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The Chemistry of the Triazolopyridines: an Update

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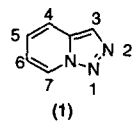
I. Introduction

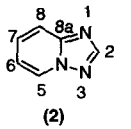
Since the first review (83AHC79) there have been two further reviews of substance (96CHEC-2(7)363) and (96CHEC-2(8)367), each covering part of the original scope, and these were necessarily compressed as part of a much larger general survey of heterocyclic chemistry. The last twenty years have seen much consolidation of synthetic methods and reactions, the development of some new areas such as the chemistry of ylides, and a great increase in the pharmaceutical and other industrial uses of the various triazolopyridines. The general structure of the previous review (83AHC79) has been retained but two new subsections have been added.

The formulae, names, and numbering system of the five triazolopyridines **1–5** are shown.



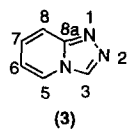
(1)

[1,2,3]Triazolo[1,5-*a*] pyridine



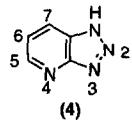
(2)

[1,2,4]Triazolo[1,5- *a*] pyridine



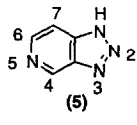
(3)

[1,2,4]Triazolo[4,3- *a*] pyridine



(4)

1*H*-[1,2,3]Triazolo[4,5-*b*] pyridine



(5)

1*H*-[1,2,3]Triazolo[4,5 -*c*] pyridine

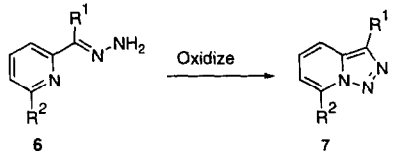
II. Syntheses of the Triazolopyridines

For each heterocycle **1–5** in turn, the syntheses are subdivided into those from pyridines, those from triazoles, and the much smaller number starting from other materials, this last class including syntheses by rearrangement of other heterocycles. Within the major groups the syntheses are arranged according to the increasing number of bonds formed, starting with those involving the formation of only one bond.

A. Synthesis of [1,2,3]Triazolo[1,5-*a*]Pyridines

1. *Syntheses from Pyridines*

a. *Formation of One Bond.* The most commonly used synthesis remains that from the hydrazones of 2-pyridylcarboxaldehydes or ketones by oxidation. It is reported (94JCS(D)2651) that the hydrazone of di-(2-pyridyl) ketone **6a** gives a low yield of the triazolopyridine **7a** when boiled in methanol in the presence of air, but all other reported cases, including the closely related 2-benzoylpyridine hydrazone, require an added oxidant. Recent examples of the use of the most common oxidants illustrate the versatility of the synthesis. Nickel peroxide was used to oxidize the hindered 2-pivaloylpyridine hydrazone **6b** to 3-*t*-butyl-triazolopyridine **7b** (90JCR(M)346), potassium ferrocyanide and bicarbonate to produce the 7-substituted triazolopyridines **7c** and **7d** (96MI1), air and a copper-II salt (93CPB1944) or manganese dioxide (99JOC6635) for 3-phenyltriazolopyridine **7e**, and a new reagent (diacetoxyiodo)benzene (00SC417) for a range of 3-substituted compounds.

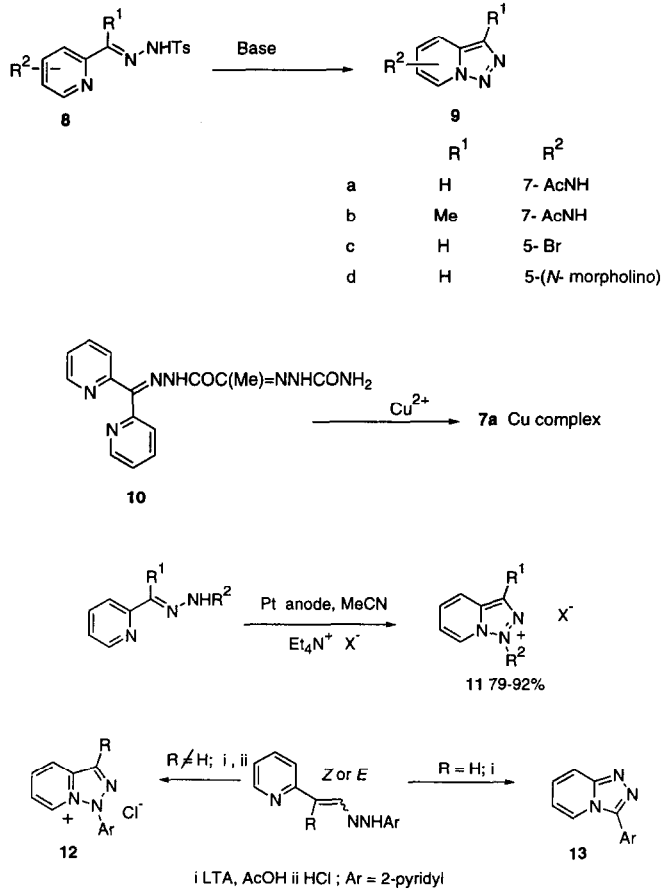


6 **7**

	R^1	R^2
a	2-Pyridyl	H
b	*t*-butyl	H
c	Ph	Me
d	Ph	Cl
e	Ph	H

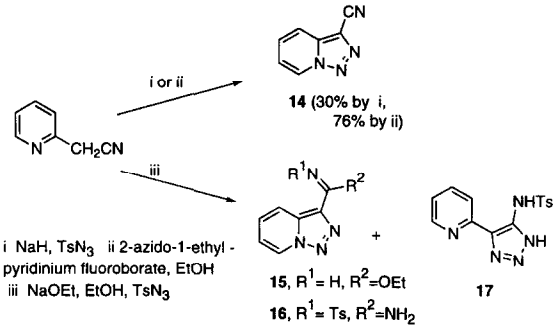
The alternative route, from tosylhydrazones **8** by treatment with base, usually morpholine, has been used for high yields of sensitive materials. Examples are the 7-acetylamino derivatives **9a** and **9b** (89T7041) and the 5-bromo derivative

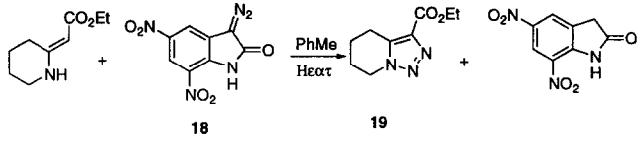
9c (97T8257), although in this case there was slight contamination by the 5-morpholino compound **9d**. A single example, possibly of the same type, is the formation of 3-(2-pyridyl)triazolopyridine **7a** copper complex when the hydrazone derivative **10** is treated with a copper-II salt (93MI2). When N2-substituted hydrazones are used, the products are necessarily quaternary. The formation of compounds **11** illustrates this, and also the use of anodic oxidation (81MI1). In a study of cyclization of the N2-arylhydrazones using lead tetraacetate, it is reported that the products can be either the [1,2,3]triazolo[1,5-*a*]pyridinium salts **12** (when R is not H) or the [1,2,4]triazolo[4,3-*a*]pyridine **13** (single example of R = H) (84JCS(P1)2109).



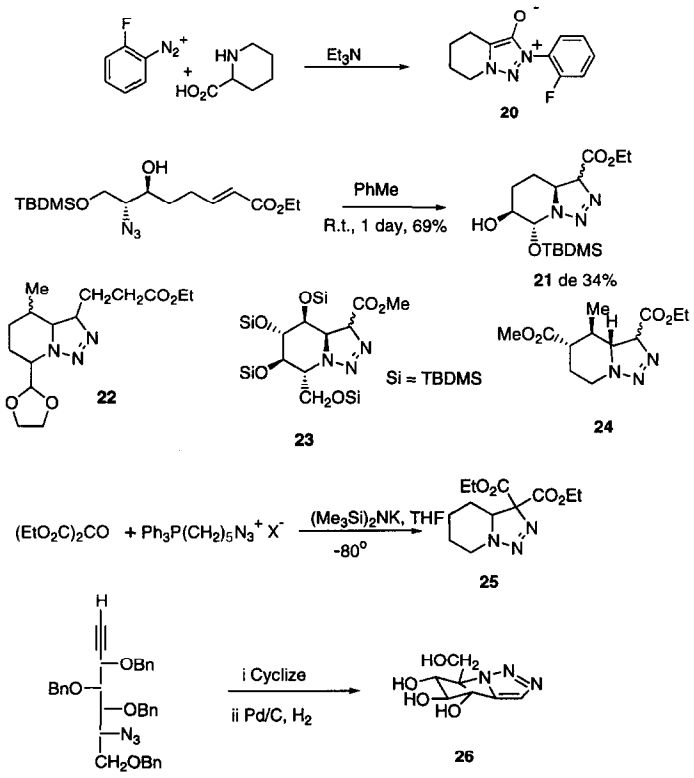
b. *Formation of Two Bonds.* The diazo transfer method, successfully applied by Regitz and Leidhegener to the synthesis of 3-substituted triazolopyridines

(66CB2918) has been found to be inefficient when applied to the production of the 3-cyano compound **14** (95T10969). Using sodium hydride as base and tosyl azide as diazo source the best yield of the nitrile **14** was 30%; under the more conventional conditions with sodium ethoxide in ethanol the products were the amidate **15**, the amidine **16**, and the triazolylpyridine **17**. The authors conclude that consistently high yields using the Regitz synthesis are obtained only with pyridyl ketones as substrates. Reaction of 2-pyridylacetonitrile with 2-azido-1-ethylpyridinium fluoroborate prepared *in situ* as described for other active methylene compounds by Monteiro (87SC983) gives a good yield of compound **14**. An alternative diazo transfer reaction uses diazocarbonyl compound **18** with a cyclic enaminoester to provide the tetrahydrotriazolopyridine **19** (94T6723).





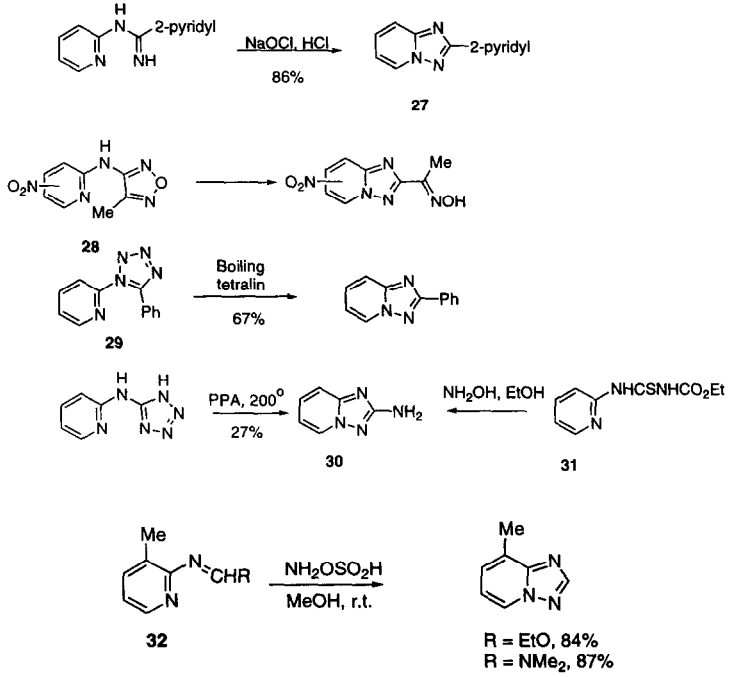
The reaction between aromatic diazonium salts and pipecolic acid to give tetrahydrotriazolopyridinium-3-oxides has been exploited to produce a range of herbicides, such as compound **20** (84EUP116928). Many examples have been given of intramolecular cycloaddition of azides to alkenes and alkynes to produce hexahydro- and tetrahydro-triazolopyridines. The reactions are often stereoselective and provide access to a range of products with oxygen functions on the six-membered ring. An example showing the production of hexahydro derivatives is compound **21** (99EJOC1407), and similar compounds from other groups are **22** (98JOC9910), **23** (97TA3807), and **24** (94T4025). In each case, references to further compounds are quoted. A one-pot Wittig condensation and cyclization gives the simpler compound **25** (92JCR(M)554), and an example of Vasella's syntheses of tetrahydro derivatives is provided by compound **26** (96HCA2190).



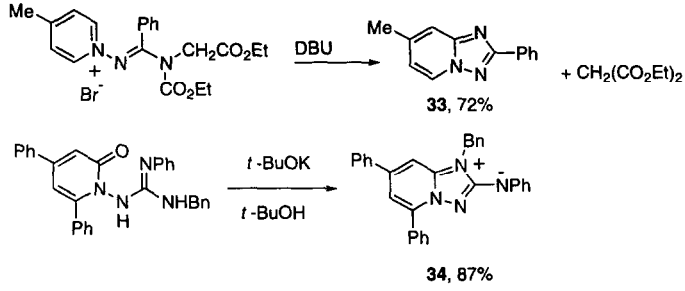
B. Synthesis of [1,2,4]Triazolo[1,5-*a*]Pyridines

1. *Syntheses from Pyridines*

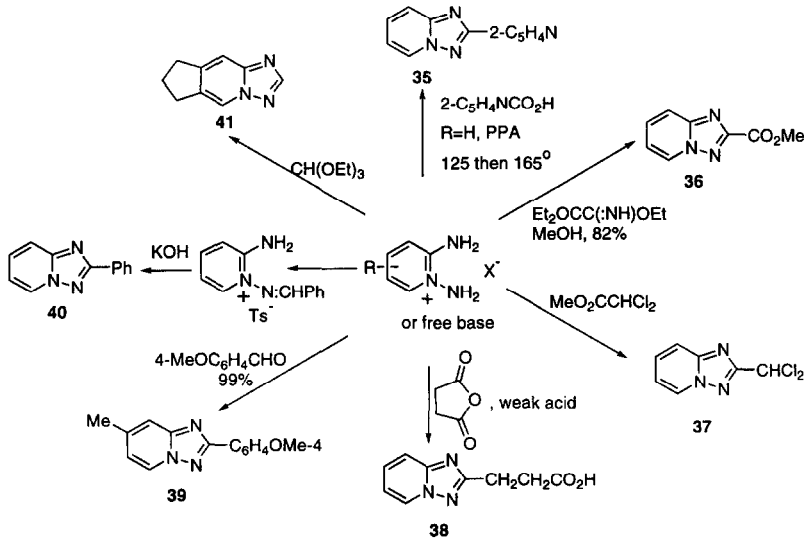
a. *Formation of One Bond.* The popular route from 2-pyridylamidines by cyclization with hypochlorite (formation of bond 3,4) gives high yields, as in the preparation of the bronchodilator **27** (81JAP(K)100783). Other approaches to formation of the 3,4 bond involve the ring opening of an oxadiazolylaminopyridine **28** (93H(36)1577) or thermal elimination of nitrogen from *N*-(2-pyridyl) tetrazoles **29** (83IJC(B)117). If the substituent is a tetrazolylamino group, the product is the 2-aminotriazolopyridine **30**, also obtained by reaction of the thioamide **31** with hydroxylamine (83M789). Closure of the 2,3 bond occurs in the reaction between hydroxyaminesulfonic acid and the formamidine derivatives **32**, amination and cyclization occurring at room temperature (81JOC3123).



Two examples of closure of the 1,8a bond are base catalyzed; synthesis of compound **33** starts from a quaternary salt (87CPB156), and compound **34** from a 2-pyridone (83TL3523).



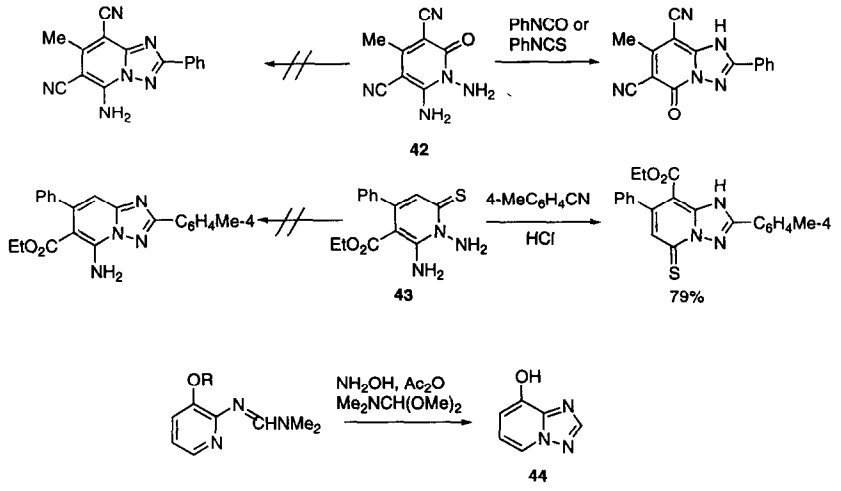
b. *Formation of Two Bonds.* The synthesis from 1,2-diaminopyridines or their salts continues to be much used, but has been widened in scope. As well as carboxylic acids and their acid chlorides, the one-carbon fragment can be an ester, an anhydride, an *ortho*-ester, or an aldehyde. These possibilities are illustrated in Scheme 1 by the production of compounds **35–39**. In most cases the free



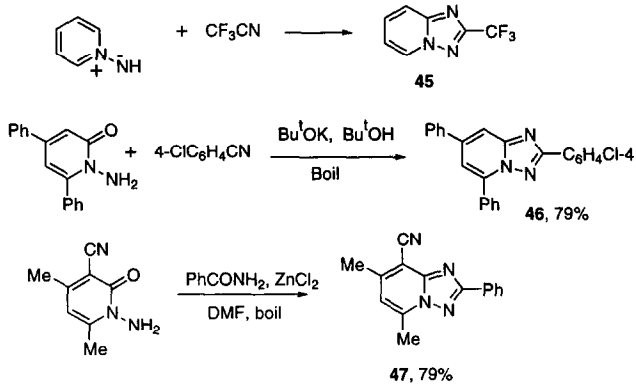
Scheme 1

bases are used, prepared for example by the action of Amberlite basic resin on the salt (86T2625), but the salts cyclize, as for example in the extremely acidic conditions used for compound **35** (81MIP1). Other points to note are the preferential cyclization of the ester over the imidate for compound **36** (with transesterification) (86T2625), and the possibility for further elaboration provided by the concealed aldehyde in compound **37** (81FRP2450259) or by the side chain acid formed from the anhydride in compound **38** (90GEP(E) 280108). When aldehydes are used (with aromatization by some oxidation procedure) the reaction can be one-stage from the free base, as shown for compound **39** (90GEP(E)280107) or two-stage as in the synthesis of compound **40** (95M1213). Ketones have also been used to give 2-*spiro*-triazolopyridines (97MI4). Triazolopyridines unsubstituted in position 2 can be obtained from formaldehyde (95M1213), or *ortho*-esters to give for example compound **41** (90GEP(E)280109) or from the sodium salt of acetoacetaldehyde by loss of acetone (94JHC1157). Dibromomalononitrile gives a 2,2-dicyanotriazolopyridine-5-one (98SC3331).

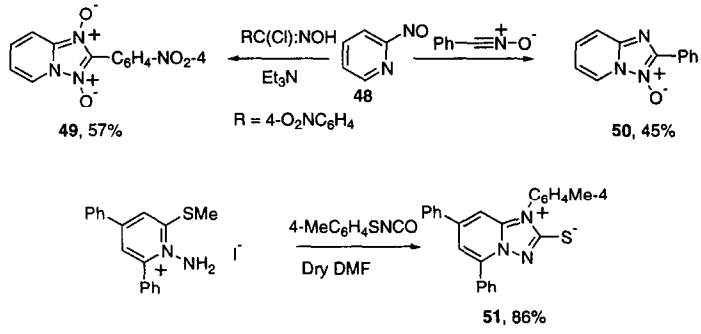
It is worth noting that the 2-pyridone **42** (99MI1) and thione **43** (88H(27)733), which could react in either of the two ways as shown, with an isocyanate or isothiocyanate and with a nitrile respectively, actually give a one-carbon insertion. There is a case of formation of 2,3 and 3,4 bonds in the preparation of 8-hydroxytriazolopyridine **44** (83MI1).



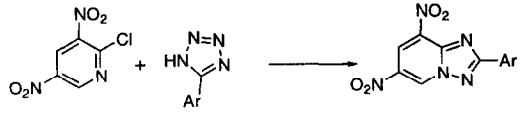
Syntheses in which a nitrile provides atoms 1 and 2 start from an ylide (82JFC373), or a 1-amino-2-pyridone (82S974) to give compounds **45** and **46**. Other two atom fragments used with 1-amino-2-pyridones are amides which give compounds such as **47** (86S860).



Cycloaddition of 2-nitrosopyridine **48** with nitrile oxides can give either di-*N*-oxides such as **49** or 3-mono-*N*-oxides such as **50** (93JHC287). In general, greater electron withdrawing character in the aromatic substituent appears to favor formation of the di-*N*-oxides. Sulfur ylides such as compound **51** are obtained from aryl isothiocyanates and 1-amino-2-methylthiopyridinium iodides (84JCS(P1)1891); nitrogen ylides can be obtained from a similar reaction (86H(24)3363).

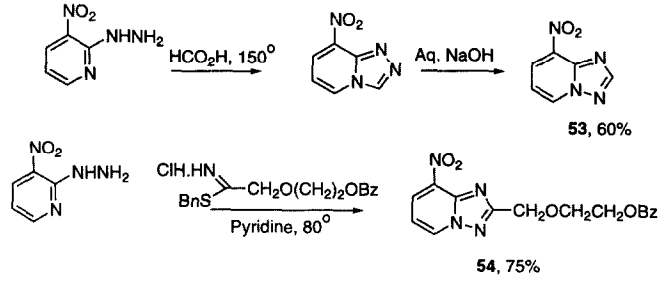


A three-atom addition is observed when the tetrazoles **52** are heated with 2-chloro-3,5-dinitropyridine (99RCB1391).

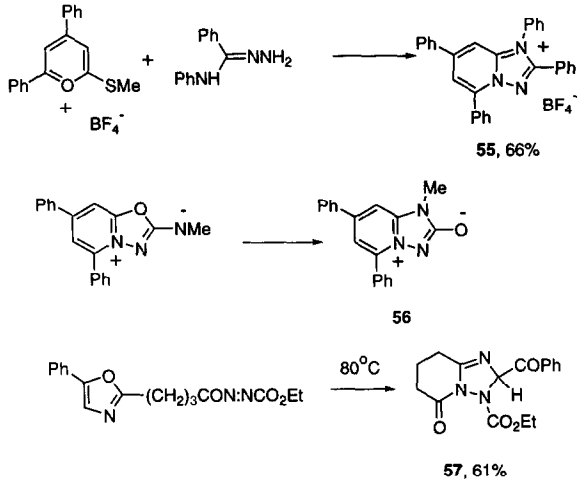


52

c. *By Rearrangement from Other Heterocycles.* The tendency of [1,2,4] triazolo [4,3-*a*]pyridines with electron withdrawing substituents to undergo rearrangement in the presence of a base means that 2-pyridylhydrazines can be precursors for the synthesis of [1,2,4]triazolo[1,5-*a*]pyridines. A two-stage synthesis of compound **53** (90JHC1649) and a one-stage synthesis of compound **54** (83JHC1169) are shown.



Molina's group have reported syntheses from pyrylium salts to give, for example, compound **55** (82TL2985, 83JCS(P1)1395) and rearrangement of an oxadiazolopyridinium ylide to give the ylide **56** (88CB1495). Intramolecular cycloaddition of the side chain aza group to an oxazole gives the triazolopyridone **57** (91JOC3419).



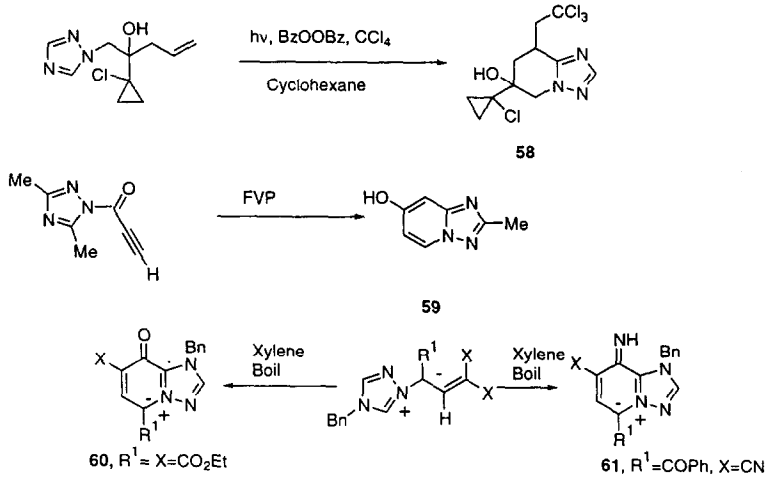
55, 66%

56

57, 61%

2. *Syntheses from Triazoles*

a. *Formation of One Bond.* An *N*-substituted triazole leads to formation of the 8,8a bond. Photochemical cyclization of an alkene, initiated by a trichloromethyl radical gives compound **58** (93GEP4204816). An alkyne under FVP conditions gives, after N1 to N2 rearrangement and cyclization, compound **59** (94AJC991), and thermal cyclization of ylides gives the 5*H*-carbonyl compound **60** or the 5*H*-imino compound **61** (00H(53)213).



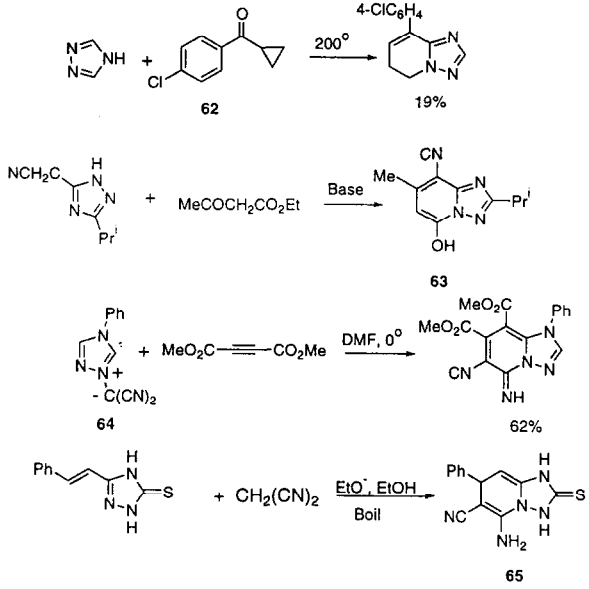
58

59

60, R^1 = X=CO_2Et

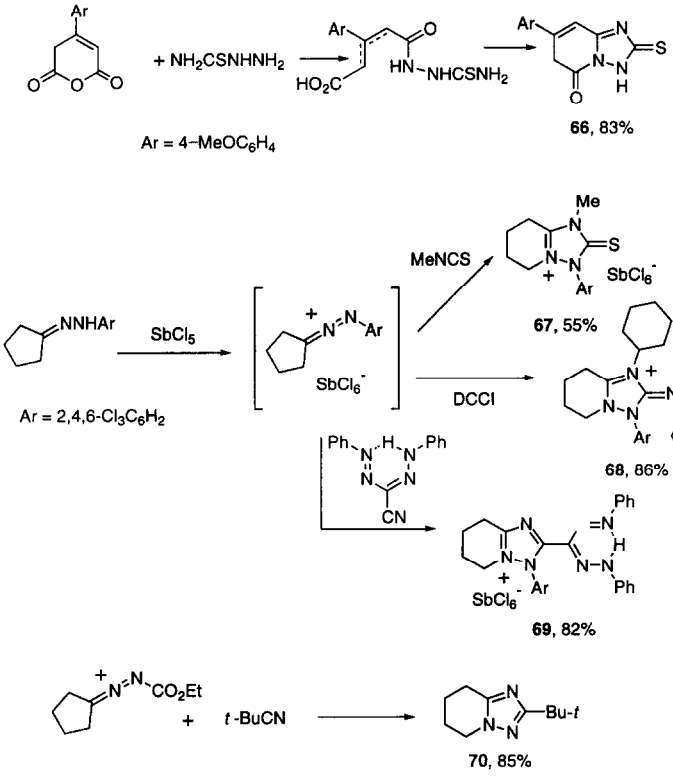
61, R^1=COPh, X=CN

b. *Formation of Two Bonds.* Heating [1,2,4]triazole with the cyclopropyl ketone **62** gives a poor yield of 5,6-dihydrotriazolopyridine; 4-chlorobutyrophenone gave a slightly better yield (87JOC1863). A 3-cyanomethyltriazole condenses with ethyl acetoacetate to give the 5-hydroxy derivative **63** (95GEP4326758). The ylide **64** reacts with acetylenic esters to give highly substituted triazolopyridines, presumably via a five-membered ring intermediate; the reaction with methyl propiolate is regiospecific (83JCS(P2)1317). A Michael addition of malononitrile to a styryltriazolothione gives compound **65** (98JCR(M)2056).

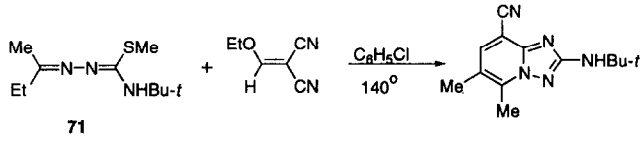


3. *Syntheses from Acyclic Fragments*

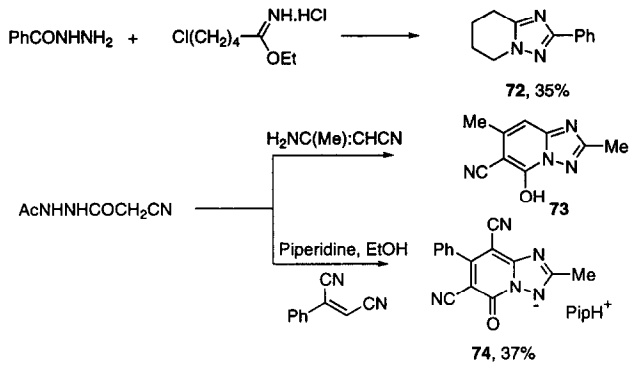
a. *Two Acyclic Fragments.* From an unsaturated anhydride and thiosemicarbazide a 2-thione **66** is obtained, directly or in a two-stage reaction (85IJC(B)330). A similar reaction gives fully reduced thiones (88JHC1471). An arylhydrazone of cyclopentanone reacts with a thiocyanate in the presence of antimony pentachloride to give the salt **67** (99JCS(P1)1999). The same intermediate reacts with a di-imide to give compound **68** (93CB2519), and with a tetrazene gives compound **69** (97T8507), and a similar salt, with *t*-butyl cyanide, gives compound **70** (93T9973).



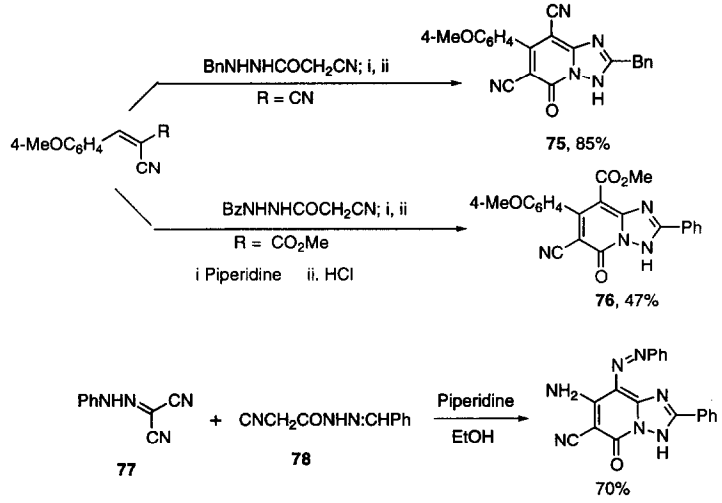
The alkylthiodi-imide **71** reacts with ethoxymethylenemalononitrile at 140°C to give a dimethylcyanotriazolopyridine (94JCS(P1)825).



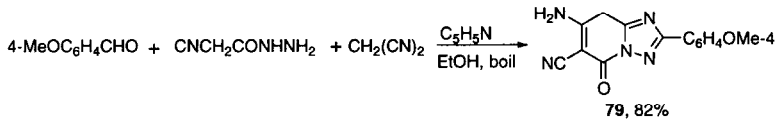
A vinyl ether and an aryl hydrazide react to give compound **72** (83JHC1657). A large number of compounds have been made from α,β-unsaturated nitriles. Crotononitriles react with *N*-acetylcyanoacetohydrazide and with cyanocinnamonitrile to give compounds such as **73** (91GEP3926770), and compound **74** (90JOC2259), respectively.



A wide range of arylmethylenemalononitriles react with cyanoacetohydrazides to give analogues of compound **74**, such as **75** (90JCS(P1)1687, 93JCS(P1)1045). Similar condensations occur with other unsaturated components, for example cyanoesters (92JHC1229), to give compounds such as **76**. If an unsaturated cyanoketone is used, the products are pyrazolopyridines (93JCS(P1)1743). The nitrile **77** and the hydrazide **78** give a highly substituted triazolopyridine (96JCR(S)296).



b. *Three Acyclic Fragments.* Products different from compound **74** are obtained if an aldehyde, malononitrile, and the free cyanoacetohydrazide are condensed with basic catalysis; here the aryl group is in position 2 as in compound **79** (96MI7, 96PHA982).



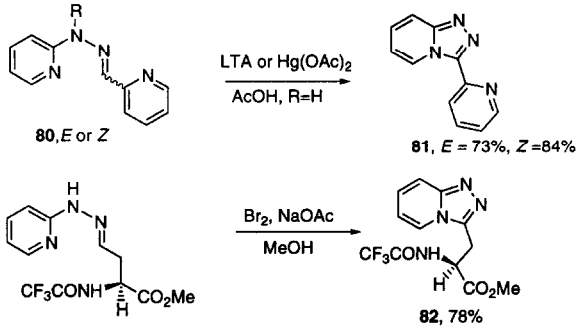
79, 82%

C. Synthesis of [1,2,4]Triazolo[4,3-*a*]Pyridines

In all syntheses of [1,2,4]triazolo[4,3-*a*]pyridines it should be remembered that electron withdrawing substituents on the pyridine ring can cause Dimroth rearrangement of the initially formed compounds into derivatives of [1,2,4]triazolo[1,5-*a*]pyridines (see Section B.2.c).

1. *Syntheses from Pyridines*

a. *Formation of One Bond.* The route mostly used is the oxidative cyclization of 2-pyridylhydrazones (94SL667). Butler and Johnson made a thorough study of the mechanism of cyclization of hydrazones of general type **80** in acetic acid with LTA or mercuric acetate (81CC376, 84JCS(P1)2109), noting that *E* or *Z* forms were equally effective when R = H giving compound **81**, but when group R was not hydrogen [1,2,3]triazolo[1,5-*a*]pyridines were formed (Section II.A.1.a). Other chemical oxidizing agents used are chloramine-T (93SC3195), bromine in acetic acid (91EUP430385) or in methanol with sodium acetate (94JHC1259). The latter case illustrates the synthesis of a compound **82** where stereochemical integrity is retained in a substituent.



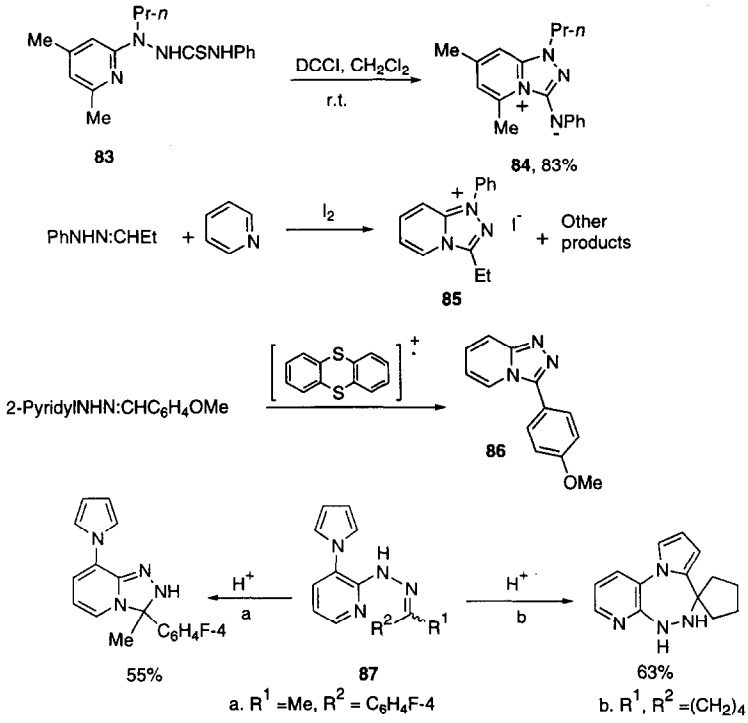
80, *E* or *Z*

81, *E* = 73%, *Z* = 84%

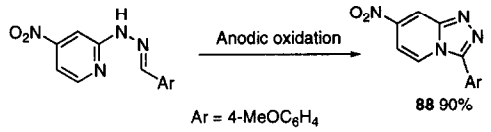
82, 78%

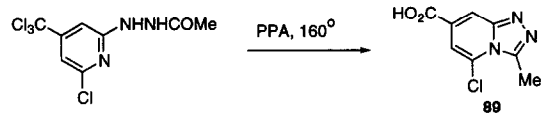
DCCI reacts with hydrazone derivatives or with the thiourea **83** to give nitrogen ylides such as **84** and hence by protonation 3-aminotriazolopyridines (88CC506, 93JCS(P1)705). A solution of iodine in pyridine reacts with propional

phenylhydrazone to give a mixture of products including a triazolopyridinium salt **85**, apparently via an unusual 1,8a cyclization (90T395). The thianthrene cation radical converts suitable hydrazones into 3-aryltriazolopyridines such as compound **86** (97MI1), and ketone hydrazones **87** are cyclized by ethanolic HBr or HCl in acetic acid to give dihydrotriazolopyridines (91CPB81). The alternative cyclization to give pyridopyrrolotriazepines is favoured when the ketone has small substituents.

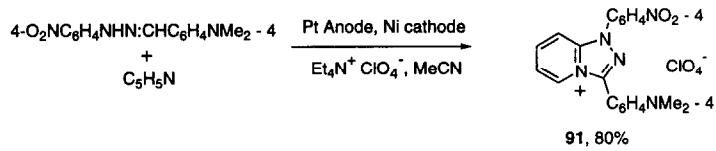


Anodic oxidation of 2-pyridylhydrazones has been thoroughly studied, a mechanism established, and yields optimized as in the production of compound **88** (83ACS(B)527, 90MI3). Cyclization of 2-pyridyl hydrazides by PPA gives a range of 3-substituted triazolopyridines such as **89** (87EUP210648), and similar derivatives of piperidine give tetrahydro derivatives such as **90** (97HCA979).

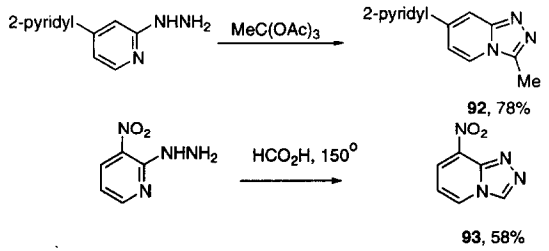




b. *Formation of Two Bonds.* Anodic reduction of the 4-nitrophenylhydrazones of aryl aldehydes in the presence of pyridine gives good yields of salts such as **91**; the mechanism proposed involves a two-stage addition of the oxidized hydrazone to the pyridine (85ZC443, 88JOC5081).

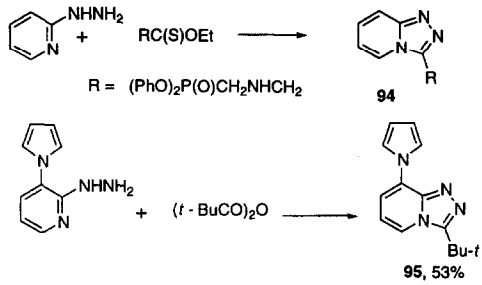


Many syntheses start from 2-pyridylhydrazine, forming the 2,3 and 3,4 bonds, by reaction with *ortho*-formates or -acetates as in example **92** (85USP4550166, 86JHC1071), formic acid to give 8-nitro derivative **93** (90JHC1649), acid

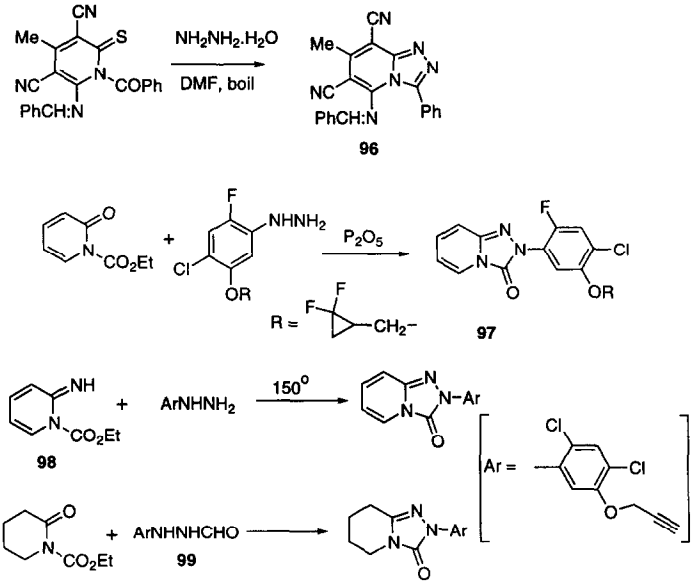


chlorides (96MI2), a thioester to give compound **94** (92MI2), and anhydrides including pivalic anhydride which gives compound **95** (85CPB4769).

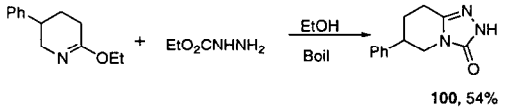
Chloroformates or carbonyl chloride react with 2-piperidone hydrazones to give triazolopyridine-3-ones (86JAP(K)69776), and there are further examples of the production of 3-thiols from a hydrazine and carbon disulfide (83USP4419516, 88EUP254623).



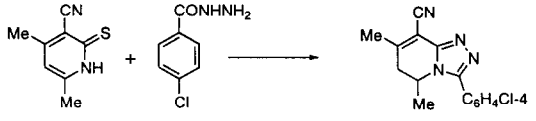
Addition of hydrazine to a 1-acetyl-2-pyridone (90MI1) or 1-benzoyl-2-pyridinethione (93JCR(M)0155) gives 3-substituted triazolopyridines such as **96**. On the other hand, 1-alkoxycarbonyl-2-pyridones give triazolopyridin-3-ones, such as **97** (88GEP3635309); the tetrahydroderivatives (89EUP317947) or the corresponding imino compounds such as **98** (98USP5705639) also give triazolopyridinones. The similar reaction between a carbamate and *N*-formylarylhydrazine **99** appears to involve loss of the formyl group (97EUP784053); 2-chloro-1-chlorocarbonyl-5,6-dihydro-4*H*-pyridine can also be used (97GEP19601189).



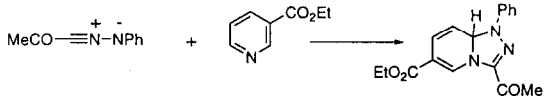
There are a few syntheses which involve addition of a three-atom fragment to a pyridine derivative to make bonds 3,4 and 1,8a. Semicarbazide with 2-chloropyridine gives an adduct which, after hydrolysis forms triazolopyridin-3-one (81USP4254124). A 2-ethoxy-3,4,5,6-tetrahydropyridine, boiled with ethyl carbazate, gives compound **100** (82JHC193), and aroylhydrazines react with a pyridine-2-thione to produce compounds such as **101** (96JICS141). The 1,3-dipoles derived from α-chlorohydrazones react with pyridines to produce dihydro derivatives such as **102** (92LA885).



100, 54%



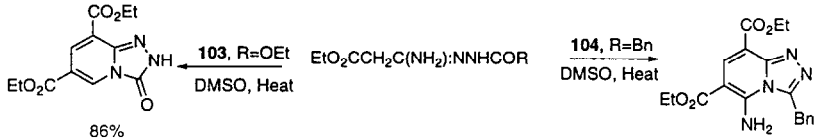
101, 62%



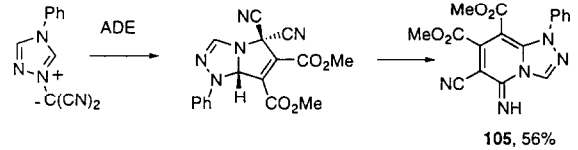
102, 90%

2. *Syntheses from Acyclic Compounds and Other Heterocycles*

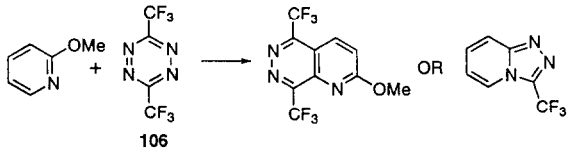
Ethoxymethylenecyanoacetate and the hydrazone 103 give a triazolopyridinone; other hydrazones, such as **104** give 7-aminotriazolopyridines (91JHC797).



86% 84%



105, 56%



106

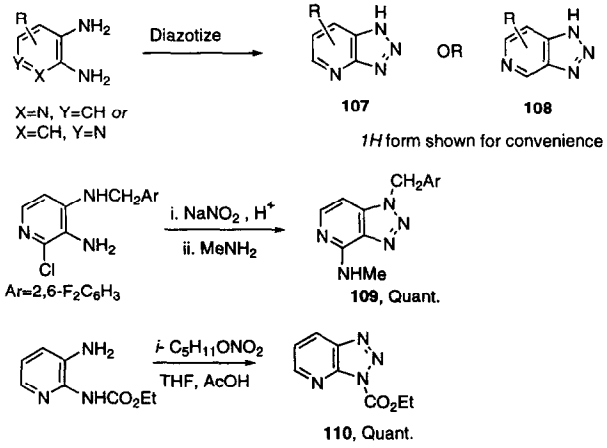
A triazolium ylide reacts with acetylene dicarboxylate to produce compound **105** via a pyrrolotriazole (83JCS(P1)1317), and 2-methoxypyridine can react with the tetrazole **106** to give either a triazolopyridine or a pyridopyrazine (93AP (326)427).

D. Synthesis of [1,2,3]Triazolo[4,5-*b*]Pyridines and [1,2,3]Triazolo[4,5-*c*]Pyridines

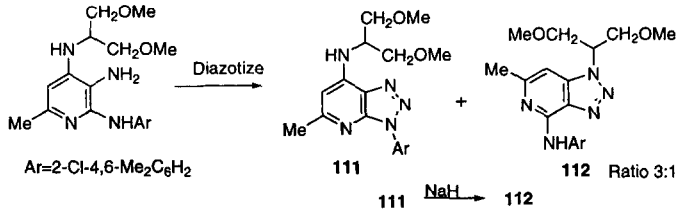
1. *Syntheses from Pyridines*

There are no new syntheses involving formation of one bond.

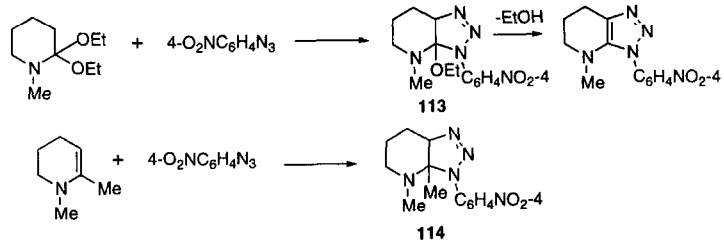
a. *Formation of Two Bonds.* The most versatile route is still via the diazotization of 2,3-diaminopyridines to give triazolo[4,5-*b*]pyridines **107** or of 3,4-diaminopyridines to give triazolo[4,5-*c*]pyridines **108**. The parent, **108** (R = H), has been obtained in 80% yield (97TL8607), and trisubstituted derivatives of **108** in 81–97% yields (82JHC1481). A substituent on one of the amino groups appears in the corresponding position in the triazolopyridine, as shown by the synthesis of compounds **109** (95JMC4131) and **110** (85JHC313).



In the case of a 2,3,4-triaminopyridine, diazotization of the 3-amino group gives a mixture of the two possible cyclized products, **111** and **112**, interconverted by sodium hydride (98MIP42706).

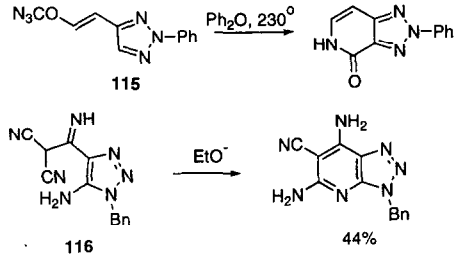


The diethylketal of *N*-methylpiperidone or 3,4,5,6-tetrahydropyridines add to 4-nitrophenyl azide to give respectively compounds **113** (86CB3591) and **114** (86AP(319)1049). For compound **113** elimination of ethanol gives the tetrahydrotriazolopyridine.



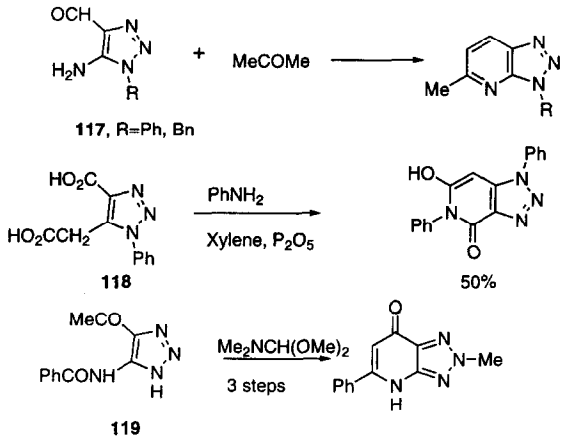
2. *Syntheses from Triazoles*

a. *Formation of One Bond.* Thermolysis of the azide **115** gives a triazolopyridinone (85LA1922), and base treatment of the aminotriazole **116** gives a highly substituted triazolo[4,5-*b*]pyridine (87JHC997).



b. *Formation of Two Bonds.* The 5-amino-4-formyltriazoles **117** undergo various pyridine syntheses; the reaction with acetone is shown (88BSB85).

Other 4,5-disubstituted triazoles used as precursors for triazolopyridines are the diacid **118** or its anhydride, reacting with aniline (83IJC(B)125) and the ketoamide **119** (90IZV1392).



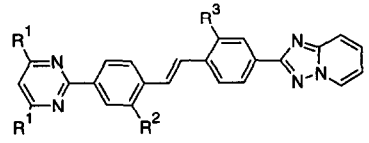
III. Physical Properties and Theoretical Chemistry

A. Electronic Spectra

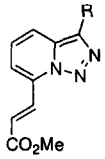
Many papers on triazolopyridines include some data on electronic spectra, but there have been few which represent studies of such spectra. A considerable number of dyes and photographic materials include triazolopyridine derivatives in their chromophores. Such compounds appear in Section VI. Photochemical reactions are dealt with in Section IV.G. A study of fluorescence spectra of a series of 2-pyrimidinyl stilbenes with a variety of other heterocycles at position 4′ include the triazolopyridine derivatives **120** (81HCA113). The absorbing frequencies range from 353 to 373 nm, and the fluorescence maxima from 393 to 498 nm, with ϕ values of 0.38–0.73. A study of the fluorescence properties of some 7-substituted [1,2,3]triazolo[1,5-*a*]pyridines showed that only compounds **121** showed relatively high fluorescence in methanol with excitation between 352 and 384 nm, and emission between 458 and 520 nm (96JHC991). A preliminary study has been made of the solvatochromism in 17 solvents of some stable ylides of triazolo-pyridine- **122**, **123**, and -quinoline **124** (00MI1). Correlation with Reichardt's empirical parameters for the solvents E_T^N (83LA721) was good in some cases.

B. Infrared Spectra

Many individual compound reports contain infrared spectral information, but there is only one in which detailed analysis appears. The 3-hydroxytriazolopyridine **125** used as a catalyst for peptide coupling (Section IV.J) has been studied in the solid and in solution, in association with a crystallographic study, and shown to exist as a dimer in solution (99MI1).

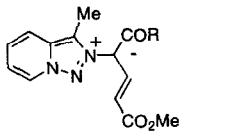


120 R^1=H, OMe; R^2=H, Cl; R^3=H, Cl

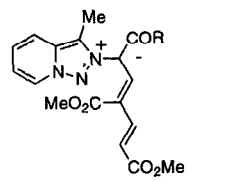


121

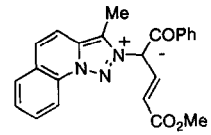
R	λ_{max} Absorption	λ_{max} Emission
H	352	458
Me	368	483
Bu^t	369	481
Ph	384	520



122, R = OMe, OEt, and Ph



123, R = OMe and OEt



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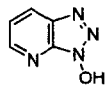
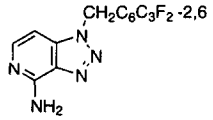


125

C. Mass Spectra

There are many reports of the use of mass spectroscopy coupled to chromatography outlets for detection and identification of drugs and metabolites. An example is compound **126** (99MI2, 99MI3). Carboxylic acids have been converted into hydrazides and hence into 3-substituted [1,2,4]triazolo

[4,3-*a*]pyridines; a combination of GC/MS then allowed the location of branches and double bonds (88OMS566). Intramolecular redox reactions were observed in ionized 3-aryl[1,2,3]triazolo[4,5-*b*]- and -[4,5-*c*]pyridines where the aryl group has an *o*-nitro group. Compound **127** lost nitrogen and produced the ionized cyclopentadienone (89MI1) while other compounds produced ionized azafulvenones (88MI1).



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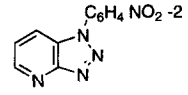


127

D. Nuclear Magnetic Resonance Spectra

1. *^{1}H-NMR Spectra*

Most new triazolopyridines reported include data on ^{1}H-NMR spectra, but there are no new studies of general correlations.

2. *^{13}C-NMR Spectra*

Detailed assignments are available for compounds **1**, **2**, and **3**, and are given in Table I. Jones and Sliskovic (84OMR192) used deuterium labeling to correct earlier assignments for the shifts of compound **1** in acetone-d_6 (80JMS15), and reported that better resolution was obtained with solutions in $CDCl_3$. Coupling constants which were assigned are given in Table II. The shifts for compounds **2** and **3** were based on single frequency decoupling for most carbons bearing hydrogen atoms and correlation diagrams for the quaternary and a few hydrogen bearing carbon atoms (87JHC805). The spectra form part of a series of aza- and polyaza-indolizines from which chemical shifts have been correlated with the position of the nitrogen substituents.

Table I. ^{13}C-Chemical Shifts for Triazolopyridines **1**, **2**, and **3**

Compound	Solvent	C1	C2	C3	C5	C6	C7	C8	C8a	References
1	Acetone-d_6	126.1	–	–	125.8	116.1	126.1	116.1	134.5	84OMR192
1	$CDCl_3$	125.2	–	–	124.7	115.0	125.0	117.6	133.3	84OMR192
2	DMSO	–	153.88	–	129.1	114.2	130.1	116.2	150.0	87JHC805
3	DMSO	–	–	136.5	125.1	113.5	128.0	115.0	148.6	87JHC805

Table II. *J* values (Hz, ±0.15 Hz) for compound **1**

Carbon Atom	^1J (CH)	^2J (CH)	^3J (CH)	^4J (CH)
1	184.3	–	–	–
5	172.7	–	–	–
6	167.8(5)	1.2	7.5	1
7	174.6	1.0	7.0	–
8	170.9	1.2	7.6	–

For convenience, all three compounds are numbered as shown for compounds **2** and **3**.

Table III. ^{15}N-Chemical Shifts for Triazolopyridines **1**, **2**, and **3**

	Solvent	N1	N2	N3	N4
1	DMSO[a]	–	+24.9	+44.2	+120.4
2	Acetone[a]	+142.5	–	+103.8	+150.2
3	Acetone[a]	+89.3	+56.8	–	+187.5

[a] With added $Cr(AcAc)_2$

3. *^{15}N-NMR Spectra*

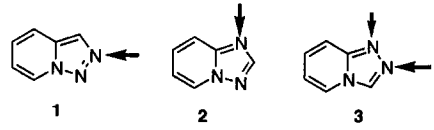
A detailed study of ^{15}N spectra of compounds **1**, **2**, and **3** has been published as part of a general study of azolopyridines (84OMR209). The shifts are shown in Table III. The ^{15}N shifts have been used to determine the structure of 7-amino-triazolopyridines **128** and **129** (89T7041). The shifts recorded were 56.8, 56.2 (N1), 245.4, 246.3 (N2), 320.6, 316.8 (N7a), all from nitromethane as standard at 380 ppm; the absorption for the amine was at 345.5, 350 ppm in accordance with the amino structure shown, rather than the imino forms **128a** and **129a**.

128, R=H
129 R=Me

128a, R=H
129a, R=Me

E. Theoretical Chemistry

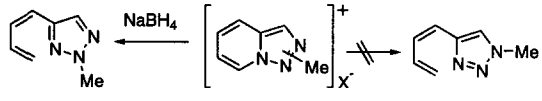
Semiempirical AM1 and *ab initio* calculations using GAUSSIAN 86 with the STO-3G basis set were used to explain the site of alkylation in compounds **1**



1 2 3

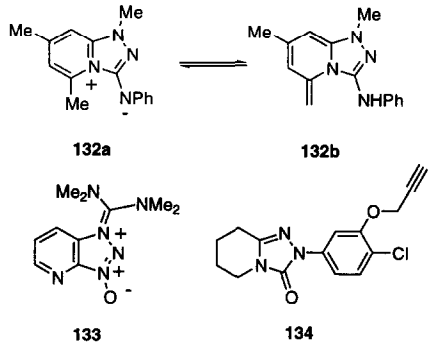
Fig. 1 Site of alkylation in compounds **1**, **2**, and **3**. Compound **3**, ratio of alkylation at N1 and N2 is 2:1.

and **2**, and to predict the site of alkylation in compound **3** (93T4307). These sites of alkylation are shown in Fig. 1. The important point was the use of the highest orbital with σ symmetry, not the HMO which is of π symmetry. The same authors have used similar reasoning to explain the observation that salt **130** is attacked by hydride at C7 with ring opening while **131** is not.



130, 3-Me
131, 2-Me

MEP maps have been produced for a number of nitrogen-containing heterocycles, including compound **2** (98MI1). A PM3 calculation on the ylide **132a** shows the phenyl ring at position 3 twisted and the tautomer **132b** to be only marginally less stable than form **132a** (97JCS(P2)49). Semiempirical calculations were performed on compound **133**, a catalyst for peptide bond formation, in the gas phase and in solution (96JCR(S)302) and on compounds **134** which has herbicidal properties (94MI1). Calculation of Hammett–Brown constants for a series of heteroaryl-substituted phenyl groups showed the triazolopyridyl system **2** to have a slight electron-withdrawing character (97JHC289).



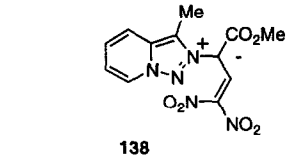
132a **132b**

133 **134**

F. X-Ray Crystallography

There are now a number of X-ray structures for simple triazolopyridines, ylides, and metal complexes which show the molecular dimensions. The 3-pyridyl derivative **135** (94JCS(D)2651), the ester **136** (83AX(C)391), and the 3-hydroxy derivative **137** (99JMS(476)289) provide dimensions for systems **1**, **2**, and **4**, and are shown in Fig. 2.

Increased interest in the chemistry of ylides has produced X-ray structures for compounds **123** (R = OMe) (91T5277) and **138** (92H(34)1005), while possibilities of complex formation have led to structures for bidentate copper complex of **135** (94JCS(D)2651), monodentate copper complex of the 3-phenyltriazolopyridine **139**, monodentate (through N2) dinitrato ligand of 3-methyltriazolopyridine **140** (99MI4), and dinitrato bidentate copper complex of



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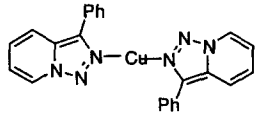

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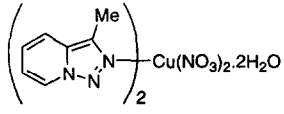

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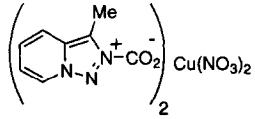

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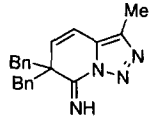
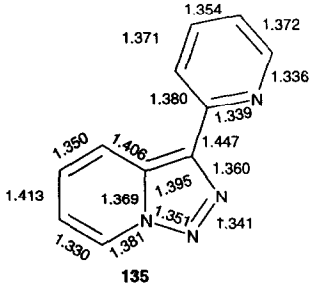


142

zwitterion **141**, where complexing occurs through the carboxylate ion (96MI3). The structure of compound **16** (Section II.A.1.b) was confirmed by X-ray



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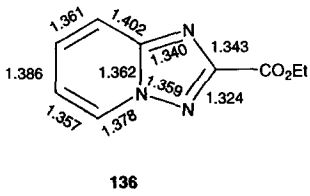

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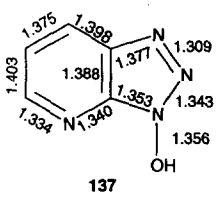


137

Fig. 2 Bond lengths of triazolopyridines.

diffraction (95T10969), as were compounds of type **76** (as piperidine salt). (92JHC1229) (Section II.B.3.a), and unusual product **142** from alkylation of a 7-aminotriazolopyridine (93T703). The determination of the crystal structure of 3-methyl[1,2,3]triazolo[1,5-*a*]pyridine has been reported from X-ray powder diffraction data (93MI1)

IV. Chemical Properties

Chemical properties are grouped under reaction type, and each of the five systems is dealt with sequentially in each subsection.

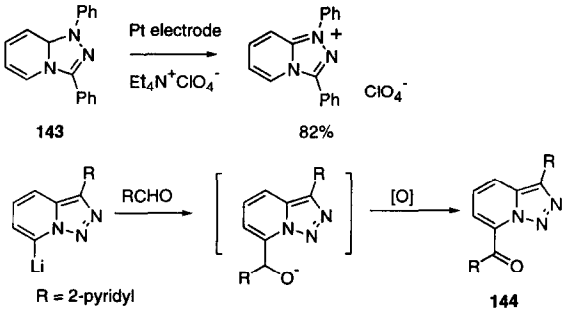
A. Oxidation

1. *Oxidation of the Ring*

The only examples of ring oxidation are the one-electron anodic oxidation of N1-aryl[1,2,4]triazolo[4,3-*a*]pyridines such as compound **143** to give quaternary salts (88ZC187), and the voltammetric oxidation of the anti-depressant Trazodone (Section V.A) (87MI1).

2. *Oxidation of Substituent Groups*

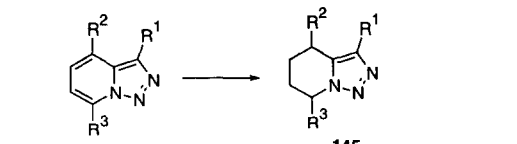
Spontaneous aerial oxidation of the initially formed alkoxide is reported in the reaction between a 7-lithiotriazolopyridine and pyridine-2-carboxaldehyde, to give ketone **144** (98T15287).



B. Reduction

1. *Reduction of the Nucleus*

A detailed study of the reduction of a range of [1,2,3]-triazolo[1,5-*a*]pyridines has produced some intriguing results (99T12881). Under standard conditions (Pd/C, MeOH, r.t.), with 3-alkyl, aryl and electron withdrawing substituents the 4,5,6,7-tetrahydro derivatives **145** are formed. The introduction of 4- or 7-alkyl groups or the electron donating 3-(2-thienyl) group prevent hydrogenation. In the case of the 3-cyano derivative there are two products, one the tetrahydro derivative **146** and the other the compound **147**, rationalized as a condensation product between compound **146** and the starting material.



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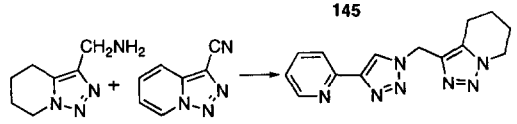
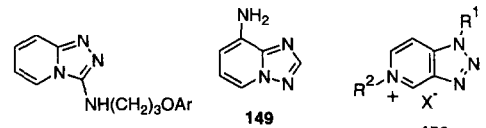


146 **147**

A compound **148** which shows stomach secretion inhibition (80EUP48555) and the aminotriazolopyridine **149** (90JHC1649) are reduced catalytically to the 5,6,7,8-tetrahydro derivatives. The polarographic behaviour of Trazodone has been studied (87MI2). The quaternary salts **150** are reduced by borohydride to the 4,5,6,7-tetrahydro derivatives (94ZOK440).

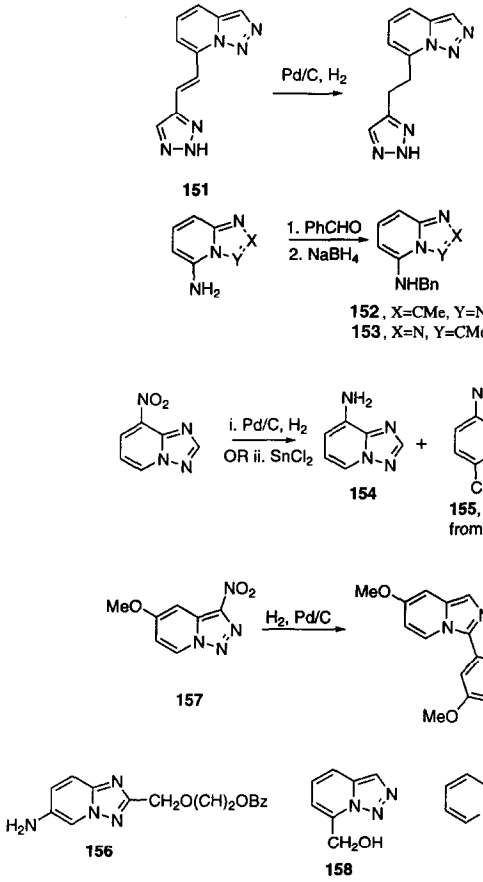


148 Ar = $C_6H_4CH_2NC_5H_{10}$ **149** **150**

2. *Reduction of Substituent Groups*

In the study of nuclear reduction of [1,2,3]triazolo[1,5-*a*]pyridine (99T12881), a number of substituents were also reduced. The cyano group was reduced to give

compound **146** and the double bond in compounds **151** to the alkane (the presence of an alkyl group in position 7 inhibits reduction of the ring). Condensation of benzaldehyde with amines gives aldimines, reduced by borohydride to secondary amines **152** (82USP4358453, 82USP4358454) and **153** (82USP4358453). Nitro groups have been reduced catalytically to give primary amines such as compounds **154** (90JHC1649) and **155** (83JHC1169). In the former case, an attempt to use stannous chloride for the reduction gives a small yield of the 5-chloro compound **155**, isolated as the acetyl derivative. Reduction of 3-nitro-5-methoxy-triazolopyridine **157** gives a 3-(2-pyridyl)imidazopyridine (83JCR(M)1338). The primary alcohol **158** is obtained by borohydride reduction of the aldehyde (95JHC787), and the *N*-oxide **159** is deoxygenated by phosphorus trichloride (93JHC287).

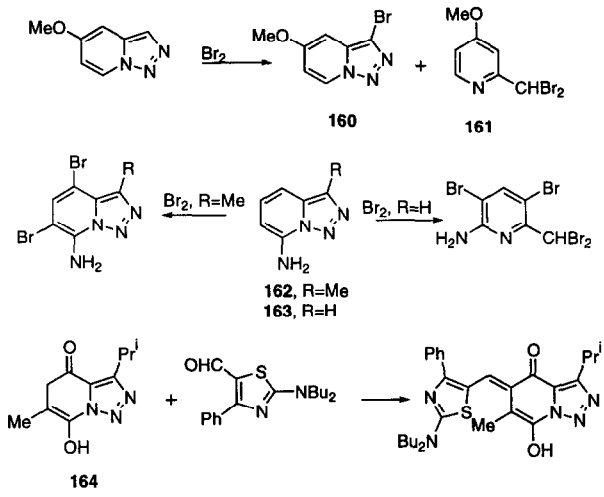


C. Reaction with Electrophiles

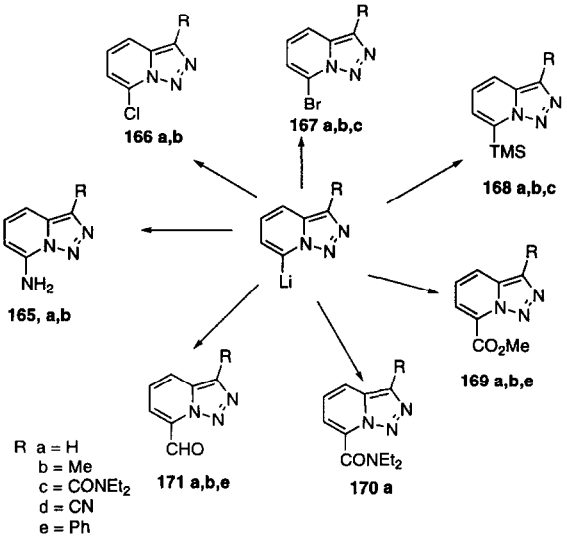
Ylide chemistry has become important enough to appear as a separate section (IV. I).

1. *Electrophiles Other than Alkylating Agents*

Most reactions with electrophiles have been reported on compound **1** and its derivatives. Bromination of the 5-methoxy derivative gives a mixture of the 3-bromo compound **160** with ring-opened product **161** (83JCR(M)1338) (see Section F). The 7-amino compound **162** gives the 4,6-dibromo derivative, while the compound **163** with a free position 3 gave only a dibromomethylpyridine (93T703). An aldol condensation on the triazolopyridinone **164** gives a transfer dye (95GEP4406167).



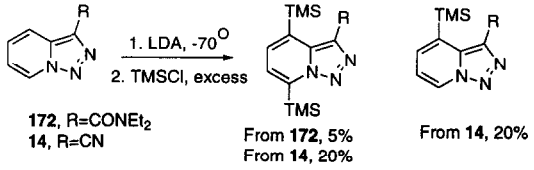
Most interest is centred on directed lithiation, with subsequent reaction with electrophiles. Lithiation occurs at position 7. Many successful replacements have been achieved, the most significant being shown in Scheme 2. Styryl azide gave a poor yield of the 7-amino derivatives **165** (89T7041) (see Section II.A for synthesis). Hexachloroethane gives the 7-chloro- and 1,2-dibromotetrachloroethane the 7-bromotriazolopyridines **166** (unpublished results) and **167** (87JCS(P1)1865). TMS chloride gives the 7-TMS derivative **168** (87JCS(P1) 1865), carbon dioxide the 7-carboxylic acid, isolated as the methyl ester **169**



Scheme 2

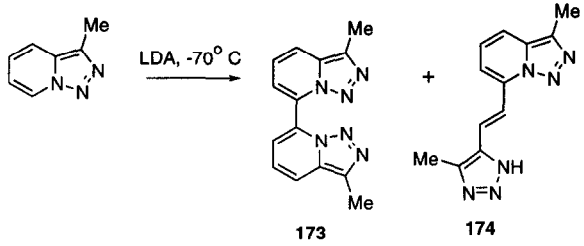
(95JHC787), *N,N*-diethylcarbamoyl chloride the amide **170** (95T10969), and, contrary to earlier reports, DMF gives the 7-formyl derivative **171** (95JHC787).

Attempts have been made to extend the directed lithiation procedure to secure substitution at other positions than 7. Lithiation of the 3-diethylcarbamoyl derivative **172** and quenching with TMS chloride gave a small yield of the 4,7-disubstituted derivative; the use of 3-cyanotriazolopyridine **14** gave more of the 4,7-disubstituted compound and, surprisingly, an equal amount of the 4-TMS derivative (95T10969). An attempt to use a 7-amido group to direct lithiation to position 6 failed, the lithium replacing the amide group with substitution at position 7. The only successful reaction on a TMS derivative was protodesilylation of compound **168c** (95T10969).

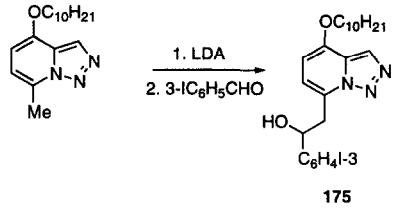


If the mixture of 3-methyltriazolopyridine and LDA is left at –70°C without adding electrophile two products are formed, one the dimer **173**, and the

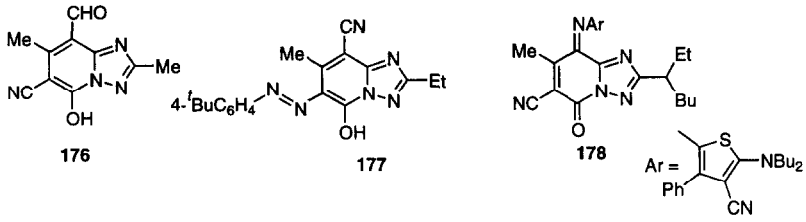
other, **174**, the product of a known ring opening reaction (97T8257). Ring opening of compounds of type **173** gives 2,2′-bipyridyls (98T15287) (see Section IV.F).



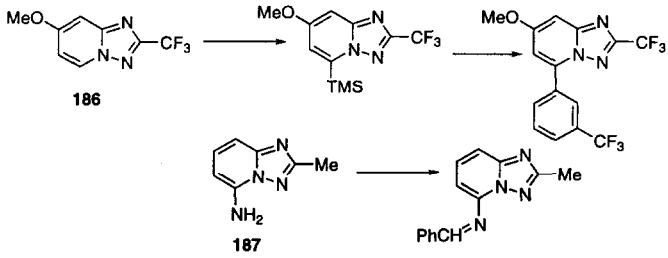
Lithiation at methyl groups allows elaboration of side chains, as in the production of compounds **175** (91MIP18880); the 5-methyl group is similarly functionalized (93JMC3321).



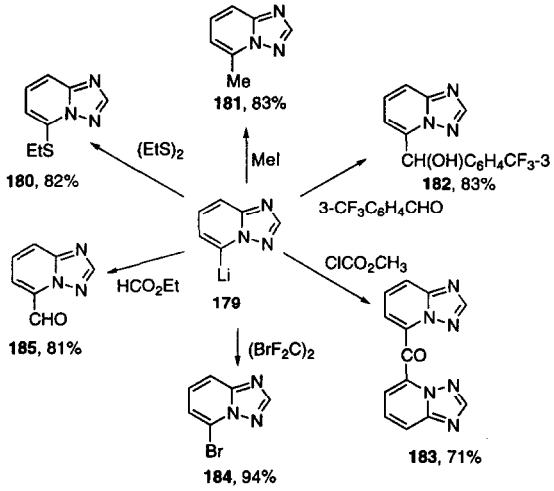
Derivatives of compound **2** bearing activating substituents react with electrophiles in the pyridine ring. Compounds thus prepared are formyl derivatives such as **176** (91GEP3926770), azo dyes such as **177** from diazocoupling (92GEP4020768, 96GEP4329296), and the imino derivative **178** by condensation with a nitrosothiophen (94GEP4232557).



Lithiation of compound **2**, by analogy with compound **1** gives the 5-lithio derivative **179** whose reactions with electrophiles give compounds **180–185** as shown in Scheme 3 (92JOC5538). The lithio derivative of **186** gives the 5-TMS derivative which couples with an aryl halide to give a 5-aryl derivative (92MI1). The 5-aminotriazolopyridine **177** condenses with benzaldehyde to give an imine, subsequently reduced by borohydride to the secondary amine (82USP4358454).

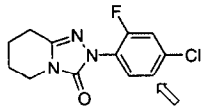


There are no reports of direct electrophilic substitution on system **3**. The triazololpyridinone **188** is chlorosulfonated on the benzene ring (92GEP4020629)



Scheme 3

and the only electrophilic substitution on the compound **189**, a derivative of system **5**, is nitration at position 7 (86ZOK1793).



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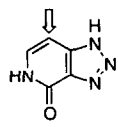
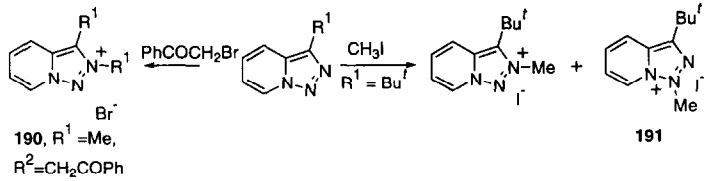


189

2. *Alkylation, Arylation, and Acylation*

Substitution on the ring is first dealt with before alkylation of substituents. The position of alkylation on the compounds **1–3** has been predicted and confirmed (see Section III.E) (93T4307). The substitution of compound **1** has been amply confirmed by preparation of a series of precursors for ylides such as compound **190**, the position of the substituent being confirmed by DIFNOE (90JCR(M) 346). In the same paper it is recorded that alkylation can be forced to position 1 by steric hindrance from a *t*-butyl substituent in position 3 (but not by a mesityl group) giving compound **191**. Methylation of 7-aminotriazolopyridines also gives 2-methylated quaternary salts **192** (89T7041).

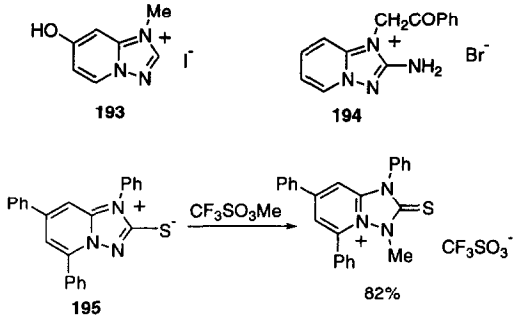


190, R^1 =Me, R^2=CH_2COPh

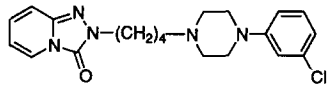
191

192

Alkylation of compound **2** has been confirmed at position 1 as predicted for methylation (dimethyl sulfate) and ethylation (triethyloxonium fluoroborate) (93T4307), and in the simple case of compound **193** (94AJC1009), and in the compound **194** (82MI1). The ylide **195** (84JCS(P1)1891) is substituted at position 3.



Compound **3** can alkylate at positions 1 and 2 (93T4307). Most interest has been on alkylation of the anion of the triazolopyridin-3-one to give compounds related to Trazodone, such as **196** (81EUP25603, see also 90MIP50817; 93MIP14091) where alkylation is exclusively at position 2. There is an interesting dichotomy in reactions of the triazolopyridinone shown in Scheme 4; alkylation of the neutral molecule can give a quantitative yield of 2-substitution (methyl iodide, acetone) or mixtures of 1- and 2-substitution (benzyl bromide). Scheme 4 (83BCSJ2969) shows that reactions with acyl chlorides (including carbonyl chloride) give 2-substituted compounds, while alkoxycarbonyl chlorides and all reactions on the TMS derivative give 1-substituted derivatives.



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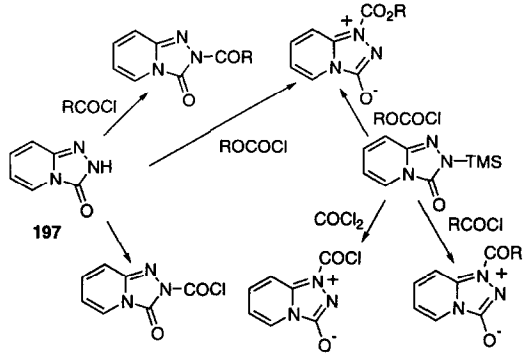
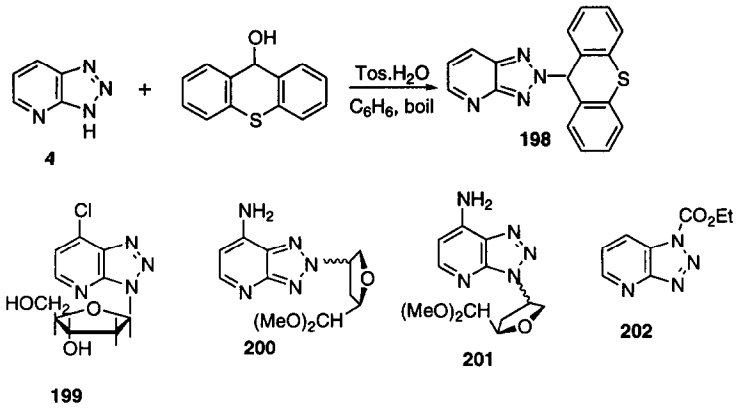


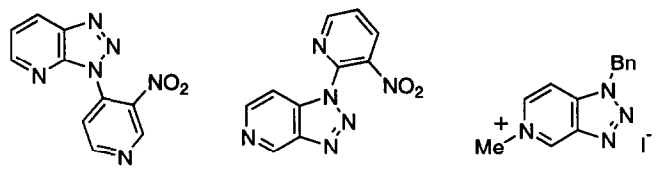
Scheme 4

Alkylation of compound **4** using a carbocation gives the compound **198** (99JHC927). Glycosidation of the anion from the 7-chloro derivative gives compound **199** (92MI3), while alkylation with a tosylate, using potassium carbonate and 18-crown-6 gives a mixture of 2- and 3-substituted products **200** and **201** in a ratio of 45:23 (94JMC3534). Acylation of compound **4** with chloroformates gives 1-substituted derivatives such as **202** (85JHC313, 86JHC1459), and arylation with 2- or 4-chloropyridines gives 3-substituted derivatives such as **203** (97TL8607).



4 **198** **199** **200** **201** **202**

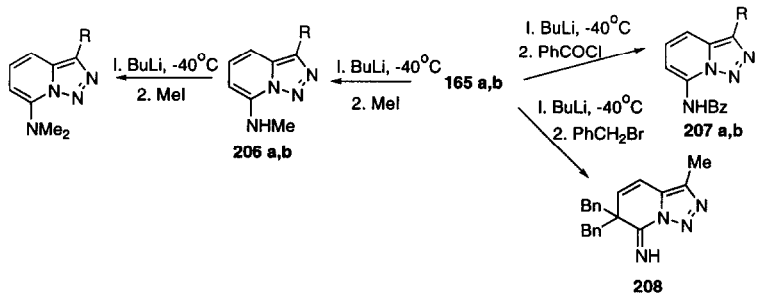
Arylation of compound **5** with a 2-chloropyridine gives compound **204** (97TL8607). Alkylation of 1-substituted derivatives gives quaternary salts such as **205** (94ZOK440).



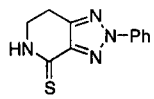
203 **204** **205**

There are many examples of alkylation using complex side chains, where the triazolopyridine is one of many heterocyclic termini in antibiotics. Mention of these will be found in Section V.B.

Alkylation of the anions of 7-aminotriazolopyridines **165a** and **165b** with methyl iodide and aroylation with benzoyl chloride gave the monosubstituted amines **206** and **207** (93T703). The dimethyl amines are obtained by a further sequence of lithiation and methylation, but not directly. Evidence that the anion is ambident is provided by the isolation of a C-alkylated derivative **208** when benzyl bromide is the alkylating agent. Ring opening is also observed (see Section IV.F).



The hydroxy compound **59** has been acetylated (94AJC991), and many glycosides have been protected by acetylation. The 4-thione **209** (85LA1922) and the 3-thiol **210** (83USP4419516) have been alkylated using methyl iodide with potassium hydroxide and chloroacetonitrile with triethylamine respectively.



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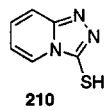
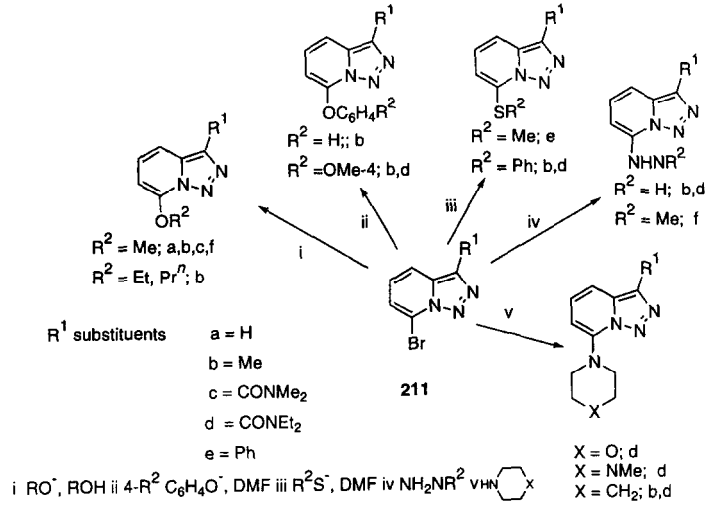


210

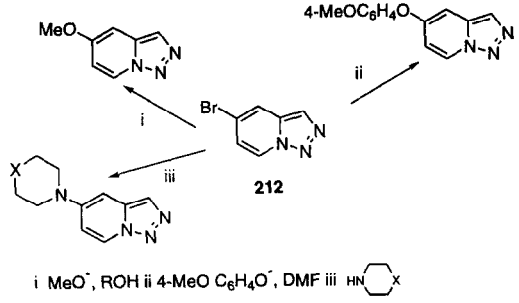
D. Reactions with Nucleophiles Giving Substitution Products

1. *Substitutions on the Ring*

Bromine substituents in compound **1** undergo nucleophilic substitution if sited at positions 5 or 7. Nucleophilic substitutions at position 7 in compounds **211** are shown in Scheme 5 (86TL3543, 88T3005, 96MI1), and at position 5 in compounds **212**, shown in Scheme 6 (97T8257); 5-chloro-triazolopyridine **213** and 6-bromotriazolopyridine **214** were completely inert to hot phenoxide and methoxide over long periods, and reaction of 7-bromo derivatives was much more rapid than that of 5-bromo derivatives.



Scheme 5

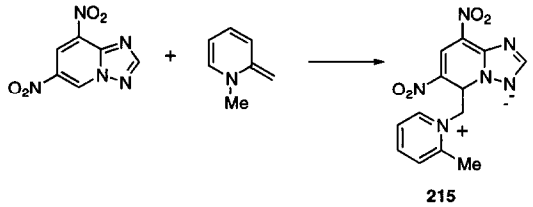


Scheme 6

213 214

The dinitro derivative of compound **2** reacts with anhydro bases of pyridine and quinoline to give zwitterions such as **215** (99RCB1391). Compound **216** has been made from the 3-bromo derivative of compound **3** by reaction with an amine, as an intermediate in the production of stomach secretion inhibitors (80EUP48555),

and compound **217** is phenylated by phenyllithium, zinc chloride, and a Pd(0) catalyst (86JHC1071).



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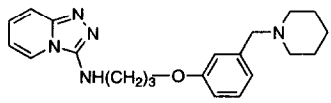

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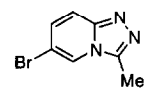
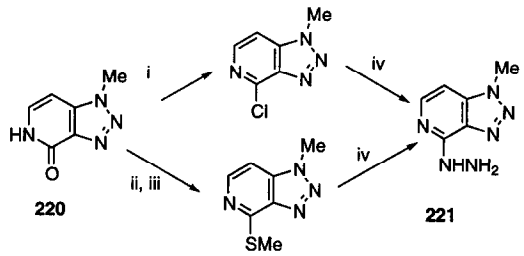


217

Compounds **4** and **5** have reactions in the six-membered ring similar to those of pyridine. As examples, compound **199** is aminated (92MI3), and compound **218** reacts with a number of primary and secondary amines to give compounds such as **219** (97UKZ64). Triazolopyridinone **220** can be converted into the hydrazine **221** either via the chloro compound or via the thione and methylthiol (85LA1922).

218 **219**

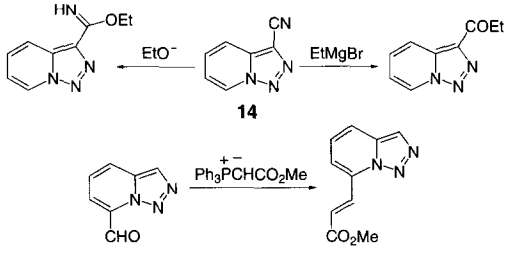


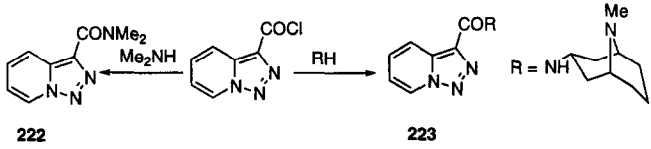
220 **221**

i. $POCl_3$ ii, P_2S_5 ii MeI, KOH iv NH_2NH_2

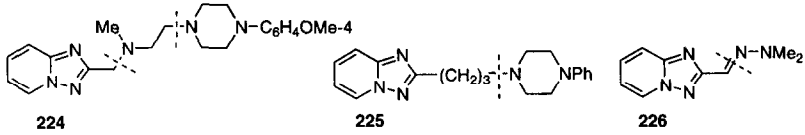
2. *Substitutions on Side Chains*

The acid chloride of the 3-carboxylic acid of compound **1** reacts with dimethylamine to give amide **222** (97T8257). The acid chloride also gives 5-HT_3 antagonists such as compound **223** (92MIP15593). The 3-cyanotriazolopyridine **14** reacts with ethoxide to give an iminoether and with a Grignard reagent to give a ketone (95T10969). The 7-formyl derivative **171a** reacts with a Wittig reagent to give acrylate **121a** (95JHC787).



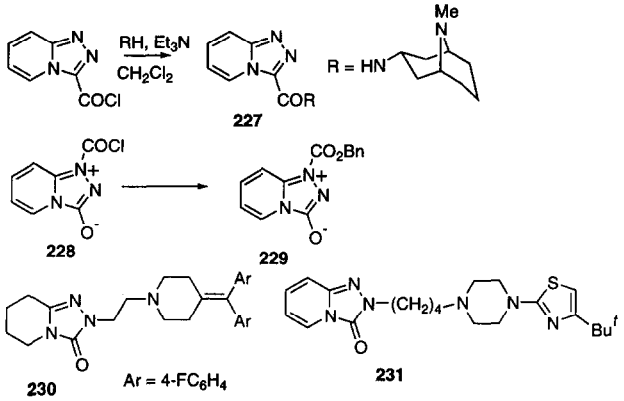


Side chain reaction in derivatives of compound **2** has largely been concerned with the production of compounds with pharmaceutical activity by reaction between chloroalkyl side chains in position 2 and suitable amines. A selection of such compounds are **224** (82JAP(K)206684), and **225** (81FRP2450259); both are antihypertensive. Use of a dichloromethyl side chain provides an unsaturated amine, as in compound **226** (81FRP2450259).

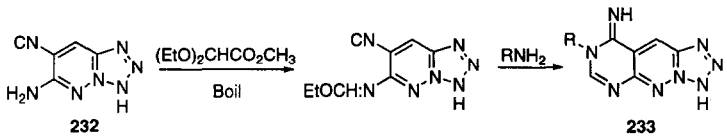


An acid chloride of compound **3** reacts with a bicyclic amine to give compound **227** (88EUP254584) while the zwitterion **228** reacts with a range of alcohols to give esters such as **229** (83BCSJ2974); the 2-isomer reacts similarly

(83BCSJ2969). Most nucleophilic substitution has been involved with the production of analogues of Trazodone; two of the many variants are shown in **230** (92JMC189), and **231** (86MIP904945).

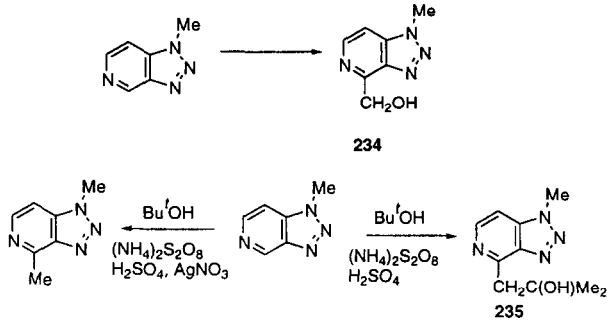


As part of a strategy for adding rings to system **4** the cyanide **232** was converted into the iminoether and treated with amines to give tricycle **233** (96JHC319).



E. Homolytic Reactions

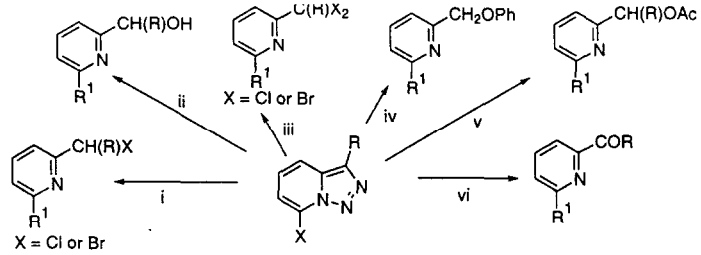
There are very few homolytic reactions on triazolopyridines. A suggestion that the ring opening reactions of compound **1** involved free radical intermediates is not substantiated (98T9785). The involvement of radical intermediates in additions to ylides is discussed in Section IV.I. The reaction of radicals with compound **5** and its 1-substituted derivatives gives 4-substituted compounds such as **234** (96ZOK1085). A more detailed study of the reaction of the 1-methyl and 1-phenyl derivatives with *t*-butanol and ammonium persulfate produced 4-methyl substitution with a silver nitrate catalyst, and the side chain alcohol **235** without the catalyst (96ZOK1412).



F. Ring Opening Reactions and Rearrangements

The ring opening reactions of ylides are dealt with in Section IV.I. The opening of the five-membered ring in derivatives of compound **1** by electrophiles has been extensively used in the period since the first review (83AHC79). The effect of different reagents is reported (85JCS(P1)2719) and confirms the stabilizing effect of a substituent on position 3. The reagents which have been used are hydrochloric, hydrobromic, and sulfuric acids in aqeous and non-aqueous media, glacial acetic and propionic acids, chlorine or bromine, phenol, and selenium dioxide (best in dichlorobenzene). The reagents and products are shown in Scheme 7.

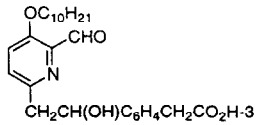
The mechanism of the ring opening has been thought to involve electrophilic attack (85JCS(P1)2719), but it has been suggested more recently (98T9785) that free radicals are involved, as in some of the ring opening reactions of ylides (Section IV.I). The reactions have been used to provide pyridines with 2,6-disubstitution, the 2-substituent being a side chain alcohol or ester, or a ketone or



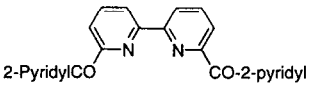
Reagents; i. HCl or HBr ii.H_2SO_4, H_2O iii. Cl_2 or Br_2 iv. PhOH, R=H only v.AcOH, glacial vi SeO_2, $C_6H_4Cl_2$

Scheme 7

aldehyde, and a wide range of 6-substituents (Section IV.D). Notable examples of this useful synthetic procedure are provided by the synthesis of intermediates for LTB_4 antagonists such as **236** (91MIP18879, 91MIP18880, 93JMC3308, 93JMC3321), and of the helicating ligand **237** (98T15287).

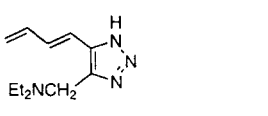


236

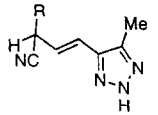


237

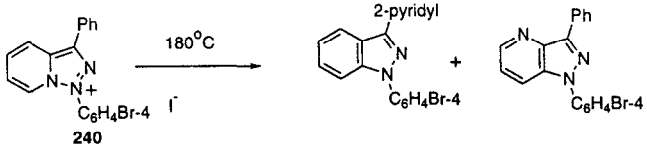
The discovery of a triazolylbutadiene **238** among the reduction products of a 3-diethylcarbamoyl derivative (85JCS(P1)2719) indicated a potential for ring opening under strongly basic conditions, which has subsequently been observed during the alkylation of 7-aminotriazolopyridines (93T703) (Section IV.D) producing compounds **239**, and in the dimerization which occurs during lithiation of compound **1**, producing compound **151** (99T12881). The quaternary salt **240** opens thermally to give a mixture of an indazole and a pyridopyrazole (97JOC1136). There are a number of examples of the equilibrium between hexahydrotriazolopyridines and the monocyclic diazo compounds exemplified by compound **241** (99EJOC1407).



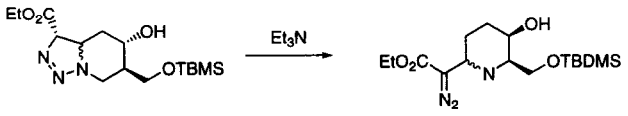
238



239 R = Me, Et, Bn

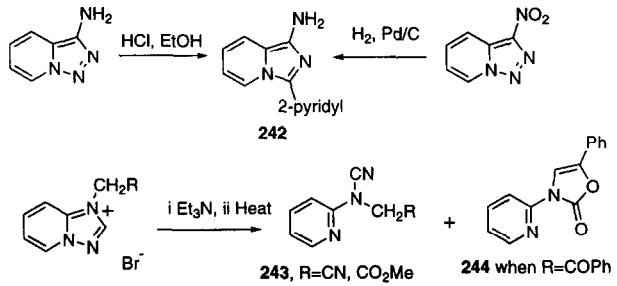


240

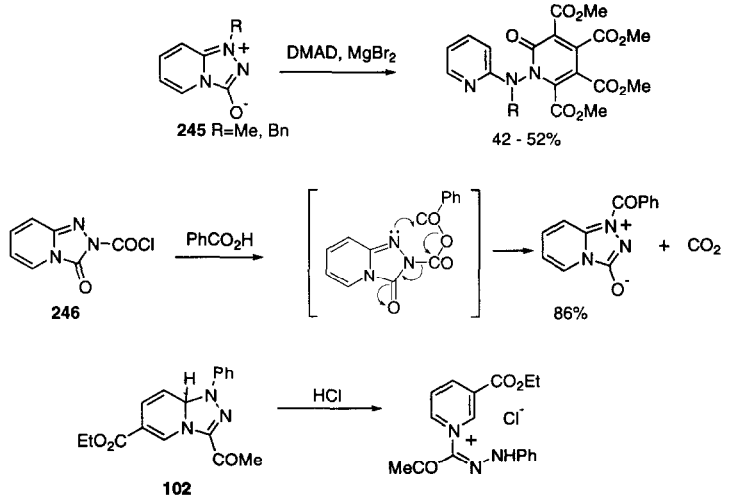


241

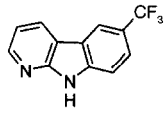
Treatment of a 3-aminotriazolopyridine with acid gave the imidazopyridine **242** (81T1787), also obtained from the 3-nitro derivative by catalytic reduction (83AHC79). Quaternary salts derived from compound **2**, when treated with triethylamine and subsequently heated give 2-pyridylcyanamides **243** or 2-(oxazol-1-yl)pyridines **244** depending on the alkyl group (86H(24)2563); the ylides are presumably intermediates (see also Section IV.I).



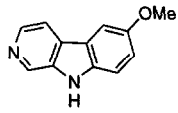
Of derivatives of compound **3**, the zwitterions **245** react with DMAD if magnesium bromide is added to give aminopyridine derivatives (00H(53)265). Compounds such as **102** are opened by acid to give quaternary pyridinium salts (92LA885). There are various interconversions of 2-substituted triazolopyridin-3-ones into 1-substituted zwitterions. An example is the reaction of **246** (83BCSJ2969); the reverse conversion is also reported.



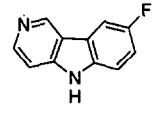
Pyrolyses of N1- or N3-substituted derivatives of compounds **4** and **5** have continued to find use as routes to azacarbazoles, although the yields are often indifferent and there are no recent examples. The photochemical reactions are dealt with in Section IV.G. Pyrolysis media are paraffin (P) or PPA, and examples of products are compounds **247** (P, cytostatic) (83MI2), **248** (P) (84MI1), and **249** (from a 1-substituted derivative) (86MI2). Indications of diradical intermediates are provided by the thermolysis of compound **250** (P) (83MI2) where one product is a dimer.



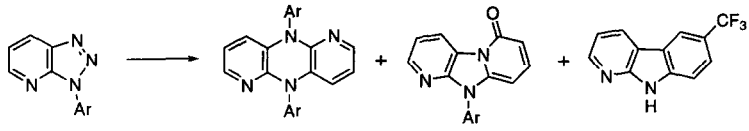
247



248



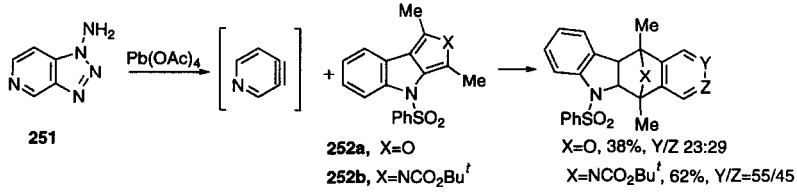
249



250 Ar = $C_6H_4CF_3$-4

22% 10.5% 16%

The 1-aminotriazolopyridine **251** reacts with lead tetraacetate to generate 3,4-pyridyne. Diels–Alder addition with compounds **252a** (84JOC4518) and **252b** (92T10645) give mixtures of regioisomers in approximately equal proportions. The nitro derivative **253** reacts with hydrazine hydrate with recyclization to give a triazolopyridazinone (86ZOK1793).



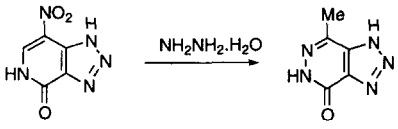
251

252a, X=O

252b, X=NCO_2Bu^t

X=O, 38%, Y/Z 23:29

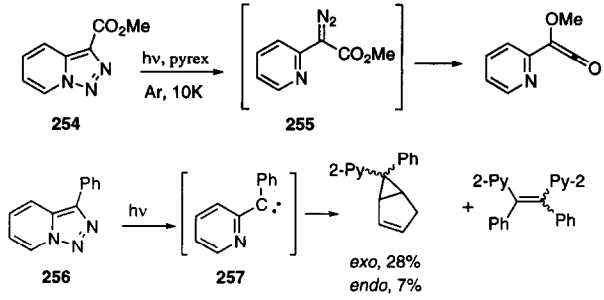
X=NCO_2Bu^t, 62%, Y/Z=55/45



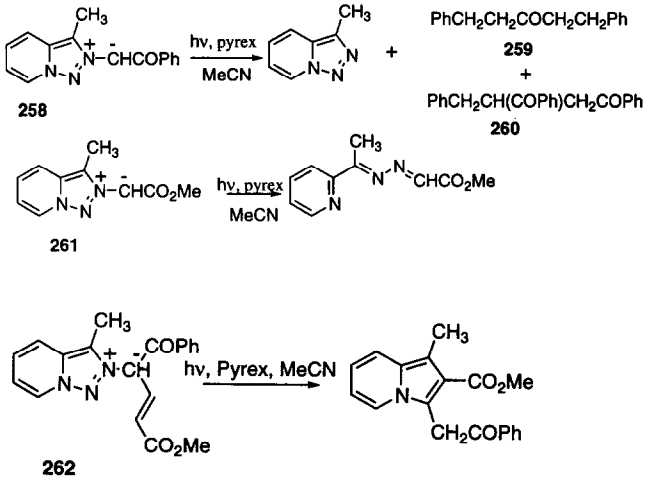
253

G. Photochemical Reactions

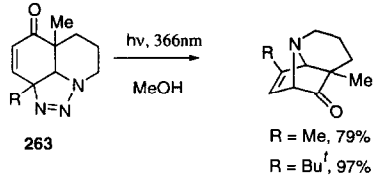
There has been new information on the products of photolysis of derivatives of compound **1**. Low temperature irradiation of the ester **254** gives a ketene (93JACS8621); the isolation of an isomeric ketene from a 3-pyridyldiazo ester suggests the involvement of the open chain form **255**. Photolysis of the 3-phenyl derivative **256** in the presence of cyclopentadiene gives *exo* and *endo* cyclopropanes and a dipyridylstilbene, suggesting the intermediacy of the carbene **257** (99JOC6635).



A study of the photochemical reactions of some ylides of compound **1** showed the expected fragmentation to give, from compound **258** for example, 3-methyltriazolopyridine and the products **259** and **260** postulated as derived from a carbene intermediate (00MI2). Ester **261** gives a hydrazone, and ylide **262** an indolizine. Thermal reactions of ylides are in Section IV. I.

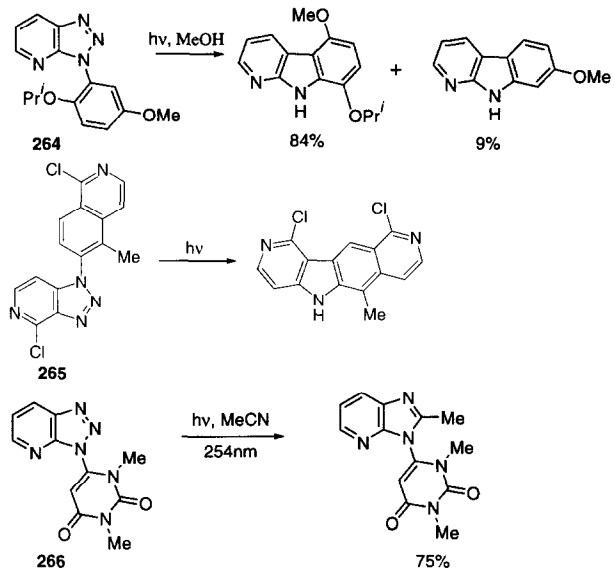


Partly saturated derivatives of compound **1** undergo normal loss of nitrogen to form new rings, as shown by compounds **263** (83JACS3273; another example is in 90HCA940).



263

Photolysis of derivatives of compounds **4** and **5** has been further studied as a route to azacarbazoles. The example **264** shows normal behavior as well as elimination of an alkoxy group, and the report includes examples of derivatives of compound **5** as well as references to earlier work (93JCS(P1)1261). Production of an intermediate for an anti-tumour ellipticine analogue is shown by example **265** (84MI1), and incorporation of acetonitrile solvent by example **266** (91TL323).

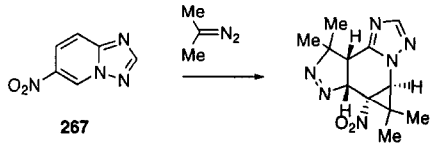


264 **265** **266**

H. Reactions with Acetylenic Carboxylates, Acrylates, and 1,3-Dipoles

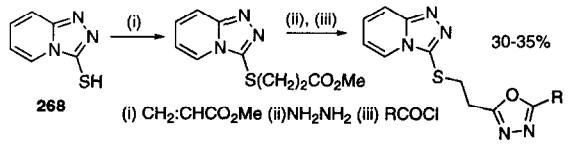
There are a number of reactions between ylides and ADE in Section IV.I. Compound **1** has been found to be completely inert to acetylenic esters over a

period of years (83AHC79). Compound **267** reacts with 2-diazopropane to give an adduct; an X-ray structure is given (89H(28)259).



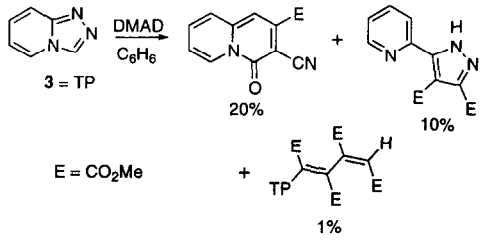
The structure of the main product from compound **3** with DMAD (81IJC(B)10) has been corrected, and two other products characterized (Scheme 8) (82JCS(CC)1280).

The 3-oxidotriazolopyridinium zwitterions **245** fail to react with DMAD unless magnesium bromide is present, when ring opening occurs (2000H(53)265) (Section IV.F). The thiol **268** adds methyl acrylate as expected; the resulting ester is converted via the acid hydrazide, to an oxadiazole (89IJC(B)170).



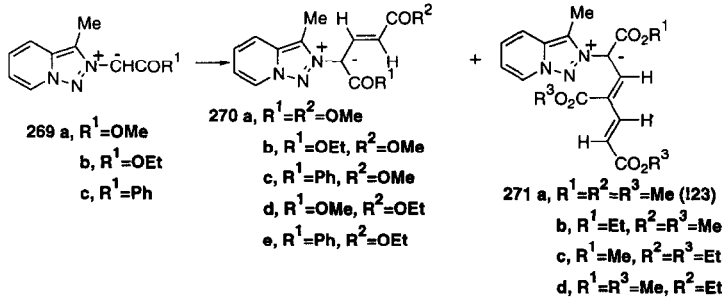
I. Reactions of Ylides

A number of reactions of ylides have been reported, in some cases giving new ring systems. Reaction between the ylides **269** (from 3-methyltriazolopyridine) and propiolates or acetylene dicarboxylates in acetonitrile gave orange 1:1 and 1:2 adducts, **270** and **271** (91T5277). Only 1:1 adducts are formed from 2-phenacyl salts; this is attributed to greater delocalization of the negative charge



Scheme 8

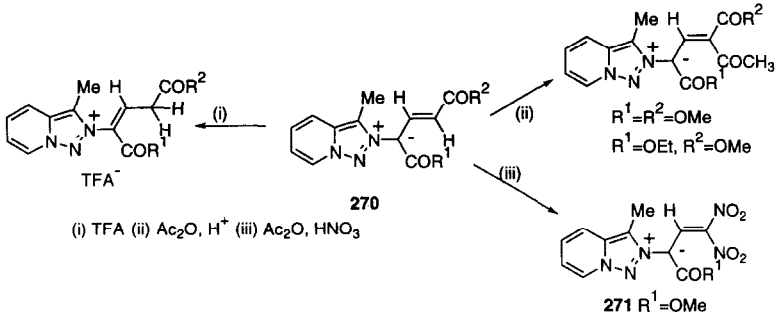
on to the carbonyl oxygen, confirmed by ^{1}H-NMR shifts. An X-ray diffraction study of compound **123** showed the plane of the side chain to be at an angle of 93.7° to the plane of the heterocyclic ring.



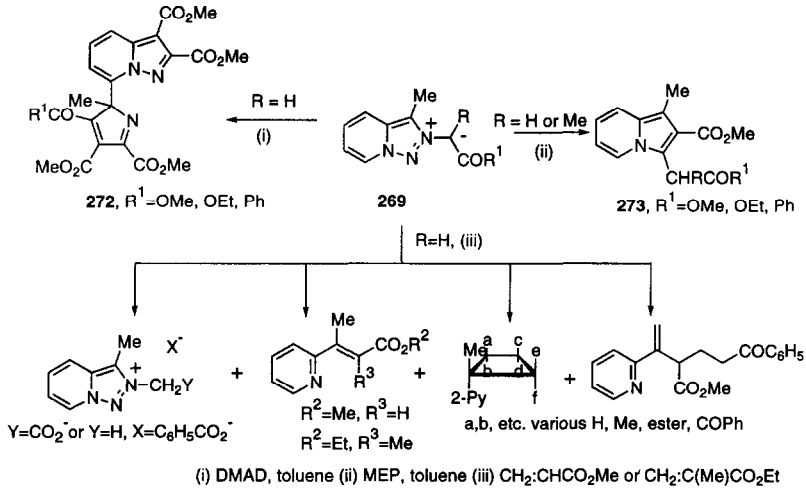
The extended ylides **270** react with electrophiles at the end of the side chain, as shown in Scheme 9 (92H(34)1005). The most unusual reaction is the nitration which requires a decarbalkoxylation, but the structure **271** is confirmed by X-ray diffraction.

With a change to non-polar solvent, the reaction of ylides **269** with alkynes and alkenes changed dramatically, as shown in Scheme 10. With DMAD in toluene the ylides give pyrazolopyridines **272** in good yield (91TL4977), and with methyl propiolate (MEP) give indolizines **273** (92H(33)203). The reaction with acrylates is much less clean, but the variety of products is said to be formed from a diazene intermediate, which splits to give a diradical (93H(35)851).

The stable dicyanomethylides **274**, made directly from the triazolopyridines and tetracyanoethylene oxide (TCNEO) reacts more slowly with MEP in acetonitrile to give mainly indolizines, with cyclazines as secondary products formed



Scheme 9



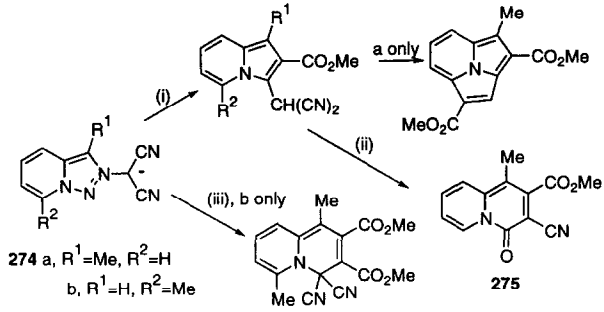
Scheme 10

by addition of a further molecule of MEP (96T10519). The quinolizinones **275** were shown to be derived from the indolizines during purification, and could be obtained in excellent yield by use of damp silica in air. Reaction of compound **274b** with DMAD gave a 4*H*-quinolizine. These reactions are summarized in Scheme 11.

The ylides **276** derived from compound **2** undergo ring opening on thermolysis to give 2-pyridylcyanamides (Section IV.F), and react with acetylenic esters to give pyrazolopyridines (Scheme 12) (86H(24)2563). In the addition of DMAD some intermediate dihydro derivative is obtained and dehydrogenated with chloranil. An ylide of system **3** is used as a catalyst (Section IV.J)

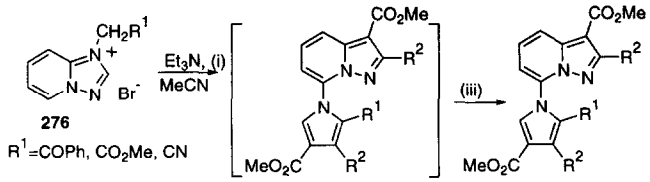
J. Uses as Catalyst or Reagent

The major reports in this section concern derivatives of compound **4**, but there is a report of the use of the ylide **277** as one among a number of catalysts in benzoin condensations (96HCA61), and in reverse benzoin condensations as a route to ketones (98CPB6). The 1-acetyl- or 1-oxycarbonyl derivatives **278** are used as acylating agents for amines or phenols, with preference for the amine in an aminophenol (86TL5029, 86JHC1459). The 3-Boc derivative acylates faster, but isomerizes to the 1-substituted derivative; the latter is easier to prepare, and is therefore recommended. The chiral aminoester **279** is acetylated on nitrogen without racemization. Compounds **278** are also used as catalysts in the



(i) MEP, MeCN, boil, 2 days (ii) SiO_2, H_2O, toluene (iii) DMAD, MeCN, boil, 1.5h.

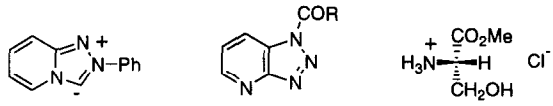
Scheme 11



(i) R^2—≡—CO_2Me (ii) Chloranil when R^2=CO_2Me

Scheme 12

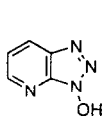
epoxidation of alkenes (stilbene, cholestenyl acetate) (87JHC1363) and in conversion of sulfides to sulfoxides (87SC515) using hydrogen peroxide in a biphasic system. The yields are high (82–99%).



277 278 R=Me, EtO, BnO 279

A very considerable body of work has been published on the use of 3-hydroxytriazolopyridine (HOAt) **280** and its derivatives as peptide coupling catalysts,

much of it from Carpino and his co-workers There are 83 references in the period covered by this review, and detailed coverage is not appropriate, but the principal points will be reported. There is a recent short review (98JPC581), and a number of papers in reports of symposia (93MI3, 94MI2, 94MI3, 96MI4, 96MI5, 96MI6, 98MI2, 98MI3, 98MI4, 98MI5). Early papers showed that both HOAt and its amine derivatives **281** were effective catalysts for peptide formation with low levels of racemization, using a carbodiimide (93JACS4397, 94JOC695, 95JOC3561). The correct structures for the compounds **281**, R = NMe_2 and R = 1-pyrrolidinyl (94MI 4, 98MI 6) have been established by X-ray diffraction, and the structure of the dimethylamino derivative explained for gas phase and solution by semiempirical calculations (96JCR(S)302). The use of phosphorus derivatives **282** is well discussed in a paper which also contains a useful review of earlier work (98JOC9678). An exhaustive comparison of the use of HOAt and hydroxybenztriazole (HOBt) claimed superiority for the former (99T6813). In stepwise assembly by solid phase techniques it is found that addition of a hindered base enhanced the step involving preactivation of the carboxyl group, and subsequent addition of the usual base DIEA enhanced the coupling stage. Some new reagents based on benztriazole are reported to be more efficient than the best based on triazolopyridine (2000TL721).



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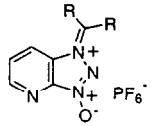
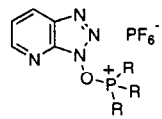


281, R=NMe_2, etc.



282, R=NMe_2

A selection of reports from 1999 and 2000 follow. Compounds **281** and **282** are used to couple nucleosides to solid phase supports (99MI5). HOAt is used to synthesize peptides used in colorimetry and fluorimetry (99MI6), compound **281** to prepare large quantities of insoluble *trans*-membrane peptide (99MI7), HOAt in racemization-free coupling of peptides having *N*-methylaminoacids at the carboxyl terminus (99CPB576), HOAt is used with sequestering resins to simplify removal of byproducts from activated amide preparations (99TL239), and compound **281** is used to prepare dendritic polylysines (2000CL144). Among the patented applications are the use of HOAt for recovery of optically pure aminoacids from waste liquors (96EUP729942), peptide coupling for antisense oligodeoxyribonucleotide duplexes (98USP5780607), for hapten-carrier conjugates for use in drug abuse (98MI7), for oligopeptide Vinca alkaloid conjugates for cancer treatment (99MI8) and for matrix metalloprotease inhibitors (99MIP35124).

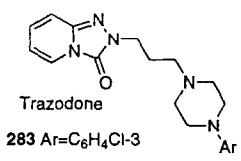
V. Pharmaceutical and Industrial Uses of Triazolopyridines

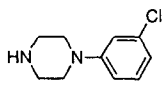
This section reports compounds of pharmaceutical interest, one section on Trazodone, and a second on other pharmaceutical compounds. The third section reports on other industrial uses.

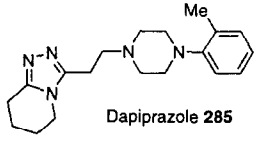
A. TRAZODONE

In the period of this review there are 519 references to Trazodone **283**. Most of these are not relevant to this review; a selection of references to chemical aspects of Trazodone and its principal metabolic product **284** will be given. There are six general reviews (81MI2, 81MI3, 82MI2, 84MI2, 88MI2, 99MI9), a review on chemical methods of analysis and of metabolism of Trazodone hydrochloride (87MI3), and one on metabolism of antidepressants in general (99MI10). There are seven references to pharmacology (81MI4, 82MI3, 82MI4, 82MI6, 84MI3, 86MI4), and one on pharmacokinetics (80MI1). There is a review on the cardiovascular side effects (81MI5) one on the postmarketing adverse reactions (86MI5, 87MI4).

The physicochemical characterization of Trazodone hydrochloride are reported (93CPB325). The effect of pH on the redox potential of Trazodone (90MI2), and the two-step irreversible oxidation by voltammetry (86MI5, 87MI1) have been reported. Voltammetry of Trazodone is also used for determination in tablets (99MI11), and potentiometric titration of drugs on a polymer modified graphite electrode also includes Trazodone (86MI6). There are a very large number on procedures reported for analysis of Trazodone; recent examples will be given of the principal methods. HPLC is widely used; there are examples of photodiode array for detection (95JC(A)(692)103, 97JC(A)(763)149), and of miniaturization and use of mobile phases for online LC-MS analysis (99MI12). GC methods are also widely used; examples are the use of solid phase extraction and wide-bore capillary with N sensitive detection (88MI3) and an automated sample preparation interfaced with capillary GC, optimized for Trazodone in plasma (95MI1). TLC procedures for drug analysis often include Trazodone (89MI2, 91MI1, 99MI13). Other techniques are capillary electrophoresis (00MI3), capillary zone electrophoresis (99MI14) and ion selective electrodes (99MI15).

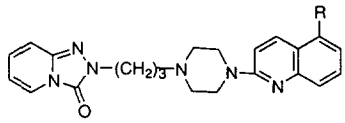




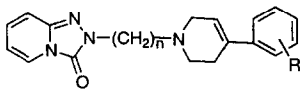


B. Pharmaceutical Applications Other than Trazodone

The most widely reported compound after Trazodone is Dapiprazole **285** with 31 references over this period. The compound is an α-adrenergic blocker (97MI2) used in antiglaucoma therapy (82AF678). A large number of modifications of the Trazodone molecule have been reported to have pharmaceutical activity. A number of compounds are shown to exemplify various modifications. Variations in the alkyl side chain have included branching (93MIP14091), replacement by a cyclohexane ring (81MI6), increase to four carbons (with concomitant change of terminal aromatic to a thiazole) as in compound **231** (87GEP3620643), change of the aromatic ring to a quinoline as in **286** (92MI4). A triple bond has also been introduced into the alkyl chain, with a more complex triazolodiazepinothienyl terminus (89EUP 320992). The pyrazine ring has been alkylated (95MIP01354, 99JMC336), and replaced by a 4-substituted piperideine, as shown in compound **287** (82US4340597) or still further modified as in **288**, which are 5-HT_2 antagonists (92JMC189). Similar side chains have been attached to the 2 position of compound **2** (Section IVD. 2).



286 Antidepressant R = H, Ph



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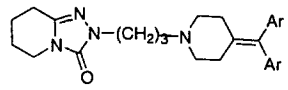
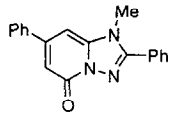


288 5-HT_2 antagonists

There are many examples where a triazolopyridine is attached to an antibiotic such as milbomycin. For the rest of this section illustrative examples of derivatives of each of systems **2–5** will be given; there are virtually none derived from compound **1**. Of compound **2** the 2-(2-pyridyl) derivative is antihypertensive and bronchodilatory (81JAP(K)100783), and compounds such as **289** are antiinflammation inhibitors and analgesics (81BRP1588166). Compounds of type **290** are positive inotropics (90GEP(E)280110). Many derivatives of compound **3** have pharmaceutical activity. Simple substitution at position 3 gives the analgesic **291** (98AF745) and the MMP-9 inhibitor **292** (00MIP11766). Simple substitution in ring B by pyridyl groups produces anxiolytics such as **293** (85USP4550166) while a range of trisubstituted derivatives such as **294** are antiallergics (87EUP 210648). Tetrahydro compounds such as **295** have been examined as inhibitors of β-D-glucosidase (97HCA979).



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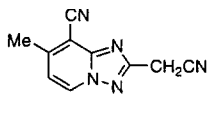

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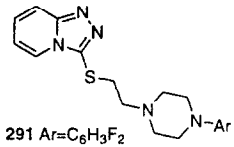
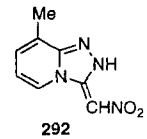


291 Ar=$C_6H_3F_2$



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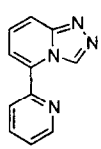

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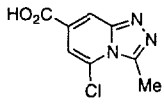

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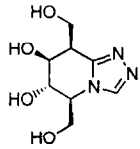
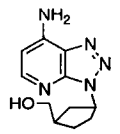


295

The obvious resemblance between compounds **4** and **5** and purine have led to glycosyl derivatives such as **296**, tested against HIV-1 (94MI5, also 94JMC 3534), and D-ribosyl derivatives (92MI3). Some 3-aryl derivatives of compound **5** such as **297** are CRF receptor antagonists (98MIP08847). Most active compounds derived from compound **5** are 4-amino compounds. The 1-β-D-ribofuranosyl compound is active against coxsackie B1 (93MI4), and numerous 1- or 3-aryl compounds such as **298** (anticonvulsant) (95JMC4131) and **299** (used to study CRF receptor binding (99JMC833)).



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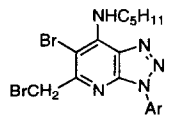
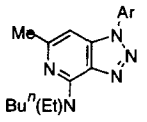
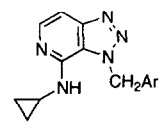


297 Ar =2,4,6-Me_3-C_6H_2



298 Ar=2,6-F_2-C_6H_3



299 Ar=2,6-F_2-C_6H_3

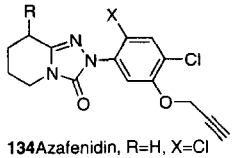
C. Other Industrial Uses

There are 110 references to industrial uses of triazolopyridines, of which 46 are to herbicides and 26 to dyes. A selection of references will be given in each category.

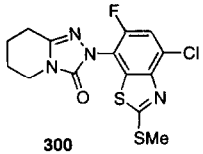
1. *Herbicides, Microbiocides*

Most reports concern Azafenidin, **134** (97MI3). There are numerous structural variants, mainly involving different 2-aryl substituents, such as **300**

(94GEP4241658), but also substitution on the reduced ring (98USP5728651). Derivatives of triazolopyridine **1** with herbicidal activity are 1-biphenyl-4-yl derivatives (96MI1) and compound **20** (84EUP116928). Two examples derives from compound **2** are the sulfonamide **301** (96MIP01826) and the trifluoromethyl derivative **302** (90EUP353902). Apart from Azafenidin analogues there are a few herbicides derived from compound **3**; an example is **303** (91EUP430385). Compounds derived from triazolopyridine **4** are of type **304** (91EUP453065). Compound **305** is a microbiocide and materials preservative (98GEP19708688).



134 Azafenidin, R=H, X=Cl



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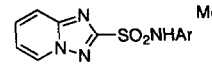
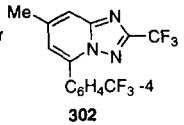


301 Ar =2-ClC$_6$H$_4$



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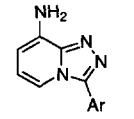
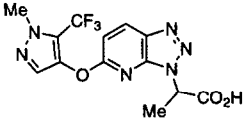


303 Ar =2-FC$_6$H$_4$



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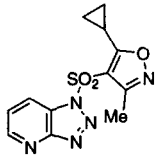

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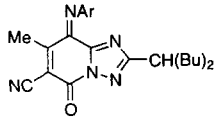
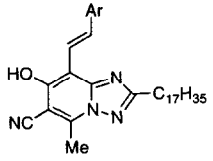
2. *Dyes, Printing, and Inks*

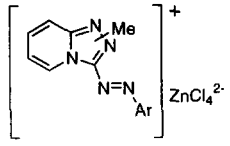
Almost all dyes are quinones or azaquinones of compound **2**. The majority are used for thermal transfer processes; a recent example is compound **306** (98USP5792587). The second major class are azo dyes, prepared either from aromatic diazonium salts as in compound **307** (95GEP4319296) or from a triazolopyridine 3-diazonium salt as in **308** (81BRP2054630).



306 Ar= 4-(Bu)$_2$NC$_6$H$_4$



307 Yellow, polyester
Ar = 4-O$_2$NC$_6$H$_4$

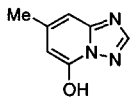


308 Violet, acrylate
Ar = 4-EtBnNC$_6$H$_4$

3. *Miscellaneous Uses*.

Various triazolopyridines have been incorporated into photographic emulsions for a variety of reasons. Compound **309** is a fog inhibitor (92JAP(K)179953),

compound **310** gives improved quality in high temperature rapid processing (83GEP3438249), and compound **311** is a nucleation accelerator in direct positive colour photographic materials (88GEP3721570). Among catalysts for polymerization is **312** (98MIP40420). Compounds **4** and **5** have been used as corrosion inhibitors for copper (98MI7).



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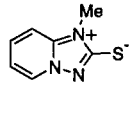

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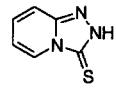

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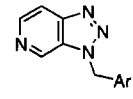

312 Ar = 2,6-(Pr^iNPh)$_2$C$_6$H$_3$

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ADVANCES IN HETEROCYCLIC CHEMISTRY, VOL. 83

Thiazole and Thiadiazole *S*-oxides

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I. Introduction

The chemistry of the 1,2,3-, 1,2,4-, 1,2,5-, and 1,3,4-thiadiazoles, together with thiazole and isothiazole (1,2-thiazole) is reviewed regularly in *Progress in Heterocyclic Chemistry* (97PHC(9)170, 98PHC(10)172, 99PHC(11)184). Full reviews have appeared in *Comprehensive Heterocyclic Chemistry I* (84CHEC-I(6)132, 84CHEC-I(6)235, 84CHEC-I(6)447, 84CHEC-I(6)463, 84CHEC-I(6)513, 84CHEC-I(6)545) and *II* (96CHEC-II(3)320, 96CHEC-II(3)373, 96CHEC-II(4)289, 96CHEC-II(4)307, 96CHEC-II(4)355, 96CHEC-II(4)379). Some specific topics have been dealt with in *Advances in Heterocyclic Chemistry*. The scope of the present chapter is to summarize the last five years of the literature correlating to the monocyclic *S*-monoxides and *S,S*-dioxides of these five-membered heterocycles.

II. Isothiazole *S*-oxides

A review (97JPR(339)1) covering the literature from 1984 to 1995 on the synthetic methods, reactions and biological applications of mono- and bicyclic *S*-oxides and *S,S*-dioxides was published in 1997 by B. Schultze and K. Ilgen.

A. Structural and Physical Properties

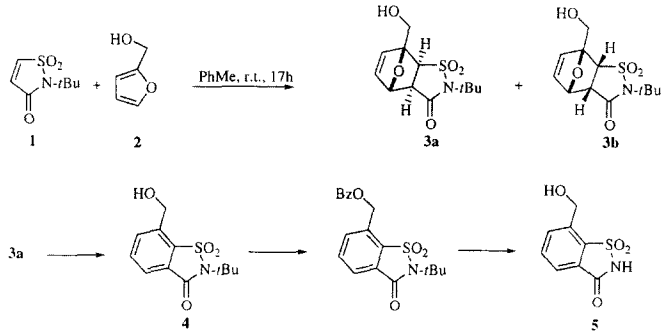
Many papers extensively discussing the structure and properties of isothiazoles have already been reviewed (84CHEC-I(6)132, 96CHEC-II(3)320). Recently, a discussion on the heteroaromaticity of isothiazole *S,S*-dioxide compared with thiazole and thiadiazole *S,S*-dioxides was presented (97MI1). The electronic characteristics of isothiazole *S,S*-dioxide have also been explored by carrying out a comparative study aiming to elucidate the method that can better describe this ring (97IJQ(62)477). The author found the CHELPG and Mulliken methods at the MP2/6-31G*//HF/631G* level provide the best charge distribution. Accurate dipole moments and charge distribution were obtained, giving a good description of the S=O double bond and showing a lack of π delocalization in the ring. Crystallographic studies (95ZK(210)206) and spectroscopic investigations on several derivatives, such as triorganotin derivatives (95JPC(337)242, 95MI1) synthesized by previously known methods, were published.

B. Reactivity

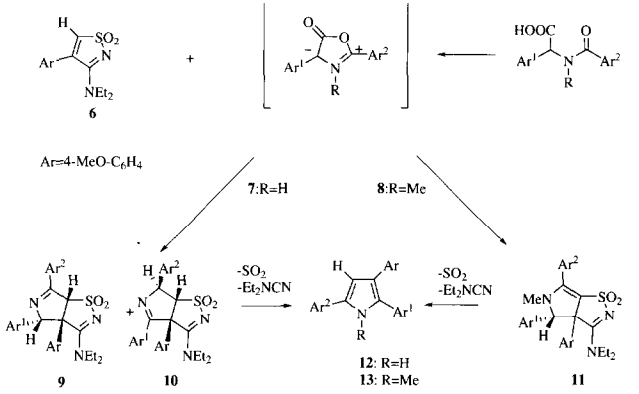
1. *Cycloaddition Reactions*

a. *Isothiazole S,S-dioxides.* Isothiazol-3-one *S,S*-dioxide **1** readily enters into Diels-Alder reactions with dienes such as furan. The Diels-Alder reaction with

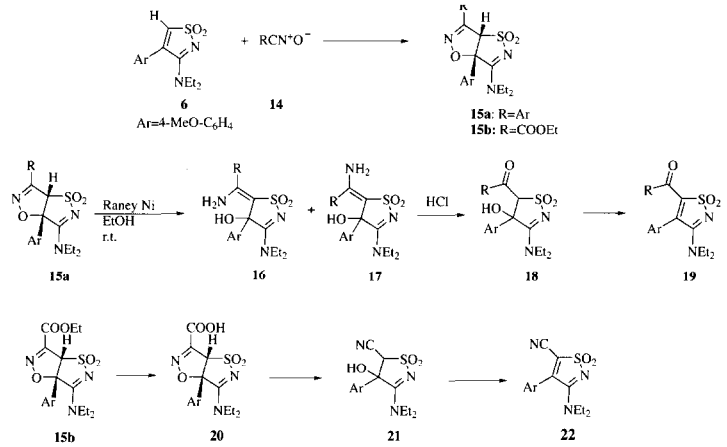
furfuryl alchol **2** (98TL(39)1483) afforded compounds **3a** and **3b** in excellent yield (90%) with the regioselectivity predicted by *ab initio* molecular calculations. The aromatic 4-hydroxymethylbenzoisothiazolone *S,S*-dioxide **4** could be obtained using LHMDS (lithium hexamethyldisilazanide) in the presence of TMSCl (trimethylsilyl chloride) from the *exo*-isomer **3a**. The same reaction when performed on the *endo*-isomer **3b** afforded almost quantitatively the same dienophile **1** through a retro-Diels-Alder reaction. After protection of the benzylic hydroxyl group of **4** and removal of the *N-tert*-butyl group, the saccharin derivative **5** was obtained and could be used as the key starting material for further functionalization to provide new benzisothiazolones with interesting biological activity.



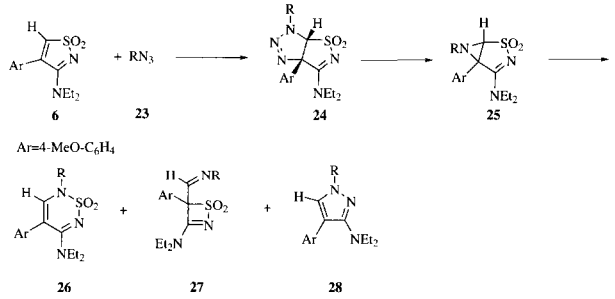
3-Diethylamino-4-(4-methoxyphenyl)-isothiazole *S,S*-dioxide **6** is (95T(51)2455) a highly reactive partner in 1,3-dipolar cycloadditions with several dipoles. Azomethine ylides, such as oxazolones **7** and münchnones **8**, afforded with **6** bicyclic pyrrolo[3,4-*d*]isothiazole *S,S*-dioxides **9**, **10**, **11** in satisfactory yield. The regioselectivity of the reaction was excellent. The thermal behavior of these new bicyclic systems was investigated. When heated at their melting point or slightly above, triarylpyrroles **12**, **13** were obtained through SO_2 and *N,N*-diethylcyanamide elimination.



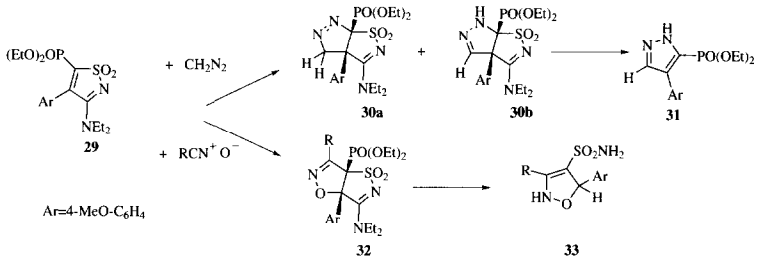
Compound **6** with nitrile oxides **14** (95T(51)12351) gave isothiazolo[5,4-*d*]isoxazolines **15a,b** through highly regioselective cycloadditions. The reduction of the isoxazoline ring with Raney Nickel or $NaBH_4$–$CoCl_2$, afforded the stereoisomeric enamines **16** and **17** which could be transformed into the ketones **19** through hydrolysis followed by dehydration of the resulting β-hydroxyketone **18**. Cycloadduct **15b** was hydrolyzed to the corresponding acid **20**. When this was heated slightly above its melting point, decarboxylative ring opening took place affording the nitrile **21**, which spontaneously eliminated water giving **22**.



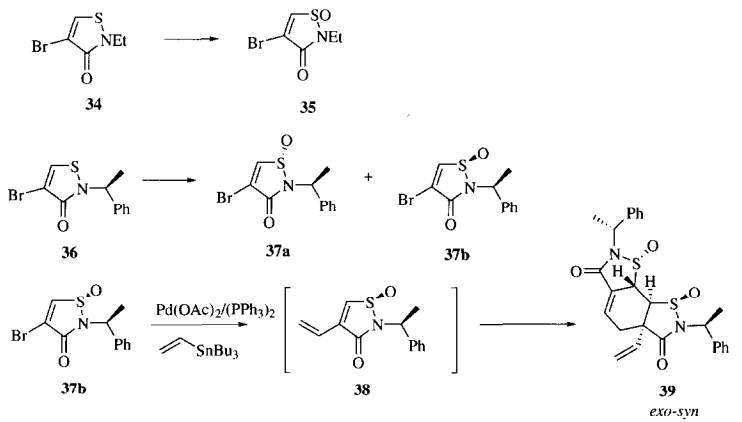
The cycloaddition reaction of compound **6** with *N*-aryl- and *N*-aralkylazides **23** was also investigated (96T(52)7183). Thiadiazabicyclo[3.1.0]hexene derivatives **25** were obtained from the labile triazoline intermediate **24** through nitrogen elimination. This bicyclic system underwent thermal transformation, producing thiadiazine dioxides **26** as the main product together with thiazete dioxides **27** and pyrazoles **28**.



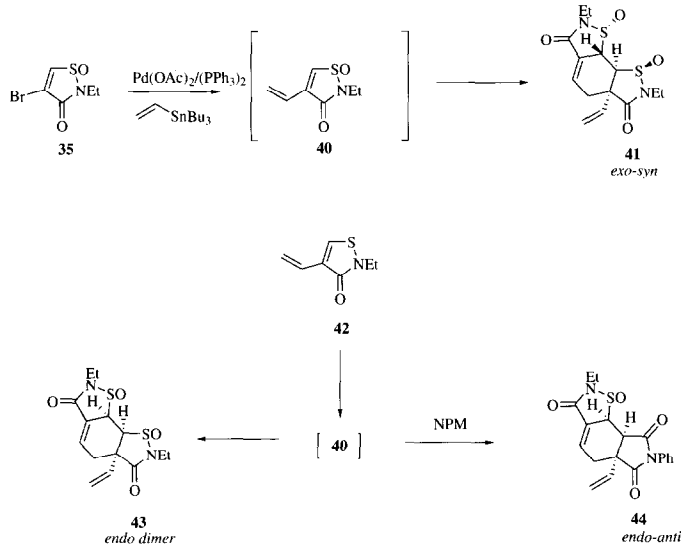
Isothiazolylphosphonate **29** (Section II.B.2) reacted with 1,3-dipoles such as diazomethane and nitrile oxides, affording regioselectively **30a,b** or **32**. By reacting **30b** and **32** with bases, pyrazolylphosphonate **31** and isoxazolylsulfonamide **33** were obtained (01T(57)5453).



b. *Isothiazole S-oxides.* The sulfinyl group had attracted particular attention due to its ability to induce a high degree of diastereoselectivity in cycloadditions. *N*-Substituted 1,2-isothiazolin-3-one *S*-oxides were obtained by oxidation with MCPBA of the corresponding 1,2-isothiazolin-3-one (95TL(36)7713, 99T(55)12313). From **34** the racemic mixture **35** was obtained; from **36** two separable diastereomers **37a** and **37b** were obtained in a mixture where the *S* configuration of the sulfoxide was predominant. On the 4-bromoisothiazolin-3-one *S*-oxide **37b** a Stille reaction was done with the aim of producing a 4-vinylsubstituted compound **38**. The only product obtained, **39**, appeared to be the result of a diastereoselective Diels-Alder dimerization of **38**. The authors predicted an *exo–syn* transition state explained *via* a stabilizing metal chelation to the sulfoxide oxygens of both addends.



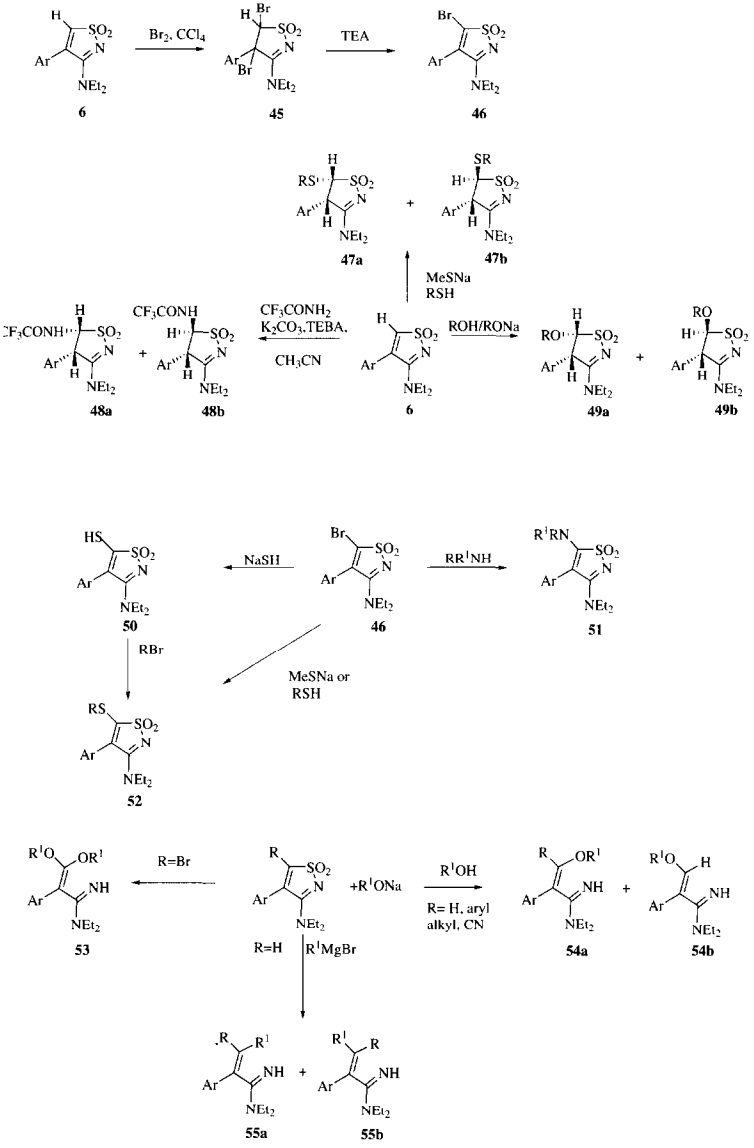
The validity of the model was demonstrated by reacting **35** under the same reaction conditions: as expected, only one diastereoisomer **41** was formed, the structure of which was confirmed by X-ray analysis. When the vinylation was carried out on the isothiazolinone **42** followed by oxidation to **40**, the dimeric compound **43** was obtained, showing that the *endo–anti* transition state is the preferred one. To confirm the result, the vinyl derivative **42** was oxidized and the intermediate **40** trapped *in situ* with *N*-phenylmaleimide. The reaction appeared to be completely diastereoselective and a single diastereomer *endo–anti* **44** was obtained. In addition, calculations modelling the reactivity of the dienes indicated that the stereochemistry of the cycloaddition may be altered by variation of the reaction solvent.



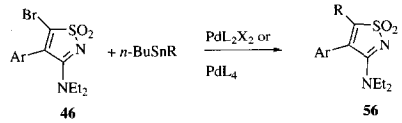
2. *Reactivity at Ring Atoms*

A simple method to functionalize 3-amino-4-arylisothiazole dioxides with a heteroatom on C-5 was developed (99T(55)2001) starting from unsubstituted **6** or 5-bromoisothiazole dioxides **46**. The latter could be obtained in high yield by reacting **6** with Br_2 affording the intermediate **45**, followed by treatment with TEA, or by simple heating. Sulfur, oxygen and nitrogen nucleophiles readily reacted with compound **6**, by a Michael addition, affording the 4,5-dihydroderivatives **47a,b**, **48a,b**, and **49a,b** as diastereoisomeric mixtures where the *trans*-isomer is the major one. When the 5-bromo derivative **46** was used as the reactant, an addition–elimination reaction took place allowing the regeneration

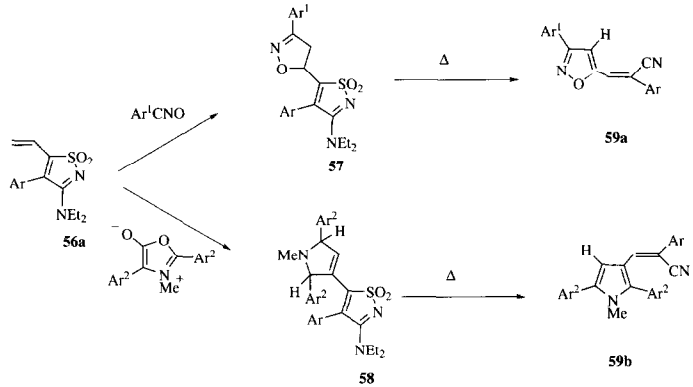
of the 4,5-double bond in compounds **50**, **51**, **52**. A ring-opening reaction took place (99T(55)14975) when two equivalents of nucleophilic base (alkoxides or Grignard reagents) were used making 3-substituted acrylamidines **53**, **54a,b**, and **55a,b** readily available.



A mild and efficient method (97T(53)15859) to functionalize 3-amino-4-arylisothiazole dioxides was achieved in the palladium-catalyzed cross-coupling reaction of 5-bromoisothiazole dioxide **46** with aryl-, heteroaryl-, vinyl-, and alkynyl-stannanes, giving derivatives **56**. In this way 3-diethylamino-4-(4-methoxyphenyl)-5-vinyl-isothiazole 1,1-dioxide **56a** was synthesized, and its reactivity with several 1,3-dipoles such as nitrile oxides and münchnones was evaluated (98T(54)11285). The cycloaddition reaction was highly regioselective and very chemoselective because only the vinyl group was involved. The thermal behavior of the cycloadducts **57**, **58** has been investigated and ring-transformation reactions were observed affording new α,β-unsaturated nitriles **59a,b** substituted in the β-position with various heterocycles.

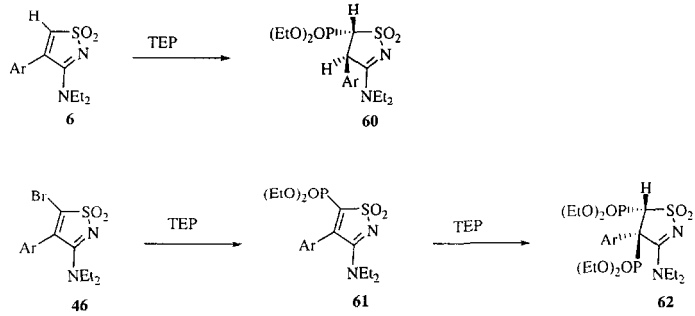


46 **56**



56a **57** **59a** **58** **59b**

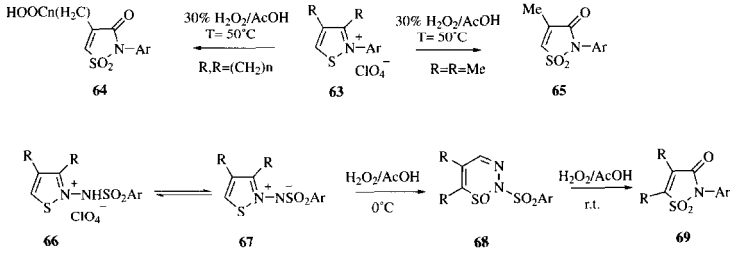
Reacting **6** with triethyl phosphite (TEP) as the solvent gave compound **60** (01T(57)5453). The bromo derivative **46**, with an equimolecular amount of TEP, afforded **29**, which could be trasformed into **61** by reacting with an excess of TEP, showing a reversal of the usual regiochemistry observed in the nucleophilic addition of other 3-aminosubstituted isothiazole *S,S*-dioxides. Reactivity of this new class of isothiazole dioxides was studied (Section II.B.1.a).



6 60 46 61 62

C. SYNTHESIS

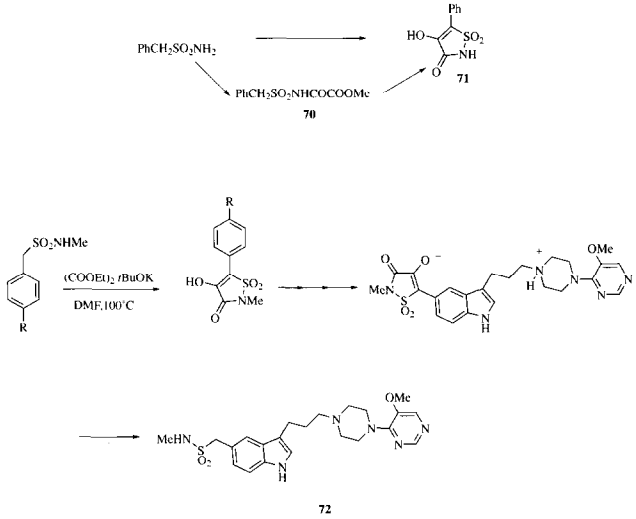
Several *N*-aryl substituted isothiazol-3(2*H*)one *S*,*S*-dioxides **63**, **64** could be obtained (98JPC(340)361) by oxidation of the corresponding isothiazolium salts **62a**,**b**. From the bicyclic salts **62b** (00JPC(342)675) the corresponding carboxylic acid **63** is formed through a Criegee-type rearrangement. When the oxidation was performed at r.t. on the *N*-benzenesulfonylamino-isothiazolium salt **65**, or the corresponding isothiazole imines **66** (99JHC(36)1081), compounds **68** were obtained through formation of the intermediate ring-enlargement product 1,2,3-thiadiazine *S*-oxide **67**, which could be isolated and characterized when performing the oxidation at 0°C.



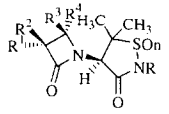
64 63 65 66 67 68 69

The formation of methyl(benzylsulfonyl)oxamate **70** as the reactive intermediate in the reaction of arylmethanesulfamide **69** and diethyl oxalate, giving 5-aryl-4-hydroxy-3(2*H*)-isothiazolone **71**, has been reported (99MI1).

Isothiazolone dioxide rings are readily cleaved in diluted aqueous alkaline solution at r.t. and this feature allows their use, in some cases, as a protecting group (95TL(36)6227). An example is the efficient Fischer indole synthesis of **72**.

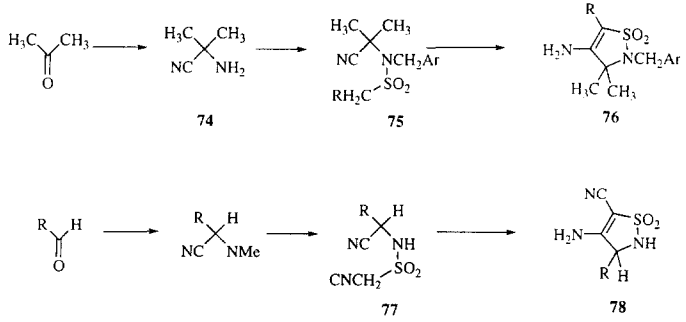


The preparation of isothiazolidin-3-one *S*-oxide and *S,S*-dioxide derivatives of azetidin-3-ones was described (99EUP100069), starting from penicillanic acid sulfoxide amides in the presence of halogenating agents in anhydrous inert solvents or even without them. Through rearrangement and oxidation with conventional methods, compounds **73** could be obtained. For some derivatives the usefulness, as intermediates for the preparation of novel β-lactam analogs or active substances in formulations for antimicrobial therapy, is claimed.

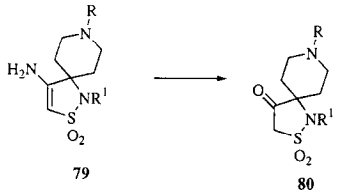


73

4-Amino-2,3-dihydroisothiazole *S,S*-dioxides have been synthesized through base-catalyzed ring closure, starting from the appropriate sulfonamide (97TL(38)4835). In this synthetic pathway, acetone is transformed into the corresponding aminonitrile **74** followed by reaction with alkane-sulfonyl chloride, affording the sulfonamide **75**. The cyclization was performed at r.t. with DBU or NaH. Compound **76** (97T(53)17795) was evaluated for its activities against human immunodeficiency virus type 1 and HIV-2(ROD) in human *T*-lymphocyte cells (MT4), but no interesting activities were observed. The same methodology could be applied to cyanoalkylsulfonamide **77** derived from aliphatic aldehydes (98TL(39)4123, 00T(56)2523) affording **78**.

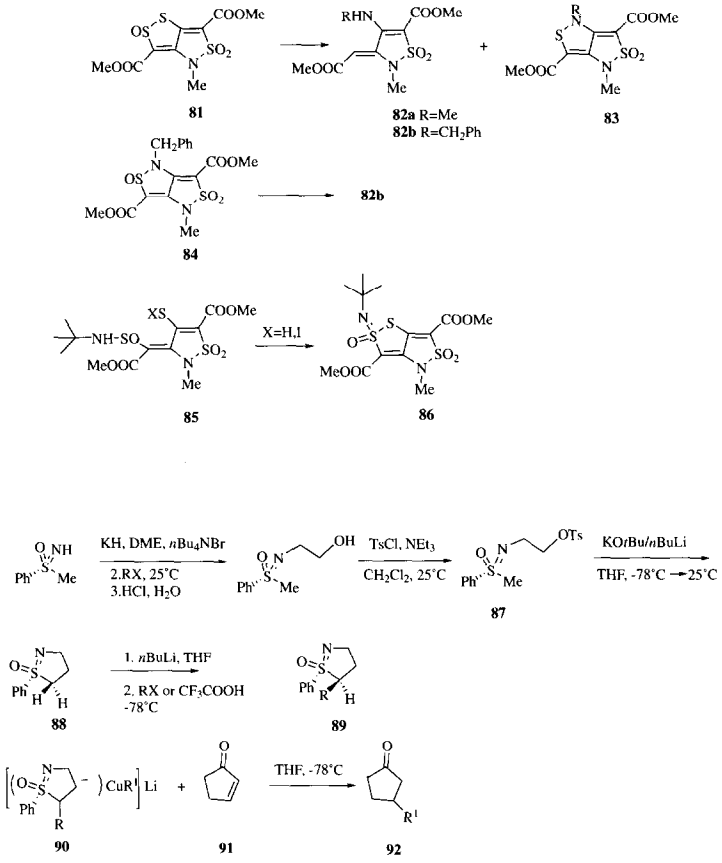


Thus, simple ketones or aliphatic aldehydes may be successfully used as starting materials in the CSIC (Carbanion mediated Sulfonate Intramolecular Cyclization) reaction. *N*-alkylsulfonamides could be also cyclized under CSIC conditions (99T(55)7625) affording the spiroisothiazoline **79**. By treatment with TMSCl, NaI in acetonitrile at r.t., hydrolysis of the enamine and formation of the corresponding keto derivative **80** was obtained.

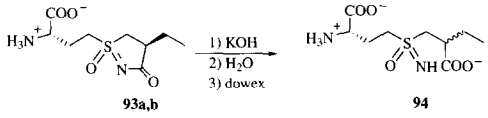


Bicyclic isothiazole dioxides **81** (99JHC(36)161), on treatment with *N*-nucleophiles such as benzylamine, afforded isothiazole dioxides **82a,b** together with a minor amount of compounds **83**. Alternatively, **82b** could be obtained from **84** by reduction with 1,2-dimethylhydrazine and DBU. By using *t*-butylamine as the *N*-nucleophile, due to steric reasons, the formation of the isothiazole dioxide **85** could also be observed followed by transformation in the bicyclic system **86**.

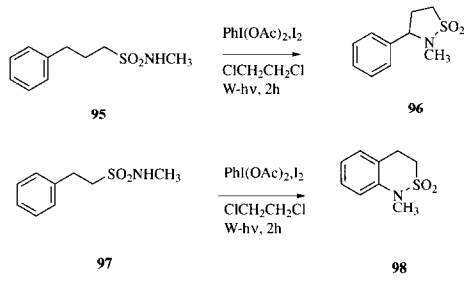
Asymmetric induction by sulfoxide is a very attractive feature. Enantiomerically pure cyclic α-sulfonimidoyl carbanions have been prepared (98S919) through base-catalyzed cyclization of the corresponding tosyloxyalkylsulfoximine **87** to **88** followed by deprotonation with BuLi. The alkylation with MeI or BuBr affords the diastereomerically pure sulfoximine **89**, showing that the attack of the electrophile at the anionic C-atom occurs, preferentially, from the side of the sulfoximine O-atom independently from the substituent at Cα-carbon. The reaction of cuprates **90** with cyclic α,β-unsaturated ketones **91** was studied but very low asymmetric induction was observed in **92**.



The cyclic sulfoximine **93a,b**, a key intermediate in the synthesis of sulfoximine **94** designed as inhibitors of *Escherichia Coli* γ-glutamyl synthetase, was synthesized stereoselectively (96BMC(6)1437, 98BMC(6)1935). X-ray analysis (99AX(C55)1598) of **93b** was performed, elucidating the configuration.



Cyclization of *N*-methyl-3-phenyl-propanesulfonamide **95** afforded 3-phenyl-*N*-methyl-isothiazolidine *S*,*S*-dioxide **96** (00JOC(65)926). The photochemical treatment in dichloroethane with diacetoxyiodobenzene in the presence of iodine was carried out at room temperature. By using 2-phenyl-ethanesulfonamide **97**, the cyclization occurred giving the corresponding benzothiazine *S*,*S*-dioxide **98**.

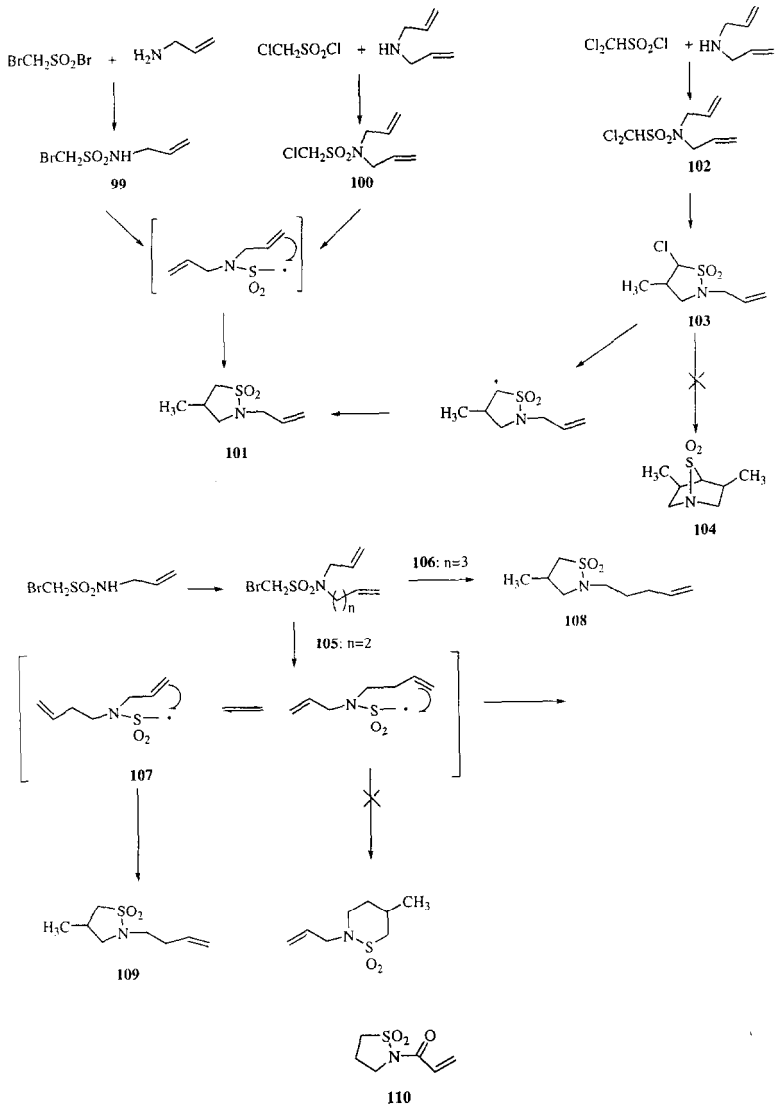


A five-membered heterocyclic ring was formed by radical cyclization of several omologous α-methylsulfonamides with tributyltin hydride under AIBN catalysis (99JOC(64)9225). By using sulfonamides **99** and **100**, compound **101** was readily obtained as expected. The formation of the same compounds from **102** also was not so evident. The initially formed **103** produce a second radical that is converted by hydrogen transfer to **101**. The cyclization affording the bicyclic system **104** did not take place, probably due to high strain. From **105** and **106** the five-membered rings **108** and **109** are the preferred (or the sole) product demonstrating that the transition state **107** is preferentially adopted. The study and evaluation of the intramolecular cyclization capability of these highly reactive intermediates resulted in a preparative useful methodology to isothiazolidine *S*,*S*-dioxides.

In the synthesis of polymers it is very important to control the configuration of the multiple stereogenic centers but free radical methods generally fail to give significant stereochemical control (96T(52)4181). To compare the effects of several chiral and achiral auxiliary groups, acrylamides of type **110** were studied.

3-Amino-isothiazole *S*,*S*-dioxides with different substituents on C-5 could be obtained with various original methodologies already cited (Section II, B, 2).

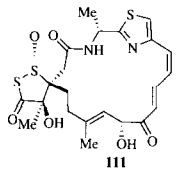
A lot of compounds were synthesized by using conventional methods, in most cases with the aim to produce compounds with pharmacological properties (98JMC(41)3261, 99BMC(9)1409, 00MI1).



D. Biological Properties and Other Applications

The isothiazole ring has been incorporated into a wide range of known biologically active compounds, either as a substituent or taking the place of another ring. Compounds of general formula **112** were synthesized (99JMC(42)1330,

00MI2) as stable derivatives of Leinamycin **111**, a novel antitumor antibiotic isolated from a culture broth of *Streptomices* sp. These new compounds contain in their structure the 3-isothiazolidinone *S*-oxide moiety and could be prodrugs that provide dithiolanone compound in biological media. Compound **113** appeared to be a very potent antitumor drug against human tumor xenograft,



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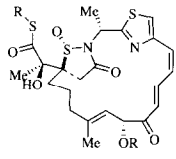

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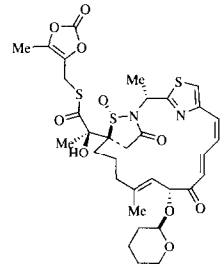
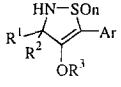


113

such as lung, liver, ovary, prostate and colon carcinomas. Isothiazolidinone *S*,*S*-dioxides and *S*-oxides **73** were prepared (Section II.C) as intermediates for β-lactam antibiotics (99EUP100069). Isothiazolidine *S*,*S*-dioxide derivative **114** was reported to possess herbicidal activity (95MI2). 4-Hydroxy- or 4-amino-isothiazoline 1,1-dioxides such as **115**, **116** were prepared as agrochemical fungicides, herbicides and pesticides (94USP336571, 96GEP19620135, 99EUP100069, 99GEP19924668). A series of isothiazolidine dioxide derivatives **117a** and **117b** were prepared (98JP4774, 98JP4775, 00JMC(43)2040) by a known methodology by cyclization of the 3-chloropropanesulfonamide followed by coupling with an aldehyde by an aldol-like reaction and dehydration to the benzylidene derivatives. By this way a di-*tert*-butylphenol functionality can be linked to the γ-sultam skeleton resulting in novel antiarthritic agents. Diverse biological activity was claimed for **118** (97GEP19700061). Compound **119** (00MI1) was synthesized to test its antitumor and antiepileptic activity, while isothiazolidine *S*,*S*-dioxide moiety is present in compounds under study as endothelin antagonists (98JMC(41)3261) or glycine receptor ligands (99BMC (9)1409). Several isothiazolidin-3-one *S*,*S*-dioxides were used as scaffolds in the design and synthesis of serine proteinases inhibitors (95USP236, 98BMC(8)539).

114



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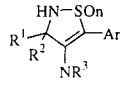

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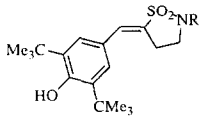
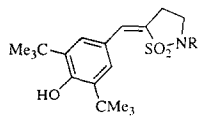
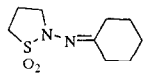


117a



117b



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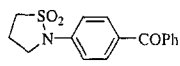


119

III. Thiazole *S*-oxides

Although thiazole chemistry has been extensively reviewed, *S*-oxide and *S,S*-dioxide derivatives had not been previously extensively treated. As already cited some aspects appeared regularly in *Progress in Heterocyclic Chemistry* (Section I).

A. Structural and Physical Properties

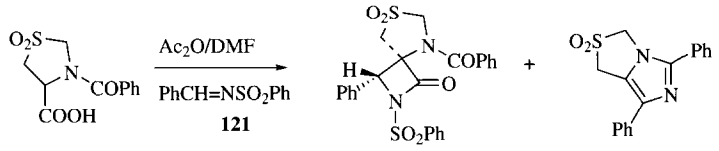
Papers dealing with this topic are exhaustively reviewed in *Comprehensive Heterocyclic Chemistry I* (84CHEC-I(6)235) and *II* (96CHEC-II(3)373). Nevertheless, little information is available on the *S*-oxides. Recently, the heteroaromaticity of thiazole compared with isothiazole and thiadiazole *S,S*-dioxide systems was studied (97MI1). Quantum-chemical calculations and X-ray studies were performed on 3,3′-di[1,3-thiazolidin-4-one] derivatives (95JCC(25)589) studied for their potential biological activity (97FA(52)43).

B. Reactivity

1. *Cycloaddition Reactions*

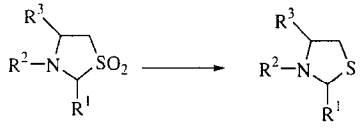
An example of 1,3-dipolar cycloaddition involving a thiazole dioxide derivative was described (99T(55)201). *N*-Benzoyl-(*R*)-thiazolidin-4-carboxylic acid *S,S*-dioxide **120** was cyclized to the bicylic mesoionic thiazolo-oxazolium *S,S*-dioxide with Ac_2O and reacted with the imine **121** in DMF

solution affording the spiro-β-lactam **122** and the bicyclic adduct **123** in a 22% total yield.



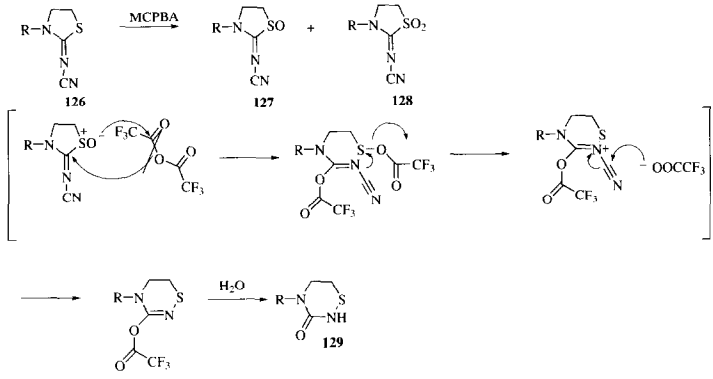
2. *Reactivity at Ring Atoms*

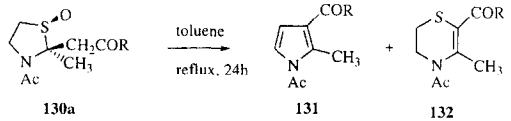
Thiazolidine *S,S*-dioxides **124** were transformed into the corresponding thiazolidines **125** by reduction with methyltrichlorosilane/NaI (97JSC(62)117). 2-(*N*-cyanoimino)-thiazolidine **126** by treatment with MCPBA (97SL316) afforded the sulfoxide **127** and the sulfone **128**, in mixture. The oxidation reaction occurred selectively on the sulfur atom generating compounds where the SO functionality is conjugated with the cyanoimino group. The new 2-(*N*-cyanoimino)-thiazolidine *S*-oxides **127** were studied under Pummerer-type reaction conditions. Reacting with TFAA at 0°C in dichloromethane afforded 4-substituted-2*H*-1,2,4-thiadiazin-3(4*H*)ones **129** as a result of ring expansion. Monocyclic 1,2,4-thiadiazin-3-one derivatives are very uncommon and, particularly, this synthesis seems to be the first one referred to a 1,2,4-thiadiazin-3-one bearing a divalent sulfur.

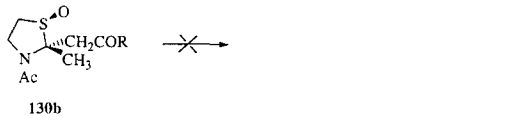


The rearrangement of cyclic sulfoxide **130a**, which could be obtained from the corresponding thiolsulfinate **163** (Section III.C.1), was studied in different experimental conditions. The *cis*-sulfoxide refluxed in toluene for 24 h gave a 1:1 mixture of the pyrrole **131** and the dihydro-1,4-thiazine **132**.

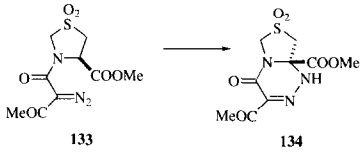
A completely different behavior was observed for the *trans*-sulfoxide **130b** which remained substantially unchanged after prolonged heating in toluene. An explanation of this difference was proposed (99JHC(36)271).



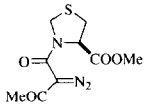




The base-induced cyclization of thiazolidine-4-carboxylate *S,S*-dioxide **133** to the bicyclic thiazolo-triazine **134** was studied (99JCS(P1)1067). In analogy with the corresponding thiazolidine derivative **135**, compound **133** underwent stereoselective cyclization with retention of configuration. When the same reaction was performed on the thiazolidine *S*-oxides **136a,b** in a 65:35 mixture, the cyclization occurred affording the bicyclic systems **137a,b** in a 63:37 mixture. By using the pure sulfoxide **136a** a 61% yield of the bicyclic **137a** was obtained. It seems that the cyclization occurred through a planar ester enolate intermediate **138**, which possesses axial chirality, and that the stereodirecting effect of the sulfinyl group is overriden. The stereoselectivity of the sulfoxidation reactions of the bicyclic sulfide **139** was also investigated and it was observed that the oxidant delivers its oxygen atom preferentially to the *exo*-orientated lone pair of the sulfur atom.



133 134



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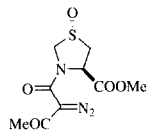
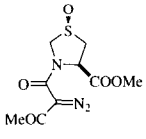


136a



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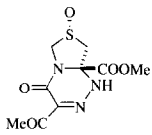
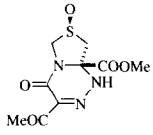


137a



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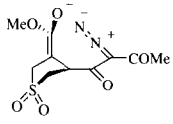

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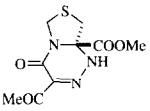
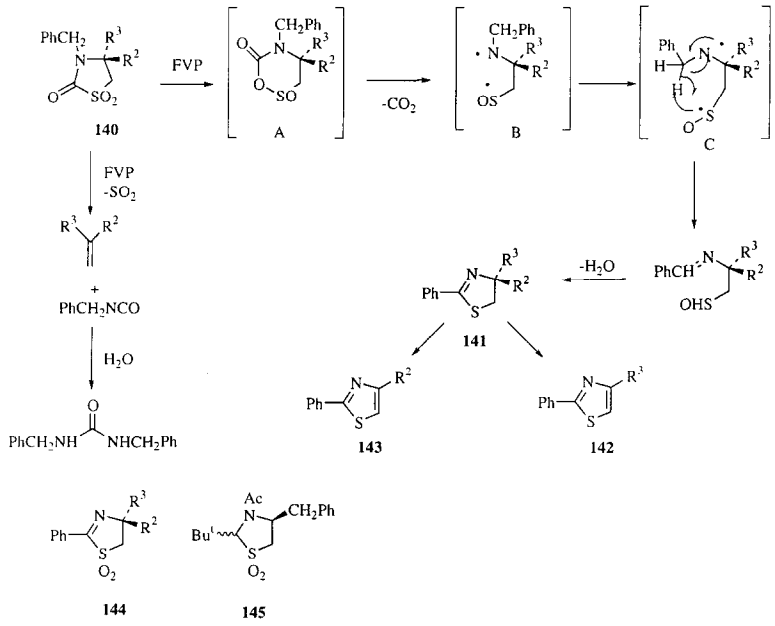


139

3. *Pyrolytic Behavior*

The thermal fragmentations of several heterocyclic systems have been studied and reviews have been reported by Atkins and coworkers (92PHC(4)1, 93PHC(5)1). The SO_2 thermal extrusion from heterocyclic systems is a common event and is the basis for several synthetic applications, such as the formation of β-lactams from appropriate thiazolidin-4-one *S*,*S*-dioxides (72TL(35)3633, 75HCA(58)2509, 83JOC(48)494) or malonic acid imides from thiazolidine-2,4-dione *S*,*S*-dioxides (73JOC(38)2652, 86LA1787). The thermal behavior upon flash vacuum pyrolysis of several thiazoline and thiazolidine *S*,*S*-dioxides was studied. Thiazolidine-2-one *S*,*S*-dioxides **140** underwent complete reaction at the relatively mild temperature of 650°C to give a rather complex mixture of products with SO_2 extrusion and complete fragmentation of the ring (97JCS(P1)2139). An unprecedented heterocyclic transformation was observed in the formation of small but significant quantities of compounds **141**, **142** and **143**. Compound **140** appeared to be substantially less reactive in photochemical conditions, affording, in low yield, an aminosulfonic acid deriving from the hydrolysis, decarboxylation and oxidation. The thiazoline *S*,*S*-dioxides **144** (97JCS(P1)935) and thiazolidine *S*,*S*-dioxides **145** (98JCR(S)76) underwent essentially quantitative loss of SO_2, affording products deriving from the opening

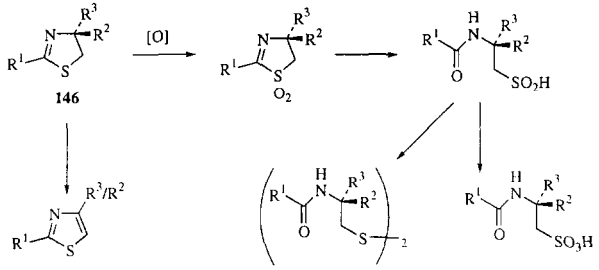
of the ring. Other examples of 1,2-thiazolidine *S,S*-dioxides have apparently not been studied previously.

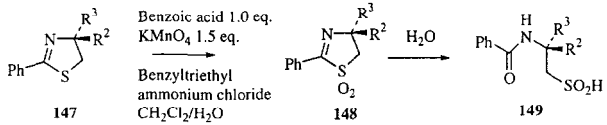


4. *Oxidation Methodologies*

a. *Thiazoline S-oxides.* The oxidation of 4,5-dihydro-1,3-thiazoles has been little investigated and there are only two previous reports on 4,5-dihydro-1,3-thiazole *S,S*-dioxides that are formed from the corresponding thiazoline using *meta*-chloroperbenzoic acid (76TL(15)1137), or using $KMnO_4$ (82MI1), and both involving rather hindered compounds. The behavior of chiral 4,5-dihydro-1,3-thiazoles towards a variety of common oxidants was investigated (97JCS (P1)935). A series of 2-substituted thiazolines **146** was treated with oxone®, *m*-chloroperbenzoic acid, peracetic acid, oxaziridine, *t*-butyl hydroperoxide, and $KMnO_4$ in different conditions. A rather complex pattern was observed. The authors finally observed serendipitously that by using 1 equivalent of benzoic acid, 1.5 eq. of $KMnO_4$ and catalytic benzyltriethylammonium chloride in a CH_2Cl_2–water medium, the conversion of 2-phenyl-4,5-dihydro-1,3-thiazoles **147** into the corresponding *S,S*-dioxides **148** was completed in excellent yields. Once thiazoline dioxides were obtained, they appeared very moisture sensitive and easily hydrolyzed to acylamino sulfinic acid **149**. This feature explains why by using all other oxidants tested, the analogous thiazoline dioxides were never isolated in good

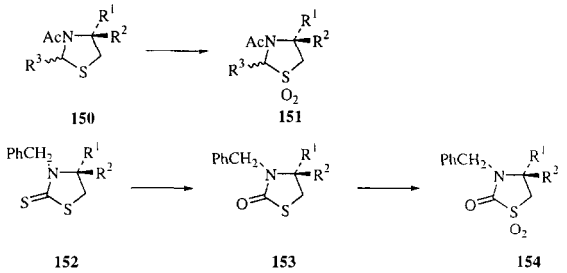
yields: 2-thiazoline *S,S*-dioxides could be generated in all cases but underwent hydrolysis in situ. The precise nature of the oxidizing species remains unknown.





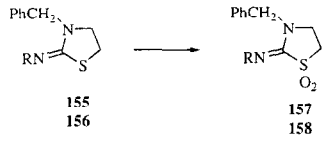
147 148 149

b. *Thiazolidine S-oxides.* Several oxidizing reagents producing sulfones or sulfoxides from thiazolidines have been previously exhaustively reported (96CHEC-II(3)390). The method above described (Section III.B.4.a) could be applied for the oxidation of a range of sulfides **150** to the corresponding sulfones **151** in high yield and (97S787) to directly transform thiazolidine-2-thione **152** into **154** by using 5 eq. of $KMnO_4$ through the formation of the isolable intermediate **153**.



150 151 152 153 154

Several *N*-benzyl-thiazolidin-2-ylidene derivatives **155**, **156** (95MI3) were oxidized to the corresponding *S,S*-dioxides **157**, **158** with 2,2 eq. of *m*-chloroperbenzoic acid. Although mild and controlled conditions were adopted, it was impossible to isolate the intermediate *S*-oxide which was probably very prone to oxidation to **157**, **158**.

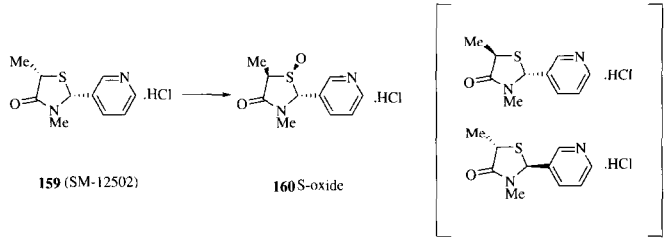


155 **157**
156 **158**

155, 157 R=$ArSO_2$;
156, 158 $Ar(R^1)C{=}N$-

An interesting application is the *S*-oxidation reaction for a sulfur-containing drug **159** (SM-12502, (+)-*cis*-3,5-dimethyl-2-(3-pyridyl)thiazolidin-4-one hydrochloride) by rat FMO1 expressed in yeast (95MI4). The authors demonstrated that the *S*-oxidation of the mixture of the two enantiomers **161** (SM-9979 (±)-*trans* compound) to **160** is four-fold greater than the oxidation of SM-12502 ((+)-*cis* compound), and enantioselectivity and diastereoselectivity was observed. Recombinant yeast could be used as a stereospecific bioreactor for obtaining *S*-oxide compounds. This bioreactor system using enzymes and microorganisms described in the article has a great potential advantage: that the *S*-oxidase reaction was stereoselective and that metabolite production could be mantained for long periods of time.

c. *Thiazole S-oxides.* Concerning thiazoles, there is a lack of information regarding the oxidation to sulfoxide or sulfone derivatives. Thiazoles, as previously reported, appear to be very resistant (96CHEC-II(3)390).



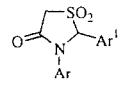
159 (SM-12502) **160** S-oxide **161** (SM-9979)

C. SYNTHESIS

1. *Conventional Methods*

3,4-Diaryl-thiazolidin-4-one *S,S*-dioxides **162** were obtained by reacting thioglycolic acid with Schiff bases, followed by oxidation at the sulfur atom

(00MI3) and their potential biological activity was tested (Section III.D). The thiolsulfinate **163**, refluxed in toluene, produced thiazole derivatives **130a** (Section III.B.2) and **166** (97H(45)1999, 99JHC(36)271). The presence of a weak S–S bond and a labile α-sulfenyl hydrogen rendered the thiolsulfinate keen to decomposition, allowing the formation of sulfenic acid **164** and thioaldehyde **165** as the nonisolable intermediate of the reaction. The cyclization to the thiazolidine *S*-oxide **130a** is completely stereospecific, affording only the *cis*-isomer. The *trans*-isomer **130b** of the thiazolidine could be obtained in mixture with the *cis*-one by a previously published procedure (89JHC(26)1447), involving the oxidation of the parent thiazolidine with aqueous hydrogen peroxide and benzene seleninic acid as the catalyst.



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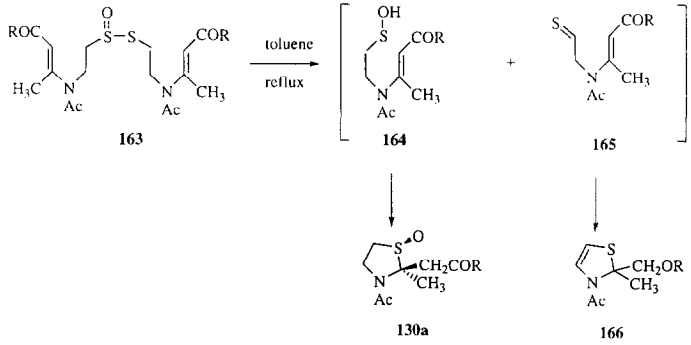
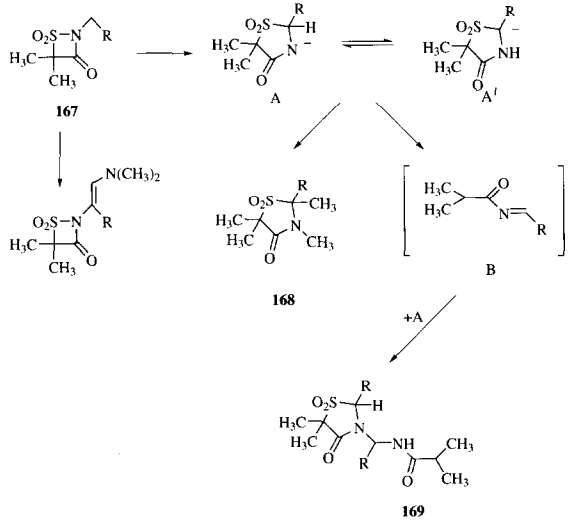
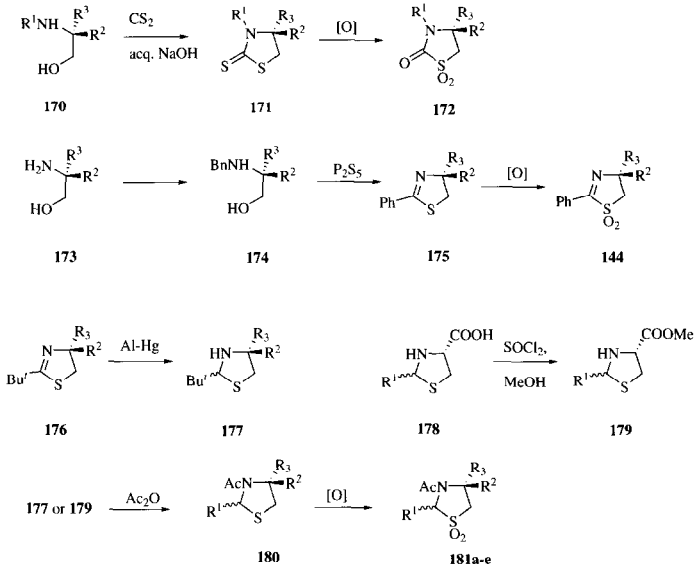


163 **164** **165** **130a** **166**

An interesting result was obtained by treating *N*-alkylated 3-oxo-β-sultams **167** with NaH in DMF (97HCA(80)671). The course of the reaction strongly depends on the conditions (amount of DMF, temperature). By controlling these parameters the 1,3-thiazolidin-4-one *S*,*S*-dioxide derivatives **168** and/or **169** could be obtained in satisfactory yields by deprotonation of the CH_2N group and ring opening to give an unstable intermediate which on cyclization gave the more favored five-membered ring. Compound **168** could be obtained by alkylation of tautomers A/A^1 by adding dimethyl sulfate to the reaction mixture before work-up. For the formation of a very unusual 1,3-thiazolidin-4-one *S*,*S*-dioxide **169**, a Michael addition of the acylimine B to the anion A is proposed.



Chiral thiazolidin-2-one *S,S*-dioxides **172** were prepared (97JCS(P1)2139) by the reaction of the appropriate aminoalcohol **170** with CS_2 in acqueous NaOH followed by oxidation of **171**. Chiral thiazoline *S,S*-dioxides **144** (Section III.B.3) have been prepared (97JCS(P1)935), starting from the corresponding aminoalcohol **173**, which was acylated to **174** and cyclized with P_2S_5 to **175**. The oxidation with $KMnO_4$/Benzoic acid/Benzyltriethylammonium chloride in dichloromethane/water medium (Section III.B.4) afforded **144**. The same pathway when applied to thiazolines with different substituents at C-2 (e.g. Me, *t*Bu) was unsuccessful, resulting in ring opening during the oxidation process (Section III.B.4). Several thiazolidine *S,S*-dioxides have been prepared by two pathways (98JCR(S)76). Compound **181a** could be obtained directly by reduction of the corresponding enantiomerically pure **176** to **177**, followed by acylation to **180** and oxidation; **181a** was obtained in a 75:25 mixture of diastereoisomers. Thiazolidine *S,S*-dioxides **181b–e** have been prepared by oxidation of the corresponding **180**, which could be obtained by an already known method from cysteine and aldehydes followed by esterification of the intermediate **178** to **179** and acylation. In recent literature many thiazoles, thiazolines, thiazolidines oxidized at sulfur atoms can be found. Most are part of very complex structure and represent simple substituents. (95JMC(38)508, 95MI5, 96BMC(6)2745, 97FA(52)43, 99BMC(7)509; 99JMC(42)3134).



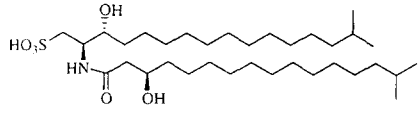
2. *Solid Phase Synthesis*

The growing interest in combinatorial solid phase synthesis prompted several groups to find a simple route to produce thiazolidine derivatives. Pàtek and coworkers (95TL(36)2227) developed a methodology starting from protected aminoacids, aldehydes and *N*-acylating agents. The amino acid was attached directly to TentaGel S OH resin and both protecting groups were removed by treatment with 20% piperidine/DMF and TFA/5% iBu$_3$SiH/DCM. Reaction with the opportune aldehyde, *N*-acylation and, finally, hydrolytic cleavage from the resin, afforded the thiazolidine in satisfactory yield. Routine oxidation of the sulfide group enables access to a variety of acid stable sulfoxide analogues. Solid phase synthesis of thiazolidinones as peptidomimetics was also patented. A library was prepared using TentaGel S resin functionalized with a photolinker and compounds tested for *K*-opioid activity (95USP7988).

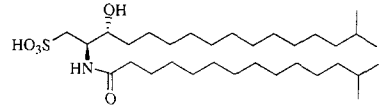
D. Biological Properties and Other Applications

Thiazoles have a wide variety of uses as biologically active compounds in agriculture and in medicine. In the last decade, lot of activities concerning monoxides

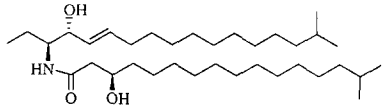
and dioxides have been claimed for a number of thiazole derivatives such as progesterone receptor binding agents (99USP29601), platelet activating factors (95MI5), calcium antagonists (99JMC(42)3134), herbicides (95BRP1224, 96EUP4014, 99EUP306382), antiinflammatory (97FA(52)43), antitussive (95JMC(38)508), antibacterial, antipsychotic, analgesic, anticonvulsant and anxiolytic agents (95EUP113757) or for treatment of multiple sclerosis (96EUP300415) or ischemic disease (97USP944550) or as inhibitors of prolyl endopeptidase (94JP1033), phosphodiesterase 4 (99BMC(7)509), dipeptidyl peptidase IV (96BMC(6)2745) and metallo beta lactamase (96EUP4014). Dipeptides were prepared as HIV-inhibitors (96EUP304764). 3,4-Diaryl-thiazolidin-4-one *S,S*-dioxides **162** (Section III.C.1) were screened for their antibacterial and anticancer activity (00MI3). Various trifluoromethyl substituted indoles and spiroindoles containing the thiazole ring were synthesized and investigated for antifungal activity (97MI2). It has to be noted that in several cases the sulfoxide and the sulfone derivatives are not the finally desired compounds but appeared very useful as the key intermediates in the synthesis of active compounds. In 1999 K. Mori and coworkers published the synthesis, from L-cysteine, of sulfobacin A,



Sulfobacin A = Flavocristamide B



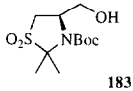
Sulfobacin B



Flavocristamide A

A

182



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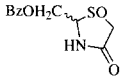

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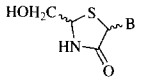


185

B= cytosine, 5-fluorocytosine, thymine

B and flavocristamide A, new sulfonolipids isolated from *Chriseobacterium* sp. (98TL(39)6931, 99JCS(P1)2467). In the synthetic plan one of the key steps involved the formation of the sulfinic acid A from compound **182** in which the sulfone group is a part of the acetonide group and by consequence a sulfinic acid equivalent. By reacting with HCl the cleavage of the acetonide protecting group resulted in the unexpected formation of the sultine **183** instead of the expected sulfinic acid. Nevertheless, the sultine resulted a good protecting group for the OH group and therefore was very useful in subsequent steps. It is well known that the sugar modification influences the biological and toxicological properties of nucleosides. The ribose ring has been replaced by a 1,3-thiazolidin-4-one moiety (95MI6). This has never been used in nucleoside chemistry. Among the different proposed synthetic pathways, the condensation of various nucleic bases using TMSOTf and triethylamine as coupling reagents on a key sulfoxide thiazolidinone intermediate **184** led to the desired compounds **185** in a one pot procedure.

IV. Thiadiazole *S*-oxides

The thiadiazole system contains the following members: 1,2,3-thiadiazoles, 1,2,4-thiadiazoles, 1,2,5-thiadiazoles and 1,3,4-thiadiazoles.

A. Structural and Physical Properties

Concerning 1,2,3-, 1,2,4-, 1,3,4-thiadiazole isomers, some information is found in *Comprehensive Heterocyclic Chemistry* (84CHEC-I(6)447, 84CHEC-I(6)460), particularly regarding rings which are not oxidized at the sulfur atom. 1,2,5-Thiadiazole *S*,*S*-dioxides and *S*-oxides are surely the most studied isomers of the thiadiazole family. Many papers discuss extensively their structure and properties and have already been reviewed (88AHC(44)133, 96CHEC-II(4)365). A discussion on the heteroaromaticity of 1,2,5-thiadiazole *S*,*S*-dioxide compared with the other 3 isomers and with thiazole and isothiazole *S*,*S*-dioxides was presented (97MI1). 1,2,5-Thiadiazole *S*,*S*-dioxide appeared to be the most aromatic molecule of the entire group studied. The electronic characteristics of 1,2,5-thiadiazole *S*,*S*-dioxide have also been explored, carrying out a comparative study aiming to evidentiate the method that can better describe this ring (97IJQ(62)477). The author found the CHELPG and Mulliken methods at the MP2/6-31G*//HF/631G* level provide better charge distribution. Accurate dipole moments and charge distributions were obtained that gave a good description of the S=O double bond and showed a lack of π delocalization along the double bond. Crystallographic studies and molecular orbital calculations of some derivatives were performed (98JPO(11)91).

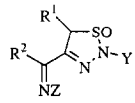
Experimental (NMR and IR) and theoretical studies of the conformations of a 1,2,5-thiadiazole *S*-oxide have also been performed (99MI2).

V. 1,2,3-Thiadiazole *S*-oxides

A. Synthesis and Reactivity

1,2,3-Thiadiazole *S*-oxides and *S,S*-dioxides are the least studied among the four possible isomers of thiadiazole system. The main summary is in the first and the second editions of *Comprehensive Heterocyclic Chemistry* (84CHEC-I(6)447, 96CHEC-II(4)289). Apparently the *S*-oxide and the *S,S*-dioxide derivatives have not yet been reviewed. There are very few papers in the literature treating these derivatives, and most of these are regarding polycyclic systems.

The Hurd–Mori synthesis of 1,2,3-thiadiazoles from α-methylene ketones developed in 1955 is, even today, the method of choice for a number of 1,2,3-thiadiazole derivatives. Both the mechanism and the regiochemistry have been extensively studied, but since the isolation of the intermediate by Hurd and Mori (84CHEC-I(6)460), there has been no further work supporting the formation of this intermediate or its conversion into the aromatization product. In 1995 Kobori and coworkers published the isolation of several 1,2,3-thiadiazolin-1-oxides **186**, finally demonstrating their participation in the formation of 1,2,3-thiadiazoles. Substituents R^1 and R^2 play an important role in the isolation of 1,2,3-thiadiazolin-1-oxide (95H(41)2413).



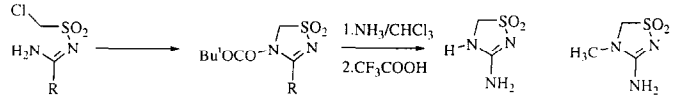
186

VI. 1,2,4-Thiadiazole *S*-oxides

A. Synthesis and Reactivity

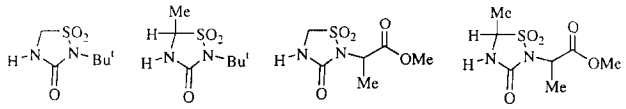
1,2,4-Thiadiazole *S*-oxides and *S,S*-dioxides cannot be prepared by direct oxidation (84CHEC-I(6)463, 96CHEC-II(4)315), and the known dioxide derivatives are prepared by cyclization of intermediates containing the sulfone group (69JCS(C)652, 70JCS(C)1429, 74BSF1580). More recently, a synthesis of 3-amino-1,2,4-thiadiazoline *S,S*-dioxide **189** and of the 4-methyl derivative **190** was carried out by cyclization of the intermediate chlorosulfonamide

187 with sodium hydroxide in the presence of 2-(*t*-butoxycarbonyloxyimino)-2-phenylacetonitrile affording **188**, which was readily converted into the product by reacting with NH_3 in $CHCl_3$, and then deprotecting with CF_3COOH. By using methyl iodide instead of 2-(*t*-butoxycarbonyloxyimino)-2-phenylacetonitrile, the *N*-methyl analogue **190** could be obtained after treating the intermediate product with liquid ammonia (97AJC(50)1027).



187 **188** **189** **190**

Several examples of 1,2,4-thiadiazolidin-3-one *S*,*S*-dioxides **191–194** were isolated as by-products in the synthesis of sulfonopeptides. These are formed by refluxing in benzene or toluene the corresponding acylazides. These sulfonyl-hydantoins are extremely labile in protic solvents (96T(52)5303).

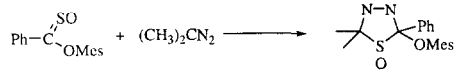


191 **192** **193** **194**

VII. 1,3,4-Thiadiazole *S*-oxides

A. Synthesis and Reactivity

Despite great interest in 1,3,4-thiadiazole chemistry and the usefulness they show in agriculture, medicine and several other fields, direct oxidation to form *S*-oxides or *S*,*S*-dioxides has not been reported. Only a restricted number of papers dealing with *S*-oxides and *S*,*S*-dioxides appeared in the literature (96CHEC-II(4)402) and, apparently, only two papers have been published in the last five years. The first one describes the synthesis of thiadiazoline **197** through a cycloaddition reaction of diazopropane **196** to the sulfine **195** (96PS(108)289). Such cycloadditions are typical for sulfines (72JCS(P1)2490). The other is the already cited study on the heteroaromaticity of sulfur heterocycles (97MI1), where all the thiadiazole *S*,*S*-dioxide isomers were considered.



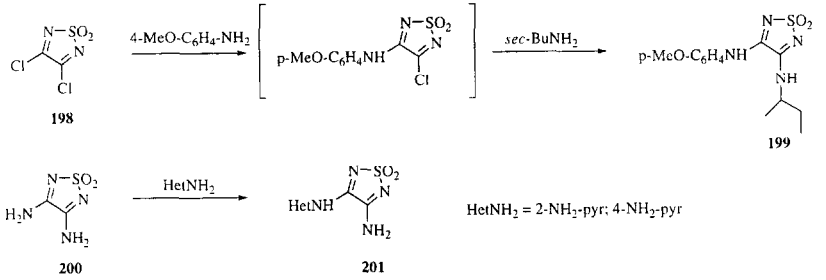
195 196 197

VIII. 1,2,5-Thiadiazole *S*-oxides

1,2,5-Thiadiazole *S*,*S*-dioxides and *S*-oxides are considered non aromatic and have been proved to be less thermally stable than the aromatic form. They belong to a group of heterocycles containing the sulfamide moiety that have been shown to possess interesting chemical properties. Furthermore, a variety of applications like biologically active compounds and fine chemicals have been found. A detailed review has been written by Aran and coworkers (88AHC(44)81), and information regarding the more recent advances in this field has been reported in *Comprehensive Heterocyclic Chemistry* (96CHEC-II(4)365). Concerning their reactivity, the most important reactions are, surely, the nucleophilic displacements of heteroatom-containing groups at C-3 and C-4.

A. Reactivity

a. *1,2,5-Thiadiazole S-oxides.* It is well known that 1,2,5-thiadiazoles readily react with nucleophiles and that the chloro, alkoxy and amino groups in the 3 and 4 position could easily be displaced by nucleophiles. On this basis a synthetic methodology affording nonsymmetrically arylamino, alkylamino 3,4-disubstituted 1,2, 5-thiadiazole *S*,*S*-dioxides has been developed (98JHC(35)297). By reacting 3,4-dichloro derivatives **198** with an arylamine and then with an alkylamine without isolating the intermediate, a nonsymmetrical desired product **199** was obtained.



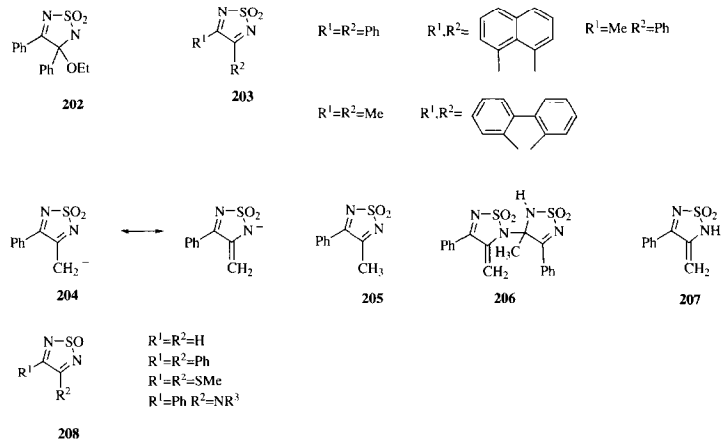
198 199 200 201

HetNH$_2$ = 2-NH$_2$-pyr; 4-NH$_2$-pyr

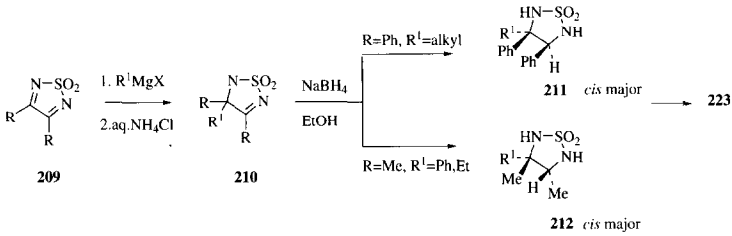
The transamination reaction on 3,4-diamino-1,2,5-thiadiazole *S*,*S*-dioxide **200** with pyridylamines afforded the 3-monoheteroarylamino thiadiazole

S,*S*-dioxides **201**. Vasorelaxant properties of the new compounds were also evaluated.

It is known that the adduct **202** is formed in ethanolic media (93JPO(6)341). The behavior of other 3,4-disubstituted analogs **203** with several nucleophiles was investigated (96CJC(74)1564, 00JPO(13)272). The equilibrium constants are measured by either spectroscopic or voltammetric experiments. The formation of the carbanion **204** was observed in basic nonaqueous media. This could add to **205**, producing a dimer **206**. The neutralization of the basic ethanolic solution of **204** causes the precipitation of the tautomer **207**. Voltammetric properties were also investigated (01JPO(14)217). Vasini and coworkers studied not only the electrochemistry of 1,2,5-thiadiazole *S*,*S*-dioxide derivatives (99CJC(77)511) but also the behavior of 1,2,5-thiadiazole *S*-oxides **208**, whose properties appear to be largely unexplored (00TL(41)3531).

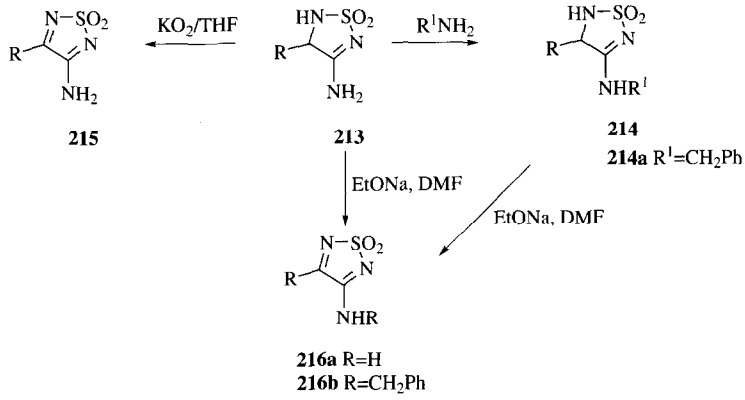


A stereoselective route to **211**, **212** was carried out by sequential functionalization at C-3 and C-4 of the thiadiazole *S*,*S*-dioxides **209** by reacting, at first,



with Grignard reagents and then by reducing the intermediate thiadiazoline *S,S*-dioxides **210** with $NaBH_4$ in ethanol. The thiadiazolidines can be converted into the vicinal diamines **223** (98SL623).

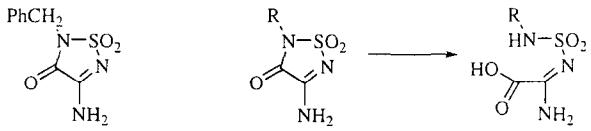
b. *1,2,5-Thiadiazoline S-oxides.* 3-Aminothiadiazoline *S,S*-dioxides **213** afforded 3-amino-substituted thiadiazoline *S,S*-dioxides **214** by reacting with the appropriate amine. The same starting compounds could be oxidized by KO_2 in dry THF to 3-amino thiadiazole *S,S*-dioxides **215** (95MI7, 96MI1). The same authors demonstrated that **213** and **214a** could also be transformed into **216a,b** by reacting with EtONa in DMF (98MI1)



215 **213** **214** **214a** $R^1=CH_2Ph$

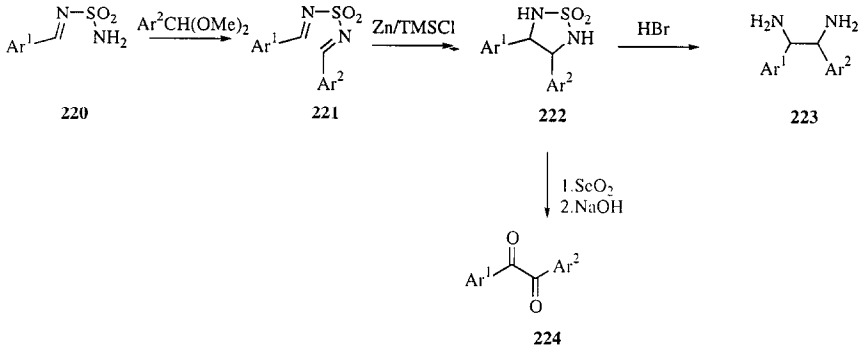
216a R=H
216b $R=CH_2Ph$

c. *1,2,5-Thiadiazolin-3-one S-oxides.* It is known that 4-amino-2-benzyl-1,2,5-thiadiazolin-3-one *S,S*-dioxide **217** hydrolyzes in basic solution (87JCS(P1)955, 89LA1135). The kinetic of the hydrolysis of several analogs **218** was investigated (98JPO(11)489). 2-Amino-2-[*N*-substituted-sulfamoyl imino]acetic acid salts **219** were identified as the labile products, which hydrolyze further to sulfamide and oxalic acid derivatives.



217 **218** **219**

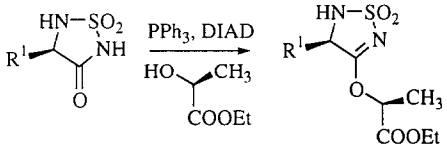
d. *1,2,5-Thiadiazolidine S,S-dioxides.* 1,2,5-Thiadiazolidine *S,S*-dioxides **222** which could be obtained from **220** through **221** were reacted with HBr with added



220 221 222 223 224

phenol for solubilization, affording the free chiral diamines **223** (52–75% yield). Treatment of the same 1,2,5-thiazolidine *S,S*-dioxides with SeO_2 followed by the hydrolysis of the crude oxidation product with aq. NaOH, furnished the aryl α–diketones **224** (97SL671). This method appears particularly interesting for the synthesis of unsymmetrical 1,2-diaryl-1,2-ethanediones.

e. *1,2,5-Thiadiazolidin-3-one S,S-dioxides.* An unusual behavior of 1,2,5-thiadiazolidine-3-ones was observed toward oxygen nucleophiles under Mitsunobu conditions (98TL(39)7435). When the cyclic sulfahydantoins **225** were reacted with hydroxyesters in the presence of triphenyl phosphine and diisopropyl azodicarboxylate (DIAD), the Mitsunobu reaction afforded selectively O-alkylation products **226** instead of the expected *N*-alkylation products. A "*pseudo*-Mitsunobu" mechanism was proposed.



225 226

B. SYNTHESIS

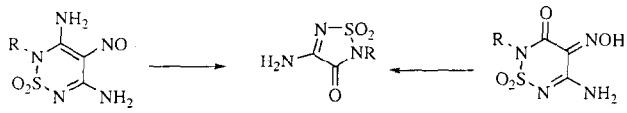
1. *Conventional Methods*

a. *1,2,5-Thiadiazole S-oxides.* As already cited, the oxidation of compound **213** with KO_2 in THF afforded the corresponding 1,2,5-thiadiazole *S,S*-dioxide

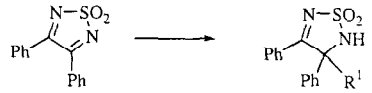
derivatives **215** (95MI7). By treating **213** or **214a** with EtONa in DMF **216a,b** were formed (98MI1).

b. *1,2,5-Thiadiazoline S-oxides.* 4-Amino-3-*oxo*-1,2,5-thiadiazoline *S,S*-dioxides **227** were obtained through strong acid hydrolysis of 3,5-diamino-4-nitroso-2*H*-1,2,6-thiadiazines **228** or 5-amino-3-*oxo*-thiadiazines **229** (96JCS(P2)293). The strong conditions needed for the hydrolysis of the 5-amino group provided the products in very poor yield.

A new method for the synthesis of 1,2,5-thiadiazoline *S,S*-dioxides **231** was achieved by reacting activated aryl nucleophiles to the C=N double bond of the corresponding thiadiazoles **230** in the presence of $AlCl_3$ as a catalyst at room temperature (00MI4). The yields of 4-aryl-derivatives ranged from 38 to 92%.

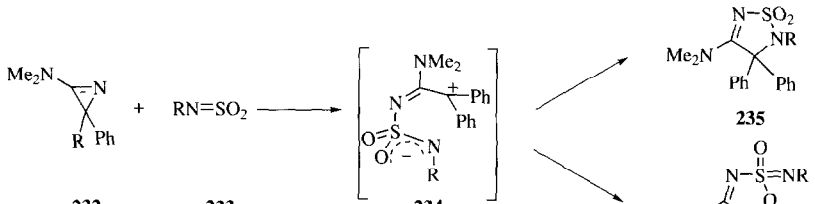


228 **227** **229**



230 **231**

An interesting reaction affording 1,2,5-thiadiazoline *S,S*-dioxides was applied by reacting in situ generated derivatives **233** with 3-dialkylamino-2*H*-azirines **232** (96JCS(P1)1629). Thiadiazolines **235** could be obtained directly or through the isomerization of the 1,2,3-oxathiazole **236**, which is the result of the ring closure of the intermediate **234** involving the sulfonyl oxygen. The latter **236** isomerizes quantitatively to the thermodynamically favored thiadiazoline **235**. The influence on the course of the reaction and on the composition of



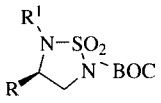
232 **233** **234** **235** **236**

the reaction mixture exerted by the *N*-substitution of *N*-sulfonylamines and by the substitution of C-3 on the azirines was analyzed.

A transamination reaction on **213** afforded 3-aminosubstituted-thiadiazoline *S,S*-dioxides **214** by reacting with the appropriate amine (96MI1).

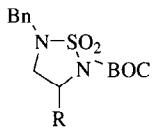
c. *1,2,5-Thiadiazolidine S-oxides.* Synthesis of 1,2,5-thiadiazolidine *S,S*-dioxides **222** (as a 2:1 mixture of *cis/trans* isomers) was achieved as previously cited (Section VIII, A, d) from **220** through **221**, with a quite general procedure applicable to a variety of aromatic aldehydes (96TL(37)2859). A stereoselective route to **211** and **212** was carried out as seen above (98SL623).

A convenient access to a series of 1,2,5-thiadiazolidines *S,S*-dioxides **237a–g** was described by Dewinter and coworkers, starting from the appropriate aminoacids and chlorosulfonyl isocyanate. The derivatization of amino acids can produce compounds **237e–g** leading at C-4 a group with a well-defined configuration (00T(56)381). 3-Substituted regioisomers **238** were obtained by using an alternative synthesis. Starting from chlorosulfonyl isocyanate and α-amino acid esters, 4,4-disubstituted 1,2,5-thiadiazolidin-3-one *S,S*-dioxides could be synthesized (00JHC(37)773). This paper describes an improved synthetic procedure affording compounds **239** in very good yield.



237 a-g

a R=R^1=H
b R=H; R^1=Me
c R=H; R^1=[CH$_2$]$_2$Cl
d R,R^1=[CH$_2$]$_3$
e R=Me; R^1=Bn
f R=*i*Pr; R^1=Bn
g R=R^1=Bn



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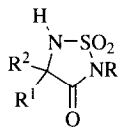
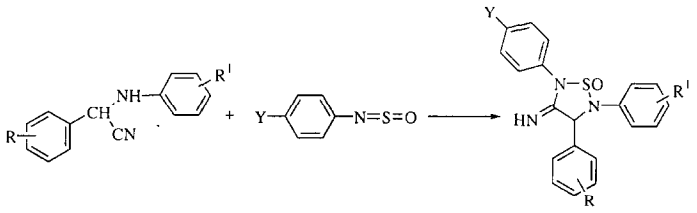


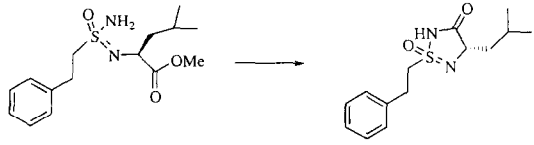
239

An approach to 2,3,5-triaryl-4-imino substituted 1,2,5-thiadiazolidin *S*-oxides **242** is the cycloaddition reaction between *N*-(α-cyano-α-aryl)-methylanilines **240** and sulphinylanilines **241** (99SC(29)911). In this way a number of thiazolidine *S*-oxides **242** could be obtained in satisfactory yield (54–70%).



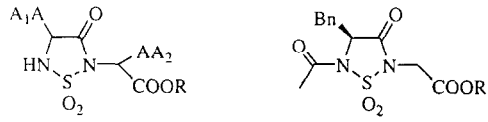
240 **241** **242**

The unusual **244** was obtained (no yield given) from the cyclization of the sulfonimidamide **243** in ethyl acetate/hexane 1/20 at 60°C. This compound appears to be very stable both in acidic and in basic solution (99BMC (9)1527).



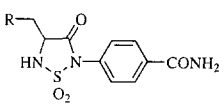
243 244

The design of conformationally constrained analogs of bioactive peptides has raised the attention of a lot of scientists in the last decade. This strategy proved to be very useful in establishing three-dimensional active structures and in developing new pharmaceutical products. The 1,2,5-thiadiazolidine or 1,2,5-thiadiazolidin-3-one moieties can be considered as a constraining element to be used in the synthesis of bioactive peptides. This goal could be reached by selective N-2 alkylation and N-5 alkylation of chiral 1,2,5-thiadiazolidine *S,S*-dioxides. Some potential applications were envisaged and reported. Groutas and coworkers have demonstrated that this ring is an effective peptidomimetic scaffold suitable for inhibition of serine proteinases especially elastase (97B(36)4737, 98BMC(8)539, 98BMC(6)661, 01MI1). With the aim to synthesize di- or tripeptides containing the sulfahydantoine unit, symmetric and asymmetric sulfamide derivatives of a series of aminoacid esters were cyclized in the presence of alkoxide as the base to **245** (99EJO(9)2275). The cyclization on dissymmetric compounds occurred on the most hindered amino acid. As a consequence, the regioselectivity depends on the nature of the constituent amino acid. Furthermore, epimerization of the exocyclic chiral carbon atom and retention of the configuration of the endocyclic one were observed. To prevent transesterification and ring opening process, *t*-butoxide as a less nucleophilic and more basic anion was used. Acylation reaction on the dipeptide was also studied as a model for the synthesis of tripeptides. Epimerization of the endocyclic α-CH was observed in **246**, due to steric decompression involved with the enolization process of the heterocyclic structure.

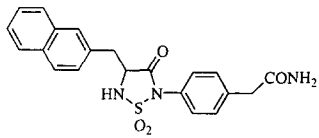


245 246

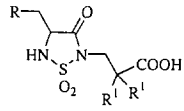
Another application was investigated by Olson and coworkers (99HCA(82) 2432). 4-Substituted-*N*-alkyl- and *N*-aryl-1,2,5-thiadiazolidin-3-ones **247–249** were prepared and evaluated for their MHC class-II inhibitor activity.



247

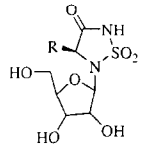


248



249

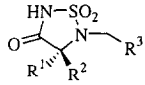
Chiral 1,2,5-thiadiazolidin-3-one *S,S*-dioxides **250** were synthesized by way of conventional methods, with the intention of introducing them in new pseudo-nucleosides as aglicone (96T(52)993). The synthetic methodology, in accord with previous reports, gave the 1,2,5-thiadiazolidin-3-ones in good overall yield (35–55%). The glycosilation was performed on the protected heterocycles to prevent the condensation involving the N-2 atom, the most acidic reactive site. As expected only one anomer was obtained that is the β-one.



250

2. *Solid Phase Synthesis*

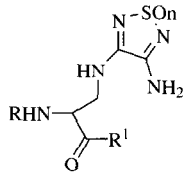
A new solid phase method to synthesize libraries of compounds based on 1,2,5-thiadiazolidine heterocycle was developed (00TL(41)3161). Starting from the coupling of the protected aminoacid to the resine functionalized with *p*-alkoxybenzylalcohol as the linker, a series of sulfahydantoins **251** could be obtained. The method is applicable to aminoacids with a basic side chain, aliphatic aldehydes or aldehydes with basic functionalities.



251

C. Biological Properties and Other Applications

Thiadiazole *S*-oxides and *S,S*-dioxides have applications in several fields (96USP760157, 96USP760156, 98BRP2062) but the main interest surely resides in their pharmaceutical applications. A number of patents and papers could be found in the literature claiming several interesting properties. Some 1,2,5-thiadiazole *S,S*-dioxides and *S*-oxides **252** were introduced in *N*-arylsulfonylarginine amides as bioisosteric replacements of the guanidine/arginine moiety and were studied as trombin inhibitors. These derivatives were prepared to test the hypothesis that different heterocycles with potentially H-bonding nuclei might act as surrogates for guanidine (95BMC(3)1145). The vasorelaxant properties of several arylamino, alkylamino-3,4-disubstituted-1,2,5-thiadiazole *S,S*-dioxides **201** were tested but without significant results (98JHC(35)297). 1,2,5-Thiadiazolidine *S,S*-dioxide moieties have also attracted attention due to the possibility of use as cyclic scaffolds in structure of new HIV protease- (96USP724563, 97USP1610, 00BMC (10)1159), or serine protease- (01MI1, 99EJO(9)2275, 97B(36)4737, 99HCA(82)2432, 98BMC(8)539, 98BMC(6)661, 98USP17406, 95USP236, 99JA(121)8128, 00BMC(8)1713, 00BMC(8)1005, 99BMC(9)2199), or human leukocyte elastase–inhibitors (94USP348440, 94USP348421).



252

As cited before (Section VIII.B.1.c), some chiral 1,2,5-thiadiazolidin-3-one *S,S*-dioxides were introduced in new pseudonucleosides as aglicone **250** (96T(52)993). Some 1,2,5-thiadiazolidin-3-one *S,S*-dioxides were prepared for treatment of degenerative disease (95USP15565, 95USP15504, 95USP15562). Very often the thiadiazole *S,S*-dioxide ring was introduced in complex active structure as a substituent, with hope of an enhancement in pharmacological efficacy (95JAN(49)199, 98FA(53)293, 99JCS(P1)2699). A few examples of *S*-oxides were found (95BMC(3)1145, 96BMC(6)2187, 98FA(53)536).

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Organometallic Complexes of Polyheteroatom Azoles Other than Pyrazole

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I. Imidazole, Biimidazole, and Benzannulated Imidazoles

A. Introductory Remarks on the Ligand Properties of Imidazole

Our generalization of the organometallic complexes of heterocycles (99AHC1) has already covered five-membered rings with one heteroatom (01(78)AHC1, 01AHC(79)115) and pyrazoles (01AHC(80)157). We now turn our attention to nitrogen azoles other than pyrazole, namely, imidazole, benzimidazole, 2,2′-biimidazole, 2,2′-bibenzimidazole, 1,2,3-triazole, benzotriazole, 1,2,4-triazole, and their derivatives. We formulate the problem of pentazole as the prospective

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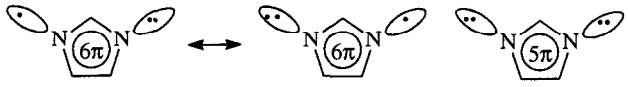
ligand for development of organometallic compounds of azoles. This aspect of the problem has been the subject of several extensive reviews (73UK177, 90CRV(106)227, 96ANH179 and references therein).

Imidazole is characterized by the resonance aromatic stabilization (61ZE369, 62JCS2927, 63T1175, 81ZN(A)1378, 92T335, 96T9945, 97T3319, 97T13111). The imidazole ring is characterized by poorer π-acceptor properties than pyridine (74JA381) due to the π-donor properties of the pyrrole-type nitrogen atom (67MI1). Trends in basicity of imidazoles (83JCS(P2)1869, 86JA3237, 88JA4105, 90JA1303, 96JMS1173, 97JPC(A)7885, 97JPOC669, 98JA11732) help us to understand their prevalent coordination via the pyridine type nitrogen atom. Imidazoles are protonated at the N-3 nitrogen (84CS84, 86JOC1105). Trends in the electronic structure and geometry of coordinated imidazoles make them useful models for the histidine residues in enzymes (97JMS(T)55). Speculations with regards to the possible donor function of the pyrrole-type nitrogen atom of the imidazole ring (64B750, 71AX(B)2089, 71IC2692, 72IC457, 74CRV471, 74JA2743) are usually not confirmed (67AX(B)406, 75JA1403). Coordination via the N^1 site would disrupt the π-aromatic system (75JA1403).

Another possibility is the η^5- (π-) donor function of the imidazole ring. Fully or partially, this problem can be resolved by studying the properties of the 1-imidazolyl radical that can be of the σ-(**1**) or π-(**2**) type. In the first case, **1**, the unpaired electron is located on one of the nitrogen lone pair σ-orbitals. The reactivity would resemble that of the phenyl radical. In the second case, **2**, it embraces all the five heterocycle atoms, and the situation would correspond to the behavior of a typical amino radical. The ESR spectra (73JPC1629) and theoretical computations (76T1555, 89JA7740) are in favor of the π-radical. Since imidazole is close to the π-neutrality, the possibility of the η^5-donor function cannot be excluded completely. The imidazolate anion ligand is known as an electron-transfer promoter (83PIC1, 87IC4148).



1 **2**

Nucleophilic imidazol-2-ylidene carbene ligands (62AGE75) deserve special attention among Fischer carbenes (00CRV3591). They are characterized by the strong σ-donor character (83MI1) and strong basicity exceeding that of phosphines, although poor π-acceptor properties (97AGE687). Moreover, they

are stable (68JA5457, 84JHC1785, 90JCS(P2)51, 91AGE674, 91JA361, 91JPC4180, 92JA5530, 93S561, 94CEJ20, 94JA6812, 94TL1365, 95JA572, 95JA11027, 96AGE725, 96CEJ114, 96CEJ229, 96CEJ772, 96JA2023, 96JA2039, 96TL149, 97AGE1478, 97AGE1709, 97AGE2607, 97AGE2719, 97CEJ232, 97JA12742, 97LAR305, 98AGE1963, 98OM2352, 98OM5801, 99ACR913, 99CEJ1590, 99OM1862, 99TL2057, 00JOM(608)122), easily form stable adducts with nontransition and transition metal compounds (64AGE580, 68AGE950, 74AG651, 83ZN(B)1313, 83ZN(B)1598, 91JA9704, 92JA9724, 93CB2041, 93CB2047, 93IC1541, 93JCS(CC)1136, 93JCS(CC)1778, 93ZN(B)973, 94JOM(480)C7, 95OM1085, 95PIC1, 97AGE2162, 99TL14523, 00AGE4036, 00JOM(600)12), and constitute a group of new valuable catalysts (81MI1, 84JOM(264)117, 95AGE2371, 95AGE3005, 95JOM(498)114, 96AGE725, 96AGE2805, 96MI1, 96OM2434, 97AGE2631, 97CB1253, 97JMC(A)L1, 97JOM(543)249, 97JOM(547)357, 97JPC397, 97T(A)3571, 98AGE1124, 98AGE2490, 98EJIC913, 98JCS(CC)869, 98JOM(557)93, 98OM1608, 99ADOC175, 99AGE262, 99JCS(CC)241, 99JOC3804, 99JOM(576)239, 99OL1307, 99OM1596, 00AGE1602, 00AGE3898, 00CEJ1773, 00CRV39, 00CRV1565, 00JOC2204, 00OM1123, 00SCI834).

One method to transform imidazolium salts (00AGE3773) into carbene ligands, imidazol-2-ylidenes, is by deprotonation with sodium hydride or other suitable hydride in a mixture of THF and liquid ammonia (73JCS(D)514, 96CEJ1627, 98IC6412).

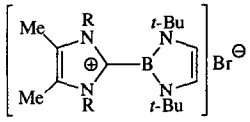
The structural features of imidazol-2-ylidenes (decreased NCN angle at the carbene center and long C_2–$N_{1(3)}$ bonds show that these compounds are characterized by a π-delocalization significantly lower compared to that of their precursors, the imidazolium salts (86SCI1100, 91JPC4180). The stabilizing factors for these carbenes are the π-donor effect of the N_1–C_4=C_5–N_3 system on the out-of-plane p-orbital of the carbene center (C_2) and influence of the σ-electronegativity (62AGE75, 94JA6641) as well as the steric effect of the 1,3-substituents such as adamantyl (91JA361, 98CZ6). However, π-electron delocalization cannot be the stabilizing factor (93IJQC(S)309, 94CPL(217)11, 94JA6361, 94JA6812, 96LAC2019, 96TCA(93)17, 96ZN(A)951). These compounds are nucleophilic and lack electrophilic reactivity.

Carbenes have an enhanced Lewis basicity, and adducts are characterized by the negligible π-back-bonding and high metal-ligand bond strength (96AGE1121, 98JA11526). An interesting perspective may be elaboration of the silicon and germanium analogs of imidazol-2-ylidenes, where Si or Ge atom replaces the nucleophilic carbon center (92AGE1485, 00JOM(600)168, 00OM3263, 00OM4726). These will be considered in a separate chapter devoted to analogs of azoles.

B. Nonmetal and Non-transition Metal Organometallic Complexes of Imidazoles

1,3-Dimesitylimidazol-2-ylidene forms a stable adduct with 1,3-dimesitylimidazolium hexafluorophosphate or triflate (95JA572). Another adduct of this nature contains the C–C bond and follows from 1,3-R_2-4,5-dimethylimidazol-2-ylidene (R=Me, Et, *i*-Pr) and pentafluoropyridine (98ZN(B)881). 1,3,4,5-Tetramethyl- and 1,3-di-*iso*-propyl-4,5-dimethylimidazol-2-ylidene with 1-bromo-2,5-di-*tert*-butyl-1,3-diazaborole form adducts **3** (97CB705). 1,3-R_2-4,5-Dimethylimidazol-2-ylidenes (R=Me, Et, *i*-Pr) react with CS_2, and the di-*iso*-propyl derivative also reacts with CO_2 to yield the adducts **4** (R=Me, Et, *i*-Pr; X=S; R=*i*-Pr, X=O) (94ZN(B)1473, 97JCS(CC)627, 99ZAAC851, 99ZN(B)427, 99ZN(B)434). 1,3-Di-*iso*-propyl-4,5-dimethylimidazol-2-ylidene forms the adduct **5** (X=Cl) with diphenylchlorophosphine and **5** ($X=AlCl_4$) if this reaction is run in the presence of aluminium trichloride (99ZAAC729).

The neutral C–P carbene adduct is formed from 1,3-dimesitylimidazol-2-ylidene and $PhPF_4$ (97JA3381). The nucleophilicity of imidazol-2-ylidenes is so strong that they appear to be able to depolymerize $(PPh)_5$, $(PCF_3)_4$, $(AsPh)_6$, and $(AsC_6F_5)_4$, and form the corresponding adducts (97ACR445, 97CL143, 97IC2151, 97JCS(CC)981). 1,3-Di-*iso*-propyl-4,5-dimethylimidazol-2-ylidene (L) with sulfur dichloride or thionyl chloride gives adducts $[ECl_2(L)]$ (E=S, S=O) (96CB1579). Selenium and tellurium adducts are known and prepared from elemental selenium or tellurium (93CB2047, 93HC409, 93ZN(B)973, 99CEJ1931).



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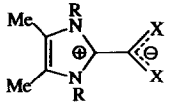

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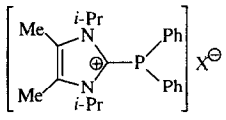
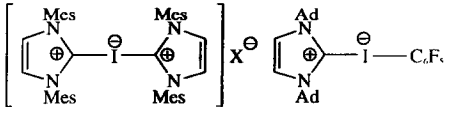


5

1,3-Dimesitylimidazol-2-ylidene with 2-iodo-1,3-dimesitylimidazolium iodide or tetraphenylborate gives the bis-carbene iodine(1+) complexes **6** (X=I, BPh_4) (94JA3625). Other iodide complexes are **7** and **8** (R=H, Me; X=I, I_3) (91JA9704). The structural proof of **8** (X=I) is provided (93JCS(CC)1778). Related dichlorine adducts can be made from 1,3-R_2-4,5-dimethylimidazol-2-ylidenes (R=Me, Et, *i*-Pr) and 1,2-dichloroethane (98ZN(B)720). In this respect, it is interesting that 1,3-di-*iso*-propyl-4,5-dimethylimidazol-2-ylidene with SO_2Cl_2, SO_2FCl, SO_2F_2 and SF_4 forms the carbene species **9** (X=Cl, Y=SO_2Cl, SO_2F; X=F, Y=SO_2F, SF_3) (94JCS(CC)2283).



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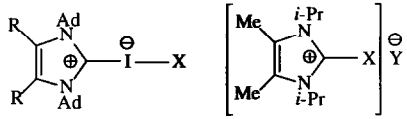
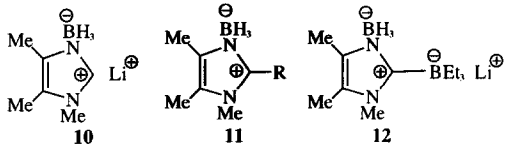


8 9

Lithiated imidazol-2-ylidenes are presented as dimers or tetramers (95AGE4, 97CB1201, 97CB1213). Lithium is coordinated via the carbene carbon and the N3 atom simultaneously. 1,3-Dimethylimidazol-2-ylidene (L) reveals strong σ-donor properties in the species $[ClBeL_3]Cl$ (95JOM(501)C1). 1,3-Bis(1-adamantyl)imidazol-2-ylidene and 1,3-dimesitylimidazol-2-ylidene with Et_2Mg and Et_2Zn form the stable 1:1 adducts of the carbene type (93JOM(462)13).

1,4,5-Trimethyl-3-boraneimidazole (98EJIC843) on lithiation with *n*-butyllithium gives the anionic carbene **10**. With bis(dimethylamino)chloroborane it forms **11** ($R = B(NMe_2)_2$). Numerous other azoles may be prepared in the same way (99EJIC789). Adduct-formation occurs when **10** reacts with triethylborane to yield **12**.

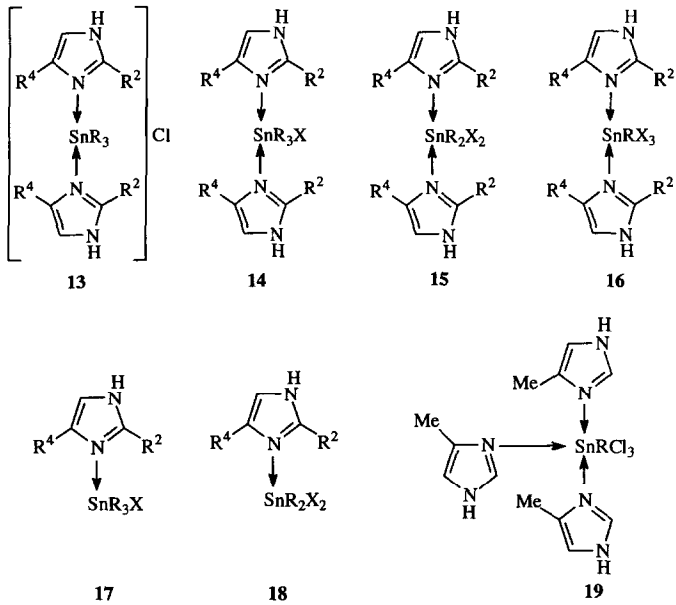


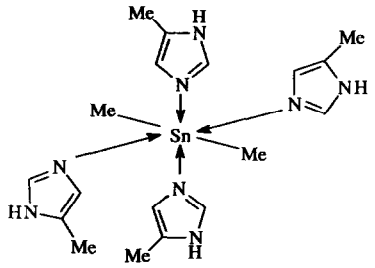
10 11 12

1,3-Bis(mesityl)imidazol-2-ylidene forms the stable alane adduct of the carbene type with $Me_3N{\cdot}AlH_3$ (92JA9724). The range of alane and gallane complexes known is broader and includes, for example, the adducts of 1,3-di-*iso*-propyl-4,5-dimethyl-imidazol-2-ylidene with trimethyl alane and trimethyl gallane (96JCS(CC)2683). 1,3-Di-*iso*-propyl-4,5-dimethylimidazol-2-ylidene also forms stable carbene adducts with $InCl_3$, $InBr_3$, and InH_3 (97JCS(D)4313, 98JCS(CC)869, 98JCS(D)3249). 1,3-Dimesitylimidazol-2-ylidene forms the InH_3 1:1 carbene adduct by reacting with $LiInH_4$ or $InH_3(NMe_3)$ (00OM4852). With quinuclidine hydrochloride, this adduct is converted into the corresponding InH_2Cl-derivative, and with dichloromethane it gives the $InCl_3$-derivative. Imidazol-2-ylidene complexes with main group metallocenes are known (98OM3375).

Tetrachorosilane monomeric complexes of the carbene type with imidazol-2-ylidenes are known (95CB245), as well as the adducts with ER_2 (E=Si, R=1, 2-$(NCH_2(t\text{-Bu}))_2C_6H_4$; E=Ge, R=I; E=Sn, R=Cl; E=Sn, Pb, R=2,4,6-$(i\text{-Pr})_3C_6H_2$) (95CB245, 95JCS(CC)1157, 99JCS(CC)755, 99JCS (CC)1131). The 1:1 adduct with germanium(II) iodide is also known (93IC1541).

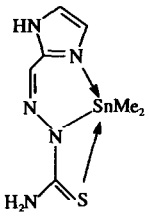
Organotin derivatives of 2- and 4-methyl-, 2-*iso*-propyl, 4-phenyl-, 1-benzyl-, and 1-methylimidazole form a wide range of different species (92ICA(191)75, 95JOM(493)107, 96JOM(515)119, 96P1263, 98P561). 2- and 4-Methyl as well as 2-*iso*-propylimidazole with organotin(IV) compounds R_nSnX_{4-n}(R=Me, Et, *n*-Bu, Ph; X=Cl, Br; *n*=1–3) yield **13** (R^2=Me, R^4=H, R=Me; R^2=H, R^4=Me, R=Me, *n*-Bu), **14** (R^2=H, R^4=Me, R=Me, X=Cl; R^2=*i*-Pr, R^4=H, R=Me, Ph, X=Cl), **15** (R^2=Me, R^4=H, R=Me, X=Cl; R^2=H, R^4=Me, R=Me, Et, *n*-Bu, X=Cl, Br, R=Ph, X=Cl; R^2=*i*-Pr, R^4=H, R=Me, X=Cl), **16** (R^2=Me, R^4=H, R=*n*-Bu, Ph, X=Cl; R^2=H, R^4=Me, R=Me, X=Cl), **17** (R^2=H, R^4=Me, R=Ph, X=Cl; R^2=*i*-Pr, R^4=H, R=Me, Ph, X=Cl), **18** (R^2=*i*-Pr, R^4=H, R=Ph, X=Cl), and **19** (98P561). Compound **15** (R^2=Me, R^4=H, R=Me, X=Cl) can be converted to **15** (R^2=Me, R^4=H, R=Me, X=I, ONO_2) by the reaction with sodium iodide or silver nitrate, respectively. With sodium tetraphenylborate, however, complex **20** is obtained.





20

Imidazole-2-carbaldehyde thiosemicarbazone forms the *N,N,S*-chelate complex **21** upon reaction with dimethyltin oxide (00JCS(D)2267).

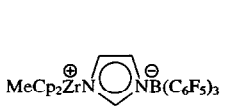


21

C. Organotransition Metal Complexes of Imidazoles

1. *Titanium, Chromium, and Manganese Groups*

Imidazole reacts with dimethylzirconocene in the presence of a strong Lewis base, tris(pentafluorophenyl)borane, to yield the betaine species **22** (96JOM(518)17), which when exposed to the atmosphere is hydrolyzed to **23**.



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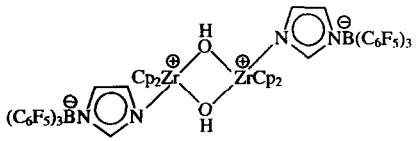
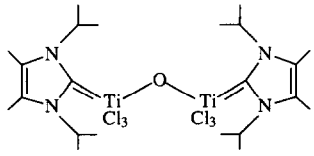


23

1,3-Dimethylimidazol-2-ylidene (L) complexes $MCl_4 \cdot 2L$ (M = Ti, Zr, Hf) are known (94JOM(480)C7). 1,3-R_2-4,5-Dimethylimidazol-2-ylidenes (R = Me, Et, *i*-Pr) with $TiCl_4$ form the C-coordinated carbene species $TiCl_4 \cdot L$

(95ICA(238)179). Further reaction of the 1,3-di-*iso*-propyl-derivative with water gives the dinuclear species **24**.



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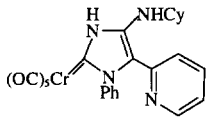
Basic method of preparation of the imidazol-2-ylidene carbene complexes starts with the heterocycles in their cationic or carbene form (74JCS(D)102, 74JCS(D)760, 75JOM(100)139, 83AGE993, 83JOM(259)C21, 88JOM(358)185, 89JOM(375)147, 90JCS(CC)1722, 93CRV1243). A special synthetic technique for the preparation of homoleptic carbene complexes is the cyclization reaction based on isocyanide metal precursors and amines (72IC2069, 74AGE599, 82ZN(B)1044, 85CB2235, 85JA2171, 86ZN(B)1005, 92ZN(B)79). The imidazol-2-ylidene carbene complexes **25** and **26** prepared by cyclization reaction are known (94ICA(222)275, 95JOM(491)135). Another representative, **27**, on decomplexation releases imidazole **28** (94ICA(222)275).



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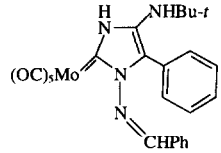

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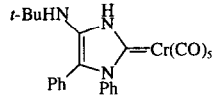

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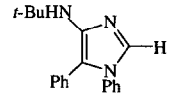
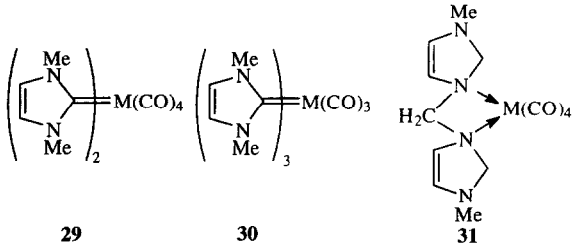


28

1,3-Dimethylimidazolium iodide with $K_4[M_4(\mu_3\text{-}OMe)_4(CO)_{12}]$ (M = Cr, Mo, W) gives the bis-carbenes **29** (92CB1795, 95JOM(498)1). With $[M(CO)_3(AN)_3]$, it gives the tris-carbenes **30** (M = Cr, Mo, W). Under the similar conditions 1,3-bis(methylimidazol-2-ylidene)methylene gives **31**.

1,3-Bis(arylmethyl)imidazol-2-ylidene (aryl = phenyl, naphthyl) with tungsten hexacarbonyl produces the products of monosubstitution of the carbonyl group with the η^1(C)-coordinated carbene ligand (97OM2472). Analogues of these complexes are known (94JOM(470)C8, 94JOM(479)C32, 96CEJ772),

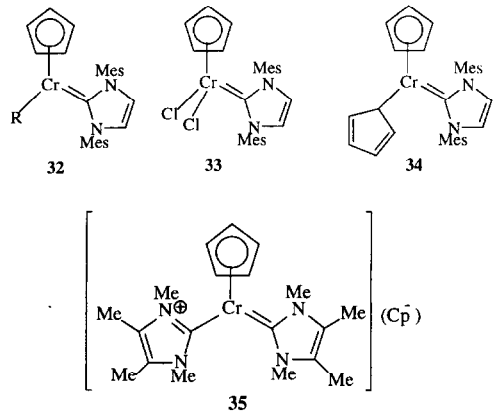


29 30 31

e.g. 1,3,4,5-tetramethylimidazol-2-ylidene with $M(CO)_6$ (M = Cr, Mo, W); 1,3-diethyl-4,5-dimethylimidazol-2-ylidene and 1,3-di-*iso*-propyl-4,5-dimethylimidazol-2-ylidene with $W(CO)_6$ (94JOM(470)C8).

1,3-Dimethylimidazolium salt of anion $[HCr(CO)_5]^-$ gives the $Cr(CO)_5^-$ carbene complex (69AGE916, 70JOM(22)C9, 00EJIC1377). The carbene complex $[(\eta^1(C)\text{-}1,3\text{-dimethylimidazol-2-ylidene})_2Mo(CO)_4]$ (70AGE739, 76CB1749, 76JA6735) enters the photochemical substitution with pyridine to yield $[(\eta^1(C)\text{-}1,3\text{-dimethylimidazol-2-ylidene})_2Mo(CO)_3(py)]$ (80AGE538). The pyridine ligand in the latter is easily replaced by CyNC, PEt_3, and PPh_3. Imidazol-2-ylidene complexes of this nature are quite spread (68AGE141, 68JOM(12)P42, 69AGE916, 70CB177, 70CB1037, 70LAC176, 72CRV545, 73ZN(B)306, 76CB1749, 76ZN(B)1070).

1,3-Dimesitylimidazolium chloride with chromocene gives the carbene **32** (R = Cl) (99OM529). With phenylmagnesium chloride, **32** (R = Cl) gives **32** (R = Ph), the product of substitution of the chloride ligand by phenyl radical. In chloroform, **32** (R = Cl) gives the chromium(III) species **33**. In contrast, 1,3-dimesitylimidazol-2-ylidene with chromocene gives **34** (99JA2329), a 14-electron but thermally stable species. 1,3,4,5-Tetramethylimidazol-2-ylidene and chromocene give the bis-carbene **35**.

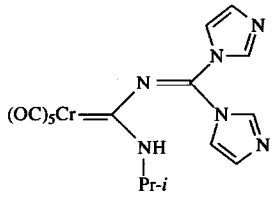


32 33 34 35

1,3-Dimethylimidazol-2-ylidene (L) with $MO_2Cl_2(THF)_2$ forms the adducts $[L_3MO_2Cl]Cl$ and $[L_2MO_2Cl_2]$ (M = Mo, W) (96JOM(520)231).

Compound $[(\eta^6\text{-}C_6H_6)Mo(py)_3]PF_6$ with *N*-methylimidazole yields the N-coordinated $[(\eta^6\text{-}C_6H_6)Mo(1\text{-}MeimH)_3]PF_6$ (78JCS(CC)1009, 79IC1835). Imidazole with $[(\eta^5\text{-Cp})M(CO)_3Cl]$ (M = Mo, W) gives $[(\eta^5\text{-Cp})M(CO)_2(imH)_2]Cl$ or $[(\eta^5\text{-Cp})M(CO)_2(imH)Cl]$ (77IC3372). The nature of the product depends on the ratio of the reactants.

Imidazole with $[Cr(CO)_5CNCCl_3]$ gives a simple product of substitution of three chlorine atoms followed by deprotonation, $[Cr(CO)_5CNC(im)_3]$ (95JOM(489)27). The product reacts further with *iso*-propylamine and pyrrolidine to give amino(alkylideneamino)carbenes **36** and **37**, respectively.



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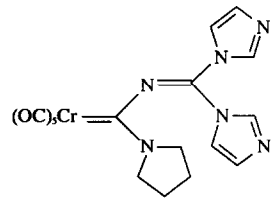
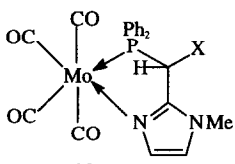


37

2-Diphenylphosphinomethyl-1-methylimidazole (99JCS(D)1655) with $Mo(CO)_6$ gives the chelate complex **38** (X = H) where the ligand is coordinated via the nitrogen heteroatom and the phosphorus site (99JCS(D)3499). The product has a versatile reactivity pattern via the methylene hydrogen: lithiation with methyl or *n*-butyl lithium to give **38** (X = Li); deuteration of the lithium derivative by D_2O to yield **38** (X = D); alkylation with methyl or ethyl iodide to **38** (X = Me, Et); derivatization of similar nature by allyl bromide, trimethylchlorosilane, diphenylchlorophosphine, and benzoyl chloride to afford, respectively, **38** ($X = CH_2CH{=}CH_2$, $SiMe_3$, PPh_2, COPh). Acetyl chloride produces species **39**.



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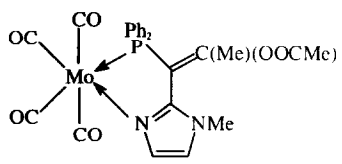
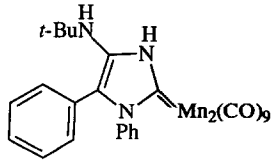


39

Imidazole with $[Re(CO)_3(phen)Cl]$ or $[Re(CO)_3(phen)(CF_3SO_3)]$ in the presence of sulfuric acid gives $[Re(CO)_3(phen)(im)]_2SO_4$ (95ICA(240)169). Imidazole with $[Mn_2(CO)_{10}]$ gives $[Mn_2(CO)_9(imH)]$ (84P707). This path involves the nucleophilic substitution of the carbonyl ligand. However, it is complicated by some redox

transformations (81JOM(214)C11, 81JOM(214)C13, 81ZN(B)400). Among their products are $[Mn(imH)_4(solv)][Mn(CO)_5]_2$ (solv = EtOH, THF) (84P707).

Reaction of *tert*-butyl isocyanide, benzaldehyde, aniline hydrochloride, and $(NEt_4)[Mn_2(CO)_9(CN)]$ gives the imidazole carbene complex **40** (95JOM (491)135). The [2 + 2 + 1] cyclization occurs between $[(\eta^5\text{-Cp})Mn(CO)_2(\equiv CPh)]^+$ and excess $N\equiv CNR_2$ (R = Me, Et, *i*-Pr) to yield the η^2-coordinated imidazolium complex **41** (93MI1).



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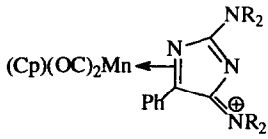


41

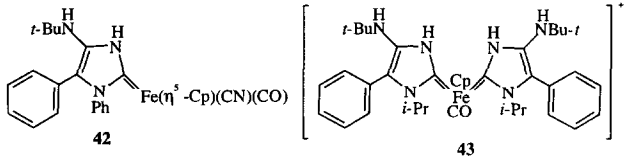
2. *Iron Group*

Imidazole with $[Fe(CO)_5]$, $[Fe_2(CO)_9]$, and $[Fe_3(CO)_{12}]$ gives the products of nucleophilic substitution of the carbonyl group, $[Fe(CO)_4(imH)]$ accompanied in the latter cases by the fission of the iron–iron bond (83JOM(241)C41). The parallel redox pathway (71DAN1112) gives $[Fe(im)_6][Fe_3(CO)_{11}]$ (84P707). With ferrocene, molten imidazole gives $[Fe_3(im)_6(imH)_2]$ (97JA8675).

Imidazole is able to substitute for carbon monoxide in $[Fe(NO)_2(CO)_2]$ to yield $[Fe(NO)_2(CO)(imH)]$ (68JA2536). 1-Formylimidazole with $Na_2[Fe(CO)_4]$ in the presence of trimethoxyboron gives $NaFeCHO(CO)_4$ and the adduct of imidazolate of composition $NaC_3H_3N_2 \cdot 2B(OMe)_3$ (82JA627). *N*-Methylimidazole substitutes the iodide ligand in the μ-silanediyl complex $[(\eta^5\text{-Cp})(OC)Fe(\mu\text{-CO})(\mu\text{-}t\text{-BuSiI})Fe(CO)(\eta^5\text{-Cp})]$ to yield $[(\eta^5\text{-Cp})(OC)Fe(\mu\text{-CO})(\mu\text{-}t\text{-BuSi(N-Meim)})Fe(CO)(\eta^5\text{-Cp})]$(I) (91AGE843). 1-Methylimidazole (L) with sulfur and $Fe(CO)_5$ gives $[FeL_6](S_8)$ (92IC153). With less amount of sulfur, $[FeL_6][Fe_2S_{12}]$ results. Another example is the interaction of 2-methylimidazole (L) with $[Fe(N_4)(AN)(CO)]$ (N_4 is the tetradentate macrocycle, bis-difluoro(dimethylglyoximato)borate) to yield $[Fe(N_4)L_2]$, the product of substitution of both carbon monoxide and the solvent (91ICA (188)139).

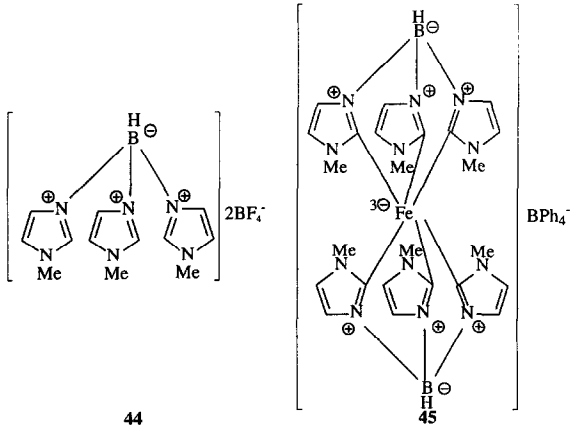
1,3-Dimethylimidazol-2-ylidene (L) is able to substitute an axial carbonyl group of $[Fe(CO)_5]$ to yield $[(\eta^1(C)\text{-L})Fe(CO)_4]$ (72CB529, 72CB2714). Another route to this complex is the rearrangement of the 1,3-dimethylimidazolium salt bearing the anion $[HFe(CO)_4]^-$ (72CB529). $[(\eta^1(C)\text{-L})Fe(CO)_3(PEt_3)]$ is also known (86JOM(315)27).

Cyclization takes place when *tert*-butylisocyanide, benzaldehyde, anilinium chloride, and carbonyl(dicyano)cyclopentadienyl ferrate are reacted, the carbene complex **42** being the result (95JOM(491)135). *Iso*-butyraldehyde, *tert*-butyl isocyanide, ammonium hexafluorophosphate, and $[(\eta^5\text{-Cp})Fe(CO)(CN)_2]^-$ give the cationic bis-carbene **43**.



42 43

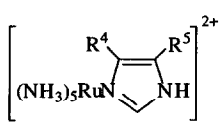
It is noteworthy that carbene function may be manifested in the derivatives of tris(imidazol-1-yl)borate **44** (96AGE310). Its reaction first with *n*-butyllithium, then with iron(II) chloride, and finally with sodium tetraphenylborate gives the iron(III) carbene derivative **45**.



44 45

The acid-catalyzed aquation of complexes **46** ($R^4 = R^5 = H$, Me; $R^4 = H$, $R^5 =$ Me) gives the η^1(C)-coordinated carbene derivatives **47** ($R^4 = R^5 = H$, Me; $R^4 = H$, $R^5 =$ Me; L = H_2O) (74JA381). Carbonylation of the product gives **47** ($R^4 = R^5 =$ H, Me; $R^4 = H$, $R^5 =$ Me; L = CO). Benzimidazole forms similar products and is also characterized by the re-switch of the coordination mode.

1,3-Dimesitylimidazolium chloride in the presence of potassium *tert*-butylate reacts with $[RuCl_2(PCy_3)_2(=CHPh)]$ or $[RuCl_2(PCy_3)_2(=CHCH=CMe_2)]$ to yield the mixed phosphine–carbene complexes $[RuCl_2(L)(PCy_3)(=CHPh)]$ or



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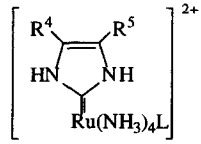
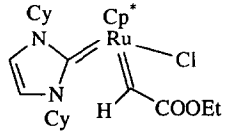


47

$[RuCl_2(PCy_3)(L)(=CHCH=CMe_2)]$, where L is 1,3-dimesitylimidazol-2-ylidene (00OM2055). 1,3-Dimethylimidazol-2-ylidene (L) and $[(\eta^6\text{-}p\text{-}MeC_6H_4Pr\text{-}i)ClRu(\mu\text{-}Cl)RuCl(\eta^6\text{-}p\text{-}MeC_6H_4Pr\text{-}i)]$ give the mononuclear η^1(C)-coordinated carbene complex $[(\eta^6\text{-}p\text{-}MeC_6H_4Pr\text{-}i)RuCl_2L]$ (96CEJ772). Similar reactions are known (99OM3760). This ligand with $[(OC)_4Os(\mu\text{-}Cl)_2Os(CO)_4]$ affords $[(OC)_4OsCl(L)]$ of the same nature. A series of complexes $[RuCl_2(=CHPh)L_2]$ where L is 1,3-dicyclohexyl-, 1,3-di(1-phenylethyl)-, or 1,3-di(1-naphthylethyl) imidazol-2-ylidene is known (98AGE2490). Reaction of the same ligands (L) with $[RuCl_2(=CHPh)(PCy_3)_2]$ gives a series $[RuCl_2(=CHPh)(PCy_3)L]$ (99JOM (582)362). When L is 1,3-dicyclohexylimidazol-2-ylidene, the product further reacts with $[(\eta^6\text{-}p\text{-cymene})RuCl_2]_2$ and yields $[(\eta^6\text{-}p\text{-cymene})ClRu(\mu\text{-}Cl)_2RuCl(=CHPh)(L)]$ (99AGE2416). $[RuCl_2(=CHPh)L_2]$ (L = 1,3-dicyclohexylimidazol-2-ylidene) reacts with $[(\eta^5\text{-}Cp^*)RhCl_2]_2$ to give the heterodinuclear species $[(\eta^5\text{-}Cp^*)ClRh(\mu\text{-}Cl)_2RuCl(=CHPh)(L)]$. 1,3-Dicyclohexyl-, 1,3-di-*p*-tolyl-, 1,3-bis(4-chlorophenyl)-, 1,3-diadamantyl-, 1,3-dimesityl-4,5-dichloroimidazol-2-ylidenes (L) react with $[(\eta^5\text{-}Cp^*)RuCl]_4$ to give the coordinatively unsaturated carbenes $[(\eta^5\text{-}Cp^*)Ru(L)Cl]$ (98JCS(CC)1315, 99JA2674, 99JA9899, 99JOM(586)263, 99OM2370, 99OM5375). Other imidazol-2-ylidene ruthenium compounds are also known (99TL2247, 99TL4787).

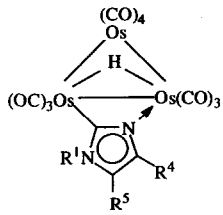
1,3-R_2-Imidazolium chloride (R = Cy, Mes) with $[(\eta^5\text{-}Cp^*)Ru(OMe)]_2$ give the 16-electron monocarbenes $[(\eta^5\text{-}Cp^*)Ru(L)Cl]$, where L is the relevant imidazol-2-ylidene (00JOM(593)489). Addition reactions of carbon monoxide, triphenylphosphine, and pyridine to the coordinatively unsaturated $[(\eta^5\text{-}Cp^*)Ru(L)Cl]$ (L = 1,3-dicyclohexylimidazol-2-ylidene) give the 18-electron species $[(\eta^5\text{-}Cp^*)Ru(L)(L')Cl]$ (L′ = CO, PPh_3, py). With ethyl diazoacetate, the mixed carbene complex **48** follows, where both nucleophilic and electrophilic carbenes are present in the coordination sphere.



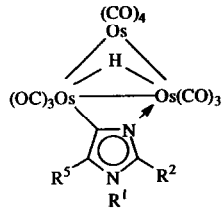
48

Imidazole with $[(\eta^6\text{-}C_6H_6)RuCl_2]_2$ in the presence of sodium methylate gives most probably the tetrameric $[(\eta^6\text{-}C_6H_6)RuCl(\mu\text{-im})]_4$ where the imidazolate anion performs the *N*, *N*-bridging function (93ICA(206)15).

Imidazole and *N*-methylimidazole with $[Os_3(CO)_{10}(AN)_2]$ produce a mixture of two isomers, major, **49** (R^1 = H, Me; $R^4 = R^5$ = H), and minor, **50** (R^1 = H, Me; $R^2 = R^5$ = H) (82IC634, 83JOM(256)349, 84P1175). 4(5)-Methylimidazole gives **49** ($R^1 = R^4$ = H, R^5 = Me), **49** ($R^1 = R^5$ = H, R^4 = Me), and **50** ($R^1 = R^2$ = H, R^5 = Me). 2-Methylimidazole gives a single isomer **50** ($R^1 = R^5$ = H; R^2 = Me). More detailed study shows that 1-vinylimidazole and imidazole at the first stage of the process of interaction with $[Os_3(CO)_{11}(AN)]$ gives the η^1(N)-coordinated species **51** (R = H, Vin) (95JOM(492)135). Thermolysis of the products gives isomers **49** and **50** where R^1 = H, Vin; $R^2 = R^4 = R^5$ = H. With $Ru_3(CO)_{12}$, imidazole and 1-vinylimidazole form analogs of isomer **49**.



49



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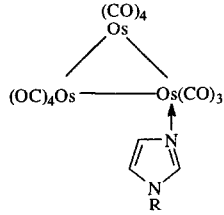
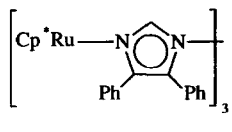
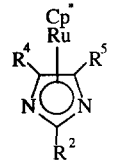


51

Potassium 4,5-diphenylimidazolate with $[Cp^*RuCl]_4$ gives the trimer **52** containing the μ-η^1 : η^1 mode (00OM5263), which under reflux gives the η^5-coordinated species **53** ($R^4 = R^5$ = Ph, R^2 = H). The structure of the latter was confirmed by X-ray analysis. In similar conditions 2,4-dimethylimidazole gives species **53** ($R^2 = R^4$ = Me, R^5 = H) straightforwardly.

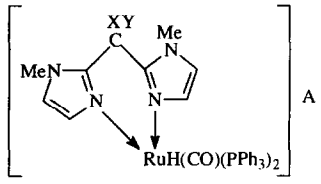


52



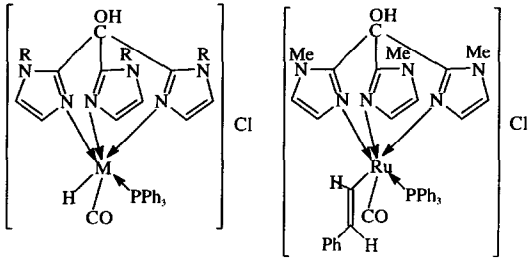
53

Bis-imidazole ligands based on 1-methylimidazol-2-yl framework with $[Ru(PPh_3)HCl(CO)]$ yield complexes **54** (XY = (=O), A = Cl, BF_4; XY = HOH, A = Cl, OH; XY = HH, A = Cl) (97JCS(D)2341). The BF_4 complex follows from **54** (XY = (=O), A = Cl) and sodium tetrafluoroborate, while the OH derivative — from **54** (XY = HOH, A = Cl) and water.



54

Tris(1-methylimidazol-2-yl)methanol and tris(1-ethoxymethylimidazol-2-yl)methanol with $[M(PPh_3)_3HCl(CO)]$ (M = Ru, Os) give species **55** (R = Me, CH_2OEt; M = Ru, Os) (97JOM(538)119). One of the products (R = Me, M = Ru) with phenylacetylene forms the alkenyl **56**.

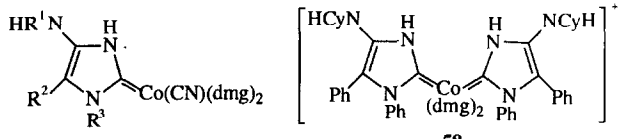


55 56

In the complex $[(\eta^6\text{-}p\text{-}MeC_6H_4Pr\text{-}i)ClRu(\mu_2\text{-}HL)(\mu\text{-}Cl)Ru(\eta^6\text{-}p\text{-}MeC_6H_4Pr\text{-}i)]$, 4,5-diphenylimidazole-2-thiol (HL) performs the chelating and bridging functions simultaneously (93ICA(208)145). Besides, the trinuclear C-metallated species $[Ru_3(\mu\text{-}L)(\mu\text{-}Cl)Cl_2(\eta^6\text{-}p\text{-}MeC_6H_4Pr\text{-}i)_3]$ can be formed.

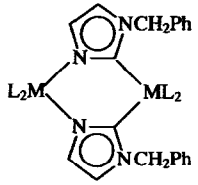
3. *Cobalt Group*

Cyclization of aldehyde, isonitrile, amine hydrochloride, and $(n\text{-}Bu_4N)[Co(CN)_2(dmgH)_2]$ depending on the nature and amounts of the reactants gives neutral carbenes, **57** (R^1 = Cy, R^2 = Ph, *p*-Tol, R^3 = Ph; R^1 = *t*-Bu, R^2 = *p*-Tol, R^3 = Ph), or cationic bis-carbene **58** (95JOM(491)135).



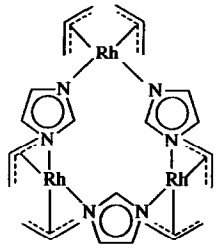
57 58

The mononuclear species $[(\eta^4\text{-cod})MCl(1\text{-}PhCH_2im)]$ (M = Rh, Ir) are known (83AGE993, 89JOM(369)253). Imidazolato ligands tend to form the *N,N'*-bridged complexes of high nuclearity with rhodium(I) and iridium(I) (81JOM(221)249, 81TMC103, 82JOM(224)207, 85TMC28), for example $[M_x(\mu\text{-im})_x(L_2)_x]$ (M = Rh, Ir; L_2 = cod, $(CO)_2$, x = 3, 4) or $[Rh_4(\mu\text{-2-Meim})_4(CO)_8]$ (82JOM(224)207). Lithium 1-benzylimidazolate with $[M(\mu\text{-Cl})L_2]_2$ (M = Rh, L_2 = cod, nbd; M = Ir, L_2 = cod) yields the N^3, C^2-coordinated dinuclear species **59** (94JOM(465)267). Carbonylation gives **59** (M = Rh, Ir; L = CO).



59

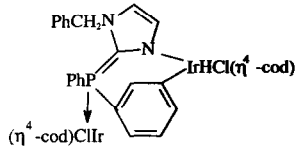
Imidazole with $[(\eta^3\text{-}C_3H_5)_2Rh(acac)]$ gives the trinuclear complex **60** (86JCS(D)2193).



60

1-Benzyl-2-imidazolyldiphenylphosphine with the dimer $[(\eta^4\text{-cod})Ir(\mu\text{-Cl}]_2$ gives the iridium(I)–iridium(III) complex **61**, in which the C–H bond activation has occurred (00OM3115). In excess ligand complex **62** results, which can regenerate **61** on addition of the starting iridium(I) dimer. The reaction of species **62** with $[(\eta^4\text{-cod})(AN)_2](BF_4)$ gives **63** with the P,N-coordination of the imidazole ligand.

1,3-Dimethylimidazol-2-ylidene (L) with $[(\eta^4\text{-cod})M(\mu\text{-Cl})]_2$ give the carbene species $[(\eta^4\text{-cod})M(L)Cl]$ (M = Rh, Ir) (96CEJ772). Carbonylation of the rhodium complex gives $[Rh(CO)_2(L)Cl]$. Excess the imidazol-2-ylidene produces $[(\eta^4\text{-cod})ML_2]Cl$, and metathesis with silver acetate yields $[(\eta^4\text{-cod})ML_2](MeCOO)$. Complex $[(\eta^4\text{-cod})RhL_2]Cl$ has a *cis*-geometry with respect to the carbene ligands.



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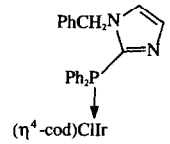
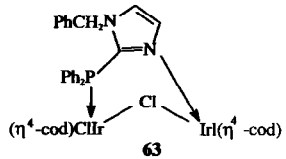
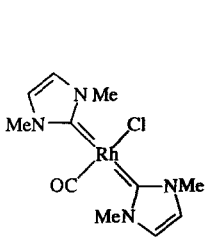


62

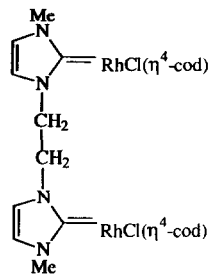


63

On carbonylation in methylene chloride it undergoes the substitution of the diene ligands, rearrangement, and *cis–trans* isomerization to yield **64** (97JOM(530) 259). 1,1′-(1,2-Ethylene)-3,3′-imidazol-2,2′-diylidene and the dimer $[(\eta^4\text{-cod})\text{Rh}(\mu\text{-Cl})]_2$ form the dinuclear species **65**.



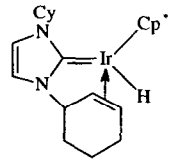
64



65

1,3-Bis(arylmethyl)imidazol-2-ylidene (aryl = phenyl, naphthyl) with the dimer $[(\eta^4\text{-cod})\text{RhCl}]_2$ gives $[(\eta^1(\text{C})\text{-1,3-arylmethyl})\text{Rh}(\eta^4\text{-cod})\text{Cl}]$ (aryl = phenyl, naphthyl) (97OM2472). 1,3-Bis(diphenylmethyl)imidazolium bromide with $[(\eta^4\text{-cod})\text{M}(\mu\text{-OMe})_2\text{M}(\eta^4\text{-cod})]$ (M = Rh, Ir) yields the carbene species $[(\eta^4\text{-cod})\text{M(L)Br}]$, where L is 1,3-bis(diphenylmethyl)imidazol-2-ylidene (97JOM(532)261, 98OM2162). The product (M = Rh) can be carbonylated to yield $[(\text{OC})_2\text{Rh(L)Br}]$, and one of the carbonyl ligands is displaceable by triphenylphosphine or triphenylphosphite.

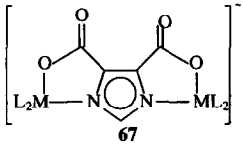
1,3-Dicyclohexylimidazol-2-ylidene (L) and $[(\eta^5\text{-Cp}^*)\text{IrCl}_2]_2$ lead to the monocarbene $[(\eta^5\text{-Cp}^*)\text{IrCl}_2\text{(L)}]$ (00OM1692). Methyl magnesium chloride causes the exchange of the chloride ligands for the methyl groups to yield $[(\eta^5\text{-Cp}^*)\text{IrMe}_2\text{(L)}]$. Reaction of the latter with triflic acid appeared very unusual, and instead of the substitution Me/OTf, the activation of one of the cyclohexyl radicals occurred accompanied by the β-hydrogen migration, formation of the Ir–H bond and appearance of the η^2-coordinated cyclohexenyl compound **66**.



66

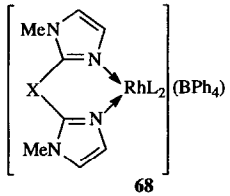
1,3-Dimesitylimidazol-2-ylidene (L) with Wilkinson's complex $[RhCl(PPh_3)_3]$ gives $[RhCl(PPh_3)_2(L)]$, which can be carbonylated to $[RhCl(CO)(PPh_3)(L)]$ (00OM3459). Both carbene species are efficient catalysts of the hydroformylation reaction. Related systems are known (00OM1194).

Rhodium(I) and iridium(I) dinuclear species **67** ($L_2 = (CO)_2$, $(CO)(PPh_3)$, cod) are of interest because of the perspective electroconducting properties in the solid state (87ASI(B)365, 87JCS(D)3003, 88JA7042, 89JCS(CC)1022, 92JCS(D)487). These complexes as well as those of 4,5-dicarboxy-2-methylimidazole are prepared from the appropriate ligand, $[(\eta^4\text{-cod})MCl]_2$ (M = Rh, Ir), and NR_4OH ($R_4 = Me_4$, HEt_3, $n\text{-}Bu_4$) in the presence of triethylamine (87JCS(D)3003). Further carbonylation leads to the complete substitution of the diene ligands. Carbonyl ligands in turn may be partially substituted by the triphenylphosphine molecules. The crystal structure is such that there is the stacking arrangement of the adjacent anionic complexes with rather short metal-metal contacts. Complexes **67** (M = Ir), where as counter-ions $(n\text{-}Bu_4)N^+$ and $(n\text{-}Pr)_4N^+$ are utilized, experience partial oxidation and formation of $(NR_4)[Ir_2(L)(CO)_4]$ (R = *n*-Pr, *n*-Bu; L = 2-methylimidazole-4,5-dicarboxylate), and the electroconducting surface film grows on the electrode. The same feature can be noted for $(TTF)[Rh_2(L)(CO)_4]$. The combinations of 4,4′,5,5′-tetracyano-2,2′-biimidazole (H_2L) (87MI1) anionic complex $[Ir(CO)_2(L)]^-$ (86SC(A)741) with various tetraalkylammonium salts, $(Et_3MeN)[Ir(CO)_2(L)]\cdot 1/2$ AN, $(Et_2Me_2N)[Ir(CO)_2(L)]$, and $(Et_2MeN(CH_2)_4NMeEt_2)[Ir(CO)_2(L)]_2$ possess thermochromic properties (88JA7042). They experience electrochemical oxidation and produce the mixed-valence compounds, e.g. $(NEt_3Me)_4[Ir(CO)_2(L)]_6$, $(NEt_3Me)_5[Ir(CO)_2(L)]_6(BF_4)$, where cation and tetrafluoroborate anion originate from the supporting electrolyte. Species $(NEt_3Me)_4[Ir(CO)_2(L)]_6$ with $[Pt(CN)_2L]^{2-}$ gives $(NEt_3Me)_3[Ir(CO)_2L]_2[Pt(CN)_2L]\cdot 3AN$. Stacking arrangements in this compound are such (85JA279) that it is regarded as a one-dimensional electroconducting alloy.



67

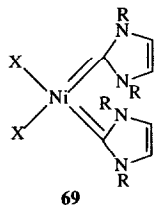
Bis(1-methylimidazol-2-yl)methane and -ketone with the dimer $[Rh(CO)_2Cl]_2$ in the presence of sodium tetraphenylborate give the dicarbonyl complexes **68** (X = CH_2, CO; L = CO) where the carbonyl ligands may easily be substituted by the triphenyl phosphine ligands to yield **68** (X = CH_2, CO; L = PPh_3) (99JOM(588)69). The bis(1-methylbenzimidazol-2-yl)methane analogs of **68** (X= CH_2; L = CO, PPh_3) can be prepared similarly.



68

4. *Nickel Group*

Reaction of 1,3-bis(phenylmethyl)imidazol-2-ylidene with nickel tetra carbonyl gives [(η^1(C)-1,3-bis(phenylmethyl)imidazol-2-ylidene)Ni$(CO)_3$] (97OM2472). Complexes of composition $[Ni(CO)_2L_2]$ with imidazol-2-ylidenes are also known (93JOM(459)177). Another species to be mentioned in this respect is bis(1,3-dimesitylimidazol-2-ylidene)nickel(0) (94JA4391). 1,3-Dicyclohexylimidazol-2-ylidene substitutes triphenylphosphine or THF from $[NiX_2L_2]$ (X = Cl, Br; L = PPh_3, THF) to yield the stable nickel(II) complexes **69** (X = Cl, Br; R = Cy) (97OM2209). Another preparation of nickel(II) derivatives is the interaction of 1,3-dimethylimidazolium iodide with nickel(II) acetate to yield **69** (X = I, R = Me).



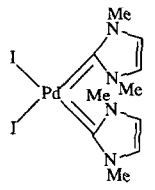
69

1,3-Bis(2,6-dimethyl-4-bromo)imidazol-2-ylidene (L) with nickelocene gives the adduct [(η^5-Cp)(η^1-Cp)NiL] (99JA2329).1,3,4,5-Tetramethylimidazol-2-ylidene (L) and nickelocene give the cationic bis-carbene [(η^5-Cp)NiL_2](Cp). 1,3-Dimesitylimidazolium chloride with nickelocene gives the carbene complex [(η^5-Cp)NiCl(L)] (L = 1,3-dimesitylimidazol-2-ylidene), in which the chloride ligand can be substituted by a methyl group by reacting the product with methyllithium (00JOM(596)3).

1,1′-Methylenebis(3-*tert*-butylimidazol-2-ylidene) and 1,1′-ethylenebis(3-*tert*-butylimidazol-2-ylidene) (L_2) with $[NiCl_2(PMe_3)_2]$ give the cationic carbenes $[(L_2)NiCl(PMe_3)]Cl$ (99OM4584). Further reaction of the methylene derivative with 1,1′-methylenebis(3-*tert*-butylimidazol-2-ylidene) gives the dicationic carbene chelate salt $[(L_2)_2Ni]Cl_2$.

Co-condensation reaction of the vapors of 1,3-di-*tert*-butylimidazol-2-ylidene and nickel, palladium, or platinum gives the coordinatively unsaturated 14-electron sandwiches $[L_2M]$ (M = Ni, Pd, Pt) of the carbene type (99OM3228). Palladium(0) carbene complexes can also be prepared by the direct interaction of 1,3-R_2-imidazol-2-ylidenes (R = *i*-Pr, *t*-Bu, Cy, Mes) (L) with the palladium(0) compound $[Pd(P(o\text{-Tol})_3)_2]$ (00JOM(595)186), and the product at the first stage is $[(L)PdP(o\text{-Tol})_3]$, and then in excess free carbene $[PdL_2]$.

1,3-Dimethylimidazolium iodide and 3,3′-dimethyl-1,1′-methylenebis(imidazolium) diiodide with palladium(II) acetate form the carbene complexes **70** and **71**, respectively (95AGE2371, 96CEJ772, 99OM4082, 00OM1123), which are efficient catalysts for the Heck coupling of aryl halides. 1,1′-Methylene-3,3′-dimethylbis(imidazolium) diiodide or -diethylbis(imidazolium) ditetrafluoroborate with palladium(II) iodide in the presence of *n*-butyllithium give the carbene chelate complexes **72** (R = Me, Et) (95JOM(490)149). 1,3-Dimesitylimidazol-2-ylidene with $[(\eta^4\text{-cod})_2M]$ give the homoleptic 14-electron adducts of the type **72** (M = Ni, Pt; R = Mes) (94JA4391). Precursors **73** (M = Pd, Pt) undergo a unique ring closure reaction to give **74** (94ZN(B)494, 95JOM(490)149). 1,1′-Dimesityl-3,3′-methylenediimidazolium dibromide (L) and palladium(II) acetate lead to $[LPdBr_2]$ (99JOM(572)239). Bromides are easily replaced by iodides using the reaction with sodium iodide. With sodium hexafluorophosphate in acetonitrile medium, $[Pd(AN)_2L](PF_6)_2$ results. This product catalyzes copolymerization of ethylene and carbon monoxide. Some other palladium–iodide carbene complexes are known (96CB1483, 98JOM(554)175, 98JOM(565)165). Homoleptic nickel(II) and palladium(II) complexes of 1,1′-R_2-3,3′-methylenediimidazol-2,2′-ylidene (L_2) (R = Me, *i*-Pr, Cy) follow from the relevant imidazolium iodide salt and nickel or palladium acetate (99JOM(575)80). For nickel, these complexes have the composition $[Ni(L_2)_2]I_2$ (R = Me, *i*-Pr, Cy), for palladium - $[PdL_2I_2]$. The latter in excess imidazolium salt and in the presence of sodium acetate gives $[Pd(L_2)_2]I_2$ (R = Me). Similar reaction course is taken by 1-R-3-R′-imidazolium iodides (R = R′ = $(CH_2)_2C_6F_{13}$, C_8H_{17}; R = $(CH_2)_2C_6F_{13}$, C_8H_{17}, R′ = Me), and it leads to the homoleptic bis-carbenes $[PdL_2I_2]$, where L is the respective imidazol-2-ylidene (00JOM(598)409). 1,3-Bis(2′-pyridyl)imidazolium bromide with palladium acetate gives $[PdL_2Br]Br$ where L = 1,3-bis(2′-pyridyl)imidazol-2-ylidene (00OM5113). The 2′-pyridyl nitrogen of one of the ligands is involved in coordination. The same synthetic ideas can be applied to the synthesis of palladium complexes that originate from the imidazolium linked cyclophanes (01JCS(D)111).



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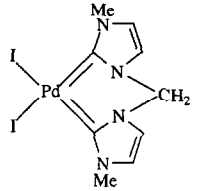

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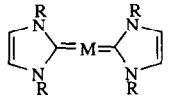

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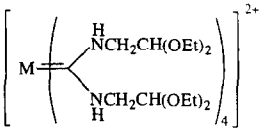

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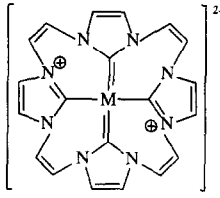
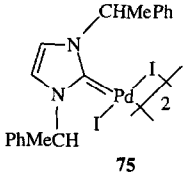


74

Dimeric carbene complex of 1-methylimidazol-2-ylidene (L) has the composition $[PdL_4]_2$ (87CB2031). The carbene complex **75** (96CB1483) with triphenylphosphine gives **76** (99JOM(585)348). Dimer **77** (98JOM(554)175, 98JOM(565)165) with carbon monoxide gives complex **78** (00OM4918).



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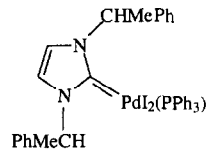

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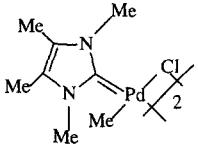

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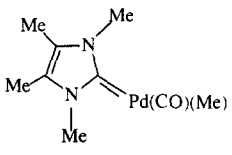
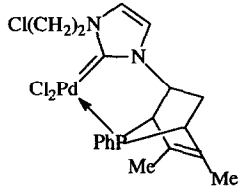


78

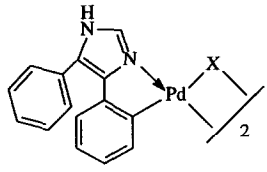
Reaction of the 3,4-dimethyl-1-phenylphosphole (L) complex $[PdL_2Cl_2]$ with 1-vinylimidazole in the presence of silver perchlorate carried out in

dichloroethane is a unique example of Diels–Alder transformation to yield the carbene **79** (98JCS(D)2109).



79

4,5-Diphenylimidazole with palladium acetate forms the cyclometallated complex **80** (X = OAc) (97AOC491). The acetate group is replaced by chloride or bromide when **80** (X = OAc) reacts with sodium chloride or lithium bromide, respectively, to give **80** (X = Cl, Br). Bromide with diethyl sulfide forms the mononuclear complex **81**. Similar reactions are known for 1-acetyl-2-phenylimidazole (96JOM(522)97). 1,5-Bis(*N*-methylimidazol-2-yl)pentane with palladium(II) acetate gives the cyclometallated complex **82** (00JOM (607)194).



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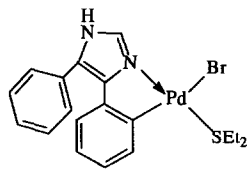

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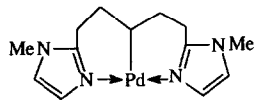
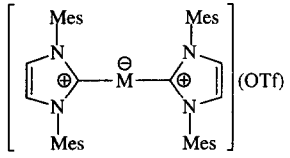


82

5. *Copper and Zinc Groups, Lanthanides*

1,3-Dimesitylimidazol-2-ylidene and copper(I) triflate or silver(I) triflate form the cationic bis-carbene adducts **83** (M = Cu, Ag) (93OM3405). 1-Methylimidazol-2-yllithium reacts first with CuX (X = Cl, I, OTf) and then with methyl triflate (an alkylating agent) to afford the copper(I) mono- and

bis-carbenes of 1,3-dimethylimidazol-2-ylidene (94AGE672, 95JCR(S)184, 95JCS(D)313). 1,3-Diferrocenylimidazolium tetraphenylborate with silver(I) oxide gives the bis-carbene $[L_2Ag](BPh_4)$ (99OM4325). Similarly, the functionalized imidazolium bromides ($R = CH_2COPh$, CH_2COMe) and iodide ($R = CH_2py$) give the dicarbenes **84** ($X = Br$, $R = CH_2COPh$, CH_2COMe; $X = I$, $R = CH_2py$) (00OM741). These serve as a basis for numerous palladium(II) carbene derivatives.



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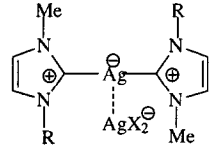
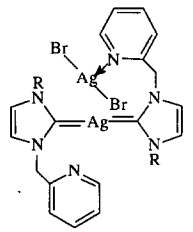


84

A variety of silver(I) carbenes can be prepared by interaction of a series of imidazolium salts with silver(I) oxide or silver(I) carbonate (00JCS(D) 4499). With 3-*tert*-butyl-1-(2′-pyridylmethyl)imidazolium bromide hydrate and 3-(2″, 6″-di-*iso*-propylphenyl)-1-(2′-pyridylmethyl)imidazolium bromide hydrate, complexes **85** ($R = t$-Bu, 2″,6″-i-$Pr_2C_6H_3$) result. 3-(2″,4″,6″-Trimethylphenyl)-1-(2′-pyridylmethyl)imidazolium bromide in turn leads to **86** ($R = 2'',4'',6''$-$Me_3C_6H_2$). 3-(2″,6″-Di-*iso*-propylphenyl)-1-(2′-pyridyl) imidazolium bromide gives the monocarbene **87**. 1-R-3-(N,N Diethylcarbamoylmethyl) imidazolium bromide ($R = t$-Bu, 2′,4′,6′-$Me_3C_6H_2$) gives **88** ($R = t$-Bu, 2′,4′,6′-$Me_3C_6H_2$). 1-(2-Benzylideneamino-3′,5′-di-*tert*-butylbenzyl)-3-*tert*-butylimidazolium bromide gives **89**, and finally, 3,3′-R_2-1,1′-*o*-phenylenedimethylenebisimidazolium dibromides give **90** ($R = t$-Bu, 2,4,6-$Me_3C_6H_2$, 2,6-i-$Pr_2C_6H_3$).



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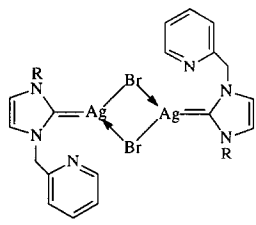

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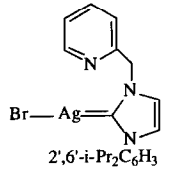

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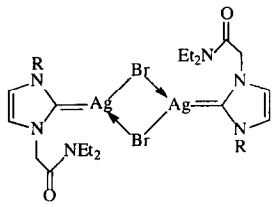

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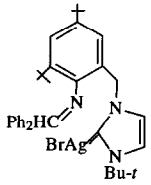

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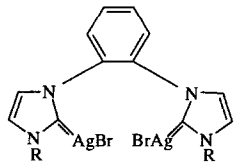
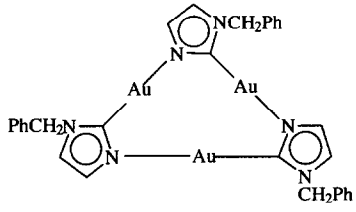


90

Gold(I) tends to form oligomeric N^3,C^2-coordinated complexes with imidazolato groups (91JOM(408)271, 92AX(C)1600), for example the trimer bearing the bridging 1-benzylimidazolato-N^3,C^2-coordinated bridging ligands (89JOM(375)147). This trimer, **91**, with ClCOOEt gives **92** (R = COOEt, X = Cl), with PhCOCl gives **92** (R = COPh, X = Cl) (93JOM(452)287), both carbene complexes (94JOM(470)275). With ethyl iodide, the dicarbene **93** (R = Et), monocarbene **92** (R = Et, X = I), and AuI_2^- are the products. Addition of $SOCl_2$ retains the trimeric framework, but increases the oxidation number of each gold site from +1 to +3 giving **94**. Another product of this reaction is the monocarbene **92** (R = H, X = Cl). Molecular iodine oxidatively adds only to one of the gold(I) centers of **91** to yield **95**. Lithium 1-benzylimidazolate with triphenylphosphine gold(I) chloride gives the dicarbene **93** (R = H). Complex **91** on reaction with silver tetrafluoroborate or thallium hexafluorophosphate intercalates Ag^+ and Tl^+ ions sandwiching them between the planar trinuclear frameworks in the chain-like structures (98JCS(CC)95, 00IC3158).



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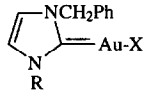

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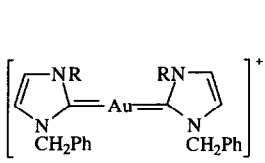

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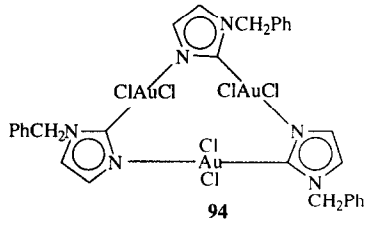

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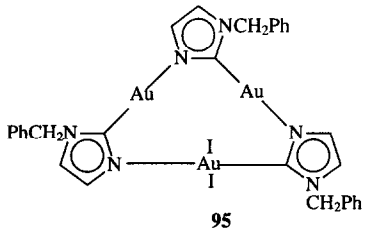
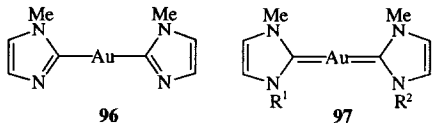
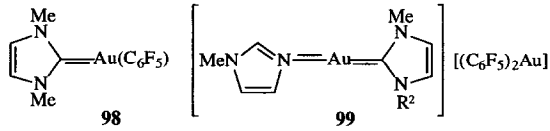


95

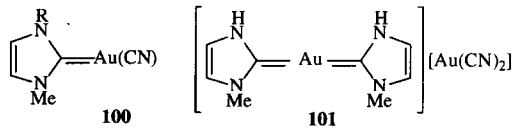
An alternative way to the preparation of the carbene gold complexes is through 1-methylimidazol-2-yllithium, which with [AuCl(THT)] gives **96** (96JOM(511)177, 97JOM(544)91, 98JOM(552)69). Protonation with triflic acid or alkylation with methyl triflate gives the carbenes **97** ($R^1 = R^2 = H$, Me). Simultaneous addition of triflic acid and methyl triflate allows preparing the mixed-ligand carbene **97** ($R^1 = H$, $R^2 = Me$) (95AX(C)1814, 96JOM(511)177). The same set of products, **97** ($R^1 = R^2 = H$, Me), follows from [AuCl(PPh_3)]. In contrast, addition of [Au(C_6F_5)(THT)] leads to the monocarbene **98**, while protonation step gives species **99**. Gold(I) cyanide gives after a similar sequence of transformations, monocarbenes **100** (R = H, Me), and the one with R = H undergoes an easy transformation to the bis-carbene **101**.



96 97

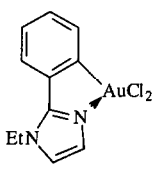


98 99



100 101

The N-coordinated compound $[AuCl_3L]$ (L = 1-ethyl-2-phenylimidazole) with silver tetrafluoroborate gives the cycloaurated species **102**, which on further reaction with triphenylphosphine and sodium tetrafluoroborate or ammonium hexafluorophosphate forms the cationic complexes **103** ($X = BF_4$, PF_6) (00JCS(D)271).



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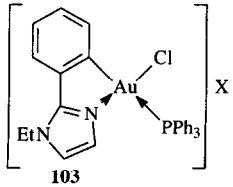


103

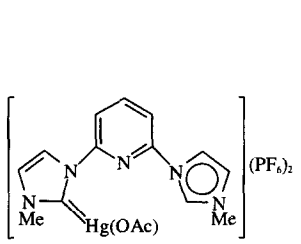
The methylmercury(I)–imidazole system in solution contains $[MeHg(Him)]^+$, [MeHg(im)] and $[(MeHg)_2Im]^+$ species (77JA8106). In the latter the imidazolate ligand fulfils a bridging function and is coordinated via both nitrogen heteroatoms.

Diethylzinc 1,3-bis(1-adamantyl)imidazol-2-ylidene adduct is known (93JOM(462)13). Bis(1,3-diphenylimidazol-2-ylidene) mercury(II) carbene complexes follow from the corresponding imidazolium perchlorate and mercury(II) chloride (68AGE682).

1,3-Dimethylimidazolium perchlorate with mercury(II) chloride gives the dicationic carbene complex carrying two 1,3-dimethylimidazol-2-ylidene ligands and two perchlorates as counter-ions (70CB1037, 96HC421). Bis(*N*,*N*-diphenyl-2-imidazolium)mercury perchlorate contains the η^1(C)-coordinated azolium ligand (71AX(B)2276). 2,6-Bis(1-methylimidazolium-3-yl)pyridine dihexafluorophosphate with mercury(II) acetate gives the carbene type species **104** and **105** where the carbene carbons, but not the nitrogen heteroatom of the pyridine ring, are involved in coordination (00JCS(D)839). 1-Methylimidazole-2-thiol (L) forms the monodentate S-coordinated species [HgMeL] (83CJC1536).

Imidazol-2-ylidenes in the lanthanide complexes behave as the nucleophilic ligands, and no back-bonding is required to describe the bonding situation (94AGE1733, 94AGE2165, 94CB2369, 94JA7927). 1,3,4,5-Tetramethylimidazol-2-ylidene (L) with $[(\eta^5\text{-}Cp^*)_2Sm(THF)]$ gives the stable adduct $[(\eta^5\text{-}Cp^*)_2Sm(L)]$ (94JA7927). When excess carbene is added, $[(\eta^5\text{-}Cp^*)_2Sm(L)_2]$ is formed. With $[M(thd)_3]$, the adducts $[M(thd)_3L]$ (M = Eu, Y) result. 1,3,4,5-Tetramethylimidazol-2-ylidene and 1,4-di-*iso*-propyl-2,3-dimethylimidazol-2-ylidene with $[(\eta^5\text{-}C_5Me_4Et)_2M(THF)]$ (M = Sm, Yb), $[(\eta^5\text{-}Cp^*)Yb(THF)]$, and $[(\eta^5\text{-}C_5H_3(t\text{-}Bu)_2)_2Yb(THF)]$ form a wide variety of the 1:1 C-coordinated adducts (94AGE1733, 94CB2369). 1,3-Dimethylimidazol-2-ylidene (L) with $ErCl_3(THF)_{3.25}$ yields the tris-carbene species $[ErCl_3L_3]$ (97OM682). With

$[Ln(N(SiMe_3)_2)_3]$, it produces the monocarbenes $[Ln(N(SiMe_3)_2)_3L]$ (Ln = Y, La) and with $[Y(N(SiHMe_2)_2)_3(THF)_2]$ it can give both mono-, $[Y(N(SiHMe_2)_2)_3L]$, and bis-carbene, $[Y(N(SiHMe_2)_2)_3L_2]$ species, depending on the amount of the imidazol-2-ylidene participating in the reaction.



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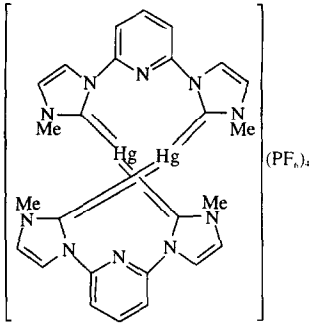
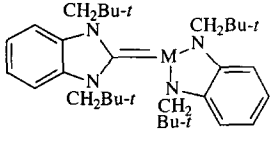


105

D. Organometallic Complexes of Benzimidazoles

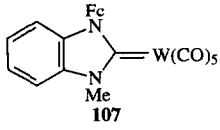
Benzimidazole is also aromatic (65AX573, 97T13111), less acidic and more basic in the gas phase than imidazole (83AGE323), although in solution the basicity trend is reverted. This is ascribed to the polarization effects of the annulation.

1,3-Di-*t*-BuCH_2-benzimidazol-2-ylidene forms adducts with its silicon, germanium, tin, and lead analogues, which have structures **106** (M = Si, Ge, Sn, Pb) (00JCS(D)3094).



106

Deprotonation of 1-methyl-3-ferrocenylimidazolium tetrafluoroborate or iodide (98JOM(552)45) by lithium di-*iso*-propylamide and subsequent reaction with $W(CO)_5$·THF gives the carbene complex **107** and bis-carbene **108**, even when excess $W(CO)_5$·THF is applied (99JOM(572)177). Numerous ferrocenyl benzimidazoles are known (97RCR613, 99JOM(580)26).



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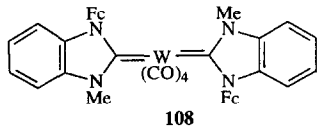
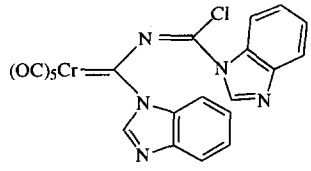


108

Benzimidazole with $[Cr(CO)_5CNCCl_3]$ gives the *N,N'*-carbenes **109** and **110**, the products of simultaneous attack at trichloromethyl and isocyano groups simultaneously (95JOM(489)27). The probability of the formation of the primary product $[Cr(CO)_5(C(L)N{=}CCl_2]$ is low (88AGE1344, 89ZN(B)1414).



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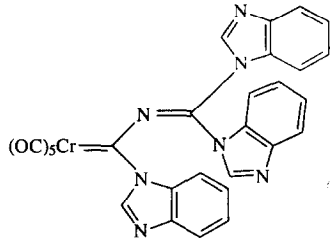
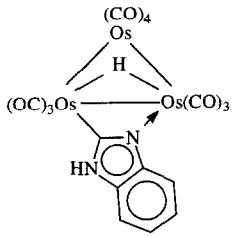


110

Benzimidazole with $[Os_3(CO)_{10}(AN)_2]$ gives two isomers, **111** and **112** (82IC634). Only species similar to **111** follows from the interaction with $[Ru_3(CO)_{12}]$ (88JCS(D)1437, 98JA11522). With triphenylphosphine, a mixture of three isomers is formed, the derivative **113** being the predominating isomer (90JCS(D)1509). Benzimidazole-2-thione with $Ru_3(CO)_{12}$ gives **114** (99JOM(585)100).



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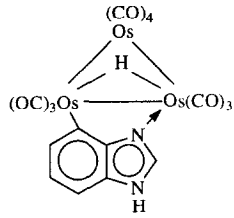
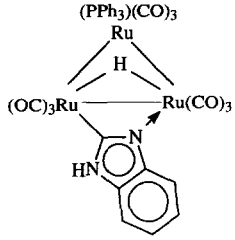


112

Imidazo[1,2-a]pyridine with $[Os_3(CO)_{10}(AN)_2]$ gives a mixture of the products **115** and **116** (99JOM(588)211). With $[Os_3(CO)_{11}(AN)]$ or $[Os_3(CO)_{12}]$ in the presence of Me_3NO it gives **117**, which produces **115** and **116** on thermolysis.

Species **115** and **116** react with imidazo[1,2-a]pyridine further and afford compounds **118** and **119**, respectively.



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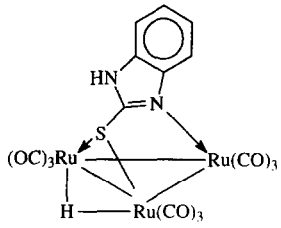

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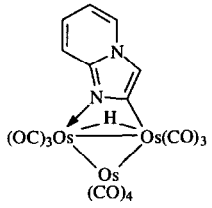

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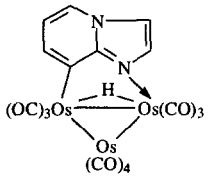

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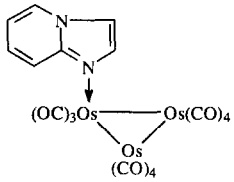

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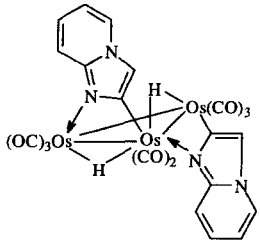

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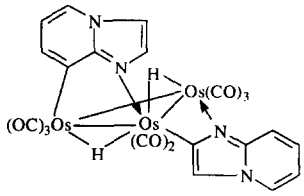
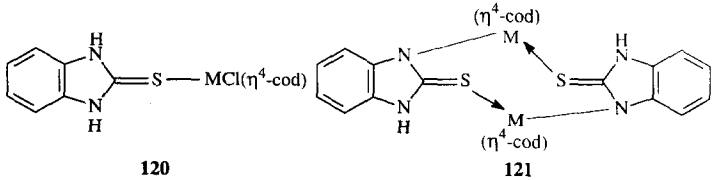


119

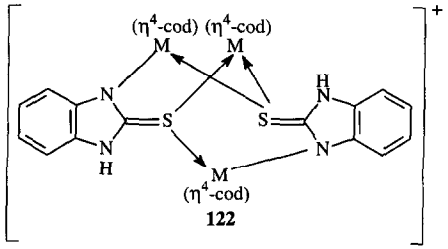
1,3-Dimethylbenzimidazolium iodide with $[(\eta^4\text{-cod})Rh(\mu\text{-OMe})_2Rh(\eta^4\text{-cod})]$ gives the carbene-based complex $[(\eta^4\text{-cod})Rh(L)I]$, where L is 1,3-dimethylbenzimidazol-2-ylidene (97JOM(532)261). Similar complexes are known (94JOM(481)89).

Benzimidazole-2-thiol is a classical representative of the family of N,N-, N,O- (85JCS(D)1891, 86ICA(111)L1, 87JCS(D)981) and N,S- (85CCR(61)115, 86NJC75, 88AGE402, 91JCS(D)255, 94CCR(129)91, 94JOM(482)53, 96CCR(153)199) ligands with a wide variety of coordination modes. This ligand with $[(\eta^4\text{-cod})M(\mu\text{-Cl})]_2$ gives the mononuclear η^1(S)-coordinated species **120** (M = Rh, Ir) (96IC4360). These products further react with potassium hydroxide and afford the dinuclear N,S-coordinated complexes **121** (M = Rh, Ir). The latter

still preserve the properties of the ligands and enter the reaction with $[(\eta^4\text{-cod})M(Me_2CO)_2]^+$, the result being the trinuclear cationic species **122**. With $[(\eta^4\text{-cod})M(\mu\text{-OMe})]_2$ (M = Rh, Ir), they undergo deprotonation and form the tetranuclear complexes **123** (M = Rh, Ir). Reaction of **121** (M = Rh) with $[(\eta^4\text{-cod})Rh(\mu\text{-Cl})]_2$ gives the tetranuclear complex **124** (98IC3954). 1-Methyl-2-(alkylthiomethyl)-1H-benzimidazoles (alkyl = methyl, *tert*-butyl) (L) with $[(\eta^5\text{-Cp}^*)M(\mu\text{-Cl})Cl]_2$ (M = Rh, Ir) and excess Bu_4NPF_6 give the N, S-coordinated chelate complexes $[(\eta^5\text{-Cp}^*)MCl(L)](PF_6)$ (M = Rh, Ir) (00JOM(596)84).



120 **121**



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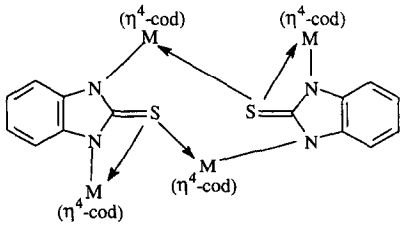

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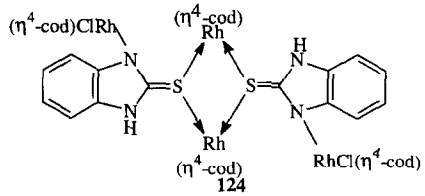

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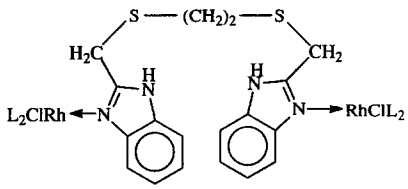

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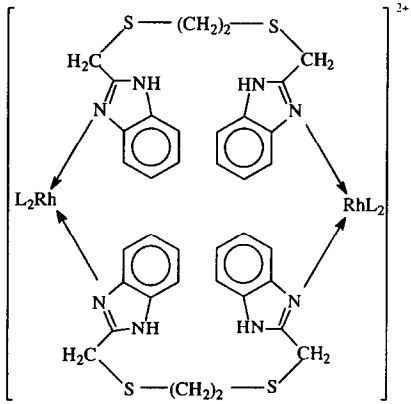
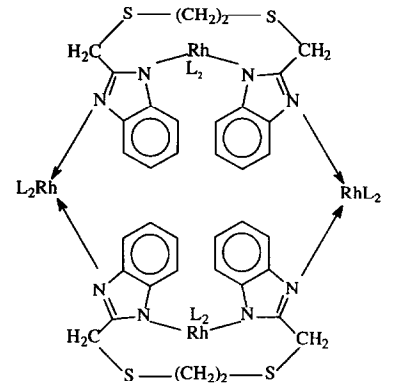


126

1,6-Bis(2′-benzimidazolyl)-2,5-dithiahexane (80RCT367) with $[(\eta^4\text{-}L_2)RhCl]_2$ (L_2 = tfb, cod) yields the η^1(N)-coordinated dinuclear complexes **125** (83ICA(71)115). In the presence of triethylamine this complex is converted to the tetranuclear species **127**. The same ligand added to $[Rh_2L_2](ClO_4)$ gives the dicationic dinuclear complex **126**

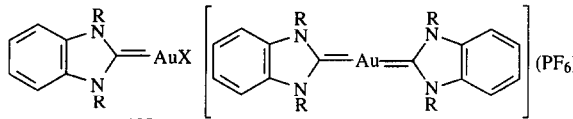


127

1,3-Dimethylbenzimidazolium iodide serves as a starting material for free carbenes (99CEJ1931, 99JA10626, 00AGE541) and carbene complexes (99JOM(585)241). Thus, with palladium(II) acetate it gives $[L_2PdI_2]$ where L is 1,3-dimethylbenzimidazol-2-ylidene. Similarly, 1,1′-methylenebis(3-methylbenzimidazolium) diiodide (L) with palladium(II) acetate gives $[PdLI_2]$, where the ligand is in the benzimidazol-2-ylidene form. 1-Methyl-3-ferrocenylbenzimidazolium iodide with palladium acetate yields the bis-carbene $[PdL_2]$ where L is 1-methyl-3-ferrocenylbenzimidazol-2-ylidene (99JOM(572)177).

Benzimidazole-2-thiol (L) forms the chelating N,S-coordinated complex of composition $(n\text{-}Bu_4N)[Ni(C_6F_5)_2L]$ (92JOM(435)193). 2-(2′-Pyridyl)benzimidazole can be used as a bridging ligand in the heteronuclear Rh-M complexes (M = Pd, Pt, Au, and Ag) (83JOM(247)205).

1,3-Dimethyl- and 1,3-diethylbenzimidazolium bromides with $[Au(SMe_2)Cl]$ in the presence of Ag_2O give **128** (X = Cl; R = Me, Et) (96OM1055, 97AGE1850, 98OM972, 99CM1237, 99OM1216). The product reveals an interesting reactivity pattern (99OM1216). With silver tetrafluoroborate and then potassium bromide or iodide **128** (X = Br, I; R = Me, Et) results. Addition of the relevant imidazolium hexafluorophosphate gives **129**. With phenylacetylene in the presence of potassium carbonate **128** (X = C≡CPh; R = Me, Et), and with phenyl sulfide and potassium hydroxide - **128** (X = SPh) are the products. Similar carbene complexes are known (96JCS(CC)181, 96JCS(D)3699, 96JCS(D)4227, 97JCS(CC)1850).



128 **129**

1-Methyl-3-ferrocenylbenzimidazolium iodide with mercury(II) acetate gives the cationic bis-carbene complex of composition $[HgL_2]I_2$, where L is 1-methyl-3-ferrocenylbenzimidazol-2-ylidene (99JOM(572)177).

E. Organometallic Complexes of Biimidazoles and Bibenzimidazoles

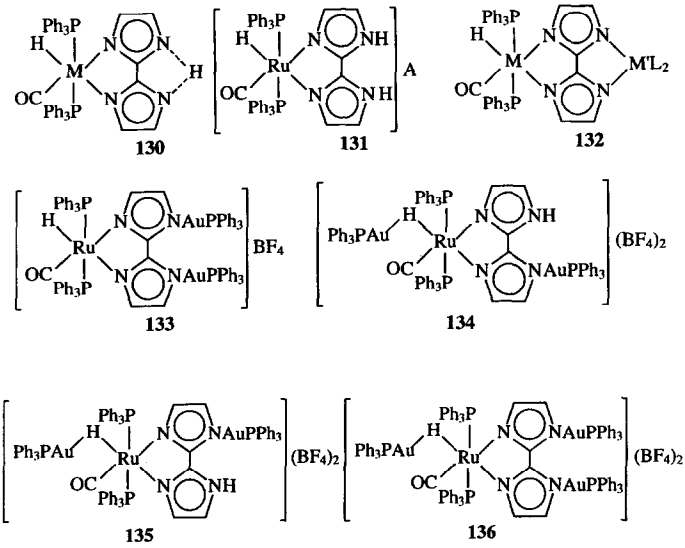
For biimidazole (97JCS(F)2967), two basic coordination modes are common. The neutral molecule, monoanion, and dianion can be bidentate chelating ligands, while the dianion can also reveal the quadridentate coordination (72CB1419, 76IC2681, 76IC2688, 80JOM(197)291, 81JOM(209)271, 81JOM(220)173).

Bis((1,1,4,7,7-pentamethyldiethylenetriamine)lithium)biimidazole and -bibenzimidazole (L) with $[(\eta^5\text{-Cp})_2TiCl]_2$ give the dinuclear species $[(\eta^5\text{-Cp})_2Ti(\mu\text{-L})Ti(\eta^5\text{-Cp})_2]$ (78IC2078). 1-Methylbibenzimidazole analogue with only one N^1 atom carrying the methyl substituent (L) gives the mononuclear complex $[(\eta^5\text{-Cp})_2TiL]$, where one of the nitrogen atoms remains uncomplexed. The dinuclear species are characterized by the antiferromagnetic exchange coupling.

Biimidazole with $[(\eta^5\text{-Cp})Mo(\eta^3\text{-}C_3H_5)(CO)_2]$ in the presence of HBF_4 gives $[(\eta^5\text{-Cp})Mo(CO)_2(H_2bim)](BF_4)$ with coordination via both pyridine-type nitrogen heteroatoms (98P1091). Reduction by sodium hydride allows to prepare $Na[(\eta^5\text{-Cp})Mo(CO)_2(bim)]$. With $XReO_3$ (X = Me, Cl), the dinuclear complexes $[(\eta^5\text{-Cp})(OC)_2Mo(\mu\text{-bim})ReO_3X]$ result. On treatment with biimidazole, $[(\eta^5\text{-Cp})_2Mo(AN)_2](BF_4)_2$ gives the product of substitution $[(\eta^5\text{-Cp})_2Mo(H_2bim)](BF_4)_2$ giving rise to $[(\eta^5\text{-Cp})_2Mo(bim)]$ by reacting with sodium hydride.

2,6-Bis(2-benzimidazolyl)pyridine, 4,4′,5,5′-tetramethyl-2,2′-biimidazole, and 2,2′-bibenzimidazole (L) react with $[Re(CO)_5Cl]$ to yield $[Re(L)(CO)_3Cl]$ (99ICA(288)150).

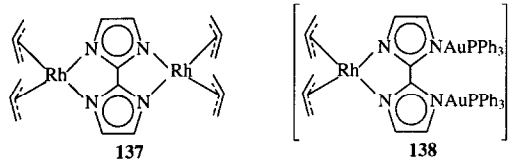
Biimidazole and bibenzimidazole often reveal their ligating properties in the doubly deprotonated form when they act as bridging ligands (83JCS(D)323). This property is well manifested in the heteronuclear species $[(Ph_3P)_2(OC)HRu(\mu\text{-bim})M(\eta^4\text{-cod})]$ (M = Rh, Ir) (88JCS(CC)793). It can be prepared in several steps starting from the reaction of 2,2′-biimidazole (H_2L) and $[RuH(CO)Cl(PPh_3)_3]$ in methanolic potassium hydroxide leading to $[RuH(CO)(HL)(PPh_3)_2]$. The next step involves the reaction of the product and $[(\eta^4\text{-cod})M(OMe)]_2$ (M = Rh, Ir). Treatment of $[MHCl(CO)(PPh_3)_3]$ (M = Ru, Os) with biimidazole in alkaline medium gives **130** (M = Ru, Os), while the same reaction run in the presence of sodium perchlorate gives only the cationic ruthenium species **131** ($A = ClO_4$) (90JCS(D)3465). Species **130** (M = Ru) can be converted into **131** ($A = ClO_4$) by protonation with perchloric acid, and the reverse process of deprotonation can be achieved using methanolic potassium hydroxide. Both **130** (M = Ru, Os) with $[M'(\mu\text{-OMe})(\eta^4\text{-}L_2)]_2$ (M′ = Rh, Ir; L_2 = cod, tfb) give a series of heterodinuclear products **132** (M = Ru, M′ = Rh, Ir, L_2 = cod, tfb; M = Os, M′ = Ir, L_2 = cod). Meanwhile, $[MHCl(CO)(PPh_3)_3]$ with excess biimidazole gives the homodinuclear $[\{RuHCl(CO)(PPh_3)_2\}_2(\mu\text{-bim})]$. Species **130** (M = Ru) also reacts with one equivalent of $[Au(PPh_3)]BF_4$ to yield the trinuclear complex **133** together with **131** ($A = BF_4$). Two equivalents of $[Au(PPh_3)]BF_4$ give a couple of isomeric heterotrinuclear species, **134** and **135**. With three equivalents of $[Au(PPh_3)]BF_4$, the tetranuclear species **136** results. The ruthenium product similar to **130** can be prepared for bibenzimidazole. With $[Rh(\mu\text{-OMe})(\eta^4\text{-cod})]_2$ it gives an analog of **132** (M = Ru, M′ = Rh, L_2 = cod), and carbonylation leads to the bibenzimidazole analog **132** (M = Ru, M′ = Rh, L_2 = CO).

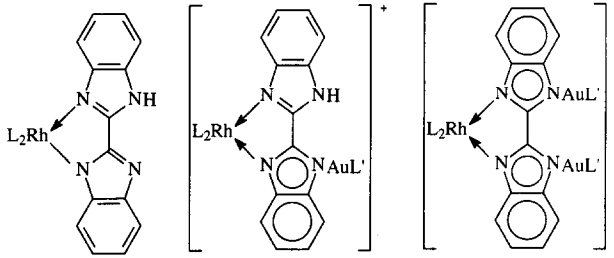


Another sequence leading to the heterodinuclear complexes starts with 2,2′-biimidazole and $[OsH_6(P(i\text{-}Pr)_3)_2]$, which give $[OsH_3(Hbim)(P(i\text{-}Pr)_3)_2]$, where the hydrogen atom is shared between two nitrogen heteroatoms (96IC7811), the situation similar to that observed before (94IC787). The product with $[(\eta^4\text{-cod})M(\mu\text{-OMe})]_2$ gives $[H_3((i\text{-}Pr)_3P)_2Os(\mu\text{-bim})M(\eta^4\text{-cod})]$ (M = Rh, Ir) (96IC7811).

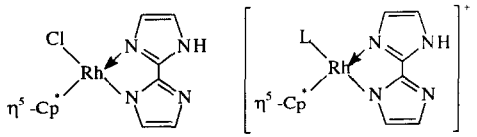
2,2′-Biimidazole with the dimer $[(\eta^4\text{-cod})Rh(OMe)]_2$ in the presence of the methoxide anion gives $[(\eta^4\text{-cod})Rh(Hbim)]$ (75JA425), where biimidazole is deprotonated and uses only two nitrogen sites for coordination. The diene ligand is readily substituted by carbon monoxide to yield $[(OC)_2Rh(Hbim)]$. Similar transformations are possible for the analogous iridium species. In excess biimidazole, the homodinuclear complex $[L_2M(\mu\text{-bim})ML_2]$ ($L_2 = \eta^4$-cod, $(CO)_2$; M = Rh, Ir) can be prepared. Excess 2,2′-biimidazole with $[M(CO)_2(acac)]$ (M = Rh, Ir) gives $[M_4(CO)_8(\mu\text{-bim})_2]$ (76IC2688). Reaction of $[(\eta^4\text{-cod})Rh(Hbim)]$ with $[Rh(CO)_2(acac)]$ gives $[(\eta^4\text{-cod})_2Rh_4(CO)_4(\mu\text{-bim})_2]$. $[(\eta^4\text{-cod})Rh(bim)]_2$ (76IC2681, 76IC2688), $[Rh_4(CO)_8(bim)_2]$, (89JCS(D)S1), $[Rh_2(\mu\text{-bim})L_2]$ (L_2 = cod, nbd, tfb) (76IC2681, 76IC2688), and $[Rh_4(\mu_3\text{-bim})_2(CO)_4L_4]$ (L = CO (75JA425, 76IC2681, 76IC2688), PPh_3 (85P325)) are known. 2,2′-Biimidazole and $[(\eta^3\text{-}C_3H_5)_2Rh(acac)]$ give the binuclear complex **137** (86JCS(D)2193). $[Au_2(bim)(PPh_3)_2]$ with $[(\eta^3\text{-}C_3H_5)_2Rh(Me_2CO)_x]ClO_4$ forms the heterotrinuclear species **138**. The bibenzimidazole analogue containing cyclooctadiene-1,5 instead of allyl can be prepared in a similar fashion (83JCS(D)323). Thus, reaction of 2,2′-bibenzimidazole with $[(\eta^4\text{-}L_2)Rh(acac)]$

(L_2 = cod, nbd) gives **139** (L_2 = cod, nbd). The latter with [AuClL′] (L′ = $P(OMe)_3$, PPh_3) give the heterodinuclear species **140** (L_2 = cod, nbd; L′ = $P(OMe)_3$, PPh_3). The complex ligands [Au_2L″L′$_2$] (L″ = 2,2′-bibenzimidazolate; L′ = $P(OMe)_3$, PPh_3; L′$_2$ = dppm, dppe) with [(η^4-cod)Rh($OCMe_2$)$_x$] ClO_4 give the heterotrinuclear species **141** (L_2 = cod; L′ = $P(OMe)_3$, PPh_3; L′$_2$ = dppm, dppe). Carbonylation of **139** (L_2 = cod, nbd), **140** (L_2 = cod, nbd; L′ = $P(OMe)_3$), or **141** (L_2 = cod; L′ = $P(OMe)_3$, PPh_3) leads to the substitution of a diene ligand and formation of the corresponding dicarbonyl complexes. Reaction of **140** (L_2 = cod, nbd; L′ = PPh_3) with carbon monoxide, however, gives [$(Ph_3P)_2Au_2$(μ-L)Rh$(CO)_2$](ClO_4) and [Rh(H_2L)$(CO)_2$](ClO_4)] (81TMC103, 83JCS(D)323). As usually, one of the carbonyl groups in a Rh$(CO)_2$ framework is readily substituted by the phosphine ligands like $P(OMe)_3$ and PPh_3.





2,2′-Biimidazole with [(η^5-Cp*)RhCl(acac)] gives **142** (86JCS(D)15). A series of cationic species **143** (L = py, *t*-BuNC, $P(OEt)_3$, PPh_3) follows from 2,2′-biimidazole and [(η^5-Cp*)RhL(acac)](ClO_4) (L = py, *t*-BuNC, $P(OEt)_3$, PPh_3). Complex **142** further reacts with [Rh(acac)L_2] (L_2 = $(CO)_2$, tfb) to yield the homotetranuclear species **144** (L_2 = $(CO)_2$, tfb). Complexes **143** (L = py, *t*-BuNC, $P(OEt)_3$, PPh_3) also give rise to the tetranuclear rhodium(I)–rhodium(III) dicationic species **145** (L = py, *t*-BuNC, $P(OEt)_3$, PPh_3; M = Rh; L′$_2$ = $(CO)_2$, tfb, nbd) by reacting with [Rh(acac)L′$_2$] (L′$_2$ = $(CO)_2$, tfb, nbd). [(η^4-tfb)Ir(acac)] gives rise to the heterotetranuclear iridium(I)–rhodium(III) dications **145** (L = py, $P(OEt)_3$, PPh_3; M = Ir; L_2′ = tfb).



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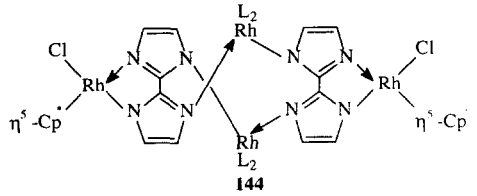

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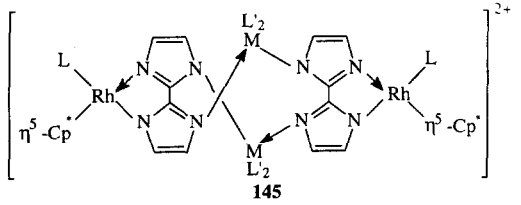


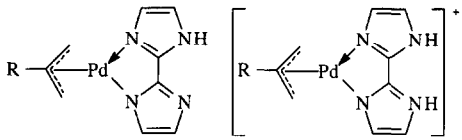
145

4,4′,5,5′-Tetracyano-2,2′-biimidazole contains electron-withdrawing cyano substituents (82JA6155). This facilitates the formation of the di- and polynuclear complexes of rhodium and iridium, since the corresponding reaction does not require addition of a base. This ligand with the dimers $[(\eta^4\text{-cod})RhCl]_2$ or $[(\eta^4\text{-cod})Rh(OMe)]_2$ or a monomer $[(\eta^4\text{-cod})Rh(acac)]$ forms $[(\eta^4\text{-cod})Rh(\mu\text{-}(CN)_4bim)Rh(\eta^4\text{-cod})]$ (84IC338, 84IC343). The iridium analogue can be prepared from $[(\eta^4\text{-cod})Ir(acac)]$. Iridium in the dimer formed tends to increase its coordination number and with triphenylphosphine forms $[(\eta^4\text{-cod})_2Ir_2(PPh_3)_2(\mu\text{-}(CN)_4bim)]$, and with bromine gives the iridium(III)–iridium(III) oxidative addition product of formulation $[(\eta^4\text{-cod})(Br)_2Ir(\mu\text{-}(CN)_4bim)Ir(Br)_2(\eta^4\text{-cod})]$. Both rhodium(I)–rhodium(I) and iridium(I)–iridium(I) dimers are easily carbonylated to give $[M_4(CO)_8(\mu\text{-}(CN)_4bim)_2]$ (M = Rh, Ir). With triphenylphosphine, the iridium tetramer forms the substitution product $[Ir_4(CO)_4(PPh_3)_4(\mu\text{-}(CN)_4bim)_2]$. Tetracyanobiimidazole and $[(\eta^4\text{-cod})MCl]_2$ (M = Rh, Ir) but in the presence of the carbonates $M_2'CO_3$ (M′ = NMe_4^+, NEt_4^+, $CH_6N_3^+$, Na^+, and K^+) give the monomeric complexes $M'[(\eta^4\text{-cod})M((CN)_4bim)]$ (M = Rh, Ir; M′ = NMe_4^+, NEt_4^+, $CH_6N_3^+$, Na^+, and K^+), in which the coordination potential of the biimidazole ligand is not fully utilized. The iridium complex $(NEt_4)[(\eta^4\text{-cod})Ir((CN)_4bim)]$ adds triphenylphosphine to yield $(NEt_4)[(\eta^4\text{-cod})Ir((CN)_4bim)(PPh_3)]$. Carbonylation of the products is a normal ligand substitution process leading to

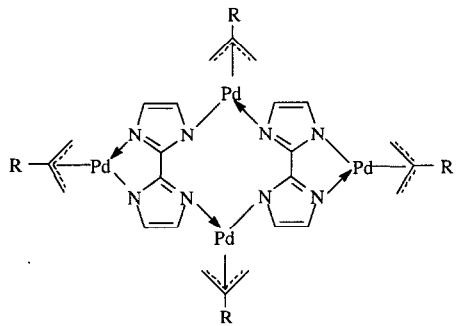
$M'[(OC)_2M((CN)_4bim)]$. The $[(OC)_2Ir((CN)_4bim)]^-$ anions reveal the stacking type of behavior in the crystalline state. Molecular bromine and iodine oxidatively add to $(NEt_4)[(\eta^4\text{-cod})Ir((CN)_4bim)]$ in a normal fashion. Electrolysis of the iridium(I) precursor in acetonitrile gives the iridium(II) dimer $[Ir_2((CN)_4bim)_2(CO)_4(AN)_2]$ (85JA279). It contains the iridium–iridium bond but no bridging ligands. With triethylphosphine, $[Ir_2((CN)_4bim)_2(CO)_2(PEt_3)_2(AN)_2]$ results.

Palladium(II) and platinum(II) complexes [M(dppe)(L)] (M = Pd, Pt; L = bibenzimidazolate) contain the chelating L with two uncoordinated nitrogen atoms and serve as ligands with respect to $[(\eta^4\text{-cod})Rh(Me_2CO)_x](ClO_4)$ to yield the heterobinuclear species $[(dppe)M(\mu\text{-L})Rh(\eta^4\text{-cod})](ClO_4)$ (M = Pd, Pt; L = bibenzimidazolate) (83P163). Carbonylation gives $[(dppe)M(\mu\text{-L})Rh(CO)_2](ClO_4)$ (M = Pd, Pt; L = bibenzimidazolate). Ligand substitution using triphenylphosphine affords $[(dppe)M(\mu\text{-L})Rh(CO)(PPh_3)](ClO_4)$ (M = Pd, Pt; L = bibenzimidazolate).

Biimidazole and bibenzimidazole with $[(\eta^3\text{-}2\text{-}RC_3H_4)Pd(\mu\text{-Cl})]_2$ (R = H, Me) taken in the 2 : 1 molar ratio in the presence of methanolic potassium hydroxide give complexes of the type **146** (83JCS(D)1729) and with $[(\eta^3\text{-}2\text{-}RC_3H_4)Pd(Me_2CO)_x](ClO_4)$ – **147**. When the ratio of 2,2′-biimidazole or 2,2′-bibenzimidazole and $[(\eta^3\text{-}2\text{-}RC_3H_4)Pd(\mu\text{-Cl})]_2$ (R = H, Me) is 1 : 1, the homotetranuclear species **148** result. Heterotetranuclear palladium(II)–rhodium(I) complexes **149** (L_2 = cod) follow from $[(\eta^4\text{-cod})Rh(Hbim)]$ and $[(\eta^3\text{-}2\text{-}RC_3H_4)Pd(acac)]$. They are readily carbonylated with complete substitution of

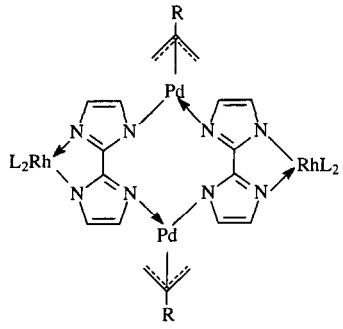


146 **147**



148

the diene ligands to yield **149** (L = CO). The 2,2′-bibenzimidazolate (L) species of the type **149** can in turn be prepared from $[(\eta^3\text{-2-R-}C_3H_4)Pd(HL)]$ and $[(\eta^4\text{-cod})Rh(acac)]$. Carbonylation of these derivatives proceeds differently and gives $[(\eta^3\text{-2-R-}C_3H_4)_4Pd_4(\mu\text{-L})_2]$ and $[Rh_4(CO)_8(\mu\text{-L})_2]$.



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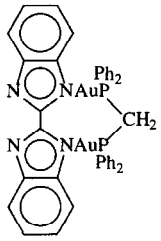
Biimidazole, tetramethylbiimidazole, and bibenzimidazole react with the anionic palladium(II) species $(n\text{-}Bu_4N)[Pd(C_6F_5)(acac)]$ to yield the dinuclear $(n\text{-}Bu_4N)[(C_6F_5)Pd(\mu\text{-L})Pd(C_6F_5)_2]$ (81ICA(50)173). Similarly, the same group of ligands with $[Pd(C_6X_5)(acac)(PPh_3)]$ (X = F, Cl) gives $[(Ph_3P)(C_6X_5)Pd(\mu\text{-L})Pd(C_6X_5)(PPh_3)]$. Tetranuclear palladium(II) species $[(\eta^3\text{-}C_3H_5)_4Pd_4(\mu_3\text{-bim})_2]$ as well as heterotetranuclear compounds of composition $[(\eta^3\text{-}C_3H_5)_2Pd_2(\mu_3\text{-bim})_2Rh_2L_2]$ (L = nbd, CO) are known (83JCS(D)1729). Organopalladium derivatives can be prepared from the species where the bibenzimidazolate ligand is in composition of the gold complex **150** (81ICA(54)L95). Reaction of **150** with $[(THT)(C_6F_5)Pd(\mu\text{-Cl})_2Pd(C_6F_5)(THT)]$ gives coordinatively saturated species **151** (R = Cl). Similarly, with $[(C_6F_5)_2Pd(\mu\text{-Br})_2Pd(C_6F_5)_2]$ **151** ($R = C_6F_5$) results. The range of such products can be extended to $[(dppm)Au_2(\mu\text{-L})Pd(C_6X_5)_2]$ (L = bibenzimidazolate; X = F, Cl), $[(dppm)Au_2(\mu\text{-L})Pd(C_6F_5)Cl]$ (L = bibenzimidazolate) (82ICA(63)91).



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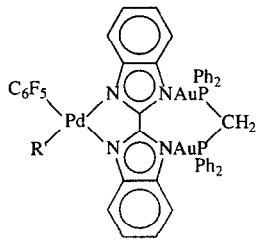


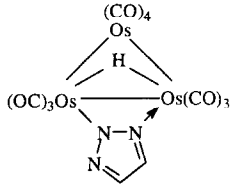
151

Interaction of the latter with triphenylphosphine in the presence of sodium perchlorate leads to the cationic complex $[(dppm)Au_2(\mu\text{-}L)Pd(C_6F_5)(PPh_3)]ClO_4$. Reactions of $[L'Au(\mu\text{-}L)AuL']$ (L = bibenzimidazolate; L′ = PPh_3, dppm)] with $[Pd(OClO_3)(C_6F_5)(PPh_3)_2]$ do not lead to the tetranuclear products. Only the bibenzimidazolate (L) dinuclear product $[(PPh_3)(C_6F_5)Pd(\mu\text{-}L)Pd(C_6F_5)(PPh_3)]$ could be isolated in both cases.

II. Triazoles, Tetrazole, and Pentazole

A. Organometallic Complexes of 1,2,3-Triazole and Benzotriazole

1,2,3-Triazole forms a single isomer **152** on interaction with $[Os_3(CO)_{10}(AN)_2]$ (97JOM(540)67).



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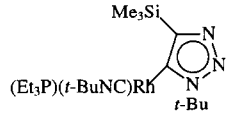
4,5-Dicarboxy-1,2,3-triazole (HL) with $[(\eta^4\text{-cod})M(\mu\text{-Cl})]_2$ (M = Rh, Ir) and R_4NOH (R = Me, *n*-Pr, *n*-Bu) give $(NR_4)[(\eta^4\text{-cod})M(\mu\text{-}L)M(\eta^4\text{-cod})]$ (R = Me, *n*-Pr, *n*-Bu; M = Rh, Ir) (93IC5313). Carbonylation gives $(NR_4)[(OC)_2M(\mu\text{-}L)M(CO)_2]$ (R = Me, *n*-Pr, *n*-Bu; M = Rh, Ir). Metathesis reactions yield $(TTF)[(OC)_2Rh(\mu\text{-}L)Rh(CO)_2]$ as well as $(p\text{-}MeC_6H_4N_2)[(OC)_2Rh(\mu\text{-}L)Rh(CO)_2]$. Triphenylphosphine substitutes half of the carbonyl ligands in some of the complexes to give $(R_4N)[(Ph_3P)(OC)Rh(\mu\text{-}L)Rh(CO)(PPh_3)]$ (R = Me, *n*-Bu). Interaction of $(n\text{-}Bu_4N)[(OC)_2Rh(\mu\text{-}L)Rh(CO)_2]$ with $C_7H_7BF_4$ or $NOBF_4$ gives the solvate of the neutral species $[(OC)_2Rh(\mu\text{-}L)Rh(CO)_2]$. Electrochemical oxidation of $(NR_4)[(OC)_2Ir(\mu\text{-}L)Ir(CO)_2]$ (R = *n*-Pr, *n*-Bu) gives $(NR_4)_{0.5}[(OC)_2Ir(\mu\text{-}L)Ir(CO)_2]$, an electroconducting material.

Interaction of $[(Et_3P)_3Rh(C{=}N{=}N)(SiMe_3)]$ with *tert*-butyl isocyanide is an example of [3 + 2] dipolar cycloaddition and leads to the η^1(C)-coordinated 1,2,3-triazole complex **153** (91JCS(CC)809, 96OM1166). Another way of cyclization toward the 1,2,3-triazol-5-ylidene carbene species lies through *N*-isocyanimine ligands (85CB51).



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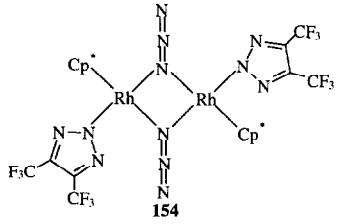
$[(\eta^5\text{-Cp}^*)(N_3)Rh(\mu\text{-}N_3)_2Rh(N_3)(\eta^5\text{-Cp}^*)]$ with hexafluorobut-2-yne reacts in two steps (79JCS(D)371). At the first step both bridging azide groups are retained giving **154**, while at the second one of the bridging azides undergoes transformation affording **155**. $[(\eta^5\text{-Cp}^*)Rh(N_3)_2(PPh_3)]$ and hexafluorobut-2-yne give **156**.



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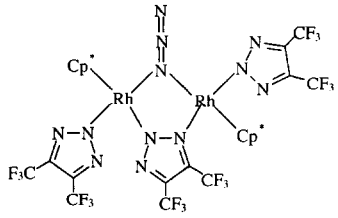

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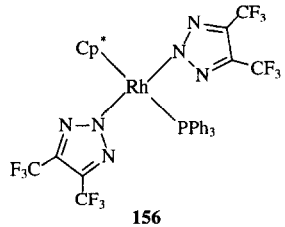


156

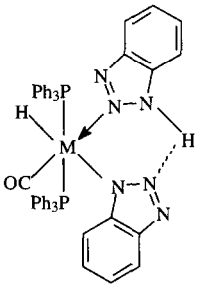
Benzotriazolate anion (84MI1) is capable of the monodentate (N^1 or N^2), bridging bidentate (N^1N^2 or N^1N^3) and tridentate ($N^1N^2N^3$) coordination (86AICR1, 88AIC171).

Benzotriazole (HL) with $[(\eta^5\text{-Cp})Mo(CO)_3Cl]$ gives the monodentately coordinated $[(\eta^5\text{-Cp})M(CO)_2(HL)Cl]$ (77IC3372).

In (1-allylbenzotriazole)tricarbonyliron, the ligand is coordinated via the N^2 site as well as the allyl group attached to the N^1 atom (77JOM(137)207).

Benzotriazole with $[MH_2(CO)(PPh_3)_3]$ (M = Ru, Os) gives **157** (M = Ru, Os), where the heteroaromatic framework is presented as the composite unit consisting of benzotriazole and benzotriazolate linked by a hydrogen bond (88P1781, 90JCS(D)621). This entity appears to be a ligand revealing the chelate function. 5,6-Dimethylbenzotriazole reacts similarly. $[MHCl(CO)(PPh_3)_3]$ in these conditions provide species **158** (M = Ru, Os), where benzotriazole is characterized by

the monodentate $\eta^1(N^3)$-coordination. With $[MH_2(PPh_3)_4]$ (M = Ru, Os) the isomer couple, **159** and **160**, is formed. In both of these isomers, there is a mixed coordination situation, described by the chelating function of the composite benzotriazole–benzotriazolate unit and $\eta^1(N)$ mode. The latter can be via N^2 or N^3 atom, this is the reason why two isomers emerge in this reaction in almost equivalent amounts.



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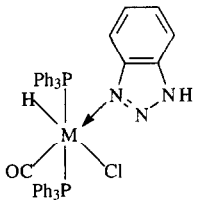

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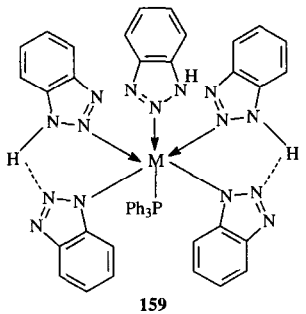

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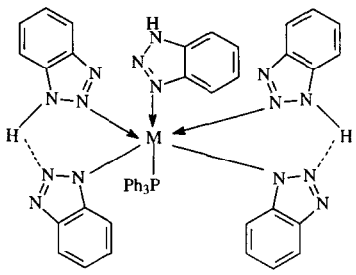

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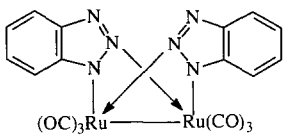
With $[Ru_3(CO)_{12}]$, dinuclear species **161** emerges (88JCS(D)1437). In contrast, with $[Os_3(CO)_{10}(AN)_2]$, two isomers, **162** and **163**, result (88JOM (353)251). Isomer **162** enters the CO/AN monosubstitution reaction in acetonitrile in the presence of $Me_3NO{\cdot}2H_2O$, the product on subsequent thermolysis forms the hexanuclear complex **164**.



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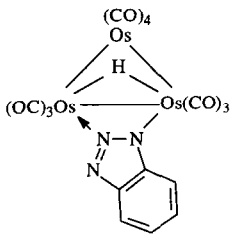

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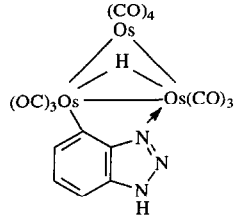

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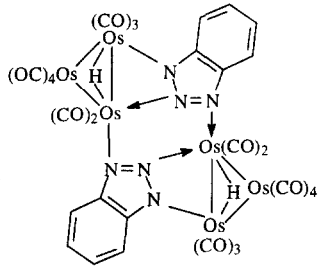
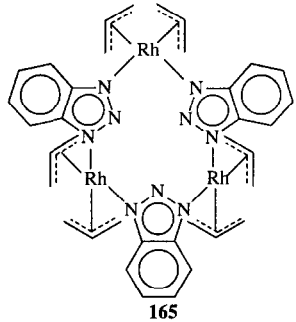


164

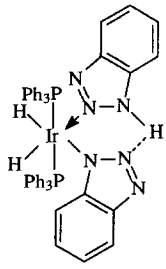
Benzotriazole with $[(\eta^3\text{-}C_3H_5)_2Rh(acac)]$ gives the trinuclear complex **165** (86JCS(D)2193).



165

Reaction of benzotriazole (HL) with $[IrCl(CO)(PPh_3)_2]$ in the presence of triethylamine gives the benzotriazolate derivative *trans*-$[IrL(CO)(PPh_3)_2]$ (78IC3026, 85JOM(280)261, 88P1781, 90JCS(D)621) together with the product of oxidative addition of benzotriazole, $[IrHClL(CO)(PPh_3)_2]$ (90JCS(D)621). With $[IrH_3(PPh_3)_3]$, the composite benzotriazole–benzotriazolate ligand forms the chelate **166**. Thallium benzotriazolate (TlL) with $[Ir(CO)(acetone)(PPh_3)]_2(PF_6)$ forms $[Ir(L)(CO)(PPh_3)]_4$ (78IC3026). The

rhodium analogue has the composition $[Rh(L)(CO)(PPh_3)]_6$. Thallium benzotriazolate with $[IrCl(CO)(PPh_3)_2]$ in benzene–acetone gives $[IrL_2(CO)(PPh_3)Tl]\cdot C_6H_6$, which tentatively has the structure **167**. In solution **167** gradually transforms into **168**.



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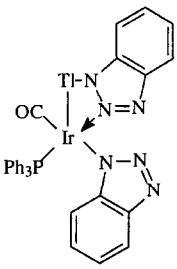

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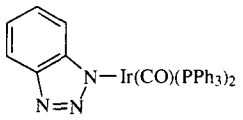
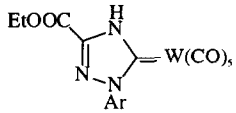


168

Benzotriazole (HL) with Me_2SAuCl in alkaline medium gives the polymeric $[AuL]_n$ (79IC658). Another synthetic approach is based on interaction of benzotriazole with Ph_3PAuCl in the presence of potassium hydroxide, which yields first Ph_3PAuL and then the decomposition product $[AuL]_n$.

B. Organometallic Complexes of 1,2,4-Triazole

Free carbenes based on 1,2,4-triazole are not as numerous as those based on imidazole (70ZN(B)1421, 95AGE1021, 97JA6668, 98JA9100). The carbene complex **169** (Ar = Ph, *p*-Tol) is prepared by the [3+2] cycloaddition route from $[W(CO)_5(C^+{=}NC^-HCOOEt)]^-$ and aryldiazonium (93OM3241). Oxidative decomplexation causes tautomerization of the 1,2,4-triazole ligand, the products being **170** (Ar = Ph, *p*-Tol).



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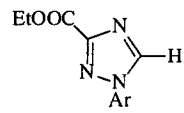
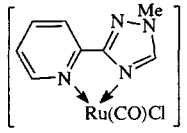


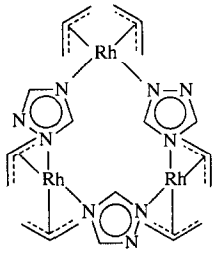
170

1-Methyl-3-(pyridin-2-yl)-1,2,4-triazole and $RuCl_3\cdot 3H_2O$ in refluxing DMF give **171** (90JCS(D)121). The chloride ligand in the product is replaceable by pyridine, acetonitrile, NCS^-, and sodium borohydride.



171

1,2,4-Triazole (HL′) tends to destroy the acetylacetonate framework from [Rh(acac)L_2] complexes (L_2 = $(CO)_2$, diene) (84JCS(CC)1687, 86JCS(D)1087). This, in particular, happens during the formation of [$Rh_3(\mu_3$-L′)(μ-Cl)Cl(η^4-tfb)$(CO)_4$], the complex with the intermolecular stacking arrangement of units. This complex follows from [Rh(acac)(tfb)], 1,2,4-triazole, and [$RhCl(CO)_2]_2$. 1,2,4-Triazole with [(η^3-$C_3H_5)_2$Rh(acac)] gives the trinuclear rhodium(III) complex **172** (86JCS(D)2193). This product with [Rh(μ-Cl)$(CO)_2]_2$ produces the mixed-valence trinuclear species **173** (L = CO) and with [(η^3-$C_3H_5)_2$Rh(μ-Cl)]$_2$ - **173** (L = C_3H_5). 1,2,4-Triazole with the dimers [(η^4-cod)M(μ-Cl)]$_2$ (M = Rh, Ir) in the presence of triethylamine gives **174** (M = Rh, Ir; L_2 = cod) (86JCS(D)1087). Further carbonylation yields **174** (M = Rh, Ir; L_2 = $(CO)_2$). One of the carbonyl ligands can be substituted with triphenylphosphine, the product being **174** (M = Rh, Ir; L_2 = (CO)(PPh_3)). Another way of preparation of dirhodium complexes **174** (M = Rh, L_2 = cod, nbd, tfb, 1,3,8-Me_3tfb, $(CO)_2$) originates from 1,2,4-triazole and [Rh(acac)L_2]. Complexes **174** contain the 1,2,4-triazolate ligand with uncoordinated nitrogen donor sites. Therefore, species **174** (M = Rh, L_2 = cod) experiences further reaction with [(η^4-cod)M′ (μ-Cl)]$_2$ or [Rh(μ-Cl)$(CO)_2]_2$ to yield **175** (M = Rh, M′ = Rh, Ir, L_2 = cod, L'_2 = cod; M = M′ = Rh, L_2 = cod, L_2' = $(CO)_2$). Carbonylation of **175** (M = M′ = Rh, L_2 = L_2' = cod) gives **175** (M = M′ = Rh, L_2 = L_2' = $(CO)_2$). Two-fold excess of the dimer [Rh(μ-Cl)$(CO)_2]_2$ when reacted with **174** (M = Rh, L_2 = cod, nfb, tfb; M = Ir, L_2 = cod) gives **176** (X = Y = Cl, M = Rh, L_2 = cod, nbd, tfb; X = Y = Cl, M = Ir, L_2 = cod). Species **174** (M = Rh, L_2 = $(CO)_2$) with excess [Rh(μ-Cl)$(CO)_2]_2$ gives **176** (X = Y = Cl, M = Rh, L_2 = $(CO)_2$). Traces of water in the solvent may cause the formation of the μ-hydroxo-complex **176** (M = Rh, L_2 = $(CO)_2$, X = OH, Y = Cl).



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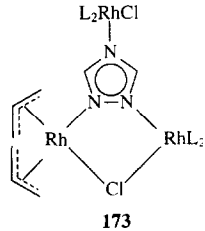

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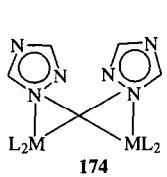

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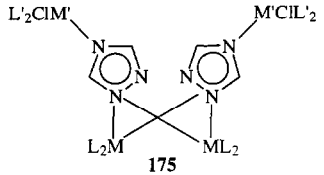

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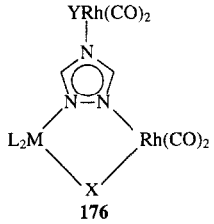
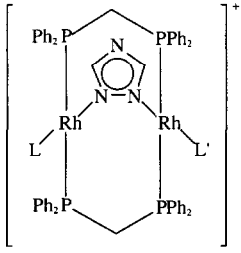


176

Lithium 1,2,4-triazolate (LiL) with $[(\eta^4\text{-cod})Rh(\mu\text{-Cl})(\mu\text{-PPh}_2)Rh(\eta^4\text{-cod})]$ gives $[(\eta^4\text{-cod})Rh(\mu\text{-L})(\mu\text{-PPh}_2)Rh(\eta^4\text{-cod})]$ (96JOM(509)89). Complex $[(\eta^4\text{-cod})Rh(\mu\text{-L})Rh(\eta^4\text{-cod})]$ with $[(\eta^4\text{-cod})Rh(\mu\text{-PPh}_2)Rh(\eta^4\text{-cod})]$ yields the hetero-bridged species $[(\eta^4\text{-cod})Rh(\mu\text{-L})(\mu\text{-PPh}_2)Rh(\eta^4\text{-cod})]$.

Lithium 1,2,4-triazolate with $[Rh_2(\mu\text{-Ph}_2PCH_2PPh_2)(CO)_2(\mu\text{-Cl})]PF_6$ gives the A-framed complex **177** (L = L′ = CO) (86IC4597). With one equivalent of *tert*-butyl isocyanide, substitution of one carbon monoxide ligand takes place to yield **177** (L = CO, L′ = *t*-BuNC), whereas two equivalents of *tert*-butyl isocyanide lead to the product of complete substitution, **177** (L = L′ = *t*-BuNC). The starting complex (L = L′ = CO) oxidatively adds molecular iodine to give the rhodium(II)–rhodium(II) cationic species **178**.



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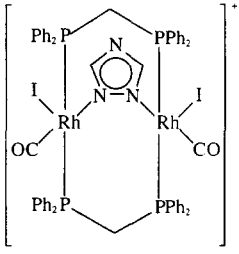


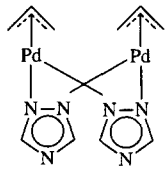
178

1,4-Dimethyl-1,2,4-triazolium iodide with nickel(II) acetate gives the carbene complex $I_2Ni(1,4\text{-dimethyl-}1,2,4\text{-triazol-}5\text{-ylidene})_2$ (97OM2209).

1,2,4-Triazole and $[Pd(\mu\text{-Cl})]L]_2$ (L = η^3-C_3H_5, η^3-C_4H_7) in the presence of potassium hydroxide give the dinuclear species **179** (L = η^3-C_3H_5, η^3-C_4H_7)

(86JCS(D)1087). Complexes **179** (L = η^3-C_3H_5, η^3-C_4H_7) experience further reaction with $[Rh(\mu\text{-}Cl)(CO)_2]_2$ and give the tetranuclear products **180** (allyl shown is η^3-C_3H_5 or η^3-C_4H_7). 1,2,4-Triazole reacts first with $[Pd_2Cl_2(\eta^3\text{-}L)]$ (L = C_3H_5, C_4H_7) and then $[Rh(acac)(CO)_2]$ to yield the tetranuclear species **180** (85ICA(100)L5), where the heterocyclic ligands are tridentate. The product reacts with the rhodium(I) dimer $[Rh(CO)_2Cl]_2$ to give the trinuclear complex **181**. In the solid state, the molecules of this complex form the intermolecular stacks along the *z*-axis.

1,4-Dimethyl-1,2,4-triazolium iodide with palladium acetate yields the carbene adduct **182** (97JOM(530)259). Under water it undergoes *cis-trans* isomerization to **183**. Some other derivatives were reported in 1981 (81BCSJ800). 1,1′-Methylenebis(4-alkyl-1,2,4-triazolium)diiodides (alkyl = *i*-Pr, *n*-Bu, octyl) with palladium(II) acetate give the mononuclear complexes $[L_2PdI_2]$ (99EJIC1965), where L_2 = 1,1′-methylenebis(4-R-1,2,4-triazol-2-ylidene) (R = *i*-Pr, *n*-Bu, octyl). Thermolysis of the products in THF gives the *trans*-dinuclear complexes **184**



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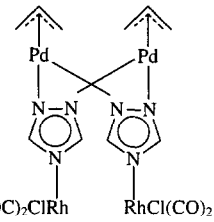

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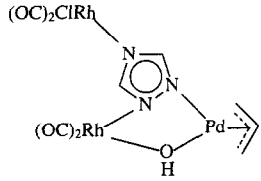

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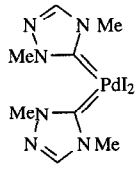

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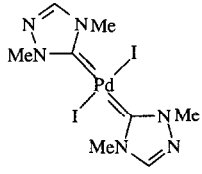

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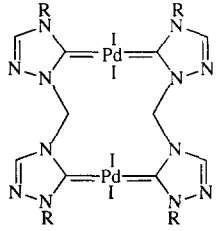
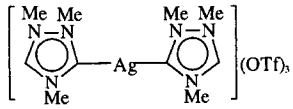


184

(R = *i*-Pr, *n*-Bu, octyl). The reaction of 1,1′-methylenebis(4-methyl-1,2, 4-triazolium)diiodide with palladium(II) acetate however proceeds differently and gives the cationic dicarbene $[L_2Pd(O_2CMe)]I$.

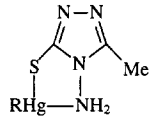
1,2,4-Triazole (HL) with Me_2SAuCl, the gold(I) species, in the presence of potassium hydroxide gives the polymeric complexes $[AuL]_n$ with exobidentate coordination mode of the azolate ligand (79IC658).

The dicationic ditriflate salt of 1,2,4-trimethyltriazolium with silver acetate gives the bis-carbene complex **185** (00JOM(600)112). In excess silver acetate, the one-dimensional polymeric species with alternating silver ions and 1,2,4-triazol-3,5-diylidene carbenes result, where both carbon atoms of each heteroring are engaged in coordination.



185

4-Amino-3-methyl-5-thione-1,2,4-triazole with [HgR(MeCOO)] (R = Me, Ph) gives complexes **186**, where coordination occurs via the sulfur and amino nitrogen atoms (93JOM(450)41). In the crystalline state, intermolecular interaction of the mercury site with the endocyclic nitrogen atom of the neighboring unit is also observed.

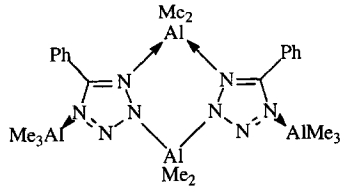


186

C. Organometallic Complexes of Tetrazole

Tetrazole exists as two tautomers, 1-H and 2-H, and although the tetrazolate anion is potentially tetradentate, all four nitrogen atoms function as donor centers extremely rarely. The mono- or bidentate donor functions predominate (88AIC171), in particular in the lithium μ_3-tetrazolate polymeric complex (93JOM(455)29) and the μ_4-tetrazolate silver salts (99AGE3488). Another unusual bridging mode μ-η^1:η^2 occurs in the organolanthanide complexes (98JOM(563)101).

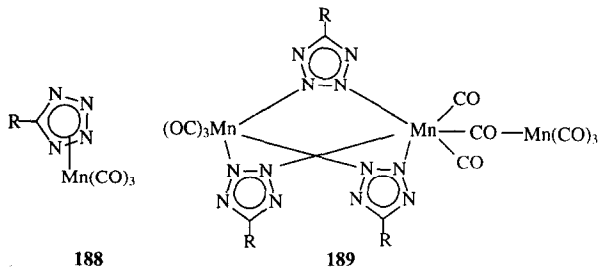
5-Phenyltetrazole (HL) with AlR_3 gives a variety of species $[R_{3-n}AlL_n]$ (n = 1, R = Me, Et, *i*-Bu; n = 2, 3, R = Me) (98P2237). Compound $[Me_2AlL]$ with $AlMe_3$ yields a dimer **187**. The cycloaddition reaction of diphenylthallium azide and



187

benzonitrile gives 1-diphenylthallium-5-phenyltetrazole (00JCS(D)1053). Some tin chemistry of 5-phenyltetrazole is also known (89JOM(361)C5, 94JOM(484)33, 94P2809, 96JCS(D)835, 96JCS(D)847, 96JCS(D)1857, 99JCS(D)1851, 99JOM(587)101, 99P2961, 00JCS(D)1663).

Sodium tetrazolates carrying the fluoro-containing substituents F_2NCF_2 and CF_3 at the carbon atom with $BrMn(CO)_5$ give products **188** ($R = F_2NCF_2$, CF_3) (89IC893). The η^5-coordination in solution follows from the fact that tetrazolates are isoelectronic with cyclopentadienyl and from some spectral data but not from the accurate structural determination, and therefore, should be regarded as tentative. As the solvent is removed, species **189** ($R = F_2NCF_2$, CF_3) with the normal bridging mode result. Dissolution of **189** ($R = CF_3$) in diglyme, petroleum ether, and methylene chloride gives the anionic species **190**, where $Na(diglyme)_2^+$ serves as the counter-ion.



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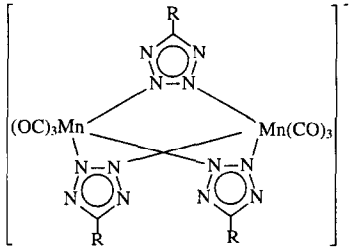
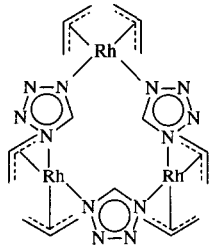


190

Tetrazole with $[(\eta^3\text{-}C_3H_5)_2Rh(acac)]$ gives the trinuclear complex **191** (86JCS(D)2193). This product with $[Rh(\mu\text{-}Cl)(CO)_2]_2$ produces the mixed-valence trinuclear species **192.**



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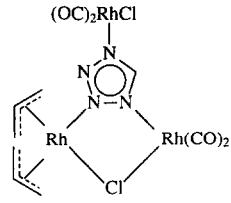

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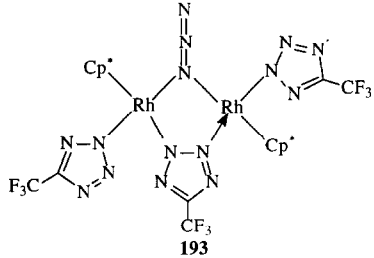
Tetrazole (HL) with $[(\eta^4\text{-}L'_2)Rh(\mu\text{-}Cl)]_2$ (L′ = cod, tfb) in the presence of triethylamine gives $[(\eta^4\text{-}L'_2)Rh(\mu\text{-}L)]_2$ (88JCS(D)1927), which on carbonylation is converted to $[(OC)_2Rh(\mu\text{-}L)]_2$. Tetrazole with $[(\eta^4\text{-}L'_2)Rh(\mu\text{-}Cl)]_2$ (L′ = cod, tfb), $[Rh(acac)L''_2]$ (L″$_2$ = cod, tfb; L″ = CO), and sodium azide produces a series of the heterobridged species $[(\eta^4\text{-}L_2')Rh_2(\mu\text{-}L)(\mu\text{-}N_3)L''_2]$ ($L_2' = L_2''$ = cod, tfb; L_2' = cod, L″ = CO). These products still have uncoordinated nitrogen centers, and further reaction with $[Rh(\mu\text{-}Cl)L'''_2]_2$ (L‴$_2$ = cod, L‴ = CO) provides the trinuclear products $[Rh_3(\mu_3\text{-}L)(\mu\text{-}N_3)ClL'_2L''_2L'''_2]$ ($L'_2 = L''_2$ = cod, L_2''' = cod, $(CO)_2$; $L'_2 = L''_2$ = tfb, L‴$_2$ = $(CO)_2$; L'_2 = cod, $L''_2 = L'''_2 = (CO)_2$). The product of the reaction of $[(\eta^4\text{-}L'_2)Rh(\mu\text{-}Cl)]_2[Rh(acac)L''_2]$ and tetrazole, $[(\eta^4\text{-cod})Rh(\mu\text{-}L)(\mu\text{-}Cl)Rh(\eta^4\text{-cod})]$, with $[Rh_2(\mu\text{-}Cl)_2(CO)_4]$ also gives the trinuclear species $[Rh_3(\mu_3\text{-}L)(\mu\text{-}Cl)Cl(\eta^4\text{-cod})_2(CO)_2]$, which on carbonylation gives $[Rh_3(\mu_3\text{-}L)(\mu\text{-}Cl)Cl(CO)_6]$. The latter forms stacks through the Rh···Rh intermolecular contacts. Lithium tetrazolate (LiL) with $[(\eta^4\text{-cod})Rh(\mu\text{-}Cl)(\mu\text{-}PPh_2)Rh(\eta^4\text{-cod})]$ gives $[(\eta^4\text{-cod})Rh(\mu\text{-}L)(\mu\text{-}PPh_2)Rh(\eta^4\text{-cod})]$, the product of substitution of the bridging chloride ligand by the tetrazolate group (96JOM(509)89).

The azido complex $[(\eta^5\text{-}Cp^*)(N_3)Rh(\mu\text{-}N_3)_2Rh(N_3)(\eta^5\text{-}Cp^*)]$ with trifluoroacetonitrile gives the tetrazole complex with two terminal and one bridging tetrazolate ligands as well as one unreacted bridging azido group, **193**



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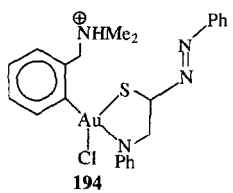
(79JCS(D)371). The same rhodium precursor with a series of isocyanides RNC (R = *t*-Bu, Cy, $CH_2CH_2CH_2Cl$, $CH_2CH{=}CH_2$, CH_2COONa) gives [(η^5-Cp^*)Rh(RNC)(CN_4R)], a carbene series containing the C-coordinated tetrazoles (00JOM(613)159).

1-R-5-Tetrazolyllithiums (R = Me, Cy) with [$(Et_3P)_2NiCl_2$] give bis(1-R-5-tetrazolate)nickel(II) (R = Me, Cy), which contain the nickel–carbon bond (66JA4266, 68JA309). The structure of the complex is postulated to be polymeric and octahedral, in which each nickel atom is coordinated via one carbon and two nitrogen atoms of the tetrazolate ring. The azide ion and platinum methyl isocyanide complexes $[(Ph_3P)_2Pt(CNMe)_2]^{2+}$ produce the C-bonded tetrazolate species $[(Ph_3P)_2Pt(CNMe)(CN_4Me)]^+$ and $[(PPh_3)_2Pt(CN_4Me)]$ (71JA5424). Complexes $[(Me_3P)_2M(Me)(CN_4R)]$ (M = Pd, Pt; R = Me, Ph) can also be obtained by the azide–isocyanide method (97JOM(538)189). $Na_2[Pd(N_3)_4]$ with isocyanides RNC (R = *t*-Bu, Cy, $(CH_2)_2CH_2Cl$, $CH_2CH{=}CH_2$) gives *cis*-$[Pd(CN_4R)_2(CNR)_2]$ (R = *t*-Bu, Cy, $(CH_2)_2CH_2Cl$, $CH_2CH{=}CH_2$) together with the polymeric products $[Pd(CN_4R)_2]_n$ (R = Cy, $(CH_2)_2CH_2Cl$, $CH_2CH{=}CH_2$) (00JOM(613)159). $[PtCl_2(dppe)]$ with tetrazole (HL) in the presence of potassium hydroxide gives the tetrazolate complex $[PtL_2(dppe)]$ (79JCS(D)1851) with the *N*-bonded tetrazolate ligands.

Tetraphenylarsonium tetraazidoaurate(III) (69CB1976) and cyclohexyl isonitrile give the *C*-bound tetrazolate complex $(AsPh_4)[Au(CN_4Cy)_4]$ (67AGE169, 72ZN(B)745). The range of such complexes can be further extended to R = Me, CF_3, *i*-Pr, CH_2Ph, Ph, *p*-Tol (68INCL143, 69CB3637, 71CB1818, 79CB468). For the case R = *i*-Pr, the X-ray structural proof exists (72JA3370). Sodium and lithium tetraazidoaurates(III) with isocyanides RNC (R = *t*-Bu, Cy) give the carbene species lithium and sodium tetrakis(1-*tert*-butyl-tetrazol-5-ato)aurate(III) (00JOM(613)159). Protonation of the products occurs at the N^4 atom and leads to the neutral products.

Sodium 1-methyl-5-mercaptotetrazolate reacts with species **194** to yield the neutral complex **195** (99P749). Similar species are known [96JCS(D)1011, 98ICC873)].



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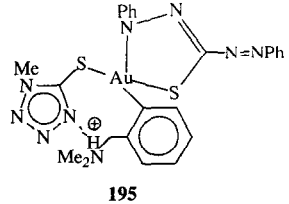

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D. The Problem of Pentazole

1-Phenylpentazole (56AG705, 57CB2914) contains a heteroaromatic ring (75JCMS137, 83JCS(CC)910). Parent pentazole is however not known and the pentazolate anion has been mentioned only as a possible intermediate (81JA6248). Theoretical estimates (83CJC1435, 85P1721, 90JPC6923, 92JA8302, 93JPC8200, 96IC7124) are in favor of the possibility of its existence, although there are some doubts with respect to its kinetic stability (93AGE230). Pentazole is a direct analog of cyclopentadienyl, and the possibility of the η^5-complex-formation of N_5^- ions is intriguing (85P1721).

III. Conclusion

1. Imidazole is characterized mainly by the $\eta^1(N)$ coordination mode, where N is the nitrogen atom of the pyridine type. The rare coordination modes are η^5- (π-) realized in the ruthenium complexes, μ-$\eta^2(C,N)$- in organoruthenium and organoosmium chemistry. Imidazolium salts and stable 1,3-disubstituted imidazol-2-ylidenes give a vast group of mono-, bis-, and tris-carbene complexes characterized by stability and prominent catalytic activity. Benzimidazole follows the same trends. Biimidazoles and bibenzimidazoles are ligands as the neutral molecules, mono- and dianions. A variety of the coordination situations is, therefore, broad, but there are practically no deviations from the expected classical trends for the mono-, di-, and polynuclear *N*-complexes.

2. For 1,2,3-triazole, the $\eta^1(N^1)$, μ-$\eta^2(N^1,N^2)$, and $\eta^1(C)$ carbene coordination modes prevail in organometallic compounds. Benzotriazole has the same general pattern but often operates as a composite unit of benzotriazole and benzotriazolate linked by the hydrogen bond. In some organoosmium compounds, the μ-$\eta^2(N^1,C^6)$ mode is realized, where the C^6-center refers to the annulated benzene ring. In some variations, together with the μ-$\eta^2(N^1,N^2)$ mode, the $\eta^1(N^3)$ monodentate coordination occurs. The μ-$\eta^2(N^1,N^3)$ mode can also be traced.

3. 1,2,4-Triazole reveals the $\eta^1(C)$ carbene function, μ-$\eta^2(N^1,N^4)$ bridges with subsequent coordination via the N^2 site, μ-$\eta^2(N^1,N^2)$ bridges with subsequent coordination to the N^4 site.

4. Tetrazole forms $\eta^1(C)$-carbenes, μ-$\eta^2(N^1,N^2)$: $\eta^1(N^4)$, and μ-$\eta^2(N^2,N^3)$: μ-$\eta^2(N^1,N^4)$ mode complexes. Suspected η^5-mode of coordination still remains unconfirmed. The organometallic chemistry of pentazole is the challenge for the further developments.

Abbreviations

Ac	acetyl
acac	acetylacetonate
AN	acetonitrile
bim	biimidazolate
Bu	butyl
cod	cycloocta-1,5-diene
Cp	cyclopentadienyl
Cp^*	pentamethylcyclopentadienyl
Cy	cyclohexyl
DMF	dimethylformamide
dmgH	dimethylglyoxime
dppe	1,2-bis(diphenylphosphino)ethane
dppm	bis(diphenylphosphino)methane
Et	ethyl
Fc	ferrocenyl
imH	imidazole
Me	methyl
Mes	mesityl
nbd	norborna-2,5-diene
Ph	phenyl
phen	1,10-phenanthroline
Pr	propyl
py	pyridine
solv	solvent
tfb	tetrafluorobenzobarrelene
thd	tris(2,2,6,6-tetramethylheptane-3,5-dionato)
THF	tetrahydrofuran
THT	tetrahydrothiophene
Tol	tolyl
TTF	tetrathiofulvalene
Vin	vinyl

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ADVANCES IN HETEROCYCLIC CHEMISTRY, VOL. 83

Aromatic Nucleophilic Denitrocyclization Reactions

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I. Introduction

Sufficiently activated aromatic nitro groups are known to undergo replacement by various nucleophiles (51CR273, 78T2057, 91MI1, 95CR2261). The intramolecular version of this reaction, where the nucleophilic group is incorporated into the formed ring, is called "aromatic nucleophilic denitrocyclization". The rings formed are usually five-, six-, or less commonly seven- or eight-membered; O^-, S^-, Se^-, RN^- or carbanions have been involved as nucleophiles. In the simplest case of benzene derivatives, the denitrocyclization reaction can be exemplified by (Eq. 1), where R is an activating group, A is a moiety incorporated into the formed ring, and X^- is a sufficiently reactive nucleophilic anion.

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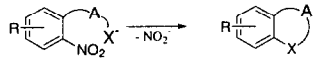


(1)

In general, the reactivity of a nitro group in nucleophilic displacement reactions is considered to be higher than that of the corresponding chloro and comparable to the fluoro derivatives (72JCS(P2)385, 80C1). However, for some weakly activated compounds the mobility of the nitro group is comparable or even higher than that of fluorine atom. In spite of these facts, synthetic use of the nucleophilic displacement reactions of the nitro group is negligible compared to the same displacement of halogens.

However, especially for intramolecular nucleophilic displacements the nitro group is a very useful leaving group. The starting nitro compounds are often easily available and the special features of the nitro group cause the high reactivity. For useful reactivity, the molecule to be cyclized should be able to adopt a conformation where the reacting centers are at an appropriate distance (77ZFK279, 79JST211). The energetically advantageous conformation can be influenced by the H-bonds formed in the molecule. This influence can be either positive, if the stabilized conformation is suitable for the cyclization, or negative, if the stabilized structure cannot cyclize. In case of negative influence, it can be circumvented either by alkylation or acylation of the H-donor atom. Another possibility is to work in solvents which are able to act as H-bond acceptors, e.g., DMSO.

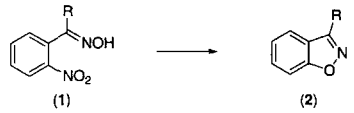
Aromatic denitrocyclizations have been used for many years in some well-known synthetic reactions. Probably the best known example is the Turpin synthesis of phenoxazines and similar synthesis of phenothiazines. The classical setup used usually base-catalyzed reactions in polar protic solvents, very often alcohols. In many cases using polar aprotic solvents was found advantageous. Besides the mentioned influence of the H-bonding, better ionization and lower solvation of the nucleophile are also important. S_NAr reactions proceed through strongly polarized complexes, which are well soluble and highly polarized in polar aprotic solvents.

Nevertheless, the advantages of the denitrocyclization strategy are usually based not on the denitrocyclization step but on the easy availability of the starting compounds. The presence of the nitro group, which is then displaced in the denitrocyclization step, is often necessary for a previous reaction step that is enabled by its electronegative nature. For this reason, schemes given in this review often show also such reaction steps. With the exception of a minireview (93MI1) and a review in Russian (82KGS867), there is no review available dealing specifically with this subject. This paper should fill the gap and help to widen utilization of the denitrocyclization reactions, the synthetic potential of which is far from being exhausted.

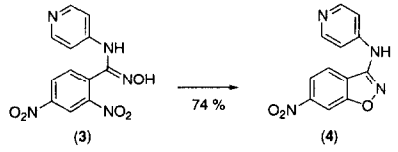
II. Cyclization Leading to Five-Membered Rings

A. Reactions Involving Attack by Oxygen Nucleophiles

One of the longest known denitrocyclizations is formation of benzisoxazoles **2** from oximes of the corresponding *ortho*-nitrophenyl ketones **1** under alkaline conditions (Eq. 2) (1893CB1250). The reaction does not require presence of additional activating groups, but the yields are relatively low due to the fact that only the *cis*-isomers are able to cyclize. The nucleophilic substitution reaction is successful with a wide variety of substituents on the aromatic ring, including an electron-donating substituent *para* to the nitro group (09CB1310, 09CB3596, 12LA(390)23, 19BSF190, 19HCA84, 26JCS810, 58MI1, 64CB1902). For the synthesis of benzisoxazole-3-carboxylic acids (**2**; R = COOH), it is necessary to use the corresponding esters since the oximes of 2-oxo acids easily decarboxylate and dehydrate to give 2-nitrobenzonitriles (75JA7305, 75JA7312, 94JMC2308). A report describing synthesis of 3-amino derivative **4** from the corresponding amidoxime **3** using potassium *tert*-butoxide in THF has recently been published (Eq. 3). Unlike ketoximes, the *N*-monosubstituted amidoximes are conformationaly labile and therefore high yields of **4** were achieved even from isomeric mixtures of amidoximes where the *trans*-isomer prevailed (96TL995).

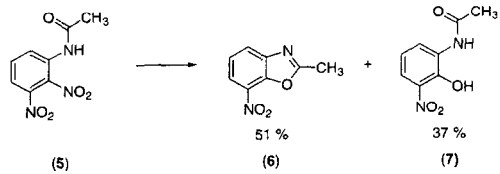


(2)



(3)

Heating 2,3-dinitroacetanilide (**5**) with sodium ethoxide in DMF gave a mixture of 2-methyl-7-nitro-benzoxazole (**6**) and 2-nitro-6-acetamidophenol (**7**) (Eq. 4). The latter is also formed under the same conditions from **6**. Consequently, the probable mechanism of the reaction involves primarily the denitrocyclization reaction leading to **6**, which is then partially hydrolyzed to **7** (80KGS417).

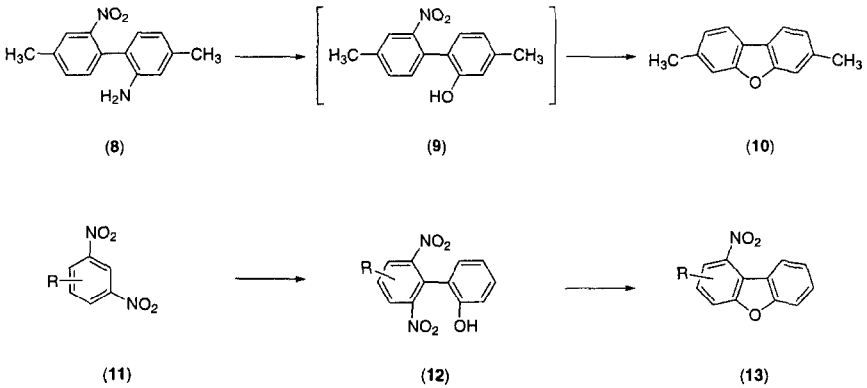


(5) (6) (7) (4)

During the diazotization of 2-nitro-2′-aminobiphenyl derivatives, e.g. 2-nitro-2′-aminobiphenyl **8**, the primarily formed hydroxy derivative **9** underwent cyclization to the final product **10** (01CB3325, 30G967). Several hydroxy biphenyl derivatives prepared by this or other methods were later used for the denitrocyclization reaction (30G967, 84KGS1690). High yields were obtained especially in the cyclization by sodium hydride in HMPT at room temperature. The present methodology allows access to a number of 1-nitro substituted dibenzofurans **13** from appropriately substituted 1,3-dinitrobenzenes **11** and aryl iodides. The nitro group could then serve as a source of other functionalities thus leading to a wide range of 1-substituted dibenzofurans (Scheme 1) (83AJC1281).

By analogy, thermal cyclization was described also for 6-nitro-2′-hydroxybiphenyl-2-carboxylic acids, e.g. **14**, obtained by other methods. The same product **15** was also formed from lactone **17**, prepared by oxidation of fluorenone **16** (Scheme 2). If the reaction was performed in DMF, the corresponding dimethylamide was isolated (82KGS703, 86KGS852, 87KGS314, 89MI1).

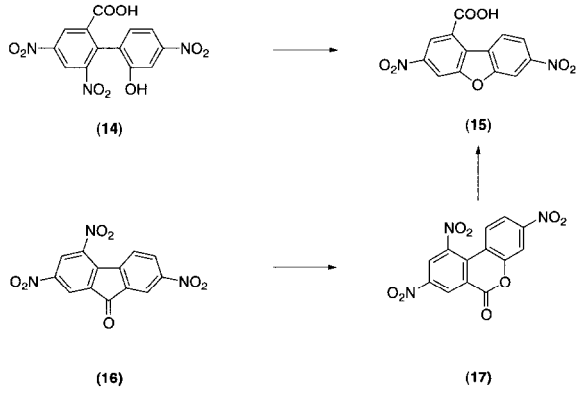
Attempts to prepare hydroxybiphenyl derivative **19** by treatment of tetranitro derivative **18** with sodium benzaldoxime led to a mixture of the required phenol **19** and dibenzofuran **20** (Eq. 5) (82JCS(P1)2299).



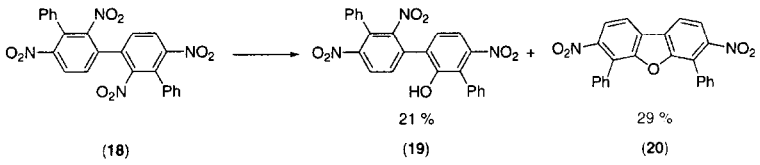
(8) (9) (10)

(11) (12) (13)

Scheme 1

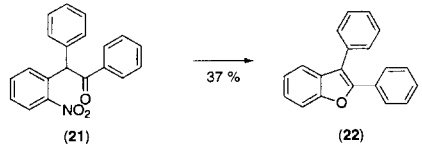


Scheme 2



(5)

Suitably stabilized enol forms also behave as oxygen nucleophiles, e.g., phenyl diphenylmethyl ketone **21**, β-diketones **23** (R^2 = R^3 = alkyl), or β-ketoesters **23** (R^2 = alkoxy, R^3 = alkyl) or **25** (Eqs 6–8) (78PJC1837, 87ZOR606). The reaction was used also for the synthesis of some aza analogs, e.g. **26** (73BCJ3144, 77BCJ237, 95MI1). The reaction combined with the vicarious nucleophilic substitution invented by Makosza (91S103, 97LA1805, 97PAC559) can represent an attractive route to this type of compounds.



(6)

(7)

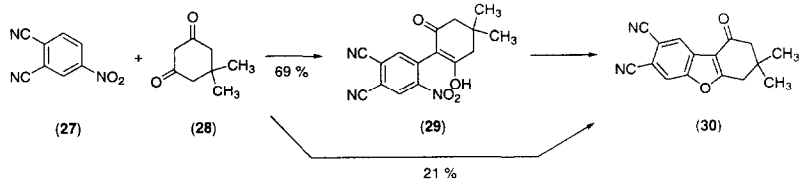
(25) (26) (8)

A similar reaction is probably involved in the reaction of 4-nitrophthalodinitrile (**27**) with dimedone (**28**), which provided under milder condition compound **29** and at a higher temperature tricyclic compound **30** (87ZOR2629). Similarly as in the vicarious nucleophilic reactions, intermediate **29** is formed by nucleophilic displacement of the *ortho*-hydrogen atom in **27** (Scheme 3).

1-Methyl-3,5-dinitro-1,4-dihydropyridin-4-one (**31**) treated with ethyl acetoacetate anion **32** is reported to provide σ-type adduct **33**, which then undergoes denitrocyclization reaction to give low yields of furo[3,2-*b*]pyridine derivative **34** (Scheme 4) (80BCJ2891).

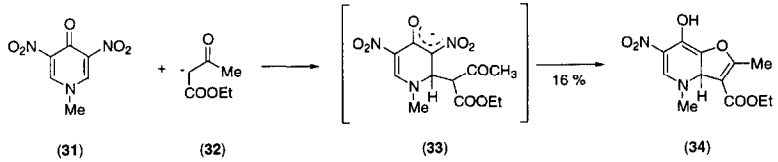
Low yields of 5-acyl-2,3-dihydropyrrolo[2,1-*b*]oxazoles (**37**) were obtained by treatment of 2-acyl-5-nitropyrrole (**35**) with ethylene oxide. Better yields are reported starting from hydroxy derivative **36a** or its acetate **36b** using sodium hydride in THF. The presence of an acyl group at the position 2 was found necessary for the cyclization (Scheme 5) (71JCS(C)2554).

Analogous reactions of 2,4-dinitroimidazole **38** with oxiranes gave mixtures of the major opened products **39** and minor 2,3-dihydroimidazo[2,1-*b*]oxazoles **40** (79JHC1499, 79JMC583, 84IJC(B)363). Similar behavior was also described



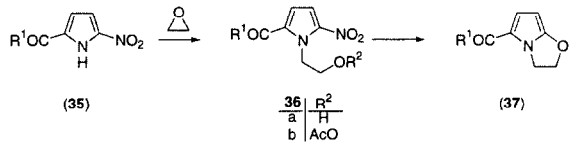
(27) (28) (29) (30)

Scheme 3



(31) (32) (33) (34)

Scheme 4

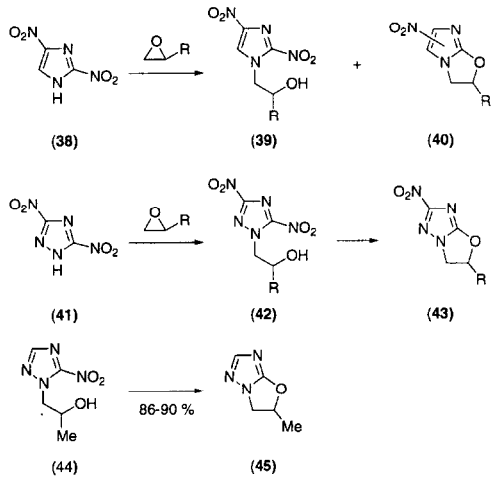


Scheme 5

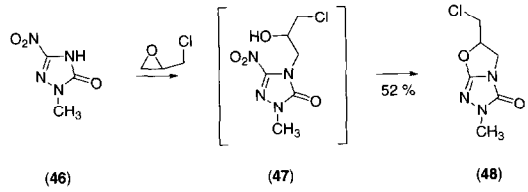
for 4,5-dinitroimidazoles (89PHA817) and 8-nitrotheophyllin (75JPC745). 3,5-Dinitro-1,2,4-triazole (**41**) provided intermediates **42**, which under mild conditions cyclized to give high yields of the only possible denitrocyclization products **43** (75KGS705). Easy intramolecular denitrocyclization was also observed when 5-nitro-1,2,4-triazole derivative **44** was treated with triethylamine and the corresponding product **45** was obtained in 86–90% yield (Scheme 6) (90T3211). Formation of triethylammonium nitrite in the reaction mixture was observed by ^{1}H-NMR spectroscopy.

Nitrotriazolone **46** with epichlorohydrine yielded intermediate **47**, which under similar conditions gave rather lower yield (52%) of **48** (Scheme 7) (77KGS1407).

Dinitro ketone **49** with potassium cyanide provided 5,6-dihydrooxazolo [3,2-*b*][1,2,4]triazole **51**. Its formation is due to the fact that primary attack by the cyanide anion is not directed at the ring C5 atom but rather at the carbonyl group to give the corresponding cyanohydrin **50** and the subsequent intramolecular displacement of the nitro group gives the final product (Scheme 8) (81KGS1403).

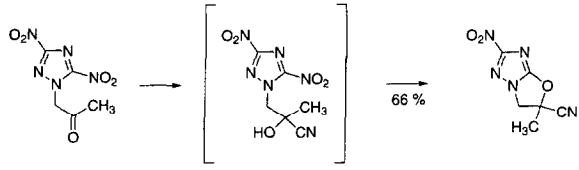


Scheme 6



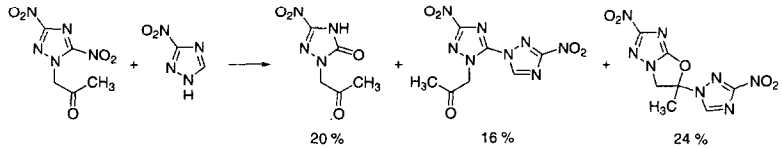
(46) (47) (48)

Scheme 7



(49) (50) (51)

Scheme 8



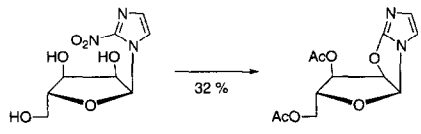
(49) (52) (53) (54) (55)

Scheme 9

The corresponding 6,7-dihydro-5*H*-[1,2,4]triazolo[5,1-*b*][1,3]oxazine can be obtained analogously.

The same compound treated with 3-nitro-1,2,4-triazole (**52**) in alkaline solutions provided a mixture of the corresponding 1,2,4-triazol-5-one (**53**), 5-substituted 1,2,4-triazole **54** and the product of denitrocyclization **55** (Scheme 9) (95ZOR1223).

Nucleoside analog **56** treated with sodium methoxide yielded a mixture, which after acetylation and chromatographic purification provided 27% of triacetate of the starting compound and 32% of diacetate **57** (Eq. 9) (78JOC4784).



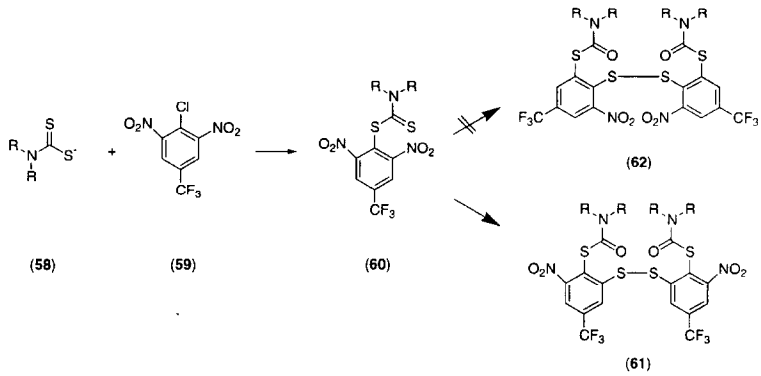
(56) (57) (9)

B. Reactions Involving Attack by Sulfur Nucleophiles

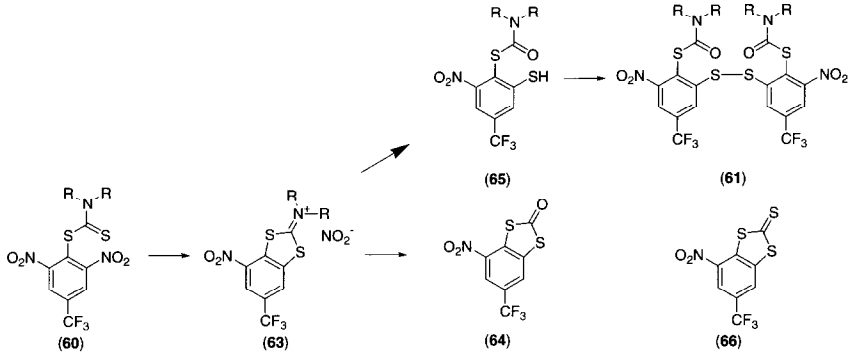
Dithiocarbamates **58** react with 2,6-dinitrochlorobenzene derivatives **59** under mild conditions to give 2,6-dinitrophenyl dithiocarbamates **60** (65JIC412). In polar aprotic solvents at elevated temperature, disulfides are formed. The structure suggested by D'Amico et al. based on the X-ray spectra as **61** (76JOC3564) was revised by Rasheed and Warkentin (77JOC1265) as **62**. However, the same authors later accepted the originally suggested structure (79JOC267) and found that the disulfides are usually only minor products (Scheme 10); the major products being the otherwise difficult to obtain 1,3-benzodithiol-2-ones **64**. The formation of **64** is explained by the intermediacy of **63**, which also explains formation of the mentioned disulfides via thiol **65**. This reaction was also applied for preparation of the corresponding aza analogs (81JHC1581). Minor modification of the reaction conditions enabled synthesis of the corresponding thiones **66** (Scheme 11) in good yields (80JOC4041).

Some 2,4-dinitrohalobenzene derivatives provide stable intermediates, e.g. **68** which undergo denitrocyclization on heating in suitable solvents. High yields of the corresponding 1,3-benzodithiol-2-ones **69** with reduced disulfide formation were observed especially with compounds bearing a dialkylamino group between the two nitro groups (Scheme 12) (77JOC1265). In the case of pyrimidine derivative **70** such treatment provided a good yield of **71**, which easily cyclized to the final product **72** (95KGS208).

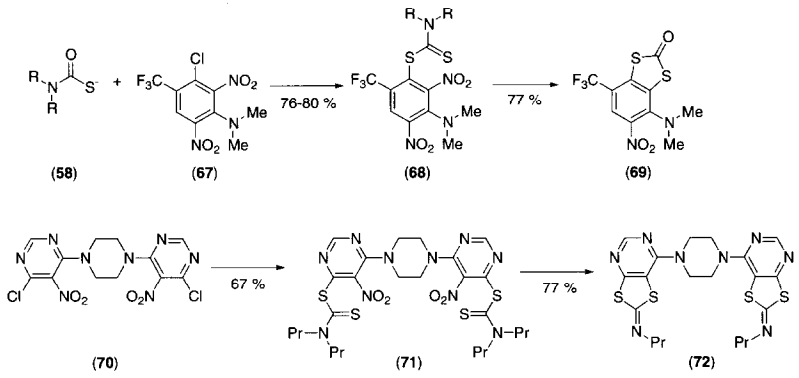
Low yields (9–40%) of 4-nitro-3*H*-benzothiazole-2-thiones **74** were obtained by treatment of the corresponding dinitroanilines **73** in DMF with carbon disulfide in the presence of sodium hydride (Eq. 10) (81JHC1597).



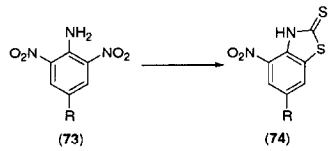
Scheme 10



Scheme 11

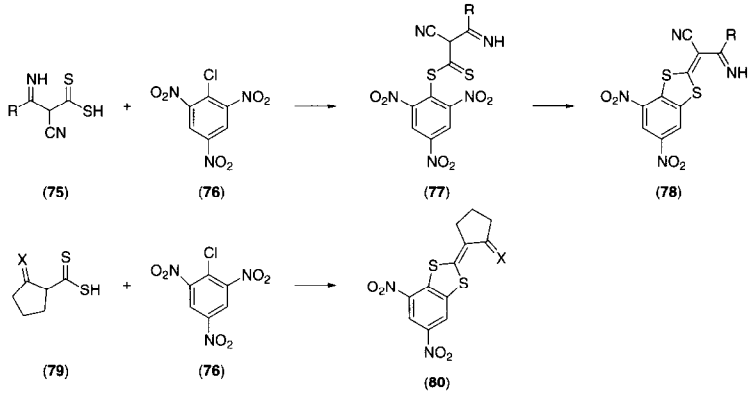


Scheme 12



(10)

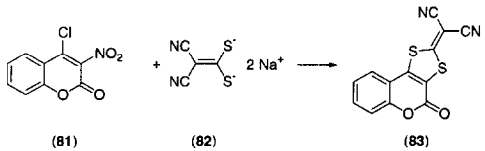
Similar reaction of dithiocarboxylic acids **75** with 2,4,6-trinitrochlorobenzene (**76**) in ethanol at 0°C yields thioesters **77**, which are then cyclized at room temperature to the final product **78** (77JCS(P1)1273). 2-Oxo- and 2-iminocyclopentane derivatives **79** provided compounds **80a** and **80b**, respectively (Scheme 13) (73JCS(P1)1009, 75JCS(P1)1277).



79,80	X	Yield
a	O	39 %
b	NH	62 %

Scheme 13

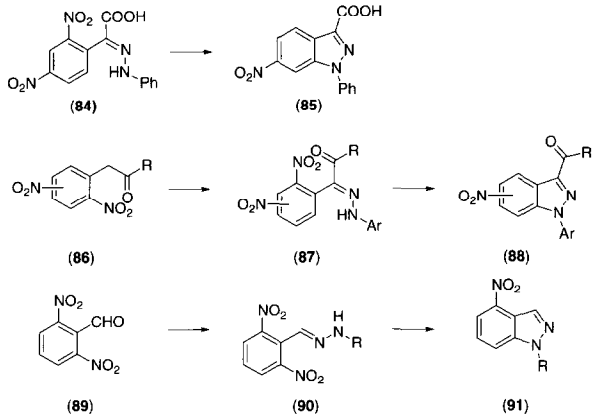
Disodium salt of 2-(dimercaptomethylene)malonodinitrile (**82**) afforded with **81** tricyclic compound **83** (Eq. 11) (91ZOR185).



(11)

C. Reactions Involving Attack by Nitrogen Nucleophiles

In 1889, Victor Meyer described the synthesis of indazolecarboxylic acid **85** by heating of phenylhydrazone **84** with sodium or potassium hydroxide (1889CB319). The usefulness of this simple reaction for the synthesis of many indazoles of a general structure **88** has been fully proven since (Scheme 14) (09CB601, 19HCA84, 34LA(510)287, 36LA(522)285, 38HCA1084, 64LA(677)157, 66JIC529). The presence of an additional nitro group in position 4 or 6 is necessary for the reaction. The starting phenylhydrazones **87** are usually prepared by coupling of the appropriate diazonium salts with 2-nitrophenylacetone or 2-nitrophenylacetic acid derivatives **86**. Analogously, a series of 2,6-dinitrobenzaldehyde hydrazones **90**, easily available from the corresponding aldehydes **89**, were converted to the corresponding 3-unsubstituted indazoles **91**;

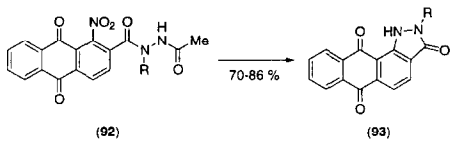


Scheme 14

beside a number of 1-aryl-4-nitroindazoles, 1-methyl-4-nitroindazole and 1-benzyl-4-nitroindazole were also prepared (13CB2380, 25CB1369).

Evidently, analogously to the mentioned cyclization of similar oximes to benzisoxazole derivatives (See Section II.A), reaction can take place only in compounds with suitable configuration. However, in case of hydrazones, due to the tautomeric equilibrium of both possible configurations, the reaction usually achieves complete conversion. The usual setup involves heating with the respective hydroxide; if an ester group is present, it is partially or completely hydrolyzed to the corresponding acids, which, in addition, can also undergo decarboxylation.

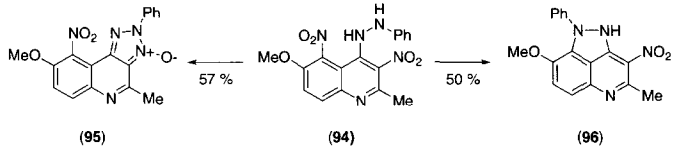
A series of anthraquinone derivatives **92** are reported to provide good yields of **93** (Eq. 12) (83KGS1621, 85ZOR1959).



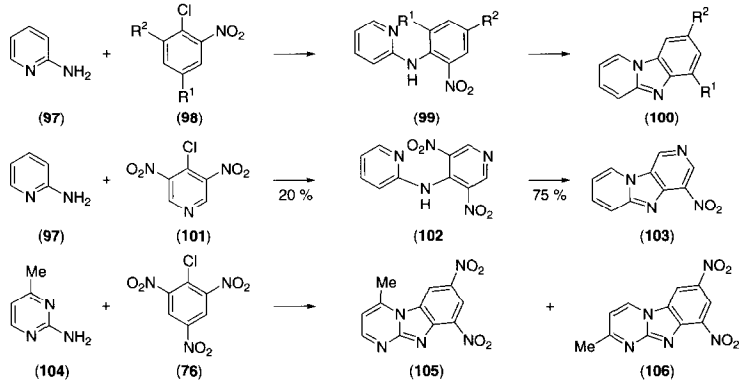
(12)

Dinitroquinoline derivative **94** under alkaline conditions condensed to give triazolo[4,5-*c*]quinoline oxide **95**. On the other hand, heating **94** in aqueous acetic acid is reported to provide 50% yield of **96** (Scheme 15) (80M963).

2,4-Dinitrochlorobenzene **98a** ($R^1 = NO_2$) or 2,6-dinitrochlorobenzene **98b** ($R^2 = NO_2$) derivatives treated with 2-aminopyridine (**97**) at room temperature



Scheme 15

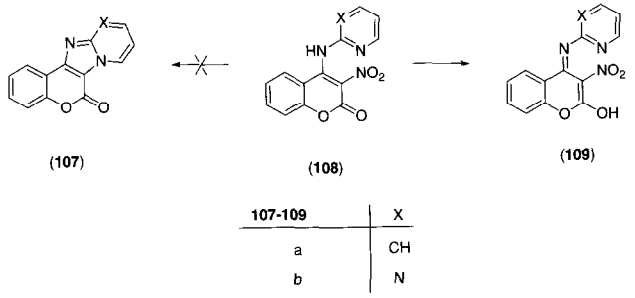


Scheme 16

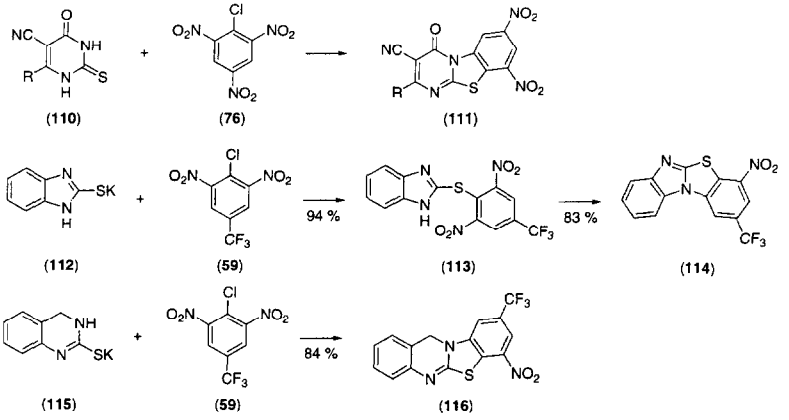
provided products of arylation of the exocyclic amino group **99**, which cyclized to benzo[4,5]imidazo[1,2-*a*]pyridines **100** by heating in *N*,*N*-dimethylaniline (Scheme 16). 2-Aminoqinoline and 9-aminophenanthridine provided analogous polycyclic products (38JCS1292, 39JCS1057, 55JCS3275, 80KGS1200, 86JHC1091). Similarly, reaction of 2-aminopyridine (**97**) with 3,5-dinitro-4-chloropyridine (**101**) provided, after cyclization, dipyrido[1,2-*a*;4′,3′-*d*]imidazole (**103**) (46JCS588). Low yields of analogous products were also obtained from the reaction of 1-chloro-2-nitroanthraquinone and 2-bromo-3-nitroanthraquinone with 2-aminopyridine (60T107). A high yield of a mixture of both possible benzo[4,5]imidazo[1,2-*a*]pyrimidines **105** and **106** was obtained analogously from 2-amino-4-methylpyrimidine (**104**) by Ochiai and Yanai (40YZ493). However, other authors failed to obtain high yields of the products although they studied the reaction systematically (Scheme 16) (52JCS784).

On the other hand, alkaline treatment of coumarin derivatives **108** did not lead to the expected cyclization products **107**, but isomerization to the corresponding chromenes **109** took place instead (Scheme 17) (96JHC351).

2-Thioxo-4-oxopyrimidines **110** treated with 2,4,6-trinitrochlorobenzene (**76**) are first arylated on the exocyclic thio group and the intermediates are then



Scheme 17

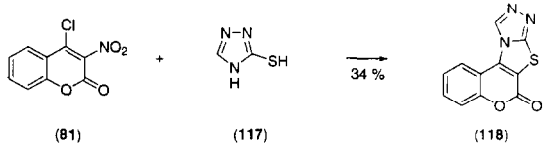


Scheme 18

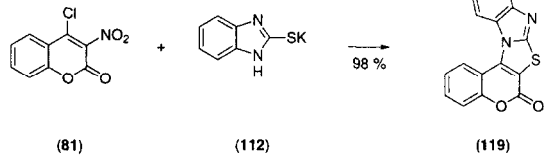
cyclized to the tricyclic compounds **111** (Scheme 18) (87LA797, 88LA1089, 89IJC(B)159, 89JPR893, 90EJM533, 92EJM851, 93IJC(B)876). Similarly, potassium salt of 2-mercaptobenzimidazole (**112**) treated with **59** at room temperature gave *S*-arylation product **113**, which was then cyclized at elevated temperature to give **114** (77JOC600). The 4,7-diaza analog of **112** (1*H*-imidazo-[4,5-*b*]pyrazine-2-thiol) under the same conditions provided a mixture of the corresponding opened intermediate and product of the denitrocyclization reaction (81JHC751). Similar reaction of quinazoline derivative **115** provided tetracyclic derivative **116** in 84% yield (Scheme 18) (87AP569).

1,2,4-Triazole-3-thiol (**117**) and 2-mercaptobenzimidazole (**112**) treated with **81** at ambient temperature are reported to provide 34% and 98% yield of products **118** and **119**, respectively (Eqs 13, 14) (85H2539). Though the assignment

was based mainly on the ^{13}C-NMR and the spectra were announced to be published elsewhere, the announced paper could not be located.



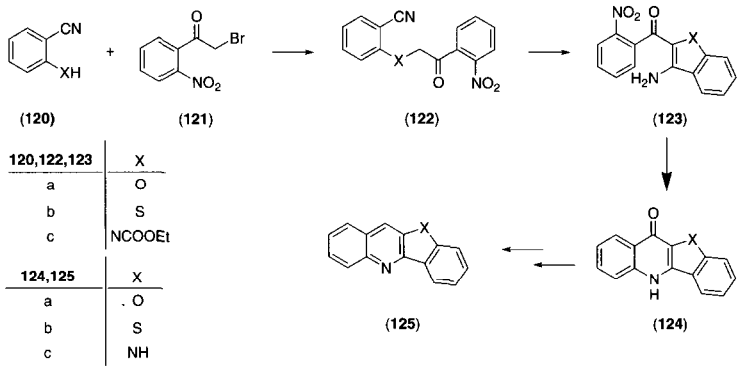
(13)



(14)

The denitrocyclization approach was applied to the synthesis of tetracyclic compounds **124**, which can be easily transferred in two steps into alkaloid quindoline (**125c**) or its analogs. This methodology starting from easily available nitriles **120** and 2-bromo-1-(2-nitro-phenyl)-ethanone (**121**) is based on an addition to the cyano group in **122** and following denitrocyclization of intermediates **123** (Scheme 19). Compared to the same strategy using fluoro derivatives, the nitro derivatives provided usually higher yields of the products under comparable conditions (000JHC855).

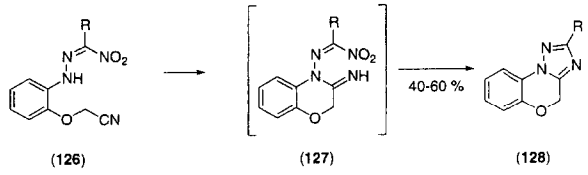
A similar reaction pathway is even described for an aliphatic nitro group nucleophilic displacement. Nitrohydrazones **126** with sodium hydride provide acceptable yields (40–60%) of tricyclic [1,2,4]triazolo[5,1-*c*][1,4]benzoxazines **128**



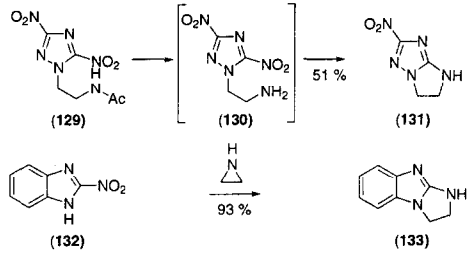
120,122,123	X
a	O
b	S
c	NCOOEt

124,125	X
a	O
b	S
c	NH

Scheme 19



Scheme 20

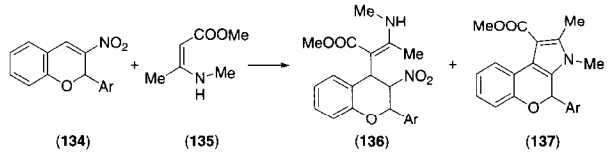


Scheme 21

(79S909). First, an addition of the cyano group takes place to give intermediate **127**, in which nucleophilic substitution of aliphatic nitro group provides the final product **128** (Scheme 20).

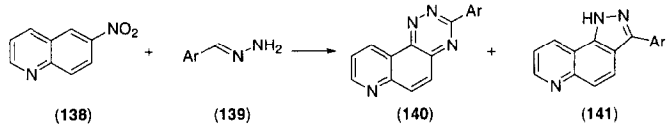
Acidic deacetylation of **129** followed by alkaline treatment of the intermediate **130** provided denitrocyclization product **131** in 51% overall yield (77KGS1271). A similar cyclized product was reported to be formed from 2-nitrobenzimidazole (**132**), which when treated with aziridine, instead of the corresponding aminoethyl derivative, provided 93% of benzimidazo[2,1-*b*]imidazole **133** (Scheme 21) (82JMC1342).

Reaction of nitro-2*H*-chromene derivatives **134** with **135** in methanol at room temperature afforded a mixture of the *Z*-isomer **136** and tricyclic compound **137**, which could be formed by denitrocyclization reaction of the corresponding primarily formed *E*-isomer and the following dehydrogenation (Eq. 15). The structural identification was based on the MS and ^{1}H-NMR, however, it is not sufficiently documented and similar examples are not known (91IJC(B)297).

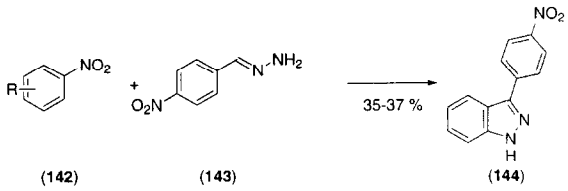


(15)

6-Nitroquinoline (**138**) undergoes direct cyclocondensation with aromatic hydrazones **139** in the presence of sodium hydride in DMF to give low yields of the corresponding [1,2,4]triazino[6,5-*b*]quinolines **140** and pyrazolo[3,4-*f*] quinolines **141** (Eq. 16). The mode of the cyclocondensation was found to depend considerably on the electronic nature of ring substituents of the aromatic hydrazones **139**. The electron-donating groups favor the ring closure with a neighboring nitro group to afford [1,2,4]triazino[6,5-*b*]quinoline ring system, while the electron-withdrawing nitro group tends to result in the denitrocyclization reaction to produce the pyrazolo[3,4-*f*]quinoline ring system. The best yield (50%) of a pyrazolo[3,4-*f*]quinoline compound was obtained with 4-nitrobenzaldehyde hydrazone **143**. This hydrazone treated with appropriate nitrobenzene derivatives **142** provided analogous indazole derivatives **144** in 35–37% yields (Eq. 17). The reaction was described for 1,3-dinitro-, 1,4-dinitro- and 4-chloronitrobenzene (000OL413).

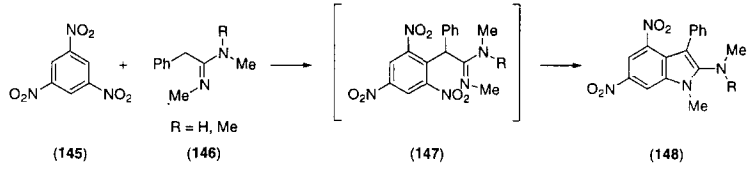


(16)

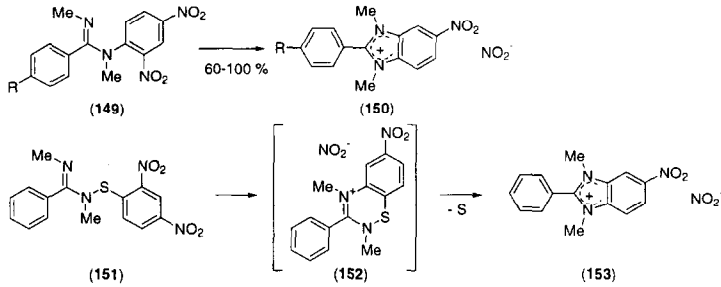


(17)

Highly electron-deficient 1,3,6-trinitrobenzene (**145**) treated with phenyl acetamidines **146** in ethanol provided low yields of a dinitroindole derivatives, probably 4,6-dinitroindoles **148** (77JOC435). Formation of indole derivatives **148** can be explained by nucleophilic substitution of the activated aromatic hydrogen leading to intermediates **147**, which then cyclized to the final products **148** (Scheme 22).



Scheme 22



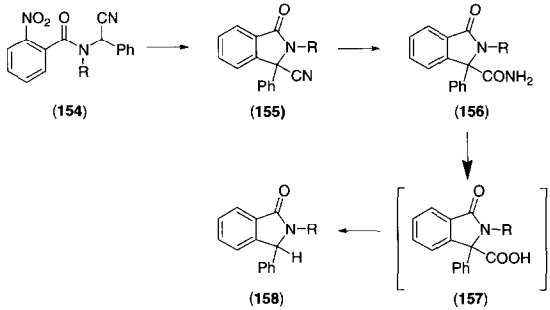
Scheme 23

Thermal cyclization of 2,4-dinitrobenzamidines **149** in boiling bromobenzene gave high yields of the corresponding benzimidazolinium nitrites **150**; quantitative yields are reported for trinitro derivative **149** (R = NO_2). The same moiety was obtained also by heating of **151**, probably intermediate **152** was formed first and subsequent extrusion of elemental sulfur provided the final product **153** (Scheme 23) (77TL3453). For reviews on the extrusion of sulfur see (87MI1, 88T6241, 96AHC39).

D. Reactions Involving Attack by Carbon Nucleophiles

Nucleophilic attack by carbanion occurs in the reaction of 2-nitrobenzamides **154** treated with sodium ethoxide (72JCS(P1)835). The reaction mixtures usually contain small amounts of nitrile **155** and carboxamide **156**, the product of decarboxylation **158** being usually the principal product (Scheme 24). The corresponding bromo derivatives under the used conditions did not react.

Formally similar intramolecular denitrocyclization reaction takes place during a fluoride-catalyzed Michael addition of nitrotoluenes **159** to unsaturated

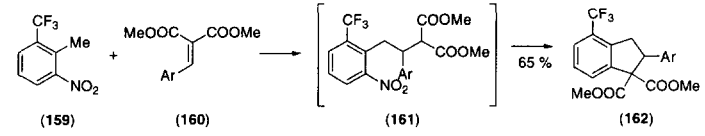


Scheme 24

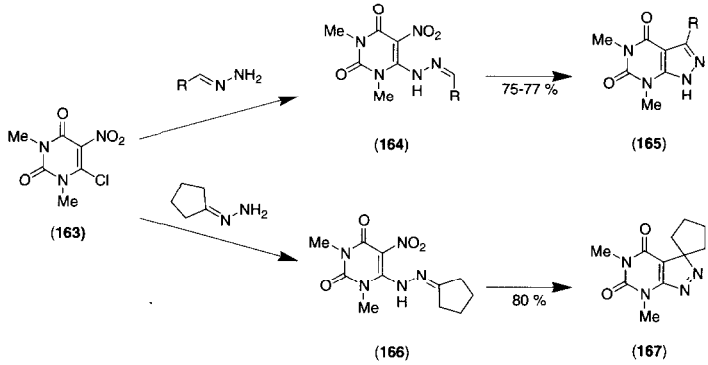
esters **160**. Intermediate Michael addition product **161** under the reaction conditions undergoes intramolecular nucleophilic displacement to give indanes **162** (Scheme 25). When a sterically demanding chiral camphorsulfonamide auxiliary was used as one of the ester group in **160**, a high degree of stereoselectivity was achieved. This reaction could be a useful route to chiral indane derivatives (94TL6595).

A series of interesting pyrazolo[3,4-*d*]pyrimidine derivatives was obtained by a thermal denitrocyclization reaction of hydrazones, e.g. **164** or **166**, easily formed from the corresponding aldehyde or ketone hydrazones with halonitrouracil derivatives, e.g. **163** (71CC1442, 72CC298). Intermediates **164** or **166** can be isolated and their cyclization in suitable solvents (methanol, DMF, DMSO) provided high yields of the products. Aldehyde hydrazones yielded the corresponding 1,7-dihydropyrazolo[3,4-*d*]pyrimidines, e.g. **165**, whereas ketone hydrazones gave 1,5-dihydropyrazolo[3,4-*d*]pyrimidine derivatives, e.g. spirocyclic compound **167** (Scheme 26).

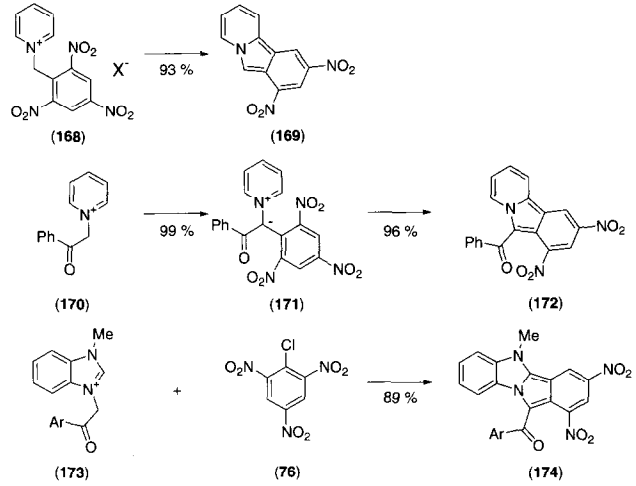
A different type of denitrocyclization reaction reported by Kröhnke et al. involving C-nucleophiles is represented by treatment of some *N*-(2,4,6-trinitrobenzyl)pyridinium salts, e.g. **168**, with sodium hydroxide providing high



Scheme 25



Scheme 26



Scheme 27

yields of benzo[*a*]indolizine derivatives **169** (66LA(697)158). Using betaines of a general formula **171**, easily available from **170** and 2,4,6-trinitrochlorobenzene (**76**), the reaction can be carried out with piperidine in DMSO at room temperature (Scheme 27). The same methodology was used also with other heterocyclic quarternary salts, e.g. **173**; the intermediate betaines were not isolated. The synthetic potential of this reaction can be further widened by the fact that the acyl groups in the products can be easily split off using sulfuric acid (66LA(697)158, 71CB2103).

III. Cyclization Leading to Six-Membered Rings

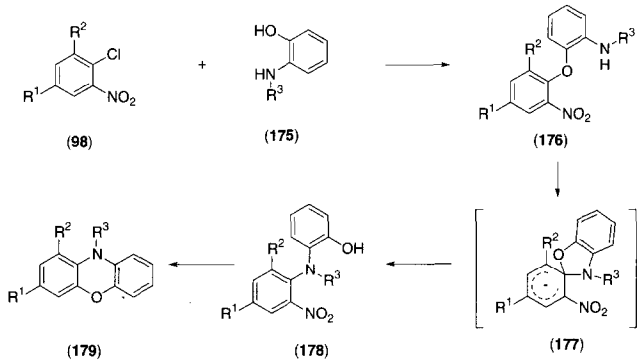
A. Reactions Involving Attack by Oxygen Nucleophiles

The best-known example of the denitrocyclization reactions is probably the Turpin synthesis of phenoxazines **179** (1891JCS714, 1899CB2601, 1899CB2605, 1899CB2686, 09LA(366)79, 11CB3730). The reaction starts from suitably activated *N*-(2-nitrophenyl)aminophenols **178**, which are usually synthesized by nucleophilic reactions of polynitrochlorobenzenes **98** with the corresponding aminophenol **175**; often **178** are not isolated. The classical setup used reflux of both starting compounds with aqueous ethanolic solution of sodium hydroxide, sodium acetate, or their mixture (56JIC671, 60ZOB1893, 61CB2551, 63CB1936, 66JCS(B)266, 68JIC1100, 68JMC913). The appropriate

O-aryl derivatives **176** are first formed and these intermediates then undergo the Smiles rearrangement to the corresponding *N*-aryl derivatives **178** (34JCS727, 35JCS196, 35JCS1309, 80ZOR876). For a review on the Smiles rearrangement and similar reactions see (66WCH155, 70OR99). Formation of the Meisenheimer complex **177** in the course of this rearrangement is supposed, and for some cases has been proved (Scheme 28) (80ZOR876).

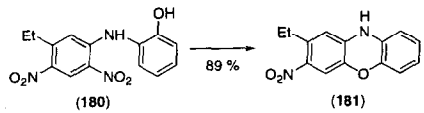
1–Nitrophenoxazine (**179**; $R^1 = R^3 = H$, $R^2 = NO_2$) can be prepared under relatively moderate conditions by denitrocyclization of 2′-hydroxy-2,6-dinitrodiphenylamine (**178**; $R^1 = R^3 = H$, $R^2 = NO_2$). On the other hand, similar cyclization of 2-hydroxy-2,4-dinitrodiphenylamine (**178**; $R^2 = R^3 = H$, $R^1 = NO_2$) is described to give only several percent yields of the corresponding phenoxazine under rather severe conditions (sodium acetate, glycerol, 200–300°C) (20CB2265). Brady and Waller did not succeed even under these harsh conditions (30JCS1218). This fact is explained by the easy formation of H-bonds between the NO_2 and the NH groups in the *N*-unsubstituted 2′-hydroxy-2-nitrodiphenylamines **178** ($R^3 = H$) and the nitro group not being accessible for the denitrocyclization. In 2,6-dinitro- or 2,4,6-trinitro derivatives, however, the formation of such H-bond complexes does not prevent the denitrocyclization reaction of the other *ortho*-nitro group. This explanation is supported by the fact, that the reaction of **178** ($R^2 = R^3 = H$, $R^1 = NO_2$) easily proceeds under relatively mild conditions (100°C) in DMSO where the NH group forms preferentially H-bond with the solvent and the nitro group is available for the cyclization reaction (63CB1927).

The presence of groups other than nitro (e.g. CH_3, OCH_3, I) at the position 6 also facilitates the Turpin reaction (30JCS1218, 60JIC647, 65JIC101). In this case, the steric influence of the groups must play an important role. A similar effect was also described for the 5-ethyl group; ethyl derivative **180** provided



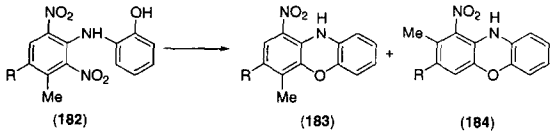
Scheme 28

under the classical Turpin's conditions the corresponding phenoxazine **181** in 89% yield (Eq. 18) (57JIC877). The same influence was found with an additional benzene ring condensed to the positions 5,6 of the benzene ring of the diphenylamine containing the nitro group (28HCA489). EWG-containing aminophenols provide usually significantly lower yields of the final phenoxazines. For example, 2-amino-5-nitrophenol with 2,4,6-trinitrochlorbenzene in DMF gave only 17% yield of the corresponding product (80ZOR876). Some probably erroneous papers decribe formation of phenoxazines without considering the Smiles rearrangement, i.e. (57MI1).



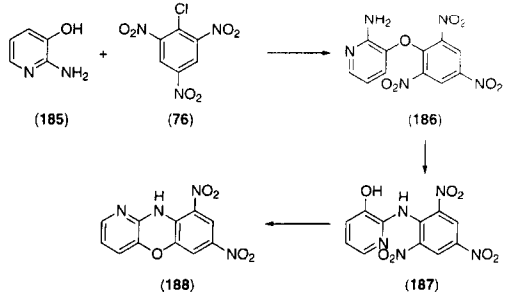
(18)

A more complex situation has been observed in case of 2-halo-6-nitro-2′-hydroxydiphenylamines, where both the halogen atom and the nitro group can serve as leaving groups. The preference of the chlorine atom to the nitro group is usually described. On the other hand, the nitro group is preferred to iodo substituent (24JCS2481, 52JIC193, 59JIC329, 63JIC400, 63JIC973, 65JIC101). Diarylamines unsymmetrically substituted in the benzene ring containing the leaving nitro group usually provide mixtures of all possible isomeric phenoxazines. An interesting selectivity was observed in a series of 2,6-dinitro-3-methyl-2′-hydroxydiphenylamines **182**, where the more sterically hindered nitro group in the vicinity of the methyl group was preferred as a leaving group giving isomers **183** as the major products while only small amounts, if any, of **184** were formed (30JCS1218, 80ZOR876) (Eq. 19).



(19)

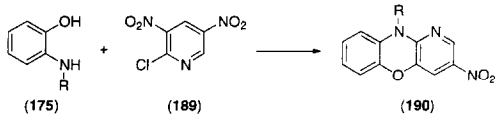
The Turpin reaction was done with a broad range of substituted diphenylamines, as well as their benzo (08CB3932, 23CB2385, 28HCA489) and aza analogs. The aza analogs are often prepared from the appropriate aminohydroxypyridines, e.g. **185**. Again, the Smiles rearrangement of the primarily formed ethers, followed by the denitrocyclization reaction providing the corresponding products,



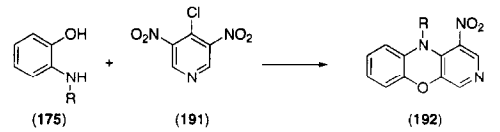
Scheme 29

e.g. **188**, was observed (Scheme 29). The reported yields range from low to nearly quantitative (36RZC502, 45JCS313, 59JA6049, 76JHC107).

Halonitropyridines also easily react with aminophenols to give the corresponding intermediates, which are suitable for the Turpin reaction. Eqs 20 and 21 show two literature examples of this reaction providing azaphenoxazines **190** and **192**, respectively (45JCS313, 58CPB46, 58CPB378).



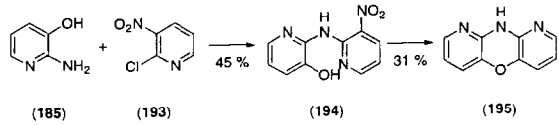
(20)



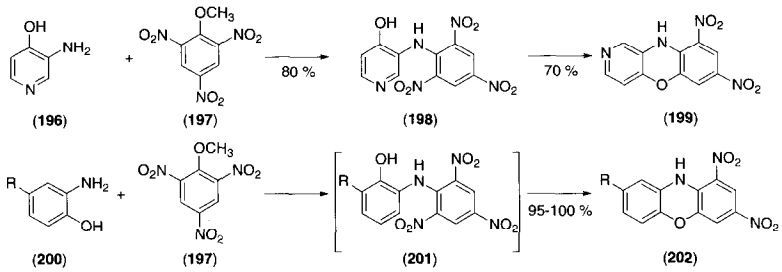
(21)

Treatment of 2-amino-3-hydroxypyridine (**185**) with 2-chloro-3-nitropyridine (**193**) easily provided intermediate **194**. Attempts to cyclize **194** with potassium hydroxide in aqueous ethanolic solutions failed, probably due to strong H-bonding. Similarly as with phenoxazines, the cyclization smoothly proceeded in DMSO to give low yield (31%) of 1,9-diazaphenoxazine (**195**) (Scheme 30) (74CC878, 76JHC107, 77H391).

2,4,6-Trinitrochlorobenzene (**76**) forms quarternary salts with some pyridine derivatives, e.g. with 3-amino-4-hydroxypyridine (**196**), and this fact narrows the



Scheme 30

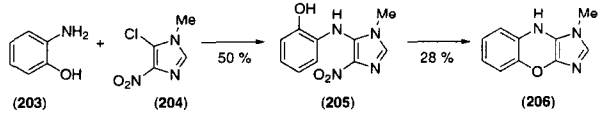


Scheme 31

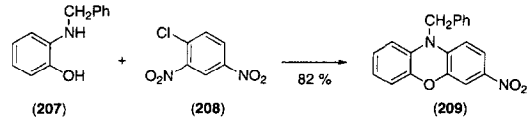
possibility to use it for the synthesis of the intermediate diarylamines. In such cases, the Misslin modification (19HCA285) using trinitroanisole (**197**) can be used (45JCS313, 58CPB46, 71IJS(B)345) (Scheme 31). This methodology was used also for the synthesis of some nitrophenoxazines **202**; nearly quantitative yields of the crude products were reported (19HCA285, 72MI1).

5-Chloro-1-methyl-4-nitroimidazole (**204**) was also used as a heterocyclic component in the Turpin reaction. Intermediate **205** was formed under mild conditions and its cyclization was achieved by heating with ethanolic dimethylamine in a sealed tube to give a blue-colored substance, which was attributed structure **206** (Scheme 32) (52JCS784).

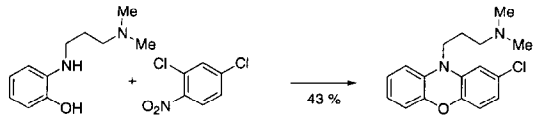
Sufficiently activated *N*-alkyl- (35JCS1312, 53JCS1499, 53JCS1504, 66JCS(B)266) and *N*-aryl- (35JCS1309) diphenylamino derivatives react especially easily in the Turpin reaction. This is exemplified by the preparation of 1-benzyl-3-nitrophenoxazine (**209**), which was prepared from **207** and **208** in 82% yield under the standard conditions used by Turpin after only 1 hour reaction time (Eq. 22) (53JCS1499). The *N,N*-dimethylaminopropyl group was also used as the *N*-alkyl group giving directly compound **212**, the phenoxazine analog of antipsychotic phenothiazine drug chloropromazine (Eq. 23). In this case, however, the achieved yields were lower than with the use of other known methods (61JOC2797, 62JOC4272). There are also several reports of the advantageous use of the *N*-acetyl derivatives in the Turpin reaction (19HCA285, 68MI1).



Scheme 32

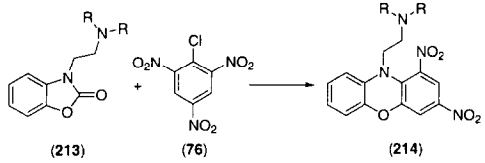


(22)

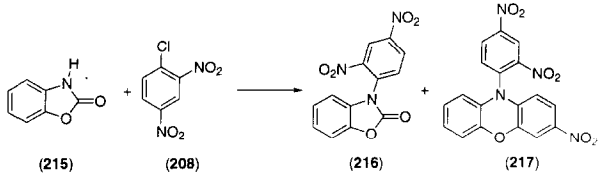


(23)

N-Alkyl-benzoxazolin-2-ones, easily obtained from the corresponding aminophenol and urea, can be used as synthetic equivalents of *N*-alkylaminophenols in the Turpin reaction. The reaction is exemplified by reaction of **213** with 2,4,6-trinitrochlorobenzene (**76**) giving phenoxazine **214** (Eq. 24). The corresponding *N*-alkylamino phenols are probably generated *in situ* (61AP57; 70MI1). This method was used also for preparation of some aza analogs (58CPB378). *N*-Unsubstituted benzoxazolinone (**215**) provided a mixture of *N*-arylbenzoxazolin-2-one **216** and *N*-arylphenoxazine **217** (Eq. 25) (85JHC1577). The same compound can be also prepared from 2-(2,4-dinitrophenylamino)-phenol with 2,4-dinitrochlorobenzene (35JCS1309).



(24)



(25)

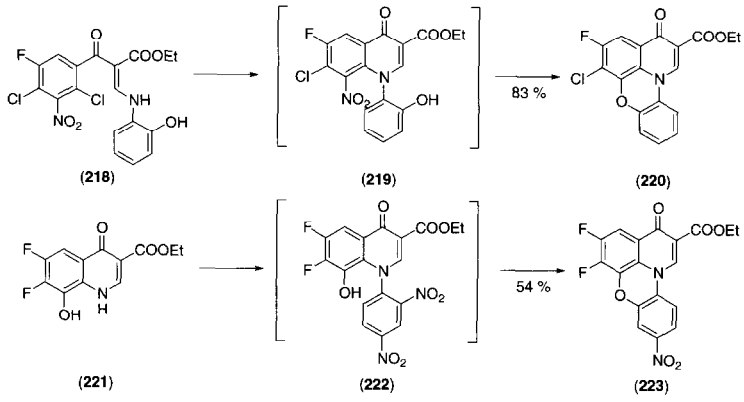
Denitrocyclization was useful also in the synthesis of pyrido[3,2,1-*kl*]phenoxazines **220** and **223** from the corresponding *N*-arylquinolones. Intermediate 8-nitro-*N*-arylquinolones, e.g. **219**, were prepared by nucleophilic cyclization of **218** (87GEP3600891). 8-Hydroxyquinolones, e.g. **221,** react with 2,4-dinitrochlorobenzene (**208**) under very mild conditions, e.g. refluxing in aqueous ethanolic solutions of sodium hydrogen carbonate or sodium carbonate, to give acceptable yields of the corresponding pyrido[3,2,1-*kl*]phenoxazine derivatives **223** (Scheme 33) (89CCC506). If the ester group in **221** is not present, the reaction can be done in DMF, however, the yields are much lower.

The 8-nitro group in intermediate quinolone **225** can be easily displaced even with aliphatic oxygen nucleophiles. Starting compound **224** under various conditions provided directly tricyclic compound **226** and all attempts to isolate the expected intermediate **225** failed (Scheme 34) (91CCC1937).

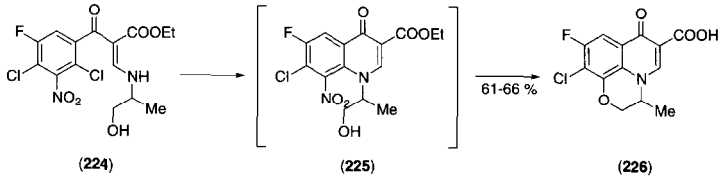
Treatment of **228** with 2,4-dinitrofluorobenzene (**227**) provided **230**. The assumed intermediate *N'*-benzoyl-*N*-(2,4-dinitrophenyl)-*N*-phenylhydrazine (**229**) underwent the denitrocyclization reaction in its enol form (80JOC3677). Similar reaction is probably involved also in the thermal cyclization of antraquinone **231** leading to **232** (Scheme 35), which took place even during attempts to crystallize the compound (60T107).

Nucleophilic displacement of the nitro group in **233** by oxygen is also involved in the synthesis of benzoxadiazine **236**. Structure **234** originally suggested by Werner and Herberger (1899CB2686) was revised and the correct structure **236** was assigned by Gilchrist (76JCS(P1)2161). It is evident, that the Smiles rearrangement product **235** serves as an intermediate (Scheme 36).

In 1901, Hillyer reported that 1,2-dihydroxybenzene (catechol) with 2,4,6-trinitrochlorobenzene (**76**) in the presence of alkali provided 1,3-dinitrodioxin

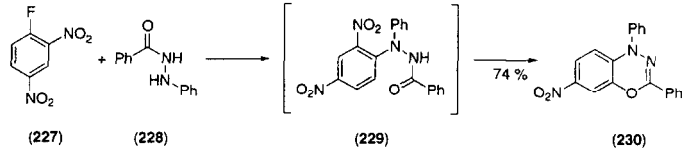


Scheme 33

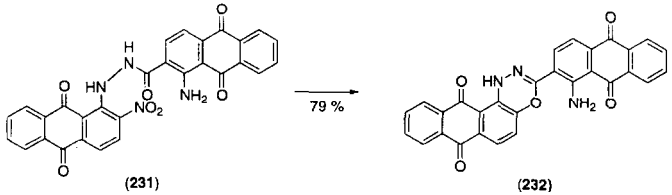


(224) (225) (226)

Scheme 34

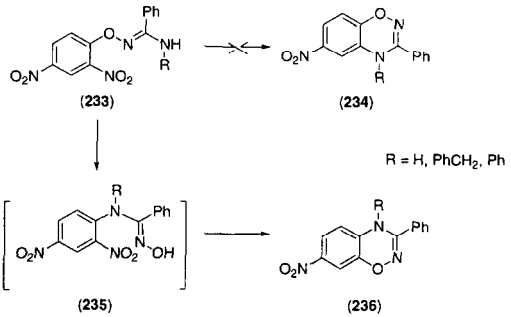


(227) (228) (229) (230)



(231) (232)

Scheme 35

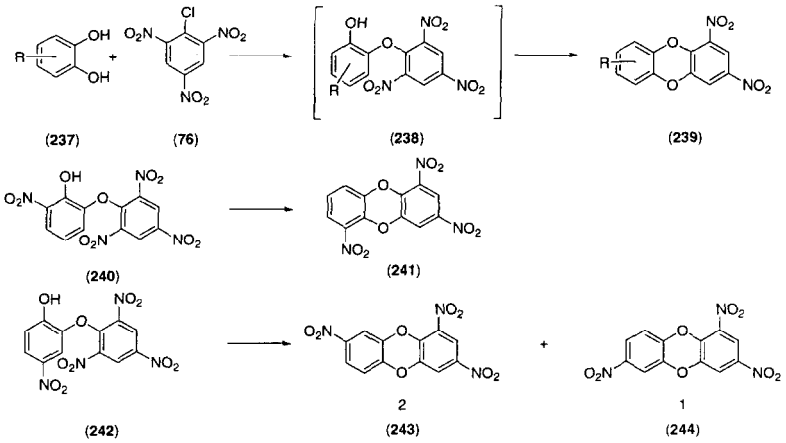


(233) (234) (235) (236)

Scheme 36

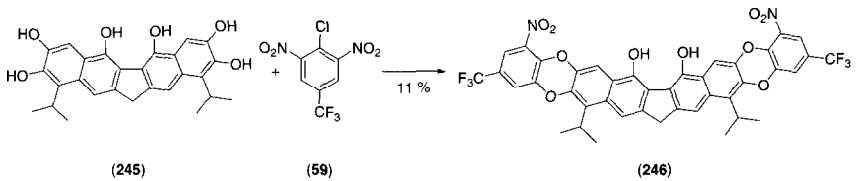
(00MI1, 01MI1). Similar reactions of 1,2-dihydroxybenzene derivatives **237** with various less activated 2,6-dinitrochlorobenzene derivatives provided usually low yields of the corresponding dioxins (59JCS1899, 84JHC1073). To improve the yields, especially with less activated chloronitro compounds, a two-step

procedure was developed (74ZOR826, 93ZOB1831). Using crown ethers (94KGS902) or HMPT as solvent was also found useful (90JCS(P1)1071, 92JMC258, 98JA13342). Unsymmetrically substituted dihydroxybenzene derivatives usually provided mixtures of both possible products. It can be, at least in part, caused by the Smiles rearrangement of intermediates **238**. When isolated diphenyl ether intermediate **240** was cyclized, dioxin **241** was formed as the only product. On the other hand, compound **242** provided a 2:1 mixture of compound **243**, the cyclization product without rearrangement, and compound **244**, the product of cyclization with rearrangement (Scheme 37) (82ZOR1683, 83ZOB451). A recent review in Russian on methods of preparation and danger assesment of dioxins is available (96MI1).



Scheme 37

Compound **245** provided 11% yield of polycyclic compound **246** even under relatively mild conditions, using Et_3N in THF at ambient temperature (Eq. 26). Other possible isomers were not described (89JFC279).

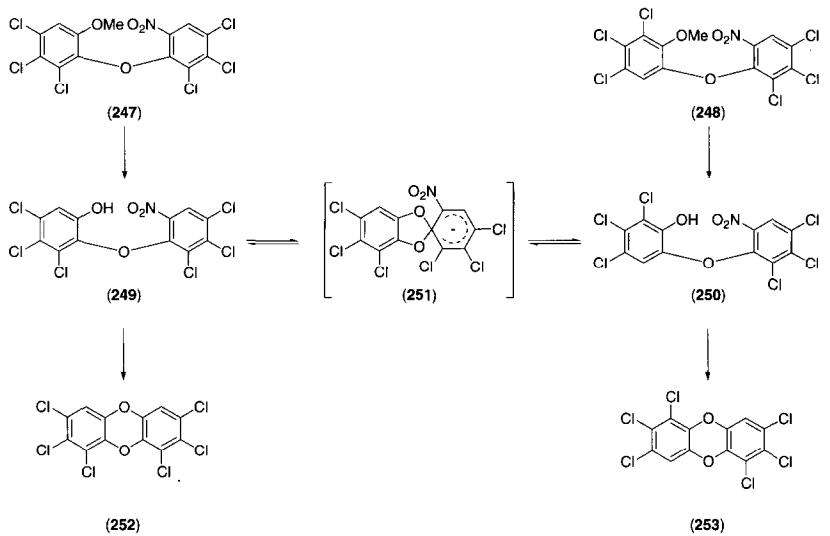


(26)

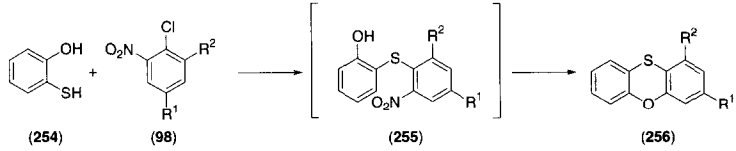
Recently, the denitrocyclization methodology was used for the synthesis of highly toxic polychlorinated dibenzodioxins (72MI2, 75TL2873, 75TL2877, 76JOC2435, 93MI2, 95CJC826, 98MI1, 98MI2, 99MI1). In attempts to prepare single isomers starting from pure methoxy derivative **247** or **248**, a 2.5:1 mixture of both possible isomers **252** and **253** was formed in both cases. This fact is a consequence of the rearrangement of primarily formed hydroxy derivatives **249** or **250** to the Meisenheimer σ-complex **251** (75TL2873, 75TL2877). In this case, the low difference in the nucleophilicity of both anionic centers causes that the equilibrium of both isomers **249** and **250** is formed and the following cyclization provided the mentioned mixture (Scheme 38).

Formation of phenoxathiins **256** by reaction of *ortho*-chloronitrobenzene derivatives **98** with mercaptophenol **254** or its derivatives was described as early as in 1905 and later in several papers (05CB1411, 06CB1340, 28M251, 29M90, 75ZOR1440, 81JHC431, 98JHC699). However, the mechanism involving O^- as nucleophile giving intermediate **255** was first proved by Stevens and Smiles in 1931 (Scheme 39) (31JCS718). In simple reactions of this type, no S–O Smiles rearrangement has been reported.

On the other hand, reaction of the *S*-protected intermediate **261** with 2,5-difluoronitrobenzene (**258**) provided better yields (61%) of the same product **260** as the reaction without the protection that gave 45% yield of this compound (Scheme 40). The fact that the same product was formed in both cases suggests that the Smiles O–S rearrangement took place during the reaction (98JHC699).

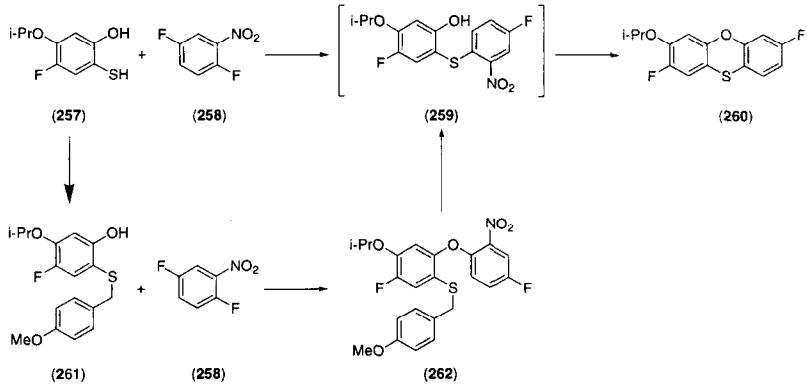


Scheme 38



(254) (98) (255) (256)

Scheme 39



(257) (258) (259) (260)

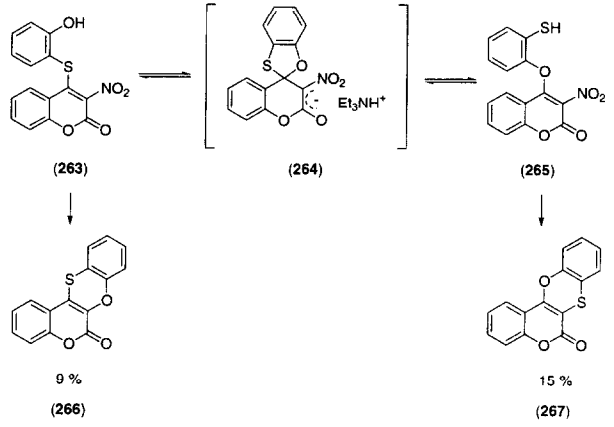
(261) (258) (262)

Scheme 40

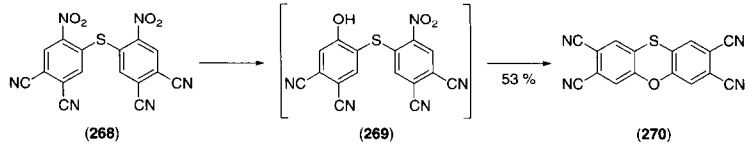
However, treatment of 4-chloro-3-nitrocoumarin (**81**) with 2-mercaptophenol (**254**) provided the product of displacement of the chlorine atom **263**. Treatment of compound **263** with triethylamine gave a mixture from which low yields of **266** and **267** were isolated (92ZOR1489). This fact can be explained by the formation of the σ-complex **264**. This complex is stabilized by carbonyl group participation and therefore an equilibrium of **263** and **265** can be expected. This is in accordance with the formed products (Scheme 41). A similar situation was described earlier for the reaction of 4,5-dichloropyridazin-6(1*H*)-one with the disodium salt of 2-mercaptophenol (82JHC1447).

Quite recently, it was reported that heating of tetracyano derivative **268** with potassium nitrite and potassium carbonate in DMF provided 53% of phenoxathiin **270** (Scheme 42) (001H1161). The probable mechanism is, that one activated nitro group in **268** is displaced with a nitrosoxy group by nucleophilic substitution of nitrite ion, followed by hydrolysis to **269**, which then undergoes denitrocyclization reaction to the final product.

Smiles rearrangement was observed also in base-catalyzed cyclization of 2-hydroxy-2′-nitrodiphenylsulfones leading to low yields (about 5%) of phenoxathiine 10,10-dioxides (34JCS422, 56JA5357). However, this type of compounds can be easily prepared by other methods (05CB1411, 06CB1340).



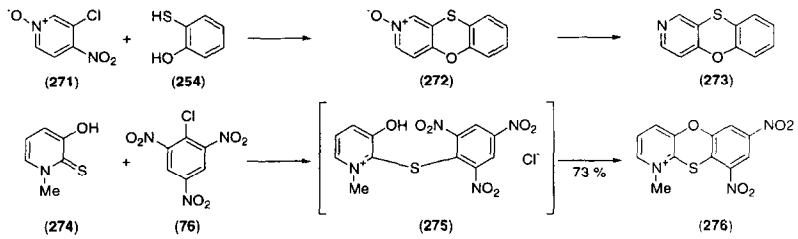
Scheme 41



Scheme 42

There are many examples of the denitrocyclization synthesis of various aza analogs of phenoxathiins (81JHC479), e.g., 1-aza (77JHC1067, 77JHC1249, 78JHC609, 78JHC721, 80JMC333), 2-aza (80JHC989), 3-aza (81JHC479), 4-aza (96JOC662), 1,6-diaza (96JOC662), 1,7-diaza (80JHC1153), 1,8-diaza (87JHC211), 1,9-diaza (79TL5035, 80JHC1153), and 2,6-diaza analogs (96JOC662). In these cases, no special activation requirements are necessary for the cyclization and no products involving the Smiles rearrangement from S to O are present. Similarly, from the reaction of 1,3-dichloro-4,6-dinitrobenzene with disodium salt of 2-mercaptopyridin-3-ol, small amounts of the corresponding product of double denitrocyclization reaction without the Smiles rearrangement was isolated (78JHC101). When 3,5-dinitro-1, 2,4-trichlorobenzene was used, the corresponding nonlinear product, which was found to be the major cyclization product, was obtained in 2.7% yield (79JHC57).

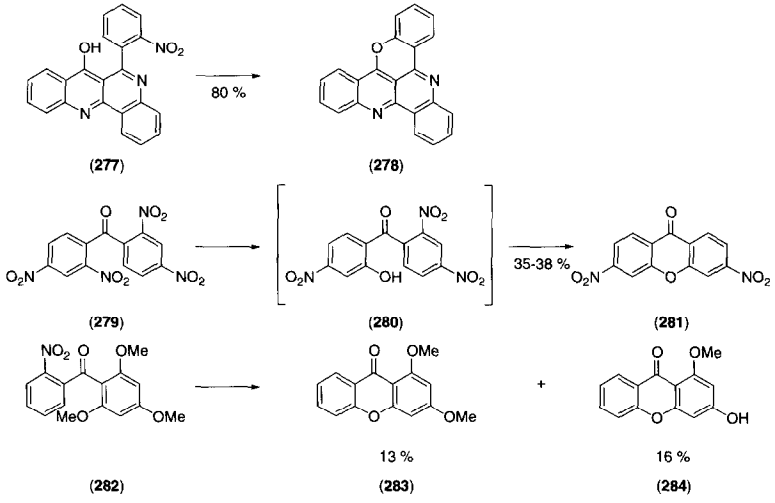
Use of some pyridinium oxides in this reaction was also described and the formed azaphenoxathiin *N*-oxides can be easily converted to their mother heterocycles (80JHC989, 87JHC211). When 3-chloro-4-nitropyridine 1-oxide (**271**) was used, small amounts of products of Smiles rearrangement were



Scheme 43

identified (80JHC989, 87JHC211). Terrier (91MI2) explained this fact by an initial displacement of the nitro group by the thiolate anion followed by intramolecular substitution of the remaining chlorine atom rather than by the Smiles rearrangement. Recently also formation of quarternary salt **276** was described. Treatment of thione **274** with 2,4,6-trinitrochlorobenzene (**76**) in acetone at room temperature provided first a mixture of **275** and **276**, which treated with hydrogen chloride gave 73% yield of **276** (Scheme 43) (95ZOR121).

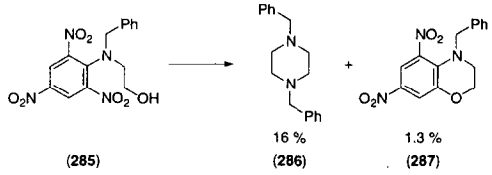
Denitrocyclization reaction was also used for the preparation of hexacyclic derivative **278**, which was obtained in 80% yield by heating of **277** with a solution of sodium hydroxide in aqueous DMF (66JCS(C)1245, 70JCS(C)2647). Low to moderate yields of 3,6-dinitroxanthen-9-one (**281**) is formed by a treatment of tetranitro derivative **279** with either potassium hydroxide or sodium



Scheme 44

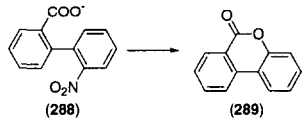
nitrite (79JCS(P1)1364). Attempts to selectively demethylate trimethoxy derivative **282** by heating with piperidine led to low yields of **283** and **284** (Scheme 44). This result can be explained by prior demethylation followed by denitrocyclization reaction (81T209).

Drozd and co-workers described cyclization of *N*-benzyl derivative **285**, which takes place without any signs of possible rearrangement providing besides 1,4-dibenzylpiperazine (**286**) also very low yields of dihydrobenzoxazine derivative **287** (Eq. 27) (77ZOR396).



(285) (286) (287) (27)

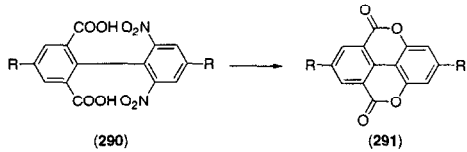
Carboxylic anion can also serve as nucleophile in denitrocyclization reactions. Reaction of suitably substituted biphenyl derivatives leading to benzo[*c*] coumarins is the best known reaction of this type (Eq. 28). The reaction was described both for 2′-nitrobiphenyl-2-carboxylic acid (**288**), and for a wide range of similar substituted compounds containing both electron-withdrawing and electron-donating groups, to give the corresponding benzo[*c*]coumarins **289** in acceptable to high yields (09CB1310, 09CB3596, 36G421, 62JCS4579, 64TL1743, 77KGS703, 79ZOR567, 91ZOR158). Several modifications of this useful reaction were published, including heating of the corresponding potassium salts or heating the corresponding acid in boiling quinoline. Comparing the yield of the thermal denitrocyclization of potassium salt of **288** (89%) with the yields of cyclizations of the corresponding compounds having fluoride (13%) or bromide anions (20%) as leaving groups, the denitrocyclization reaction is substantially more advantageous [68JCS(C)1030]. This fact is explained by finding that the nitro group containing benzene ring is much more deflected from the plane of the other benzene ring than in the case of fluoro or bromo derivatives (79JST211).



(288) (289) (28)

Easy cyclization of 2′,6′-dinitrobiphenyl-2,6-dicarboxylic acids **290** during their heating in dipolar aprotic solvents providing high yields of tetracyclic

derivatives **291** has also been described (Eq. 29) (78ZOR668). On the other hand, cyclization of 6,6′-dinitrobiphenyl-2,2′-carboxylic acid **292** (R = H) is very slow, probably due to the H-bonds, which stabilize conformation unsuitable for the cyclization. Good yields of **293** (R = H) were also obtained by sublimation of the dipotassium salt of **292** (85ZFK1782). An older reference reported only low yields of the product (64JCS5135). However, more activated acid **292** (R = NO_2) gave high yields of the corresponding cyclization product **293** (Eq. 30) (77KGS703, 77ZOR463, 78ZOR668, 80MI2).



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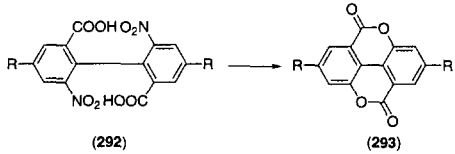
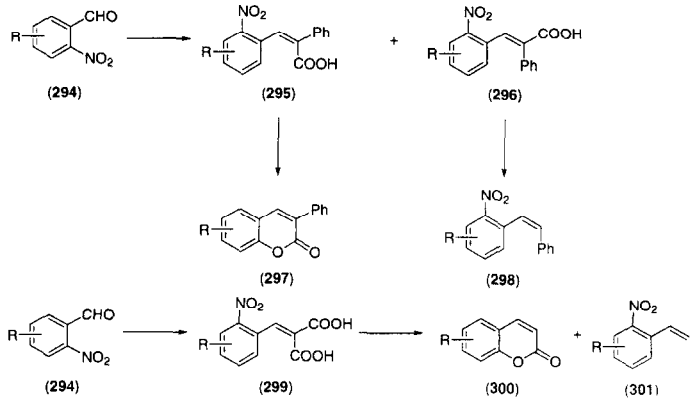
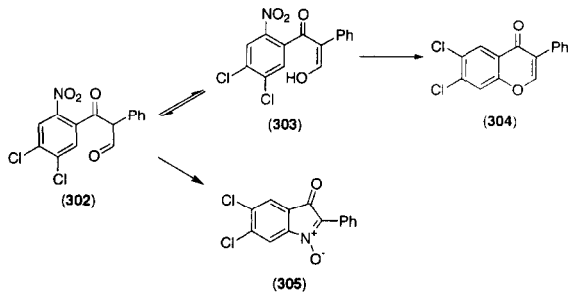


(30)

Analogously as the above mentioned synthesis, coumarin derivatives can be prepared starting from appropriately substituted 2-nitrobenzaldehydes **294** (Scheme 45). In this case, the nucleophilic carboxylic group is not placed on an aromatic ring but on the double bond of intermediates **295** in the *cis*-position to the benzene ring bearing the leaving nitro group. *E*-isomers **296** decarboxylated



Scheme 45



Scheme 46

under the conditions of the reaction (commonly heating in quinoline) to give compounds **298** (34JIC743). The reaction is compatible with a wide range of substituents, the yields of coumarin derivatives **297** range from low to very good. 3-Unsubstituted coumarins **300** were obtained in very good yields (80–90%) from suitable 2-nitrobenzaldehydes **294** and malonic acid in two steps. Intermediates **299** heated in quinoline provided directly 3-unsubstituted compounds **300** and only small amounts of nitrostyrene derivatives **301**; the corresponding coumarin 3-carboxylic acid was not isolated from the reaction mixture (62YZ1185, 62YZ1188, 86S1026, 87CPB1796).

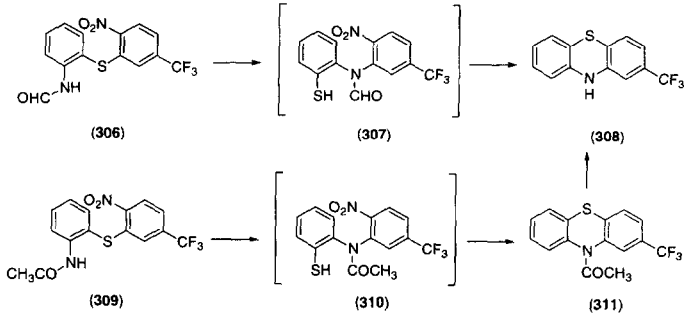
Unusual formation of isoflavone **304** during reaction of **302** is explained by equilibrium between **302** and its enol form **303**, which is able to undergo denitrocyclization reaction to the isoflavone (Scheme 46) (81IJC(B)495, 81IJC(B)1094). The other product **305** is formed by a different type of participation of the *ortho*-nitro group combined with a deformylation. For a review on this type of reaction, see (72CR627).

B. Reactions Involving Attack by Sulfur Nucleophiles

The best explored reaction of this type is the synthesis of phenothiazines first described in 1899 (1899CB2605, 09LA(366)79, 10CB927, 11CB3011, 13CB3014, 23CB2385, 28M213, 35JCS340, 35JCS1263, 36JCS1607, 53JCS4192, 55JA2270, 56YZ566, 57JA4375, 58JA1651, 58JIC202, 58JOC1804, 61JOC824, 67TL1657, 69JCS(C)2148, 70KGS1041, 71M760, 76BCJ2026, 78JHC969, 79IJC(B)626, 79SC457, 80JHC1325, 81ZOR2376, 87SC229). Thanks to the important role of phenothiazines in medicinal chemistry, various phenothiazines were prepared by this method, which was frequently shown to be a method of choice for their preparation. The reaction is in many aspects analogous to the Turpin reaction; the Smiles rearrangement takes place during the reaction, the reaction is often carried out using aminothiophenols

and nitrohalobenzenes without isolation of the intermediates. However, the reaction has lower requirements for the activation. Good yields are often achieved without an additional nitro group (69TL4483, 84H1169). In spite of this, especially previous works used the same relatively harsh conditions as in the Turpin reaction. The reaction can also be done in pyridine, or in DMF using potassium carbonate and copper powder (71IJC(B)1236). High yields of phenothiazines were obtained also by heating of the corresponding zinc thiophenolate with appropriate chloronitrobenzene in ethanolic potassium hydroxide (58JOC1018, 82IJC(B)1118, 89JFC201). Using milder conditions, sometimes also small extent of cyclization without the Smiles rearrangement was observed (79ZOR2561).

An important improvement of the reaction, especially with slightly activated compounds, was achieved by using *N*-acyl derivatives. *N*-Formyl (46JA2673, 55JOC1577, 58JOC1018, 64JOC2453, 69JCS(C)2148, 69JHC631, 71IJC(B)1236, 74KFZ23, 80H831, 81H1527, 84H1169, 84JHC893, 86PHA830, 92JHC1703, 93JFC191, 93PHA620, 94PHA453, 99JFC153) and *N*-acetyl derivatives (55JA2270, 56YZ566, 57JA4375, 57YZ3, 58JOC1804, 61JOC824, 69JHC631, 71IJC(B)1236, 74KFZ23) are commonly used. Though a previous work reported that use of an *N*-benzoyl derivative gives a phenothiazine without the Smiles rearrangement (12CB131), the result was later questioned and *N*-benzoyl derivatives are occasionally also used (13CB2809, 35JCS340). In some cases using *N*-acetyl and *N*-benzoyl derivatives, the corresponding *N*-substituted phenothiazines can be isolated. On the other hand, *N*-formyl derivatives in all cases provided *N*-unsubstituted products. The reaction is exemplified by two possible ways leading to an important pharmaceutical intermediate **308** starting either from *N*-formyl derivative **306** or its *N*-acetyl analog **309** via intermediates **307** or **310**, respectively (Scheme 47). A better total yield of **308** was obtained when the *N*-acetyl derivative **309** was used. Sometimes *N*-formyl



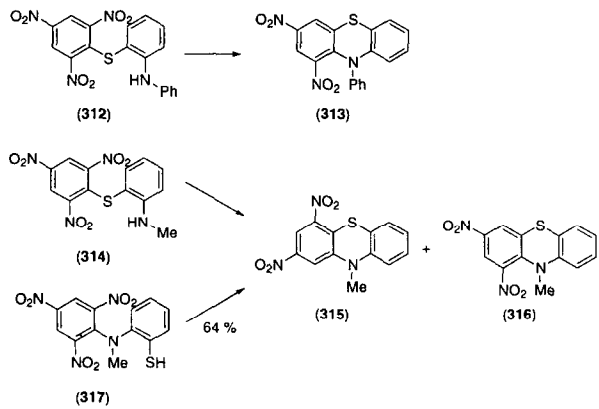
Scheme 47

derivatives are reported to cyclize in cases where cyclization of the corresponding *N*-acetyl derivatives failed (64JOC2453). However, the failure to cyclize some *N*-formyl compounds has also been reported (46JA2673, 55JOC1577).

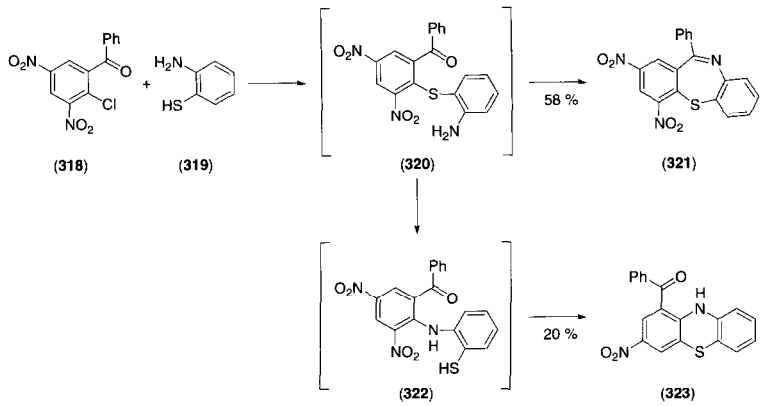
Intramolecular denitrocyclization reaction of activated 2-aminodiphenylsulfides and their *N*-acyl derivatives provided in all cases products of previous Smiles rearrangement. Similarly, 2-phenylaminodiphenylsulfide **312** provided the corresponding product of cyclization after the Smiles rearrangement **313** (80MI1). On the other hand, cyclization of *N*-methyldiphenylsulfide **314** treated with potassium *tert*-butoxide in various solvents provided mixtures of both possible products **315** and **316** (78ZOR893, 79ZOR2561). Similarly *N*-methyldiphenylamine **317** treated with triethylamine in DMSO provided a 1 : 1 mixture of both products **315** and **316** in the overall yield of 64% (81ZOR2376) (Scheme 48).

2-Chloro-5-nitrobenzaldehyde, -acetophenone, or -benzophenone derivatives treated with 2-aminothiophenol under alkaline conditions provided good yields of the corresponding dibenzo[*b*,*f*][1,4]thiepins. Similar treatment of 2-chloro-3,5-dinitrobenzophenone (**318**) provided 58% of dibenzo[*b*,*f*][1,4]thiepin **321** and 20% of phenothiazine **323**. Its formation can be easily explain by the Smiles rearrangement of the initially formed intermediate **320** into diphenylamine derivative **322**, followed by denitrocyclization reaction leading to the corresponding product of denitrocyclization **323** (Scheme 49). When the reaction was done in pyridine, only this product was isolated in 50% yield (57JCS3818).

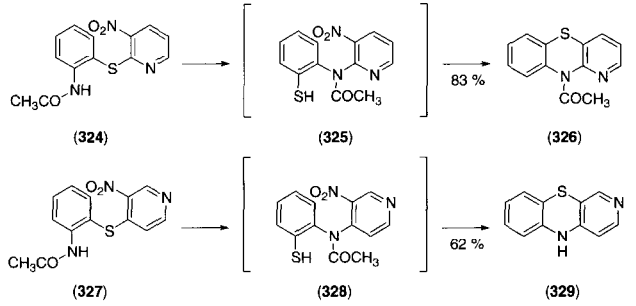
Synthesis of a wide range of 1-aza (58CPB369, 58JA1651, 59JOC1156, 87MI2), 2-aza (57YZ862), 3-aza (45JCS591, 56YZ566, 61JOC1126, 68CPB559), and 4-aza analogs (54CPB382, 55CPB92, 57YZ485, 57YZ862, 63MI1) has been described. In most cases, *N*-acetyl- or *N*-formyl derivatives were used. Selected examples are shown in Scheme 50.



Scheme 48

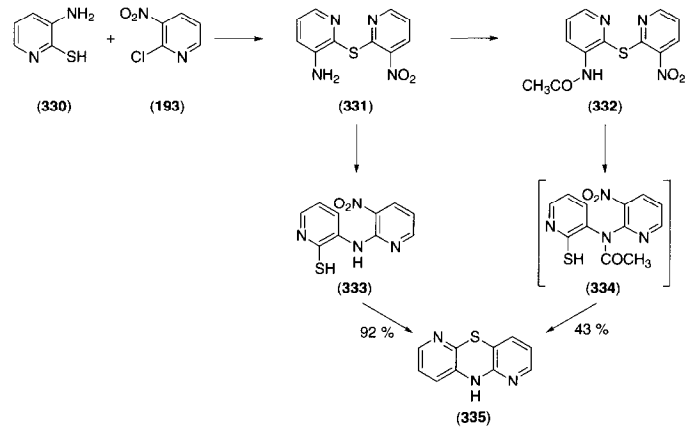


Scheme 49



Scheme 50

Synthesis of 1,6-diaza (54CPB382, 57YZ485, 58CPB369, 58YZ417, 66JMC116) and 3,6-diazaphenothiazines (67JOC2006) by this method have been reported. 1,6-Diazaphenothiazine (**335**) was prepared from 3-amino-2-thiopyridine (**330**) and 2-chloro-3-nitropyridine (**193**) via the intermediate **331**. Its acetylation to **332** followed by treatment with potassium hydroxide gave the Smiles rearrangement product **334**, which then provided the denitrocyclization product **335** in 43% yield accompanied by 25% of **333** formed by simple deacetylation of **332** followed by the Smiles rearrangement the primarily formed **331** (66JMC116). Attempts to use *N*-unsubstituted derivative **331** provided under the same conditions only the Smiles rearrangement product **333** (58YZ417, 66JMC116). This compound, due to the strong H-bond between the nitro group and the NH group, is not able to cyclize under the used conditions. However, in DMSO the required product **335** was obtained in 92% yield (66JMC116).

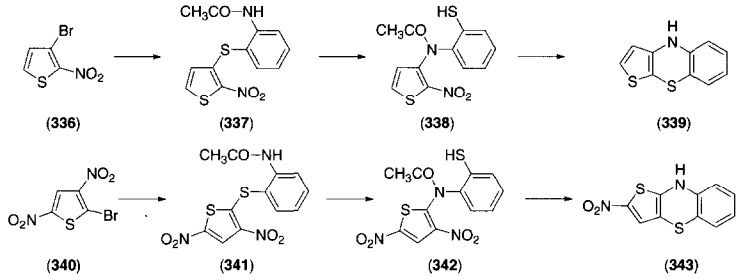


Scheme 51

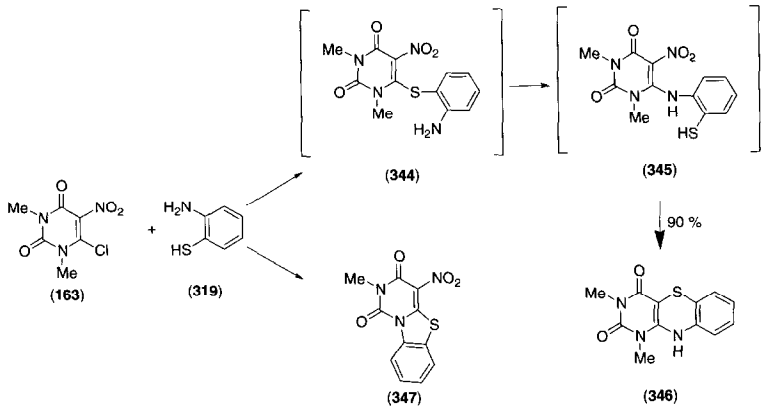
Similarly, reaction of 3-aminopyridine-2-thiol (**330**) with 4-chloro-5-nitropyrimidine derivatives provided usually high yields of the corresponding triazaphenothiazines (75JOC2753, 77EJM249).

Denitrocyclization strategy is potentially useful for the synthesis of a wide range of tricyclic compounds. The approach was found useful for the synthesis of thienobenzothiazole **339** and **343** starting from the corresponding bromonitrothiophenes **336** and **340**, respectively (Scheme 52) (68MI2, 72IJS(B)109).

An interesting S–N Smiles rearrangement was reported in some reactions of uracil derivative **163**. Starting 5-nitro-6-chlorouracil **163** with 2-mercaptoaniline (**319**) under alkaline conditions provided tricyclic product **346**, probably via intermediates **344** and **345**. For example, in the presence of triethylamine, compound **346** was obtained in 90% yield (74CPB1265, 80T2097). On the other hand, under acidic conditions, high yields of **347**, a product of the cleavage of the uracil ring, were obtained (Scheme 53). Denitrocyclization reactions analogous to



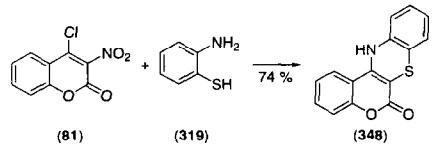
Scheme 52



Scheme 53

the formation of **346** were described also for 5-amino-4-mercapropyrimidine and 3-amino-2-mercaptopyridine derivatives (85KGS131).

4-Chloro-3-nitrocoumarin (**81**) was found to react easily with 2-mercaptoaniline (**319**) to give the corresponding denitrocyclization product **348** (Eq. 31) (85H2539).

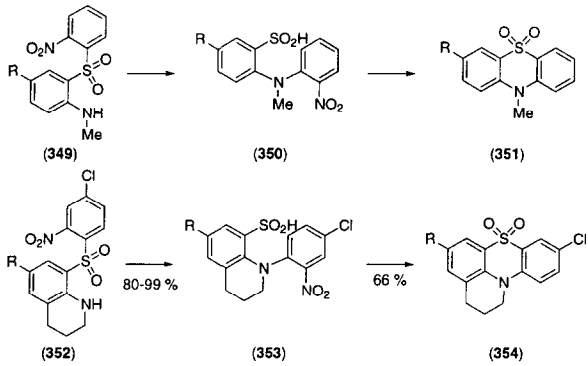


(31)

Smiles rearrangement followed by denitrocyclization reaction was described also for some aminosulfones **349**. Under alkaline conditions the reaction is very slow and only low yields of the products **351**, if any, are obtained (32JCS2774, 34JCS422, 35JCS181, 56JA5357, 56JA5363). However, good yields were obtained when the starting sulfones were heated in acetic acid (72JHC699). The phenothiazine dioxides formed can be also easily prepared by oxidation of the corresponding phenothiazines (71M760, 79ZOR2561, 82IJC(B)1118, 99JFC153).

The Smiles rearrangement of sulfones **352** led to intermediates **353**; the final ring closure was done in glacial acetic acid to provide the corresponding products of denitrocyclization **354** in 66% yield (Scheme 54) (72JHC699).

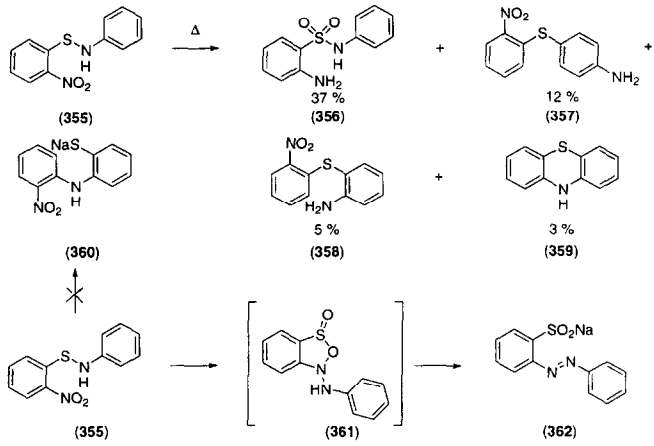
Several reactions take place during heating of 2-nitrobenzenesulphenanilides **355** without solvent or in excess of the corresponding aniline at 195 °C. Originally 4-amino derivative **357** was reported to be the main product (35JA1517). However, later reinvestigation found sulfonamide **356** as the principle product. It was also



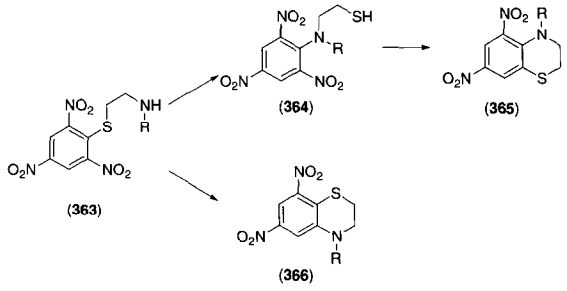
Scheme 54

shown, that denitrocyclization reaction of primarily formed 2-amino-diarylsulfides **358** takes place giving small amounts of phenothiazine **359** (70CC678, 71JOC799). This is with accordance to the finding that heating of 2-amino-2′-nitrodiphenylsulfide under very similar conditions provides a mixture of the starting compound together with phenothiazine and 4-nitrodibenzothiophene (69TL4483). Under alkaline conditions, 2-nitrobenzenesulphenanilides were formerly reported to undergo rearrangement to sodium salt of 2-mercapto-2′-nitrodiphenylamine **360** (35JA2234, 36JA1091, 36JA1960). This was in contradiction to the finding of Evans and Smiles who failed to isolate free 2-mercapto-2′-nitrodiphenylamines due to the rapid formation of the corresponding phenothiazines (35JCS1263). This discrepancy was later explained by reinvestigation of this reaction, which revealed azobenzenesulfinate **362** as the main product, formed probably via 3*H*-benzo[1,2,5]oxathiazole **361** (Scheme 55) (36JA5444, 69CC100).

Denitrocyclization reaction with the Smiles rearrangement was observed with trinitroderivative **363**, which yielded benzothiazine **365**. Product of cyclization without the Smiles rearrangement **366** was also present in the reaction mixture, the ratio seems to be dependent both on nucleophilicity of the amino group and the used base (Scheme 56). Similarly, intramolecular nucleophilic substitution of the *ortho*-nitro group in 1-(*N*-methylaminoethylthio)-2,4- and 1-(*N*-methylaminoethylthio)-2,6-dinitrobenzenes took place with a preliminary reversible Smiles rearrangement, as a result of which both possible regioisomeric 2,3-dihydro-1,4-benzothiazines were formed. The products of prior Smiles rearrangement **365** are strongly preferred when weak bases are used while strong bases in dipolar aprotic solvents prefer products of cyclization without the Smiles rearrangement **366** (76TL4825, 77ZOR1255, 78ZOR105, 81ZOR2376). In contrast to this, the corresponding *N*-phenyl derivatives gave only the rearranged heterocycles (76TL4825, 77ZOR1255).

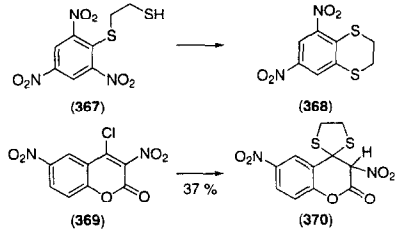


Scheme 55



Scheme 56

Similar cyclization of **367** leading to low yields (20%) of benzodithiine **368** was observed with triethylamine in DMSO (Eq. 32) (76ZOR844). On the other hand, coumarin derivative **369** treated with 1,2-ethanedithiole in the presence of triethylamine provided relatively stable spiro compound **370** (Eq. 33) (89ZOR669).



(32)

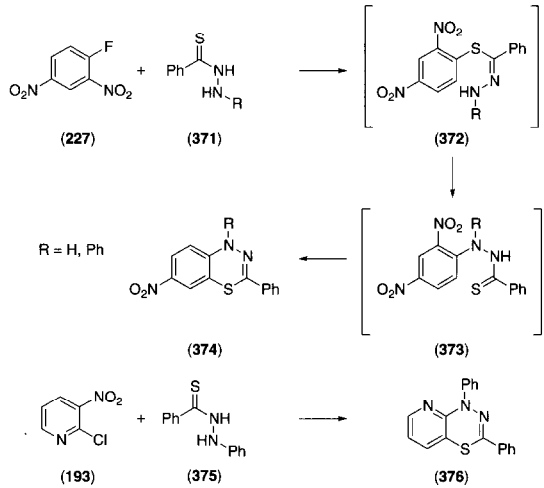
(33)

2,4-Dinitrofluorobenzene (**227**) with hydrazides of thiobenzoic acid **371** yielded **374**; this reaction can be explained by the *S*-alkylation of **371** leading to **372**, which is then rearranged to **373**. Aza analogs, e.g. **376**, were prepared similarly starting from 2-chloro-3-nitropyridines, e.g. **193** (Scheme 57). *N*-Phenylhydrazides generally provided good yields of the final products while the yields of *N*-unsubstituted products were low (77JCS(P1)192, 80JOC3677, 81JHC799).

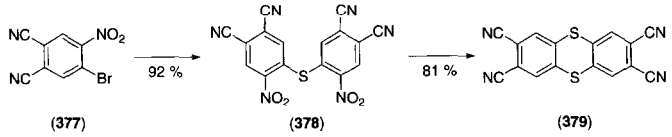
Relatively little attention has been paid to previous synthesis of thianthrenes by denitrocyclization (07CB2489, 75ZOR1440). This methodology is described mainly for the synthesis of the respective aza and diaza analogs. Quite recently, a report describing a high yield procedure leading to tetracyanophenanthrene **379** has been published (001H1161). Starting dinitrile **377** treated with half equivalent of thioacetamide in the presence of triethylamine provided intermediate **378**, the prolonged treatment of this intermediate with additional thioacetamide then provided the final product **379** (Scheme 58).

2-Azathianthrene (**382**) was prepared in good yield via the corresponding *N*-oxide **381**, obtained by treating 3-chloro-4-nitropyridine-1-oxide (**271**) with **380** (86JHC785, 87JHC1357). High yields were also achieved in the preparation of 4-nitroderivative **384** from 4-chloro-3,5-dinitropyridine (**383**) (Scheme 59) (86JHC785).

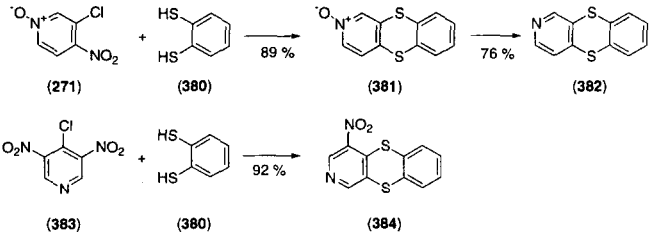
Reaction of disodium salt of pyridine-2,3-dithiol (**385**) with 1-chloro-2-nitrobenzene provided in 45% yield the corresponding aza analog **386** (82JHC1441). Similar treatment with 2-chloro-3-nitropyridine (**193**) provided



Scheme 57



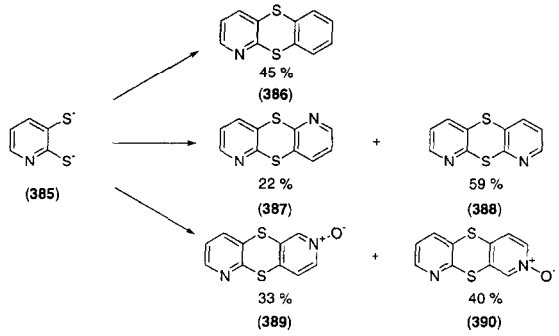
Scheme 58



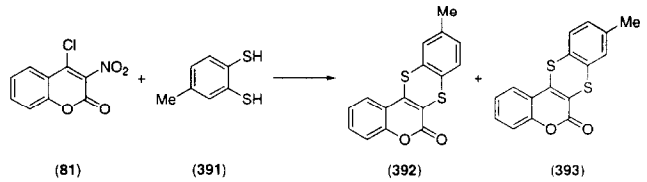
Scheme 59

a mixture of both possible diaza derivatives **387** and **388** (87JHC1357). Analogously, 3-chloro-4-nitropyridine-1-oxide (**271**) gave a mixture of **389** and **390** (Scheme 60) (87JHC1357).

Similarly, compound **81** treated with **391** provided a mixture of both possible tetracyclic compounds **392** and **393** in overall yield of 99% (Eq. 34) (91ZOR185).

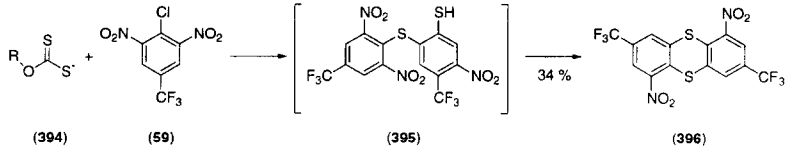


Scheme 60



(81) (391) (392) (393) (34)

A different approach leading to thianthrene derivatives starts from *O*-ethyl or *O*-isopropyl dithiocarbonate **394**, when heated with chlorodinitrobenzene derivative **59** provided intermediate **395**, the compound having all features necessary for denitrocyclization reaction to the final product **396**, which was the only isolated compound (Scheme 61). Its structure was assigned by X-ray crystallography (77JOC2896).



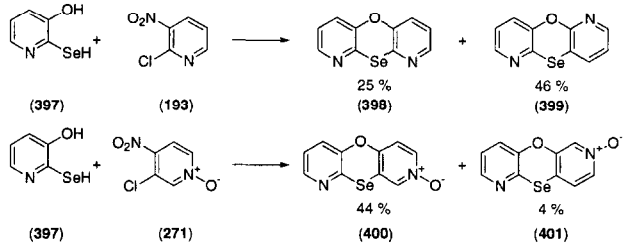
(394) (59) (395) (396)

Scheme 61

C. Reactions Involving Attack by Selenium Nucleophiles

Several 1-azaphenoxaselenines were prepared from 3-hydroxypyridine-2-selol (**397**) by the method routinely used for the synthesis of analogous phenoxathienes (86JCS(P1)2075). Using 2-chloro-3-nitropyridine (**193**), a mixture of 1,9-diazaphenoxaselenine (**398**) (product of direct cyclization) and 1,6-diazaphenoxaselenine (**399**) (product of cyclization after the Smiles rearrangement) was analogously obtained. The mixture after a workup provided these compounds in 25% and 46% yields, respectively. On the other hand, 3-hydroxypyridine-2-selol (**397**) treated with 3-chloro-4-nitropyridine-1-oxide (**271**) provided mainly the product of direct cyclization **400** (44%) and only a small amount (4%) of the product after the Smiles rearrangement **401** (Scheme 62) (87JCS(P1)2839).

Formation of 1,3-dinitro- and 1,3,6-trinitroselenazine derivatives by a method analogous to the synthesis of phenothiazines have been also described (14CB1873).

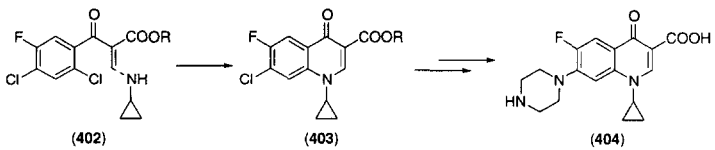


Scheme 62

D. Reactions Involving Attack by Nitrogen Nucleophiles

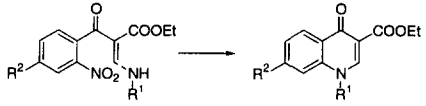
There are several methods of preparation of antibacterial quinolones, drugs widely used in the therapy of various bacterial diseases. The most general method is based on the nucleophilic cyclization of 2-halobenzoyl derivatives **402**, leading to the key intermediates **403**. The methodology is exemplified in Scheme 63 by the synthesis of a broad-spectrum drug ciprofloxacin **404** (92H2143).

The corresponding 2-nitro derivatives **405** were also used in this way to prepare compounds **406** (R^1 = *c*-Pr, $R^2 = NO_2$; $R^1 = NMe_2$, R^2 = H) (87JHC181, 87LA29, 87LA871). Our group prepared a series of quinolones **406** without additional activation (R^1 = H), bearing at the 1-position various substituents (Et, *c*-Pr, *t*-Bu, Ph) (Eq. 35) (002UP1). We also prepared a series of 3-unsubstituted quinolones **408**. Cyclization is facilitated by the presence of the ester group in **405** (Eq. 36): the cyclization of **407** leading to **408** was slower and gave lower yields than gave the corresponding analogs **406** under the same conditions. The ease of the cyclization was also affected by steric demands of the *N*-1 substituents; *N*-methyl, *N*-ethyl and *N*-phenyl substituted compounds cyclized under much milder conditions than compounds bearing *c*-Pr or *tert*-butyl substituents (002UP1). The described methodology was applied also for the preparation of **410**, a key intermediate of antibacterial drug levofloxacin, from



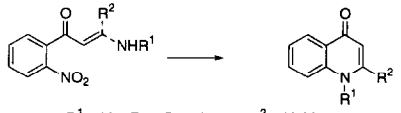
Scheme 63

acetoxy derivative **409** (Eq. 37). In this case, the corresponding quinolone intermediate was successfully isolated in 96% yield and cyclized to **410** (97H137).



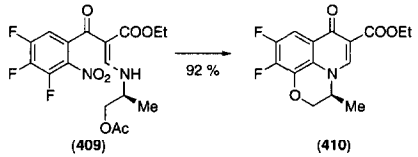
R^1 = Et, *c*-Pr, *t*-Bu, Ph, NMe_2; R^2 = H, NO_2

(405) **(406)** (35)



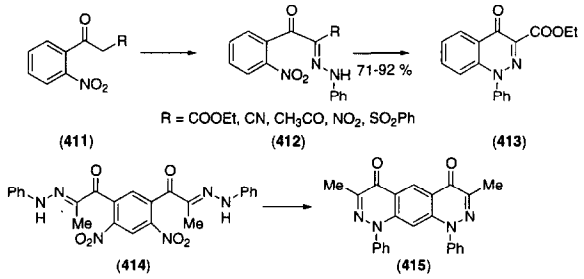
R^1 = Me, Et, *c*-Pr, *t*-Bu, Ph; R^2 = H, Me

(407) **(408)** (36)



(409) **(410)** (37)

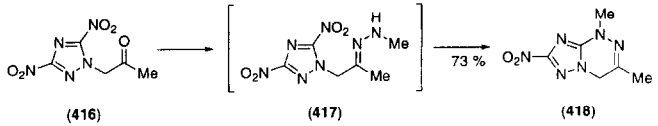
Similar high-yield syntheses of cinnolines **413** have also been described. The presence of the electron-attracting group is probably necessary only for the preparation of the intermediate phenylhydrazones **412** from the corresponding benzoyl derivatives **411**. Nevertheless, the second step is apparently also influenced by a character of the R substituent; the easiest cyclization was observed even in warm aqueous ethanolic sodium acetate for **412** having R = CN and NO_2 groups (74CC752). Similar bis-cyclization of **414** leading to **415** was also described (Scheme 64) (38HCA1084).



(411) **(412)** **(413)**

(414) **(415)**

Scheme 64

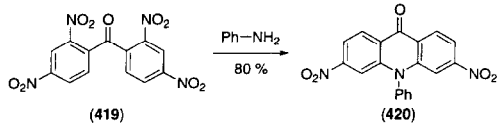


(416) (417) (418)

Scheme 65

Similarly, methylhydrazone **417**, formed *in situ* from ketone **416** and methylhydrazine, cyclized to give good yield of **418** (Scheme 65) (82KGS1113).

Good yields of 10-aryl-3,6-dinitroacridones were obtained merely by heating 2,2′,4,4′-tetranitrobenzophenone (**419**) with an excess of the corresponding aryl amines at 125°C. For example, aniline provided **420** in 80% yield (Eq. 38). The reaction is fairly general for *meta*- and *para*-substituted anilines, though it proceeds less readily with *ortho*-substituted compounds (79JCS(P1)1364). A method of isolation of the intermediate diarylamine in the synthesis of certain 10-aryl-3,6-dinitroacridones from 2,2′,4,4′-tetranitrobenzophenone has also been described (93JCR(M)2779).

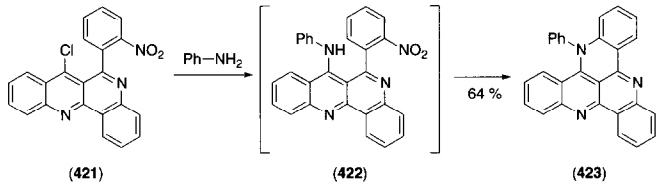


(419) (420) (38)

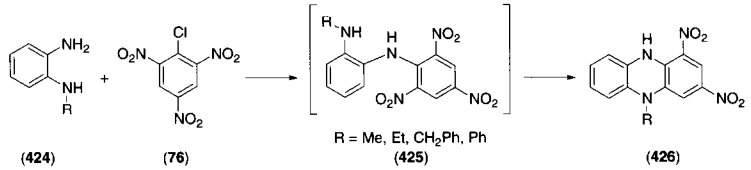
Chloronitro derivative **421** in boiling aniline provided 64% yield of **423**. Presumably, intermediate **422** is first formed and its denitrocyclization reaction provides the polycyclic product **423** (Scheme 66) (66JCS(C)1245).

The synthesis of dihydrophenazines **426** shown in Scheme 67 is analogous to the Turpin reaction. Available literature data indicate that the reaction requires even higher activation than the Turpin reaction (1892JPR574, 1893CB2372, 1899CB2605, 08CB1306, 09LA(366)79, 11CB2622, 21HCA517, 64JIC52, 70KGS1428, 82IJC(B)365). All the described examples involve the trinitrophenyl derivatives; *N*-unsubstituted derivatives do not cyclize or provide only very low yields under harsh conditions (1893CB2372, 08CB1306). Apparently, the less substituted amino group of **424** is arylated with 2,4,6-trinitrochlorobenzene (**76**) to give intermediates **425**; no reports on the Smiles rearrangement were published. Use of 4-chloro-3,5-dinitropyridine in the synthesis of the corresponding aza analogs was also described (46JCS588).

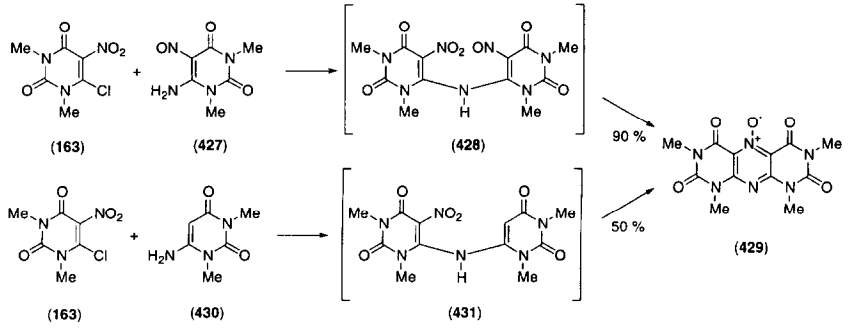
Formally analogous reaction is the reaction of aminouracil **427** with chloronitrouracil derivative **163** in refluxing DMF providing high yields of pyrimido[4,5-*g*]pteridin *N*-oxide **429**, probably via intermediate **428** (71TL4271).



Scheme 66



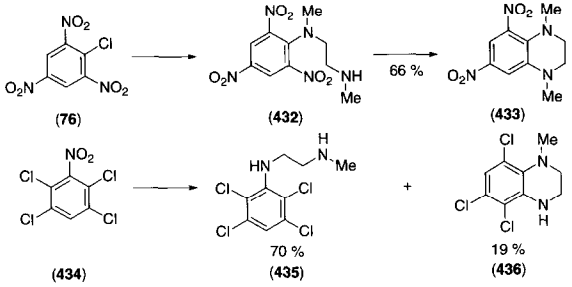
Scheme 67



Scheme 68

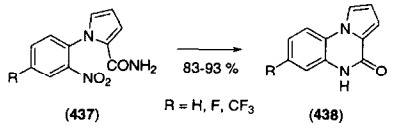
However, mechanism of this reaction is not quite known and since the same product can be also prepared by the same treatment of the corresponding derivative without the nitroso group **430**, the real mechanism can be quite different (Scheme 68).

Compound **432**, which can be easily prepared from trinitrochlorobenzene (**76**), treated with triethylamine in dipolar aprotic solvents provided good yield of the denitrocyclization product **433** (80JCS(P1)2205). Reaction of 2,3,5,6-tetrachloronitrobenzene (**434**) with various 1,2-diamines under high pressure provided mixtures of the corresponding open products of the nitro group displacement, e.g. **435**, and cyclized products, e.g. **436** (Scheme 69). Compound **436** was formed by denitrocyclization reaction, since compound **435** did not cyclize under the used conditions (94BCJ196, 95BCJ3227).



Scheme 69

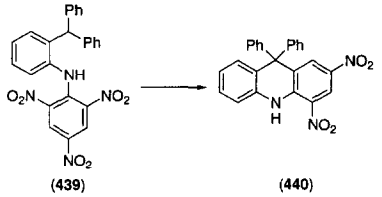
Denitrocyclization involving the primary amide group in **437** gave good yields of pyrrolo[1,2-*a*]quinoxaline derivatives **438** (Eq. 39) (91SC1567).



(39)

E. Reactions Involving Attack by Carbon Nucleophiles

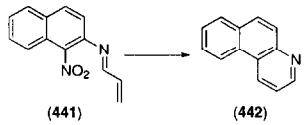
Strongly activated 2-(diphenylmethyl)diphenylamine derivatives **439** are able to cyclize to the corresponding acridine derivatives **440**. The reaction requires both a strong activation of the leaving nitro group (dinitro derivatives do not react) and stabilization of the intermediate carbanion by a suitable substitution. The only described example of this type is the reaction of triphenylmethane derivative **439** giving 74% yield of diphenylacridine **440** (Eq. 40). The corresponding diphenylmethane derivative does not react in this way (21HCA538).



(40)

Formal denitrocyclization reaction occurs also during thermal reaction of **441** leading to benzoqinoline **442** under the conditions used for the Skraup's method

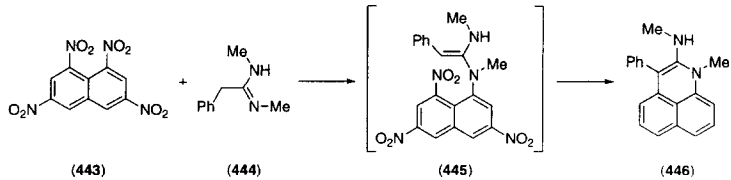
of preparation of quinolines (Eq. 41). The reaction was described by Lellmann and Schmidt as early as in 1887, but no more recent example of this reaction is available (1887CB3154).



(441) (442) (41)

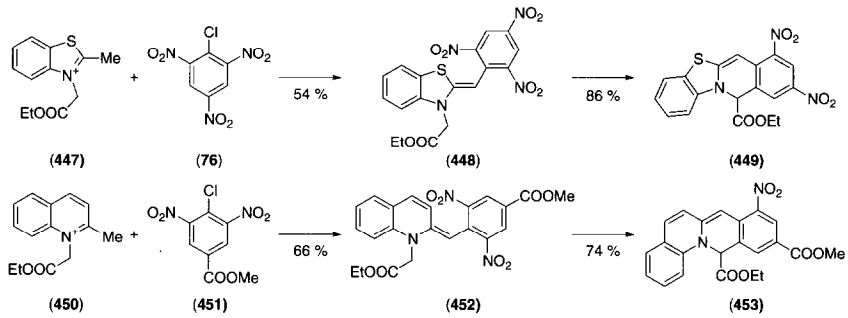
Highly electron-deficient 1,3,6,8-tetranitronaphthalene **443** was reported to react in ethanol with *N*-methyl phenylacetamidines, e.g. **444**, to give the corresponding benzoquinoline derivatives, e.g. **446** (77JOC435). Though the reaction mechanism of this double nitro group displacement is not known, formation of intermediate **445** and its following cyclization is probably the most reasonable explanation (Scheme 70).

Many interesting polycyclic compounds containing an isoquinoline moiety are available in good yields by a several step sequence involving denitrocyclization reaction. Typical examples of this useful reaction are given in Scheme 71.



(443) (444) (445) (446)

Scheme 70



(447) (76) (448) (449)

(450) (451) (452) (453)

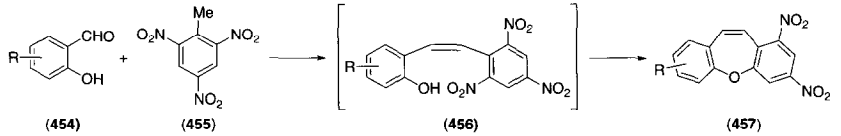
Scheme 71

2-Methyl cyclimonium salts, e.g. **447** or **450**, treated with triethylamine condensed with 2,6-dinitrochlorobenzene derivatives bearing at the position 4 an additional activating group, e.g. **76** or **451**, at the 2-methyl group to give intermediates **448** or **452**, respectively. These compounds treated with piperidine form six-membered rings by a denitrocyclization pathway to give good yields of the corresponding compounds **449** or **453** (71CB2103, 71CB2110).

IV. Cyclization Leading to Seven-Membered Rings

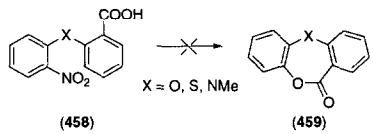
A. Reactions Involving Attack by Oxygen Nucleophiles

The only known example of this type of cyclization is the synthesis of dibenz[*b*,*f*]azepines **457** from appropriate salicylaldehyde **454** and 2,4,6-trinitrotoluene (**455**) via the corresponding intermediate **456** (Scheme 72) (62M766).



Scheme 72

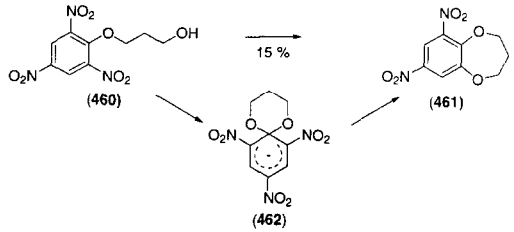
The smooth intramolecular nucleophilic displacement of biphenyl carboxylic acids leading to benzocoumarins (See Section II.A.) inspired also investigation of the behavior of similar diphenyl ether, diphenyl sulfide and *N*-methyldiphenyl amine derivatives **458** under similar conditions. However, all these attempts to achieve cyclization to tricyclic compounds **459** were unsuccessful, probably due to the unfavorable stereochemistry for the formation of the required seven-membered transition states and also to the presence of the deactivating bridge groups X (Eq. 42) [68JCS(C)1030].



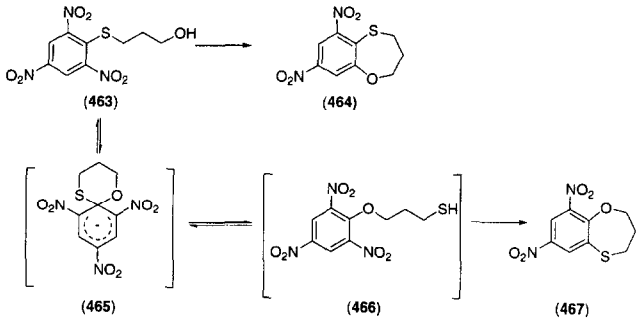
(42)

Treatment of **460** with triethylamine in DMSO gave 15% of **461**. This compound was also obtained from spiro complex **462** formed from **460** by the action of potassium *tert*-butoxide (Scheme 73) (74ZOR826, 78ZOR105).

Similar reaction was described also for **463**, the reaction mixture contained 95% of **464** and 5% of **467**, the product of cyclization of the rearranged intermediate **466**. The proposed mechanism of this rearrangement is shown in Scheme 74 (78ZOR105).

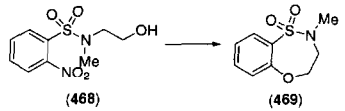


Scheme 73



Scheme 74

An interesting denitrocyclization reaction of **468** providing 28% yield of **469** is shown in Eq. 43 (68AG284).



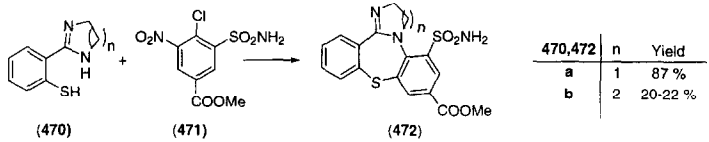
(43)

B. Reactions Involving Attack by Sulfur Nucleophiles

A series of 4,5-dihydro-1*H*-imidazole derivatives **470a** (n = 1) were treated with several 1-chloro-2-nitro derivatives, e.g. **471**, in ethanolic sodium acetate to give good yields of tetracyclic 2,3-dihydroimidazo[1,2-*d*][1,4]thiazepines, e.g. **472a** (n = 1). On the other hand, similar 1,4,5,6-tetrahydropyrimidine derivatives **470b** (n = 2) provided only small yields of the corresponding 3,4-dihydro-2*H*-pyrimido[1,2-*d*][1,4]thiazepines **472b** (n = 2) (Scheme 75) (78LA259).

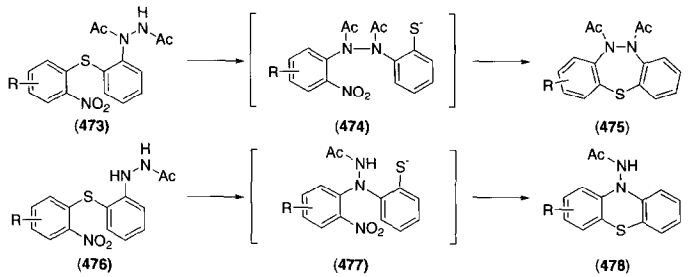
Diacetyl derivatives **473** after a short reflux with potassium carbonate in DMF provided high yields of **475** (82JOC2214). On the other hand, the corresponding monoacetyl derivatives **476** under the same conditions gave good yields of phenothiazines **478** (Scheme 76) (78JHC1137).

2,4,6-Trinitrochlorobenzene (**76**) treated with 1,3-propanedithiole and one equivalent of a base provided compound **479** and its treatment with additional base was reported to provide only small yields of benzodithiepine **480** (74CC672). A more recent work described that good yield (80%) of **480** was obtained by a treatment of **479** with triethylamine in benzene (76ZOR844). Similar treatment of **81** provided first spiro complex **481**, which refluxed in acetone in the presence of triethylamine gave good yield of the denitrocyclization product **482** (Scheme 77) (92ZOR1496).

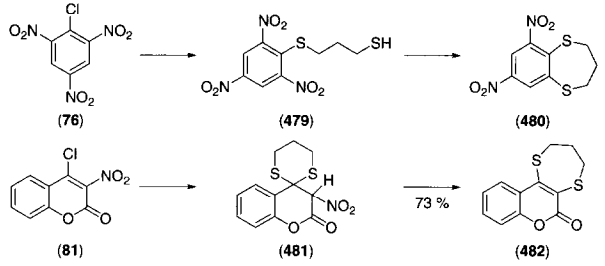


470,472	n	Yield
a	1	87 %
b	2	20-22 %

Scheme 75

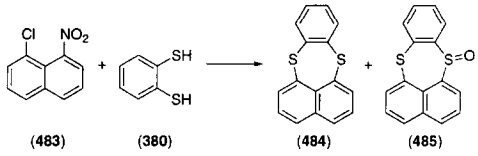


Scheme 76



Scheme 77

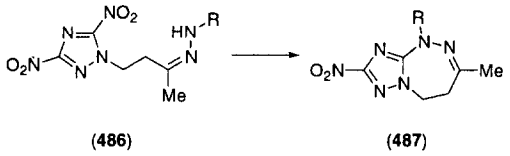
Condensation of the dianion of 1,2-dimercaptobenzene (**380**) with 1-chloro-8-nitronaphthalene (**483**) in DMF provided 45% of benzo[2,3]naphthalene [5,6,7-*i,j*][1,4]dithiepin (**484**) and a small amount of its *S*-oxide **485** (Eq. 44) (89JHC667). Though the structure of **485** was adequately determined (NMR studies, X-ray crystallography), its formation was not definitely explained.



(44)

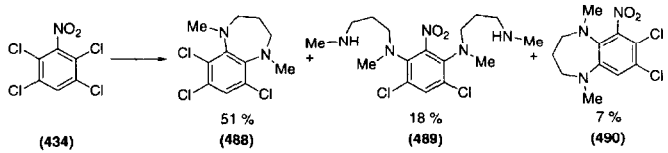
C. Reactions Involving Attack by Nitrogen Nucleophiles

Analogously to the reaction of compound **416** leading to 1,4-dihydro[1,2,4]triazolo[5,1-*c*][1,2,4]triazine moiety (See Section III.D.), hydrazone **486** undergoes denitrocyclization reaction giving 4,5-dihydro-1*H*-[1,2,4]triazolo[5,1-*c*][1,2,4]triazepine **487**, as shown in Eq. 45 (82KGS1113).



(45)

Treatment of **434** with *N,N'*-dimethylpropane-1,3-diamine gave a complex mixture, from which the product of possible denitrocyclization reaction **488** was obtained in 51% yield (Eq. 46) (95BCJ3227).



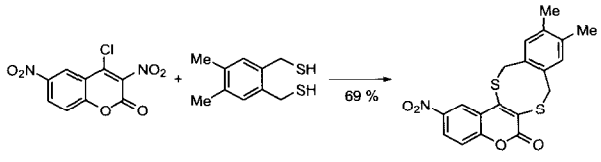
51 % 18 % 7 %

(434) (488) (489) (490)

(46)

V. Cyclization Leading to Eight-Membered Rings

A good yield of **492** was obtained by reaction of **369** with dithiol **491** (Eq. 47). This reaction is probably the only example of the eight-membered ring formation by denitrocyclization reaction described so far (91ZOR185).



(369) (491) (492)

(47)

VI. Conclusion

Intramolecular nucleophilic displacement reactions of aromatic nitro group by various nucleophiles include cyclization reactions, which provide practical methods for the synthesis of a variety of heterocycles. I hope that the text of this review suggests a wide range of potential of this reaction in organic synthesis of various heterocycles. However, it is necessary to stress that some structural types described in this review could be prepared with similar, or even better yields by other methods. In spite of this, there are many heterocyclic systems for the synthesis of which the denitrocyclization strategy is a method of choice.

As it was mentioned in the text, first reactions of this type are more than a century old. Whilst a number of major advances have been made since, many important questions still remain unanswered or incompletely addressed. One of

them is also the issue of safety. It is well known, that many energy rich polynitro derivatives, e.g. 2,4,6-trinitrotoluene (TNT) or 2,4,6-trinitrophenol (picric acid), are highly explosive (91MI1). Therefore this issue should be considered in planning any denitrocyclization strategy, especially for larger amounts.

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Preface

Gurnos Jones of the University of Keele, UK covers recent advances in the chemistry of triazolopyridines ring systems, which are of considerable importance in medicinal chemistry, in an update of his 1983 review in Volume 34 of *Advances in Heterocyclic Chemistry*.

Heteroaromatic sulfur compounds do form sulfoxides and sulfones, but these derivatives have their own special reactivity. Francesca Clerici (Milan, Italy) has now provided an up-to-date survey of the preparation and properties of the *S*-oxides of thiazoles and thiadiazoles, collecting literature scattered in many publications.

The third chapter of Volume 83 of *Advances in Heterocyclic Chemistry* is Part 5 in the series by Alexander Sadimenko (Fort Hare, Republic of South Africa) and covers organometallic complexes of azoles other than pyrazoles. This chapter continues the series of which parts 1–4 were published in volumes 78, 79, 80, and 81 of *Advances in Heterocyclic Chemistry*, respectively.

Finally, aromatic nucleophilic denitrocyclization reactions are reviewed for the first time by Stanislav Rádl (Prague, Czech Republic). The nitro functionality is a good leaving group, especially for intramolecular reactions, and many such reactions lead to polycyclic heterocyclic ring systems. Frequently, these transformations are a method of choice for preparative purposes.

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