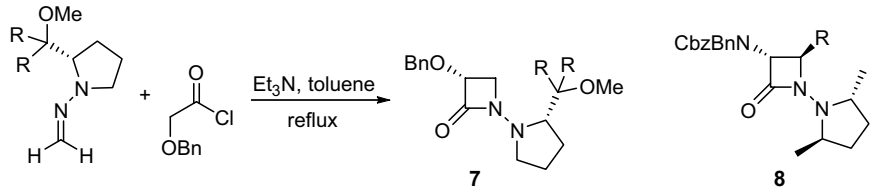
The vast number of syntheses of β-lactams amply illustrates the ongoing vitality of 2-azetidinone chemistry. Obviously, this chapter cannot offer a comprehensive description of all the aspects of the various types of β-lactam syntheses emanating from research groups active in this area, and so we have concentrated our efforts on the more relevant aspects. Major synthetic routes, for example, the cycloaddition of ketenes and imines, cannot be covered completely and readers are advised to consult reviews on this topic for more details.

24.1.4.1 **Ketene-Imine Cycloaddition (Staudinger Reaction)**

[2 + 2] Cycloaddition reactions between ketenes, bearing amino-, oxy-, or halo-groups, and imines are recognized as being among the most important and direct routes to β-lactams [22]. Alkyl-substituted ketenes also furnish the corresponding β-lactams upon reaction with activated imines (iminoesters). In general, ketenes are generated from the appropriate acid chloride and a tertiary amine. The major or sole product of the cycloaddition is usually the *cis*-β-lactam, although a few exceptions showing trans selectivity are known. In this way β-lactams with a widely varying

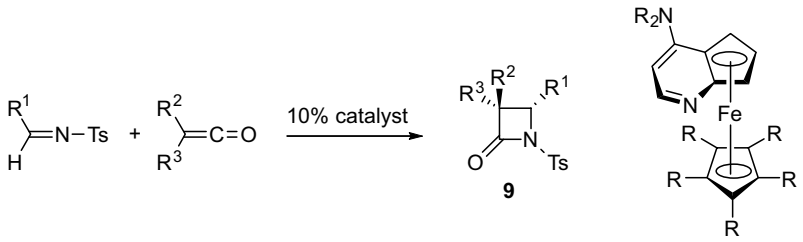
substitution pattern at the C3 and C4 positions of the ring are constructed stereoselectively. The diastereoselection of the cycloaddition process can be controlled with variable success from chiral groups attached to either the ketene or the imine component, or alternatively to both. More recently, chiral catalysts have been used in the asymmetric Staudinger reaction.

Staudinger-like cycloaddition between proline-derived formaldehyde hydrazones and functionalized ketenes constitutes an efficient methodology for the stereoselective construction of 4-unsubstituted β-lactams **7** (yield: 80–96%, dr up to 99 : 1) (Scheme 24.1) [23]. Enantiopure *N,N*-dialkylhydrazones react with *N*-benzyloxycarbonyl-*N*-benzyl glycine as an aminoketene precursor to afford *trans*-3-amino-4-alkylazetidin-2-ones **8** as single diastereomers [24a]. Oxidative N−N bond cleavage of cycloadducts **7** and **8** afforded free N-H-azetidinones in high yields [24b].



Scheme 24.1

Lectka and colleagues have reacted achiral ketenes with achiral imines to achieve asymmetric induction in the synthesis of *cis*-β-lactams through the use of a bifunctional catalyst system consisting of a chiral nucleophile (benzoylquinine) and an achiral Lewis acid [25], while a catalytic, highly diastereoselective process for the synthesis of *trans*-β-lactams has been reported based on a phosphonium fluoride precatalyst that both activates the nucleophile and directs the reaction process for high yield and diastereoselectivity [26a]. It has been demonstrated as well that a planar-chiral azaferrocene derivative of 4-(pyrrolidino)pyridine is an excellent catalyst for the enantioselective Staudinger reaction, providing β-lactams **9** with very good stereoselection and yield (Scheme 24.2) [26b].

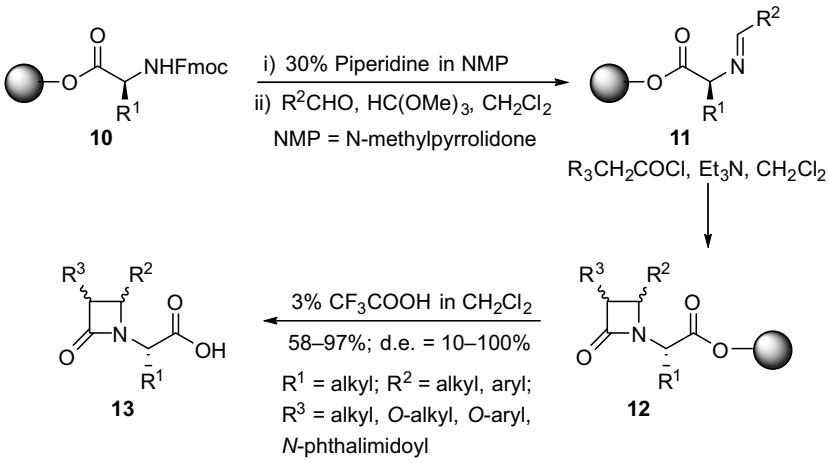


Scheme 24.2

More recently, azolium salts that belong to the extraordinary class of N-heterocyclic carbenes (NHCs) have been found to be efficient catalysts for the enantioselective

synthesis of β-lactams through Staudinger reaction of ketenes with *N*-tosyl, *N*-benzyloxycarbonyl, *N*-*tert*-butoxycarbonyl, or *N*-(4-nitrobenzenesulfonyl) imines [27].

The rapid development of solid-supported combinatorial chemistry has increased in a spectacular way the complexity and the diversity of reactions by using solid support. Among others, the Staudinger reaction has found various uses in polymer-assisted synthesis [28]. Sasrin, preloaded with an Fmoc-protected (Fmoc = 9-fluorenylmethoxycarbonyl) amino acid, has been used by Gallop as the starting material **10** (Scheme 24.3) [29]. After deprotection, the resin yields a free primary amine, which can be reacted with aldehydes, in the presence of trimethyl orthoformate as a desiccant, to afford the desired polymer-bound imines **11**. These, in turn, are treated with an acid chloride in the presence of triethylamine to produce the polymer-supported β-lactams **12**, which are liberated from the resin to give in good yields 2-azetidinones **13** by treatment with CF_3COOH. The polymer-bound lactams can be further derivatized by Suzuki and Heck coupling reactions, upon selection of properly functionalized aldehydes, to form the imines. The Staudinger reaction on a solid phase has also been accomplished using imines obtained from commercially available fluorinated α-amino acids. Thus, the β-lactam formation on a solid phase can be monitored by ^{19}F NMR spectroscopy [30].



Scheme 24.3

The stereochemical selectivity of this procedure, through the effect of chiral ketenes and chiral imines, has also been investigated [31]. In both cases only cis-diastereomers are observed. The diastereoselectivities of the β-lactams produced were in a range of 8 : 1 to greater than 25 : 1 when using a ketene bearing a chiral oxazolidinone moiety, and a range of 2 : 1 to greater than 25 : 1 when using chiral aldehydes to form the imines.

In the previous examples, the imine intermediate is generated from a polymer-bound amine, but it may also be generated from a polymer-bound aldehyde [32]. The use acetoxyketene [33] allows further modifications to give carbamate products. This

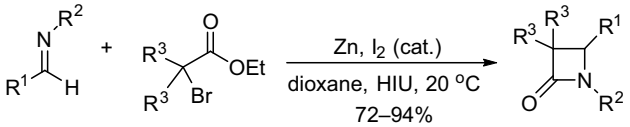
chemistry has been extrapolated to the synthesis of enantiomerically enriched β-lactams starting from a polymer-bound version of Garner's aldehyde [34]. A polymer-supported Mukaiyama-type reagent has been used for the preparation of β-lactams, using the Staudinger reaction. The products were obtained by generating the ketene from a carboxylic acid under sonication with the resin followed by reaction with the imine [35]. These approaches also exclusively produce the cis-diastereomers of the lactams. The solid-phase synthesis of *trans*-3-alkyl-β-lactams from non-activated acid chlorides has been reported recently [36].

Lectka has devised a method in which a polymer-bound base, used as a packing material for a jacketed column cooled to −78 °C, effects the dehydrohalogenation of acyl halides to generate ketenes [37]. When a solution of the acid chloride is added to the top of the column, a solution of the ketene percolates at the bottom and can be either trapped by another reagent or eluted through another column packed with a different polymer-bound reagent/scavenger for further transformations. The use of a polymer-bound cinchona alkaloid as both the nucleophilic catalyst and the base effecting the dehydrohalogenation has been reported [38]. This polymeric reagent was regenerated *in situ* with K_2CO_3 or sodium hydride in a rather unusual solid-gel shuttle deprotonation between a solid and a gel. Although this β-lactam formation involves a single step, the presence of a regenerating base seems to induce some scrambling in its stereoselectivity. All of the polymers can be recycled by simply eluting washing solutions through the columns, which seems to have only a marginal effect on the reaction results.

24.1.4.2 **Metalloester Enolate-Imine Condensation**

The metalloester enolate-imine condensation represents one of the most popular entries to β-lactams [39]. Various ester types and imine types can be utilized in this one-pot reaction between imines and metal ester enolates (or their synthetic equivalents, the silylketene acetals). The reaction can be promoted by various metals, including aluminium, boron, indium, lithium, titanium, zinc and zirconium.

The Reformatsky addition reaction to imines has been employed as a method to synthesize β-lactams. For example, in the presence of Zn/Cp_2TiCl_2 (cat.), α-bromoacetates, or γ-bromocrotonates, react with imines in one-pot to form β-lactams, at room temperature without the need for pretreatment of the solvent and Zn [40]. Reformatsky reactions between enolizable and non-enolizable aldimines and α-bromoesters of differing steric demands, in the presence of zinc dust and a catalytic amount of iodine in dioxane under high intensity ultrasound (HIU) irradiation afford short reaction times and high yields of β-lactams **14** (Scheme 24.4) [41]. In a similar way, indium can mediate the synthesis of 3-unsubstituted β-lactams [42].



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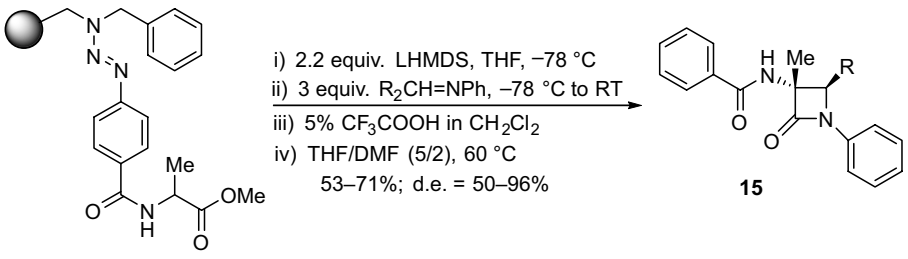
Scheme 24.4

The use of silyl enolates or S-thioester, instead of carboxylic ester, metal enolates in the condensation with imines provides a mild route to 2-azetidinones. 2,2′-Dibenzothiazolyl disulfide is a versatile reagent that provides a convenient and efficient route for the synthesis of β-lactams from Schiff's bases and alkoxy/aryloxy acetic acids. The process involves the formation of thioester of the corresponding acid. Finally, condensation of titanium enolates, derived from these esters, with imines completes the synthesis of 2-azetidinones [43]. Highly substituted β-lactams have been synthesized by addition of air-stable ethyl(trimethylsilyl)acetate derivatives to *N*-(2-hydroxyphenyl)aldimine sodium salts [44].

The asymmetric version of the metalloester enolate-imine condensation route has been explored using a chiral enolate. The diastereoselectivity of the reaction of the lithium enolate of menthyl isobutyrate with imines has been improved by the addition of a catalytic amount (5 mol%) of a chiral tridentate aminodiether ligand to give the corresponding β-lactams in high enantioselectivities [45a]. Matching and mismatching phenomena were observed by the reaction of L- and D-menthyl isobutyrates. The asymmetric Reformatsky-type reaction of (–)-menthyl bromodifluoroacetate with imines in the presence of $RhCl(PPh_3)_3$ affords (*S*)-difluoro-β-lactams in moderate to good yields and high diastereoselectivities through spontaneous removal of the auxiliary [45b]. A systematic investigation of chiral ligand mediated addition of imines to lithium ester enolates to give β-lactams has been carried out to study the effects of the variation of the alkoxy group in the latter reagent [46]. A maximum of 93% ee was obtained.

The ester enolate-imine condensation route to β-lactams via an immobilized ester enolate has been achieved [47]. The key reaction in the synthesis is the cyclization of the resin-bound ester dianion and an imine. Traceless cleavage from the T1-triazene linker system yields the desired β-lactams (Scheme 24.5).

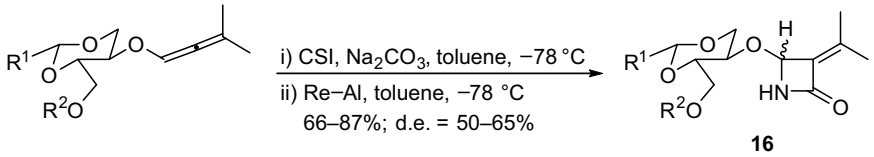


Scheme 24.5

24.1.4.3 **Isocyanate-Alkene Cyclocondensation**

The reaction of isocyanates with alkenes to give β-lactams requires activation of the isocyanate moiety by electron-withdrawing substituents or activation of the alkene partner by electron-donating groups. 4-Aryl-2-azetidinones have been prepared by reacting *N*-chlorosulfonyl isocyanate with styrene and 4-methylstyrene [48]. The reaction between the same isocyanate with an enantiopure *(E)*-vinyl sulfide gives a 2.5 : 1 diastereomeric mixture of phenylthioazetidinones [49]. The facial selectivity

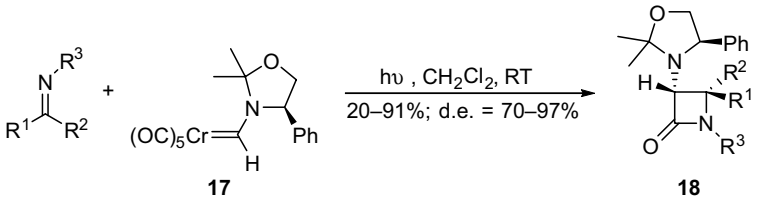
in the cycloaddition is explained by the conformational preference of the allylic groups in the transition structure. The [2 + 2] cycloaddition of chlorosulfonyl isocyanate (CSI) to alkoxyallenes derived from ethylidene and benzylidene erythritols and threitols proceeds with a moderate asymmetric induction in the case of the erythritols (Scheme 24.6) and with a very low induction in the case of threitols. This indicates that the erythritol derivatives may exist in solution in one predominant conformation while the threitol derivatives behave as a conformational ensemble [50].



Scheme 24.6

24.1.4.4 Chromium Carbene-Imine Cyclization

The preparation of 2-azetidinones through the photochemical reaction of chromium carbene complexes with imines is a convenient method [51]. A vast array of imines, including simple imines, α-iminoketones, α-diimines, iminodithiocarbonates, and ferrocene imines [52], can be used. The asymmetric version of this route can be accomplished on using enantiopure chromium carbenes, such as the *(R)*-phenylglycine derivative **17**, which allowed the preparation of optically active β-lactams **18** (Scheme 24.7) [53]. A theoretical-experimental approach to the mechanism of the photocarbonylation of chromium(0) (Fischer)-carbene complexes and their reaction with imines to give β-lactams has been published [54].

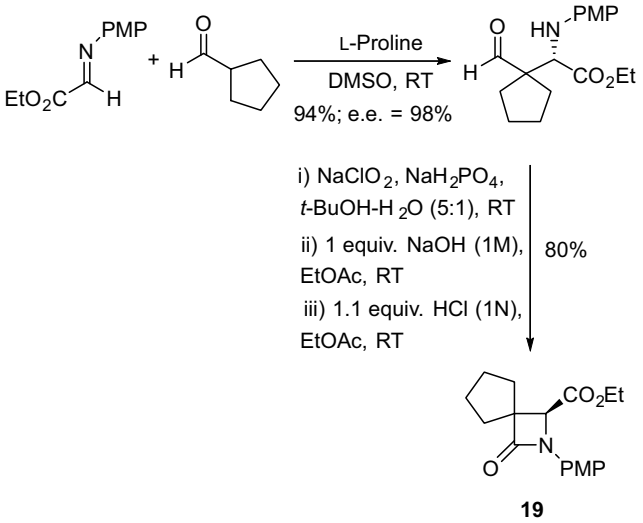


Scheme 24.7

24.1.4.5 Cyclization of β-Amino Acids and Derivatives

The cyclization of β-amino acids to give β-lactams can be achieved through the use of a numerous reagents and conditions [55]. Interesting examples include the preparation of C3 unsubstituted β-lactams by using *tert*-butylmagnesium chloride [56], the synthesis of 2-azetidinones bearing a C4 quaternary stereocenter by using 4-pyrrolidinopyridine [57], the preparation of the key β-lactam precursor in the total synthesis of lankacidin C [58], the preparation of the chartelline framework by simple heating [59], the LHMDS-promoted cyclization of an aspartic acid derivative to

provide a carbapenem PS-6 precursor [60] and the preparation of the spirocyclic β-lactam **19** by sequential base and acid treatment (Scheme 24.8) [61].



19

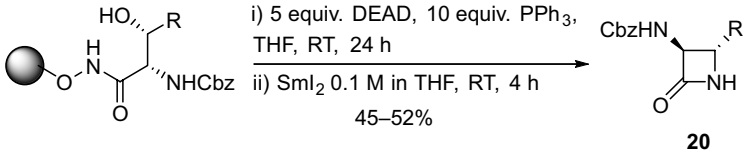
Scheme 24.8

24.1.4.6 **Hydroxamate Cyclization**

The cyclization of a β-hydroxyhydroxamate derived from an amino acid is a straightforward approach to 2-azetidinones [62]. The stereoselective synthesis of 3,4-substituted β-lactams by bromine-induced oxidative cyclization of *O*-acyl β,γ-unsaturated hydroxamic acid derivatives is a classical example [63]. The intramolecular Mitsunobu reaction of a β-hydroxy hydroxamic acid derivative has been used for the preparation of the β-lactam precursors in the preparation of cobactin analogs and in the total syntheses of pateamine A and sitagliptin [64]. A related contribution is the cyclization of β-hydroxy-α-thioalkylhydroxamates in the presence of $AgClO_4$ [65]. The hydroxamate synthesis of β-lactams carried out on solid phase has been reported [66]. The strategy chosen was to link the amino acid derivative to a polystyrene-supported hydroxylamine, and finally carry out the cyclization under Mitsunobu conditions. This approach is particularly suitable for solid-phase synthesis as the supported β-lactam can be easily separated from the by-products of the Mitsunobu reaction. The linker employed was a polystyrene resin carrying a *O*-trityl-hydroxylamine linker. The cyclization occurred in THF using freshly distilled DEAD and PPh_3. The resin was treated with a commercially available solution of SmI_2 in THF, and free 2-azetidinones **20** were recovered from the solution after hydrolytic workup and passage through a short silica gel column (Scheme 24.9).

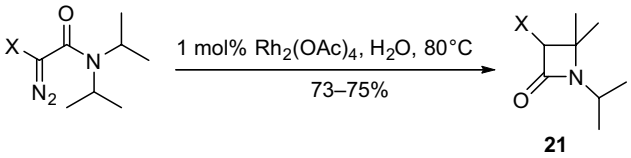
24.1.4.7 **Metal-Catalyzed Insertions of Diazo Compounds**

In recent years, metal-catalyzed intramolecular C−H insertion has emerged as a general strategy for the construction of numerous cyclic and heterocyclic



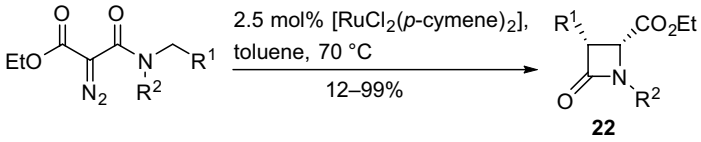
Scheme 24.9

compounds, among which β-lactams are especially noteworthy [67]. The success of this approach is related to the level of regio- and stereocontrol and, in some cases, to the high enantioselectivity of the C−H insertion process. It has been recently demonstrated that water is an efficient solvent for the $Rh_2(OAc)_4$-catalyzed intramolecular C−H insertion of a range of diazo substrates to yield 2-azetidinones **21** without competitive water insertion (Scheme 24.10) [68]. Owing to the high solubility and stability of the catalyst in water, the catalyst can be efficiently reused.



Scheme 24.10

An operationally simple catalytic system based on $[RuCl_2(p\text{-cymene})]_2$ has been developed for the stereoselective cyclization of α-diazoacetamides by intramolecular carbenoid C−H insertion, and β-lactams **22** have been produced in excellent yields and >99% cis-stereoselectivity (Scheme 24.11) [69a]. The Ru-catalyzed reactions can be performed without the need for slow addition of diazo compounds and inert atmosphere. The stereoselectivity of the related polymer-supported ruthenium-catalyzed intramolecular carbenoid C−H insertion of α-diazoacetamides to yield β-lactams has been shown to be similar to the analogous reactions with the homogeneus $[RuCl_2(p\text{-cymene})]_2$ catalyst [69b].

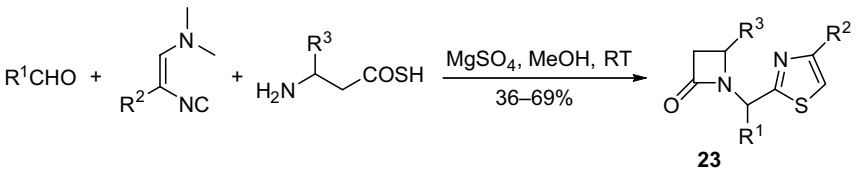


Scheme 24.11

Aryl tosylhydrazones are converted into β-lactams in good yields and remarkable cis selectivity (up to 99%) using a ruthenium porphyrin-catalyzed stereoselective intramolecular carbenoid C−H insertion [70].

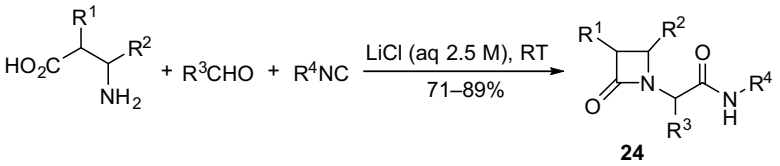
24.1.4.8 **Multicomponent Reactions**

Multicomponent reactions (MCRs) have recently emerged as a highly valuable synthetic tool in the context of modern drug discovery. The atom economical and convergent character, the simplicity of a one-pot procedure, the possible structural variations, the accessible complexity of the molecules, as well as the very large number of accessible compounds are among the described advantages of MCRs. Thus, for example, the reactivity of transition-metal catalysts can be exploited to design one-step methods to convert readily available building blocks directly into a diverse array of products, including β-lactams [71]. A multicomponent reaction of β-aminothiocarboxylic acids, aldehydes and 3-dimethylamino-2-isocyanoacylate has been used for the preparation of β-lactams **23** (Scheme 24.12) [72]. During this reaction two heterocyclic moieties, a thiazole and a 2-azetidinone ring, are formed simultaneously and under mild conditions. The increase in molecular complexity here is dramatic as two C−N, two C−S and one C−C bonds are formed in a new "one-pot" multicomponent reaction.



Scheme 24.12

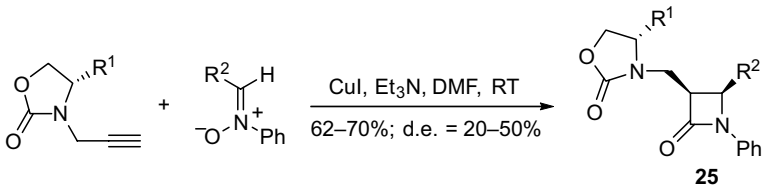
A tandem Petasis–Ugi multicomponent condensation strategy and 1,3-diisopropylcarbodiimide condensation reaction can be used to prepare aza-β-lactams containing two to four elements of diversity [73a]. Although the yields are only moderate, the methods provide rapid entry into this interesting structural class of molecules. The creation of the β-lactam ring by Ugi reaction with β-keto-acids is unknown in organic solvents, as exemplified by the complete failure of the reaction in MeOH, THF or CH_2Cl_2. However, this reaction proceeds well in water to give 2-azetidinones **24** (Scheme 24.13) [73b]. A library of 32 β-lactams has been created by Ugi reaction in water. The HPLC purity of the crude reactions products was 70–99%, and the yields of these products were 71–89%.



Scheme 24.13

24.1.4.9 Coupling of Terminal Alkynes and Nitrones (Kinugasa Reaction)

The Kinugasa reaction is a convergent route to β-lactams through the reaction of a copper acetylide with a nitrone [74]. Appealing features of this process include the ready availability of the starting materials and its high functional group tolerance. The Kinugasa reaction has been used for the asymmetric synthesis of β-lactams **25** via cycloaddition between chiral oxazolidinyl propynes (or related chiral ynamides) and nitrones, in the presence of cuprous iodide (Scheme 24.14) [75].

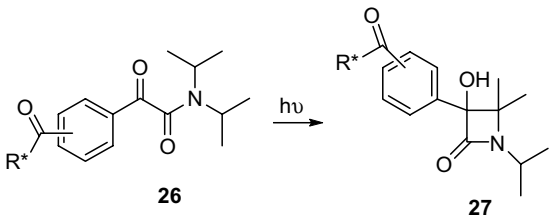


Scheme 24.14

Recently, asymmetric Kinugasa reactions have been accomplished using enantioselective catalysis. Thus, 3-exomethylene β-lactams have been obtained via Cu(I)-mediated cycloaddition between propargyl alcohol and nitrones in the presence of L-proline [76a], while 3,4-diaryl β-lactams have been observed for the asymmetric intermolecular Kinugasa reaction using P,N-ligands [76b]. A chiral bis(oxazoline)/$Cu(OTf)_2$ derivative, a chiral tris(oxazoline)/Cu(II) system, and a chiral *i*-Pr-trisoxazoline/$Cu(ClO_4)_2 \cdot 6H_2O$ complex under air atmosphere catalyzed the coupling of terminal alkynes and nitrones to afford β-lactams with reasonable enantioselectivities [77]. A versatile system for the copper-catalyzed asymmetric coupling of alkynes with nitrones to form *cis*-β-lactams has been developed using a bis(azaferrocene) ligand [78].

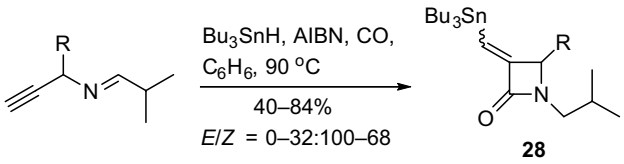
24.1.4.10 Photochemical and Radical Methods

α-Oxoamides **26** undergo γ-hydrogen (with respect to the benzylic carbonyl) abstraction under photochemical treatment in the crystalline state, leading to β-lactams **27** in which a new chiral center is generated at the benzylic carbon (Scheme 24.15) [79]. It has been shown that the crystal lattice preorganizes the reactant molecules towards a single diastereomer of the β-lactam and prevents large motions of the 1,4-diradical intermediate that would result in the loss of stereochemical memory.



Scheme 24.15

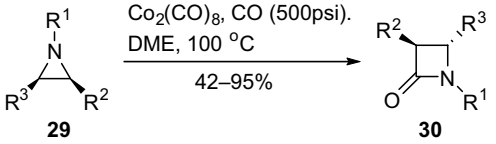
Photosensitized decomposition of oxime oxalate amides and α-oxoamides is a useful new route to carbamoyl radicals that may cyclize to afford β-lactams [80]. The kinetics of the 4-*exo* cyclizations of these carbamoyl radicals onto C=C and C=NO bonds, leading to β-lactam-containing species, have been studied by EPR spectroscopy [81]. Similarly, β-lactams have been prepared via ring closures of unsaturated carbamoyl radicals derived from 1-carbamoyl-1-methylcyclohexa-2,5-dienes [82]. The free-radical mediated stannylcarbonylation of azaenynes provides a 4-*exo* annulation approach leading to α-stannylmethylene β-lactams **28** (Scheme 24.16) [83]. The stereochemical results of β-lactam formation with respect to newly formed C−C double bonds depend strongly on the substitution pattern at the propargylic position. Thus, if the substituent is anything other than hydrogen, the tributyltin group tends to be disposed syn to the carbonyl group to avoid strain.



Scheme 24.16

24.1.4.11 Synthesis from Carbo- or Heterocycles

The regioselectivity and efficiency of the ring opening of aziridines has been exploited for the synthesis of β-lactams through carbonylation of the aziridine nucleus in the presence of a catalytic amount of $[Rh(CO)_2Cl]_2$ [84a], or using a four-component reaction [84b]. The carbonyl insertion is regio- and stereospecific, occurring at the most substituted carbon–nitrogen bond in the aziridine ring, and proceeding with retention of stereochemistry of the substituents linked to the aziridinic carbon atoms. The four-component reaction for the rapid synthesis of 1,3,4,4-tetrasubstituted β-lactams from methyleneaziridines consists of a sequence that involves aziridine opening, C-alkylation, and Staudinger [$2\pi + 2\pi$] cycloaddition. *cis*-Aziridines **29** have been employed in the carbonylation reaction by treatment with $Co_2(CO)_8$, giving rise to *trans*-β-lactams **30**, which were obtained as single diastereo- and regioisomers in good yields (Scheme 24.17) [85a]. Nucleophilic ring opening of the cis starting material results in inversion of configuration, thus leading to the *trans*-β-lactam. The exclusive formation of the 2-azetidinones **30** is a consequence of the completely regioselective ring opening of the aziridine [85b].

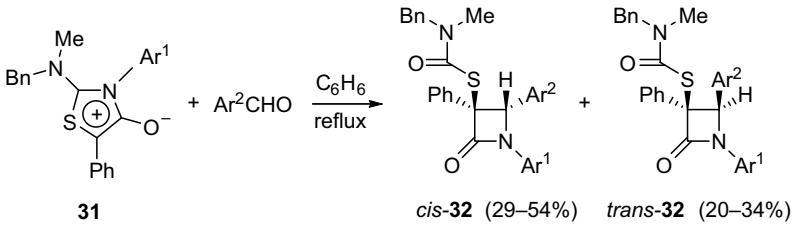


Scheme 24.17

A theoretical investigation of the related $Co_2(CO)_4^-$-catalyzed carbonylative ring expansion of *N*-benzoyl-2-methylaziridine to β-lactams has been performed [85c].

The synthesis of 3-unsubstituted 4,4-disubstituted β-lactams by silver-induced ring expansion of the corresponding 2,2-disubstituted *N*-chloro-1-hydroxycyclopropylamines is, according to theoretical calculations, a very efficient process that yields a regio- and stereoselective product [86]. This process presents a two-step mechanism proceeding through a nitrenium intermediate. The rate-determining step corresponds to the extrusion of AgCl. This pathway could be an interesting new synthetic route for obtaining the useful 3-unsubstituted 4-alkoxycarbonyl-4-alkyl-2-azetidinones.

A single-pot, mild conversion of β-lactones into *N*-benzyloxy-β-lactams has been accomplished by a ring opening/Mitsunobu sequence [87]. The transformation proceeded with high stereochemical fidelity, with the Mitsunobu reactions proceeding as expected with inversion of configuration at the β-carbon. In contrast to what was expected, the reaction of 1,3-thiazolium-4-olates (thioisomünchones) **31** with aromatic aldehydes yielded β-lactams **32** bearing a sulfur-containing side chain (Scheme 24.18) [88]. In every case, β-lactams **32** were formed as a mixture of cis and trans isomers (with respect to the orientation of aryl substituents at C–3 and C–4). Individual diastereomers were separated either by fractional crystallization or preparative chromatography. A plausible rationale to account for the formation of β-lactams involves first a [3 + 2] cycloaddition in which thioisomünchones play the role of the dipole to produce a transient cycloadduct that undergoes a spontaneous C−N bond cleavage, followed by a rearrangement under the reaction conditions.

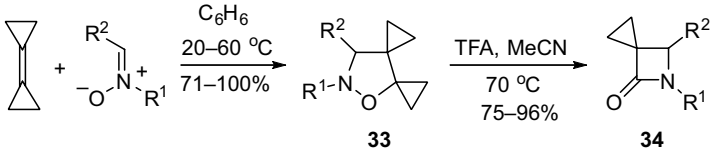


31 *cis*-**32** (29–54%) *trans*-**32** (20–34%)

Scheme 24.18

1,3-Dipolar cycloaddition of nitrones to bicyclopropylidene or fluoroalkenes gives the corresponding cycloadducts [89]. Catalytic hydrogenolysis of the N−O bond of the fluorinated isoxazolidine derivatives leads to α-trifluoromethylated β-lactams, while treatment of the bis-spirocyclopropanated isoxazolidines **33** with trifluoroacetic acid in acetonitrile furnishes the corresponding 3-spirocyclopropanated β-lactams **34** in good yields. Thus, this new method affords compounds with a 5-azaspiro[2.3]hexan-4-one skeleton in 68–94% overall yield in two simple steps (Scheme 24.19).

1-(*o*-Nitrobenzyl)-2-acylpyrazolidin-3-ones upon irradiation through Pyrex and then through Vycor yield 1-(acylamino)azetidin-2-ones. Removal of the acyl residue from the extraannular nitrogen produces 1-aminoazetidin-2-ones. The suggested mechanism for this tandem photochemical synthesis of β-lactams involves initial

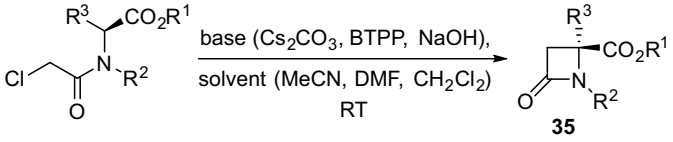


Scheme 24.19

removal of the N1 *o*-nitrobenzyl substituent, followed by ring contraction via a diazabicyclo[2.1.0]pentane intermediate [90]. Highly enantioselective photocyclization in the solid state of 1-alkyl-2-pyridones has been achieved in inclusion crystals with optically active host compounds to give cyclobutene fused β-lactams, which after sequential treatment with ozone and sodium borohydride afford the corresponding monocyclic β-lactams [91].

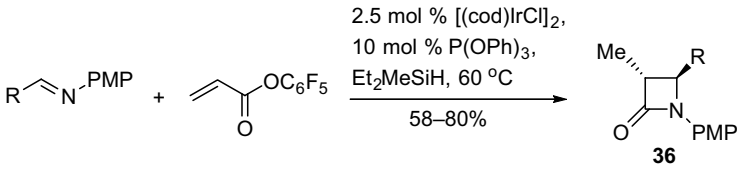
24.1.4.12 **Miscellaneous**

The asymmetric synthesis of 4-alkyl-4-carboxy-2-azetidinones **35** has been achieved through base-mediated intramolecular cyclization of the corresponding *N*-α-chloroacetyl derivatives bearing (+)- or (−)-10-(*N*,*N*-dicyclohexylsulfamoyl)isoborneol as chiral auxiliary (ee up to 82%) [92]. More recently, it has been noted that the asymmetric induction observed during cyclization of *N*-alkyl-*N*-chloroacetyl amino acid derivatives to β-lactams **35** may be ascribed to chirality memory, being dependent on the substituents on the starting material, and can be controlled by the appropriate choice of the base and solvent (Scheme 24.20) [93].



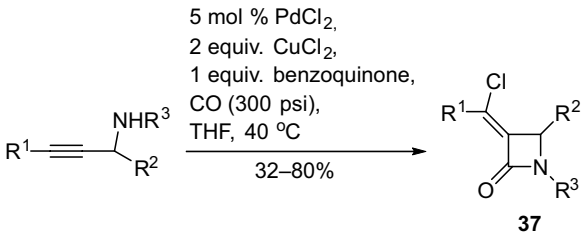
Scheme 24.20

Cycloaddition of lithium ynolates to *N*-sulfonyl imines has been reported to afford 2-azetidinones [94]. Unactivated imines such as *N*-4-methoxyphenyl imines are, however, much less reactive in this reaction. The benzylic lithiation of substituted acrylamides bearing a β-electron-withdrawing group, followed by 4-*exo*-*trig* cyclization, has yielded β-lactams in modest yields [95]. Iridium-catalyzed reductive coupling of acrylates and imines provides *trans* β-lactams **36** with high diastereoselection (Scheme 24.21) [96]. The optimal catalyst allows for the synthesis of *trans* β-lactams bearing aromatic, alkenyl and alkynyl side chains. This reaction appears to proceed through a reductive Mannich addition–cyclization mechanism. Examination of substituent effects reveals a linear Hammett correlation for both the N-aryl group on the imine and the aryloxy group on the acrylate, thereby pointing to rate-determining cyclization in the reaction mechanism.



Scheme 24.21

Allyl halides of different structures, under CO pressure, undergo a [2 + 2] cycloaddition with imines in the presence of $Pd(OAc)_2$, PPh_3, and Et_3N to afford 2-azetidinones [97]. The $PdCl_2$-catalyzed cyclocarbonylation of propargylic amines with $CuCl_2$ and benzoquinone affords *(E)*-α-chloroalkylidene-β-lactams **37** in moderate to good yields (Scheme 24.22) [98]. Formation of the corresponding *(Z)*-isomers or five-membered products was not observed. The stereoselectivity in this reaction is different from that observed with propargylic alcohols.



Scheme 24.22

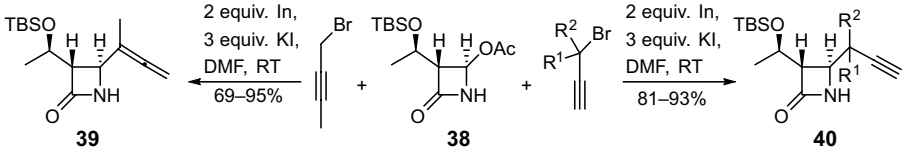
The electrochemically induced synthesis of β-lactams by C3−C4 bond formation has been accomplished [99]. 4-Alkylidene *gem*-difluoro β-lactams have been synthesized through intramolecular hydroamination reaction of difluoropropargyl amides via a Baldwin disfavored 4-*exo-digonal* cyclization using palladium acetate as the catalyst [100a], while 4-alkylidene β-lactams have been obtained by Cu(I)-catalyzed intramolecular C−N coupling of amides with vinyl bromides, revealing that the 4-*exo* ring closure is preferred over other modes (5-exo, 6-exo, and 6-endo) [100b]. A copper-catalyzed skeletal rearrangement of *O*-propargyl arylaldoximes has produced the corresponding 4-arylidene-2-azetidinones in good yields [101]. It was found that the thermal rearrangement of aminocyclobutenones in the presence of an appropriate amine produced either *cis*- or *trans*-β-lactams with high selectivities [102].

24.1.5 Reactivity of the 2-Azetidinone Ring

24.1.5.1 Nucleophilic Attack at Carbon

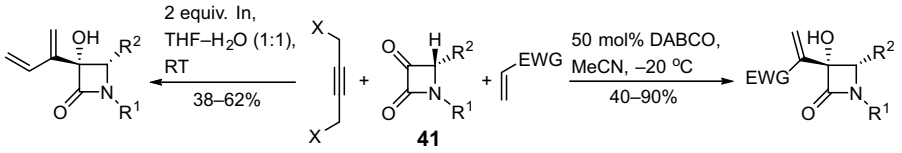
The functionalization of 4-acetoxy-β-lactams at the C4 position is a key step in the synthesis of 1-β-methylcarbapenems. Most of these efforts have been devoted to the stereoselective introduction of different moieties on the commercially available

4-acetoxy-β-lactam **38**, including a highly diastereoselective condensation between the titanium enolate of 2′-hydroxypropiophenone with 2-azetidinone **38** followed by ozonolysis of the resulting ketone to the carboxylic acid [103], the synthesis of 4-(2-oxoethylidene)azetidin-2-ones by a Lewis acid mediated reaction of acyldiazo compounds with 4-acetoxy derivative **38** [104], the reaction of **38** with organoindium reagents generated *in situ* from indium powder and γ-substituted propargyl bromides in the presence of KI in DMF to selectively produce 4-allenyl-2-azetidinones **39** in good to excellent yields, the reaction of 4-acetoxy-2-azetidinones with organoindium reagents generated *in situ* from indium and 1,4-dibromo-2-butyne in the presence of LiCl in DMF to selectively produce 2-azetidinones that contain a 1,3-butadienyl-2-yl group at the C4-position in good yields [105], the reaction of 4-acetoxy-β-lactams with organoindium reagent generated *in situ* from indium and 1,6-dibromo-2,4-hexadiyne in the presence of LiCl in DMF to selectively produce 2-azetidinones possessing 1,2,4,5-hexatetraen-3-yl group on the C4-position [106], as well as the coupling with α-substituted propargyl bromides to give 4-propargyl-2-azetidinones **40** selectively (Scheme 24.23) [107].



Scheme 24.23

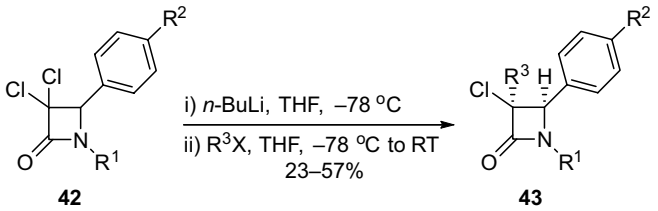
The stereoselective anti S_N2' attack of NaN_3 to 3-alkenyl-3-bromo-azetidin-2-ones gives a mixture of diastereomeric azides in rapid equilibrium. The [3,3]-sigmatropic rearrangement of allylic azides occurs with complete stereocontrol, allowing the equilibrium to be directed preferentially toward the *(E)*- or *(Z)*-isomer, which are useful precursors of 3(2′-amino)-β-lactams [108]. Azetidine-2,3-diones **41** and various stabilized organic halides undergo coupling under Barbier-type conditions in the presence of different metals (indium, tin, zinc) and additives [ammonium chloride, hydrobromic acid, bismuth(III) chloride, hafnium(IV) chloride]. The regiochemistry of the processes (carbonyl-allylation [109], bromoallylation [110], 1,3-butadien-2-ylation [111], propargylation [112] or allenylation [112] reactions) are generally excellent. Similarly, the reaction of various activated vinyl systems, including 2-cyclopenten-1-one, with enantiopure azetidine-2,3-diones **41** has been promoted by DABCO to afford the corresponding optically pure Baylis–Hillman adducts without detectable epimerization [110]. In addition, the reactions of enantiopure azetidine-2,3-diones with unmodified ketones or nitromethane were catalyzed by proline and *N*-methylephedrine, respectively, to give the corresponding aldol and nitroaldol adducts [113]. On this basis, simple and fast protocols for the synthesis of the bioactive 3-substituted 3-hydroxy-β-lactam moiety have been developed (Scheme 24.24).



Scheme 24.24

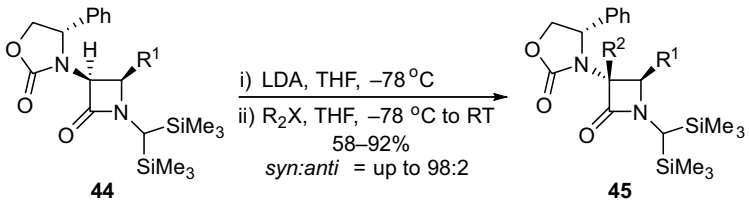
24.1.5.2 Electrophilic Attack at Carbon

Using a halogen–lithium exchange reaction on 4-aryl-3,3-dichloro-2-azetidinones **42**, followed by treatment with alkyl halides as electrophiles, the synthesis of *cis*-3-alkyl-3-chloro-4-arylazetidin-2-ones **43** has been accomplished (Scheme 24.25) [114].



Scheme 24.25

It has been reported that the achiral bis(trimethylsilyl)methyl group acts as an efficient stereochemical determinant of the α-alkylation reaction in β-branched α-phenyloxazolidinyl-β-lactams **44** and provides stereocontrolled access to *syn*-α-amino-α,β-dialkyl(aryl)-β-lactams **45** (Scheme 24.26) [115], which are readily transformed into type II β-turn mimetic surrogates [116]. *In situ* generated organozinc reagents of 3-alkenyl-3-bromoazetidin-2-ones react with aromatic and aliphatic aldehydes to give the corresponding alcohol derivatives, which could be of interest on account of their structural similarity with known cholesterol adsorption inhibitors [117].

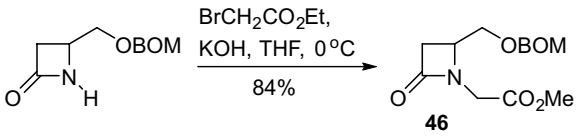


Scheme 24.26

24.1.5.3 Electrophilic Attack at Nitrogen

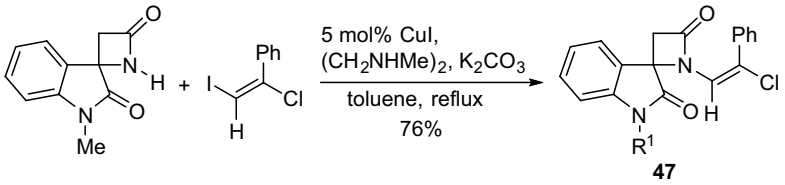
Conventionally, an alkyl or acyl side chain is introduced at the N1 position by base-mediated N-alkylation or N-acylation of the nitrogen atom with the appropriate alkyl

or acyl halide [118]. A representative example is shown in Scheme 24.27 for the preparation of 2-azetidinone **46** [119]. However, some unexpected results have been reported. For example, in a tentative acylation reaction of the β-lactam nitrogen atom of *(E)*- and *(Z)*-4-alkylidene-β-lactams with acetic anhydride under basic conditions it was found that the *(E)* isomer is readily acylated, whereas the *(Z)*-isomer reacted sluggishly, rearranging to the corresponding oxazin-6-one. The N-acylation of *(Z)*-isomers has been successful, though, with oxalyl- or malonyl chlorides in benzene at reflux [120]. The treatment of *NH*-β-lactams with aldehydes under heat or sonication formed the corresponding *N*-hydroxyalkyl-2-azetidinones [121].



Scheme 24.27

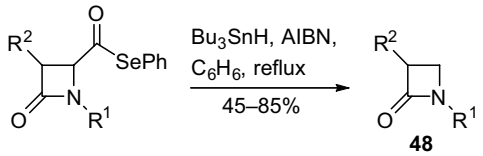
The copper-catalyzed couplings of *NH*-β-lactams with aryl and vinyl halides have been developed as an efficient procedure for the preparation of unsubstituted *N*-aryl and *N*-vinyl-2-azetidinones [122]. This protocol has been fruitful for the synthesis of the spiro-β-lactam **47**, which contains the enamide moiety of natural chartellines (Scheme 24.28) [123].



Scheme 24.28

24.1.5.4 **Radical Transformations**

The treatment of 4-thiophenyl-2-azetidinones with tributyltin hydride in the presence of AIBN initiator yields the corresponding C4-desulfenylated β-lactam [124]. The generation of radicals at C4 has been used for the synthesis of C4-unsubstituted β-lactams **48**, which are conveniently prepared using as the key step a radical reductive decarbonylation of 4-carboxy derivatives through their phenyl selenoesters (Scheme 24.29) [125]. 3,3-Dibromosubstituted β-lactams can be dehalogenated or C3-functionalizated by treatment with methyl acrylate under radical conditions [126]. Upon using triethylborane as the radical initiator, β-lactamido *N*-sulfonyl radicals could be allylated and added onto electron-rich olefins [127]. The radicals do not undergo desulfonylation and are electrophilic in nature.

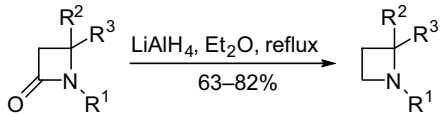


48

Scheme 24.29

24.1.5.5 **Reduction Reactions**

The application of metal hydrides in the search for general and efficient methods for the one-step conversion of β-lactams into different building blocks has been examined. The reaction of different β-lactams with diborane gives rise to γ-amino alcohols [128]. Lithium aluminium hydride (2 molar equiv) in diethyl ether under reflux for 7–16 h converted 1,4,4-trisubstituted β-lactams into azetidines **49** in good yields 63–82% yield (Scheme 24.30) [129]. By contrast, treatment of 4-(1-chloroethyl)-β-lactams with two molar equivalents of lithium aluminium hydride in diethyl ether at 0 °C for two hours afforded 3-chloropyrrolidines [130], while various novel *syn*-2-alkoxy-3-amino-3-arylpropan-1-ols, easily converted into antimalarial *cis*-5-alkoxy-4-aryl-1,3-oxazinanes, have been prepared through $LiAlH_4$-promoted reductive ring-opening of *cis*-3-alkoxy-4-aryl-β-lactams in Et_2O [131].



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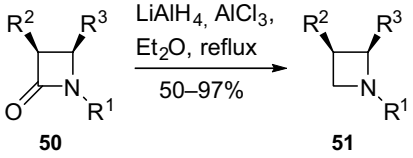
Scheme 24.30

Attempted reduction by BH_3.THF (22 h in refluxing dioxane) and $NaBH_4$–$AlCl_3$ (3.5 h in refluxing ether) resulted in a complete recovery of the starting 2-azetidinone. The reduction with $LiAlH_4$, $LiBEt_3H$ or LiB-*sec*-Bu_3H in THF at room temperature gave exclusively the corresponding γ-amino alcohol through 1,2-bond fission. It was found that the reduction of various 2-azetidinones with DIBAL-H in THF affords the corresponding azetidines in reasonable yields, although a small amount of γ-amino alcohols was also produced. The use of alane (AlH_3) for the reduction of the azetidinone nucleus results in the formation of a mixture of compounds, with the four-membered heterocycle and the γ-amino alcohol being the minor and major component, respectively [132]. Examination of the reactivities of monochloroalane (AlH_2Cl) and dichloroalane ($AlHCl_2$) toward β-lactams has revealed that AlH_2Cl and $AlHCl_2$ prepared *in situ* from $LiAlH_4$ and $AlCl_3$ in ether converts 2-azetidinones **50** into azetidines **51** in quite high yields (50–97%) without being accompanied by γ-amino alcohols (Scheme 24.31) [133]. The reduction of 2-azetidinones by metal hydrides to afford azetidines is not compatible with the presence of ester groups. Reduction with diphenylsilane and catalytic amounts of tris(triphenylphosphine)

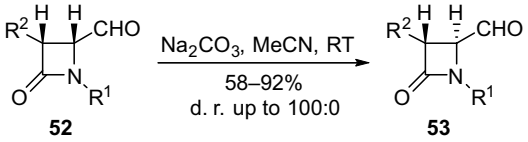


Scheme 24.31

rhodium(I) carbonyl hydrides is a chemoselective method for the transformation of β-lactams into the corresponding azetidines [134].

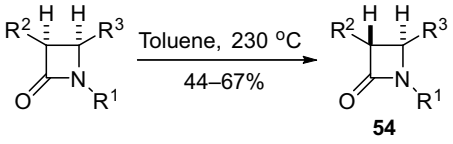
24.1.5.6 **Cis/Trans Isomerization**

Regarding the stereochemical outcome of the routes to prepare β-lactams, a very strong preference for *cis*-β-lactam formation, a kinetic control product, is observed. Consequently, the development of different strategies to access to *trans*-2-azetidinones is of interest. Isomerization of *cis*-β-lactams to *trans*-β-lactams usually requires as starting materials 2-azetidinones bearing acid or basic sensitive moieties (e.g., aldehyde, ketone, ester, amine, amide) at the position susceptible to epimerization. Epimerization at C3 and/or C4 is effected by different reagents, such as CF_3COOH [135], Me_3SiOTf [136], DBN [137], DBU [138] and NaOH/BuLi [139]. A more recent report involves Na_2CO_3-promoted regiospecific C4-epimerization of *cis*-4-formyl-β-lactams **52** into *trans*-4-formyl-β-lactams **53** (Scheme 24.32) [14b].



Scheme 24.32

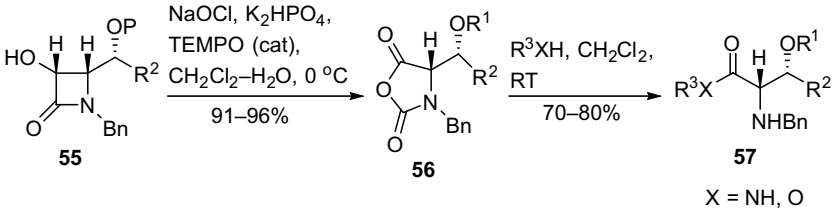
A thermal conversion method for switching the stereochemistry of the 4-aryl-β-lactam ring from cis to trans involving a homolytic cleavage of the C3−C4 bond has been reported (Scheme 24.33) [140]. These results are the only available examples of isomerization in β-lactams induced by heat.



Scheme 24.33

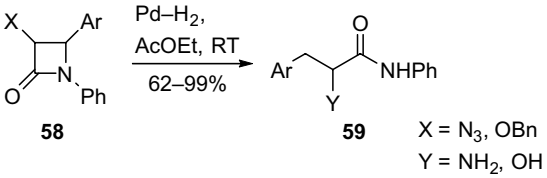
24.1.5.7 Ring-Opening and Rearrangement Reactions

In recent years many 2-azetidinone-based methods for the synthesis of nitrogen-containing compounds of biological relevance have appeared [141]. β-Lactams are precursors to α- and β-amino acids. They have been used to introduce the C13 side-chain of the anticancer compound paclitaxel (taxol) and related analogues [142]. The ring expansion of α-hydroxy β-lactams **55** through a regioselective Baeyer–Villiger rearrangement of an *in situ* generated azetidine-2,3-dione by means of sodium hypochlorite and a catalytic amount of TEMPO, affords *N*-carboxy anhydrides (NCAs) **56**, which after coupling with amines or alcohols produces α-amino acid derivatives **57** (Scheme 24.34) [143]. A related one-pot procedure starting from azetidine-2,3-diones has been documented [144].



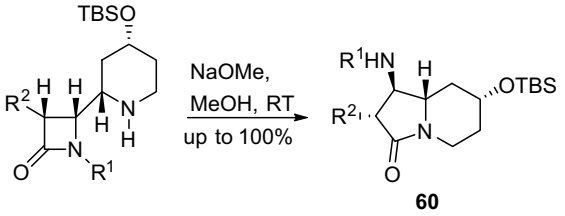
Scheme 24.34

Palladium-catalyzed hydrogenolysis of 4-aryl-β-lactams **58** proceeds exclusively to give α-amino acid derivatives **59** (Scheme 24.35). The ring strain of the 2-azetidinone nucleus greatly accelerates the cleavage of the N1−C4 bond, rather than the more usual N1−C2 bond breakage, when an aryl substituent is attached to the C4 position [145]. Addition reaction of 2-(trimethylsilyl)thiazole to *cis*- or *trans*-4-formyl-β-lactams has been reported to give enantiopure α-alkoxy-γ-keto acid derivatives [146]. Also, the first organocatalytic N1−C4 bond breakage of the β-lactam skeleton has been uncovered, providing a direct method for the preparation of enantiopure 5-arylimino-pyrrolidin-2-ones as well as pyrrolidin-2,5-diones (succinimides) from 4-(arylimino)-methyl-azetidin-2-ones [147]. In addition, a single-step catalytic ring expansion approach from 4-oxoazetidine-2-carbaldehydes to enantiopure succinimides has been achieved by the use of a base (DBU) and a thiazolium salt precatalyst [148], and its mechanism has been studied using DFT methods [149].



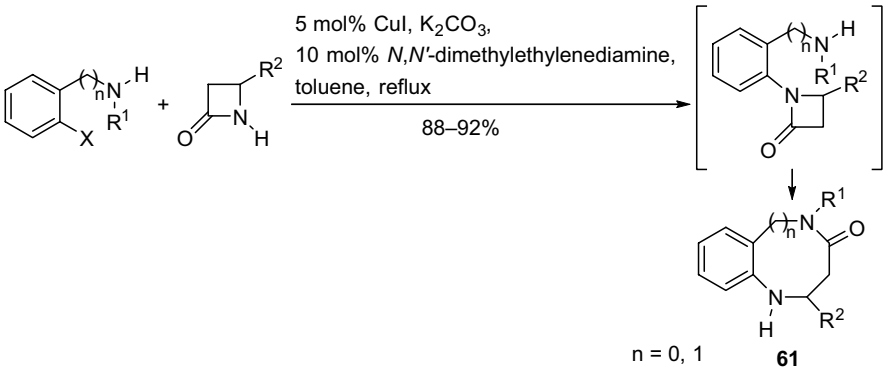
Scheme 24.35

The stereoselective synthesis of different sized heterocycles has been accomplished from conveniently functionalized 2-azetidinones. Ring sizes from three through to complex macrocycles have been synthesized using β-lactams. For example, indolizidine type-alkaloids **60** have been prepared using β-lactams as chiral building blocks by an aza-Diels–Alder reaction of 2-azetidinone-tethered imines combined with amide bond breakage and rearrangement reactions on the β-lactam ring (Scheme 24.36) [150].



Scheme 24.36

The synthesis of medium-sized azalactams **61** fused to a benzene ring via a tandem copper-catalyzed C−N bond formation–β-lactam ring-expansion process has been accomplished recently (Scheme 24.37) [151]. Starting from β-lactam cyanohydrin hybrids, two concise, complementary stereocontrolled routes to optically pure orthogonally protected *anti,anti*-4-amino-3,5-piperidine diols have been achieved [152]. In addition, molecular iodine (10 mol.%) efficiently catalyzes the ring expansion of 4-oxoazetidine-2-carbaldehydes in the presence of *tert*-butyldimethyl cyanide to afford protected 5-cyano-3,4-dihydroxypyrrolidin-2-ones with good yield and high diastereoselectivity, through a novel C3–C4 bond cleavage of the β-lactam nucleus [153]. A new one-pot approach, which relies on the regiocontrolled cyclization of β-allenamine intermediates derived from the ring opening of 2-azetidinone-tethered allenols, to both racemic and enantiopure densely substituted pyrroles has been developed from β-lactams [154]. The total synthesis of several

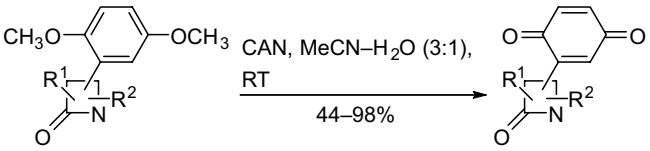


Scheme 24.37

natural products such as biotin [155], cribrostatin 4 [156], and himandrine [157] has also been carried out using 2-azetidinones as important building blocks. The syntheses of pyrrolizidines [158], fused prolines [159], oxazinones [160], amino glycals [161], aminocyclobutanes [162], bicyclic γ-lactams [163], medium-sized heterocycles [164], and complex macrocycles [165] deserve to be mentioned as well.

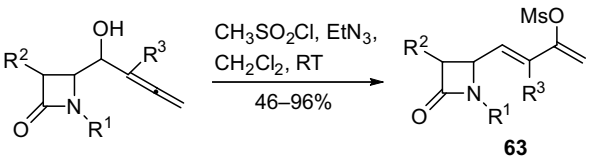
24.1.5.8 Reactions of Substituents Attached to Carbon Atoms

The oxidation of α-ethylidene β-lactams is a useful method to prepare azetidine-2,3-diones [166]. A general and efficient synthesis of cis and trans β-lactams bearing a quinone moiety at N1, C3 or C4 positions, which can be regarded as hybrids of the pharmacologically relevant subunits of β-lactam and quinone, has been developed. The target molecules **62** are smoothly prepared via oxidative demethylation of the appropriate 2,5-dimethoxyphenyl substituted-β-lactams using ceric ammonium nitrate (CAN) in aqueous acetonitrile (Scheme 24.38) [167].



Scheme 24.38

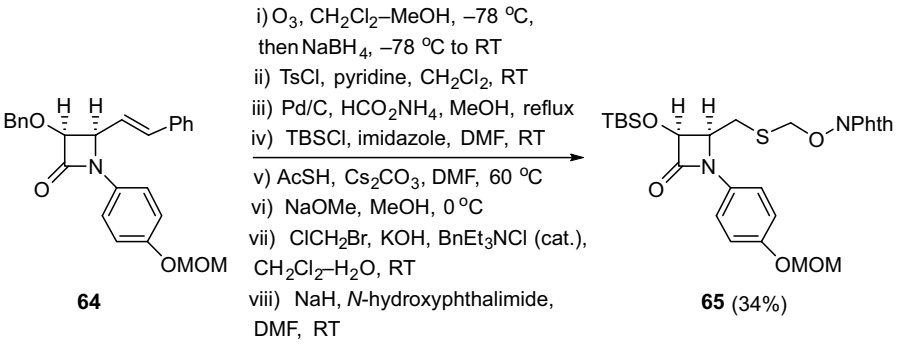
A stereoselective synthesis of 1,2,3-trisubstituted β-lactam-1,3-dienes **63** has been developed from 2-azetidinone-tethered α-allenols just by treatment with a methanesulfonyl chloride/tertiary amine system. This transformation might be tentatively explained through a migration of the methanesulfonyl group in the initially formed α-allenic methanesulfonate to give the corresponding mesyloxy-diene via [3,3]-sigmatropic rearrangement (Scheme 24.39) [168]. Mesylates of 2-azetidinone-tethered homoallylic alcohols by gentle heating in benzene or toluene in the presence of DBU have been used for the stereoselective preparation of 4-butadienyl-2-azetidinones [169].



Scheme 24.39

The benzylidene moiety of β-lactam **64** is cleaved by ozonolysis and reductive treatment with $NaBH_4$ to afford the primary alcohol, which is then activated as the tosylate. After replacement of the benzyl group with the TBS group, a four-step sequence including S_N2 reaction of caesium thioacetate, methanolysis of the

thioacetate, chloromethylation of the thiol, and S_N2 reaction of *N*-hydroxyphthalimide sodium salt, gives the protected N-alkoxyamine **65** (Scheme 24.40), which bears the side chain required for the construction of the oxathiazepin ring of natural eudistomins [170]. N-Terminal chain elongation on amido substituents at the C3-position of the β-lactam moiety has been achieved using conventional peptide synthesis (saponification, activation as pentafluorophenyl esters and subsequent cleavage of the N-terminal Boc-protecting group) [171]. The olefin cross metathesis of α-methylene-β-lactams [172] and the selective Diels-Alder reaction of α-dienyl-β-lactams [173] have been developed. Vinylic halogenation and halodecarboxylation reactions of 4-alkylidene-β-lactams have been performed [174]. It has been reported that, by adopting Pd(II)-catalyzed conditions, the cycloisomerization/dimerization ratio of 4-buta-2,3-dienoyl-azetidin-2-ones is controlled by the substitution of the allene moiety: unsubstituted allenones mainly afford dimerization, whereas allenones bearing an internal substituent favor the formation of cycloisomerization products [175].

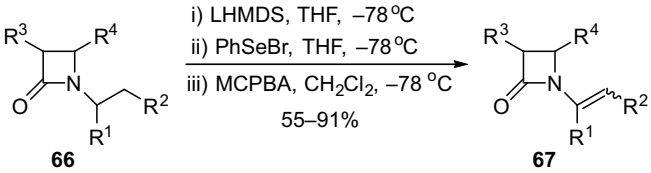


64 **65** (34%)

Scheme 24.40

24.1.5.9 **Reactions of Substituents Attached to Nitrogen Atom**

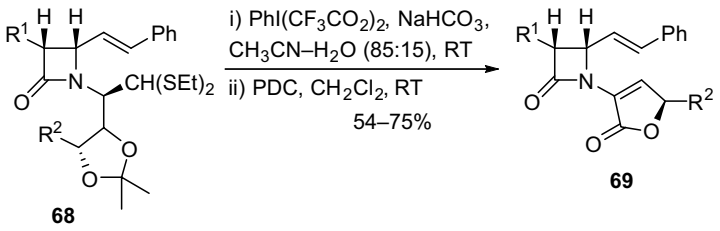
A three-step synthesis of *N*-vinyl-2-azetidinones starting from α- or β-amino ester imines has been developed [176]. Enolate formation on the amino ester moiety of the 2-azetidinone **66**, selenylation and finally MCPBA treatment affords *N*-vinyl-2-azetidinones **67** in good yields (Scheme 24.41).



66 **67**

Scheme 24.41

The selective N-oxidation of the most nucleophilic amino nitrogen atom of the hydrazide moiety in 1-dialkylamino azetidin-2-ones is central for the cleavage of their N−N bonds under oxidative conditions by treatment with peracids such as magnesium monoperoxyphthalate hexahydrate (MMPP·$6H_2O$) or *meta*-chloroperbenzoic acid (MCPBA) [177]. A Grubbs' carbene catalyzed isomerization of *N*-allyl β-lactams into *N*-vinyl β-lactams affords, after $RuCl_3$–$NaIO_4$ treatment, the corresponding *NH*-β-lactams [178]. It has been shown that *N*-(4-methoxy or 4-ethoxyphenyl) groups can be oxidatively removed by silica gel supported ceric ammonium nitrate under mild conditions in solution and on column [179]. The *cis*-2-azetidinones **68** have been reacted with $PhI(CF_3CO_2)_2$ and $NaHCO_3$ and the crude reaction products purified by column chromatography on silica gel to give a diastereomeric mixture of hemiketals, which was quantitatively converted into the lactones **69** by oxidation with PDC (Scheme 24.42) [180].

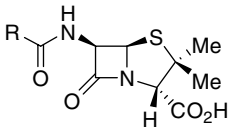


Scheme 24.42

24.2 Penicillins and Cephalosporins

24.2.1 Introduction

The antibacterial effect of β-lactam antibiotics such as penicillins (**70**) and cephalosporins (**71**) is due to their capacity to disrupt bacterial cell wall biosynthesis [181]. This is achieved by the antibiotics acting as inhibitors of penicillin binding proteins (PBPs), which are membrane bound serine peptidases. PBPs recognize D-alanyl-D-alanine peptide termini and the structural and conformational similarity of the β-lactam antibiotics to these natural peptide substrates for PBPs is believed to ensure their acceptance by the target proteins. The high reactivity of the fused β-lactam ring towards nucleophiles then results in the formation of a covalent PBP–antibiotic complex that prevents the PBPs from taking further part in bacterial cell wall synthesis.



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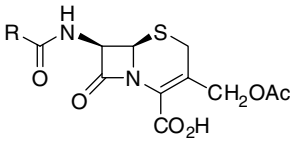

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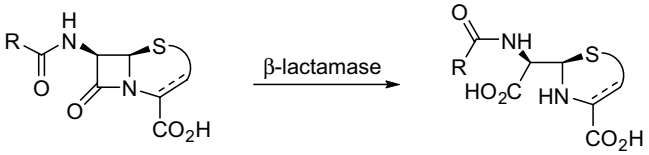
β-Lactamase hydrolytic enzymes are the most common, and growing, form of bacterial resistance to their normally lethal action [182]. β-Lactamases catalyze the hydrolysis of the β-lactam antibiotic to give the ring opened and bacterially inert β-amino acid (Scheme 24.43). The problem of β-lactamases became critical in 1960 when widespread use of penicillin G led to an alarming increase of *Staphylococcus aureus* infections. These problem strains had gained the lactamase enzyme and had thus gained resistance to the drug. At one point, 80% of all *Staphylococcus aureus* infections in hospitals were due to virulent, penicillin-resistant strains. Alarmingly, these strains were also resistant to all other available antibiotics.



Scheme 24.43

Two main therapeutic strategies have been adopted to counteract bacterial resistance to β-lactam antibiotics. One strategy consists of modifying the structure of the β-lactam antibiotic, aiming to render it insensitive to the β-lactamase attack. Recently, trinems antibiotics (Figure 24.1) have been the subject of considerable study owing to their broad spectrum of antibacterial activity, resistance to β-lactamases and stability to renal dehydropeptidases [183]. As a result of their impressive biological activity, tricyclic β-lactams have become interesting targets for synthesis. A second approach uses a reagent, typically a β-lactam derivative, which incapacitates the β-lactamase, in synergy with the β-lactam antibiotic. Clavulanic acid (Figure 24.1) is the archetype of β-lactamase inhibitors [184]: in synergistic mixture with amoxicillin (Figure 24.1), under the name "augmentin," it arrived at the practice some years ago. Both

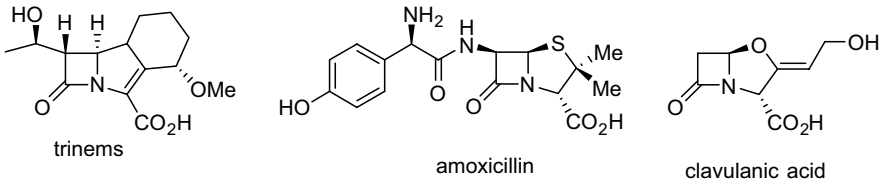


Figure 24.1 New generation β-lactam antimicrobials: trinems and "augmentin."

approaches have produced results and a new generation of antibiotics has been developed.

24.2.2 Physicochemical Data

24.2.2.1 Computational Chemistry

The calculated STO-3G energy of formamide in a penicillin-like geometry is only 2.8 kcal mol^{-1} higher than the planar geometry [185]. In addition, the geometrical parameters associated with the 2-azetidinone nucleus generally suffer a slight variation with changes in the hybridization at nitrogen. However, the C−N bond length becomes longer as the nitrogen atom becomes pyramidal.

Two penicillin derivatives, the active penamecillin and the inactive penamecillin-1β-sulfoxide, have been used to study the relationship between their charge density and their activity [186]. Single crystals of both compounds have been measured at the synchrotron beamline F1 at the HASYLAB/DESY, at 100 K and up to resolutions of around 0.4 Å. Experimental charge densities have been obtained by using the Hansen–Coppens multipole formalism. The cleavage of the amide bond in the β-lactam ring is of paramount importance in the mechanism of action of penicillins. Topological analysis of this bond in terms of Bader's AIM theory showed that its strength is equal in both compounds; therefore, a direct influence of bond strength on the activity can be ruled out. However, the two derivatives differ significantly in their experimental electrostatic potentials. These differences provide further insight into the chemistry and activity of penicillins.

Theoretical results have been reported on the conformational properties of benzylpenicillin, which are characterized by means of quantum chemical calculations (MP2/6-31G* and B3LYP/6-31G*) and classical molecular dynamics simulations (5 ns) both in the gas phase and in aqueous solution [187]. In the gas phase, the benzylpenicillin conformer in which the thiazolidine ring has the carboxylate group oriented axially is the most favored one. Both intramolecular CH ⋯ O and dispersion interactions contribute to stabilize the axial conformer with respect to the equatorial one. In aqueous solution, a molecular dynamics simulation predicts a relative population of the axial : equatorial conformers of 0.70 : 0.30 in consonance with NMR experimental data. Overall, the quantum chemical calculations as well as the simulations give insight into substituent effects, the conformational dynamics of benzylpenicillin, the frequency of ring-puckering motions, and the correlation of side chain and ring-puckering motions.

The mechanisms of antibiotic resistance have been studied using a combined quantum mechanical and molecular mechanical (QM/MM) modeling of the acylation reaction of a class A β-lactamase with benzylpenicillin [188]. Hybrid Car–Parrinello QM/MM calculations have been used to investigate the reaction mechanism of hydrolysis of a common cephalosporin-type substrate (cefotaxime) by the monozinc β-lactamase from *Bacillus cereus* [189]. Theoretical studies on the conformational similarity of penicillins and cephalosporins to X-D-alanyl-D-alanine and correlation of their structure with activity has been examined by stereochemical

criteria, concluding that the conformation of these β-lactam antibiotics is similar to X-D-alanyl-D-alanine due to the presence of the lactam ring [190].

24.2.2.2 Experimental Structural Methods

The degree of coplanarity of the β-lactam nitrogen atom in β-lactam antibiotics can be expressed either by the perpendicular distance, *h*, of the nitrogen from the plane of its three substituents or by the sum of the bond angles about nitrogen. The former is easier to visualize and the nitrogen ranges from being essentially in the plane of its three substituents in monocyclic β-lactams to being 0.5 Å out of the plane in bicyclic systems [191]. There is no direct correlation between *h* values and chemical reactivity. In non-planar penicillins and cephalosporins there is a general trend for the C−N bond length to increase as the C=O bond length decreases. However, this trend is by no means linear. Bond lengths for C=O vary from 1.17 to 1.24 Å and for C−N from 1.33 to 1.46 Å. There is also a tendency for the C−N bond length to increase with *h*. It is difficult to discern reasons and reactivity consequences of these differences in bond length. Penicillin V (**70** R = $PhOCH_2$) shows the longest C–N bond length of 1.46 Å and yet the C=O bond length (1.21 Å) is identical to that commonly found in planar monocyclic β-lactams. In monocyclic β-lactams the nitrogen is coplanar with its three substituents and yet the bond length differences are also in the direction predicted by inhibition of amide resonance. The degree of non-planarity in penicillin V and ampicillin [**70** R = $PhCH(NH_2)$] is similar ($h = 0.40$ and 0.38 Å, respectively) and yet the C−N bond length in the former is 0.10 Å longer than in the latter. Structural data have also been used to support the suggestion that enamine resonance is important in cephalosporins and that this also reduces amide resonance [192]. However, there is no significant difference in the C−O and C−N bond lengths in cephalosporins from the general trend exhibited by penicillins. It became apparent that variations in bond lengths within penicillins and cephalosporins are due to the nature of substituents and the minimization of unfavorable strain energies caused by the geometry of the molecule rather than to the inhibition of the amide resonance.

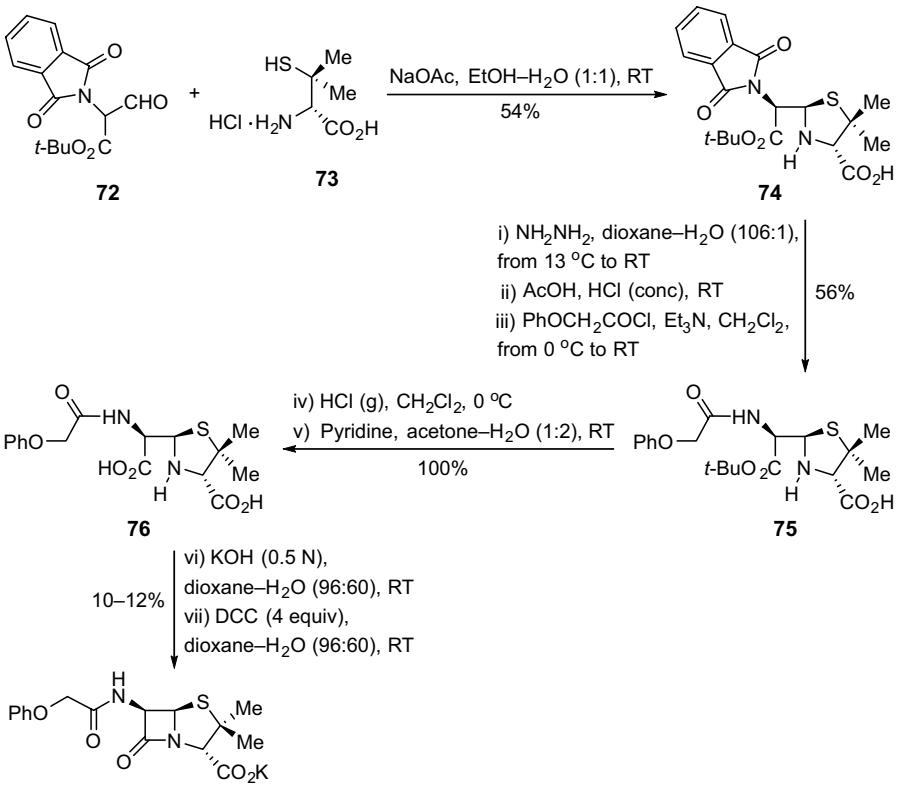
The ^{13}C NMR spectra of bicyclic β-lactam antibiotic show the carbonyl resonance at about 165 ppm. The 2-azetidinone carbonyl carbon in penicillins resonates around 10 ppm to lower field than that in cephalosporins. The chemical shifts for the biologically active Δ^3- and the inactive Δ^2-cephalosporins are similar. The ^{15}N NMR spectra show an upfield shift of 30 ppm in the β-lactam nitrogen on going from non-planar penicillins to planar 2-cephems [193]. The infrared C=O absorption frequency for the bicyclic β-lactam antibiotics is in the 1760–1780 cm^{-1} range. The frequency in cephalosporins increases by about 5 cm^{-1} when the ring sulfur is substituted by oxygen but decreases by a similar amount when the 7-α-hydrogen is replaced by a methoxy group. Structural studies confirm that N-fused β-lactam systems generally have a higher C=O stretching frequency than the C-fused structures, indicating a greater amount of ring strain and chemical reactivity toward nucleophiles [194]. N-Fused lactams are highly respondent to the geometric constraints imposed by the second ring to which it is fused, as evidenced from the increase in the infrared absorption frequency for the lactam carbonyl as the size of the second ring is decreased. ^{13}C NMR spectroscopic data for third-generation cephalosporins, such as

cefotaxime, cefixime, cefdinir, and cefpodoxime proxetil, have been assigned by combination of one- and two-dimensional experiments; the effect of the substitution at C3, C7, and C4 acid group positions on the chemical shifts of the cephem nucleus is discussed [195].

24.2.3
Synthesis of Penicillins and Cephalosporins

24.2.3.1 Classical Syntheses

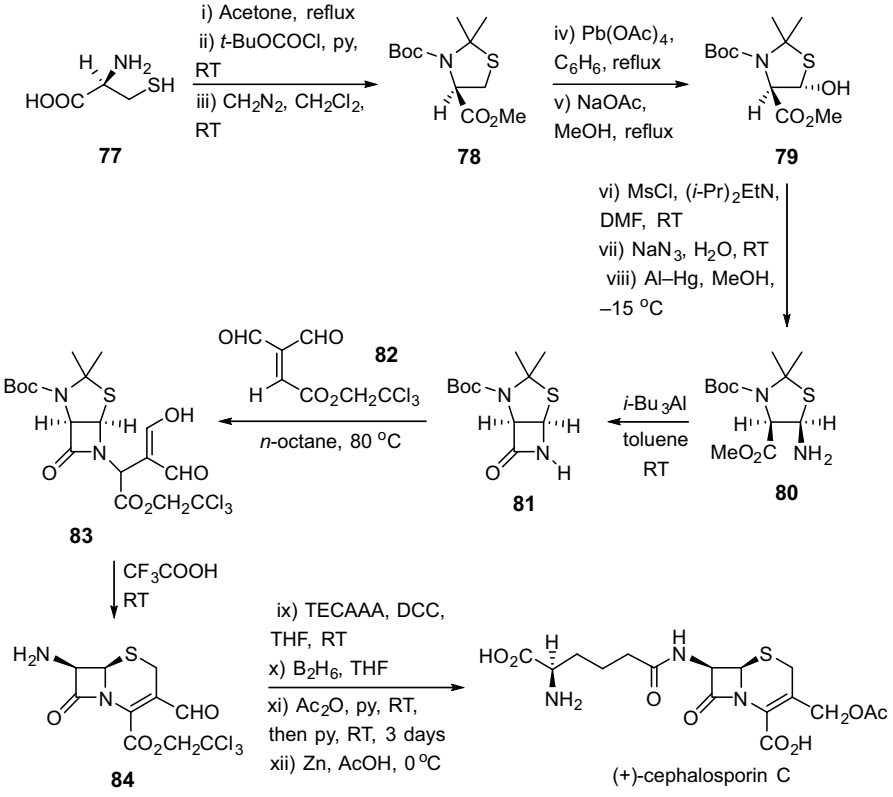
Sheehan published in 1957 the first total synthesis of a natural penicillin, penicillin V (Scheme 24.44) [196]. At the time of this synthesis it was believed that the instability of penicillin was due to the presence of the strained four-membered β-lactam ring. Therefore, the creation of the 2-azetidinone nucleus was postponed for as long as possible in the synthetic sequence. *t*-Butyl phthalimidomalonaldehydate (**72**) was condensed with D-penicillamine **73** to afford the thiazolidine **74** as a mixture of two of the four possible stereoisomers. The configuration of one of the isomers



Scheme 24.44

corresponded to the stereochemistry found in natural penicillin. The other stereoisomer could be epimerized into the required isomer by simple heating in the presence of pyridine. Sequential hydrazinolysis of the phthalimido group and acylation of the free amine with phenoxyacetyl chloride gave the phenoxyacetamide **75**. The *t*-butyl ester was then cleaved with dry hydrogen chloride to produce the diacid **76**. The β-lactam formation, the final step of the synthesis, was achieved through the use of a reagent introduced by Sheehan for amide bond formation, the dicyclohexylcarbodiimide.

Another masterly synthesis of β-lactam antibiotics is Woodward's total synthesis of cephalosporin C (Scheme 24.45) [197]. Complete stereocontrol was afforded by starting from enantiopure L-cysteine **77**, which was protected and activated at its methylene group as the cyclic thiazolidine **78**. Oxidative cleavage using lead tetraacetate gave the corresponding acetate accompanied by a small amount of its cis epimer, which could be separated. Transesterification liberated alcohol **79**, which was transformed into aminoester **80** by sequential mesylation, azide displacement with inversion, and final reduction with aluminium amalgam. Triisobutylaluminium

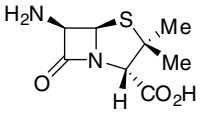


Scheme 24.45

effected smooth conversion of aminoester **80** into the bicyclic 2-azetidinone **81**, which is a key intermediate containing the basic structural features common to both penicillins and cephalosporins. Conjugate addition of the β-lactam nitrogen atom to ester **82**, which was obtained through the condensation between malondialdehyde and trichloroethyl glyoxylate, generated compound **83**. All the functionalities required for the cephem skeleton formation are present in fused 2-azetidinone **83**. Treatment of **83** with trifluoroacetic acid induced cyclization with concomitant deprotection of both the amino and mercapto groups to give bicycle **84**. The total synthesis of cephalosporin C was completed after acylation with a protected *N*-β,β,β-trichloroethyloxycarbonyl-D-α-amino adipic acid, followed by aldehyde reduction with diborane, acetylation, isomerization of the olefin under basic conditions, and treatment with zinc in acetic acid. This last step was the first use of the trichloroethyl moiety as protecting group in synthesis.

24.2.3.2 Industrial Production of β-Lactam Antibiotics

The industrial production of β-lactam antibiotics by fermentation over the past 50 years is one of the outstanding examples of biotechnology [198]. Today, β-lactam antibiotics, particularly penicillins and cephalosporins, are the world's major biotechnology products with worldwide dosage form sales of ~US$ 15 billion or ~65% of the total world market for antibiotics. Over the past five decades, major improvements in the productivity of the producer organisms, *Penicillium chrysogenum* and *Acremonium chrysogenum* (syn. *Cephalosporium acremonium*) and improved fermentation technology have culminated in enhanced productivity and substantial cost reduction. Major fermentation producers are now estimated to record harvest titers of 40–50 g L^{-1} for penicillin and 20–25 g L^{-1} for cephalosporin C. Recovery yields for penicillin G or penicillin V are now >90%. Chemical and enzymatic hydrolysis process technology for 6-aminopenicillanic acid (6-APA) **85** or 7-aminocephalosporanic acid (7-ACA) **86** is also highly efficient (~80–90%), with new enzyme technology leading to major cost reductions over the past decade.



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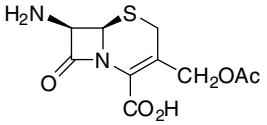

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24.2.3.2.1 Commercial Production of Penicillins

The fermentation production of penicillin-G or -V is a fed-batch process carried out aseptically in stainless steel tank reactors of 30 000–100 000 gallon capacity. The fermentation usually involves two to three initial seed growth phases followed by a fermentation production phase having a time cycle ranging from 120 to 200 h. High dissolved oxygen levels are critical, especially during peak growth periods that often occur at the 40–50 h time-period of the cycle. The fermentation mode is fed-batch and crude sugar and precursor are fed throughout the cycle. Current penicillin fermentations are highly computerized and automated. Temperature, pH, dissolved oxygen, carbon dioxide, sugar,

precursor, ammonia, and so on are closely monitored and controlled for optimal antibiotic production [199]. Various carbon sources have been adopted for the fermentation, including glucose, sucrose and other crude sugars. About 65% of the carbon is metabolized for cellular maintenance, 20–25% for growth and 10–12% for penicillin production [200]. Sugar and precursor are fed continuously and the sugar is also used to help regulate the pH of the fermentation to between 6.4–6.8 during the active penicillin production phase. Corn steep liquor and cottonseed or soybean meal, ammonia and ammonium sulfate represent major nitrogen sources. The essential precursor substances are phenylacetic acid (for penicillin G) or phenoxyacetic acid (for penicillin V) that are either fed or batched.

Mini-harvest protocols are often used in penicillin fermentations. This "batch-fill and withdraw" system involves the removal of 20–40% of the fermentor contents with replacement with fresh sterile medium. This procedure can be repeated several times during the fermentation without yield reduction and, in reality, can enhance the total penicillin yield per fermentor. Penicillin is excreted into the medium and is recovered at the end of the fermentation. Whole broth extraction is usually performed at acidic pH by most manufacturers and has resulted in a 2–5% improvement in overall extraction efficiency by the elimination of the rotary vacuum filtration step. Solvent extraction of chilled acidified broth is carried out with amyl, butyl or isobutyl acetate. Multiple back-extractions into buffer and solvent at varying pH using countercurrent contactors has led to considerable penicillin concentration in the early recovery stages of the purification process. Pigments and other broth impurities are removed by the use of activated charcoal. The penicillin is crystallized upon the addition of potassium acetate and is isolated as a crystalline potassium salt. Additional carbon treatments and solvent washes result in a highly purified final product.

Approximately 75% of the total bulk penicillin volume produced in 1995, ~33 000 tons, was used for the production of semi-synthetic penicillins and cephalosporins. The penicillin nucleus (6-APA) has enabled researchers to develop many excellent semi-synthetic penicillins. 6-APA can also be chemically ring-expanded to 7-ADCA to generate several important orally-active cephalosporins (cephalexin, cephradine, cefadroxyl, etc.). 6-APA has now grown to be the world's largest selling β-lactam bulk intermediate.

24.2.3.2.2 **Commercial Production of Cephalosporin C** High-yielding strains of *A. chrysogenum* are used in large-scale, fed-batch fermentations. Major fermentation producers of cephalosporin C obtain harvest titers in the range of 20–25 g L^{-1}. Production-scale fermentations are fed-batch with carbon supplied as simple or complex carbohydrate feeds during the growth phase of the fermentation. As the fermentation progresses, sugar feeds are reduced and are usually replaced by higher energy oils such as soybean oil or peanut oil. Energy conservation from oil as a substrate is considerably less efficient and leads to slower growth, with the vegetative mycelium becoming largely transformed into multicellular arthrospores. The arthrospore stage leads to greater oxygen availability to the organism and results in rapid cephalosporin production. DL-Methionine addition, which also results in the onset of arthrospore formation, is often added to the medium during the early growth

phase of the fermentation. The formation of arthrospores is also correlated with improved dissolved oxygen concentration in the broth and is critical for maximal expression of the important biosynthetic cyclase and expandase enzymes. Organic nitrogen is often supplied as a combination of soybean and cottonseed meals supplemented with ammonium sulfate and ammonia that is also used to help control the pH throughout the fermentation. Corn steep liquor is also supplied as a cheap nitrogen source and is rich in amino acids, vitamins, organic acids and trace elements. The pH of the fermentation is maintained between 6.2 and 7.0 and the temperature range is controlled between 24 and 28 °C.

A major problem associated with cephalosporin C fermentation is the inherent chemical instability of the cephalosporin C molecule. This is probably one of the major reasons why long-cycle cephalosporin C fermentations often result in reduced cephalosporin production compared to typical long-cycle penicillin fermentations. Cephalosporin C is readily degraded to 2-(D-4-amino-4-carboxybutyl)-thiazole-4-carboxylic acid, which can account for as much as a ~40% loss of the cephalosporin C produced [201]. The biosynthetic precursor molecules of cephalosporin C, deacetylcephalosporin C and DAOC have much more chemical stability. Strains of the yeast *Rhodosporidium toruloides* possess a potent acetyl esterase and, when the organism is added to active cephalosporin C fermentations, result in increased levels of deacetylcephalosporin C with an increase in total cephalosporin nucleus levels of ~40%. Over the past decade, the cloning of many of the genes involved in the biosynthetic pathway of cephalosporins has resulted in more productive strains.

The purification and recovery of harvest cephalosporin C broth begins with the rapid chilling of the active broth to 3–5 °C followed by removal of the mycelial solids either by filtration or by centrifugation. The active broth contains not only the desired cephalosporin C component but also small quantities of the biosynthetic precursors penicillin N, DAOC, deacetylcephalosporin C and the degraded cephalosporin C product, 2-(D-4-amino-4-carboxybutyl)-thiazole-4-carboxylic acid. Two major strategies can be used for the recovery and purification of cephalosporin C. One strategy involves the use of activated carbon or the use of a non-ionic resin. Because of the high selectivity of the resin, cephalosporin C is preferentially adsorbed over penicillin N or the contaminating biosynthetic precursor molecules. Most of the penicillin N is removed in the pH 2.0 acidification step. An additional anion- and cation-exchange step usually results in high quality cephalosporin C. A large fraction of the cephalosporin C is converted into 7-ACA and derivatized to semi-synthetic cephalosporins. A second purification strategy involves the substitution of the amine moiety on the α-aminoadipyl side-chain at C7. Two substituted derivatives, *N*-2,4-dichlorobenzoyl cephalosporin C and tetrabromocarboxybenzoyl cephalosporin C, can be crystallized from acidic aqueous solution. Alternatively, salts can be formed between the N-substituted derivatives, and an organic base such as dicyclohexylamine or dimethylbenzylamine results in cephalosporin salts that are solvent extractable. Bristol-Myers Squibb uses a solvent-extractable process resulting in the isochlorobutylformate (ICBF) ester of cephalosporin C, termed cephalosporin D. Several extraction steps are usually necessary to achieve the final desired purity.

N-Substituted cephalosporin C salts containing small amounts of contaminants can be effectively converted into 7-ACA. Efficient enzymatic processes are now utilized for the conversion of cephalosporins into 7-ACA, which has resulted in a dramatic cost reduction for this important bulk intermediate. Two key genetically engineered enzymes are involved. The initial step is reaction of the α-aminoadipyl group with D-amino acid oxidase to produce glutaryl-7-ACA. This reaction proceeds through a keto-7-ACA intermediate that undergoes an oxidative decarboxylation in the presence of hydrogen peroxide. A glutaryl acylase is used to remove the glutaryl side-chain to produce 7-ACA. Two-thirds of the commercial cephalosporins are derived from 7-ACA that is produced from cephalosporin C by either chemical or enzymatic deacylation. In the chemical process, after protection of the amino and carboxyl groups, reaction with potassium pentachloride in the presence of base forms an iminochloride derivative. The iminoether is formed on the addition of alcohol. The iminoether is hydrolyzed to form 7-ACA.

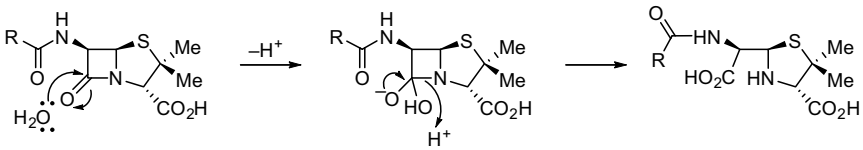
24.2.4 Reactivity of Penicillins and Cephalosporins

24.2.4.1 Basicity of β-Lactam Nitrogen

If amide resonance in penicillins is inhibited because of the pyramidal nature of the β-lactam nitrogen, penicillins should show enhanced basicity compared with normal amides. By contrast, penicillins appear to show reduced basicity and cannot be detectably protonated even in 12 M hydrochloric acid [202]. Another indication of increased nitrogen basicity would be a large binding constant of penicillin to metal ions. The equilibrium constant for metal-ion coordination between the carboxyl group and the β-lactam nitrogen in penicillins is about 100–200 M^{-1} for various metal ions [203], which is the same order of magnitude expected for coordination between a normal amide and a carboxyl group. Therefore, it became evident that there is not a substantial enhancement for the electron pair donating ability either to a proton or to a metal in penicillins.

24.2.4.2 Hydrolysis

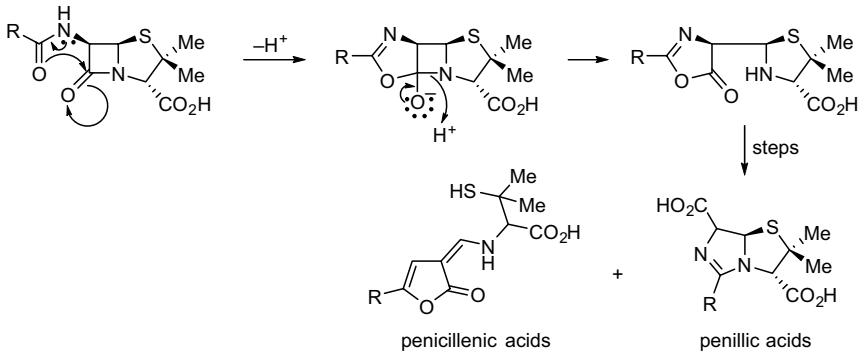
The bicyclic system in penicillin consists of a four-membered ring and a five-membered ring. As a result, penicillin suffers large angle and torsional strains. Ring opening relieves these strains by cleavage of the more highly strained four-membered lactam ring (Scheme 24.46).



Scheme 24.46

The carbonyl group in the β-lactam ring is highly susceptible to nucleophiles and as such does not behave like normal tertiary amides, which are usually quite resistant to nucleophilic attack. This difference in reactivity is due mainly to the fact that stabilization of the carbonyl is possible in the tertiary amide but impossible in the β-lactam nucleus. The β-lactam nitrogen is unable to feed its lone pair of electrons into the carbonyl group since this would require the bicyclic rings to adopt an impossibly strained flat system. As a result, the lone pair is localized on the nitrogen atom and the carbonyl group is far more electrophilic than one would expect for a tertiary amide.

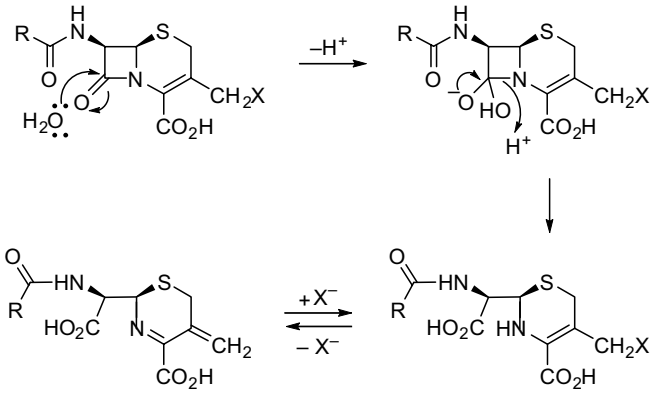
The acyl side chain can actively participate (neighboring group participation) in a mechanism to open up the 2-azetidinone moiety (Scheme 24.47). Thus, penicillins have a built-in self-destruct mechanism. However, if a good electron-withdrawing group is attached to the carbonyl group, then the inductive pulling effect should draw electrons away from the carbonyl oxygen and reduce its tendency to act as a nucleophile.



Scheme 24.47

Enzyme-catalyzed hydrolysis of the β-lactam ring uncovers the thiazolidine-ring nitrogen as a nucleophile that drives a rapid intramolecular displacement on the side chain. Attachment of 7-hydroxy-4-methylcoumarin as the releasable group of this side chain generates a penicillin structure that can function as a fluorescence-based reporter substance/diagnostic for the presence of low levels of β-lactamase enzyme in solution [204].

The major structural differences between penicillins and cephalosporins are that the five-membered thiazolidine ring of penicillins is replaced by a six-membered dihydrothiazine ring in cephalosporins and that the degree of pyramidalization of the β-lactam nitrogen is generally smaller in cephalosporins. In addition, many cephalosporins bear a potential leaving group at the C3′ position (pyridine, acetate, or thiol), which is expelled during the hydrolysis of the 2-azetidinone nucleus to give an exo-methylene cyclic imine (Scheme 24.48). Experimental observations have led to the conclusion that β-lactam C–N bond fission is not concerted with the departure of the leaving group, and that the tetrahedral intermediate breaks down by proton



Scheme 24.48

transfer to generate an intermediate enamine, which subsequently, in a separate step, expels the leaving group [205]. The similarity in the second-order rate constants for the hydroxide-promoted hydrolysis of penicillins and cephalosporins points to an absence of influence of the leaving group at C3′ in cephalosporins.

The hydrolysis of an acetoxy ester side chain at C3 in cephalosporins is competitive with the hydrolysis of the β-lactam ring. It may be due to the comparable reactivity of the 2-azetidinone nucleus of cephalosporins and a simple ester such as ethyl acetate. No significant spontaneous hydrolysis is observed in the pH–rate profile for the hydrolysis of penicillins, but the β-lactam moiety does undergo an acid-catalyzed degradation. By contrast, the hydrolysis of cephalosporins shows a spontaneous pH-independent hydrolysis and is less reactive by a factor of about 10^4 towards acid than are penicillins [206]. Penicillins undergo an acid- and a base-catalyzed hydrolysis, but there is no significant uncatalyzed reaction, the pH minimum being around 7 for spontaneous or water-induced degradation. However, cephalosporins often exhibit a significant pH-independent reaction in the pH range 3–7. The evaluation of different glutaryl acylase mutants to improve the hydolysis of cephalosporin C in the absence of hydrogen peroxide has been reported [207].

24.2.4.3 **Alcoholysis, Thiolysis, and Aminolysis**

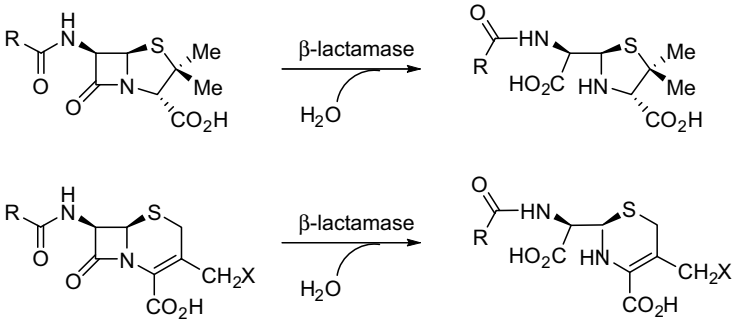
The reactions of β-lactam antibiotics and their derivatives with nucleophiles have been studied extensively. For example, nucleophilic substitution at the β-lactam carbonyl center of penicillins occurs, in water, with amines [208], alcohols [209], and thiols [210] in competition with that by hydroxide ion. These are acyl transfer processes involving covalent bond formation between the carbonyl carbon and the nucleophile and C−N bond fission of the β-lactam. In general, covalent bond formation to the incoming nucleophile occurs before β-lactam C−N bond fission, resulting in the reversible formation of a tetrahedral intermediate. The rate-limiting step in these reactions is thus commonly ring opening and breakdown of the tetrahedral intermediate. Formation of the tetrahedral intermediate also changes the basicity of the leaving group amine, as amide resonance in the β-lactam is lost and

proton transfer to nitrogen changes from an unfavorable to a thermodynamically favorable process. Thus, many of these reactions require general acid catalysis and protonation of the amine nitrogen leaving group to facilitate C−N bond fission and avoid amine anion expulsion. Although the release of strain energy, which accompanies ring opening, could possibly decrease the need for protonation, C−N fission in penicillins appears to require some form of catalysis. For example, the alcoholysis and thiolysis of penicillins occur with rate-limiting breakdown of the tetrahedral intermediate facilitated by proton transfer from solvent water to the departing amine. Exceptionally, the thiolysis of some cephalosporins appears to involve the breakdown of the tetrahedral intermediate by the expulsion of an enamine anion [211].

Unlike the strongly base catalyzed aminolysis of β-lactam antiobiotics, such as penicillins and cephaloridines, the rate law for the aminolysis of *N*-aroyl β-lactams is dominated by a term with a first-order dependence on amine concentration in its free base form, which is indicative of an uncatalyzed aminolysis reaction that proceeded by a concerted mechanism [212]. The relative sequence of bond making and breaking between heavy atoms in the aminolysis of β-lactam antibiotics is a result of subtle effects that often involve proton transfer. A step-wise process for aminolysis occurs through the formation of a tetrahedral intermediate, resulting from the attack on the carbonyl center by an amine, which gives rise to a large change in the pK_a of the amine NH as a result of covalent bond formation. Proton transfer from the amine nucleophile to a base catalyst thus occurs *after* full covalent bond formation, as it changes from a thermodynamically unfavorable to a favorable process. Hence aminolysis usually requires general base catalysis to remove a proton from the attacking amine and this is the dominant term in the rate law – in fact it is experimentally difficult to determine the rate constant for any uncatalyzed reaction. With penicillins and cephalosporins this proton transfer occurs after initial C−N bond formation in a rate-limiting step that is diffusion controlled. The aminolysis of β-lactam antibiotics also requires β-lactam C−N bond fission and expulsion of an amine. The rate of aminolysis of benzylpenicillin and cephaloridine by hydroxylamine, unlike other amines, shows only a first order dependence on amine concentration [213]. The rate enhancement compared with that predicted from a Brønsted plot for other primary amines with benzylpenicillin is greater than 10^6. This is much more than an α-effect and is compatible with rate-limiting formation of the tetrahedral intermediate due to a rapid intramolecular general acid catalyzed breakdown of the intermediate. For cephaloridine, the rate enhancement is greater than 10^4, which demonstrates that β-lactam C−N bond fission and expulsion of the leaving group at C3′ are not concerted.

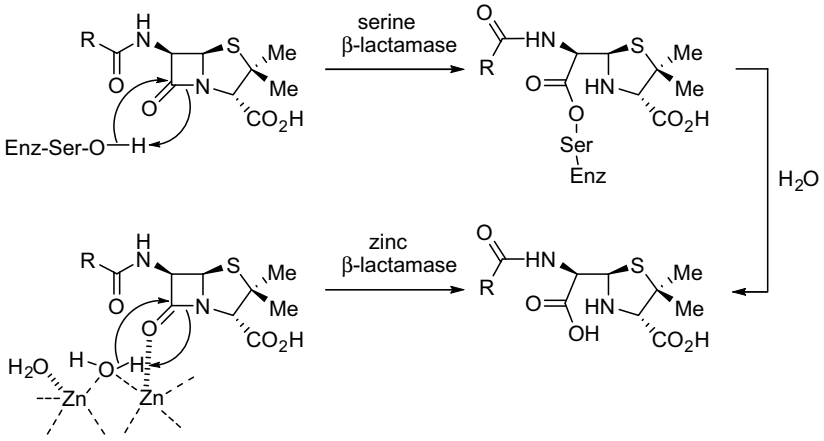
24.2.4.4 **Destruction of β-Lactam Antibiotics by β-Lactamases**

β-Lactamases hydrolyze the four-membered β-lactam ring in both penicillin and cephalosporin classes of antibiotics (Scheme 24.49). They thereby destroy the antibacterial activity by deactivating the chemical warhead in the molecule [182], the strained β-lactam that is the chemically reactive acylating group for modifying the active-site serine side chains in the penicillin-binding proteins (PBPs) (the transpeptidases and carboxypeptidases in peptidoglycan [PG] crosslinking).



Scheme 24.49

β-Lactamase activity was detected a few years before clinical use of penicillins in humans, indicating its presence in soil bacteria that combat the natural product penicillins, and to date more than 190 β-lactamases have been described [214], and categorized into class A, B, C and D lactamases [215]. The A, C and D classes are active-site serine enzymes, with architectural and mechanistic similarities to the PBPs [216], suggesting evolution from PBPs. In the A, C and D classes of β-lactamases the same type of penicilloyl-*O*-Ser enzyme covalent intermediate is formed as in the catalytic cycle of PBPs that attack and open the 2-azetidinone ring and become self-acylated. There is no such covalent penicilloyl enzyme intermediate in the catalytic cycle of the zinc-dependent class B β-lactamases, which has consequences for the failure of class B β-lactamases to be inhibited by certain drugs, because direct attack by water is carried out (Scheme 24.50).



Scheme 24.50

A simple, novel gold nanoparticle based colorimetric method has been developed for efficient screening of class A β-lactamase activity and inhibitors *in vitro* and in

bacterial strains [217]. A novel protein labeling system that combines a genetically modified, noncatalytic β-lactamase variant and specific mechanism-based fluorescent probes has also been developed [218].

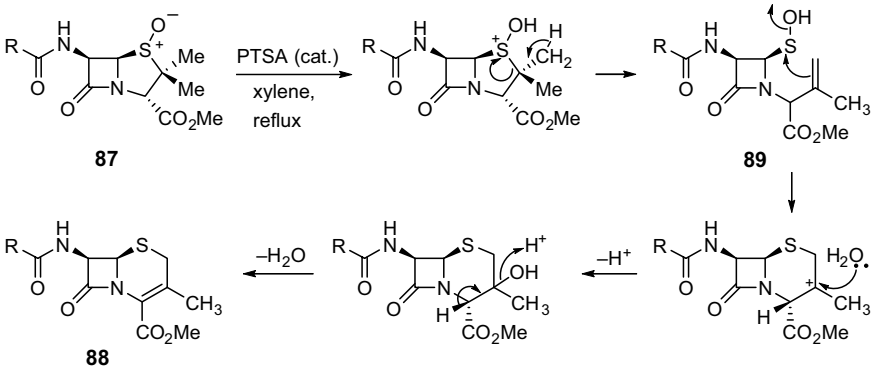
BcII is a B1 metallo-β-lactamase that is found in both mononuclear and dinuclear forms. Despite very elegant studies, there is still controversy over the nature of the active BcII species. A non-steady-state study of the hydrolysis of penicillin G catalyzed by Co(II)-substituted BcII has been carried out, and the modifications occurring at the active site of the enzyme have been followed. Working at different metal/enzyme ratios it has been demonstrated that both mono-Co(II) and di-Co(II) BcII are active metallo-β-lactamases. In addition, evidence has been presented that during penicillin G hydrolysis catalyzed by mono-Co(II) BcII the metal is localized in the DCH site (the Zn_2 site in B1 enzymes) [219].

To probe the role of the Zn(II) sites in metallo-β-lactamase L1, mononuclear metal ion containing and heterobimetallic analogues of the enzyme have been generated and characterized using kinetic and spectroscopic studies. Mononuclear Zn(II)-containing L1, which binds Zn(II) in the consensus Zn_1 site, was shown to be slightly active; however, this enzyme did not stabilize a nitrocefin-derived reaction intermediate that had been previously detected. Mononuclear Co(II)- and Fe(III)-containing L1 were essentially inactive, and NMR and EPR studies suggest that these metal ions bind to the consensus Zn_2 site in L1. Heterobimetallic analogues (ZnCo and ZnFe) analogues of L1 have been generated, and stopped-flow kinetic studies revealed that these enzymes rapidly hydrolyze nitrocefin and that there are large amounts of the reaction intermediate formed during the reaction. These studies demonstrate that the metal ion in the Zn_1 site is essential for catalysis in L1 and that the metal ion in the Zn_2 site is crucial for stabilization of the nitrocefin-derived reaction intermediate [220].

24.2.4.5 **Conversion of Penicillins into Cephalosporins**

The chemical relationship of the penicillin (thiazolidine) and the cephalosporin (dihydrothiazine) skeletons was established in the early 1960s, when it was demonstrated that penicillin sulfoxides could be rearranged to form 3-methylated cephalosporins [221]. Treatment of phenoxymethylpenicillin sulfoxide methyl ester **87**, which can be obtained from phenoxymethyl penicillin via periodate oxidation followed by esterification with diazomethane, with a trace of *p*-toluenesulfonic acid in xylene at reflux temperature gave the cephalosporin derivative **88**. A plausible pathway for this acid-catalyzed ring-expansion involves a sulfoxide elimination to intermediate **89**, subsequent addition of the sulfenic acid to the double bond with the sulfur becoming attached to the primary carbon and the loss of a proton to yield **88** (Scheme 24.51).

Eventually, a more efficient process was developed using silyl protection during the ring expansion rearrangement. Silyl protection chemistry has led to efficient chemical production of 7-ADCA and has led to highly efficient production of the oral cephalosporins, cephalexin and cephradine. Cephadroxyl is synthesized after silylation of 7-aminocephalosporanic acid (7-ACA) followed by acylation with a mixed anhydride prepared from a salt of *p*-hydroxyphenylglycine and ethylchloroformate.

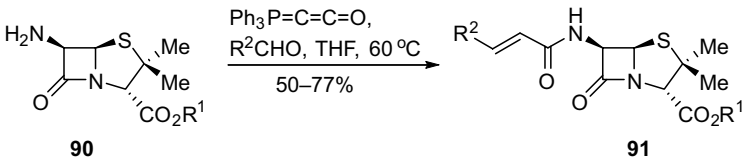


Scheme 24.51

Amoxicillin is synthesized using a similar process. An important Lilly product, cefaclor, involves a ring enlargement of a penicillin V ester to an expanded cephalosporin-S oxide with an exocyclic double bond. The product is a useful intermediate in that it can be converted into 3-substituted cephalosporins and into cefaclor, a highly prescribed oral cephalosporin with chlorine on the C3 position.

24.2.4.6 **Reactions for the Transformation of Functional Groups in Side Chains**

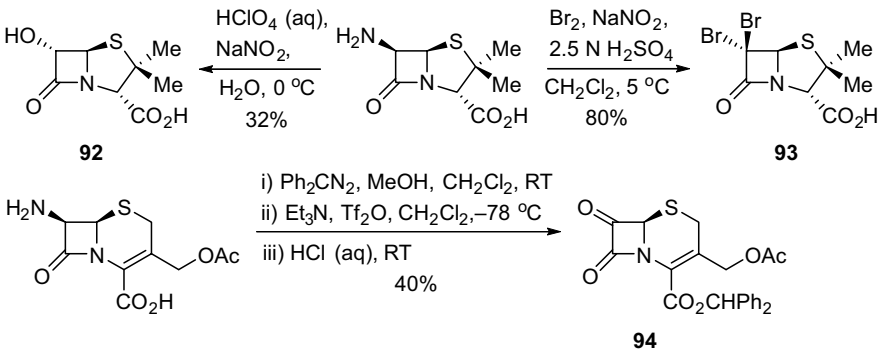
This chapter cannot give a complete overview of all the possible transformations for penicillins and cephalosporins at a specific position, because of the enormous variety of reactions involved. We focus instead on some of the most relevant reactions [181, 222]. The most important transformation for the amino function in penicillins and cephalosporins is the protection, which is introduced in general as amide by acylating the 6-APA or 7-ACA [223]. In a recent contribution, 6-aminopenicillanates **90** have been N-acylated in a three-component reaction with an aldehyde and Ph_3PCCO to give the corresponding 6-[*(E)*-2′-alkenoyl]amides **91** via a domino addition–Wittig alkenation sequence (Scheme 24.52) [224]. In addition to the amide group, several different protective groups are used for the transformation of the amino moiety of penicillins and cephalosporins. The amine can be converted into a carbamate group, to give the corresponding Boc [225], Cbz [226] or Teoc [227] derivatives. The Dane protecting group is very suitable for penicillins and cephalosporins, because the



Scheme 24.52

proton remaining on the nitrogen is stabilized by hydrogen bonding with the ester carbonyl group, which allows reactions that are normally possible only in doubly protected derivatives [228]. Double protection of the amino group is desirable in many operations, particularly with strongly basic reagents, and imines are often used [229].

The amino moiety of penicillins and cephalosporins can be transformed into different heteroatomic groups, as shown in Scheme 24.53. 6-Hydroxypenicillanic acid (**92**) has been synthesized by treatment of a solution of 6-APA in aqueous perchloric acid with sodium nitrite [230], while 6,6-dibromopenicillanic acid **93** has been prepared on reacting 6-APA with bromine [231]. A regiospecific methodology for the preparation of penicillate derivatives 6α-(1*R*-hydroxyoctyl)penicillanic acid and 6β-(1*R*-hydroxyoctyl)penicillanic acid – which will be valuable tools in the investigation of mechanistic and structural details of class D β-lactamases – has been described from 6,6-dibromopenicillanic acid **93** [232]. Esterification of 7-ACA followed by sequential treatment with excess triethylamine and trifluoromethanesulfonic anhydride gives an imine, which can then be hydrolyzed to generate the 7-oxo-cephalosporanate **94** [233]. A carbenechromium(0)-containing tether may be incorporated into penicillin G or cephalotin by using a (bromopropylamino) carbenechromium(0) complex to give metalla-penicillin and-cephalosporin derivatives, stable compounds which can be transformed into antibiotic derivatives bearing tripeptide side-chains [234].

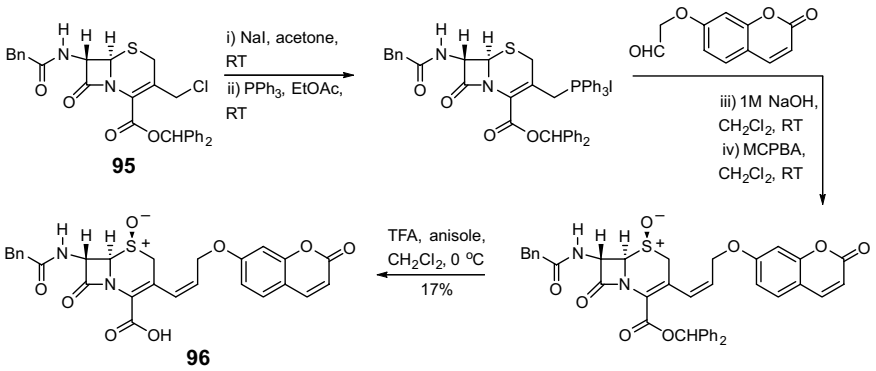


Scheme 24.53

6-Aminopenicillanic acid and two of its derivatives, 6-APA benzyl ester and penicillin G, have been evaluated as catalysts for use in direct cross-aldol reactions in different solvents and mixtures [235]. A thermal decarbonylation of penam β-lactams has been reported [236]. With the exception of monobactams, a carboxylic acid function α to the β-lactam nitrogen is essential for good antibacterial activity, and it is nearly always necessary to protect this carboxylic acid function during the preparation of derivatives. The first esterification of the carboxylic acid of penicillins was achieved on preparing penicillin G benzhydryl ester [237]. For penicillins and

cephalosporins, the most often used protective groups are functionalities that can be removed under acidic conditions, such as benzhydryl [238], *tert*-butyl [239] and *p*-methoxybenzyl [240]. A procedure that has been employed for some time to improve the absorption of penicillins and cephalosporins after oral administration is the use of special esters that readily undergo enzymatic hydrolysis *in vivo*, with liberation of the active drug. These esters, which are mostly bis-acyl derivatives of formaldehyde or acetaldehyde, can also provide protection for carboxylic acid functions during derivatization and synthetic transformations [222].

Transformations of 3-acetoxymethyl cephalosporins are of central importance. The cleavage of the acetyl residue can be carried out both enzymatically [241] and chemically [242] under mild conditions. Oxidation of alcohols obtained in this way allows preparation of the corresponding 3-formylcephalosporins, which can suffer further transformations such as the Wittig olefination [243] or Barbier-type allylation [244]. 3-Halomethyl cephalosporins can be synthesized via substitution reactions in 3-acetoxy(hydroxy)methyl cephalosporins [245]. These 3-halo derivatives usually act as building blocks for more complex derivatives. For example, the cephalosporin derivative **96**, which has been confirmed as a novel fluorogenic substrate for imaging β-lactamase gene expression, has been prepared from the 3-chloromethyl cephalosporin **95** (Scheme 24.54) [246]. A practical route to the preparation of nitrocefin from a 3-chloromethyl cephalosporin related to **95** has been reported using a similar synthetic sequence [247]. Employing a multivalent approach to drug discovery, vancomycin and cephalosporin synthons have been chemically linked to yield heterodimer antibiotics, which simultaneously target the principal cellular targets of both glycopeptides and β-lactams [248].



Scheme 24.54

The sulfur in penicillins and cephalosporins can be oxidized, leading to sulfoxides or sulfones [224, 231, 246, 249]. This oxidation is usually accomplished for one of three reasons: (i) sulfoxide formation to obtain reactive intermediates for further transformations; (ii) sulfoxide formation with subsequent reduction in cephems to shift the double bond from position 2 to position 3; (iii) preparation of sulfones as β-lactamase or elastase inhibitors.

Abbreviations

AIBN	α,α′-azoisobutyronitrile
7-ACA	7-aminocephalosporanic acid
6-APA	6-aminopenicillanic acid (6-APA)
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOM	benzyloxymethyl
BTPP	phosphazene base P_1-*t*-Bu-tris(tetramethylene)
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
Cp	cyclopentadienyl
CSI	chlorosulfonyl isocyanate
DABCO	1,4-diazabicyclo[2.2.2]octane
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DIBAL-H	(diisobutyl)aluminium hydride
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
de	diastereomeric excess
dr	diastereomeric ratio
ee	enantiomeric excess
Fmoc	9-fluorenylmethoxycarbonyl
HIU	high intensity ultrasound
HMDS	hexamethyldisilazane
HPLC	high-performance liquid chromatography
IR	infrared
LHMDS	lithium hexamethyldisilazane
LDA	lithium diisopropylamide
MCPBA	*meta*-chloroperoxybenzoic acid
MCR	multicomponent reaction
MOM	methoxymethyl
MM	molecular mechanical
MMPP	magnesium monoperoxyphthalate
MS	mass spectrometry
NCA	*N*-carboxy anhydride
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
PBP	penicillin binding protein
PDC	pyridinium dichromate
Phth	phthalimidoyl
PMB	*p*-methoxybenzyl

PMP	*p*-methoxyphenyl
PPTS	pyridinium *p*-toluenesulfonate
PTSA	*p*-toluenesulfonic acid
QM	quantum mechanical
RCM	ring closing metathesis
RT	room temperature
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
Ts	tosyl

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25
The Chemistry of Benzodiazepines

Carlos Valdés and Miguel Bayod

25.1
Introduction

25.1.1
General Introduction

The discovery of the psychotropic activity of 1,4-benzodiazepine derivatives (Figure 25.1) [1] opened a whole new area of activity in the treatment of mental diseases associated with depressive processes and affective alterations. More recently, compounds featuring the basic structure of 1,4-benzodiazepine, and exhibiting non-psychotropic biological activity, such as anti-cancer [2], anti-HIV [3], and anti-Alzheimer [4] activities have been discovered. Prominent examples are the benzodiazepinic alkaloids circumdatin A, B, and C, **1**–**3**, which are employed in the treatment of gastrointestinal disorders [5], and the naturally occurring pyrrolo[2,1-*c*][1,4]benzodiazepines (**4**), which are potent antitumor antibiotics isolated from various species of *Streptomyces* (Figure 25.2) [6].

Currently, the structure of 1,4-benzodiazepine represents one of most important *privileged structures* in medicinal chemistry, a term coined by Evans to define "a single molecular framework able to provide ligands for diverse receptors" [7]. In fact, the development of benzodiazepines chemistry has been directed to the search for new and more active compounds.

The introduction of chlordiazepoxide (**5**) (Figure 25.3) in clinical medicine, in 1961, can be regarded as the starting point of the benzodiazepine era. Since then, thousands of these compounds have been synthesized through conventional and combinatorial techniques. Currently, over 50 benzodiazepines find clinical application in different regions of the world. Most of the benzodiazepines that have reached the market were selected due to their high anxiolytic potency due to their depressing function of the central nervous system. Most of them feature some sedative hypnotic properties to various extents, and therefore also find clinical application as sleep promoters. Moreover, their low tendency to induce lethal depression of the CNS has

Modern Heterocyclic Chemistry, First Edition.
Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.

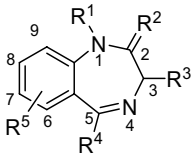
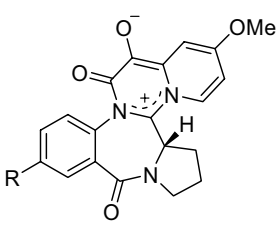
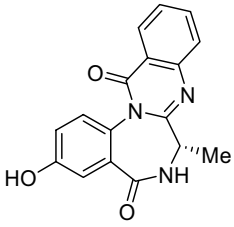


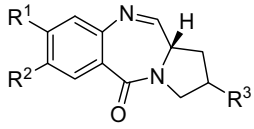
Figure 25.1 General Structure of 1,4-benzodiazepines.



1 R = OMe, Circumdatin A
2 R = H, Circumdatin B



3 Circumdatin C



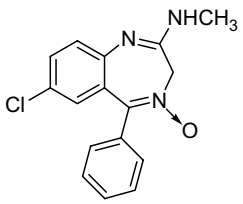
4 Pyrrolo[2,1-*c*] [1,4]benzodiazepines

Figure 25.2 Some compounds that feature the basic structure of 1,4-benzodiazepine and exhibit non-psychotropic biological activity.

ensured that benzodiazepines have replaced almost completely the barbiturics as sedative hypnotics.

Over the last decade it has been shown that the effects of most of the 1,4-benzodiazepines with clinical application result from benzodiazepine's modulation of γ-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the central nervous system, by influencing the $GABA_A$ receptor complex [8]. Benzodiazepines bind to the $GABA_A$ receptor, reducing the quantity of GABA required to open the chloride channel, hyperpolarize the neuron, and inhibit neurotransmission [9].

Benzodiazepines are lipo-soluble substances that are easy to crystallize and have basic character. The common characteristic of benzodiazepines is a bicyclic structure composed of a benzene ring fused to a diazepine (a seven-membered ring with two nitrogen atoms). In addition, most of the biologically active benzodiazepines feature substitution at C5 with an aromatic ring. Each particular benzodiazepine is derived



5 Chlordiazepoxide

Figure 25.3 Structure of chlordiazepoxide (**5**).

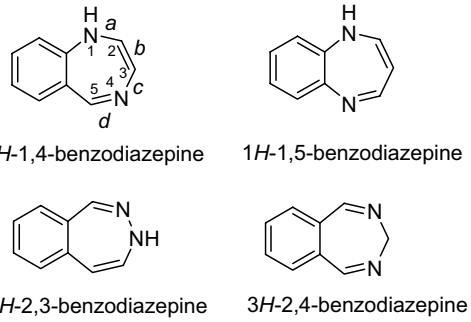


Figure 25.4 Basic structures of benzodiazepines.

by the incorporation of different substituents at the different positions of the basic structure [10].

25.1.2
Structural Classification of Benzodiazepines

Depending on the position of the two nitrogen atoms in the seven-membered heterocyclic ring, the benzodiazepines can be classified in four main different groups (Figure 25.4):

- 1,4-benzodiazepines
- 1,5-benzodiazepines
- 2,3-benzodiazepines
- 2,4-benzodiazepines.

By far, 1,4-benzodiazepines are the most interesting derivatives, due to their clinical applications. In addition, some examples of therapeutic applications of 1,5- and 2,3-benzodiazepines exist. Thus, this chapter will focus mainly on the chemistry of 1,4-benzodiazepines, and in particular on the biologically more active members of this family. Nevertheless, 1,5- and 2,3- derivatives are covered in Sections 25.7 and 25.8, respectively.

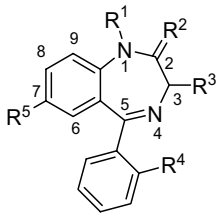
25.2
Relevant Benzodiazepines

25.2.1
Most Common 1,4-Benzodiazepines

Table 25.1 gives the particular structures of some of the most important 1,4-benzodiazepines with clinical applications.

Variations on the substituents denoted by R^1, R^2, R^3, R^4, and R^5 are responsible for the different biological activity of 1,4-benzodiazepines.

Table 25.1 Chemical structure of the most common 1,4-benzodiazepines.



Compound	Name	R^1	R^2	R^3	R^4	R^5
6	Bromazepam	H	O	H	[a]	Br
7	Camazepam	Me	O	$OCONMe_2$	H	Cl
8	Clonazepam	H	O	H	Cl	NO_2
9	Clorazepate	H	O	CO_2K	H	Cl
5	Chlordiazepoxide[b),c)]	—	NHMe, H	H	H	Cl
10	Demoxepam[c)]	H	O	H	H	Cl
11	Diazepam	Me	O	H	H	Cl
12	Fletazepam	CH_2CF_3	H, H	H	F	Cl
13	Flunitrazepam	Me	O	H	F	NO_2
14	Flurazepam	$(CH_2)_2NEt_2$	O	H	F	Cl
15	Fosazepam	CH_2POMe_2	O	H	H	Cl
16	Halazepam	CH_2CF_3	O	H	H	Cl
17	Lorazepam	H	O	OH	Cl	Cl
18	Lormetazepam	Me	O	OH	Cl	Cl
19	Medazepam	Me	H, H	H	H	Cl
20	Metaclazepam	Me	CH_2OMe, H	H	Cl	Br
21	Nimetazepam	Me	O	H	H	NO_2
22	Nitrazepam	H	O	H	H	NO_2
23	Nordazepam	H	O	H	H	Cl
24	Oxazepam	H	O	OH	H	Cl
25	Pinazepam	CH_2CCH	O	H	H	Cl
26	Prazepam	CH_2—	O	H	H	Cl
27	Quazepam	CH_2CF_3	S	H	F	Cl
28	Temazepam	Me	O	OH	H	Cl
29	Tetrazepam	Me	O	H	[d)]	Cl
30	Tifluadom	Me	[e)]	H	F	H
31	Uldazepam[b)]	—	[f)]	H	Cl	Cl

[a)] 2-Pyrido as substituent at C5.
[b)] Double bond between N1 and C2.
[c)] Oxygen at N4.
[d)] 1-Cyclohexenyl as substituent at C5.
[e)] Thieno-2-carbonylaminomethyl.
[f)] Allyloxiamino.

Regarding the benzene ring, only substitution at C7 (R^5) presents pharmacological interest. Moreover, usually anionic derivatives are more interesting than cationic forms. Substitution at positions 6, 8, and 9 diminishes substantially the activity or even makes the benzodiazepines biologically inert.

Alterations in the substituent attached at C5 render some compounds pharmacologically interesting. For instance, bromazepam (**6**) with anxiolytic activity, features a 2-pyridyl substituent, and the muscle relaxant tetrazepam (**29**) a cyclohexenyl group.

Modifications in the diazepinic ring give rise to most of the benzodiazepines with pharmacological activity. For example, methylation of the amide nitrogen of position 1 ($R^1 = Me$; $R^2 = =O$) is found in diazepam (**11**), while the addition of longer alkyl chains is detrimental to the anxiolytic activity. Other variations of R^1 determine the formation of compounds with a high sedative effect: flurazepam (**14**, $R^1 = (CH_2)_2NEt_2$), anticonvulsant; halazepam (**16**, $R^1 = CH_2CF_3$), with activity similar to chlordiazepoxide (**5**); and pinazepam (**25**, $R^1 = CH_2C \equiv CH$) and prazepam (**26**, $R^1 = CH_2$-cyclopropyl) with diazepam-like activity.

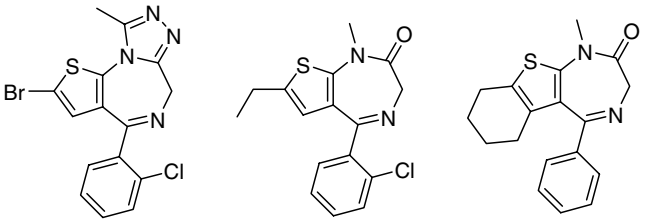
The introduction of modifications at position 2 leads to chlordiazepoxide (**5**), metaclazepam (**20**), and uldazepam (**31**). The 2-acylaminomethyl derivatives do not have affinity for the same receptor, and therefore lack anxiolytic activity. However, these type of derivatives act selectively on the opiaceous receptors. This is the case for tifluadom (**30**), which has shown K-selective agonist activity, with a potential of action over this subgroup of receptors 25-fold superior than that of morphine [11].

The introduction of functionality at position 3 leads to a new family of benzodiazepines, with camazepam (**7**), clorazepate (**9**), lorazepam (**17**), and oxazepam (**24**) as the most distinguished members. Camazepam (**7**) has shown excellent anxiolytic activity, with low sedative and relaxant effects. Reduction of the lactam of camazepam leads to fletazepam (**12**) and medazepam (**19**), compounds with lower pharmacological activity.

The structural variants in which the benzene ring is replaced by a heterocycle hold great interest, since they exhibit similar pharmacological properties to the classic benzodiazepienes, and extend the therapeutic scope of these drugs. In this context, thienodiazepines, such as brotizolam (**32**), clotiazepam (**33**), and bentazepam (**34**) (Figure 25.5) have been extensively studied.

25.2.2
1,4-Benzodiazepines with a Heterocycle Condensed at sides *a* or *d*

Another interesting variation of pharmacological interest is present in systems that feature an additional five- or six-membered nitrogenated heterocycle condensed at



32 Brotizolam **33** Clotiazepam **34** Bentazepam

Figure 25.5 Thienodiazepines brotizolam (**32**), clotiazepam (**33**), and bentazepam (**34**), which have been studied extensively in terms of their pharmacological properties.

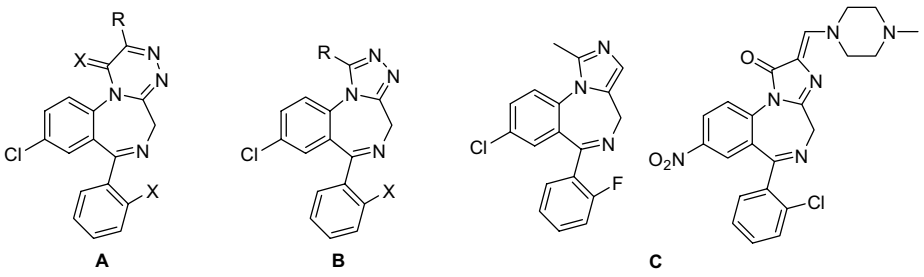


Figure 25.6 Benzodiazepines with a heterocycle condensed at the *a* face.

the *a* face of the benzodiazepine. Triazino-, triazolo-, and imidazobenzodiazepines (**A**,**B**, and **C** respectively in Figure 25.6) have been studied thoroughly. Triazinobenzodiazepines (**A**) have shown an effect similar to diazepam (**11**) (with the exception of the anticonvulsant effect), but the derivatives featuring a nitrogenated five-membered ring have attracted more interest in the pharmaceutical industry.

Figure 25.6 shows some of the most relevant members of this type of benzodiazepines. Triazolam (**36**) is the most active triazolo-benzodiazepine. Both triazolam and estazolam (**35**) have exhibited excellent action as hypnotic agents. Of particular interest is alprazolam (**37**), which features rapid and strong anxiolytic activity, and antidepressive effects [12]. Regarding the imidazobenzodiazepines **C**, worth noting is midazolam (**38**), a benzodiazepine with relatively short action, which holds anxiolytic, hypnotic anticonvulsive, amnesic, and muscle relaxant effects [13].

Among the cyclofunctionalized 1,4-benzodiazepines, another interesting subgroup is formed by structures that feature a fused heterocycle at the *d* face (N4-C5) of the diazepine ring (Figure 25.7). In particular, oxazolobenzodiazepines and oxazinobenzodiazepines have been studied extensively. Representative members of these families of heterocycles are oxazolam (**40**), cloxazolam (**41**), and mexazolam

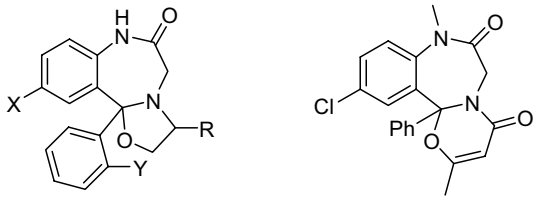


Figure 25.7 Benzodiazepines with a heterocycle condensed at the *d* face.

(**42**) for the oxazolobenzodiazepines, and ketazolam **43** for the oxazinobenzodiazepines. The latter is an analog of diazepam (**11**) that features good anxiolytic activity with low secondary effects.

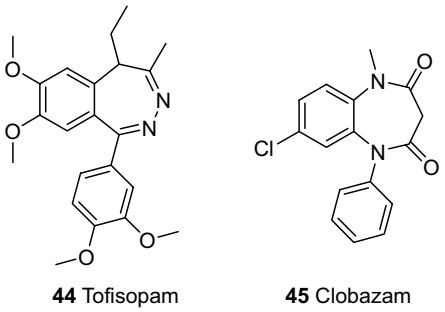
25.2.3
Other Benzodiazepines with Clinical Application

Although 1,4-benzodiazepines represent the vast majority of benzodiazepines with pharmaceutical applications, some other examples exist of benzodiazepine drugs that feature the nitrogen atoms in different positions. This is the case of tofisopam (**44**), a 2,3-benzodiazepine with anxiolytic properties, and clobazam (**45**), a 1,5-benzodiazepine employed in the treatment of several psychotic disorders (Figure 25.8).

25.2.4
Naturally Occurring Benzodiazepines

Many years after the discovery of synthetic 1,4-benzodiazepines as biologically active substances, several natural alkaloids featuring the basic 1,4-benzodiazepine substructure have been discovered. The benzodiazepine-quinazoline scaffold is found in several alkaloids with interesting biological activity. The simplest member is sclerotigenin, isolated from the sclerotia of *Penicillium sclerotigenum* [14]. More complex structures are found in benzomalvins A–C, isolated from the fungus *Penicillium* sp. [15], asperlicins [16] (Figure 25.9), and circumdatins A–G (Figure 25.2), isolated from the fungus *Aspergillus ochraceous* [5, 17].

Another important class of natural products that contains the 1,4-benzodiazepine structure are pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs). These compounds are a family of naturally occurring of antitumor antibiotics that have attracted great attention in recent years. Section 25.6 provides more detailed coverage of these systems.



44 Tofisopam **45** Clobazam

Figure 25.8 Tofisopam (**44**), a 2,3-benzodiazepine with anxiolytic properties, and clobazam (**45**), a 1,5-benzodiazepine used in the treatment of several psychotic disorders.

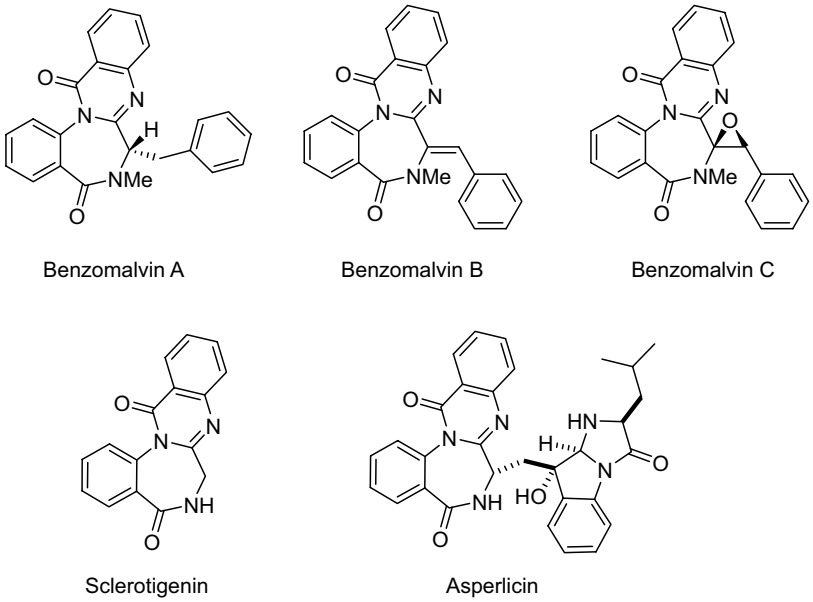


Figure 25.9 Compounds containing the benzodiazepine-quinazoline scaffold.

25.3
1,4-Benzodiazepines: General Synthetic Methods

25.3.1
1,4-Benzodiazepines Ring Synthesis: Introduction

Since 1960, when the first benzodiazepine with clinical applications (chlordiazepoxide, **5**) was introduced onto the pharmaceutical market, several methods have been developed for the preparation of a large variety of members of this family of products. With the advent of parallel and combinatorial techniques, the solid-supported synthesis of 1,4-benzodiazepines has been thoroughly developed. The synthetic strategies applied are common to both solution- and solid-supported synthesis. For this reason, the different methodologies will be presented regardless of whether they are employed in solution or solid support.

This section is divided in two parts, dedicated to the most important members of this family, namely, 1,4-benzodiazepin-2-ones and 1,4-benzodiazepin-2,5-diones (Figure 25.10).

25.3.2
Ring Synthesis of 1,4-Benzodiazepin-2-ones

25.3.2.1 Quinazoline *N*-Oxide Route: Sternbach's Classical Synthesis

The synthesis of chlordiazepoxide (**5**) was reported by Leo Sternbach back in 1961 [18] by treatment of quinazoline N-oxide **48** with amines, followed by ring expansion of

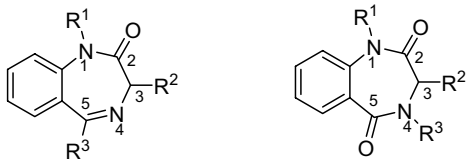
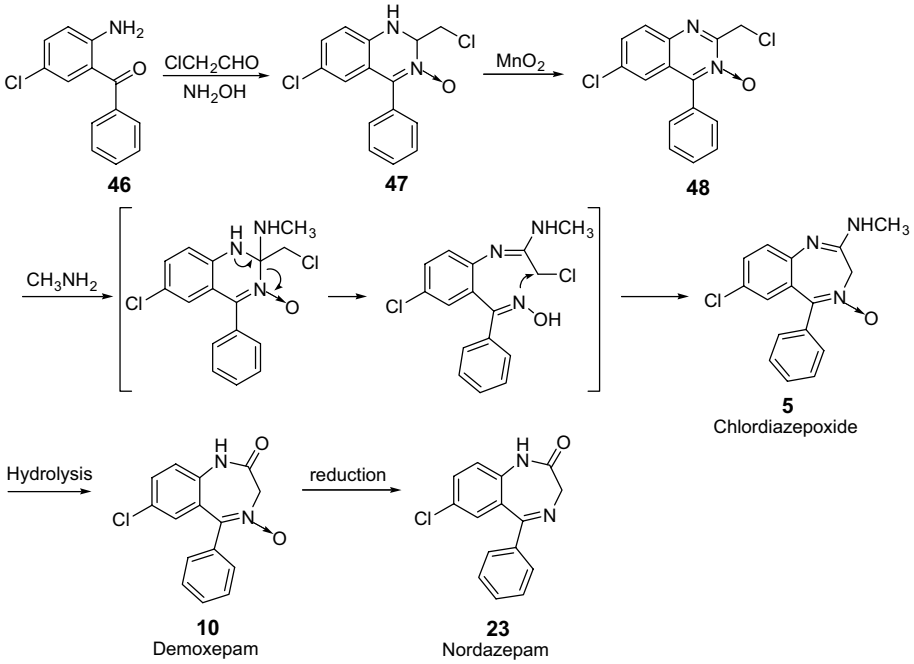


Figure 25.10 The two most important members of the 1,4-benzodiazepine family.

the piperazine ring formed (Scheme 25.1). Hydrolysis of the amidine function of chlordiazepoxide gives rise to the corresponding lactam demoxepam (**10**) and further reduction of the N-oxide provides nordazepam (**23**) (Scheme 25.1).

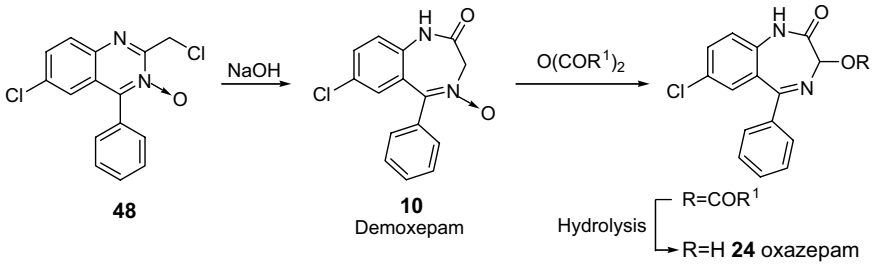
The discovery of the first benzodiazepine by Sternbach is a fascinating example of a serendipitous discovery that turned out to have an enormous impact in our society. Readers are encouraged to read Sternbach's own version [1]. Chlordiazepoxide (**5**) had been prepared inadvertently and its structure had been wrongly assigned in 1955 during a synthetic project aimed at substituted quinazoline N-oxides (Scheme 25.1). Treatment of quinazoline N-oxide (**48**) with methylamine led to chlordiazepoxide (**5**) through an unexpected nucleophilic addition/ring-opening/ring-closure sequence, instead of the desired S_N2 reaction. The crystals of chlordiazepoxide, which had remained in a flask in the bench for two years, were discovered during a laboratory



Scheme 25.1 Sternbach's synthesis of chlordiazepoxide (**5**).

clean-up operation and then submitted for pharmacological testing. The unparalleled properties found for that compound triggered the development of this important type of drugs in pharmaceutical industry.

Demoxepam (**10**) can be directly obtained from 2-chloromethylquinazoline N-oxide **48** by treatment with base [19]. In addition, reaction with anhydrides or acid chlorides leads to 3-acyloxy derivatives through the Polonovsky rearrangement [20], which upon hydrolysis gives 3-hydroxybenzodiazepines. This route has been employed for the synthesis of highly active benzodiazepines such as lorazepam (**17**) [21], lormetazepam (**18**) [22], oxazepam (**24**), and temazepam **28**, which are marketed as anxiolytic, anticonvulsants, or hypnotics (Scheme 25.2).

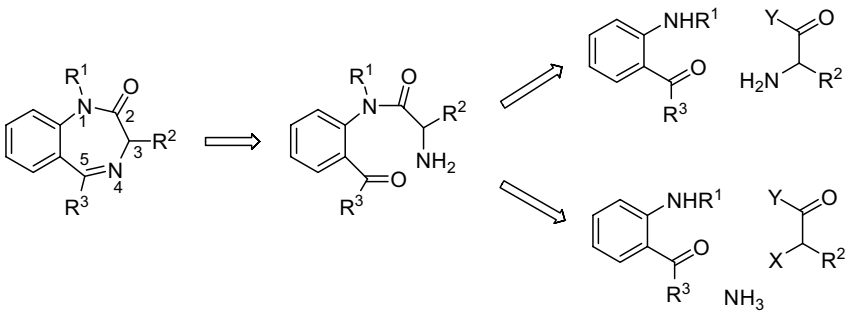


Scheme 25.2 Synthesis of 3-hydroxy-1,4-benzodiazepines from 2-chloromethylquinazoline *N*-oxide **48**.

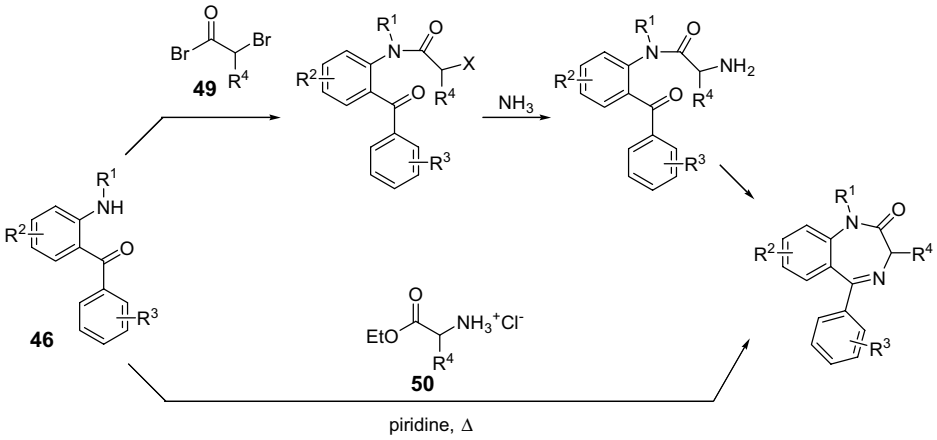
25.3.2.2 **2-Aminobenzophenone Route**

Scheme 25.3 presents the typical disconnections for the synthesis of 1,4-benzodiazepine-2-ones: (i) formation of an amide bond between N1 and C2; (ii) imine condensation between N4 and C5.

Thus, the most straightforward strategies for the preparation of 1,4-benzodiazepin-2-ones are based on the condensation of 2-aminobenzophenones and α-functionalized carboxylic acid derivatives. Scheme 25.4 depicts the most typical synthetic routes.



Scheme 25.3 Retrosynthetic analysis of 1,4-benzodiazepines.



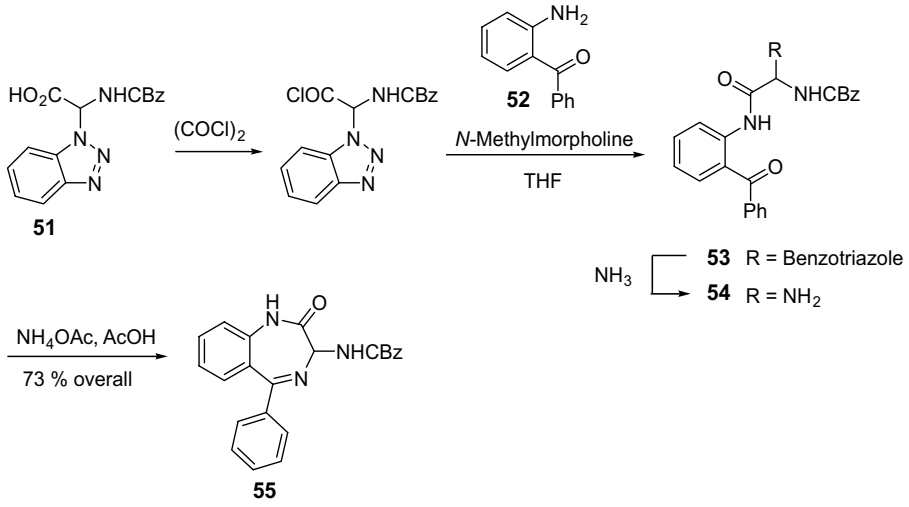
Scheme 25.4 Synthesis of 1,4-benzodiazepin-2-ones from *o*-aminobenzophenones.

The first procedure consists in the treatment of the aminobenzophenone **46** with a bromoacetyl bromide **49** followed by reaction with ammonia [23]. Then, intramolecular condensation occurs easily in the reaction media to provide the 1,4-benzodiazepine without the need to isolate the open chain intermediates. The second approach implies the treatment of the o-aminobenzophenone (**46**) with the hydrochloride of an amino ester **50** in pyridine, which leads directly to the final benzodiazepine. This procedure is particularly useful for the introduction of different substituents (R^4) at C3 [24]. Typical examples of this procedure are the classical syntheses of bromazepam (**6**) [25].

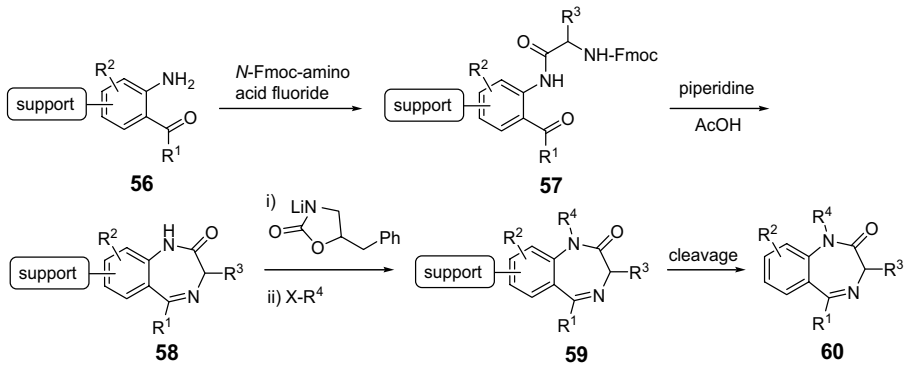
This methodology has been adapted to the preparation of 3-amino-1,4-benzodiazepines. A very convenient methodology employs α-benzotriazol-1-yl-N-(benzyloxycarbony1)glycine (**51**) as synthetic equivalent of α-aminoglycine [26]. After acylation of the NH_2 group of 2-aminobenzophenone **52**, treatment with ammonia yields the open chain derivative **54**, which features a free NH_2 and undergoes cyclization to the 3-aminobenzodiazepine **55** (Scheme 25.5).

The condensation of 2-aminobenzophenones with α-amino acids was also applied by Ellman in one of the first examples of solid-supported synthesis of benzodiazepines (Scheme 25.6) [27]. To the aminoketone attached at the polymeric support (**56**) is coupled a Fmoc-protected amino acid. Deprotection of the Fmoc group followed by treatment with acid leads to the solid supported benzodiazepine **58**. Additional diversity is achieved by alkylation of the N1 nitrogen to give solid-supported benzodiazepines **59**. Final cleavage from the resin gives rise to the free benzodiazepine **60** featuring four points of diversity.

A different strategy for the solid supported synthesis of 1,4-benzodiazepine-2-ones was reported by DeWitt *et al.* in 1993 (Scheme 25.7) [28]. Reaction of 2-aminobenzophenone imines **61** with solid-supported amino acids **62** renders the intermediate imine **63**, which provides the benzodiazepine upon cyclization. Interestingly, the cyclization-release strategy allows for the obtention of the benzodiazepines **64** with very high purity.



Scheme 25.5 Synthesis of 3-amino-1,4-benzodiazepin-2-ones.



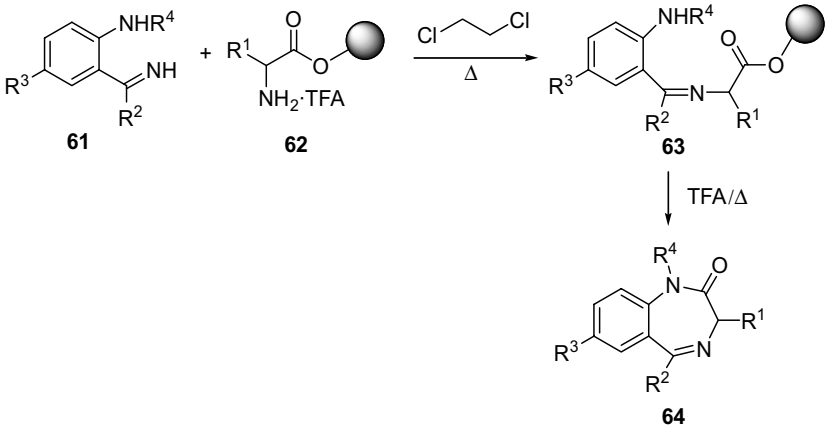
Scheme 25.6 Ellman's solid-phase synthesis of 1,4-benzodiazepine-2-ones.

25.3.3

Synthesis of 1,4-Benzodiazepine-2,5-diones

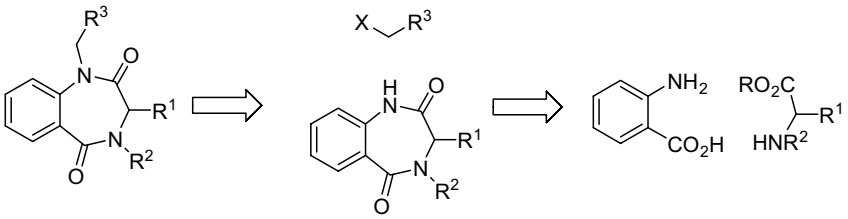
25.3.3.1 **Standard Synthesis: from Anthranilic Acid and α-Amino Acid Derivatives**

Among the different classes of structures featuring the benzodiazepine structure, 1,4-benzodiazepine-2,5-diones hold a prominent position, not only because they are direct precursors of 1,4-benzodiazepine-2-ones, but also due to the diverse of biological properties that they feature. The retrosynthetic analysis of 1,4-benzodiazepine-2,5-diones is very obvious, as they are generally prepared by the condensation of an anthranilic acid and an α-amino acid. Finally, treatment with an alkylating



Scheme 25.7 DeWitt's solid-phase synthesis of 1,4-benzodiazepine-2-ones.

reagent introduces the substitution at N1 (Scheme 25.8). Most modern advances regarding the preparation of such molecules have concentrated on the development of high-throughput methodologies that could be adapted to combinatorial techniques.

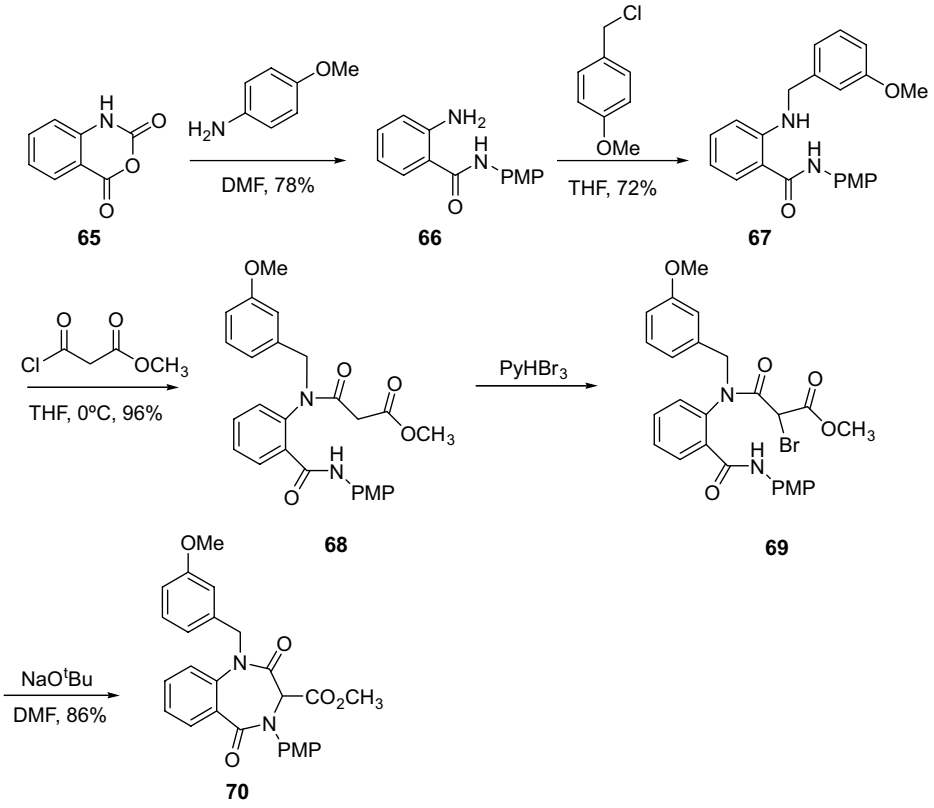


Scheme 25.8 Retrosynthesis of 1,4-benzodiazepine-2,5-diones.

In the following schemes are represented two different synthetic routes that employ isatoic anhydride (**65**) as synthetic equivalent of anthranilic acid. Treatment of **65** with an aniline gives rise to o-amino amide **66**. Alkylation of the amino group, followed by acylation with methyl malonyl chloride gives **68**, which is treated with a brominating agent to produce the intermediate **69**, which undergoes cyclization by treatment with base to produce the benzodiazepine-dione **70** (Scheme 25.9) [29].

The 1,4-benzodiazepine-2,5-dione **71** can be constructed in a single step by reaction of isatoic anhydride **65** with an α-amino ester (Scheme 25.10). Further substitution at both nitrogens to obtain **73** can be achieved by sequential alkylation. Notably, the N1 nitrogen on **71** can be selectively alkylated to form **72** by taking into account the higher acidity of the anilide nitrogen.

Microwave irradiation promotes the cyclization between isatoic anhydride and α-amino acids very efficiently, as represented by the solvent-free synthesis of pyrrolo



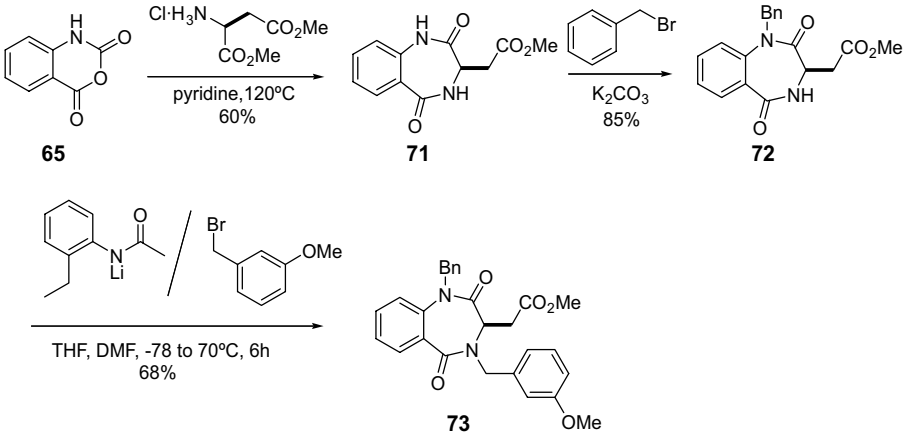
Scheme 25.9 Synthesis of 1,4-benzodiazepine-2,5-diones employing isatoic anhydride (**65**).

[2,1-c][1,4]benzodiazepine-5,11-diones **75** from isatoic anhydride and a proline derivative **74** (Scheme 25.11) [30].

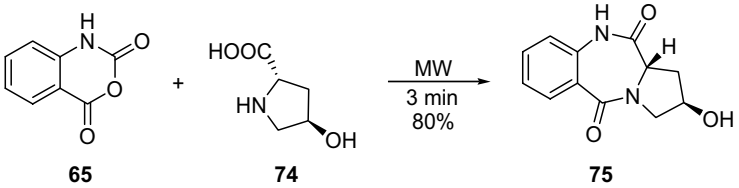
o-Nitroacyl chlorides **76** and o-azidoacyl chlorides **79** [31] can be employed as starting point for the preparation of 1,4-benzodiazepine-2,5-diones. Condensation with an amino ester provides the N-acylated precursors **77** and **80**, respectively, that can be cyclized directly into the benzodiazepine-1,3-diones **78** and **81** upon reduction of the masked amine functionality (Scheme 25.12).

25.3.3.2 Ugi 4CC Reaction in the Synthesis of 1,4-Benzodiazepines-2,5-diones

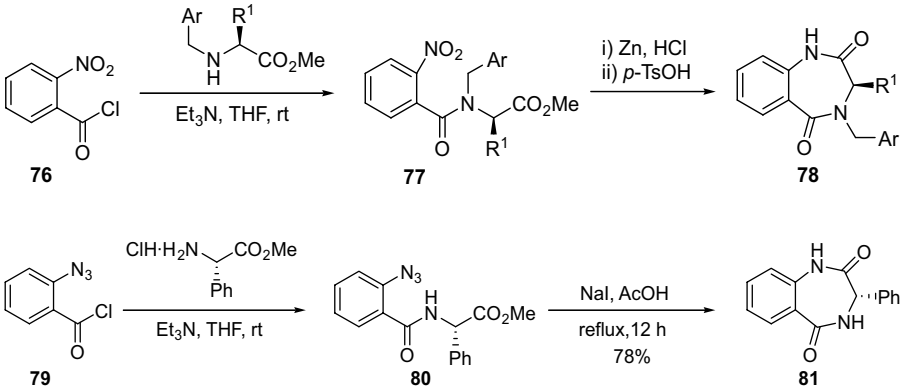
A particularly appealing advance in the synthesis of benzodiazepines was the incorporation of the Ugi four-component condensation reaction to prepare the intermediate that ultimately leads to the benzodiazepine upon cyclization. The Ugi four-component condensation (4CC) consists of the reaction of a carboxylic acid, an amine, a carbonyl compound (ketone or aldehyde), and an isocyanide to provide an α-acylamino amide **82** (Scheme 25.13), and has been extensively employed in diversity oriented synthesis [32].



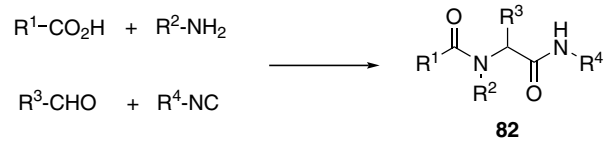
Scheme 25.10 One-step synthesis of the 1,4-benzodiazepine-2,5-dione ring from isatoic anhydride (**65**).



Scheme 25.11 Microwave-promoted synthesis of 1,4-benzodiazepine-2,5-diones.

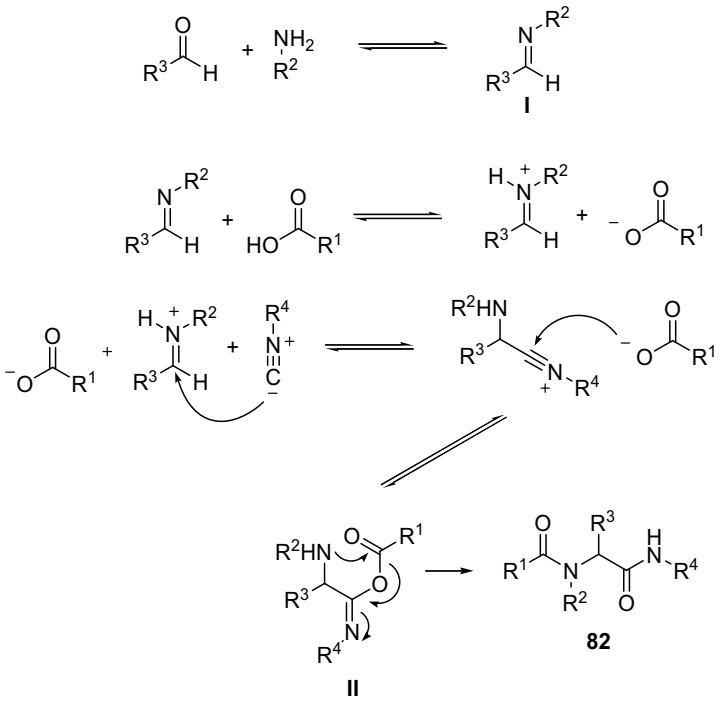


Scheme 25.12 Synthesis of 1,4-benzodiazepine-2,5-diones employing *o*-nitroacyl chlorides **76** and *o*-azidoacyl chlorides **79** as anthranilic acid equivalents.



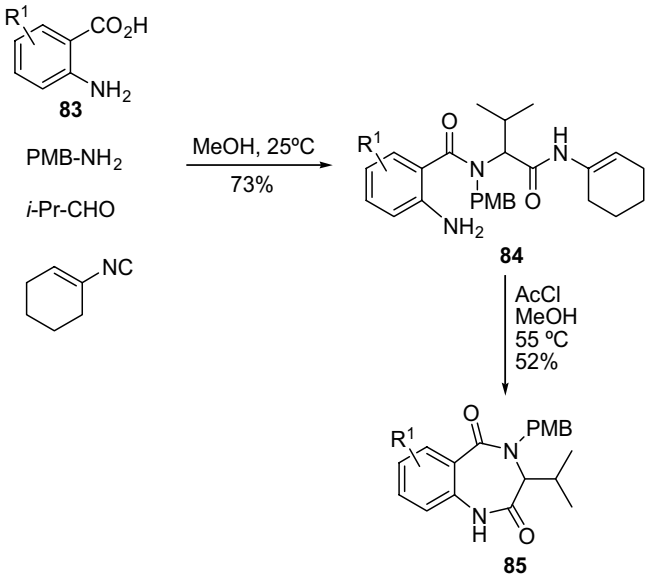
Scheme 25.13 The Ugi four-component condensation (4CC).

The mechanism proposed for the Ugi reaction (Scheme 25.14) involves formation of an imine **I** by condensation of the amine with the aldehyde, followed addition of the carboxylic acid oxygen and the imino carbon across the isocyanide carbon. The resulting acylated isoamide **II** then rearranges by acyl transfer to give the final product.



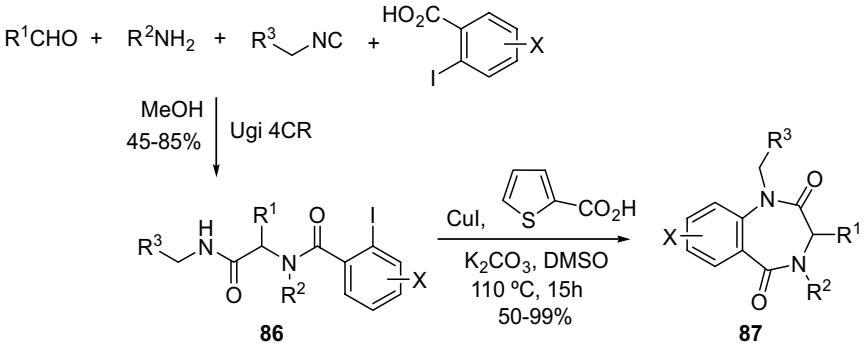
Scheme 25.14 Plausible mechanism of the Ugi 4CC.

When the Ugi reaction is conducted employing an anthranilic acid derivative (**83**) as carboxylic acid component, the resulting α-acylamino amide **84** suffers an intramolecular cyclization in acidic media that leads to the 1,4-benzodiazepine-2,5-dione **85** (Scheme 25.15) [33]. Several modifications of this synthetic route have been adapted to combinatorial solid-phase synthesis [34].



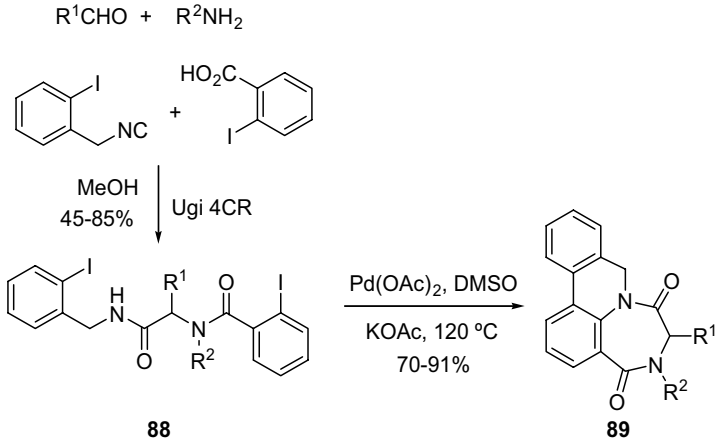
Scheme 25.15 Synthesis of 1,4-benzodiazepine-2,5-diones employing the Ugi 4CC.

A completely different approach to the synthesis of 1,4-benzodiazepin-2,5-diones relies on an intramolecular transition metal catalyzed arylation of o-iodoamides **86** The cyclization reaction is carried out employing either Pd [35] or Cu [36] catalysts, depending on the nature of the starting iodoamide [37]. This strategy allows for the preparation of structurally diverse 1,4-benzodiazepines-1,5-diones, as the starting amides are readily prepared through the Ugi 4CC reaction. Copper-catalyzed cyclizations of iodoamides **86** lead to typical benzodiazepine-diones **87** (Scheme 25.16). A similar approach employing o-bromobenzoic acids has been reported recently [38].



Scheme 25.16 Synthesis of 1,4-benzodiazepine-2,5-diones by Cu-catalyzed intramolecular amidation.

In contrast, the Pd-catalyzed reaction of diamides **88**, which feature two iodo-substituted benzene rings, provides the benzodiazepine containing tetracycles **89** (Scheme 25.17).



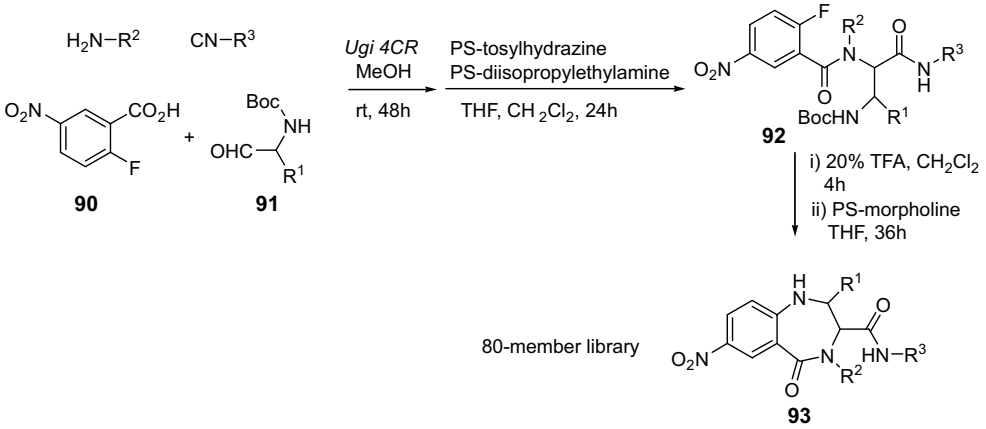
Scheme 25.17 Palladium-catalyzed intramolecular amidation in the synthesis of 1,4-benzodiazepine-2,5-diones.

The cyclization reaction to build the seven-membered ring of benzodiazepines has been also accomplished by a S_NAr reaction on the corresponding fluoro-substituted amides **92**. Again, a diverse range of the acyclic precursors **92** can be prepared employing the Ugi 4CC, consisting of in this case 2-fluoro-4-nitrobenzoic acid (**90**), a N-Boc-protected amino aldehyde **91**, a primary amine, and the isonitrile. The S_NAr cyclization occurs upon deprotection of the Boc group. Interestingly, the whole sequence has been performed employing solid-supported scavenging reagents, and, thus, the benzodiazepines **93** are isolated without the need of further purification. An 80-member library has been synthesized employing this methodology (Scheme 25.18) [39].

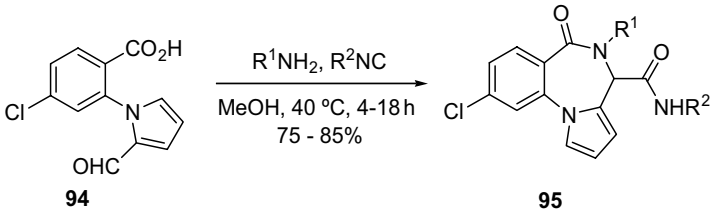
The intramolecular Ugi 4CC reaction has been employed in the preparation of pyrrolobenzodiazepines **95** and structurally related systems. Thus, employment of the bifunctional pyrrole **94**, which features both the carboxylic acid and the aldehyde functionalities in the Ugi condensation, leads directly to the benzodiazepines with the pyrrole fused at the a side (Scheme 25.19) [40].

25.3.4
Other 1,4-Benzodiazepines

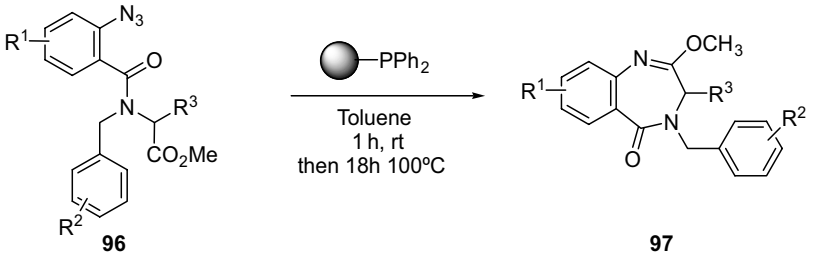
An intramolecular aza-Wittig reaction is the key step for the preparation of 1,4-benzodiazepine-5-ones **97** from azido esters **96** [41]. Scheme 25.20 presents an example that employs a solid supported equivalent of triphenylphosphine and allows for the very easy isolation of the pure benzodiazepines [42].



Scheme 25.18 Synthesis of 1,4-benzodiazepine-2,5-diones by a Ugi 4CC/S_NAr sequence.



Scheme 25.19 Synthesis of a 1,4-benzodiazepine-5-one through an intramolecular Ugi condensation.



Scheme 25.20 Synthesis of 1,4-benzodiazepine-5-ones.

25.4
Modifications of the 1,4-Benzodiazepine Ring

25.4.1
Introduction

Modifications on the 1,4-benzodiazepine skeleton have led to the discovery of new therapeutic agents with diverse functions. As presented in Figure 25.11, the

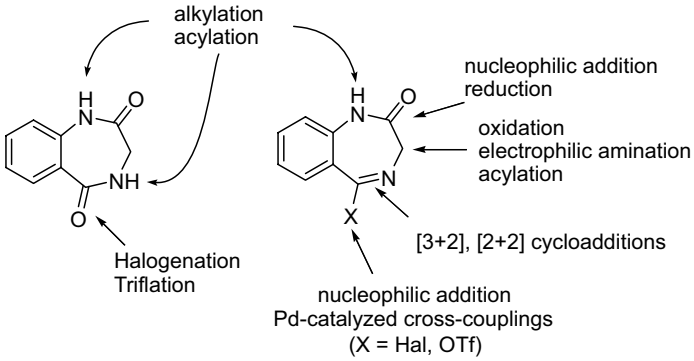


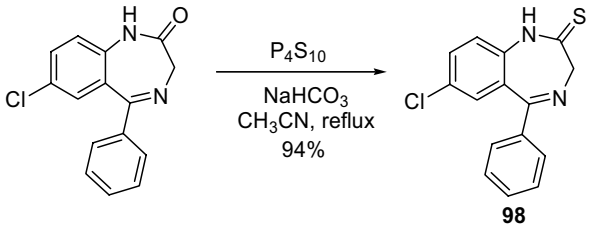
Figure 25.11 General picture of the modifications of the 1,4-benzodiazepine basic skeleton.

diazepine ring in 1,4-benzodiazepin-2,5-diones and 1,4-benzodiazepin-2-ones can be subjected to several different types of reactions oriented to the preparation of more elaborated drug candidates.

Amide NH groups can be acylated and alkylated employing conventional chemistry. Several examples have been shown in the previous sections, see for instance Scheme 25.10, and will not be further discussed. The carbonyl groups can undergo nucleophilic additions, reductions, and, moreover, can also be transformed into imidoyl halides or triflates and subjected to nucleophilic additions and cross-coupling reactions. The C3 methylene can be acylated, oxidized to introduce an oxygen functionality, or subjected to electrophilic amination to introduce a nitrogenated function. Finally, the iminic double bond can be reduced and also participate in [2 + 2] and [3 + 2] cycloaddition reactions.

25.4.2
Reactions of the C2 Carbonyl Group

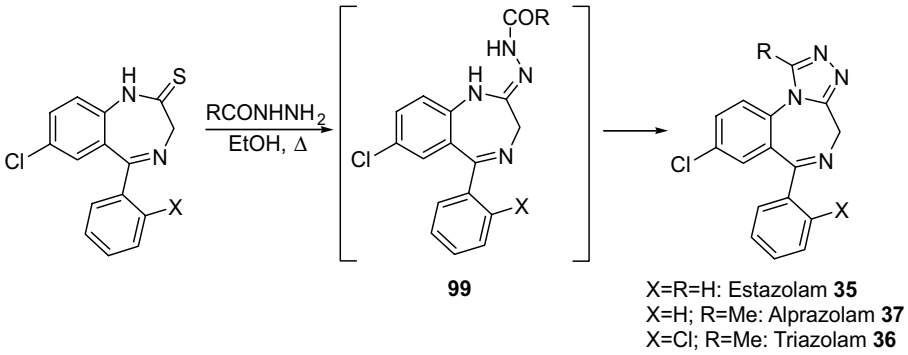
The C2 carbonyl of benzodiazepines is fairly unreactive, and therefore it requires activation prior to any type of reaction. Formation of thiolactam **98** is one of the most frequent solutions for the activation of position 2 of benzodiazepines, because it is a very reactive functional group towards nucleophilic attack. This transformation is carried out employing phosphorous sulfide as thiolating agent (Scheme 25.21). The original procedure developed by Sternbach [43], which employed phosphorous



Scheme 25.21 Formation of a thiolactam of a 1,4-benzodiazepine-2-one.

sulfide in pyridine as solvent, can be modified to employ more environmentally benign solvents, for instance, reflux of acetonitrile in the presence of sodium bicarbonate [44].

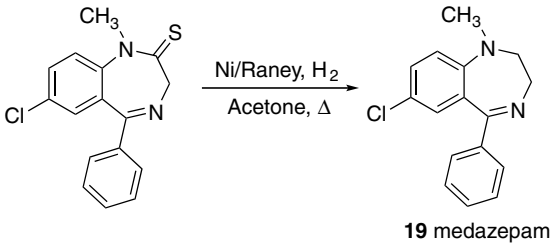
An example of nucleophilic addition on the thiolactam is the hydrazination reaction, which gives rise to the important triazolobenzodiazepines after intramolecular cyclization of intermediate **99**. This route has been employed in the synthesis of triazolam, alprazolam, estrazolam, and more elaborated triazolobenzodiazepines (Scheme 25.22) [45].



Scheme 25.22 Hydrazination of C3 thiolactam *en route* to the synthesis of [1,2,4]triazolo[4,3-*a*][1,4] benzodiazepines.

On the other hand, reduction of the thiolactam by treatment with Ni/Raney represents the classical route for the synthesis of medazepam (**19**) from diazepam thiolactam (Scheme 25.23) [46].

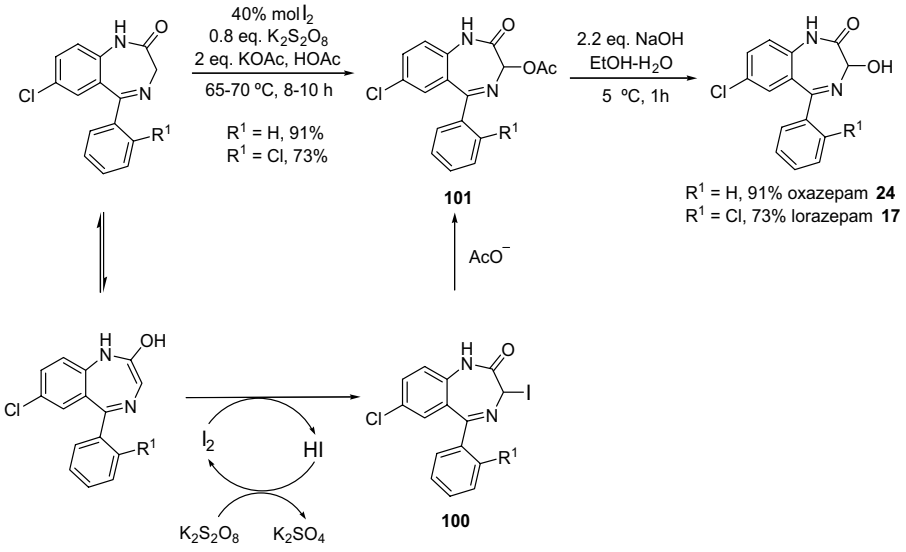
Other methods for the activation of the C2-carbonyl include the formation of imidoyl chlorides and imidoyl phosphates (examples of these transformations are provided in Section 25.5.1, Scheme 25.30).



Scheme 25.23 Thiolactam reduction in the synthesis of medazepam.

25.4.3
Functionalization at C3

The standard way to introduce a hydroxy functionality at C3 in 1,4-benzodiazepines is by oxidation of the 4-nitrogen to obtain the N-oxide, followed by treatment with acetic anhydride, leading to the 3-acetoxy compound via a Polonovsky rearrangement (Scheme 25.2). Recently, a new direct acetoxylation procedure has been developed that uses catalytic amounts of iodine (20–50 mol.%) and $K_2S_2O_8$ as the stoichiometric oxidant. This method has been reliably scaled up for the synthesis of oxazepam and lorazepam, with overall yields of 83% and 64%, respectively (Scheme 25.24) [47].

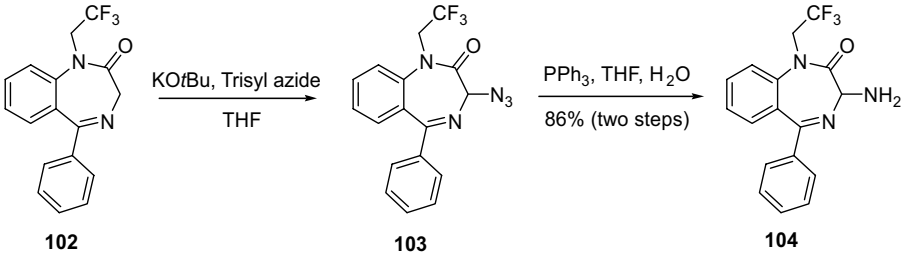


Scheme 25.24 Hydroxylation of 1,4-benzodiazepines.

The reaction most likely involves the formation of the 3-iodobenzodiazepine **100**, which undergoes nucleophilic substitution to give the acetoxy derivative **101**.

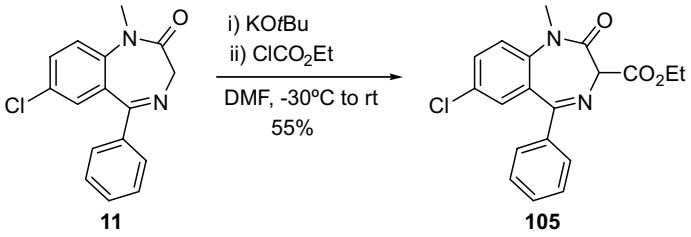
The 3-amino-1,4-benzodiazepine structure is present in several pharmacologically relevant molecules. 3-Amino-1,4-benzodiazepines can be prepared through two different approaches: from 2-aminobenzophenones and α-aminoglycine derivatives (previously discussed see Scheme 25.6) or by electrophilic amination of a 1,4-benzodiazepin-2-one (**102**). The amination takes advantage of the acidity of the hydrogens at C3, and can be carried out by, among other methods [48], azidation with trisyl azide under basic media to form 3-azidobenzodiazepine **103**, followed by reduction by treatment with triphenylphosphine to furnish 3-aminobenzodiazepine **104** (Scheme 25.25) [49].

Carbon substituents at can be introduced at C3 by treatment with the corresponding electrophile under basic media. For instance, acylation of diazepam (**11**) to obtain



Scheme 25.25 Synthesis of 3-amino-1,4-benzodiazepines.

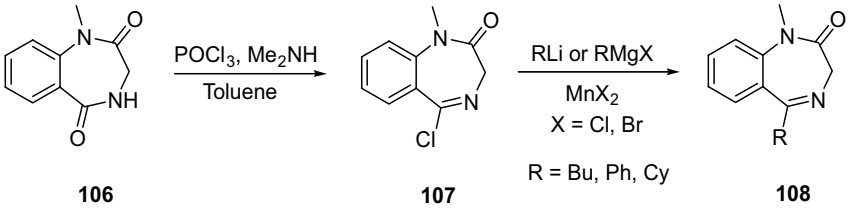
ethoxycarbonyl benzodiazepine **105** is performed by reaction with ethyl chloroformate in the presence of KO^{t}Bu (Scheme 25.26).



Scheme 25.26 Synthesis of 3-ethoxycarbonyl-1,4-benzodiazepines.

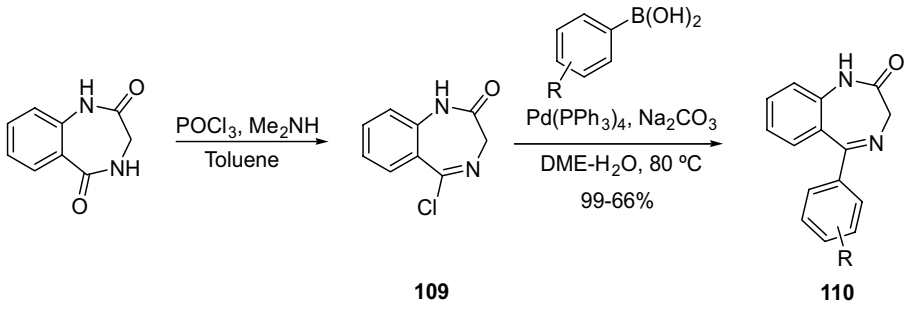
25.4.4
Substitutions at C5

In the standard methods for the synthesis of 1,4-benzodiazepin-2-ones the substituent at C5 is established in the initial condensation step and cannot be further modified. However, it is possible to introduce different substituents on 1,4-benzodiazepin-2,5-diones **106** upon transformation into imidoyl chloride **107** by treatment with phosphorous oxychloride [50]. A patent by Sanofi [51] describes the formation of different 5-substituted 1,4-benzodiazepin-2-ones **108** by nucleophilic addition of organomanganese derivatives to the imidoyl chlorides (Scheme 25.27).



Scheme 25.27 Synthetic strategy for the introduction C-substituents at C5.

More recently, the imidoyl chlorides **109** have been employed as substrates for Pd-catalyzed Suzuki, Negishi, and Sonogashira cross-couplings leading to the corresponding 5-aryl substituted benzodiazepines (Scheme 25.28) [52].



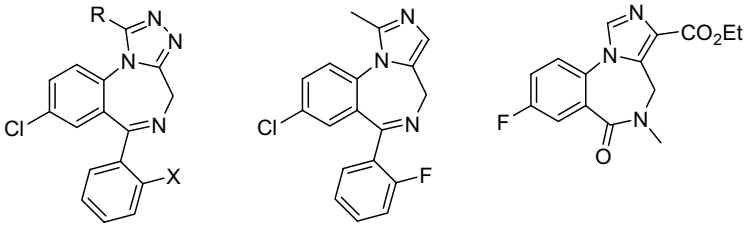
Scheme 25.28 Suzuki reactions on imidoyl chlorides derived from 1,4-benzodiazepine-2,5-diones.

25.5
1,4-Benzodiazepines with a Fused Heterocycle

The introduction of a heterocyclic ring fused with the seven-membered ring of a benzodiazepine is a type of modification that renders in many examples new benzodiazepines with enhanced or modified biological activities. For this reason, since the beginning of the benzodiazepine era much effort has been devoted to the preparation of benzodiazepines featuring additional heterocyclic rings fused at different positions of the original structure.

25.5.1
Benzodiazepines with a Heterocycle Fused at the *a* Side (N1-C2 Position)

Estazolam (**35**) [53], triazolam (**36**) [54], and alprazolam (**37**) (Figure 25.12), which bear an additional triazole ring fused at the N1-C2 positions of the benzodiazepine,



35 R=H, X=H, Estazolam
36 R=Me, X=Cl, Triazolam
37 R=Me, X=H, Alprazolam

38 Midazolam

111 Flumazenil

Figure 25.12 Benzodiazepines with a heterocycle fused at the *a* side.

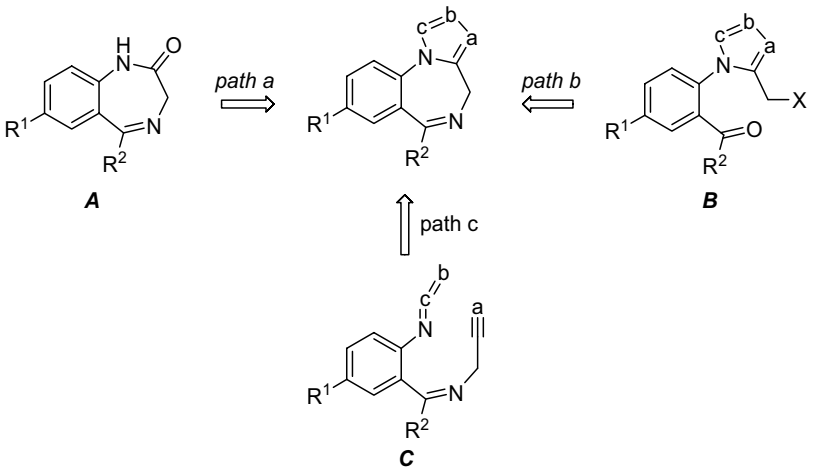
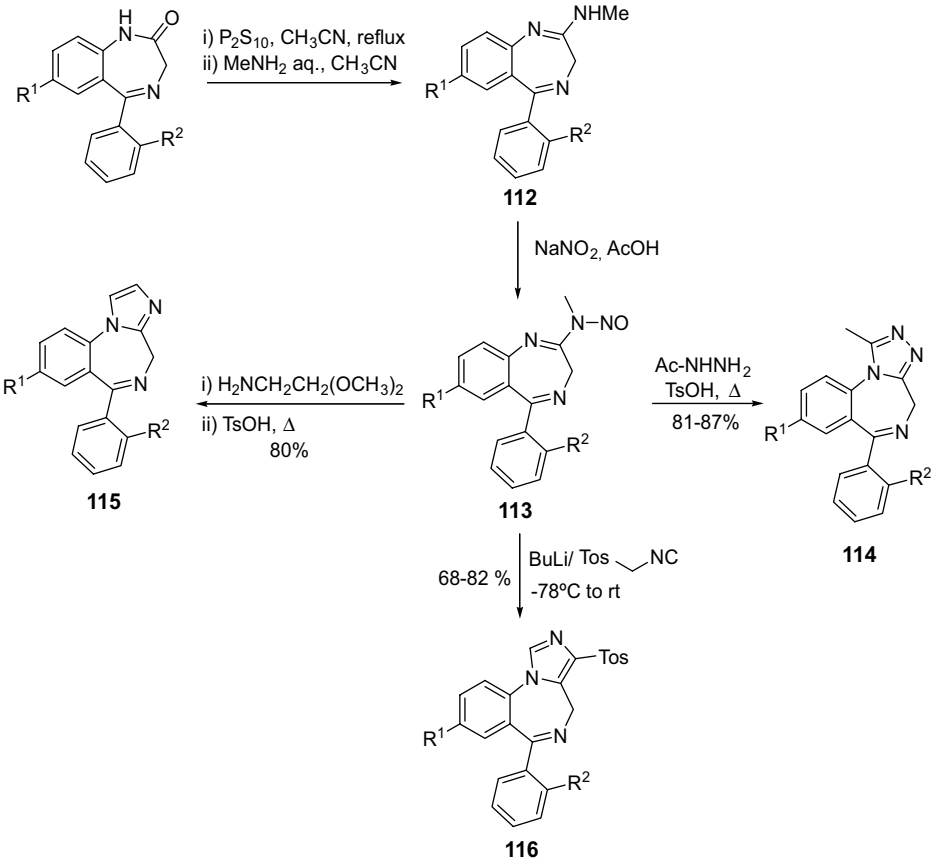


Figure 25.13 General strategies for the synthesis of benzodiazepines with a heterocycle fused at the *a* side.

feature interesting anxiolytic properties, and are among the most commonly prescribed benzodiazepines. The imidazole-containing midazolam (**38**) possesses sedative and hypnotic properties, and is employed in the treatment of insomnia. Another important benzodiazepinic drug is flumazenil (**111**) [55], an analog of 1,4-benzodiazepines-2,5-diones, which features an imidazole ring at the N1-C2-positions, and is employed as a benzodiazepine antagonist and also as a cognitive enhancer in Alzheimer's patients.

These classes of benzodiazepines can be synthesized through three different general strategies: (i) incorporation of the five-membered ring by modification of a preformed benzodiazepine (**A**) (Figure 25.13, path a); (ii) formation of the benzodiazepine ring from an appropriate benzophenone (**B**) that contains the additional heterocycle (Figure 25.13, path b); (iii) intramolecular dipolar cycloaddition on an appropriate acyclic precursor (**C**) that creates simultaneously both the five- and the seven-membered rings (Figure 25.13, path c).

The most general approach is path a. This route requires the activation of the C2 carbonyl group, which is usually achieved by formation of the corresponding thiolactam (Scheme 25.22) followed by the addition of the appropriate nucleophiles (Section 25.4.2) [56–62], Of particular interest is the transformation into *N*-nitrosoamidines **113**, which are prepared from benzodiazepines in a sequence that includes (i) activation of C2 by formation of a thiolactam, (ii) conversion into amidine **112** by treatment with methylamine, and (iii) nitrosation with $NaNO_2$ in acetic acid (Scheme 25.29). Nitrosoamidines **113** have been employed extensively since the mid-1970s in the preparation of heterocycle fused benzodiazepines [63]. For instance, in some recent examples, reaction with acetylhydrazine gives rise to [1,2,4]triazolo[4,3-*a*][1,4]benzodiazepines **114**, treatment with aminoacetaldehyde dimethyl acetal yields imidazo[1,2-*a*][1,4]benzodiazepines **115** [64], and reaction with TosMIC

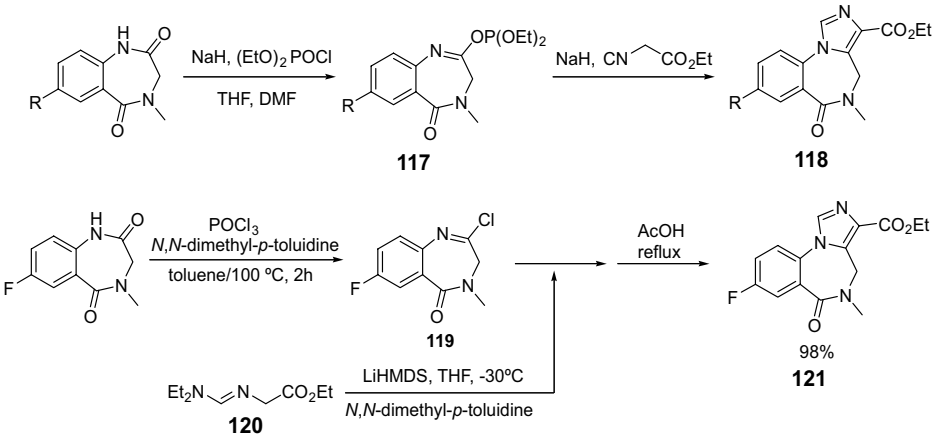


Scheme 25.29 Synthesis of [1,2,4]triazolo[4,3-*a*][1,4]benzodiazepines and imidazo[1,5-*a*][1,4] benzodiazepines.

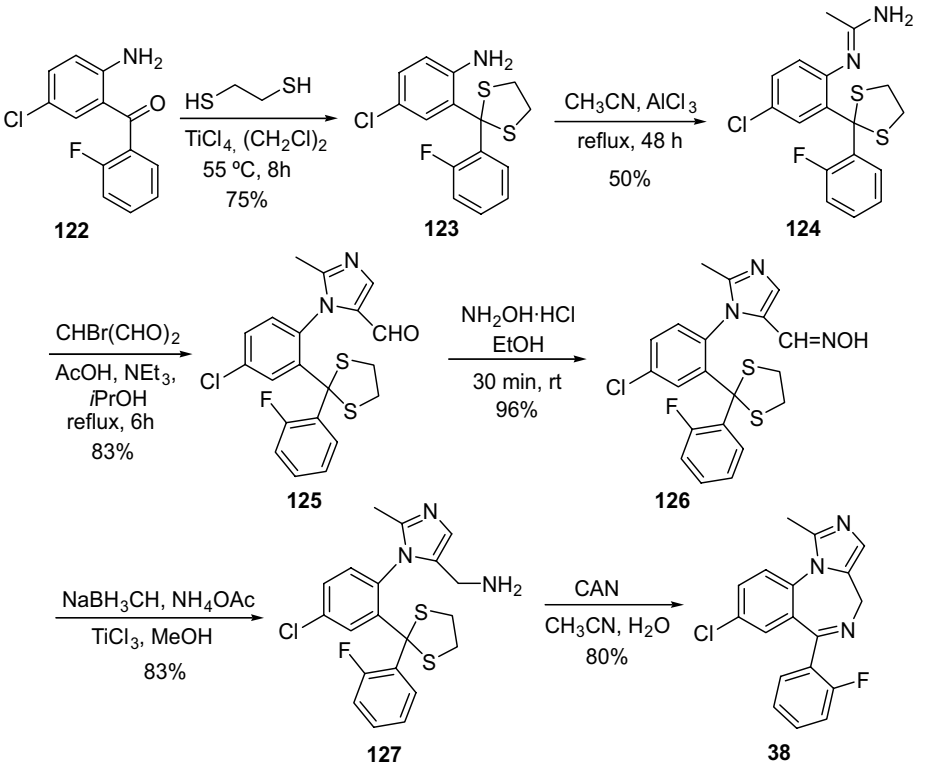
(tosylmethyl isocyanide) [65] leads to imidazo[1,5-*a*][1,4]benzodiazepines **116** (Scheme 25.29) [66].

The C2 position can be also activated by formation of an imidoyl phosphate **117** or an imidoyl chloride **119**, as illustrated in two different syntheses of flumazenil derivatives (Scheme 25.30). In the first case, the enol phosphate is reacted with the anion of an isonitrile to build the imidazole moiety of **118** [67, 68]. In the second example, amidine **120** is employed as an efficient synthetic equivalent of the isonitrile to build the imidazolebenzodiazepine [69].

The strategy sketched in Figure 25.13, path b usually requires multistep synthetic sequences, and the employment of protecting groups. Scheme 25.31 presents one example of this approach, taken from a 1998 patent for the synthesis of midazolam [7070b]. The synthesis starts with benzophenone **122**, then, after protection of the ketone functionality as thioacetal **123**, the 2-carboxaldehydeimidazole **125** is built via amidine **124**. The intermediate **127** required for the cyclization is obtained by



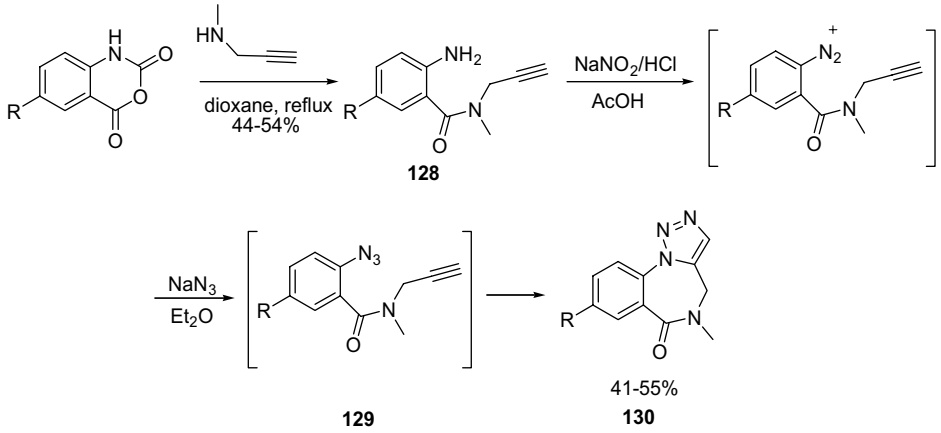
Scheme 25.30 Synthesis of flumazenil derivatives from enolphosphates and imidoyl chlorides.



Scheme 25.31 Multistep synthesis of midazolam (**38**).

formation of an oxime **126** and reduction with $NaBH_3CN$. Cyclization to form midazolam **38** occurs upon cleavage of the thioacetal with ceric ammonium nitrate (CAN).

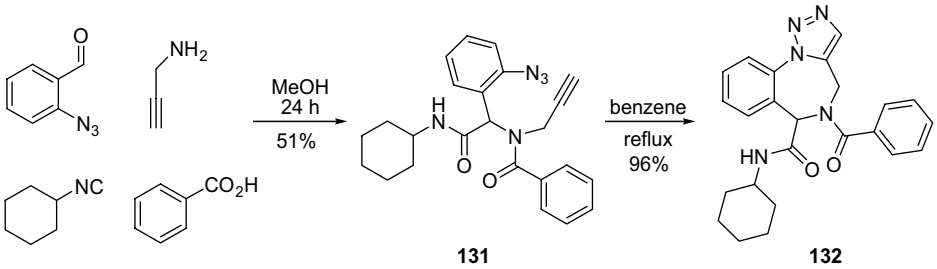
A more convergent approach is path c in Figure 25.13, since both the five- and seven-membered rings are built in a single synthetic operation. This pathway is particularly useful for the preparation of [1,2,3]triazolo[5,4-*a*][1,4]benzodiazepines **130**, by application of the alkyne azide dipolar cycloaddition [71]. In the example presented in Scheme 25.32 the azido alkyne **129** required for the cyclization is easily prepared from the amino alkyne **128**, which results from the reaction of isatoic anhydride and *N*-methylpropargylamine (Scheme 25.32). Diazotization followed by substitution with NaN_3 gives intermediate **129**, which suffers intramolecular dipolar cycloaddition to form **130**. Notably, the transformation from **128** into **130** occurs in a one-pot process without the isolation of the intermediates.



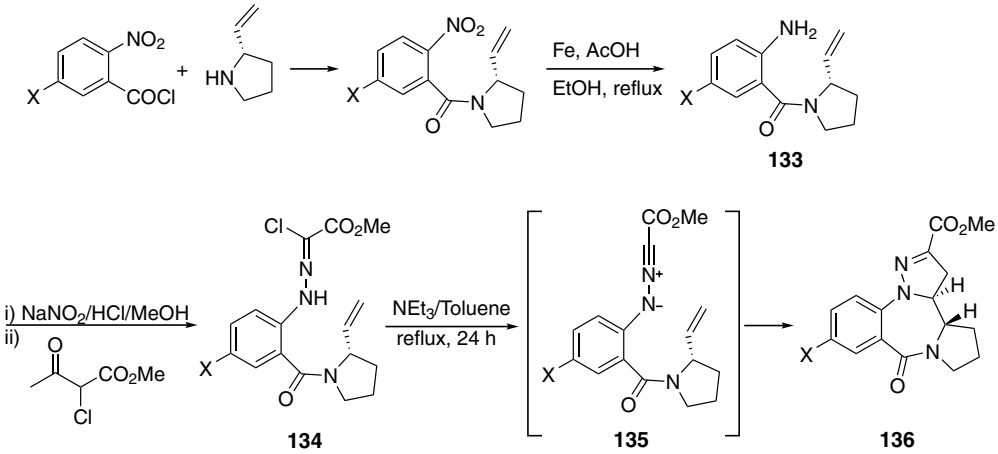
Scheme 25.32 Synthesis of [1,2,3]triazolo[5,4-*a*][1,4]benzodiazepines by intramolecular azide-alkyne [3 + 2] cycloaddition.

Interestingly, this approach has been combined with the Ugi 4CC to implement a multicomponent synthesis of [1,2,3]triazolo[4,3-*a*][1,4]benzodiazepines **132**. To this end, the alkyne and azide functionalities have to be incorporated in the amine, aldehyde, or carboxylic acid components. In the example presented in Scheme 25.33 the Ugi 4CC conducted employing propargylamine and *o*-azidobenzaldehyde gives the azido alkyne **131**, which undergoes thermally induced cyclization to form the triazolobenzodiazepine **132** [72].

The intramolecular dipolar cycloaddition has been also applied to prepare pyrazolo [1,5-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepines **136**, employing a nitrilimine as dipole [73]. The intermediate **135** that suffers the intramolecular cycloaddition is generated *in situ* from hydrazonyl chloride **134** (which is easily prepared employing conventional chemistry) (Scheme 25.34).

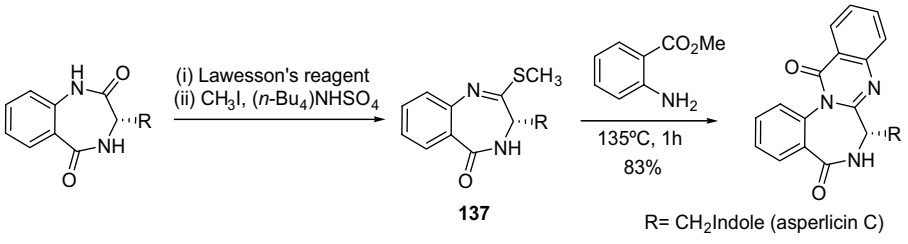


Scheme 25.33 Multicomponent synthesis of [1,2,3]triazolo[5,4-*a*][1,4]benzodiazepines by a Ugi 4CC/intramolecular azide-alkyne [3 + 2] cycloaddition sequence.



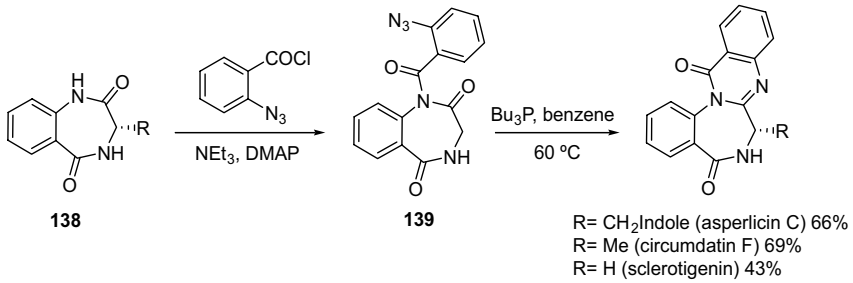
Scheme 25.34 Synthesis of pyrazolo[1,5-*a*]pyrrolo[2,1-*c*][1,4]benzodiazepines by intramolecular alkene-nitrilimine [3 + 2] cycloaddition.

Many naturally occurring alkaloids feature a benzodiazepine ring fused at the *a* face with a quinazoline ring (Section 25.2.4). The benzodiazepine-quinazoline skeleton has been constructed following different strategies. The synthesis of asperlicins C and E was first achieved by Bock *et al.* in 1987. In their approach, the quinazoline ring was prepared from the corresponding 1,4-benzodiazepine-2,5-dione and methyl anthranilate (Scheme 25.35). To activate the C2 position, the benzodiazepinedione was converted into the methyl imino thioether **137** [74].



Scheme 25.35 Synthesis of asperlicin C.

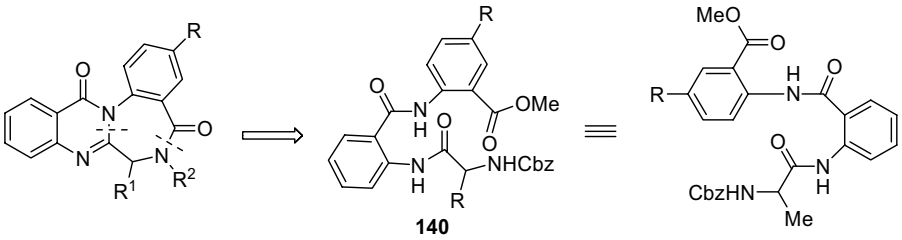
A different approach from 1,4-benzodiazepine-2,5-diones involves an intramolecular aza-Wittig reaction as key step. Selective acylation of the more acidic anilide nitrogen of the corresponding 1,4-benzodiazepine-2,5-dione **138** with *o*-azidobenzoyl chloride gives the acylated benzodiazepine **139**. Then, aza-Wittig cyclization promoted by Bu_3P [75] leads to the benzodiazepine-quinazoline hybrids (Scheme 25.36) [76]. A similar procedure has been applied for the preparation of a library of circumdatin analogs employing a solid-supported phosphine [77].



138 **139**

Scheme 25.36 Synthesis of quinazolobenzodiazepine alkaloids through an aza-Wittig reaction.

Circumdatins C and F have been synthesized by the stepwise dehydration of tripeptidic acyclic precursors **140** following the disconnections depicted in Scheme 25.37 [78].



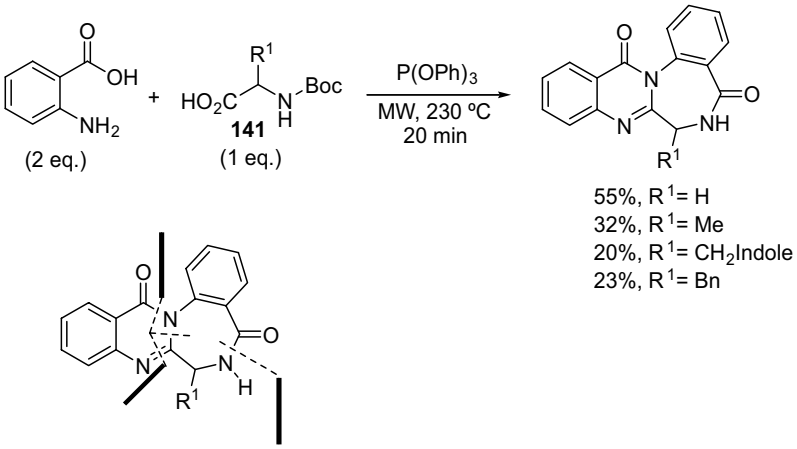
140

Scheme 25.37 Synthesis of circumdatins by condensation of an acyclic tripeptide.

Finally, a very direct synthesis of quinazolinobenzodiazepines has been recently disclosed by condensation of two molecules of anthranilic acid with one molecule of a N-Boc protected amino acid **141**. This *one-pot* domino process takes place in only 20 min under microwave heating (Scheme 25.38) [79].

25.5.2
Benzodiazepines with a Heterocycle Fused at the *d* Side (N4-C5 Position)

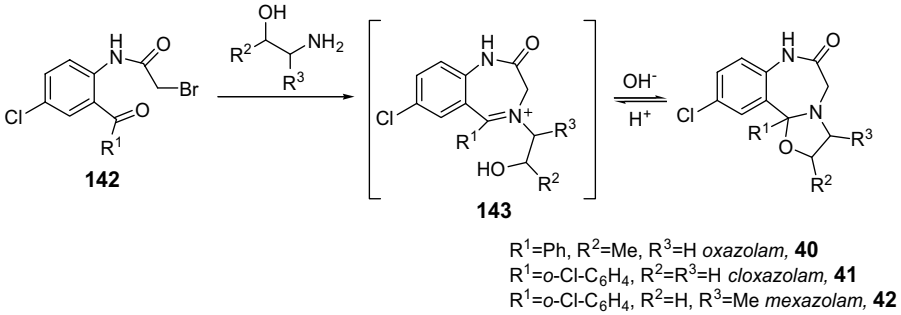
The presence of a heterocycle at the N4-C5 positions also renders biologically active benzodiazepines with therapeutic application. The most important structures are



Scheme 25.38 Microwave-promoted synthesis of quinazolobenzodiazepines.

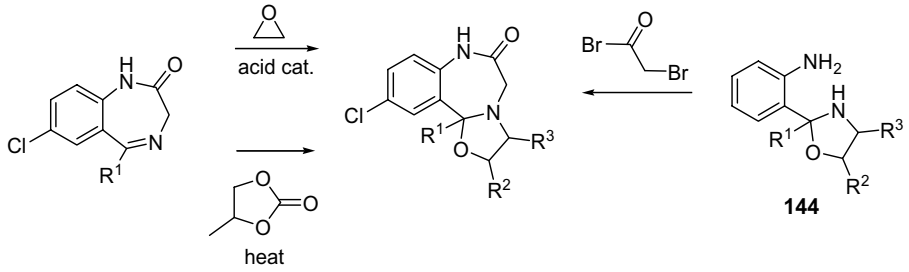
oxazolam (**40**) [80], cloxazolam (**41**) [81], and mexazolam (**42**) [82] that incorporate an oxazolidine, and ketazolam (**43**), which features an oxazino ring (Figure 25.7) [83].

As shown in Scheme 25.39, the oxazolo derivatives are generally prepared *N*-(2-bromoacetyl)benzophenones **142**, generated by reaction of benzophenones with bromoacetyl bromide. Reaction with the appropriate amino-alcohol gives rise to the tricyclic systems **40–42** upon cyclization of the intermediate iminium cation **143** (Scheme 25.39) [84–86]. Variations of this methodology include the reaction of 1,4-benzodiazepines with the carbonate of 1,2-propylene [87] or epoxides [88]. An alternative route is the cyclization of a conveniently substituted 2-aryloxazolidine **144** with bromoacetyl bromide (Scheme 25.40) [89].

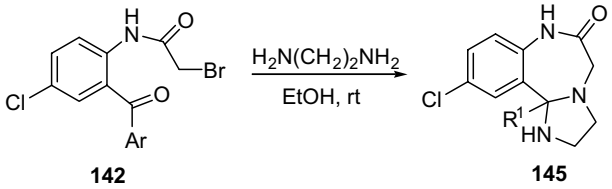


Scheme 25.39 Synthesis of oxazolo[3,2-*d*][1,4]benzodiazepines.

The same strategy can be applied to the incorporation of different heterocycles. For instance, the reaction of **142** with ethylenediamine gives imidazolino[1,4]benzodiazepine derivatives **145** (Scheme 25.41) [43].



Scheme 25.40 Other synthetic routes to oxazolo[3,2-*d*][1,4]benzodiazepines.



Scheme 25.41 Synthesis of imidazolino[1,4]benzodiazepines **145**.

25.5.3
Cycloaddition Reactions in the Synthesis of 1,4-Benzodiazepines with Fused Heterocycles

The presence of the imine functionality at the N4-C5 positions in 1,4-benzodiazepines makes them viable substrates for cycloaddition reactions. In fact, many examples have been described of [2 + 2] and [3 + 2] cycloadditions.

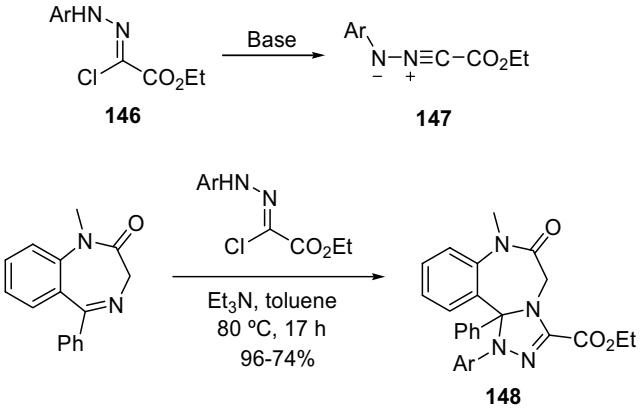
25.5.3.1 [3 + 2] Cycloadditions

The reaction of 1,4-benzodiazepin-2-ones with nitrile imines **147** generated *in situ* from hydrazinoyl chlorides **146** gives rise to new benzodiazepines **148** incorporating an additional 1,2,4-triazolino ring, in a process that proceeds with total regioselectivity (Scheme 25.42) [43, 90, 91].

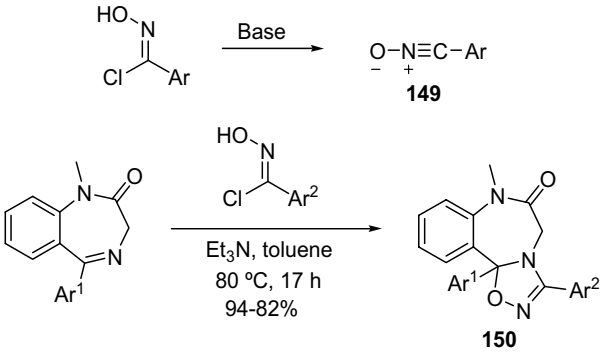
Analogously, the reaction with nitrile oxides **149** give rise to [1,2,4]oxadiazolo[4,5-*d*][1,4]benzodiazepine derivatives **150**, again as single regioisomers (Scheme 25.43) [92].

The less common 1,4-Benzodiazepin-5-ones **153** and 1,4-benzodiazepin-3-ones [93] also react with nitrilimines. In this case the N1-C2 imine acts as dipolarophile, to provide [1,2,4]triazolo[4,3-*a*][1,4]benzodiazepines **154** [94]. Interestingly, the initial 1,4-benzodiazepin-5-ones **153** are prepared in a sequence that includes formation of an unstable [1,2,3]triazolino[3,4-*a*][1,4]benzodiazepine **152** through an intramolecular [3 + 2] cycloaddition of the azide **151**, followed by N_2 extrusion (Scheme 25.44).

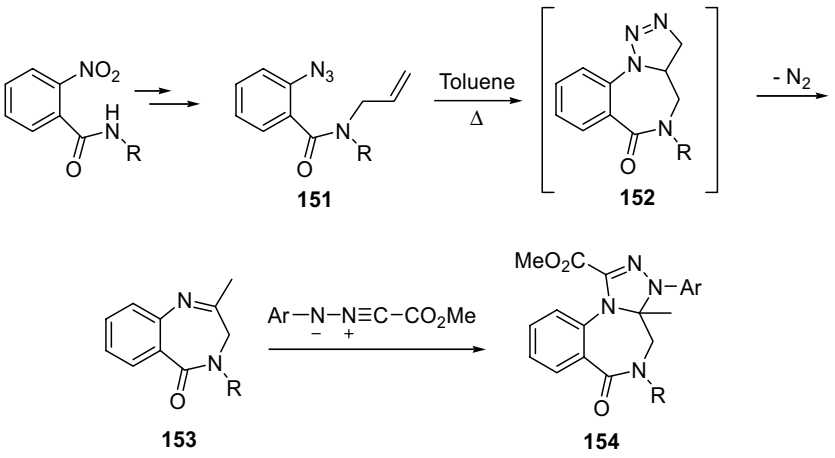
The nitrone moiety, a typical dipole, is present in 1,4-benzodiazepine *N*-oxides **155** (Figure 25.14); these systems react as dipoles in [3 + 2] cycloadditions with electrophilic dipolarophiles such as α,β-unsaturated carbonyl compounds and sulfones [95], maleimides, and alkyl isocyanides [96].



Scheme 25.42 Synthesis of tetrahydro-1*H*-s-triazolo[4,3-*d*][1,4]benzodiazepin-2-ones.



Scheme 25.43 Dipolar cycloaddition of nitrile oxides with the N4 = C5 benzodiazepine double bond.



Scheme 25.44 Dipolar cycloadditions of 1,4-benzodiazepine-5-ones with nitrilimines.

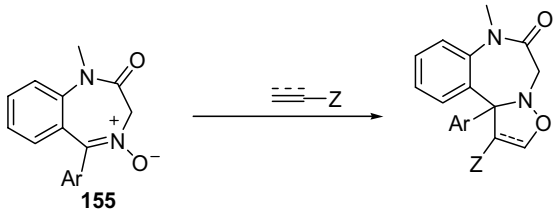
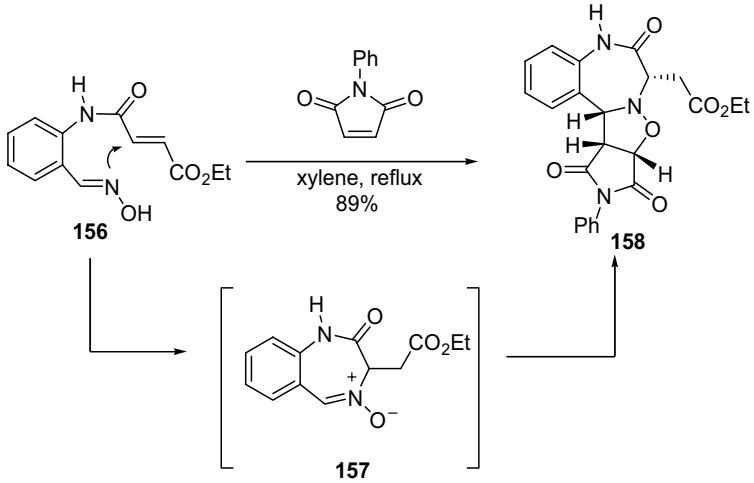


Figure 25.14 1,4-benzodiazepine-*N*-oxides as dipoles for [3 + 2] cycloadditions.

The generation of the 1,4-benzodiazepine *N*-oxide **157** and the cycloaddition can be carried out in a one-pot sequential process from the acyclic oxime **156**. In the example presented in Scheme 25.45, intramolecular dipole formation–intermolecular cycloaddition with *N*-phenylmaleimide gives rise to the corresponding isoxazolobenzodiazepinone **158** as a single diastereoisomer [97].

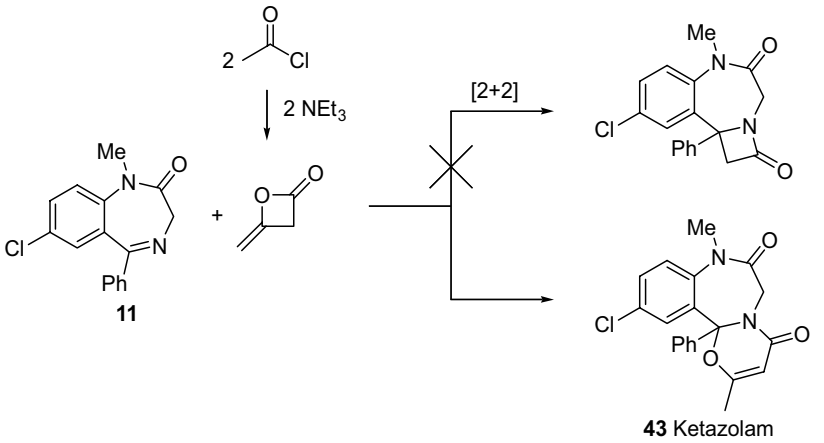


Scheme 25.45 Dipolar cycloadditions of 1,4-benzodiazepine *N*-oxide.

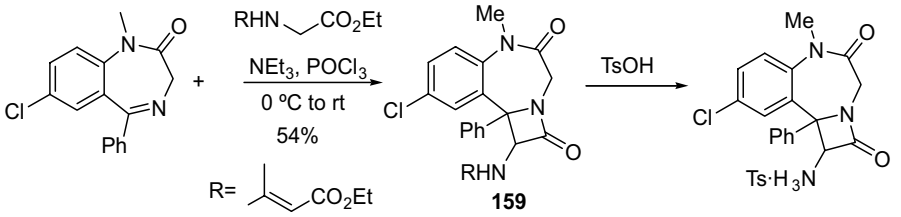
25.5.3.2 **[2 + 2] Cycloadditions**

The first reaction between ketenes and 1,4-benzodiazepines was carried out in 1970, employing diazepam **11** and acetyl chloride in the presence of triethylamine. The reaction furnished the oxazinobenzodiazepine **43**, commercially known as ketazolam [98]. The reaction is the result of the addition of diketene to the iminic bond of diazepam, instead of the expected [2 + 2] adduct (Scheme 25.46).

The first example of the synthesis of 1,4-benzodiazepines fused with β-lactams was reported by Gunda and Enebäck in 1983 [99]. The azetidino[1,2-*d*][1,4]benzodiazepines **159** were prepared by reaction of 1,4-benzodiazepine-2-ones with the ketene generated from glycine Dane-salt, phosphorous oxychloride, and triethylamine (Scheme 25.47).



Scheme 25.46 Synthesis of ketazolam by reaction of diazepam with diketene.

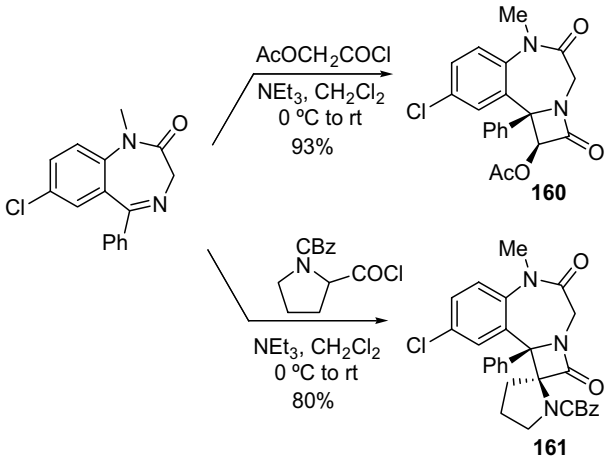


Scheme 25.47 Synthesis of 1-amino-azetidino[1,2-d][1,4]benzodiazepin-2-ones **159**.

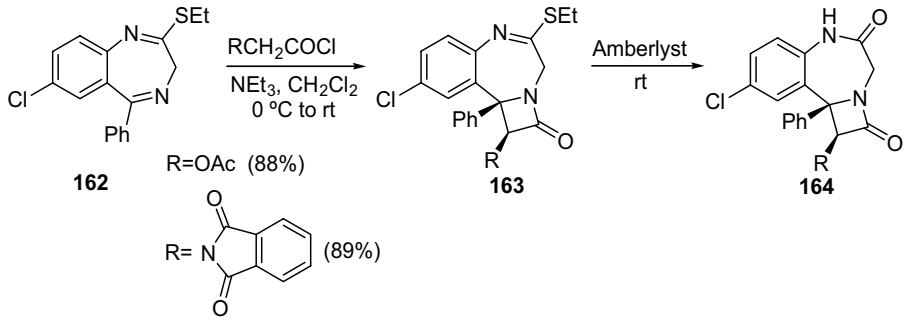
More recently, the cycloaddition of ketenes with 1,4-benzodiazepines has been conducted under the typical conditions of Staudinger-type reactions, in which the ketene partner is generated *in situ* by the dehydrohalogenation of an acid chloride with triethylamine as base. The reactions proceed with high stereoselectivity, leading to 1-heterosubstituted and 1-spiro azeto[1,2-*d*][1,4]benzodiazepin-2,5-ones **160** and **161**, respectively [100]. In all cases the heterosubstituent coming from the ketene is placed cis to the aromatic substituent of the benzodiazepine (Scheme 25.48).

For the preparation of the N-H analogs of **160** an alternative Staudinger reaction has been developed, employing derivatives **162** that have the *a* bond amide group of the 1,4-benzodiazepine masked as a thioimidate. The NH-derivatives **164** are obtained after treatment of the intermediate adduct **163** with Amberlyst (Scheme 25.49).

The [2 + 2] cycloaddition of benzodiazepines with ketenes has also been employed as key step in the preparation of β-amino acids containing the benzodiazepine substructure **166**, as potential antagonists of the endothelin receptor. The [2 + 2] cycloaddition with the ketene derived from benzylacetic acid occurs with very high yield and stereoselectivity under Staudinger conditions, leading to adduct **165** (Scheme 25.50). Interestingly, after derivatization, the β-lactam can be selectively hydrolyzed to obtain β-amino acid derivatives **166** [101].



Scheme 25.48 Staudinger reaction of the N4 = C5 imine of 1,4-benzodiazepines with ketenes.



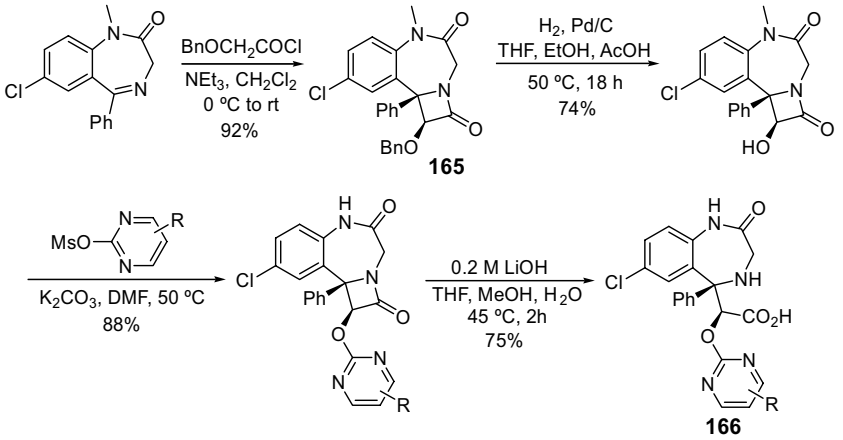
Scheme 25.49

The [2 + 2] reaction can be also applied to introduce modifications to 1,4-benzodiazepines with a heterocycle fused at the *a* side, such as midazolam (**38**), alprazolam (**37**), and triazolam (**36**). Following the typical conditions of Staudinger reactions the β-lactams **167** are obtained with moderate yield and cis stereoselectivity (Scheme 25.51).

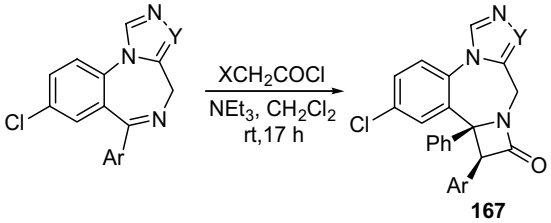
25.6 Pyrrolo[2,1-*c*][1,4]Benzodiazepines (PBDs)

Pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs) are a class of DNA-interactive potent antitumor agents that are produced by various species of *Streptomyces* [102]. Figure 25.15 shows some examples [103].

These compounds exert their cycotoxic effect due to the covalent union between the iminic C11 (or the carbonylamino equivalent) of the PDB and the NH_2 group of



Scheme 25.50 Synthesis of azetidino[1,2-*d*][1,4]benzodiazepines as intermediates in the synthesis of β-amino acids.



Scheme 25.51 Synthesis of heterocycle[*a*]azeto[1,2-*d*][1,4]benzodiazepines.

the guanine base [104], in the minor groove of the DNA double helix, with preference to the purine-guanine-purine sequences (Figure 25.16) [105].

The PBDs have also been employed as scaffolds to attach different organic substituents, mainly attached at C2 and C8, in the search for new conjugates with enhanced biological properties, such as sequence-selective DNA-cleaving or cross-linking activity, and enhanced DNA-binding affinity and selectivity [106].

The key step in the synthesis of PBDs is the formation of the carbinolamino or imino N10–C11 bond, which is usually incorporated in the last step of the synthetic sequence, due to its lability. Nevertheless, there are in the literature numerous methods for the synthesis of these systems [107]. Most of the methodologies share the retrosynthetic analysis shown in Scheme 25.52 and, thus, the pyrrolobenzodiazepine ring **169** is prepared from an acyclic precursor **168** that has both amino and aldehyde (X = O) functionalities, and which is accessible, for instance, from 2-nitrobenzoic acid and a proline derivative [108]. The different methodologies differ in the way the amino and the aldehyde groups are masked along the synthesis.

A widely used method implies the intramolecular cyclization of the readily available amino dithioketals **170**, promoted by mercury chloride, to yield the final

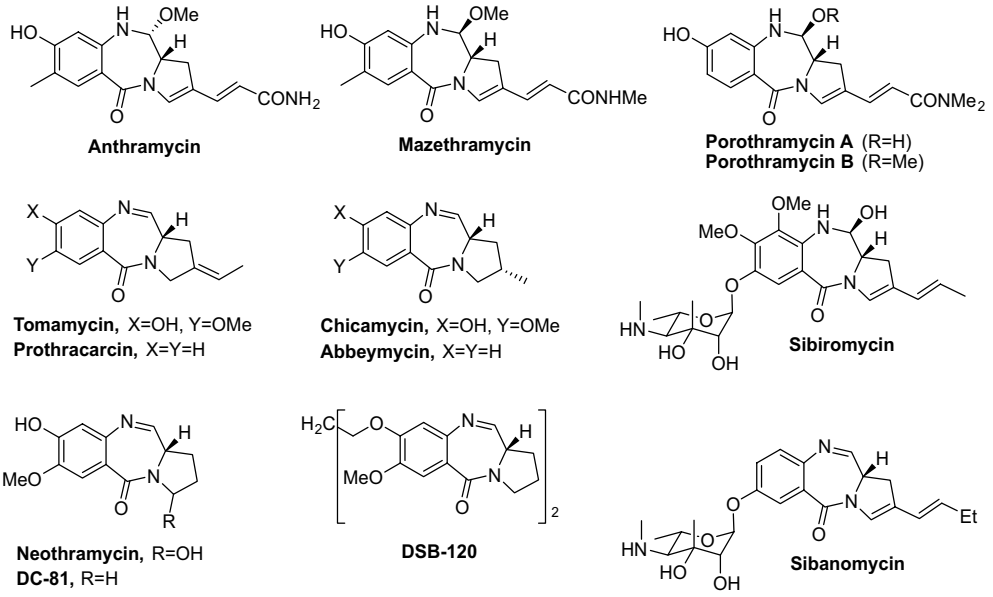


Figure 25.15 Some naturally occurring pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs).

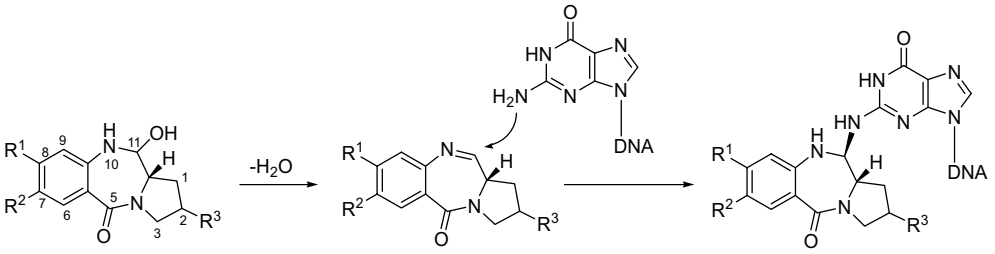
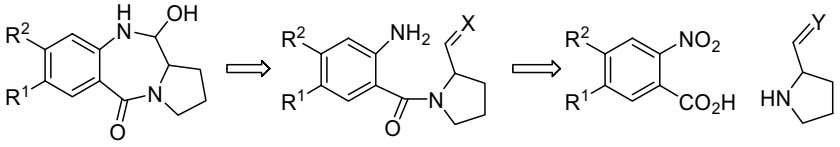


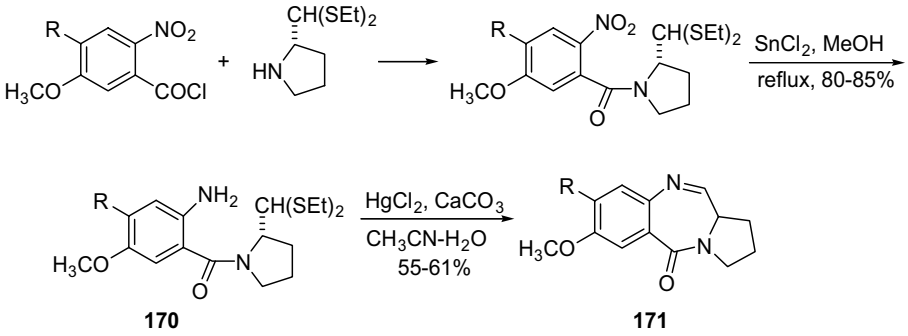
Figure 25.16 Possible mechanism for the formation of the PBD-DNA adduct.

iminic derivatives. This strategy has been applied to the preparation of DC-81 (**171**) (Scheme 25.53) [109].

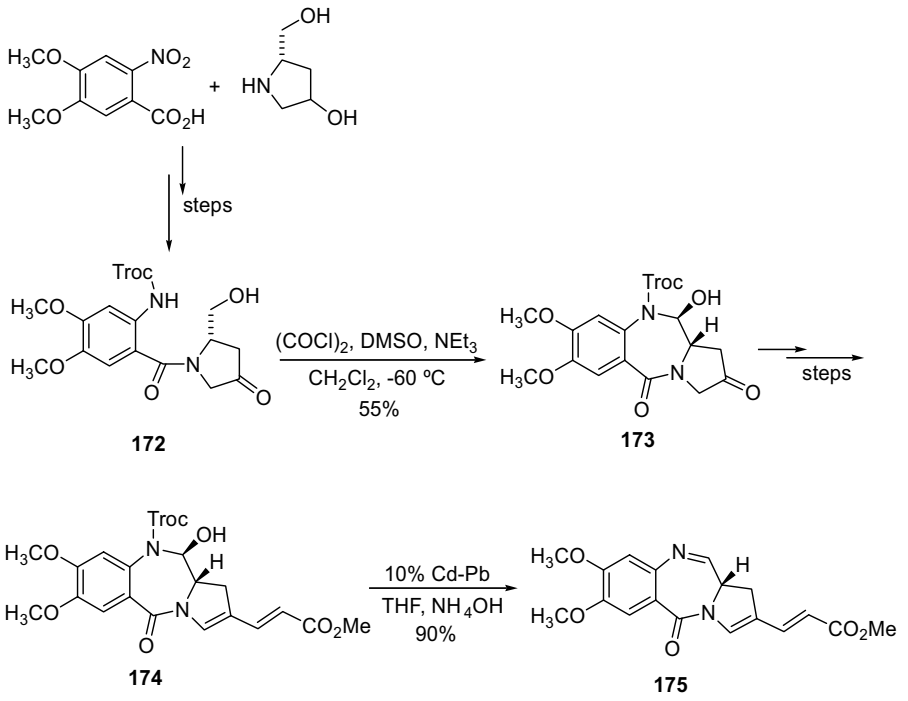
A different cyclization methodology, which provides the carbinolamino functionality is based on the Swern oxidation of a N-protected amino alcohol such as **172** (Scheme 25.54), to give N-protected PBD **173**. In the example featured in Scheme 25.54, after some chemical transformations to give **174**, cleavage of the Troc protecting group at N10 leads to the imine-containing PDB **175** [110, 111].



Scheme 25.52 General approaches for the synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs).



Scheme 25.53 Synthesis of PBDs from amino dithioketals.



Scheme 25.54 PBDs synthesis triggered by Swern oxidation.

25.7
1,5-Benzodiazepines

The discovery that certain 1,5-benzodiazepines indeed produced similar pharmacological effects to the 1,4-derivatives fostered considerable interest for their synthesis. In addition to their known psychotropic potential, the biological interest of 1,5-benzodiazepines has been expanded to other therapeutic applications in diseases

such as cancer [112], viral infections (non-nucleoside inhibitors of HIV reverse transcriptase) [113], and cardiovascular disorders [114]. Moreover, the 1,5-benzodiazepine scaffold is found in compounds that are active against various peptidic hormones such as CCK [115], interleukin-converting enzymes [116], and potassium blockers (I_K) [117].

25.7.1 General Methods of Synthesis of 1,5-Benzodiazepines

Most of the methods of synthesis of 1,5-benzodiazepines are based on the condensation of a benzene-1,2-diamine or a synthetic equivalent with a 1,3-dielectrophile such as a dicarbonyl or dicarboxy compound (Figure 25.17).

Clobazam **45**, which has been marketed as an anxiolytic since 1975 and is the most representative compound of 1,5-benzodiazepines, is prepared by a variation of this route. The ring is synthesized by intramolecular cyclization of ethyl *N*-phenyl-*N*-(2-nitro-5-chlorophenyl)malonate **177**. The regioselectivity of the reaction is determined by employing a starting material that features two nitrogenated functionalities of different nature, such as 3-chloro-6-nitro-*N*-phenylaniline (**176**). Reaction of **176** with ethyl 2-(chlorocarbonyl)acetate, followed by reduction of the nitro group of **177** gives amino ester **178**, which undergoes cyclization to 1,5-benzodiazepine **179** by treatment with dilute acid. The synthesis of clobazam **45** is completed by final methylation of the amide NH (Scheme 25.55) [118].

Several variations of this methodology have been developed [119], but most of them rely on the employment of *o*-nitroanilines **180** as synthetic equivalent of the *o*-phenylenediamine that acts as double nucleophile. The starting *o*-nitroanilines can be easily obtained, for instance, from *N*-unsubstituted *o*-nitroanilines **181** or by nucleophilic aromatic substitution on *o*-halonitrobenzene derivatives **182** (Scheme 25.56).

This methodology has also been adapted to solid-phase organic synthesis. As presented in Scheme 25.57 the solid-phase anchored benzodiazepine **183** is prepared following the methodology discussed in Schemes 25.55 and 25.56. Then, a high degree of diversity can be generated by the incorporation of different substituents R^2

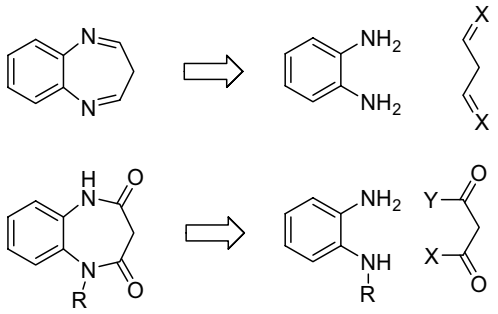
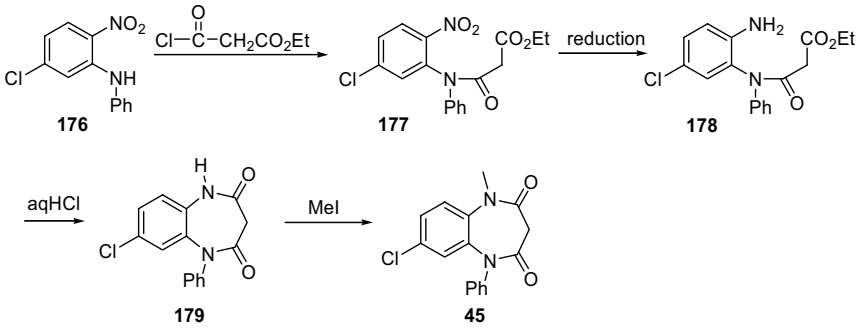
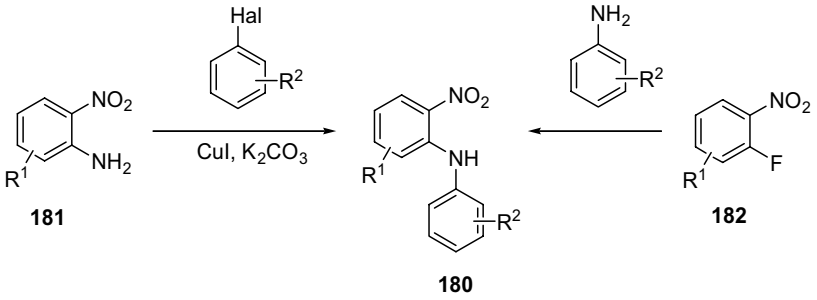


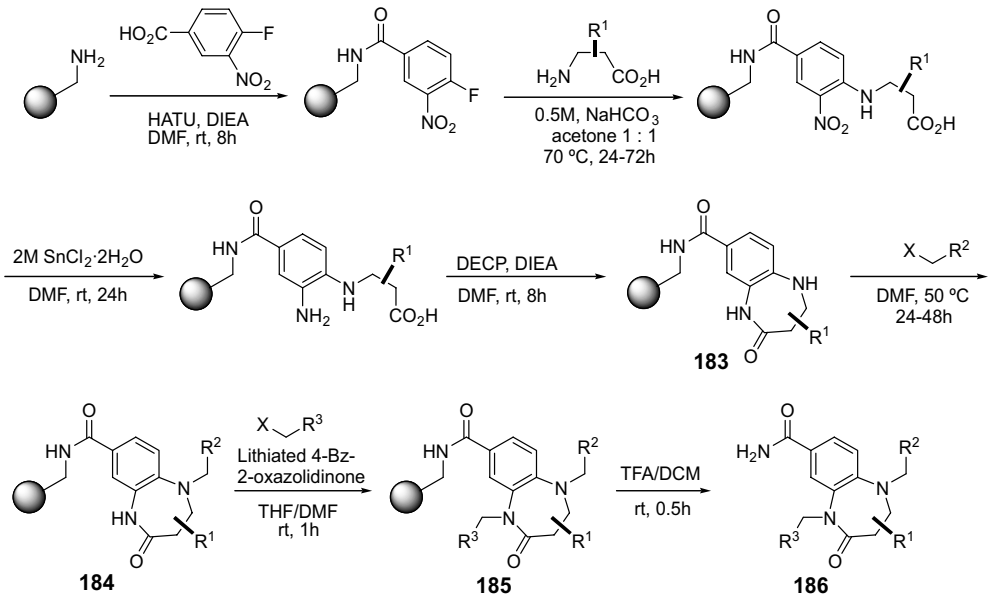
Figure 25.17 General method for the synthesis of 1,5-benzodiazepines.



Scheme 25.55 Synthetic route to clobazam (**45**).



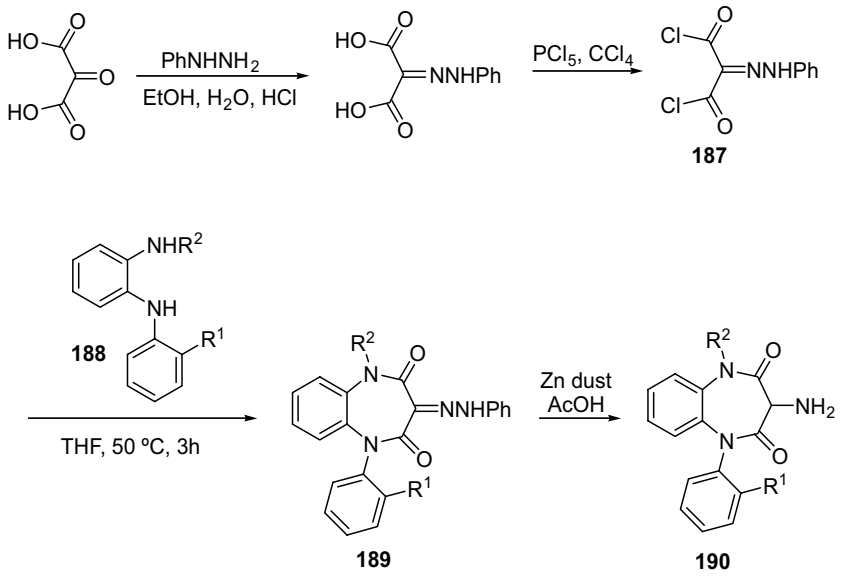
Scheme 25.56 Approaches to *o*-nitroanilines, the direct precursors of 1,5-benzodiazepines.



Scheme 25.57 Solid-supported synthesis of 1,5-benzodiazepines.

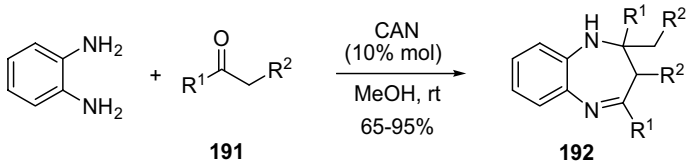
and R^3, by selective alkylation of the aniline NH to obtain **184**, followed by alkylation of the anilide NH, which gives **185**. The final 1,5-benzodiazepine-2-one **186** is obtained after cleavage from the solid support [120].

1,5-Benzodiazepines featuring an amino group at C3 are particularly interesting, due to the biological activity of some of their members. They are synthesized by a similar strategy, by condensation of the diacid chloride **187** with an *o*-phenylene diamine **188**. Final reduction of the hydrazone functionality of **189** yields the 3-amino-1,5-benzodiazepine **190** (Scheme 25.58) [121].



Scheme 25.58 Synthesis of 3-amino-1,5-benzodiazepines **188**.

Derivatives of 1,5-benzodiazepines **192** have also been prepared by condensation of *o*-phenylene diamines with two equivalents of an enolizable ketone (**191**) (Scheme 25.59). Numerous reagents, such as BF_3-etherate, polyphosphoric acid, SiO_2, $MgO/POCl_3$, $Yb(OTf)_3$, $Sc(OTf)_3$, Al_2O_3/P_2O_5, AcOH under microwave and ionic liquids, and NBS [122] have been utilized to promote this condensation reaction. In the example shown, ceric ammonium nitrate is employed to promote



Scheme 25.59 1,5-Benzodiazepines from *o*-phenylenediamine and ketones.

the condensation [123]. Obviously, this three-component reaction is limited to the incorporation of two identical ketone subunits.

25.7.2
1,5-Benzodiazepines with a Fused Heterocycle

Similar to the analogous 1,4-benzodiazepines, the incorporation of an additional fused ring renders interesting biological properties to 1,5-benzodiazepines. For instance, *s*-triazolo[4,3-*a*][1,5]benzodiazepines **193** [124], imidazo[1,2-*a*][1,5]benzodiazepines **194** [125], and also thiazolo[3,2-*a*] derivatives **195** [126] show moderate anticonvulsant and SNC depressor properties in animals (Figure 25.18).

These types of benzodiazepines can be readily prepared by 1,3-dipolar cycloadditions on one iminic double bond. For instance, cycloaddition of the imine of a 1,5-benzodiazepinone (**196**) with a nitrilimine leads to triazolo-1,5-benzodiazepines **197** [127–129]. Analogously, the dipolar cycloaddition reaction with nitrile oxides provides oxadiazolo-1,5-benzodiazepines **198** [130] (Scheme 25.60).

25.8
2,3-Benzodiazepines

The chemistry of 2,3-benzodiazepines has attracted great attention since the discovery that some members of this family serve as orally active anticonvulsant and noncompetitive antagonists of the AMPA subtype of glutamate excitatory amino acid receptors [131]. Tofisopam (**44**) and talampanel (**199**) (Figure 25.19) are the most representative 2,3-benzodiazepines. Tofisopam (**44**) possesses anxiolytic properties [132] and is prescribed in the treatment of anxiety and alcohol withdrawal. Talampanel (**199**) has been studied to treat epilepsy, multiple sclerosis, and Parkinson's disease, and also in the treatment of brain tumors and traumatic brain injuries [133].

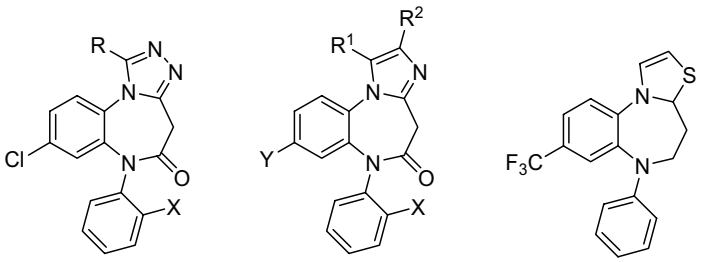
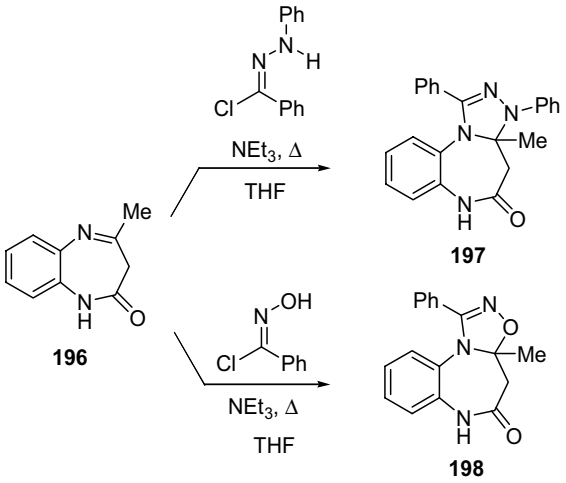


Figure 25.18 Tricyclic 1,5-benzodiazepines.



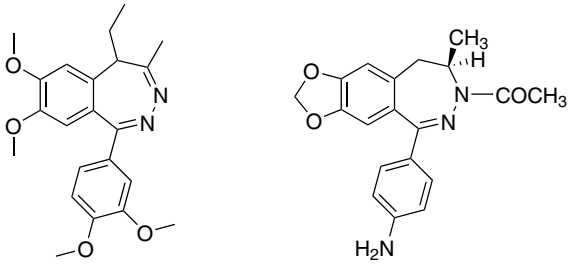
Scheme 25.60 Synthesis of [1,2,4]triazolo[4,3-*a*][1,5]benzodiazepines and [1,2,4]oxadiazolo[4,5-*a*][1,5]benzodiazepines by 1,3-dipolar cycloadditions with nitrilimines and nitrile oxides, respectively.

25.8.1
2,3-Benzodiazepine Ring Synthesis

The obvious strategy for the construction of the 2,3-benzodiazepine ring involves the double condensation of a proper dielectrophile with hydrazine or a hydrazine derivative (Figure 25.20).

The first strategy is exemplified by the synthesis of GYKI 52 466 (**201**), a direct precursor of talampanel. The 2,3-benzodiazepine is constructed by condensation of hydrazine hydrate with benzophenone derivative **200**, which features a carbonyl and a ketal functionalities in the appropriate positions (Scheme 25.61) [134].

1-Aryl-3,5-dihydro-4*H*-2,3-benzodiazepin-4-ones **206** are prepared by reaction of hydrazines with ketoacid **205**. The ketoacid **205** is prepared in two steps from phenethyl alcohols **202** and aromatic aldehydes **203**. Condensation in hydrogen



44 Tofisopam **199** Talampanel

Figure 25.19 Important 2,3-benzodiazepines.

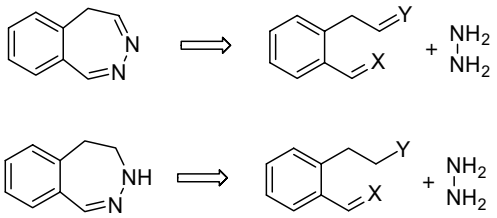
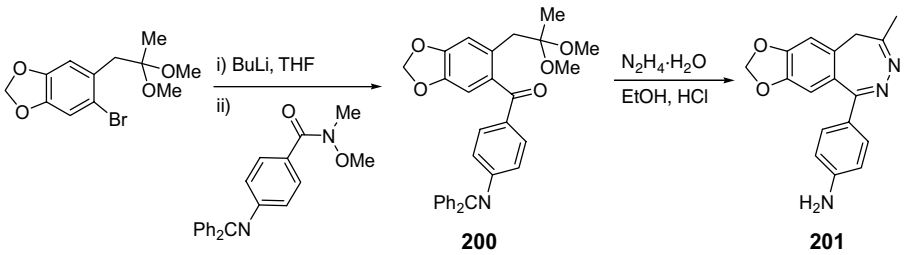
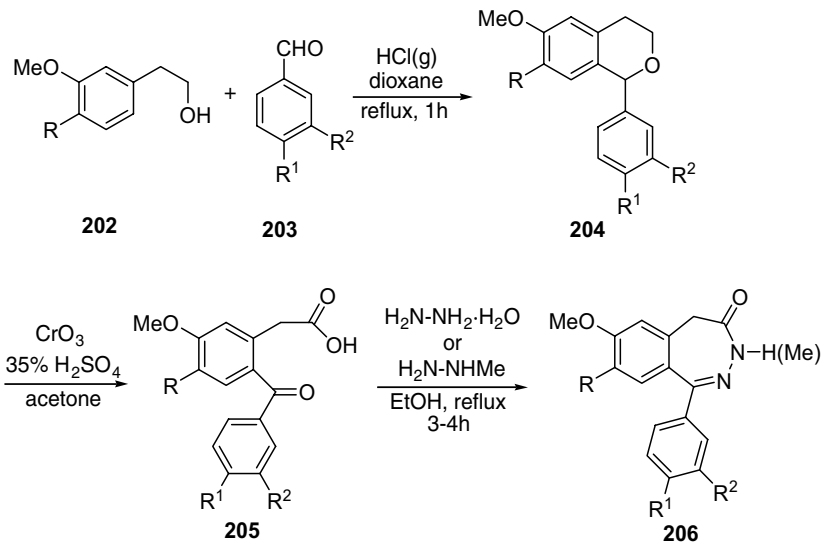


Figure 25.20 Benzodiazepine ring synthesis.



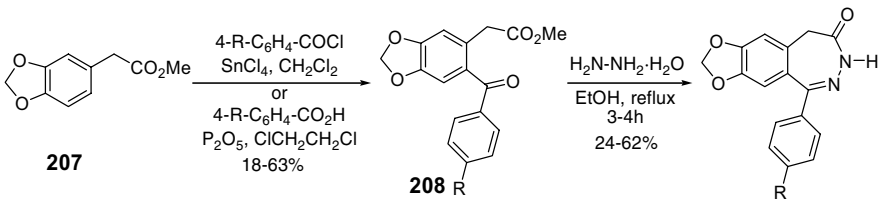
Scheme 25.61 Synthesis of GYKI 52 466 (**201**).

chloride saturated dioxane gives rise to 1-arylisochromans **204**. Then, oxidation with CrO_3 provides the ketoacid, which is further condensed with hydrazine (Scheme 25.62) [135].



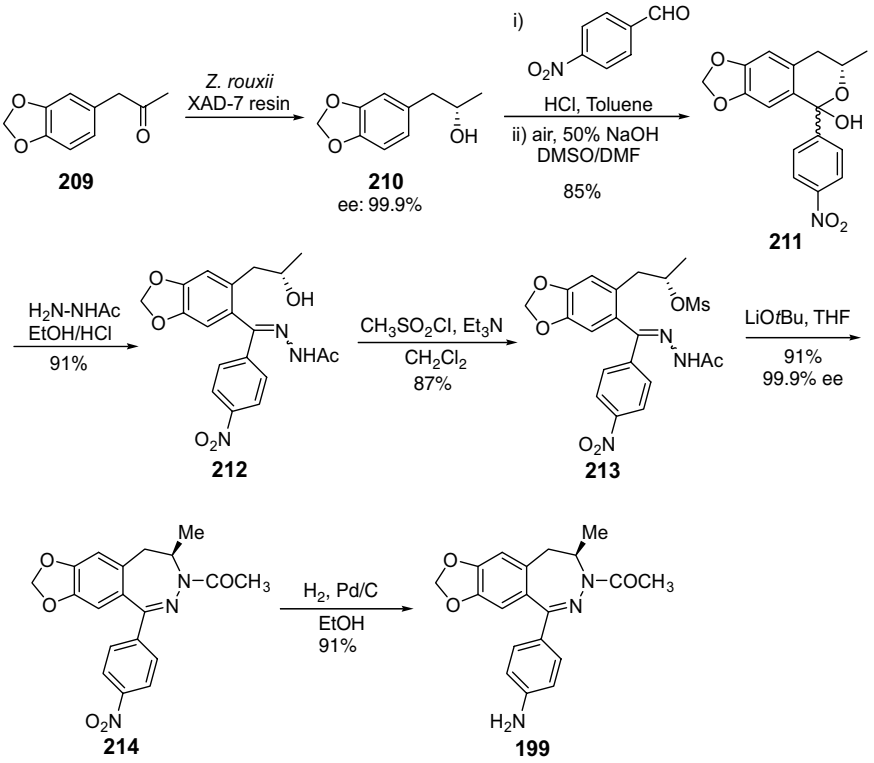
Scheme 25.62 Synthesis of 2,3-benzodiazepines from a ketoacid and hydrazine.

Alternatively, precursor ketoester **208** can be prepared by Friedel–Crafts acylation of phenylacetic acid derivative **207** (Scheme 25.63) [136, 137]. Notably, a solid-supported version of this strategy has been also developed [138].



Scheme 25.63

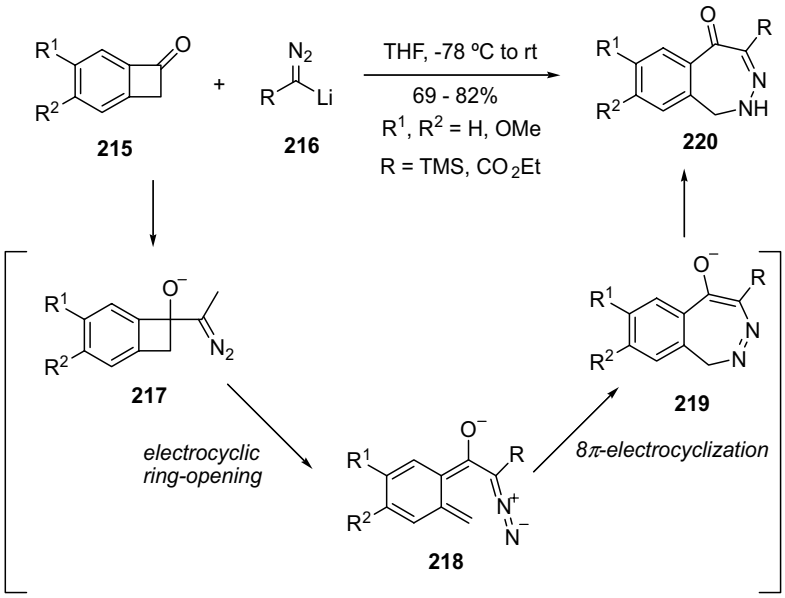
Talampanel (**199**) features a chiral center in the seven-membered ring. Chirality can be introduced by selective reduction of the N3-C4 iminic double bond from a 5*H*-2,3-benzodiazepine (**201**) [139]. Otherwise, the stereocontrolled synthesis of this molecule can be achieved by cyclization through an intramolecular S_N2 reaction of enantiomerically pure mesylate **213**. The synthesis starts from ketone **209**, which is biocatalytically reduced to alcohol **210** in 99.9% ee (Scheme 25.64) [140]. Conden-



Scheme 25.64 Synthesis of talampanel (**199**).

sation with *p*-nitrobenzaldehyde followed by air autoxidation gives hemiketal **211**. The substrate for the intramolecular cyclization is then generated by formation of hydrazone **212** followed by mesylation of the alcohol to give **213**. The intramolecular S_N2 reaction proceeds with total inversion of configuration, leading to **214**. Finally, reduction of the nitro group gives talampanel (**199**). A modification of this strategy has been applied to the preparation of analogs with diverse substitution at N4 [141].

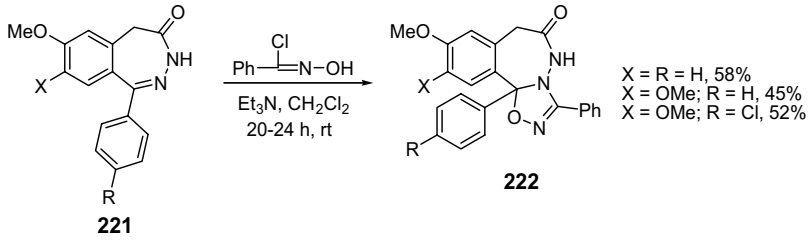
Very recently, it has been shown that 2,3-benzodiazepine **220** derivatives can be obtained from benzocyclobutenones **215** and lithiated diazo compounds **216**. The process involves nucleophilic addition of the lithiated diazo compound **216** to the carbonyl group of **215**, to give alkoxide intermediate **217**, which easily undergoes an oxy-anion-accelerated ring opening to generate *o*-quinodimethane **218**. Then, a formal 8π-electrocyclic ring closure recovers the aromaticity of the benzene ring to form **220** via its enolate form **219** (Scheme 25.65).



Scheme 25.65 2,3-Benzodiazepines from benzocyclobutenones and lithiated diazo compounds.

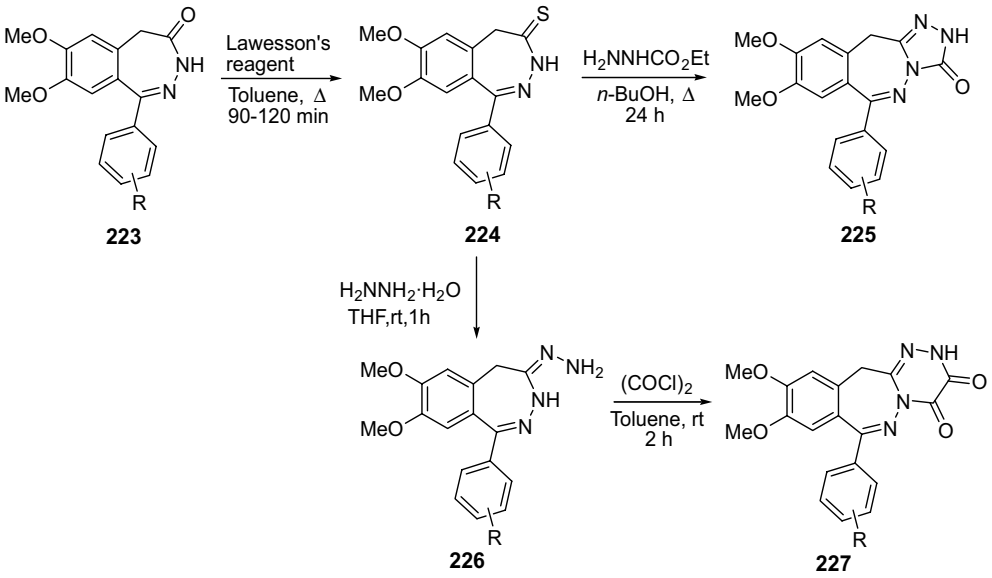
25.8.2
2,3-Benzodiazepines with a Fused Heterocycle

In the search for new 2,3-benzodiazepines with enhanced pharmacological properties, derivatives featuring a condensed heterocyclic ring have been prepared. A heterocycle has been attached at the C1-N2 face by dipolar cycloaddition. For instance reaction of 3,5-dihydro-4*H*-2,3-benzodiazepin-5-ones **221** with benzonitrile oxide leads to new benzodiazepines **222** with an oxadiazole ring condensed at the C1-N2 face (Scheme 25.66) [142].



Scheme 25.66 [3 + 2] Dipolar cycloadditions of 2,3-benzodiazepines.

A fused heterocycle can be incorporated at the N3-C4 position through stepwise procedures similar to those described for 1,4-benzodiazepines. In a first step 3,5-dihydro-4*H*-2,3-benzodiazepin-5-ones **223** are activated by thiolation with Lawesson's reagent [143]. Reaction of **224** with ethyl carbazate affords 11*H*-[1,2,4]triazolo[4,5-*c*][2,3]benzodiazepin-3(2*H*)-one derivatives **225**. Moreover, condensation of **224** with hydrazine gives rise hydrazinyl derivatives **226**, which are converted into 2,12-dihydro-[1,2,4]triazino[4,3-*c*][2,3]benzodiazepine-3,4-dione derivatives **227** by treatment with oxalyl chloride (Scheme 25.67) [144].



Scheme 25.67 Synthesis of benzodiazepines with a fused-heterocycle at the N3-C4 side.

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26
Porphyrins: Syntheses and Reactions

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26.1
Introduction

26.1.1
General Introduction

Porphine (**1**) is the parent form of porphyrin (Figure 26.1). Porphyrin is a tetrapyrrolic pigment (**2**–**4**) with various substitutions on the macrocycle. Based on the substitution, they are known as octaethyl porphyrins (OEPs), tetra phenyl porphyrins (TPPs) and octaethyl tetra phenyl porphyrins (OETPPs). It is recognized chiefly for the role of its metal complexes in oxygen transport/storage in animals and for the conversion of carbon dioxide into oxygen in plants, apart from a multitude of diverse functions that it executes in various other biological processes [1, 2]. This has led it to acquiring the sobriquet "Pigment of Life" [3].

From a chemist's point of view, it has been fascinating to study the properties of this macrocycle to understand its role in biology. From an organic perspective, it has four pyrrole sub-units that are interlinked through four methine (or *meso*) carbons in a cyclic fashion. Its stability is attributed to the aromatic character due to the delocalization of π electrons. The conjugated pathway accounts for a formal 18π system, which satisfies Huckel's $4n + 2$ rule for aromaticity. Owing to this conjugation, porphyrin absorbs strongly in the visible part of the electromagnetic spectrum. A characteristic porphyrin spectrum has an intense absorption band around 420 nm, also known as the Soret band, followed by weak absorptions in the region 500–650 nm [1]. Its ability to absorb visible light and to carry out energy/electron transfer has been the backbone of photosynthesis in plants. Based on this natural phenomenon, several attempts are being directed towards artificial photosynthesis to harness solar energy. From the inorganic viewpoint, the core of the porphyrin ring is an excellent binding site for various metal ions due to the presence of imino and amino type nitrogen of the pyrrole rings [2]. Porphyrin complexes, with biological significance, of Fe, Mg, and Co are found abundantly in nature.

Modern Heterocyclic Chemistry, First Edition.
Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.

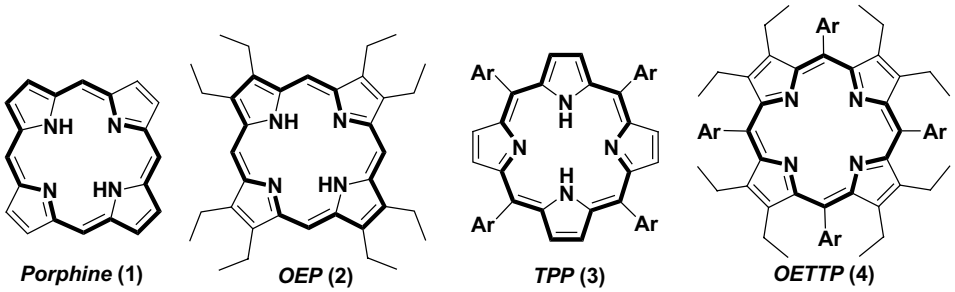


Figure 26.1 Tetrapyrrolic pigments.

In fact, it is a versatile ligand for complexing not only metals, but also for a few metalloids [4] in the periodic table.

With such diverse functionality, porphyrin has attracted many researchers across the globe, who have explored its role in various applications. New synthetic strategies have evolved to fine-tune the properties of the macrocycle for applications ranging from microelectronics [5] to medicine [6]. The outcome of this process has led to new derivatives such as contracted porphyrins [7], expanded porphyrins [8], confused porphyrins [9], and core-modified porphyrins [10]. In this chapter, we highlight recent advancements in the synthesis of porphyrin and porphyrinoids (porphyrin-like macrocycles) and their reactions with various reagents.

26.1.2 System Isomers

26.1.2.1 Tetrapyrrolic Systems

Isomers of porphyrin have the same number of pyrrolic subunits but with altered links between the heterocyclic units. One of the ways to name porphyrin and its isomers is through numbering the *meso* carbons and the manner in which the heterocyclic units are linked to each other. Each *meso* carbon is identified by one (1) and each direct link between two adjacent heterocyclic units is given a zero (0). For example, porphine (**1**) and its isomer porphycene (**5**) [11] are recognized as [1.1.1.1] and [2.0.2.0] 18π tetrapyrrolic systems, respectively (Figure 26.2). Similarly, **6**–**8** are identified as [2.1.0.1], [2.1.1.0], and [3.0.1.0] 18π tetrapyrrolic systems. Their trivial names are corrphycene [12], hemiporphycene [13] and isoporphycene [14], respectively.

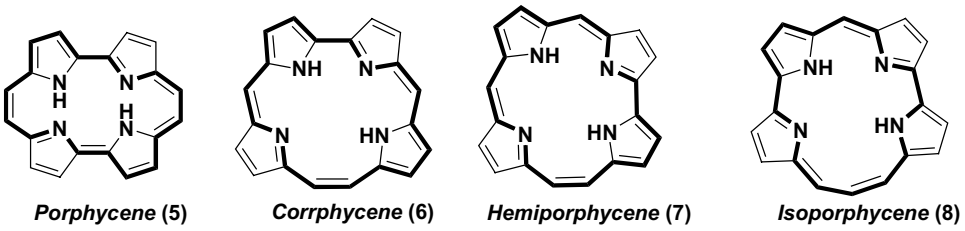


Figure 26.2 Examples of isomers of porphyrin.

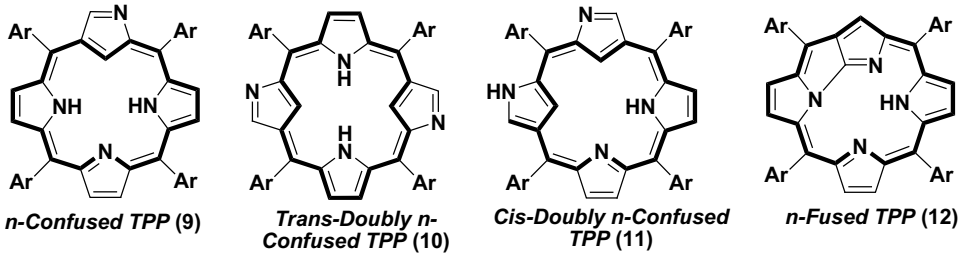


Figure 26.3 Pyrrole inverted systems.

26.1.2.2 **Pyrrole Inverted Systems**

In some cases, a pyrrole sub-unit exhibits α and β connectivity leading to, for example, N-confused porphyrin **9** (Figure 26.3) [15]. Instead of two alpha connectivities, a beta and an alpha carbon become part of the conjugated framework. Furuta and Latos-Grazynski independently reported the formation of such porphyrins, wherein a sp^2 carbon replaces one of the nitrogens in the core of the macrocycle. The skeleton structure is similar to that of porphyrin, except for the inversion of a pyrrole ring. Possible isomers with more than one confused pyrrole ring were reported later and these are called doubly confused porphyrins. Depending on the location of the confused pyrrole rings with respect to each other, they are identified as trans-doubly N-confused porphyrin (**10**) [16] and cis-doubly N-confused porphyrin (**11**) [17]. Depending on the location of hydrogen on the pyrrolic nitrogen atoms, different tautomeric structures have been identified through proton NMR. N-Confused porphyrin **9** is also found to form a fused structure known as N-fused porphyrin, **12.** Some expanded porphyrins with confused pyrrole rings have also been reported.

26.1.2.3 **Core-Modified Porphyrins**

Another kind of porphyrin isomer is known as core-modified porphyrins [10]. Here, one or more pyrrole rings in porphyrins can be replaced by other heterocyclic units such as furan/thiophene/selenophene/tellurophene. Depending on the number of heteroatoms in the macrocycle they are named as mono or di-oxa/thia/selena porphyrins [18, 19] (**13** and **14**, Figure 26.4). Some representative examples are shown below. Porphyrins can also have a confused non-pyrrolic heterocyclic ring.

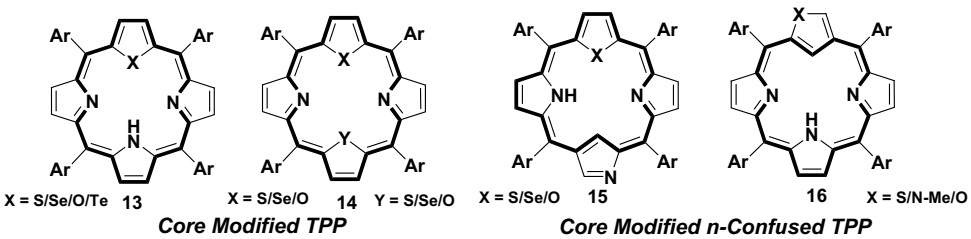
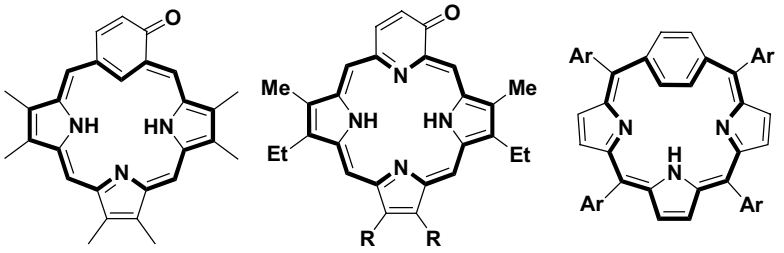


Figure 26.4 Core-modified porphyrins.



***Oxybenziporphyrin* (17)** ***Oxypyriporphyrin* (18)** ***p-Benziporphyrin* (19)**

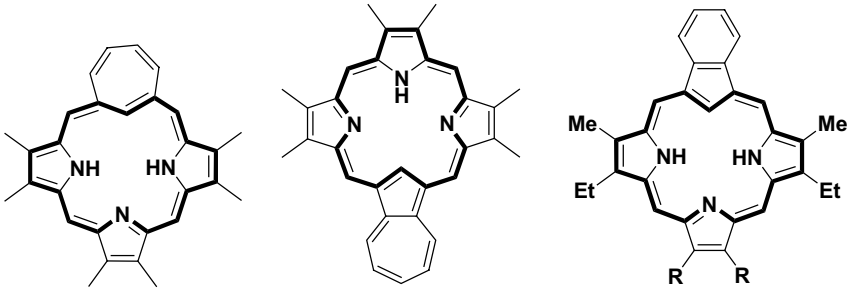
Figure 26.5 Examples of a six-membered ring within the porphyrin framework.

In some macrocycles, pyrrole or the other heterocyclic ring have α and β links in the macrocycle. They are known as core-modified N-confused porphyrins (**15** and **16**) [20, 21]. They all exhibit properties similar to that of porphyrin and can bind metal ions in a few cases. Since elements like S/Se are considered as poor donors, they are ideal ligands to stabilize metal ions in lower oxidation states.

Apart from five-membered heterocycles, six-membered rings such as benzene [22] and pyridine can also replace pyrrole in the porphyrin framework. Some examples are oxybenziporphyrin (**17**) [23], oxypyriporphyrin (**18**) [24] and *p*-benziporphyrin (**19**) [25] (Figure 26.5).

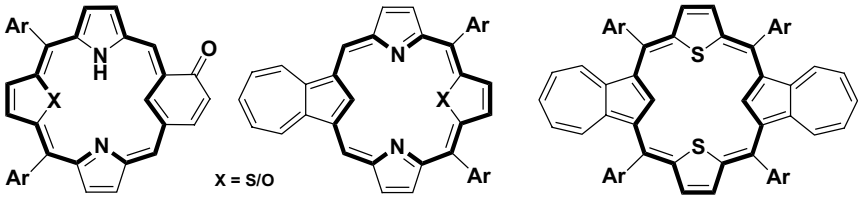
Larger carbon rings such as a seven-membered cycloheptatrienyl ring and fused cyclic derivatives such as indene and azulene can also replace a pyrrole ring to form, for example, tropiporphyrin (**20**) [26], azuliporphyrin (**21**) [27] and benzocarbaporphyrin (**22**) [28] (Figure 26.6). They exhibit interesting features in terms of π electron delocalization and their effect on diatropic ring currents. In some cases they are found to be aromatic and in others the ring current is disrupted based on the nature of the six- or five-membered ring present in the conjugated pathway.

A six-membered cyclic sub-unit and a non-pyrrolic heterocycle can also be a part of the porphyrin framework. Macrocycles such as core-modified oxybenziporphyrin (**23**) [29], azuliporphyrin (**24**) [30] and dithiadiazuliporphyrin (**25**) [31] represent a combination of five- and six-membered cyclic sub-units within a porphyrin framework (Figure 26.7).



***Tropiporphyrin* (20)** ***Azuliporphyrin* (21)** ***Benzocarbaporphyrin* (22)**

Figure 26.6 Inclusion of larger carbon rings in the porphyrin framework.



***Core Modified Oxybenziporphyrin* (23)** ***Core Modified Azuliporphyrin* (24)** ***Dithia Diazuliporphyrin* (25)**

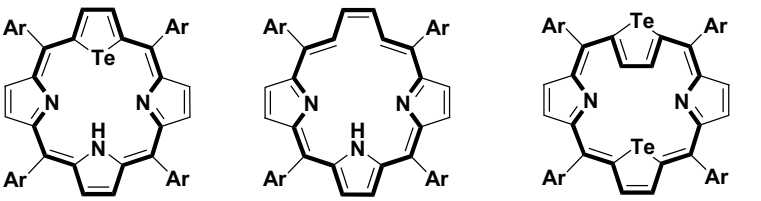
Figure 26.7 Combinations of five- and six-membered cyclic sub-units within a porphyrin framework.

In the case of telluraporphyrin (**26**) [32], the carbon–tellurium bond can be broken, leading to the formation of vacataporphyrin (**27**) [33] (Figure 26.8).

26.1.2.4 Expanded Porphyrins

The delocalization of π electrons in porphyrin can be extended either by increasing the number of heterocyclic units or *meso* carbons linking them in a cyclic fashion. Molecules synthesized based on this concept are called expanded porphyrins [8]. Even though this was not realized by any forethought, the serendipitous discovery of a 22π five pyrrolic macrocycle by Woodward and coworkers [34] generated a new trend towards the design and synthesis of giant conjugated macrocycles. Expanded porphyrins synthesized through an increased number of *meso* carbons are called vinylogous porphyrins. The groups of Markl [35] and Franck [36] have independently synthesized tetraoxa and tetrapyrrolic vinylogous porphyrins with multiple methine bridges between four heterocyclic rings (Figure 26.9).

Expanded porphyrins with more heterocyclic rings have attracted attention for their potential in various applications [8]. Synthetically, they challenge chemists to create large, flat conjugated macrocycles. To date, a maximum of 24 pyrrole units have been linked to each other in a cyclic fashion [37]. Unlike the parent porphyrin, these macrocycles have a combination of *meso* carbon bridges and direct carbon–carbon bonds between two or more heterocycles as bridges to link each other in a circular fashion. They have been studied extensively for their potential in applications such as molecular recognition [38], nonlinear optics [39] and as sensitizers for photodynamic



Telluraporphyrin (26) ***Vacataporphyrin* (27)** **Ditelluraporphyrin (28)**

Figure 26.8 Tellurium-containing porphyrins and one of their derivatives (**27**).

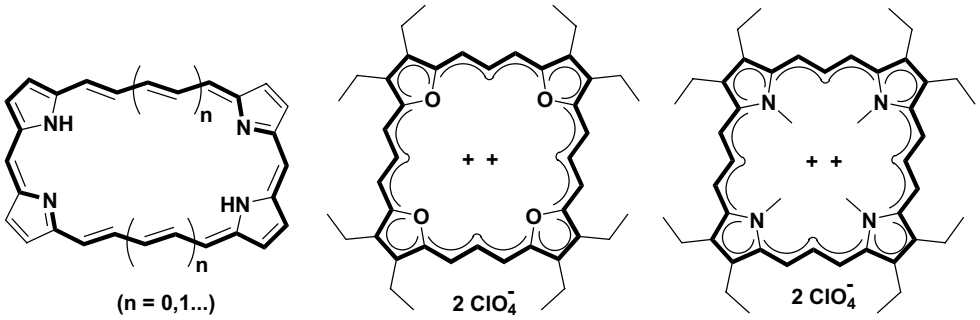


Figure 26.9 Examples of expanded porphyrins.

therapy. Their photo-physical properties can be altered by replacing pyrrole rings with other heterocyclic units such as furan/thiophene/selenophene/tellurophene and even other six-membered cyclic sub-units such as benzene and pyridine.

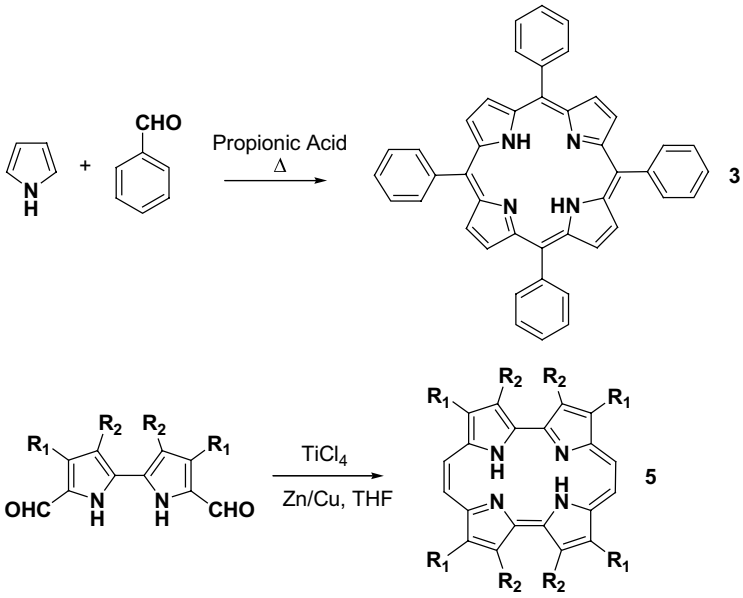
Even though various macrocycles have been described above, their synthesis is mainly dependent on either acid-catalyzed condensations or oxidative coupling reactions under acidic conditions [8]. But most of them are made in poor to moderate yields due to the tendency of pyrrole to polymerize under acidic conditions. An overview of the synthesis of these macrocycles along with interesting examples is discussed below.

26.2
Synthetic Chemistry of Porphyrins and Expanded Porphyrins

The Rothemund reaction [40] of pyrrole and benzaldehyde in refluxing propionic acid is the simplest way to synthesize porphyrin in general and TPP (**3**) in particular (Scheme 26.1). Most porphyrin isomers such as porphycene, corrphycene, hemiporphycene and isoporphycene have substituents on the β positions of the pyrrole rings. In general, the synthesis of β-substituted porphyrins is a multi-step process. Vogel and coworkers [11] were the first to synthesize porphycene (**5**) through a McMurry coupling of bipyrrole dialdehydes in 10–25% yield depending on the nature of the substitutent on the pyrrole ring.

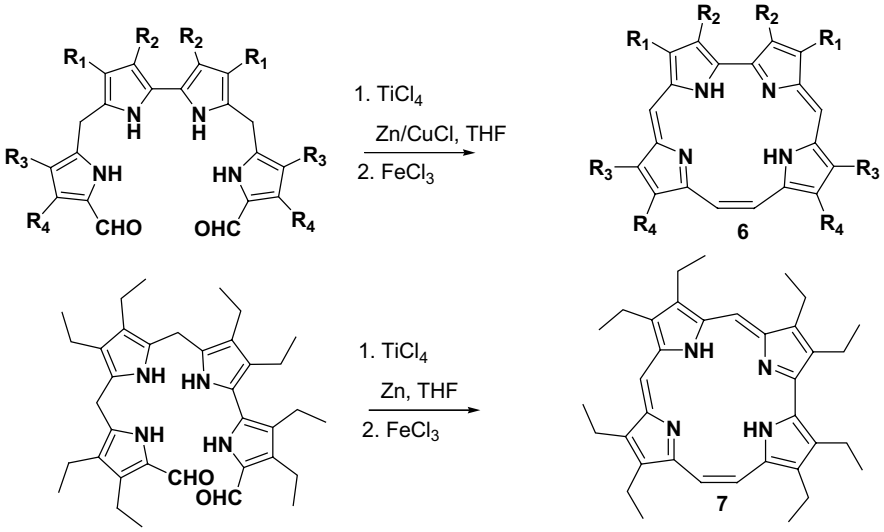
Corrphycene (**6**) has also been synthesized by a McMurry-type coupling of a tetrapyrrolic dialdehyde in 15–20% yield (Scheme 26.2) [12]. The next isomer, hemiporphycene (**7**) was discovered by Callot [41] and coworkers through a ring contraction of homoporphyrin through a demetallation–metallation sequence as shown in Scheme 26.2. Later, Vogel and Sessler developed a rational synthesis for **7** through a McMurry coupling of a tetrapyrrole dialdehyde in 25% yield.

Isoporphycene (**8**) has also been synthesized, through Pd-catalyzed condensation of tetrapyrrole vinylogousaldehyde in 3% yield (Scheme 26.3) [14]. This molecule is thermally stable, but can undergo interconversion at the double bounds upon exposure to light.

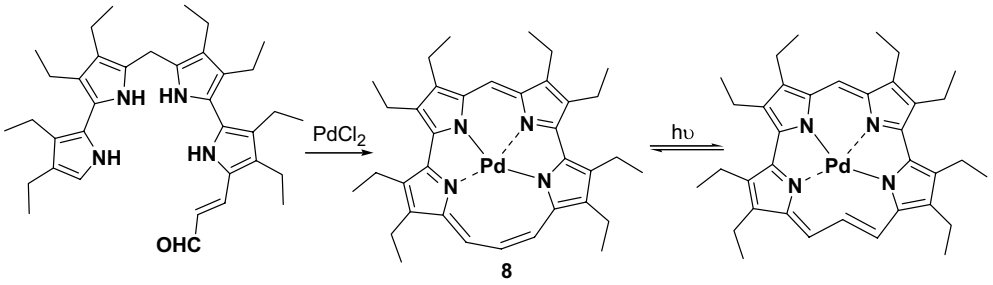


Scheme 26.1

Owing to similar 18π conjugation, all the porphyrin isomers described above display physical characteristics comparable to the parent porphyrin system. They also exhibit intense Soret-like absorption in the vicinity of 400 nm along with relatively intense Q-type bands in the lower energy region 500–700 nm. Owing to these

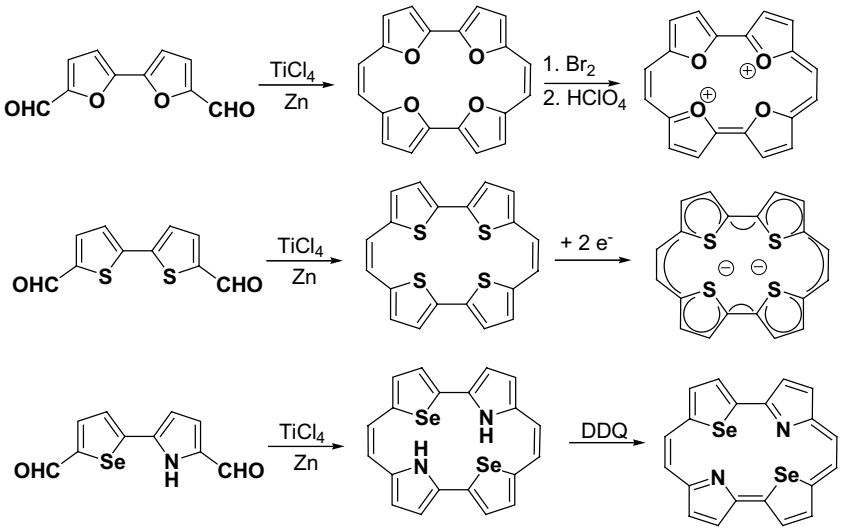


Scheme 26.2



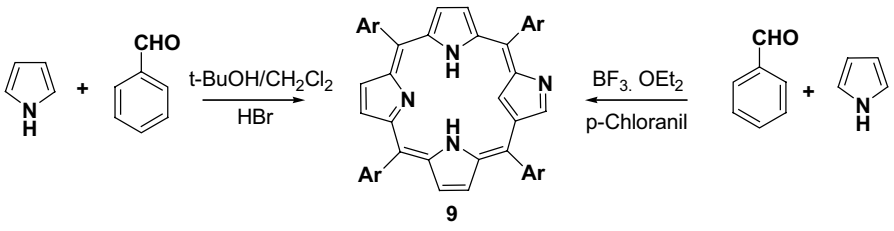
Scheme 26.3

characteristics they appear attractive as sensitizers for their use in photodynamic therapy (PDT). The synthesis of porphycene led to many reports on core-modified porphycene isomers [42] by replacing some or all pyrrole rings by other heterocyclic systems such as furan, thiophene or selenophene (Scheme 26.4). Most of them were synthesized through low-valent titanium coupling of appropriate dialdehyde precursors.



Scheme 26.4

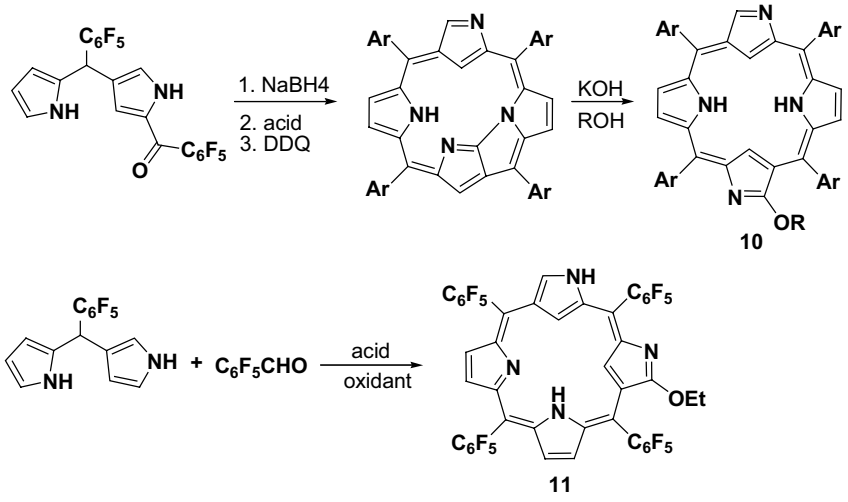
The N-confused porphyrins **9**–**12** and analogues are recent entries into the growing list of porphyrin isomers. The first synthesis of **9** was reported simultaneously and independently by the groups of Furuta and Latos-Grazynski (Scheme 26.5) [15]. Both groups were able to isolate the novel isomer under different reaction conditions depending on the nature of the acid catalyst and the time required to complete the reaction. In either case, the product yield was very low (4–7%). Subsequently, Lindsey and coworkers [43] performed a detailed study on modified Rothemund reaction conditions to optimize the yield of N-confused porphyrin and were able to improve



Scheme 26.5

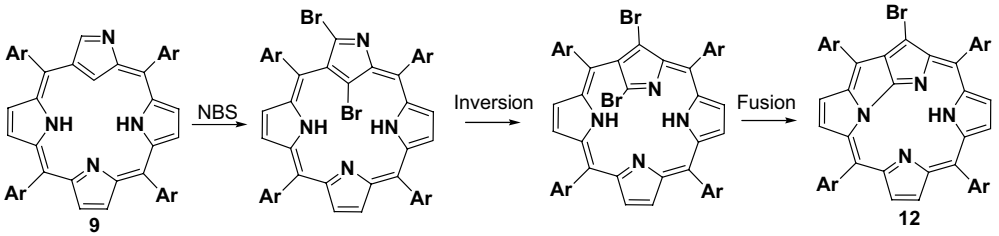
the yields up to 39%. These porphyrinoids were also prepared in a stepwise manner using MacDonald-type [2 + 2] condensation by Dolphin's group in 25% yields [49], respectively.

Furuta and coworkers have developed the chemistry of N-confused porphyrins further by the synthesis of doubly N-confused porphyrins **10** and **11** (Scheme 26.6). They are synthesized in a step-wise manner from modified dipyrromethanes, in which one of the pyrrole rings has a β link to the *meso* carbon. In the *cis* case, the two inverted rings are adjacent [17], while they are diagonally opposite in the trans case [16].



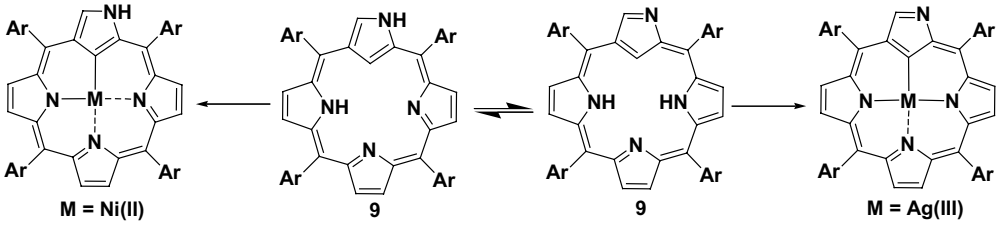
Scheme 26.6

The inverted pyrrole ring, in **9**, can be dibrominated with *N*-bromosuccinimide (NBS) under ambient conditions. It undergoes a transformation, under basic conditions, by losing HBr, leading to the formation of N-fused porphyrin **12** (Scheme 26.7) [44]. This is the first report of the formation of covalent bonds between nitrogen and carbon inside the core of porphyrin; **12** can be converted back into **9** upon treatment with a strong base such as NaOMe in 72% yield. All the macrocycles described above have 18π electron conjugation and show physical characteristics similar to that of the parent porphyrin.



Scheme 26.7

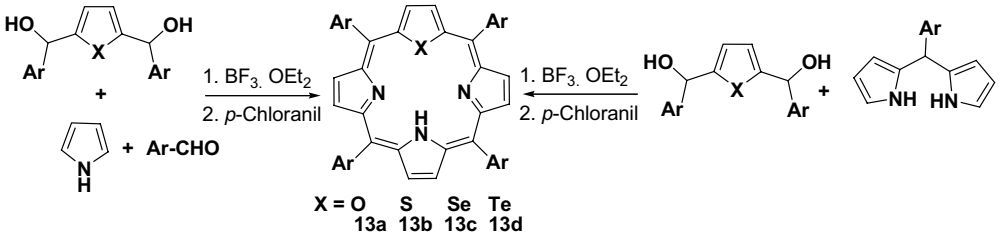
Porphyrin **9** can have different isomers depending on the location of hydrogen on the nitrogen of the pyrrole rings. This enables it to act as a ligand for stabilizing either $+2$ or $+3$ oxidation states of transition metal ions. Latos-Grazynski and coworkers [15] were the first to report the formation of a metal–carbon bond in a porphyrin macrocycle. Porphyrin **9** forms a Ni(II) metal complex with a metal–carbon bond in the core of the porphyrin ring (Scheme 26.8). Furuta and coworkers [17] have isolated the Ag(III) complex of **9**, with a metal–carbon bond in the core of the porphyrin ring. Metal complexes of **9**–**11** have been reported, with some having coordination with metal ions both inside and on the periphery of the macrocycle [45].



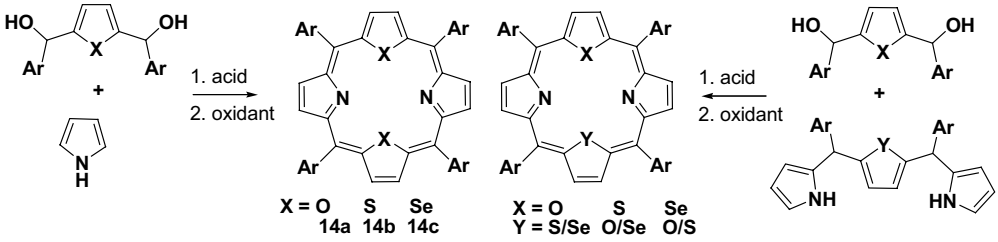
Scheme 26.8

In porphyrins, one or more pyrrole rings can be replaced by other heterocyclic units such as *N*-methylpyrrole, furan, thiophene, selenophene, and tellurophene [10]. This can accommodate other elements such as O, S, Se, and Te, leading to a modified core of the porphyrin ring. Therefore, they are called core-modified porphyrins (e.g., **13** and **14**). They can be synthesized easily from 2,5-diols of heterocyclic units under acid-catalyzed conditions (Schemes 26.9 and 26.10). The diols of such heterocycles are synthesized in good yields by bis-lithiation at the 2- and 5-positions of the heterocyclic units followed by addition of aryl aldehydes. Porphyrins with a single non-pyrrolic unit can be synthesized in two different ways (Scheme 26.9) [46].

With the same approach, two similar or different non-pyrrolic units can replace two pyrroles in a porphyrin. Such compounds can be synthesized by a one-pot synthesis or from modified tripyrrane precursors depending on the kind of the core-modification desired in the porphyrin [47].

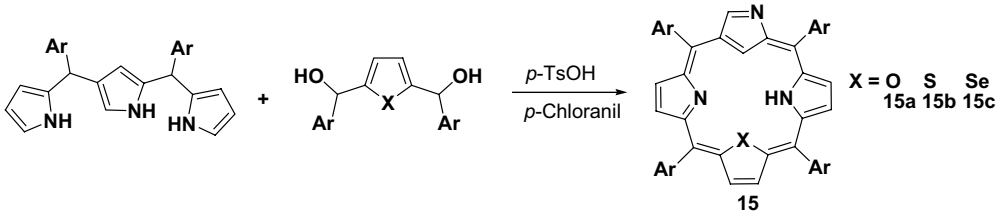


Scheme 26.9



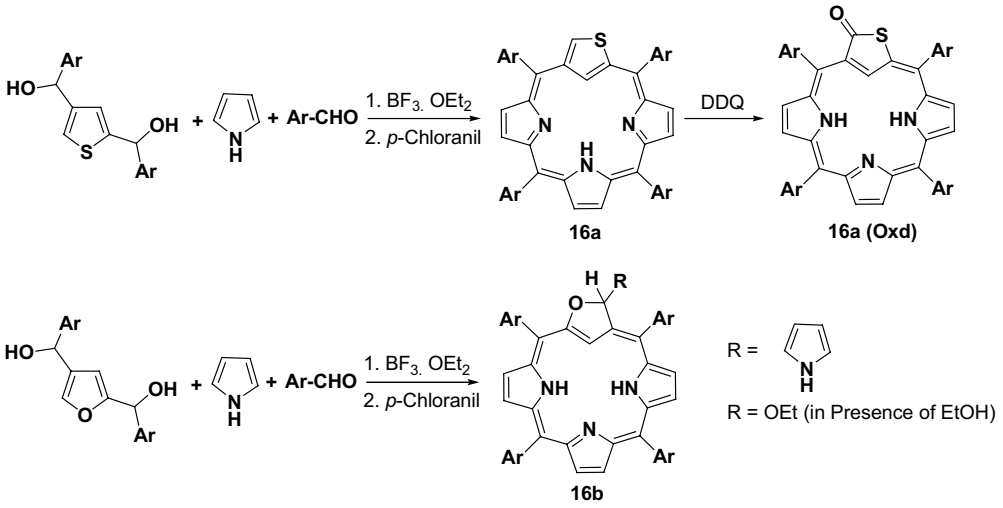
Scheme 26.10

N-confused porphyrin **9** is also a core-modified porphyrin, since one of the four nitrogens is replaced by carbon. In N-confused porphyrins, one of the normal pyrrole rings can also be replaced by other heterocyclic units, such as furan, thiophene or selenophene, giving rise to core-modified N-confused porphyrins (e.g., **15**). Our group has reported three different core-modified N-confused porphyrins bearing oxa, thia or selena (**15a–c**) derivatives [21]. They can be synthesized in moderate yields by condensing N-confused tripyrrane with 2,5-diols of heterocyclic units followed by oxidation (Scheme 26.11).



Scheme 26.11

The confused pyrrole ring can also be replaced by another inverted non-pyrrolic heterocyclic ring. Latos-Grazynski and coworkers have synthesized S-confused and O-confused porphyrins, **16**, bearing an inverted thiophene ring (**16a**) and furan ring (**16b**) (Scheme 26.12) [20]. They were synthesized by condensing the 2,4-diol of thiophene or furan, respectively, with pyrrole and benzaldehyde in 4–5% yields.



Scheme 26.12

They are highly susceptible to further oxidations or substitutions on the free alpha position of the confused ring. A pyrrole is added to the furan ring in **16b** under the reaction conditions employed, but can be altered to an ethoxy derivative by changing the solvent system from dichloromethane to ethanol. The thiophene keto derivative **16a (Oxd)** is obtained upon prolonged oxidation.

The possibility of replacing the pyrrole ring in a porphyrin by five- or six-membered cyclic π sub-units has been explored extensively. In this process, many aromatic units like pyridine, benzene, azulene and similar such units have successfully replaced one or more pyrrolic units in the macrocycle. Earlier attempts by Breitmaier and coworkers [48] yielded only the non-aromatic form of a benziporphyrin. This was attributed to the fact that the thermodynamically more stable 6π aromaticity of benzene could not be disrupted to be part of an 18π system. Therefore, early reports suggested that benzene and porphyrinoid aromaticity were mutually exclusive in benziporphyrin-type macrocycles. Lash and coworkers were also unsuccessful in their attempts to synthesize aromatic pyriporphyrins, and could isolate only non-conjugated *meso-meso* dimers or *meso*-keto derivatives (Figure 26.10).

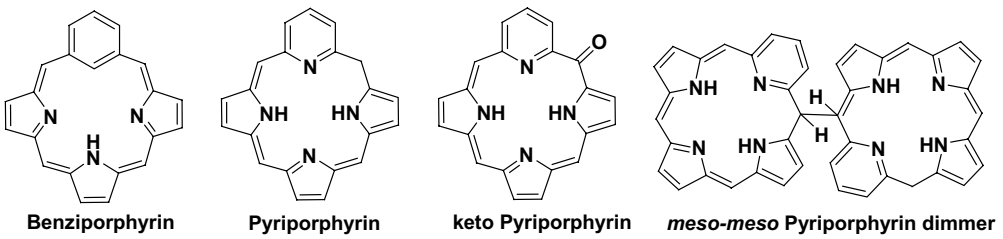
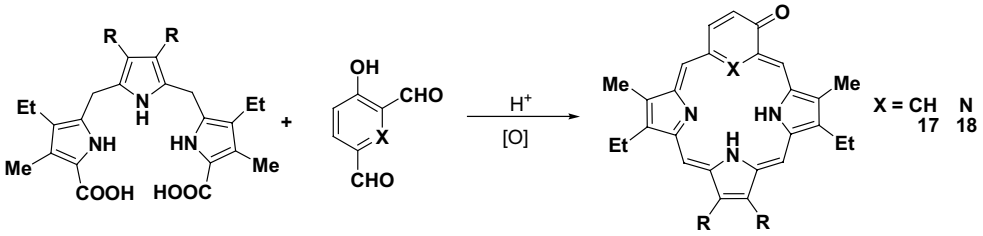


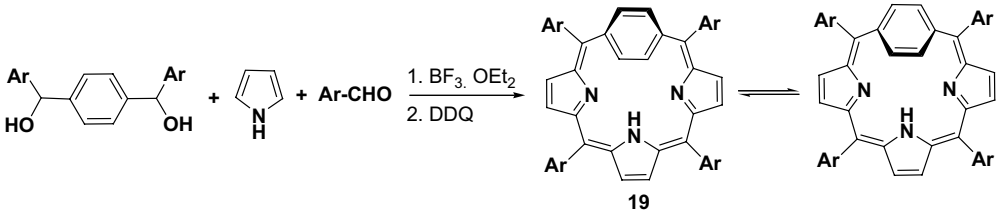
Figure 26.10 Examples of porphyrins containing a six-membered cyclic π sub-unit.

However, they were successful in the synthesis of oxybenziporphyrin (**17**) [23] and oxypyriporphyrins (**18**) [24], wherein the benzene or the pyridine ring was substituted with a keto group upon the formation of the macrocycle. The synthesis involved condensation of tripyrrane dicarboxylic acid and 2,4-diformylphenol or 3-hydroxy-2,6-diformylpyridine under acidic conditions, with yields up to 44% and 86%, respectively (Scheme 26.13). These macrocycles were found to be aromatic, as analyzed by NMR spectroscopy, since the 6π conjugation of the benzene or the pyridine could be disrupted by the exocyclic keto group, thereby favoring stabilization of the 18π system over the benzenoid aromaticity.



Scheme 26.13

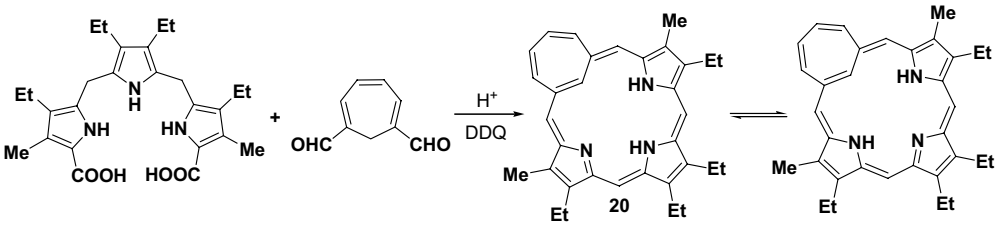
In both the macrocycles **17** and **18** benzene is connected by two meta links within the porphyrin ring. Latos-Grazynski and coworkers [25] have reported an isomer of benziporphyrin (**19**) by changing the nature benzene ring incorporation within the porphyrin framework. When the benzene ring was connected by a 1,4 (para) link it exhibited aromatic features indicating the flow of 18π conjugation through the benzene ring. Compound **19** was synthesized by acid-catalyzed reaction of a 1,4-diol of benzene with pyrrole and benzaldehyde in 1% yield (Scheme 26.14). ^{1}H NMR studies showed that the benzene ring rotates very rapidly at room temperature but is stable at low temperatures. Two doublets seen at 7.68 and 2.32 ppm at 168 K are indicative of a diatropic ring current, which deshields protons outside the ring and shields the protons inside the ring.



Scheme 26.14

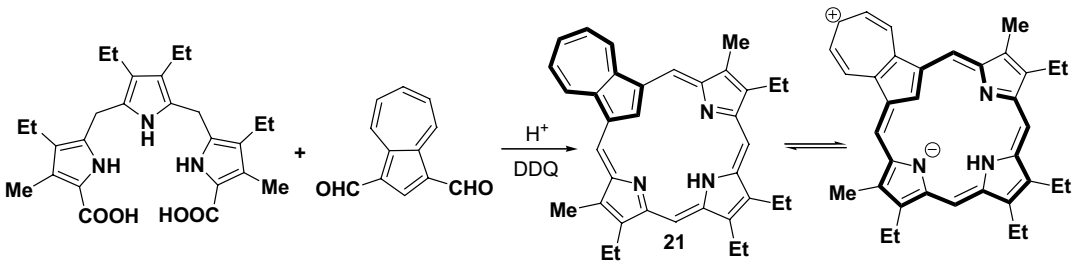
The flow of conjugation in such systems is of great interest and porphyrins with different cyclic units have been the targets of synthetic chemists. This has led to the formation of a new class of macrocycles called carbaporphyrinoids, wherein a

carbon acts as a coordinating site for metal ions inside the cavity of the porphyrin ring. Even though some of them were envisaged as probable macrocycles they were not realized due to lack of easy and efficient synthetic routes. Tropiporphyrin (**20**) is one successful example synthesized by Lash and Chaney. After the initial attempts of Breitmaier and coworkers [48], they were able to synthesize aromatic tropiporphyrin (**20**) with modified reaction conditions in 23% yield (Scheme 26.15) [26]. Unlike benziporphyrin, interestingly, the meta link of cycloheptatriene-1,6-dicarboxaldehyde is attuned to accommodation into the 18π conjugated network of the macrocycle.



Scheme 26.15

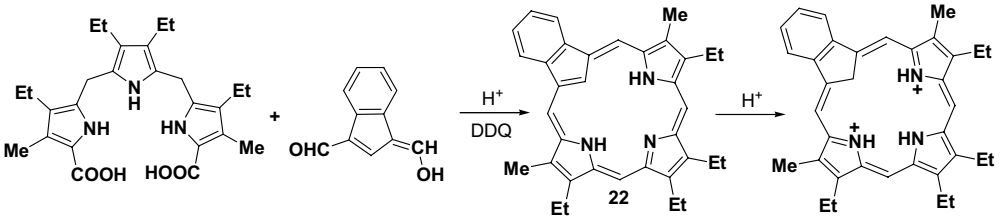
Azuliporphyrin (**21**) [27] and benzocarbaporphyrin (**22**) [28] are remarkable examples of incorporating five-membered carbon rings inside the 18π aromatic porphyrin ring. Compound **21** can be synthesized by reacting azulene-1,3-dicarboxaldehyde with tripyrrane in a MacDonald-type condensation (Scheme 26.16). With trifluoroacetic acid (TFA) as the catalyst, Lash and Chaney isolated **21** in 28% yield. The azulene unit interrupts the 18π aromaticity of the macrocycle, and hence it would seem that the molecule cannot be aromatic. However, the observed aromatic nature of **21** is attributed to its dipolar resonance contributor, which allows both the porphyrinoid and tropylium aromaticity to be attained simultaneously.



Scheme 26.16

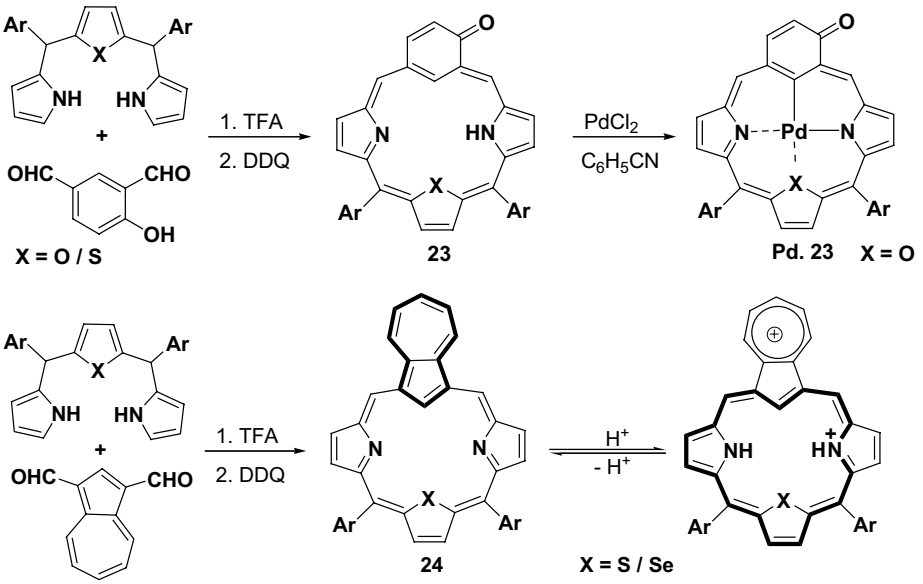
Breitmaier and coworkers had carried out the same reaction with HBr as the acid catalyst and obtained **21** along with various benzocarbaporphyrins in low yields [49]. Subsequently, Lash and Hayes established a rational synthetic route for **22**, by

reacting 1,3-diformylindene with tripyrrane using TFA as the catalyst, with yields of up to 43% (Scheme 26.17) [28]. Upon protonation, the carbon is protonated, leading to an altered 18π conjugated pathway.



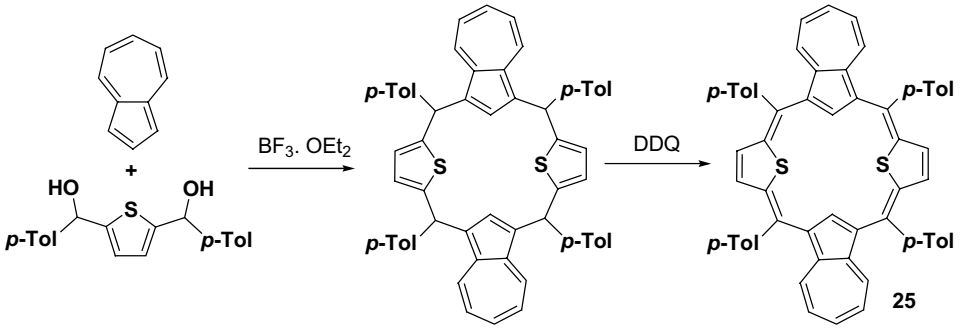
Scheme 26.17

These molecules have different isomers depending on the location of the proton on the nitrogen of the pyrrole rings. Owing to this, they display interesting solution state dynamics in free base and in protonated form, too. We have also noted such an interesting observation in core-modified oxybenziporphyrin (**23**) [29] and core-modified azuliporphyrin (**24**) [30]. They were synthesized under similar conditions as described above – using diformylphenol and diformylazulene, respectively, and modified *meso* aryl tripyrrane – in 28% and 51% yield, respectively (Scheme 26.18). Compound **23** forms palladium metal complexes, with metal–carbon bonds in the center of the macrocycle, in 77% yield.



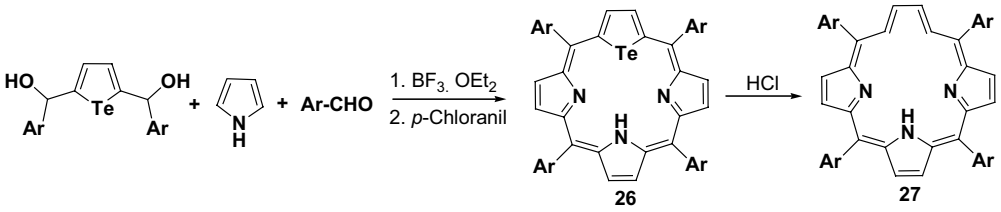
Scheme 26.18

When two azulene rings are incorporated inside a porphyrin framework, the macrocycle cannot be oxidized to obtain an aromatic macrocycle alone. Latos-Grazynski and coworkers [31] have reported the synthesis of dithiadiazuliporphyrin **25** in moderate yields (Scheme 26.19). Upon oxidation, however, **25** forms a mixture of its radical cation and its dication. The authors employed successfully NMR characterization under controlled conditions and also single-crystal crystallography to confirm the exact structure of the macrocycle.



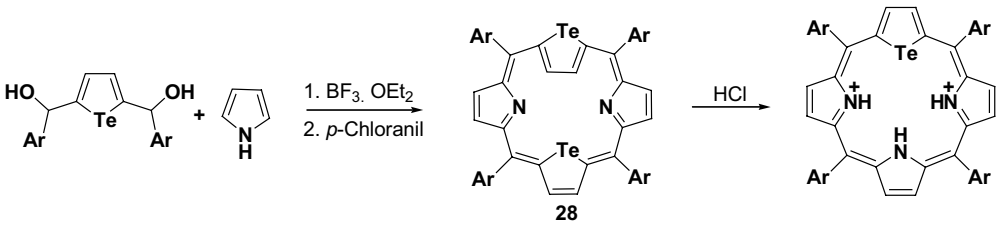
Scheme 26.19

Of all the core-modified porphyrins, telluraporphyrins, both mono and ditellura derivatives, show remarkable traits in terms of reactivity and structural features. Latos-Grazynski and coworkers have reported the synthesis a telluraporphyrin (**26,** Scheme 26.20) [32]. It can undergo transformation to form mono-oxa porphyrin. But of more interest is its interaction with acids like HCl. The macrocycle loses the tellurium atom owing to a weak C—Te bond under acidic conditions. This gave rise to a new macrocycle, named vacataporphyrin **27** (*vacata*, meaning vacancy, in the place of N in porphyrin) [33]. It was found to be aromatic in nature as determined by proton NMR spectroscopy.



Scheme 26.20

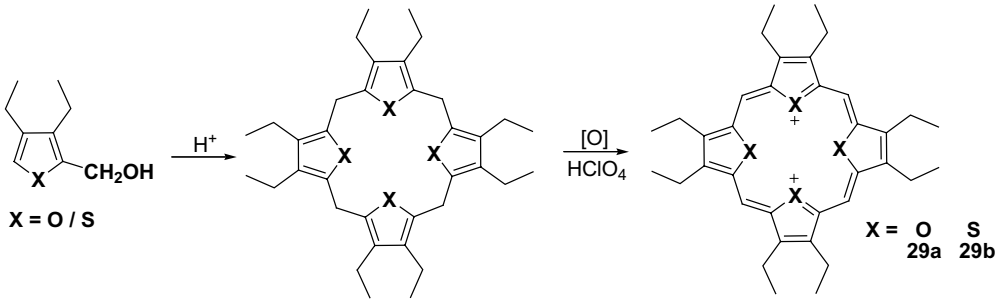
Latos-Grazynski and coworkers reported the first ditelluraporphyrin (**28**) (Scheme 26.21) [50]. The most interesting feature was the ring inversion of a tellurophene ring such that the tellurium atom was outside the core of the porphyrin ring. This differs from **9,** in the sense that the heterocyclic ring undergoes a complete



Scheme 26.21

inversion for both β carbon atoms to be inside the core of the ring. Upon protonation with TFA, the tellurophene ring flips back to a regular structure. This is the first observation of ring inversion in an 18π porphyrin macrocycle.

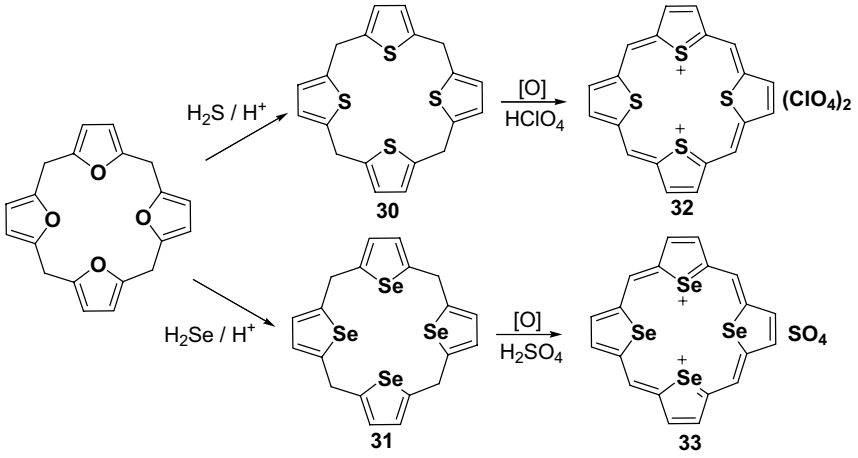
So far we have seen only one or two non-pyrrolic heterocyclic rings in an 18π porphyrin ring. Vogel and coworkers [51] reported the first ever non-pyrrolic porphyrin-like macrocycles bearing four furan, thiophene or selenophene rings. In freebase form they account for a 20π conjugated pathway, but can be oxidized by perchlorates or perchloric acid to obtain an aromatic 18π dication. Tetraoxa- and tetrathia-porphyrinogens are synthesized from 2-hydroxymethyl-3,4-diethylthiophene/furan, which upon further oxidation forms the aromatic tetraoxaporphyrin, **29a**, and tetrathiaporphyrin, **29b**, dications (Scheme 26.22).



Scheme 26.22

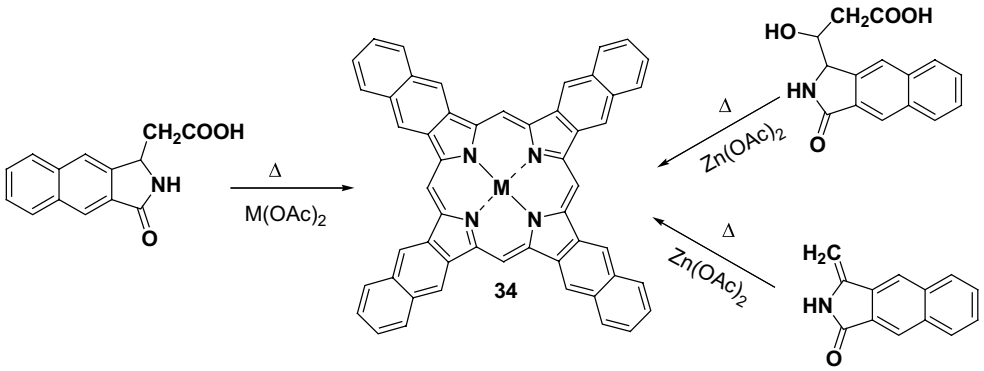
Interestingly, the tetraoxa-porphyrinogen acts as a precursor to generate tetrathia (**30**) or tetraselena (**31**) derivatives by treating it with H_2S or H_2Se under acidic conditions (Scheme 26.23) [52].

Apart from modifying the core of the porphyrin ring, periphery modifications in terms of extended conjugation is attracting considerable attention due to the photophysical properties of the products. Owing to their strong absorption in the red region of the visible spectrum, they are potential chromophores for sensitizers in photodynamic therapy (PDT). Various porphyrins with extended conjugation on the pyrrole rings have been synthesized in this regard. A few representative examples, which have the maximum redshifted absorption with respect to the 18π porphyrin



Scheme 26.23

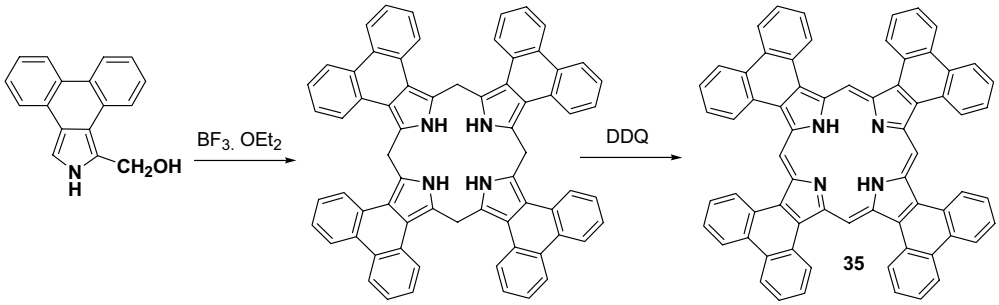
system, are described below. In addition, the group of Kopranenkov [53] and Rein and Hanack [54] have explored the synthesis of zinc tetra-(2,3-naphtho)porphyrin (**34**) by employing zinc acetate (Scheme 26.24).



Scheme 26.24

Lash and Novak [55] have demonstrated the synthesis of tetraphenanthropoprhyrin (**35**) by self-condensation of phenanathropyrrole carbinol under modified Rothemund conditions (Scheme 26.25). Its solubility in freebase was poor in common organic solvents compared to its diprotonated derivative.

Further, Lash and coworker [56] were able to synthesize *meso*-aryl tetracenaphthoporphyrin, **36**, by condensing acenaphtho[1,2-*c*]pyrrole with aryl aldehydes under Lindsey conditions (Scheme 26.26) [57]. The corresponding *meso*-free tetracenaphthoporphyrin was highly insoluble, whereas **36** is deep violet in chloroform, which is indicative of extended conjugation. It displayed a record-breaking bathochromic

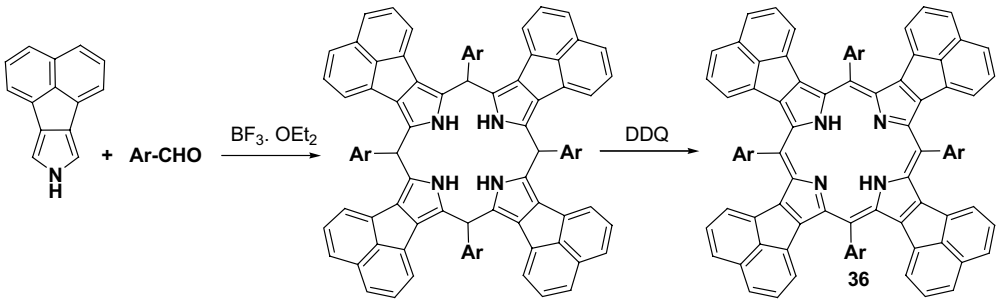


Scheme 26.25

shift, with an intense Soret-like absorption at 556 nm and Q-like bands at 638, 705, and 790 nm.

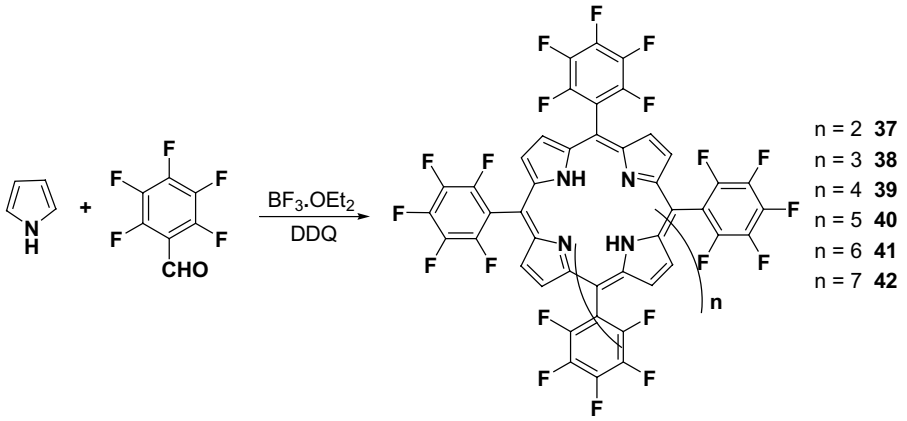
By incorporating chromophoric groups on the pyrrole ring or on *meso* carbons, the photophysical properties can be tuned to make the porphyrin absorb light of lower energies. A similar effect can be achieved by increasing the conjugation pathway to more than 18π electrons. This can be carried out by either adding more carbon bridges between the heterocyclic rings or by increasing the number of heterocyclic units in the porphyrin ring. Such molecules are known as expanded porphyrins. The concept of expanded porphyrins is directly linked to the serendipitous discovery of sapphyrin, a pentapyrrolic 22π system, by Woodward and coworkers [34] during their attempts to synthesize the naturally occurring corrin ring. Expanded porphyrins provide novel insights into extended conjugation and their effect on aromatic behavior in general. Several expanded porphyrins, from 22π to 96π systems, are known in the literature [8]. Further, they exhibit properties such as binding anions, cations and neutral guests, in some cases, which are unknown to porphyrins. Most of them are synthesized by similar methodologies employed for various porphyrin systems. A brief description based on common methods engaged in the synthesis of expanded porphyrins and their interesting structural features with specific examples is given below.

The one-pot synthesis discovered by Osuka and Furuta and coworkers [58] is the simplest way to generate expanded porphyrins, **37**–**42**, with five to ten pyrrolic units



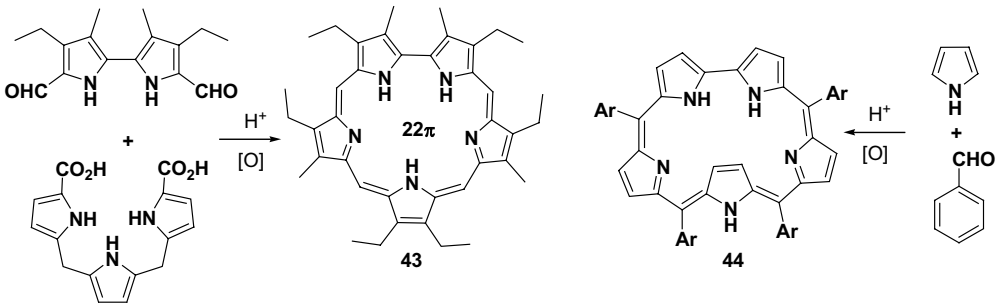
Scheme 26.26

(Scheme 26.27). They all exhibit different structural features, contrasting sharply with the parent porphyrin system (**3**). The macrocycles with seven or more pyrrole rings (**39**–**42**) were non-planar.



Scheme 26.27

The synthesis of expanded porphyrins with 22π and 26π electrons is well established and various isomers have been reported in the literature [59]. They can be classified as aza macrocycles and core-modified macrocycles. In the case of aza macrocycles, the porphyrinoid has only nitrogen in the core, while the core-modified macrocycles can have other chalcogens such as O, S, or Se, too, apart from carbon. They are exclusively synthesized by acid-catalyzed condensation of bi-heterocyclic or heterocyclic diols with appropriate precursors. Scheme 26.28 shows representative syntheses for various expanded porphyrins.



Scheme 26.28

Sapphyrin is the most studied 22π pentapyrrolic systems. The β substituted sapphyrin **43** and the *meso* phenyl sapphyrin [60] **44** are structurally different. In free base, **44**, the pyrrole ring opposite to bipyrrole is inverted and undergoes a ring inversion protonation. Hence all the nitrogens point towards the center of the

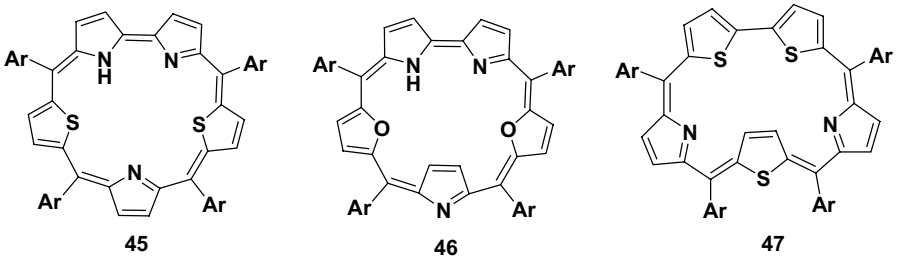
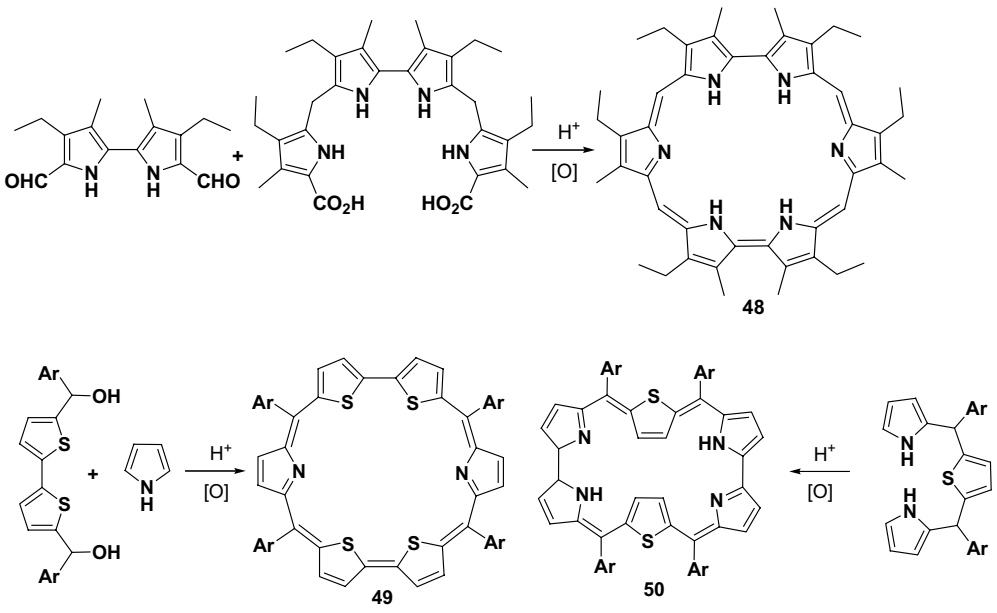


Figure 26.11 Core-modified sapphyrins.

macrocycle, as in **43**. A few core-modified sapphyrins [61] show ring inversions both in freebase and in protonated forms. Depending on the nature of the heteroatom, some macrocycles are planar and others exhibit inverted structures. For example, dithia-sapphyrin (**45**) is planar, while dioxa-(**46**) and trithia-(**47**) sapphyrins display inverted ring systems (Figure 26.11).

Rubyrins are 30π macrocycles with six heterocyclic rings and are aromatic in nature. Sessler and coworkers [62] reported the first example of a hexapyrrolic 26π rubyrin, **48**, by a [4 + 2] condensation of a tetrapyrrole and diformyl-bipyrrole under acidic conditions (Scheme 26.29).

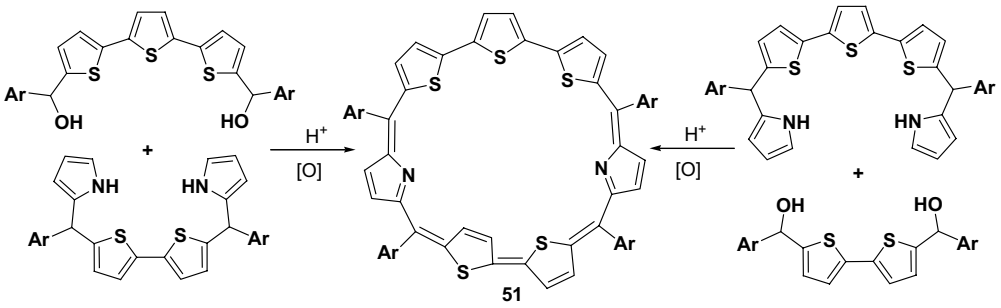


Scheme 26.29

Other kinds of hexapyrrolic systems are also known in the literature [8]. Rubyrins with non-pyrrolic rings show interesting structural diversity, in comparison to all-aza isomers. Our group has synthesized two different kinds of rubyrins, **49** and **50**,

having two or four non-pyrrolic rings [63] by an acid-catalyzed condensation of bithiophene diols with pyrrole or by oxidative coupling reactions of thia-tripyrranes. Even furan and selenophene derivatives of such macrocycles are synthesized under similar reaction conditions. They are 26π aromatic macrocycles and exhibit different structures depending on the nature and the number of heteroatoms present in the macrocycle.

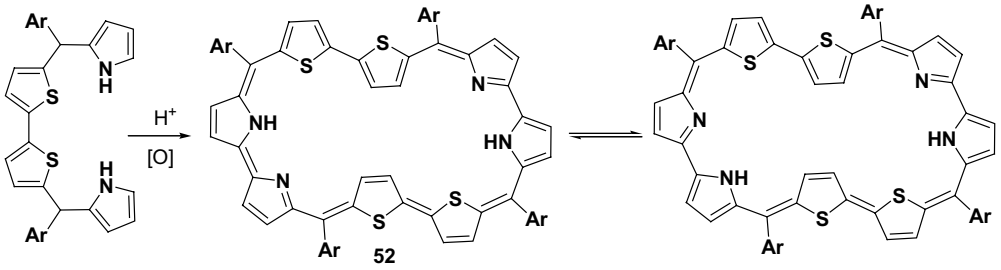
Further, aromatic 30π heptaphyrins have been synthesized by MacDonald-type [3 + 4] or [5 + 2] condensation of appropriate precursors [64]. Even though several seven-membered macrocycles are known, very few of them are aromatic. We have employed terthiophene diol or bithiophene diol with dithia-tetrapyrranes or trithia-pentapyrrane to obtain core-modified heptaphyrin **51** (Scheme 26.30). Analogous macrocycles with bifuran and biselenophene are also synthesized under similar reaction conditions.



Scheme 26.30

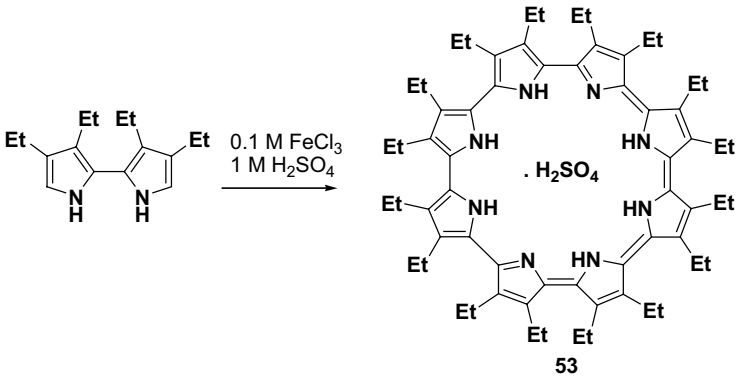
Octapyrrolic macrocycles are known as octaphyrins. Invariably porphyrinoids with seven or more heterocyclic rings undergo a twist and hence are non-planar. Sessler and coworkers were the first to identify such a twisted conformation for turcasarin, a decapyrrolic system. Subsequently, various research groups across the globe have reported various octapyrrolic macrocyclic systems that are non-planar. Their aromatic behavior is strongly dependent on the topology of the macrocycle. A $4n + 2\pi$ system was found to be non-aromatic in nature due to the non-planar geometry [65]. Only two macrocycles – **52** and **53** – stand out prominently for displaying a flat structure and aromatic characteristics. We have reported a series of flat core-modified 34π octaphyrins with thiophene, selenophene or furan, in which two heterocyclic rings are inverted [66]. The 34π tetrathiaoctaphyrin, **52**, is synthesized by the oxidative coupling of dithia-tetrapyrrane (Scheme 26.31) (cf. 26π dithia-rubyrin, **50**). To date, **52** and its analogues of furan and selenophene are the largest aromatic molecules to be characterized in the solid state.

Later, Sessler and coworkers reported a flat 30π octapyrrolic macrocycle, **53**, with no *meso*-carbon bridges between the heterocyclic rings [67]. β-Substituted bipyrrole



Scheme 26.31

can be coupled under acidic conditions to form the flat eight-membered macrocycle in over 70% yield (Scheme 26.32). Owing to the β-substitution, the pyrrole rings do not undergo ring inversion, thereby allowing all the nitrogens to face the center of the macrocycle. The cavity was found to bind a molecule of sulfuric acid upon protonation of **53**.



Scheme 26.32

Expanded porphyrins with more than eight rings generally show a figure-of-eight conformation. Figure 26.12 shows the structures for some of them (**54**–**56**). Setsune and coworkers have reported a one-pot synthesis for the largest expanded porphyrin to-date [37, 68]. It contains 24 pyrrole rings with a twisted conformation and accounts for 96π electrons. The 64π hexadecaphyrin **56** is the largest expanded porphyrin to be characterized in the solid state [37].

The synthetic methodologies described above do not give an exhaustive account of the synthesis of porphyrin isomers or expanded porphyrins. It is a glimpse of the current trend in heterocyclic chemistry, towards the generation of large macromolecules so far unknown in the literature. It paves the way to understanding the fundamental concept of aromaticity with respect to conjugation in giant macrocycles.

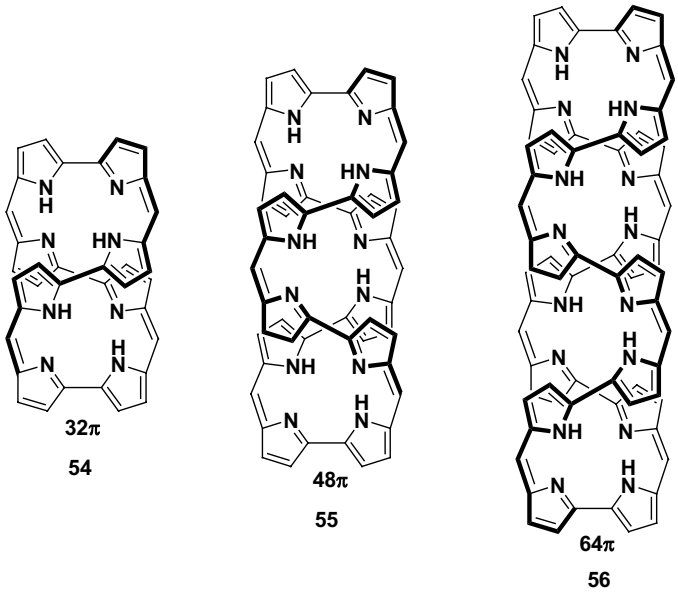


Figure 26.12 Expanded porphyrins showing a figure-of-eight structure.

26.3 Reactivity of Porphyrins

Porphyrins undergo series of electrophilic and nucleophilic reactions. One or two double bonds on the periphery can undergo addition reactions, without losing the aromaticity, to form chlorins (**57**), bacteriochlorins (**58**) and isobacteriochlorins (**59**) (Figure 26.13). The electrophilic aromatic substitutions can occur either at the four *meso* or the eight β-pyrrolic positions with concomitant loss of a proton. In some cases, the substitution occurs by an alternative mechanism such as addition followed by elimination, or via oxidation with formation of intermediate π-cation radicals.

Porphyrins readily form complexes with various metals. The central metal ions have an inductive effect with the π-electron of the macrocycles, which greatly influences the chemical reactivity and biological functions. Metalloporphyrins containing electrophilic metals such as Fe(III) and Sn(IV) favor substitution at

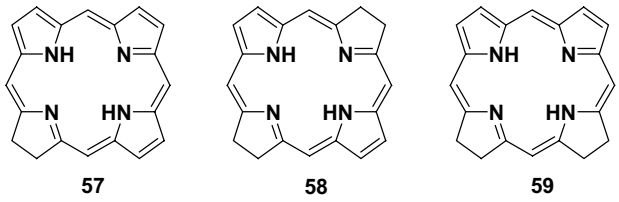


Figure 26.13 Examples of partially saturated porphyrins.

the β-pyrrolic positions, while divalent metals such as Mg, Zn, Ni, Cu, and Pd tend to facilitate substitution at the *meso* positions. Most of the electrophilic substitutions occur in the presence of divalent metal complexes since these are more stable to electrophilic attack. Steric effects are also an important consideration for electrophilic substitution, especially if bulky electrophiles are involved in the reaction, in which case substitution occurs at the β-positions. In contrast, directive effects, which are the combination of both steric and electronic effects of the substituents, affect the electron distribution of the macrocycle. For example, diformylation of metallo-octaalkyl porphyrin furnishes 5,10- and 5,15-regioisomers, whereas the 5-nitro and/or 5-halo derivatives of octaalkyl porphyrins favor the formation of 5,15-disubstituted products rather than the 5,10-disubstituted regioisomers.

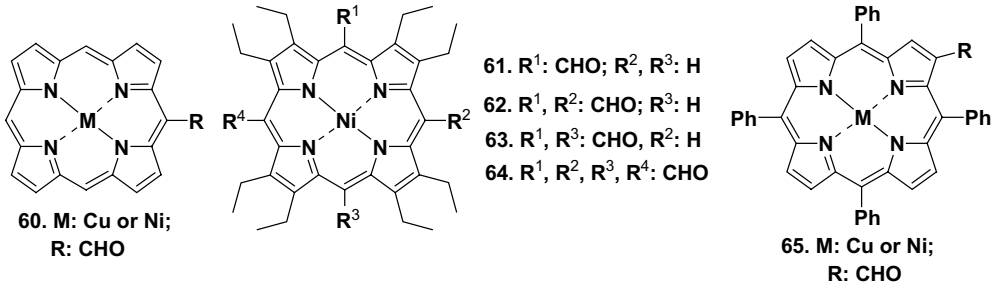
Here, we describe a series of electrophilic substitution reactions, such as formylation, halogenation, nitration, acylation and cyanation reactions. The first two are the most widely studied reactions and have been used as potential starting materials for many derivatives. Finally, we discuss nucleophilic substitution reactions. This is often the chosen methodology for direct functionalization of readily oxidizable macrocycles.

26.3.1 Electrophilic Reactions

26.3.1.1 Formylation

A formyl group was first introduced in the *meso* position of the metallo β-substituted porphyrin by Inhoffen and his group, affording high yields of corresponding formylated products [69]. The formylation reactions generally utilize DMF/$POCl_3$ to produce the reactive Vilsmeier complex, which undergoes basic hydrolysis of the iminium salt intermediate, by using NaOH or Na_2CO_3 or NaOAc. As the free base porphyrin (**1**) was easily protonated under acidic conditions, metallated complexes, such as with Cu(II), were used for the formylation reactions. The Cu(II) complexes of **1** were treated with one equivalent of Vilsmeier reagent to form *meso*-substituted 5-formylporphyrin (**60**) in excellent yield, suggesting the higher reactivity of the *meso*-positions [70].

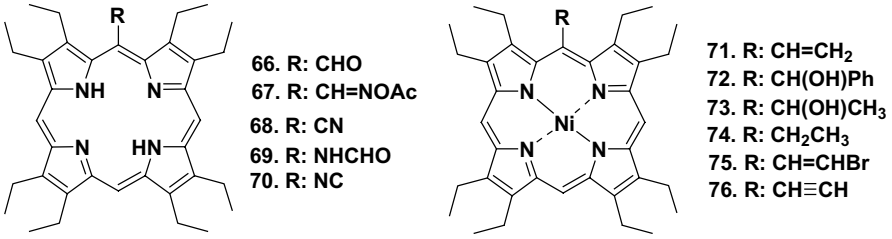
The Ni(II) and Cu(II) complexes of metallo-β-octa substituted porphyrins, under Vilsmeier reaction conditions, afford the corresponding metallo-5-formyl derivatives (**61**), while increasing the Vilsmeier reagents to two equivalents gives the metallo-*meso*-5,10- and metallo-5,15-formylated regioisomers (**62**, **63**) in good yield (Scheme 26.33). All four *meso*-positions are formylated (**64**) by prolonged treatment with excess Vilsmeier reagent [71]. The Cu(II) complex usually gives higher yields than the corresponding Ni(II) derivatives. The electron-rich Mg(II) and Zn(II) complexes are easily demetallated under Vilsmeier conditions, while trivalent complexes such as Mn(III) and Fe(III) are less reactive towards electrophilic formylation reactions, affording lower yields of the formylated products. In contrast, metallo-*meso*-tetra-aryl porphyrins under Vilsmeier conditions form the 2-formyl derivative (**65**) in good yield [72].



Scheme 26.33

26.3.1.2 Reactions of Formyl Porphyrins

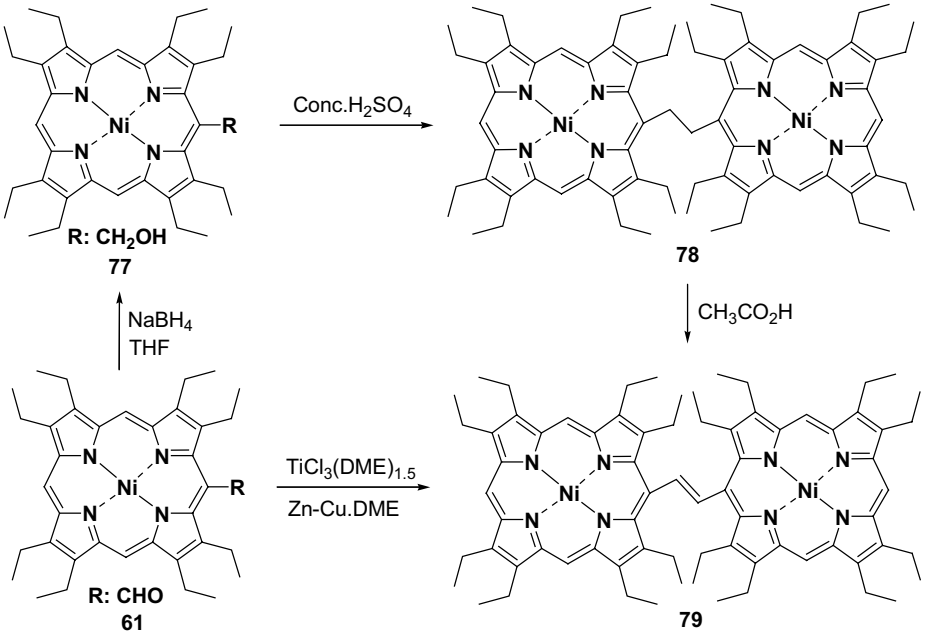
The metal-free 5-formylporphyrin (**66**) can be easily converted into a wide variety of functional groups (Scheme 26.34). For example, **66** gives predominantly the oxime acetate (**67**), which on heating with acetic anhydride forms the 5-cyano (**68**) and 5-formamido (**69**) derivatives [73]. Dehydration of **68**, in the presence of phosgene and base or in refluxing acetic anhydride, affords isocyanoporphyrin (**70**).



Scheme 26.34

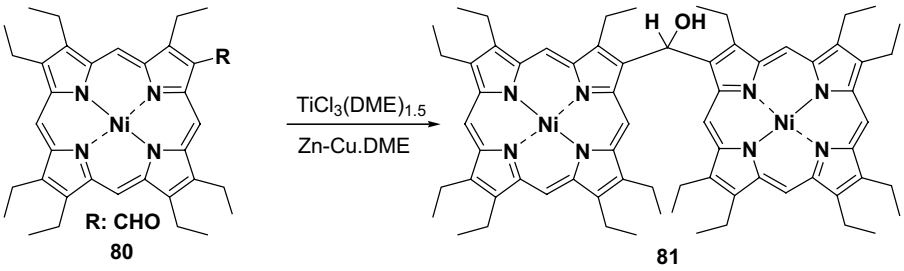
The metallo-vinyl porphyrins (**71**) are easily obtained by the Wittig reaction, by using $Ph_3P{=}CH_2$ and metallo-formyl porphyrins (**61**) [74]. Compound **61** further reacts with Grignard and aryllithium reagents to produce the corresponding alcohol derivatives, such as phenyl hydroxy methyl (**72**) or methyl hydroxy methyl (**73**) derivative [75]. Dehydration of **73** in the presence of *p*-TSA gives the vinylporphyrin (**71**), which is further converted into the ethyl derivative (**74**) by catalytic hydrogenation. Selective bromination of **71**, using pyridinium hydrobromide, gives a mixture of *trans*- (major) and *cis*-2-bromovinyl derivatives (**75**), which undergo dehydrobromination, by using sodium hydride in refluxing 1,2-dimethoxyethane, to form the ethynyl compound (**76**) [75].

Reduction of **61** with $NaBH_4$ gives the corresponding hydroxy-methyl derivatives (**77**), whereas reduction with $NaBH_4$ in acetic acid directly affords to *meso*-methyl derivatives (Scheme 26.35) [76]. In the presence of conc. H_2SO_4, **77** dimerizes to produce a dimer linked by a CH_2-CH_2 bridge (**78**), which on further heating with acetic acid yields the *trans*-ethylene-bonded porphyrin dimer (**79**) [77]. A similar dimer was also obtained by treating **61** with an excess of $TiCl_3(DME)_{1.5}$ in the



Scheme 26.35

presence of a Zn-Cu couple. Apart from the trans-dimer, the kinetically stable cis-dimer was also formed, which was further converted into the thermodynamically stable trans-dimer by heating or irradiation [78]. Under similar reaction conditions, Ni(II)formylheptaethylporphyrin (**80**) produced a hydroxymethylene-bridged dimer (**81**) by loss of one of the formyl groups (Scheme 26.36) [78].



Scheme 26.36

26.3.1.3 **Halogenation**

Porphyrins can undergo a series of halogenation reactions, such as fluorination, chlorination, bromination and iodination; the latter is less favored due to steric and electronic factors. The site of the halogenation is determined by the size and reactivity of the halogen.

Figure 26.14 Examples of fluorinated porphyrins.

26.3.1.3.1 **Fluorination** The electrophilic fluorination of **2** using caesium fluoroxysulfate in dioxane gives a mixture of mono-, di-, tri- and tetra-fluorinated (**82–85**, Figure 26.14) compounds [79]. Better yields of fluorinated **2** were obtained by using an excess of N-fluoropyridinium triflates in hexafluorobenzene [80]. In the presence of a metal fluoride (CoF_2 or AgF_2), under an inert atmosphere, a refluxing solution of the Zn(II) complex of *meso*-tetra-aryl porphyrin in $CHCl_3$ affords the octafluorinated derivative **86** [81].

26.3.1.3.2 **Chlorination** Chlorination of **2** with HCl/H_2O_2 in aqueous THF affords the 5-mono- (**87**) and 5,15-dichloro products (**88**), while the *meso*-tri (**89**) and *meso*-tetra chlorinated products (**90**) have been obtained by using HCl/H_2O_2 in acetic acid (Figure 26.15) [82]. In the presence of *N*-chlorosuccinimide (NCS) and AIBN, only the 5- and 5,15-dichlorinated products (**87, 88**) were produced [83]. Metallated derivatives [Ni(II) or Cu(II) complex] of **2** react with PhSeCl or $PhSeCl_3$ in $CHCl_3$ to form *meso*-mono-, di-, tri- and tetra-chlorinated products (**91–94**) [84]. Octa-chlorination and octa-bromination of *meso*-tetraarylporphyrins are achieved by refluxing solution of metalloporphyrin [Ni(II) or Cu(II)] in CH_3OH or CCl_4, in the presence of an excess NCS and NBS (**95**) [85]. Similarly, mono-chlorination and -bromination has been

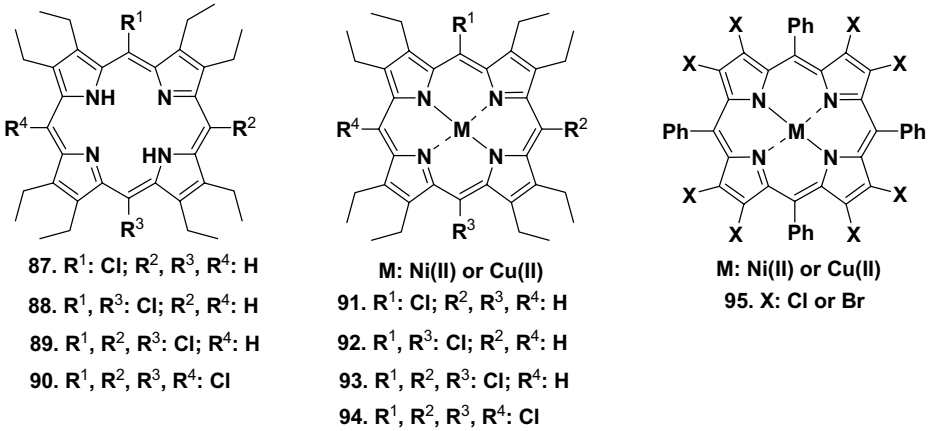
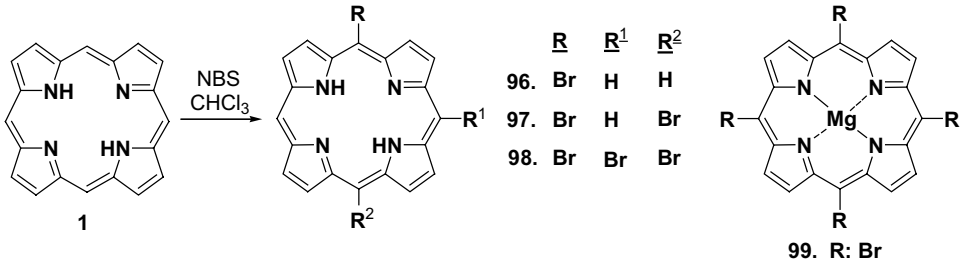


Figure 26.15 Examples of chlorinated porphyrins.

achieved by using one equivalent of NCS or NBS, although dihalogenated products are also formed in lesser yield. Furthermore, chlorine gas in the presence of $FeCl_3$ or bromine in CH_3OH, $CHCl_3$ or in a 1: 1 $CHCl_3$–CCl_4 mixture have also been used for the chlorination or bromination of *meso*-tetra-aryl-metallo-porphyrins. Under these conditions, halogenation mainly occurs at the β-position [85].

26.3.1.3.3 **Bromination** Lango and coworkers have discussed the bromination of free-base porphyrin (**1**), where **1** was brominated predominantly at the *meso* positions in the presence of NBS in $CHCl_3$, or pyridinium bromide perbromide, or bromine in $CHCl_3$ or acetic acid, to give the 5-mono- (**96**), 5,15-di- (**97**), and 5,10,15-tribromo-porphyrins (**98**), respectively (Scheme 26.37) [86]. In contrast, the Mg(II) complex of **1** affords the *meso*-tetrabromoporphyrin (**99**) in the presence of an excess of *N*-bromoacetamide [70].



Scheme 26.37

Meso-bromination of **2** does not occur, due to overcrowding at the pyrrolic β-positions [87], while the metallated-OEP [Cu(II) or Ni(II)] complexes react with PhSeBr or $PhSeBr_3$ in $CHCl_3$ to form the *meso*-mono bromo derivative (**100**) as a major yield [84]. 5,15-Diphenylporphyrin, in contrast, when treated with two equivalents of NBS in $CHCl_3$, furnishes the *meso*-tetra-substituted porphyrin (**101**) (Figure 26.16) [70].

26.3.1.3.4 **Iodination** Iodination of **2** has not been reported, due to the size of the atom to be introduced at the sterically crowded *meso*-positions. However,

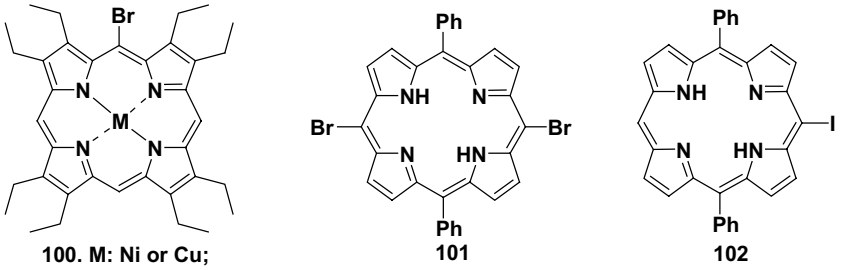


Figure 26.16 Examples of brominated and iodinated porphyrins.

5,15-diphenylporphyrin reacts with bis(trifluoroacetoxy)iodobenzene–iodine to form the mono iodo derivative (**102**), while the diiodo porphyrin was also formed, where the second iodo group occupies the β-position instead of the readily available other *meso*-positions [88].

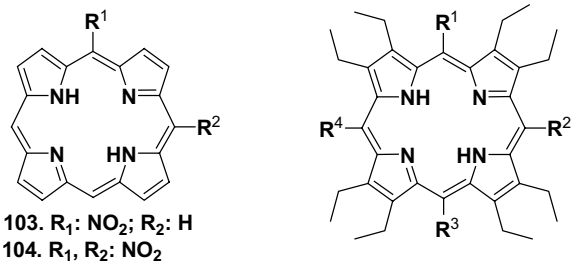
Metallobromoporphyrins undergo nucleophilic substitution reactions with CuCN in quinoline and with thiolate ions to form the corresponding metallo-cyanoporphyrins and thiol-substituted macrocycles [89]. Metallated mono-bromo and mono-iodo porphyrins also undergo a Pd-catalyzed Heck-type reaction with various terminally substituted acetylenic derivatives [89, 90]. With aryl- and alkyl-boronic acids, the β-bromo tetra-aryl porphyrins undergo a Suzuki cross-coupling reaction to form the β-substituted aryl or alkyl derivatives [91]. This is the most suitable method for the synthesis of β-octasubstituted tetra-aryl porphyrins.

26.3.1.4 **Nitration**

Electrophilic nitration can be achieved with a mixture of nitric acid in acetic or sulfuric acid, $PhSeNO_2$ in THF or with nitrate salts in acetic anhydride. Like halogenation reactions, nitration also occurs in the 5,15-positions of the H_2(OEP) derivatives.

In the presence of nitric acid in sulfuric acid, porphyrin (**1**) is exclusively nitrated at the *meso* positions to form, predominantly, the *meso*-5-nitro (**103**) and 5,10-dinitro derivatives (**104**), instead of the *meso*-5,15-dinitro derivatives [92]. The m*eso*-mono-nitro derivative of **2** is formed by using nitric acid in acetic acid (**105**), whereas *meso*-di (**106**, **107**), and tri- (**108**) derivatives are formed by using nitric acid in sulfuric acid at 0 °C. The *meso*-di-substituted products (both **106** and **107**) are formed roughly in 1: 1 ratio (Figure 26.17). The m*eso*-tetra-substituted product (**109**) is not formed under this methodology [93]. Extensive nitration of **2** is achieved by using $Zn(NO_3)_2$ in acetic anhydride, affording the Zn(II) complexes of 5-mono, 5,15-di, 5,10,15-tri and 5,10,15,20-tetra-*meso*-nitrated derivatives. Under these reaction conditions, 5,15-disubstituted products are formed predominantly as compared to the 5,10-disubstituted derivative [94].

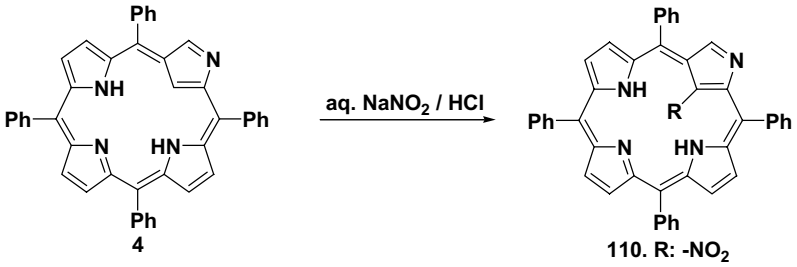
The room temperature reaction of *meso*-aryl-N-confused porphyrin **4**, in contrast, with aqueous $NaNO_2$/HCl or with aqueous 30 wt% nitric acid without sulfuric acid affords the inner C-nitrated derivative of **4** in moderate to excellent yields (**110**, Scheme 26.38) [95].



103. R_1: NO_2; R_2: H
104. R_1, R_2: NO_2

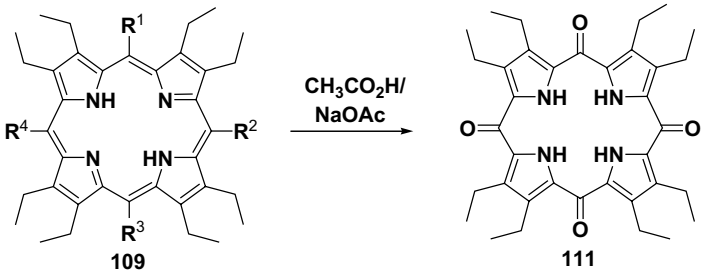
105. R^1: NO_2; R^2, R^3, R^4: H
106. R^1, R^2: NO_2; R^3, R^4: H
107. R^1, R^3: NO_2; R^2, R^4: H
108. R^1, R^2, R^3: NO_2; R^4: H
109. R^1, R^2, R^3, R^4: NO_2

Figure 26.17 Nitro derivatives of porphyrins.



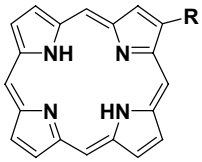
Scheme 26.38

Meso-tetra-nitro substituted H_2(OEP) (**109**, $R = NO_2$) undergoes aromatic nucleophilic substitution reactions with HCl and HBr, where the nitro groups are replaced by the respective halide ions. Under bromide reaction conditions, a side reaction was also observed that furnishes a lesser amount octaethylxanthoporphyrinogen (**111**). The yield can be improved by treating **109** with acetic acid in sodium acetate or with acetic acid in sulfuric acid (Scheme 26.39) [96].



Scheme 26.39

The 2-nitro substituted *meso*-tetra-aryl porphyrin undergoes reduction with tin (II)chloride in conc. HCl [93] or with $NaBH_4$ and 10% Pd-C in methanol [97] to afford the corresponding amino derivative, which can be further functionalized. For example, with sodium nitrite in the presence of acid the corresponding diazonium salts are formed [98] that react with aldehydes to afford the corresponding Schiff base complexes [99]; in addition, they react with acetic anhydride and pyridine to produce the respective acylated derivatives [93]. In contrast, metallated 2-nitro-*meso*-tetraphenyl porphyrin undergoes reduction with $NaBH_4$ to form the nitrochlorins, which further react with tributyltin hydride in the presence of AIBN to afford denitrated chlorins or are converted into porphyrins upon heating on silica [100]. In addition, metallated derivatives react with Grignard and organolithium reagents, yielding β-alkyl-tetraaryl porphyrins [101], and with α-isocyanoacetic esters, malonates and malononitriles in the presence of base to form β-fused pyrroloporphyrins, cyclopropanochlorins and functionalized *trans*-chlorins [102].



112. R: $COCH_3$
113. R: $CH(OH)CH_3$
114. R: $CH=CH_2$

Figure 26.18 Products derived from the acylation of **1**.

26.3.1.5 **Acylation**

Friedel–Crafts acylation of **2** is usually unreactive due to the presence of two ethyl groups near the *meso* positions. The Ni(II) and Cu(II) complexes of unsubstituted β-pyrrolic porphyrins are normally used for the electrophilic acylation reactions, to form the 2-acylated derivative (**112**), while the Fe(III) and V(II) complexes also undergo Friedel–Crafts acylation in the presence of stonger Lewis acids.

The peripheral acetyl derivative **112** undergoes reduction reaction with $NaBH_4$ to form the 2-methyl hydroxy methyl derivative (**113**), which further reacts with *p*-TSA in 1,2-dichlorobenzene, or with DMF and benzoyl chloride, to afford the corresponding vinylporphyrins (**114**) (Figure 26.18) [103].

26.3.1.6 **Cyanation**

The electrophilic cyanation of metalloporphyrins is accomplished by Friedel–Crafts cyanation – boiling under reflux the metalloporphyrin in a $CHCl_3$ solution of cyanogen bromide and $AlCl_3$ or $SnCl_4$ results in moderate yields after demetallation [104]. More practical methods of cyanation reactions have been introduced. Some of them are: (i) Vilsmeier formylation, converted into oxime, followed by dehydration, (ii) nucleophilic displacement of bromoporphyrins, and (iii) reaction of cyanide ion with metalloporphyrin π-cation radicals.

26.3.2
Nucleophilic Reactions

26.3.2.1 **Reactions of π-Cation Radicals**

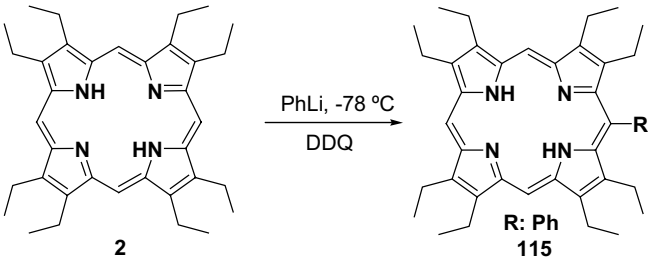
The π-cation radicals of the metalloporphyrins, particularly **2,** are usually formed by various oxidizing agents such as iodine, thallium(III) nitrate, tris(*p*-bromophenyl)ammonium hexachloroanitimonate (TBAH) and *N*-chlorobenzotriazole, which are stable in methanolic solution but do react with various nucleophiles such as cyanide, thiocyanate, chloride, imidazole, acetate, azide, pyridine and triphenylphosphine to produce the corresponding *meso*-substituted macrocycles [105]. For example, the Mg(II), Zn(II) and Co(II) complexes of **2** react with N_2O_4 in CH_2Cl_2 to produce the corresponding *meso*-nitro derivatives in good yield [106].

The Zn(II) complex of **3** is oxidized into its π-cation radical by using iodine/silver perchlorate or dibenzodioxin/sodium dichromate and, analogously, reacts with nitrite ion to form the β-substituted [107] as well as the *meso*-substituted ring-opened

products [106]. Selective *meso*-nitration of 5,15-diphenylporphyrin is accomplished by using the same methodology [108].

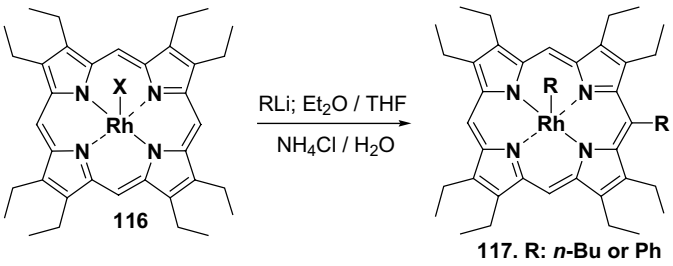
26.3.2.2 Substitution Reactions. Reactions with H_2(OEP)

H_2(OEP) (**2**) and several of its metal complexes undergo nucleophilic substitution reactions by using alkyl- and aryl-lithium reagents at low temperatures, to form the corresponding *meso*-substituted alkyl or aryl porphyrins (**115**) by oxidation via porphodimethene intermediates (Scheme 26.40). By using this methodology, mono-, di-, tri- and tetra-*meso*-substituted H_2(OEP) can be obtained [109].



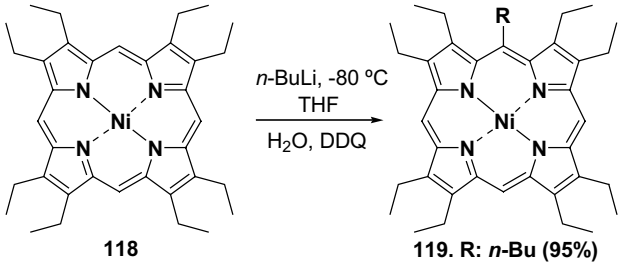
Scheme 26.40

Nucleophilic attack of organolithium reagents with Rh(III)-OEP (**116**) occurs in two stages: initially at the Rh atom and subsequently at the *meso*-position via the Rh(III)phlorin complex, which undergoes further oxidation to form the corresponding *meso*-substituted product (**117**, Scheme 26.41) [110].



Scheme 26.41

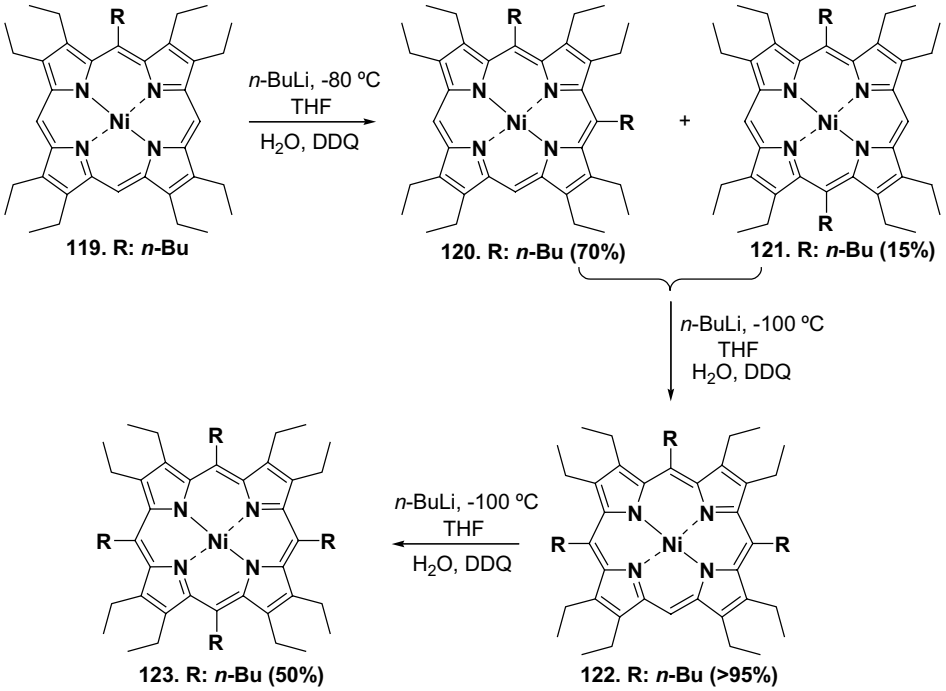
Most detailed studies on Ni(II)-OEP (**118**) with *n*-BuLi showed that the porphyrin had undergone a *meso*-alkylation reaction (**119**) (Scheme 26.42) [109]. Comparative investigations with other metal complexes such as Zn(II), Co(II), and Cu(II) also showed similar results, with the yield ranging from 40% to 90%, while a similar reaction was not successful with the Fe(II) complex due to degradation of the porphyrin unit. The reaction was further extended to various organolithium reagents, including those yielding porphyrins suitable for subsequent chemical transformations and C–C coupling reactions [111]. Except for *t*-BuLi, the organolithium reagents



Scheme 26.42

gave good to excellent yields. In contrast, Ni(II)-OEP gives a lower yield with aryllithium reagents than with alkyllithium reagents, while the reaction of free-base porphyrins with aryllithium reagents afford better yields. Thus, alkyllithium reagents with metalloporphyrin give higher yields, while the aryllithium reagents with free-base porphyrin afford better yields.

Under similar reaction conditions, *meso*-mono-alkyl metalloporphyrin **119** forms the *meso*-di-5,10- (**120**) and -5,15-dialkyl (**121**) derivatives, with **120** as the predominant product (Scheme 26.43) [109, 111]. Both **120** and **121** further react with *n*-BuLi at −100 °C to afford the *meso*-tri-substituted derivative (**122**), which under similar reaction conditions forms the *meso*-tetra-substituted product (**123**) in 50% yield.

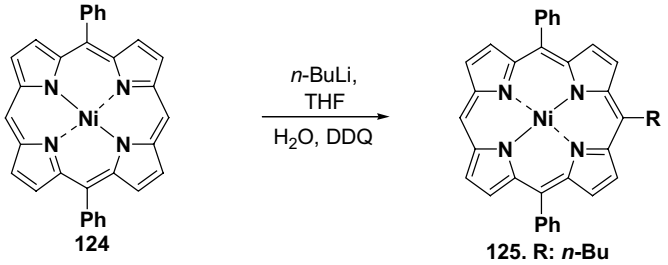


Scheme 26.43

As expected, gradual introduction of *meso*-butyl residues led to a bathochromic shift of the absorption bands, suggesting an increase in macrocyclic distortion [112]. Using this methodology, various *meso*-aryl and -alkyl residues of dodecasubstituted derivatives have been synthesized with over all yields of 20–40% [113].

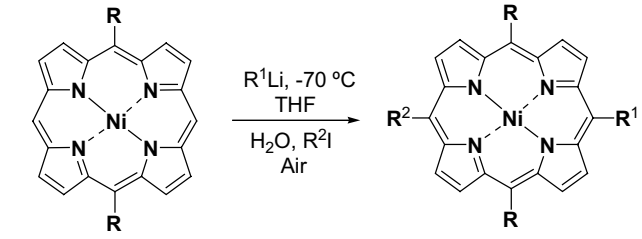
26.3.2.3 Reactions with 5,15-Disubstituted Porphyrins

Krattinger and Callot have reported that the reaction of *meso*-tetra-aryl porphyrin with *n*-BuLi and *t*-BuLi leads to both the *meso*- and β-alkylated products [114]. Unlike *meso*-tetra-aryl porphyrin, *meso*-5,15-diaryl metallated porphyrins (**124**), in the presence of a linear alkyllithium, afforded the A_2B type porphyrins (*meso*-tri-substituted products) (**125**) in good to excellent yields, showing complete regioselectivity towards the *meso*-position (Scheme 26.44) [115].



Scheme 26.44

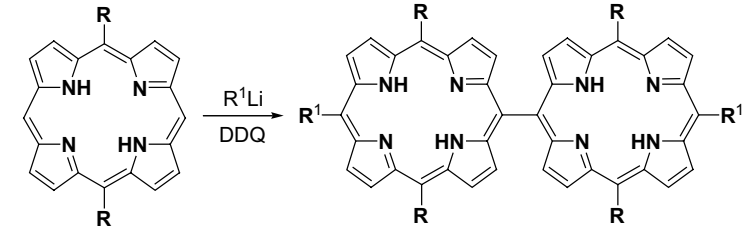
Treatment of *meso*-5,15-diaryl- (**124**) and dialkyl-metallated (**126**) porphyrins with *n*-alkyl or aryl-lithium, under similar reaction conditions, followed by hydrolysis of excess RLi and addition of alkyl iodides gives A_2BC (**127–130**) type porphyrins in good to excellent yield (Scheme 26.45). This simple two-step, one-pot reaction is suitable for the synthesis of three different *meso*-substituted porphyrins [116].



	R	R^1	R^2	Yield
127.	Ph	*n*-Bu	*n*-Bu	92%
128.	Ph	Ph	*n*-Bu	90%
129.	Ph	*n*-Bu	$(CH_2)_4I$	79%
130.	Ph	Ph	$(CH_2)_4I$	71%

Scheme 26.45

In contrast, *meso*-5,15-dialkyl- (**131**) and diaryl- (**132**) substituted free-base porphyrins – under similar reaction conditions as mentioned above, but omitting the final hydrolysis step – afforded the *meso-meso* linked bisporphyrins in good yields (**133, 134**) (Scheme 26.46) [117]. The dimerization proceeds via oxidation of the initial



	R	R^1	Yield
133.	Ph	*n*-Bu	75%
134.	Ph	Ph	79%
135.	*n*-Bu	Ph	55%

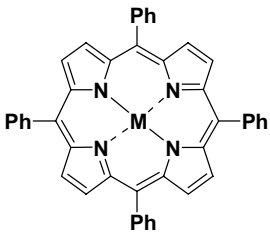
131. R: *n*-Bu; 132. R: Ph

Scheme 26.46

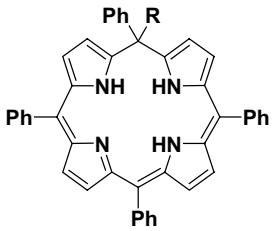
intermediate of the π-stabilized radical, followed by radical dimerization. Apart from the bisporphyrins, *meso*-5,10,15-tri-substituted and *meso*-5,10,15,20-tetra-substituted porphyrins are also formed. Under similar reaction conditions, the Ni complex of **124** and **126** afforded only *meso*-substituted products, instead of the bis-porphyrin derivatives. This method gives convenient access to bisporphyrins with mixed substituents by using simple starting materials and complements Ag(I)-promoted coupling of Zn(II) porphyrins, which is a facile method for the synthesis of unsubstituted bis- and oligoporphyrins [118].

26.3.2.4 Reactions with H_2TPP

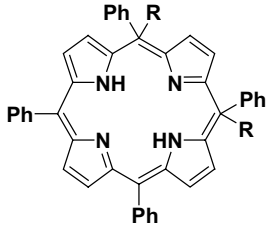
In 1996, Callot reported the nucleophilic substitution reaction of the Co(III) complex of *meso*-tetra-aryl porphyrins (**136**) [119]. In the presence of *n*-BuLi at



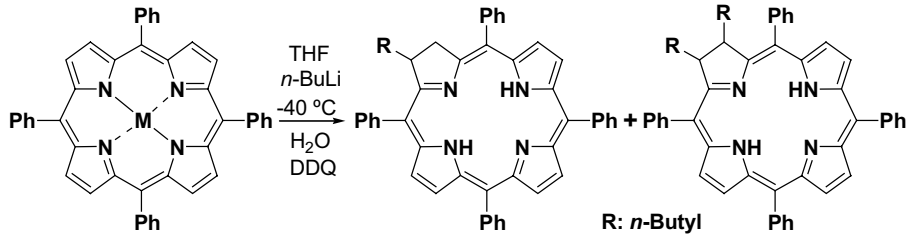
136. Co(III)Ar; 3. 2H
137. Zn(II)



138. R: *n*-Butyl



141. R: *t*-Bu

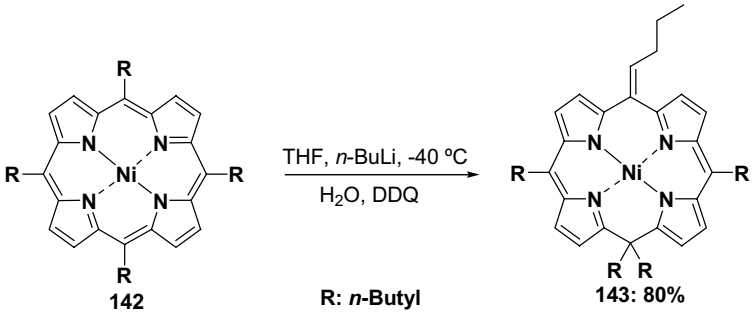


137: Zn(II) 139 R: *n*-Butyl 140

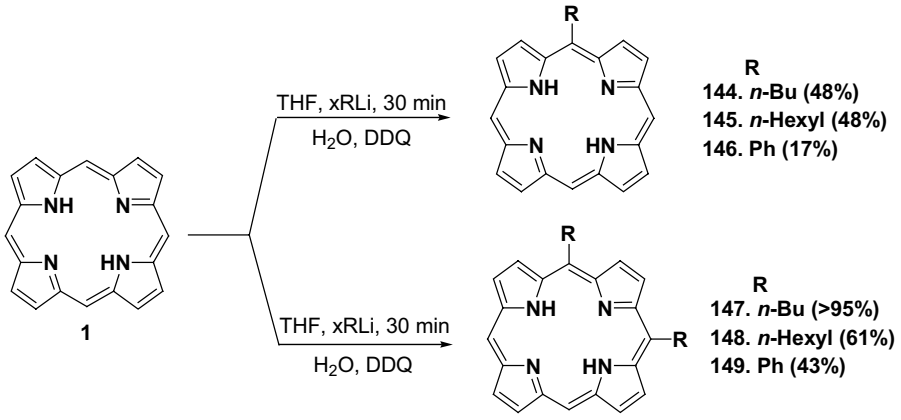
Scheme 26.47

0 °C, apart from the axial ligand exchanging product he observed numerous other products, such as mono-, di- and tri-β-butylated porphyrins and chlorins, with <3% yield [120]. Reaction of the free-base H_2TPP (**3**), under similar reaction conditions, forms phlorin **138** (28% yield) and chlorin **139** (18%) [114, 120], while the Zn(II) complex (**137**) gives mono- (**139**) and di-butylated chlorin (**140**) (Scheme 26.47) [109, 111]. The use of *s*-BuLi, instead of *n*-BuLi, leads to similar chlorins, among other products, while the more hindered *t*-BuLi produces a mixture of β-alkylated chlorins and 5,10-di-*tert*-butylated porphyrins (**141**) in <5% yield [121]. Thus, H_2TPP and other *meso*-aryl porphyrins can undergo both *meso*- and β-addition reactions.

In contrast to metal-free *meso*-tetra-aryl porphyrins, the Ni(II) **142** reacts with *n*-BuLi to form in quantitative yield the porphodimethene, which is further oxidized at the *meso*- and *ipso*- positions to produce the novel 5,5′-didehydroporphodimethenes (**143**) with an exocyclic double bond (Scheme 26.48) [109, 111]. Depending on the steric bulk of the *meso*-alkyl substituents, the macrocycle



Scheme 26.48



Scheme 26.49

conformation varies from planar to highly ruffled [122]. Similar results are observed, with porphyrins bearing *iso*-butyl, 1-ethylpropyl or *tert*-butyl residues. Thus, *meso*-alkyl porphyrins react with sterically unhindered organolithium reagents to form exclusively the *meso*-substituted product. This is a further indication of the higher reactivity of the *meso*-position toward nucleophilic attack.

26.3.2.5 **Reactions with Porphine**

Porphine (**1**) reacts with *n*-alkyl or aryl-lithium reagents to form 5-monosubstituted (**144–146**) and 5,10-disubstituted porphyrins (**147–149**) in low to excellent yields, depending on the number of equivalents of RLi used in the reaction (Scheme 26.49) [123].

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27
New Materials Derived From Heterocyclic Systems

Javier Santamaría and José L. García- Álvarez

27.1
Introduction

The understanding and applicability of the properties exhibited by natural and synthetic compounds has long been an important target for the chemical community. Heterocycles, due to their special structure, have contributed greatly to this purpose.

In this sense, this chapter briefly summarizes the different properties induced, enhanced or simply modified by the participation of heterocyclic systems in a material. Some of them have fulfilled important gaps in terms of applicability and are now in common use in modern society.

27.2
Color and Fluorescent Agents

27.2.1
Heterocyclic Pigments and Industrial Applications

There are numerous natural pigments, as expressed by the wide range of colors we can find in nature [1]. In the vast majority, the presence of organic compounds with one or more heterocycles in the skeleton is largely responsible for their colorful properties. Remarkable examples are the red iron complex heme (**1**) in hemoglobin and the green chlorophyll (**2**), a magnesium complex present in green plants. Both these compounds belong to the porphyrin family (Figure 27.1) [2].

Another family of heterocycles usually present in a large variety of plants and involved in their color is the flavonoids, which contain a benzopyran skeleton. Figure 27.2 shows the structure of flavone (**3**) and its derivative flavonol (**4**). These natural products are compounds with almost no light absorption in the visible region but are responsible for the white color of the splendid spring postcards of flowered apple and cherry trees [3].

Among the flavonoids with intense color are anthocyanidin derivatives. Several examples of anthocyanidins are present in nature such as the brilliant red

Modern Heterocyclic Chemistry, First Edition.
Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.

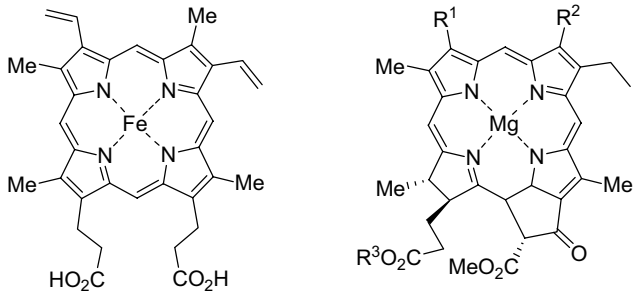


Figure 27.1 Structures of the porphyrins heme (**1**) and chlorophyll (**2**).

pelargonidin (**5**), responsible for the color of geranium petals [4], and the crimson cyanidin (**6**) found in apples [5] and raspberries [6]. Other examples are blue to dark purple delphinidin (**7**), which colorizes some types of grapes [7], and dark purple malvidin (**8**) as the main pigment of red wines (Figure 27.3) [8]. A combination of different anthocyanidins results in a wide range of colors in flowers such as tulips [9].

Other natural pigments, not belonging to the flavonoid family, are pterins. These are present in some insects, such as butterflies, as part of the coloration of their wings. Figure 27.4 shows the structures of yellow xanthopterin (**9**) (2-amino-1,5-dihydro-4,6-pteridinedione) and white leucopterin (**10**) (7-hydroxyxanthopterin) the two first pteridine pigments isolated and characterized from butterfly wings [10]. Other pterin pigments are 7-methylxanthopterin, a yellow pigment known as chrysopterin (**11**), and red erythropterin (**12**) [11].

Humanity has taken advantage of the presence of pigments in nature, from paints in prehistoric caves to the modern ages. Nowadays it is difficult to imagine life without the use of pigments. Notable examples of famous pigments extracted from nature, and slightly modified for use as a dye, are the indole derivatives indigo (**13**) [12] (blue) and its derivative tyrian purple (**14**) [13] (Figure 27.5).

However, extracting pigments from nature suffers from a major inconvenience: the usually very low availability of some of them. In some cases, a very large amount of plants or animal parts need to be processed to obtain just a few milligrams. This is why cloth dyed with a particular pigment was originally considered as a symbol of power. Tyrian purple **14** (also known as Royal purple), discovered by the

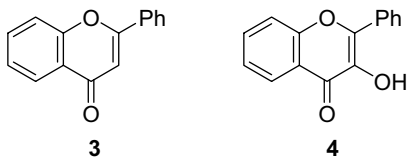


Figure 27.2 Flavone (**3**) and flavonol (**4**).

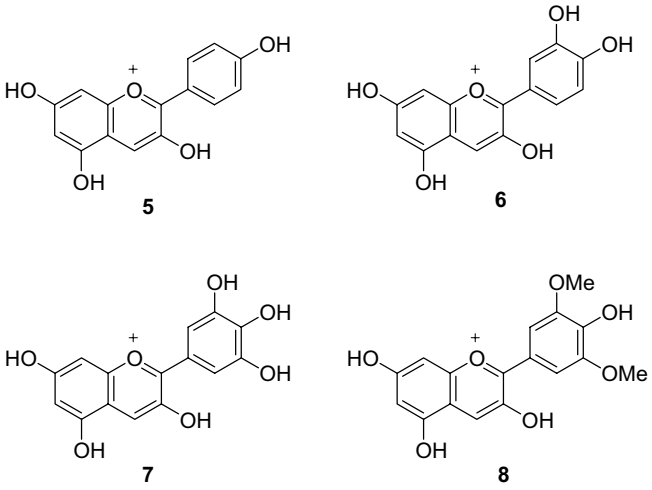


Figure 27.3 Examples of pigments belonging to the anthocyanidin family.

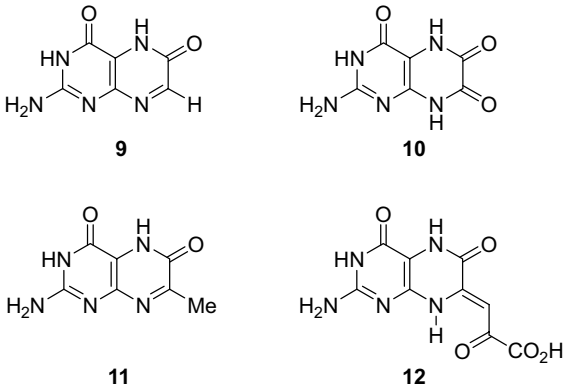


Figure 27.4 Examples of pigments belonging to the pterin family.

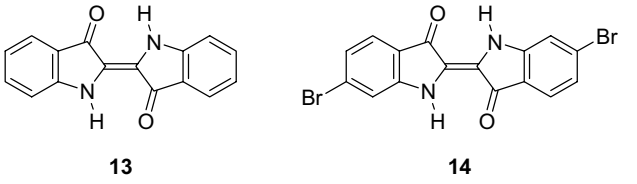
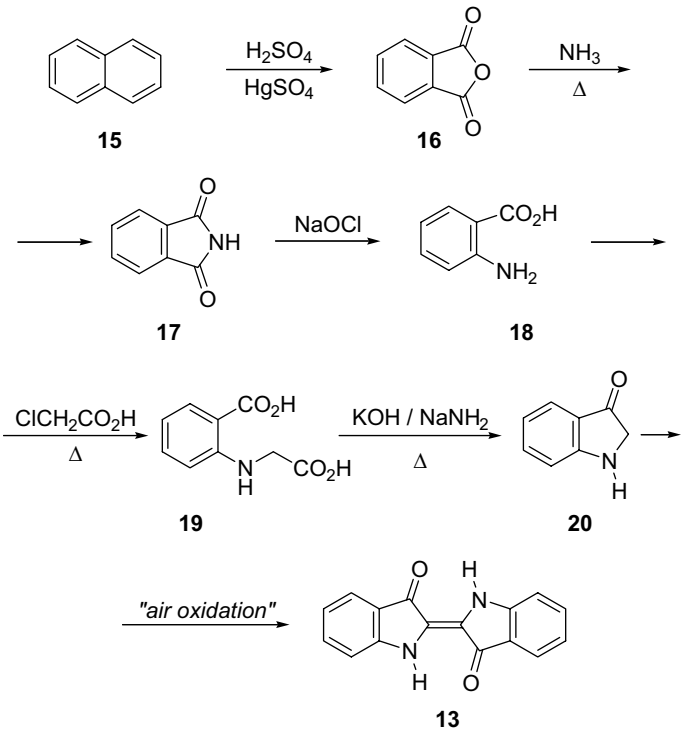


Figure 27.5 Structures of indigo (**13**) and tyrian purple (**14**) (6,6′-dibromoindigo).

Phoenicians [14], is perhaps the most representative example of this, as it was restricted to dye coats for kings, emperors and popes. In some periods tyrian purple (**14**) was worth 10–20 times its weight in gold.

Additionally, some natural pigments lack the necessary thermal, chemical and photochemical stability to be commonly used as dyes.

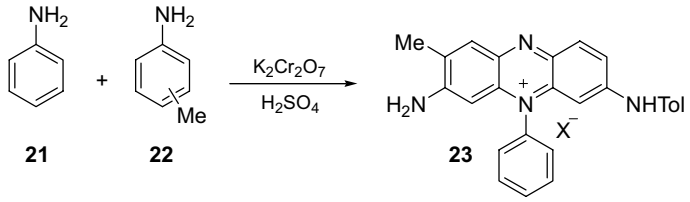
These two major limitations of natural pigments began to be overcome with the development of modern organic chemistry, allowing the preparation of synthetic pigments in large quantities and at low cost. Synthetic indigo (**13**) and its derivatives are good examples. Scheme 27.1 shows the first synthetic procedure for commercial indigo (**13**), accomplished by BASF in 1897. Consequently, although the purple color of the tyrian purple (**14**) is considered by tradition to be a symbol of power it has, in fact, lost such significance.



Scheme 27.1 BASF synthesis of indigo (**13**).

Slight modifications in the structure of pigments can be used to modulate their physical or chemical properties, affecting not only their stability but also the coloration. With these two premises in mind, it is easy to imagine that almost every color of pigment can be obtained for use as a dye for most purposes.

The first unnatural pigment synthesized in an organic laboratory – a few years before the synthesis of indigo – was the phenazine derivative mauveine (**23**) [15], used to incorporate mauve coloration to some textile fibers such as silk. Scheme 27.2 shows the original, serendipitous, synthesis of mauveine, accomplished by Perkin in 1856, from aniline (**21**) and different toluidines **22**.



Scheme 27.2 First reported synthesis of mauveine (**23**).

In modern industry, there are many synthetic pigments that can be used as a dye. Of the heterocyclic synthetic dyes, the family of the quinolinium blue dye cyanine **24** is worth mentioning (Figure 27.6).

A cyanine dye usually consists in a cationic molecule with a bridge of conjugated bonds between two rings, at least one of them heterocyclic in nature. One side of the system, the cationic ring, acts as acceptor and the other side, a neutral heterocycle or an aromatic ring with a heteroatomic substituent, as donor. This electronic delocalization is mainly responsible for the coloration of the cyanine dyes. Figure 27.7 shows the structure of two quinolinium salts commonly used as dyes, namely, pseudocyanine (**25**) [16] and pinacyanol chloride (**26**) (quinoline blue) [17].

The family of cyanines is not restricted to quinolinium compounds, as different types of heterocycles can appear in the molecule. As selected examples, Figure 27.8 shows the structures of indolinium cyanines Basic Yellow 21 (**27**) [18], benzothiazolium Basic Blue 41 (**28**) [19] and triazolium Basic Red 46 (**29**) [20]. Additionally, the bridge chain is not restricted to carbon atoms as carbocyanines, they can also be nitrogen atoms (azamethines) or the two rings can even be directly connected (apocyanines) [21].

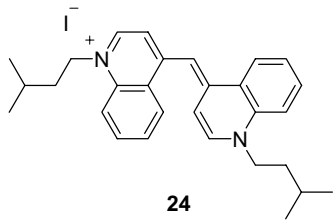
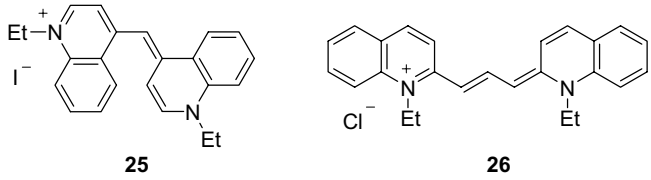


Figure 27.6 Structure of cyanine.

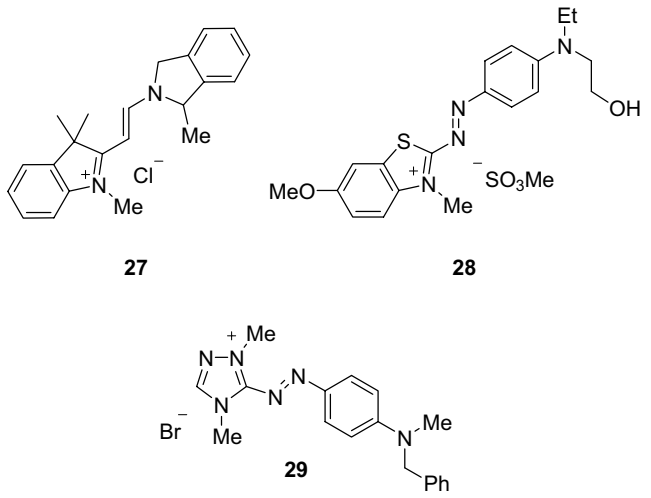


25 26

Figure 27.7 Quinolinium salts as dyes.

Other types of dyes, very commonly used in laboratories as stains of bacteria or blood cells, are azine, oxazine or thiazine dyes. The structure of these dyes consists of two six-membered rings containing amino or imino groups and bridged by nitrogen, oxygen or sulfur atoms, respectively. These systems are cationic dyes with the positive charge delocalized on both nitrogen atoms at the ends of the molecule, and on the nitrogen, oxygen or sulfur atoms of the bridge. Azine neutral red (**30**), oxazine brilliant cresyl blue (**31**) and thiazines thionin (**32**) and methylene blue (**33**) are characteristic examples of these compounds, used for DNA detection [22] (Figure 27.9).

Of great importance for the synthetic dye industry was the accidental discovery – by De Diesbach in the late 1920s – of a family of phthalo-derivatives named phthalocyanines (**34**) (Figure 27.10) [23]. These compounds are not related to the cited cyanines but have been named as cyanines due to its blue color. In fact, these compounds are structurally related to porphyrins. Their main structural characteristics are the presence of benzene rings fused to the pyrrole β-positions and a porphyrin core where the carbons at the *meso*-positions have been replaced by nitrogen atoms.



27 28 29

Figure 27.8 Dyes belonging to the cyanine family.

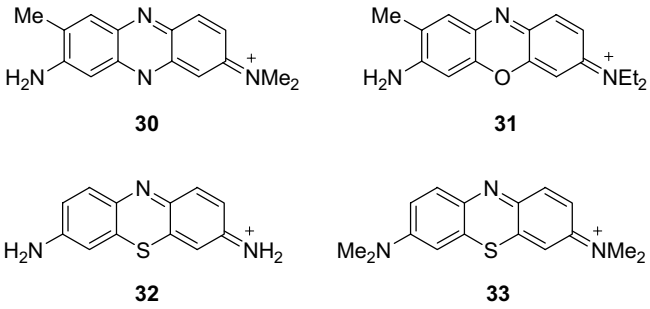
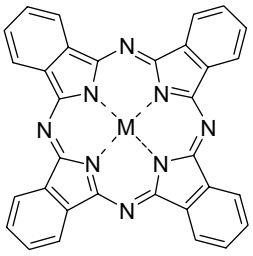


Figure 27.9 Heterocyclic stains.

Porphyrins have not found widespread application in the dye industry due to the usually low intensity of the absorption bands (Q bands) in the visible region, having instead more intense bands in the near-UV region (Soret band). In contrast, phthalocyanines have also bands in the near-UV region but the highest intense bands have shifted into the visible region (600–700 nm) absorbing red light and resulting in their characteristic intense blue color. These differences in UV/visible spectra derive from two fundamental structural changes: (i) replacement of the carbon atoms at the *meso*-positions by more electronegative nitrogen atoms, which attract the π-electron density to themselves, (ii) the presence of fused benzene-pyrrole rings, which extend the π-electron density.

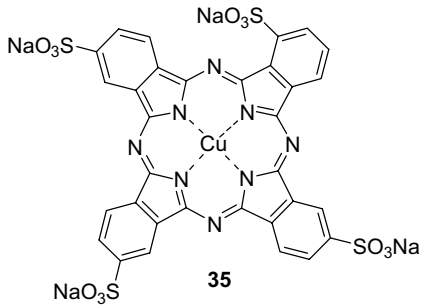
On the other hand, phthalocyanines are very stable. As a notable example, iron is not removed from a phthalocyanine core in concentrated sulfuric acid and the intense blue coloration is not modified up to 500 °C. This stability together with the intense coloration has rendered phthalocyanines as powerful pigments for the dye industry. A good example of the industrial applicability of phthalocyanines is the use of remazol turquoise blue (**35**) as a textile dye (Figure 27.11) [24].



M = Fe(III), Cu(II)

34

Figure 27.10 General structure of phthalocyanine.



35

Figure 27.11 Structure of the remazol turquoise blue.

27.2.2

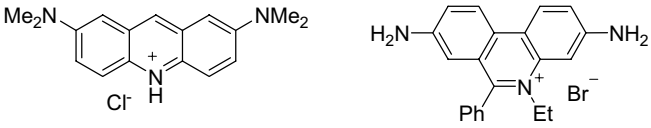
Fluorescence and Fluorescent Heterocycles

A luminescent or photoluminescent agent is a molecule that upon excitation with ultraviolet or short wavelength visible light can spontaneously emit a photon to recover the original energy state. Among the two different kinds of luminescence, fluorescence or phosphorescence, fluorescence does not involve a spin change in the excited electron, since the transition occurs from a singlet excited state to the singlet ground state. Conversely, phosphorescence involves a transition from a triplet excited state to the singlet ground state, a forbidden transition by the selection rules and, as a consequence of this, it is less common than fluorescence.

Luminescence can operate in numerous compounds but it is easier in those with a narrow energy gap between the HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital). In this sense, two important factors that contribute to narrow this energetic gap are the presence of π-conjugated bonds and conjugated electron-donating or electron-withdrawing groups. On the other hand, contributions to the energy dissipation (rotation, vibration, etc.) are responsible for falls in the emitted energy related to the energy of excitation. As a result of this, the wavelength of the luminescent is always longer than that of the absorbed light. Thus, molecular rigidity favors luminescence that avoids energy dissipation through vibration modes.

Among the different molecules that can exhibit the so-called luminescent properties (luminophores), heterocycles are good candidates because of their π-extended conjugation, together with the rigidity induced by the usual heteroatom participation in the conjugation. Selected examples from the many fluorescent heterocycles are described below.

In the field of medicine, fluorescent agents – especially those containing heterocycles – are important as chemical markers. In this sense, fluorescence *in situ* hybridization (FISH) is a good example of practical application for early cancer detection that has been applied to studies in colon [25], lungs [26], prostate [27], and so on. In addition, specific fluorescent heterocyclic molecules have been designed to be selectively attached to biological substances to serve as tracers of these components.



36 **37**

Figure 27.12 Examples of chemical markers used as medical tracers.

Figure 27.12 shows acridine orange (**36**) [28] and ethidium bromide (**37**) [29], pyridinium derivatives used to distinguish cancerous from healthy cells.

A different, but no less important, medical application is the use of fluorescent substances, for example fluorescein (**38**), to check the quality of the blood vessel walls (Figure 27.13). A very small concentration of fluorescein salt injected in the blood flow can be followed by fluorescent detectors to obtain information related to the permeability of the vessels [30].

The application of fluorescent heterocycles as markers is not restricted to the medical field. Fluorescent dyes also have found industrial application in the detection of small fissures in different types of materials [31]. The piece to be checked is immersed in the fluorescent agent and, after the corresponding washing, a fluorescent detector looks for small amounts of the agent in microfissures of the tested material.

Fluorescence has also emerged as a valuable tool for ecophysiologists. Thus, a noninvasive technique known as chlorophyll fluorescence is routinely used to monitor the photosynthetic performance of plants. Light energy absorbed by chlorophyll **2** (Figure 27.1) in plants is put to three possible uses: to drive photosynthesis, dissipated as heat or re-emitted as light-chlorophyll fluorescence [32]. Detection of an increase in the yield of chlorophyll fluorescence gives information about a decay in photochemistry efficiency, as all three processes are in competence. Among the wide range of applications for agriculture are the improvement of crop productions by plant selection [33], studies of adaptation of maize to low temperature [34], responses to water stress in grapevine leaves [35], early detection of interactions of tobacco mosaic virus and chloroplasts [36], and so on.

Related to industrial applications of fluorescent chemicals in modern industry is the preparation of fluorescent paints. These substances increase the brightness of the reflected light upon irradiation and their use over a surface permits its identification

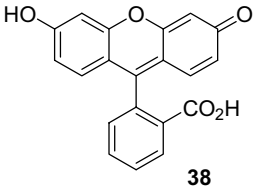


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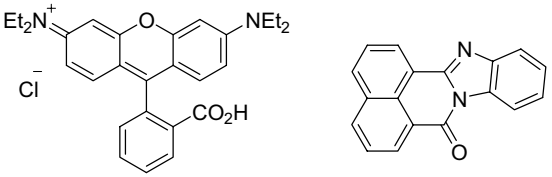
Figure 27.13 Structure of fluorescein.



39 40

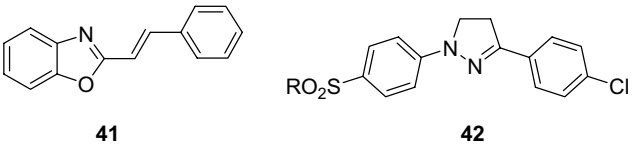
Figure 27.14 Dyes for fluorescent paints.

even at night. Thus, fluorescent paints are very commonly used for road markings, traffic signals, coloration of safety cloths, and so on [37]. Figure 27.14 shows two examples of heterocycles with this property, xanthene **39** and benzimidazole **40**.

The application of fluorescence phenomena to the whitening of different materials such as paper or white cloths is very interesting. The whiteness of these materials can be increased upon treatment with substances known as "optical bleachers." These compounds are colorless fluorescent agents that after absorbing energy reemit a part of it by fluorescent in the blue region of the visible spectrum, thereby creating the appearance of an increased whiteness [38]. "Optical bleachers" can be included in the synthetic fibers or used as part of washing mixtures.

Several systems incorporating heterocyclic compounds exhibit this property. Figure 27.15 shows three of them: oxazole **41**, pyrazoline **42**, and triazinylaminostilbene derivative **43** [39].

Many other applications are possible using fluorescent or simply luminescent heterocycles but remarkable among them is the participation in laser devices. The use of laser devices has increased progressively to the point where they play now an important role not only in industrial or research fields but in everyday life as well. Representative examples of these applications are lasers in medical surgery, supermarket code readers, credit cards readers, musical devices, computers, and so on.



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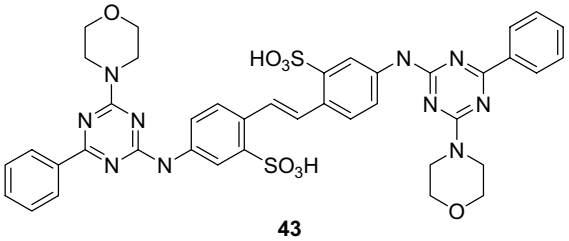

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Figure 27.15 Example of "optical bleachers."

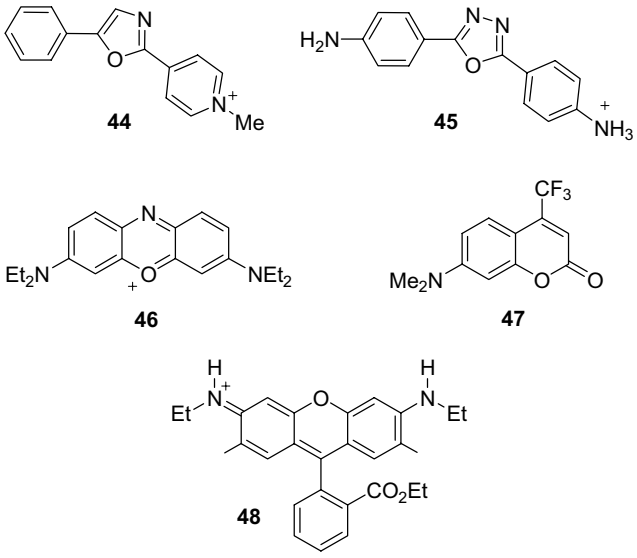


Figure 27.16 Some heterocycles employed in liquid lasers.

A solution of heterocyclic fluorescent compounds contributes, in liquid lasers, to transform the energy into the necessary coherent light for the laser functionality. Many heterocyclic compounds are used for laser devices. Figure 27.16 shows a selection of them: oxazole **44**, oxadiazole **45** [40], oxazine **46** [41], coumarin **47** [42], and xanthenes such as Rhodamine 6G (**48**) [43].

The advantage of liquid lasers, compared with solid or gas lasers, lies in the fact that, although they are not very powerful, they are usually easy to smoothly modulate in terms of the operating wavelength.

Finally, another interesting application of fluorescent heterocycles is their use as detectors for ionizing particles. 2,5-Diphenxyloxazole (PPO) (**49**), 1,3,5-triphenyl-Δ^2-pyrazoline (**50**) and 1,4-bis-2-(5-phenyloxazolyl)benzene (POPOP) **51** are heterocyclic compounds commonly used as counters (Figure 27.17). These substances emit short

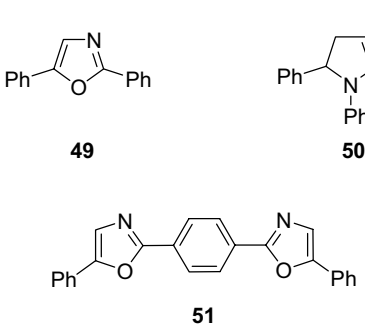


Figure 27.17 Fluorescent compounds used in counters for ionizing particles.

lived flashes when they are struck by ionizing particles. This use of heterocycles as counters has found applications in space investigations to detect neutrons, neutrinos and α-, β-, or γ-rays [44].

27.3
Self-Assembling Materials and Molecular Containers

27.3.1
Introduction

As a reflection of increasing interest in knowledge of the mechanistic bases of life at the molecular level, molecular recognition has been the focus of increasing effort in recent decades. This discipline can be considered as an art involving the creation and/or study of supramolecular structures held together through complementarity in size, shape, non-covalent or even electrostatic interactions, among others. As pioneers in this field, Jean-Marie Lehn, Donald J. Cram, and Charles J. Pedersen were awarded with the Nobel Prize in Chemistry in 1987 "for their development and use of molecules with structure-specific interactions of high selectivity".

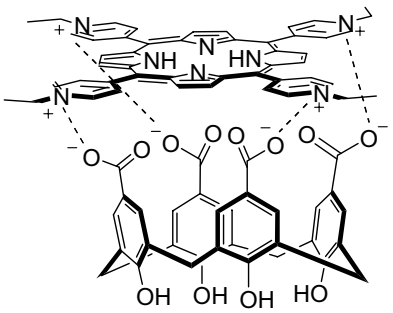
This section gives a brief compilation of several macrostructures assembled by non-covalent bonds, with the crucial participation of one or more heterocyclic rings. It is divided in three sub-sections according to the type of interaction involved: electrostatic and π-stacking interactions, coordination chemistry and hydrogen-bond interactions. A fourth section covers a special type of assemblies capable of encapsulating small molecules.

27.3.2
Assembly Mediated by Electrostatic and π-Stacking Interactions

Electrostatic interactions play an important role in the formation of a large number of assemblies. A good example is the early work done by Nobel Laureate Charles J. Pedersen in late 1950s with the synthesis of crown ethers and the formation of simple assemblies with cations [45]. From this work to now, numerous supramolecular structures have been described using electrostatic interactions as the main driving force.

Heterocycles, especially nitrogenated heterocycles such as pyridines, have actively participated in the formation of assemblies in their cationic forms. A representative example of this type of work is shown in Figure 27.18 with the formation of the assembly **52** between a tetrapyridilium porphyrin and a tetracarboxylate calyx[4]arene derivative [46]. The assembly is highly dependent on the pH of the media, pointing to the electrostatic interactions between pyridinium and carboxylate ions as the most important driving forces involved in the assembly.

Many other examples can be mentioned for the formation of supramolecular structures through electrostatic interactions, including their participation together with other non-covalent forces. In this sense, these electrostatic interactions emerge



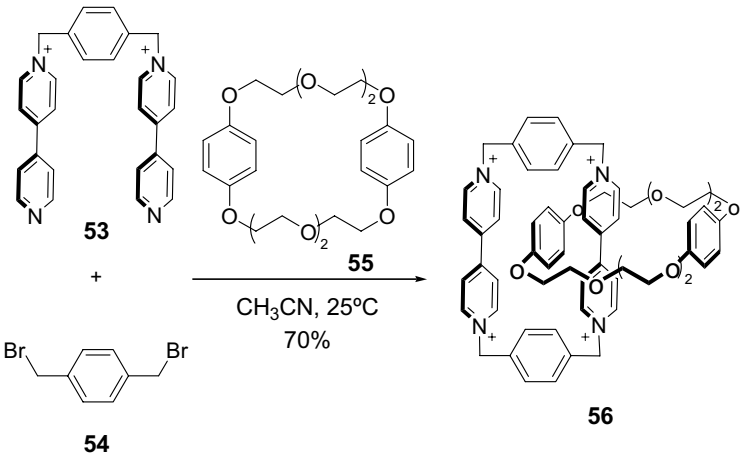
52

Figure 27.18 Example of an ionic assembly.

in many cases as the main factor in the control of protein interactions [47], and are the ultimate cause of some biological properties.

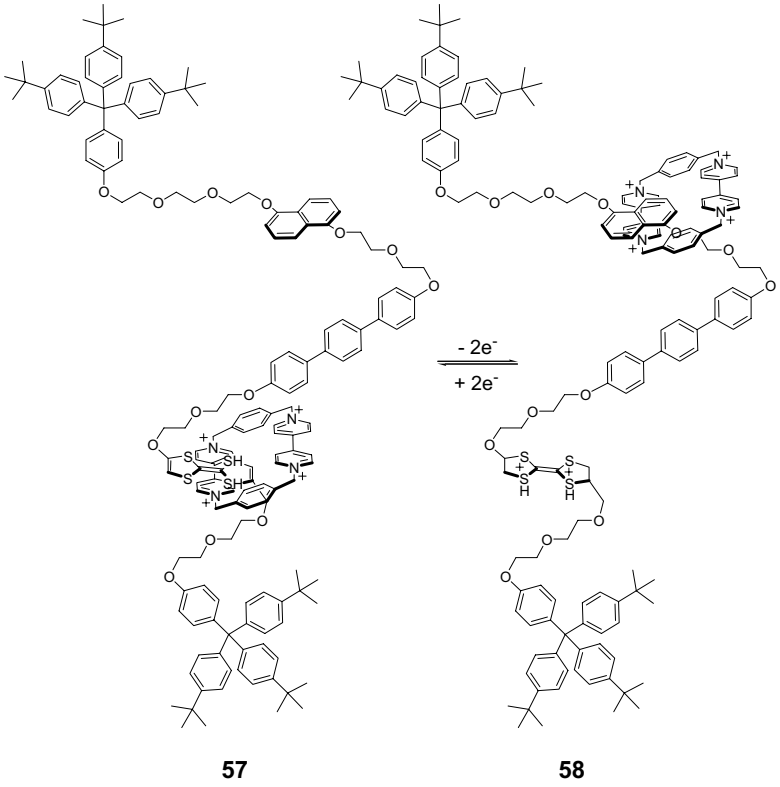
Particular types of non-covalent forces, with an important component of electrostatic interaction, are π-stacking interactions. These interactions between two aromatic systems are considered to have two main components: electrostatic interactions and van der Waals forces [48].

The formation of supramolecular assemblies such as catenanes and rotaxanes are ruled out in many cases by π-stacking interactions between a donor group, usually an electron-rich aromatic ring, and an acceptor one as a heterocyclic cation. A good exponent of this work is Stoddart and coworkers. Since the formation of their first catenane **56** (Scheme 27.3) [49], numerous interlocked self-assembled superstructures [50], including molecular switches [51], have been produced.



Scheme 27.3 Synthesis of a catenane.

Additionally, a change in the electronic properties of the molecules can be used to modify the assembly. In this regard, Scheme 27.4 shows a [2]rotaxane, assembled by π-stacking interaction of the tetracationic derivative with the tetrathiafulvalene unit [52]. This interaction prevails over the interaction with the 1,5-dioxynaphthalene unit present in the same rotaxane **57**. However, a redox-switching can be accomplished through an oxidation of the tetrathiafulvalene, which promotes a switch of the cationic unit to the 1,5-dioxynaphthalene.



57 **58**

Scheme 27.4 [2]-Rotaxane as a molecular switch.

27.3.3
Self-Assembly Through Coordination Chemistry

The formation of labile metal–ligand bonds has emerged, in the last two or three decades, as an important tool in the field of supramolecular chemistry. Examples of this type of behavior can be taken from nature, like the selective coordination exhibited by metalloproteins, such as hemoglobin. The selective and reversible binding of different molecules to the metal centre is one of the most crucial factors in the control of the protein activity.

In this sense, chemists, taking advantage of increasing knowledge of metal coordination, have been able to design and construct architectures of increasing complexity. Although many factors affect the formation of these supramolecular structures it can be controlled by taking account of three major aspects:

- The shape of the self-assembled structure is highly dependent on the metal coordination geometry. Thus, metals with different coordination possibilities can drive different to architectures.
- The choice of the ligands also plays an important role through the orientation of their interaction sites, usually heteroatom functions.
- Finally, although metal–ligand interactions are stronger than other weak forces (hydrogen bonds, wan der Waals forces, etc.), metal–heteroatom bonds are thermally labile. On the one hand, the higher strength of the metal–ligand bonds helps to overcome the entropic cost of the supramolecular assembly, as several discrete molecules have to be held together. On the other hand, the lability of the bond gives rise to the formation of the thermodynamically most favored assembly, through a process that involves the self-correction of initially formed kinetic structures.

As mentioned earlier, heterocyclic systems have been widely selected for the formation of supramolecular coordination structures due to the ability of heteroatoms to act as donors to the metal acceptor centre. A brief selection of these supramolecular architectures, accomplished through metal coordination of different heterocyclic rings, is given below.

A wide variety of heterocycles, especially nitrogen heterocycles, can act as metal ligand and can be potentially used as ligands in self-assembly coordination chemistry [53]. However, pyridine derivatives, due to their well known ability to form complexes with a large number of metals, have been used in most cases. This is also favored by the back-bonding from the metals into the π^*-orbitals of the pyridine rings.

Figure 27.19 shows an example of two different binuclear assemblies through the coordination of pyridine rings. The driving force for the assembly formation emerges from the silver [54] and palladium [55] coordination, respectively.

Pyridine derivatives participate in numerous self-assembly processes even with two different metals [56], resulting in structures with diverse sizes and forms. An interesting example of this, carried out by Fujita *et al.* [57], is shown in Scheme 27.5. This work resulted in the formation of tetranuclear **61** or trinuclear **62** complexes in equilibrium, assembled from the nucleation of bipyridine ligands around palladium atoms.

As a representative example of the increasing complexity in the supramolecular structures with pyridine or bipyridine ligands, it is worth mentioning the work of Lehn and collaborators. Scheme 27.6 describes the formation of pentanuclear **64** [58] or hexanuclear **65** [59] iron helicates with the same trisbipyridyl ligand **63**. The formation of one double helicate over the other is dependent on the counterion size, which acts as a template. Thus, chloride drives the assembly to the pentameric helicate **64**, isolated with a chloride ion within its central cavity, whereas sulfate gives rise to the hexameric helicate **65**.

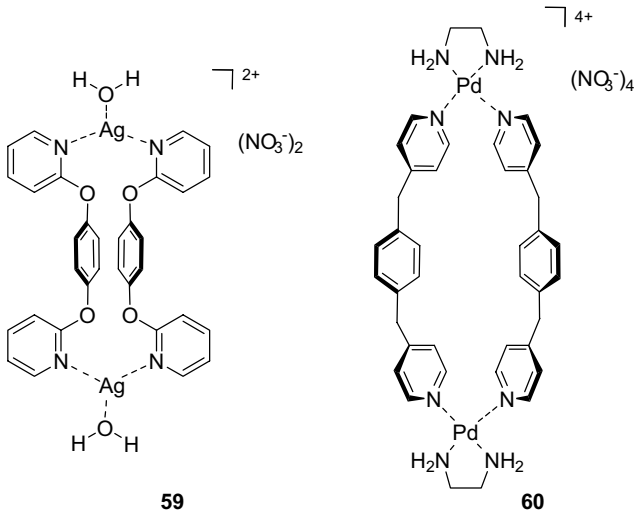
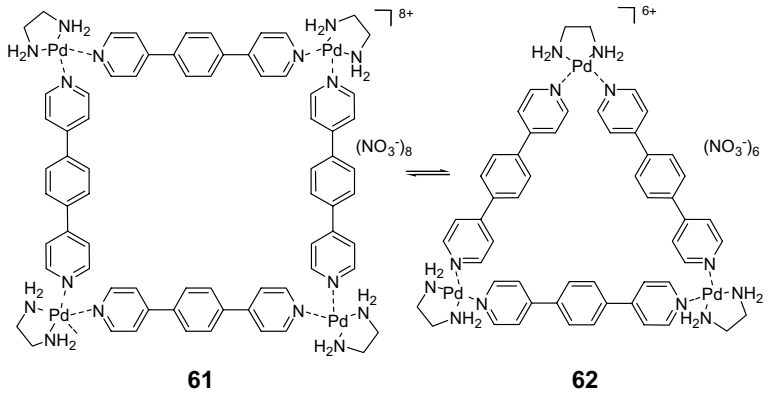


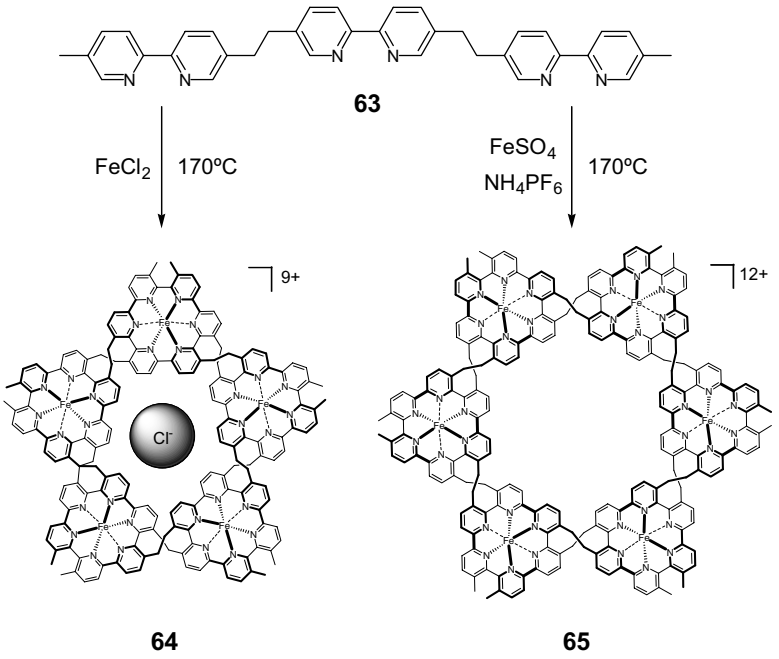
Figure 27.19 Silver and palladium dimeric assemblies.



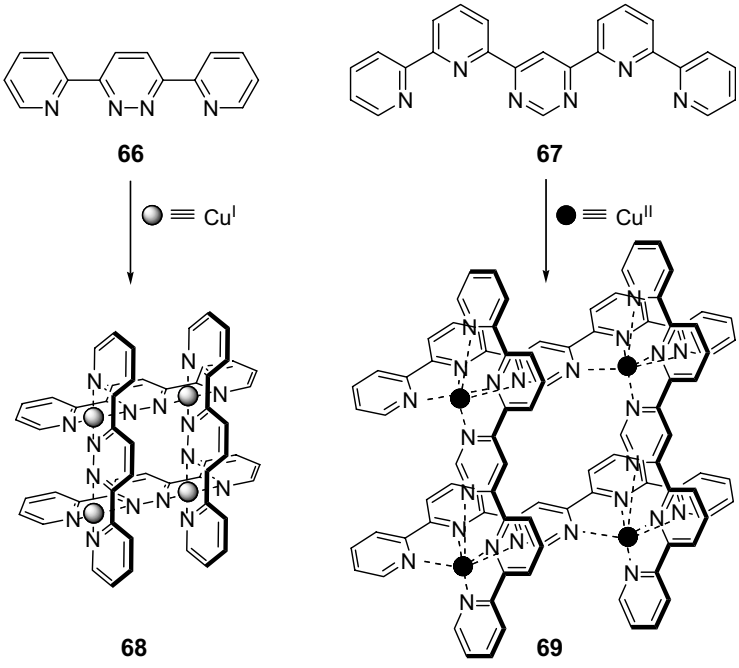
Scheme 27.5 Tetra- and trinuclear self-assembled complexes.

A careful design of ligands, which combines pyridine with pyridazine, pyrimidine or pyrazine rings, together with the appropriate selection of the metal has allowed the design and building of grid-type architectures of diverse size and complexity [60]. Scheme 27.7 shows two of the simplest examples of these type of complexes: the tetrameric compounds **68** and **69**, containing bis(pyridyl)pyridazine (**66**) [61]and bis (terpyridine) **67** [62] ligands, respectively. Owing to the structure of the ligands, the metal is coordinated tetrahedrally in the first case and octahedrally in the second.

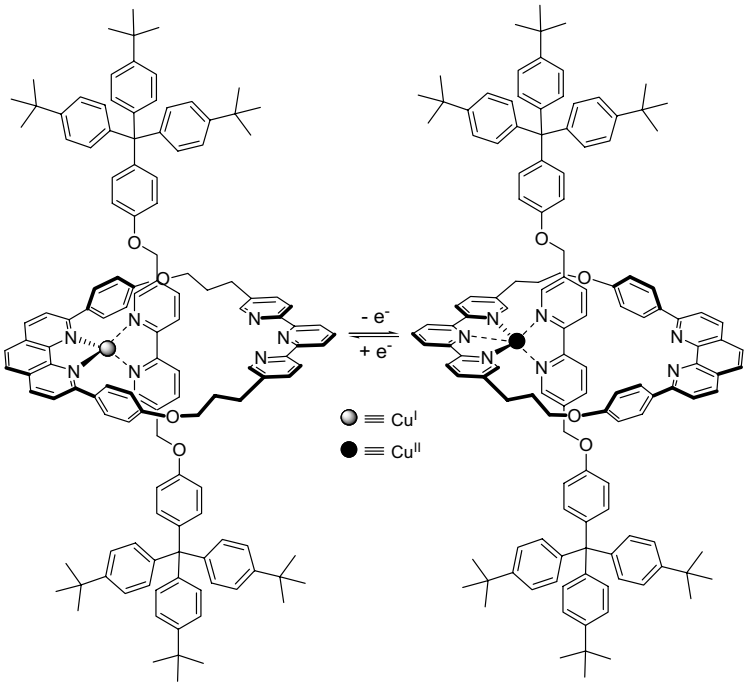
Metal coordination assemblies can also act as molecular machines. Scheme 27.8 shows a [2]rotaxane produced by Sauvage and coworkers [63]. The axle of the rotaxane,



Scheme 27.6 Preparation of pentameric and hexameric helicates.



Scheme 27.7 Grid-type self-assembled complexes.



70 **71**

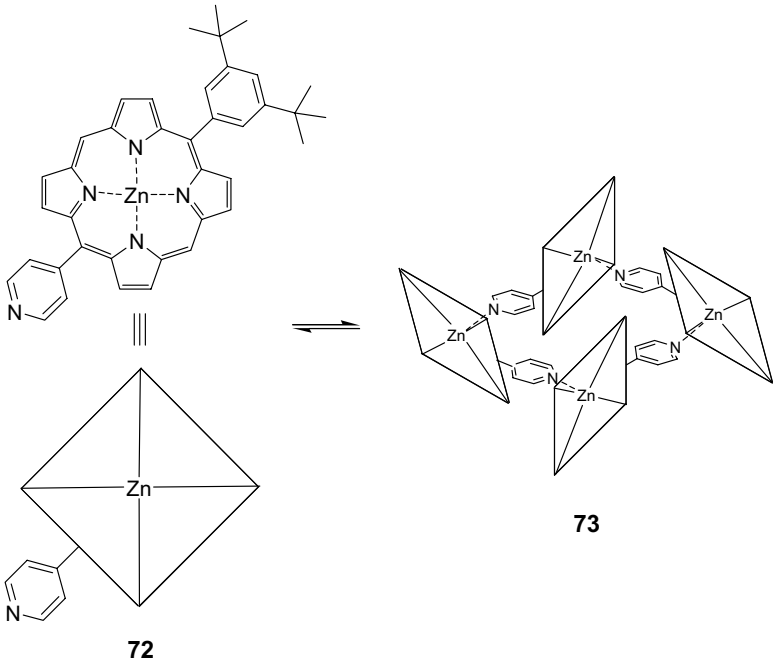
Scheme 27.8 Example of a redox molecular switch.

assembled by bipyridine–copper coordination, can be electrochemically switched between the two coordination sites of the ring. A change in the copper oxidation state promotes the rotation of the ring and the metal changes from tetra- to pentacoordination and vice versa.

In addition to the six-membered nitrogen heterocyclic rings (pyridines, pyridazines, pyrimidines, pyrazines or tetrazines [64]) and combinations of these heterocycles, five-membered rings have also been involved in self-assembly metallomolecular arrays. Scheme 27.9 presents the tetrameric structure **73**, which involve double zinc porphyrin-pyridine coordination [65]. Each zinc atom is surrounded by the porphyrin core and by a pyridine ligand, placed at the *meso*-position of a different porphyrin unit.

Five-membered rings with two or more nitrogen atoms such as pyrazole [66], imidazole [67], triazole [68], benzotriazole [69], or tetrazole [70] have also participated in this type of assemblies. Figure 27.20 shows the hexameric assembly **74** involving a copper metal and a ligand bearing an imine and pyridine and imidazole rings [71]. The fourth coordination site of the copper is saturated with a second imidazole nitrogen atom of a different ligand.

Finally, although the participation of heteroatoms other than nitrogen is not very common in metal coordination assemblies, heterocycles such as thiazoline [72] have been used in this type of supramolecular architecture.



Scheme 27.9 Tetrameric porphyrin assembly.

27.3.4
Self-Assembly Through Hydrogen-Bond Chemistry

Hydrogen-bonding interactions can be considered as a weak force that, taking advantage of the principle of cooperativity [73], can be used to hold together large

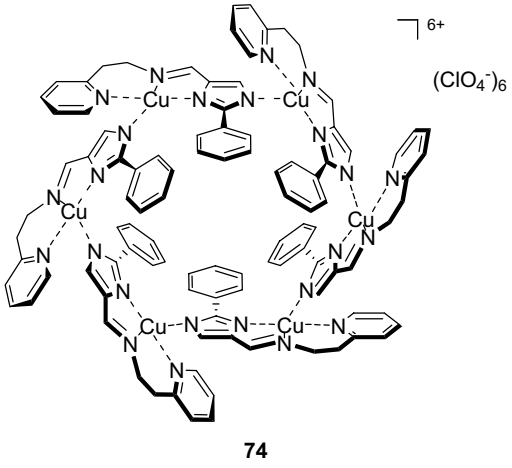


Figure 27.20 Hexameric structure assembled through copper coordination.

structures consisting of several discrete molecules. Owing to the weakness of this type of interactions and the entropic cost of keeping several molecules together, assemblies based on an isolated hydrogen bond lack stability. In this sense, cooperativity is crucial as the stability of the assemblies increases exponentially with the number of hydrogen bonds.

However, the weakness of the single hydrogen bond facilitates two important features:

- The low energy of the hydrogen bond carries a selection capability as hydrogen bonds are made and broken until stable structures are reached.
- This property habilitates, as nature does, the transfer of biological information. In this sense, the transcription and translation of the genetic information represents a noteworthy example. During that processes both single strands of the DNA and RNA double helix, which are held together by hydrogen bonds, are partially taken apart and regenerated after the information has been transferred.

Owing to the difference in electronegativity between nitrogen or oxygen and hydrogen, these are the two most common atoms acting as proton donors and also as proton acceptors in hydrogen bonds. Heterocycles bearing these types of atoms commonly participate in supramolecular assemblies through hydrogen bonding.

To show here all the different heterocycles that participate in the formation of supramolecular assemblies is far from the aim of this section and so only a brief compilation of some relevant examples is given. Perhaps the most important example of this type of assemblies, in terms of life implication, is the self-complementarily of DNA double helix through Watson–Crick base pair interactions [74] (adenine–thymine and guanine–cytosine). Figure 27.21 shows the structure of the purine (fused pyrimidine-imidazole) nucleosides adenine (**75**) and guanine (**77**) and pyrimidones thymine (**76**) and cytosine (**78**). The pairs adenine–thymine and guanine–cytosine are held together with the formation of two and three hydrogen bonds, respectively, contributing to the overall stability of the DNA double helix [75].

In addition to observations from nature, scientists have also focused a great deal of effort to designing and synthesizing molecules with the appropriate complementarily, to create new superstructures held together through hydrogen bonding.

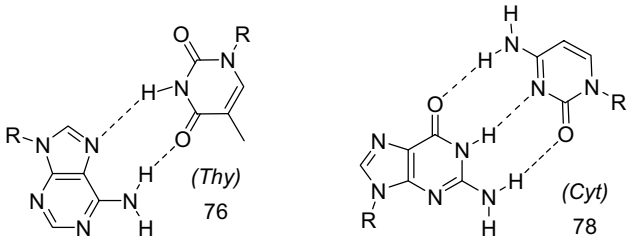
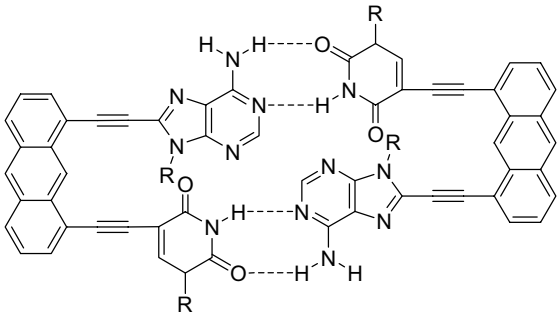


Figure 27.21 Watson–Crick base pairs.

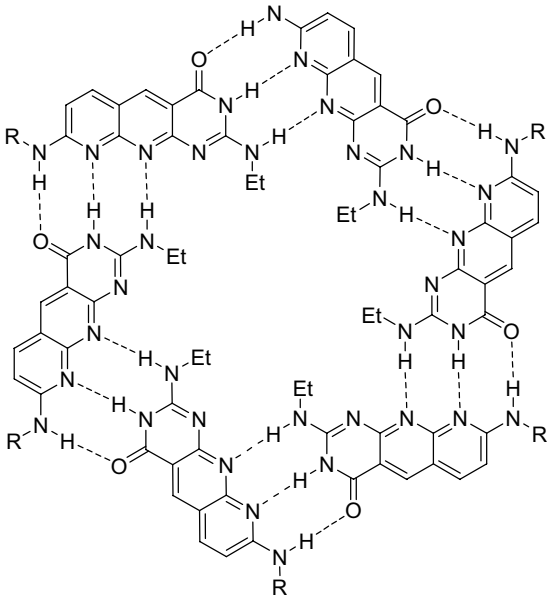


79

Figure 27.22 Self-assembled artificial nucleotide.

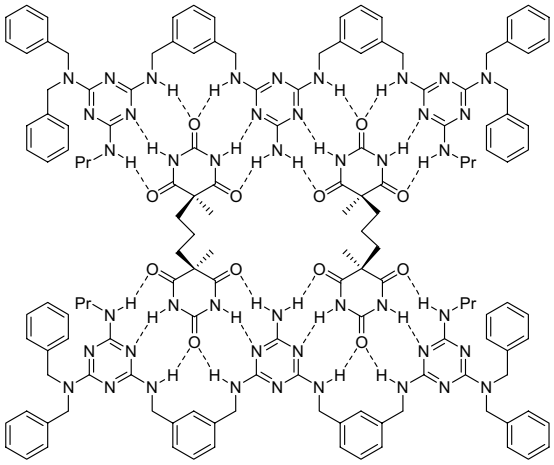
Thus, Sessler *et al.* [76] have described an artificial dinucleotide with purine and piperidindione derivatives, which can self-assemble, leading to the corresponding dimer **79** (Figure 27.22).

Assemblies are not restricted to dimers as supramolecular structures with different numbers of monomerical components have also been realized. Figure 27.23 shows a circular array, developed by Zimerman *et al.*, as a hexameric assembly of fused pyridines and pyrimidinones. Thus, the complementarily of both edges of the monomer, in the adequate angular disposition (60°), results in the formation of the hexameric structure **80**, which is held together with 18 hydrogen bonds [77].



80

Figure 27.23 Hexameric structure assembled through hydrogen bonding.



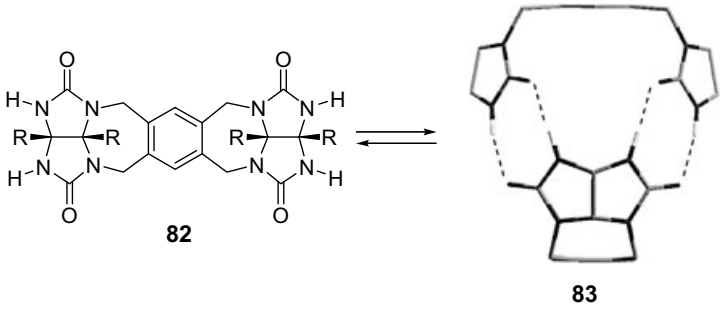
81

Figure 27.24 Melamine–barbituric acid assembly.

In a similar approach, a hexameric assembly starting from fused pyrimidinones has also been described by Lehn and coworkers [78].

Linear, even polymeric [79], structures have also been described. For example, Timmerman has reported the formation of the linear discrete assembly **81** through hydrogen-bond interactions between a trimer of the triazine derivative melamine and a bis(barbituric acid) derivative [80]. The cyclic-ureido structure of the bis(barbituric acid) can connect two linear strands of melamine components. Figure 27.24 shows the structure of four components, which involves the formation of 24 hydrogen bonds.

Finally, in the literature it is also possible to find three-dimensional structures – assembled by hydrogen-bond self-complementarity – with different sizes and shapes. Rebek's "tennis ball" (**83**) is a good example (Scheme 27.10) [81]. This supramolecular structure is held together by eight hydrogen bonds between two self-complementary



82 **83**

Scheme 27.10 A self-assembled "tennis ball."

units. The monomer **82** consists of two glycoluril subunits attached to a central skeleton that provides the necessary curvature.

Other glycoluril capsules have also been attained [82] and some of these capsules are able to host discrete molecules inside. Encapsulation features are described in the next section.

27.3.5
Capsules and Encapsulation Behavior

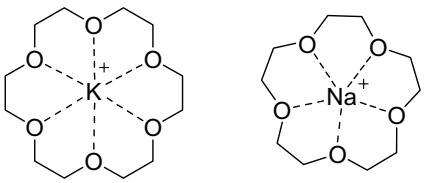
Synthetic molecular recognition and host–guest chemistry have their origin in the complementarity of three main characteristics: size, shape and chemical interaction. This is very well illustrated in the pioneering work of Pedersen, in the 1960s, by the synthesis and study of crown ethers [45]. Pedersen demonstrated that these heterocycles can selectively bind cations of only a given size (Figure 27.25).

This concept of "molecules within molecules," a term coined by Nobel Prize winner Donald Cram [83], has been extended to modern supramolecular chemistry and an increasing number of molecules can be almost completely surrounded by self-assembled capsules. In the last decade, host–guests chemistry has been a field of increasing interest and capsules of different shapes and sizes have been synthesized [84].

Apart from, or perhaps due to, the selective binding, these capsules are able to feature special properties such as catalysis, chiral discrimination, intermediate stabilization, traces capture, and so on. A brief compilation of some of these features is given below.

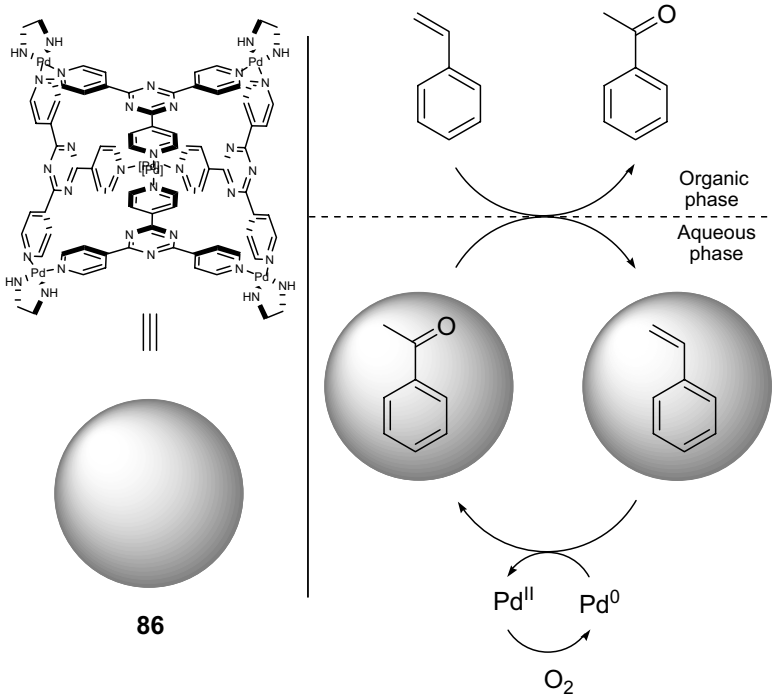
A very interesting observation made by several authors is that self-assembled capsules can accelerate or even catalyze different reaction processes. Of note in this regard is the report by Fujita of an octahedral capsule acting as a phase-transfer catalyst [85]. The water-soluble capsule **86** is assembled from pyridine ligands coordinated to palladium complexes. Capsule **86** encapsulates styrene, which lacks water solubility, allowing its effective participation in a Wacker oxidation (Scheme 27.11).

In addition, Rebek *et al*. have reported the participation in a catalytic process of glycoluril-based capsule **88**, which is assembled through the formation of 16 hydrogen bonds (Scheme 27.12). A Diels–Alder reaction between *p*-benzoquinone



84 **85**

Figure 27.25 Crown ethers and cationic recognition.



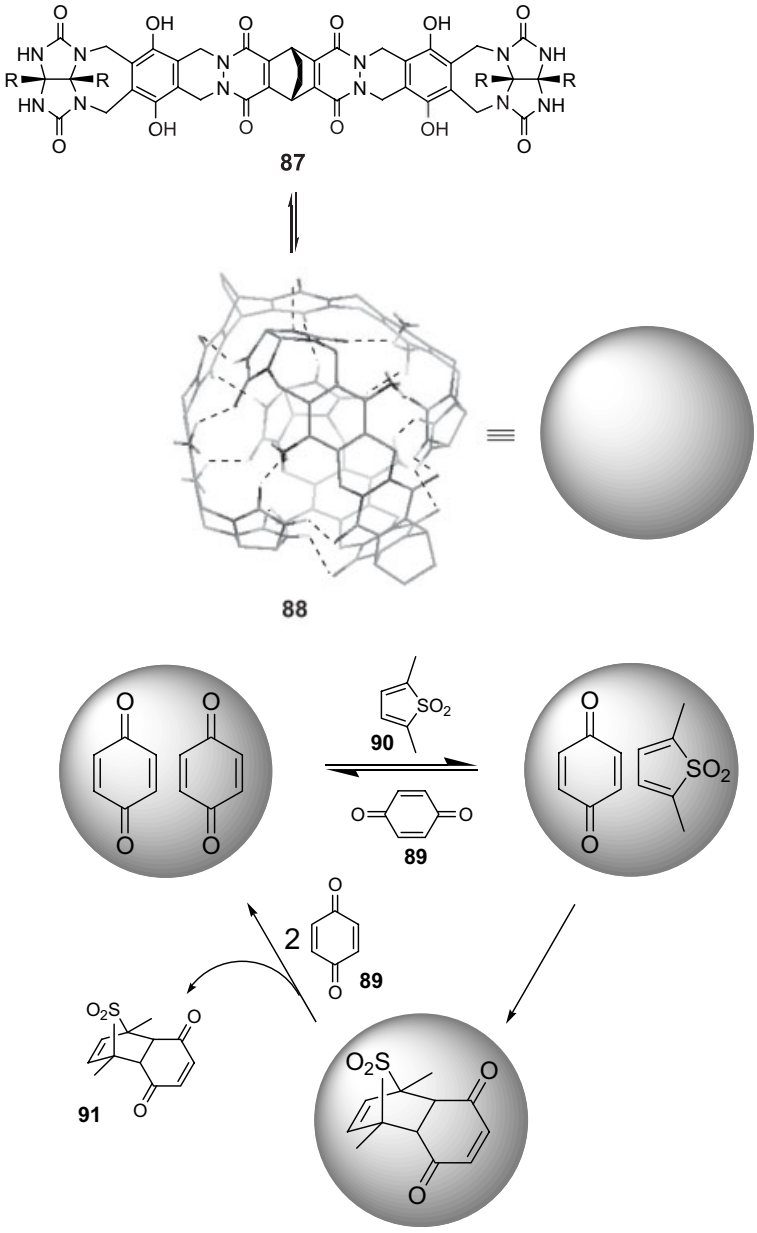
Scheme 27.11 Example of the use of a capsule as a phase-transfer catalyst.

(**89**) and 2,5-dimethylthiophene **90** is catalyzed in the presence of the capsule **88** [86]. Thus, one of the two molecules of *p*-benzoquinone **89**, which initially fills the capsule, is replaced by one molecule of 2,5-thiophene **90**. After the Diels–Alder reaction takes place the product **91** is replaced by more *p*-benzoquinone **89** due to its poor affinity for the capsule, and a new cycle begins.

The capsule **88** also participates in the acceleration of Diels–Alder reactions with other substrates [87]. However, in these cases, the high affinity of the reaction product for the capsule prevents its replacement by more reagents and no true catalysis is observed. This product inhibition has also been observed by other authors [88].

Asymmetric behavior has also been observed in self-assembled capsules. For example, Rebek *et al*. have synthesized a glycoluril-based dimeric capsule starting from achiral monomer **92**. These capsules can be assembled in two different enantiomeric forms, as a racemic mixture (Scheme 27.13) [89]. Enantiopure guests can be selectively recognized by one of the enantiomers, affording an enriched diastereomeric mixture of capsules. Additionally, taking advantage of the much faster guest exchange compared with capsule dissociation, an enantiomerically enriched mixture of capsules **93** and **94** is obtained, replacing the chiral by an achiral guest [90].

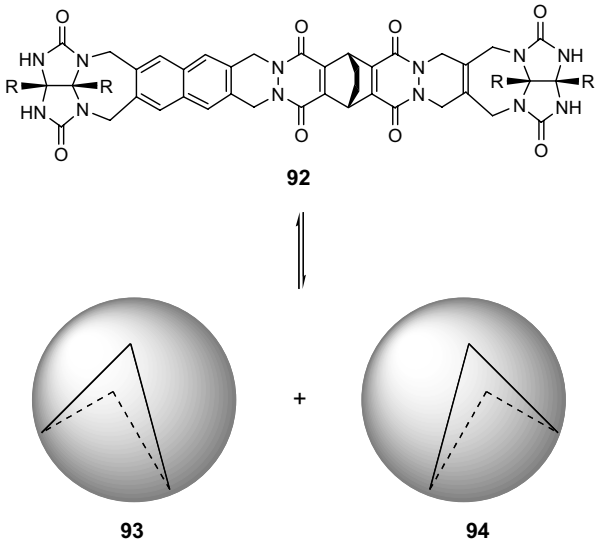
Examples of chiral discrimination have also been reported from metal coordinated nanocages [91]. Thus, a racemic mixture of supramolecular structures assembled by



Scheme 27.12 Diels–Alder catalysis through encapsulation.

pyridine coordination to palladium can be discriminated by the addition of chiral guests.

Finally, among the special features that can be addressed by a self-assembled capsule is the stabilization of reactive intermediates. A relevant example is the



Scheme 27.13 Chiral capsules.

formation of the highly reactive trimer of phenyltrimethoxysilane inside a capsule similar to **86** [92]. Owing to the special characteristics of the host–guest size and shape complementarity, polymerization of this intermediate is avoided inside the capsule. Similar behavior has been observed in the stabilization of benzoyl peroxide inside an hydrogen-bond self-assembled capsule [93].

27.4
Unnatural Enzyme Models

The quest for synthetic molecules to mimic one or more features of enzymatic systems is ongoing. These organic molecules, known as enzyme models, are structurally simpler than enzymes, as they usually lack the peptide chain, and are used to reproduce the characteristics and properties of the enzyme active site. The simplicity of the coenzyme model, compared to the biomolecule, and the possibilities of manipulation of its structure facilitates the study of a specific property of the enzyme.

Because many coenzymes belong to the family of nitrogen molecules, heterocycles – specifically nitrogen heterocycles – have been widely used as enzyme models. Among such heterocycles, porphyrin derivatives, imidazole rings and pyridines are perhaps the most commonly described. Several examples of such systems are, briefly, given in this section.

Several molecules have been synthesized to simulate the active site of the cytochrome P450's, a very important family of enzymes involved in the biocatalysis

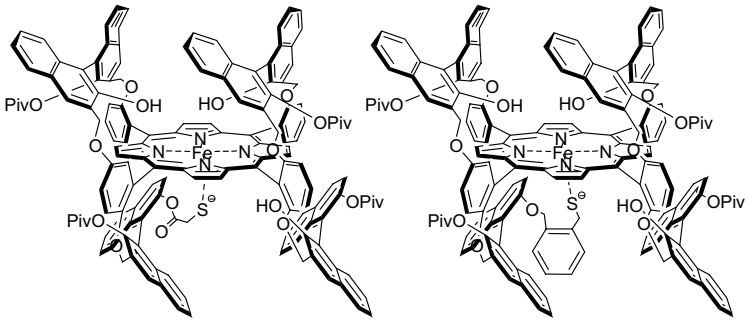


Figure 27.26 Enzyme models for cytochrome $P450_{cam}$.

of several organic compounds from dioxygen. The structure of the $P450_{cam}$ [94], –one of the best characterized P450s – is a hemoprotein with a special characteristic that bears a thiolate group – belonging to a cysteine amino-acid – as a ligand to the heme. A number of porphyrin derivatives have been synthesized to mimic the coenzyme of this cytochrome P450 [95]. Figure 27.26 shows two remarkable examples, **95** and **96**.

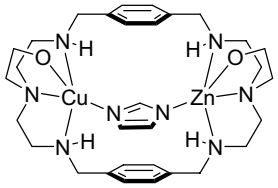
In both cases, porphyrins **95** and **96** have a thiolate group covalently attached to the porphyrin and coordinated to the iron centre [96]. Additionally, they have on both sides of the porphyrin hydrophobic cavities protected with binaphthyl moieties. The binaphthyl walls of one side protect the iron centre from a possible autoxidation. On the other side, these moieties protect the thiolate from oxidation and disulfide formation. Finally, the hydroxyl groups attached to the binaphthyls on the open side of the iron centre interact with the bound dioxygen through hydrogen bonding.

This enzyme model has been used in studies of binding and activation of dioxygen by cytochrome P450. The dioxygen adduct has been characterized and direct evidence of hydrogen bonding of the hydroxyl groups to the bound dioxygen has been obtained.

Owing to the complexity of the active site of the enzymes, a precise combination of heterocycles and metals could also be required for the synthesis of an enzyme model. For example, the active site of the copper-zinc superoxide dismutase consists of a bimetallic Cu(II)-Zn(II) core bridged by an imidazolate moiety [97].

Few systems have been synthesized to reproduce this coenzyme due to the special characteristics of the bimetallic bridged core [98]. Figure 27.27 shows an enzyme model of superoxide dismutase (**97**) accomplished with a macrocyclic nitrogenated ligand [99] that selectively coordinates a copper cation on one side and a zinc on the other.

The appropriate distance between the two coordination sites in **97** makes it suitable for the coordination of imidazolate as a bridge between the two metallic centers. Finally, the fifth coordination sites in both metals are saturated by oxygen atoms.



97

Figure 27.27 Enzyme model for copper-zinc superoxide dismutase.

Experimental measures of the catalytic activity towards the dismutation of superoxide show that complex **97** is a good enzyme model, although its activity is lower than the native enzyme.

An interesting, third example, of heterocyclic participation in the synthesis of an enzyme model is the recent use of a macroheterocycle that includes a terpyridine derivative. This macrocycle has been used to simulate the active site of the enzyme Rubisco, which is involved in the fixation of carbon dioxide by green plants and the formation of a carbamate moiety [100]. The natural enzyme fixes carbon dioxide by reaction with the nitrogenated amino acid lysine, with the participation of a magnesium or manganese complex.

This feature, the formation of a carbamate from atmospheric carbon dioxide and its stabilization, has been reproduced by an artificial model (Figure 27.28) [101].

In this case, the enzyme model **98** involves the participation of a copper cation coordinated to a terpyridine included in a nitrogenated macrocycle. The copper complex acts as Lewis acid, facilitating the carbon dioxide reaction and helping carbamate stabilization by coordination.

Finally, we end this section by mentioning other systems that can be considered as enzyme models although they do not mimic any particular natural enzyme. These compounds are included here because they reproduce some enzymatic properties

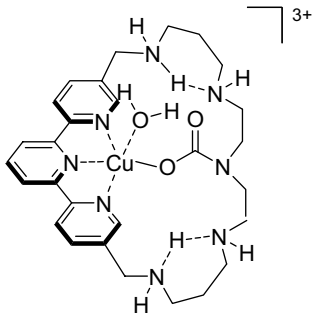


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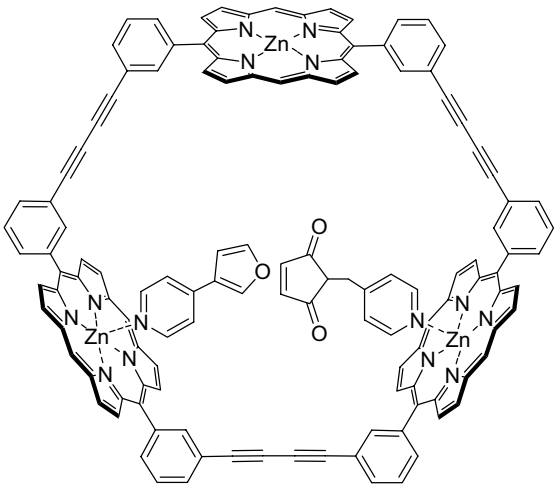
Figure 27.28 Model of the enzyme Rubisco.



99

Figure 27.29 Diels–Alder acceleration inside a porphyrin trimer.

such as catalysis or chiral recognition. Examples have been given in Section 27.3.5, where we describe Diels–Alder reactions catalyzed or simply accelerated by a self-assembled glycoluril capsule [86, 87]. These systems follow the "Michaelis kinetics" typically observed in enzymology.

Similarly, Diels–Alder acceleration has been accomplished inside the cavity of the covalently bonded porphyrin trimer **99** [102]. The reagents have been attached to a pyridine moiety and Diels–Alder acceleration takes place through coordination of the pyridine rings to the metallic centre of the porphyrin core (Figure 27.29).

Although the acceleration is truly remarkable, it cannot be considered true catalysis due to product inhibition. The Diels–Alder adduct binds to the trimer and so the complex lacks catalytic turnover.

Chiral recognition by organic synthetic molecules has also been observed by self-complementarity in size and shape between the host and one of a pair of enantiomers. Rebek *et al*. have described an example of this approach [89] (Section 27.3.5).

In a different approach, chiral discrimination can also be accomplished by the differences between both enantiomers in number and quality of the interactions with the host.

For example, Figure 27.30 show a bowl shape complex **100** that binds selectively (−)-morphine **101** (natural morphine) 43-fold versus (+)-morphine **102** [103]. This "bowl" is formed by a porphyrin core covalently surrounded by four cholate units.

The difference in selectivity towards the natural isomers lies in the fact that (−)-morphine **101** has three binding-points to the host: coordination of the nitrogen to the zinc and formation of two hydrogen bonds through the hydroxyl groups, whereas the non-natural morphine **102**, apart from the nitrogen–zinc coordination, is only able to make a single hydrogen bond with the "bowl" **100**.

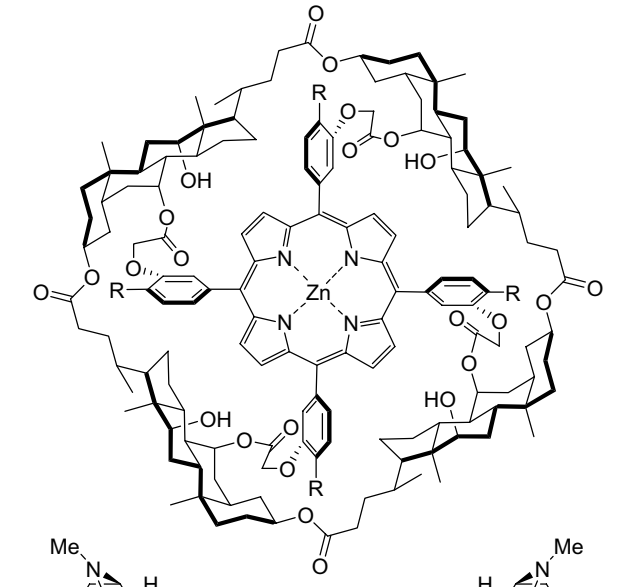


Figure 27.30 Chiral recognition by a synthetic "bowl".

27.5 Organic Conductors

27.5.1 Introduction

Low-cost, lightweight and flexibility are the main requirements for electronic devices used on a massive scale [104]. The latest research on this technology demonstrates that organic-based materials fulfill those requirements. In fact, thin film displays based on organic light emitting devices (OLEDs) are already commercial. Obviously, the organic compounds useful for these purposes are those with semiconducting or conducting properties.

Many heterocyclic structures are included in materials showing electronic conductivity, especially those heterocyclic rings with a heteroatom that is part of an aromatic ring. The common role played by the heterocycle is to modify the electronic properties of the material. In this sense, electron-rich heterocycles make the material easier to oxidize, so they will be a better carrier of holes. In contrast, electron-poor

heterocycles make the material easier to reduce, and so will be better electron carriers. Taking this into account, the conductive characteristics may be tuned by adequate selection or combination of the appropriate heterocycles.

Applying the same terminology used for semiconductors, donor (electron-rich) heterocycles are p-type molecules, and acceptor heterocycles (electron poor) n-type molecules. Additionally, the term "doping" is used in the sense of oxidizing (generation of a positive charge) or reducing (generation of a negative charge) the molecule chemically or electrochemically.

As with other organic compounds, the conductivity of one heterocycle may be modified by a change in its chemical structure or by interactions between molecules in the solid state. The chemical substitution of the molecule modulates the oxidation or reduction potentials, and the interactions between molecules greatly modify the conductivity of the bulk material.

This section discusses the conductivity of several heterocyclic materials. The synthesis and properties of heterocyclic polymers is discussed first, followed by a description of the conductivity of heterocyclic molecules in the bulk and how the structure of the bulk material in the solid state affects the final properties. Finally, single-molecule conductivity is described.

27.5.2 Conducting Heterocyclic Polymers

From the mid-1970s, conjugated polymers have attracted increasing interest due to their electronic properties and the applications derived from them. In 2000, Heeger, MacDiarmid and Shirakawa were awarded the Nobel Prize in Chemistry for the discovery of metallic-type electronic conductivity in doped poly(acetylene). As there are only a few conjugated polymers with only carbon in the backbone, the incorporation of heterocyclic structures permits different kinds of conjugated polymers with tunable properties. Some of these properties are related to enhanced stability; it is generally agreed that heterocyclic polymers are more stable than all-carbon conducting polymers. Other properties depend on the energy of the band gap between the conduction and the valence band, which is typically 1 to 3 eV in the neutral state. As the excitation of carriers in the neutral state would occur at energy levels less than 2 eV, these polymeric systems would be insulators or, at best, semiconductors [105], and they only become conductors when they are doped. Recent efforts in conducting polymers have focused on diminishing the band gap, but conjugated polymers with a vanishing band gap have not yet been synthesized [106].

Figure 27.31 shows a selection of the most important heterocyclic conducting polymers: poly(thiophene)s **103**, poly(thiazole)s **104**, poly(pyrrole)s **105**, poly(selenophene)s **106**, poly(furan) (**107**), poly(pyridine-2,5-diyl) (**108**), poly(pyridazine-3,6-diyl) (**109**), poly(quinolinediyl-5,8-diyl) (**110**), poly(isoquinoline-1,4-diyl) (**111**), poly(1,5-naphthyridine-2,6-diyl) (**112**), and poly(quinoxaline-5,8-diyl) **113**. In general, these polymers are synthesized by two different methodologies: electrochemically and/or chemical coupling. As the final properties very much depend on the synthetic

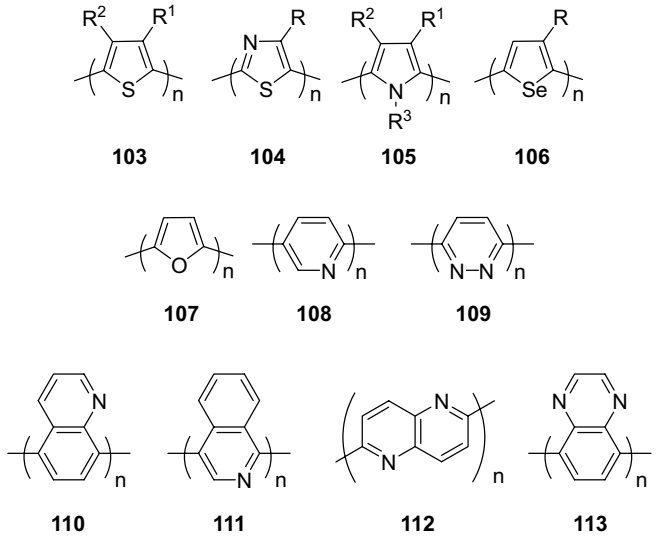


Figure 27.31 Structure of some heterocyclic conducting polymers.

method used, we discuss the alternative synthetic methods for each polymer and the consequences of selecting one or the other.

Poly(thiophene)s **103** are the most extensively studied conducting heterocyclic polymers. The first electrochemical synthesis, directly from thiophene, was developed in 1982 [107], yielding an oxidized doped, black film over the electrode. The material was insoluble in common organic solvents. However, some physical properties could be measured, such as the band gap [108] and conductivity [107], from the film removed from the electrode. The neutral polymer was obtained by carrying out a reduction over the electrode.

Several improvements to the reaction conditions, changing concentration, electrolyte, solvent, electrode material and electrical conditions [109], have produced poly (thiophene)s with increased conductivity [110]. Another approach for the electrosynthesis of high-conducting polymers is the use of substituted thiophenes. The aim of such substitution is to make the material more ordered and more processable, facilitate the electropolymerization by reduction of the oxidation potential, and, in some cases, make the polymer more stable in air. Consequently, the electropolymerization of many different substituted thiophenes has been reported; Figure 27.32 shows a selection of the most relevant.

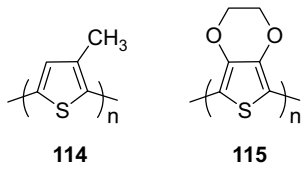


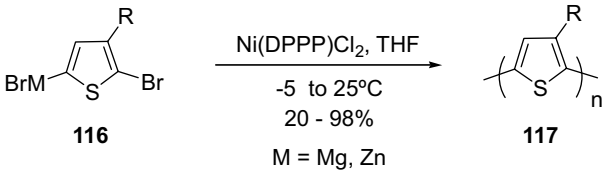
Figure 27.32 Substituted polythiophenes.

Polymer **114** has been used as a model compound owing to its better stereoregularity and conductivity [111], which are intimately related. Polymer **115** (PEDOT) is a processable polymer with an environmental stability that makes it a commercial polymer solution [112].

Poly(thiophene)s are also prepared by chemical methods, following two general approaches: chemical oxidation (typically using Fe^{3+} as oxidant), resulting in polymers in their oxidized state, and chemical coupling of organometallic compounds as the best method for directly synthesizing polymers in their neutral state.

The most efficient method for the preparation of stereoregular poly(thiophene)s is the chemical coupling of organometallic thiophene derivatives. The stereoregularity is an important issue in conducting polymers because it affects directly the transport of carriers between chains. A good stereoregularity in 3-substituted thiophenes is achieved with a head to tail coupling along the polymer chain.

Two approaches to total regioregular polymers have been independently developed by McCullough [113] and Rieke [114] using magnesium and zinc organometallic derivatives, respectively (Scheme 27.14). For example, a polymer with $R = CH_2O(CH_2)_2O(CH_2)_2OCH_3$ has been prepared with very high regioselectivity by McCullough [115], showing, to the best of our knowledge, the highest conductivity reported for a polythiophene.



Scheme 27.14 Organometallic synthesis of polythiophenes.

Poly(thiazole)s **104** have been prepared by dehalogenation–polycondensation of 2,5-dibromothiazoles [116] using a Ni(0) complex. This synthetic method does not allow the preparation of regioregular polymers head to tail, and mixtures of head to tail and head to head are obtained along the polymeric chain. In this sense, the polymerization of 5,5′-dibromo-2,2′-bithiazoles is more convenient [117], resulting in polymers with the structure shown in Figure 27.33.

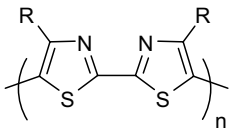


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Figure 27.33 Poly(2,2′-bithiazole-5,5′-diyl)s (**118**).

As expected for these polymers, the introduction of an imine nitrogen in the heterocyclic structure makes the material more electron poor than the equivalent poly (thiophene)s, which is demonstrated by a shift in the redox potential [117]. These polymers are insulators in their neutral state, but the conductivity increases in the n-doped state (with sodium naphthalide in THF [117]).

Poly(pyrrole)s **105** were the first conducting heterocyclic polymer directly synthesized [118] by electropolymerization (of pyrrole), although they showed moderate conductivities. Substitution by a methyl group at the 3-position of the pyrrole ring improves the stereoregularity and conductivity of these polymers [119]. Chemical oxidative coupling, using $FeCl_3$ as oxidant, allows its synthesis with a conductivity similar to the best poly(pyrrole) prepared by electropolymerization [120].

Poly(selenophene)s **106** and poly(furan) (**107**) are prepared by direct electropolymerization of selenophene [121] and furan [122], respectively. The both show low conductivity.

Polymers **108–113**, having one or more imine nitrogens, have been prepared by dehalogenation–polycondensation of the appropriate dihalogen monomer, using zero-valent Ni complexes [123], except for poly(pyridazine-3,6-diyl) (**109**) [124], which has been prepared by the electrochemical polymerization of pyridazine. In the neutral state, the conductivity of these polymers is very low, but when doped with sodium naphthalide the conductivity increases, in some cases by several orders of magnitude.

The electronic properties of heterocyclic conducting polymers have been taken account for their application in several devices [125, 126]. Although much work is necessary to use conducting polymers in the same way as metals (copper has a conductivity of $50\,000\ S\,cm^{-1}$, and in the best case for polythiophenes the conductivity is $5500\ S\,cm^{-1}$), in some cases very good behavior as semiconductors is found. These applications are divided into two groups, depending on the oxidation state of the polymers. Thus, in the oxidized or reduced forms, conducting polymers may act as anticorrosion protectors (mainly polymers with conductivities that are not pH dependent), sensors and electrochemical devices, batteries, electrochromic cells, controlled-release applications, radar applications, infrared polarizers, and so on. In the neutral state, they have been used as OLEDs and TFTs (thin film transistors).

27.5.3
Conducting Heterocyclic Molecules in the Bulk

Well-ordered systems based on heterocyclic molecules also show very interesting electronic properties, related to their semiconductor character. To obtain good performance of the devices made with these compounds (OLEDs, TFTs and solar cells), they have to be disposed over a surface with the maximum of interactions between the molecules, allowing a good mobility of hole and electron carriers [127]. There are several methods by which to create such well-ordered arrangements of molecules: crystallization, chemical vapor deposition (CVD), Langmuir–Blodgett films, mesomorphic structures arrangements, and so on.

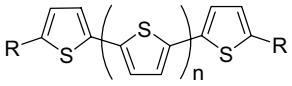

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Figure 27.34 Thiophene oligomers useful as TFTs.

Thiophene oligomers **119**, or structures based in the thiophene ring, are among the most interesting heterocyclic molecules with applications in TFTs (Figure 27.34) [128]. These compounds are mainly p-type semiconductors; although there are some n-type, it is well known that p-type heterocyclic molecules are more stable than n-type [129]. The main reason for the high mobility of carriers lies in their ability to form π-stacking face to face structures in the solid state after deposition over a surface, which facilitates charge transport between the molecules [130].

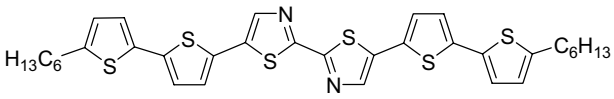
Of the synthesized oligomers **119**, from tetramer to octamer, the hexamer **120** with $R = C_6H_{13}$ shows the best behavior [131]. To increase the air stability of oligothiophenes, the p character has been lowered by incorporation of electron-poor thiazole (Figure 27.35) [132]. Air stability is crucial for application in real devices.

Commercially available pentacene, a non-heterocyclic compound used for TFT purposes, shows promising results. Consequently, some heterocyclic compounds with a related structure have been prepared and tested (Figure 27.36). Dimer **121** [133] and dialkyl anthradithiophene **122** [134] show very good performances in TFTs devices.

Tetrathiafulvalene derivatives (Figure 27.37) have been extensively used as charge-transfer salts and are discussed below. However, in the context of TFTs, some derivatives have prepared recently and their electronic properties studied. Compound **123** [135] shows the best performance, although tetrathiafulvalene **124** [136] with electron-poor nitrogen heterocycles is more stable in air.

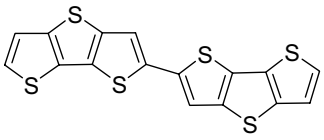
Thiophenes may also act as n-type semiconductors if appropriate groups are linked to the thiophene ring. Thus, alkyl fluorinated oligomers of thiophene (from two to six thiophene rings) have been studied [137]. Among them, the best performance was found for tetramer **125** (Figure 27.38). The inclusion of ketone groups in **125** (**126**) increases the performance by several orders of magnitude and also improves air stability [138].

Although thiophene oligomers are the most commonly used heterocyclic compounds for TFT devices, other heterocycles can also participate, and several studies of

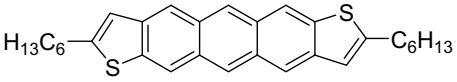


120

Figure 27.35 Thiophene-thiazole oligomer with p-type semiconductor character.

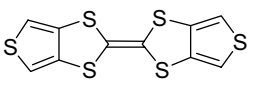


121

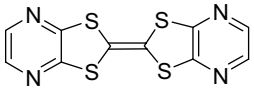


122

Figure 27.36 Fused heterocyclic aromatic molecules **121** and **122**.



123



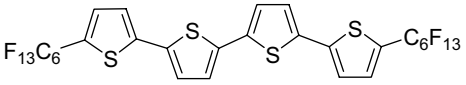
124

Figure 27.37 Tetrathiafulvalene derivatives useful as TFTs.

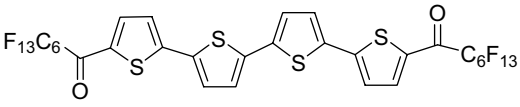
TFT devices based on nitrogen heterocycles have been performed. For example, very good results have been obtained with compound **127**, a p-type semiconductor derived from carbazole (Figure 27.39) [139].

Finally, an interesting heterocyclic skeleton that has been used as an n-type charge carrier is the metallophthalocyanine **128** substituted with 16 fluoro atoms [140] (Figure 27.40). Molecule **128** with M = Cu in combination with hexamer **119** (R = H) has found application in large-scale complementary integrated circuits [141].

Other types of organic molecular conductors are those formed by charge-transfer complexes. The discovery of the high conductivity (10 000 S cm^{-1} at 54 K) of the 1 : 1 donor–acceptor charge-transfer complex salt between tetrathiafulvalene (**129**) and tetracyano-*p*-quinodimethane (**130**) [142] (Figure 27.41) has opened a new field in

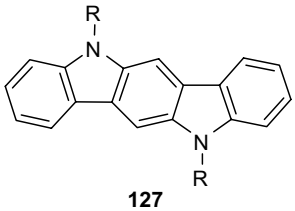


125



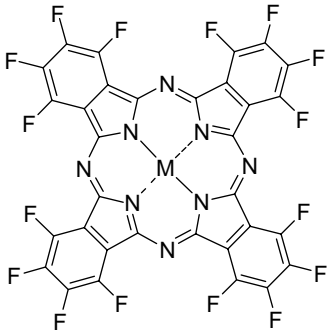
126

Figure 27.38 Perfluoroalkylquaterthiophenes **125** and **126**.



127

Figure 27.39 Carbazole-derivative p-type semiconductors.



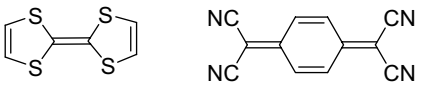
128

Figure 27.40 Perfluorinated metallophthalocyanine: an n-type semiconductor.

materials, with conductive properties varying from semiconductors to superconductors. A brief description of several heterocycles used as donors or acceptors for charge-transfer complexes is given below.

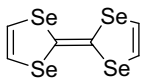
Several modifications of compound **129** have been made to obtain new molecules so as to increase the interactions in the crystalline state and reduce the ionic potential, to favor the electron donation. Some of those heterocyclic compounds, shown in Figure 27.42 [143, 144], exhibit either metallic conduction, when they interact with organic acceptors, or even superconduction when crystallized with some inorganic anions.

The incorporation of heteroatoms other than O, S and Se also produces materials for charge-transfer complexes salts. The structure of these compounds (**136**) is

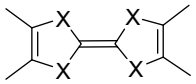


129 **130**

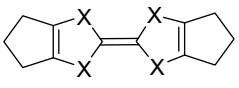
Figure 27.41 The first reported acceptor–donor charge-transfer organic complex salt.



131

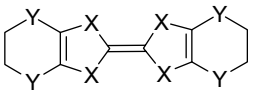


132

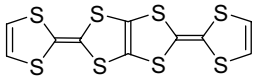


133

X = S, Se
Y = O, S, Se



134



135

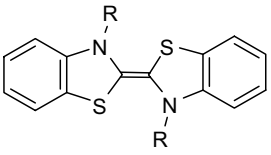
Figure 27.42 Structures of some modified acceptors for charge-transfer complexes.

similar to that of tetrathiafulvalenes although they present lower air stability (Figure 27.43) [145].

In general, all these molecules present conductivity when they form charge-transfer complexes. Of particular note is the remarkable superconductivity transition at low temperature for molecule **132** (X = Se; Figure 27.42) when salts are formed with anions such as PF_6^-, AsF_6^-, SbF_6^-, TaF_6^-, BF_4^-, ClO_4^-, ReO_4^-, or NO_3^- [146].

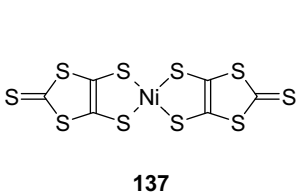
Although less work has been carried out on charge-transfer complexes with acceptors derived from heterocycles, several compounds have been reported (Figure 27.44) [147, 148]. Molecule **137**, a Ni complex with heterocyclic ligands, forms an interesting charge-transfer salt with Li(15-crown-5-ether), which is, at the same time, electron conductor by **137** and ionic conductor by the crown ether [149].

Very interesting systems are those in which the conduction is tailored to a preferred direction, such as in columnar discotic mesogens. These systems are packed in columns and have the appropriate electronic characteristics. They can transport electron or hole carriers along the column direction. Several heterocyclic structures, mainly based on pyridine derivatives, have been described for the

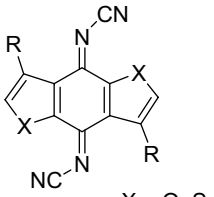


136

Figure 27.43 Donors with nitrogen atoms.



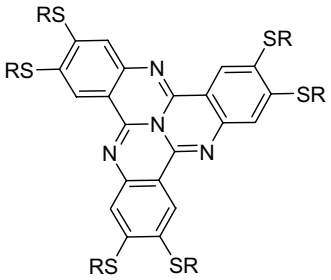
137



X = O, S

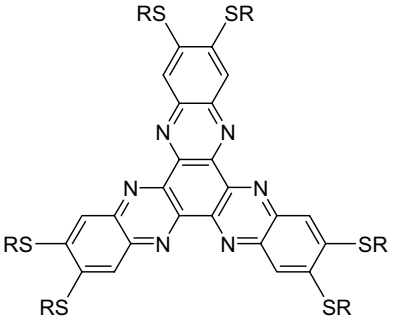
138

Figure 27.44 Structures of some alternative acceptors to **130**.



$R = C_6H_{13}$

139



$R = C_6H_{13}, C_8H_{17}, C_{10}H_{21}, C_{12}H_{25}$

140

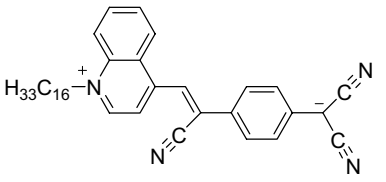
Figure 27.45 Structures of molecules **139** and **140** for discotic liquid crystals.

preparation of n-type molecules capable of being ordered in columnar discotic mesophases. Figure 27.45 shows two examples of well-characterized compounds of this type [150, 151].

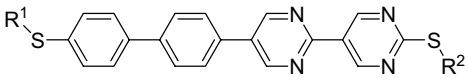
27.5.4
Single Molecule Conductivity

A very intriguing technological challenge is the reduction of the size of the components in computers and computerized machines. Surprisingly, this reduction has followed the "Moore's law" for the last 30 years, which predicts that the number of components per chip doubles every 18 months [152]. It is expected that technology based on silicon will not be useful when a certain size is reached, and, consequently, it will be necessary to change that technology. In an extreme approach, the electronic components could be formed by appropriate monomolecules [153].

One of the most studied devices at the molecular level has been the rectifier. The structure of molecules that shows a rectifier effect follows two proposals: the first is a



141



$R^1 = CH_2CH_2CN$, $R^2 = CH_2CH_2SiMe_3$

142

Figure 27.46 Two molecules showing a rectifier effect.

linkage between donor and acceptor parts of the molecule through a σ-bridge, as suggested Aviram and Ratner [154], and the second is related to the p-n junction in silicon diodes. Figure 27.46 shows two molecular examples related to the latter.

Compound **141** [155], which can form Langmuir–Blodgett films, has been layered over a metal surface and the I–V (intensity of electric current versus electric potential) curves obtained using STM (scanning tunneling microscopy). The curve is asymmetric, as it is expected for a rectifier. Molecule **142** [156] has been directly linked to a gold surface at one extreme and to a gold nanoparticle at the other extreme, allowing a more convenient way to measure the rectifier effect by STM. Moreover, the rectifier effect observed for this molecule can be inverted by protonation.

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28
Solid Phase and Combinatorial Chemistry in the Heterocyclic Field

José M. Villalgordo

28.1
Introduction

Over recent years, disciplines like molecular biology, biochemistry and genomic sciences, have undergone enormous development and an ever increasing number of potentially relevant biological targets (e.g., receptors, enzymes, transcription factors, modulators, chaperones) have been identified, expressed and isolated in pure form and in macroscopic quantities, allowing the study their structure, function and biological role in living systems. In addition, the elucidation of the entire human genome is expected to further expand the number of novel biological targets. Through techniques of crystallization and co-crystallization, numerous crystal structures of pharmacologically relevant proteins (e.g., HIV-proteinase [1], insulin receptor kinase domain [2, 3], calcineurin/FKBP12-FK506 complex [4], platelet derived growth factor (PDGF) [5, 6] and collagenase [7]) became available, opening the way to drug development programs that turned out to be very successful. As a direct consequence, during last 20 years, drug discovery has been strongly influenced by structural knowledge of target proteins and molecular modeling techniques, which have allowed in some cases the design of tailor-made ligands through the so-called "rational drug design approach."

The discovery of novel biological targets has been paralleled by the development of novel assays. Usually, after a target protein has been identified and selected it is expressed and purified using modern biochemical techniques. Once the material is available in pure form and sufficient quantity, the phases of structural determination and assay development generally start simultaneously. The use of modern informatic systems, robotics and miniaturization has allowed successful transfer of the new developed assays into a format suitable for high-throughput screening (HTS). By using HTS techniques it is possible to test several thousand compounds per day against a given biological target (Figure 28.1).

Depending on the type of biological assay, once it is transferred to a suitable HTS format, the compound collection is screened (as individual compounds or as mixtures) in a completely random fashion, or, in turn, only a subset is selected

Modern Heterocyclic Chemistry, First Edition.
Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.

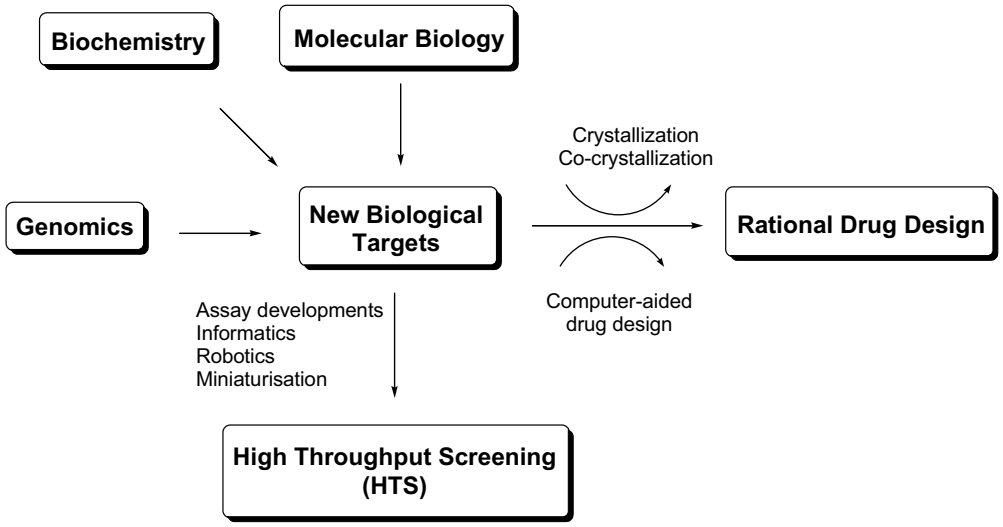


Figure 28.1 Flow chart outlining the steps in modern drug discovery.

based on 2D- and 3D-clustering techniques [8] and then screened. After an active ligand molecule has been identified it can serve as a starting point for hit-to-lead and lead optimization programs. Alternatively, in the case where crystals suitable for X-ray crystallography are available, the ligand molecule can be co-crystallized and the resulting structural information used for structure-based "de novo" design to find more potent ligands. In the ideal situation the rational and random approaches converge into lead compounds showing common structural features that are ultimately transferable into a development compound.

In addition, since a successful clinical candidate originates on average from the evaluation of a pool of 10 000 related analogues, the appearance of this literal burst of novel biological targets together with the introduction of HTS techniques has created an increasing need for novel sources of structurally and chemically diverse compound collections.

How could we then satisfy this increasing demand for novel compounds that can feed our HTS systems in the different drug discovery programs? The different sources for novel lead compounds can be grouped basically into the categories given below.

28.1.1 Natural Products

Natural products isolated from plants, microorganisms and animals of terrestrial or marine origin have a long tradition in medicine [9]. Nature offers a virtually unlimited plethora of diverse chemical scaffolds, often going beyond human imagination.

Natural products are, structurally and chemically, the most diverse source for finding new lead compounds; with a molecular weight within the range ~400 to ~1000 Da, they are often biologically active (biological activity through evolution). For example, taxol [10], monensin [11], avermectin [12], mitomycin [13–15], FK506 [16], and epothilones are just a few natural products that have served as inspiration sources for intense lead optimization programs (Figure 28.2). Usually, natural products display such enormous structural complexity that, often, the process of lead optimization is very time consuming. In addition, the development of a technical

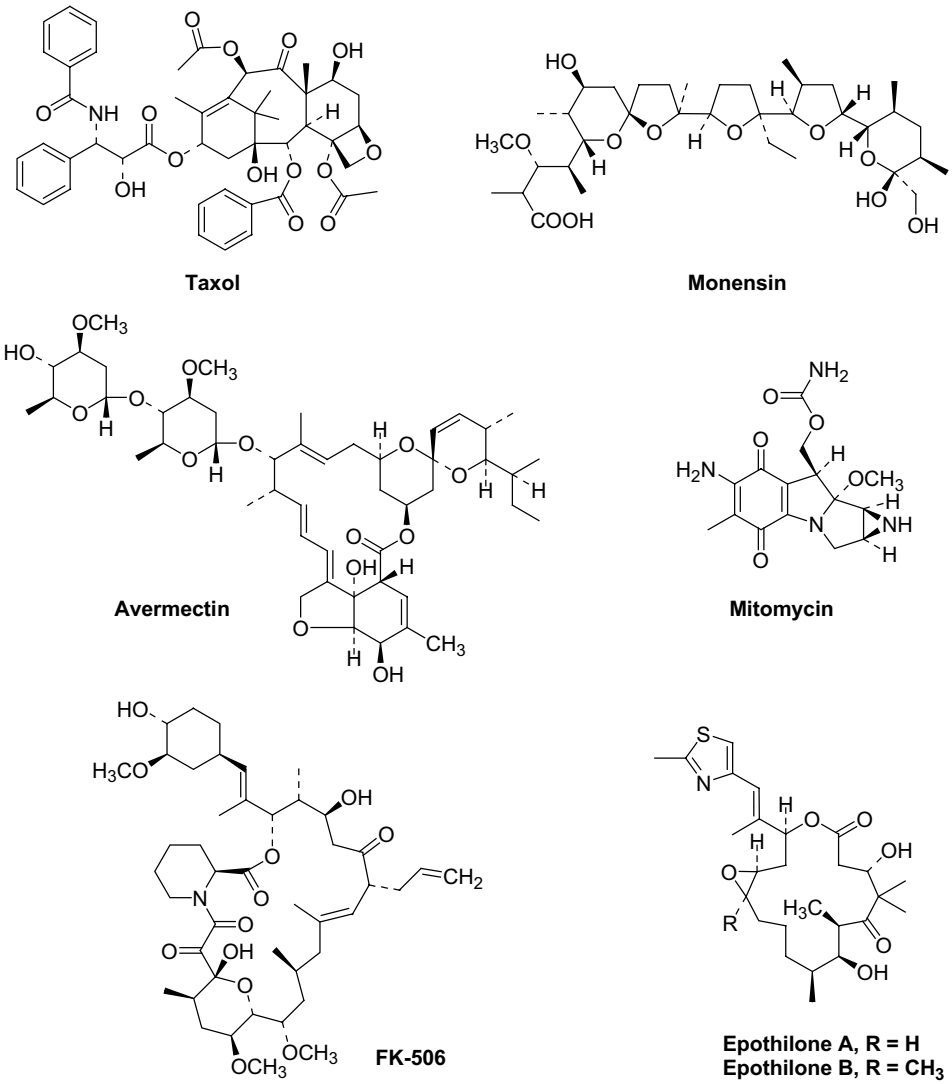


Figure 28.2 Some natural products used in lead optimization programs.

synthesis is generally very challenging and therefore the manufacturing costs of the final drugs are very high. Despite these drawbacks, natural products will undoubtedly always play a key role in finding leads.

28.1.2 Peptides, Peptoids and Peptidomimetics

Peptides are another source for feeding HTS systems for novel lead finding. There are many bioactive peptides known and their preparation is generally fast through linear assembly of similar building-blocks. They have usually a molecular weight higher than 600 Da and in general they have a low bioavailability, undergo easy proteolytic degradation and, therefore, are usually "drug-like." The transformation of a bioactive peptide into a molecule that maintains biological activity, while removing the undesired properties (conformational flexibility, low bioavailability, etc.), requires the design and preparation of peptidomimetic structures. This is, however, a complex and non-trivial task that usually requires several trial and error cycles.

Therefore, although peptides are not usually good candidates for effective drugs, many pharmacologically relevant target receptors exhibit large surface spanning areas where it is still very difficult to find small molecules as inhibitors. For such purpose, peptoids, peptides and peptidomimetics derived from structural information of the targets can be of great value as tools for finding leads.

28.1.3 Small Synthetic Organic Molecules

A highly useful source for finding novel lead compounds is compound collections of synthetic small-molecular-weight compounds that have been accumulated over the past in industrial companies and academic institutions. These compound collections are usually derived from a limited amount of "privileged" core structures such as benzodiazepines, pyridines, dihydropyridines, pyrimidines, phenothiazines and others and, therefore, they exhibit a more limited chemical and structural diversity than natural products, but, in turn, due to their usually simpler structure, a given hit or lead can be subsequently optimized in a rather straightforward manner, resulting in low manufacturing and development costs.

In fact, examination of the list of the most successful prescription drugs already on the market (data from 2004), reveals that most of them are small-molecular-weight compounds that generally bearing a heterocyclic nucleus (Figure 28.3).

Hence, chemists have been challenged to develop new high throughput synthesis techniques to satisfy this growing demand for screening compounds and allow a reasonable rate to be maintained for the detection of valuable hits and leads for subsequent lead optimization. This new demand stands behind the birth of combinatorial and parallel chemistry. Small-molecular–weight compound libraries from combinatorial and parallel chemistry are excellent tools to complement other feeding sources of HTS systems in terms of numbers and diversity. Hits and leads that have emerged from such a library are especially valuable since the optimization process is

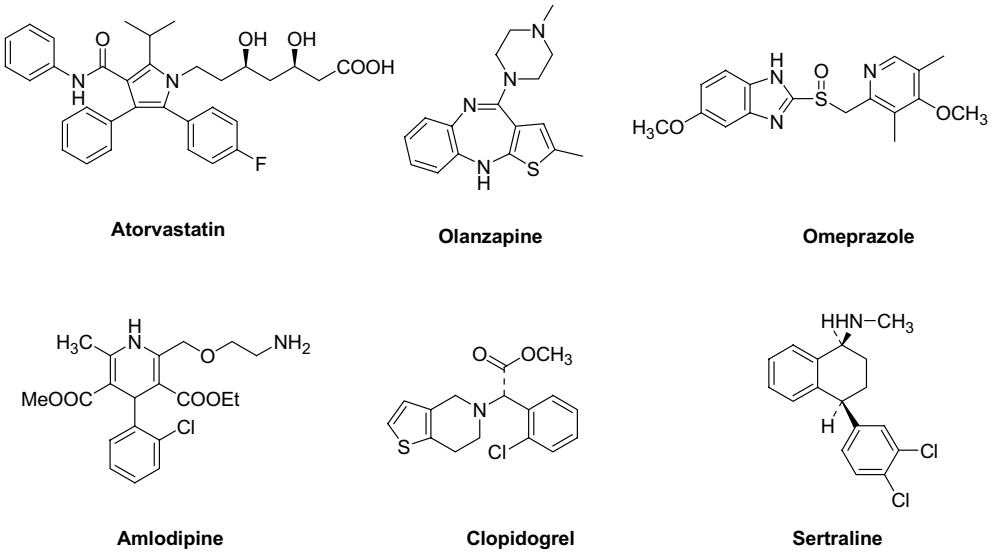


Figure 28.3 Some small-molecular-weight compounds currently employed as successful prescription drugs (data from 2004).

speeded up by the usually fast and convergent assembly strategies that have been used to synthesize the compounds. The structural complexity of the resulting compounds is only limited by the possible chemical strategies, the reactive monomers or building-blocks that can be employed and the number of those that are available and can be engaged for the final derivatization of a given library.

Combinatorial chemistry was initially developed to generate vast arrays of different peptidic molecules and can be performed in solution and/or on solid support. The resulting products can be obtained as individual compounds (parallel synthesis) or as mixtures of defined composition. In fact, combinatorial chemistry was inspired by nature. Nature, starting from just 20 simple amino acids, can obtain large combinations of different peptides with different functions. In conventional organic synthesis, one building block of type **A** (e.g., an acid chloride) is allowed to react with another building-block of type **B** (e.g. an amine) to afford one product **C** (e.g., an amide). If, however, we can employ ten different building-blocks of type **A** and ten different building-blocks of type **B**, all possible combinations of the available monomers would afford up to 100 different compounds of type **C**, and that just in one single synthetic step (Figure 28.4).

In a multistep, linear assembly, a synthetic sequence for instance, the combinatorial capacity is of course greatly expanded. This is shown schematically in Figure 28.5, where in a four-step synthesis, simply by using ten different building-blocks of each class for every step, their combinations could afford potentially up to 10 000 different compounds.

Organic synthesis in solution requires that, for every single synthetic step, the product or intermediate produced be isolated and purified. Common techniques

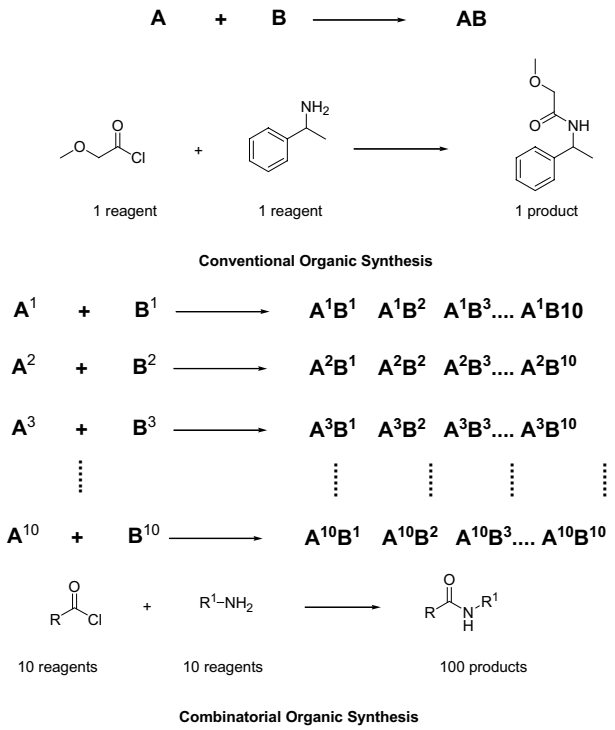


Figure 28.4 Simple comparison between conventional and combinatorial organic chemistry.

used in organic synthesis for the isolation and purification of the compounds are extraction, distillation, chromatography and crystallization. The fastest way to isolate a compound in pure form is crystallization: The product is precipitated with a suitable solvent, filtered off, washed and used readily in the next step. This is only possible of course when the product is a solid. This is then the rationale behind the use of solid-phase organic synthesis (SPOS).

Schematically, SPOS consists in having a suitable solid support that is chemically modified to introduce a linker that in turn bears a given available functional group where the synthetic procedure can begin. The targeted molecule is then grown onto

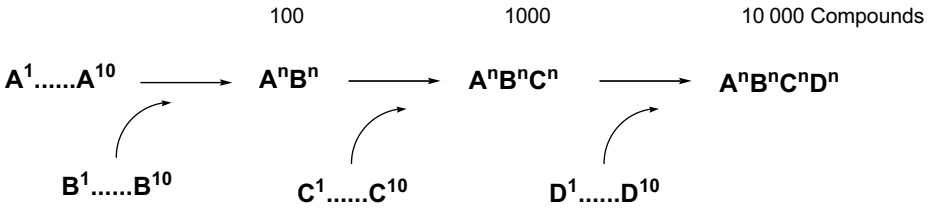


Figure 28.5 Multi-step combinatorial synthesis.

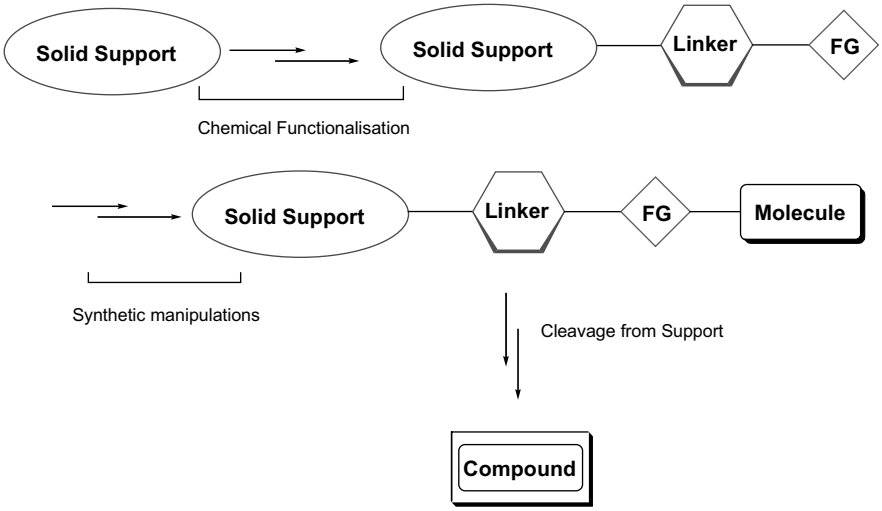


Figure 28.6 Schematic outline of solid phase organic synthesis (SPOS).

the solid support through suitable synthetic procedures and, finally, cleaved from the support (Figure 28.6).

28.2 Solid Supports

For many years, polymeric supports have been mainly used to immobilize substrates, reagents, and catalysts. In addition, insoluble polymeric matrices are widely used in solid–liquid separations processes. The polymers that have been used in the synthesis of small organic molecules can be grouped into the following classes:

- **Crosslinked organic polymers**: these are insoluble in organic solvents. They can be in the form of microporous polymers or gels [e.g., polystyrene, poly(4-vinylpyridine)] or as a macroporous polymers (e.g., polystyrene-derived beads).
- **Linear organic polymers**: these are usually soluble in certain organic solvents but insoluble in others [e.g., poly(ethylene glycol) (PEG), polystyrene].
- **Dendrimers**: their solubility depends on size and shape.
- **Inorganic supports**: such as silica gel, alumina, clays, graphite or porous glass.

Solid phase chemistry began with Merrifield's seminal polypeptide synthesis [17]. Owing to the highly repetitive cycles of removal of protecting groups, washing and coupling procedures, peptide synthesis became an ideal target for solid-phase synthesis. In recent decades, solid-phase peptide synthesis has matured to become a highly automated and powerful technology. Closely related to the linear assembly strategy of polypeptides, other biopolymers like oligonucleotides [18, 19] and oligosaccharides [18, 20] have also attracted great interest. In recent years, and due

to the increasing demand for novel molecules for HTS, the synthesis of small molecules on solid supports has been generally performed by using either soluble linear polymers (usually PEG [21, 22] or polystyrene-derived supports [23–26]) or insoluble matrices. With the former, the polymer-bound substrates are isolated and purified by precipitation [21, 22, 24, 25], ultrafiltration [27], or dialysis or gel filtration [23]. This technology takes advantage of combining the well-established solution chemistry with simple purification procedures. These purification procedures, however, are often very time-consuming and not generally easily adapted to automated systems.

However, the vast majority of applications in the field of solid-supported organic synthesis use insoluble polymeric matrices – some advantages of which can be summarized as follows:

- Purification can be performed by simply washing and filtration cycles.
- The use of large excesses of reagents is allowed, with the general benefit of driving the reactions to total completion. The excess of reagents are easily removed by washing with suitable solvents.
- Reaction, washing and filtration steps can be easily automated.

Among the polymeric supports that have been employed in solid phase synthesis, polystyrene-derived resins crosslinked with varying amounts of divinylbenzene (DVB, typically 1–5%) are of the most widespread use. These resins are simply spherical beads of different sizes. Depending on the polymerization protocol, these resins can be micro- or macroporous. Resins that have found wide applications in organic synthesis are:

- Micro- and macroporous polystyrene/DVB-crosslinked resin beads (Merrifield type-resins). These resins are fairly available, can be easily functionalized with high loading (between 1 and 3.5 mmol g^{-1}) and are widely used in solid-supported polypeptide as well as in small molecule synthesis.
- Polystyrene/DVB-crosslinked polymeric matrix coated with poly(ethylene glycol) spacers of various sizes (e.g., Tentagel). These resins are less hydrophobic and show better swelling properties in aqueous and in alcoholic solvents, but in turn they are usually mechanically less stable and show a lower loading degree than the Merrifield-type resins. They have found widespread use in solid-supported peptide- and small molecule synthesis.
- Polystyrene/DVB-derived resin beads sealed in a porous polypropylene bag (tea-bags), developed originally by Houghten *et al.*, have been also used, mainly for the combinatorial and parallel synthesis of peptides. Each bag contains one type of polymer-bound molecule. Different tea-bags can be mixed and are allowed to react with the same building-block, can be washed in parallel and then be separated. Since the reactions take place in separate compartments there will be only one type of well specified molecule in each bag. This protocol allows the synthesis of larger amounts of material and similar to the "split-mixed" technology the number of coupling steps is reduced while all benefits of solid-supported chemistry are maintained.

- Polystyrene- or polymethacrylamide-dimethylacrylamide-(copolymerized) derived matrices grafted onto polyethylene crowns that are attached to the top of pins are another system widely used for solid-support organic synthesis. These pins are usually assembled in the 96-deepwell plate format. This technology, originally developed by Geysen *et al.* [28–30] for the parallel synthesis of peptide libraries, has also found applications in the synthesis of small-molecular-weight compound collections [31–34].
- Other solid supports include foils [35] and cellulose disks [36].

28.2.1
Crosslinked Polystyrene-Derived Matrices

Crosslinked polystyrene beads are obtained by free radical initiated copolymerization of styrene and variable amounts of divinylbenzene (DVB). A suspension of water, styrene and DVB are mixed in the presence of a free radical initiator like dibenzoyl peroxide or azoisobutyronitrile (AIBN) and heated to a suitable temperature for polymerization. The aqueous phase initiates a fine dispersion of the mixture of monomers that serves as a medium to control the reaction temperature but does not participate in the reaction. Coalescence of monomer droplets leads to association and the formation of conglomerates. Suspension stabilizers such as poly(vinyl alcohol) or derivatives of cellulose are added to avoid these aggregations and to ensure a reproducible polymerization process. These aggregation phenomena can also be suppressed by addition of salts to the aqueous phase, producing a change in the surface interface forces. Thus, the polymerization proceeds in each droplet and initiates the formation of a polymer bed. The size of the bed can be controlled by the stirring speed, the relative ratio between aqueous and monomer phase, the amount and nature of the suspension stabilizers and by the reaction temperature.

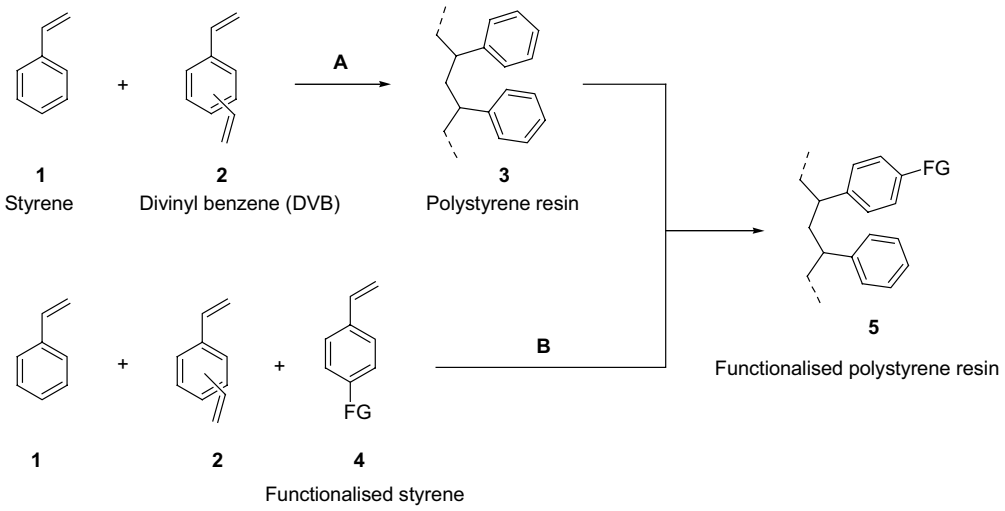
In essence, the swelling properties of the resin beads depend on the crosslinking degree and, therefore, on the relative amount of DVB in the core monomer [37, 38]. Resins containing a low crosslinking degree (typically 1–2% DVB) show a higher swelling capacity than those with a higher content of DVB (>5%) [39]. The size and shape of the resin particles can be controlled to some extent by suspension polymerization.

28.2.2
Functionalized Polystyrene Resins

The application of polystyrene-derived resins is widespread because styrene consists of a chemically inert alkyl backbone carrying chemically reactive aryl side chains that can be easily modified. Nowadays, a wide range of different types of polystyrene resins with various physical properties can be easily generated by simply modifying the crosslinking degree. In addition, numerous styrene-derived monomers are commercially available. The main feature of polystyrene, and hence one of the main reasons for its widespread use, is that it is chemically stable to many reaction

conditions, while the benzene moiety can be easily functionalized in many ways through electrophilic aromatic substitutions or through lithiations.

In general, there are two main ways of obtaining functionalized polystyrene/DVB-copolymers. As shown in Scheme 28.1, in approach **A**, a polystyrene crosslinked with DVB (**3**) is obtained through copolymerization of styrene monomers (**1**) with varying amounts of DVB (**2**) followed by subsequent chemical introduction of the corresponding functional group; in approach **B**, the functional group is already incorporated in a modified styrene-derived monomer (**4**).



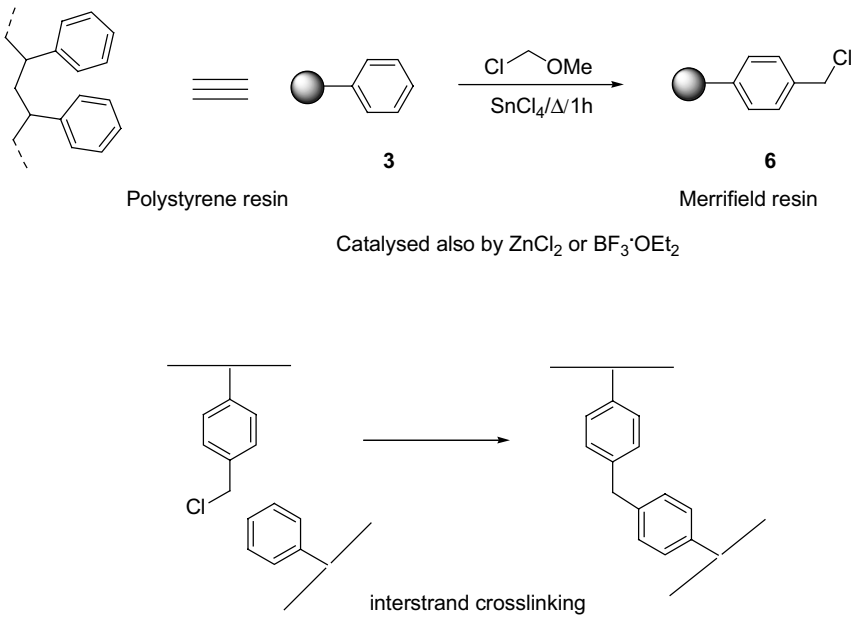
Scheme 28.1

The chemical modification of crosslinked polystyrene (approach **A**) offers the advantage that only accessible benzene rings and positions on the aromatic rings are functionalized. In turn, the disadvantage of this approach is that the reactions on polymers are usually slower and difficult to monitor. This can significantly affect the yields due to side reactions and thus the loading degree. Approach **B** assures the exact positioning of the functional groups and usually a high loading degree, but it needs prior synthesis of the appropriate monomers. Since the first functionalization determines the loading of the resin, it is important that these reactions proceed with high yields and reproducibility.

28.2.3 Chloromethylated Polystyrenes

Although chloromethyl polystyrene was first used as an intermediate for the synthesis of anion exchange resins [40], it was not until the introduction by Merrifield [17] of the solid-phase peptide synthesis that its use attracted a burst of attention. Chloromethylated polystyrenes (**6**) are best synthesized by Friedel–Crafts

alkylation of polystyrene with methoxymethylene chloride in the presence of a Lewis acid such as $SnCl_4$ (Scheme 28.2) [17, 40].



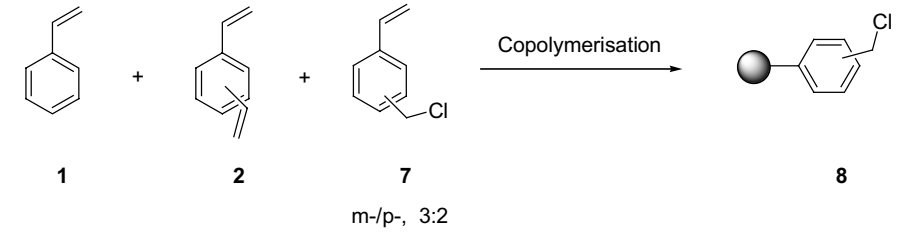
Scheme 28.2

Regarding the swelling properties of chloromethylated polystyrenes, it has been shown [41] that up to a chlorine content of 19% (about 0.75 chlorine atoms per aromatic ring) there is no significant drop in swelling. An increase of loading, however, leads to a markedly less swelling capacity, indicating a higher degree of crosslinking by "interstrand" couplings (Scheme 28.2).

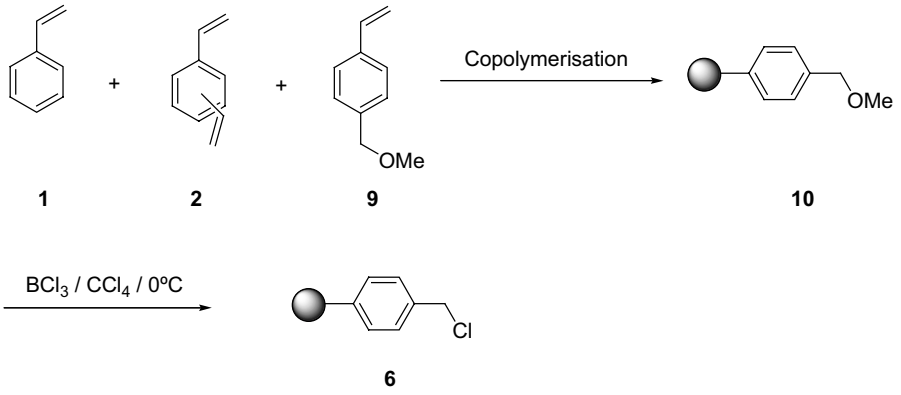
For soluble polystyrenes (without DVB crosslinking), it has been shown by NMR that the ratio of para- to ortho-chloromethylation was 95 : 5 [42]. The same ratio, therefore, can be expected for resins with a low degree of crosslinking. The use of $ZnCl_2$ instead of $SnCl_4$ in the chloromethylation reaction with methoxymethylene chloride leads to a resin with a low degree of functionalization [43]. In addition, by using $BF_3.OEt_2$ as catalyst and ethoxymethylene chloride as alkylating agent, the loading degree can be controlled by the amount of catalyst used [44].

Chloromethylated resins have also been synthesized by copolymerization of styrene, divinylbenzene and chloromethylstyrene **7** (usually as a 3 : 2 mixture of meta and para isomers), although this approach can lead to substantial losses of chlorine content [45–47] (Scheme 28.3).

Merrifield resin **6** with a chlorine content up to 22% (which corresponds to 1.0 chlorine atom per aromatic ring) can be obtained by copolymerization of 4-methoxymethylstyrene (**9**) and DVB and subsequent conversion using BCl_3 in CCl_4 (Scheme 28.4) [47].

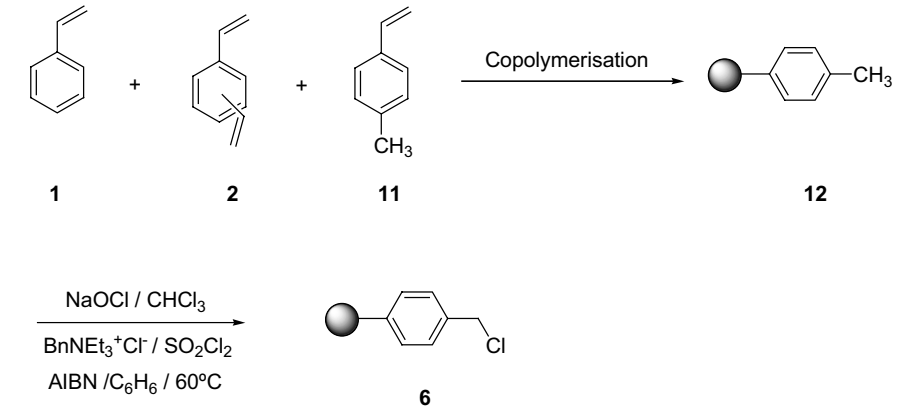


Scheme 28.3



Scheme 28.4

Chlorination of 4-methylpolystyrene **12** (obtained by copolymerization of styrene, DVB and 4-methylstyrene) with NaOCl in the presence of a phase-transfer catalyst [48] proved to be a valuable method for the preparation of microporous (1% DVB crosslinking) as well as macroporous (20% DVB-crosslinking) chloromethylpolystyrene **6** (Scheme 28.5).

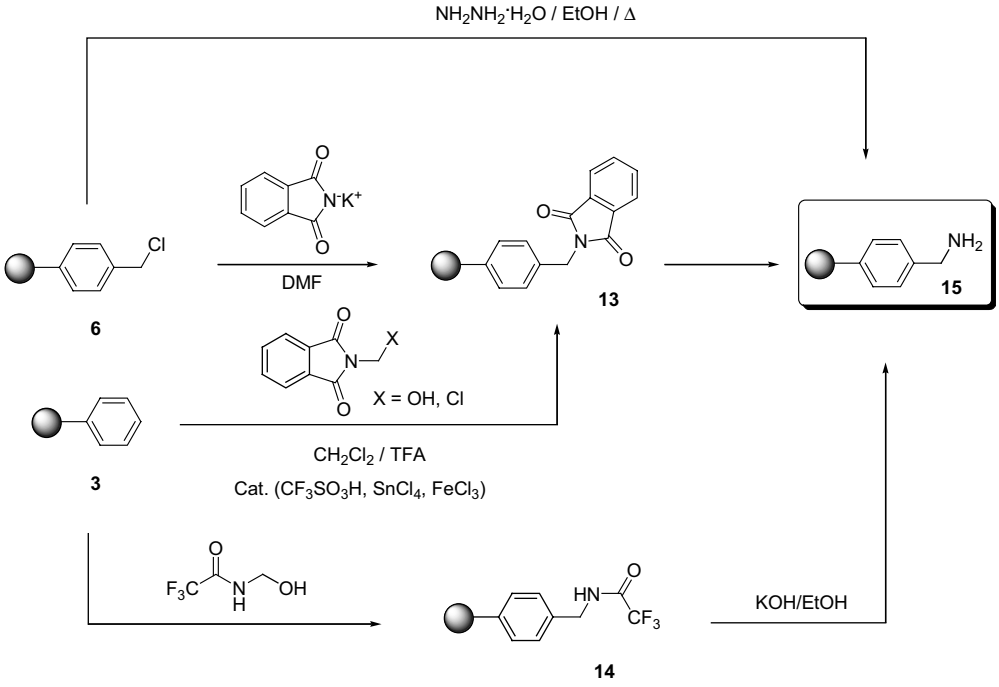


Scheme 28.5

Again, through NMR techniques, it could be shown that for a loading degree higher than 2.5 mmol g^{-1} dichloromethyl groups were also present [48]. Since the elemental combustion analysis gave higher chlorine contents than those determined by NMR, it was concluded that partial chlorination of the backbone also occurs.

28.2.4
Aminomethylated Polystyrene Resins

Aminomethylated, crosslinked polystyrenes constitute very valuable and versatile resins for various applications. The amino group can be easily acylated for the introduction of spacer and linker molecules [49–52]. It has been used also for the synthesis of polymer-bound carbodiimides [53–55]. Scheme 28.6 shows some of the most common synthetic procedures for the synthesis of aminomethylpolystyrenes.



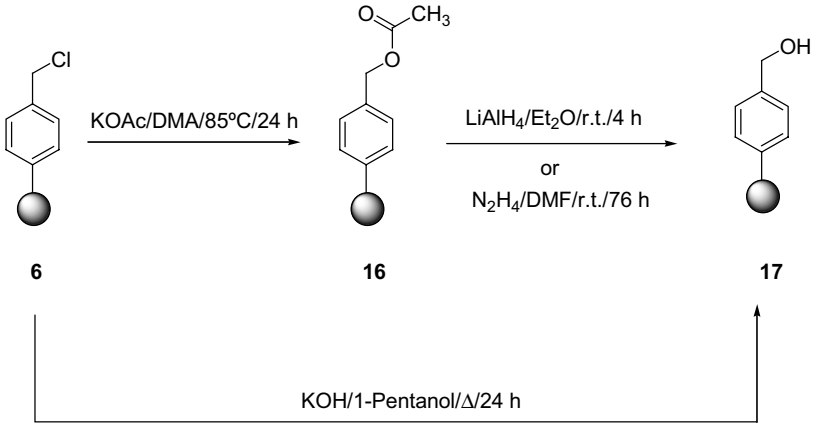
Scheme 28.6

Although aminomethyl resins **15** can be obtained through reaction of chloromethylated polystyrene (**6**) with non-aqueous ammonia [56] with good conversion, the reaction is rather slow. Excellent conversions are obtained, however, by using potassium phthalimide [51, 53–55, 57] instead, followed by treatment with hydrazine. The same phthalimido intermediate can be obtained from polystyrene **3** and *N*-(hydroxymethyl)- or *N*-(chloromethyl)phthalimide in the presence of an acid

catalyst such as HF, CF_3SO_3H or $SnCl_4$ [49, 50]. The loading degree (typically 0.05–3.6 mmol g^{-1}) can be controlled by the amount of reagent and the concentration of the catalyst by using *N*-(chloromethyl)phthalimide in CH_2Cl_2 and using $FeCl_3$ as catalyst [58]. Loadings as high as 7.3 mmol g^{-1} can be achieved, but the resultant resins show very limited swelling properties. Aminomethylated resins can also be obtained through the reaction of polystyrene with *N*-(hydroxymethyl)trifluoroacetamide followed by hydrolysis with KOH in EtOH [50].

28.2.5
Other Functionalized Polystyrene Resins

Besides aminomethylpolystyrene **15**, many other functionalized polystyrene resins can be prepared from chloromethyl resin through nucleophilic displacement. For instance, when Merrifield resin **6** is treated with KOAC in DMA at 85 °C, acetylated polymer **16** is obtained [59, 60]. Reduction of **16** with $LiAlH_4$ or hydrazinolysis at room temperature affords hydromethyl polystyrene resin [60] **17**. Alternatively, **17** can be obtained directly by reaction of **6** with KOH in refluxing 1-pentanol (Scheme 28.7) [61].

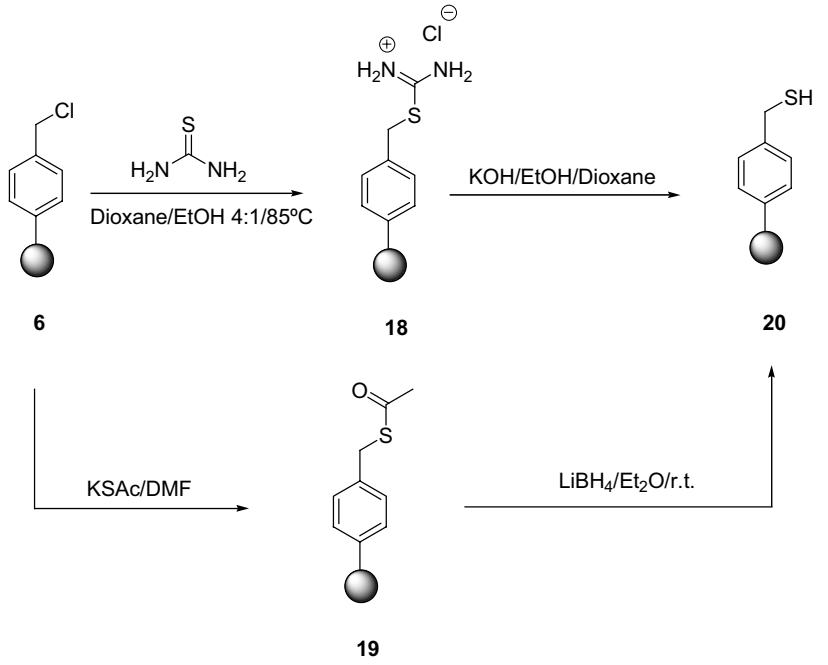


Scheme 28.7

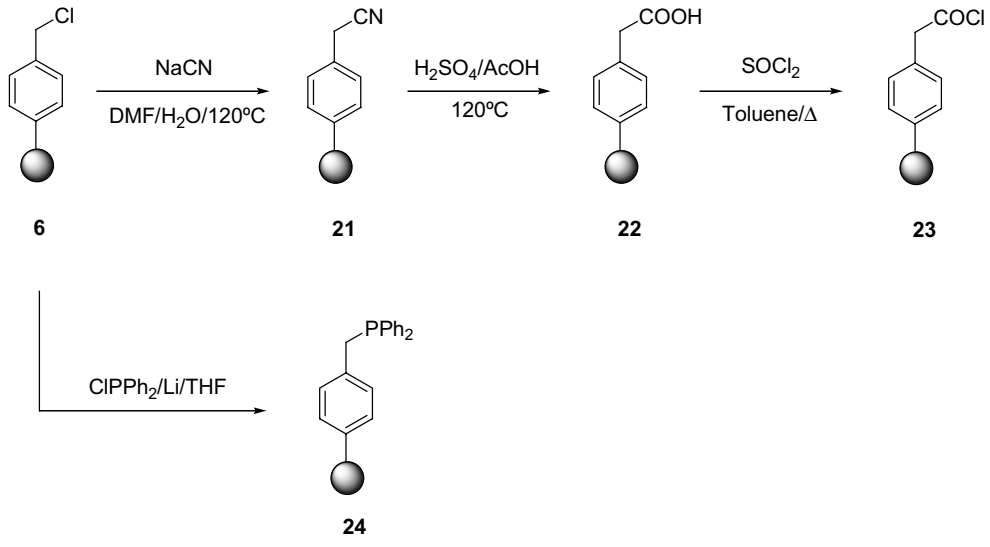
Reaction of **6** with thiourea in refluxing ethanol/dioxane leads to polymer-bound thiouronium salt [62] **18** that can be hydrolyzed to thiol **20**. Alternatively, reaction of **6** with KSAc in DMF affords **19**, which can be also reduced with $LiBH_4$ to give the thiol resin (Scheme 28.8) [63].

In addition, Merrifield resin **6** is easily transformed into cyanide derivative **21**, which in turn can be transformed into the corresponding carboxylic acid **22** or acid chloride [64] **23**. Phosphine **24** is also easily available by reaction with $Li/ClPPh_2$ (Scheme 28.9) [65].

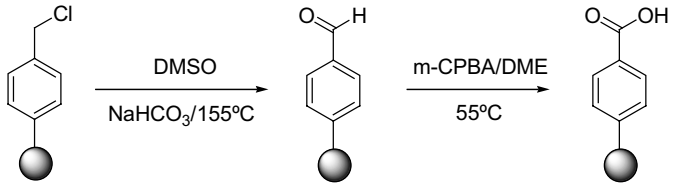
Finally, oxidation of Merrifield resin **6** can also afford the corresponding benzaldehyde resin **25** and, hence, polymer-bound benzoic acid **26** (Scheme 28.10) [66, 67].



Scheme 28.8



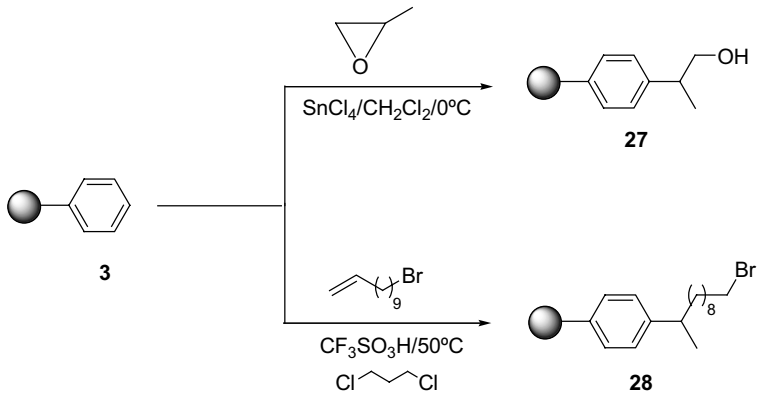
Scheme 28.9



6 **25** **26**

Scheme 28.10

The synthesis of other functionalized polymers containing spacer or linker units usually starts with a Friedel–Crafts alkylation of the basic polystyrene resin **3**. Reaction of polystyrene with propylene oxide in the presence of $SnCl_4$ yields a resin containing a β-hydroxyl group (**27**). Prior to addition of the reagent, the resin is treated with the Lewis acid catalyst to afford a complex [68]. Alkylation of polystyrene resins with ω-bromoalkenes in the presence of trifluoromethane sulfonic acid yields bromoalkyl polystyrene **28**. This reaction presumably proceeds without additional crosslinking, as shown, in comparison to similar experiments with soluble polymers (Scheme 28.11) [69].

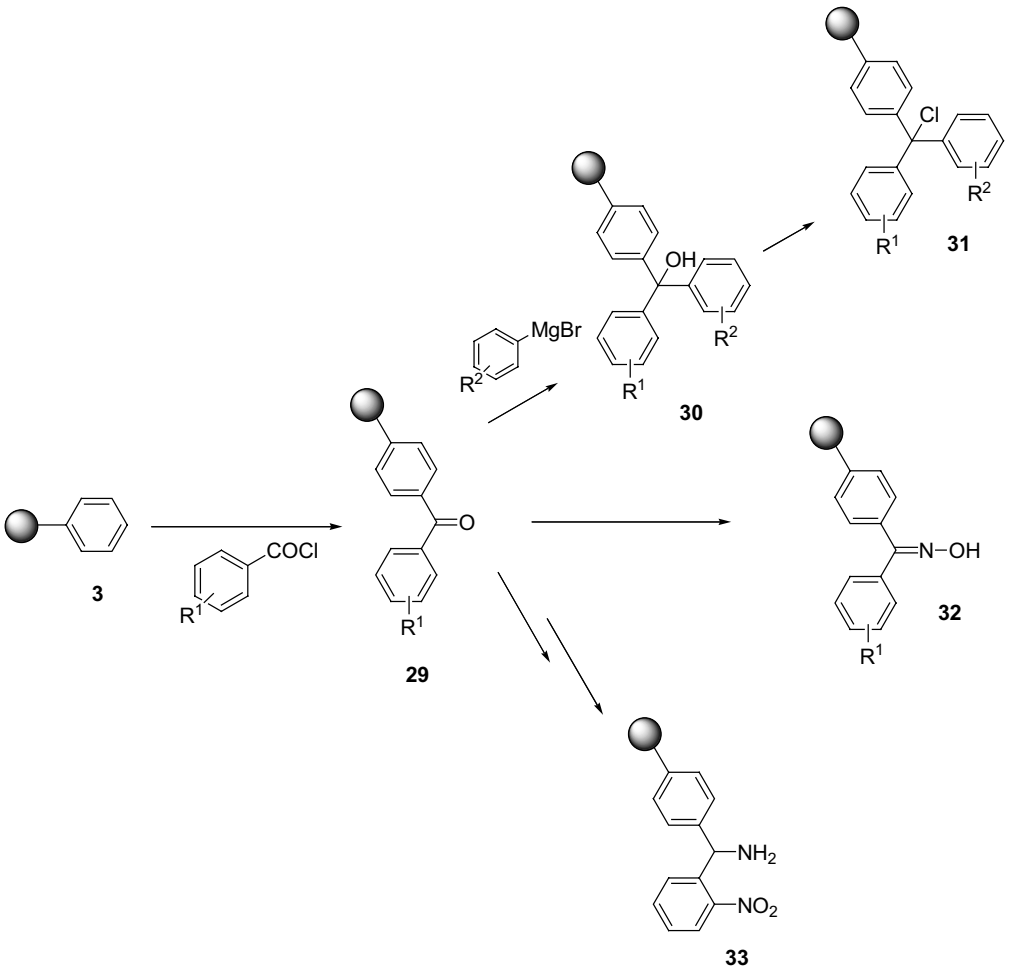


Scheme 28.11

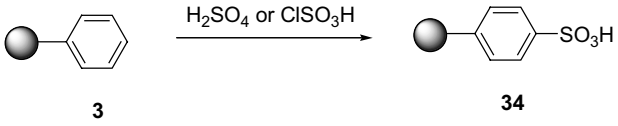
Friedel–Crafts acylation of micro- and macroporous polystyrene resins yields the corresponding benzophenone-derived resins **29**. These functionalized resins can be further transformed into trityl- (**30** and **31**), oxime-derived (**32**) or into photolabile o-nitrobenzhydryl derived resins (**33**), which have been widely used in peptide synthesis and oligonucleotide chemistry (Scheme 28.12) [70–72].

Strongly acidic cation-exchange resins of type **34** can be obtained by sulfonylation of polystyrene using H_2SO_4 or $ClSO_3H$ (Scheme 28.13).

Nitration of polystyrene resins **3** followed by reduction with $SnCl_2$ results in the formation of aniline **36**, which can be further transformed into the corresponding isothiocyanate **37** (Scheme 28.14). This polymer has found applications as an insoluble reagent for Edman degradation [73].

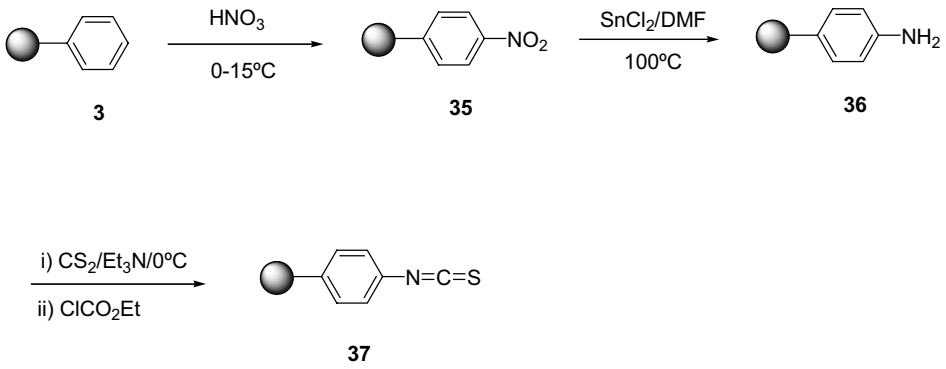


Scheme 28.12



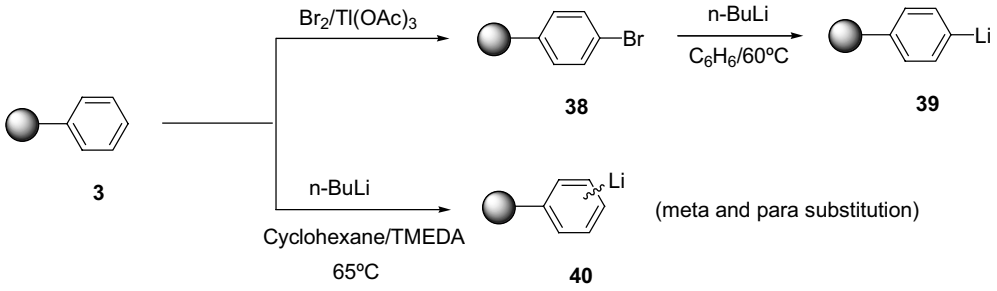
Scheme 28.13

As discussed above, many different functionalized polystyrene-derived resins can be obtained through electrophilic aromatic substitution reactions; however, another valuable synthetic route to other functionalized resins is based on the lithiation of polystyrenes.



Scheme 28.14

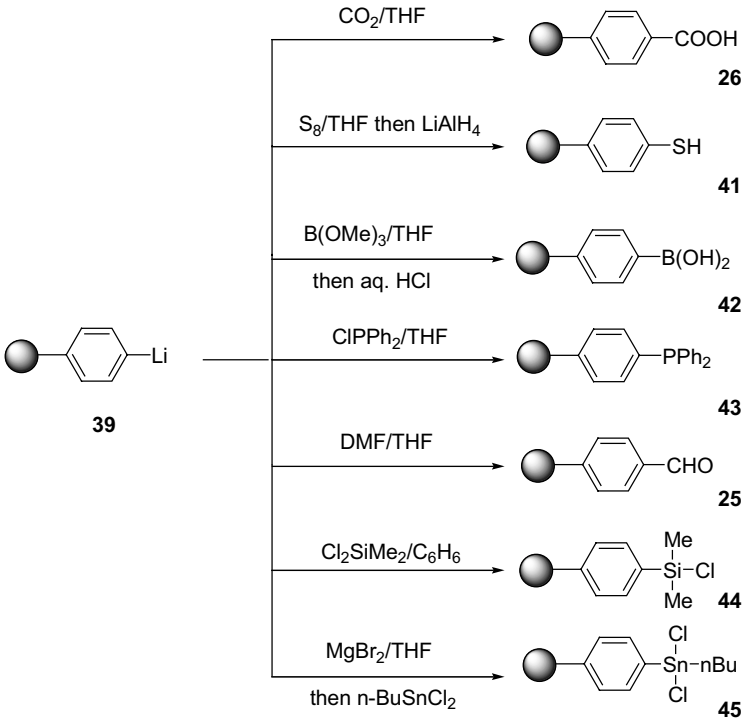
Lithiated polystyrene resins can be obtained either via convenient bromine–lithium exchange using n-BuLi, starting from 4-bromo-substituted polystyrene [65, 74–78], or by direct lithiation of polystyrene using n-BuLi in cyclohexane in the presence of TMEDA [74, 79]. The latter method, however, yields a mixture of para and meta isomers (**40**). Bromination of microporous resins in the presence of a Lewis acid catalyst is generally carried out in the dark, whereby the loading degree can be conveniently controlled by the amount of bromine used in the reaction [74]. Macroreticular resins can be brominated using Br_2 and $FeCl_3$ [39], or by using a stoichiometric amount of thallium acetate as Lewis acid catalyst (Scheme 28.15) [76, 77].



Scheme 28.15

The bromine–lithium exchange on macroreticular polystyrene resins can be driven to completion by using iterative lithiation reactions with n-BuLi in THF [74]. Highly loaded microporous resins can be lithiated successfully in toluene or benzene. Direct lithiation reaction of microporous polystyrene-derived resins (2% DVB) using n-BuLi in cyclohexane in the presence of TMEDA is much faster than that of macroreticular resins (20% DVB) [79]. Notably, for this reaction, THF and benzene are not adequate solvents. The use of cyclohexane as solvent allows the synthesis of resins with a low or medium loading degree (up to 2.0 mmol g^{-1}). For higher loadings, the bromination–lithiation route needs to be used.

Lithiated polystyrene is a very versatile intermediate, since many differently functionalized polystyrene-derived resins can be obtained through different chemical reactions [76, 78, 80]. Scheme 28.16 shows several examples.

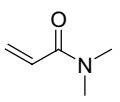


Scheme 28.16

28.2.6
Polyacrylamide Resins

In microporous resins, the corresponding functional groups can only react when the polymers show a high degree of swelling. These swelling properties depend largely on the nature of the functional groups present. Thus, during a synthesis on a polymeric support, the swelling properties of the resin can undergo significant changes. For instance, in the Merrifield peptide synthesis, the starting polystyrene-derived resin is highly hydrophobic but becomes increasingly hydrophilic as the synthesis of the peptide evolves and the peptidic chain grows. Owing to such phenomena, certain peptide sequences are rather difficult to synthesize on standard Merrifield resins. To improve this situation, Sheppard *et al.* [81] have altered the hydrophobic nature of the polystyrene polymer backbone by introducing a polyacrylamide polymer backbone, which they felt is quite similar to a peptide.

The first polyacrylamide resins were prepared by copolymerization of *N*,*N*-dimethylacrylamide (**46**) (basic monomer), ethylenebisacrylamide (**47**) (crosslinking agent) and *N*-acryloyl-*N*′-(*tert*-butoxycarbonyl-β-alanyl)hexamethylene diamine (**48**) (functionalized monomer) (Scheme 28.17) [82]. Monomer **48** is essentially used to functionalize the polyacrylamide polymer after liberation of the primary amino group of the β-alanine moiety. The hexaethylenediamine groups serve as spacers to separate the reactive groups. Monomer **48** was later replaced by acryloylsarcosin methyl ester (**49**) [83], which is chemically very similar to the basic monomer, to achieve a homogenous distribution of the functional groups. Copolymerization of monomers **46**, **47**, and **49** initiated by persulfate in an emulsion with 66% aqueous DMF, 1,2-dichloroethane and cellulose acetate or butyrate yields beads with a high swelling degree (in H_2O, DMF, MeOH, Py or CH_2Cl_2, the volume increases ten times with respect to the original volume; in 1,4-dioxane about five times) [81, 83]. Aminolysis of the ester groups using ethylenediamine affords resins containing free primary amino groups.



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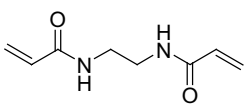

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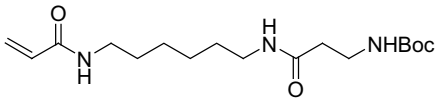

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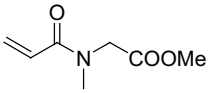

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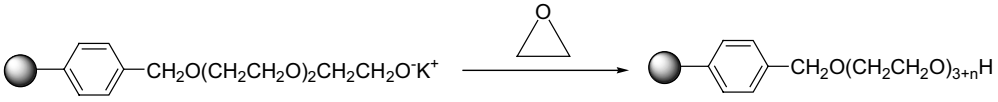
Scheme 28.17

28.2.7
TentaGel Resins

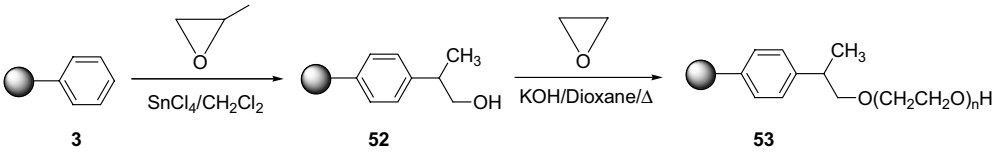
TentaGel polymers, originally developed by Bayer and Rapp [84, 85], consist of a polystyrene matrix covalently coated with poly(ethylene glycol) (PEG) chains and were intended initially for solid-phase peptide synthesis in analogy to the polyacrylamide resins. Subsequently, TentaGel resins have found wide applications in the field of solid-supported synthesis of small molecule libraries [33, 86]. The PEG chains are introduced by anionic polymerization of ethylene oxide with hydroxylated crosslinked polystyrene beads (Scheme 28.18).



50 **51**

Scheme 28.18

An alternative procedure towards TentaGel resins uses the functionalization of β-hydroxy-polystyrenes, which avoids the grafting of acid-labile benzylether groups to the polymeric backbone (Scheme 28.19) [68].



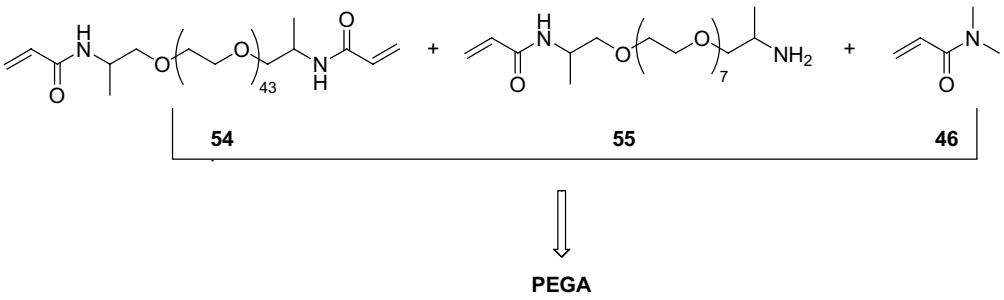
Scheme 28.19

TentaGel resins are composed up to 60–80% w/w of PEG units. These PEG units largely determine their physical properties. Thus, they show good swelling properties in protic and polar solvents such as H_2O, MeOH, CH_2Cl_2, MeCN, THF or DMF, whereas in apolar solvents, like diethyl ether, they hardly swell at all. In general, they show complementary swelling properties to polystyrene resins.

Important features of TentaGel resins are those derived from the high flexibility imparted by the PEG chains, which can be observed in NMR [84, 85]. The reactive centers are allocated at the end of the PEG spacers and are, therefore, easily accessible. However, loadings of commercially available TentaGel resins range between 0.15 and 0.3 mmol g^{-1}, which are significantly lower than those of polystyrene resins.

28.2.8
Novel Polymeric Supports

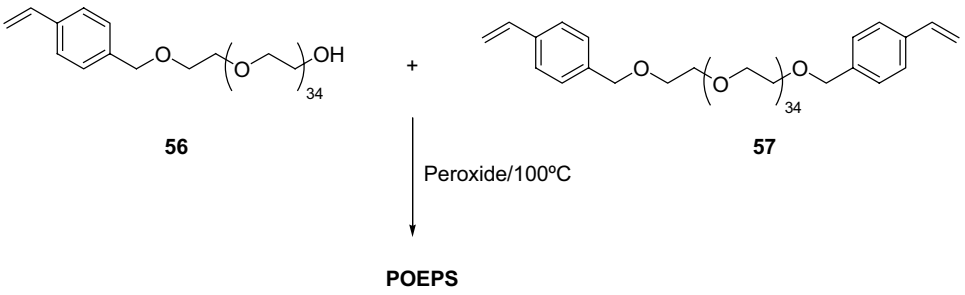
PEGA is a copolymerizate of bis(2-acrylamidoprop-1-yl)-PEG1900 (**54**), 2-acrylamidoprop-1-yl[2-aminoprop-1-yl] PEG300 (**55**) and *N*,*N*-dimethylacrylamide (**46**) (Scheme 28.20) [87].



Scheme 28.20

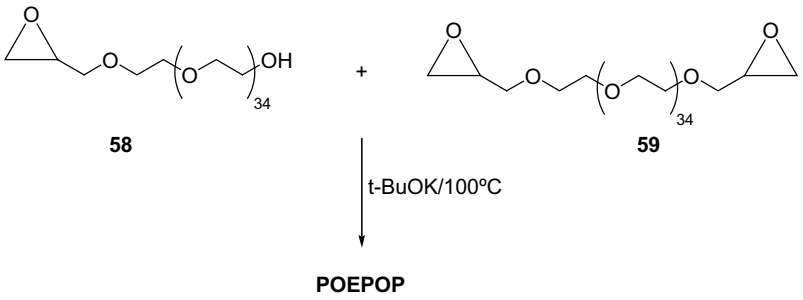
PEGA can be obtained by bulk-polymerization followed by granulation of the polymerizate or alternatively by suspension polymerization resulting in the formation of suitable beads for synthesis. The PEGA beads show excellent swelling properties in non-protic solvents like CH_2Cl_2 and DMF and also in protic solvents like alcohols, H_2O and even aqueous buffers. For difficult peptide synthesis on other polymeric supports, the corresponding amino acid coupling reactions proceeds faster and with higher efficiency on PEGA resins. In addition, PEGA resins are also compatible with enzyme-catalyzed reactions and have been employed for the enzymatic synthesis of a glycopeptide using a β-(1–4)-galactosyltransferase [88].

In recent years, two novel PEG-crosslinked resins derived from polyoxyethylene polystyrene (POEPS) and polyethylene polyoxypropylene (POEPOP) have been made available for solid-phase organic synthesis. These resins lack the amide-derived polymer backbone and, thus, show increased chemical stability [89]. POEPS has been obtained by radical polymerization of monomers **56** and **57** as shown in Scheme 28.21.



Scheme 28.21

POEPOP resins are obtained by anionic polymerization of monomer **58** and **59** (Scheme 28.22).

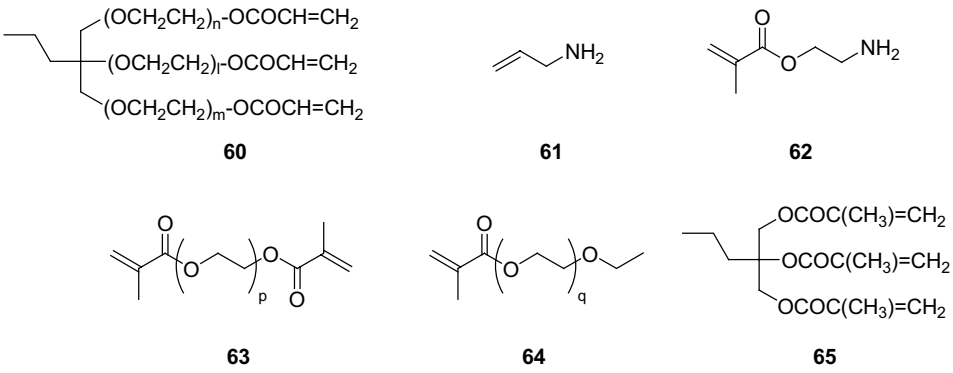


Scheme 28.22

The loading capacity can be controlled by the corresponding ratio of the monomers. Both POEPS and POEPOP resins show excellent swelling properties in solvents such as CH_2Cl_2, DMF and H_2O.

28.2.9
CLEAR Resins

CLEAR resins (cross-linked ethoxylate acrylate resins) belong to a group of highly crosslinked resins with good swelling properties. They are obtained by polymerization of monomers **60–65**. CLEAR resins differ from the standard crosslinked polymers by the incorporation of branched molecules such as **60** and **65**. The amino groups present in monomers **61** and **62** constitute the attachment points for potential linker groups (Scheme 28.23). CLEAR resins show excellent swelling properties in protic and aprotic polar solvents such as DMF, TFA, H_2O, MeOH, MeCN, THF and CH_2Cl_2, whereas they swell gradually in more lipophilic solvents such as toluene, AcOEt and hexanes. In addition, these resins show a high mechanical stability. Their properties have been compared with polystyrene, PEGA and TentaGel resins [90].



60 **61** **62**

63 **64** **65**

Scheme 28.23

28.3
Linkers for Solid-Phase Organic Synthesis

Linker molecules play a key role in every successful synthetic strategy on solid support. They covalently link the polymeric support and the molecules that are being synthesized. Linkers are usually bifunctional spacer molecules that contain on one end an anchoring group for attachment to the solid support and on the other end a selectively cleavable functional group used for the subsequent chemical transformations and cleavage procedures. Whereas linkers were traditionally designed to release

one specific functional group (e.g., carboxylic acids and amides in peptide synthesis), the synthesis of diverse small-molecular-weight compound libraries has required the introduction of new additional linkers and hence of new cleavage strategies. Among those, the use of traceless linkers, and linkers that allow cyclization-assisted cleavage and multidirectional cleavage, has emerged as a powerful tool in solid-phase organic synthesis.

A given linker should allow the easy attachment of the starting material to the solid support through a given functional group. It should be also chemically inert during the construction of the target molecules and, therefore, be stable under a wide variety of reaction conditions. Finally, it should allow for a selective cleavage under very specific reaction conditions without damage of the final targeted product. Upon cleavage, either the originally attached or a new functional group may be generated. In addition, the so-called "safety-catch" linker principle has been rediscovered for combinatorial synthesis. A "safety-catch" linker is usually converted from a chemically inert entity into reactive species in the very last step before cleavage.

Linker molecules, and therefore cleavage strategies, can be grouped into the following categories:

- Linker molecules releasing one specific functional group; monofunctional cleavage.
- Linkers that allow for cyclization-assisted cleavage.
- Linkers that allow for multidirectional cleavages, by:
  - direct nucleophilic or electrophilic substitutions,
  - using "traceless linkers,"
  - activation of the linker molecules ("safety-catch principle").

28.3.1 Linker Molecules Releasing One Specific Functional Group. Monofunctional Cleavage

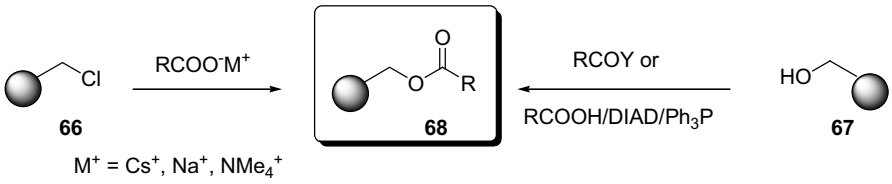
Monofunctional resin-cleavage has attracted wide interest in the field of organic synthesis on a solid support [91, 92]. Monofunctional resin-cleavage strategies are well suited for the construction of focused combinatorial libraries, where a given important pharmacophoric group, which remains constant, is released in the very last step. Hence, the linkage to the resin also serves as a protective group throughout the entire synthesis. The linkers may be classified according to the functional groups that are released from the resin. Thus, we have linkers releasing:

- carboxylic acids
- amides
- sulfonamides
- amines
- alcohols and phenols
- other functional groups.

28.3.1.1 Linkers Releasing Carboxylic Acids

The largest number of linkers described so far is for those releasing carboxylic acids (and also amides) as they are closely related to peptide synthesis. In addition, many relevant classes of pharmacologically active compounds contain this moiety. Therefore, strategies on a solid phase that lead to compounds containing a carboxylic acid, which is generally released at the very end of the synthesis, are of interest for many compound classes.

Three different strategies are generally used for the attachment of carboxylic acids to resins: (i) acylation of resin-bound benzyl alcohols **67** [93–95], (ii) O-alkylation of carboxylates by resin-bound benzylic halides **66** [96–98], or (iii) O-alkylation of carboxylic acids under Mitsunobu conditions [99, 100] (Scheme 28.24).



Scheme 28.24

Linkers releasing a carboxylic acid group can be grouped according to the cleavage method (Table 28.1); thus, there are linkers that are cleaved under acidic conditions (Table 28.1 entries 1–8), under basic or neutral conditions (entries 9–14), under transition metal catalysis (entry 15), and linkers that are photocleavable (entries 16 and 17).

28.3.1.2 Linkers Releasing Amides

As in the case of linkers releasing carboxylic acids, there are a large number of linkers known that, upon cleavage, release an amide functional group. Table 28.2 shows widely used linkers that release an amide group, gathered according to the cleavage conditions: acidic conditions (entries 1–6) and photocleavable linkers (entries 7 and 8).

28.3.1.3 Linkers Releasing Amines

Some of the most widely used linkers that release an amine group are depicted and grouped according to their releasing reaction conditions in Table 28.3.

28.3.1.4 Linkers Releasing Alcohols, Diols and Phenols

Various linker strategies for the attachment of alcohols and phenols have been developed and some of the most widely employed examples are shown in Table 28.4.

28.3.1.5 Linkers Releasing Hydroxamic Acids

Matrix metalloproteinases (MMPs) such as collagenase, gelatinase and others [132] have emerged as prime targets in several therapeutic areas (e.g., in antiinflammatory

Table 28.1 Some of the most widely used linkers that release a carboxylic acid.

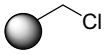
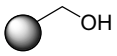
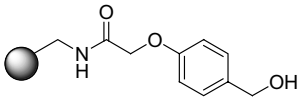
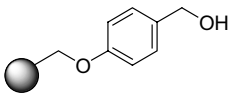
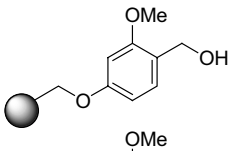
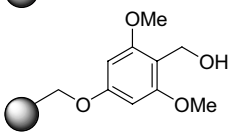
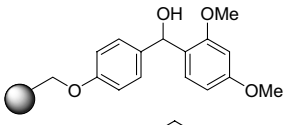
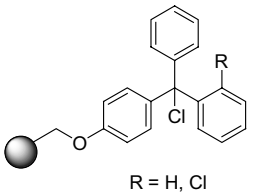
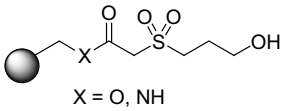
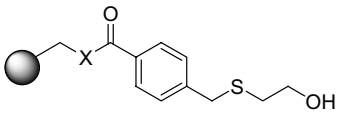
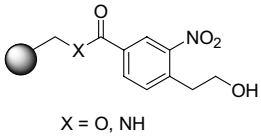
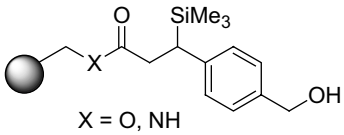
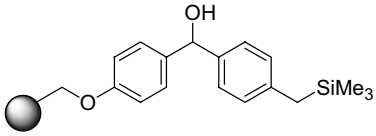
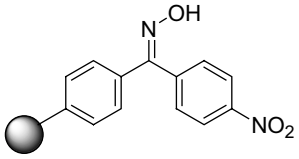
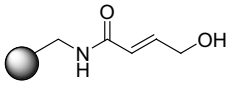
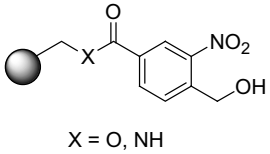
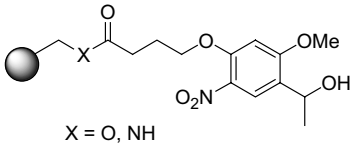
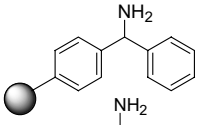
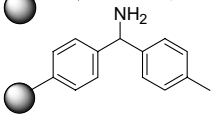
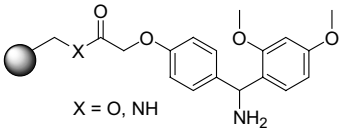
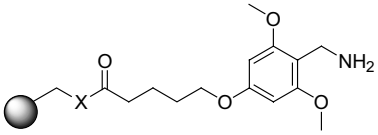
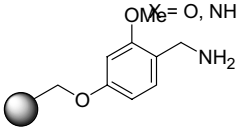
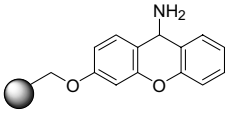
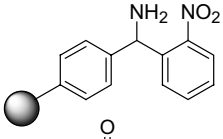
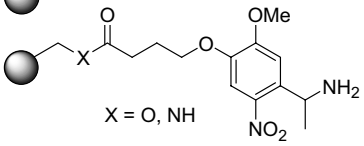
Entry	Name	Structure	Cleavage	Reference
1	Merrifield resin		HF, CF_3SO_3H	[101]
2	Hydroxymethyl resin		HF, CF_3SO_3H	[102]
3	Pam resin		HF/TFA	[103]
4	Wang resin		50% TFA	[104]
5	Sasrin resin		1% TFA	[105]
6	HAL resin		0.1% TFA	[106]
7	Rink resin		1% TFA	[107]
8	Trityl resin	 R = H, Cl	1% TFA/ AcOH	[108]
9	—	 X = O, NH	NaOH	[109]
10	—	 X = O, NH	NH_3/TFE	[110]

Table 28.1 (*Continued*)

Entry	Name	Structure	Cleavage	Reference
11	—		DBU/ piperidine	[111]
12	—		Bu_4NF	[112]
13	—		Bu_4NF, CsF	[113]
14	Kaiser resin		N_2H_4	[70]
15	—		$Pd(PPh_3)_4$	[114]
16	—		*hν*/ 350 nm	[56]
17	—		*hν*/ 350 nm	[115]

and in oncology). An important class of inhibitors of MMPs is hydroxamic acids; several drugs or drug candidates contain a hydroxamic acid moiety. Therefore, linker molecules releasing the hydroxamic acid moiety are very valuable tools for the construction of focused libraries toward MMPs. Table 28.5 shows some linkers that release the hydroxamic acid functional group.

Table 28.2 Some of the most widely used linkers that release an amide group.

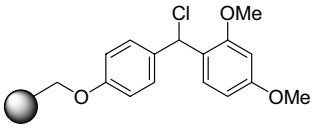
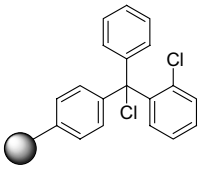
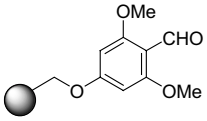
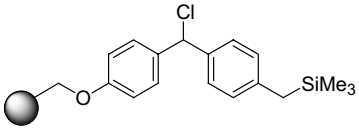
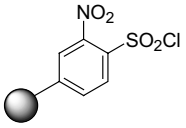
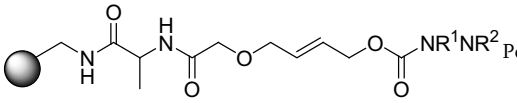
Entry	Name	Structure	Cleavage	Reference
1	BHA		HF, CF_3SO_3H	[116]
2	MBHA		HF, CF_3SO_3H	[117]
3	Rink-Amide resin		TFA	[107]
4	PAL resin		TFA	[118]
5	—		TFA	[119]
6	Sieber resin		1% TFA	[120]
7	—		*h*ν/350 nm	[121]
8	—		*h*ν/350 nm	[122]

28.3.2
Cyclization-Assisted Cleavage

Among the various cleavage strategies described in the literature, cyclization-assisted-cleavages are extensively used since they offer advantages:

- First, only those molecules attached to the solid support that have gone through the entire synthetic sequence necessary for the cyclization reaction will be cleaved.

Table 28.3 Some of the most widely used linkers that release an amine group.

Entry	Name	Structure	Cleavage	Reference
1	Rink chloride		TFA	[123]
2	Chlorotrityl resin		TFA	[124]
3	BAL resin		TFA/ Et_3SiH	[125]
4	—		Bu_4NF/ CsF	[113]
5			PhSH, K_2CO_3	[126]
6			Pd(0)	[127]

- Secondly, even in those cases where single synthetic steps do not proceed quantitatively, the cyclization will nevertheless lead to pure products.

As expected, cyclization-assisted cleavage is largely independent of the nature of the linker molecule (it depends only on the synthetic sequence that is necessary to create the corresponding precursors) and therefore many available linkers are perfectly compatible with cyclization-assisted cleavage procedures. One of the first examples described in the literature was the pioneering benzodiazepine solid-phase synthesis by Camps *et al.* in 1974 [136].

Table 28.4 Linkers that release alcohols, diols and phenols.

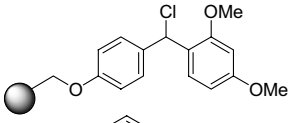
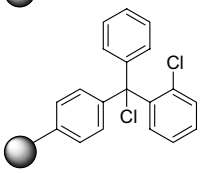
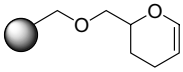
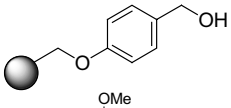
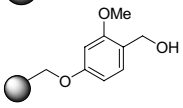
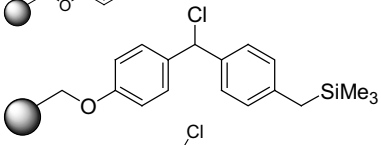
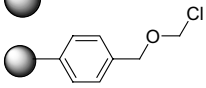
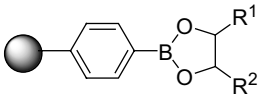
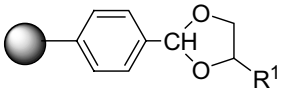
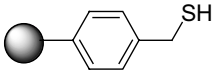
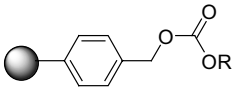
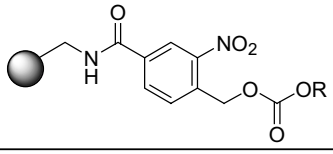
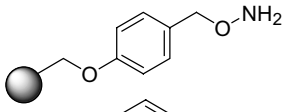
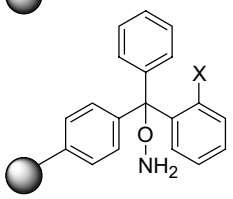
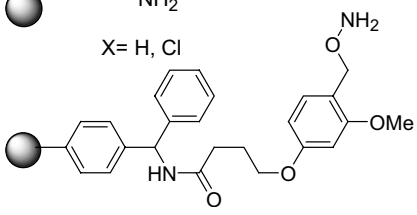
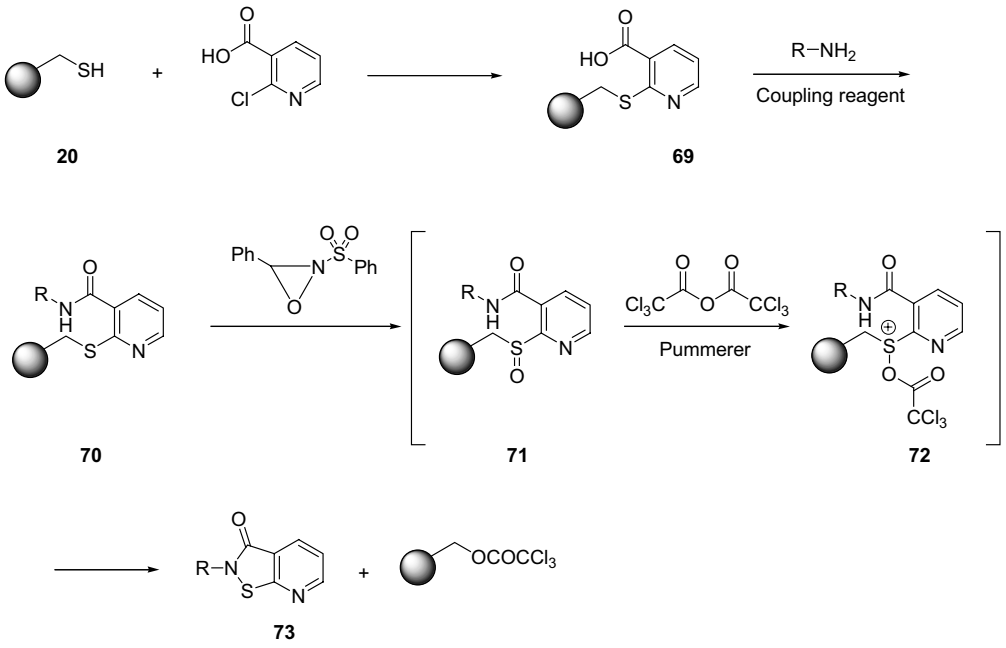
Entry	Name	Structure	Cleavage	Reference
1	Rink chloride		TFA	[123]
2	Chlorotrityl resin		TFA	[124]
3	—		TFA, PPTS/EtOH	[128]
	Wang Resin		TFA	[104]
	Sasrin resin		1% TFA	[105]
4	—		Bu_4NF/CsF	[113]
5	—		TFA	
6	—		H_3O^+	[129]
7	—		H_3O^+	[129]
8	—		$LiBH_4$	[130]
9			HF, anisole	[131]
10			*hν*/350 nm	[131]

Table 28.5 Linkers that release hydroxamic acid functional groups.

Entry	Name	Structure	Cleavage	Reference
1	—		TFA/iPr_3SiH	[133]
2	Trityl resin	 X= H, Cl	TFA/Et_3SiH	[134]
3			TFA/iPrSiH	[135]

A more recent prominent example is shown in Scheme 28.25, where 2-chloro nicotinic acid (**69**) is attached to benzyl thiol resin **20** in basic media. Introduction of different amines through standard amide couplings affords amides of type **70**. Oxidation to the corresponding sulfoxide **71** through Davis' reagent followed by



Scheme 28.25

Pummerer rearrangement affords heterocyclic derivatives of type **73** with concomitant release from the resin [137, 138].

28.3.3 Multidirectional Cleavage Strategies

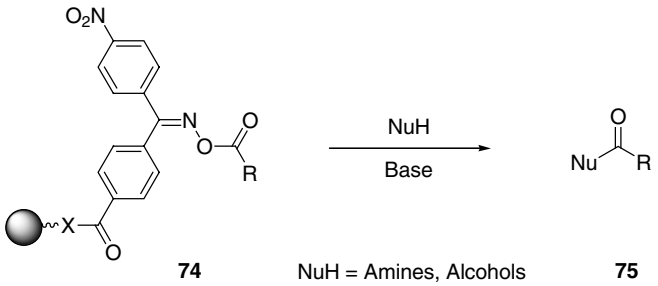
Monofunctional resin cleavage procedures are well suited for the generation of targeted libraries where the given key pharmacophoric group that remains constant forms the link between the resin and the molecules that are being synthesized. Multidirectional cleavage, in addition, offers the advantage that, in the final cleavage step, an additional element of diversity is incorporated into the final compound being produced. Thus, the number of compounds is multiplied by the number of elements that can be incorporated. Most the linkers that have been described for multidirectional cleavage procedures are also termed "traceless" linkers as no element of the linker remains in the final molecules.

The main strategies include:

- direct cleavage by nucleophilic substitution reactions;
- direct cleavage by electrophilic substitution reactions;
- cleavage through cross-coupling reactions;
- activation of the linker group prior to cleavage ("safety-catch" principle).

28.3.3.1 Direct Cleavage by Nucleophilic Substitution

The following schemes show some representative examples of linkers and strategies that allow the final multidirectional cleavage from the resin using nucleophiles such as amines, alcoholates, thiolates and C-nucleophiles such as organolithium or Grignard reagents. Thus, for instance, carboxylic acids attached to Kaiser resins type **74** react with different nucleophiles [70, 139] (e.g., amines, alcoholates) to afford different amides/esters of type **75** with simultaneous release from the polymeric support (Scheme 28.26).

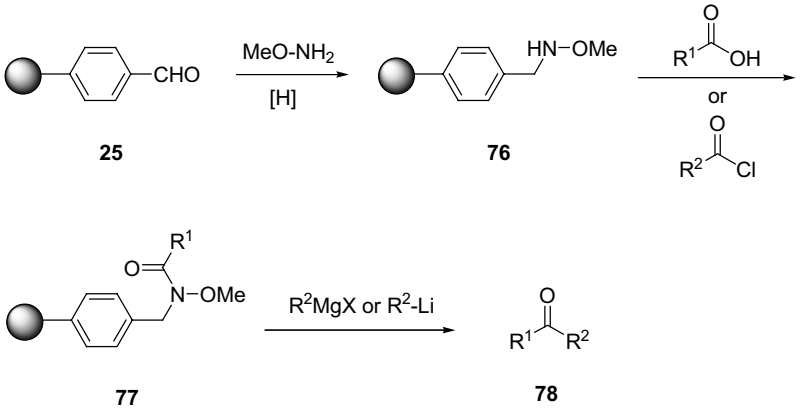


74 NuH = Amines, Alcohols **75**

X = O, NH

Scheme 28.26

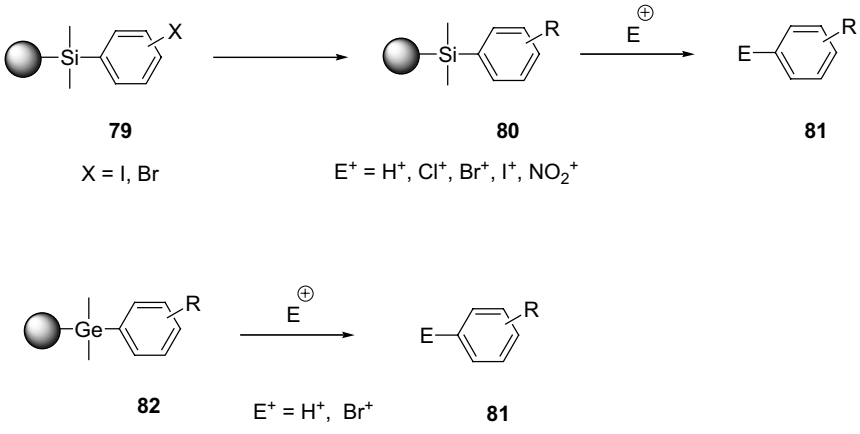
Another illustrative example of multidirectional cleavage through nucleophilic substitution is the one shown in Scheme 28.27, which is based on Weinreb amides (**77**). Again, the introduction of a new element of diversity and release from the polymeric support are simultaneous [139].



Scheme 28.27

28.3.3.2 **Direct Cleavage by Electrophiles**

Most of the developed linkers that allow multidirectional electrophilic cleavage from the resin are based on the chemistry of silicon and also to a less extent on germanium [140–142]. Silyl linkers have broad appeal in solid-phase synthesis. Many encoded diversity-oriented synthesis (DOS) libraries rely almost exclusively on immobilizing alcohol building-blocks via the silyl ether [143, 144]. Cleavage conditions are tunable, depending upon the type of alkyl substituents present on the silicon atom. Scheme 28.28 shows a few early interesting examples.



Scheme 28.28

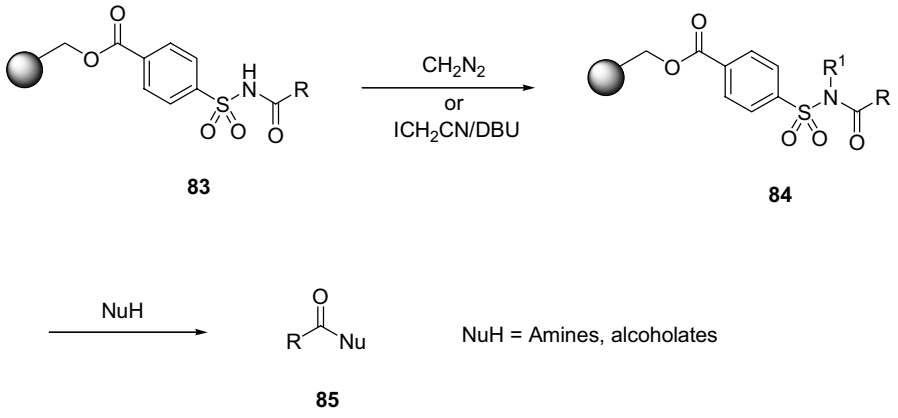
28.3.3.3 "Safety-Catch" Linkers

Among the several successful linker strategies that are being developed specifically for the solid-supported synthesis of small organic molecules, the "safety-catch" principle has gained wide acceptance as it offers several advantages:

- Through the entire synthetic sequence of the library, the linker moiety is completely stable under a wide range of reaction conditions.
- The linkage between the resin and the molecule can be specifically designed according to the structure and chemical stability of the desired final products.
- The linker group can often be reduced to a single atom such as sulfur, silicon, tin and others. Thus, full advantage can be taken of the rich chemistry of these elements, integrating the final activation and cleavage step into the whole synthetic strategy.
- The "safety-catch" principle generally leads to multidirectional resin cleavage, which allows multiplication of the final library members both in terms of structural and functional diversity.

The safety-catch principle was first described by Kenner *et al.* [145] in the field of peptide chemistry and was originally based on the reactivity of the sulfonimide group.

As shown in Scheme 28.29, after suitable synthetic manipulations on molecule **83**, alkylation of the polymer-bound sulfonimido nitrogen atom with diazomethane or iodoacetonitrile activates the linker towards the action of a nucleophile (e.g., amines, alcoholates), thereby introducing a new element of diversity with simultaneous release from the resin (multidirectional cleavage) to afford compounds of type **85** in high yields [145, 146].

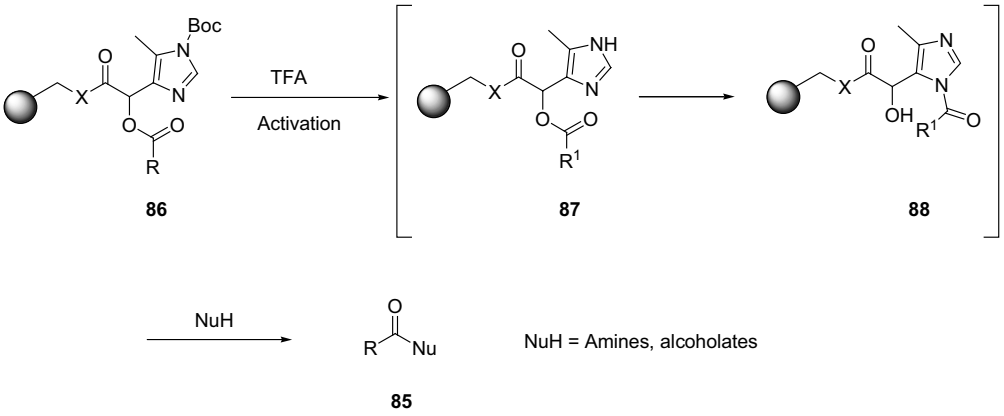


83 **84** **85**

Scheme 28.29

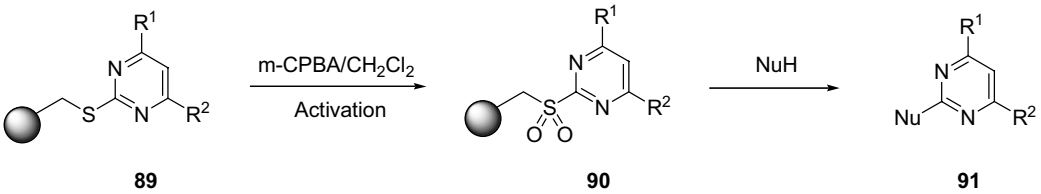
A further example that illustrates the safety-catch principle, designed by Frank *et al.*, is based on imidazole chemistry. Thus, Boc-protected polymer-bound

imidazole **86** is activated by cleavage of the Boc protective group. Acyl transfer in **87** and subsequent nucleophile cleavage leads to products of type **85** [147, 148] in a multidirectional cleavage (Scheme 28.30).



Scheme 28.30

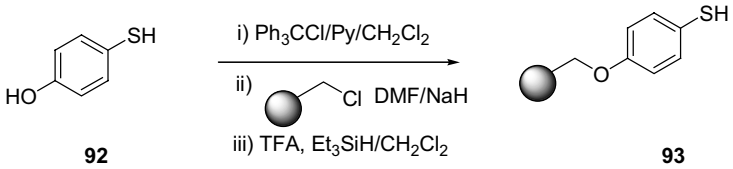
In addition, a novel safety-catch principle for the multidirectional cleavage of pyrimidines and related heterocycles was first developed by Obrecht *et al.* [62, 149]. Here, polymer bound thiopyrimidines of type **89** are activated at the end of the synthesis to the corresponding sulfones **90** by oxidation. Multidirectional cleavage with various nucleophilic agents such as amines, alcoholates and C-nucleophiles allows the formation of diverse pyrimidines of type **91** with simultaneous release from the resin (Scheme 28.31).



Scheme 28.31

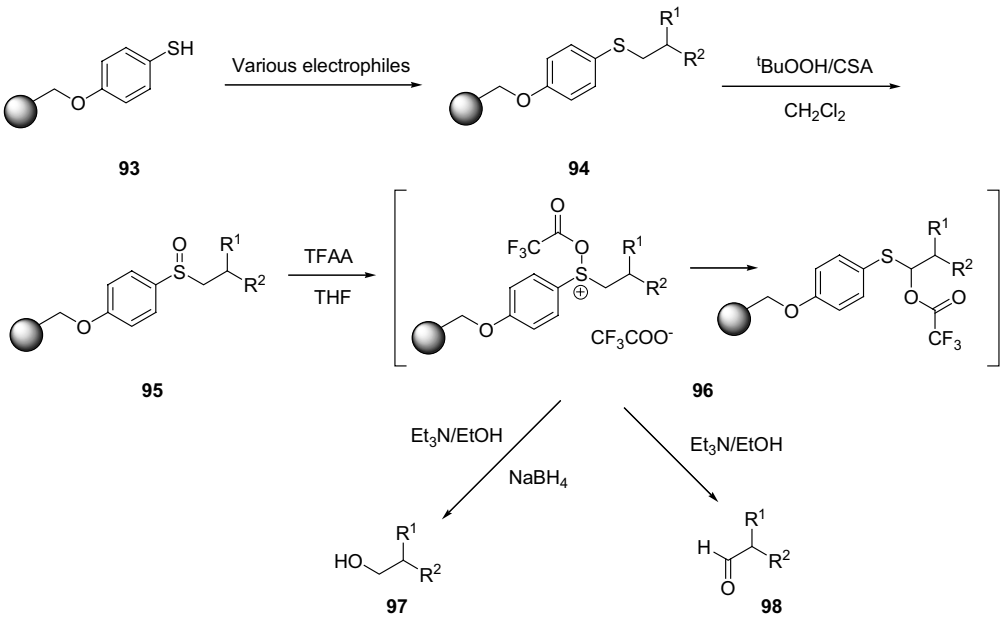
More recently, other novel safety-catch linkers have been developed. Starting from 4-hydroxythiophenol (**92**), S-tritylation, coupling to the Merrifield resin (**6**) and detritylation afford linker **93** (Scheme 28.32).

Safety-catch linker **93** reacts with various electrophiles, such as halides and sulfonate esters (NaH is required as the base) and epoxides (Et_3N is required as a base), or alcohols under Mitsunobu conditions, yielding a sulfide resin **94**. This



Scheme 28.32

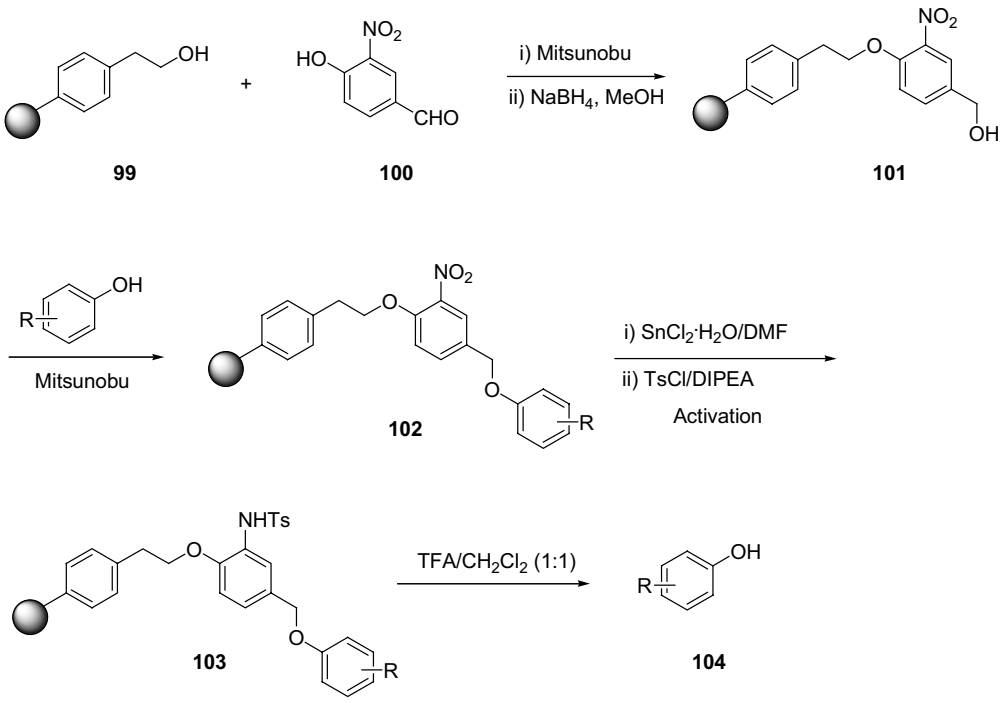
sulfide linker is stable to a wide range of reaction conditions. Subsequent activation through the corresponding sulfoxide followed by Pummerer rearrangement promoted by trifluoroacetic acid anhydride releases alcohols **97** or aldehydes **98** depending upon the reaction conditions used (Scheme 28.33) [150].



Scheme 28.33

Nitrobenzyl linker **101** has been designed as a new safety-catch linker for solid-phase synthesis, possessing both acid and base stability. This is a Wang-type resin whose acid stability is dramatically improved by virtue of the nitro substituent. It is activated by reduction of the nitro group to the corresponding aniline followed by sulfonylation (also acylation); the corresponding synthesized products are then released from resin upon exposure to mild acid. Linker **101** has been prepared upon Mitsunobu coupling of 4-hydroxy-3-nitrobenzaldehyde (**100**) to

2-hydroxyethylpolystyrene (**99**) followed by aldehyde reduction with $NaBH_4$ (Scheme 28.34) [151].



Scheme 28.34

28.4 Heterocyclic Synthesis on Solid-Phase

As discussed earlier, for more than two decades most developments in solid-phase synthesis focused on the preparation of biopolymers. In recent years, interest in other synthetic targets including heterocycles has begun to grow. Today the field of solid-phase heterocyclic chemistry is rapidly expanding and numerous preparations and methodologies have been reported. Heterocycles are very important compounds due to their chemical, biological and technical significance: heterocycles count among their number many natural products, such as vitamins, hormones, antibiotics, alkaloids, as well as pharmaceuticals herbicides, dyes and other products of technical importance.

Interest in solid-phase heterocyclic chemistry originated mainly from the pharmaceutical industry. Heterocycles not only enable the spatial fixation of a set of structural elements relevant to reversible binding to proteins but can also have a strong influence on the solubility and on other physicochemical properties of a

compound. Heterocycles play a key role in the development of new drugs. Therefore, synthetic methodologies that enable the rapid production of arrays of heterocycles are of critical importance to the pharmaceutical industry.

Several review articles have appeared covering the synthesis of heterocycles on insoluble supports for the production of compound libraries [152–154].

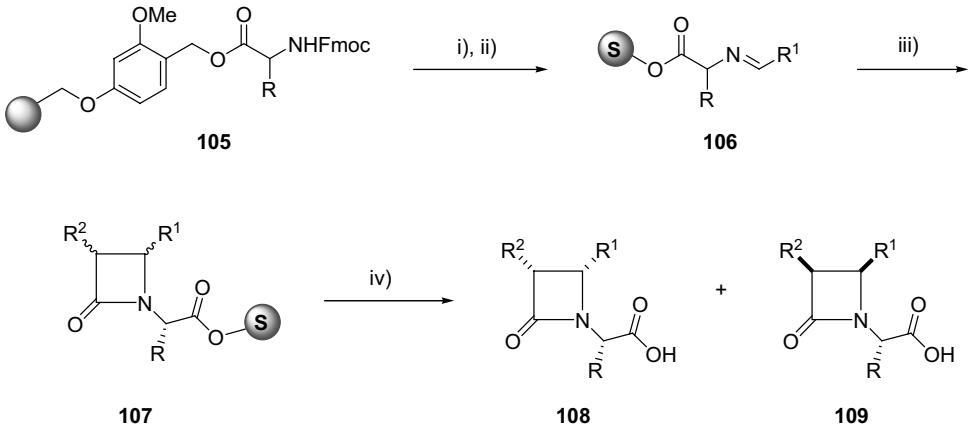
It is not the purpose of this chapter to comprehensively review all synthetic methodologies available for the preparation and further manipulation of all heterocycles classes on solid supports. Instead, we illustrate how the technical developments on solid-phase chemistry and the concepts previously discussed have been successfully translated to the heterocyclic field.

For this purpose, recent prominent examples according to the type of heterocycle prepared and its relevance are presented here.

28.4.1
Synthesis of β-Lactams

β-Lactams are clinically valuable pharmacophores. There preparation on a solid support can be best achieved by reaction between resin-bound imines and ketenes. Owing to the highly reactive nature of ketenes, resin-bound ketenes are less suitable intermediates for the preparation of β-lactams. An illustrative example has been reported by Gallop *et al.* [155].

Fmoc-amino acids tethered to the acid labile Sasrin resin (**105**) have been condensed quantitatively to imines **106** by using a large excess of alkyl, aryl or α,β-unsaturated aldehydes in a mixture of CH_2Cl_2 and trimethylorthoformate (as dehydrating agent) (Scheme 28.35). Optimization studies of the [2 + 2] cycloaddition



Reagents and conditions: i) 30% piperidine in NMP, 45 min., r.t.; ii) 0.8 M R^1-CHO in $(MeO)_3CH/CH_2Cl_2$ (1:1), 3 h; iii) 0.8 M R^2CH_2COCl, 1.1 M Et_3N in CH_2Cl_2, 0ºC to r.t., 16 h; iv) 3% TFA in CH_2Cl_2

Scheme 28.35

step showed that conversion into β-lactams **107** could only take place by slow addition of acid chlorides to a suspension of the imine resin at 0 °C in the presence of Et_3N. By using a large excess of ketene at high concentration, the cycloaddition of imines derived from even sterically hindered amino acids (e.g., valine) could be carried out with full conversion. After mild TFA cleavage from the resin and preparative HPLC purification, β-lactams **108** and **109** were isolated in yields of 55–97% (Scheme 28.35).

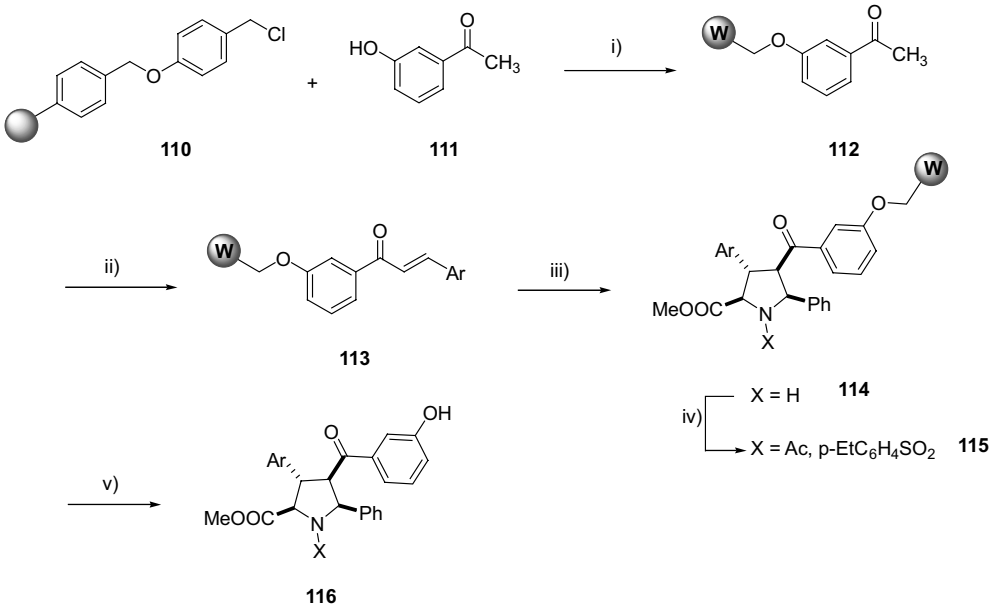
Although the formation of the corresponding β-lactams occurred with high cis selectivity, the diastereoselection induced by the asymmetric center of the amino acid was only moderate. Higher induction could be achieved, however, with an optically active ketene.

28.4.2
Synthesis of Pyrrolidines

1,3-Dipolar cycloaddition reactions are important processes for the preparation of several heterocyclic systems due to the generally mild reaction conditions and the simultaneous formation of several bonds in a single operation. The preparation of pyrrolidines via cycloaddition reactions of azomethine ylides is a well-known process and has been extensively studied. One of the earliest described examples of preparation of pyrrolidines on solid support was reported by Hollinshead [156], who developed a solid-phase protocol for the preparation of highly functionalized pyrrolidines based on the reaction of azomethine ylides with polymer-bound α,β-unsaturated ketones. Thus, chlorinated Wang resin **110** [157] is coupled to 3-hydroxyacetophenone **111** with Cs_2CO_3/NaI in DMF, affording acetophenone tethered to the solid support (**112**). Knoevenagel condensation with different aromatic aldehydes using a 0.5 M solution of MeONa/MeOH affords the corresponding enones **113**. These α,β-unsaturated ketones attached to the solid support are then subjected to standard 1,3-dipolar cycloaddition with N-metallated azomethine ylides in the presence of DBU and LiBr as Lewis acid to give highly substituted pyrrolidine derivatives **114** with high regio- and diastereoselectivity. Derivatives **114** can be further manipulated by introducing acyl or sulfonyl groups on the pyrrolidine nitrogen atom (Scheme 28.36).

Monofunctional cleavage of pyrrolidines of type **116** from Wang resin is then achieved under standard acidic conditions (50% TFA in CH_2Cl_2) for this linker to afford a collection of compounds that can be purified by chromatography or crystallization.

In a similar approach, but generating the corresponding azomethine ylide on the solid support, Gallop *et al*. [158] have developed a protocol for the solid-phase synthesis of highly substituted pyrrolidines. Starting from Fmoc-amino acids tethered to the acid labile Sasrin resin **105**, deprotection of the Fmoc group with piperidine and subsequent condensation reaction with different aromatic and heteroaromatic aldehydes at room temperature in neat trimethylorthoformate as dehydrating agent provides the corresponding resin-bound aryl imines **106**. Lewis acid-promoted formation of N-metalloazomethine ylides and subsequent



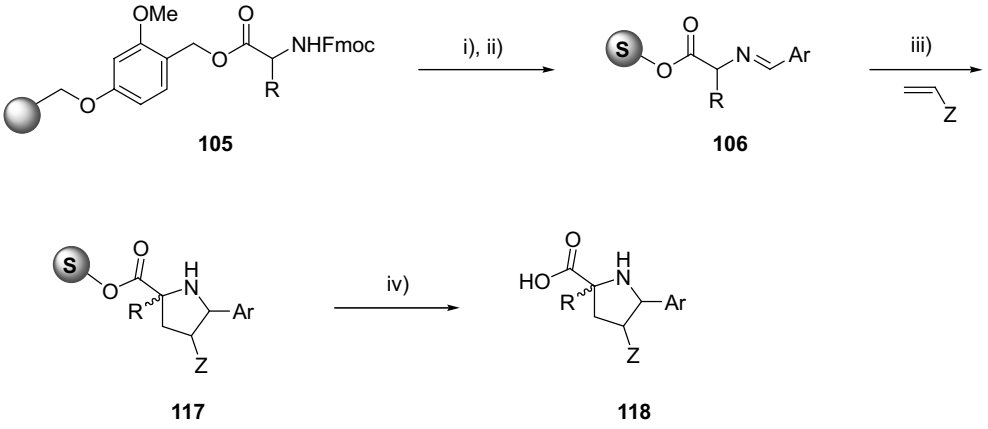
Reagents and conditions: i) Cs_2CO_3, NaI, DMF; ii) Ar-CHO (12 eq.), NaOMe (0.5 M in MeOH, 12 eq.), THF; iii) $PhCH{=}NCH_2CO_2Me$, LiBr, DBU, THF; iv) Acylating agent, Py, DMAP, CH_2Cl_2; v) TFA/CH_2Cl_2 1:1

Scheme 28.36

cycloaddition reaction with different electron-deficient olefins (e.g., acrylates, cinnamates, conjugated enones, maleinimides, etc.) under basic conditions affords pyrrolidines **117**. Representative proline analogues **118** have been characterized by mild acid cleavage from the resin by means of 10% TFA in yields ranging between 50 and 80% and with diastereoselectivities ranging from 2.5 : 1 to greater than 10 : 1 (Scheme 28.37).

Again in this case, a strategy based on monofunctional cleavage (releasing a carboxylic acid) was used. In this particular case, since functionalized prolines and proline analogues are frequently found as C-terminal residues in numerous ACE inhibitors, this chemistry was used to generate a focused library of mercaptoacyl prolines as potential ACE inhibitors whereby the release of a carboxylic acid group had to remain constant.

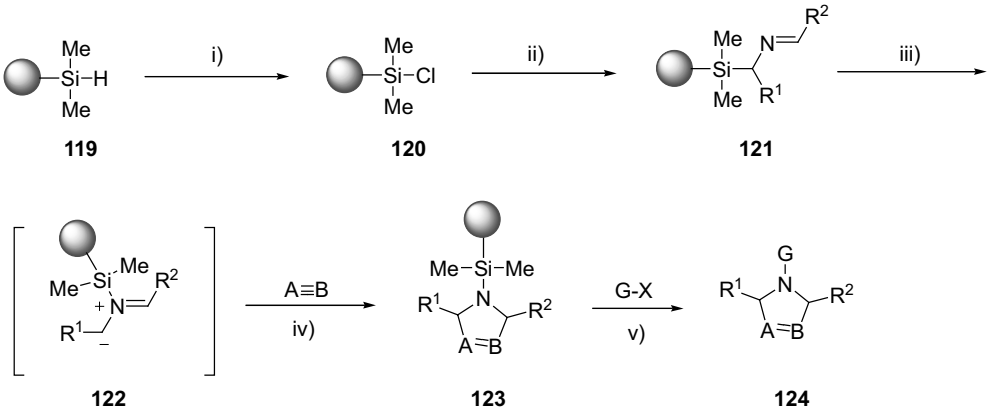
A further example of pyrrolidine synthesis on solid support employs a silicon-based traceless linker of type **119** that is chlorinated with 1,3-dichloro-5,5-dimethylhydantoin under mild conditions to afford **120**. Reaction with azaallyl anions generated *in situ* from N-alkylidene N-benzylamines and LDA yields the corresponding polymer-bound α-silylimines **121**. Thermal 1,2-silatropic shift affords **122**, which reacts *in situ* with the corresponding dipolarophiles to provide pyrrolidines **123**.



Reagents and conditions: i) 20% piperidine in DMF, 20 min., r.t.; ii) 1 M Ar-CHO in $(MeO)_3CH$, 4h; iii) 1 M olefin, 1 M $AgNO_3$, 1 M Et_3N in MeCN, 8 h; iv) 10% TFA in CH_2Cl_2

Scheme 28.37

A further element of diversity can be introduced into the pyrrolidine ring during the cleavage step (multidirectional electrophilic cleavage) with different electrophiles (HCl, acid chlorides, allyl iodide, and so on) to furnish collections of pyrrolidines of type **124** in good yields (Scheme 28.38) [159].

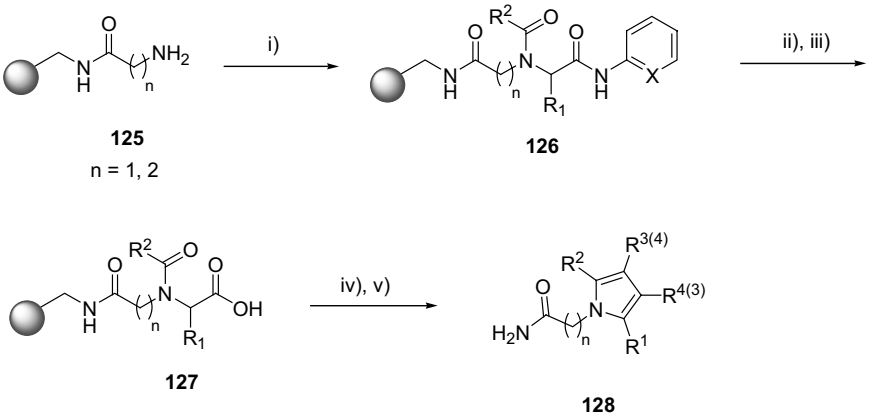


Reagents and conditions: i) 1,3-dichloro-5,5-dimethylhydantoin, CH_2Cl_2, r.t.; ii) LDA, THF, -78ºC, $R^1CH_2N{=}CHR^2$; iii) Heat; iv) Dipolarophile; v) Electrophile

Scheme 28.38

28.4.3
Synthesis of Pyrroles

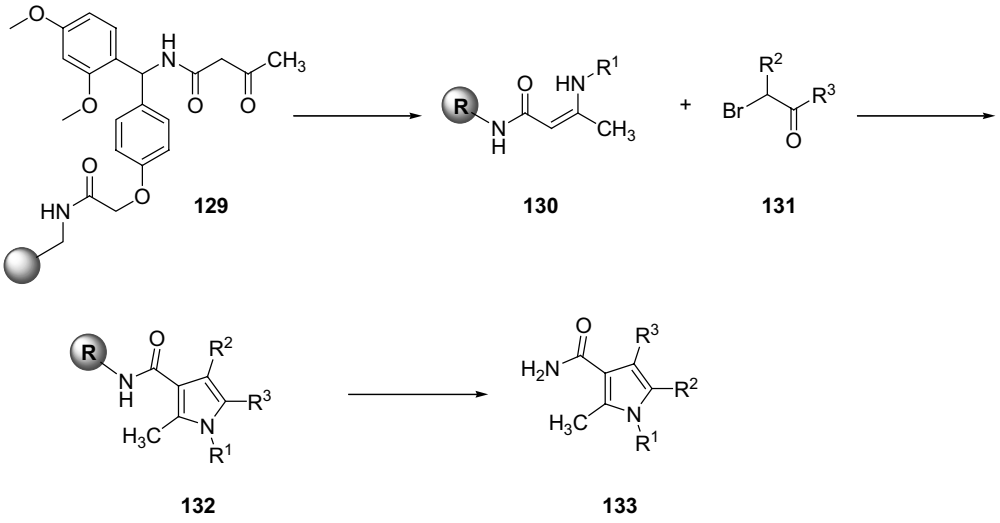
Substituted pyrroles are commonly found in natural products [160, 161], drugs [162, 163], conducting materials [164, 165] and insecticides [166]. The pyrrole ring system has been synthesized on solid-supports by few methods. An early example is shown in Scheme 28.39, where pentasubstituted pyrroles are synthesized using a multi-component condensation. The condensation of a resin-bound amine **125** to an aldehyde, followed by the addition of carboxylic acid and isocyanide (Ugi reaction), results in the formation of resin-bound N-alkyl-N-acyl-α-amino amides **126**, which are acylated and hydrolyzed in one-pot to **127**. Treatment with neat acetic anhydride or isobutyl chloroformate and triethyl amine in toluene, followed by the addition of a series of acetylenic esters, provides the polymer-bound pentasubstituted pyrroles **126**. The reaction proceeds via *in situ* cyclization of the intermediate through a [3 + 2] cycloaddition with various alkynes. The corresponding products are released from the resin with 20% TFA to afford **128** (monofunctional cleavage releasing amides) in 35–75% overall yield over eight steps. For asymmetrically substituted alkynes, an isomeric mixture of pyrroles **128** in an approximately 4 : 1 ratio has been obtained.



Reagents and conditions: i) R^1-CHO, R^2-COOH, PhNC (or PyNC), $CHCl_3$-Py-MeOH (1:1:1), 65ºC, 48 h; ii) $(Boc)_2O$, CH_2Cl_2; iii) (1N LiOH-5% H_2O_2)-THF, 4:1; iv) $R^3{-}{\equiv}{-}R^4$, Ac_2O, 65-100ºC; v) 20% TFA/CH_2Cl_2

Scheme 28.39

Another method toward the solid-phase of pyrroles was developed by Jung *et al.* [167]. by adapting the Hantzsch pyrrole synthesis to the solid support. Thus, acetoacetylated Rink amide resin **129** has been converted into resin-bound enaminones **130** upon reaction with primary amines. These enaminones **130** react with α-bromoketones **131** to yield polymer-bound pyrroles **132**. Cleavage with 20% TFA in CH_2Cl_2 affords pyrrole-3-carboxamides **133** in excellent purities (Scheme 28.40).



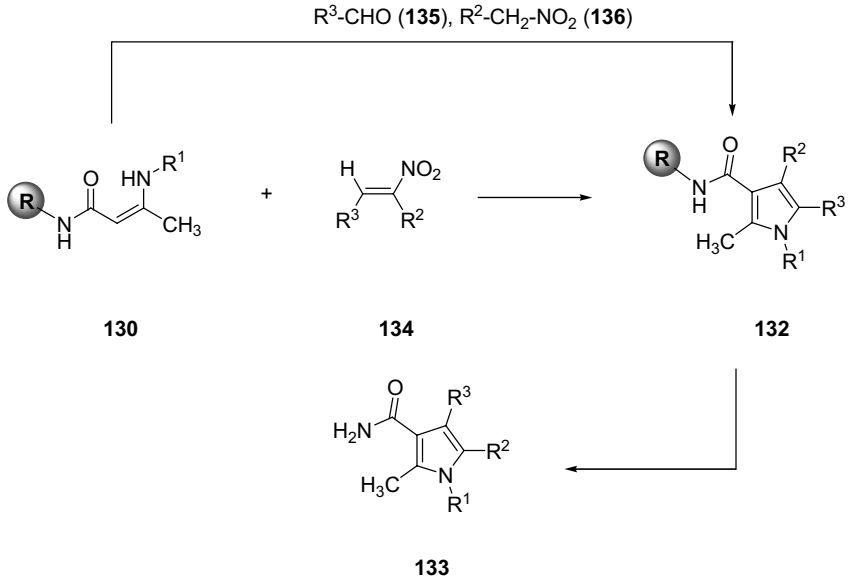
Scheme 28.40

Furthermore, related resin-supported Hantzsch methodology has used been successfully for the cyclocondensation of nitroalkenes **134** with enaminones **130–** or, alternatively, in a three-component pathway with aldehydes **135** and nitroalkanes **136**– to furnish polymer-bound resin **132.** As in the previous case, monofunctional cleavage under acidic conditions (releasing an amide group) affords pyrrole carboxamide derivatives (**133**, Scheme 28.41) [168].

Other prominent recent examples for the solid-phase synthesis of pyrroles include the Paal–Knorr condensation of polymer-supported 1,4-diketones with primary amines [169]. In another approach, 1,3-dipolar cycloadditions onto polymer-bound vinyl sulfones and subsequent pyrrole annulation have been reported to deliver isoxazolinopyrrole-2-carboxylates [170, 171].

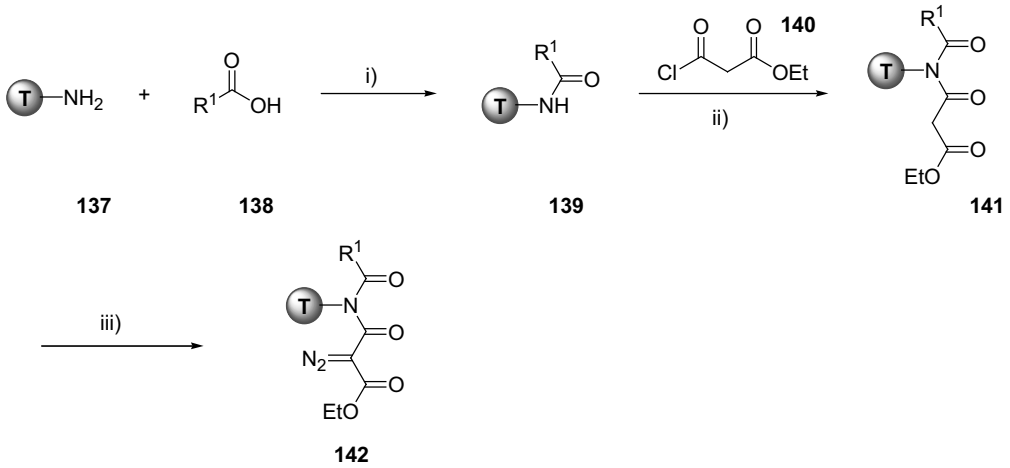
28.4.4
Synthesis of Furans

A traceless linker strategy for the synthesis of substituted furans based on the generation on a solid support of mesoionic isomünchnones has been developed by Gallop *et al.* The key step of this protocol takes advantage of an efficient [3 + 2] cycloaddition reaction with electron-deficient acetylenes, followed by a thermally promoted cycloreversion reaction. For this synthesis, an amino TentaGel resin (**137**) was employed. Thus, **137** was primarily acylated with different carboxylic acids **138** using diisopropyl carbodiimide (DIC) in the presence of catalytic amounts of DMAP. The amide **139** was converted into imide **141** by treating the resin twice with a 1 : 1 (v/v) mixture of malonyl chloride **140** in benzene at 60 °C. Quantitative diazo-transfer reaction to diazoimide **142** was effected at room temperature using tosyl azide in



Scheme 28.41

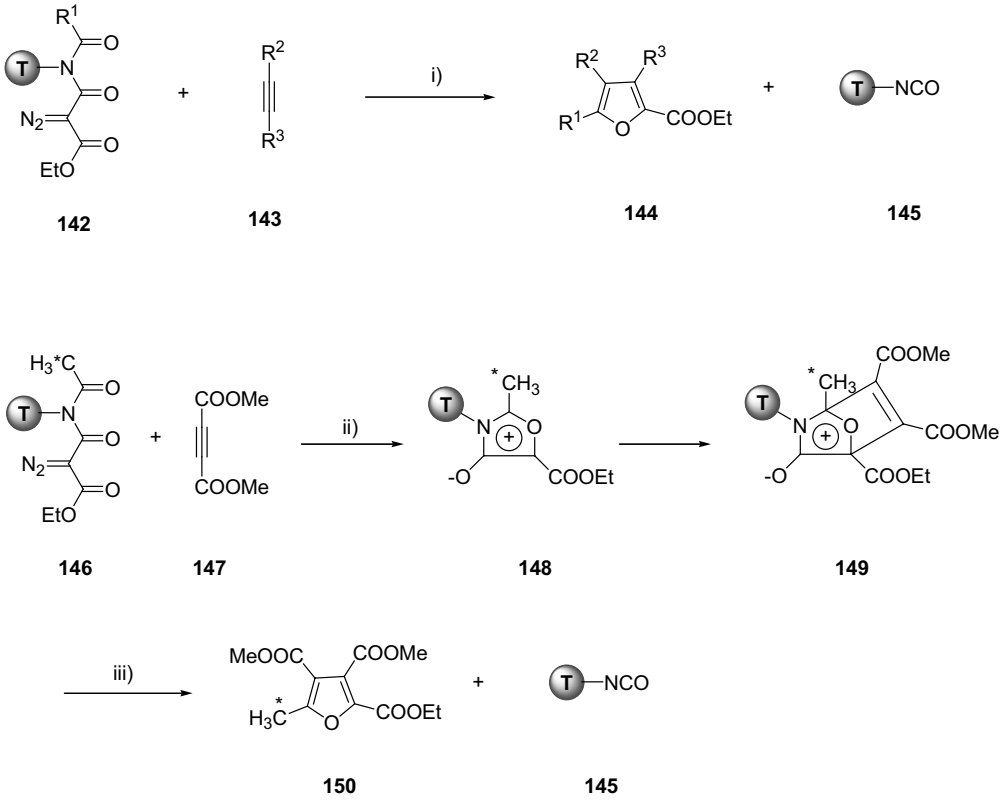
CH_2Cl_2/Et_3N. Optimization of this reaction sequence was facilitated by using gel-phase ^{13}C NMR, by monitoring these transformations with initially acetylated resin with 2-^{13}C-labeled Ac_2O. The analysis indicated that both the imide and diazoimide formation proceeded with >95% conversion (Scheme 28.42).



Reagents and conditions: i) DIC, DMAP, DMF; ii) **140**, benzene, 60ºC; iii) TsN_3, Et_3N, CH_2Cl_2, 18 h.

Scheme 28.42

Resin-bound diazoimides **142** have subsequently been allowed to react with different electron-deficient acetylenes **143** in benzene at 80 °C for 2 h in the presence of $Rh_2(OAc)_4$ as a catalyst (Scheme 28.43). Analysis of the crude products showed exclusively the presence of the desired furans **144** and excess of unreacted acetylene, which, when sufficiently volatile (e.g., propiolate esters), is eliminated in vacuo to provide furans **144** of high purity. To avoid contamination of the desired furan product with residual, non-volatile acetylene, a two-step sequence has been implemented for the cycloaddition reaction. Thus, ^{13}C-labeled diazoimide **146** has been allowed to react with a large excess (10 equivalents) of dimethyl acetylenedicarboxylate (DMAD) **147** in the presence of $Rh_2(OAc)_4$ at room temperature in anticipation of trapping the bicyclic intermediate **149** on the polymeric support. After washing the beads with suitable solvents to remove excess acetylene, resin **148** is suspended in fresh benzene and heated at 80 °C to promote cycloreversion. HPLC analysis of the



Reagents and conditions: i) $Rh_2(OAc)_4$, benzene, 80ºC; ii) $Rh_2(OAc)_4$, benzene, r.t.; iii) benzene, 80ºC

Scheme 28.43

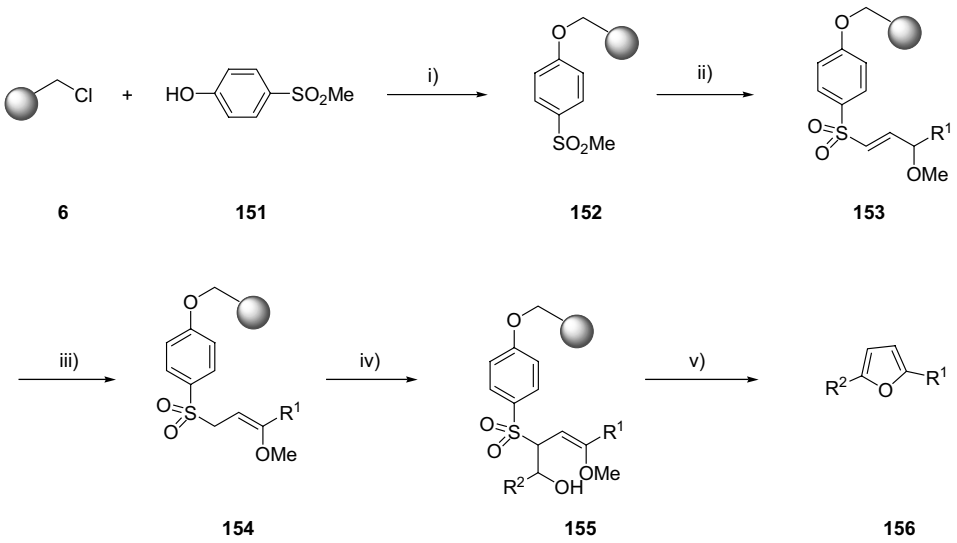
crude product from this reaction showed the presence of pure furan **150** with neither starting acetylene nor any other impurities. Resin washings did not contain any ^{13}C label, indicating that no cycloreversion occurs at room temperature, while gel-phase ^{13}C NMR of the resin after thermolysis showed no resonances from enriched carbons, suggesting that the cycloaddition to the polymer-bound isomünchnone **148** proceeds efficiently at room temperature.

This stepwise (room temperature/thermal) cycloreversion sequence failed, however, to provide furans from acetylene derivatives activated by just a single electron-withdrawing moiety (e.g., propiolate esters). These derivatives, less reactive than DMAD, do not undergo cycloadditions to the immobilized dipoles at an appreciable rate at room temperature.

In another traceless strategy, 2,5-disubstituted furans have been synthesized on solid support through hydroxyalkylation of polymer-bound allylsulfones. Thus, 4-hydroxyphenylsulfonylmethane (**151**) is attached directly to Merrifield resin (**6**) to give the corresponding resin-bound arylsulfonylmethane **152**. Deprotonation of this resin with LDA and treatment with diethylchlorophosphate and subsequent addition of 2-methoxy aldehydes (Horner–Wadsworth–Emmons reaction) affords resin-bound vinyl sulfones **153**. Treatment with *t*-BuOK allows isomerization to alkoxyallyl aryl sulfones **154** that when treated with a strong base at 0 °C react with aldehydes to afford **155**. Optimal conversion into hydroxyalkylated resins **155** was observed when DMPU was used as an additive. Finally, treatment of resins **155** with two equivalents of TFA in CH_2Cl_2 at room temperature effects the formation of 2,5-disubstituted furans **156** with simultaneous release from the resin. The overall yields for this five-step sequence range from 13 to 32%, but no other purification other than removal of the solvents under reduced pressure was necessary [172] (Scheme 28.44).

28.4.5
Synthesis of Thiophenes

Based on an aminoalkylurethane linker attached to the Wang resin **157**, Zaragoza *et al.* [173] have developed a solid-phase synthesis of substituted 3-aminothiophenes by adapting Laliberté's thiophene synthesis [174, 175]. Thus, as shown in Scheme 28.45, Wang resin **157** was primarily treated with 4-nitrophenyl chloroformate (**158**) in the presence of pyrimidine to give **159** and then reacted with piperazine in DMF to produce **160**, which on treatment with cyanoacetic acid afforded **161**. Subsequent reaction of the resin-bound (cyanoacetyl)piperazine **161** with aliphatic or aromatic isothiocyanates in the presence of DBU, followed by S-alkylation with α-haloketones under slightly acidic or neutral conditions gave the intermediates **162** and **163** (the predominant form being determined by the electronic properties of the substituents R^1–R^3). Treatment of intermediates **162**/**163** with DBU in DMF and subsequent acidolytic cleavage of the resin with TFA yielded 3-aminothiophene **164** as trifluoroacetates (monofunctional cleavage releasing an amide group). This synthetic sequence toward **164** has, however, some



Reagents and conditions: i) K_2CO_3, n-Bu_4NI, acetone; ii) LDA, THF, $(EtO)_2POCl$, -78ºC, then $R^1CH(OMe)CHO$; iii) t-BuOK, t-BuOH/THF; iv) LDA, R^2CHO, THF, DMPU, 0ºC; TFA (2 eq), CH_2Cl_2, r.t.

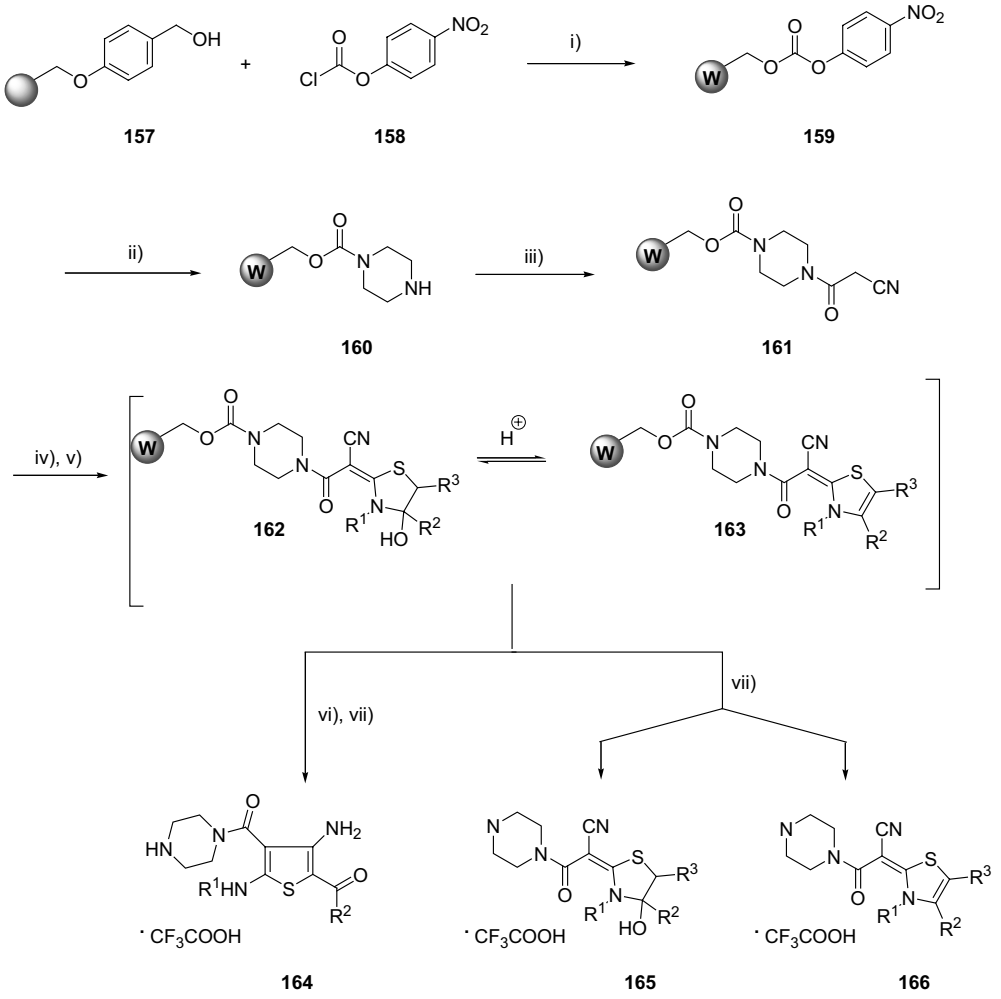
Scheme 28.44

limitations. For instance, a complex mixtures of products is obtained in those cases, where strongly electron-donating isothiocyanates or α-haloketones are used and, in general, no thiophenes results from aliphatic haloketones.

In contrast, direct treatment of the intermediates **162** and **163** with TFA yields the 2-methylene-2,3-dihydrothiazoles **165** and **166** of unknown configuration. The reaction sequence leading to **165** and **166** shows higher tolerance towards variation of the substitution pattern. Generally pure products are obtained for both electron-donating and electron-withdrawing isothiocyanates and α-haloketones. For most of the studied cases, dehydrated 2-methylenethiazoles **166** are obtained as single products. 4-Hydroxythiazolidines of type **165** result only in those cases where R^2 is a strongly electron-withdrawing group (Scheme 28.45).

Since thiophene is sufficiently acidic to be metallated directly by treatment with n-BuLi, this direct lithiation can also be carried out with polystyrene-bound thiophenes. The resulting organolithium compounds react as expected with several electrophiles such as amides (to yield ketones), alkyl halides, aldehydes and Me_3SiCl [176]. In addition, polymer-bound bromothiophenes can be metallated by treatment with Grignard reagents. The resulting thienylmagnesium compounds can be directly treated with carbon nucleophiles to afford the corresponding derivatized thiophenes [177].

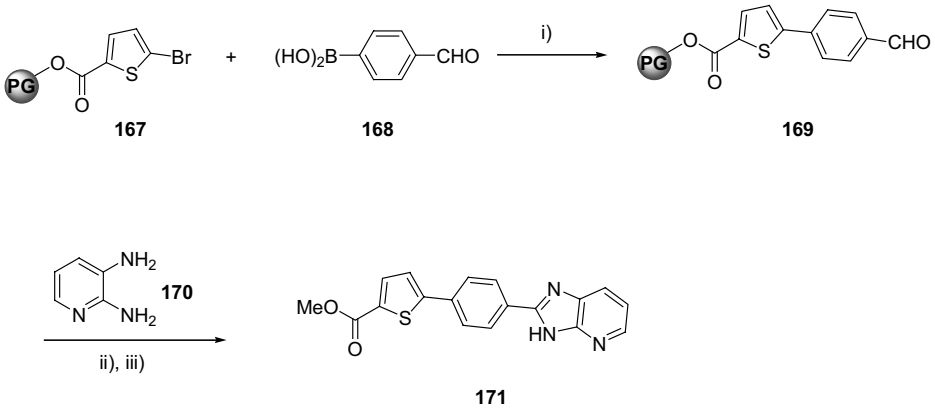
Polymer-bound halothiophenes are also good substrates for Suzuki, Heck, Negishi, and Stille coupling reactions [178, 179]. For instance, the Suzuki coupling



Reagents and conditions: i) CH_2Cl_2/Py, then **158**; ii) piperazine, DMF, r.t., 13 h; iii)cyanoacetic acid, DIC, DMF; iv) R^1-NCS, DBU, DMF, 18 h; v) R^2-COCH(R^3)X, DMF, AcOH; vi) DBU, DMF, 20 h; vii) 50% TFA in CH_2Cl_2

Scheme 28.45

of soluble PEG-bound bromothiophene **167** and *p*-formylphenylboronic acid (**168**) provide biaryl **169**. Owing to the high solubilizing power of PEG, the reaction is conducted as a liquid-phase synthesis. Treatment of **169** with *o*-pyridinediamine **170** results in a two-step-one-pot heterocyclization through an imine intermediate. Nitrobenzene serves as an oxidant in the ring closure step. Finally, transesterification with NaOMe in MeOH furnishes thiophene derivative **171** (Scheme 28.46).



Reagents and conditions: i) $Pd(PPh_3)_4$, 2M Na_2CO_3, DMF, 110ºC, 10 h.; ii) **170**, nitrobenzene, 180ºC, 72 h.; iii) NaOMe/MeOH

Scheme 28.46

28.4.6
Synthesis of Imidazoles

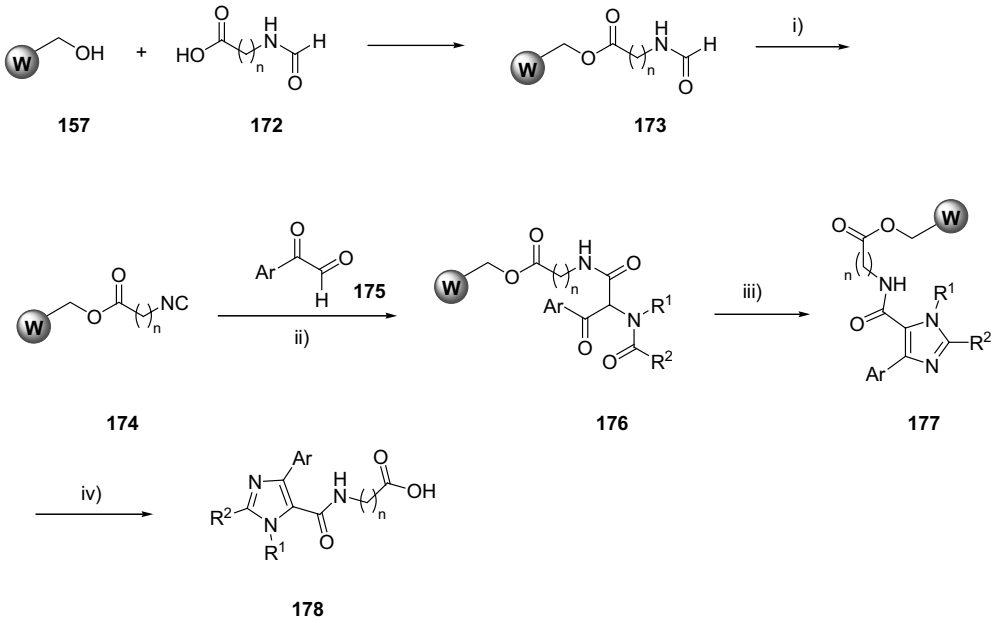
The imidazole ring system is of particular interest since it is a component of histidine and its decarboxylation metabolite histamine. The wide application of the imidazole pharmacophore can be attributed to its hydrogen bond donor–acceptor capability as well as its high affinity for metals (e.g., Zn, Fe, Mg) that are present in many protein active sites.

Based on a four-component condensation reaction (the Ugi reaction), Mjalli *et al.* [180] have developed a solid-phase protocol for the synthesis of tetrasubstituted imidazoles. Because of the limited number of commercially available isocyanides, the selected strategy started with the generation of an isocyanide component tethered to the Wang resin.

A series of N-formylated aliphatic amino acids **172** have been attached to Wang resin **157** (Scheme 28.47), affording **173**. Dehydration of **173** provides resin-bound isocyanides **174**. Multicomponent condensation of resin **174** with arylglyoxals **175**, primary amines and carboxylic acids the affords resin-bound α-(*N*-acyl-*N*-alkylamino)-β-ketoamides **176** that further react with excess of NH_4OAc in AcOH to give immobilized imidazoles **177**. Final monofunctional cleavage with 10% TFA provides imidazoles **178**.

The length of the isocyanide linker, the electronic nature of the aryl glyoxals, the use of different primary amines (except anilines), and the use of both aliphatic and aromatic carboxylic acids showed no effects on the yields of imidazoles **178**.

This methodology has been further extended [181] by attaching the aldehyde or amine component to the Wang resin. Hence, functionalized polymers **180** and **182**



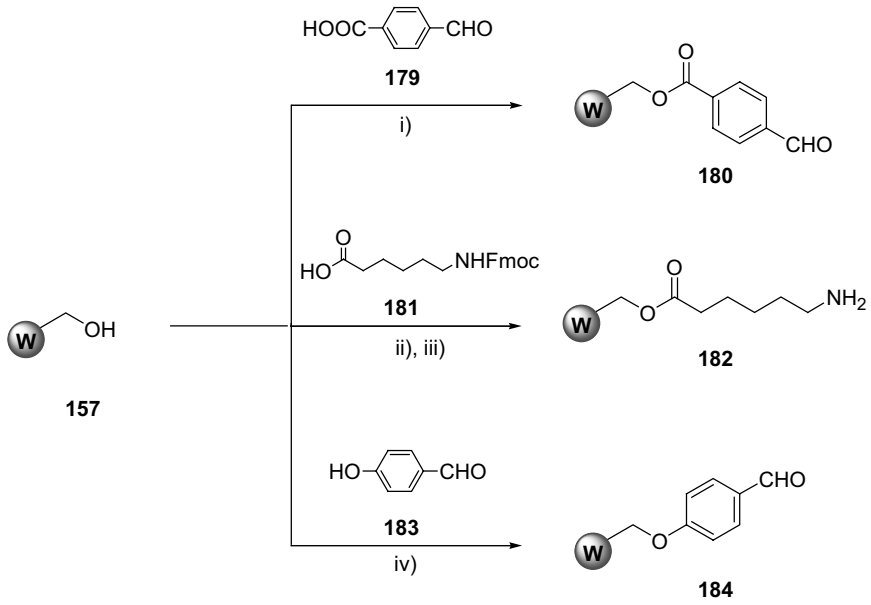
Reagents and conditions: i) Ph_3P, CCl_4, Et_3N, CH_2Cl_2; ii) **175**, R^1-NH_2, R^2-COOH; iii) NH_4OAc, 100°C; iv) 10% TFA in CH_2Cl_2

Scheme 28.47

have been prepared by standard coupling methods of carboxybenzaldehyde **179** and *N*-Fmoc-6-aminohexanoic acid (**181**), respectively. Resin **184** has been prepared via a modified Mitsunobu coupling of 4-hydroxybenzaldehyde (**183**) to Wang resin **157** (Scheme 28.48).

The protocol for the preparation of solid supported imidazoles **185** and **186** involves the condensation of resins **180** and **182** with a large excess of 1,2-dicarbonyl compounds, NH_4OAc and primary amines or aldehydes. Imidazoles of type **187** have been prepared in a similar manner by replacing primary amines with NH_4OAc. Subsequent monofunctional resin cleavage with 20% TFA afforded imidazoles **188**, **189**, and **190** in high yields and purities (Scheme 28.49).

Tetrasubstituted imidazoles of type **196** have also been prepared by using polymer-bound sodium benzenesulfinate as a traceless linker. Thus, polystyrene 1% DVB sodium sulfinate **191** was allowed to react with concentrated HCl in DMF–H_2O (3 : 1) at room temperature. Condensation of **192** with an aldehyde and a primary amide in the presence of Me_3SiCl at 50 °C afforded resin **193**. The α-ketoamide **195** was generated by treatment of resin **193** with excess triethylamine in the presence of thiazolium catalyst **194** in CH_2Cl_2. Concentration of the reaction product **195** and *in situ* treatment with primary amines in refluxing EtOH/AcOH affords imidazoles **196**,



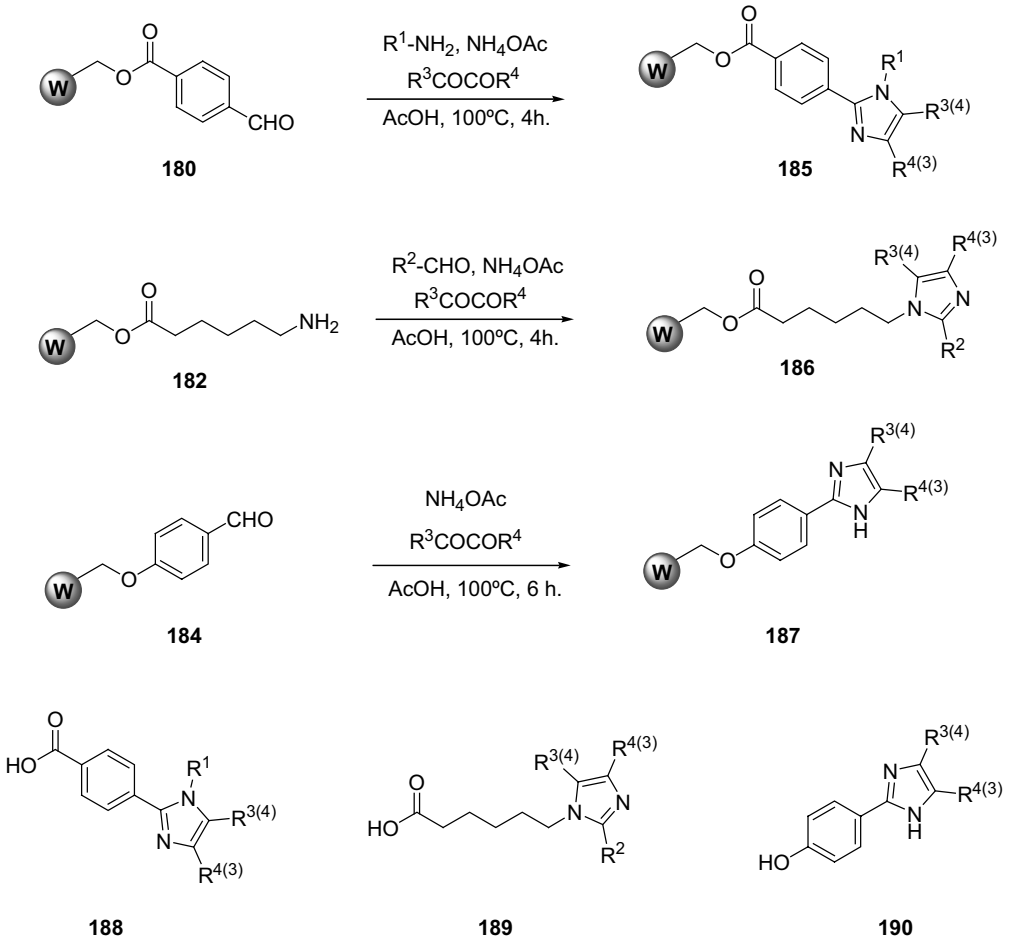
Reagents and conditions: i) DIC, DMAP, THF, 23ºC, 48 h.; ii) DIC, DMAP, CH_2Cl_2, 23ºC, 24 h.; iii) 20% piperidine, DMF; iv) N-ethylmorpholine, DIAD, Ph_3P, sonicate for 1 h., then stirring 23ºC, 16 h.

Scheme 28.48

which were isolated in pure form after flash-chromatography in 24–40% overall yields [182] (Scheme 28.50).

In addition to imidazoles **196**, the α-ketoamido intermediates **195** have also been used to obtain thiazoles **197** and oxazoles **198** by reaction with Lawesson's reagent and PPh_3/I_2 respectively (Scheme 28.51).

Another approach, reported recently [183], involves a simple, efficient synthesis of 1-alkyl-4-imidazolecarboxylate derivatives on solid support through a cyclization-assisted cleavage strategy (which in general is largely independent of the linker type). By this approach, N-methylaminomethylated polystyrene **199** was allowed to react with alkylisocyanate **200** in the presence of *N*-formyl imidazole diethylacetal **201** under acid-catalyzed conditions (10% CSA) in DMF to afford functionalized support **202** (Scheme 28.52). Although this transformation could be achieved on heating the mixture at 80 °C for 36 h, the reaction was preferentially conducted under microwave heating to reduce the reaction time to just 10 min. The free amine on the polymer was monitored using the chloranil test [184]. This rather sensitive assay enables the detection of even very small amounts of free secondary amines on the resin, a negative test indicating complete anchoring to the solid support. Treatment of the resin **202** with a primary amine **203** in n-butanol affords the isomerically pure



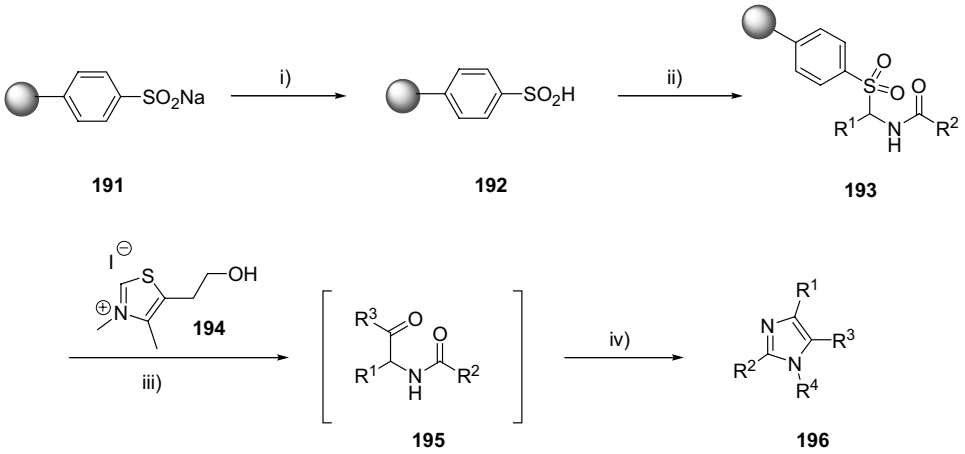
Scheme 28.49

1-substituted-4-imidazolecarboxylate derivatives **204** in excellent yields (80–97%, overall, two steps).

A particular feature of this approach is that the solid-support **199** can be regenerated and used for 3–4 cycles with similar levels of yields and purities of desired imidazoles **204**. A similar strategy has employed resin-bound 3-*N,N*-dimethylamino-isocyanoacrylate for the regioselective synthesis of 1-substituted-4-imidazolecarboxylates [185].

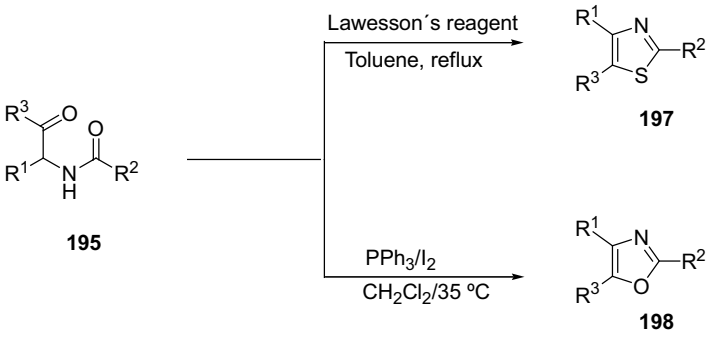
28.4.7
Synthesis of Thiazoles

Most of the solid-phase syntheses described so far are based on the cyclocondensation reaction between thioamides or thioureas and α-halocarbonyl compounds.



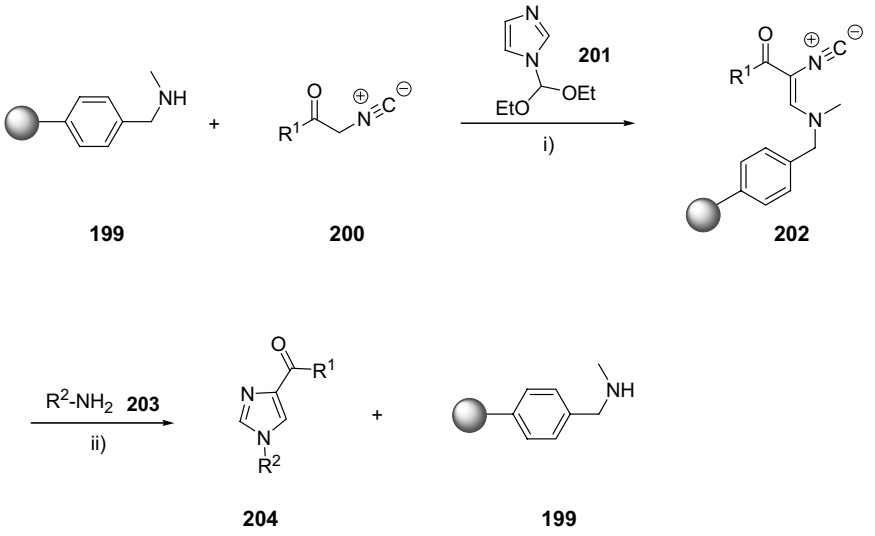
Reagents and conditions: i) HCl $_{(c)}$, DMF-H_2O, r.t., 4 h.; ii) R^1-CHO, R^2-$CONH_2$, Me_3SiCl, MeCN, 50ºC, 8 h.; iii) **194** (cat.), R^3-CHO, Et_3N, CH_2Cl_2, 35ºC, 10 h.; iv) EtOH, AcOH, R^4-NH_2, reflux, 12 h.

Scheme 28.50



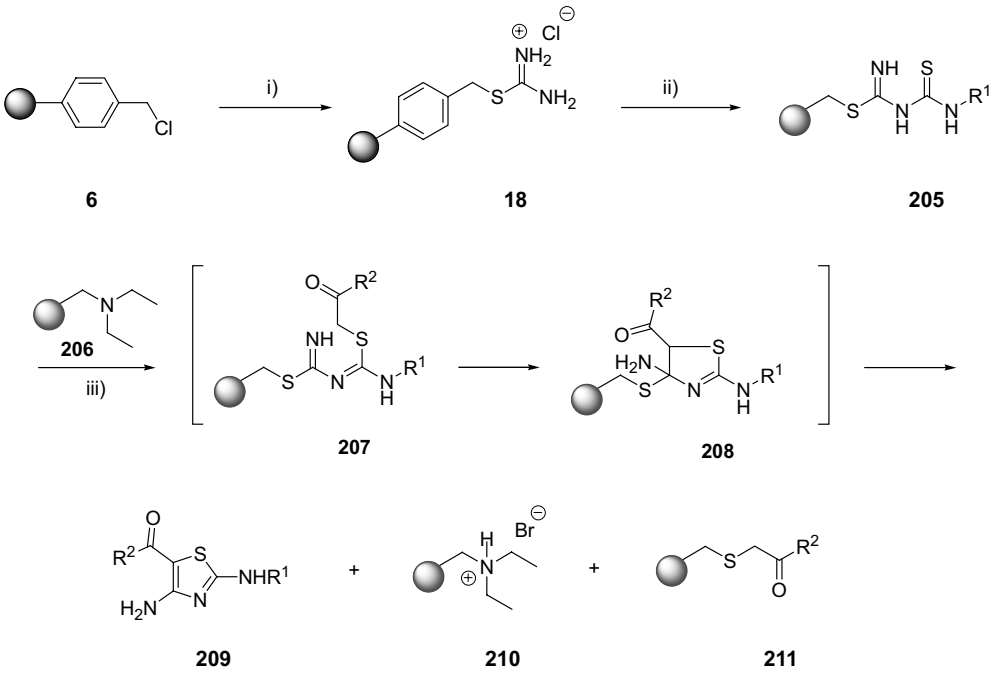
Scheme 28.51

Using this general strategy, Masquelin *et al.* [186] have developed a solid-phase synthesis of highly diverse 2,4-diaminothiazoles through a cyclization-assisted cleavage approach. Starting from Merrifield resin (**6**), reaction with thiourea in DMA affords polymer-bound thiouronium salt **18**. Subsequent reaction with several isothiocyanates in DMF at room temperature in the presence of DIPEA leads to the formation of thioureido thioureas attached to the polymer support of type **205**. Next, the reaction of resins of type **205** with a slight excess of different α-bromoketones in DMF at room temperature in the presence of diethylaminomethylpolystyrene **206** for several hours affords the corresponding 2,4-diaminothiazoles **209** in high yields (49–96%) and purities (Scheme 28.53).



Reagents and conditions: i) **201**,CSA $_{(cat.)}$, DMF, MW (80ºC), 10 min.; ii) **203**, n-BuOH, 114ºC, 30 min. (2 cycles)

Scheme 28.52



Reagent and conditions: i) Thiourea, DMA, r.t.-85ºC; ii) R^1-NCS, DIPEA, DMF, r.t., 3 h.; iii) R^2COCH_2Br, **206**, DMF, r.t., 18 h.

Scheme 28.53

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Modern Heterocyclic Chemistry, First Edition.
Edited by Julio Alvarez-Builla, Juan Jose Vaquero, and José Barluenga.

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