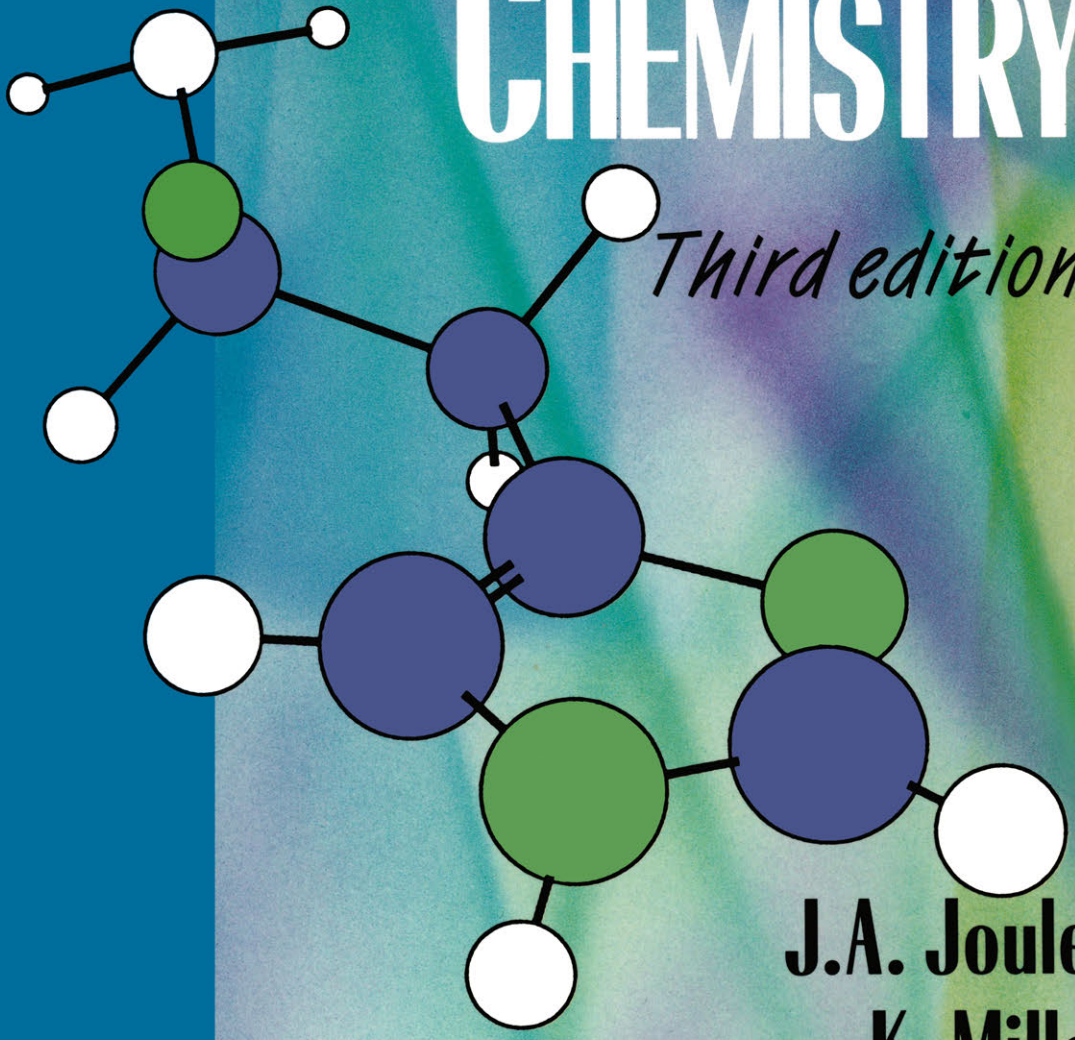
Heterocyclic Chemistry

Third edition



J.A. Joule
K. Mills
G.F. Smith

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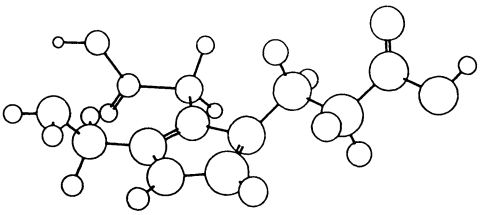

For my A from her A

HETEROCYCLIC CHEMISTRY

Third edition

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First edition 1972
Second edition 1978
Third edition 1995

Originally published by Chapman & Hall in 1995

Typeset by Columns Design and Production Services Ltd, Reading, England

ISBN 978-0-412-41340-7 ISBN 978-1-4899-3222-8 (eBook)
DOI 10.1007/978-1-4899-3222-8

A catalogue record for this book is available from the British Library


Printed on permanent acid-free text paper, manufactured in accordance with ANSI/NISO Z39.48-1992 and ANSI/NISO Z39.48-1984 (permanence of Paper).

Contents

Preface

Since the preparation of the second edition, one of us (GFS) has retired from the University of Manchester, UK, the better to pursue botanical interests. This revision has been prepared by the other original author (JAJ) in collaboration with one of his former research students (KM), now a Principal Research Chemist with Glaxo Research and Development, Ware, UK. Heterocyclic compounds are of particular interest in medicinal chemistry, and this has catalysed the discovery and development of much new heterocyclic chemistry and methods. The preparation of a third edition has allowed us to review thoroughly the material included in the earlier editions, to make amendments in the light of new knowledge, and to include much recent work.

We here record our thanks to several colleagues who read part, or all, of the manuscript and made valuable comments: Professor C. W. Rees, Dr D. I. C. Scopes and Ms S. A. Roberts. The following Manchester post-graduate research students worked through the exercises: Neil Barnwell, Jacqueline Birks, Jason Kettle, James Lovell, Max Pendleton and David Peters. JAJ thanks Professor Catherine Fenselau and her colleagues for their hospitality and stimulating discussions, during a period of sabbatical leave at the University of Maryland, Baltimore County Campus, Baltimore, USA, when the revision was begun. We thank Glaxo Research and Development, Ware, UK, for assistance and support during the preparation of this edition, not the least in granting KM permission to participate in the project, and for hosting a dinner at which David Scopes suggested the JAJ/KM collaboration which has brought this revision to a conclusion. KM thanks his colleagues at Glaxo for many helpful discussions.

INTRODUCTION TO THE THIRD EDITION

We have maintained the principal aim of the earlier editions – to teach the fundamentals of heterocyclic reactivity and synthesis in a way which is understandable by undergraduate students. However in addition, and in recognition of

the level at which much heterocyclic chemistry is now normally taught, we have included some more advanced and current material which will also make the book appropriate both for post-graduate level courses, and as an introductory text for those involved in heterocyclic chemistry in industry. These modified goals have occasioned important changes in the format of the book:

(1) In the earlier Editions, the essential explanatory 'teaching' material was given in small chapters, preceding the main chapters which discussed 'reactions and synthesis' of particular heterocyclic systems. This didactically vital material has now been incorporated partly into a larger, general discussion of heterocyclic reactivity (chapter 2), and partly into six small summary-chapters, such as 'typical reactivity of pyridines, quinolines and isoquinolines' (chapter 4), which aim to capture the essence of that typical reactivity in a very concise resumé. These are therefore suitable either as an introduction to the chemistry of that heterocyclic system or, in the didactical context, as a revision-summary of the typical chemistry of that system.

(2) Original references have been given throughout the text: most of these have been chosen as good leading references and are, therefore, not necessarily the first mention of that particular topic or method; some are included as benchmark papers and others for their historical interest. Many review references are also included: for these we give the title of the article; titles are also given for books to which we refer. This change, a response to comments we have received, improves the relevance of the book to post-graduate teaching and to research workers without, we hope, interfering with the readability of the text for the undergraduate student.

(3) We have added exercises, with solutions given in an appendix at the end of the book, designed to help the reader to understand, learn and apply the principles of heterocyclic reactivity. We believe that this departure considerably improves the usefulness of the book as an instrument for the teaching of heterocyclic chemistry. References have not been given for the exercises, though all are 'real' examples culled from the literature.

(4) Photochemical reactions[1] are now incorporated into the 'Reactions and synthesis' chapters, rather than being given in a separate chapter.

We have avoided the use of 'R' and 'Ar' for substituents in schemes, and instead give actual examples. We believe this makes the chemistry easier to assimilate, especially for the undergraduate reader. It also avoids implying a generality which may not be justified.

Structures and numbering for heterocyclic systems are given at the beginnings of chapters. Where the commonly-used name differs from that used in *Chemical Abstracts*, the name given in square brackets is the official *Chemical Abstracts* name, thus: indole [1*H*-indole]. We believe that the systematic naming of heterocyclic substances is of importance, not least for computer data bases, but it serves little purpose in teaching or for the understanding of the subject and, accordingly, we have devoted little space to nomenclature. The reader is referred to an exposition on this topic[2] and also to the Ring Index of

Chemical Abstracts in combination with the Chemical Substances Index, from whence both standardised name and numbering can be obtained for all known systems.

There are several general reference works concerned with heterocyclic chemistry, which have been gathered together as a set at the end of this preface, and to which the reader's attention is drawn. NB: In order to save space, these vital sources are not referred to again in this book: particular volumes (say those on thiophenes) are not mentioned in particular chapters (thiophenes chapter), however all the topics covered in this book are covered in them, and recourse to this information should form the early basis of any literature search.

The literature of heterocyclic chemistry is so vast that the series of four listings – *The literature of heterocyclic chemistry, Parts I–IV*[3] – is of enormous value at the start of a literature search. These four listings appear in *Advances in Heterocyclic Chemistry*, itself a prime source for key reviews on heterocyclic topics; the journal, *Heterocycles,* also carries many useful reviews specifically in the heterocyclic area. Essential at the beginning of a literature search is a consultation with the appropriate chapter(s) of *Comprehensive heterocyclic chemistry*[4] or, for a useful introduction and overview, to the 'handbook' which is Volume 9.[5] There have been many instances of interconversion of heterocyclic systems, with changes of hetero atom components and/or ring size; these are gathered together in one useful volume.[6] A book,[7] which has provided considerable inspiration for two decades, highlights the utility of heterocycles, often as 'carriers' of functionality, in a general synthetic context.

There are three comprehensive compilations of heterocyclic facts: the early series[8] edited by Elderfield discusses pioneering work. The still-continuing and still-growing series of monographs[9] dealing with particular heterocyclic systems, edited originally by Arnold Weissberger, and latterly by Edward C. Taylor, is a vital source of information and reviews for all those working with heterocyclic compounds. Finally, the heterocyclic volumes of *Rodd's chemistry of carbon compounds*[10] contain a wealth of well-sifted information and data.

HOW TO USE THIS TEXTBOOK

As indicated above, by comparison with earlier editions, this 3rd edition of *Heterocyclic Chemistry* contains more material, including more which is appropriate to study at a higher level, than that generally taught in a first degree course. Nevertheless we believe that undergraduates will find the book of value and offer the following *modus operandi* as a means for their use of this text.

The undergraduate student should first read chapter 1, which will provide a structural basis for the chemistry which follows. We suggest that the material dealt with in chapter 2 be left, for study at later stages, and that the undergraduate student proceed next to those chapters (4, 7, 10, 12, 16, and 20) which explain heterocyclic principles in the simplest terms and which should be easily

assimilable by students who have a good grounding in elementary reaction chemistry, especially aromatic chemistry.

The student could then proceed to the main chapters, dealing with 'reactions and synthesis of . . .' in which will be found full discussions of the chemistry of particular systems – pyridines, quinolines, etc. These utilise many cross references which seek to capitalise on that important didactical strategy – comparison and analogy with reactivity already learnt and understood.

Chapter 2 is an advanced essay on heterocyclic chemistry. Sections can be sampled as required – 'Electrophilic substitution' could be read at the point at which the student was studying electrophilic substitutions of, say, thiophene – or it can be read as a whole. We have devoted considerable space in chapter 2 to discussions of radical substitution, metallation, and palladium-catalysed reactions. These topics have grown enormously in importance since the last edition of the book, are of great relevance to heterocyclic chemistry, and are relatively poorly explained in general textbooks.

GENERAL HETEROCYCLIC CHEMISTRY REFERENCES

1 'Photochemistry of heterocycles', Reed, S. T., *Adv. Heterocycl. Chem.*, **1970**, *11*, 1; 'Photochemistry of nitrogen-containing heterocycles', *ibid.*, **1982**, *30*, 239; 'Photochemistry of heterocyclic compounds', Buchardt, O., Wiley-Interscience, New York, **1976**.

2 'The nomenclature of heterocycles', McNaught, A. D., *Adv. Heterocycl. Chem.*, **1976**, *20*, 175.

3 Katritzky, A. R. and Weeds, S. M., *Adv. Heterocycl. Chem.*, **1966**, *7*, 225; Katritzky, A. R. and Jones, P. M., *ibid.*, **1979**, *25*, 303; Belen'kii, L. I., *ibid.*, **1988**, *44*, 269; Belen'kii, L. I. and Kruchkovskaya, N. D., *ibid.*, **1992**, *55*, 31.

4 'Comprehensive heterocyclic chemistry. (The structure, reactions, synthesis, and uses of heterocyclic compounds)', Eds Katritzky, A. R. and Rees, C. W., Vols 1–8, Pergamon Press, Oxford, **1984**.

5 'Handbook of heterocyclic chemistry', Katritzky, A. R., Pergamon Press, Oxford, **1985**.

6 'Ring transformations of heterocycles', Vols 1 and 2, van der Plas, H. C., Academic Press, New York, **1973**.

7 'Heterocycles in organic synthesis', Meyers, A. I., Wiley-Interscience, New York, **1974**; for a more recent article in the same vein see: 'Five-membered heteroaromatic rings as intermediates in organic synthesis', Lipshutz, B. H., *Chem. Rev.*, **1986**, *86*, 795.

8 'Heterocyclic compounds', Ed. Elderfield, R. C., Vols 1–9, Wiley, **1950–1967**.

9 'Heterocyclic compounds', Series Eds Weissberger, A. and Taylor, E. C., Vols 1–47, Wiley-Interscience, **1950–1990**.

10 'Rodd's chemistry of carbon compounds', Eds Coffey, S. then Ansell, M. F., Vols IVA–IVL, and Supplements, Elsevier, Amsterdam, **1973–1990**.

Definitions of abbreviations

p-An = *para*-anisyl [4-MeO-C_6H_4]
aq. = aqueous
9-BBN triflate = 9-borabicyclo[3.3.1]nonyl trifluoromethanesulfonate
Bn = benzyl [$PhCH_2$]
Boc = *tertiary*-butoxycarbonyl [$Me_3COC{=}O$]
i-Bu = *iso*-butyl [Me_2CHCH_2]
n-Bu = *normal*-butyl [$Me(CH_2)_3$]
s-Bu = *secondary*-butyl [$MeCH_2C(Me)H$]
t-Bu = *tertiary*-butyl [Me_3C]
c. = concentrated
c = cyclo as in *c*-C_5H_9 = cyclopentyl
CDI = 1,1′-carbonyldiimidazole [$(C_3H_3N_2)_2C{=}O$]
cp = cyclopentadienyl [*c*-$C_5H_5^-$]
m-CPBA = *meta*-chloroperbenzoic acid [3-Cl-C_6H_4-CO_3H]
DBU = diazabicycloundecane
DCC = N,N′-dicyclohexylcarbodiimide [*c*-$C_6H_{11}N{=}C{=}N$-*c*-C_6H_{11}]
DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD = diethyl azodicarboxylate [$EtO_2CN{=}NCO_2Et$]
DIBALH = diisobutylaluminium hydride [$(Me_2CHCH_2)_2AlH$]
DMAP = 4-dimethylaminopyridine
DMF = dimethylformamide [$Me_2NCH{=}O$]
DMFDMA = dimethylformamide dimethyl acetal [$Me_2NCH(OMe)_2$]
DMSO = dimethylsulfoxide [$Me_2S{=}O$]
dppb = 1,4-bis(diphenylphosphino)butane [$Ph_2P(CH_2)_4PPh_2$]
ee = enantiomeric excess
ESR = electron spin resonance
Et = ethyl [CH_3CH_2]
f. = fuming
FVP = flash vacuum pyrolysis
Het = general designation for a heterocyclic nucleus

HOMO = highest occupied molecular orbital
hν = ultraviolet or visible irradiation
LDA = lithium diisopropylamide [LiN*i*-Pr_2]
LiTMP = lithium 2,2,6,6-tetramethylpiperidide
liq. = liquid
LUMO = lowest unoccupied molecular orbital
Me = methyl [CH_3]
Ph = phenyl [C_6H_5]
Phosphorus oxychloride = $POCl_3$
Phosphoryl chloride = $POCl_3$
PMP = 1,2,2,6,6-pentamethylpiperidine
(PP) = pyrophosphate [OP(=O)(OH)OP(=O)OH]
PPA = polyphosphoric acid
i-Pr = *iso*-propyl [Me_2CH]
n-Pr = *normal*-propyl [$CH_3CH_2CH_2$]
proton sponge = 1,8-bis(dimethylamino)naphthalene
rp = room (atmospheric) pressure
rt = room temperature
salcomine = *N*,*N*′-bis(salicylidene)ethylenediaminocobalt(II)
SEM = trimethylsilylethoxymethyl [$Me_3Si(CH_2)_2OCH_2$]
SET = single electron transfer
SOMO = singly occupied molecular orbital
TASF = tris(dimethylamino)sulfur (trimethylsilyl)difluoride [$(Me_2N)_3S(Me_3SiF_2)$]
TBAF = tetra-*normal*-butylammonium fluoride [n-$Bu_4N^+ F^-$)
TBDMS = *tertiary*-butyldimethylsilyl [$Me_3C(Me)_2Si$]
THF = tetrahydrofuran [2,3,4,5-tetrahydrofuran]
TIPS = tri-*iso*-propylsilyl [*i*-Pr_3Si]
TMEDA = N,N,N′,N′tetramethylethylenediamine [$Me_2N(CH_2)_2NMe_2$]
TMS = trimethylsilyl [Me_3Si]
TMSOTf = trimethylsilyl triflate
p-Tol = *para*-tolyl [4-Me-C_6H_4]
o-Tol = *ortho*-tolyl [2-Me-C_6H_4]
TOSMIC = tosylmethyl isocyanide [4-$MeC_6H_4SO_2CH_2NC$]
TfO^- = triflate
triflate = trifluoromethanesulfonate [$CF_3SO_3^-$]
Ts = tosyl [4-$MeC_6H_4SO_2$]

(dR) = deoxyribose

(R) = ribose

(S) = a sugar, usually a derivative of ribose or deoxyribose, attached to heterocyclic nitrogen, in which the substituents have not altered during the reaction shown

))) = sonication

1 Structures and main physical properties of aromatic heterocycles

This chapter describes the structures of aromatic heterocycles and gives a brief summary of some physical properties.[1] The treatment we use is the valence-bond description, which we believe is sufficient for the understanding of all heterocyclic reactivity, perhaps save some very subtle effects, and is certainly sufficient for a general text-book on the subject. The more fundamental molecular-orbital description of aromatic systems is still not so relevant to the day-to-day interpretation of heterocyclic reactivity, though it is necessary in some cases to utilise frontier orbital considerations,[2] however such situations do not fall within the scope of this book.

1.1 CARBOCYCLIC AROMATIC SYSTEMS

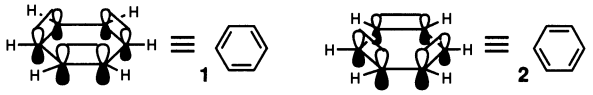
1.1.1 Structures of benzene and naphthalene

The concept of aromaticity as represented by benzene is a familiar and relatively simple one. The difference between benzene on the one hand and alkenes on the other is well known: the latter react by **addition** with electrophiles, such as bromine, whereas benzene reacts only under much more forcing conditions and then nearly always by **substitution**. The difference is due to the cyclic arrangement of six π-electrons in benzene: this forms a conjugated molecular orbital system which is thermodynamically much more stable than a corresponding non-cyclically conjugated system. The additional stabilisation results in a diminished tendency to react by addition and a greater tendency to react by substitution for, in the latter manner, survival of the original cyclic conjugated system of electrons is ensured in the product. A general rule proposed by Hückel in 1931 states that aromaticity is observed in cyclically conjugated systems of $4n + 2$ electrons, that is with 2, 6, 10, 14, etc., π-electrons; by far the majority of monocyclic aromatic, and heteroaromatic, systems are those with 6 π-electrons.

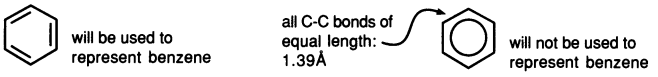
In this book we use the pictorial valence-bond resonance description of structure and reactivity. Even though this treatment is not rigorous it is still the standard means for the understanding and learning of organic chemistry, which can at a more advanced level give way naturally to the much more complex, and mathematical, quantum mechanical approach. We begin by recalling the structure of benzene in these terms.

In benzene the geometry of the ring, with angles of 120°, precisely fits the geometry of a planar trigonally hybridised carbon atom, and allows the assembly of a σ-skeleton of six sp^2 hybridised carbon atoms in a strainless planar ring. Each carbon then has one extra electron which occupies an atomic p orbital orthogonal to the plane of the ring. The p orbitals interact to generate π-molecular orbitals associated with the aromatic system.

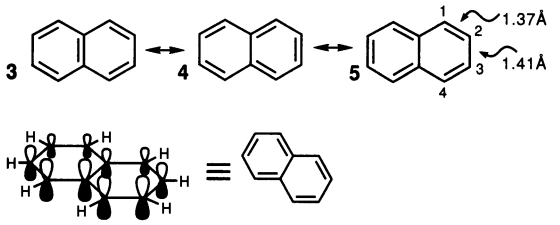
Benzene is described as a resonance hybrid of the two extreme forms which correspond, in terms of orbital interactions, to the two possible spin-coupled pairings of adjacent p-electrons – structures **1** and **2**. These are known as canonical structures, have no existence in their own right, but serve to illustrate two extremes which contribute to the 'real' structure of benzene.



Sometimes, benzenoid compounds are represented using a circle inside a hexagon; although this emphasises their delocalised nature and the close similarity of the ring bond lengths (all exactly identical only in benzene itself), it is not helpful in interpreting reactions, and we do not use this method here.



Treating naphthalene comparably reveals three canonical structures, **3**, **4**, and **5**. Note the standard use of a double-headed arrow to interrelate resonance contributors. This must never be confused with the use of opposing straight 'fish-hook' arrows which are used to designate an equilibrium between two species: **resonance contributors have no separate existence; they are not in equilibrium one with another**.



This valence bond treatment predicts quite well the non-equivalence of the bond lengths in naphthalene: in two of the three contributing structures C-1/C-2 is double and in one it is single, whereas C-2/C-3 is single in two and double in one. Statistically, then, the former may be looked on as 0.67 of a double bond and the latter as 0.33 of a double bond: the measured bond lengths confirm that there indeed is this degree of bond fixation, with values closely consistent with statistical prediction.

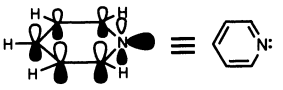
1.1.2 Aromatic resonance energy[3]

The difference between the ground-state energy of benzene and that of hypothetical, non-aromatic, 1,3,5-cyclohexatriene corresponds to the degree of stabilisation conferred to benzene by the special cyclical interaction of the six π-electrons. This difference is known as aromatic resonance energy. Of course, quantification depends on the assumptions made in estimating the energy of the 'non-aromatic' structure and, for this reason and others, a variety of values have been calculated for the various heteroaromatic systems; perhaps their absolute values are less important than their relative values. What one can say with certainty is that the resonance energy of bicyclic aromatics, like naphthalene, is considerably less than twice that of the corresponding monocyclic system, implying a smaller loss of stabilisation energy on conversion to a reaction intermediate which still retains a complete benzene ring, for example during electrophilic substitution (section 2.2.2). The resonance energy of pyridine is of the same order as that of benzene, that of thiophene is lower, with pyrrole and lastly furan of lower stabilisation energy still. Actual values for the stabilisations of these systems vary according to assumptions made, but are in the same relative order (kJ mol^{-1}): benzene (150), pyridine (117), thiophene (122), pyrrole (90), and furan (68).

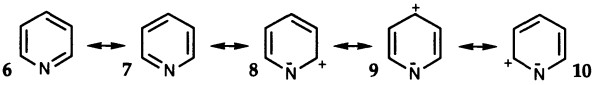
1.2 STRUCTURE OF SIX-MEMBERED HETEROAROMATIC SYSTEMS

1.2.1 Structure of pyridine

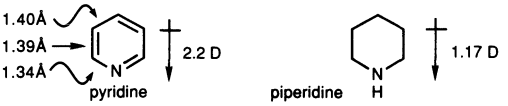
The structure of pyridine is completely analogous to that of benzene, being related by replacement of CH by N. The key differences are: (i) the departure from perfectly regular hexagonal geometry caused by the presence of the hetero atom, in particular the shorter carbon–nitrogen bonds, (ii) the replacement of a hydrogen in the plane of the ring with an unshared electron pair, likewise in the plane of the ring, located in an sp^2 hybrid orbital, and **not at all involved in the aromatic π-electron sextet**; it is this nitrogen lone pair which is responsible for the basic properties of pyridines, and (iii) a strong permanent dipole, traceable to the greater electronegativity of the nitrogen compared with carbon.



It is important to realise that the electronegative nitrogen causes inductive polarisation, mainly in the σ-bond framework, and additionally, stabilises those polarised canonical structures in which nitrogen is negatively charged – **8**, **9**, and **10** – which, together with contributors **6** and **7**, which are strictly analogous to the Kekulé contributors to benzene, represent pyridine. The polarised contributors imply a permanent polarisation of the π-electron system too (these equate, in the more rigorous molecular orbital treatment, to a consideration of the relative magnitudes of orbital coefficients in the HOMO and LUMO).

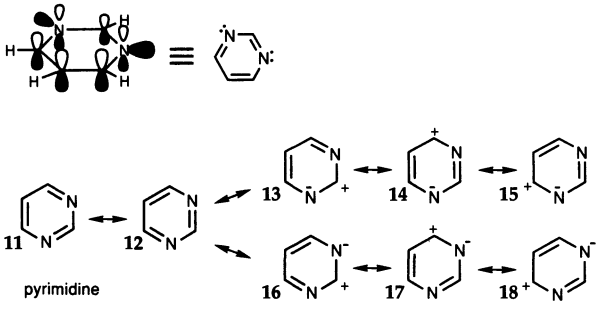


Because inductive and mesomeric effects work in the same sense in pyridine, there results a permanent dipole towards the nitrogen atom. It also means that there are fractional positive charges on the carbons of the ring, located mainly on the α- and γ-positions. It is because of this general electron-deficiency at carbon that pyridine and similar heterocycles are referred to as 'electron-poor', or sometimes 'π-deficient'. A comparison with the dipole moment of piperidine, which is due wholly to the induced polarisation of the σ-skeleton, gives an idea of the additional polarisation associated with distortion of the π-electron system.



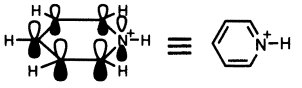
1.2.2 Structure of diazines

The structures of the diazines (six-membered systems with two nitrogen atoms in the ring) are analogous, but now there are two nitrogen atoms and a corresponding two lone pairs; as an illustration, the main canonical contributors (**11–18**) to pyrimidine are shown below.

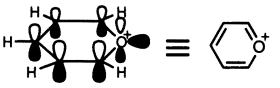


1.2.3 Structures of pyridinium and related cations

Electrophilic addition to the pyridine nitrogen generates pyridinium ions, the simplest being 1*H*-pyridinium formed by addition of a proton. 1*H*-Pyridinium is actually isoelectronic with benzene, the only difference being the nuclear charge of nitrogen, which makes the system, as a whole, positively charged. Thus **pyridinium cations are still aromatic**, the diagram making clear that the system of six p orbitals required to generate the aromatic molecular orbitals is still present, though the formal positive charge on the nitrogen atom severely distorts the π-system, making the α- and γ-carbons in these cations carry fractional positive charges which are higher than in pyridine, with a consquence for their reactivity towards nucleophiles. Electron density at the pyridinium β-carbons is also reduced relative to these carbons in pyridines.

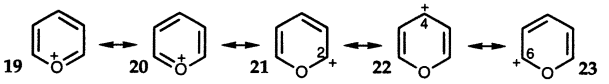


1*H*-pyridinium cation



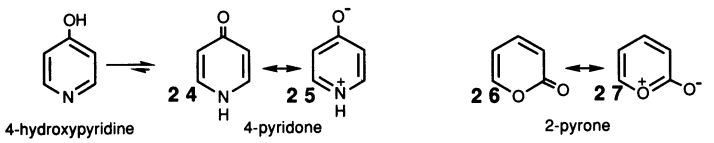
pyrylium cation

In the pyrylium cation, the positively charged oxygen also has an unshared electron pair, in an sp^2 orbital in the plane of the ring, exactly as in pyridine. Once again, a set of resonance contributors, **19–23**, makes clear that this ion is strongly positively charged at the 2-, 4- and 6-positions, in fact, because the more electronegative oxygen tolerates positive charge much less well than nitrogen, the pyrylium cation is certainly a less stabilised sytem than a pyridinium cation.



1.2.4 Structures of pyridones and pyrones

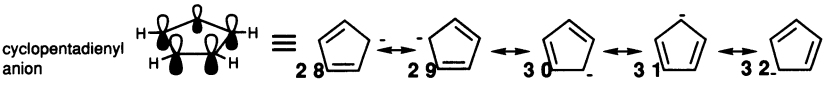
Pyridines carrying 2- and 4-hydroxyl substituents exist predominantly as carbonyl tautomers, which are therefore known as pyridones[4] (see also section 1.5). In the analogous oxygen systems, no alternative tautomer is possible; the systems are known as pyrones. The extent to which such molecules are 'aromatic' has been a subject for considerable speculation and experimentation, and estimates have varied considerably. The degree of aromaticity depends on the contribution which dipolar structures, **25** and **27**, with a 'complete' pyridinium (pyrylium) ring make to the overall structure. Pyrones are less aromatic than pyridones, as can be seen from their tendency to undergo addition reactions (section 8.2.2.4), and as would be expected from a consideration of the 'aromatic' contributors, **25** and **27**, which have a positively charged hetero atom, oxygen being less easily able to accommodate this requirement.



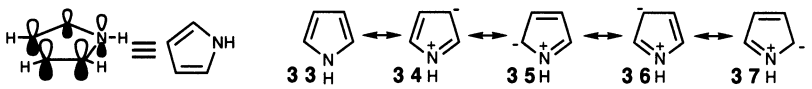
1.3 STRUCTURE OF FIVE-MEMBERED HETEROAROMATIC SYSTEMS[5]

1.3.1 Structure of pyrrole

Before discussing pyrrole it is necessary to recall the structure of the cyclopentadienyl anion, which is a 6-π-electron aromatic system produced by the removal of a proton from cyclopentadiene. This system serves to illustrate nicely the difference between aromatic stabilisation and reactivity, for it is a very reactive, fully negatively charged entity, and yet is 'resonance stabilised' – everything is relative. Cyclopentadiene, with a pK_a of about 14, is much more acidic than a simple diene, **because** the resulting anion is resonance stabilised. Five equivalent contributing structures, **28–32**, show each carbon atom to be equivalent and hence to carry one fifth of the negative charge.

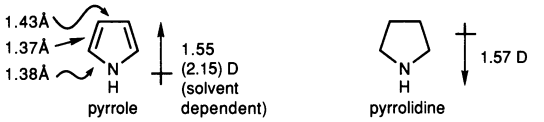


Pyrrole is isoelectronic with the cyclopentadienyl anion, but is electrically neutral because of the higher nuclear charge on nitrogen. The other consequence of the presence of nitrogen in the ring is the loss of radial symmetry, so that pyrrole does not have five equivalent canonical forms: it has one with no charge separation, **33**, and two pairs of equivalent forms in which there is charge separation, indicating electron density drift **away from the nitrogen.** These forms do not contribute equally; the order of importance is: **33** > **35,37** > **34,36.**



Resonance leads, then, to the establishment of partial negative charges on the carbons and a partial positive charge on the nitrogen. Of course the inductive effect of the nitrogen is, as usual, towards the hetero atom and away from carbon, so that the electronic distribution in pyrrole is a balance of two opposing effects, of which the mesomeric effect is probably the more significant. The lengths of the bonds in pyrrole are in accord with this exposition, thus the 3,4-bond is very much longer than the 2,3-/4,5-bonds, but appreciably shorter than a normal single bond betwen sp^2 hybridised carbons, in accord with contributions

from the polarised structures **34–37**. It is because of this electronic drift away from nitrogen and towards the ring carbons that five-membered heterocycles of the pyrrole type are referred to as 'electron-rich', or sometimes 'π-excessive'.



It is most important to recognise that the **nitrogen lone pair in pyrrole forms part of the aromatic 6-electron system.**

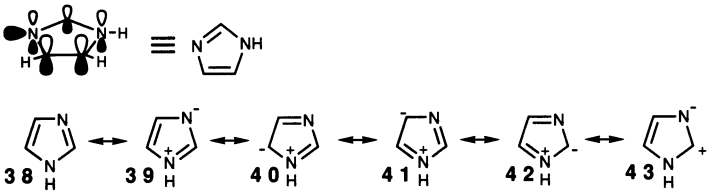
1.3.2 Structures of thiophene and furan

The structures of thiophene and furan are closely analogous to that discussed in detail for pyrrole above, except that the NH is replaced by S and O respectively. A consequence is that the hetero atom in each has one lone pair as part of the aromatic sextet, as in pyrrole, but also has a second lone pair which is not involved, and is located in an sp^2 hybrid orbital in the plane of the ring. Canonical forms exactly analogous to those (above) for pyrrole can be written for each, but the higher electronegativity of both sulfur and oxygen means that the polarised forms, with positive charges on the hetero atoms, make a smaller contribution. The decreased mesomeric electron drift away from the hetero atoms is insufficient, in these two cases, to overcome the inductive polarisation towards the hetero atom (the dipole moments of tetrahydrothiophene and tetrahydrofuran, 1.87 D and 1.68 D, respectively, both towards the heteroatom, are in any case larger) and the net effect is to give dipoles directed towards the hetero atoms in thiophene and furan.

The larger bonding radius of sulfur is one of the influences making thiophene more stable (more aromatic) than pyrrole or furan – the bonding angles are larger and angle strain is somewhat relieved, but in addition, a contribution to the stabilisation involving sulfur d orbital participation may be significant.

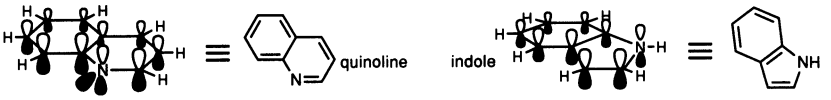
1.3.3 Structures of azoles

The 1,3- and 1,2-azoles, five-membered rings with two hetero atoms, present a fascinating combination of hetero atom types – in all cases, one must be of the five-membered heterocycle (pyrrole, thiophene, furan) type and one of the azomethine type, as in pyridine; imidazole with two nitrogen atoms illustrates this best. Contributor **39** is a particularly favourable one.

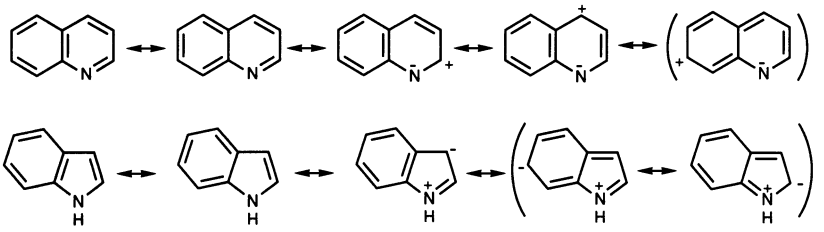


1.4 STRUCTURES OF BICYCLIC HETEROAROMATIC COMPOUNDS

Once the ideas of the structures of benzene, naphthalene, pyridine and pyrrole, as prototypes, have been assimilated it is straightforward to extrapolate to those systems which combine two (or more) of these types, thus quinoline is like naphthalene, only with one of the rings a pyridine, and indole is like pyrrole, but with a benzene ring attached.



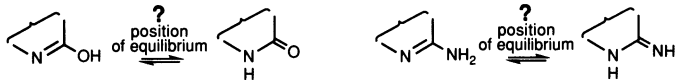
Resonance representations must take account of the pattern established for benzene and the relevant heterocycle. Contributors in which both aromatic rings are disrupted make a very much smaller contribution.



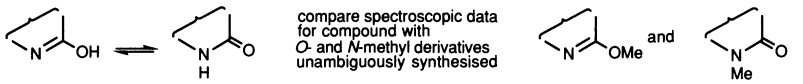
1.5 TAUTOMERISM IN HETEROCYCLIC SYSTEMS[6]

A topic which has attracted an inordinately large research effort over the years is the determination of precise structure of heterocyclic molecules which are potentially tautomeric – the pyridinol/pyridone relationship (section 1.2.4) is

one such situation. In principle, when a hydroxyl is located on a carbon α or γ to nitrogen, two tautomeric forms can exist; the same is true of amino groups.



Early attempts to use the results of chemical reactions to assess the form of a particular compound were misguided, since these can give entirely the wrong answer: the minor partner in such a tautomeric equilibrium may be the one which is the more reactive, so a major product may be actually derived from the minor component in the tautomeric equilibrium. Most secure evidence on these questions has come from comparisons of spectroscopic data for the compound in question with unambiguous models – often *N*- and *O*-methyl derivatives.

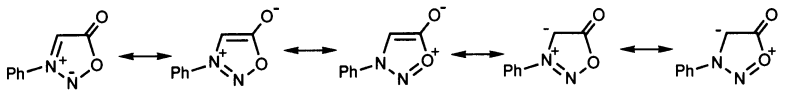


After all the effort that has been expended on this area, the picture which emerges is fairly straightforward: α and γ oxy-heterocycles generally prefer the carbonyl form; amino-heterocycles nearly always exist as amino tautomers. Sulfur analogues – potentially thiol or thione – tend to exist as thione in six-membered situtations, but as thiol in five-membered rings.

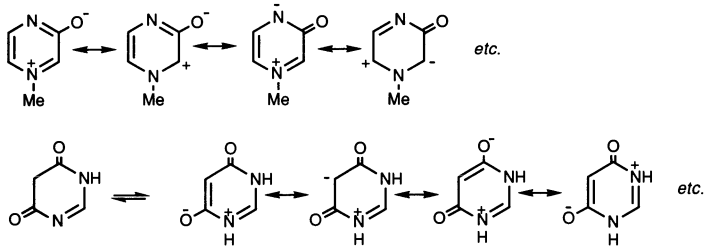
The establishment of tautomeric form is perhaps of most importance in connection with the purine and pyrimidine bases which form part of DNA and RNA, and, through H-bonding involving carbonyl oxygen, provide the mechanism for base pairing (cf. section 23.1).

1.6 MESOIONIC SYSTEMS[7]

There are a substantial number of heterocyclic substances for which no plausible, unpolarised canonical structure can be written: such systems are termed 'mesoionic'. Despite the presence of a nominal positive and negative charge in all resonance contributors to such compounds, they are not salt-like, are of course overall neutral, and behave like 'organic' substances, dissolving in the usual solvents. Examples of mesoionic structures occur throughout the text. Amongst the earliest mesoionic substances to be studied were the sydnones, for which several contributing structures can be drawn.



Mesoionic structures occur amongst six-membered systems too – two are illustrated below:



If there is any one feature which characterises mesoionic compounds it is that their dipolar structures lead to reactions in which they serve as 1,3-dipoles in cycloadditions.

1.7 SOME SPECTROSCOPIC PROPERTIES OF SOME HETEROAROMATIC SYSTEMS

The use of spectroscopy is at the heart of chemical research and analysis, but a knowledge of the particular chemical shift of, say, a proton on a pyridine, or the particular UV absorption maximum of, say, an indole, is only of direct relevance to those actually pursuing such research and analysis, and adds nothing to the understanding of heteroaromatic reactivity. Accordingly, we give here only a brief discussion, with relatively little data, of the spectroscopic properties of heterocyclic systems, anticipating that those who may be involved in particular research projects will turn to reviews[1] or the original literature for particular data.

The ultraviolet and infrared spectra of heteroaromatic systems are in accord with their aromatic character. Spectroscopic investigation, particularly ultraviolet/visible (UV/VIS) and nuclear magnetic resonance (NMR) spectroscopies, is particularly useful in the context of assessing the extent of such properties, in determining the position of tautomeric equilibria, and in testing for the existence of non-isolable intermediates.

1.7.1 Ultraviolet/visible (electronic) spectroscopy

The simple unsubstituted heterocyclic systems show a wide range of electronic absorption, from the simple 200 nm band of furan, for example, to the 340 nm maximum shown by pyridazine. As is true for benzenoid compounds, the presence of substituents which can conjugate causes profound changes in electronic absorption, but the many variations possible are outside the scope of this section.

The UV spectra of the monocyclic azines show two bands, each with fine

structure: one occurs in the relatively narrow range of 240–260 nm and corresponds to the $\pi \rightarrow \pi^*$ transitions, analogous with the $\pi \rightarrow \pi^*$ transitions in the same region in benzene (see table 1.1). The other band occurs at longer wavelengths, from 270 nm in pyridine to 340 nm in pyridazine and corresponds to the interaction of the hetero atom lone pair with aromatic π electrons, the $n \rightarrow \pi^*$ transitions, which of course cannot occur in benzene. The absorptions due to $n \rightarrow \pi^*$ transitions are very solvent dependent, as is exemplified in table 1 by the case of pyrimidine. With pyridine, this band is only observed in hexane solution, for in alcoholic solution the shift to shorter wavelengths results in masking by the main $\pi \rightarrow \pi^*$ band. Protonation of the ring nitrogen naturally quenches the $n \rightarrow \pi^*$ band, by removing the hetero atom lone pair; protonation also has the effect of considerably increasing the intensity of the $\pi \rightarrow \pi^*$ band, without changing its position significantly, the observation of which can have considerable diagnostic utility.

Table 1.1 Ultraviolet spectra of monocyclic azines (fine structure not given)

Heterocycle (solvent)	$n \rightarrow \pi^*$ $\lambda_{max.}$ (nm)	ε	$\pi \rightarrow \pi^*$ $\lambda_{max.}$ (nm)	$\pi \rightarrow \pi^*$	ε	ε
Pyridine (hexane)	270	450	195	251	7500	2000
Pyridine (ethanol)	–	–	–	257	–	2750
Pyridinium(ethanol)	–	–	–	256	–	5300
Pyridazine (hexane)	340	315	–	246	–	1400
Pyrimidine (hexane)	298	326	–	243	–	2030
Pyrazine (hexane)	328	1040	–	260	–	5600
Pyrimidine (water)	271	410	–	243	–	3210
Pyrimidine (water)	–	–	–	242	–	5500
Pyrylium (90% aq. $HClO_4$)	–	–	220	269	1400	8500
Benzene (hexane)	–	–	204	254	7400	200

The bicyclic azines have much more complex electronic absorption, and the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ bands overlap; being much more intense, the latter mask the former. Broadly, however, the absorptions of the bicyclic azines resemble that of naphthalene (table 1.2).

Table 1.2 Ultraviolet spectra of bicyclic azines (fine structure not given)

Heterocycle	$\lambda_{max.}$ (nm)	$\lambda_{max.}$ (nm)	$\lambda_{max.}$ (nm)	ε	ε	ε
Quinoline	313	270	226	2360	3880	35500
Quinolinium	313	–	233	6350	–	34700
Isoquinoline	317	266	217	3100	4030	37000
Isoquinolinium	331	274	228	4170	1960	37500
Quinolizinium	324	284	225	14500	2700	17000
Naphthalene	312	275	220	250	5600	100000

The UV spectra of the simple five-membered heteroaromatic systems all show just one medium-to-strong low-wavelength band with no fine structure. Their absorptions have no obvious similarity to that of benzene, and no detectable $n \rightarrow \pi^*$ absorption, not even in the azoles, which contain a pyridine-like nitrogen (tables 1.3 and 1.4).

Table 1.3 Ultraviolet spectra of monocyclic five-membered heterocycles

Heterocycle	$\lambda_{max.}$(nm)	$\lambda_{max.}$(nm)	ε	ε
Pyrrole	210	–	5100	–
Furan	200	–	10000	–
Thiophene	235	–	4300	–
Imidazole	206	–	3500	–
Oxazole	205	–	3900	–
Thiazole	200	239	10000	3400

Table 1.4 Ultraviolet spectra of bicyclic compounds with five-membered heterocyclic rings

Heterocycle	$\lambda_{max.}$(nm)	$\lambda_{max.}$(nm)	$\lambda_{max.}$(nm)	ε	ε	ε
Indole	288	261	219	4900	6300	25000
Benzo[*b*]thiophene	288	257	227	2000	5500	28000
Benzo[*b*]furan	281	–	244	2600	–	11000
2-*t*-Bu-isoindole	233, 266	270, 277	289, 329	48000, 1800	1650, 1850	1250, 3900
Isobenzofuran	215, 244, 249	254, 261, 313 –	319, 327, 334, 343	14800, 2500, 2350	2250, 1325, 5000	5000, 7400, 4575, 6150
Indolizine	347	295	238	1950	3600	32000
Purine	263	–	–	7950	–	–

1.7.2 Nuclear magnetic resonance (NMR) spectroscopy[8]

The chemical shifts of protons attached to, and in particular of the carbons in, heterocyclic systems, can be taken as relating to the electron-density at that position, with lower fields corresponding to electron-deficient carbons. For example, in the ^1H spectrum of pyridine, the lowest field signals are for the α-protons (table 1.5), the next lowest is that for the γ-proton and the highest field signal corresponds to the β-protons, and this is echoed in the corresponding ^{13}C shifts (table 1.6). A second generality relates to the inductive electron withdrawal by the hetero atom – for example it is the hydrogens on the α-carbons of pyridine which are at lower field than that at the γ-carbon, and it is the signals for protons at the α-positions of furan which are at lower field than those at the β-positions. Protons at the α-positions of pyrylium cations present the lowest

Table 1.5 ^{1}H chemical shifts (ppm) for heteroaromatic ring protons

Heterocycle	δ_1	δ_2	δ_3	δ_4	δ_5	δ_6	δ_7	δ_8	others
Pyridine	–	8.5	7.1	7.5	–	–	–	–	–
2-Pyridone	–	–	6.6	7.3	6.2	7.3	–	–	–
Quinoline	–	8.8	7.3	8.0	7.7	7.4	7.6	8.1	–
Quinoline *N*-oxide	–	8.6	7.3	7.7	–	–	–	8.8	–
Isoquinoline	9.1	–	8.5	7.5	7.7	7.6	7.5	7.9	–
Isoquinoline *N*-oxide	8.8	–	8.1	–	–	–	–	–	–
Pyridazine	–	–	9.2	7.7	–	–	–	–	–
Pyrimidine	–	9.2	–	8.6	7.1	–	–	–	–
Pyrimidine *N*-oxide	–	9.0	–	8.2	7.3	8.4	–	–	–
Pyrazine	–	8.5	–	–	–	–	–	–	–
Pyrylium	–	9.6	8.5	9.3	–	–	–	–	in SO_2 (liq.)
Pyrrole	–	6.6	6.2	–	–	–	–	–	–
Thiophene	–	7.2	7.1	–	–	–	–	–	–
Furan	–	7.4	6.3	–	–	–	–	–	–
Indole	–	6.5	6.3	7.5	7.0	7.1	7.4	–	
Benzo[*b*]furan	–	7.5	6.7	7.5	7.1	7.2	7.4	–	–
Benzo[*b*]thiophene	–	7.3	7.3	7.7	7.3	7.3	7.8	–	–
Indolizine	6.3	6.6	7.1	–	7.8	6.3	6.5	7.2	–
Imidazole	–	7.7	–	7.1	–	–	–	–	–
1-Methylimidazole	–	7.4	–	6.9	7.1	–	–	–	–
Pyrazole	–	–	7.6	6.3	–	–	–	–	–
1-Methylpyrazole	7.3	6.1	7.4	–	–	–	–	–	3.8 (CH_3)
Thiazole	–	8.9	–	7.4	8.0	–	–	–	–
Oxazole	–	7.9	–	7.1	7.7	–	–	–	–
Purine	–	9.0	–	–	–	9.2	–	8.6	–
Benzene	7.27	–	–	–	–	–	–	–	–
Anisole	–	6.9	7.2	6.9	–	–	–	–	–
Aniline	–	6.5	7.0	6.6	–	–	–	–	–
Nitrobenzene	–	8.2	7.4	7.6	–	–	–	–	–
Naphthalene	7.8	7.5	–	–	–	–	–	–	–

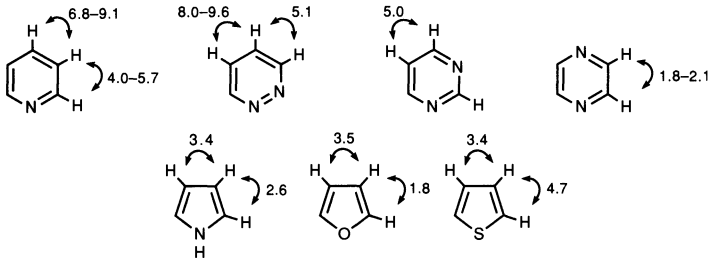
field ^{1}H signals. In direct contrast, the chemical shifts for *C*-protons on electron-rich heterocycles, such as pyrrole, occur at much higher fields.

Coupling constants between 1,2-related (*ortho*) protons on heterocyclic systems vary considerably. Typical values round six-membered systems show smaller values closer to the hetero atom(s). In five-membered heterocycles, altogether smaller values are typically found, but again those involving a hydrogen closer to the hetero atom are smaller, except in thiophenes, where the larger size of the sulfur atom influences the coupling constant. The magnitude of such coupling constants reflects the degree of double bond character (bond fixation) in a particular C–C bond.

Table 1.6 ^{13}C Chemical shifts (ppm) for heteroaromatic ring carbons

Heterocycle	δ_1	δ_2	δ_3	δ_4	δ_5	δ_6	δ_7	δ_8	$\delta_{\text{ring junction}}$	$\delta_{\text{ring junction}}$	other
Pyridine	–	150	124	136	–	–	–	–	–	–	–
1*H*-Pyridinium	–	143	129	148	–	–	–	–	–	–	–
Pyridine *N*-oxide	–	139	126	126	–	–	–	–	–	–	–
1-Me-pyridinium I^-	–	146	129	146	–	–	–	–	–	–	50 (CH_3)
2-Pyridone	–	165	121	142	107	136	–	–	–	–	–
4-Pyridone	–	140	116	176	–	–	–	–	–	–	–
Quinoline	–	151	122	136	128	127	130	131	129 (4*a*)	149 (8*a*)	–
Isoquinoline	153	–	143	120	126	130	127	128	136 (4*a*)	129 (8*a*)	–
Pyridazine	–	–	153	128	–	–	–	–	–	–	–
1*H*-Pyridazinium	–	–	152	138	–	–	–	–	–	–	–
Pyrimidine	–	158	–	156	121	–	–	–	–	–	–
1*H*-Pyrimidinium	–	152	-	159	125	–	–	–	–	–	–
Pyrazine		146	–	–	–	–	–	–	–	–	–
1*H*-Pyrazinium	–	143	–	–	–	–	–	–	–	–	–
Pyrylium (BF_4^-)	–	169	128	161	–	–	–	–	–	–	–
2-Pyrone	–	162	117	143	106	152	–	–	–	–	–
2,6-Me_2-4-pyrone	–	166	114	180	–	–	–	–	–	–	–
Coumarin	–	161	117	144	129	124	132	117	119 (4*a*)	154 (8*a*)	–
Chromone	–	156	113	177	125	126	134	118	125 (4*a*)	156 (8*a*)	–
Pyrrole	–	117	108	–	–	–	–	–	–	–	–
Thiophene	–	126	127	–	–	–	–	–	–	–	–

Furan	–	144	110	–	–	–	–	–	–	–	–
Indole	–	124	102	121	122	120	111	–	128 (3*a*)	136 (7*a*)	–
Oxindole	–	179	36	124	122	128	110	–	125 (3*a*)	155 (7*a*)	–
Benzo[*b*]furan	–	145	107	122	123	125	112	–	128 (3*a*)	155 (7*a*)	–
Benzo[*b*]thiophene	–	126	124	124	124	124	123	–	140 (3*a*)	140 (7*a*)	–
Indolizine	100	114	113	–	126	111	117	120	133 (3*a*)	–	–
Imidazole	–	135	–	122	–	–	–	–	–	–	–
1-Methylimidazole	–	138	–	130	120	–	–	–	–	–	33 (CH_3)
Pyrazole	–	–	135	106	135	–	–	–	–	–	–
Thiazole	–	154	–	143	120	–	–	–	–	–	–
Isothiazole	–	–	157	123	148	–	–	–	–	–	–
Oxazole	–	151	–	125	138	–	–	–	–	–	–
Isoxazole	–	–	150	105	159	–	–	–	–	–	–
Purine	–	152	–	155	131	146	–	146	–	–	–
Uracil	–	151	–	142	100	164	–	–	–	–	–
Benzene	129	–	–	–	–	–	–	–	–	–	–
Anisole	160	114	130	121	–	–	–	–	–	–	–
Aniline	149	114	129	116	–	–	–	–	–	–	–
Nitrobenzene	149	124	130	135	–	–	–	–	–	–	–
Naphthalene	128	126	–	–	–	–	–	–	133 (4*a*)	–	–



Recently the use of ^{15}N NMR spectroscopy has come to the fore, and is of obvious relevance to the study of nitrogen-containing heterocycles – it can for example be used to estimate the hybridisation of nitrogen atoms.[9]

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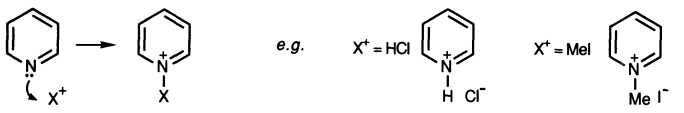
2 Reactivity of aromatic heterocycles

This chapter describes in general terms the types of reactivity found in the typical six- and five-membered aromatic heterocycles. Considerable space is devoted to radical substitution, metallation and palladium-catalysed reactions, since it is in these areas that there has been most progress and change since the earlier editions of this book, and we feel that for a proper appreciation of their importance in the heterocyclic context, an introduction to these topics is required, their being only poorly covered in general text-books. Emphasis on the typical chemistry of individual heterocyclic systems is to be found in the summary/revision chapters (4, 7, 10, 12, 16 and 20) and a more detailed examination of typical heterocyclic reactivity, and many more examples for particular heterocyclic systems are to be found in the chapters – 'Pyridines: reactions and synthesis' etc. For the advanced student, it is recommended that this present chapter should be read in its entirety before moving on to the later chapters, and that the introductory summary/ revision chapters, like 'Typical reactivity of pyridines, quinolines and isoquinolines' should be read before the more detailed discussions.

2.1 ELECTROPHILIC ADDITION AT NITROGEN

Heterocycles which contain an azomethine unit (C=N) as part of their ring structure – pyridines, quinolines, isoquinolines, 1,2- and 1,3-azoles, etc. – do not utilise the nitrogen lone pair in their aromatic π-system (cf. section 1.2) and therefore it is available for donation to electrophiles, just as in any simpler amine. In other words, such heterocycles are basic and will react with protons, or other electrophilic species, **at nitrogen**, by **addition**. In many instances the product salts, from such additions, are isolable.



For reversible additions, for example of a proton, the position of equilibrium depends on the pK_a of the heterocycle,[1] and this in turn is influenced by the substituents present on the ring: electron-releasing groups enhance the basicity and electron-withdrawing substituents reduce the basic strength. The pK_a of simple pyridines is of the order of 5, while those for 1,2- and 1,3-azoles depend on the character of the other hetero atom: pyrazole and imidazole, with two nitrogen atoms, have values of 2.5 and 7.1 respectively.

Related to basicity, but certainly not always mirroring it, is the *N*-nucleophilicity of azomethine-containing heterocycles. Here, the presence of substituents adjacent to the nitrogen can have a considerable effect on how easily reaction with alkyl halides takes place and indeed whether nitrogen attacks at carbon, forming N^+-alkyl salts,[2] or by deprotonation, bringing about a 1,2-dehydrohalogenation of the halide, the heterocycle then being converted into an N^+-hydrogen salt. The classical study of the slowing of *N*-alkylation by the introduction of steric interference at α-positions of pyridines showed one methyl to slow the rate by about threefold, whereas 2,6-dimethyl substitution slowed the rate between 12 and 40 times.[3] Taking this to an extreme, 2,6-di-*t*-butylpyridine will not react at all with iodomethane, even under high pressure; the very reactive methyl fluorosulfonate will *N*-methylate it, but only under high pressure.[4] The quantitative assessment of reactivity at nitrogen must always take into account both steric (especially at the α-positions) and electronic effects: 3-methylpyridine reacts faster (× 1.6) but 3-chloropyridine reacts slower (× 0.14) than pyridine. *Peri* substituents have a significant effect on the relative rates of reaction with iodomethane: for pyridine, isoquinoline (no *peri* hydrogen), quinoline and 8-methylquinoline, rates are 50, 69, 8 and 0.008, respectively.

Other factors can influence the rate of quaternisation: all the diazines react with iodomethane more slowly than does pyridine. Pyridazine, much more weakly basic (pK_a 2.3) than pyridine, reacts with iodomethane faster than the other diazines, a result which is ascribed to the 'α effect', i.e. the increased nucleophilicity is deemed to be due to electron repulsion between the pair of immediately adjacent lone pairs.[5] Reaction rates of iodomethane with pyridazine, pyrimidine and pyrazine are respectively 0.25, 0.044 and 0.036 relative to the rate with pyridine.

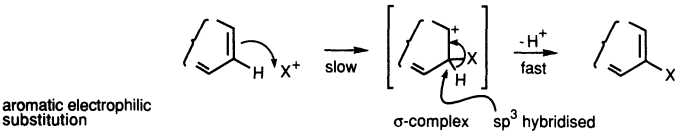
2.2 ELECTROPHILIC SUBSTITUTION AT CARBON[6]

The study of aromatic heterocyclic reactivity can be said to have begun with the results of electrophilic substitution processes – these were traditionally the means for the introduction of substitutents onto heterocyclic rings. To a considerable extent that methodology has been superseded, especially for the introduction of carbon substituents, by methods relying on the formation of heteroaryllithium nucleophiles (section 2.6) and on palladium-catalysed processes (section 2.7). Nonetheless the reaction of heterocycles with electrophilic

reagents is still extremely useful in many cases, particularly for electron-rich, five-membered heterocycles.

2.2.1 Aromatic electrophilic substitution – mechanism

Electrophilic substitution of aromatic (and heteroaromatic) molecules proceeds *via* a two-step sequence, initial **addition** (of X^+) giving a positively charged intermediate (a σ-complex, or Wheland intermediate), then **elimination** (normally of H^+), of which the former is usually the slower (rate-determining) step. Under most circumstances such substitutions are irreversible and the product ratio is determined by kinetic control.

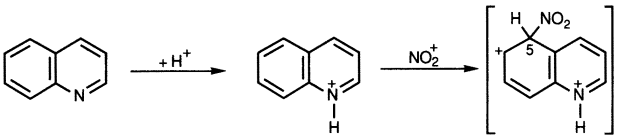


2.2.2 Six-membered heterocycles

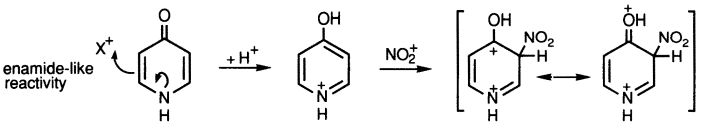
An initial broad division must be made in considering heteroaromatic electrophilic substitution, into those heterocycles which are basic and those which are not, for in the case of the former the interaction of nitrogen lone pair with the electrophile (cf. section 2.1), or indeed of any other electrophilic species in the proposed reaction mixture (protons in a nitrating mixture, or aluminium chloride in a Friedel-Crafts combination) will take place far faster than any *C*-substitution, thus converting the substrate into a positively charged salt and therefore hugely reducing its susceptibility to attack by X^+ at carbon. It is worth recalling the rate reduction attendant upon the change from benzene to *N,N,N*-trimethylanilinium cation (PhN^+Me_3) where the electrophilic substitution rate goes down by a factor of 10^8 even though in this instance the charged atom is only attached to, and not a component of, the aromatic ring. Thus all heterocycles with a pyridine-type nitrogen (i.e. those containing C=N) do not easily undergo *C*-electrophilic substitution, unless (i) there are other substituents on the ring which 'activate' it for attack, or (ii) the molecule has another, fused benzene ring in which substitution can take place, or (iii) there is a second hetero atom in a five-membered ring, which can release electrons to the attacking electrophile. For example, simple pyridines do not undergo many useful electrophilic substitutions, but quinolines and isoquinolines undergo substitution in the benzene ring. It has been estimated that the intrinsic reactivity of a pyridine (i.e. not protonated) to electrophilic substitution is around 10^7 times less than that of benzene, that is to say, about the same as that of nitrobenzene.

When quinoline or isoquinoline undergo nitration in the benzene ring the

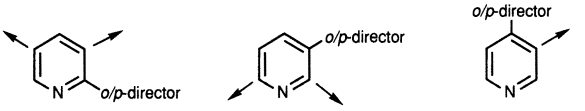
actual species attacked is the *N*-protonated heterocycle, and even though substitution is taking place in the benzene ring, it must necessarily proceed through a doubly charged intermediate: this results in a much slower rate of substitution than for the obvious comparison, naphthalene – the 5- and 8-positions of quinolinium are attacked at about a 10^{10} slower rate than the 1-position of naphthalene, and it was estimated that the nitration of pyridinium cation is at least 10^5 slower still.[7] A study of the bromination of methylpyridines in acidic solution allowed an estimate of 10^{-13} for the partial rate factor for bromination of a pyridinium cation.[8]



'Activating' substitutents,[9] i.e. groups which can release electrons either inductively or mesomerically, make the electrophilic substitution of pyridine rings to which they are attached faster, for example 4-pyridone nitrates at the 3-position *via* the *O*-protonated salt.[10] In order to understand the activation, it is helpful to view the species attacked as a (protonated) phenol-like substrate. Electrophilic attack on neutral pyridones is best visualised as attack on an enamide. Dimethoxypyridines also undergo nitration *via* their cations, but the balance is often delicate, for example 2-aminopyridine brominates at C-5, in acidic solution, *via* the free base.[11]



Pyridines carrying activating substituents at C-2 are attacked at C-3/C-5, those with such groups at C-3 are attacked at C-2, and not at C-4, whilst those with substituents at C-4 undergo attack at C-3.



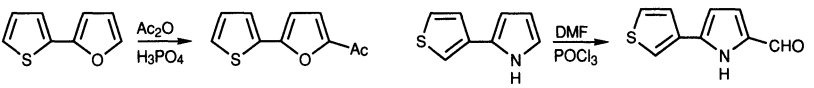
Substituents which reduce the basicity of a pyridine nitrogen can also influence the susceptibility of the heterocycle to electrophilic substitution, in these cases by increasing the quantity of neutral (more reactive) pyridine present at equilibrium: 2,6-dichloropyridine nitrates at C-3, as the free base, and only 10^3 times as slowly as 1,3-dichlorobenzene. As a rule-of-thumb it has been suggest-

ed that (i) pyridines with a $pK_a > 1$ will nitrate as cations, slowly unless strongly activated, and at an α- or β-position depending on the position of the substituent, (ii) weakly basic pyridines, $pK_a < -2.5$, nitrate as free bases, and at an α- or β-position depending on the position of the substituent.[11]

Pyridines carrying strongly electron-withdrawing substituents, or heterocycles with additional hetero atoms, diazines for example, are so deactivated that electrophilic substitutions do not take place.

2.2.3 Five-membered heterocycles

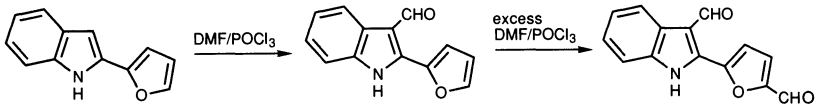
For five-membered, electron-rich heterocycles the utility of electrophilic substitutions is much greater.[12] Heterocycles such as pyrrole, thiophene and furan undergo a range of electrophilic substitutions with great ease, at either type of ring position, but with a preference for attack adjacent to the hetero atom – at their α-positions. These substitutions are facilitated by electron-release from the hetero atom and, as a consequence, pyrroles are more reactive than furans which are in turn more reactive than thiophenes. Quantitative comparisons[13] of the relative reactivities of the three heterocycles vary from electrophile to electrophile, but for trifluoroacetylation, for example, the pyrrole : furan : thiophene ratio is: $5 \times 10^7 : 1.5 \times 10^2 : 1$;[14] in formylation, furan is 12 times more reactive than thiophene,[15] and for acetylation, the value is 9.3.[16] In hydrogen exchange (deuteriodeprotonation) the partial rate factors for the α- and β-positions of *N*-methylpyrrole[17] were shown to be 3.9×10^{10} and 2.0×10^{10} respectively; for this same process, the values for furan were 1.6×10^8 and 3.2×10^4 and for thiophene, 3.9×10^8 and 10^5 respectively,[18] and in a study of thiophene, α : β ratios ranging from 100 : 1 to 1000 : 1 were found for different electrophiles.[19] Relative substrate reactivity parallels positional selectivity i.e. the α : β ratio decreases in the order furan > thiophene > pyrrole.[20] Nice illustrations of these relative reactivities are found in acylations of compounds containing two different systems linked together.[21]



The positional selectivity of attack on pyrroles can be completely altered by the presence of bulky groups on nitrogen: 1-(*t*-butyldimethylsilyl)pyrrole and 1-(tri-*i*-propylsilyl)pyrrole are attacked exclusively at their β-positions.[22] Extremely electrophilic reagents (hard electrophiles) such as trimethylsilyl triflate attack *N*-methylpyrroles exclusively at a β-position.[23]

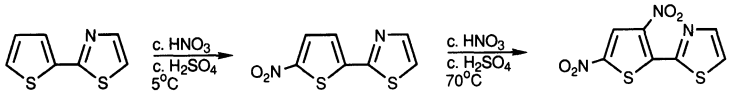
Indoles are only slightly less reactive than pyrroles, electrophilic substitution taking place in the heterocyclic ring, at a β-position: in acetylation using a Vilsmeier combination (*N*,*N*-dimethylacetamide/phosgene), the rate ratio compared with pyrrole was 1 : 3.[24] In contrast to pyrrole there is a very large

difference in reactivity betwen the two hetero-ring position in indoles: 2600 : 1, β : α, in Vilsmeier acetylation. With reference to benzene, indole reacts at its β-position around 5×10^{13} times as fast.[25] Again, these differences can be illustrated conveniently using an example[26] which contains two types of system linked together.



The reactivity of an indole is very comparable to that of a phenol: typical of phenols is their ability to be substituted even by weak electrophiles, like benzenediazonium cations, and indeed indoles (and pyrroles) also undergo such couplings; depending on p*H*, indoles can undergo such processes *via* a small equilibrium concentration of anion formed by loss of *N*-proton (cf. section 2.5); of course this is an even more rapid process, shown to be 10^8 faster than for the neutral heterocycle.[27] The Mannich substitution (electrophile, $CH_2{=}N^+Me_2$) of 5- and 6-hydroxyindoles, takes place *ortho* to the phenolic activating group on the benzene ring, and not at the indole β-position.[28] Comparisons of the rates of substitution of the pairs furan/benzo[*b*]furan and thiophene/benzo[*b*]thiophene showed the bicyclic systems to be less reactive than the monocyclic heterocycles, the exact degree of difference varying from electrophile to electrophile.[29]

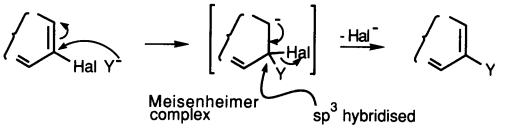
Finally, in the 1,2- and 1,3-azoles there is a fascinating interplay of the propensities of an electron-rich five-membered heterocycle with an azomethine, basic nitrogen. This latter reduces the reactivity of the heterocycle towards electrophilic attack at carbon, both by inductive and by mesomeric withdrawal, and also by conversion into salt in acidic media. For example, depending on acidity, the nitration of pyrazole can proceed by attack on the pyrazolium cation,[30] or *via* the free base.[31] A study of acid-catalysed exchange showed the order: pyrazole > isoxazole > isothiazole, paralleling pyrrole > furan > thiophene, but each is much less reactive than the corresponding heterocycle without the azomethine nitrogen, but equally, that each is still more reactive than benzene, the partial rate factors for exchange at their 4-positions being 6.3×10^9, 2.0×10^4 and 4.0×10^3 respectively. Thiophene is 3×10^5 times more rapidly nitrated than 4-methylthiazoles;[32] the nitration of a thienylthiazole illustrates the relative reactivities.[33]



2.3 NUCLEOPHILIC SUBSTITUTION AT CARBON[34]

2.3.1 Aromatic nucleophilic substitution – mechanism

Nucleophilic substitution of aromatic compounds proceeds *via* an **addition** (of Y^-) then **elimination** (of a negatively charged entity, most often Hal^-) two-step sequence, of which the former is usually rate-determining. It is the stabilisation (delocalisation of charge) of the negatively charged intermediates (Meisenheimer complexes) which is the key to such processes, for example in reactions of *ortho* and *para* chloronitrobenzenes the nitro group is involved in the charge dispersal.

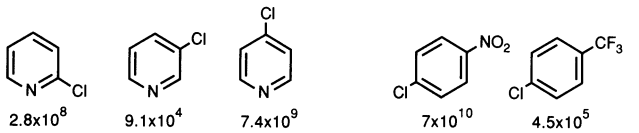


2.3.2 Six-membered heterocycles

In the heterocyclic field, the displacement of good leaving groups, often halide, by a nucleophile is a very important general process, especially for six-membered electron-poor systems. In the chemistry of five-membered aromatic heterocycles, such processes only come into play in special situations such as where, as in benzene chemistry, the leaving group is activated by an *ortho* or *para* nitro group, or in the azoles, where the leaving group is attached to an azomethine link.

Positions α and γ to an azomethine nitrogen are activated for the initial addition of a nucleophile by two factors: (i) inductive and mesomeric withdrawal of electrons by the nitrogen and (ii) inductive withdrawal of electrons by the halogen. The σ-adduct intermediate is also specially stabilised when attack is at α- and γ-positions, since in these intermediates the negative charge resides largely on the nitrogen: α- and γ-positions are much more reactive in nucleophilic displacements than β-positions. A quantitative comparison for displacements of chloride with sodium methoxide in methanol showed the 2- and 4-chloropyridines to react at roughly the same rate as 4-chloronitrobenzene, with the γ-isomer somewhat more reactive than the α-halide.[35] It is notable that even 3-chloropyridine, where only inductive activation can operate, is appreciably more reactive than chlorobenzene.

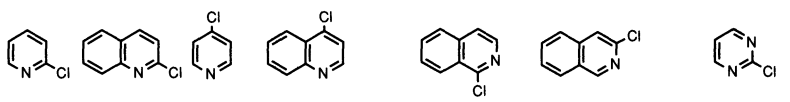
Rates of reaction with MeO^-, relative to chlorobenzene, at 50°C



The presence of a formal positive charge on the nitrogen, as in *N*-oxides and *N*-alkylpyridinium salts, has a further very considerable enhancing effect on the rate of nucleophilic substitutions, *N*-oxidation having a smaller effect than quaternisation – in the latter there is a full formal positive charge on the molecule but *N*-oxides are overall electrically neutral. In reactions with methoxide, the 2-, 3- and 4-chloropyridine *N*-oxides are 1.9×10^4, 1.1×10^5, and 1.1×10^3 times more reactive than the corresponding chloropyridines, and displacements of halide in the 2-, 3- and 4-chloro-1-methylpyridinium salts are 4.6×10^{12}, 2.9×10^8, and 5.7×10^9 times more rapid. Another significant point to emerge from these rate studies concerns the relative rate enhancements, at the three ring positions: the effect of the charge is much greater at an α than at a γ position such that in the salts the order is 2 > 4 > 3, as opposed to both neutral pyridines, where the order of reactivity is 4 > 2 > 3, and *N*-oxides, where the α-positions end up at about the same reactivity as the γ-position.[36] The utility of nitrite as a leaving group in heterocyclic chemistry is emphasised by a comparison of its relative reactivity to nucleophilic displacement: 4-nitropyridine is ~ 1100 times more reactive than 4-bromopyridine. A comparison of the rates of displacement of 4-methylsulfonylpyridine with its *N*-methyl quaternary salt showed a rise in rate by a factor of 7×10^8.[37] Although methoxide is not generally a good leaving group, when attached to a pyridinium salt it is only about 4 times less easily displaced than iodide, bromide and chloride; fluoride in the same situation is displaced about 250 times faster than the other halides.[38]

Turning to bicyclic systems, and a study of reaction with ethoxide, a small increase in the rate of reaction relative to pyridines was found for chloroquinolines at comparable positions.[39] In the bicyclic compounds, quaternisation again greatly increases the rate of nucleophilic substitution, having a larger effect (~ 10^7) at C-2 than at C-4 (~ 10^5).[40]

Relative rates for nucleophilic displacement with EtO^- at 20°C



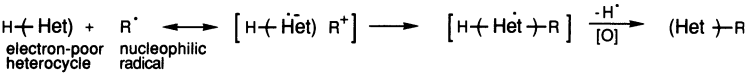
Diazines with halogen α and γ to nitrogen are **much more reactive** than similar pyridines, for example 2-chloropyrimidine is ~ 10^6 times more reactive than 2-chloropyridine.

2.4 RADICAL SUBSTITUTION AT CARBON[41]

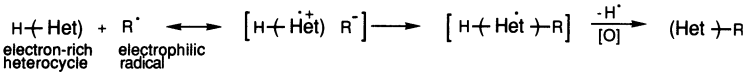
Both electron-rich and electron-poor heterocyclic rings are susceptible to substitution of H by radicals. Although electrically neutral, radicals exhibit varying degrees of nucleophilic or electrophilic character and this has a very significant effect on their reactivity towards different heterocyclic types. These electronic

properties are a consequence of the interaction between the SOMO (Singly Occupied Molecular Orbital) of the radical and either the HOMO, or the LUMO, of the substrate, depending on their relative energies; these interactions are usefully compared with charge transfer interactions.

Nucleophilic radicals carry cation-stabilising groups on the radical carbon, allowing electron density transfer from the radical to an electron-deficient heterocycle; they react therefore only with electron-poor heterocycles and will not attack electron-rich systems: examples of such radicals are $^{\bullet}CH_2OH$, alkyl$^{\bullet}$, and acyl$^{\bullet}$. Substitution by such a radical can be represented in the following general way:



Electrophilic radicals, conversely, are those which would form stabilised anions on gaining an electron, and therefore react readily with electron-rich systems: examples are $^{\bullet}CF_3$ and $^{\bullet}CH(CO_2Et)_2$. Substitution by such a radical can be represented in the following general way:



Aryl radicals can show both types of reactivity. A considerable effort (mainly older work) was devoted to substitutions by aryl radicals; they react with electron-rich and -poor systems at about the same rate and often with poor chemo- and regioselectivity.[42]

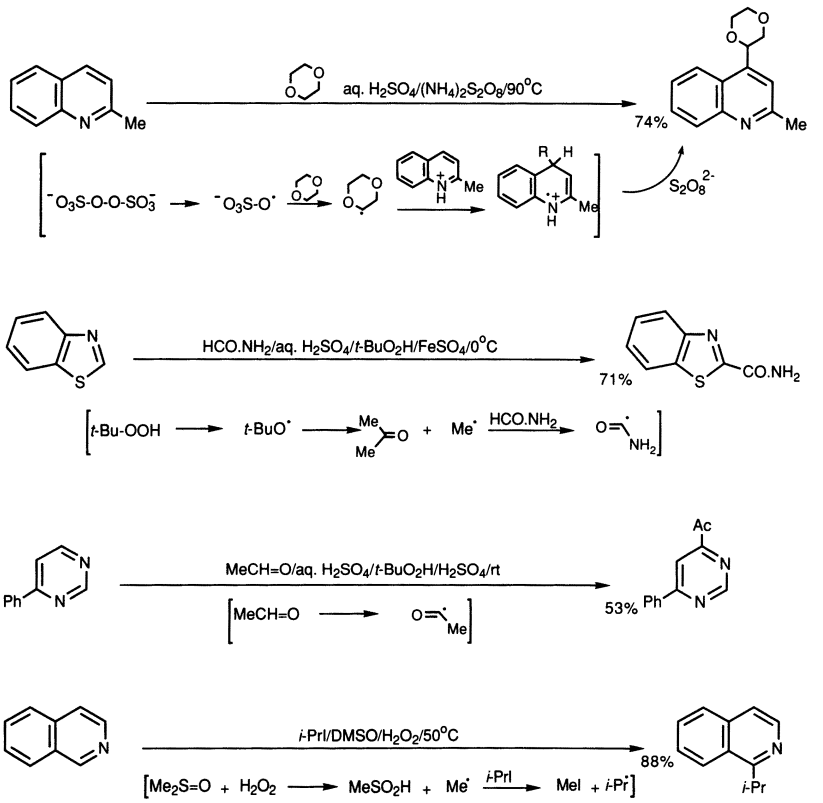
2.4.1 Reactions of heterocycles with nucleophilic radicals

2.4.1.1 *The Minisci reaction*[43]

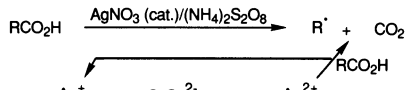
The reaction of nucleophilic radicals, under acidic conditions, with heterocycles containing a C=N unit, is by far the most important and synthetically useful radical substitution of heterocyclic compounds. Pyridines, quinolines, diazines, imidazoles, benzothiazoles, and purines are amongst the systems which have been shown to react with a wide range of nucleophilic radicals, selectively at positions α and γ to the nitrogen, with replacement of hydrogen. Acidic conditions are essential because *N*-protonation of the heterocycle both greatly increases its reactivity and promotes regioselectivity towards a nucleophilic radical, most of which hardly react at all with the neutral base. A particularly useful feature of the process is that it can be used to introduce acyl groups, directly, i.e. to effect the equivalent of a Friedel-Crafts substitution – impossible under normal conditions for such systems (cf. section 2.2.2). Tertiary radicals are more stable, but also more nucleophilic and therefore more reactive than methyl radicals in Minisci reactions. The majority of Minisci substitutions have

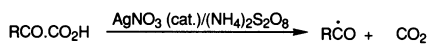
been carried out in aqueous, or at least partially aqueous, media, making isolation of organic products particularly convenient.

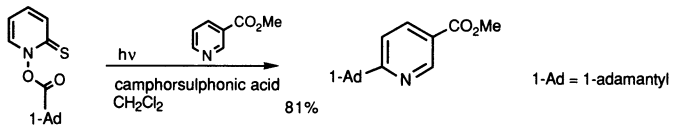
Different methods have been employed to generate the required radical, many depending on the initial formation of oxy- or methyl radicals which then abstract hydrogen or iodine from suitable substrates; both these are illustrated by the typical examples shown below.[44] The re-aromatisation of the intermediate radical-cation is usually brought about by its reaction with excess of the oxidant used to form the initial radical.



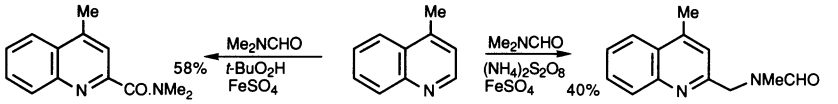
In contrast to the oxidative generation of radicals described above, reductions of alkyl iodides using tris(trimethylsilyl)silane also produces alkyl radicals under conditions suitable for Minisci-type substitution.[45] Carboxylic acids are also useful precursors for alkyl[46] and acyl[47] radicals *via* silver-catalysed peroxide oxidation, or from their 1-hydroxypyridine-2-thione derivatives using Barton's method,[48] the latter in non-aqueous conditions.



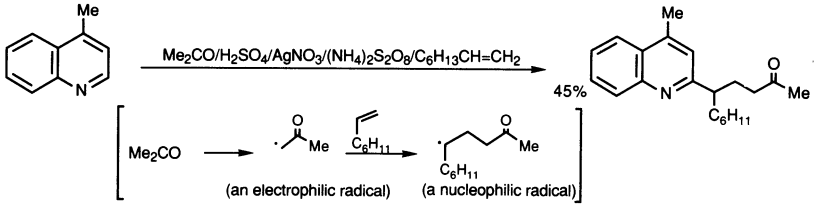




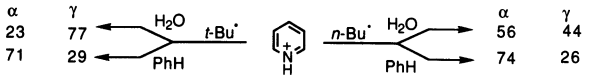
N,N-Dialkylformamides can be converted into either alkyl or acyl radicals, depending on the conditions.[49]



An instructive and useful process is the two-component coupling of an alkene with an electrophilic radical: the latter will of course not react with the protonated heterocycle, but after addition to the alkene a nucleophilic radical is generated.[50]



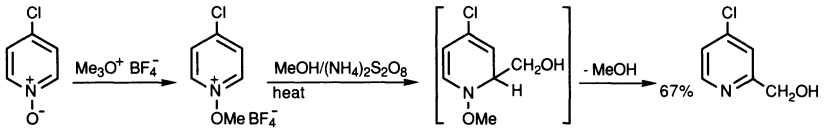
When more than one reactive position is available in a heterocyclic substrate, as is often the case for pyridines for example, there are potential problems with regioselectivity or/and disubstitution (since the product of the first substitution is often as reactive as the starting material). Regioselectivity is dependent to a certain extent on the nature of the attacking radical and the solvent, but may be difficult to control satisfactorily.[51]



A point to note is that for optimum yields, radical substitutions are often not taken to full conversion (of starting heterocycle), but as radical substitutions are usually very efficient this is usually not a problem. Ways of avoiding disubstitution include control of p*H*, (when the product is less basic than the starting

material), or the use of a two-phase medium to allow extraction (removal) of a more lipophilic product out of the aqueous acidic reaction phase.

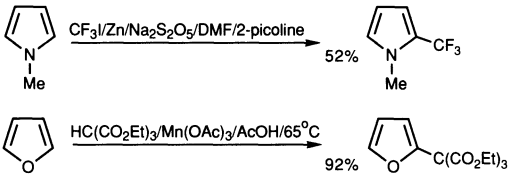
Very selective monosubstitution can also be achieved by the ingenious use of an N^+-methoxy-quaternary salt, in place of the usual protonic salt. Here, re-aromatisation is the result of loss of methanol, leaving as a product a much less reactive, neutral pyridine.[52]



In addition to substitution of hydrogen, *ipso* replacement of nitro, sulfonyl, and acyl substituents can occur, and may compete with normal substitution.[53]

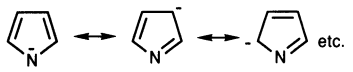
2.4.2 Reactions with electrophilic radicals

Although much less well developed than the Minisci reaction, substitution with electrophilic radicals can be used in some cases to achieve selective reaction in electron-rich heterocycles.[54]

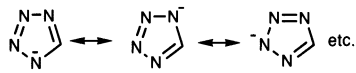


2.5 DEPROTONATION OF *N*-HYDROGEN[55]

Pyrroles, imidazoles, pyrazoles and benzo-fused derivatives which have a free *N*-hydrogen have pK_a values for the loss of the *N*-hydrogen as a proton in the region of 14–18. This is to say that they can be completely converted into anions by reaction with strong bases like sodium hydride or *n*-butyllithium. Even in the simplest of these examples, pyrrole itself, the acidity (pK_a 17.5) is very considerably greater than that of its saturated counterpart, pyrrolidine (pK_a ~ 44); similarly the acidity of indole (pK_a 16.2) is much greater than that of aniline (pK_a 30.7). One may rationalise this relatively increased acidity on the grounds that the charge is not localised, and this is illustrated by resonance forms which show the delocalisation of charge around the heterocycle. With the addition of electron-withdrawing substituents, or with the inclusion of extra hetero atoms, especially azomethine groups, the acidity is enhanced. A nice, though extreme, example is tetrazole for which the pK_a is 4.8, of the same order as a carboxylic acid.



pyrryl anion pK_a 17.5



tetrazolyl anion pK_a 4.8

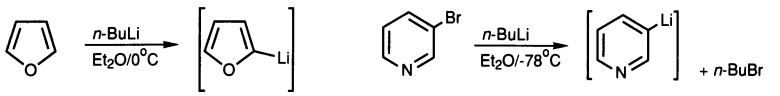
2.6 ORGANOMETALLIC DERIVATIVES

The most important developments in heterocyclic chemistry since the second edition of this book are probably in the area of organometallic chemistry, particularly transition-metal-catalysed reactions and the reactions of lithio-derivatives, reflecting development in these areas in organic chemistry as a whole.

2.6.1 Lithium derivatives[56]

While Grignard reagents have been widely used in carbocyclic chemistry, the direct preparation of heterocyclic Grignard reagents by the standard route – halo-compound plus magnesium metal – is often difficult, particularly for those containing a basic nitrogen. Haloimidazoles, halopyridines and pyridylsulfoxides have been converted[57] by exchange reactions with simple Grignard reagents into the corresponding heteroaryl magnesium species, but these appear to be significantly less reactive towards electrophiles than normal Grignard reagents, though the latter are useful in some circumstances.

Lithio-heterocycles, which react as nucleophiles with the whole range of electrophiles in a manner exactly comparable with Grignard species, have proved to be much more useful because they can often be prepared by direct metallation (*C*-hydrogen deprotonation), as well as by halogen exchange between halo-heterocycle and alkyllithium. As well as reaction with carbon electrophiles, lithiated species are the most convenient source of heterocyclic derivatives of less electropositive metals, such as zinc, boron, silicon, and tin (sections 2.6.2 and 2.6.3), which are now widely used in coupling reactions (section 2.7.2.2).

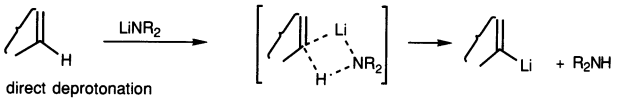


2.6.1.1 *Direct lithiation (C-hydrogen-deprotonation)*

Many heterocyclic systems react directly with alkyllithiums or with lithium amides to give the lithio-heterocycle *via* abstraction of a proton. Although a 'free' anion is never formed, the ease of lithiation correlates well with *C*-hydrogen acidity and of course this, with the stability of the corresponding conjugate base (carbanion).[58] Lithiations by deprotonation are therefore directly related to base-catalysed proton exchange[59] using reagents such as sodium methoxide, at

much higher temperatures, which historically provided the first indication that preparative deprotonations might be regioselective and thus of synthetic value.

The detail of the mechanism of metallation is still under discussion; it may involve a four-centre transition state.



The main factor giving increased acidity of heterocyclic *C*-hydrogen relative to benzenoid *C*-hydrogen is the inductive effect of the hetero atom(s) thus **metallation occurs at the carbon α to the hetero atom**, where the inductive effect is felt most strongly, unless other factors, with varying degrees of importance, intervene. These include the following.

Mesomerism

Except in the case of side-chain anions (section 2.6.3.2), the 'anion' orbital is orthogonal to the π-system and so it is not mesomerically delocalised. However, electron density and therefore *C*-hydrogen acidity at ring carbons, is affected by resonance effects.

Coordination of the metal counterion to the hetero atom

Stronger coordination between the metal of the base and a hetero atom leads to enhanced acidity of the adjacent *C*-hydrogen due to increased inductive withdrawal of electron density – it is proportionately stronger, for example, for oxygen than for sulfur.

Lone pair interactions

Repulsion between the electrons in the orbital of the 'anion' and an adjacent heteroatom lone pair has a destabilising influence. This effect is thought to be important in pyridines and other azines.[60]

Polarisability of the hetero atom

More polarisable atoms such as sulfur are able to disperse charge more effectively.

Substituent effects

Directed metallation (DoM),[61] just as in carbocyclic chemistry, is extremely useful in heterocyclic chemistry. Metallation *ortho* to the directing group is promoted by either inductive effects (e.g. Cl, F), or chelation (e.g. $CH_2OH \rightarrow CH_2OLi$), or a combination of these, and may overcome the intrinsic regioselectivity of metallation of a particular heterocycle. When present, **this is by far the most important additional factor influencing the regioselectivity of lithiation.**

It should be remembered that kinetic and equilibrium acidities may be different; thermodynamic products are favoured by higher temperatures and by more polar solvents.

Lithiating agents

Lithiations are normally carried out with alkyllithiums or lithium amides. *n*-Butyllithium is the most widely used alkyllithium but *t*-butyllithium and occasionally *s*-butyllithium are used when more powerful reagents are required. Phenyllithium was used in older work but is uncommon now although it can be of value when a less reactive, more selective base is required.[62] A very powerful metallating reagent is formed from a mixture of *n*-butyllithium and potassium *t*-butoxide: this produces the potassium derivative of the heterocycle.

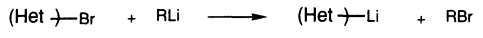
Lithium diisopropylamide (LiN(*i*-Pr)$_2$; LDA) is the most widely used lithium amide but lithium 2,2,6,6-tetramethylpiperidide (LiTMP) is rather more basic and less nucleophilic – it has found particular use in the metallation of diazines. Alkyllithiums are stronger bases than the lithium amides, but usually react at slower rates. Metallations with the lithium amides are reversible, so for efficient conversion the substrate must have a pK_a of more than four units lower.

Solvents

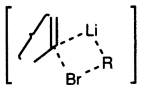
Ether solvents – Et_2O and THF – are normally used. The more strongly coordinating THF increases the reactivity of the lithiating agent by increasing its dissociation. A mixture of ether, THF and pentane (Trapp's solvent) can be employed for very low temperature reactions (< 100°C) (THF alone freezes at this temperature). To increase the reactivity of the reagents even further, ligands such as TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine; $Me_2N(CH_2)_2NMe_2$) or HMPA ($(Me_2N)_3PO$) (**CAUTION**: carcinogen) are sometimes added – these strongly and specifically coordinate the metal cation. While these additives are undoubtedly beneficial in some cases, the efficacy of TMEDA has been questioned.[63]

2.6.1.2 *Halogen exchange*

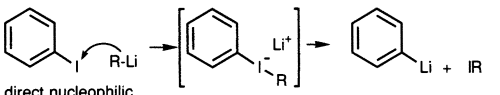
Bromo- and iodo-heterocycles react rapidly with alkyllithiums, even at temperatures as low as −100°C, to give the lithio-heterocycle. Where alternative exchanges are possible, the site of reaction is governed by the stability of the 'anion' formed, just as for direct lithiation by deprotonation. Exchange of fluorine is unknown and of chlorine, rare enough to assume that it is inert.



Mechanistically, the exchange process may involve a four-membered transition state, or may possibly proceed *via* an electron-transfer sequence, however direct nucleophilic attack, at least on iodine, has been demonstrated in the case of iodobenzene,[64] and cannot therefore be dismissed as a mechanism.



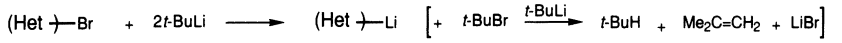
four-membered transition state



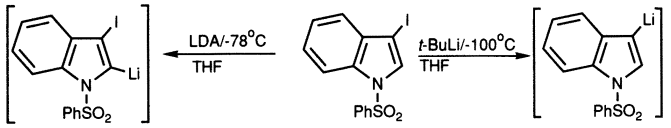
direct nucleophilic attack on halogen

Halogen exchange reagents

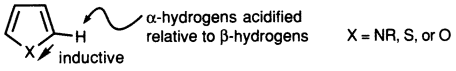
n-Butyllithium is the usual exchange reagent; the *n*-butyl bromide byproduct does not usually interfere with subsequent steps. When the presence of an alkyl bromide is undesirable, two equivalents of *t*-butyllithium can be employed – the initially formed *t*-butyl bromide is consumed by reaction with the second equivalent of alkyllithium, producing isobutene.



It is very important to differentiate between pure bases, such as lithium diisopropylamide, which act only by deprotonation, and alkyllithiums which can act as bases or take part in halogen exchange. When using alkyllithiums, exchange is favoured over deprotonation by the use of lower temperatures. The reaction of 3-iodo-1-phenylsulfonylindole with the two types is illustrative.[65]

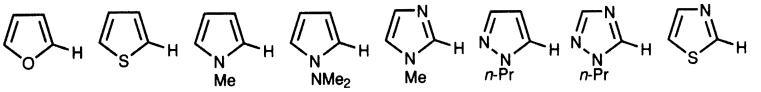


2.6.1.3 *Ring lithiation of five-membered heterocycles*

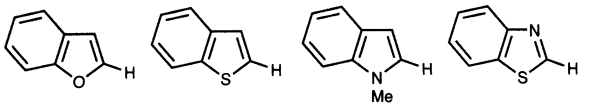


The inductive effect of the hetero atom, which withdraws electrons to a greater extent from an adjacent carbon atom (α-positions), allows direct α-lithiation of practically all five-membered heterocycles. The relative 'acidities' of α-hydrogens in some different classes are illustrated in the table below.

Equilibrium pK_a values[a] for deprotonation of some five-membered heterocycles in THF[66]



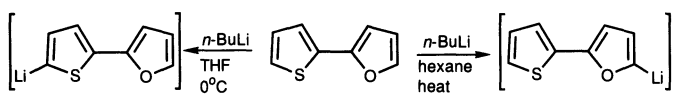
35.6 33.0 39.5 37.1 33.7 35.9 26.2 >28.3



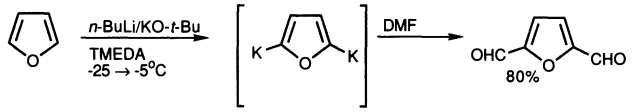
33.2 32.4 38.1 ~28

[a]Measured pK_a values vary according to solvent etc.

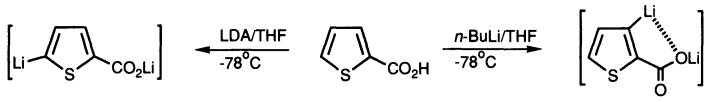
Despite the lower electronegativity of sulfur, and hence a weaker inductive effect, thiophene metallates about as readily as furan, probably in part because the higher polarisability of sulfur allows more efficient charge distribution;[67] d-orbital participation is thought to be relatively unimportant in the stabilisation of carbanionic centres adjacent to sulfur. The lithiation of 2-(2-furyl)thiophene, in either ring depending on conditions, is instructive;[68] preferential lithiation of the furan ring in the non-polar solvent is probably due to stronger coordination of lithium to the oxygen, thus increasing the inductive effect on the α-hydrogen in the furan ring.



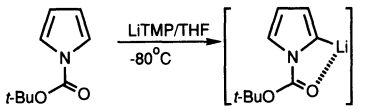
The use of stronger bases can result in dimetallation.[69]



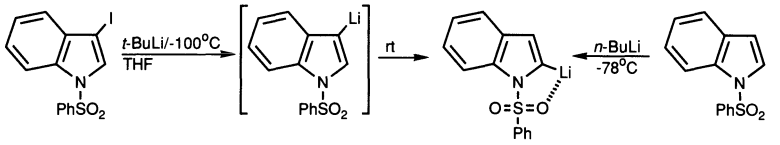
Directing groups can overcome the normal tendency for α-lithiation in five-membered heterocycles, as shown in the thiophene example below, however the use of the more weakly coordinating LDA does allow 'normal' α-lithiation.[70]



Lithiation of pyrroles is complicated by the presence of a much more acidic hydrogen on nitrogen, however 1-methylpyrrole lithiates, at C-2, albeit under slightly more vigorous conditions than for furan.[71] Removable protecting groups on the pyrrole nitrogen allow α-lithiation, *t*-butoxycarbonyl (Boc), is an example; it has additional advantages: not only is it easily hydrolytically removed, but it also withdraws electrons thus acidifying the α-hydrogen further, and finally, provides chelation assistance.[72]

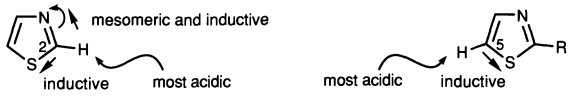


Benzo[*b*]thiophenes and -furans, and *N*-blocked indoles lithiate on the heterocyclic ring, α to the hetero atom.[73] Lithiation at the other hetero-ring position can be achieved *via* halogen exchange, but low temperatures must be maintained to prevent equilibration to the more stable 2-lithiated heterocycle.[65]



Benzene-ring-lithiated intermediates can be prepared by metal–halogen exchange, even, in the case of indoles, without protection of the NH, i.e. it is possible to produce an *N,C*-dilithiated species.[74]

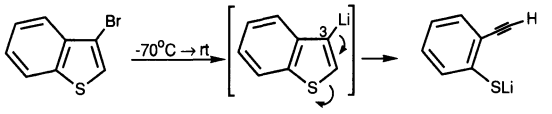
The 1,3-azoles lithiate very readily, at C-2. One may understand this in terms of a combination of the acidifying effects seen at an α-position of pyridine (both inductive and mesomeric electron withdrawal, see section 2.6.1.4) with that at the α-positions of thiophene, furan, and pyrrole (inductive only). 2-Substituted-1,3-azoles generally lithiate at C-5.[75]



For imidazoles, it is usual for the *N*-hydrogen first to be masked,[76] and a variety of protecting groups have been used for that purpose, many of which provide additional stabilisation and an additional reason for regioselective α-lithiation by coordinating the lithium: trimethylsilylethoxymethyl ($Me_3Si(CH_2)_2OCH_2$; SEM) is one such group.[77]

It is a significant comment on the relative ease of α-lithiation in six- and five-membered systems that (*N*-protected) pyrazoles lithiate at C-5, i.e. in the pyrrole-like α-position, though, again chelation assistance from the *N*-protecting group also directs to C-5.[78]

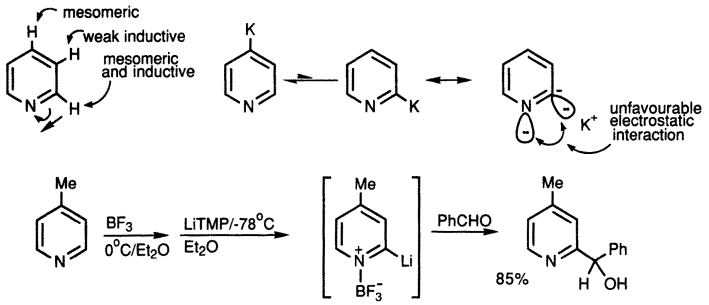
One must be aware that hetero-ring cleavage[79] can occur in β-lithiated five-membered systems, because the hetero atom can act as a leaving group, if the temperature is allowed to rise.[80]



2.6.1.4 *Ring lithiation of six-membered heterocycles*

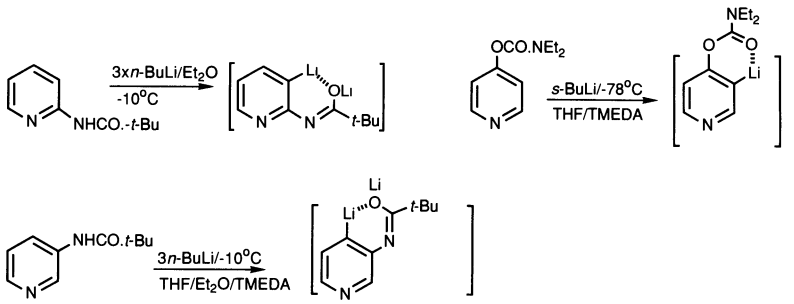
The preparation of lithiated derivatives of six-membered heterocycles like pyridines, quinolines and diazines must overcome the problem that they are sus-

ceptible to nucleophilic addition/substitution (section 2.3.2) by the lithium reagents. In contrast to the selective lithiation of five-membered rings, the direct metallation of pyridine is quite difficult and complex, but it can be achieved using the very strong base combination *n*-butyllithium/potassium *t*-butoxide. In relatively non-polar solvents (ether-hexane) kinetic 2-metallation predominates but in a polar solvent (THF-HMPA-hexane), or under equilibrating conditions, the 4-isomer is the major product. The pyridine α- and γ-positions, being more electron-deficient than a β-position, have the kinetically most acidic protons, and of the two former anions, location of negative charge at the γ-position is the more stable situation, perhaps due to unfavourable repulsion between the coplanar nitrogen lone pair and the α-'anion' only in the former. In non-polar solvents stronger coordination of the metal cation with the nitrogen lone pair will reduce this repulsive interaction and thus increase the relative stability of the α-'anion'.[81] As a corollory of this, pyridine can be selectively lithiated at C-2 when the lone pair is tied up as a complex with boron trifluoride.[82] This is consistent with much earlier studies of base-catalysed exchange when it was demonstrated that *N*-oxides and N^+-alkyl quaternary salts exchange more rapidly at an α-position.[83]

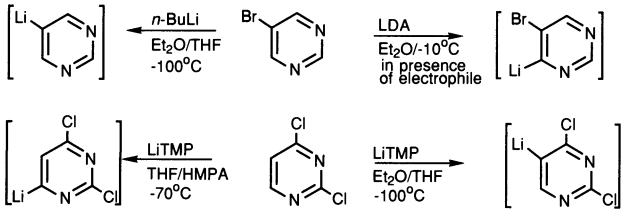


All the isomerically pure lithio-pyridines can be prepared by halogen exchange, though 3-bromopyridine requires a lower temperature to discourage nucleophilic addition; bromopicolines can be similarly converted, without deprotonation at the methyl groups (cf. section 2.6.4).

Pyridines carrying groups which direct metallation *ortho*, using chelation and/or inductive influences, can be directly lithiated without risk of nucleophilic addition. When the group is at a 2-[84] or 4-position[85], lithiation must occur at a β-carbon; pyridines with *ortho*-directing groups located at a β-position usually lithiate at C-4: this is true for example of chloro- and fluoropyridines;[86] 3-methoxymethoxy-,[87] 3-pivaloylamino-,[88] 3-trimethylsilylethoxymethoxy-.[89] 3-*t*-butylaminosulfonyl-,[90] pyridines; pyridines carrying a 3-diethylaminocarbonyloxy or 3-diethylaminothiocarbonyloxy group;[91] and the adduct from 3-formylpyridine and $Me_2N(CH_2)_2NMeLi$,[92] however 3-ethoxypyridine metallates at C-2.[93]



Quinolines react like pyridines but are more susceptible to nucleophilic addition;[94] this is also an increased problem with pyrimidines, relative to pyridines, but nevertheless they can be lithiated by deprotonation or by halogen exchange at low temperatures, around −100°C. The presence of 2- and/or 4-substituents adds some stability to lithiated pyrimidines.[95]



Pyrazines and pyridazines react in accord with the principles discussed above.[96]

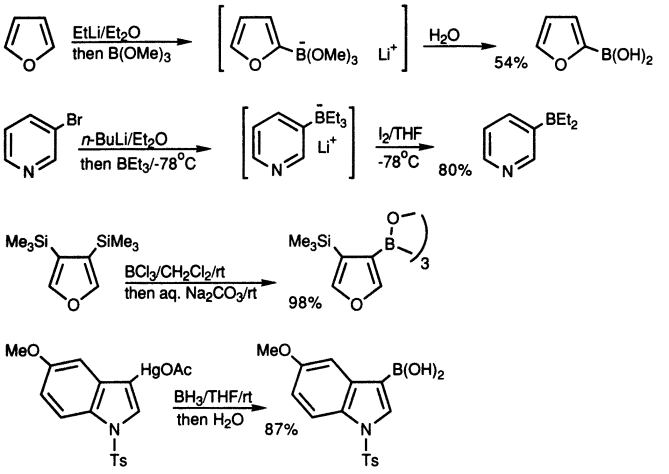
2.6.2 Boron, silicon and tin reagents

Caution: while very useful, many organotin compounds are toxic and should be handled with care. Trimethyltin derivatives in particular are highly toxic and whenever possible should be replaced by the slightly less reactive but much less toxic, tri-*n*-butyl analogues.

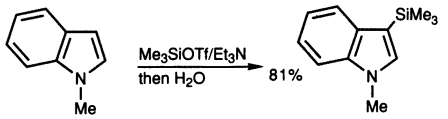
2.6.2.1 *Synthesis*

The most general preparative method for silanes,[97] stannanes, and boronic acids is the reaction of a heteroaryllithium with a chlorosilane, a chlorostannane, or with a borate ester,[98] respectively. 3-Diethylborylpyridine can be similarly prepared by reaction of the lithiopyridine with triethylborane, followed by cleavage of an ethyl group with iodine; this method does not work for electron-rich sys-

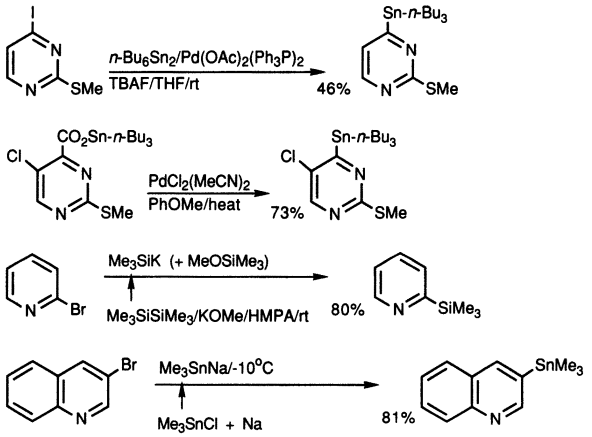
tems such as furan due to preferential cleavage of the heterocyclic group.[99] Transmetallation reactions can also be of use in specific cases.[100]



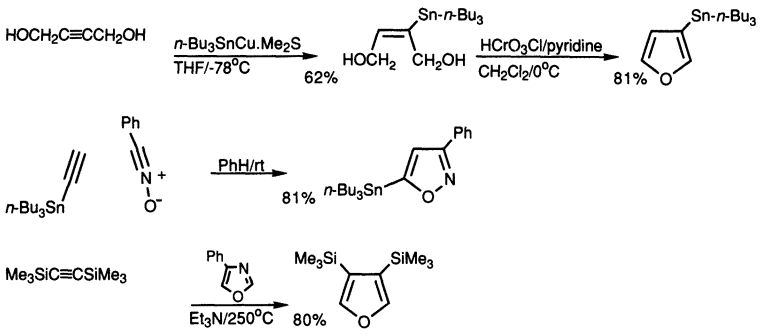
It is possible to directly silylate indoles and pyrroles *via* electrophilic substitution.[101]



Useful alternative preparations of stannanes include palladium-catalysed decarboxylation of stannyl esters or coupling of halo compounds with hexaalkyldistannanes;[102] coupling with hexaalkyldisilanes requires rather more vigorous conditions.[103] Trialkylstannyl and -silyl anions are highly reactive and will displace halogen without the use of a catalyst.[104]



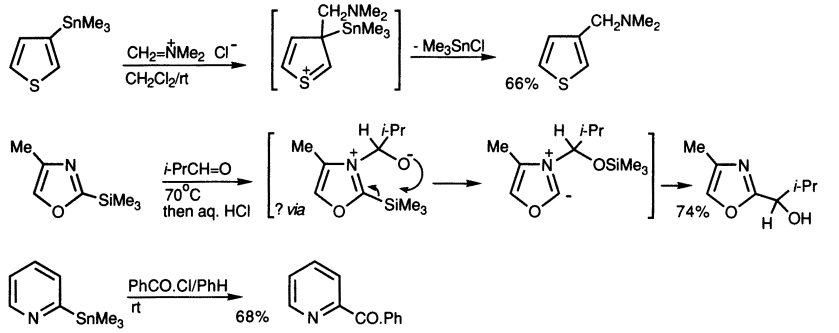
The relatively high stability of carbon–silicon/boron/tin bonds allows the 'metal' to be carried through standard heterocyclic syntheses as an inert substitutent: some examples are shown below.[105,100a]



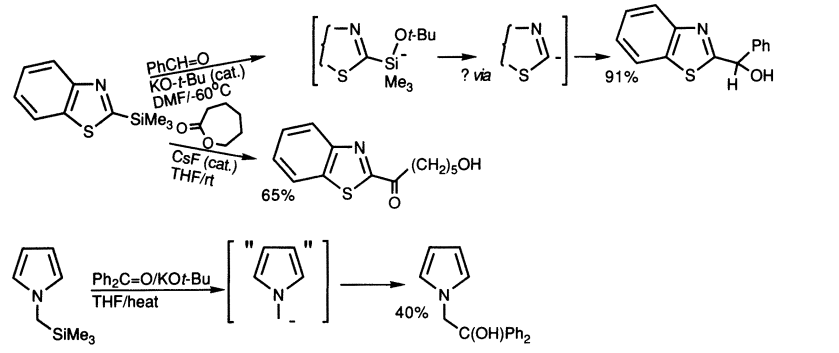
2.6.2.2 *Reactions*

The heteroaryl derivatives of boron, silicon, and tin, which show related patterns of reactivity, have found considerable application in synthesis. Unlike lithium compounds, they are generally fairly stable to air and water but will undergo a range of selective reactions under relatively mild conditions. Heteroaryl boronic acids and stannanes are particularly useful as the organometallic component in palladium-catalysed coupling reactions (section 2.7.2.2) but while benzenoid silanes also undergo couplings,[106] the only heteroaryl application so far has involved 2-trimethylsilylthiophene.[107]

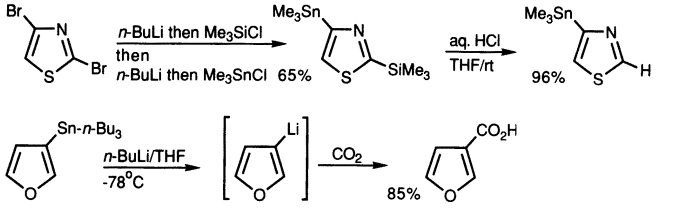
All three elements are susceptible to *ipso* replacement by electrophiles – such reactions have been studied extensively for arylsilanes and -stannanes, where they occur *via* an electrophilic addition/silicon elimination mechanism analogous to other aromatic substitutions, but at a much faster rate than the corresponding replacement of hydrogen.[108] *Ipso* substitutions also take place on heterocycles and, in the case of electron-rich systems, probably *via* the same type of mechanism. Most applications, however, have been in heterocycles containing an azomethine unit with the silicon/tin directly attached;[109] such heterocycles undergo electrophilic attack reluctantly (section 2.2.2) so a mechanism involving coordination to nitrogen may be involved;[110] for example a 2-trimethylstannylpyridine will react readily with an acid chloride but its 3-isomer is inert under the same conditions, though palladium-catalysed coupling can be achieved with the 3- and 4-isomers under different conditions and *via* a different mechanism.[111]



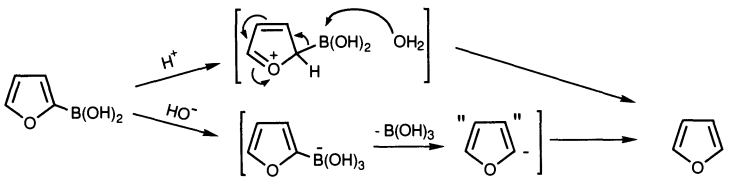
Silanes will also react with electrophiles with catalysis by fluoride or methoxide.[112] Here, an intermediate complex is formed *in situ* which reacts like a carbanion but under much milder conditions than would a lithio-derivative. This reaction can even be used to generate the equivalent of a CH_2-carbanion on a five-membered heterocyclic nitrogen.[113]



In addition to acting as a functional group, silanes can also be used as protecting groups for 'acidic' *C*-hydrogen, being removable at a later stage using fluoride or acid.[114] Stannanes are also valuable precursors for regiospecific formation of heteroaryllithiums *via* reaction with alkyllithiums.[105]

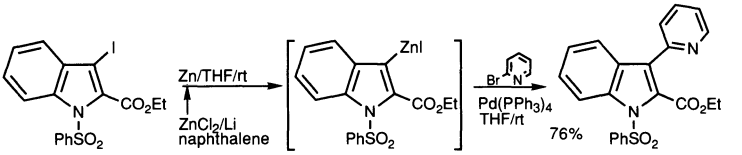


Although boronic acids are very reactive to *ipso* displacement by some electrophiles such as halonium ions, these reactions have found only occasional synthetic use. The *C*-boron bond can be cleaved by base, or acid, at rates depending on the corresponding carbanion stability or ease of protonation of the ring, respectively. When a relatively stable carbanion can be formed, such as in furan boronic acids containing electron-withdrawing groups, base-catalysed deboronation can be become an important unwanted side-reaction during palladium-catalysed boronic acid couplings.[115] Indeed, imidazole and oxazole 2-boronic acids have not yet been isolated, possibly due to their very ready deboronation.



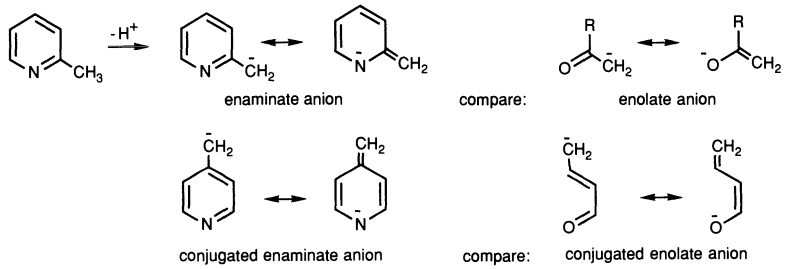
2.6.3 Zinc reagents

Heteroarylzinc compounds are of particular use in palladium-catalysed couplings, being compatible with many functional groups. They have usually been prepared by exchange reactions[116] (*in situ*) of zinc halides with heteroaryllithiums but this method limits their usefulness. Efficient methods are now available for their direct preparation from zinc metal and the heteroaryl halide in both electron-rich and electron-poor systems.[117]

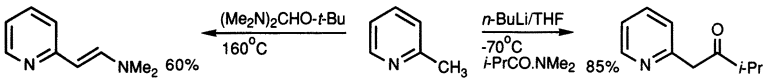


2.6.4 Side-chain metallation of 6-membered heterocycles ('lateral metallation')

Anions on alkyl side-chains and immediately adjacent to a heterocyclic ring are subject to varying degrees of stabilisation by interaction with the ring. The most favourable situation is where the side-chain is on an α- or a γ-carbon with respect to a C=N, as in the 2-, 6-, and 4-positions of a pyridine. Such anions are stabilised in much the same way as an enolate (conjugated enolate). We use the word 'enaminate' to describe this nitrogen-containing, enolate-like anion.

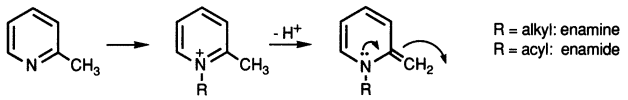


Quantitative measures for some methyl deprotonations are: 2-methylpyridine (pK_a 34), 3-methylpyridine (pK_a 37.7), 4-methylpyridine (pK_a 32.2), 4-methylquinoline (pK_a 27.5).[118] These values can be usefully compared with those typical for ketone α-deprotonation (19–20) and toluene side-chain deprotonation (~ 41). Thus strong bases can be used to convert methylpyridines quantitatively into side-chain anions, however the enolate-like stabilisation of the anion is sufficient that reactions can often be carried out using weaker bases under equilibrating conditions, i.e. under conditions where there is only a small percentage of anion present at any one time. It may be that under such conditions, side-chain deprotonation involves *N*-hydrogen-bonded or *N*-coordinated pyridines.

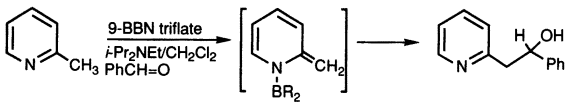


via small concentration of the side-side-chain anion — *via* complete conversion to the side-chain anion

An alternative means for effecting reaction at a side-chain depends on a prior electrophilic addition to the nitrogen: this acidifies further the side-chain hydrogens, then deprotonation generates an enamine or an enamide, each being nucleophilic at the side-chain carbon.

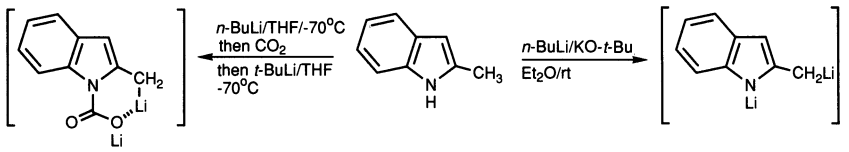


One of the most elegant examples of this principle is the generation and use of *N*-dialkylboryl derivatives.[119]



2.6.5 Side-chain metallation of five-membered heterocycles

The metallation of a side-chain on a simple five-membered heterocycle is **much more difficult** than in the six-membered series, because no enaminate stabilising resonance is available. Nonetheless it also is selective for an alkyl adjacent to the hetero atom, because the hetero atom acidifies by induction. Relatively more forcing conditions need to be applied, especially if an *N*-hydrogen is present,[120] but an elegant method has been developed for indoles, in which the first-formed *N*-anion is blocked with carbon dioxide, the lithium carboxylate thus formed then neatly also facilitating 2-methyl-lithiation by intramolecular chelation; this device has the further advantage that, following reaction of the side-chain anion with an electrophile, the *N*-protecting group is removed, simply, during aqueous processing.[121]



Side-chains at C-2 on 1,3-azoles are activated in a manner analogous to pyridine α-alkyl groups, and can be metallated, but more care is needed to avoid ring metallation.[122]

2.7 PALLADIUM-CATALYSED REACTIONS[123]

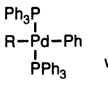
Transition metal-catalysed reactions are probably the most rapidly expanding area in organic chemistry at present and they have been used extensively in both the ring synthesis and the functionalisation of heterocycles. As well as completely new modes of reactivity, variants of older synthetic methods have been developed using the milder and more selective processes which attach to the use of transition metal catalysts. Palladium is by far the most important and widely used catalyst due to the very wide range of reaction types in which it can function. Nickel catalysts (mechanistically similar to palladium) have also been used, but for a narrower range of reactions.

In general, heterocyclic compounds undergo palladium-catalysed reactions in a way analogous to carbocycles; heterocyclic sulfur and nitrogen atoms seldom interfere with these (homogeneous) palladium catalysts, which must be contrasted with the well-known poisoning of hydrogenation catalysts such as palladium metal on carbon by sulfur- and nitrogen-containing molecules.

Palladium-catalysed processes typically utilise only 1–5 mol% of the catalyst and proceed through small concentrations of transient palladium species: there is a sequence of steps, each with an organopalladium intermediate, and it is important to become familiar with these basic organopalladium processes in order to rationalise the overall conversion. Concerted, rather than ionic, mechanisms are the rule so it is misleading to compare them too closely with apparantly similar 'classical' organic mechanisms, however 'curly arrows' can be used as a memory aid (in the same way as one may use them for cycloaddition reactions), and this is the way in which palladium-catalysed reactions are 'explained' in the following discussion.

2.7.1 Basic organopalladium processes[124]

Note: For clarity, ligands which are not involved in the transformation under consideration are omitted from the following schemes, however it is important to understand that most organopalladium compounds normally exist as 4-coordinate, square-planar complexes:



will be referred to as RPdPh

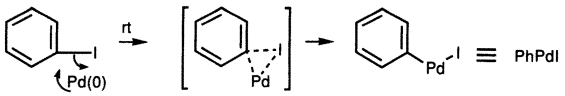
Pd(0) is usually

Despite an apparant similarity between RPdX and RMgX, their chemical properties are very different. The former are usually **stable to air and water** and **unreactive to** the usual **electrophilic centres such as carbonyl**, whereas RMgX do react with oxygen, water, and carbonyl compounds.

2.7.1.1 *Concerted reactions*

Oxidative addition

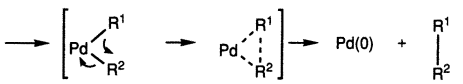
Aromatic and vinylic halides react with Pd(0) to give an organopalladium halide: aryl(or alkenyl)PdHal. This is formally similar to the formation of a Grignard reagent from magnesium metal, Mg(0), and a halide, but mechanistically, a concerted, direct 'insertion' of palladium into the carbon–halogen bond is believed to be involved. The ease of reaction: X = I > Br ~ OTf >> Cl >> F, explains why chloro and fluoro substituents can normally be tolerated, not interfering in palladium-catalysed processes. As a simple illustration, $Pd(PPh_3)_4$ reacts with iodobenzene at room temperature, but requires heating to 80°C for a comparable insertion into bromobenzene. Although alkyl halides will undergo oxidative addition to Pd(0), the products are generally much less stable.



Palladium(0) exhibits a degree of nucleophilic character, thus electron-withdrawing substituents increase the reactivity of aryl halides in oxidative additions. This is exemplified in the heterocyclic context: the inductive effect of C=N units allows 2-chloropyrimidine (it is slightly less reactive than bromobenzene), and even 3-chloropyridine[125] to react (even the moderate inductive effect at the β-position gives rise to a significantly higher rate of reaction relative to chlorobenzene) although a more reactive catalyst is required for the latter case (cf. section 2.7.2.2).

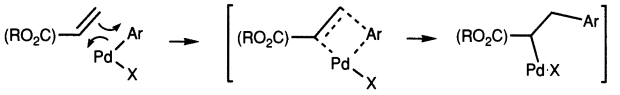
Reductive elimination

Organopalladium species with two organic units attached to the metal, R^1PdR^2, are generally unstable: extrusion of the metal, in a zero oxidation state, takes place, with the consequent linking of the two organic units. Because this is again a concerted process, stereochemistry in the organic moiety(ies) is conserved.



1,2-Insertion

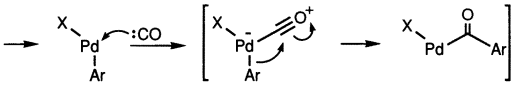
Organopalladium halides add readily to double and triple bonds in a concerted, and therefore *syn*, manner (*via* a π-complex, not shown for clarity).



This process works best with electron-deficient alkenes such as ethyl acrylate, but will also take place with isolated, or even with electron-rich, alkenes. In reactions with acrylates, the palladium becomes attached to the carbon adjacent to the ester, i.e. the aromatic moiety becomes attached to the carbon β to the ester.

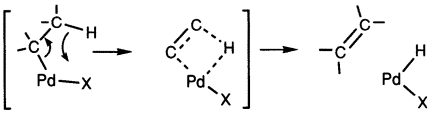
1,1-Insertion

Carbon monoxide, and isonitriles, will insert into a carbon–palladium bond.



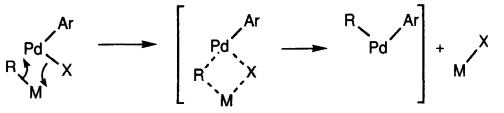
β-Hydride elimination

When a *syn* β-hydrogen is present in an alkylpalladium species a rapid elimination of a palladium hydride occurs, generating an alkene. This reaction is much faster in RPdX than in R_2Pd and is the reason that attempted palladium-catalysed reactions of alkyl halides often fail.



Transmetallation

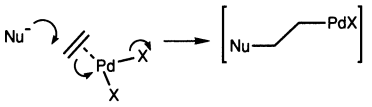
Palladium(2) compounds such as ArPdX and PdX_2 generally react readily with a wide variety of organometallic reagents, of varying nucleophilicity, such as R_4Sn, $RB(OH)_2$, RMgX, and RZnX, transferring the R group to palladium with overall displacement of X. The details of the reactions are not fully understood and probably vary from metal to metal, but a concerted transfer is probably the best means for their interpretation.



2.7.1.2 *Ionic reactions*

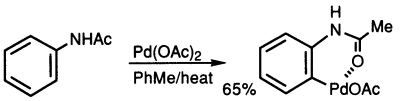
Addition to palladium-alkene π-complexes

Like those of Hg^{2+} and Br^{+}, Pd^{2+}-alkene complexes are very susceptible to attack by nucleophiles. In contrast to the reactions described in section 2.7.1.1 (1,2-insertion), this process exhibits *anti* stereospecificity.



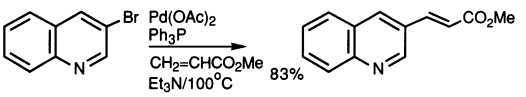
Aromatic palladation

In reactions like aromatic mercuration, palladium(2) compounds will metallate aromatic rings *via* an electrophilic substitution, hence electron-rich systems are the most reactive.[126] *ortho*-Palladation assisted by electron-releasing chelating groups has been used frequently.[127]



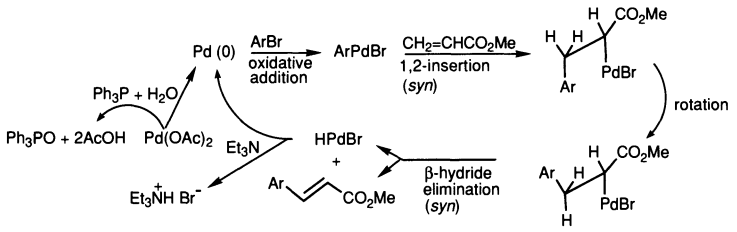
2.7.2 Palladium-catalysed reactions in heterocyclic chemistry

2.7.2.1 *Heck reactions*[128]

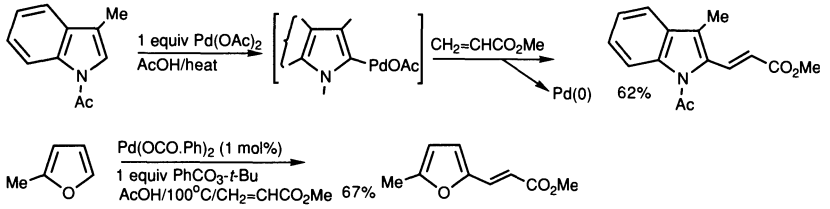


The standard Heck conditions shown in the example above[129] illustrate a common cause of confusion in understanding palladium-catalysed reactions, for while Pd(0) is actually involved in the catalytic cycle, palladium(2) acetate is generally used as an ingredient. This is just a matter of convenience because palladium acetate is stable and easily stored; it is reduced to Pd(0) by the phosphine (with a trace of water) *in situ* in a preliminary, initiating step.

The standard Heck reaction involves the reaction of an aryl halide with an alkene, commonly acrylate, to give a styrene (cinnamate) in the presence of a catalytic amount of palladium (often less than 1 mol%). The sequence involves (i) oxidative addition of the halide to Pd(0) followed by (ii) 1,2-insertion into the alkene; rotation then occurs to produce a species with hydrogen *syn* to palladium, then (iii) β-hydride elimination gives the styrene and regenerates Pd(0), which rejoins the catalytic cycle and can take part in a second oxidative addition, etc.

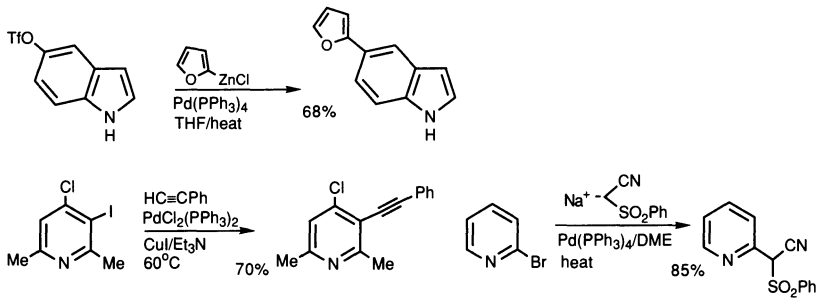


The electron-rich nature of heterocycles such as indoles, furans, and thiophenes allows a different type of Heck reaction to be carried out.[130] In this 'oxidative' modification the aryl palladium derivative is generated by electrophilic palladation with a palladium(2) reagent. This process is not catalytic in the standard way, but can be made so by the addition of a reoxidant selective for Pd(0); note, that the catalytic Pd(0) could not effect the first (electrophilic) ring palladation.[131]

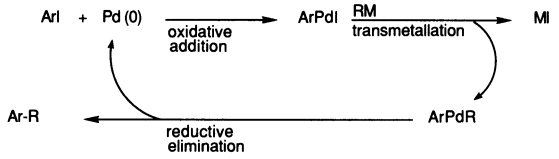


2.7.2.2 *Coupling reactions*

Heteroaryl halides (or phenolic triflates) take part in palladium-catalysed couplings with a wide range of organometallic and anionic reagents; in contrast to the Heck reaction, the catalyst is often provided as preformed Pd(0), in a complex such as tetrakis(triphenylphosphine)palladium(0), $(Ph_3P)_4Pd$.[132]

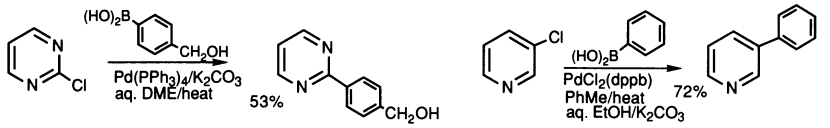


These conversions also involve catalytic cycles: (i) initial oxidative addition is again the first step, but then (ii) transmetallation, and (iii) reductive elimination give product and regenerate Pd(0).

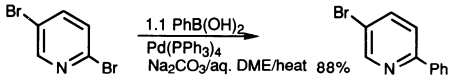


There are examples in which RM is $ArSnBu_3$, $HetSnBu_3$, $ArB(OH)_2$, $HetB(OH)_2$, $HetBEt_2$, RMgX, HetMgX, RZnX, $RTiX_3$, $RZrXL_2$, M-≡-R, $M^+ {}^-CH(CN)_2$, and $M^+ CN^-$

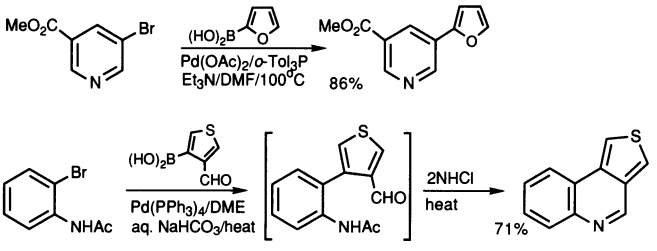
The electron-withdrawing effect of typical azines makes chlorine substituents sufficiently reactive that they can participate in palladium-catalysed reactions, even at a pyridine β-position.[125]



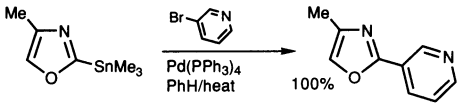
α-Activation can serve to allow regioselective reaction in the presence of a β-halogen (cf. section 2.7.1.1, oxidative addition).



Where a heterocyclic organometallic reagent is required, Grignard and zinc derivatives are often satisfactory; complications sometimes attend the use of lithio derivatives. The use of boronic acids has become very popular on account of their clean reactions, general stability to air and water, and their compatibility with practically any functional group: furan, thiophene, indole and pyridine boronic acids have all been used.[133]

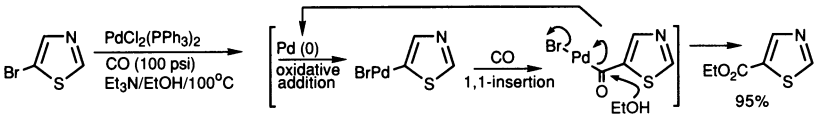


Some boronic acids may not be so stable, and in these cases tin derivatives can be used,[134] though they must be treated with caution as some are highly toxic.



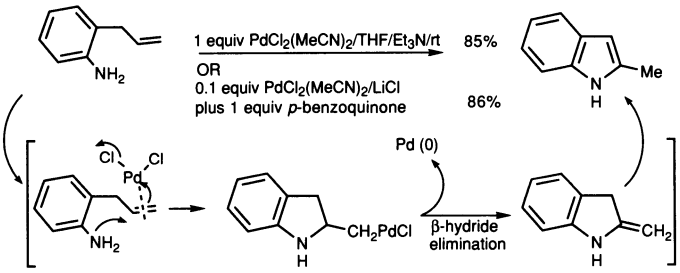
2.7.2.3 *Carbonylation reactions*

Acyl palladium species, formed by insertion of carbon monoxide into the usual aryl palladium halides, react readily with nucleophiles such as amines and alcohols to give amides and esters respectively; interception with hydride produces aldehydes.[135]

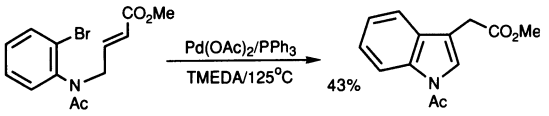


2.7.2.4 *Synthesis of benzo-fused heterocycles*

Nucleophilic cyclisations onto palladium-complexed alkenes have been used to prepare indoles, benzofurans and other fused systems. The process can be made catalytic in some cases by the use of reoxidants such as benzoquinone or Cu(2).[136]



Intramolecular Heck reactions have found quite wide use for the construction of heterocyclic rings.[137]



2.8 OXIDATION AND REDUCTION[138] OF HETEROCYCLIC RINGS

Generally speaking the electron-poor heterocycles are more resistant to oxidative degradation than are electron-rich systems – it is usually possible to oxidise alkyl side-chains attached to electron-poor heterocycles whilst leaving

the ring intact; this is not generally true of electron-rich, five-membered systems.

The conversion of monocyclic heteroaromatic systems into reduced, or partially reduced, derivatives is generally possible, especially in acidic solutions where it is a cation which is the actual species reduced. It follows that the six-membered types, which always have a basic nitrogen, are more easily reduced than the electron-rich, five-membered counterparts; heteroaromatic quaternary salts are likewise easily reduced.

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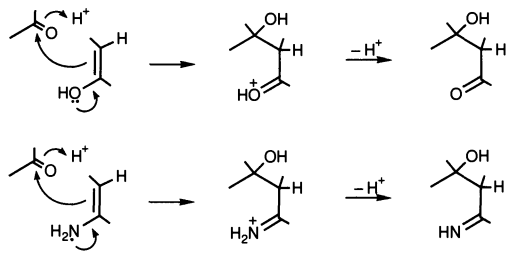
3 Synthesis of aromatic heterocycles

The preparation of benzenoid compounds nearly always begins with an appropriately substituted, and often readily available, benzene derivative – only on very rare occasions is it necessary to start from compounds lacking the ring, and to form it during the synthesis. The preparation of heterocyclic compounds presents a very different picture, for it involves ring synthesis more often than not. Of course when first considering a suitable route to a desired target, it is always important to give thought to the possibility of utilising a commercially available compound which contains the heterocyclic nucleus and which could be modified by manipulation, introduction and/or elimination of substituents[1] – a synthesis of tryptophan (section 17.12) for example would start from indole – however if there is no obvious route, a ring synthesis has to be designed which leads to an heterocylic intermediate appropriately substituted for further elaboration into the desired target.

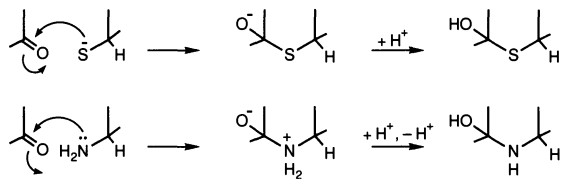
This chapter shows how just a few general principles allow one to understand the methods, at first sight apparently diverse, which are used in the construction of the heterocyclic ring of an aromatic heterocyclic compound from precursors which do not have that ring. It discusses the principles, and analyses the types of reaction frequently used in constructing an aromatic heterocycle, and also the way in which appropriate functional groups are placed, in the reactants, in order to achieve the desired ring synthesis.

3.1 REACTION TYPES MOST FREQUENTLY USED IN HETEROCYCLIC RING SYNTHESIS

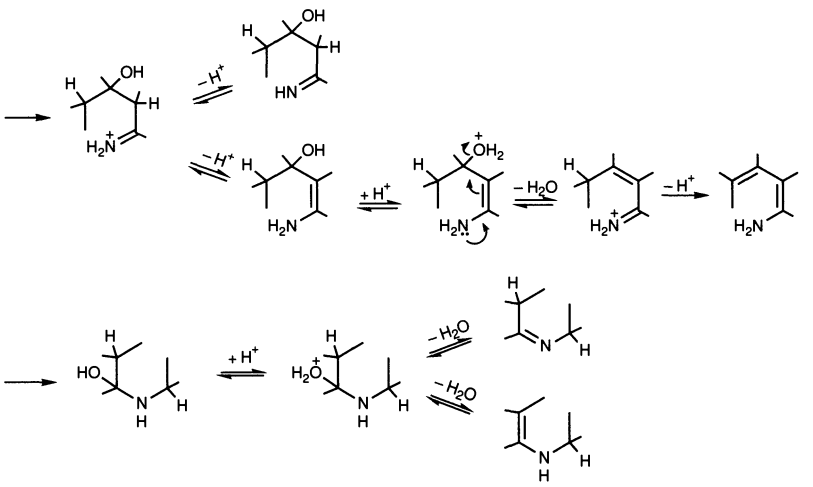
By far the most frequently used process is the addition of a nucleophile to a carbonyl carbon (or the more reactive carbon of an *O*-protonated carbonyl). When the reaction leads to C–C bond formation, then the nucleophile is the β-carbon of an enol or enolate anion, or of an enamine, and the reaction is aldol in type:



When the process leads to C–hetero atom bond formation, then the nucleophile is an appropriate hetero atom, either anionic ($-X^-$) or neutral (-XH):



In all cases, subsequent loss of water produces a double bond, either a C–C or a C–hetero atom double bond. Simple examples are the formation of an aldol condensation product, and the formation of an imine or enamine, respectively.

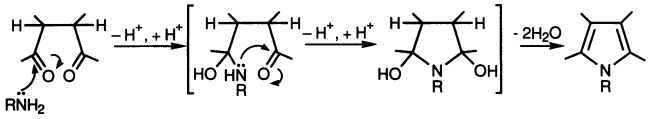


These two basic processes, with minor variants, cover the majority of the steps involved in heteroaromatic synthesis. In a few instances, displacements of halide, or other leaving groups, from saturated carbon are also involved. A completely separate category is the increasing number of ring syntheses which involve electrocyclic processes (see section 3.4).

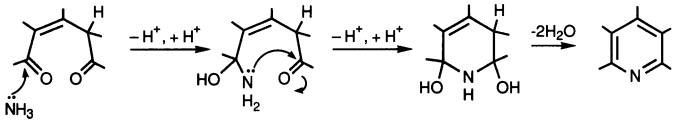
3.2 TYPICAL REACTANT COMBINATIONS

Although there are some examples of nearly all possible retrosynthetic disections and synthetic recombinations of five- and six-membered heterocycles, by far the majority of ring syntheses fall into two categories; in the first, for each ring size, only C–hetero atom bonding is needed i.e. the rest of the skeleton is present intact in one starting component; in the second, for each ring size, one C–C bond and one C–hetero atom linkage are required.

We can now look at more specific examples, and see how the principles above can lead to the aromatic heterocycles. In the first of the two broad categories, where only C–hetero atom bonds are needed, and for the synthesis of five-membered heterocycles, precursors with two carbonyl groups related 1,4 are required; 1,4-diketones, for example, react with ammonia or primary amines to give 2,5-disubstituted pyrroles.

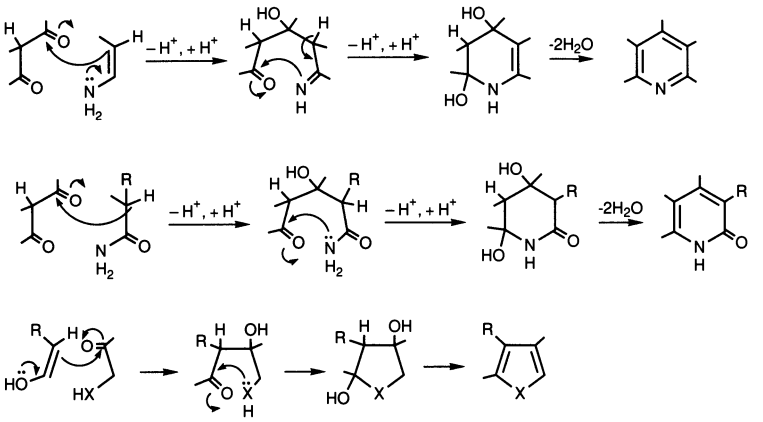


For six-membered rings, the corresponding 1,5-dicarbonyl precursor has to contain a C–C double bond in order to lead directly to the aromatic system (though it is relatively easy to dehydrogenate the dihydro-heterocycle which is comparably obtained if a saturated 1,5-dicarbonyl compound is employed).



In the second broad category, needing both C–C and C–hetero atom links to be made, one component must contain an enol/enolate/enamine, or the equivalent thereof, while the second obviously must have electrophilic centres to match.

The following generalised combinations show how this works out for the two ring sizes.



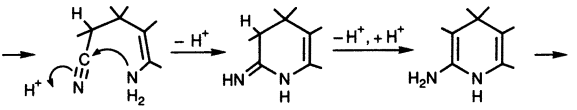
Note: (1) The R substituent shown in the last two of these schemes must be an acidifying group: ketone, ester, nitrile, or occasionally, nitro.

(2) Some of the components shown in these examples have two electrophilic centres and some have a nucleophilic and an electrophilic centre; in other situations components with two nucleophilic centres are required. In general, components in which the two reacting centres are either 1,2- or 1,3-related are utilised most often in heterocyclic synthesis, but 1,4- (e.g. HX–C–C–YH) (X and Y are hetero atoms) and 1,5-related (e.g. O=C–$(C)_3$–C=O) bifunctional components, and also reactants which provide one-carbon units (formate, or a synthon for carbonic acid – phosgene, Cl_2C=O, or a safer equivalent) are also important. Amongst many examples of 1,2-difunctionalised compounds are 1,2-dicarbonyl compounds, enols (which first react in a nucleophilic sense at carbon and then provide an electrophilic centre (the carbonyl carbon), Hal–C–C=O, and systems with HX–YH units. Amongst often used 1,3-difunctionalised compounds are the doubly electrophilic 1,3-dicarbonyl compounds and α,β-unsaturated carbonyl compounds (C=C–C=O), doubly nucleophilic HX–C–YH (amidines and ureas are examples), and α-amino- or α-hydroxycarbonyl compounds (HX–C–C=O), which have an electrophilic and a nucleophilic centre.

(3) The exact sequence of nucleophilic additions, deprotonations/protonations, and dehydrations is never known with certainty, but the sequences shown are the most reasonable ones; the exact order of steps almost certainly varies with conditions,[2] particularly p*H*.

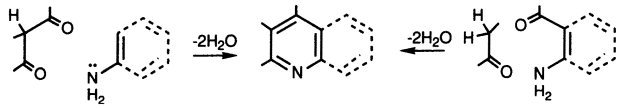
(4) When components like α-halocarbonyl compounds are utilised, and if reaction at the halogen-bearing carbon is a cyclising process, the displacement of the halogen (by enolate α-carbon or hetero atom) is an *exo-tet* process. Where a cyclisation involves attack at carbonyl carbon or nitrile carbon and is the ring-closing step, the processes are *exo-trig* and *exo-dig* respectively.[3]

(5) In the second example above, where a carbonyl component (an amide) at the oxidation level of an acid is used then the resultant product carries an oxygen substituent at that carbon (pyridone in the example). Similarly, if a nitrile group is used instead of a carbonyl group, as an electrophilic centre, then the resulting heterocycle carries an amino group at that carbon, thus:



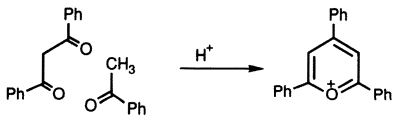
The two nucleophilic centres can both be hetero atoms, as in syntheses of pyrimidines and pyrazoles.

In syntheses of benzanellated systems, phenols can take the part of enols, and anilines react in the same way as enamines.[4]

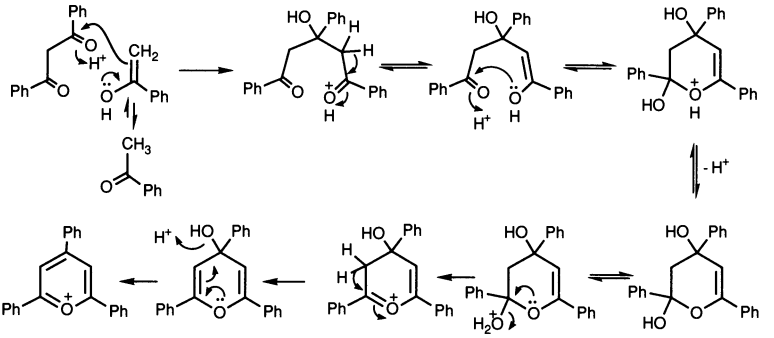


3.3 SUMMARY

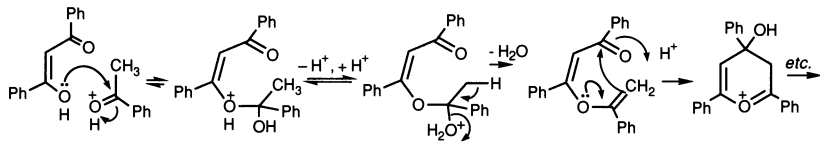
The chemical steps involved in heteroaromatic synthesis are mostly simple and straightforward, even though a first look at the structures of starting materials and product might make the overall effect seem almost alchemical. In devising a sequence of sensible steps it is important to avoid obvious pitfalls, like suggesting that electrophile react with electrophilic centre, or nucleophile with a source of electrons, but this aside it should be easy enough to devise a sensible scheme.



A complete step-by-step analysis of the reaction of 1,3-diphenylpropane-1,3-dione with acetophenone is presented below – note that many individual steps are involved but that each of them is very simple when considered separately.



The sequence shows an initiating step as nucleophilic attack by acetophenone enolate on the protonated diketone, however an equally plausible sequence, shown below, starts with the nucleophilic addition of the enolic hydroxyl of the diketone to protonated acetophenone.



A final point to be made is that most of the steps in such sequences are reversible; the overall sequence proceeds to product nearly always because the product is the thermodynamically most stable molecule in the sequence, or because the product is removed from the equilibria by distillation or crystallisation. A nice example is the interrelationship between 1,4-diketones and furans; the latter can be synthesised by heating the former, in acid, under conditions which lead to the distillation of the furan (section 15.13.1.1), but in the reverse sense, furans are hydrolysed to 1,4-diketones by aqueous acid (section 15.1.1).

3.4 ELECTROCYCLIC PROCESSES IN HETEROCYCLIC RING SYNTHESIS

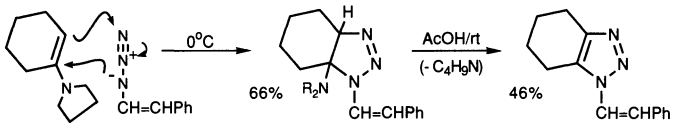
There are two types of electrocyclic process which are of considerable value for heterocyclic ring synthesis: one of these is 1,3-dipolar cycloaddition, and the second involves a Diels-Alder type addition using some type of azadiene;[5] the latter does not in general produce aromatic heterocycles and, important though it is, will not be dealt with here.

1,3-Dipoles always contain a hetero atom as the central atom of the trio, either sp or sp^2 hybridised. Amongst other examples, cycloadditions have been demonstrated with azides ($N{\equiv}N^+{-}N^-{-}R$), nitrile oxides ($R{-}C{\equiv}N^+{-}O^-$) and nitrile ylides ($R{-}C{\equiv}N^+{-}C^-R_2$) where the central atom is sp hybridised nitrogen, and with nitrones ($R_2C{=}N^+(R){-}O^-$), carbonyl ylides

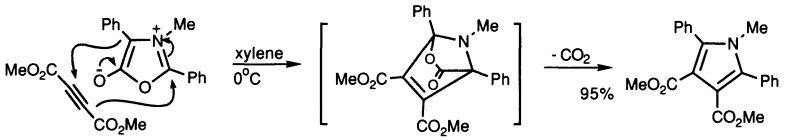
($R_2C{=}O^+{-}C^-R_2$), and azomethine ylides ($R_2C{=}N^+(R){-}C^-R_2$), where the central atom is sp^2 hybridised.

Dipolar cycloadditions[6] can, of course, only produce five-membered rings. Unless the dipolarophile is an alkyne, or is an alkene with a potential leaving group, addition generates dihydro-aromatic five-membered heterocycles. A couple of examples of the utility of these reactions are given below.

The interaction of azides, as the 1,3-dipoles, with enamines, followed by elimination of the amine, affords 1,2,3-triazoles.[7]

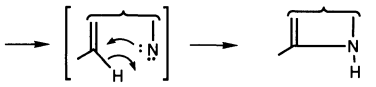


Many mesoionic substances (section 1.6) can act as 1,3-dipoles, and, after elimination of a small molecule – carbon dioxide in the example shown – produce aromatic heterocycles.[8]

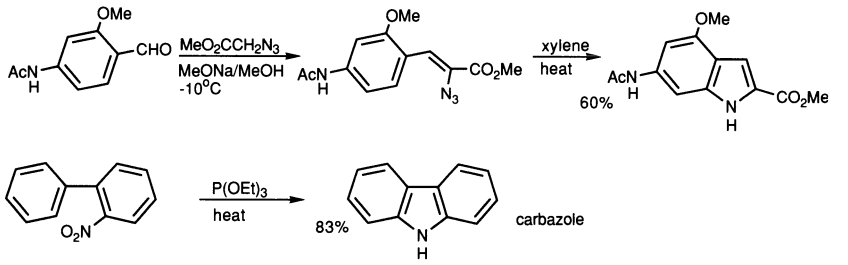


3.5 NITRENES IN HETEROCYCLIC RING SYNTHESIS[9]

The insertion of a nitrene (a monovalent, six-electron, neutral nitrogen, most often generated by thermolysis or photolysis of an azide ($RN_3 \rightarrow RN + N_2$), or by deoxygenation of a nitro group) into a C–H bond has been made the key step in several synthetic routes to both five- and six-membered aromatic systems. The process can be written in a general way:



The preparation of an indole[10] (which was elaborated into the coenzyme, methoxatin; see also section 6.16.2.4) and of carbazole[11] illustrate the power of the method.



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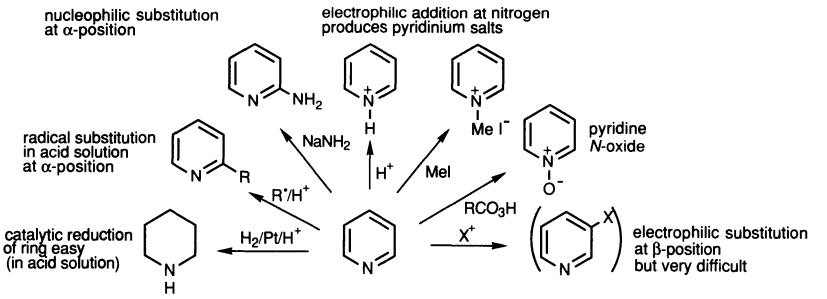
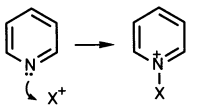
4 Typical reactivity of pyridines, quinolines and isoquinolines

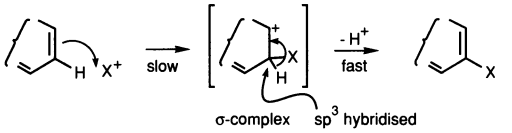
Before detailed descriptions of the chemistry of the heterocyclic systems covered in this book, and at intervals during the book, we provide six highly condensed and simplified discussions of the types of reaction, ease of such reactions, and regiochemistry of such reactions for groups of related heterocyles. In this chapter the group comprises pyridine, as **the** prototype electron-poor six-membered heterocycle, and its benzo-fused analogues, quinoline and isoquinoline. As in each of these summary chapters, reactions are shown in brief and either as the simplest possible example, or in general terms.



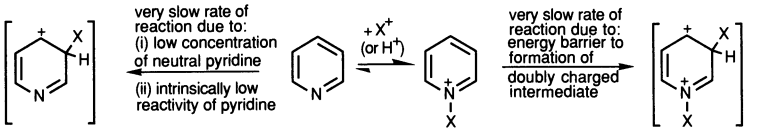
The formal replacement of a CH in benzene, by N, leads to far-reaching changes in typical reactivity: pyridines are **much less susceptible to electrophilic substitution than benzene, and much more susceptible to nucleophilic attack**. However, pyridine undergoes a range of simple **electrophilic additions**, some reversible, some forming isolable products, each involving donation of the nitrogen lone pair to an electrophile, and thence the formation of 'pyridinium' salts which, of course, do not have a counterpart in benzene chemistry at all. It is essential to understand that the ready donation of the pyridine lone pair in this way **does not destroy the aromatic sextet** (compare with pyrrole, chapter 12) – pyridinium salts are still aromatic, though of course much more polarised than neutral pyridines (see section 1.2.3).



Electrophilic substitution of aromatic compounds proceeds *via* a two-step sequence – addition (of X^+) then elimination (of H^+), of which the former is usually the slower (rate-determining) step. Qualitative predictions of relative rates of substitution at different ring positions can be made by inspecting the structures of the σ-complexes (Wheland intermediates) thus formed, on the assumption that their relative stabilities reflect the relative energies of the transition states which lead to them.



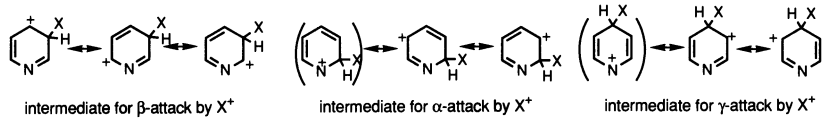
Electrophilic substitution at carbon, in simple pyridines at least, is very difficult in contrast to the reactions of benzene – Friedel-Crafts acylations, for example, do not occur at all with pyridines. This unreactivity can be traced to two factors:



(1) Exposure of a pyridine to a medium containing electrophilic species immediately converts the heterocycle into a pyridinium cation with the electrophile (or a proton from the medium, or a Lewis acid) attached to the nitrogen. The extent of conversion depends on the nature and concentration of the electrophile (or protons) and the basicity of the particular pyridine, and is usually nearly complete. Obviously, the positively charged pyridinium cation is many orders of magnitude less easily attacked at carbon by the would-be electrophile than the original neutral heterocycle. The electrophile, therefore, has Hobson's choice – it must either attack an already-positively charged species, or seek out a neutral pyridine from the very low concentration of uncharged heterocyclic molecules.

(2) The carbons of a pyridine are, in any case, electron-poor, particularly at the α- and γ-positions: formation of a σ-complex is intrinsically disfavoured. The least disfavoured, i.e. best option, is attack at a β-position – resonance contributors to the cation thus produced, do not include one with the particularly unfavourable sextet, positively-charged nitrogen situation (shown in parentheses for the α- and γ-intermediates). The situation has a direct counterpart in

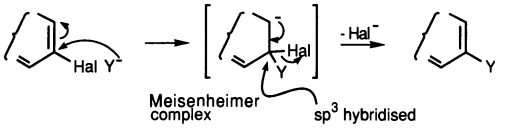
benzene chemistry where a consideration of possible intermediates for electrophilic substitution of nitrobenzene provides a rationalisation of the observed *meta* selectivity.



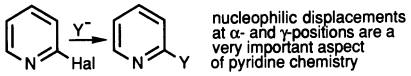
Substituents exert an influence on the ease of electrophilic attack, just as in benzene chemistry. Strongly electron-withdrawing substituents simply render the pyridine even more inert, however activating groups – amino and oxy, and even alkyl – allow substitution to take place, even though by way of the protonated heterocycle i.e. *via* a dicationic intermediate. The presence of halogen substituents, which have a base-weakening effect and are only weakly deactivating, can allow substitution to take place in a different way – by allowing an appreciably larger concentration of the un-protonated pyridine to be present.

Pyridine rings are resistant to oxidative destruction, as are benzene rings. In terms of reduction, however, the heterocyclic system is much more easily catalytically reduced, especially in acidic solution. Similarly, *N*-alkyl- and *N*-arylpyridinium salts can be easily reduced both with hydrogen over a catalyst, and by nucleophilic chemical reducing agents.

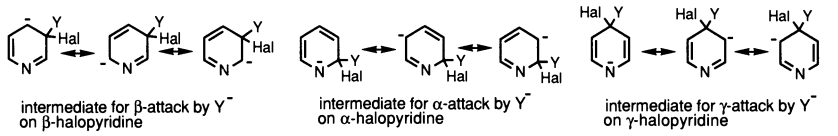
Nucleophilic substitution of aromatic compounds proceeds *via* an addition (of Y^-) then elimination (of a negatively charged entity, most often Hal^-) two-step sequence of which the former is usually rate-determining (the $S_N(AE)$ mechanism: **S**ubstitution **N**ucleophilic **A**ddition **E**limination). Rates of substitution at different ring positions can be assessed by inspecting the structures of the negatively charged intermediates (Meisenheimer complexes) thus formed, on the assumption that their relative stabilities (degree of delocalisation of negative charge) reflect the relative energies of the transition states which lead to them. For example 2- and 4-halonitrobenzenes react in this way because the anionic adduct derives stabilisation by delocalisation of the charge onto the nitro group(s).



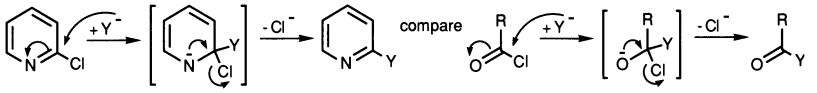
The electron-deficiency of the carbons in pyridines, particularly α- and γ-carbons, makes nucleophilic addition and, especially nucleophilic displacement of halide (and other good leaving groups), a very important feature of pyridine chemistry.



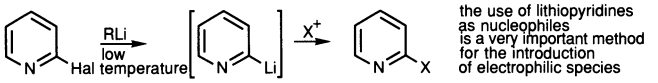
Such substitutions follow the same mechanistic route as the displacement of halide from 2- and 4-halo-nitro-benzenes, i.e. the **nucleophile first adds** and **then the halide departs**. By analogy with the benzenoid situation, the addition is facilitated by (i) the electron-deficiency at α- and γ-carbons, increased by a halogen substituent, and (ii) the ability of the hetero atom to accommodate negative charge in the intermediate thus produced. Once again, a comparison of the three possible intermediates makes it immediately plain that this latter is not available for attack at a β-position, and thus β nucleophilic displacements are very much slower.



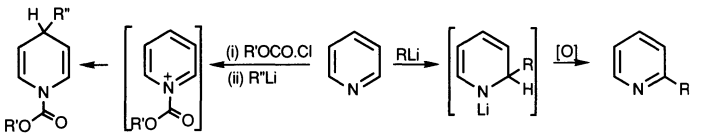
It is useful to compare the reactivity of α- and γ-halopyridines with the reaction of acid halides and β-halo-α,β-unsaturated ketones, respectively, both of which also interact easily with nucleophiles and also by an addition/elimination sequence resulting in overall displacement of the halide by the nucleophile.



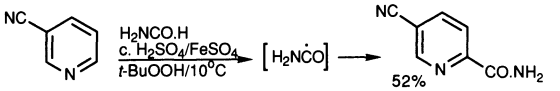
The generation of metallated aromatics has become extremely important for the introduction of substituents, especially carbon substituents, by subsequent reaction with an electrophile. It is very important, in the light of the discussion above on the ease of nucleophilic addition and substitution, to realise that iodine and bromine at all positions of a pyridine can be exchanged at low temperature without nucleophilic displacement or addition, with formation of the pyridyllithium.



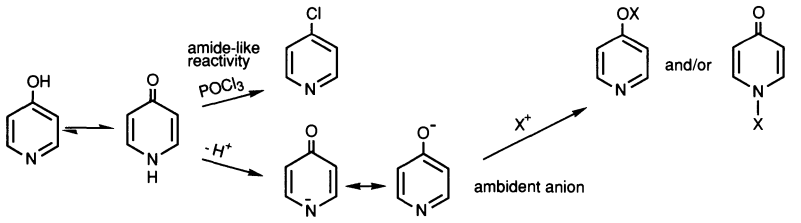
In the absence of an α- or γ-halogen, pyridines are less reactive and, of course, do not have a substituent suitable for leaving as an anion to complete a nucleophilic substitution. Nucleophilic additions do however take place, but the resultant dihydropyridine adduct requires an oxidant – to remove 'hydride' – to complete an overall substitution. Such reactions, for example with amide or with organometallic reagents, are selective for an α-position, possibly because the nucleophile is delivered *via* a complex involving interaction of the ring nitrogen with the reactant's metal cation. The addition of organometallic and hydride reagents to N^+-acylpyridinium salts is an extremely useful process: the product, dihydropyridines, are stable because the nitrogen is an amide, most often a urethane.



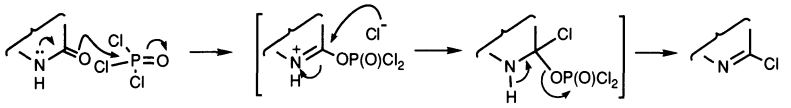
Radical substitution of pyridines, in acid solution, is now a preparatively useful process. For efficient reaction, the radicals must be 'nucleophilic', like $^{\bullet}CH_2OH$, alkyl$^{\bullet}$, and acyl$^{\bullet}$; aminocarbonylation provides an example.



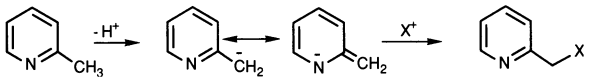
Pyridines carrying oxygen at an α- or γ-position exist as tautomers having carbonyl groups – pyridones. Nonetheless, there is considerable parallelism between their reactions and those of phenols: pyridones are activated towards electrophilic substitution, attack taking place *ortho* and *para* to the oxygen, and they readily form anions, by loss of the *N*-hydrogen, which are analogous in structure and reactivity to phenolates, though in the heterocyclic system the anion can react at either oxygen or nitrogen, depending on conditions.



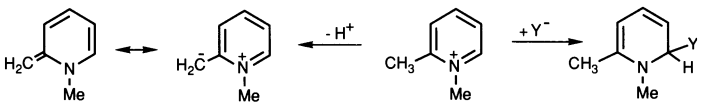
Where pyridones differ from phenols is in their interaction with phosphorus and sulfur halides, where transformation of the oxygen substituent into halide occurs. Here, the pyridones react in an amide-like fashion, the inorganic reagent reacting first at the 'amide-like' oxygen.



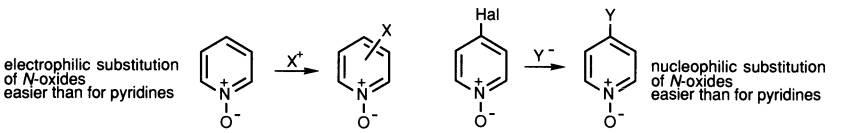
The special properties associated with pyridine α- and γ-positions show again in the reactions of alkylpyridines: the protons on alkyl groups at those positions are particularly acidified because the 'enaminate' anions formed are delocalised. The ability to form side-chain anions provides an extremely useful means for the manipulation of α- and γ-side chains.



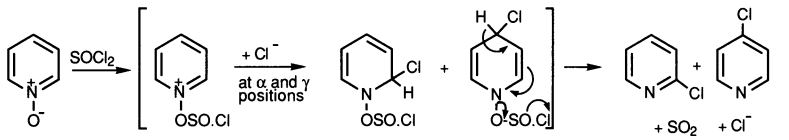
Pyridinium salts show the properties which have been discussed above, but in extreme: they are highly resistant to electrophilic substitution but, conversely, nucleophiles add very easily. The hydrogens of α- and γ-alkyl side-chains on pyridinium salts are further acidified compared with the uncharged alkylpyridine.



Pyridine *N*-oxide chemistry, which clearly has no parallel in benzenoid chemistry, is an extremely important and useful aspect of the chemistry of heterocycles of the pyridine series. The structure of these derivatives means that they are both more susceptible to electrophilic substitution **and** react more easily with nucleophiles – an extraordinary concept when first encountered. On the one hand, the nominally negatively charged oxygen can release electrons to stabilise an intermediate from electrophilic attack and, on the other, the positively charged ring nitrogen can act as an electron sink to encourage nucleophilic addition.

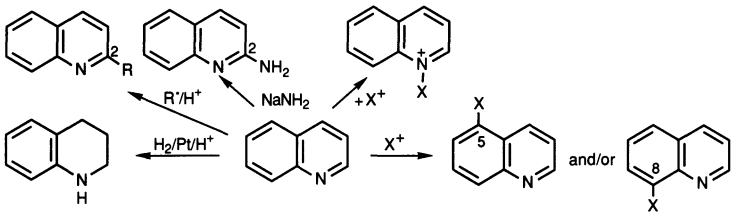


There are a number of very useful processes in which the *N*-oxide function allows the introduction of substituents usually mainly at an α-position and in the process, the oxide function is removed; reaction with thionyl chloride is an example.

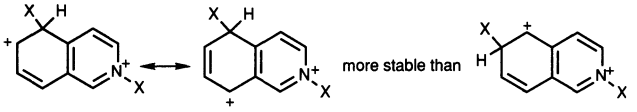


Quinoline and isoquinoline, the two possible structures in which a benzene ring is annelated to a pyridine ring, represent an opportunity to examine the effect of fusing one aromatic ring to another. Clearly, both the effect the benzene ring has on the reactivity of the pyridine ring, and *vice versa*, and comparisons with the chemistry of naphthalene must be made. Thus the regioselectivity of electrophilic substitution, which in naphthalene is faster at an α-position, is mirrored in quinoline/isoquinoline chemistry by substitution at 5-

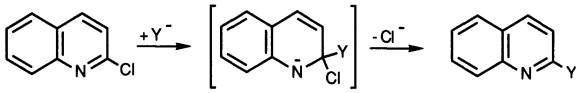
and 8-positions. It should be noted that such substitutions usually involve attack on the species formed by electrophilic addition (often protonation) at the nitrogen, which has the effect of discouraging (preventing) attack on the heterocyclic ring.



Just as for naphthalene, the regiochemistry of attack is readily interpreted by looking at possible intermediates: those for attack at C-5/8 allow delocalisation of charge without disruption of the pyridinium ring aromatic resonance, while those for attack at C-6/7 would necessitate disrupting that resonance in order to allow delocalisation of charge.

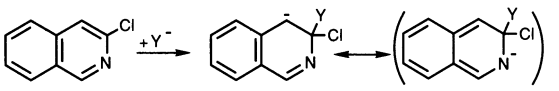


So, just as quinoline and isoquinoline are reactive towards electrophiles in their benzene ring, they are reactive to nucleophiles in the pyridine ring, especially (see above) at the positions α and γ to the nitrogen and, further, are more reactive in this sense than pyridines. This is consistent with the structures of the intermediates for, in these, a full and complete, aromatic benzene ring is retained. Since the resonance stabilisation of the bicyclic aromatic is considerably less than twice that of either benzene or pyridine, the loss in resonance stabilisation in proceeding from the bicyclic system to the intermediate is considerably less than in going from pyridine to an intermediate adduct. There is an obvious analogy: the rate of electrophilic substitution of naphthalene is greater than that of benzene for, in forming a σ-complex from the former, less resonance energy is lost.

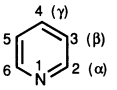


A significant difference in this typical behaviour applies to the isoquinoline 3-position – the special reactivity which the discussion above has developed for positions α to pyridine nitrogen, and which also applies to the isoquinoline 1-position, does not apply at C-3. In the context of nucleophilic displacements, for example, an intermediate for reaction of a 3-halo-isoquinoline cannot achieve delocalisation of negative charge onto the nitrogen unless the aromaticity of the

benzene ring is disrupted. Therefore, such intermediates are considerably less stabilised and reactivity considerably tempered.



5 Pyridines: reactions and synthesis

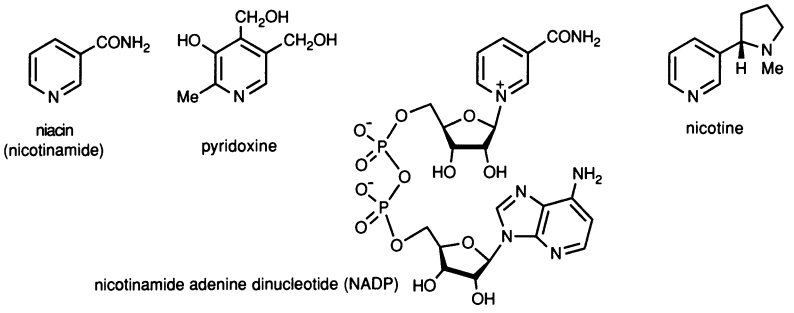


pyridine

Pyridine and its simple derivatives are stable and relatively unreactive liquids, with strong penetrating odours that are unpleasant to some people. They are much used as solvents and bases, especially pyridine itself, in reactions such as *N*- and *O*-tosylation and -acylation. Pyridine and the monomethylpyridines (picolines) are completely miscible with water.

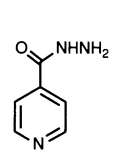
Pyridine was first isolated, like pyrrole, from bone pyrolysates: the name is constructed from the Greek for fire, '*pyr*', and the suffix '*idine*', which was at the time being used for all aromatic bases – phenetidine, toluidine, etc.

Pyridine and its simple alkyl derivatives were for a long time produced by isolation from coal tar, in which they occur in quantity. In recent years this source has been displaced by synthetic processes: pyridine itself, for example, can be produced on a commercial scale in 60–70% yields by the gas-phase high-temperature interaction of crotonaldehyde, formaldehyde, steam, air and ammonia over a silica–alumina catalyst. Processes for the manufacture of alkylpyridines involve reaction of acetylenes and nitriles over a cobalt catalyst.

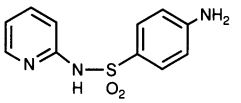


The pyridine ring plays a key role in several biological processes, most notably in the oxidation/reduction coenzyme nicotine adenine dinucleotide (NADP); the vitamin niacin (or the corresponding acid) is required for its biosynthesis. Pyridoxine (vitamin B_6) plays a key role as the coenzyme in

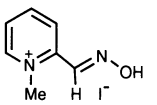
transaminases. Nicotine, a highly toxic alkaloid, is the major active component in tobacco.



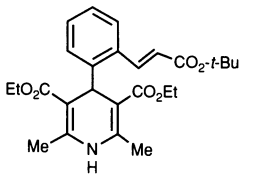
Isoniazide



Sulphapyridine

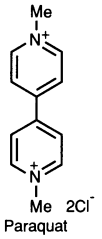


Prialdoxime

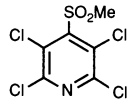


Lacidipine

Many synthetic pyridine derivatives are important as therapeutic agents, for example Isoniazide is a major antituberculosis agent, Sulphapyridine is one of the sulfonamide antibacterials, Prialdoxime is an antidote for poisoning by organophosphates, and Lacidipine is one of several antihypertensive 1,4-dihydropyridines. Some herbicides (Paraquat)[1] and fungicides (Davicil) are also pyridine derivatives.



Paraquat



Davicil

5.1 REACTIONS WITH ELECTROPHILIC REAGENTS

5.1.1 Addition to nitrogen

In reactions which involve bond formation using the lone pair of electrons on the ring nitrogen, such as protonation and quaternisation, pyridines behave just like tertiary aliphatic or aromatic amines. When a pyridine reacts as a base or a nuclophile it forms a pyridinium cation in which the aromatic sextet is retained and the nitrogen acquires a formal positive charge.

5.1.1.1 *Protonation of nitrogen*

Pyridines form crystalline, frequently hygroscopic, salts with most protic acids. Pyridine itself, with pK_a 5.2 in water, is a much weaker base than saturated aliphatic amines which have pK_a values mostly between 9 and 11. Since the gas-phase proton affinity of pyridine is actually very similar to those of aliphatic amines, the observed solution values reflect relatively strong solvation of aliphatic ammonium cations;[2] this difference may in turn be related to the mesomerically delocalised charge in pyridinium ions and the consequent reduced requirement for external stabilisation *via* solvation.

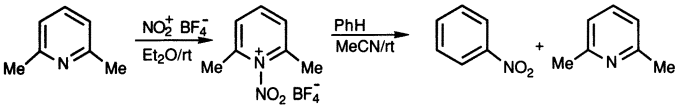
Electron-releasing substituents generally increase the basic strength;

2-methyl- (pK_a 5.97), 3-methyl- (5.68) and 4-methylpyridine (6.02) illustrate this. The basicities of pyridines carrying groups which can interact mesomerically as well as inductively vary in more complex ways, for example 2-methoxypyridine (3.3) is a weaker, but 4-methoxypyridine (6.6) a stronger base than pyridine; the effect of inductive withdrawal of electrons by the electronegative oxygen is felt more strongly when it is closer to the nitrogen, i.e. at C-2.

5.1.1.2 *Nitration at nitrogen*

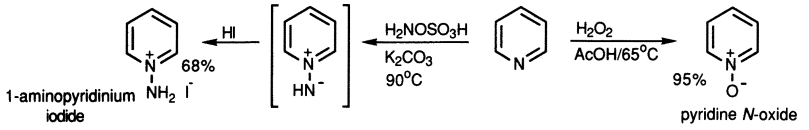
This occurs readily by reaction of pyridines with nitronium salts, such as nitronium tetrafluoroborate.[3] Protic nitrating agents such as nitric acid of course lead exclusively to *N*-protonation.

1-Nitro-2,6-dimethylpyridinium tetrafluoroborate is one of several *N*-nitropyridinium salts which can be used as non-acidic nitrating agents with good substrate and positional selectivity. The 2,6-disubstitution serves to sterically inhibit resonance overlap between nitro group and ring and consequently increase reactivity as a nitronium ion donor, however the balance between this advantageous effect and hindering approach of the aromatic substrate is illustrated by the lack of transfer nitration reactivity in 2,6-dihalo-analogues.[4]



5.1.1.3 *Amination of nitrogen*

The introduction of nitrogen at a different oxidation level can be achieved with hydroxylamine *O*-sulfate.[5]



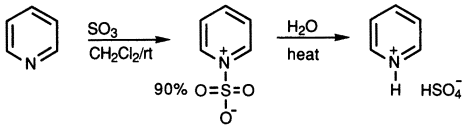
5.1.1.4 *Oxidation of nitrogen*

In common with other tertiary amines, pyridines react smoothly with percarboxylic acids to give *N*-oxides, which have their own rich chemistry (section 5.14).

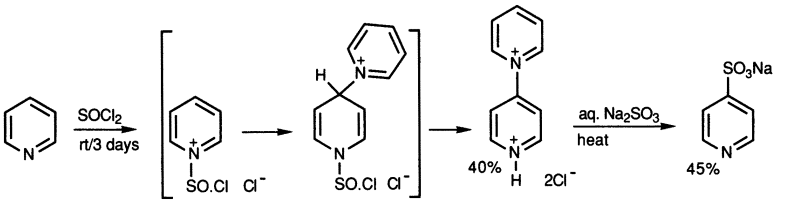
5.1.1.5 *Sulfonation at nitrogen*

Pyridine reacts[6] with sulfur trioxide to give the commerially available, crystalline, zwitterionic pyridinium-1-sulfonate, usually known as the pyridine–sulfur trioxide complex. This compound is hydrolysed in hot water to sulfuric acid and pyridine (for its reaction with hydroxide see section 5.13.4), but more

usefully it can serve as a mild sulfonating agent (for examples see sections 13.1.3 and 15.1.3) and as an activating agent for DMSO in Moffat oxidations.

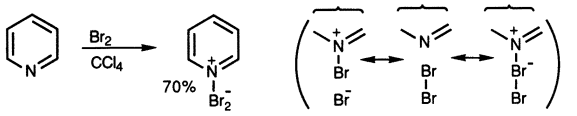


When pyridine is treated with thionyl chloride a synthetically useful dichloride salt is formed, which can, for example, be transformed into pyridine-4-sulfonic acid. The reaction is believed to involve initial attack by sulfur at nitrogen, followed by nucleophilic addition of a second pyridine at C-4 (cf. section 5.13.3).[7]

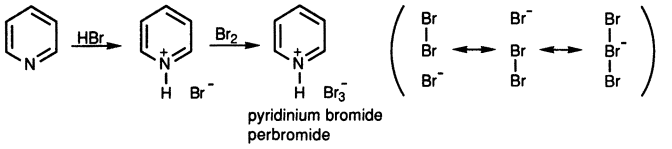


5.1.1.6 *Halogenation at nitrogen*

Pyridines react easily with halogens and interhalogens[8] to give crystalline compounds, largely undissociated when dissolved in solvents such as carbon tetrachloride. Structurally they are best formulated as resonance hybrids related to trihalide anions. 1-Fluoropyridinium triflate is also crystalline and serves as an electrophilic fluorinating agent.[9]

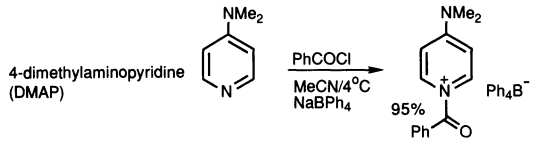


These salts must be distinguished from 'pyridinium bromide perbromide', obtained by treating pyridine hydrobromide with bromine, which does not contain an *N*-halogen bond, but does include a trihalide anion. The stable, crystalline, commercially available salt can be used as a source of molecular bromine especially where small accurately known quantities are required.



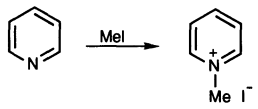
5.1.1.7 *Acylation at nitrogen*

Carboxylic and arylsulfonic acid halides react rapidly with pyridines generating 1-acyl- and 1-arylsulfonylpyridinium salts in solution, and in suitable cases some of these can even be isolated as crystalline solids.[10] The solutions, generally in excess pyridine, are commonly used for the preparation of esters and sulfonates from alcohols and amides and sulfonamides from amines. 4-Dimethylaminopyridine[11] (DMAP) is widely used (in catalytic quantities) to activate anhydrides in a similar manner. The salt derived from DMAP and *t*-butyl chloroformate is stable even in aqueous solution at room temperature.[12]

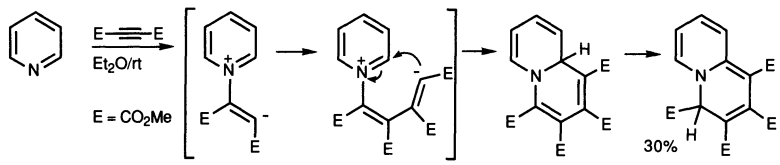


5.1.1.8 *Alkylation at nitrogen*

Alkyl halides and sulfates react readily with pyridines giving quaternary pyridinium salts. As with aliphatic tertiary amines, increasing substitution around the nitrogen, or around the halogen-bearing carbon, causes an increase in the alternative, competing, elimination process which gives alkene and tertiary salt, thus 2,4,6-trimethylpyridine (collidine) is useful as a base in dehydrohalogenation reactions.



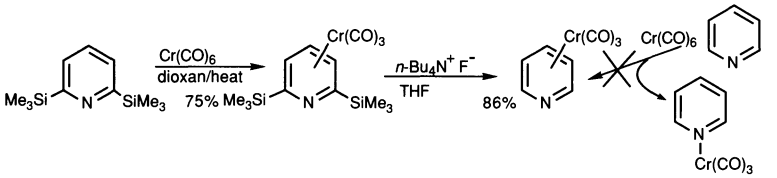
Pyridine reacts with dimethyl acetylenedicarboxylate, firstly being *N*-alkylated by the electrophilic alkyne to give a zwitterion which then adds as a nucleophile to a second equivalent of the alkyne, the process being completed by an intramolecular nucleophilic addition/cyclisation to the pyridine α-position; the initial product tautomerises to a more stable final product.[13]



5.1.1.9 *Reaction with metal centres*

The normal behaviour of pyridines in the presence of metal cations is complexation involving donation of the nitrogen lone pair to the metal centre. This means that for simple pyridines, π-complex chemistry, such as

benzene–chromium carbonyl complexes, does not exist. However, if the nitrogen lone pair is hindered, then η^6-complexes can be formed.[14]



5.1.2 Substitution at carbon

In most cases, electrophilic substitution of pyridines occurs very much less readily than for the correspondingly substituted benzene. The main reason is that the electrophilic reagent, or a proton in the reaction medium, adds preferentially to the pyridine nitrogen, generating a pyridinium cation, which is naturally very resistant to a further attack by electrophile.

When it occurs, then, electrophilic substitution at carbon must involve either highly unfavoured attack on a pyridinium cation or relatively easier attack but on a very low equilibrium concentration of uncharged free pyridine base.

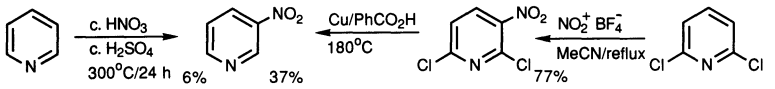
Some of the typical electrophilic substitution reactions do not occur at all – Friedel-Crafts alkylation and acylation are examples – but it is worth recalling that these also fail with nitrobenzene. Milder reagents, such as Mannich reactants, diazonium ions and nitrous acid, which in any case require activated benzenes for success, naturally fail with pyridines.

5.1.2.1 *Proton exchange*

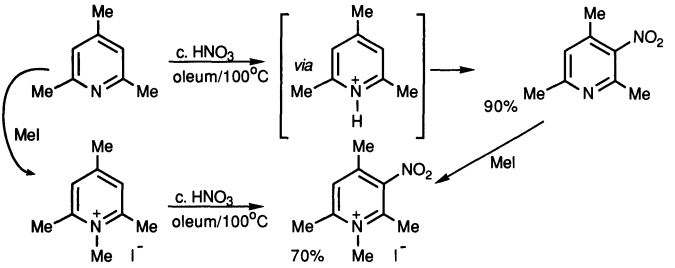
H–D exchange *via* an electrophilic addition process, such as operates for benzene, does not take place with pyridine. A special mechanism allows selective exchange at the two α-positions in DCl–D_2O or even in water at 200°C, the key species being an ylid formed by 2/6-deprotonation of the 1*H*-pyridinium cation (see also section 5.12).[15]

5.1.2.2 *Nitration*

Pyridine itself can be converted into 3-nitropyridine only inefficiently by direct nitration even with vigorous conditions, however a pair of methyl groups facilitate electrophilic substitution sufficiently to allow nitration to compete with side-chain oxidation.[16] Steric or/and inductive inhibition of *N*-nitration allows *C*-substitution using nitronium tetrafluoroborate, an example is 2,6-dichloropyridine; dehalogenation of 2,6-dichloro-3-nitropyridine provides a practicable preparation of 3-nitropyridine.[4]

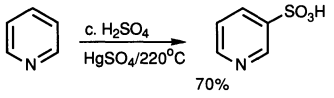


Both collidine and its quaternary salt are nitrated at similar rates under the same conditions, showing that the the former reacts *via* its *N*-protonic salt.[17]

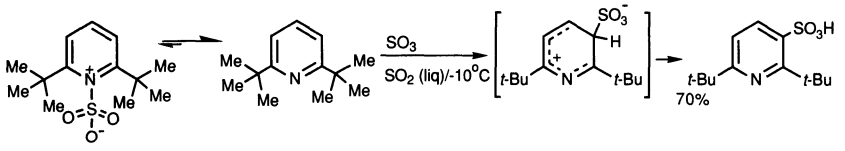


5.1.2.3 *Sulfonation*

Pyridine is very resistant to sulfonation using concentrated sulfuric acid or oleum, only very low yields of the 3-sulfonic acid being produced after prolonged reaction periods at 320°C. However, addition of mercuric sulfate in catalytic quantities allows smooth sulfonation at a somewhat lower temperature. The role of the catalyst is not established; one possibility is that *C*-mercuration is the first step (cf. section 5.1.2.5).[18]



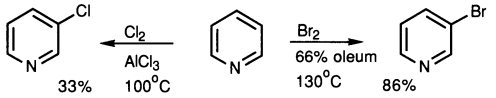
The *C*-sulfonation of 2,6-di-*t*-butylpyridine[19] is a good guide to the intrinsic reactivity of a pyridine ring, for in this situation the bulky alkyl groups effectively prevent addition of sulfur trioxide to the ring nitrogen allowing progress to a 'normal' electrophilic *C*-substitution intermediate, at about the same rate as for sulfonation of nitrobenzene. A maximum conversion of 50% is all that is achieved because for every *C*-substitution a proton is produced which 'consumes' a molecule of starting material by *N*-protonation.



5.1.2.4 *Halogenation*

3-Bromopyridine is produced in good yield by the action of bromine in oleum.[20] The process is thought to involve pyridinium-1-sulfonate as the reactive species,

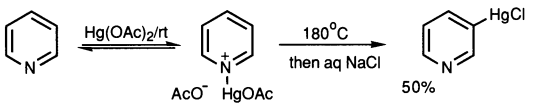
since no bromination occurs in 95% sulfuric acid. 3-Chloropyridine can be produced by chlorination at 200°C or at 100°C in the presence of aluminium chloride.[21]



2-Bromo- and 2-chloropyridines can be made extremely efficiently by reaction with the halogen, at 0–5°C in the presence of the pyridine–palladium chloride complex.[22]

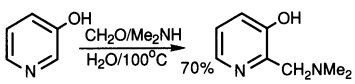
5.1.2.5 *Acetoxymercuration*

The salt formed by the interaction of pyridine with mercuric acetate at room temperature can be rearranged to 3-acetoxymercuripyridine by heating to only 180°C.[23] This process, where again there is *C*-attack by a relatively weakly electrophilic reagent, like that described for mercuric sulfate-catalysed sulfonation, may involve attack on an equilibrium concentration of free pyridine.



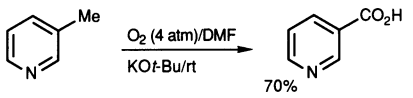
5.1.2.6 *Substitution in pyridines carrying activating substituents*

As in benzene chemistry, electron-releasing groups facilitate electrophilic substitution, thus for example 2-aminopyridine undergoes 5-bromination in acetic acid at room temperature, and this then can be nitrated, at room temperature, forming 2-amino-5-bromo-3-nitropyridine.[24] Pyridines carrying an activating substituent at C-3 undergo electrophilic substitution at C-2; thus chlorination of 3-aminopyridine affords 3-amino-2-chloropyridine;[25] nitration of 3-hydroxypyridine gives 3-hydroxy-2-nitropyridine.[26] The Mannich condensation of 3-hydroxypyridine takes place at C-2.[27]

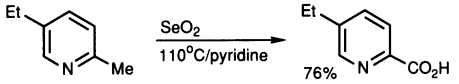


5.2 REACTIONS WITH OXIDISING AGENTS

The pyridine ring is generally resistant to oxidising agents, vigorous conditions being required, thus pyridine itself is oxidised by neutral aqueous potassium permanganate at about the same rate as benzene (sealed tube, 100°C), to give carbon dioxide. In acidic solution pyridine is more resistant, but in alkaline media more rapidly oxidised, than benzene.



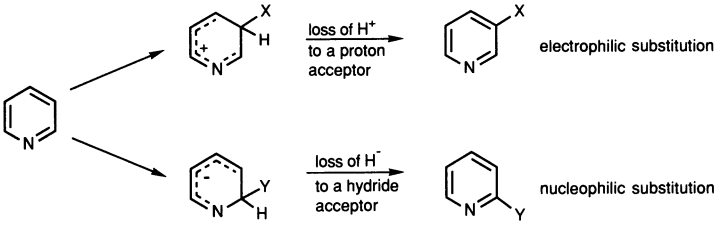
In most situations carbon-substituents can be oxidised with survival of the ring, thus alkylpyridines can be converted into pyridine carboxylic acids with a variety of reagents.[28] Some selectivity can be achieved: only α- and γ-groups are attacked by selenium dioxide.[29]



5.3 REACTIONS WITH NUCLEOPHILIC REAGENTS

Just as electrophilic substitution is the characteristic reaction of benzene and electron-rich heteroaromatic compounds (pyrrole, furan, etc.), so substitution reactions with nucleophiles can be looked on as characteristic of pyridines.

It is important to realise that nucleophilic substitution of hydrogen differs in an important way from electrophilic substitution: whereas the last step in electrophilic substitution is loss of proton, an easy process, the last step in nucleophilic substitution of hydrogen has to be a hydride transfer, which is less straightforward and generally needs the presence of an oxidising agent as hydride acceptor. Nucleophilic substitution of an atom or group which is a good anionic leaving group however is an easy and straightforward process.

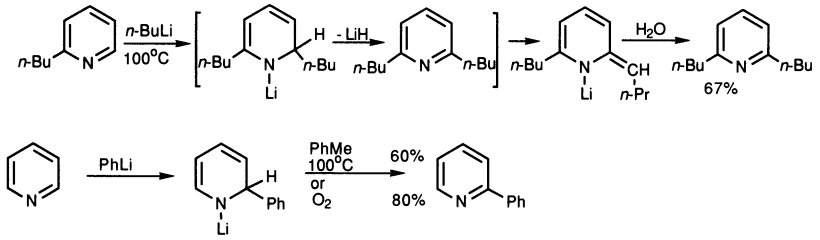


5.3.1 Nucleophilic substitution with 'hydride' transfer

5.3.1.1 *Alkylation and arylation*

Reaction with alkyl- or aryllithiums proceeds in two discrete steps: addition to give a dihydropyridine *N*-lithio-salt which can then be converted into the substituted aromatic pyridine by oxidation (e.g. by air), disproportionation, or elimination of lithium hydride.[30] The *N*-lithio-salts can be observed spectroscopically and in some cases isolated as solids.[31] Attack is nearly always at an α-position; reaction with 3-substituted-pyridines usually takes place at both available α-positions, but predominantly at C-2.[32] This regioselectivity is possibly

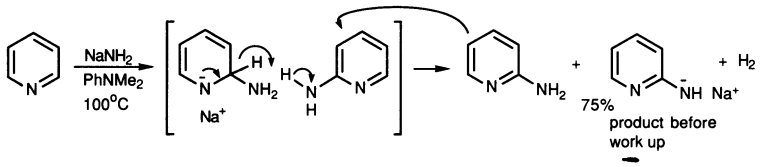
associated with relief of strain when the 2-position rehybridises to sp^3 during addition.



From the preparative viewpoint nucleophilic alkylations can be greatly facilitated by the device of prior quaternisation of the pyridine in such a way that the *N*-substituent can be subsequently removed – these processes are dealt with in section 5.13.2.

5.3.1.2 *Amination*

Amination of pyridines and related heterocycles, generally at a position α to the nitrogen, is called the Chichibabin reaction,[33] the pyridine reacting with sodamide with the evolution of hydrogen. The 'hydride' transfer and production of hydrogen probably involve interaction of aminopyridine product, acting as an acid, with the anionic intermediate. The preference for α-substitution may be associated with an intramolecular delivery of the nucleophile, perhaps guided by complexation of ring nitrogen with metal cation.



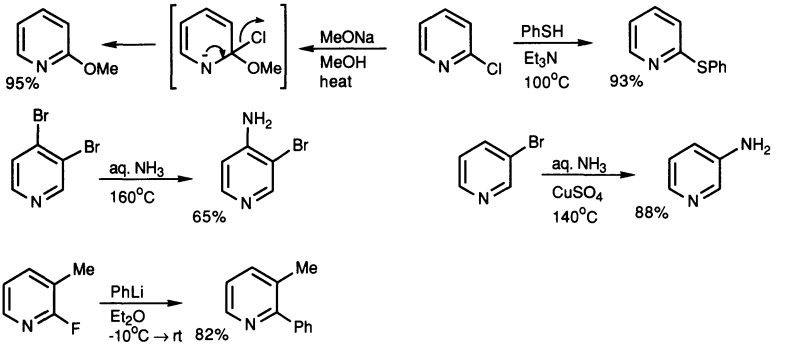
More vigorous conditions are required for the amination of 2- or 4-alkylpyridines since proton abstraction from the side-chain by the amide occurs first and ring attack must therefore involve a dianionic intermediate. Amination of 3-alkylpyridines is regioselective for the 2-position.[34]

5.3.1.3 *Hydroxylation*

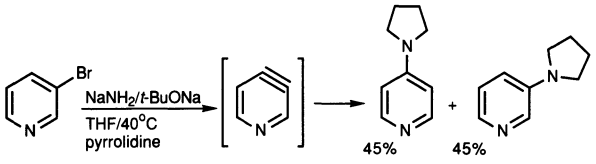
Hydroxide ion, being a much weaker nucleophile than amide, attacks pyridine only at very high temperatures to produce a low yield of 2-pyridone,[35] which can be usefully contrasted with the much more efficient reaction of hydroxide with quinoline and isoquinoline (section 6.3.1.3) and with pyridinium salts (section 5.13.4).

5.3.2 Nucleophilic substitution with displacement of good leaving groups

Halo, and also, though with fewer examples, nitro,[36] alkoxysulfonyl,[37] and methoxy[38] substituents at α- or γ-positions, but not at β-positions, are easily displaced by a wide range of nucleophiles *via* an addition–elimination mechanism facilitated by (i) electron withdrawal by the substituent and (ii) the good leaving ability of the substituent. γ-Halopyridines are more reactive than the α-isomers; β-halopyridines are much less reactive, being much closer to, but still somewhat more reactive than halobenzenes. Fluorides are more reactive than the other halides.[39] Ammonolysis can be achieved at considerably lower temperatures under 6–8 kbar pressure.[40]



In some, apparently straightforward, displacements, more detailed mechanistic study reveals the operation of alternative mechanisms. For example the reaction of either 3- or 4-bromopyridine with secondary amines in the presence of sodamide/sodium *t*-butoxide, produces the same mixture of 3- and 4-dialkylaminopyridines; this proceeds *via* an elimination process (S_N(EA) – Substitution Nucleophilic Elimination Addition) and the intermediacy of 3,4-pyridyne.[41] That no 2-aminated pyridine is produced shows a greater difficulty in generating 2,3-pyridyne; it can however be formed by reaction of 3-bromo-2-chloropyridine with butyllithium.[42]

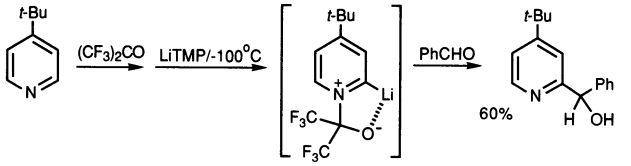


5.4 REACTIONS WITH BASES

5.4.1 Deprotonation of *C*-hydrogen

When pyridine is heated to 165°C in MeONa–MeOD, H–D exchange occurs at all positions *via* small concentrations of deprotonated species, at the relative

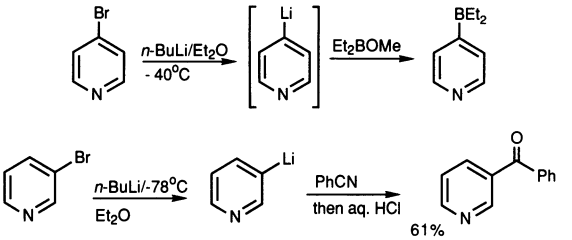
rates α : β : γ, 1.0 : 9.3 : 12.[43] However, using the combination *n*-butyllithium/potassium *t*-butoxide, efficient formation of 2-pyridylpotassium or 4-pyridylpotassium has been achieved.[44] Some pyridines have been selectively lithiated at C-2 *via* complexes with hexafluoroacetone;[45] complexation removes the lone pair (cf. section 5.5.1) and additionally provides inductive and chelation effects to assist the regioselective metallation. In practice, simple lithiopyridines are generally prepared by metal–halogen exchange (see below), however the presence of chlorine or fluorine, or other substituents which direct *ortho* metallation, allows direct lithiation (section 5.5.1).



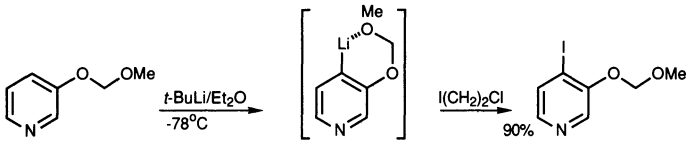
5.5 REACTIONS OF *C*-METALLATED PYRIDINES

5.5.1 Lithio derivatives

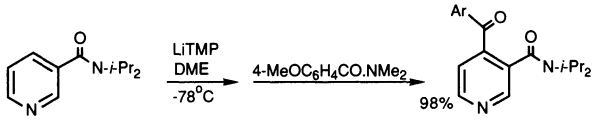
Pyridyl Grignard reagents are seldom used, being difficult to prepare by the usual methods; the corresponding lithium reagents are much more convenient and behave as typical organometallic nucleophiles,[46,47,48] thus for example, 3-bromopyridine undergoes efficient exchange with *n*-butyllithium in ether at −78°C. In the more basic THF as solvent, and at this temperature, the alkyllithium becomes more nucleophilic and only addition occurs, although the exchange can be carried out in THF at lower temperatures.[49] Even 2-bromo-6-methylpyridine can be converted into its lithio-derivative without deprotonation of the methyl.[50]



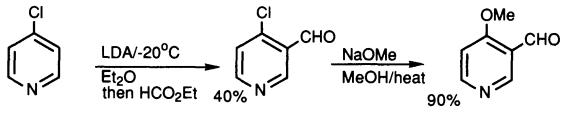
Lithiation of 2,5-dibromopyridine leads exclusively and efficiently to 2-bromo-5-lithiopyridine in a thermodynamically controlled process;[51] it has been suggested that the 2-pyridyl anion is destabilised by electrostatic repulsion between nitrogen lone pair and the adjacent anion;[43] this same factor is probably important in the greater difficulty found in generating 2,3-pyridyne (see section 5.3.2).



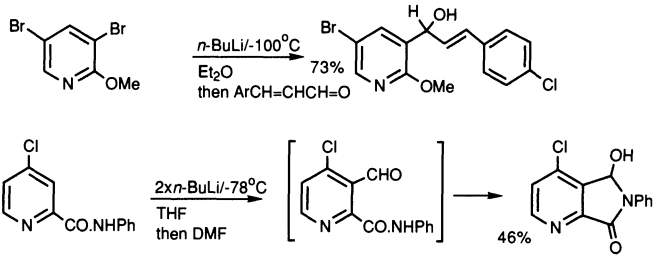
Chloro- or better, fluoropyridines undergo lithiation *ortho* to the halogen, 3-halopyridines reacting mainly at C-4,[52] however in the lithiation of methoxypyridines using mesityllithium, the 3-isomer metallates at C-2.[53] 3-Methoxymethoxypyridine,[54] 3-diisopropylaminocarbonyl-[55] and 3-*t*-butylcarbonylamino-[56] -pyridines all lithiate at C-4. Lithiation assisted by the dimethyloxazolidine group requires lithium 2,2,6,6-tetramethylpiperidide, otherwise C-4-addition of alkyllithium or Grignard occurs; subsequent aerial oxidation produces 4-alkylated derivatives efficiently.[57] The lithiated pyridines react with the normal range of electrophilic species, for example they are acylated by tertiary amides.[58]



The use of halogen to direct lithiation can be combined with the ability to subsequently displace the halogen with a nucleophile.[59]

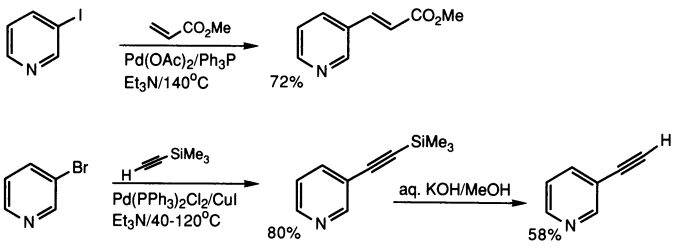


The combination of metal–halogen exchange with the presence of a directing substitutent can permit regioselective exchange;[60] the presence of two 1,3-related directing groups causes lithiation between the two groups.[61]

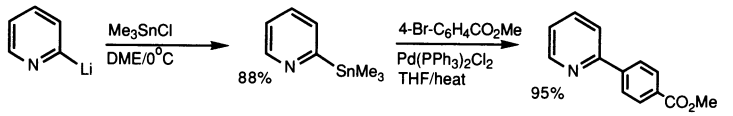


5.5.2 Palladium-catalysed reactions

Halopyridines take part in palladium-catalysed reactions, for example Heck,[62] carbonylation,[63] and coupling reactions, with, for example, alkynes.[64]



Couplings requiring pyridyl organometallic species are best achieved with boron, zinc, or tin compounds;[65] the last are available either by reaction of pyridyl halides with sodium trialkylstannate or, in the opposite sense, by the reaction of a pyridyllithium with chlorotrimethylstannane.[66]



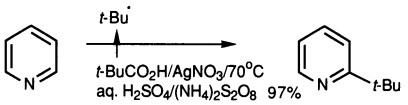
5.6 REACTIONS WITH RADICAL REAGENTS

5.6.1 Halogenation

At temperatures where bromine (500°C) and chlorine (270°C) are appreciably dissociated into atoms, 2- and 2,6-dihalopyridines are obtained *via* radical substitution.[67]

5.6.2 Carbon radicals

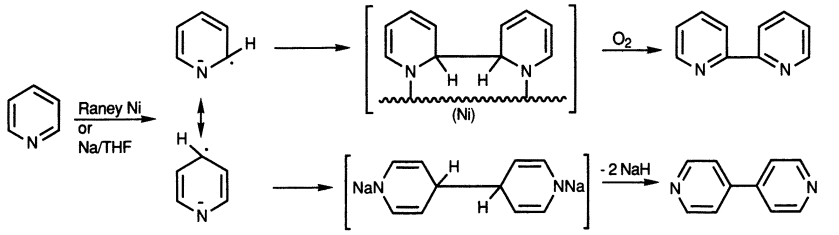
This same preference for α-attack is demonstrated by phenyl radical attack, but the exact proportions of products depend on the method of generation of the radicals.[68] Greater selectivity for phenylation at the 2- and 4-positions is found in pyridinium salts.[69]



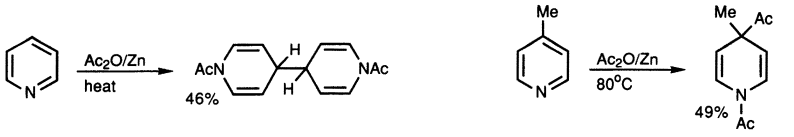
Of more preparative value are the reactions of nucleophilic radicals, such as $HOCH_2^{\bullet}$ and $R_2NCO^{\bullet}$ which can be easily generated under mild conditions. These substitutions are carried out on the pyridine protonic salt, which provides both increased reactivity and selectivity for an α-position; the process is known as the Minisci reaction (cf. section 2.4.1).[70] It is accelerated by electron-withdrawing substituents.

5.6.3 Dimerisation

Both sodium and nickel bring about 'oxidative' dimerisations,[71] despite the apparently 'reducing' conditions, the former giving 4,4′-dipyridyl (strictly 4,4′-bipyridine) and the latter 2,2′-dipyridyl.[72] Each reaction is considered to involve the same anion-radical resulting from transfer of an electron from metal to heterocycle, and the species has been observed by ESR spectroscopy when generated by SET from LDA.[73] In the case of nickel, the 2,2′-mode of dimerisation may be favoured by chelation to the metal surface. Bipyridyls are important for the preparation of Paraquat-type weedkillers.



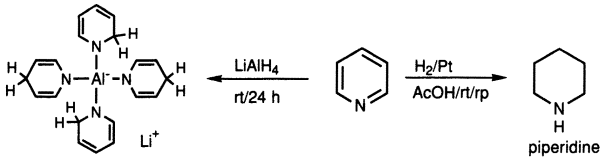
Intermediate, reduced dimers can be trapped under milder conditions,[74] and reduced monomers when the pyridine carries a 4-substituent.[75]



5.7 REACTIONS WITH REDUCING AGENTS

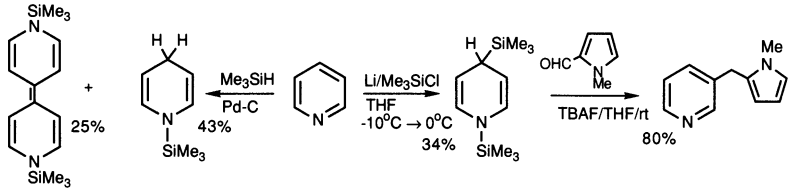
Pyridines are much more easily reduced than benzenes, for example catalytic reduction proceeds easily at atmospheric temperature and pressure, usually in weakly acidic solution but also in dilute alkali with Ni–Al.[76]

Of the hydride reagents, sodium borohydride is without effect on pyridines, though it does reduce pyridinium salts (see section 5.13.1), whereas lithium aluminium hydride effects the addition of one hydride equivalent to pyridine and thus the formation of a mixed dihydropyridines aluminate, which has been used as a selective reducing agent.[77]



Sodium in ethanol treatment generally gives mixtures in which the 1,2,5,6-tetrahydropyridine is predominant, whereas sodium in liquid ammonia, in the presence of ethanol, affords the 1,4-dihydropyridine.[78] Metal/acid combinations, which in other contexts bring about reduction of iminium groups, are without effect on pyridines.

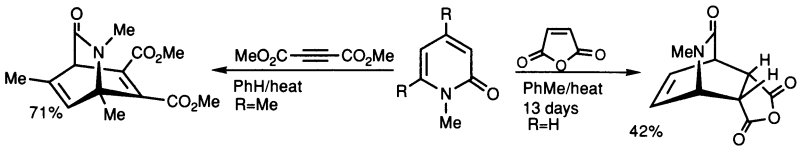
The combination lithium/chlorotrimethylsilane produces a 1,4-dihydro doubly silylated product the enamine character in which can be utilised for the introduction of 3-alkyl groups *via* reaction with aldehydes.[79] Trimethylsilane in the presence of palladium gives 1,4-dihydro-1-trimethylsilylpyridine, together with silylated dimer.[80]



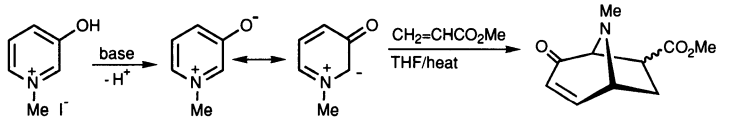
4-Pyridones are reduced to 2,3-dihydro-derivatives by lithium in liquid ammonia.[81]

5.8 ELECTROCYCLIC REACTIONS (GROUND STATE)

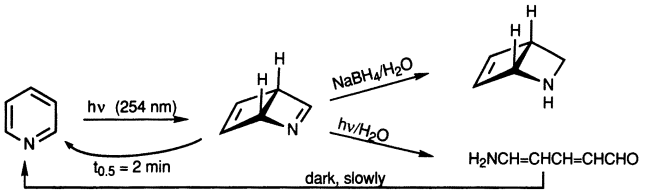
There are no reports of thermal electrocyclic reactions involving simple pyridines; 2-pyridones however participate as 4π components in Diels-Alder additions, especially under high pressure.[82]



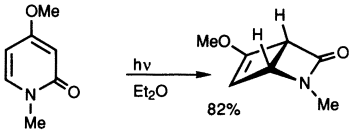
The quaternary salts of 3-hydroxypyridines are converted by mild base into zwitterionic, organic-solvent-soluble species for which no neutral canonical form can be drawn. These 3-oxidopyridiniums undergo a number of dipolar cycloaddition reactions, especially across the 2,6-positions.[83]



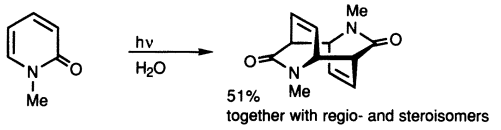
5.9 PHOTOCHEMICAL REACTIONS



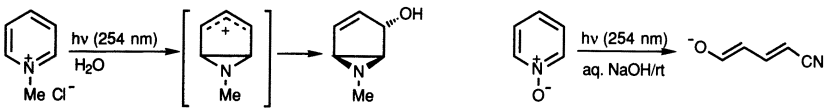
Ultraviolet irradiation of pyridines can produce highly strained species which may lead to isomerised pyridines or can be trapped. From pyridines[84] and from 2-pyridones[85] 2-azabicyclo[2.2.0]hexadienes and -hexenones are obtained; in the case of pyridines these are usually unstable and revert thermally to the aromatic heterocycle, but 2-alkylpyridines with an electron-withdrawing group on the alkyl substituent give stable products by base-catalysed proton shift.[86] Pyridone-derived bicycles are relatively stable, 4-alkoxy- and -acyloxypyridones are converted in particularly good yields.



Irradiation of *N*-methyl-2-pyridone in aqueous solution produces a mixture of regio- and stereoisomeric dimers.[87]

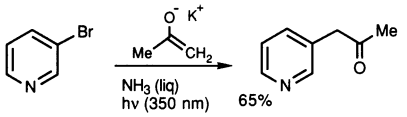


The photoreactions of quaternary pyridinium salts in water give 6-azabicyclo[3.1.0]hex-3-en-2-ols.[88] On photolysis of pyridine *N*-oxides in alkaline solution, ring opening produces cyano-dienolates.[89]



The displacement of bromine, in the relative order 2 > 3 > 4, by an enolate or related anion under irradation, known as an $S_{RN}1$ process (**S**ubstitution **R**adical **N**ucleophilic, unimolecular), involves photostimulated transfer of an electron from the enolate to the heterocycle, loss of bromide to generate a pyridyl radical which then combines with a second mol of enolate, generating the radical anion of product, transfer of an electron from which sustains the chain process.[90] The

equivalent photo-catalysed displacement of bromide by hydroxide gives 3-hydroxypyridine.[91] Irradiation of 3-iodopyridine generates the 3-pyridinyl radical which will effect radical substitution of heterocycles such as furan, thiophene and pyrrole.[92]

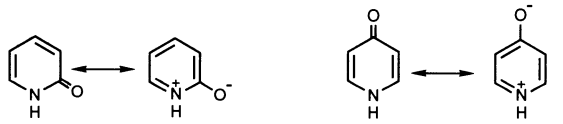


5.10 OXY- AND AMINOPYRIDINES

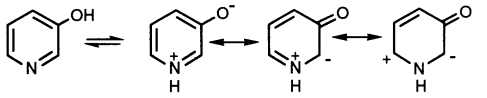
5.10.1 Structure

The three oxy-pyridines are subject to tautomerism involving hydrogen interchange between oxygen and nitrogen, but again with a significant difference between α- and γ- on the one hand and β-isomers on the other.

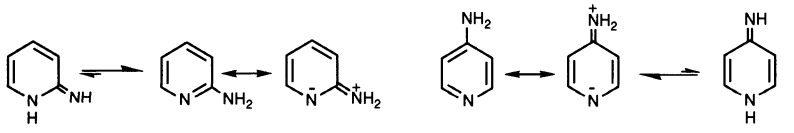
Under all normal conditions, α- and γ-isomers exist almost entirely in the carbonyl tautomeric form, and are accordingly known as pyridones; the hydroxy tautomers are detected in significant amounts only in very dilute solutions in non-polar solvents like petrol, or in the gas phase where, for the α-isomer, 2-hydroxypyridone is actually the dominant tautomer by 2.5 : 1.[93] The polarised pyridone form is favoured by solvation.[94]



3-Hydroxypyridine exists in equilibrium with a corresponding zwitterionic tautomer, the exact ratio depending on solvent.



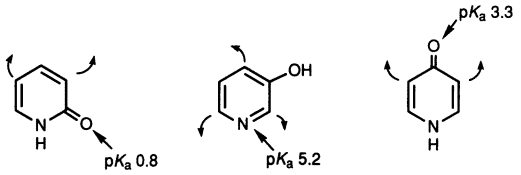
All three aminopyridines exist in the amino form; the α- and γ-isomers are polarised in a sense opposite to that in the pyridones.



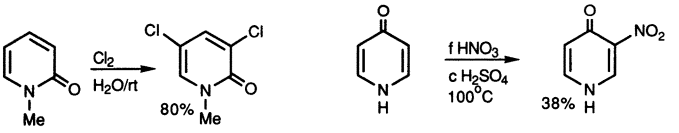
5.10.2 Reactions of pyridones

5.10.2.1 *Electrophilic addition and substitution*

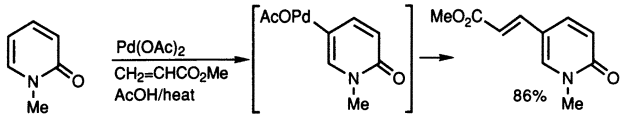
3-Hydroxypyridine protonates on nitrogen, with a typical pyridine pK_a of 5.2, the pyridones however are much less basic, and both, like amides, protonate on oxygen.[95] Electrophilic substitution at carbon can be effected more readily with the three oxy-pyridines than with pyridine itself, and it occurs *ortho* and *para* to the oxygen function, acid catalysed exchange of 4-pyridone in deuterium oxide, for example, giving 3,5-dideuterio-4-pyridone, *via* *C*-protonation of the neutral pyridone.[96]



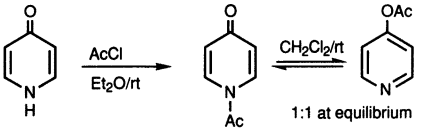
The pyridones can be readily halogenated, nitrated and sulfonated. Substitutions in acidic solutions usually proceed *via* attack on the free pyridone,[97] but in very strong acid, where there is almost complete protonation, 4-pyridone undergoes a slower nitration, *via* the *O*-protonated salt, but with the same regioselectivity.[98]



N-Methyl-2-pyridone undergoes electrophilic palladation allowing a subsequent direct coupling *via* a modified Heck reaction (cf. section 2.7.2.1).[99]

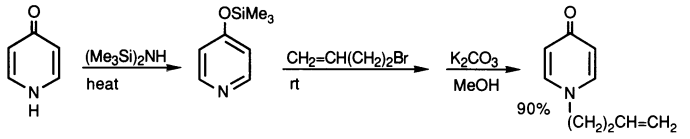


An apparent exception to the reactivity pattern described above is the reaction of 4-pyridone with acid chlorides producing *N*-acyl derivatives. 1-Acetyl-4-pyridone subsequently equilibrates in solution affording a mixture with 4-acetoxypyridine.[100] *N*-Acyl-4-pyridones can serve as acylating agents for alcohols and thiols.[101]

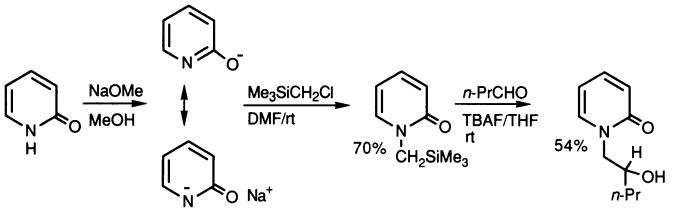


5.10.2.2 *Deprotonation and reaction of salts*

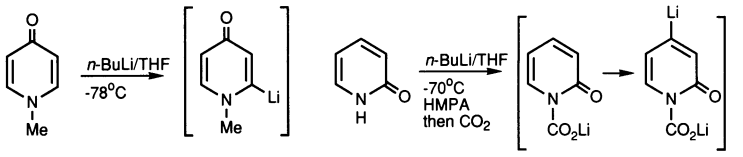
N-Unsubstituted pyridones are acidic, with pK_a values of about 11 for deprotonation giving mesomeric anions. These ambident anions can be alkylated on either oxygen or nitrogen, producing alkoxypyridines or *N*-alkylpyridones, respectively, the relative proportions depending on the reaction conditions.[102] A clean method for the synthesis of *N*-alkylated 4-pyridones is to convert the pyridone first into the *O*-trimethylsilyl ether[103] which can then be reacted selectively at nitrogen, subsequent removal of the silicon giving the *N*-alkylpyridone.[81]



Alkylation of the sodium salt of 2-pyridone with chloromethyltrimethylsilane allows subsequent introduction of further groups on to the nitrogen substituent.[104]



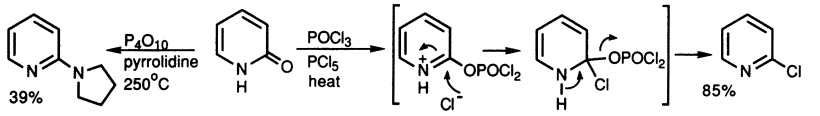
Aqueous sodium hydroxide at 100°C causes exchange of the α-protons in 1-methyl-4-pyridone[105] and synthetically useful metallation at an α-position can be effected with *n*-butyllithium;[106] 1-methyl-2-pyridone, in contrast, metallates on the methyl,[107] but 2-pyridones, protected by carboxylation at nitrogen, lithiate at C-4.[108] The metallated *N*-methylpyridones tend to dimerise in the sense that they add to free pyridone in a Michael fashion. Metallation then condensation at side chain methyl in a pyridone is also known.[109]



5.10.2.3 *Replacement of oxygen*

The conversion of the carbonyl group in pyridones into a leaving group has a very important place in the chemistry of these compounds, the most frequently encountered examples involving reaction with phosphorus oxychloride and/or pentachloride leading to the chloropyridine, *via* an assumed chloro-phosphate

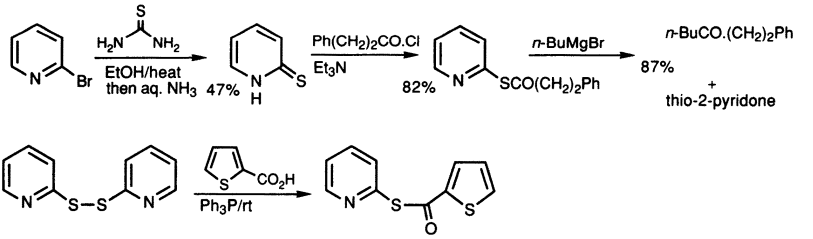
intermediate. Similarly, treatment with a secondary amine and phosphorus pentoxide, or of 2- or 4-trimethylsilyloxypyridines with secondary amines produces aminopyridines.[103]



The usual way to remove oxygen completely from a pyridone is by conversion, as described, into halogen followed by catalytic hydrogenolysis;[110] alternatively, reaction of the pyridone salt with 5-chloro-1-phenyltetrazole then hydrogenolysis of the resulting ether can be used.[111]

5.10.2.4 *Thio-2-pyridone*

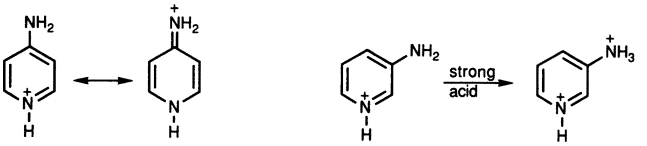
Thio-2-pyridone[112] can be converted efficiently into 2-acylthiopyridines by reaction with an acid chloride in the presence of triethylamine; the combination of an acid, triphenylphosphine, and 2,2′-pyridyldisulfide also produces such thioesters.[113] These 2-acylthiopyridines react smoothly with Grignard reagents giving ketones, the thiopyridone anion being the leaving group. 2-Acylthiopyridines have also been used as acyl-transfer reagents to nitrogen, in peptide synthesis,[114] and to oxygen in medium-sized lactone construction.[115]



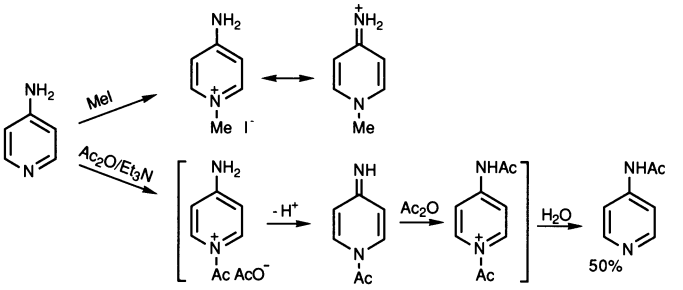
5.10.3 Reactions of aminopyridines

5.10.3.1 *Electrophilic addition and substitution*

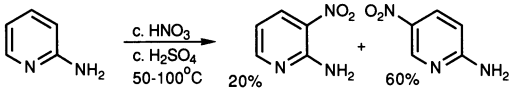
The three aminopyridines are all more basic than pyridine itself and form crystalline salts by protonation at the ring nitrogen. The α- and γ-isomers are monobasic only, because charge delocalisation over both nitrogen atoms, in the manner of an amidinium cation, prevents the addition of a second proton. The effect of the delocalisation is strongest in 4-aminopyridine (pK_a 9.1) and much weaker in 2-aminopyridine (7.2). Delocalisation is not possible for the β-isomer which thus can form a di-cation in strong acid (pK_a values 6.6 and −1.5).[116]



Whereas alkylation, irreversible at room temperature, gives the product of kinetically controlled attack at the most nucleophilic nitrogen, the ring nitrogen,[117] acetylation gives the product of reaction at a side-chain amino group. The acetylaminopyridine which is isolated probably results from side-chain deprotonation of an *N*-acylpyridinium salt followed by side-chain *N*-acylation, with loss of the ring-*N*-acetyl during aqueous work-up.

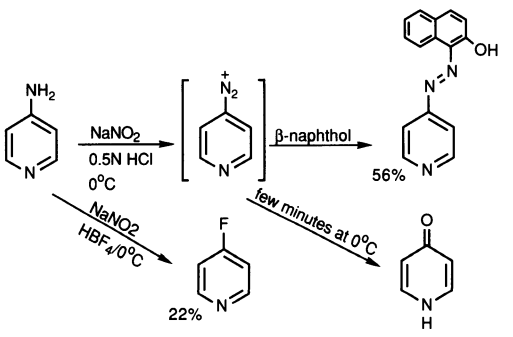


Nitration of aminopyridines is relatively easy, with selective attack of 2- and 4-isomers at β-positions. Study of dialkylaminopyridines showed reaction to take place *via* the salts.[118]



5.10.3.2 *Reactions of the amino group*

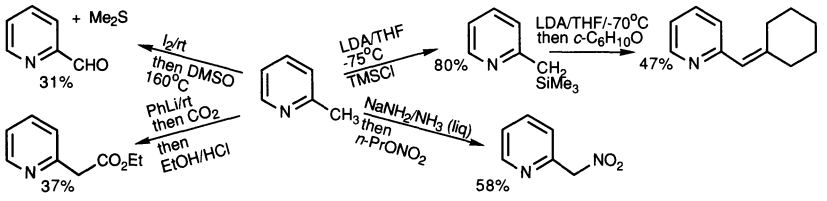
β-Aminopyridines give normal diazonium salts on reaction with nitrous acid, but with α- and γ-isomers, unless precautions are taken, the corresponding pyridones are produced *via* easy hydrolysis,[119] water addition at the diazonium-bearing carbon being rapid.[120] With care, this same susceptibility to nucleophilic displacement can be harnessed in effecting Sandmeyer-type reactions without the use of copper.[119,121]



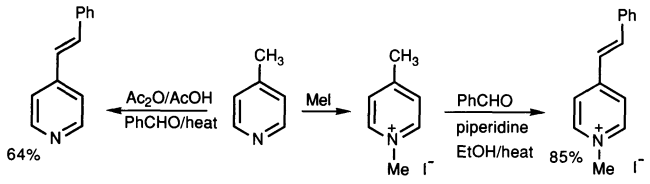
5.11 ALKYLPYRIDINES

The main feature of the reactivity of alkylpyridines is deprotonation of the alkyl group at the carbon adjacent to the ring. Measurements of side-chain-exchange in methanolic sodium methoxide, 4 : 2 : 3, 1800 : 130 : 1,[122] and of pK_a values in THF[123] each have the γ-isomer more acidic than the α-, both being much more acidic than the β-isomer, though the actual carbanion produced in competitive situations can depend on both the counterion and the solvent. Alkyllithiums selectively deprotonate an α-methyl where amide bases produce the more stable γ-anion.[124] The much greater ease of deprotonation[125] of the α- and γ-isomers is related to mesomeric stabilisation of the anion involving the ring nitrogen, not available to the β-isomer for which there is only inductive facilitation, but deprotonation can be effected at a β-methyl under suitable conditions;[126] the difference in acidity between 2- and 3-methyl groups allows selective reaction at the former.[127]

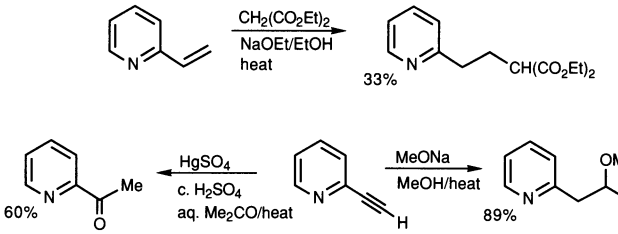
The 'enaminate' anions produced by deprotonating α- and γ-alkylpyridines can participate in a wide range of reactions,[128] being closely analogous to enolate anions. Similar side-chain carbanion formation is seen in *ortho*- but not *meta*-nitrotoluene.



In the quaternary salts of alkylpyridines, the side-chain hydrogens are considerably more acidic and condensations can be brought about under quite mild conditions, the reactive species being an enamine;[129] side-chain deprotonation of *N*-oxides can also be achieved, though it can be complicated by ring-deprotonation at C-2.[130]

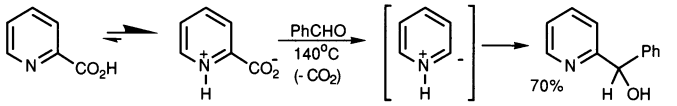


A further consequence of the stabilisation of carbanionic centres at pyridine α- and γ-positions is the facility with which vinylpyridines,[131] and alkynylpyridines, add nucleophiles, in Michael-like processes (mercury-catalysed hydration goes in the opposite sense[132]). Complimentarily, pyridin-2-yl- and 4-ylethyl esters, sulfides or sulfones can serve as protecting groups, being readily and mildly removed by pyridine quaternisation (iodomethane), causing elimination of the vinylpyridinium salt.[133]



5.12 PYRIDINE ALDEHYDES, KETONES, CARBOXYLIC ACIDS AND ESTERS

These compounds all closely resemble the corresponding benzene compounds in their reactivity because the carbonyl group cannot interact mesomerically with the ring nitrogen. The pyridine 2- (picolinic), 3- (nicotinic), and 4- (isonicotinic) acids exist almost entirely in their zwitterionic forms in aqueous solution; they are slightly stronger acids than benzoic acid. Decarboxylation of picolinic acids is relatively easy and results in the transient formation of the same type of ylid which is responsible for specific proton α-exchange of pyridine in acid solution (see section 5.1.2.1).[134] This transient ylid can be trapped by aromatic or aliphatic aldehydes in a reaction known as the Hammick reaction.[135] As implied by this mechanism, quaternary salts of picolinic acids also undergo easy decarboxylation.[136]

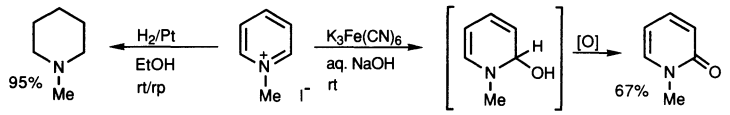


5.13 QUATERNARY PYRIDINIUM SALTS

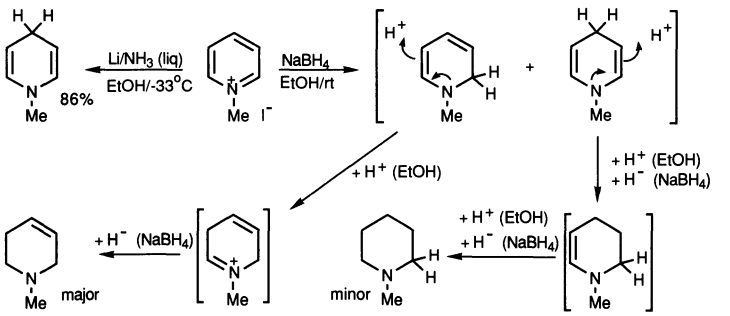
The main features of the reactivity of pyridinium salts are (i) the greatly enhanced susceptibility to nucleophilic addition and displacement at the α- and γ-positions, sometimes followed by ring opening and (ii) the easy deprotonation of α- and γ-alkyl groups (see also section 5.11).

5.13.1 Reduction and oxidation

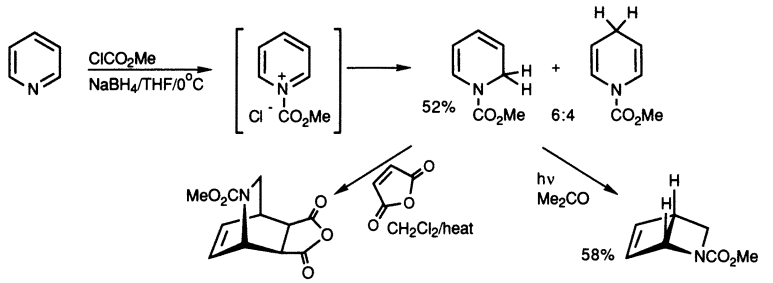
The oxidation of pyridinium salts[137] to pyridones by alkaline ferricyanide is presumed to involve a hydroxide adduct. 3-Substituted pyridinium ions are transformed into mixtures of 2- and 6-pyridones, for example oxidation of 1,3-dimethylpyridinium iodide gives a 9 : 1 ratio of 2- and 6-pyridones.



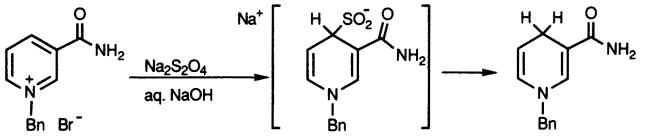
Catalytic reduction of pyridinium salts to piperidines is particularly easy; they are also susceptible to hydride addition by complex metal hydrides[138] or formate,[139] and lithium/ammonia reduction.[140] In the reduction with sodium borohydride in protic media the main product is a tetrahydro-derivative with the double bond at the allylic, 3,4-position. These cyclic allylamines are formed by initial hydride addition at C-2, followed by enamine β-protonation and a second hydride addition. Some fully reduced material is always produced and its relative percentage increases with increasing *N*-substitutent bulk, consistent with a competing mechanism having initial attack at C-4, generating a dienamine which can then undergo two successive proton-then-hydride addition steps. When 3-substituted pyridinium salts are reduced with sodium borohydride, 3-substituted-1,2,5,6-tetrahydropyridines result. Care must be taken to destroy amine-borane which can be present at the end of such reductions.[141] When 1,4-dihydro-1-methylpyridine and 1,2-dihydro-1-methylpyridine are equilibrated using strong base, the former predominates to the extent of approximately 9 : 1.[142]



N-Acyl, particularly *N*-alkoxycarbonylpyridiniums can be reductively trapped as dihydro-derivatives by borohydride;[143] no further reduction occurs because the immediate product is an enamide and not an enamine and therefore does not protonate.[144] The 1,2-dihydro-isomers, which can be produced essentially exclusively by reduction at −70°C in methanol, serve as dienes in Diels-Alder reactions. Irradiation causes conversion into 2-azabicyclo[2.2.0]hexenes; removal of the carbamate and *N*-alkylation gives derivatives which are synthons for unstable *N*-alkyldihydropyridines, and convertible into the latter thermally.[145]

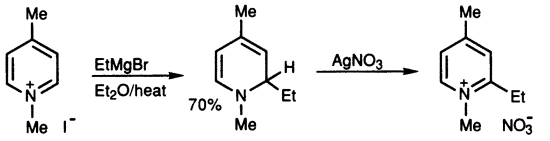


An important result, because of its relevance to nicotinamide coenzyme activity, is the specific reduction of 3-acylpyridinium salts to 1,4-dihydropyridines using sodium dithionite, the mechanism for which has addition of sulfur at C-4 as its first step.[146] 1,4-Dihydropyridines are normally air-sensitive, easily rearomatised molecules; the stability of 3-acyl-1,4-dihydropyridines is related to the conjugation between ring nitrogen and side-chain carbonyl group (see also Hantzsch synthesis, section 5.15.1.2).



5.13.2 Organometallic addition

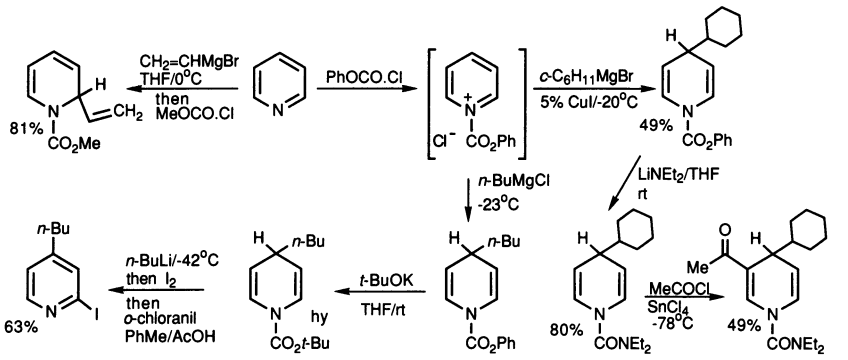
Organometallic reagents add very readily to *N*-alkyl-, *N*-aryl- and with important synthetic significance, *N*-acylpyridinium salts. In the simplest cases addition is to an α-carbon; the resulting 2-substituted-1,2-dihydropyridine can be handled and spectroscopically identified, with care, but more importantly can be easily oxidised to a 2-substituted pyridinium salt.[147]



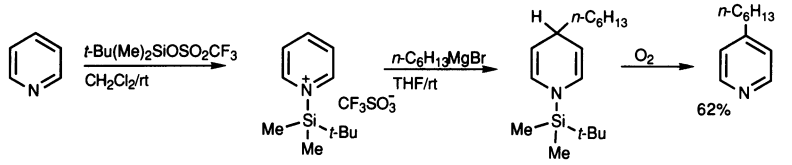
The great significance of the later discovery that exactly comparable additions to *N*-acylpyridinium cations, generated and reacted *in situ*, is that the dihydropyridines which result can be further manipulated if required and that during rearomatisation the *N*-substituent can be easily removed to give a substituted pyridine. It is worth noting the contrast to the use of *N*-acylpyridinium salts for reaction with alcohol, amine nucleophiles (section 5.1.1.7) when attack is at the carbonyl carbon; the use of an alkoxycarbonyl substituent in the present context aids this discrimination.

Generally, organometallic addition to *N*-alkoxycarbonylpyridinium salts[143]

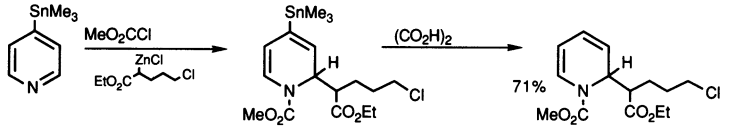
takes place at both 2- and 4-positions,[148] however higher selectivity for the 4-position can be achieved using copper reagents.[149,150] Indole, as the neutral molecule, reacts with *N*-benzoylpyridinium chloride at C-4,[151] but its anion will add to *N*-methylpyridinium salts having acyl groups at C-3 either at C-6 or at C-4, depending on the solvent.[152] High selectivity for the 2-position is found in the addition of phenyl,[153] alkenyl and alkynyl organometallics.[154] Examples of the further manipulation of dihydropyridines produced as above include introduction of substituents at a β-position, by acylation of the enamide,[150] and at an α-position, *via* 2-lithiation.[150]



Silylation at nitrogen with *t*-butyldimethylsilyl triflate, generates pyridinium salts which, because of the size of the *N*-substitutent, react with Grignard reagents exclusively at C-4;[155] montmorillonite-catalysed addition of silyl enol ethers to pyridines has a comparable effect in producing 1-trimethylsilyl-1,4-dihydropyridines carrying an acylalkyl substituent at C-4.[156]

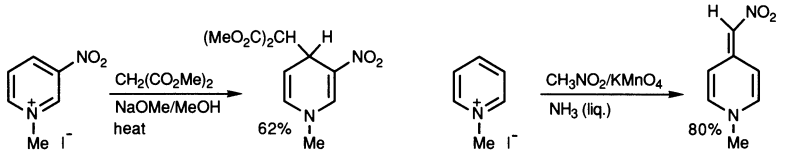


4-Substituents direct attack to an α-carbon;[157,158] the use of a removable 4-blocking group can be made the means for the production of 2-substituted isomers.[159]



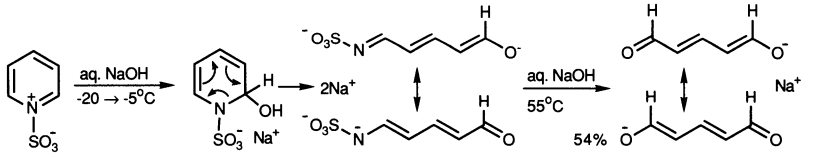
5.13.3 Other nucleophilic additions

There are a variety of examples of other nucleophiles adding to *N*-alkylpyridinium salts. A study[160] of reversible additions to 3-cyano-1-methylpyridinium iodide showed α-attack to be kinetically favoured but the γ-adduct to be the more thermodynamically stable. Similarly, in thermodynamically controlled processes, 1-methyl-3-nitropyridinium gives products resulting from addition at C-4 in which again there is stabilising conjugation between ring nitrogen and 3-substituent.[161] Products of γ-addition, even in 1-methyl- or -phenylpyridinium iodides, lacking a conjugating 3-substituent, can be trapped *via* attack by added oxidant.[162]

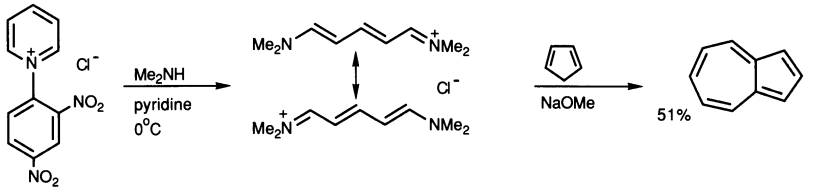


5.13.4 Nucleophilic addition followed by ring opening[163]

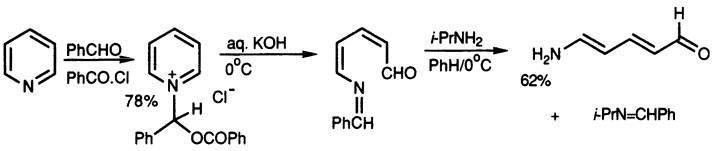
There are many examples of pyridinium salts, particularly, but not exclusively, those with powerful electron-withdrawing *N*-substituents, adding a nucleophile at C-2 and then undergoing a ring opening. Perhaps the classic example is addition of hydroxide to the pyridine–sulfur trioxide complex, which produces the sodium salt of glutaconaldehyde.[164]



Another well-known example is a synthesis of azulene which utilises the bis dimethylamine derivative of glutaconaldehyde produced with loss of 2,4-dinitroaniline from 1-(2,4-dinitrophenyl)pyridinium chloride.[165]

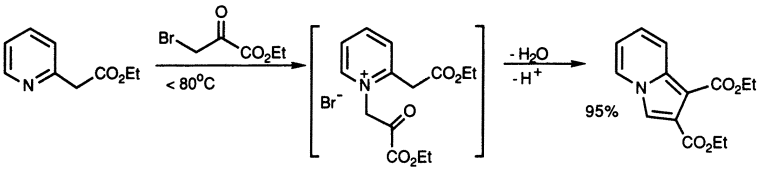


As a third example of nucleophilic addition then ring opening, it has even been possible to isolate the ring-opened 'hydrate' of pyridine.[166]

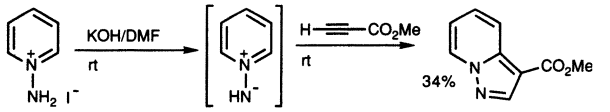


5.13.5 Cyclisations involving an α-position or an α-substituent

It is often possible to achieve cyclisation of pyridinium salts, in which the ring closure involves an α-substituent or the electrophilic nature of the α-position (see also section 5.1.1.8) and gives a neutral product. Reaction of ethyl pyridin-2-ylacetate with bromopyruvate affords a pyridinium salt which cyclises *via* an aldol condensation.[167]



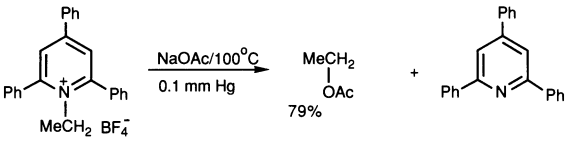
Pyridinium *N*-imide, the ylid produced by removal of a proton from 1-aminopyridinium iodide, serves as a 1,3-dipole and reacts with propiolate and fumarate to give bicyclic compounds.[168]



5.13.6 *N*-Dealkylation

The conversion of *N*-alkyl- or -arylpyridinium salts into the corresponding pyridine, i.e. the removal of the *N*-substitutent, is generally not an easy process, however triphenylphosphine[169] or simply heating the iodide salt[170] can work for metho-salts. The transfer of trityl from 1-triphenylmethyl-4-dimethylaminopyridinium chloride and of *t*-butyldimethylsilyl from 1-*t*-butyldimethylsilyl-4-dimethylaminopyridinium chloride are assumed in the use of the combinations DMAP/Ph_3CCl for *O*-tritylation and DMAP/*t*-Bu$(Me)_2SiCl$ for *O*-silylation.[171]

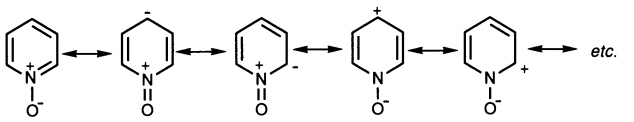
Pyridinium salts corresponding to 2,4,6-trisubstituted pyridines, which must be prepared by reacting a primary amine with 2,4,6-trisubstituted pyrylium perchlorates (see section 8.1.2.2) are attacked by a variety of nucleophiles with transfer of the *N*-substituent to the attacking reagent and as such are convenient alkylating agents,[172] and, recalling that the precursor to the pyridinium salt is the primary amine, the sequence also represents the overall transformation of a primary amine into a variety of derivatives.



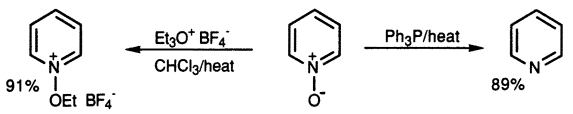
5.14 PYRIDINE *N*-OXIDES[173]

The reactions of pyridine *N*-oxides are of great interest,[174] differing significantly from those of both neutral pyridines and pyridinium salts.

A striking difference between pyridines and their *N*-oxides is the much greater susceptibility of the latter to electrophilic nitration. This can be understood in terms of mesomeric release from the oxide oxygen, and is strictly parallel to electron release and increased reactivity towards electrophilic substitution in phenols and phenoxides. One can find support for this rationalisation by a comparison of the dipole moments of trimethylamine and its *N*-oxide, on the one hand, and pyridine and its *N*-oxide, on the other: the difference of 2.03 D for the latter pair is much smaller than the 4.37 D found for the former. The smaller difference signals significant contributions from those canonical forms in which the oxygen is neutral and the ring negatively charged. Clearly, however, the situation is subtle, as those contributors carrying formal positive charges on α- and γ-carbons suggest a polarisation in the opposite sense and thus an increased susceptibility to nucleophilic attack too, compared with the neutral pyridine, and this is indeed found to be the case. Summarising: the *N*-oxide function in pyridine *N*-oxides serves to facilitate, on demand, both electrophilic and nucleophilic addition to the α- and γ-positions.

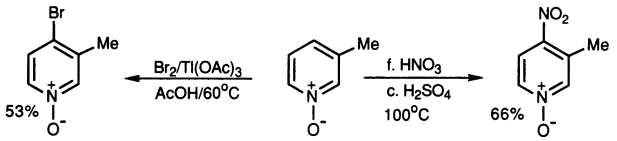


Many methods are available for the removal of oxygen from *N*-oxides: samarium iodide, chromous chloride, stannous chloride with low-valent titanium, ammonium formate with palladium, and catalytic hydrogenation all do the job at room temperature.[175] The most frequently used methods have involved oxygen transfer to trivalent phosphorus[173] or divalent sulfur.[176]

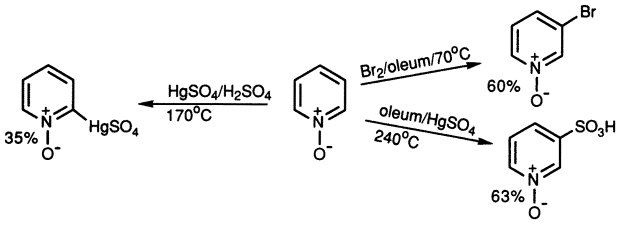


5.14.1 Electrophilic addition and substitution

Pyridine *N*-oxides protonate and are alkylated at oxygen; stable salts can be isolated in some cases.[177] Hot aqueous sodium hydroxide treatment of alkoxypyridinium salts produces aldehydes corresponding to the alkoxy substituent.[178]



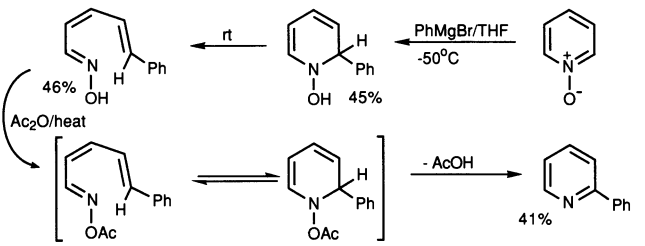
Electrophilic nitration and bromination of pyridine *N*-oxides can be controlled to give 4-substituted products[179] by way of attack on the free *N*-oxide.[180] Under conditions where the *N*-oxide is *O*-protonated, substitution follows the typical pyridine/pyridinium reactivity pattern, thus in fuming sulfuric acid bromination shows β-regioselectivity;[181] mercuration, however, takes place at the α-position.[182]



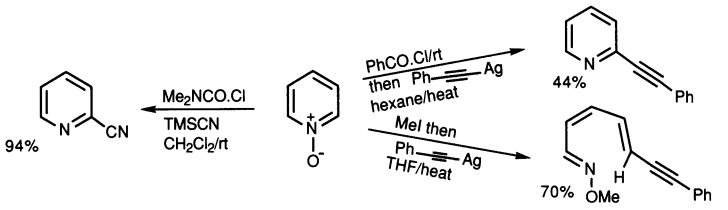
5.14.2 Nucleophilic addition and substitution

The *N*-oxide function enhances the rate of nucleophilic displacement of halogen from α- and γ-positions. The relative rates 4 > 2 > 3 found for pyridines are echoed for the *N*-oxides, but interestingly altered to 2 > 4 > 3 in methiodides.[183]

Grignard reagents add to pyridine *N*-oxide forming adducts, which can be characterised from a low temperature reaction, but which at room temperature undergo disrotatory ring opening, the isolated product being an acyclic, unsaturated oxime. Heating with acetic anhydride brings about rearomatisation, *via* electrocyclic ring closure rendered irreversible by the loss of acetic acid.[184]



Comparable addition/ring openings can be observed with 1-alkoxypyridiniums,[185,186] however prior acylation at the *N*-oxide oxygen before addition of alkyl or aryl Grignard or acetylide leads through to 2-substituted-pyridines.[186,187]

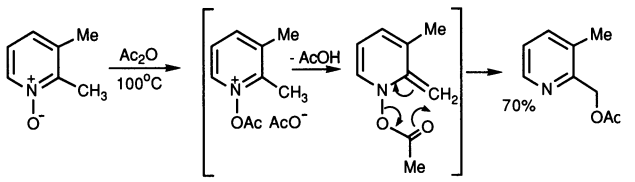


Very clean conversions of pyridine *N*-oxide into 2-cyanopyridine on prior conversion of oxide into silyloxy or carbamate,[188] displace earlier methods which utilised *N*-alkoxypyridinium salts.[189]

5.14.3 Rearrangements

A range of synthetically useful rearrangements convert pyridine *N*-oxides into variously substituted pyridines in which an α-(γ-)position, or an α-substitutent, has been modified.

2-Methylpyridine *N*-oxides react with acetic anhydride and produce 2-acetoxymethylpyridines; repetition of the sequence affords 2-aldehydes after hydrolysis.[190] The mechanism[191] of the rearrangement would seem to be most simply explained by invoking an electrocyclic sequence.



In the absence of a 2-substitutent, reaction with thionyl chloride or with acetic anhydride leads to the formation of 2- and 4-chloro- or 2-acetoxypyridines. Mechanistically, electrophilic addition to oxide is followed by nucleophilic addition to an α- or γ-position, the process being completed by an elimination.[173]

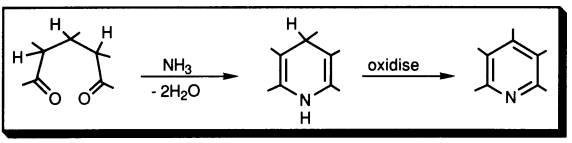
5.15 SYNTHESIS OF PYRIDINES

5.15.1 Ring synthesis

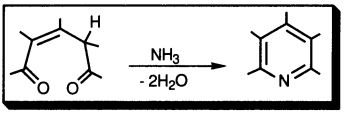
There are very many ways of achieving the synthesis of a pyridine ring; the following section describes the main general methods.

5.15.1.1 *From 1,5-dicarbonyl compounds and ammonia*

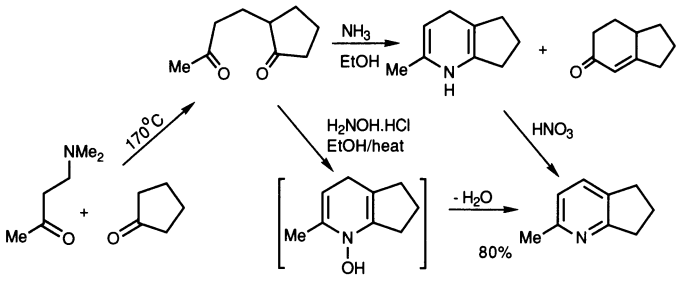
Ammonia reacts with 1,5-dicarbonyl compounds to give 1,4-dihydropyridines which are easily dehydrogenated to pyridines.



With unsaturated 1,5-dicarbonyl compounds, or their equivalents (e.g. pyrylium ions), ammonia reacts to give pyridines directly.

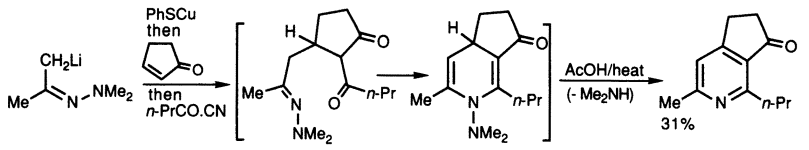


1,5-Diketones are accessible *via* a number routes, classically by Michael addition of enolate to enone (or precursor Mannich base[192]) or by ozonolysis of a cyclopentene precursor, or more recently by reaction of silyl enol ethers with 3-methoxyallylic alcohols.[193] They react with ammonia, with loss of two mol equivalents of water to produce a cyclic bis-enamine, i.e. a 1,4-dihydropyridine, which is generally unstable but can be easily and efficiently dehydrogenated to the aromatic heterocycle.

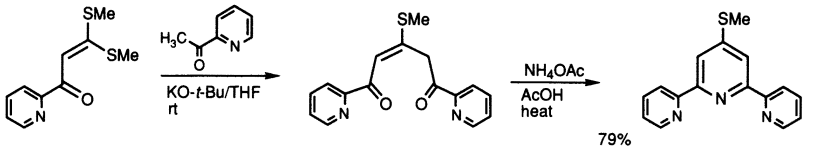


The oxidative final step can be neatly avoided by the use of hydroxylamine,[194] instead of ammonia, when a final 1,4-loss of water produces the aromatic heterocycle. In an extension of this concept, the construction of a 1,5-diketone equivalent by tandem Michael addition of dimethylhydrazone anion to

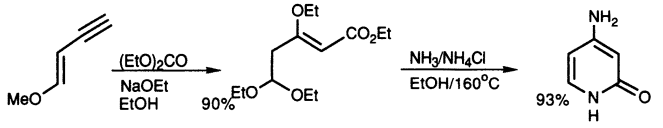
an enone, then acylation, has loss of dimethylamine from nitrogen as the final aromatisation step.[195]



It follows that the use of an unsaturated 1,5-dicarbonyl compound will also afford aromatic pyridine directly; a number of methods are available for the assembly of the unsaturated diketone, including the use of pyrylium ions or α-pyrones[196] (see chapter 8) as synthons, or the alkylation of an enolate with a 3,3-bismethylthio-enone.[197]



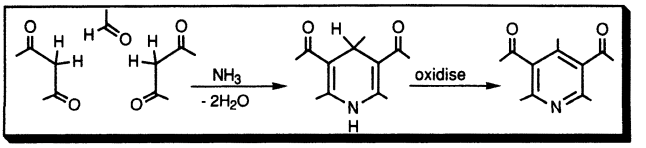
When one of the carbonyl carbons is at the oxidation level of acid (as in a 2-pyrone, section 8.2) then the product, reflecting this oxidation level, is a 2-pyridone.[198] Similarly, 4-pyrones (section 8.2) react with ammonia and primary amines to give 4-pyridones.[199]



When one of the the 'carbonyl' units is actually a nitrile, then a 2-aminopyridine results.[200]

5.15.1.2 *From an aldehyde, two equivalents of a 1,3-dicarbonyl compound, and ammonia*

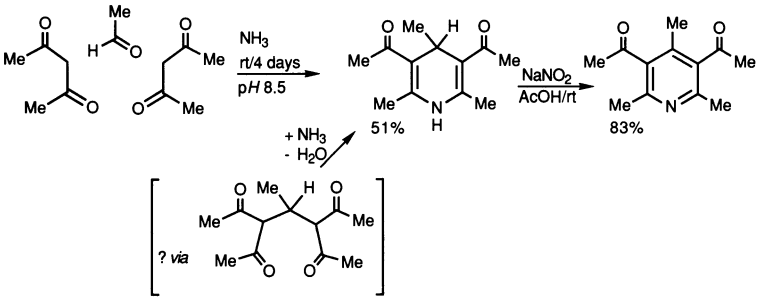
Symmetrical 1,4-dihydropyridines, which can be easily dehydrogenated, are produced from the interaction of ammonia, an aldehyde, and two equivalents of a 1,3-dicarbonyl compound which must have a central methylene.



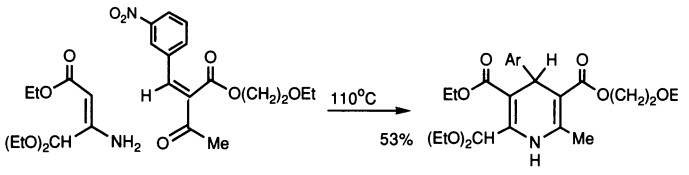
The Hantzsch synthesis[201]

The product from the classical Hantzsch synthesis is necessarily a symmetrically substituted 1,4-dihydropyridine since two mol equivalents of the one dicarbonyl component are utilised, the aldehyde carbonyl carbon becoming the pyridine C-4. The precise sequence of intermediate steps is not known for certain, and may indeed vary from case to case, for example the ammonia may become involved early or late, but a reasonable sequence would be aldol condensation followed by Michael addition generating, *in situ*, a 1,5-dicarbonyl compound.

The 1,4-dihydropyridines produced in this approach, carrying conjugating substituents at each β-position, are stable, and can be easily isolated before dehydrogenation; classically the oxidation has been achieved with nitric acid, or nitrous acid, but other oxidants such as ceric ammonium nitrate, cupric nitrate on montmorillonite, and manganese dioxide on bentonite also all achieve this objective smoothly.[202] It is a corollary that 'Hantzsch esters' can be viewed as reducing agents; they have selectivity for the carbon–carbon double bond in a nitroalkene.[203]

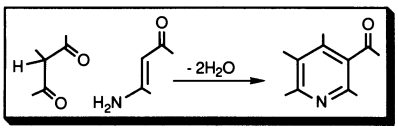


Unsymmetrical 1,4-dihydropyridines can be produced by conducting the Hantzsch synthesis in two stages, i.e. by making the (presumed) aldol condensation product separately, then reacting with ammonia and a different 1,3-dicarbonyl component, or an enaminoketone, in a second step.[204]



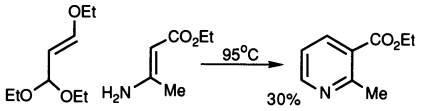
5.15.1.3 *From 1,3-dicarbonyl compounds and 3-amino-enones or -nitriles*

Pyridines are formed from the interaction between a 1,3-dicarbonyl compound and a 3-amino-enone or 3-aminoacrylate; 3-cyano-2-pyridones result if cyanoacetamide is used instead of an amino-enone.



This approach, in its various forms, is probably the most versatile and useful since it allows the construction of unsymmetrically substituted pyridines from relatively simple precursors. 3-Amino-enones or 3-amino-acrylates can be prepared by the straightforward reaction of ammonia with a 1,3-diketone or a 1,3-keto-ester. Again, in this pyridine ring construction, intermediates are not isolated and it is difficult to be sure of the exact sequence of events.

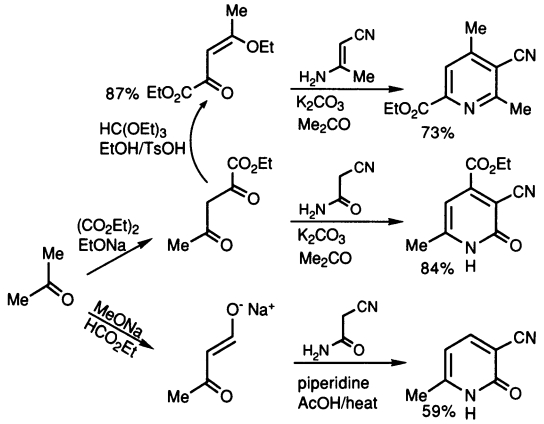
The simplest 1,3-dicarbonyl compound, malondialdehyde, is too unstable to be useful, but its readily available acetal enol ether can be used instead.[205]



The Guareschi synthesis

The variation which makes use of cyanoacetamide as the nitrogen-containing component leads to 3-cyano-2-pyridones, from which the carbonyl group and/or the cyano group can be subsequently removed.

Providing the two carbonyl groups are sufficiently different in reactivity, only one of the two possible isomeric pyridine/pyridone products is formed *via* reaction of the more electrophilic carbonyl group with the central carbon of the 3-amino-enone, 3-aminoacrylate, or cyanoacetamide.[206,207]

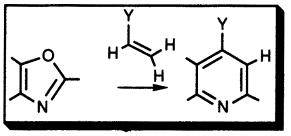


Variations include the use of yne-ones, when conjugate addition of the cyanoacetamide controls the regiochemistry of reaction,[208] and 3-alkoxy-enones (i.e. the enol ethers of 1,3-diketones) when comparably, the initial Michael-type

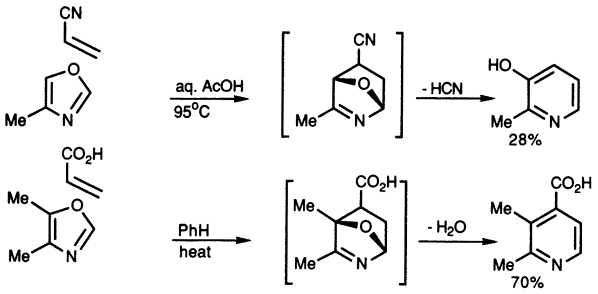
interaction dictates the regiochemistry.[206,209] Using $H_2NCO.CH_2C(NH_2)=N^+H_2$ Cl^- instead of cyanoacetamide gives 2-aminopyridine-3-carboxamides.[210]

5.15.1.4 *By cycloadditions*

Various electrocyclic additions, with subsequent extrusion of a small molecule, have been used to construct pyridines: addition to oxazoles is one of these.

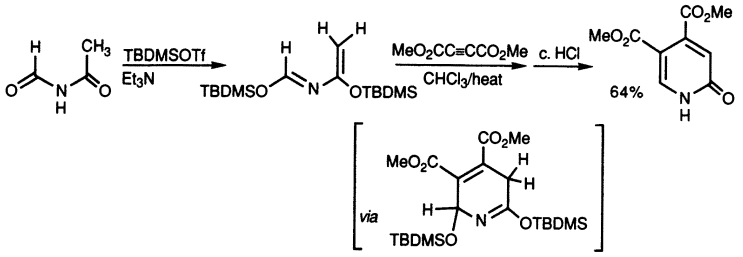


A number of 6π cycloadditions, some with inverse electron demand, have been developed into useful means for the construction of pyridines. The first of these was the addition of a dienophile to an oxazole; sometimes the oxazole oxygen is retained (giving 3-hydroxypyridines) and sometimes it is lost.[211]



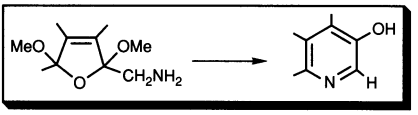
1,2,4-Triazines, acting as inverse electron demand dienes, add to enamines, and following extrusion of nitrogen and loss of amine, a pyridine is produced (section 25.2.1).[212]

The *O,O'*-bis-*t*-butyldimethylsilyl derivative of an imide serves as an azadiene in reaction with dienophiles; 2-pyridones are the result, following desilylation.[213]

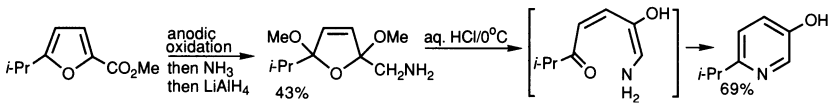


5.15.1.5 *From furans*

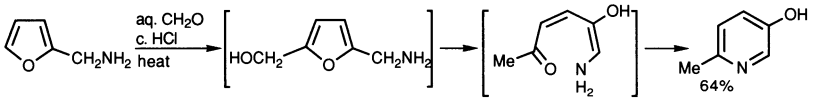
2-Furfurylamines can be converted *via* ring-opening ring-closure sequences, for example through 2,5-dimethoxy-2,5-dihydrofurans, into 3-hydroxypyridines.



Ring-opening and reclosure processes using furans include several significant methods for the construction of pyridines. 2,5-Dihydro-2,5-dimethoxyfurans (see section 15.1.4) carrying as side-chain an aminoalkyl group, give rise to 3-hydroxypyridines.[214]

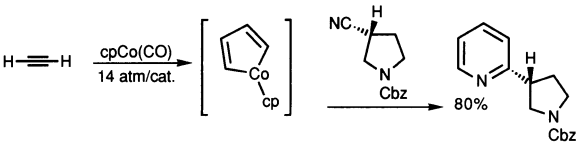


Furfurylamines react with formaldehyde, directly,[215] (or with an aromatic aldehyde *via* 5-lithiation after *N*-protection[216]) to give 3-hydroxy-6-substituted pyridines.



5.15.1.6 *Miscellaneous methods*

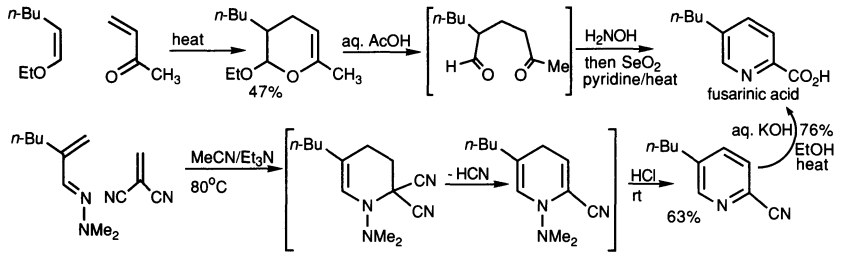
Many alkylpyridines are manufactured commercially by chemically complex processes which often produce them as mixtures. A good example is the extraordinary *Chichibabin synthesis*, in which paraldehyde and ammonium hydroxide react together at 230°C under pressure to afford 52% of 5-ethyl-2-methylpyridine; so here, four mol equivalents of acetaldehyde and one of ammonia combine.[217] Also of commercial significance is the cobalt-catalysed interaction of a nitrile and acetylene.[218]



5.15.2 Examples of notable syntheses of pyridine compounds

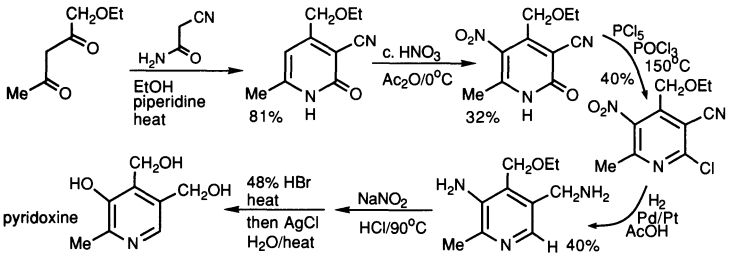
5.15.2.1 *Fusarinic acid*

Fusarinic acid is a mould metabolite with antibiotic and antihypertensive activity. Two syntheses of this substance employ cycloadditions, the earlier[219] as a means to produce a 1,5-diketone, and the second[220] to generate a 1-dimethylamino-1,4-dihydropyridine.



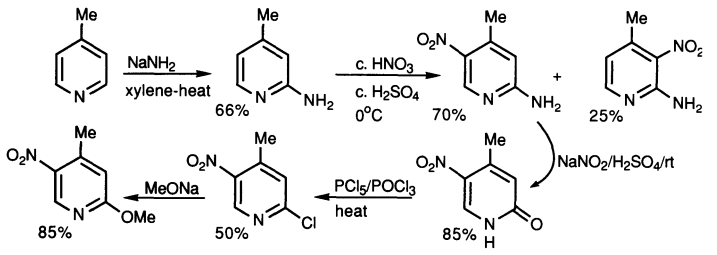
5.15.2.2 *Pyridoxine*

Pyridoxine, vitamin B_6, has been synthesised by several routes, including one which utilises a Guareschi ring synthesis, as shown below.[221]



5.15.2.3 *2-Methoxy-4-methyl-5-nitropyridine*

2-Methoxy-4-methyl-5-nitropyridine is an intermediate used in a synthesis of porphobilinogen (section 13.18.2.1).



REFERENCES FOR CHAPTER 5

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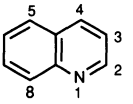
EXERCISES FOR CHAPTER 5

1. Suggest a structure for the products: (i) $C_7H_8N_2O_3$ produced by treating 3-ethoxypyridine with $fHNO_3$/c. H_2SO_4 at 100°C, (ii) $C_6H_4BrNO_2$ produced by reaction of 4-methylpyridine first with Br_2/H_2SO_4/oleum then with hot $KMnO_4$.
2. Deduce a structure for the product $C_9H_{15}N_3$ produced by reacting pyridine with the potassium salt of $Me_2N(CH_2)_2NH_2$.
3. Deduce structures for the product formed by (i) reacting 2-chloropyridine with (a) hydrazine → $C_5H_7N_3$, (b) water → C_5H_5NO; (ii) 4-nitropyridine heated with water at 60°C → C_5H_5NO.
4. Deduce structures for the products formed in turn by reacting 4-chloropyridine with (i) sodium methoxide → C_6H_7NO, A, this with iodomethane → $C_7H_{10}INO$, then this heated at 185°C → C_6H_7NO, isomeric with A.
5. Treatment of 4-bromopyridine with $NaNH_2$ in NH_3 (liq.) gives two products (isomers, $C_5H_6N_2$) but reaction with sodium methoxide gives a single product, C_6H_7NO. What are the products and why is there a difference?
6. Write structures for the products to be expected in the following sequences: (i) 4-diisopropylaminocarbonyl pyridine with LDA then with benzophenone, then with hot acid → $C_{19}H_{13}NO_2$; (ii) 2-chloropyridine with LDA then iodine → C_5H_3ClI; (iii) 3-fluoropyridine with LDA then with acetone → $C_8H_{10}FNO$; (iv) 2-bromopyridine with butyllithium at –78°C, then chlorotrimethylstannane → $C_8H_{13}NSn$.
7. A crystalline solid $C_9H_{11}BrN_2O_3$ is formed when 2-methyl-5-nitropyridine is reacted with bromoacetone, subsequent treatment with $NaHCO_3$ affords $C_9H_8N_2O_2$ – deduce the structures and write out a mechanism.
8. When the salt, $C_9H_{13}IN^+ I^-$ produced by reacting pyridine with 1,4-diiodobutane is then treated with Bu_3SnH in the presence of AIBN, a new salt, $C_9H_{12}N^+ I^-$ is formed, which had ^1H NMR signals for four aromatic protons. Suggest structures for the two salts and a mechanism of formation of the latter.
9. Deduce a structure for the product, $C_6H_{11}NO_3$, produced by exposing 4-methyl-2-pyridone to the following sequence: (i) irradiation at 310 nm, (ii) O_3/MeOH/−78°C then $NaBH_4$.
10. Write structures for the compounds produced at each stage in the following sequence: 4-methylpyridine reacted with $NaNH_2$ → $C_6H_8N_2$, then this with $NaNO_2/H_2SO_4$ at 0°C → rt → C_6H_7NO, then this with sodium methoxide and iodomethane → C_7H_9NO and finally this with $KOEt/(CO_2Et)_2$ → $C_{11}H_{13}NO_4$.
11. Nitration of aniline is not generally possible, yet nitration of 2- and 4-aminopyridines can be achieved easily – why?
12. When 3-hydroxypyridine is reacted with 5-bromopent-1-ene a crystalline salt, $C_{10}H_{14}NBrO$ is formed. Treatment of the salt with mild base gave a dipolar substance $C_{10}H_{13}NO$ which on heating provided a neutral,

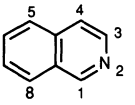
non-aromatic isomer. Deduce the structures of these compounds.

13. Give an explanation for the relatively easy decarboxylation of pyridine-2-acetic acid; what is the product?
14. Suggest a structure for the product, $C_{16}H_{22}N_2O_5$ resulting from the interaction of 4-vinylpyridine with diethyl acetamidomalonate ($AcNHCH(CO_2Et)_2$) and base.
15. Write structures for the products of reacting (i) 2,3-dimethylpyridine with butyllithium then diphenyldisulfide → $C_{13}H_{13}NS$; (ii) 2,3-dimethylpyridine with NBS then with PhSH → $C_{13}H_{13}NS$ isomeric with the product in (i).
16. Write structures for the two isomeric compounds $C_7H_6N_2O$ (formed in a ratio of 4 : 3) when 3-cyanopyridine methiodide is reacted with alkaline potassium ferricyanide.
17. Predict the sites at which deuterium would be found when 1-butylpyridinium iodide is reduced with $NaBD_4$ in EtOH forming (mainly) 1-butyl-1,2,5,6-tetrahydropyridine.
18. Deduce structures for the final product, and intermediates, in the following sequence: pyridine with methyl chloroformate and sodium borohydride gave $C_7H_9NO_2$, then this irradiated gave an isomer which had NMR signals for only two alkene protons – what are the compounds?
19. When pyridine *N*-oxide is heated with c. H_2SO_4 and c. HNO_3 a product $C_5H_4N_2O_3$ is formed; separate reactions of this with PCl_3 then H_2/Pd-C produces $C_5H_4N_2O_2$ and $C_5H_6N_2$ sequentially. What are the three products?
20. Write a structure for the cyclic product, $C_{18}H_{19}NO_4$, from the reaction of ammonia, phenylacetaldehyde ($PhCH_2CH{=}O$), and two mol equivalents of methyl acetoacetate. How might it be converted into a pyridine?
21. 2,3-Dihydrofuran reacts with acrolein to give $C_7H_{10}O_2$; reaction of this with aq. H_2NOH/HCl gave a pyridine, C_7H_9NO: deduce structures.
22. What pyridines or pyridones would be produced from the following combinations of reactants: (a) $H_2NCO.CH_2CN$ (cyanoacetamide) with (i) $EtCO.CH_2CO_2Et$; (ii) 2-acetylcyclohexanone; (iii) ethyl propiolate; (b) $MeC(NH_2){=}CHCO_2Et$ (ethyl 3-aminocrotonate) with (i) $MeCOCH_2COMe$, (ii) but-3-yn-2-one, and (iii) $MeCO.C(CO_2Et){=}CHOEt$.
23. When the sodium salt of formyl acetone ($MeCO.CH{=}CHO^-\ Na^+$) is treated with ammonia, a pyridine, C_8H_9NO is formed. Deduce a structure and explain the regiochemistry of reaction.

6 Quinolines and isoquinolines: reactions and synthesis

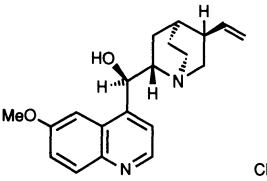


quinoline

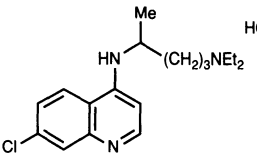


isoquinoline

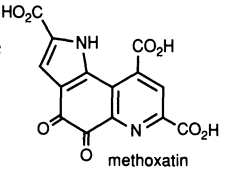
Quinoline and isoquinoline are stable; the former is a high-boiling liquid the latter a low-melting solid, each with a sweetish odour. Both bases have been known for a long time: quinoline was first isolated from coal tar in 1834, isoquinoline from the same source in 1885. Shortly after the isolation of quinoline from coal tar it was also recognised as a pyrolytic degradation product of cinchonamine, an alkaloid closely related to quinine, from which the name quinoline is derived; the word quinine, in turn, derives from *quina*, a Spanish version of a local South American name for the bark of quinine-containing *Cinchona* species. Several synthetic antimalarial drugs are based on the quinoline nucleus: chloroquine is an example.



quinine

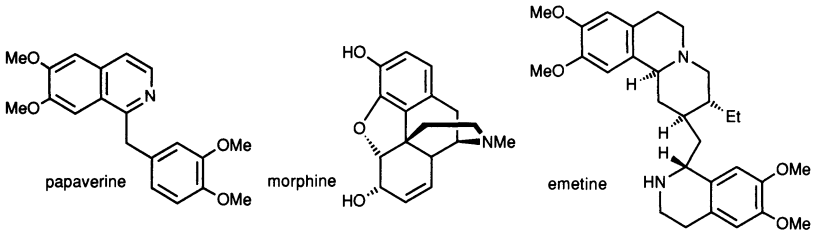


chloroquine

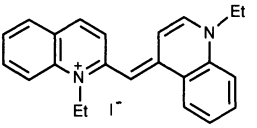


methoxatin

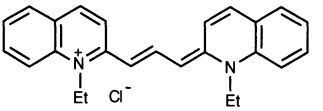
Quinolines play a relatively minor role in fundamental metabolism, methoxatin, an enzyme cofactor of methylotrophic bacteria, being one of the small number of examples. There are also comparatively few quinoline-containing secondary metabolites, in contrast to isoquinoline, which occurs, mainly at the 1,2,3,4-tetrahydro-level, in a large number of alkaloids – the opium poppy alkaloids papaverine and, in more-elaborated form, morphine are examples.[1] Emetine, with two tetrahydroisoquinoline units, is a medicinally important amoebicide.



Quinoline compounds provided the first photographic film sensitisers: the cyanine dye[2] ethyl red extended photography from the blue into the green and then in 1904, with pinacyanol, into the red. Subsequently, thousands of sensitising dyes have been made and tested and quinoline-based dyes replaced by other, more efficient systems.



ethyl red



pinacyanol

6.1 REACTIONS WITH ELECTROPHILIC REAGENTS

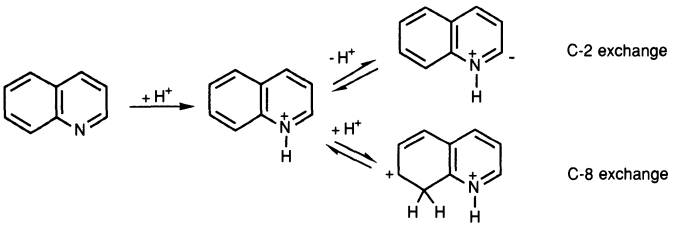
6.1.1 Addition to nitrogen

All the reactions noted in this category for pyridine (section 5.1.1), which involve donation of the nitrogen lone pair to electrophiles, also occur with quinoline and isoquinoline and little further comment is necessary, for example the respective pK_a values, 4.94 and 5.4, show them to be of similar basicity to pyridine; each, like pyridine, forms *N*-oxides and quaternary salts.

6.1.2 Substitution at carbon

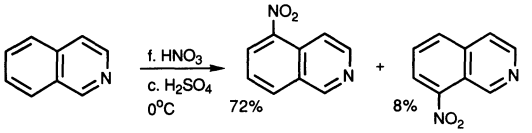
6.1.2.1 *Proton exchange*

Benzene ring *C*-protonation, and thence exchange, *via* *N*-protonated quinoline, requires strong sulfuric acid and occurs fastest at C-8, then at C-5 and C-6; comparable exchange in isoquinoline takes place somewhat faster at C-5 than at C-8.[3] At lower acid strengths each system undergoes exchange α to nitrogen, at C-2 for quinoline and C-1 for isoquinoline. These processes involve a zwitterion produced by deprotonation of the *N*-protonated heterocycle.



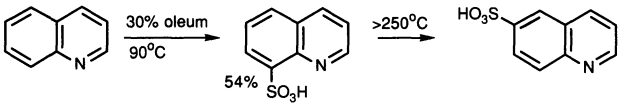
6.1.2.2 *Nitration*

The positional selectivity for proton exchange is partly mirrored in nitrations, quinoline gives approximately equal amounts of 5- and 8-nitroquinolines whereas isoquinoline produces almost exclusively the 5-nitro-isomer;[4] mechanistically, the substitutions involve nitronium ion attack on the *N*-protonated heterocycles.



6.1.2.3 *Sulfonation*

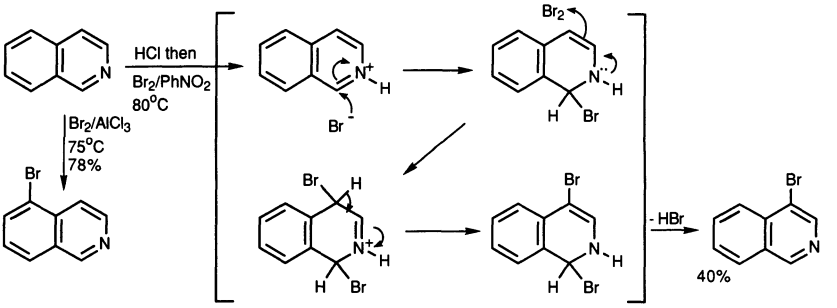
Sulfonation of quinoline gives largely the 8-isomer whereas isoquinoline affords the 5-sulfonic acid.[5] Reactions at higher temperatures produce other isomers, under thermodynamic control, for example both quinoline 8-sulfonic acid and quinoline 5-sulfonic acid are isomerised to the 6-acid.[6]



6.1.2.4 *Halogenation*

Ring substitution of quinoline and isoquinoline by halogens is rather complex, products depending on the conditions used.[7] In concentrated sulfuric acid quinoline gives a mixture of 5- and 8-bromo-derivatives; comparably isoquinoline is efficiently converted into the 5-bromo-derivative in the presence of aluminium chloride;[8] both processes involve halogen attack on a salt.

Introduction of halogen to the hetero-rings occurs under remarkably mild conditions in which the nitrogen lone pair initiates a sequence by interaction with an electrophile. Thus treatment of quinoline and isoquinoline hydrochlorides with bromine produces 3-bromoquinoline and 4-bromoisoquinoline respectively.[9]



6.1.2.5 *Acylation and alkylation*

There are no generally useful processes for the introduction of carbon substituents by electrophilic substitution into quinolines or isoquinolines, except for a few examples in which a ring has an strong electron-releasing substituent.

6.2 REACTIONS WITH OXIDISING AGENTS

It requires vigorous conditions to degrade a ring in quinoline and isoquinoline: examples of attack at both rings are known, though degradation of the benzene ring, generating pyridine diacids, should be considered usual;[10] ozonolysis can be employed to produce pyridine dialdehydes,[11] or after subsequent hydrogen peroxide treatment, diacids.[12] Electrolytic oxidation of quinoline is the optimal way to convert quinoline to pyridine-2,3-dicarboxylic acid ('quinolinic acid')[13]; alkaline potassium permanganate converts isoquinoline into a mixture of pyridine-3,4-dicarboxylic acid ('cinchomeronic acid') and phthalic acid.[14]

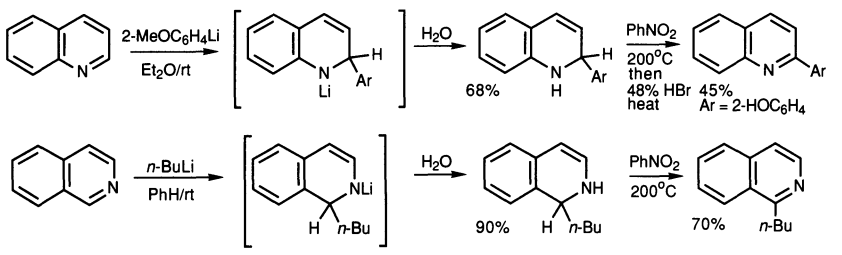
6.3 REACTIONS WITH NUCLEOPHILIC REAGENTS

6.3.1 Nucleophilic substitution with hydride transfer

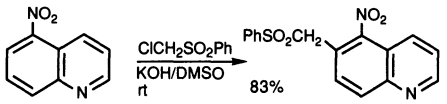
Reactions of this type occur fastest at C-2 in quinoline and at C-1 in isoquinolines.

6.3.1.1 *Alkylation and arylation*

The immediate products of addition of alkyl and aryl Grignard reagents and alkyl- and aryllithiums are dihydroquinolines and -isoquinolines and can be characterised as such, but can be oxidised to afford the *C*-substituted, rearomatised heterocycle; illustrated are a 2-arylation of quinoline[15] and an isoquinoline 1-alkylation.[16]

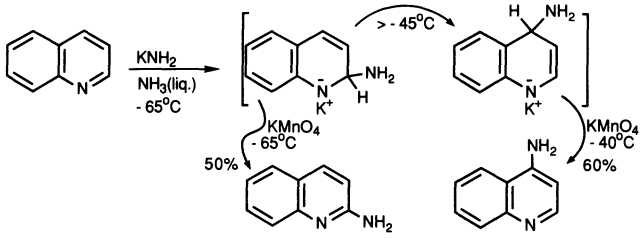


'Vicarious nucleophilic substitution' (VNS)[17] allows the introduction of substituents into nitroquinolines: cyanomethyl and phenylsulfonylmethyl groups, for example, can be introduced *ortho* to the nitro group, in 5-nitroquinolines at C-6 and in 6-nitroquinolines at C-5.[18]

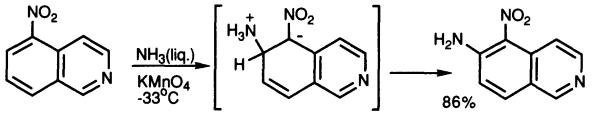


6.3.1.2 *Amination*

Sodium amide reacts rapidly and completely with quinoline and isoquinoline, even at −45°C, to give dihydro-adducts with initial amide attack at C-2 (main) and C-4 (minor) in quinoline and C-1 in isoquinoline. The quinoline 2-adduct rearranges to the more stable 4-aminated adduct at higher temperatures.[19] Oxidative trapping of the quinoline adducts provides 2- or 4-aminoquinoline;[20] isoquinoline reacts with potassium amide in liquid ammonia at room temperature to give 1-aminoisoquinoline.[21]

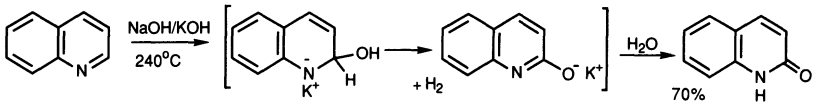


Oxidative aminations are possible at other quinoline and isoquinoline positions, even on the benzene ring, providing a nitro group is present to promote the amide addition.[22]



6.3.1.3 *Hydroxylation*

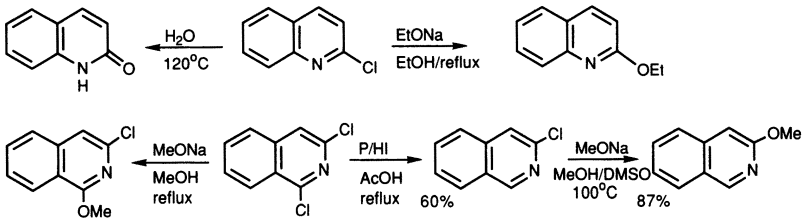
Both quinoline and isoquinoline can be directly hydroxylated with potassium hydroxide at high temperature with the evolution of hydrogen.[23] 2-Quinolone ('carbostyril') and 1-isoquinolone ('isocarbostyril') are the isolated products.



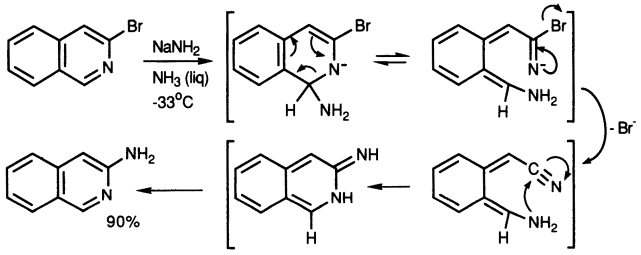
6.3.2 Nucleophilic substitution with displacement of halide

The main principle here is that halogen on the homocyclic rings of quinoline and isoquinoline, and at the quinoline-3- and the isoquinoline-4-positions behave as would halobenzenes. In contrast, 2- and 4-haloquinolines and

1-haloisoquinolines have the same susceptibility as α- and γ-halopyridines (see section 5.3.2). 3-Haloisoquinolines are intermediate in their reactivity to nucleophiles.



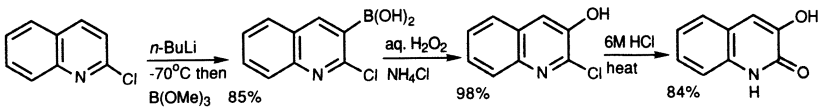
An apparent exception to the relative unreactivity of 3-haloisoquinolines is provided by the reaction of 3-bromoisoquinoline with sodium amide. Here, a different mechanism, known by the acronym ANRORC (**A**ddition of **N**ucleophile, **R**ing **O**pening and **R**ing **C**losure), leads to the product, apparently of direct displacement, but in which a switching of the ring nitrogen, to become the substituent nitrogen, has occurred.[24]



6.4 REACTIONS WITH BASES

6.4.1 Deprotonation of C-hydrogen

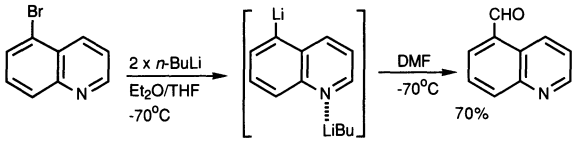
Direct lithiation, i.e. *C*-deprotonation of quinolines,[25] seems to require an adjacent substituent such as chlorine, fluorine, or methoxyl. 4-Pivaloylamidoquinoline lithiates at the *peri* position, C-5. 3-Haloquinolines lithiate at C-4, not C-2.



6.5 REACTIONS OF *C*-METALLATED QUINOLINES AND ISOQUINOLINES

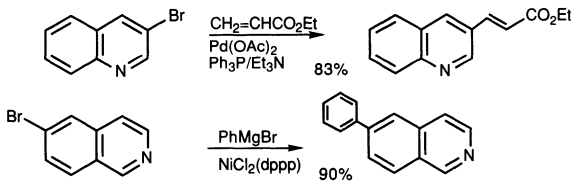
6.5.1 Lithio derivatives

The preparation of lithioquinolines and -isoquinolines *via* metal–halogen exchange is complicated by competing nucleophilic addition. Low temperatures do allow metal–halogen exchange at the pyridine,[26] and benzene ring positions[27] in quinolines, and the isoquinoline-1-[26] and 4-positions,[28] subsequent reaction with electrophiles generating *C*-substituted products. It seems that for benzene ring lithiation two mol equivalents of butyllithium are necessary to allow one lithium to associate with the ring nitrogen.



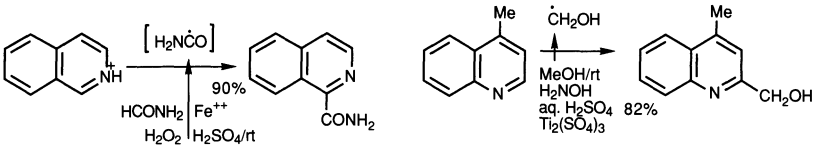
6.5.2 Palladium- and nickel-catalysed reactions

The coupling of various haloquinolines and -isoquinolines has been effected with palladium[29] or nickel reagents.[30]



6.6 REACTIONS WITH RADICAL REAGENTS

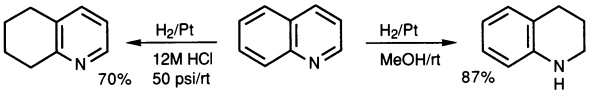
Phenyl radicals generated by the decomposition of dibenzoyl peroxide attack quinoline and isoquinoline with formation of mixtures of all the isomeric phenyl-substituted products. Much more discriminating substitutions can be achieved with more nucleophilic radicals in acid conditions (cf. section 2.4.1) .



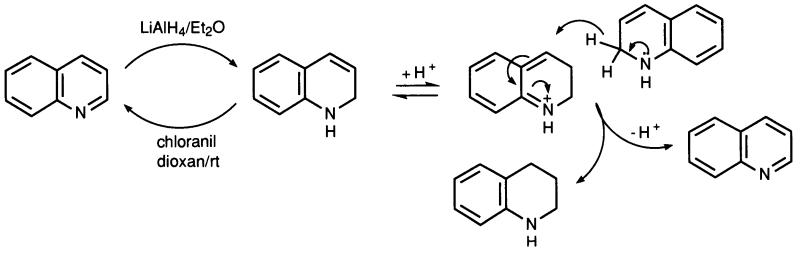
6.7 REACTIONS WITH REDUCING AGENTS

Selective reduction of either the pyridine or the benzene rings in quinolines and isoquinoline can be achieved: the heterocyclic ring is reduced by sodium

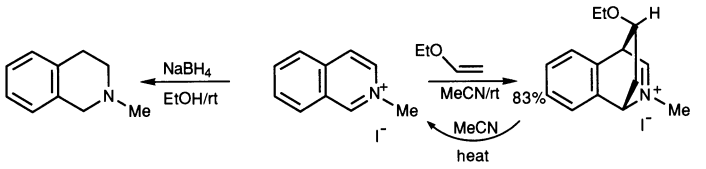
cyanoborohydride[31] in acid solution, by sodium borohydride in the presence of nickel(2) chloride[32] or, traditionally, by room temperature and room pressure catalytic hydrogenation in methanol. However, in strong acid solution it is the benzene ring which is selectively saturated;[33] longer reaction times can then lead to decahydro-derivatives. The combination – sodium borohydride and an organic acid, RCO_2H – produces *N*-alkyl-tetrahydro-derivatives where the alkyl group is RCH_2.[31]



Lithium/liquid ammonia conditions can produce 1,4-dihydroquinoline[34] and 3,4-dihydroisoquinoline[35] under certain conditions. Conversely, lithium aluminium hydride reduces generating 1,2-dihydroquinoline[36] and -isoquinoline.[37] These dihydro-heterocycles[38] can be easily oxidised back to the fully aromatic systems, or disproportionate, especially in acid solution, to give a mixture of tetrahydro- and aromatic compounds.



N^+-Alkyl salts of quinoline and isoquinoline are particularly easily reduced in the heterocyclic ring, either catalytically or with a borohydride in protic solution.

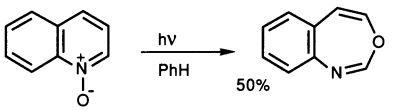


6.8 ELECTROCYCLIC REACTIONS (GROUND STATE)

The tendency for relatively easy nucleophilic addition to the pyridinium ring in isoquinolinium salts is echoed in the cycloaddition of electron-rich dienophiles such as ethoxyethene.[39]

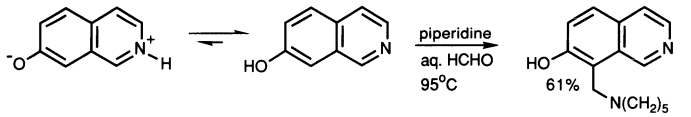
6.9 PHOTOCHEMICAL REACTIONS

Of a comparatively small range of photochemical reactions described for quinolines and isoquinolines perhaps the most intriguing are some hetero-ring rearrangements of quaternary derivatives, which can be illustrated by the ring expansions of their *N*-oxides.[40] As with 2-pyridones, 2-quinolones undergo 2 + 2 photo-dimerisation.[41]

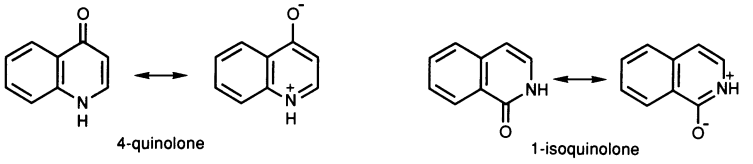


6.10 OXYQUINOLINES AND -ISOQUINOLINES

Quinolinols and isoquinolinols in which the oxygen is at any position other than 2- and 4- for quinolines and 1- and 3- for isoquinolines are true phenols, i.e. have an hydroxyl group, though they exist in equilibrium with variable concentrations of zwitterionic structures. They show the typical reactivity of naphthols.[42] 8-Hydroxyquinoline has long been used in analysis as a chelating agent, especially for Zn(2), Mg(2) and Al(3); the Cu(2) chelate is used as a fungicide.

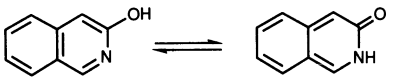


2- and 4-Quinolones and 1-isoquinolone (strictly 2-(1*H*)-quinolinone, 4-(1*H*)-quinolinone and 1-(2*H*)-isoquinolinone) are, as the nomenclature implies, completely in the carbonyl tautomeric form[43] for all practical purposes, because the hydroxyl tautomers lack a favourable polarised resonance contributor, illustrated for 4-quinolone and 1-isoquinolone. There is considerable interest in quinolones as antibacterial agents.[44]



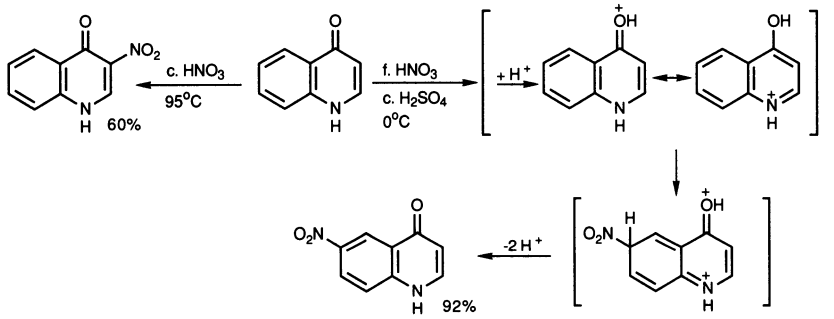
In 3-oxy-isoquinoline there is an interesting and instructive situation: here the two tautomers are of comparable stability. 3-Isoquinolinol is dominant in dry ether solution, 3-isoquinolone is dominant in aqueous solution. A colourless ether solution of 3-isoquinolinol turns yellow on addition of a little methanol because of the production of some of the carbonyl tautomer. The similar stabilities is the consequence of the balancing of two opposing tendencies: the

presence of an amide unit in 3-isoquinolone forces the benzene ring into a less favoured quinoid structure, conversely, the complete benzene ring in isoquinolinol necessarily means loss of the amide unit and its contribution to stability. One may contrast this with 1-isoquinolone which has an amide, as well as a complete benzene, unit.[45]

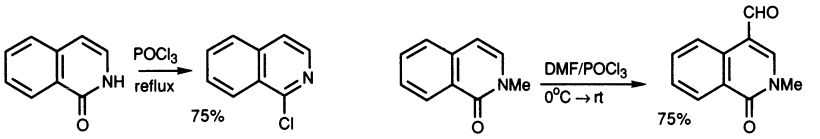


3-isoquinolinol (colourless) 3-(2H)-isoquinolone (yellow)

The position of electrophilic substitution of quinolones and isoquinolones depends upon the p*H* of the reaction medium. Each type protonates on carbonyl oxygen so reactions in strongly acidic media involve attack on this cation: the contrast can be illustrated by the nitration of 4-quinolone at different acid strengths.[46] The balance between benzene ring and unprotonated heterocyclic ring selectivity is small, for example 2-quinolone chlorinates preferentially, as a neutral molecule, at C-6, and only secondly at C-3.



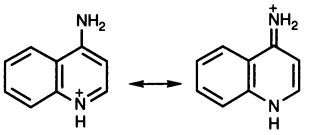
Strong acid-catalysed H-exchange of 2-quinolone proceeds fastest at C-6 and C-8; of 1-isoquinolone at C-4, then 5 ~ 7.[47] This is echoed in various electrophilic substitutions, for example formylation.[48]



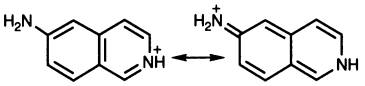
The '-one' tautomers deprotonate at N–H-generating ambident anions which can react at either oxygen or nitrogen depending on the exact conditions. They are converted, as with the pyridones, into haloquinolines and -isoquinolines[49] by reaction with phosphorus halides; the quinolinols and isoquinolinols do not react in this way.

6.11 AMINOQUINOLINES AND -ISOQUINOLINES

Aminoquinolines and -isoquinolines exist as amino tautomers and all protonate on ring nitrogen. Only 4-aminoquinoline shows appreciably enhanced basicity (pK_a 9.2); the most basic aminoisoquinoline is the 6-isomer (pK_a 7.2), indeed this is the most basic of all the benzene-ring-substituted aminoquinolines and aminoisoquinolines.



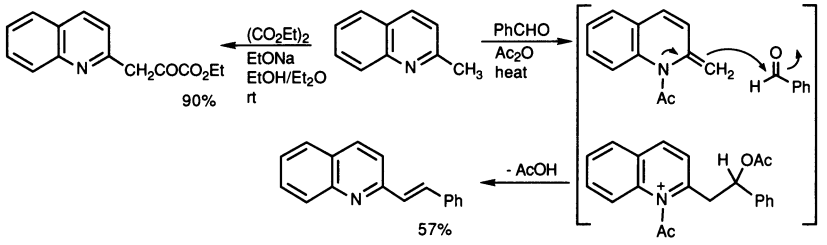
4-aminoquinolinium protocation



6-aminoisoquinolinium protocation

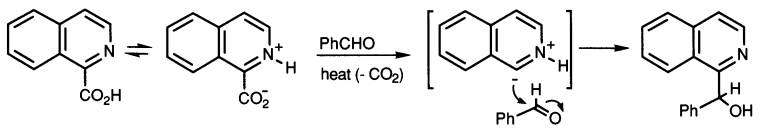
6.12 ALKYLQUINOLINES AND -ISOQUINOLINES

The particular acidity of the protons of pyridine α- and γ-alkyl groups is echoed by quinoline-2-[50] and 4-alkyl groups and by alkyl at the isoquinoline 1-position, but to a much lesser extent by alkyl at isoquinoline C-3. Condensation reactions with alkyl groups at these activated positions can be achieved in either basic or acidic media; the key nucleophilic species in the latter cases is probably an enamine,[51] or enamide as shown,[52] and in the former a side-chain carbanion.[53]



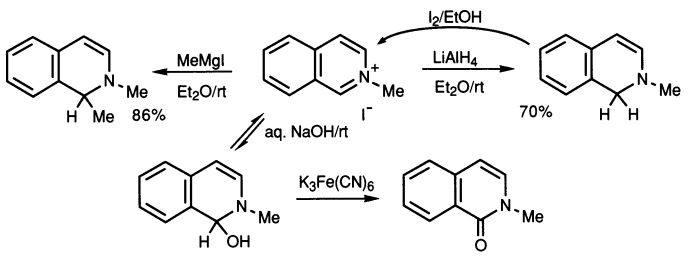
6.13 QUINOLINE AND ISOQUINOLINE CARBOXYLIC ACIDS AND ESTERS

There is little to differentiate these derivatives from straightforward aromatic acids and esters save for the easy decarboxylation of quinoline-2- and isoquinoline-1-acids, *via* an ylid which can be trapped with aldehydes as electrophiles – the Hammick reaction.[54] Loss of carbon dioxide from *N*-methylquinolinium-2- and -isoquinolinium-1-acids, and trapping of resulting ylids, can be achieved with stronger heating.[55]

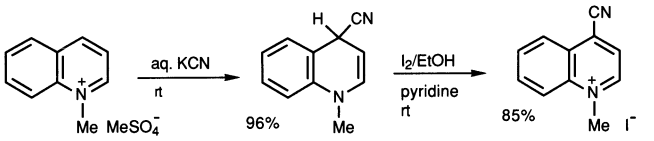


6.14 QUATERNARY QUINOLINIUM AND ISOQUINOLINIUM SALTS

The predominant property of these salts is the ease with which nucleophiles add to the quinolinium-2- and the isoquinolinium-1-positions. Hydroxide, hydride[56] and organometallic nucleophiles all add with facility, though the resulting dihydroaromatic products require careful handling if they are not to disproportionate (see also section 6.7) or be oxidised.[57]

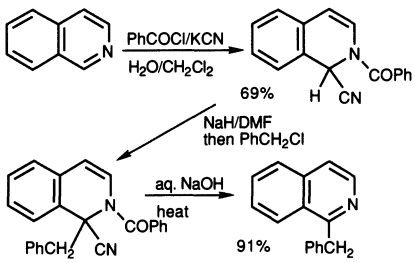


The position of fastest addition to quinolinium salts is C-2 but, with reversible reactions, a thermodynamic adduct with the addend at C-4 and the residual double bond in conjugation with the nitrogen (as an enamine) can be obtained.[58]

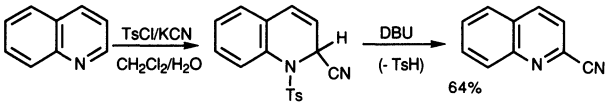


Treatment of quinoline and isoquinoline with sodium borohydride in a mixture of acetic acid and acetic anhydride gives good yields of *N*-acetyl-1,2-dihydro-derivatives.[59]

The Reissert reaction involves the kinetic trapping by cyanide of an N^+-acylquinolinium or -isoquinolinium salt; in the classical process[60] the acylating agent is benzoyl chloride. Reissert compounds[61] are usually prepared using a dichloromethane/water two-phase medium; recent improvements include utilising phase-transfer catalysts with ultrasound[62] or crown ether catalysis.[63]



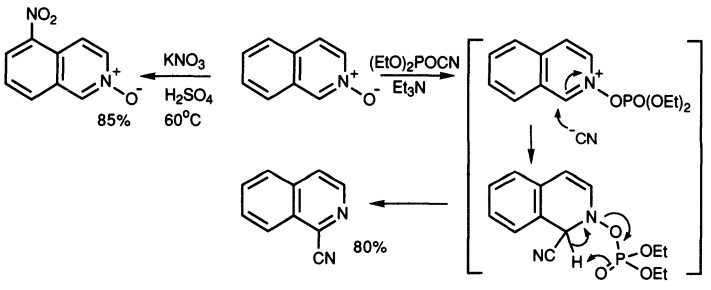
Reissert compounds have utility in a number of ways: deprotonation, alkylation and removal of acyl and cyanide groups leads to the corresponding substituted heterocycles. *N*-Sulfonyl analogues of Reissert adducts easily eliminate arylsulfinate, which provides a method for the introduction of a cyano group.[64]



6.15 QUINOLINE AND ISOQUINOLINE *N*-OXIDES

N-Oxide chemistry in these bicyclic systems largely parallels the processes described for pyridine *N*-oxide, with the additional possibility of benzene ring electrophilic substitution; for example, mixed acid nitration of quinoline *N*-oxide takes place at C-5 and C-8 *via* the *O*-protonated species, but at C-4 at lower acid strength;[65] nitration of isoquinoline *N*-oxide takes place at C-5.[66]

Diethyl cyanophosphonate converts quinoline and isoquinoline *N*-oxides into the 1- and 2-cyanoheterocycles in high yields in a process which must have *O*-phosphorylation as a first step, and in which the elimination of diethylphosphate may proceed *via* a cyclic transition state.[67]



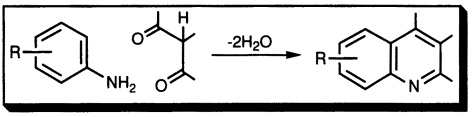
6.16 SYNTHESIS OF QUINOLINES AND ISOQUINOLINES

6.16.1 Ring syntheses

Three of the more generally important approaches to quinoline and three to isoquinoline compounds from non-heterocyclic precursors are summarised in this section.

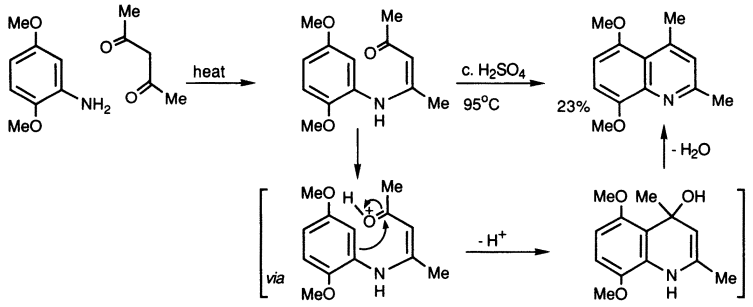
6.16.1.1 *Quinolines from arylamines and 1,3-dicarbonyl compounds*

Anilines react with 1,3-dicarbonyl compounds to give intermediates which can be cyclised with acid.



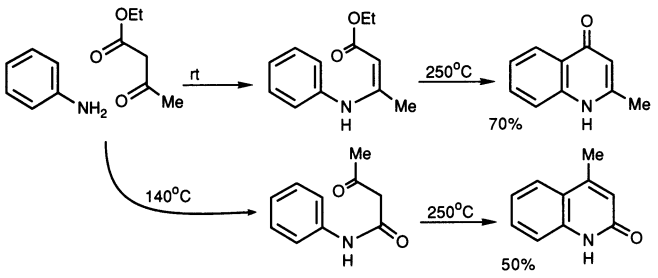
The Combes synthesis

Condensation of a 1,3-dicarbonyl compound with an arylamine gives a high yield of a β-amino-enone, which can then be cyclised with concentrated acid.[68] The cyclisation step may be an electrophilic substitution by the *O*-protonated amino-enone, as shown, followed by loss of water to give the aromatic quinoline.

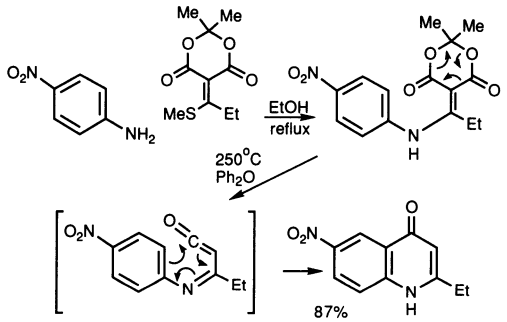


The Conrad-Limpach-Knorr synthesis

This closely-related synthesis uses β-ketoesters and leads to quinolones.[69] Anilines and β-ketoesters can react at lower temperatures to give the kinetic product, a β-aminoacrylate, cyclisation of which gives a 4-quinolone. At higher temperatures, β-ketoester anilides are formed and cyclisation of these affords 2-quinolones. β-Aminoacrylates, for cyclisation to 4-quinolones, are also available *via* the addition of anilines to acetylenic esters[70] and by reation with diethyl ethoxymethylenemalonate ($EtOCH{=}C(CO_2Et)_2$ → $ArNHCH{=}C(CO_2Et)_2$).[71]

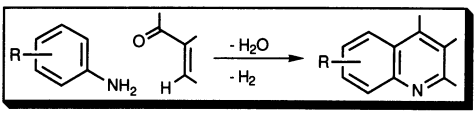


Closures onto benzene rings carrying electron-withdrawing groups can be effected in this variant below because the ring-closure substrate is simply heated strongly – the mechanism of ring closure is probably not electrophilic attack on the benzene ring but electrocyclic in nature.[72]



6.16.1.2 *Quinolines from arylamines and α,β-unsaturated carbonyl compounds*

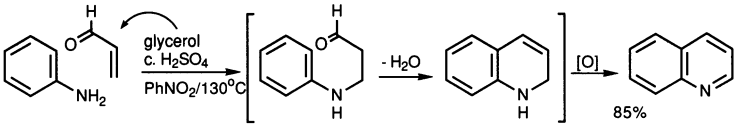
Anilines react with an α,β-unsaturated carbonyl compound in the presence of an oxidising agent to give quinolines. When glycerol is used as an *in situ* source of acrolein, quinolines carrying no substituents on the heterocyclic ring are produced.



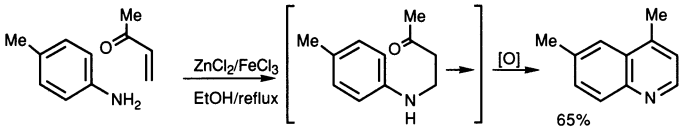
The Skraup synthesis[73]

In this extraordinary reaction, quinoline is produced when aniline, concentrated sulfuric acid, glycerol and a mild oxidising agent are heated together.[74] The reaction has been shown to proceed by dehydration of the glycerol to acrolein to which aniline then adds in a conjugate fashion. Acid-catalysed cyclisation produces a 1,2-dihydroquinoline finally dehydrogenated by the oxidising agent – the corresponding nitrobenzene or arsenic acid have been used classically,

though with the inclusion of a little sodium iodide, the sulfuric acid can serve as oxidant.[12] It is the best method for the synthesis of quinolines unsubstituted on the hetero-ring.[75]



The use of substituted carbonyl components confirms the mechanism, showing that interaction of the aniline amino group with the carbonyl group is not the first step.



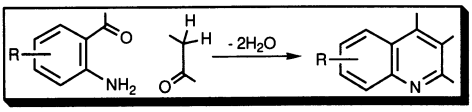
Skraup syntheses sometimes become very vigorous and extreme care must be taken to control their potential violence; preforming the Michael adduct and using an alternative oxidant (*p*-chloranil was the best) has been shown to be advantageous in terms of yield and as a better means for controlling the reaction.[76]

Orientation of ring closure

meta-Substituted anilines could give rise to both 5- and 7-substituted quinolines. In practice, electron-donating substituents direct ring closure *para*, thus producing 7-substituted quinolines; *meta*-halo-anilines produce mainly the 7-isomer. In the Skraup reaction, an electron-withdrawing *meta* substituent gives rise mainly to the 5-substituted quinoline.

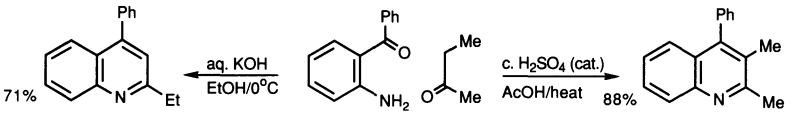
6.16.1.3 *Quinolines from ortho-acylanilines and carbonyl compounds*

ortho-Acylanilines react with ketones having an α-methylene to give quinolines.



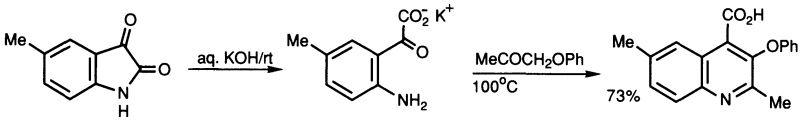
The Friedländer synthesis[77]

ortho-Acylanilines condense with a ketone or aldehyde (which must contain an α-methylene group) by base or acid catalysis to yield quinolines. The orientation of condensation depends on the orientation of enolate or enol formation.[78]



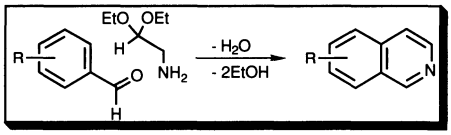
The Pfitzinger synthesis

ortho-Aminobenzaldehydes are sometimes difficult of access; in this modification, isatins (sections 17.14.3 and 17.16.4), which are easy to synthesise, are hydrolysed to *ortho*-aminoarylglyoxylates, which react with ketones affording quinoline-4-carboxylic acids.[79] The carboxylic acid group can be removed, if required, by pyrolysis with calcium oxide.



6.16.1.4 *Isoquinolines from arylaldehydes and aminoacetal*

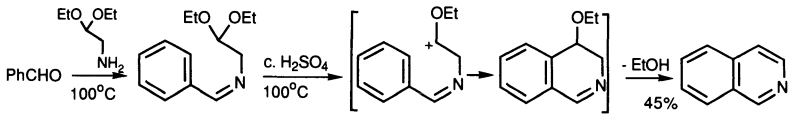
Aromatic aldehydes react with aminoacetal (2,2-diethoxyethanamine) to generate imines which can be cyclised with acid to isoquinolines carrying no substituents on the heterocyclic ring.



The Pomeranz-Fritsch synthesis[80]

The Pomeranz-Fritsch synthesis is normally carried out in two stages. Firstly, an aryl aldehyde is condensed with aminoacetal to form an aryl aldimine. This stage proceeds in high yield under mild conditions. Secondly, the aldimine is cyclised by treatment with strong acid; hydrolysis of the imine competes and reduces the efficiency of this step.

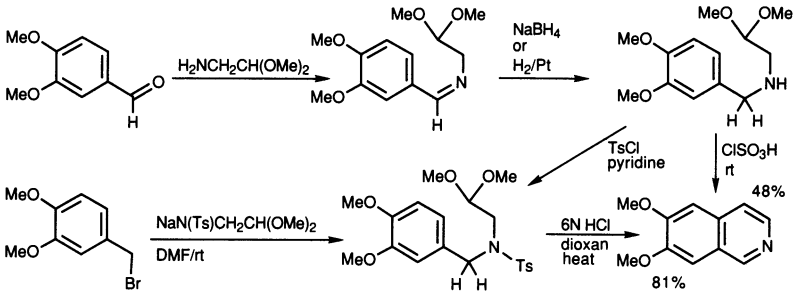
The second step is similar to those in the Combes and Skraup syntheses, in that the acid initially protonates, causing elimination of ethanol and the production of a species which can attack the aromatic ring as an electrophile. Final elimination of a second mole of alcohol completes the process.



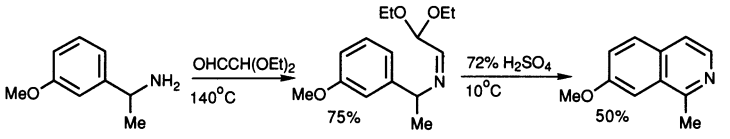
The electrophilic nature of the cyclisation step explains why the process works best for benzaldimines carrying electron-donating substituents (especially

when these are oriented *para* to the point of closure leading to 7-substituted isoquinolines) and least well for systems deactivated by electron-withdrawing groups.

The problem of imine hydrolysis can be avoided by cyclising at a lower oxidation level, with tosyl on nitrogen for subsequent elimination as toluenesulfinic acid. The ring closure substrates can be obtained by reduction and tosylation of imine condensation products[81] or by benzylating the sodium salt of 2-tosylaminoethanal acetal.[82] Cyclisation of benzylaminoethanal acetals using chlorosulfonic acid gives the aromatic isoquinoline directly.[83]

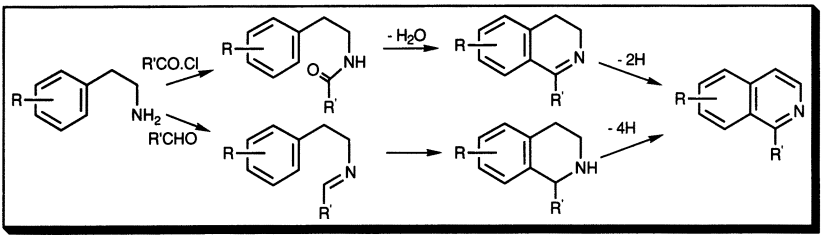


Isoquinolines substituted at C-1 are not easily formed by the Pomeranz-Fritsch procedure. The first step would require formation of a ketimine from aminoacetal and an aromatic ketone, which would proceed much less well than for an aryl aldehyde. A variation, which overcomes this difficulty, has a benzylamine condensing with glyoxal diethyl acetal; the resulting isomeric imine can be cyclised with acid.[84]



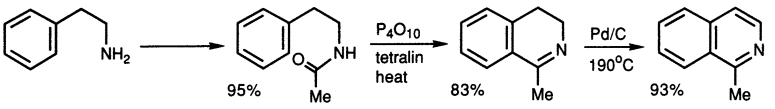
6.16.1.5 *Isoquinolines from arylethylamides*

The amide or imine from reaction of arylethylamines (2-arylethanamines) with an acid derivative or with an aldehyde, can be ring-closed to a 3,4-dihydro- or 1,2,3,4-tetrahydroisoquinoline respectively. Subsequent dehydrogenation produces the aromatic heterocycle.

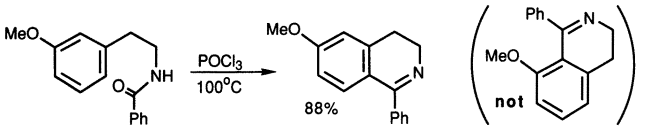


The Bischler-Napieralski synthesis[85]

In the classical process a phenylethylamine reacts with a carboxylic acid chloride or anhydride to form an amide, which can be cyclised, with loss of water, to a 3,4-dihydroisoquinoline, then readily dehydrogenated to the isoquinoline using palladium, sulfur, or diphenyl disulfide. Common cyclisation agents are phosphorus pentoxide (P_4O_{10}), phosphorus oxychloride and phosphorus pentachloride. The electrophilic intermediate is very probably an imino chloride,[86] or phosphate; the former have been isolated and treated with Lewis acids when they are converted into isonitrilium salts, which cyclise efficiently to 3,4-dihydroisoquinolines.[87]

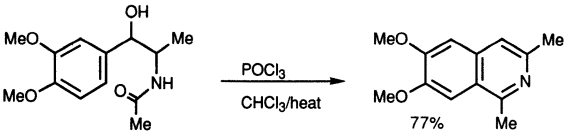


Here, once again, the cyclising step involves electrophilic attack on the aromatic ring so the method works best for activated rings, and *meta*-substituted substrates give exclusively 6-substituted isoquinolines.



Pictet-Gams modification

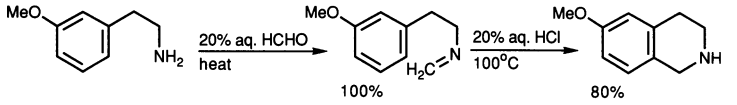
By conducting the Bischler-Napieralski sequence with a potentially unsaturated arylethylamine, a fully aromatic isoquinoline can be obtained directly. The amide of a β-methoxy- or β-hydroxy-β-arylethylamine is heated with the usual type of cyclisation catalyst. It is not clear whether dehydration to an unsaturated amide or to an oxazolidine[88] is an initial stage in the overall sequence.



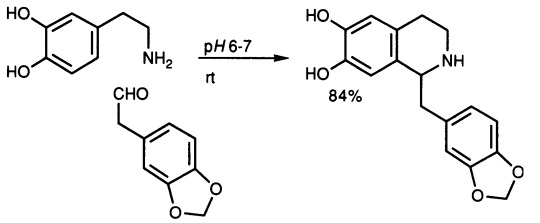
6.16.1.6 *Isoquinolines from activated arylethylamines and aldehydes.*

The Pictet-Spengler synthesis[89]

Arylethylamines react with aldehydes easily and in good yields to give imines. 1,2,3,4-Tetrahydroisoquinolines result from their cyclisation with acid catalysis. Note that the lower oxidation level imine, *versus* amide, leads to tetrahydro- not dihydroisoquinoline. After protonation of the imine, a Mannich-type electrophile is generated; since these are intrinsically less electrophilic than the intermediates in Bischler-Napieralski closure, a strong activating substituent must be present, and appropriately sited, on the aromatic ring.



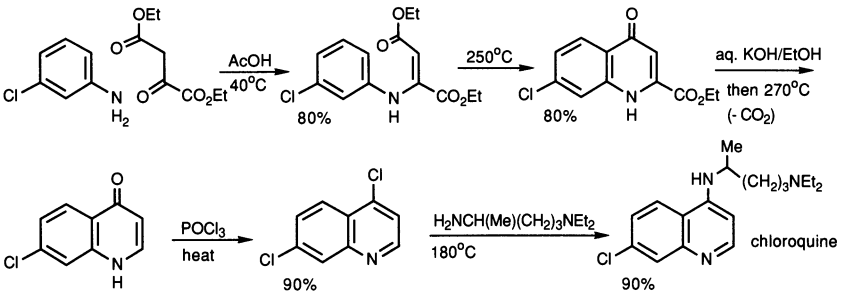
Highly activated hydroxylated aromatic rings permit Pictet-Spengler ring closure under very mild, 'physiological' conditions.[90]



6.16.2 Examples of notable syntheses of quinoline and isoquinoline compounds

6.16.2.1 *Chloroquine*

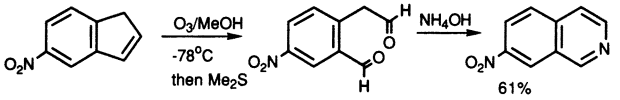
Chloroquine[91] is a synthetic antimalarial.



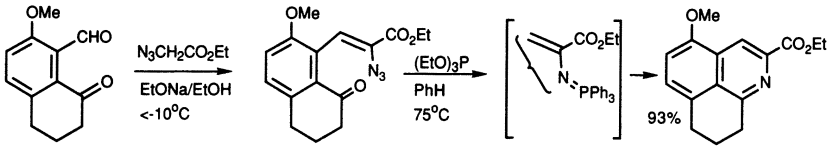
6.16.2.2 *Newer methods*

A number of recently described routes take rather different approaches to the synthesis of quinolines and isoquinolines; for example, ozonolyses of indenes

provide homophthalaldehydes which are at exactly the right oxidation level for aromatic pyridine ring closure with ammonia.[92]

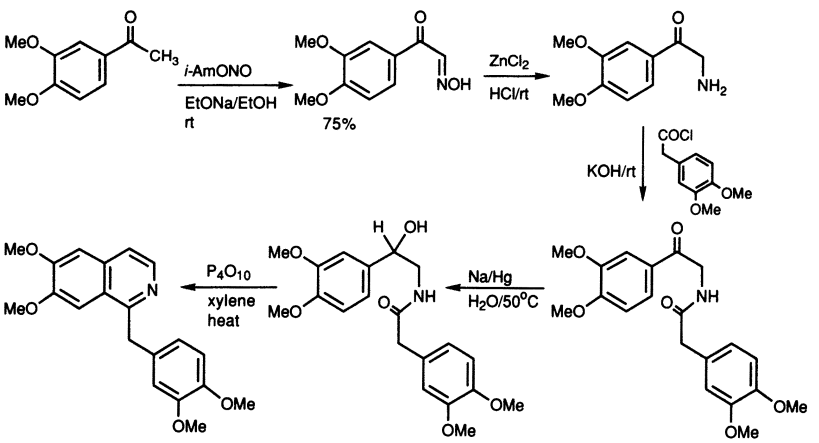


Aromatic aldehydes condense with azidoacetates to produce species which by treatment with trivalent phophorus compounds give aza-ylids which undergo intramolecular aza-Wittig condensations giving aromatic isoquinolines.[93]



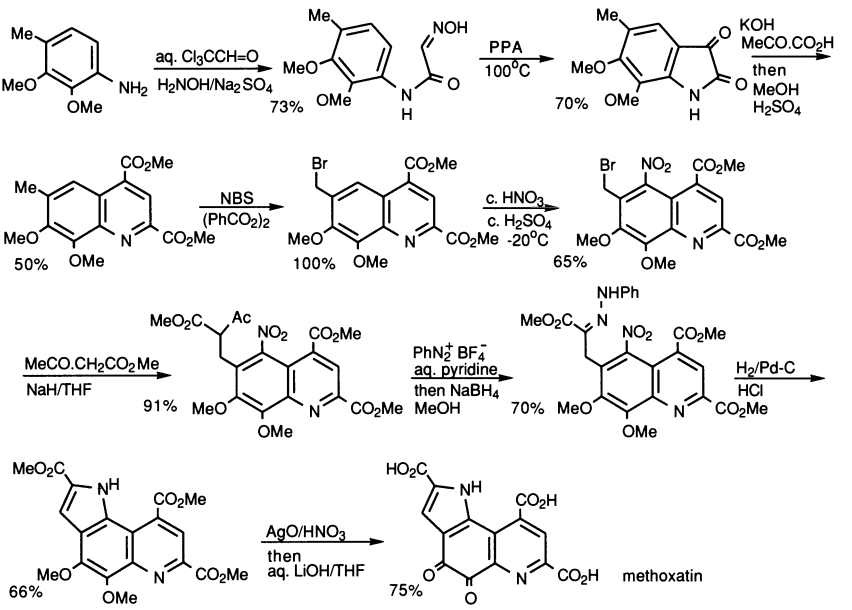
6.16.2.3 *Papaverine*

Papaverine[94] is an alkaloid from opium; it is a smooth muscle relaxant and thus useful as a coronary vasodilator – the synthesis illustrates the Pictet-Gams variation.



6.16.2.4 *Methoxatin*

Methoxatin[95] is an enzyme cofactor of bacteria which metabolise methanol. This synthesis is a particularly instructive one since it includes an isatin synthesis (section 17.16.4), a quinoline synthesis, and an indole synthesis.



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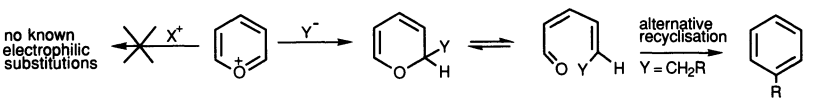
EXERCISES FOR CHAPTER 6

1. Predict the structures of the high yield mono-nitration products (i) $C_{16}H_{12}N_2O_2$ from 1-benzylisoquinoline, (ii) $C_{10}H_8N_2O_3$ from 6-methoxyquinoline, (iii) $C_{10}H_8N_2O_3$ from 7-methoxyisoquinoline.
2. Write a sequence to rationalise the conversion of quinoline into 3-bromoquinoline by reaction with Br_2 in CCl_4/pyridine.
3. Suggest a structure for product $C_{16}H_{16}ClNO_4$ from 1,3-dichloroisoquinoline and $NaCH(CO_2Et)_2$
4. Deduce a structure for the product, $C_{15}H_{18}N_2O_4S$ formed on treatment of 2-*t*-BuCONH-quinoline successively with 3 × *n*-BuLi then dimethyl disulfide.
5. Write a sequence of mechanistic steps to explain the conversion of 2-methylisoquinolinium iodide into 2-methyl-1,2,3,4-tetrahydroisoquinoline with sodium borohydride in ethanol.
6. Draw the most stable tautomer of 3-oxyquinoline, and 1-, 4- and 8-oxyisoquinolines.
7. Suggest a mechanistic sequence to rationalise the formation of methyl 2-methylquinoline-3-carboxylate from the reaction of aniline with methyl acetoacetate (→ $C_{11}H_{13}NO_2$) and then this with DMF/$POCl_3$.
8. Deduce the structure of the product quinolones: (i) $C_{12}H_{11}NO_4$ resulting from reaction of 2-methoxyaniline with dimethyl acetylenedicarboxylate then heating at 250°C; (ii) $C_{10}H_6ClNO_3$ from 3-chloroaniline and diethyl ethoxymethylenemalonate ($EtOCH{=}C(CO_2Et)_2$) then heating at 250°C, then heating with aq. NaOH.
9. Deduce structures for the quinolines produced from the following combinations: (i) $C_{16}H_{11}NO_2$ from isatin/NaOH then acetophenone; (ii) $C_{10}H_7NO_3$ from isatin/KOH then 3-chloropyruvic acid; (iii) $C_{10}H_7NO_3$ from *N*-acetylisatin and NaOH.

10. Deduce structures for the heterocyclic products from the following combinations: (i) $C_{11}H_7N_3O_2$ from 2-aminobenzaldehyde and barbituric acid (section 11.10); (ii) $C_{14}H_{11}NO_6$ from 4,5-methylenedioxy-2-aminobenzaldehyde and dimethyl acetylenedicarboxylate; (iii) $C_{14}H_{11}NS$ from 2-aminoacetophenone and 2-acetylthiophene; (iv) $C_{21}H_{19}NO$ from 2-aminobenzophenone and dimedone; (v) $C_{15}H_{12}N_2O_2S$ from 2-aminopyridine-3-aldehyde and 1-phenylsulfonylacetone; (vi) $C_{15}H_{15}N_3$ from 4-amino-pyrimidine-5-aldehyde and α-tetralone.

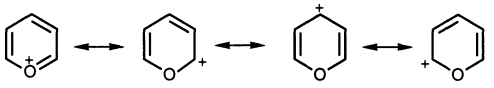
7 Typical reactivity of pyrylium and benzopyrylium ions, pyrones and benzopyrones

The pyrylium cation presents an intriguing dichotomy – it is both 'aromatic', and therefore, the beginning student would be tempted to understand, 'stable', yet it is very reactive – the tropylium cation and the cyclopentadienyl anion can also be described in this way. However, all is relative, and that pyrylium cations react rapidly with nucleophiles to produce adducts which are not aromatic, is merely an expression of their relative stability – if they were not 'aromatic' it is doubtful whether such cations could exist at all. Pyrylium perchlorate is surprisingly stable – it does not decompose below 275°C but, nonetheless, it will react with water, even at room temperature, producing a non-aromatic product.



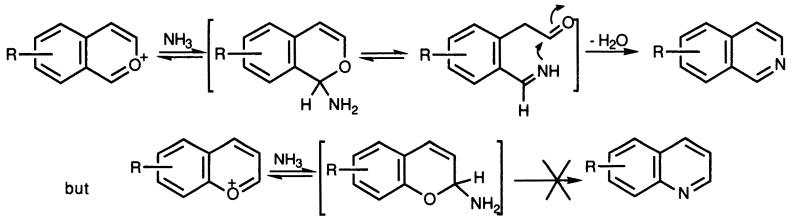
The properties of pyrylium cations are best compared with those of pyridinium cations: the system does not undergo electrophilic substitution nor, indeed, are benzopyrylium cations substituted in the benzene ring. This is a considerable contrast with the chemistry of quinolinium and isoquinolinium cations and is a comment on the stronger deactivating effect of the positively charged oxygen.

Pyrylium ions readily add nucleophilic reagents, at an α-position, generating 2*H*-pyrans which then often ring open. Virtually all the known reactions of pyrylium salts fall into this general category. Often, the initial product of ring opening also subsequently and spontaneously takes part in an alternative ring closure, generating a benzenoid aromatic system (if Y contains active hydrogen attached to carbon) or a pyridine (if Y is an amine nitrogen).



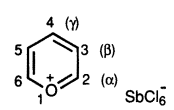
Resonance contributors to the pyrylium cation show that there is greater positive charge at the α- and γ-positions, but nearly all of the known nucleophilic additions take place at an α-position. It is relevant to recall here the greater influence of the hetero atom positive charge on pyridine α- versus the γ-positions. Pyrylium is more reactive in such nucleophilic additions than pyridinium – oxygen tolerates a positive charge less well than nitrogen. It is worth pointing out again the analogy with carbonyl chemistry – the nucleophilic additions which characterise pyrylium systems are nothing more nor less than those which occur frequently in acid-catalysed (*O*-protonated) chemistry of carbonyl groups.

Turning to benzopyrylium systems, one finds exactly comparable behaviour – a readiness to add nucleophiles, adjacent to the positively charged oxygen, in the heterocyclic ring. The interaction of the two isomeric bicycles with ammonia is instructive: one can be converted into an isoquinoline, the other cannot be converted into a quinoline for, although in the last case the addition can and does take place, in the subsequent ring-opened species, no low energy mechanism is available to allow the nitrogen to become attached to the benzene ring.

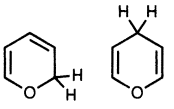


Pyrones, which are the oxygen equivalent of pyridones, are simply α- and γ-hydroxypyrylium salts from which an *O*-proton has been removed. There is little to recommend that 2- and 4-pyrones be viewed as aromatic: they are perhaps best seen as cyclic unsaturated lactones and cyclic β-oxy-α,β-unsaturated ketones, respectively, for example 2-pyrones are hydrolysed by alkali just like simpler esters (lactones). It is instructive that the pyrones are converted into pyridones by reaction with amines or ammonia, but pyridones are not transformed into pyrones by water, or hydroxide. Some electrophilic *C*-substitutions are known for pyrones and benzopyrones, the carbonyl oxygen guiding the electrophile *ortho* or *para*, however there is a tendency for electrophilic addition to a double bond of the heterocyclic ring, again reflecting their non-aromatic nature. Easy Diels-Alder additions to 2-pyrones are further evidence for 'diene', rather than aromatic, character.

8 Pyryliums, 2- and 4-pyrones: reactions and synthesis



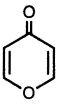
pyrylium hexachloroantimonate (5)



2*H*-pyran

4*H*-pyran

2-pyrone (α-pyrone) [2*H*-pyran-2-one]



4-pyrone (γ-pyrone) [4*H*-pyran-4-one]

Pyrylium salts,[1] especially perchlorates, tetrafluoroborates, and hexachloroantimonates (5), are stable but reactive compounds. Perchlorates have been used extensively, since pyrylium perchlorates tend to be sparingly soluble, however all perchlorates should be treated with CAUTION: perchlorates, particularly dry perchlorates can decompose explosively. No pyrylium salts have been identified in living organisms, even though the benzo[*b*]pyrylium system plays such an important role in the flower pigments (see section 9.1.6).

Almost all the known reactions of the pyrylium nucleus involve addition of a nucleophile, usually at an α-position, occasionally γ, as the first step. A feature of pyrylium chemistry is the ring opening of adducts produced by such additions, followed by cyclisation in a different manner to give a new heterocyclic or homocyclic product (ANRORC processes).

Straightforward electrophilic or radical substitutions at ring positions are unknown. Controlled oxidations, like those of pyridinium salts to 2-pyridones, are likewise not known in pyrylium chemistry.

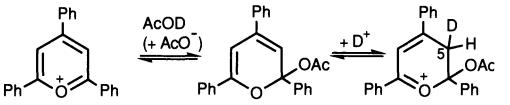
8.1 REACTIONS OF PYRYLIUM CATIONS

8.1.1 Reactions with electrophilic reagents

8.1.1.1 *Proton exchange*

2,4,6-Triphenylpyrylium undergoes exchange at the 3- and 5-positions in hot deuterioacetic acid, but the process probably involves not protonation of the

pyrylium cation, but formation of an equilibrium concentration of an adduct, with acetate added to C-2, allowing enol ether protonation and thus exchange.[2]



8.1.1.2 *Nitration*

Nitration of 2,4,6-triphenylpyrylium proceeds on the benzene rings;[3] no nitrations of pyrylium rings are known.

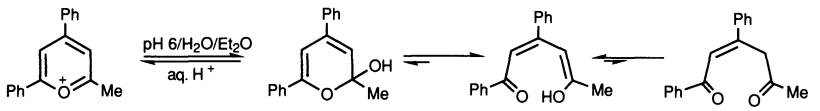
8.1.2 Addition reactions with nucleophilic reagents

Pyrylium salts usually add nucleophiles at a carbon adjacent to the oxygen, and in many ways, such reactions are analogous with those of *O*-protonated carbonyl compounds.

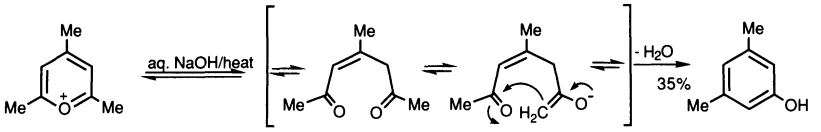
8.1.2.1 *Water and hydroxide ion*

The degree of susceptibility of pyrylium salts to nucleophilic attack varies widely: pyrylium cation itself is even attacked by water at 0°C, where 2,4,6-trimethylpyrylium is stable in water at 100°C. Hydroxide anion, however, adds very readily to C-2 in all cases.

The reaction of 2-methyl-4,6-diphenylpyrylium is typical:[4] the immediate 2-hydroxy-2*H*-pyran, which is a cyclic enol hemiacetal, is in equilibrium with a dominant concentration of the acyclic tautomer, reached probably *via* a proton-catalysed process, since methoxide adducts remain cyclic.[5] Treatment of such acyclic unsaturated diketones with acid regenerates the original pyrylium salt (section 8.3.1).

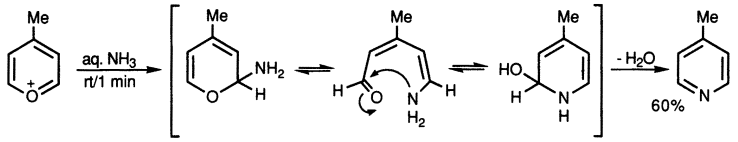


With pyryliums carrying α-alkyl groups, more vigorous alkaline treatment leads to an alternative closure producing benzenes, for example treatment of 2,4,6-trimethylpyrylium with warm alkali causes a subsequent cyclising aldol condensation of the acyclic intermediate to give 3,5-dimethylphenol.[6]

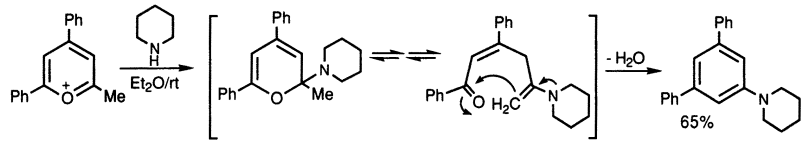


8.1.2.2 *Ammonia and primary and secondary amines*

Ammonia and primary amines react with pyrylium salts to give pyridines and *N*-alkyl- or *N*-arylpyridinium salts respectively.[6a,7] The transformation represents a good method for preparing the nitrogen heterocycles, providing the pyrylium salt can be accessed in the first place. The initial adduct exists as one of a number of ring-opened tautomeric possibilities,[8] depending upon conditions; it is probably the amino-dienone which recloses to give the nitrogen heterocycle.



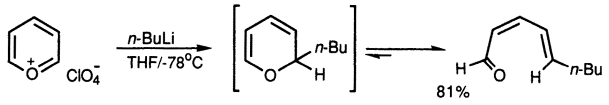
The reaction of a secondary amine cannot, of course, lead to a pyridine, however in pyryliums carrying an α-methyl, ring closure to a benzene can occur, this time *via* an enamine.[6a]



Other reactants containing a primary amino group will also convert pyryliums into *N*-substituted nitrogen heterocycles: *N*-aminoheterocycles[9] are amongst several types of hydrazine derivatives to have been utilised: these give 1-(substituted)aminopyridiniums. Reaction of pyryliums with hydroxylamine comparably leads (predominantly) to the formation of pyridine *N*-oxides.[1,10]

8.1.2.3 *Organometallic addition*

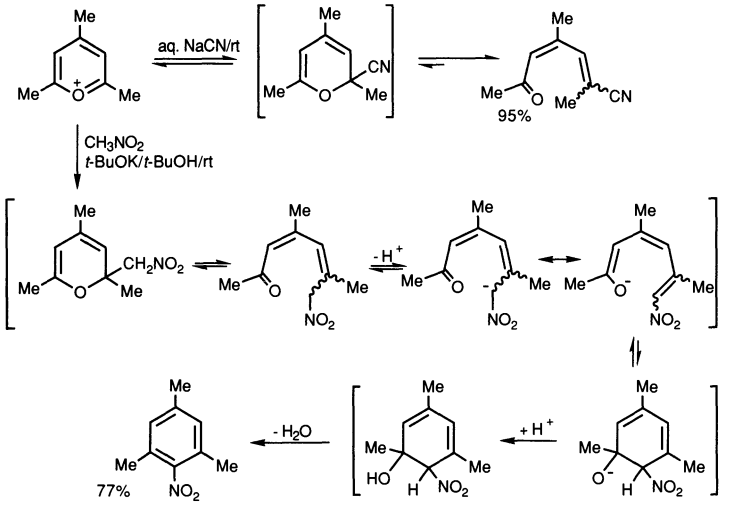
Organometallic addition takes place at an α-position, or occasionally at C-4 when the α-positions are substituted and C-4 is unsubstituted,[11] or with organocuprates.[12] The initial 2*H*-pyrans undergo electrocyclic ring opening (and more rapidly than the comparable cyclohexadiene/hexatriene transformation[13]) affording dienones or dienals.



8.1.2.4 *Other carbanionic additions*

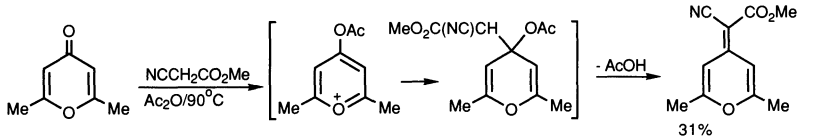
By processes comparable to organometallic addition, cyanide addition to 2,4,6-trimethylpyrylium produces a ring-opened dienone.[14] Reactions with stabilised

anions, such as those from nitromethane or 1,3-dicarbonyl compounds, proceed though a series of equilibria to recyclised, aromatic compounds.[6a]



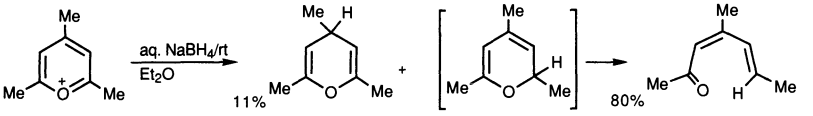
8.1.3 Substitution reactions with nucleophilic reagents

There are a small number of pyrylium reactions which fall into the category of nucleophilic substitutions. 4-Pyrones react with acetic anhydride at carbonyl oxygen to produce 4-acetoxypyryliums, *in situ*, allowing nucleophilic substitution at C-4: the reaction of 2,6-dimethylpyrone with methyl cyanoacetate is typical.[15] Phosphoryl chloride likewise converts 4-pyrones into 4-chloropyryliums.[1]



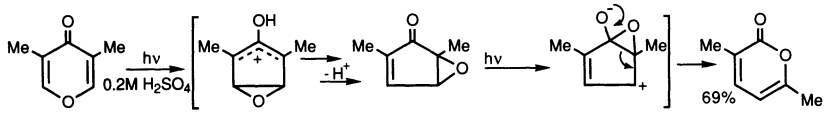
8.1.4 Reactions with reducing agents

The addition of hydride to pyryliums takes place mainly at an α-position, generating 2*H*-pyrans which rapidly open to form the isolated products, dienones best extracted immediately into an organic solvent; the minor products are the isomeric 4*H*-pyrans.[16]

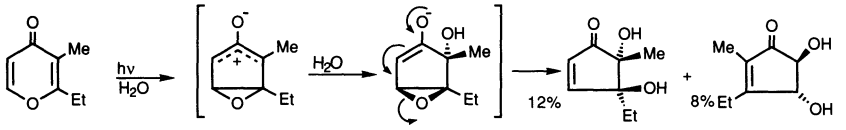


8.1.5 Photochemical reactions

At first sight, the photochemistry of 4-hydroxypyryliums, i.e. of 4-pyrones in acid solution, seems extraordinary, in that they are converted into 2-pyrones, however a rationalisation, involving first a bicyclic hydroxyallyl cation, secondly a bicyclic epoxycyclopentenone, and then a second photo-excitation, makes the transformation clear.[17]

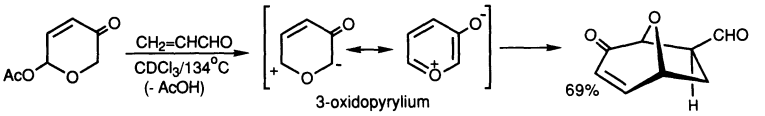


Irradiation at higher p*H* leads to a trapping of first-formed photo-intermediate by solvent and thus the isolation of dihydroxycyclopentenones.[18]



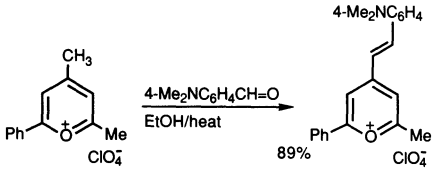
8.1.6 Reactions with dienophiles; cycloadditions

There has been quite an interest in dipolar cycloaddition reactions of 3-oxidopyryliums,[19] formally 3-hydroxypyryliums rendered overall neutral by loss of the phenolic proton, though this is not always the method for their formation. These species undergo cycloadditions across the 2,6-positions and in so doing parallel the reactivity of 3-oxidopyridiniums (section 5.9).

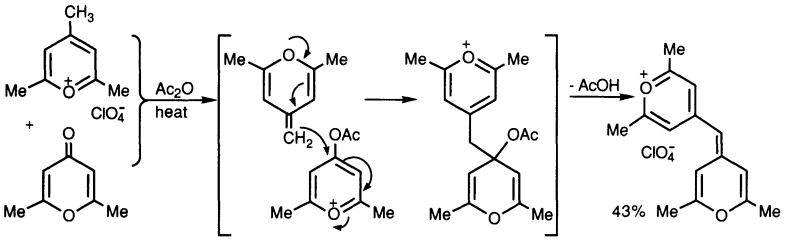


8.1.7 Alkylpyryliums[20]

Alkyl groups at the α- and γ-positions of pyrylium salts are, as might be expected, quite acidic: reaction at a 4-methyl is somewhat faster than at an α-methyl.[21] Such methyls will, for example, condense with aromatic aldehydes,[22] triethyl orthoformate[23] and dimethylformamide.[24]



The condensation between 2,4,6-trimethylpyrylium and 2,6-dimethyl-4-pyrone is particularly instructive: the latter is converted into a 4-acetoxypyrylium (see also section 8.1.3) and the former, by 4-methyl deprotonation, into a nucleophilic dienol ether.[21]



8.2 α-PYRONES AND γ-PYRONES (2*H*-PYRAN-2-ONES AND 4*H*-PYRAN-4-ONES)

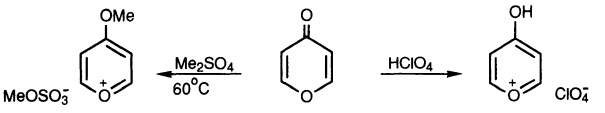
8.2.1 Structure of pyrones

The simple γ-pyrones are quite stable crystalline substances, whereas the α-pyrones are much less stable, α-pyrone itself, which has the smell of fresh-mown hay, polymerising slowly on standing. There are relatively few simple pyrone natural products in great contrast with the widespread occurrence and importance of their benzo-derivatives, the coumarins and chromones, in nature. 2- and 4-Hydroxypyrylium salts are quite strongly acidic and are therefore much better known as their conjugate bases, the 2- and 4-pyrones.

8.2.2 Reactions of pyrones

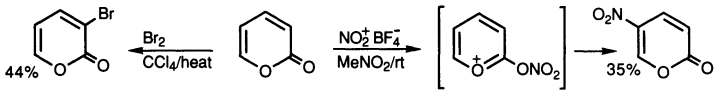
8.2.2.1 *Electrophilic addition and substitution*

γ-Pyrone is a weak base, pK_a −0.3, which is protonated on the carbonyl oxygen to afford often crystalline 4-hydroxypyrylium salts. α-Pyrones are much weaker bases and though they are likewise protonated on carbonyl oxygen in solution in strong acids, salts cannot be isolated. This difference is mirrored in reactions with alkylating agents: the former give 4-methoxypyrylium salts with dimethyl sulfate,[25] whereas α-pyrones require Meerwein salts, Me_3O^+ BF_4^-, for carbonyl-*O*-methylation. Acid-catalysed exchange in γ-pyrone, presumably *via* *C*-protonation of a concentration of neutral molecule, takes place at the 3/5-positions.[26]



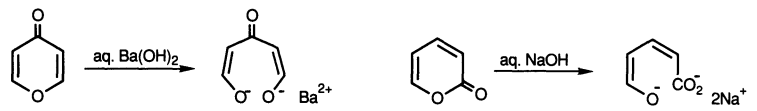
2-Pyrone forms unstable adducts with bromine[27] which give the 3-bromo-2-pyrone on warming. 5-Bromo-2-pyrone is prepared by *N*-bromosuccinimide bromination, then dehydrobromination of 5,6-dihydro-2-pyrone.[28] With nitronium tetrafluoroborate,[29] the electrophile is assumed to attack first at carbonyl oxygen leading subsequently to 5-nitro-2-pyrone.

Simple examples of electrophilic substitution of 4-pyrones are remarkably rare, however bis-dimethylaminomethylation of the parent heterocycle takes place under quite mild conditions.[30]

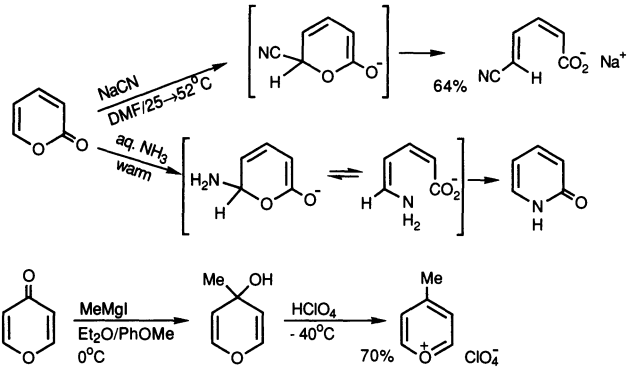


8.2.2.2 *Attack by nucleophilic reagents*

2-Pyrones are in many ways best viewed as unsaturated lactones, and as such they are easily hydrolysed by aqueous alkali; 4-pyrones, too, easily undergo ring opening with base, though for these vinylogous lactones, initial attack is at C-2, in a Michael fashion.[31]

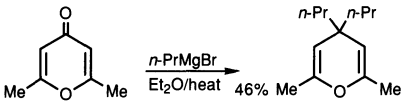


α-Pyrones can in principle add nucleophilic reactants at either C-2 (carbonyl carbon), C-4, or C-6: their reaction with cyanide anion,[32] and ammonia/amines are examples of the last, whereas the addition of Grignard nucleophiles occurs at carbonyl carbon.

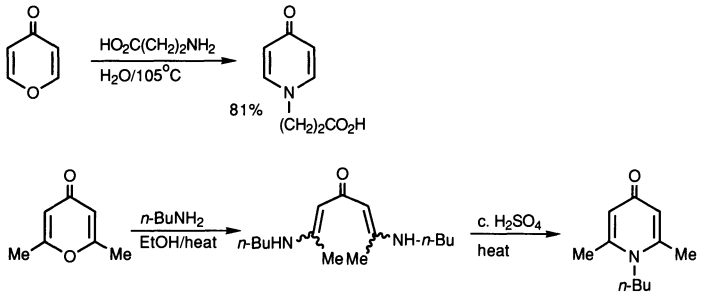


4-Pyrones also add Grignard nucleophiles at the carbonyl carbon, C-4; dehydration of the immediate tertiary alcohol product with mineral acid provides an important access to 4-mono-substituted pyrylium salts.[33] More vigorous conditions lead to the reaction of both α- and γ-pyrones with 2 mol equivalents of

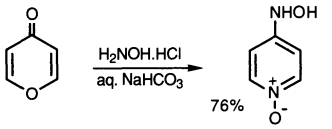
organometallic and the formation of 2,2-disubstituted-2*H*- and 4,4-disubstituted-4*H*-pyrans respectively.[34] Perhaps surprisingly, hydride (lithium aluminium hydride) addition to 4,6-dimethyl-2-pyrone takes place, in contrast, at C-6.[35]



Ammonia and primary aliphatic and aromatic amines convert 4-pyrones into 4-pyridones:[36] this must involve attack at an α-position, then ring opening and reclosure; in some cases ring-opened products of reaction with two mols of the amine have been isolated, though such structures are not necessarily intermediates on the direct route to pyridones.[37]



The reactions of 4-pyrones with hydrazines and hydroxylamine can lead to recyclisations involving the second hetero atom of the attacking nucleophile, producing pyrazoles and isoxazoles respectively; however, in the simplest examples 4-pyrones react with hydroxylamine giving either 1-hydroxy-4-pyridones or 4-hydroxylaminopyridine-*N*-oxides.[38]



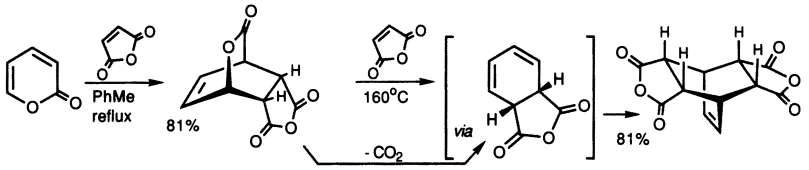
8.2.2.3 *Organometallic derivatives*

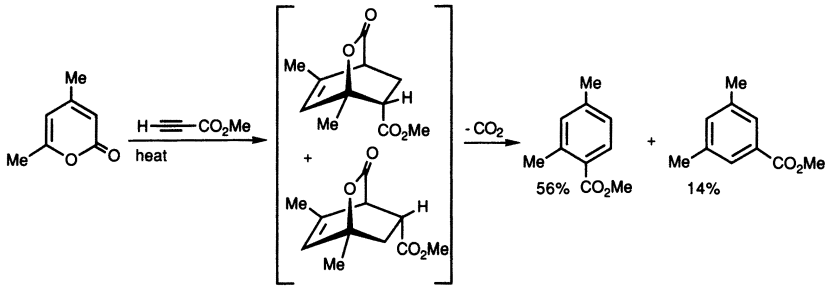
3-Bromopyrone does not undergo exchange (or C–H-deprotonation) with *n*-butyllithium, however it can be transformed into a cuprate, albeit of singularly less nucleophilic character than typical cuprates.[39]

8.2.2.4 *Cycloaddition reactions*[40]

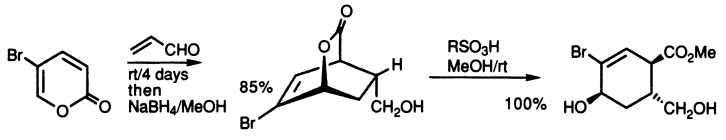
When 2-pyrone acts as a diene in a Diels-Alder a ddition the initial adduct often loses carbon dioxide, generating a second diene which then adds a second mol of the dienophile: reaction with maleic anhydride is typical – a monoadduct can

be isolated, which under more vigorous conditions loses carbon dioxide and undergoes a second addition.[41] When the dienophile is an alkyne, methyl propiolate for example, benzenoid products result from the expulsion of carbon dioxide.[42] Primary adducts, which have not lost carbon dioxide, can be obtained from reactions conducted at lower temperatures under very high pressure.[43]



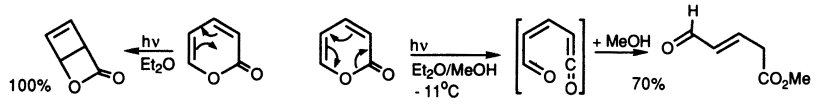


3-[44] and 5-Bromo[28] -2-pyrones present remarkable properties in their abilities to act as efficient dienes towards both electron-rich and electron-poor dienophiles; 3-(*para*-tolylthio)-2-pyrone also undergoes cycloadditions with facility, with electrophilic alkenes.[45]



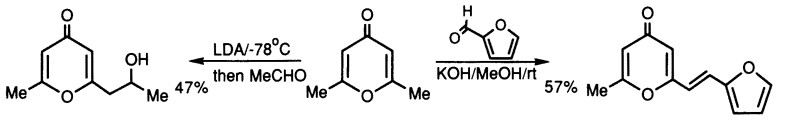
8.2.2.5 *Photochemical reactions*

In addition to the photo-catalysed rearrangement of 4-pyrones in acid solution (see section 8.1.5) the other clear-cut reactions undergone are the transformation of 2-pyrone into a bicyclic β-lactone on irradiation in a nonhydroxylic solvent and into an unsaturated ester-aldehyde on irradiation in the presence of methanol.[46]



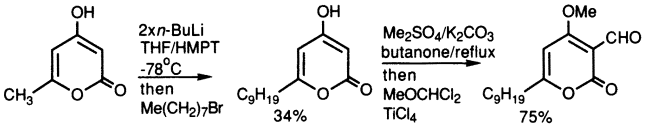
8.2.2.6 *Side-chain reactions*

2,6-Dimethyl-4-pyrone condenses with aromatic aldehydes at a methyl[47] and can be lithiated and thereby substituted.[48]



8.2.2.7 *2,4-Dioxygenated pyrones*

2,4-Dioxygenated pyrones exist as the 4-hydroxy tautomers. Such molecules are easily substituted by electrophiles, at the position between the two oxygens (C-3)[49] and can still be side-chain deprotonated.[50]

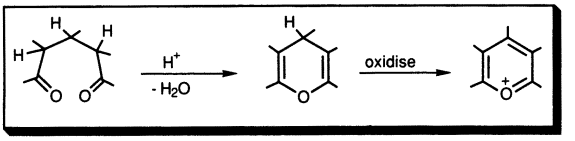


8.3 SYNTHESIS OF PYRYLIUMS[1,7a]

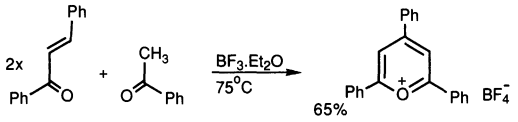
Pyrylium rings are assembled by the cyclisation of a 1,5-dicarbonyl precursor, separately synthesised or generated *in situ*.

8.3.1 From 1,5-dicarbonyl compounds

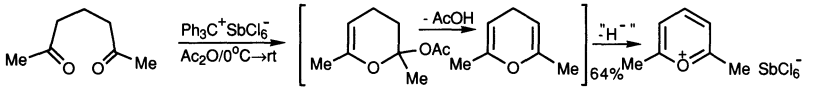
1,5-Dicarbonyl compounds can be cyclised, with dehydration and in the presence of an oxidising agent.



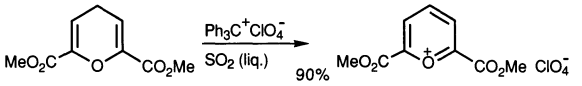
Mono-enolisation of a 1,5-diketone, then the formation of a cyclic hemiacetal, and its dehydration, produces dienol ethers (4*H*-4-pyrans) which require only hydride abstraction to arrive at the pyrylium oxidation level. The diketones are often prepared *in situ* by the reaction of an aldehyde with two mols of a ketone (compare Hantzsch synthesis, section 5.15.1.2) or of a ketone with a previously prepared conjugated ketone – a chalcone in the case of aromatic ketones/aldehydes. It is the excess chalcone which serves as the hydride acceptor in this approach.



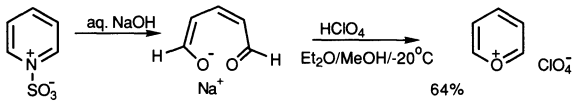
Early work utilised acetic anhydride as solvent with the incorporation of an oxidising agent (hydride acceptor), often ferric chloride (though it is believed that it is the acylium cation which is the hydride acceptor); latterly the incorporation of DDQ,[51] 2,6-dimethylpyrylium or, most often, a trityl cation[52] have proved efficient.



In some cases the 4*H*-pyran is isolated then oxidised in a separate step.[53]

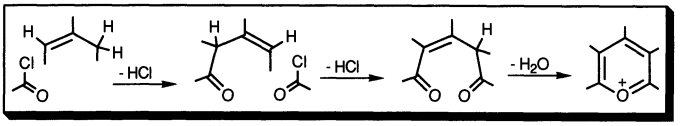


If an unsaturated dicarbonyl precursor is available then no oxidant needs to be added: a synthesis of pyrylium perchlorate itself falls into this category – careful acid treatment of either glutaconaldehyde, or of its sodium salt, produces the parent salt (CAUTION: explosive).[54]



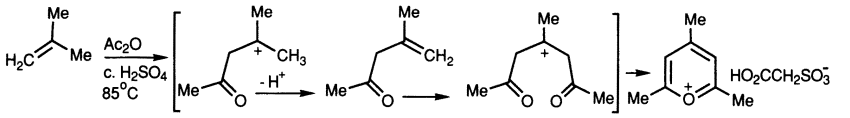
8.3.2 Alkene acylation

Alkenes can be diacylated with an acid chloride or anhydride generating an unsaturated 1,5-dicarbonyl compound which then cyclises with loss of water.

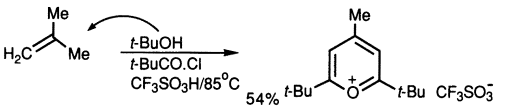


The aliphatic version of the classic aromatic Friedel-Crafts acylation produces, by loss of proton, a non-conjugated enone which can then undergo a second acylation thus generating an unsaturated 1,5-diketone. Clearly, if the alkene is not symmetrical, two isomeric diketones are formed.[55] Under the conditions of these acylations, the unsaturated diketone cyclises, loses water and forms a pyrylium salt. The formation of 2,4,6-trimethylpyrylium, best as its

much more stable and non-hygroscopic carboxymethanesulfonate,[56] illustrates the process.

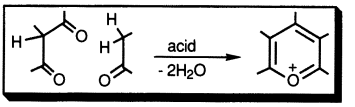


Common variations are the use of an alcohol, which dehydrates *in situ*,[57] or of a halide which similarly dehydrohalogenates[58] to give the alkene.

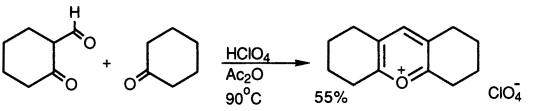


8.3.3 From 1,3-dicarbonyl compounds and ketones

The acid-catalysed condensation of a ketone with a 1,3-dicarbonyl compound, with dehydration *in situ* produces pyrylium salts.



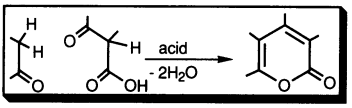
Aldol condensation between a 1,3-dicarbonyl component and a ketone carrying an α-methylene under acidic, dehydrating conditions, produces pyrylium salts.[59] It is likely that the initial condensation is followed by a dehydration before the cyclic hemiacetal formation and loss of a second water molecule. The use of the bis-acetal of malondialdehyde, as synthon for the 1,3-dicarbonyl component, is one of the few ways of making α-unsubstituted pyryliums.[1]



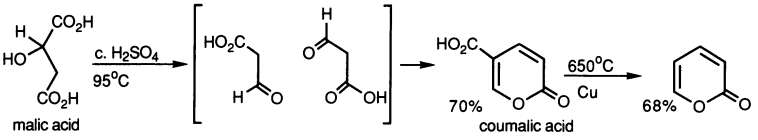
Successful variations on this theme include the use, as synthons for the 1,3-dicarbonyl component, of β-chlorovinyl ketones,[60] or conjugated alkynyl aldehydes.[61]

8.4 SYNTHESIS OF α-PYRONES

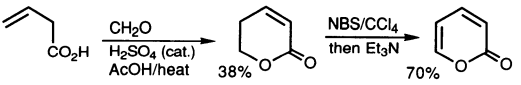
The general method for constructing α-pyrones is that based on the cyclising condensation of a 1,3-keto(aldehydo)-acid with a second component which provides the other two ring carbons.



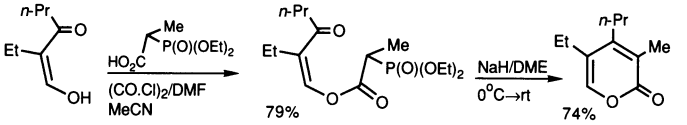
The long known synthesis of coumalic acid from treatment of malic acid with hot sulfuric acid illustrates this route: decarbonylation produces formylacetic acid, *in situ*, which serves as both 1,3-aldehydo-acid component and the second component.[62] Decarboxylation of coumalic acid is still used as an access to 2-pyrone itself.[63]



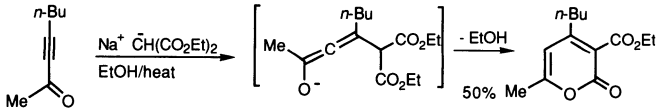
The parent 2-pyrone can also be accessed in a quite different manner: Prins alkylation of but-3-enoic acid with subsequent lactonisation gives 5,6-dihydro-2-pyrone which *via* allylic bromination and then dehydrobromination is converted into 2-pyrone.[64]



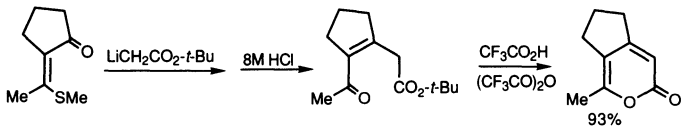
The esterification of a 1,3-ketoaldehyde enol with a diethoxyphosphinylalkanoic acid, forming the ester linkage of the final molecule first, allows ring closure *via* an intramolecular Horner-Emmons reaction.[65]



Conjugate addition of enolates to ynones[66] and to yne-esters[67] are yet further variations on the synthetic theme.

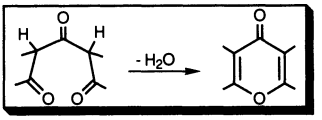


More modern variations include the use of β-methylthiovinylketones, as 1,3-dicarbonyl synthons, in combination with the enolate anion of *t*-butyl acetate.[68]

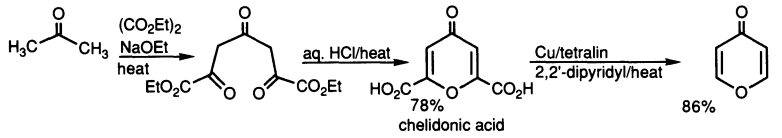


8.5 SYNTHESIS OF γ-PYRONES

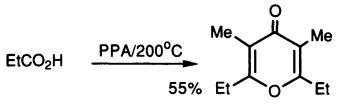
γ-Pyrones result from the acid-catalysed closure of 1,3,5-tricarbonyl precursors.



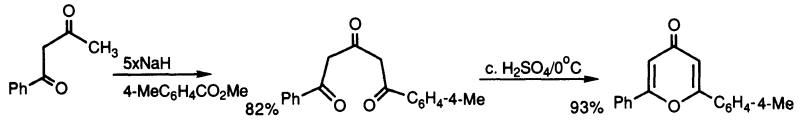
The construction of a γ-pyrone is essentially the construction of a 1,3,5-tricarbonyl compound since such compounds easily form cyclic hemiacetals then requiring only dehydration. Several methods are available for the assembly of such precursors: the synthesis of chelidonic acid (4-pyrone-2,6-dicarboxylic acid)[69] represents the obvious approach of bringing about two Claisen condensations, one on each side of a ketone carbonyl group. Chelidonic acid can be decarboxylated to produce γ-pyrone itself.[70]



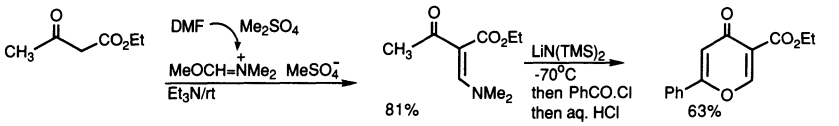
A variety of symmetrically substituted 4-pyrones can be made very simply by heating an alkanoic acid with polyphosphoric acid;[71] presumably a series of Claisen-type condensations, with a decarboxylation, lead to the assembly of the requisite acyclic, tricarbonyl precursor.



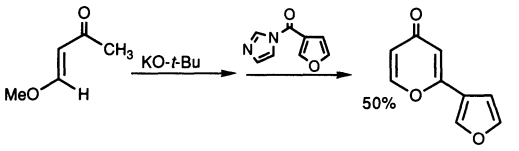
The Claisen condensation of a 1,3-diketone, *via* its dianion, with an ester,[72] or of a ketone enolate with an alkyne ester[73] also give the desired tricarbonyl arrays.



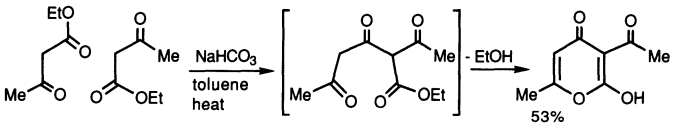
Another strategy to bring about acylation at the less acidic carbon of a β-keto ester is to condense, firstly at the central methylene, with a formate equivalent; this has the added advantage that the added carbon can then provide the fifth carbon of the heterocycle.[74]



α-Unsubstituted 4-pyrones have similarly been constructed *via* the enolate of methoxymethylene ketones.[75]



Dehydroacetic acid[76] was first synthesised in 1866;[77] it is formed very simply from ethyl acetoacetate by a Claisen condensation between two molecules, followed by the usual cyclisation and finally loss of ethanol. In a modern version, β-keto-acids can be self condensed using carbonyl diimidazole as the condensing agent.[78]



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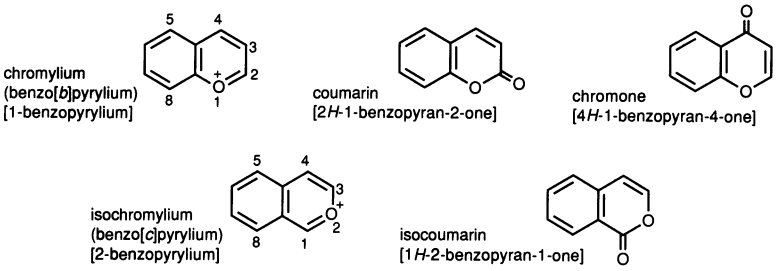
EXERCISES FOR CHAPTER 8

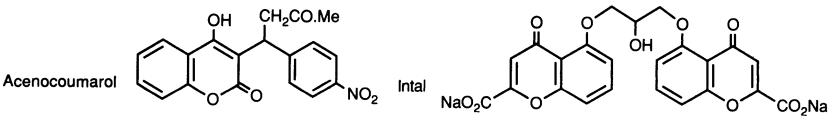
1. Write a sequence for the transformation of 2,4,6-trimethylpyrylium into 1-phenyl-2,4,6-trimethylpyridinium by reaction with aniline.
2. Devise a mechanism to explain the formation of 1,3,5-triphenylbenzene from reaction of 2,4,6-triphenylpyrylium perchlorate with 2 mol equivalents of $Ph_3P{=}CH_2$.
3. Suggest structures for the compounds in the following sequence: 2-methyl-5-hydroxy-4-pyrone reacted with MeOTf → $C_7H_9O_3^+$ TfO^- (a salt), then this with 2,2,6,6-tetramethylpiperidine (a hindered base) → $C_7H_8O_3$, a dipolar substance, and this then with acrylonitrile → $C_{10}H_{11}NO_3$.
4. Write out a mechanism for the conversion of 4-pyrone into 1-phenyl-4-pyridone by reaction with aniline. Write a structure for the product you would expect from reaction of methyl coumalate (5-methoxycarbonyl-2-pyrone) with benzylamine.
5. Deduce structures for the pyrylium salts formed by the following sequences: (i) pinacolone ($Me_3CCO.Me$) condensed with pivaldehyde ($Me_3CCH{=}O$) gave $C_{11}H_{20}O$, which was then reacted with pinacolone in the presence of $NaNH_2$, generating $C_{17}H_{32}O_2$, and this with Ph_3C^+ ClO_4^- in AcOH gave a pyrylium salt; (ii) cyclodecene and $Ac_2O/HClO_4$; (iii) PhCO.Me and $MeCO.CH_2CHO$ with Ac_2O and $HClO_4$.
6. When dehydroacetic acid is heated with c. HCl 2,6-dimethyl-4-pyrone is formed in 97% yield – explain.
7. When ethyl acetoacetate is reacted with HCl, isodehydroacetic acid (ethyl 4,6-dimethyl-2-pyrone-5-carboxylate is formed – explain.
8. Deduce structures for the pyrones formed by the following sequences: (i) $PhCO.CH_3$ with $PhC{\equiv}CCO_2Et$ in the presence of NaOEt; (ii) butanoic acid heated with PPA at 200°C; (iii) *n*-$BuCO.CH_2CO_2H$ with carbonyl diimidazole; (iv) $PhCO.CH_2CO.CH_3$ with excess NaH then methyl 4-chlorobenzoate; (v) $CH_3CO.CH{=}CHOMe$ with KO-*t*-Bu and PhCO.Cl.

9 Benzopyryliums and benzopyrones: reactions and synthesis



1-Benzopyryliums, coumarins, and chromones are very widely distributed throughout the plant kingdom where many secondary metabolites contain them. Not the least of these are the anthocyanins[1] and flavones[2] which, grouped together, are known as the flavonoids,[3] and make up the majority of the flower pigments. In addition, many flavone and coumarin[4] derivatives have marked toxic and other physiological properties in animals, though they play no part in the normal metabolism of animals. The isomeric 2-benzopyrylium[5] system does not occur naturally and only a few isocoumarins[6] occur as natural products: as a consequence much less work on these has been described.

Chemotherapeutically valuable compounds in this group are a series of coumarins, of which Acenocoumarol is one, which are valuable as anticoagulants, and Intal, which is used in the treatment of bronchial asthma. One of the earliest optical brighteners was 7-diethylamino-4-methylcoumarin.[7]



Processes initiated by nucleophilic additions to the positively charged heterocyclic ring are the main, almost the only, types of reaction known to be undergone by benzopyryliums. The absence of examples of electrophilic

substitution in the benzene ring is to be contrasted with the many examples of substitution in quinolinium and isoquinolinium salts, emphasising the greater electron-withdrawing and thus deactivating effect of positively charged oxygen.

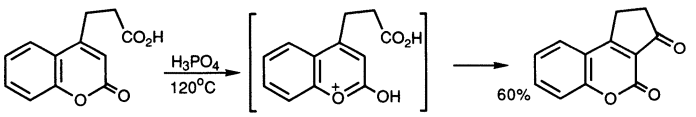
Coumarins, chromones, and isocoumarins react with both nucleophiles and electrophiles in much the same way as do quinolones and isoquinolones.

9.1 REACTIONS OF BENZOPYRYLIUMS

Much more work has been done on 1-benzopyryliums than on 2-benzopyryliums, because of their relevance to the flavylium (2-phenyl-1-benzopyrylium) nucleus which occurs widely in the anthocyanins, and much of that work has been conducted on flavylium itself. As with pyrylium salts, benzopyrylium salts usually add nucleophiles at the carbon adjacent to the oxygen.

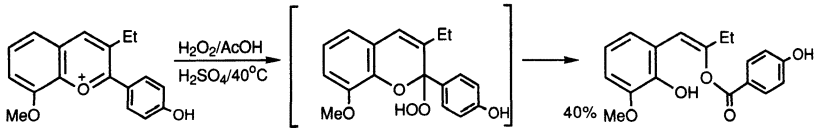
9.1.1 Reactions with electrophilic reagents

No simple examples are known of electrophilic or radical substitution of either heterocyclic or homocyclic rings of benzopyrylium salts; flavylium (2-phenyl-1-benzopyrylium)[8] and 1-phenyl-2-benzopyrylium[5] salts nitrate in the substitutent benzene ring. Having said this, the cyclisation of coumarin-4-propanoic acid may represent Friedel-Crafts type intramolecular attack on the carbonyl-*O*-protonated form, i.e. on a 2-hydroxy-1-benzopyrylium system, at C-3.[9]



9.1.2 Reactions with oxidising agents

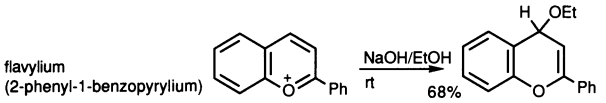
Oxidative general breakdown of flavylium salts was utilised in early structural work on the natural compounds. Baeyer-Villiger oxidation is such a process whereby the two 'halves' of the molecule can be separately examined (after ester hydrolysis of the product).[10] Flavylium salts can be oxidised to flavones using thallium trinitrate[11] and benzopyrylium itself can be converted into coumarin with manganese dioxide.[12]



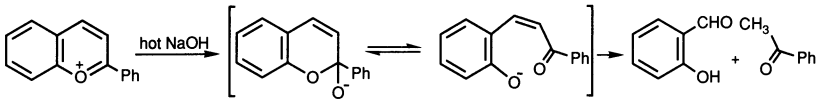
9.1.3 Reactions with nucleophilic reagents

9.1.3.1 *Water and alcohols*

Water and alcohols add readily at C-2, and sometimes at C-4, generating chromenols or chromenol ethers.[13] It is difficult to obtain 2*H*-chromenols pure since they are always in equilibrium with ring-opened chalcones.[14]

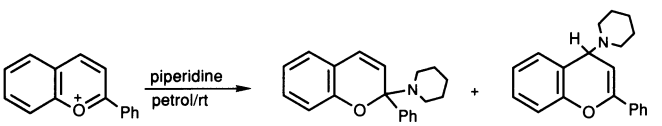


Controlled conditions are required for the production of simple adducts, for under more vigorous alkaline treatment, ring opening then carbon–carbon bond cleavage *via* a retro-aldol mechanism takes place and such processes, which are essentially the reverse of a route used for the synthesis of 1-benzopyryliums (section 9.3.1), were utilised in early structural work on anthocyanin flower pigments.

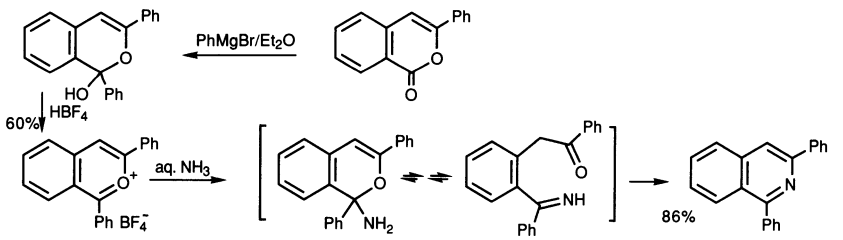


9.1.3.2 *Ammonia and amines*

Ammonia and amines add to benzopyryliums, and simple adducts from secondary amines have been isolated.[15]

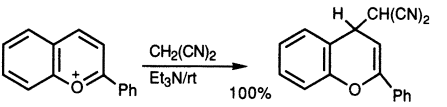


It is important to realise that 1-benzopyrylium salts cannot be converted into quinolines or quinolinium salts by reaction with ammonia or primary amines, whereas 2-benzopyrylium salts are converted, efficiently, into isoquinolines and isoquinolinium salts.[16]



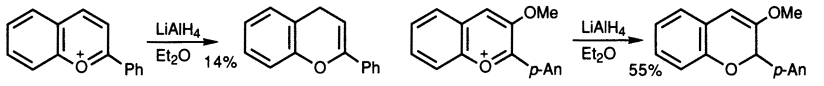
9.1.3.3 *Carbon nucleophiles*

Organometallic carbon nucleophiles add to flavylium salts[17] as do activated aromatics like phenol,[18] and enolates such as those from cyanoacetate, nitromethane[19] and dimedone,[20] all very efficiently at C-4. Cyanide and azide add to 2-benzopyryliums at C-1.[21]



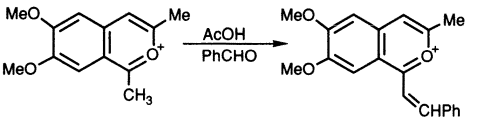
9.1.4 Reactions with reducing agents

Catalytic hydrogenation of flavylium salts is generally straightforward and results in the saturation of the heterocyclic ring. Lithium aluminium hydride reduces flavylium salts generating 4*H*-chromenes,[22] unless there is a 3-methoxyl, when 2*H*-chromenes are the products.[23] 2-Benzopyryliums add hydride at C-1.[24]



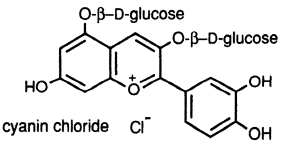
9.1.5 Alkylbenzopyryliums

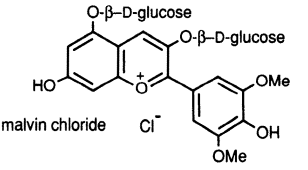
Alkyl groups oriented α or γ to the positively charged oxygen in benzopyryliums have acidified hydrogens which allow aldol-type condensations.[5,25]



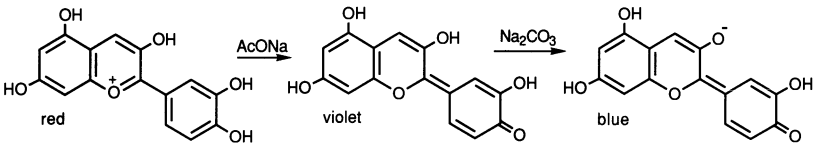
9.1.6 1-Benzopyrylium pigments; anthocyanins and anthocyanidins

The anthocyanidins are polyhydroxyflavylium salts. They occur in a large proportion of the red to blue flower pigments and in fruit skins, for example grapes and therefore in red wines made therefrom. Anthocyanidins are generally bound to sugars, and these glycosides are known as anthocyanins. As an example, cyanin (isolated as its chloride) is an anthocyanin which occurs in the petals of the red rose (*Rosa gallica*), the poppy (*Papaver rhoeas*), and very many other flowers. Another example is malvin chloride, which has been isolated from many species, including *Primula viscosa*, a mauvy-red alpine primula.





In the living cell these compounds exist in more complex bound forms, interacting with other molecules, for example flavones,[26] and the actual observed colour depends on these interactions. However it is interesting that even *in vitro*, simple p*H* changes bring about extreme changes in the electronic absorption of these molecules. For example, cyanidin is red in acidic solution, violet at intermediate p*H* and blue in weakly alkaline solution, the deep colours being the result of extensive resonance delocalisation in each of the structures.

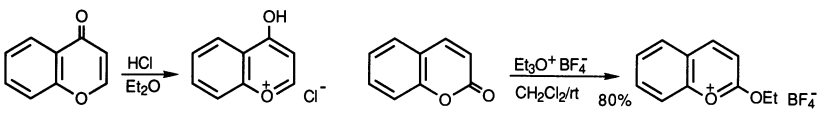


9.2 BENZOPYRONES (CHROMONES, COUMARINS AND ISOCOUMARINS)

9.2.1 Reactions with electrophilic reagents

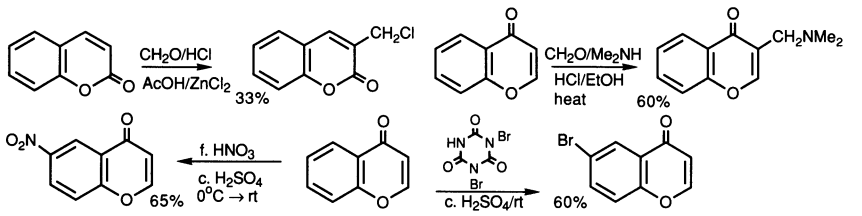
9.2.1.1 *Addition to carbonyl oxygen*

Addition to carbonyl oxygen of a proton produces a hydroxybenzopyrylium salt; chromones undergo this protonation more easily than the coumarins, for example passage of hydrogen chloride through a mixture of chromone and coumarin in ether solution leads to the precipitation of only chromone hydrochloride (i.e. 4-hydroxy-1-benzopyrylium chloride).[27] *O*-Alkylation requires the more powerful alkylating agents.[5,28]

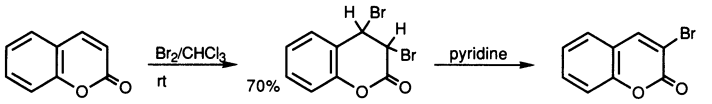


9.2.1.2 *C-Substitution*

C-Substitution of coumarins and chromones has been observed in both rings: in strongly acidic media, in which presumably it is an hydroxybenzopyrylium cation which is attacked, substitution takes place at C-6, for example nitration.[29] This can be contrasted with the dimethylaminomethylation of chromone[30] or the chloromethylation of coumarin,[31] where hetero-ring substitution takes place, presumably *via* the non-protonated (complexed) heterocycle (CAUTION: CH_2O/HCl also produces some $ClCH_2OCH_2Cl$, a carcinogen).

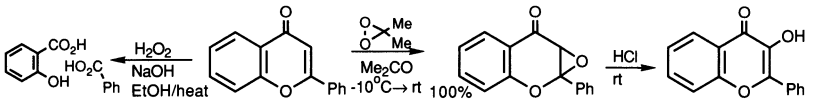


Treatment of coumarin with bromine results in simple addition to the double bond in the heterocyclic ring; 3-bromocoumarin can be obtained by then eliminating hydrogen bromide.[32] Bromine in the presence of an excess of aluminium chloride (the 'swamping catalyst' effect) converts coumarin into 6-bromocoumarin.[33] Chromone can be efficiently brominated at C-6 using dibromoisocyanuric acid (DBI);[34] treatment of chromone with bromine in carbon disulfide results in addition, elimination of hydrogen bromide on warming giving 3-bromochromone.[35]



9.2.2 Reactions with oxidising agents

Non-phenolic coumarins are relatively stable to oxidative conditions. Various oxidative methods have been extensively used in the structure determination of natural flavones.[36]

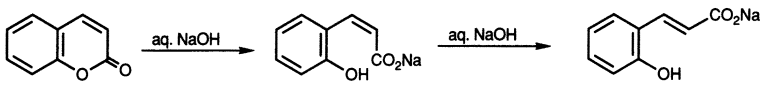


Flavones and isoflavones (3-arylchromones) are quantitatively converted into 2,3-epoxides by exposure to dimethyl dioxirane; such intermediates have obvious synthetic potential, the former oxides, for example, being quantitatively converted by acid into 3-hydroxyflavones, which are naturally occurring.[37]

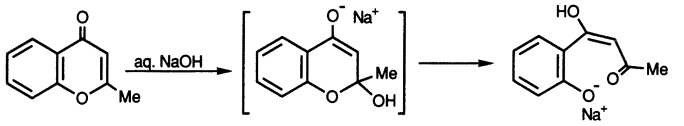
9.2.3 Reactions with nucleophilic reagents

9.2.3.1 *Hydroxide*

Coumarins (and isocoumarins) are quantitatively hydrolysed to give yellow solutions of the salts of the corresponding *cis* cinnamic acids (coumarinic acids) which cannot be isolated since acidification brings about immediate relactonisation; prolonged alkali treatment leads to isomerisation and the formation of the *trans* acid (coumaric acid) salt.

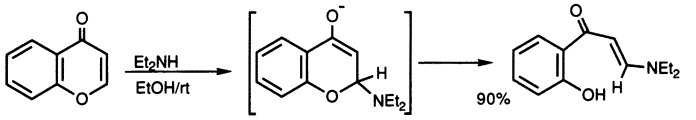


Cold sodium hydroxide comparably reversibly converts chromones into the salts of the corresponding ring-opened phenols, *via* initial attack at C-2, more vigorous alkaline treatment leading to reverse-Claisen degradation of the 1,3-diketo-side-chain.



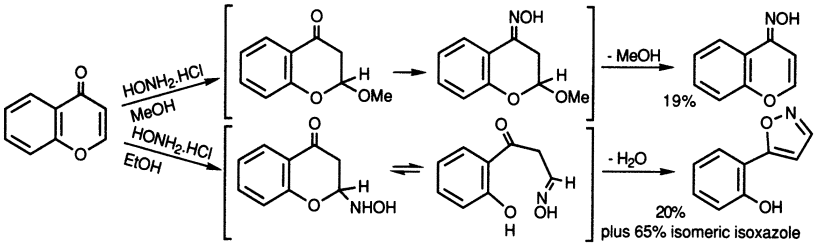
9.2.3.2 *Ammonia and amines*

Ammonia and amines do not convert coumarins into 2-quinolones, nor chromones into 4-quinolones, but isocoumarins do produce isoquinolones.[38] Ring-opened products from chromones and secondary amines can be obtained where again the nucleophile has attacked at C-2.



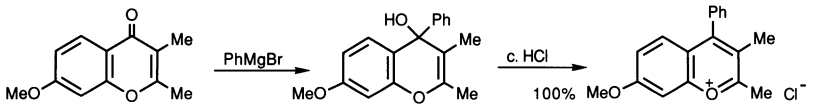
9.2.3.3 *Hydroxylamine*

Hydroxylamine reacts with chromone to give different products according to the reaction conditions: in dry methanol, hydroxylamine hydrochloride produces chromone oxime; in ethanolic solution, ring opening and re-closure produces isoxazoles.[39] Both types of product are formed *via* adducts in which a nucleophile has added to C-2. In the former case, the oxime is formed not by direct attack on the carbonyl group of the chromone but *via* a methanol C-2 adduct.

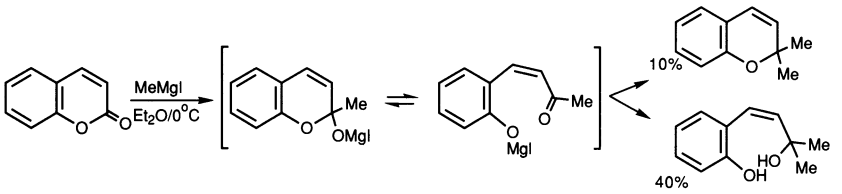


9.2.3.4 *Carbon nucleophiles*

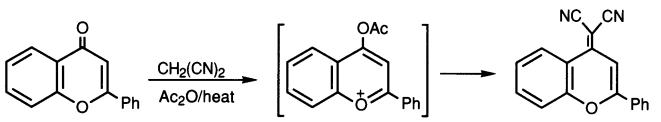
Grignard reagents react with chromones at carbonyl carbon; the resulting chromenols can be converted by acid into the corresponding 4-substituted 1-benzopyrylium salts.[25]



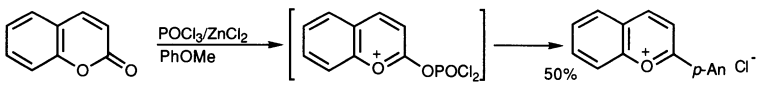
Coumarins, and isocoumarins,[16] react with Grignard reagents, as do esters, and can give mixtures of products, resulting from ring opening of the initial carbonyl adduct; the reaction of coumarin with methyl magnesium iodide illustrates this.[40]



By conversion into a benzopyrylium salt with a good leaving group, nucleophiles can be introduced at the chromone-4-position: treatment with acetic anhydride presumably forms a 4-acetoxybenzopyrylium.[41]

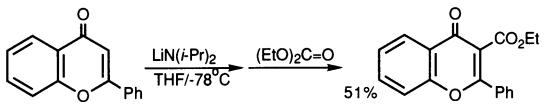


In efficient couplings, coumarin can be made to react with electron-rich aromatics using phosphorus oxychloride, alone, or with zinc chloride.[42]

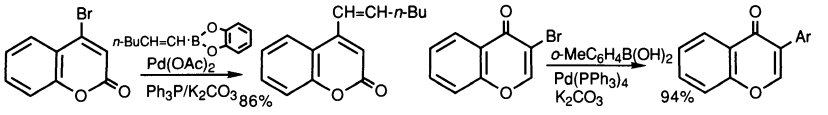


9.2.3.5 *Organometallic derivatives*

Flavone has been lithiated at C-3.[43]

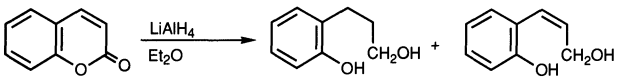


Both 3-bromochromone and 4-bromocoumarin have been successfully used in coupling reactions using palladium methodology.[44]



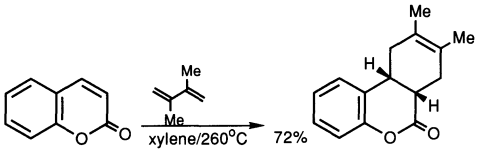
9.2.3.6 *Reactions with reducing agents*

Both coumarin and chromone are converted by diborane then alkaline hydrogen peroxide into 3-hydroxychroman.[45] Catalytic reduction of coumarin or chromone removes the C–C double bond.[46] For both systems, hydride reagents can of course react, either at carbonyl carbon or the conjugate position, and mixtures therefore tend to be produced.



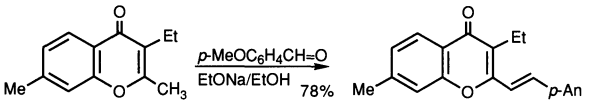
9.2.3.7 *Reactions with dienophiles; cycloadditions*

Coumarins, but not, apparently, chromones, serve as dienophiles in Diels-Alder reactions, but under relatively forcing conditions.[47]

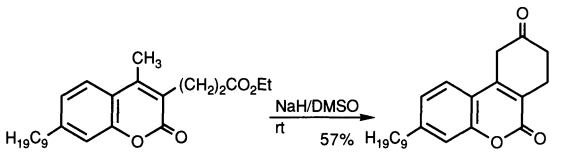


9.2.3.8 *Alkylcoumarins and -chromones*

Methyl groups at C-2, but not at C-3, of chromones undergo condensations with aldehydes, because only the former can be deprotonated to give conjugated enolates.[48]

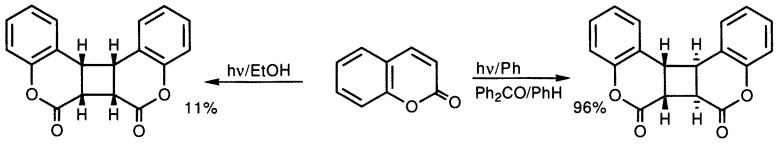


The 4-position of coumarins is the only one at which alkyl substituents have enhanced acidity in their hydrogens,[49] and this is considerably less than that of the methyl groups of 2-methylchromones.[50]

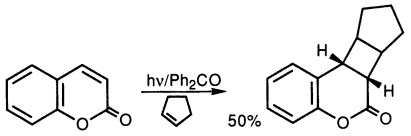


9.2.3.9 *Photochemical reactions*

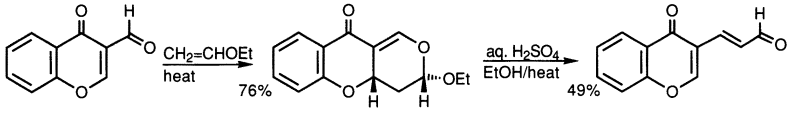
Only coumarin has been studied extensively in this context; in the absence of a sensitiser it gives a *syn* head-to-head dimer; in the presence of benzophenone, as sensitiser, the *anti* isomer is formed;[51] the *syn* head-to-tail dimer is obtained by irradiation in acetic acid.[52]



Cyclobutane-containing products are obtained in modest yields by sensitiser-promoted cycloadditions to tetramethylethene, ketene diethylacetal and cyclopentene.[53]



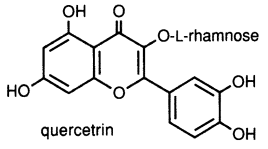
It is a measure of the low instrinsic aromaticity associated with fused pyrone rings, that 3-formylchromone undergoes hetero Diels-Alder addition with ethoxyethene.[54]

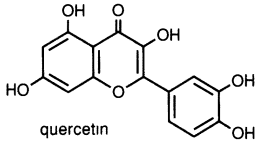


9.2.3.10 *Flavone pigments*

The naturally occurring flavones are yellow and are very widely distributed in plants. They accumulate in almost any part of a plant, from the roots to the flower petals.

Unlike the anthocyanins, which are too reactive and short-lived, the much more stable flavones have, from time immemorial, been used as dyes, for they impart various shades of yellow to wool. As an example, in the more recent past the inner bark of one of the North American oaks, *Quercus velutina*, was a commercial material known as quercitron bark and much used in dyeing: it contains quercetrin.



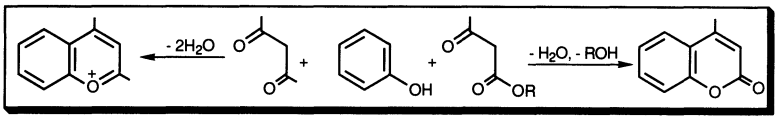


The corresponding aglycone, quercetin, is one of the most widely-occurring flavones, found, for example, in *Chrysanthemum* and *Rhododendron* species, horse chestnuts, lemons, onions and hops.

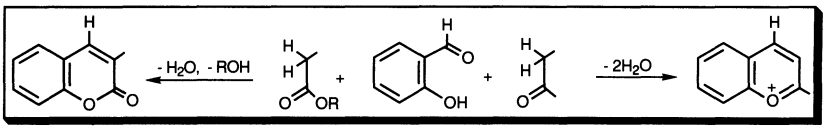
9.3 SYNTHESIS OF BENZOPYRYLIUMS, CHROMONES, COUMARINS AND ISOCOUMARINS

There are three important ways of putting together 1-benzopyryliums, coumarins and chromones; all begin with phenols. The isomeric 2-benzopyrylium and isocoumarin nuclei require the construction of an *ortho*-carboxy- or *ortho*-formyl-arylacetaldehyde (homophthalaldehyde).

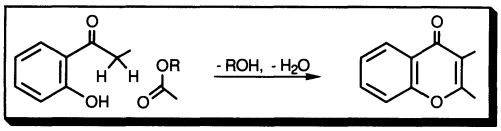
Subject to the restrictions set out below, phenols react with 1,3-dicarbonyl compounds to produce 1-benzopyryliums or coumarins depending on the oxidation level of the 1,3-dicarbonyl component.



ortho-Hydroxybenzaldehydes react with carbonyl compounds having an α-methylene, to give 1-benzopyryliums or coumarins depending on the nature of the aliphatic unit.



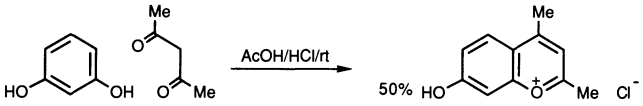
ortho-Hydroxyaryl alkyl ketones react with esters to give chromones.



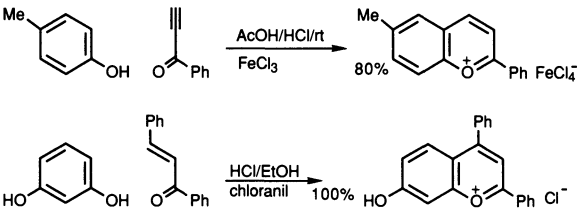
9.3.1 Ring synthesis of 1-benzopyryliums[1b]

9.3.1.1 *From phenols and 1,3-dicarbonyl compounds*

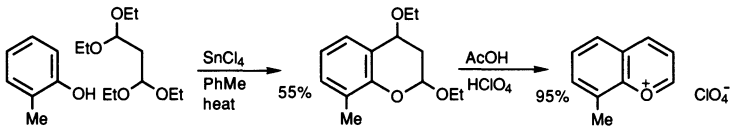
The simplest reaction, that between a diketone and a phenol, works best with resorcinol, for the second hydroxyl facilitates the cyclising electrophilic attack. This synthesis can give mixtures with unsymmetrical diketones, and it is therefore well suited to the synthesis of 1-benzopyryliums with identical groups at C-2 and C-4,[55] however diketones in which the two carbonyl groups are appreciably different in reactivity can produce high yields of single products.[56]



Acetylenic ketones, synthons for 1,3-keto-aldehydes, also take part regioselectively in condensations,[57] as do chalcones, though of course an oxidant must be incorporated in this latter case.[58]

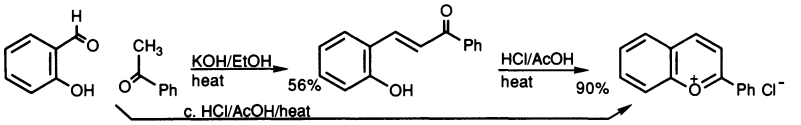


For hetero-ring-unsubstituted targets the bis-acetal of malondialdehyde can be employed; in this variant a heterocyclic acetal-ether is first obtained, from which two mol equivalents of ethanol must then be eliminated.[59]



9.3.1.2 *From ortho-hydroxybenzaldehydes and ketones*

Salicylaldehydes can be condensed, by base or acid catalysis, with ketones which have an α-methylene. When base catalysis is used the intermediate hydroxy-chalcones can be isolated,[8] but overall yields are often better when the whole sequence is carried out in one step, using acid.[60] It is important to note that because this route does not rely upon an electrophilic cyclisation on the benzene ring, benzene-ring-unsubstituted 1-benzopyryliums can be produced.

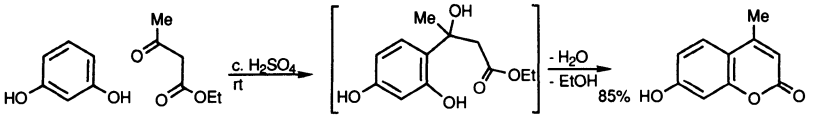


9.3.2 Ring synthesis of coumarins

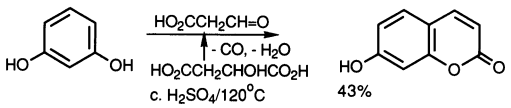
9.3.2.1 *From phenols and 1,3-ketoesters*

The Pechmann synthesis[61]

Phenols react with β-ketoesters, including cyclic keto-esters,[62] to give coumarins under acid-catalysed conditions, the usual being concentrated sulfuric acid;[63] hydrogen fluoride[64] or a cation exchange resin[65] have also been recommended.

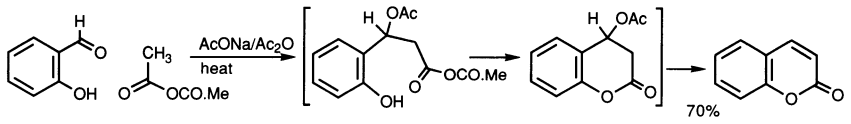


The Pechmann synthesis works best with the more nucleophilic aromatics such as resorcinols: electrophilic attack on the benzene ring *ortho* to phenolic oxygen by the protonated ketone carbonyl is the probable first step, though aryl acetoacetates, prepared from a phenol and diketene, also undergo ring closure to give coumarins.[66] The greater electrophilicity of the ketonic carbonyl determines the orientation of combination. The production of hetero-ring-unsubstituted coumarins can be achieved by condensing with formylacetic acid, generated *in situ* by the decarbonylation of malic acid.

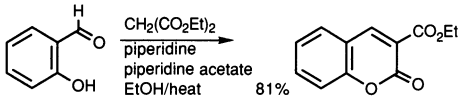


9.3.2.2 *From ortho-hydroxybenzaldehydes and anhydrides (esters)*

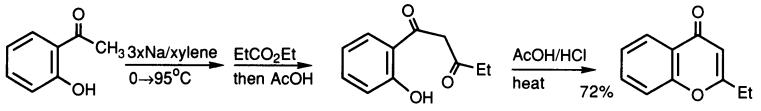
The simplest synthesis of coumarins is a special case of the Perkin condensation i.e. the condensation of an aromatic aldehyde with an anhydride. *ortho*-Hydroxy-*trans*-cinnamic acids cannot be intermediates since they do not isomerise under the conditions of the reaction; nor can *O*-acetylsalicaldehyde be the immediate precursor of the coumarin, since it is not cyclised by sodium acetate on its own.[67]



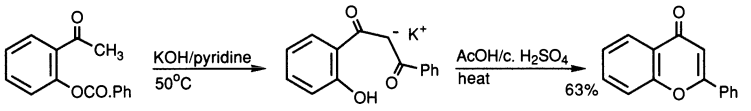
The general approach can be enlarged and conditions for condensation made milder by the use of further-activated esters, thus condensation with methyl nitroacetate produces 3-nitrocoumarins,[68] condensations with Wittig ylids allow *ortho*-hydroxyaryl ketones to be used[69] and the use of diethyl malonate (or malonic acid[70]), in a Knoevenagel condensation, produces coumarins with a 3-ester substituent,[71] which can be removed by hydrolysis and decarboxylation if required.



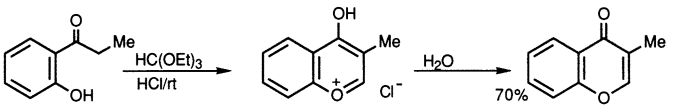
9.3.3 Ring synthesis of chromones from ortho-hydroxyacyl benzenes and esters



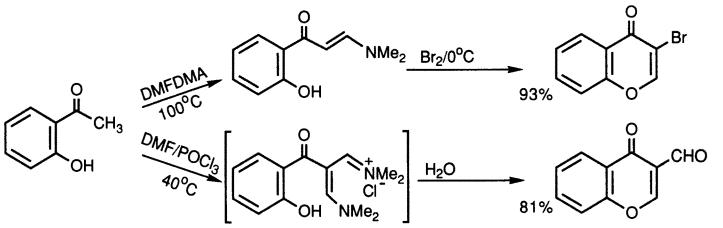
This synthesis involves a Claisen condensation between an ester and the activated methylene of the acyl benzene. The Claisen condensation can be conducted in the presence of the acidic phenolic hydroxyl by the use of excess strong base;[72] triethylamine as solvent and base has also been utilised.[73] Alternatively, the process is conducted in two steps: first, acylation of the phenolic hydroxyl, and secondly, an intramolecular[74] base-catalysed Claisen condensation, known as the Baker-Venkataraman rearrangement: a synthesis of flavone is illustrative of the latter.[75]



The production of a 2-unsubstituted chromone by this route requires the use of formate, or its equivalent, as the ester: a good method for this is the use of triethyl orthoformate;[76] the combination dimethylformamide/methanesulfonyl chloride has also been employed.[77] Another route to 2-unsubstituted chromones employs oxalic acid half-ester half-acid chloride, which gives a 2-ethoxycarbonyl chromone, hydrolysis and decarboxylation of which achieves the required result.[78] Diethyl carbonate as the ester gives rise to 2,4-dioxygenated heterocycles, which exist as 4-hydroxy-coumarins.[79]



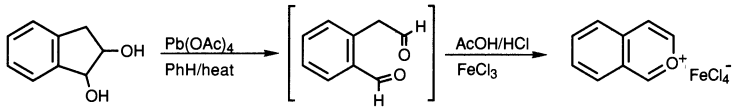
The variants on this route are many: for example, condensation of *ortho*-hydroxyacetophenone with the Vilsmeier reagent produces 3-formylchromone,[80] and combination with dimethylformamide dimethyl acetal, then bromine, gives 3-bromochromones.[81]



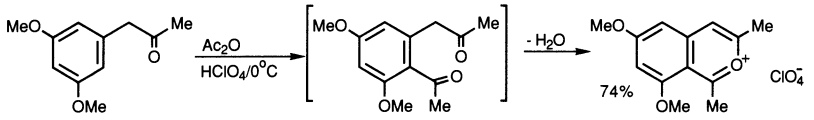
At a lower oxidation level, *ortho*-hydroxyacyl benzenes undergo base-catalysed aldol condensations with aromatic aldehydes to give α,β-unsaturated ketones known as chalcones.[82] Chalcones can be cyclised to 2,3-dihydrochromones, which in turn can be dehydrogenated to produce chromones, either by bromination/dehydrobromination or by treatment with trityl cation.[83]

9.3.4 Ring synthesis of 2-benzopyryliums

The first synthesis[84] of the 2-benzopyrylium cation provided the pattern for subsequent routes in which it is the aim to produce a homophthaldehyde, or diketone analogues, for acid-catalysed closure.

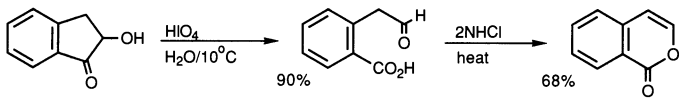


Most of the 2-benzopyrylium salts which have been synthesised subsequently have been 1,3-disubstituted and their precursors have been prepared by Friedel-Crafts acylation of activated benzyl ketones.[6,85]

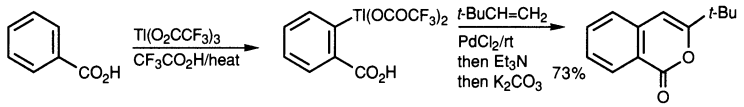


9.3.5 Ring synthesis of isocoumarins

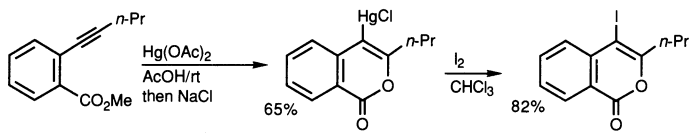
One approach to isocoumarins is comparable to that above for 2-benzopyryliums, only the ring aldehyde needing to be changed to acid.[86]



The direct introduction of the two-carbon unit of the heterocyclic ring, *ortho* to an existing carboxylic acid (ester) has been achieved in two ways: *ortho*-bromobenzoates can be coupled with π-(2-methoxyallyl)nickel bromide for the introduction of acetonyl,[87] or thallation of benzoic acids, *ortho* to the carboxyl, can be followed by palladium-catalysed coupling with alkenes.[88]



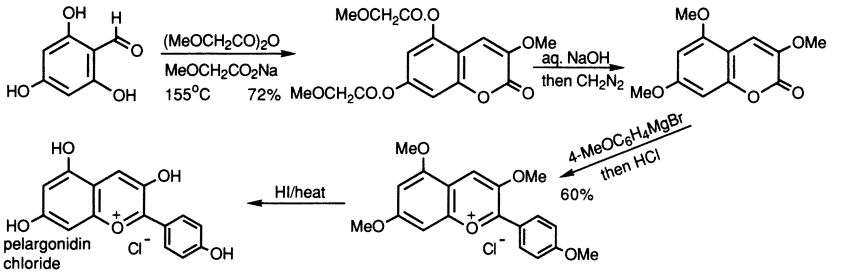
Finally, benzoates carying an *ortho* acetylenic substituent can be ring closed using mercuric acetate.[89]



9.3.6 Notable examples of benzopyrylium and benzopyrone syntheses

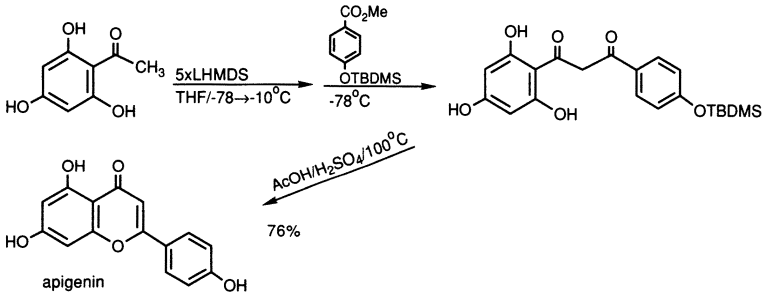
9.3.6.1 *Pelargonidin chloride*

The first synthesis of pelargonidin chloride used methyl ethers as protecting groups for the phenolic hydroxyls during the Grignard addition step.[90]



9.3.6.2 *Apigenin*

The modern use of excess of a very strong base, and the reaction of the resulting 'polyanion' obviated the need for phenolic protection in this synthesis of apigenin.[91]



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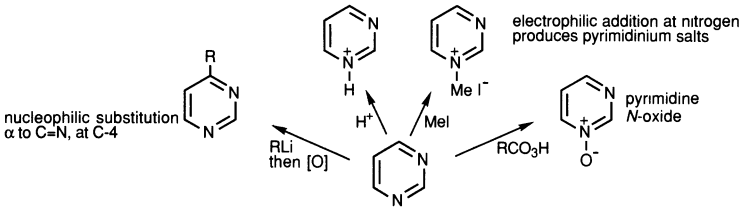
EXERCISES FOR CHAPTER 9

1. When salicaldehyde and 2,3-dimethyl-1-benzopyrylium are heated together in acid, a condensation product $C_{18}H_{15}O_2^+ Cl^-$ is formed. Treatment of the salt with a weak base (pyridine) generates a neutral compound, $C_{18}H_{14}O_2$. Suggest structures for these two products.
2. When ethyl 2-methylchromone-3-carboxylate is treated with NaOH, then HCl, a product $C_{11}H_8O_4$ is produced which does not contain a carboxylic acid group but does dissolve in dilute alkali: suggest a structure and the means whereby it could be formed.
3. Deduce the structures of intermediate and final product in the sequence: salicaldehyde/$MeOCH_2CO_2Na/Ac_2O$/heat $\rightarrow$ $C_{10}H_8O_3$, this then with 1 mol equivalent of PhMgBr $\rightarrow$ $C_{16}H_{14}O_3$ and finally this with HCl $\rightarrow$ $C_{16}H_{13}O_2^+ Cl^-$.
4. Predict the structure of the major product from the interaction of resorcinol (1,3-dihydroxybenzene) and (i) $PhCO.CH_2CO.Me$ in AcOH/HCl; (ii) methyl 2-oxocyclopentanecarboxylate/H_2SO_4.

Typical reactivity of the diazines: pyridazine, pyrimidine and pyrazine

10

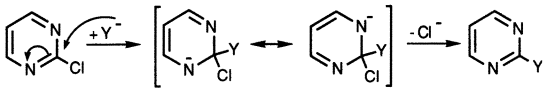
The diazines – pyridazine, pyrimidine and pyrazine – contain two azomethine nitrogen atoms, so the lessons learnt with regard to pyridine (chapter 5) are, in these heterocycles, exaggerated. Two hetero atoms withdraw electron density from the ring carbons even more than in pyridine, so the unsubstituted diazines are **even more resistant to electrophilic substitution than is pyridine**. A corollary of course, developed below, is that this same increased electron deficiency at carbon makes the **diazines more easily attacked by nucleophiles than pyridines**. The availability of nitrogen lone pair(s) is also reduced: each of the diazines is appreciably less basic than pyridine, reflecting the destabilising influence of the second nitrogen on the *N*-protocation. Nevertheless, diazines will form salts and will react with alkyl halides and with peracids to give *N*-alkyl quaternary salts and *N*-oxides, respectively. Generally speaking, such electrophilic additions take place at one nitrogen only, because the presence of the positive charge in the products renders the second nitrogen extremely unreactive towards a second electrophilic addition.



A very characteristic feature of diazine chemistry, which is associated with their strongly electron-poor nature, is that they add nucleophilic reagents easily. Without halide to be displaced, such adducts require an oxidation to complete an overall substitution. However, halo-diazines, where the halide is α or γ to a nitrogen, undergo very easy nucleophilic displacements, the intermediates being particularly well stabilised.

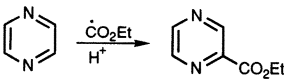
All positions on each of the diazines, with the sole exception of the 5-position

of a pyrimidine, are α and/or γ to an azomethine ring nitrogen and, in considering nucleophilic addition/substitution, it must be remembered that there is also an additional nitrogen-withdrawing electron density. As a consequence, all the monohalodiazines are more reactive than either 2- or 4-halopyridines. The 2- and 4-halopyrimidines are particularly reactive because the anionic intermediates (shown below for attack on 2-chloropyrimidine) derive direct mesomeric stabilisation from both nitrogen atoms.



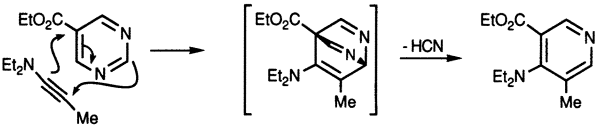
Despite this particularly strong propensity for nucleophilic addition, *C*-lithiation of diazines can be achieved either by metal–halogen exchange or by deprotonation *ortho* to chloro or alkoxyl substituents, though very low temperatures must be utilised in order to avoid nucleophilic addition of the reagent.

In line with their susceptibility to nucleophilic addition, diazines also undergo Minisci radical substitution with ease.



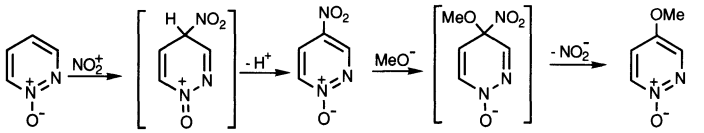
Further examples of the enhancement of those facets of pyridine chemistry associated with the azomethine electron withdrawal include a general stability towards oxidative degradation but, on the other hand, a tendency to undergo rather easy reduction of the ring.

Although there is always debate about quantitative measures of aromaticity, it is agreed that the diazines are less resonance stabilised than pyridines – they are 'less aromatic'. Thus, Diels-Alder additions are known for all three systems, with the heterocycle acting as a diene; initial adducts lose a small molecule – hydrogen cyanide in the pyrimidine example shown – to afford a final stable product.

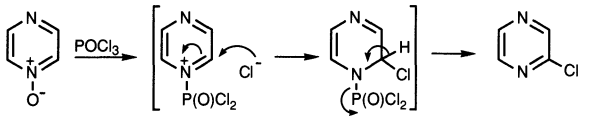


N-Oxides, just as in the pyridine series, show a remarkable duality of effect – they encourage both electrophilic substitutions and nucleophilic displacements. The sequence below shows pyridazine *N*-oxide undergoing first, electrophilic

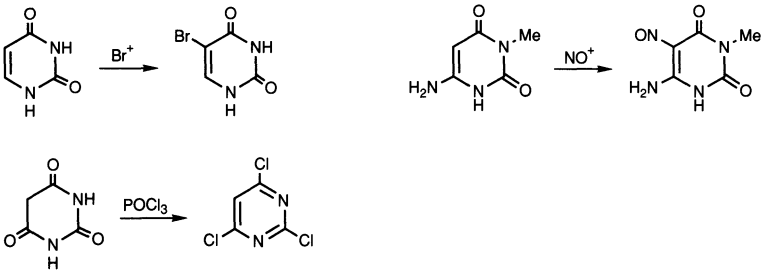
nitration, then, the product, nucleophilic displacement with nitrite as leaving group.



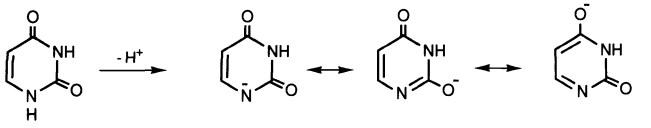
N-Oxide chemistry in six-membered heterocycles provides considerable scope for synthetic manipulations. One of the very useful transformations is the introduction of halide α to a nitrogen on reaction with phosphorus or sulfur halides, the conversion being initiated by oxygen attack on the phosphorus (sulfur). The power of this transformation can be emphasised by noting that the unsubstituted heterocycle is converted, in the two steps, into a halide with its potential for subsequent displacement by nucleophiles.



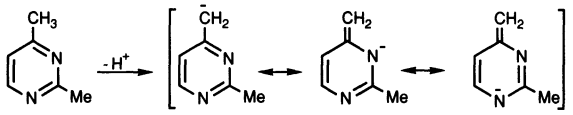
The most studied diazine derivatives are the oxy- and amino-pyrimidines since uracil, thymine and cytosine are found as bases in DNA and RNA. It is the enamide-like character of the double bonds in diazines with two oxygen substituents which allows electrophilic substitution – uracil, for example, can be brominated. One amino substituent permits electrophilic ring substitution and two amino, or one amino and one oxy, substituent, permit reaction with even weakly electrophilic reactants.



Diazinones, like pyridones, react with phosphorus halides with overall conversion into halide. Anions produced by (*N*-) deprotonation of diazinones are ambident, with a phenolate-like resonance contributor, but they generally react with electrophilic alkylating agents at nitrogen, rather than oxygen.



Diazine alkyl groups, with the exception of those at the 5-position of pyrimidine, can undergo condensation reactions which utilise the carbanion produced by removal of a proton. As in pyridine chemistry, formation of these anions is made possible by delocalisation of the charge onto one (or more) of the ring nitrogen atoms.



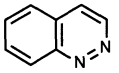
The diazines: pyridazine, pyrimidine and pyrazine: reactions and synthesis

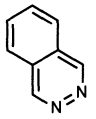
11

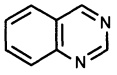

pyridazine

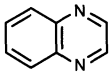

pyrimidine


pyrazine


cinnoline


phthalazine


quinazoline

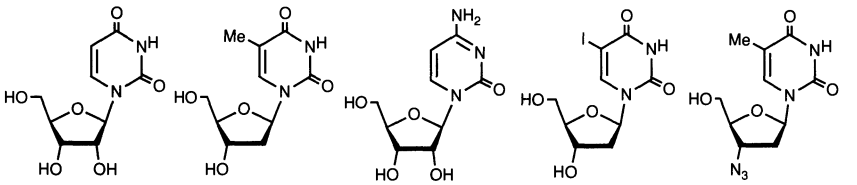

quinoxaline

The three diazines, pyridazine,[1] pyrimidine[2] and pyrazine[3] are stable, colourless compounds which are soluble in water. The three parent heterocycles, unlike pyridine, are expensive and not readily available and so are seldom used as starting materials for the synthesis of their derivatives. There are only four ways in which a benzene ring can be fused to a diazine: cinnoline, phthalazine, quinazoline and quinoxaline are the bicyclic systems thus generated.

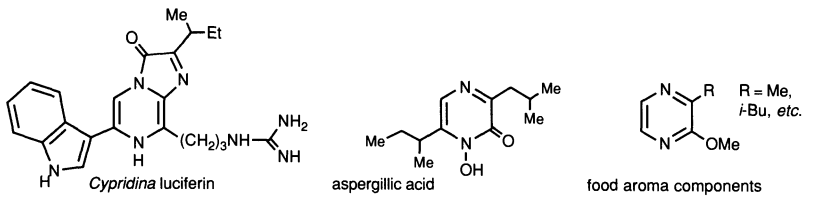
One striking aspect of the physical properties of the diazine trio is the high boiling point of pyridazine (207°C), 80–90°C higher than that of pyrimidine (123°C), pyrazine (118°C), or indeed other azines, including 1,3,5-triazine, all of which also boil in the range 114–124°C. The high boiling point of pyridazine is attributed to the polarisability of the N–N unit which results in extensive dipolar association in the liquid.

The most important naturally occuring diazines are the pyrimidine bases uracil, thymine and cytosine, which are constituents of the nucleic acids. Following from this, several pyrimidine nucleoside analogues have been developed as anti-viral agents, for example Idoxuridine is used in the treatment of *Herpes* infections of the eye, and AZT is the most widely used anti-AIDS drug.[4] The pyrimidine ring also occurs in the vitamin thiamin (chapter 21). The nucleic acid pyrimidines are often drawn horizontally transposed from the representations used in this chapter, i.e. with N-3 to the 'North-West', mainly to draw

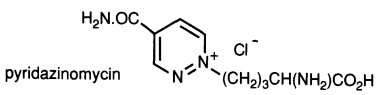
attention to their structural similarity to the pyrimidine ring of the nucleic acid purines (chapter 23), which are traditionally drawn with the pyrimidine ring on the left.



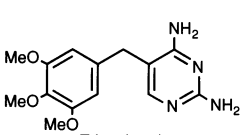
The pyrazine ring system is found in the fungal metabolite aspergillic acid and in dihydro-form in the luciferins of several beetles, including the firefly, *Cypridina hilgendorfii*, and is responsible for the chemiluminescence[5] of this ostracod. Quite simple methoxypyrazines are very important components of the aromas of many fruits and vegetables, such as peas and Capsicum peppers, and also of wines.[6] Although present in very small amounts, they are extemely odorous and can be detected at concentrations as low as 0.00001 ppm. Related compounds, probably formed by the pyrolysis of amino acids during the process of cooking, are also important in the aroma of roasted meats.



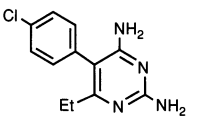
The only naturally occuring pyridazines are a few fungal metabolites from *Streptomyces* species, consisting mainly of reduced systems, and the quaternary salt pyridazinomycin.



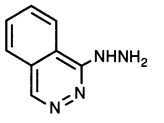
Derivatives of all three heterocyclic systems have been widely investigated for use in synthetic drugs (see also above); amongst the most commonly used compounds are the antibacterial Trimethoprim, the antimalarial Pyrimethamine and the anti-hypertensive agent Hydralazine (containing a phthalazine nucleus). Piperazine (hexahydropyrazine) is used in the treatment of intestinal nematode (worm) infections.



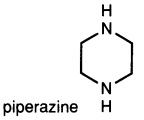
Trimethoprim



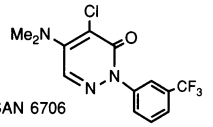
Pyrimethamine



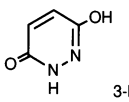
Hydralazine



piperazine



SAN 6706



3-hydroxy-6(1*H*)-pyrazinone

Pyrazinone derivatives are important as selective plant-growth regulators and have found use as selective herbicides, for example SAN 6706; 3-hydroxy-6(1*H*)-pyrazinone, is used as a lawn weedkiller.

11.1 REACTIONS WITH ELECTROPHILIC REAGENTS

11.1.1 Addition at nitrogen[7]

11.1.1.1 *Protonation*

The diazines, pyridazine (pK_a 2.3), pyrimidine (1.3) and pyrazine (0.65) are essentially monobasic substances, and considerably weaker, as bases, than pyridine (5.2). This reduction in basicity is believed to be largely a consequence of destabilisation of the mono-protonated cations due to inductive withdrawal by the second nitrogen atom. Secondary effects, however, determine the order of basicity for the three systems: lone pair repulsion between the two adjacent nitrogen atoms in pyridazine means that protonation occurs more readily than if inductive effects, only, were operating. In the case of pyrazine, mesomeric interaction between the protonated and neutral nitrogen atoms probably destabilises the cation.

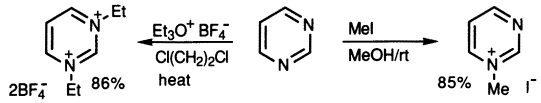
N,N'-Diprotonation is very much more difficult and has only been observed in very strongly acidic media. Of the trio, pyridazine ($pK_{a(2)}$ −7.1) is the most difficult from which to generate a dication, probably due to the high energy associated with the juxtaposition of two immediately adjacent positively charged atoms, but pyrimidine ($pK_{a(2)}$ −6.3) and pyrazine ($pK_{a(2)}$ −6.6) are only marginally easier to doubly protonate.

Substituents can affect basicity (and nucleophilicity) both inductively and mesomerically, but care is needed in the interpretation of pK_a changes, for example it is important to be sure which of the two nitrogens of the substituted azine is protonated (see also section 11.1.1.2).

11.1.1.2 *Alkylation*

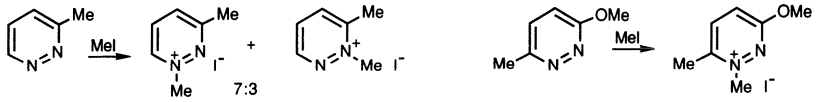
The diazines react with alkyl halides to give mono-quaternary salts, though

somewhat less readily than comparable pyridines. Dialkylation cannot be achieved with simple alkyl halides, however the very much more reactive trialkyloxonium tetrafluoroborates do convert all three systems into di-quaternary salts.[8]



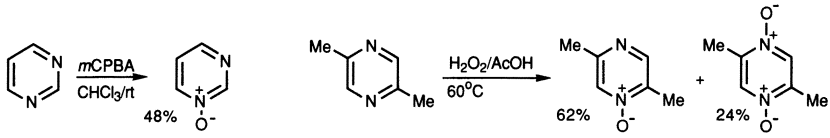
Pyridazine is the most reactive in alkylation reactions and this again has its origin in the lone pair/lone pair interaction between the nitrogen atoms. This phenomenon is known as the 'α effect' and is also responsible, for example, for the relatively higher reactivity of hydrogen peroxide as a nucleophile, compared with water.

Unsymmetrically substituted diazines can give rise to two isomeric quaternary salts. Substituents influence the orientation mainly by steric and inductive, rather than mesomeric effects. For example, 3-methylpyridazine alkylates mainly at N-1, even though N-2 is the more electron-rich site. Again, quaternisation of 3-methoxy-6-methylpyridazine takes place adjacent to the methyl substituent, at N-1, although mesomeric release would have been expected to favour attack at N-2.[9]



11.1.1.3 *Oxidation*

All three systems react with peracids,[10] giving *N*-oxides, but care must be taken with pyrimidines[11] due to the relative instability of the products under the acidic conditions. Pyrazines[10] form *N,N'*-dioxides the most easily, but pyridazine[12] requires forcing conditions and pyrimidines, apart from some examples in which further activation is present, give poor yields.[13]



The regiochemistry of *N*-oxidation of substituted azines is governed by the same factors as alkylation (section 11.1.1.2), for example 3-methylpyridazine gives the 1-oxide as main (3 : 1) product,[14] but the pattern is not a simple one, for 4-methylpyrimidine *N*-oxidises principally (3.5 : 1) at the nitrogen adjacent to the methyl.[15] The acidity of the medium can also influence the regiochemistry of oxidation, for example 3-cyanopyridazine reacts at N-1 with peracetic acid, but under strongly acidic conditions, in which the heterocycle is mainly

present as its N-1-protonic salt, oxidation, apparently involving attack on this salt, occurs at N-2.[16]

11.1.2 Substitution at carbon

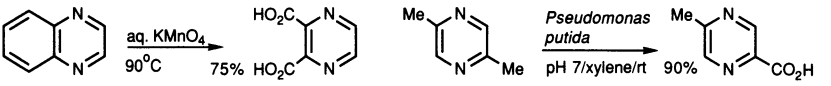
Recalling the resistance of pyridines to electrophilic substitution, it is not surprising to find that introduction of a second azomethine nitrogen, in any of the three possible orientations, greatly increases this resistance: no nitration or sulfonation of a diazine or simple alkyldiazine has been reported, though some halogenations are known. It is to be noted that C-5 in pyrimidine is the only position, in all three diazines, which is not in an α- or γ-relationship to a ring nitrogen, and is therefore equivalent to a β-position in pyridine. Diazines carrying electron-releasing (activating) substituents undergo electrophilic substitution much more easily (sections 11.10.2.1 and 11.1).

11.1.2.1 *Halogenation*

Chlorination of 2-methylpyrazine occurs under such mild conditions that it is almost certain that an addition/elimination sequence is involved, rather than a classical aromatic electrophilic substitution.[17] Halogenation of pyrimidines may well also involve such processes.[18]

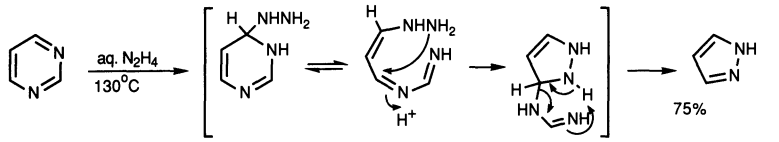
11.2 REACTIONS WITH OXIDISING AGENTS

The diazines are generally resistant to oxidative attack at ring carbon, though alkaline oxidising agents can bring about degradation *via* intermediates produced by initial nucleophilic addition (section 11.3). Alkyl substituents[19] and fused aromatic rings[20] can be oxidised to carboxylic acid residues, leaving the heterocyclic ring untouched.

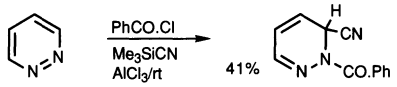


11.3 REACTIONS WITH NUCLEOPHILIC REAGENTS

The diazines are very susceptible to nucleophilic addition: pyrimidine, for example, is decomposed when heated with aqueous alkali by a process which involves hydroxide addition as a first step, and it is converted into pyrazole by reaction with hydrazine.



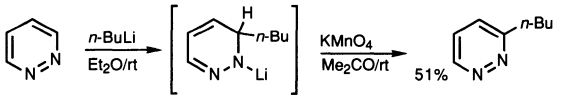
The quaternisation of a diazine naturally increases its propensity for addition of nucleophile; for example, Reissert adducts have been described for pyridazine and pyrimidine.[21]



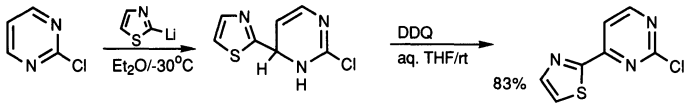
11.3.1 With replacement of hydrogen

11.3.1.1 *Alkylation and arylation*

The diazines readily add alkyl- and aryllithiums, and Grignard reagents, to give dihydro-adducts which can be aromatised by oxidation with reagents such as potassium permanganate or DDQ. In reactions with organolithiums, pyrimidines react at C-4,[13] and pyridazines at C-3, but Grignard reagents add to pyridazines at C-4.[22]



An important point is that in diazines carrying chlorine or methylthio substituents, attack does not take place at the halogen- or methylthio-bearing carbon; halogen-[23] and methylthio-containing[24] products are therefore obtained.

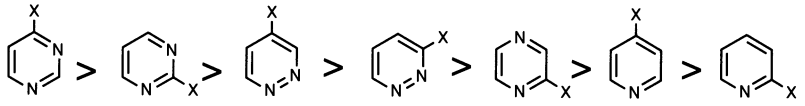


11.3.1.2 *Amination*

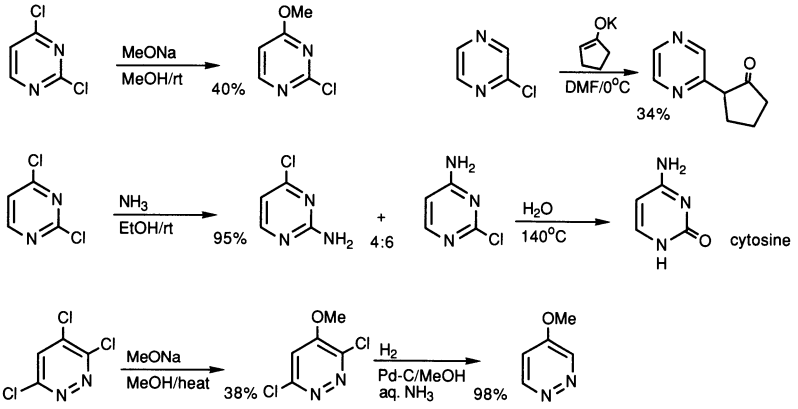
The Chichibabin reaction can be carried out under the usual conditions in a few cases,[25] but is much less general than for pyridines. This may be a consequence of the lower aromaticity of the diazines for, although the initial addition is quite easy, the subsequent loss of hydride (rearomatisation) is difficult. However, high yields of 4-aminopyridazine, 4-aminopyrimidine and 2-aminopyrazine can be obtained by oxidation of the dihydro-adduct *in situ* with potassium permanganate.[26]

11.3.2 With replacement of good leaving groups

All the halodiazines, apart from 5-halopyrimidines, react readily with 'soft' nucleophiles such as amines, thiolates, and malonate anions, with substitution of the halide. All cases are more reactive than 2-halopyridines; the relative reactivity can be summarised:

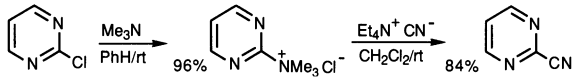


and is illustrated by the following examples:[27]

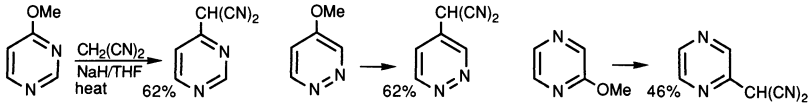


Nucleophilic displacement of halogen with ammonia[28] and amines[29] can be accelerated by carrying out the displacements in acid solution, when the protonated heterocycle is more reactive than the neutral heterocycle.[30] Halogen can also be easily removed hydrogenolytically; for example, treatment of 2,4-dichloropyrimidine, readily available from uracil, with hydrogen in the presence of palladium, or with hydrogen iodide, gives pyrimidine itself.[31]

A device which is also used in pyridine and purine chemistry is the initial replacement of halogen with a tertiary amine, the resulting salt now having a better leaving group.[32]



Even methoxy groups can be displaced by carbanions.[33]



11.4 REACTIONS WITH BASES

11.4.1 Deprotonation of *C*-hydrogen

All three diazines undergo H/D exchange at all ring positions with MeONa/MeOD at 164°C;[34] the transient carbanions which allow the exchange are formed somewhat faster than for pyridines, and again this is probably due to the acidifying, additional inductive withdrawal provided by the second nitrogen.

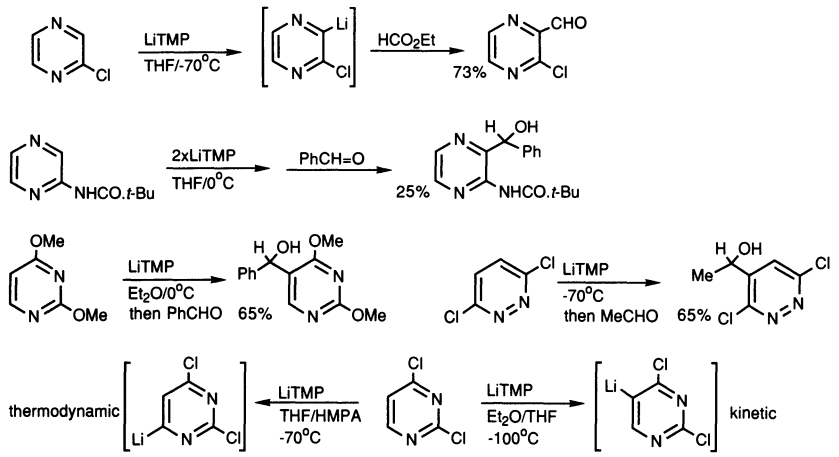
11.4.2 Metallation

Because simple diazines undergo such ready nucleophilic addition, their direct metallation has not been reported, however, metallated chloro- and methoxy-derivatives can be prepared[35] and have been widely used (see below).

11.5 REACTIONS OF *C*-METALLATED DIAZINES

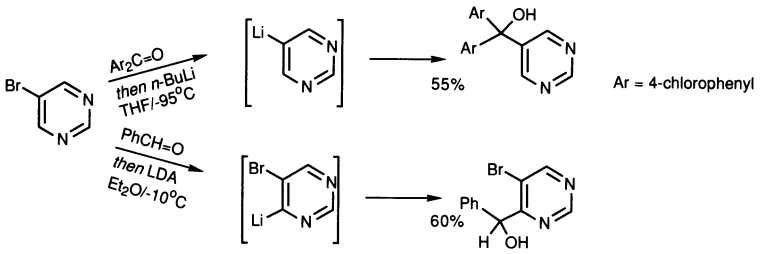
11.5.1 Lithio derivatives

Typically, lithium tetramethylpiperidide has been used for the kinetically controlled metallation of substituted diazines;[36] in some cases the use of a somewhat higher temperature allows equilibration to a thermodynamic anion.[37]



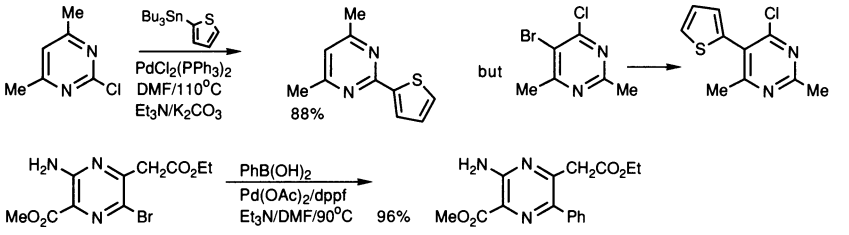
Lithiodiazines can also be prepared by halogen exchange with alkyllithiums, but very low temperatures must be used in order to avoid addition to the ring.[38] The example below shows how 5-bromopyrimidine can be lithiated at C-4, using LDA, or alternatively can be made to undergo exchange, using *n*-butyllithium.[39] Note also that, in these cases, reactions were carried out by adding the electrophile to the pyrimidine, before lithiation, a practice which incidentally

illustrates that metal–halogen exchange with *n*-butyllithium is faster than the addition of *n*-butyllithium to a carbonyl compound.[40]

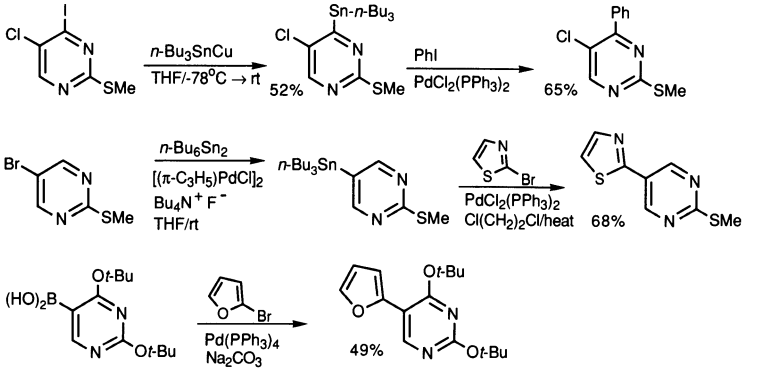


11.5.2 Palladium-catalysed reactions

Palladium- (and nickel-) catalysed coupling reactions proceed normally on halodiazines, the most significant feature, as with pyridines, being the enhanced reactivity, relative to chlorobenzene, of chlorine at positions α and γ to a nitrogen, but it is important to recognise that this activation does not overcome the higher intrinsic reactivity of bromine and iodine at any position.[41]



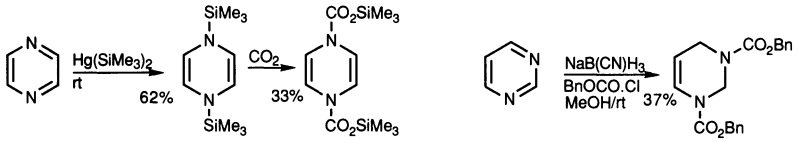
In diazine chemistry, tin derivatives have normally been used[42] for coupling reactions and have the particular advantage that they can be prepared without the use of organolithium intermediates. Boronic acids have been used occasionally,[43] but as a general rule they are difficult to prepare at positions α to azine nitrogens – a major disadvantage in diazine chemistry.



11.6 REACTIONS WITH REDUCING AGENTS

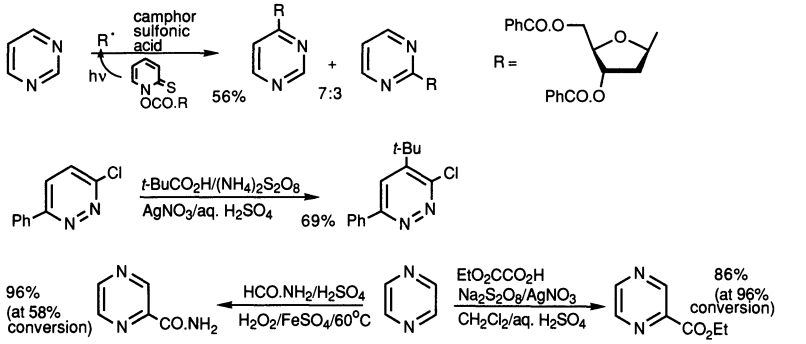
Due to their lower aromaticity, the diazines are more easily reduced than pyridines. Pyrazine and pyridazine can be reduced to hexahydro-derivatives with sodium in hot ethanol; under these conditions pyridazine has a tendency for subsequent reductive cleavage of the N–N bond.

Partial reductions of quaternary salts to dihydro compounds can be achieved with borohydride, but such processes are much less well studied than in pyridinium salt chemistry.[44] 1,4-Dihydropyrazines have been produced with either silicon[45] or amide[46] substitution at the nitrogen atoms, and all the diazines can be reduced to tetrahydro-derivatives with carbamate protection on nitrogen, which aids in stabilisation and thus allows isolation.[47]

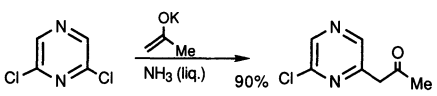


11.7 REACTIONS WITH RADICAL REAGENTS

Radicals add readily to diazines under Minisci conditions.[48] Additions to pyrimidine show little selectivity, C-2 *versus* C-4, however attack at C-5 does not take place.[49] Radical attack on pyridazines shows selectivity for C-4,[50] even when C-3 is unsubstituted. Pyrazines[51] can of course substitute in only one type of position.

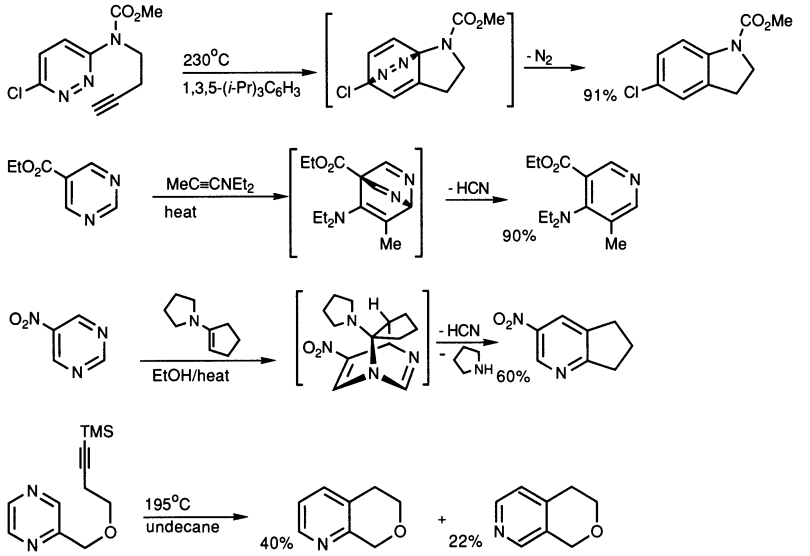


Substitutions of halide by an $S_{RN}1$ mechanism have been carried out, though AE mechanisms compete in the more reactive halides.[52]

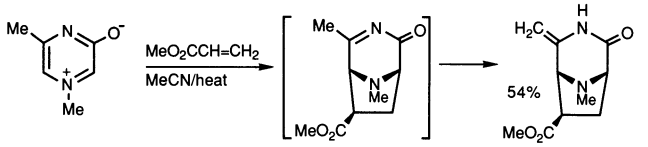


11.8 ELECTROCYCLIC AND PHOTOCHEMICAL REACTIONS

All the diazines, providing they also have electron-withdrawing substituents, undergo Diels-Alder additions with dienophiles. Intramolecular reactions occur the most readily; these do not even require the presence of activating substituents. The immediate products of such process usually lose nitrogen (pyridazine adducts) or hydrogen cyanide (adducts from pyrimidines and pyrazines) to generate benzene and pyridine products,[53] respectively, as illustrated below.[54]

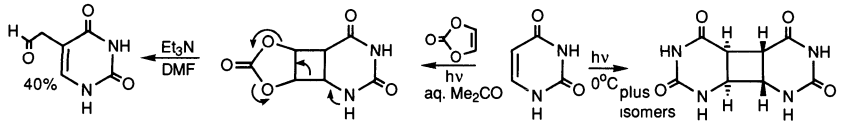


Mesoionic oxidopyraziniums undergo cycloadditions[55] similar to those known for oxidopyridiniums (section 5.9).

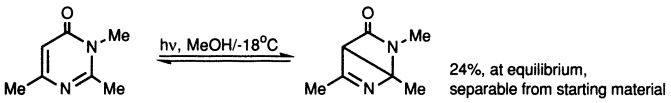


Heterodienophiles have also been studied: diethyl azodicarboxylate has been added across the 2,6-positions of a pyridazin-3-one, and singlet oxygen has been added across the 2,5-positions of pyrazines[56] and pyrazinones.[57]

Because of possible relevance to mutagenesis, considerable study has been devoted to study of the photochemical transformations of oxypyrimidines; uracil, for example, takes part in a 2 + 2 cycloaddition with itself,[58] or with vinylene carbonate (1,3-dioxol-2-one).[59]

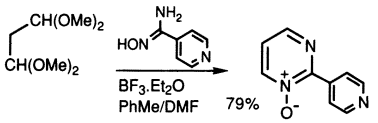


Pyrimidin-2-ones[60] and pyrimidin-4-ones[61] form bicyclic systems and pyrazine isomerises into pyrimidine, on exposure to light.[62]

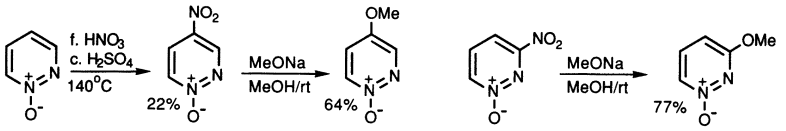


11.9 DIAZINE *N*-OXIDES[63]

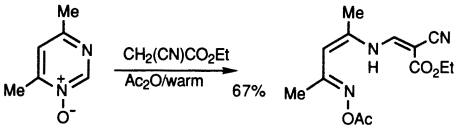
Although pyridazine and pyrazine *N*-oxides can be readily prepared by oxidation of the parent heterocycles, pyrimidine *N*-oxides are more difficult to obtain in this way but they can conveniently be prepared by ring synthesis.[64]



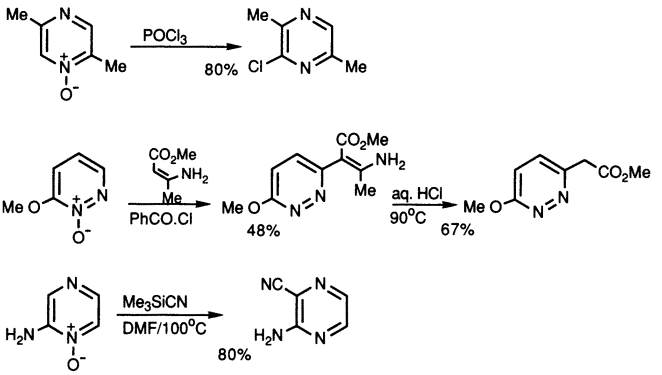
Pyridazine and pyrazine *N*-oxides behave like their pyridine counterparts in electrophilic substitution,[65] and nucleophilic displacement reactions involving loss of the oxygen. It is interesting that displacement of nitro β to the *N*-oxide function occurs about as readily as that of a γ nitro group, but certainly, displacements on *N*-oxides proceed faster[66] than for the corresponding base.



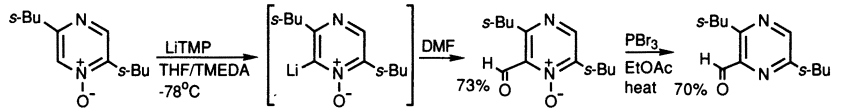
Pyrimidine *N*-oxides often behave anomalously, giving ring-opened products.[67]



Nucleophilic substitution by halide, cyanide, carbon nucleophiles such as enamines, and acetate (by reaction with acetic anhydride), with concomitant loss of the oxide function, occurs smoothly in all three systems,[68] though the site of introduction of the nucleophile is not always that (α to the *N*-oxide) predicted by analogy with pyridine chemistry, for example the reaction of pyrimidine *N*-oxide with acetic anhydride gives 4- not 2-acetoxypyrimidine.[13]

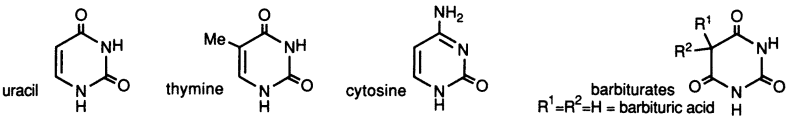


The *N*-oxide grouping can also serve as an activating substituent to allow regioselective lithiation[69] or for the further acidification (section 11.12) of side-chain methyl groups for condensations with, for example, aromatic aldehydes or amyl nitrite.[70]



11.10 OXYDIAZINES

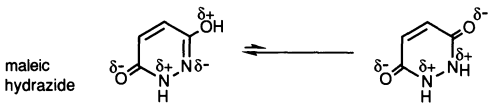
By far the most important naturally occuring diazines are the pyrimidinones uracil, thymine, and cytosine, which as the nucleosides uridine, thymidine and cytidine, are components of the nucleic acids. As a consequence, a great deal of synthetic chemistry has been directed towards these types of compound in the search for anti-viral and anti-tumour agents.[71] Among other well-known pyrimidinones are the barbiturate sedatives.[72]



11.10.1 Structure of oxydiazines

With the exception of 5-hydroxypyrimidine, which is analogous to 3-hydroxypyridine, all the mono-oxygenated diazines exist predominantly as carbonyl tautomers and are thus categorised as diazinones.

The dioxydiazines present a more complicated picture, for in some cases, where both oxygens are α or γ to a nitrogen, and both might be expected to exist in carbonyl form, one actually takes up the hydroxy form: a well-known example is 'maleic hydrazide'. One can rationalise the preference easily in this case, as resulting from the removal of the unfavourable interaction between two adjacent, partially positive nitrogen atoms in the dicarbonyl form.



On the other hand, uracil exists as the dione and most of its reactions[73] can be interpreted on this basis. Barbituric acid adopts a tricarbonyl tautomeric form.

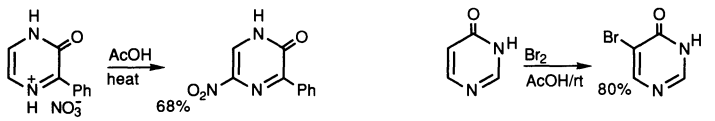
11.10.2 Reactions of oxydiazines

For many synthetic transformations, it is convenient to utilise halo- or alkoxydiazines, in lieu of the (oxidation level) equivalent -ones; often this device facilitates solubility; a final hydolysis re-converts to the 'one'.

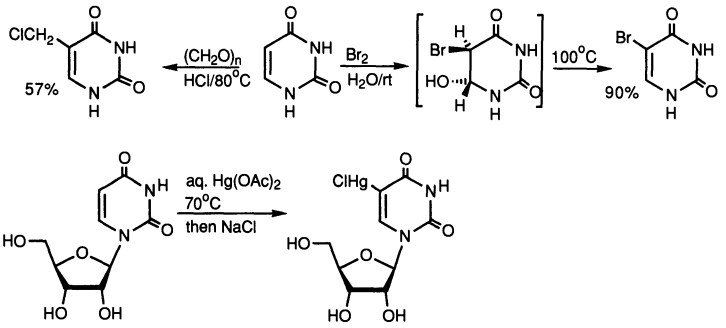
11.10.2.1 *Reactions with electrophilic reagents*

The deactivating effect of two ring nitrogens cannot always be overcome by a single oxygen substituent: 3-pyridazinone can be neither nitrated nor halogenated, or again, of the singly oxygenated pyrimidines, only 2(1*H*)-pyrimidinone can be nitrated;[74] pyrazinones seem to be the most reactive towards electrophilic substitution.

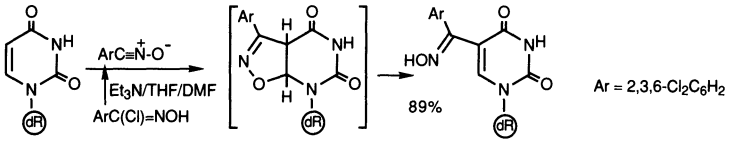
5-Hydroxypyrimidine, the only phenolic diazine, is unstable even to dilute acid and no electrophilic substitutions have been reported.



Uracils undergo a range of electrophilic substitution reactions such as halogenation, phenylsulfenylation,[75] mercuration,[76] and hydroxy- and chloromethylation.[77] Bromination of uracils has been shown to proceed *via* the bromohydrin adduct, and similarly of pyrimidin-2-one, *via* the bromohydrin-hydrate.[78]

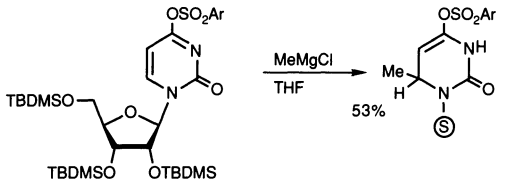


The reaction of deoxyuridine with nitrile oxides gives products of apparent electrophilic substitution, but these probably arise by ring opening of a cycloadduct.[79]

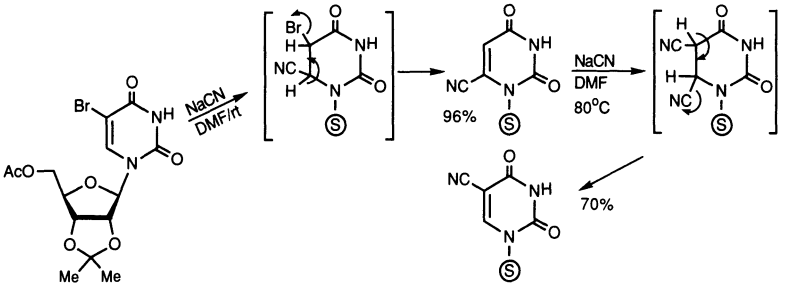


11.10.2.2 *Reactions with nucleophilic reagents*

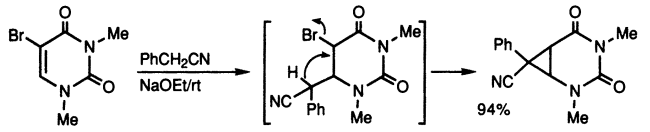
Diazinones are quite susceptible to nucleophilic attack, reaction taking place generally *via* Michael-type adducts rather than by attack at a carbonyl group, though there are exceptions[80] to this generalisation. Grignard reagents add to give dihydro-compounds and good leaving groups can be displaced.[81]



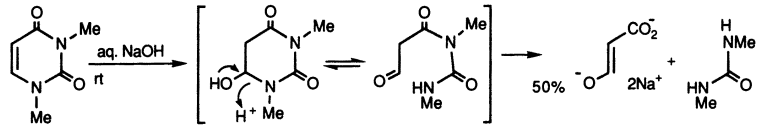
The reaction of cyanide with a protected 5-bromouridine[82] is instructive: under mild conditions, a *cine*-substituted product is obtained *via* a Michael addition followed by β-elimination of bromide, but at higher temperatures, conversion of the 6- into the 5-cyano isomer is observed, i.e. the product of apparent, direct displacement of bromide is obtained. The higher temperature product arises *via* an isomerisation involving another Michael addition, then elimination of the 6-cyano group.



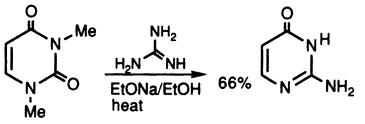
In a related reaction with the anion of phenylacetonitrile, the initial addition is followed by an internal alkylation, generating a cyclopropane.[83]



The conversion of 1,3-dimethyluracil into a mixture of *N,N'*-dimethylurea and the disodium salt of formylacetic acid begins with the addition of hydroxide at C-6.[84]



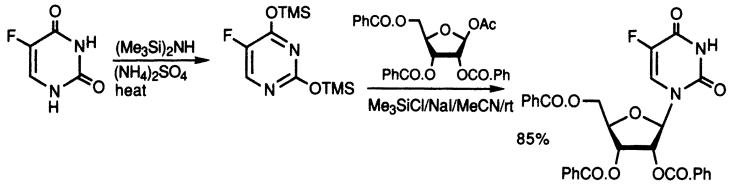
The propensity for uracils to add nucleophiles can be put to synthetic use by reaction with double nucleophiles such as ureas, when a sequence of addition, ring opening and re-closure can achieve (at first sight) extraordinary transformations.[85]



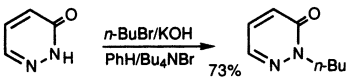
11.10.2.3 *Reactions with bases*

N-Deprotonation

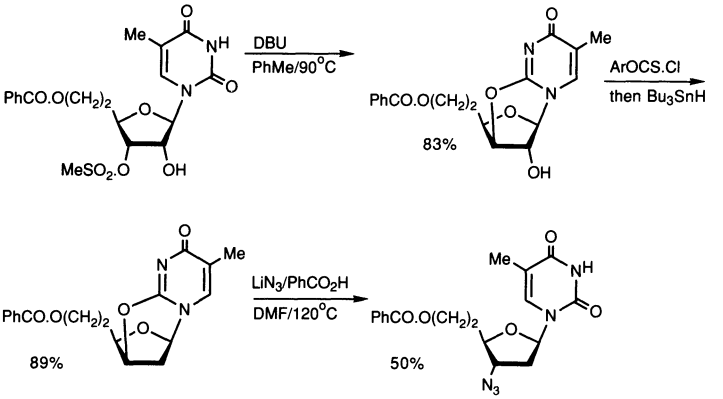
Like pyridones, oxydiazines are readily deprotonated under mild conditions to give ambident anions which can be alkylated, conveniently by phase-transfer methods, reaction usually occurring at nitrogen.[86] Alternative methods include heating with trimethyl phosphate[87] and the alkylation of *O*-silylated derivatives,[88] which is an important method for unambiguous *N*-alkylation.



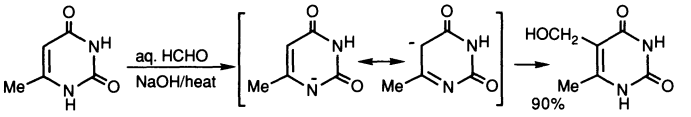
Ribosylation of uracils is usually carried out *via* bis-silyl derivatives[89] and is subject to the same stereochemical difficulties as purine ribosylation (for further discussion see section 23.2.1.2). 3-Pyridazinones alkylate cleanly on N-2 under phase-transfer conditions[90] but the regiochemistry of uracil alkylation is sometimes difficult to control.



O-Alkylation is also possible and is particularly important in ribosides, where it occurs intramolecularly, and can be used to control the stereochemistry of substitution in the sugar residue.[91]

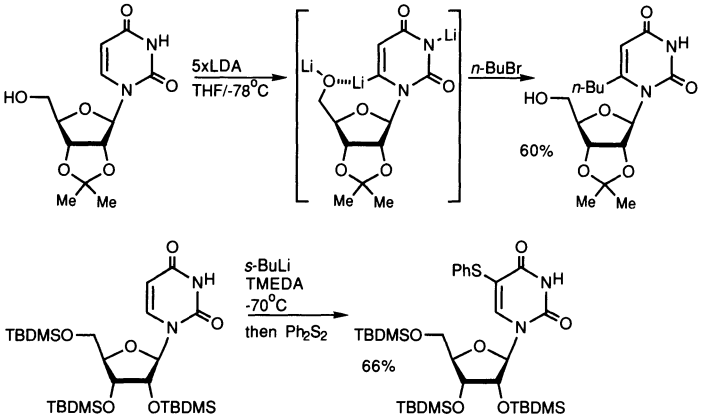


Carbon substitution can also be effected in some cases *via* delocalised *N*-anions, as in the reaction of 6-methyluracil with formaldehyde,[92] or with diazonium salts.[93]

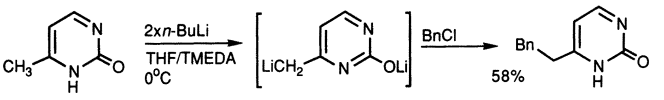


C-Metallation

C-Lithiation of uridine derivatives has been thoroughly studied as a means for the introduction of functional groups at C-5 and C-6. Chelating groups at C-5′ (hydroxyl or OMOM) favour 6-metallation,[94] as do equilibrating conditions, indicating that this is the most stable lithio-derivative. Kinetic lithiation, at C-5, can be achieved when weakly chelating silyloxy groups are used as protecting groups for the sugar.[95] It is remarkable that protection of the N–H group is not necessary.

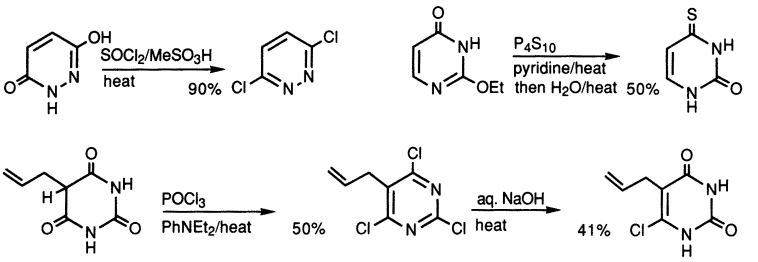


NH-Protection is also unnecessary for the side-chain metallation of 6-methylpyrimidin-2-one.[96]

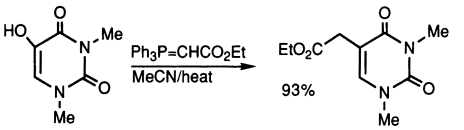


11.10.2.4 *Replacement of oxygen*

Oxydiazines, with the oxygen α to nitrogen, can be converted into halo-[28,97] and thio-compounds[98] using the same reagents as for 2- and 4-pyridones. They can also now be converted directly into aminodiazines, without the (classical) intermediacy of a halo-derivative.

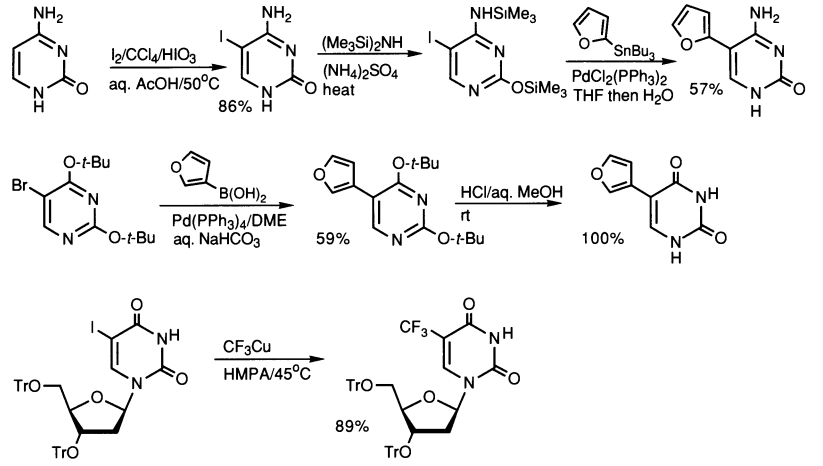


5-Hydroxypyrimidin-2,4-diones react as ketones at the 5-position and undergo Wittig condensation.[99]

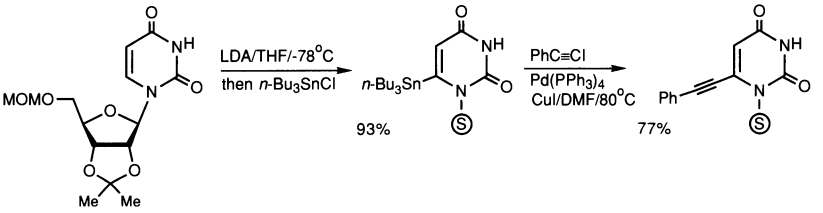


11.10.2.5 *Transition metal-catalysed reactions*

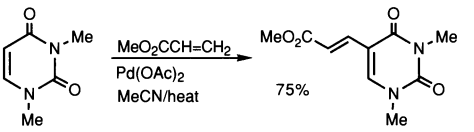
Halodiazinones undergo palladium-catalysed couplings with boronic acids and stannanes, but the reactions appear to be less consistent than with other systems. Temporary protection as silyl derivatives,[100] or the use of additives such as silver oxide,[101] are beneficial in some cases, but it is often preferable to carry out transformations on alkoxydiazines, followed by hydrolysis. Direct coupling with organocopper reagents has also been described.[102]



Stannyluridines have been used in coupling reactions, but again the use of the corresponding dialkoxypyrimidine is usually to be preferred when an organometallic derivative of the heterocycle is required.[103]

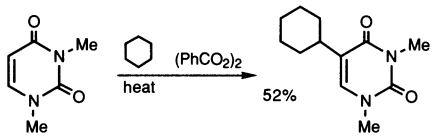


Heck reactions can be carried out on halo- or the readily available mercuri-derivatives, the latter requiring the use of one equivalent of palladium.[104] In addition, due to their susceptibility to electrophilic substitution, 'oxidative' Heck couplings (proceeding *via in situ* palladation) have found use in uracil chemistry.[105]



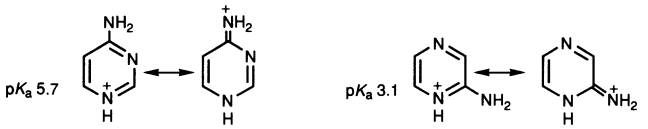
11.10.2.6 *Radical reactions*

Uracils undergo radical additions;[106] these and their photochemical reactions (section 11.8) are of possible relevance to mutagenesis mechanisms.

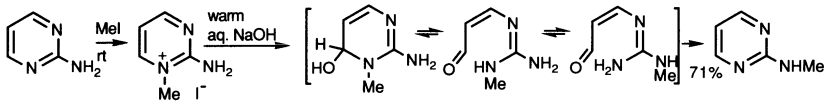


11.11 AMINODIAZINES

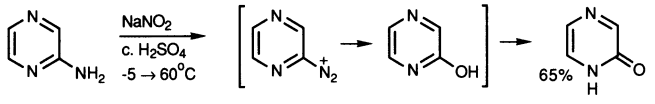
Aminodiazines exist in the amino form. They are stronger bases than the corresponding unsubstituted systems and always protonate on one of the ring nitrogen atoms: where two isomeric cations are possible, the order of preference for protonation is of a ring nitrogen which is $\gamma > \alpha > \beta$ to the amino group, as can be seen in the two examples below. A corollary of this is that those aminodiazines which contain a γ-aminoazine system are the strongest bases.



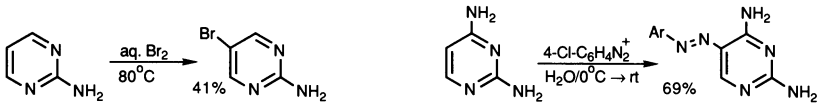
The alkali-promoted rearrangement of quaternary salts derived from 2-aminopyrimidine provides the simplest example of the Dimroth rearrangement.[107] The larger the substituent on the positively charged ring nitrogen the more rapidly the rearrangement proceeds, no doubt as a result of the consequent relief in strain between the substituent and the adjacent amino group.



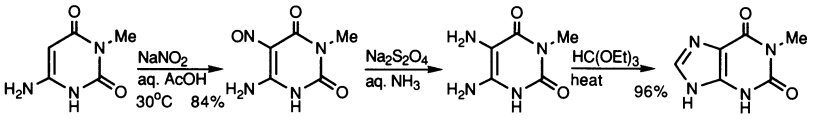
All of the aminodiazines react with nitrous acid to give the corresponding diazinones,[29] by way of highly reactive diazonium salts; even 5-aminopyrimidine does not give a stable diazonium salt, though a low yield of 2-chloropyrimidine can be obtained by diazotisation of 2-aminopyrimidine in concentrated hydrochloric acid.[108]



One amino group is sufficient in most cases to allow easy electrophilic substitution, halogenation[109] for example, and two amino groups activate the ring to attack even by weaker electrophilic reagents – for example by thiocyanogen.[110] Diaminopyrimidines will couple with diazonium salts[111] which provides a means for the introduction of a third nitrogen substituent.

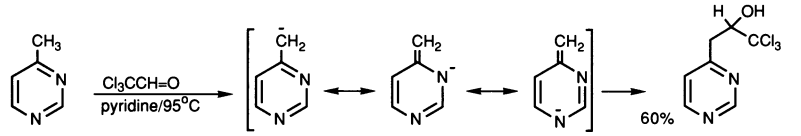


Amino-oxy-pyrimidines[112] and amino-dioxy-pyrimidines[113] can be *C*-nitrosated, and such 5,6-dinitrogen-substituted pyrimidines, after reduction to 5,6-diaminopyrimidines, are important intermediates for the synthesis of both purines (section 23.13.1.1) and pteridines (section 11.13.4.6).

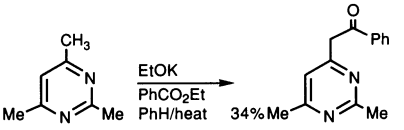


11.12 ALKYLDIAZINES

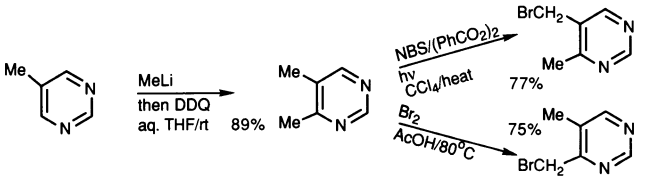
All alkyldiazines, with the exception of 5-alkylpyrimidines, undergo condensations which involve deprotonation of the alkyl group,[114] in the same way as α- and γ-picolines. The intermediate anions are stabilised by mesomerism involving one, or in the case of 2- and 4-alkylpyrimidines, both nitrogens.



In pyrimidines, a 4-alkyl is deprotonated more readily that a 2-alkyl group;[115] here again one sees the greater stability associated with a γ-quinonoid resonating ion.



Side-chain radical halogenation selects a pyrimidine 5-methyl over a pyrimidine 4-methyl; the reverse selectivity can be achieved by halogenation in acid solution – presumably an *N*-protonated, side-chain deprotonated species, i.e. the enamine tautomer, is involved.[116]



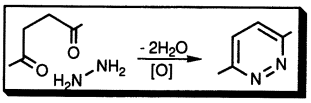
11.13 SYNTHESIS OF DIAZINES

Routes for the ring synthesis of the isomeric diazines are, as one would expect, quite different one from the other, and must therefore be dealt with separately.

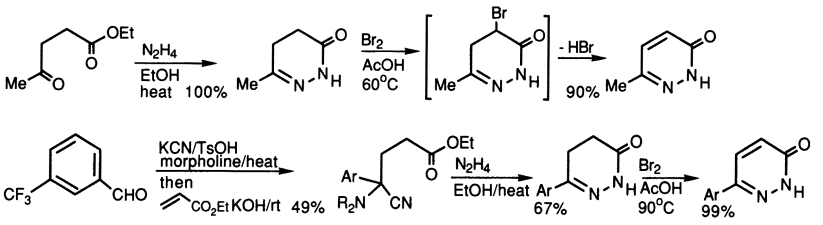
11.13.1 Ring synthesis of pyridazines

11.13.1.1 *From a 1,4-dicarbonyl compound and a hydrazine*

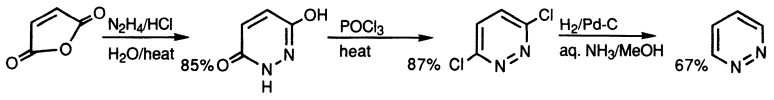
By far the most common method for the synthesis of pyridazines involves a 1,4-dicarbonyl compound reacting with hydrazine; unless the four-carbon component is unsaturated, a final oxidative step is needed to give an aromatic pyridazine.



The most useful procedure makes use of a 4-keto-ester, giving a dihydropyridazinone which can be easily dehydrogenated to the fully aromatic heterocycle, often by bromination then dehydrobromination;[117] sodium 3-nitrobenzoate as an oxidant is a good alternative if the use of halogenation has complications. A useful variant on this method allows the preparation of 6-arylpyridazinones from aromatic aldehydes, using an α-amino-nitrile as a masked ketone in the four-carbon component.[118] Friedel-Crafts acylation using succinic anhydride is an alternative route to 1,4-keto-acids, reaction with hydrazine again giving 6-arylpyridazinones.[119]

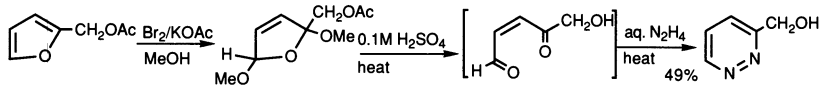


Maleic anhydride and hydrazine give the hydroxypyridazinone directly,[120] the additional unsaturation in the 1,4-dicarbonyl component meaning that an oxidative step is not required; conversion of 3-hydroxypyridazin-6-one into 3,6-dichloropyridazine makes this useful intermediate very easily available.



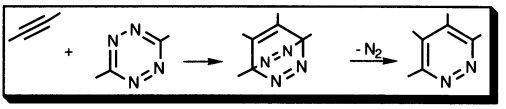
Saturated 1,4-diketones suffer, in this approach, from the disadvantage that they can react with hydrazine in two ways, giving mixtures of the desired dihy-

dropyridazine and an *N*-aminopyrrole; this complication does not arise when unsaturated 1,4-diketones are employed.[121] Synthons for unsaturated 1,4-diketones are available as cyclic acetals from the oxidation of furans (section 15.1.4), and react with hydrazines to give the fully aromatic pyridazines directly.[122]

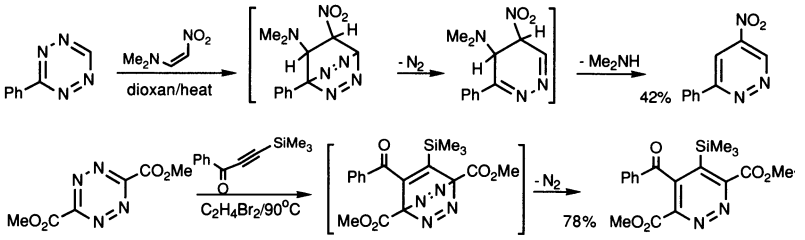


11.13.1.2 *By cycloaddition of a 1,2,4,5-tetrazine with an alkyne*

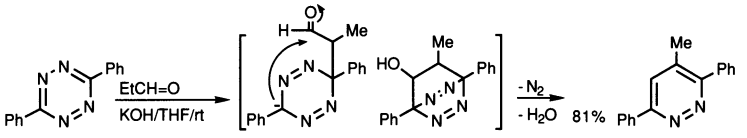
Cycloaddition of a 1,2,4,5-tetrazine with an alkyne (or its equivalent), with elimination of nitrogen gives pyridazines.



This process works best when the tetrazine has electron-withdrawing substituents, but a wide range of substituents can be incorporated on the acetylene, including nitro, trimethylsilyl, and trimethyltin, affording routes to substituted pyridazines[123] not easily available by other methods.



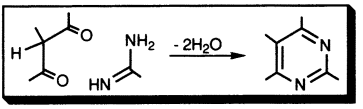
The addition of ketone and aldehyde enolates to tetrazines, though not a concerted process, has the same overall effect.[124]



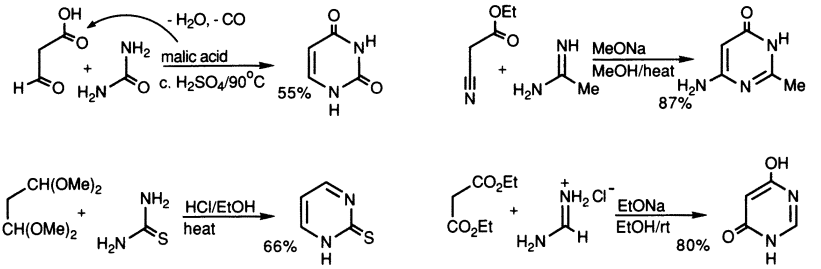
11.13.2 Ring synthesis of pyrimidines

11.13.2.1 *From a 1,3-dicarbonyl compound and an N–C–N fragment*

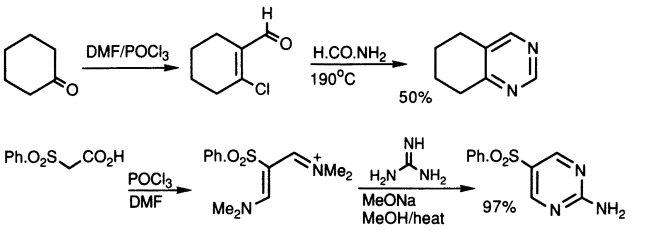
The most general pyrimidine ring synthesis involves the combination of a 1,3-dicarbonyl component with an N–C–N fragment such as a urea, an amidine or a guanidine.



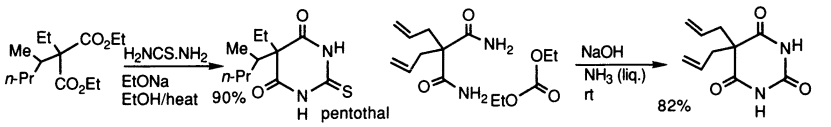
The choice of N–C–N component – amidine,[125] guanidine[126] or a urea[127] (thiourea[128]) – governs the substitution at C-2 in the product heterocycle. Although not formally 'N–C–N' components, formamide,[129] or an orthoester plus ammonia[130] can serve instead in this type of approach. The dicarbonyl component can be generated *in situ*, for example formylacetic acid (by decarbonylation of malic acid), or a synthon used (1,1,3,3-tetramethoxypropane for malondialdehyde), or a nitrile can serve as a carbonyl equivalent, the resulting heterocycle now carrying an amino substituent, as shown in the examples below.[131] The use of 2-bromo-1,1,3,3-tetramethoxypropane provides a route to 5-bromopyrimidine[132] and methanetricarboxaldehyde reacts with amidines to give 5-formylpyrimidines.[133]



Other synthons for 1,3-dicarbonyl compounds which have been successfully applied include β-chloro-α,β-unsaturated ketones and aldehydes,[134] β-amino-α,β-unsaturated ketones,[135] vinylamidinium salts,[136] and propiolic acid, reaction of which with urea gives uracil directly in about 50% yield.[137] In analogy, pyrimidines fused to other rings, for example as in quinazolines, can be made from *ortho*-aminonitriles[138] and in general, from β-enaminoesters.[139]

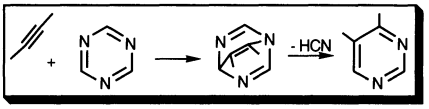


Barbituric acid and barbiturates can be synthesised by reacting a malonate with a urea,[140] or a bis primary amide of a substituted malonic acid with diethyl carbonate.[141]

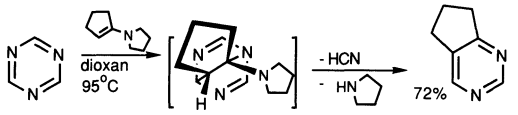


11.13.2.2 *By cycloaddition of a 1,3,5-triazine with an alkyne*

Cycloaddition of a 1,3,5-triazine with an alkyne (or its equivalent) gives pyrimidines after loss of hydrogen cyanide.

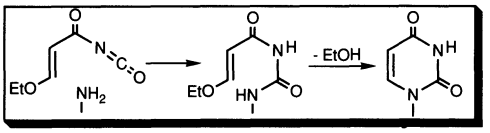


The formation of pyrimidines[142] *via* aza-Diels-Alder reactions is similar to the preparation of pyridazines from tetrazines (see also section 25.2.1).

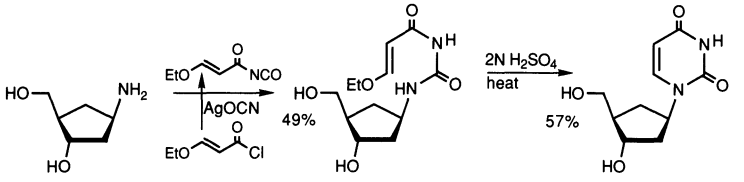


11.13.2.3 *From ethoxyacryloyl isocyanate and primary amines*

Primary amines add to the isocyanate group in ethoxyacryloyl isocyanate; ring closure then gives pyrimidines *via* intramolecular displacement of the ethoxy group.



Uracils can be prepared *via* reaction of primary amines with ethoxyacryloyl isocyanate;[143] this method is particularly suitable for complex amines and has found much use in recent years in the synthesis of, for example, carbocyclic nucleoside analogues as potential anti-viral agents.[144] The immediate product of amine/isocyanate interaction can be cyclised under either acidic or basic conditions and the method can also be applied to thiouracil synthesis.

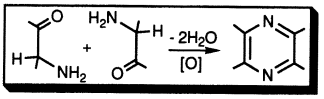


11.13.3 Ring synthesis of pyrazines

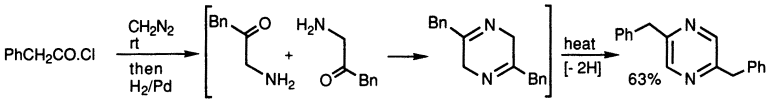
Pyrazine is not easily made in the laboratory. Commercially, the high temperature cyclodehydrogenation of precursors such as *N*-hydroxyethyl ethane-1,2-diamine is used.

11.13.3.1 *From the self-condensation of a 2-aminoketone*

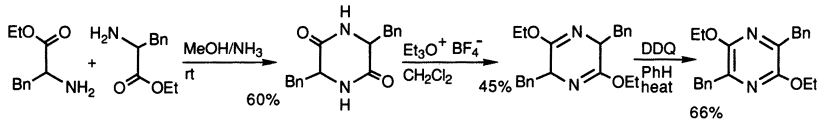
Symmetrical pyrazines result from the spontaneous self condensation of two mol equivalents of a 2-aminoketone, or -aldehyde, followed by an oxidation.



2-Amino-carbonyl compounds, which are stable only as their salts, are usually prepared *in situ* by the reduction of diazo-, oximino- or azido-ketones. The dihydropyrazines produced by this strategy are very easily aromatised, for example by air oxidation, and often distillation alone is sufficient to bring about disproportionation.[145]

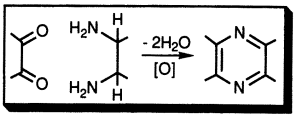


α-Amino-esters are more stable than α-amino-ketones but nonetheless easily self-condense to give heterocycles, known as 2,5-diketopiperazines. These compounds are resistant to oxidation but can be used to prepare aromatic pyrazines after first converting them into dichloro- or dialkoxy-dihydropyrazines.[146]

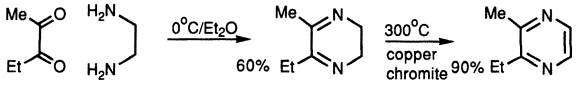


11.13.3.2 *From 1,2-dicarbonyl compounds and 1,2-diamines*

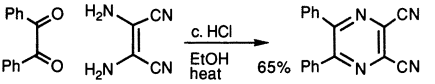
1,2-Dicarbonyl compounds undergo double condensation with 1,2-diamines; an oxidation is then required.



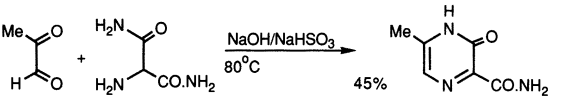
This method is well suited to the formation of symmetrical pyrazines;[147] if both diketone and diamine are unsymmetrical, two isomeric pyrazines are formed.



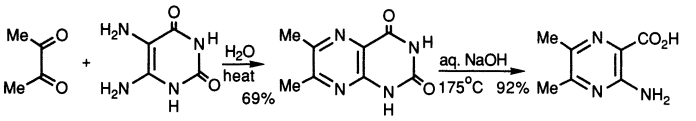
The direct synthesis of aromatic pyrazines along these lines requires a 1,2-diaminoalkene, but simple examples of such compounds are not known; however, diaminomaleonitrile[148] is stable and serves in this context.



Other dinitrogen components which also carry unsaturation are α-amino acid amides,[149] from which pyrazinones can be formed; a special example is amino-malonamide.[150]



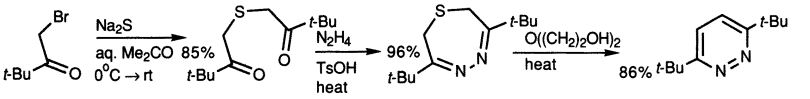
An ingenious modification of the general method uses 5,6-diaminouracil as a masked ene-1,2-diamine: the products can be hydrolysed with cleavage of the pyrimidinone ring, finally arriving at amino-pyrazine acids as products.[151]



11.13.4 Notable syntheses of diazines

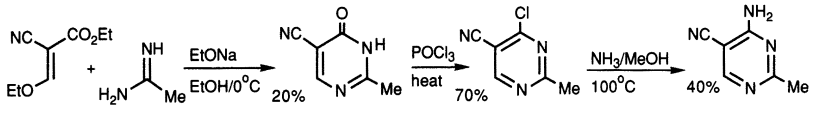
11.13.4.1 *Pyridazines via sulfides*

Symmetrically 3,6-disubstituted pyridazines, with a variety of alkyl and aryl substituents, can be constructed *via* ring contraction of a sulfide.[152]



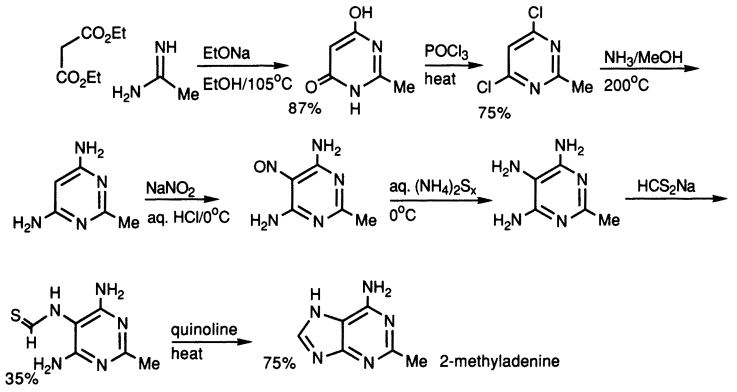
11.13.4.2 *4-Amino-5-cyano-2-methylpyrimidine*

4-Amino-5-cyano-2-methylpyrimidine[153] is an intermediate used in a synthesis of vitamin B_1.



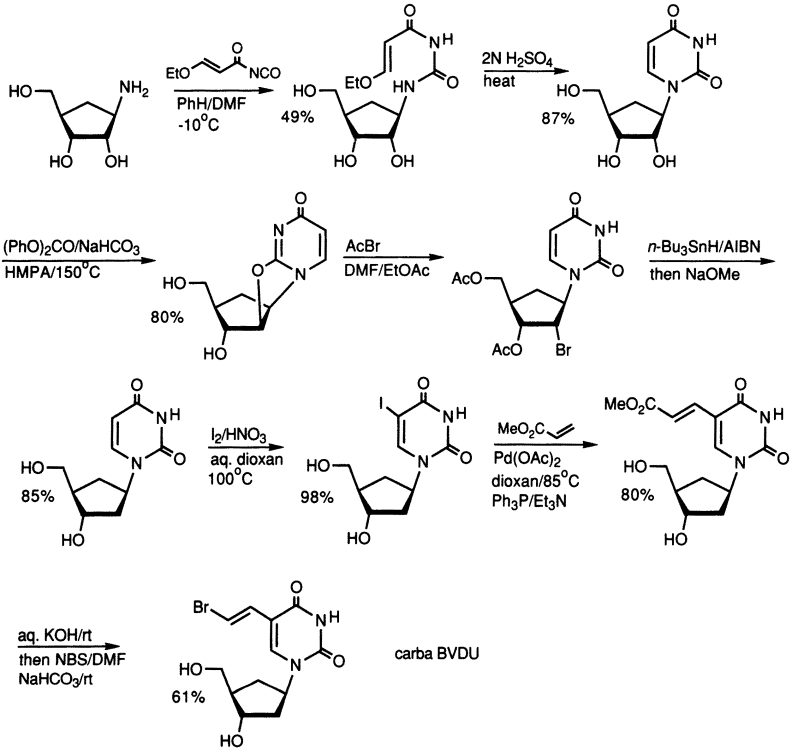
11.13.4.3 *4,6-Diamino-5-thioformamido-2-methylpyrimidine*

4,6-Diamino-5-thioformamido-2-methylpyrimidine can be converted into 2-methyladenine.



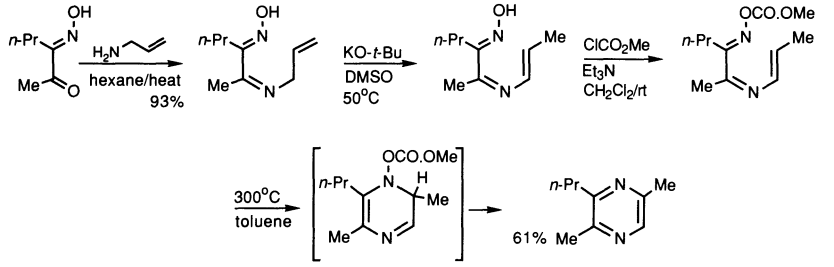
11.13.4.4 *Carbocyclic bromovinyldeoxyuridine*

Carbocyclic bromovinyldeoxyuridine (CarbaBVDU) is an anti-viral agent.[154]



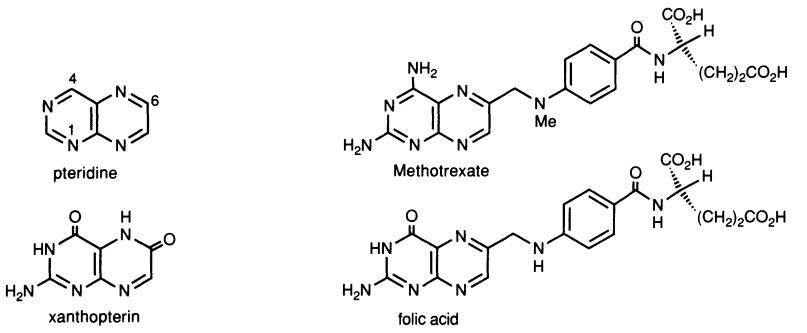
11.13.4.5 *2,5-Dimethyl-3-n-propylpyrazine*

Alkylpyrazines can be produced by an ingenious sequence involving an electrocyclic ring closure of a 1,4-diazatriene, aromatisation being completed by loss of the oxygen from the original oxime hydroxyl group.[155]



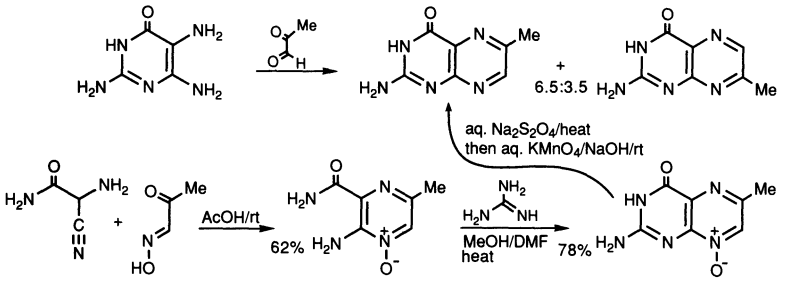
11.13.4.6 *Pteridines*

Pyrazino[2,3-*d*]pyrimidines are known as 'pteridines',[156] because the first examples of the ring system, as natural products, were found in pigments, like xanthopterin (yellow), in the wings of butterflies (*Lepidoptera*). The pteridine ring system has subsequently been found in coenzymes which use tetrahydrofolic acid (derived from the vitamin folic acid), the molybdenum cofactor of the oxomolybdoenzymes, and in the anti-cancer drug Methotrexate.



The synthesis of the ring system has been approached by two obvious routes: one is the fusion of the pyrazine ring onto a preformed 4,5-diaminopyrimidine, and the second, the elaboration of the pyrimidine ring on a preformed pyrazine. The first of these, the *Isay synthesis*, suffers from the disadvantage that condensation of the heterocyclic 1,2-diamine with an unsymmetrical 1,2-dicarbonyl compound usually leads to a mixture of two 5/6-substituted isomers.[157] It was to avoid this difficulty that the alternative strategy, the *Taylor synthesis*, now widely used, starting with a pyrazine, was developed.[158] This approach has the further advantage that because the pyrazine ring is presynthesised, using 2-cyanoglyci-

namide,[159] it eventually produces, regioselectively, 6-substituted pteridines – substitution at the 6-position is the common pattern in natural pteridines.



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EXERCISES FOR CHAPTER 11

1. What compounds are produced at each stage in the following sequences: (i) pyridazin-3-one reacted with $POCl_3$ (→ $C_4H_3N_2Cl$) and this with NaOMe (→ $C_5H_6N_2O$); (ii) 2-chloropyrazine with $BuNH_2$/120°C (→ $C_8H_{13}N_3$).
2. What are the structures of the compounds formed: (i) $C_6H_9IN_2S$ from 3-methylthiopyridazine and MeI and $C_6H_8ClIN_2$ from 3-chloro-6-methylpyridazine; (ii) $C_5H_2Cl_2N_2O$ from treatment of 2,6-dichloropyrazine with LiTMP then HCO_2Et; (iii) $C_{14}H_{12}N_2O_2$ from 2,6-dimethoxypyrazine with LiTMP, then I_2 then PhC≡CH/Pd(0); (iv) $C_6H_9N_3$ from 2-aminopyrimidine, first with $NaNO_2$/c. HCl/−15°C (and

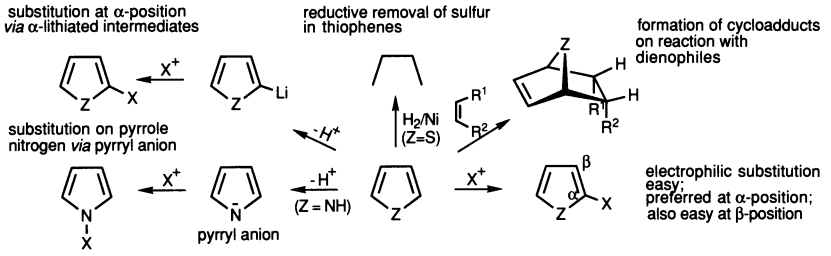
then the product with Me_2NH; (v) $C_{18}H_{14}N_2$ from 3-methyl-6-phenylpyridazine with $PhCH{=}O/Ac_2O$/heat.

3. Write sequences and structures for intermediates and final products in the following ring syntheses: (i) 4-chlorobenzene with succinic anhydride/$AlCl_3$ ($\rightarrow C_{10}H_9ClO_3$) , then this with N_2H_4 ($\rightarrow C_{10}H_9ClN_2O$) and finally this with Br_2/AcOH ($\rightarrow C_{10}H_7ClN_2O$); (ii) 2,5-dimethylfuran reacted with Br_2 in MeOH ($\rightarrow C_8H_{14}O_3$) then this firstly with aqueous acid and then hydrazine ($\rightarrow C_6H_8N_2$); (iii) 1,1-dimethoxybutan-3-one with guanidinium hydrogen carbonate ($\rightarrow C_5H_7N_3$); (iv) ethyl cyanoacetate with guanidine/NaOEt ($\rightarrow C_4H_6N_4O$); (v) ethyl cyanoacetate with urea/EtONa ($\rightarrow C_4H_5N_3O_2$); (vi) $(EtO)_2CHCH_2CH(OEt)_2$/HCl/urea ($\rightarrow C_4H_4N_2O$); (vii) $MeOCH_2COMe$ with EtO_2CH/Na ($\rightarrow C_5H_8O_3$), then this with thiourea ($\rightarrow C_6H_8N_2OS$), then this with H_2/Ni ($\rightarrow C_6H_8N_2O$); (viii) $PhCO.CH_2CO_2Et$ with $EtC(=NH)NH_2$ ($\rightarrow C_{12}H_{12}N_2O$); (ix) PhCO.CHO with $MeCH(NH_2)CO.NH_2$ ($\rightarrow C_{11}H_{10}N_2O$).

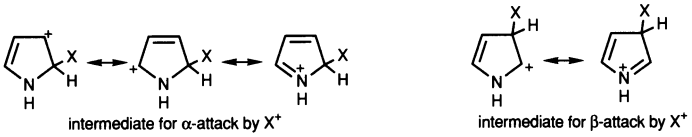
Typical reactivity of pyrroles, thiophenes and furans

12

In this chapter are gathered the most important generalisations which can be made, and the general lessons which can be learned about the reactivity, and relative reactivities, one with the other, of the prototypical five-membered, aromatic heterocycles: pyrroles, thiophenes and furans.



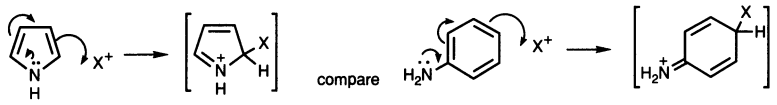
The chemistry of pyrrole, thiophene and furan is dominated by a readiness to undergo electrophilic substitution, preferentially at an α-position but, with only slightly less alacrity, also at a β-position, should the α-positions be blocked.



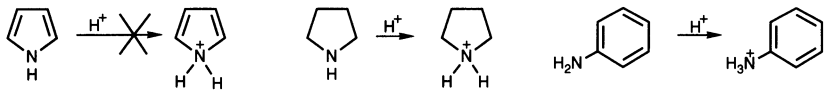
Positional selectivity in these five-membered systems, indeed their high reactivity to electrophilic attack, are well explained by a consideration of the Wheland intermediates (and by implication, the transition states which lead to them) for electrophilic substitution. Intermediate cations from both α- and β-attack are stabilised (shown for attack on pyrrole). The delocalisation, involving donation of electron density from the hetero atom, is greater in the intermediate from α-attack, as illustrated by the number of low energy resonance contributors which can be drawn. Note that the C–C double bond in the intermediate for

β-attack is not, and cannot become involved in delocalisation of the charge.

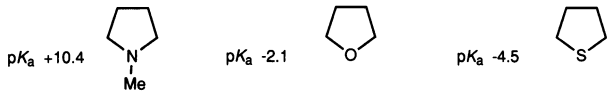
There is a simple parallelism between the reaction of a pyrrole with an electrophile and the comparable reaction of an aniline, and indeed pyrrole is in the same range of reactivity towards electrophiles as is aniline.



The five-membered heterocycles do not react with electrophiles at the hetero atom; perhaps this surprises the heterocyclic newcomer most obviously with respect to pyrrole, for here, it might have been anticipated, the nitrogen lone pair would be easily donated to an incoming electrophile, as it certainly would be in reactions of its saturated counterpart, pyrrolidine. The difference is that in pyrrole, electrophilic addition at the nitrogen would lead to a substantial loss of resonance stabilisation – the molecule would be converted into a cyclic butadiene, with an attached nitrogen carrying a positive charge localised on that nitrogen atom. The analogy with aniline falls down for, of course, anilines do react easily with simple electrophiles (e.g. protons) at nitrogen. The key difference is that, although some stabilisation in terms of overlap between the aniline nitrogen lone pair and benzenoid π-system is lost, the majority of the stabilisation energy, associated with the 6-electron aromatic π-system, is retained when aniline nitrogen donates its lone pair of electrons to a proton (electrophile).



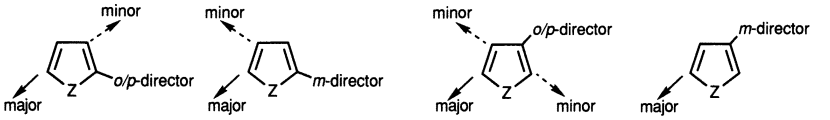
Of the trio – pyrrole, furan and thiophene – the first is by far the most susceptible to electrophilic attack: this susceptibility is linked to the greater electron-releasing ability of neutral trivalent nitrogen, and the concomitant greater stability of a positive charge on tetravalent nitrogen. This finds its simplest expression in the relative basicities of saturated amines, sulfides and ethers, respectively, which are seen to nicely parallel the relative order of reactivity of pyrrole, furan and thiophene towards electrophilic attack at carbon, but involving major assistance by donation from the hetero atom, i.e. the development of positive charge on the hetero atom.



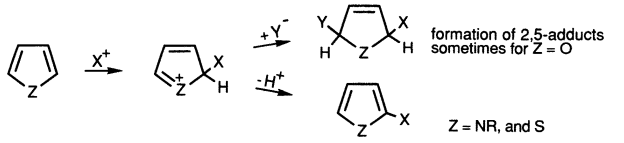
In qualitative terms, the much greater reactivity of pyrrole is illustrated by its rapid reaction with weak electrophiles like benzenediazonium cation and nitrous acid, neither of which react with furan or thiophene. It is relevant to note that

N,N-dimethylaniline reacts rapidly with PhN_2^+ and HNO_2, while anisole does not.

Substituents ranged on five-membered rings have 'directing' effects comparable to those which they exert on a benzene ring. Alkyl groups, for example, direct *ortho* and *para*, and nitro groups direct *meta* although, strictly, these two terms cannot be applied to the five-membered situation. The very strong tendency for α electrophilic substitution is however the dominating influence in most instances, and products resulting from attack following guidance from the substituent are generally minor products in mixtures where the dominant substitution is at an available α-position. The influence of substituents is felt least in furans.



An aspect of the chemistry of furans is the occurrence of a number of 2,5-additions initiated by electrophilic attack: a Wheland intermediate is formed normally but then adds a nucleophile, when a sufficiently reactive one is present, instead of then losing a proton. Conditions can, however, usually be chosen to allow the formation of a 'normal' α-substitution product if desired. The occurrence of such processes in the case of furan is generally considered to be associated with its lower aromatic resonance stabilisation energy – there is less to regain by loss of a proton and the consequent return to an aromatic furan.

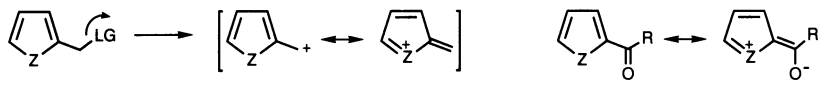


The lower aromaticity of furans also manifests itself in a much greater tendency to undergo cycloadditions, as a 4-π, 'diene' component in Diels-Alder reactions. That is to say, furans are much more like dienes, and less like six-electron aromatic systems, than are pyrroles and thiophenes. However, the last two systems can be made to undergo cycloadditions by increasing the pressure or, in the case of pyrroles, by 'reducing the aromaticity' by the device of inserting an electron-withdrawing group onto the nitrogen.

In direct contrast with electron-deficient heterocycles like pyridines and the diazines, the five-membered systems do not undergo nucleophilic substitutions, except in situations (especially in furan and thiophene chemistry) where halide is situated *ortho* or *para* to a nitro group. Deprotonations are however extremely important: furan and thiophene are deprotonated by strong bases, such as *n*-butyllithium or lithium diisopropylamide, at their α-positions, because here the hetero atom can exert its greatest acidifying influence by inductive withdrawal

of electrons, to give anions which can then be made to react with the whole range of electrophiles affording α-substituted furans and thiophenes. This methodology compliments the use of electrophilic substitutions to introduce groups, also regioselectively α, but has the advantage that even weak electrophiles can be utilised. The employment of metallated *N*-substituted (blocked) pyrroles is an equally valid strategy for producing α-substituted pyrroles. Pyrroles which have an *N*-hydrogen are deprotonated at the nitrogen, and the pyrryl anion thus generated is nucleophilic at the hetero atom, providing a means for the introduction of electrophilic groups on nitrogen.

The potential for interaction of the hetero atom (electron donation) with positive charge on a side-chain, especially at an α-position, has a number of effects: amongst the most important is the enhanced reactivity of side-chain derivatives carrying leaving groups.

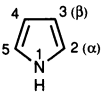


Similarly, carbonyl groups attached to five-membered heterocycles have somewhat reduced reactivity, as implied by the resonance contributor shown.

Generally speaking, the five-membered heterocycles are far less stable to oxidative conditions than benzenoid aromatic substances, with thiophenes bearing the closest similarity – in many ways thiophenes, of the trio, are the most like benzenes. Hydrogenation of thiophenes, particularly over nickel as catalyst, leads to saturation and removal of the hetero atom. Some controlled chemical reductions of pyrroles and furans are known, which give dihydro-products.

Pyrroles: reactions and synthesis

13



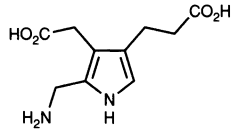
pyrrole

Pyrrole[1] and the simple alkyl pyrroles are colourless liquids, with relatively weak odours rather like that of aniline, which, also like the anilines, darken by autoxidation. Pyrrole itself is readily available commercially, and is manufactured by alumina-catalysed gas-phase interaction of furan and ammonia.

Pyrrole was first isolated in 1857 from the pyrolysate of bone: the process by which it arises is similar to an early laboratory method for the preparation of pyrrole – the pyrolysis of the ammonium salt of the sugar acid, mucic acid.

The word pyrrole is derived from the Greek for red, which refers to the bright red colour which pyrrole imparts to a pinewood shaving moistened with concentrated hydrochloric acid.

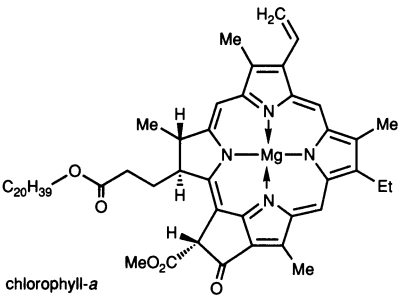
The early impetus for the study of pyrroles came from degradative work relating to the structures of two pigments central to life processes, the blood respiratory pigment haem, and chlorophyll, the green photosynthetic pigment of plants.[2] Such degradations led to the formation of mixtures of alkylpyrroles. Chlorophyll and haem are synthesised in the living cell from porphobilinogen, the only aromatic pyrrole to play a function – a vitally important function – in fundamental metabolism.[3]



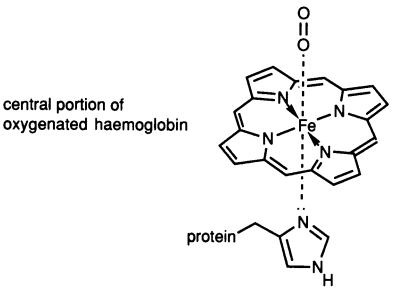
porphobilinogen

Ultimately, all life on earth depends on the incorporation of atmospheric carbon dioxide into carbohydrates. The energy for this highly endergenic process is sunlight, and the whole is called photosynthesis. The very first step in the com-

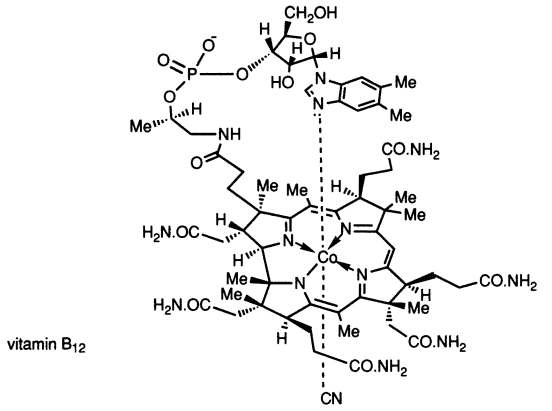
plex sequence is the absorption of a photon by pigments, of which the most important in multicellular plants is chlorophyll-*a*. This photonic energy is then used chemically to achieve a crucial C→CO_2 bonding reaction, a reductive carboxylation in which ultimately oxygen is liberated. Thus formation of the by-product of this process, molecular oxygen, allowed the evolution of aerobic organisms, of which man is one.



Haemoglobin is the agent which carries oxygen from lung to tissue in the arterial blood-stream in mammals; it is made up of the protein globin associated with a prosthetic group, the pigment haem (also spelt heme). The very close structural similarity of haem with chlorophyll is striking, suggesting a common evolutionary origin. In oxygenated haemoglobin, the iron is six-coordinate Fe(2) with an imidazolyl nitrogen of a protein histidine residue as ligand on one side of the plane of the macrocycle, and on the other, molecular oxygen. Haem without the ferrous iron is called protoporphyrin IX and the unsubstituted tetrapyrrolic macrocycle is called porphin.

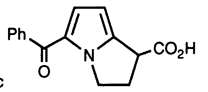


Haem is also the active site of the cytochromes,[4] which are enzymes concerned with electron transfer. Another porphobilinogen-derived system is vitamin B_{12},[5] the structure of which is significantly different, though related to chlorophyll and haem. The parent, unsubstituted macrocycle is called corrin.



vitamin B_{12}

Ketorolac, an analgesic and anti-inflammatory agent, is one of the top 100 best-selling drugs in the USA.



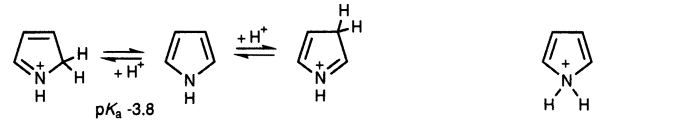
Ketorolac

13.1 REACTIONS WITH ELECTROPHILIC REAGENTS[6]

Whereas pyrroles are resistant to nucleophilic addition and substitution, they are very susceptible to attack by electrophilic reagents and react almost exclusively by substitution. Pyrrole itself, *N*- and *C*-monoalkyl and to a lesser extent *C*, *C'*-dialkylpyrroles, are polymerised by strong acids so that many of the electrophilic reagents useful in benzene chemistry cannot be used. However, the presence of an electron-withdrawing substitutent such as methoxycarbonyl (MeO_2C–), prevents polymerisation and allows the use of the strongly acidic, nitrating and sulfonating agents.

13.1.1 Protonation

Reversible proton addition occurs at all positions, being by far the fastest at the nitrogen, and about twice as fast as at C-2 as at C-3.[7] Thermodynamically the stablest cation, the 2*H*-pyrrolium ion, is that formed by protonation at C-2 and observed pK_a values for pyrroles are for these 2-protonated species. The weak *N*-basicity of pyrroles is the consequence of the absence of mesomeric delocalisation of charge in the 1*H*-pyrrolium cation.

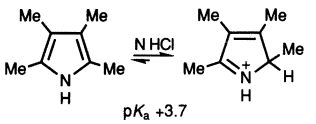


2*H*-pyrrolium cation (stablest)

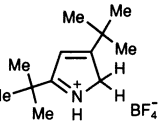
3*H*-pyrrolium cation

1*H*-pyrrolium cation (least stable)

The pK_a values of a wide range of pyrroles have been determined:[8] pyrrole itself is an extremely weak base with a pK_a value of −3.8; this, as a 0.1 molar solution in normal acid, corresponds to only one protonated molecule to about 5000 unprotonated. However, basicity increases very rapidly with increasing alkyl substitution, so that 2,3,4,5-tetramethylpyrrole, with a pK_a of +3.7, is almost completely protonated on carbon as a 0.1 molar solution in normal acid (cf. aniline, which has a pK_a of +4.6). Thus alkyl groups have a striking stabilising effect on cations – isolable, crystalline salts can be obtained from pyrroles carrying *t*-butyl groups.[9]

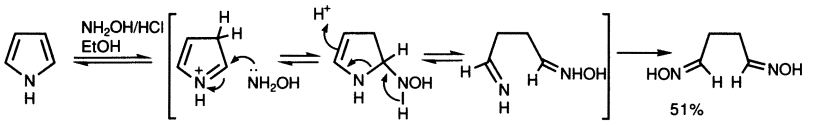


stable, crystalline salt of 2,5-di-*t*-butylpyrrole



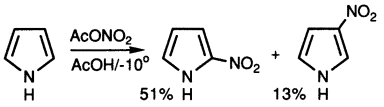
Reactions of protonated pyrroles

The 2*H*- and 3*H*-pyrrolium cations are essentially immonium ions and as such are electrophilic: they play the key role in polymerisation (section 13.1.8) and reduction (section 13.8) of pyrroles in acid. In the reaction of pyrroles with hydroxylamine hydrochloride, which produces a ring-opened 1,4-dioxime, it is probably the more reactive 3*H*-pyrrolium cation which is the starter.[10] Primary amines, RNH_2, can thus be protected, by conversion into 1-R-2,5-dimethylpyrroles (section 13.18.1.1), the protecting group being removable by this reaction with hydroxylamine.[11]

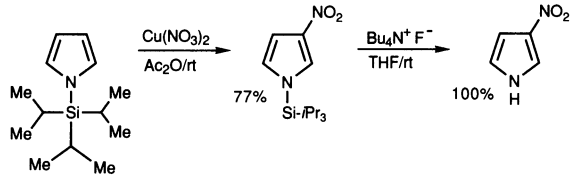


13.1.2 Nitration

Nitrating mixtures suitable for benzenoid compounds cause complete decomposition of pyrrole, but reaction occurs smoothly with acetyl nitrate at low temperature, giving mainly 2-nitropyrrole. This nitrating agent is formed by mixing fuming nitric acid with acetic anhydride to form acetyl nitrate and acetic acid, thus removing the strong mineral acid. In the nitration of pyrrole with this reagent it has been shown that C-2 is 1.3×10^5 and C-3 is 3×10^4 times more reactive than benzene.[12]

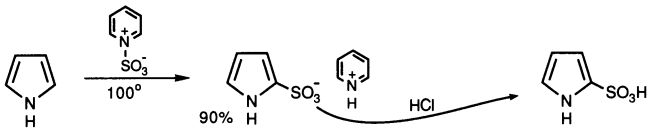


N-Substitution of pyrroles gives rise to increased proportions of β-substitution, even methyl causing the β : α ratio to change to 1 : 3, the much larger *t*-butyl actually reverses the relative positional reactivities, with a β : α of 4 : 1,[13] and the intrinsic α-reactivity can be effectively completely blocked with a very large substituent such as a triisopropylsilyl (TIPS) group, especially useful since it can be subsequently easily removed.[14]

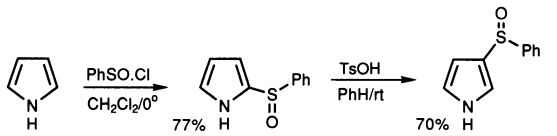


13.1.3 Sulfonation; reactions with other sulfur electrophiles

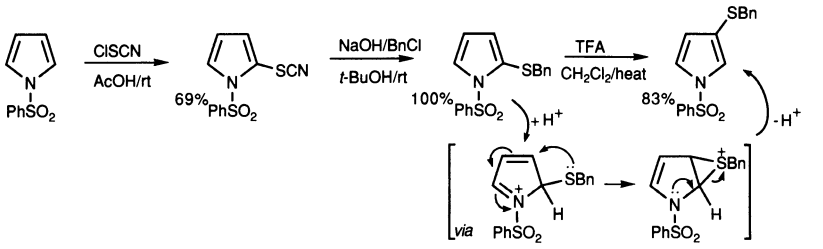
For sulfonation, a mild reagent of low acidity must be used: the pyridine–sulfur trioxide compound smoothly converts pyrrole into the 2-sulfonate.[15]



Sulfinylation of pyrrole[16] and thiocyanation of 1-phenylsulfonylpyrrole[17] also provide means for the electrophilic introduction of sulfur, but at lower oxidation levels.

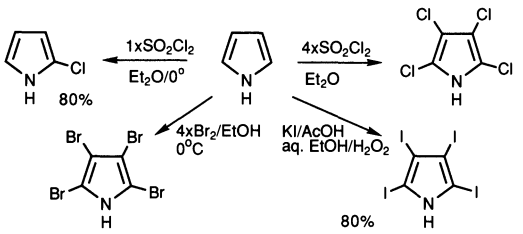


The acid-catalysed rearrangement of sulfur substituents from the α-position of kinetically-controlled attack, exemplified in these sulfur-substituted pyrroles, is a useful means for the preparation of β-substituted pyrroles (see also section 13.1.5).[17]

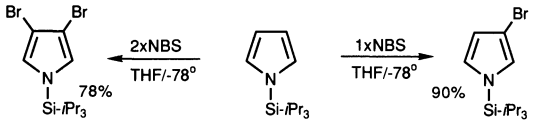


13.1.4 Halogenation

Pyrrole halogenates so readily that unless controlled conditions are used, stable tetrahalopyrroles are the only isolable products,[18] however 2-bromo- and 2-chloropyrroles, unstable compounds, can be prepared by direct halogenation of pyrrole itself.[19]

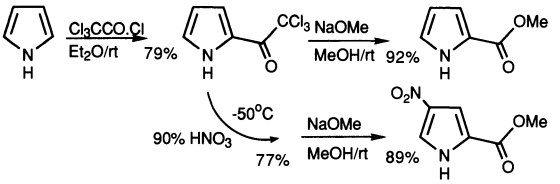


Attempts to monohalogenate simple alkylpyrroles fail, probably because of side-chain halogenation and the generation of extremely reactive pyrrylalkyl halides. However, *N*-triisopropylsilylpyrrole monobrominates and monoiodinates cleanly and nearly exclusively at C-3 and, with two mol equivalents of NBS, dibrominates at C-3 and C-4.[14,20]

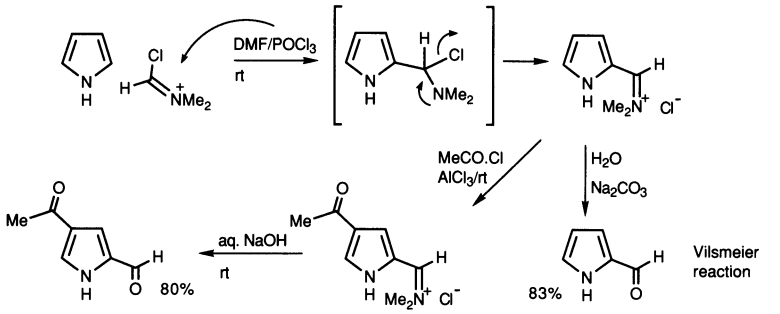


13.1.5 Acylation

Direct acetylation of pyrrole with acetic anhydride at 200°C leads to 2-acetylpyrrole as main product together with some 3-acetylpyrrole but no *N*-acetylpyrrole.[21] *N*-Acetylpyrrole can be obtained in high yield simply by heating pyrrole with *N*-acetylimidazole.[22] Alkyl substitution facilitates *C*-acylation, so that 2,3,4-trimethylpyrrole yields the 5-acetyl derivative even on refluxing in acetic acid. The more reactive trifluoroacetic anhydride and trichloroacetyl chloride react with pyrrole efficiently, even at room temperature, to give 2-substituted products, alcoholysis or hydrolysis of which provides a clean route to pyrrole-2-esters or -acids.[23] Strong electron-withdrawing (*meta*-directing) substituents at a pyrrole α-position tend to override the intrinsic pyrrole reactivity and further substitution takes place mainly at C-4, not the remaining α-position.[24]

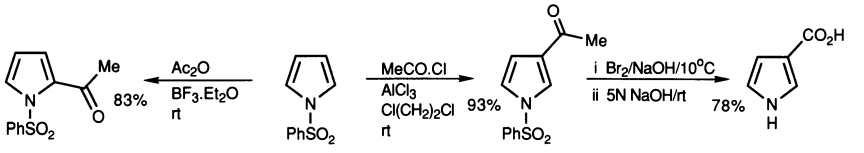


Vilsmeier acylation of pyrroles, formylation with DMF/phosphorus oxychloride in particular, is a generally applicable process.[25] Here again, the presence of a large *N*-substituent perturbs the intrinsic α-reactivity, formylation of *N*-tritylpyrrole favouring the β-position by 2.8 : 1 and trifluoroacetylation of this pyrrole giving only the 3-ketone;[26] the use of bulky *N*-silyl-substituents allows β-acylation with subsequent removal of the *N*-substituent.[27] Nitrilium salts also effect acylation of pyrroles to give 2-ketones after hydrolysis.[28]

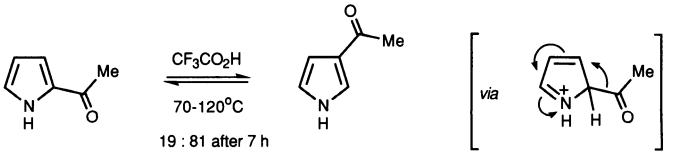


The iminium salt products from Vilsmeier reactions, before hydrolysis, can be neatly utilised for further Friedel-Crafts substitution. The substituent is strongly *meta* directing, thus leading to 2,4-diacylated pyrroles, and also serves to protect the potential aldehyde.[29]

Acylation of *N*-phenylsulfonyl pyrrole, with its deactivating substituent, requires more forcing conditions – the presence of a Lewis acid as catalyst – the regioselectivity of attack depending both on choice of catalyst and on the particular acylating agent.[30] Oxidation of 3-acetyl-1-phenylsulfonylpyrrole[31] or hydrolysis and detritylation of 3-trifluoroacetyl-1-tritylpyrrole are each efficient routes to pyrrole-3-carboxylic acid. Treatment of acylated 1-phenylsulfonylpyrroles with *t*-butylamine-borane effects conversion to the corresponding alkyl derivatives.[32]

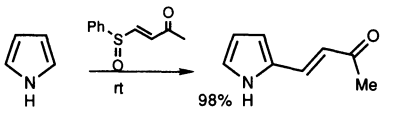


β- and α-Acylpyrroles can be equilibrated one with the other using acid; for *N*-alkyl-*C*-acylpyrroles, the equilibrium lies completely on the side of the 3-isomer.[33]



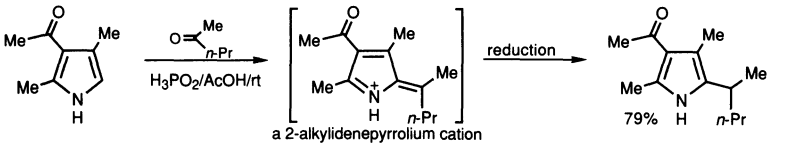
13.1.6 Alkylation

Mono-*C*-alkylation of pyrroles cannot be achieved by direct reaction with simple alkyl halides, either alone or with a Lewis acid catalyst; for example, pyrrole does not react with methyl iodide below 100°C; above about 150°C a series of reactions occurs leading to a complex mixture made up mostly of polymeric material together with some poly-methylated pyrroles. The much more reactive allyl bromide reacts with pyrrole at room temperature, but mixtures of mono- to tetrallylpyrroles together with oligomers and polymers are obtained. Alkylations with conjugated enones carrying a β-electron-withdrawing and potential leaving group have considerable synthetic potential.[34]

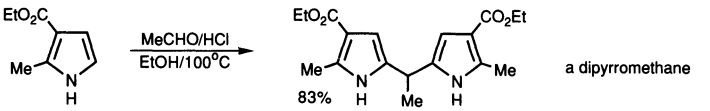


13.1.7 Condensation with aldehydes and ketones

Condensations of pyrroles with aldehydes and ketones occur easily by acid catalysis but the resulting pyrrolylcarbinols cannot be isolated, for under the reaction conditions proton-catalysed loss of water produces 2-alkylidenepyrrolium cations which are themselves highly reactive electrophiles. Thus, in the case of pyrrole itself, reaction with aliphatic aldehydes inevitably leads to resins, probably linear polymers. Reductive trapping of these cationic intermediates produces alkylated pyrroles; all free positions react and, as the example shows, acyl and alkoxycarbonyl substituents are unaffected.[35] A mechanistically related process is the clean 4-chloromethylation of pyrroles carrying acyl groups at C-2.[36]

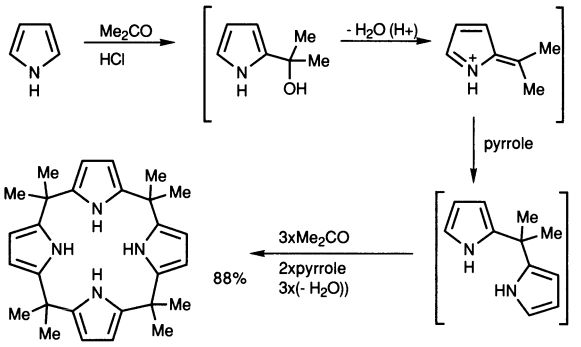


When the pyrrole ring contains an electron-withdrawing substituent and has only one free α-position, dipyrromethanes resulting from attack by a second mol equivalent of the pyrrole on the intermediate can be obtained.

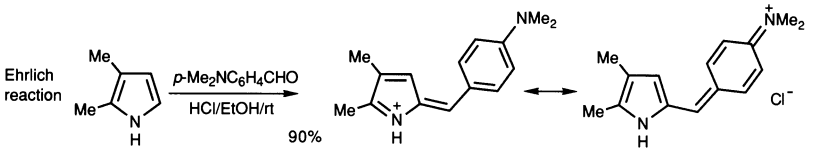


Acetone, reacting in a comparable manner, gives a cyclic tetramer in high yield, perhaps because the geminal methyl groups tend to force the pyrrole rings

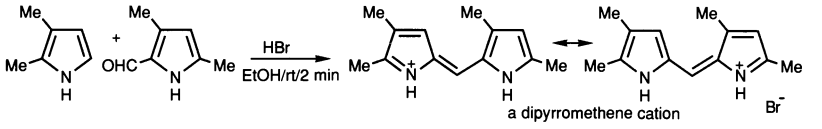
into a coplanar conformation, greatly increasing the chances of cyclisation of a linear tetrapyrrolic precursor.[37]



Condensations with aromatic aldehydes carrying appropriate electron-releasing substituents produce cations which are sufficiently stabilised by mesomerism to be isolated. Such cations are coloured: the reation with *p*-dimethylaminobenzaldehyde is the basis for the classical Ehrlich test, deep red/violet colours being produced by pyrroles (and also by furans and indoles) which have a free nuclear position.

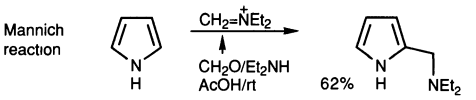


Analogous condensations with a pyrrole aldehyde lead to mesomeric dipyrromethene cations, which play an important part in porphyrin synthesis.

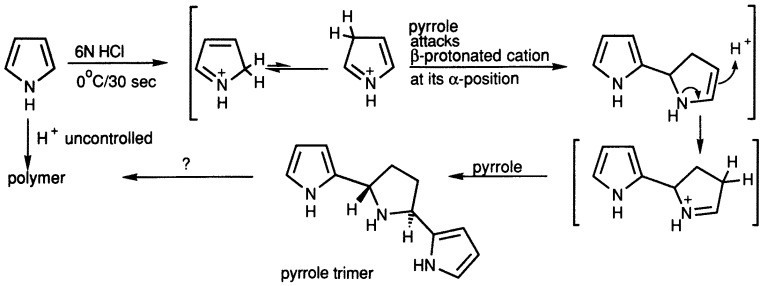


13.1.8 Condensation with imines and immonium ions

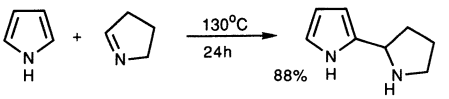
The imine and immonium functional groupings are, of course, the nitrogen equivalents of carbonyl and *O*-protonated carbonyl groups, and their reactivity is analogous. The Mannich reaction of pyrrole produces dialkylaminomethyl derivatives, the immonium electrophile being generated *in situ* from formaldehyde, dialkylamine and acetic acid.[38]



The mineral-acid-catalysed polymerisation of pyrrole involves a series of Mannich reactions, but under controlled conditions pyrrole can be converted into an isolable trimer, which is probably an intermediate in the polymerisation. The key to understanding the formation of the observed trimer is that the less stable, therefore more reactive, β-protonated pyrrolium cation is the electrophile which initiates the sequence attacking a second mol equivalent of the heterocycle. The dimer, an enamine, is too reactive to be isolable, however the trimer, relatively protected as its salt, reacts further only slowly.[39]

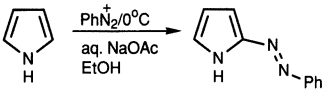


There are only a few examples of the reactions of imines themselves with pyrroles; the condensation of 1-pyrroline with pyrrole as solvent is one such example.[40]



13.1.9 Diazo-coupling[41]

The high reactivity of pyrroles is illustrated by their ready reaction with benzenediazonium salts. Pyrrole itself gives a mono-azo derivative by reacting as a neutral species below p*H* 8, but by way of the pyrryl anion (section 13.4), and 10^8 times faster, in solutions above p*H* 10. In more strongly alkaline conditions 2,5-bisdiazo derivatives are formed.



13.2 REACTIONS WITH OXIDISING AGENTS[42]

Simple pyrroles are generally easily attacked by chemical oxidising agents, frequently with complete breakdown. When the ring does survive, maleimide derivatives are the commonest products, even when there was originally a 2- or 5-alkyl substituent. This kind of oxidative degradation played an important part in early porphyrin structure determination, in which chromium trioxide in aque-

ous sulfuric acid or fuming nitric acid were usually used as oxidising agents.

Hydrogen peroxide is a more selective reagent and can convert pyrrole itself into a tautomeric mixture of pyrrolin-2-ones in good yield (section 13.17.1).

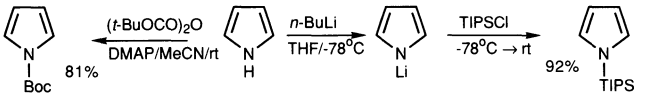
13.3 REACTIONS WITH NUCLEOPHILIC REAGENTS

Pyrrole and its derivatives do not react with nucleophilic reagents by addition or by substitution, except in the same special situations which apply in benzene chemistry, i.e. where there are powerful electron-withdrawing substituents.

13.4 REACTIONS WITH BASES

13.4.1 Deprotonation of *N*-hydrogen

Pyrrole *N*-hydrogen is much more acidic (pK_a 17.5) than that of a comparable saturated amine, say pyrrolidine (pK_a ~ 44), or aniline (pK_a 30.7), and of the same order as that of 2,4-dinitroaniline. Any very strong base will effect complete conversion of an *N*-unsubstituted pyrrole into the corresponding pyrryl anion, perhaps the most convenient being commercial *n*-butyllithium in hexane, however, reactions at nitrogen can proceed *via* smaller, equilibrium concentrations of pyrryl anion, as in the formation of 1-chloropyrrole (in solution) by treatment with sodium hypochlorite[43] or the preparation of 1-*t*-butoxycarbonylpyrrole.[44]



13.4.2 Deprotonation of *C*-hydrogen

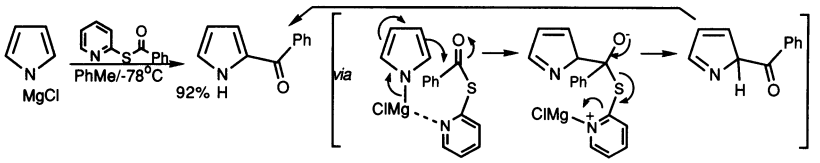
The *C*-deprotonation of pyrroles requires the absence of the much more acidic *N*-hydrogen, i.e. the presence of an *N*-substituent, either alkyl[45] or, if required, a removable group like phenylsulfonyl,[46] carboxylate,[47] trimethylsilylethoxymethyl[48] or *t*-butylaminocarbonyl.[49] Even in the absence of chelation assistance to lithiation, which is certainly an additional feature in each of the latter examples, metallation proceeds at the α-position. Deprotonation of *N*-methylpyrrole proceeds further, amazingly easily, to a dilithio derivative, either 2,4- or 2,5-dilithio-1-methylpyrrole, depending on the exact conditions.[50]

13.5 REACTIONS OF *N*-METALLATED PYRROLES

13.5.1 Lithio, sodio, potassio and magnesio derivatives

N-Metallated pyrroles can react with electrophiles to give either *N*- or *C*-substituted pyrroles: generally speaking the more ionic the metal–nitrogen bond and/or the better the solvating power of the solvent, the greater is the percentage of attack at nitrogen.[51] Based on these principles, several methods are available for efficient *N*-alkylation of pyrroles, including the use of potassium hydroxide in DMSO,[52] or in benzene with 18-crown-6,[53] thallous ethoxide,[54] using phase-transfer methodology,[55] or of course by reaction of the pyrryl anion generated using butyllithium. The thallium salt acylates[56] and the potassium salt arylsulfonylates[57] efficiently on nitrogen.

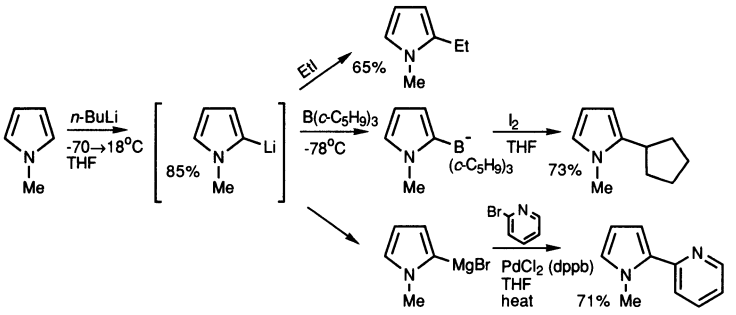
Pyrryl Grignard reagents, obtained in solution by treating an *N*-unsubstituted pyrrole with alkyl Grignard, tend to react at carbon with alkylating and acylating agents, but give mixtures of 2- and 3-substituted products with the former predominating,[58] *via* neutral non-aromatic intermediates, however clean α-acylation can be achieved using 2-acylthiopyridines (section 5.10.2.4).[59]



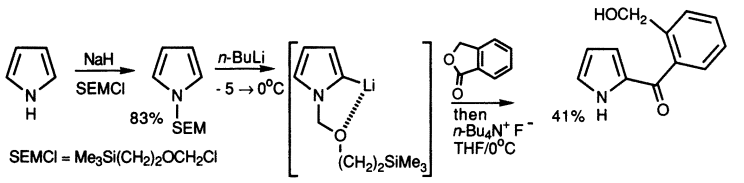
13.6 REACTIONS OF *C*-METALLATED PYRROLES

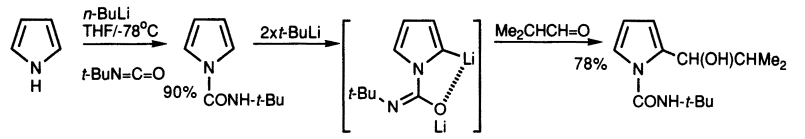
13.6.1 Lithio derivatives

Reactions of the species produced by the lithiation of *N*-substituted pyrroles are efficient for the introduction of groups to the 2-position, either by reaction with electrophiles[45–49] or by coupling processes based on boron or palladium chemistry.[60]

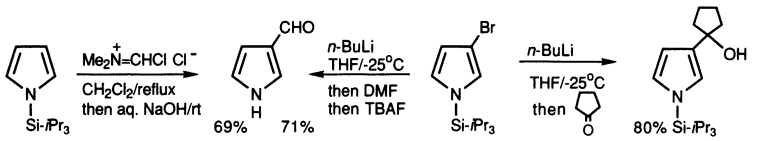


Some examples where removable *N*-blocking groups have been used in the synthesis of 2-substituted pyrroles, *via* lithiation, are shown below.



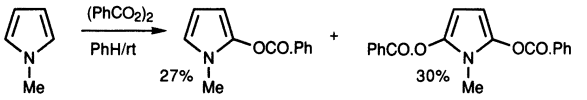


Metal/halogen exchange using 3-bromo-*N*-triisopropylsilylpyrrole very usefully allows the introduction of groups to the pyrrole β-position and can complement direct electrophilic substitution of *N*-triisopropylsilylpyrrole (see sections 13.1.2 and 13.1.4).



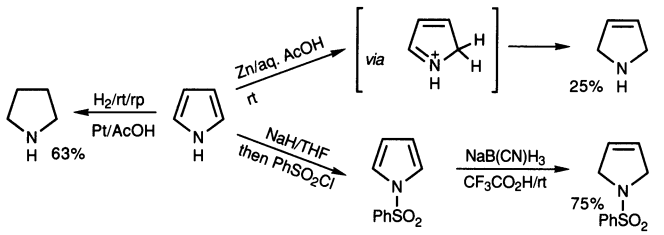
13.7 REACTIONS WITH RADICAL REAGENTS

Pyrrole itself tends to give tars under radical conditions, probably by way of initial *N*-hydrogen abstraction, but some *N*-substituted derivatives will undergo preparatively useful arylations, with attack taking place usually at the α-position.[61] More efficient routes to arylpyrroles depend on transition metal-mediated coupling processes (see section 2.7.2.2). *N*-Methylpyrrole is attacked by electrophilic benzoyloxy radicals at its α-positions.[62]



13.8 REACTIONS WITH REDUCING AGENTS

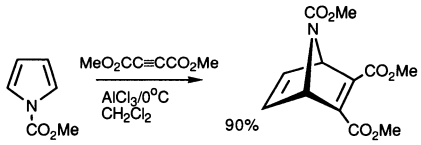
The pyrrole ring is not reduced by hydride reducing agents, diborane, or alkali metal/ethanol or /liquid ammonia combinations, but is reduced in acidic media, in which the species under attack is the protonated pyrrole. The products are 2,5-dihydropyrroles, accompanied by some of the pyrrolidine as by-product.[63]



Full reduction[64] of pyrroles to pyrrolidines can be effected catalytically over a range of catalysts, is especially easy if the nitrogen carries an electron-withdrawing group, and is not complicated by carbon–oxygen hydrogenolysis and ring opening as for furans.

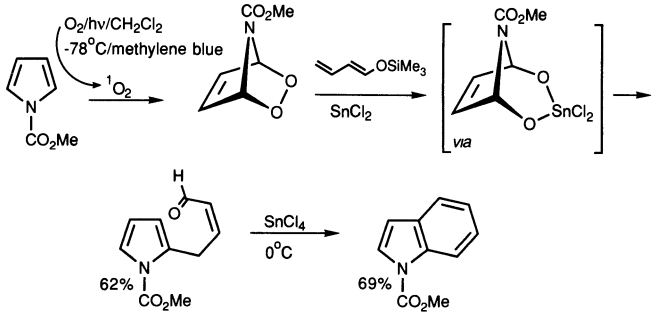
13.9 ELECTROCYCLIC REACTIONS (GROUND STATE)

Most simple pyrroles do not readily react as 4π components in cycloadditions – exposure of pyrrole to benzyne, for example, leads only to 2-phenylpyrrole, in low yield.[65] However *N*-substitution, particularly with an electron-withdrawing group, does allow such reactions to occur, thus adducts with arynes were obtained using 1-trimethylsilylpyrrole.[66]



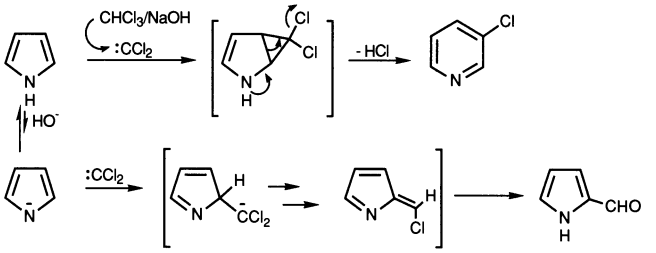
Whereas pyrrole itself reacts with dimethyl acetylenedicarboxylate only by α-substitution, even at 15 kbar,[67] 1-acetyl- and 1-alkoxycarbonylpyrroles give cycloadducts,[68] addition being much accelerated by high pressure or by aluminium chloride catalysis.[69]

A process which has proved valuable in synthesis is the addition of singlet oxygen to *N*-alkyl- and especially *N*-acylpyrroles,[70] producing 2,3-dioxa-7-azabicyclo[2.2.1]heptanes which react with nucleophiles, such as silyl enol ethers, mediated by stannous chloride, generating 2-substituted pyrroles.

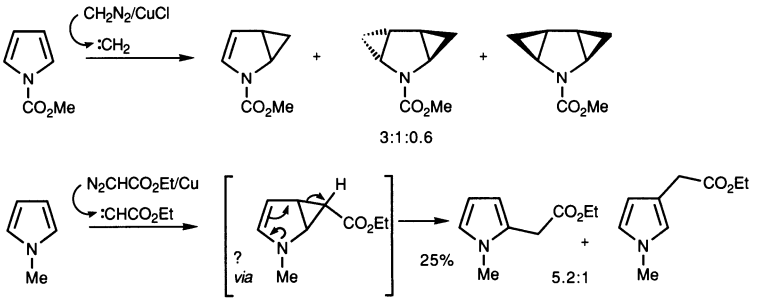


13.10 REACTIONS WITH CARBENES

The reaction of pyrrole with dichlorocarbene has been known for a long time and was at one time a main route to 2-formylpyrrole. The reaction is of mechanistic interest in that it proceeds in part *via* a dichlorocyclopropane intermediate, ring expansion of which leads to 3-chloropyridine.[71] Formation of the ring-expanded products can be encouraged by the generation of dichlorocarbene in neutral aprotic solution.[71a,72]

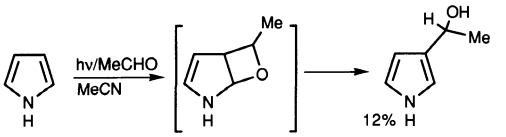


In contrast to thiophene (section 14.1.2) the only reported isolable cyclopropane-containing adducts from pyrroles are those from 1-methoxycarbonylpyrrole.[73] 1-Methylpyrrole gives only substitution products, which may be the results of opening of a cyclopropanoid intermediate (arrows show the genesis of the α-product) or the result of electrophilic attack by ethoxycarbonylcarbene.[74]

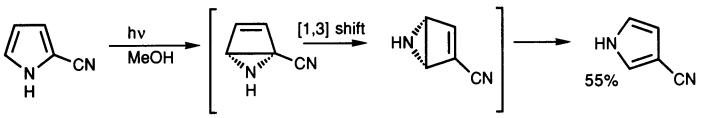


13.11 PHOTOCHEMICAL REACTIONS

Photo-catalysed β-hydroxyalkylation of pyrroles on irradiation in the presence of aldehydes or ketones may proceed *via* regioselective formation of non-isolable oxetanes.[75]

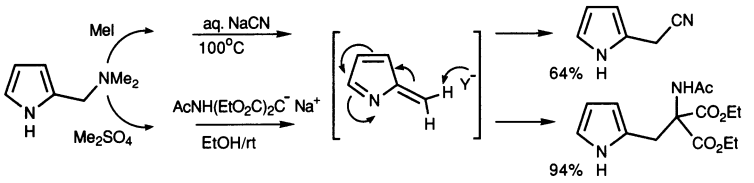


The photo-catalysed rearrangement of 2- to 3-cyanopyrroles is considered to involve a 1,3-shift in an initially formed bicyclic aziridine.[76]



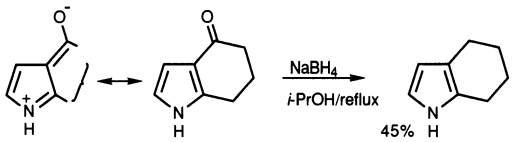
13.12 PYRRYL-C-X COMPOUNDS

Pyrroles of this type, where X is halogen, alcohol, or amine, and especially protonated alcohol or quaternised amine, easily lose X generating very reactive electrophilic species. Thus ketones can be reduced to alkane, *via* the loss of oxygen from the initially formed alcohol (cf. section 13.1.7), and quaternary ammonium salts, typified by 2-dimethylaminomethylpyrrole methiodide, react with nucleophiles by loss of trimethylamine in an elimination/addition sequence of considerable synthetic utility.[77]



13.13 PYRROLE ALDEHYDES AND KETONES

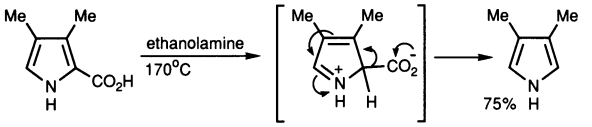
These are stable compounds which do not polymerise or autoxidise. For the most part, pyrrole aldehydes and ketones are typical aryl ketones, though less reactive, especially when at the α-position, due to the reduced electrophilicity of the carbonyl carbon resulting from mesomeric interaction with the ring nitrogen. They can be reduced to alkylpyrroles by the Wolff-Kishner method, or by sodium borohydride *via* elimination from the initial alcoholic product.[78]



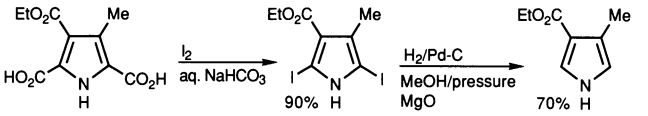
13.14 PYRROLE CARBOXYLIC ACIDS

The main feature within this group is the ease with which loss of the carboxyl group occurs. Simply heating[79] pyrrole α- or β-acids causes easy loss of carbon dioxide in what is essentially *ipso* displacement of carbon dioxide by proton.[80] This facility is of considerable relevance to pyrrole synthesis since many of the

ring-forming routes (e.g. see sections 13.18.1.2 and 13.18.1.3) produce pyrrole esters, in which the ester function may not be required ultimately.

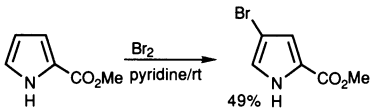


Displacement of carboxyl groups by other electrophiles such as halogen[81] or nitro is also common, for example *ipso* diazo-coupling occurs more readily than at a carbon carrying hydrogen.

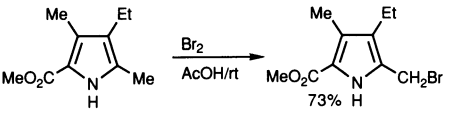


13.15 PYRROLE CARBOXYLIC ACID ESTERS

The electrophilic substitution of these stable compounds has been much studied; the *meta*-directing effect of the ester overcomes the normally dominant tendency for α-substitution.[82]



An ester group can also activate side-chain alkyl for halogenation, and such pyrrolylalkyl halides have been used extensively in synthesis.[83]



The rates of alkaline hydrolysis of α- and β-esters are markedly different, the former being faster than the latter, possibly because of stabilisation, by intramolecular hydrogen bonding involving the ring hetero atom, of the intermediate.[84]

13.16 HALOPYRROLES

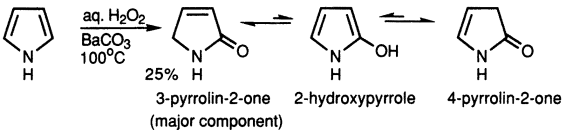
Simple 2-halopyrroles are very unstable compounds whereas 3-halopyrroles are stable, as indeed are 2-halopyrryl ketones and esters. Pyrryl halides have typical aryl halide reactivity, being inert to nucleophilic displacement but undergoing exchange with *n*-butyllithium and palladium-catalysed couplings. Pyrryl halides

undergo catalytic hydrogenolysis, which has allowed the use of halide as a blocking substituent.

13.17 OXY- AND AMINOPYRROLES

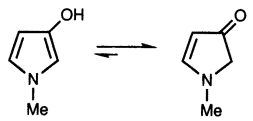
13.17.1 2-Oxypyrroles

2-Oxypyrroles exist in the hydroxyl form, if at all, only as a minor component of the tautomeric mixture which favours 3-pyrrolin-2-one over 4-pyrrolin-2-one by 9 : 1.[85]

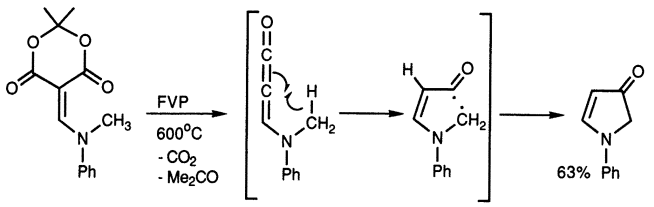


13.17.2 3-Oxypyrroles

3-Oxypyrroles exist largely in the carbonyl form, unless flanked by an ester group which favours the hydroxyl tautomer by intramolecular hydrogen bonding.[86]



A special route, involving flash vaccuum pyrolysis, can be utilised to synthesise 3-pyrrolinones.[87]



13.17.3 Aminopyrroles

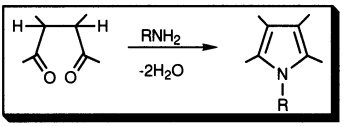
Aminopyrroles have been very little studied; the 3-isomers are more stable than 2-aminopyrroles.

13.18 SYNTHESIS OF PYRROLES[6,88]

13.18.1 Ring synthesis

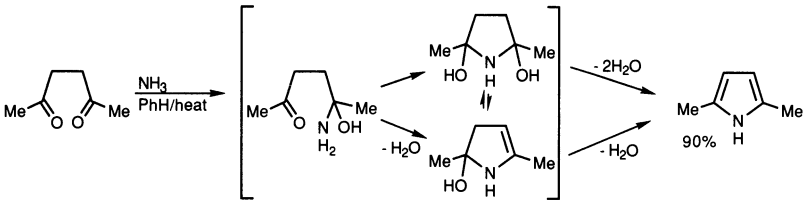
13.18.1.1 *From 1,4-dicarbonyl compounds and ammonia or primary amines*[89]

1,4-Dicarbonyl compounds react with ammonia or primary amines to give pyrroles.

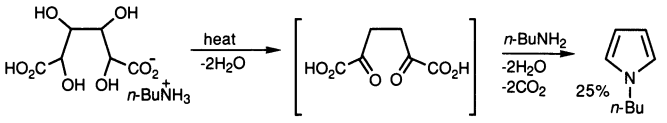


Paal-Knorr synthesis

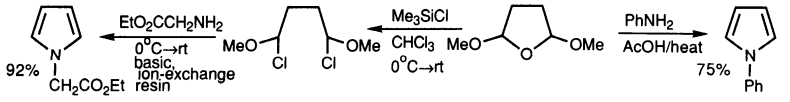
Pyrroles are formed by the reaction of ammonia or a primary amine with a 1,4-dicarbonyl compound. Successive nucleophilic additions of the amine nitrogen to the two carbonyl carbon atoms and the loss of two mol of water represent the net course of the synthesis; two reasonable sequences for this are shown.



A still-useful synthesis of *N*-substituted pyrroles, which consists of dry distillation of the alkylammonium salt of mucic or saccharic acid,[90] probably also proceeds by way of a 1,4-dicarbonyl intermediate. The overall process involves loss of four mol equivalents of water and two of carbon dioxide, and may proceed as shown.

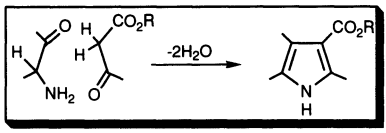


The best equivalent of unstable succindialdehyde, for the ring synthesis of *C*-unsubstituted pyrroles, is 2,5-dimethoxytetrahydrofuran (section 15.1.4),[91] or the bis(α-chloroether) obtainable from it.[92]



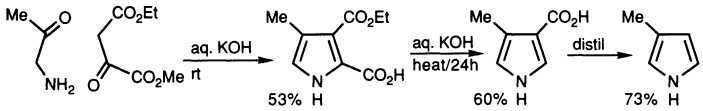
13.18.1.2 *From α-aminocarbonyl compounds*

α-Aminoketones react with carbonyl compounds which have an α-methylene grouping, preferably further activated, for example by ester, as in the illustration.



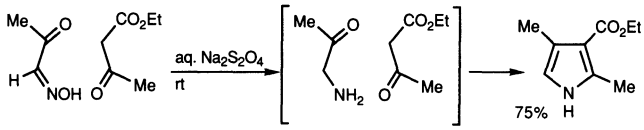
Knorr synthesis

This widely used general approach to pyrroles utilizes two components: one, the α-aminocarbonyl component, supplies the nitrogen and C-2 and C-3, and the second component supplies C-4 and C-5 and must possess a methylene group α to carbonyl. The synthesis of 4-methylpyrrole-3-carboxylic acid and therefrom, 3-methylpyrrole illustrates the process.

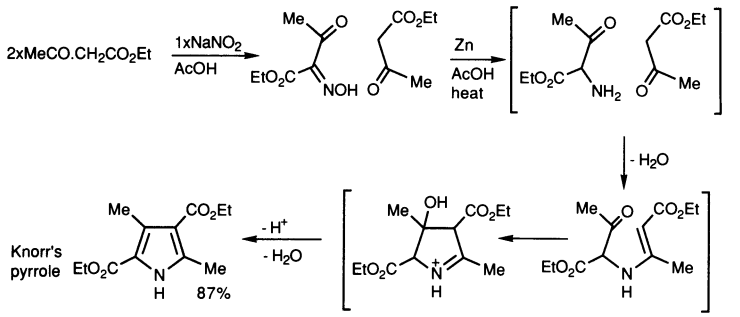


Since free α-aminocarbonyl compounds self-condense very readily producing dihydropyrazines (section 11.13.3.1), they must be prepared and used in the form of their salts, to be liberated for reaction by the base present in the reaction mixture. The Knorr synthesis works well only if the methylene group of the second component is further activated (e.g. as in acetoacetic ester) to enable the desired condensation leading to pyrrole to compete effectively with the self-condensation.

An alternative way of avoiding the difficulty of handling α-aminocarbonyl compounds is to prepare them in the presence of the second component, with which they are to react. Zinc–acetic acid or sodium dithionite[93] can be used to reduce oximino groups to amino while leaving ketone and ester groups untouched.



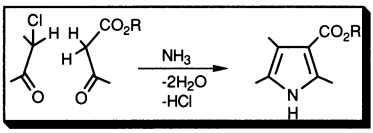
In the classical synthesis, which gives this route its name, the α-aminocarbonyl component is simply an amino-derivative of the other carbonyl component, and it is even possible to generate the oximino precursor of the amine *in situ*.[94]



It is believed that in the mechanism, shown for Knorr's pyrrole, an N–C2 bond is the first formed, which implies that the nitrogen becomes attached to the more electrophilic of the two carbonyl groups of the other component. Similarly, the C3–C4 bond is made to the more electrophilic carbonyl group of the original α-aminocarbonyl component, where there is a choice.

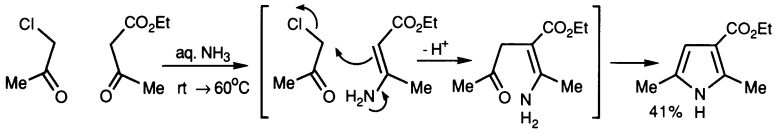
13.18.1.3 *From α-halocarbonyl compounds*

An alternative strategy for combining a pair of two-carbon units employs an α-halocarbonyl compound, a β-keto-ester, and ammonia.



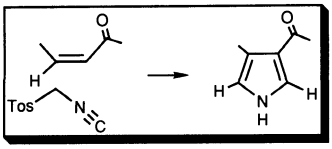
Hantzsch synthesis

In this modification of the Feist-Benary synthesis of furans (section 15.13.1.4) ammonia, or a primary amine, is incorporated. The pyrrole is probably formed by initial interaction of ammonia (an amine) with the β-ketoester, the resulting β-aminocrotonate then being alkylated by the halo-ketone or -aldehyde.[95]

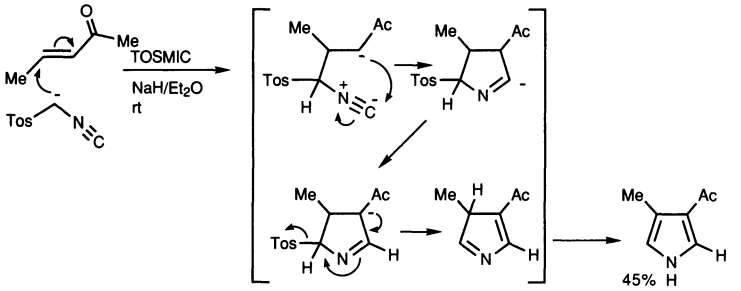


13.18.1.4 *From tosylmethyl isocyanide and α,β-unsaturated esters or ketones*[96]

Tosylmethyl isocyanide anion reacts with α,β-unsaturated esters, ketones, or sulfones with loss of toluenesulfinate.

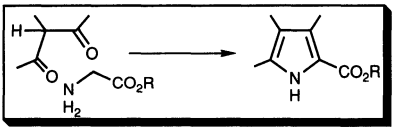


The stabilised anion of tosylmethyl isocyanide (TOSMIC) adds in Michael fashion to unsaturated ketones and esters, with subsequent closure onto isocyanide carbon generating the ring. Proton transfer, then elimination of toluenesulfinate, generates a 3*H*-pyrrole which tautomerises to the aromatic system.

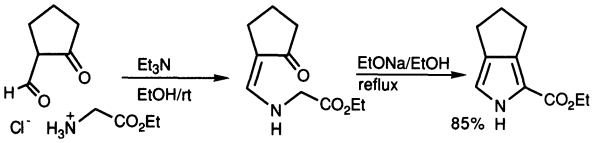


13.18.1.5 *From 1,3-dicarbonyl compounds and glycine esters*[97]

1,3-Dicarbonyl compounds, or oxidation level equivalents, react with glycine esters to give pyrrole-2-esters.

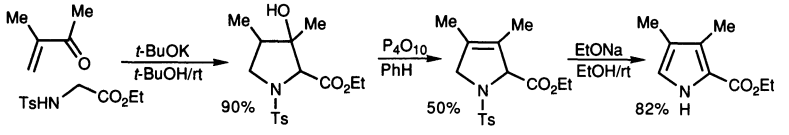


A variety of methods have been employed to effect the condensation between a 1,3-diketone and a glycine ester; perhaps the simplest is condensation using triethylamine as base to produce an intermediate enamino-ketone, this then ring closed in a second step.



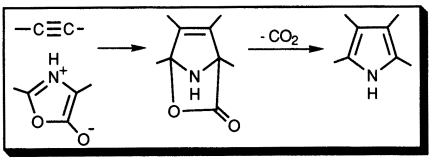
The Kenner synthesis

A related process uses a lower oxidation-level C_3-component – an α,β-unsaturated ketone – and provides the means for achieving pyrrole oxidation level in a tosyl group on glycine nitrogen, eliminated as toluenesulfinate later.[98]

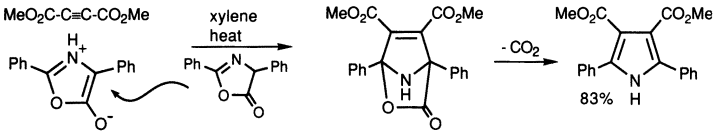


13.18.1.6 *From alkynes and oxidooxazoliums*[99]

Dipolar cycloaddition of alkynes to mesoionic oxido-oxazoliums, followed by expulsion of carbon dioxide, yields pyrroles.



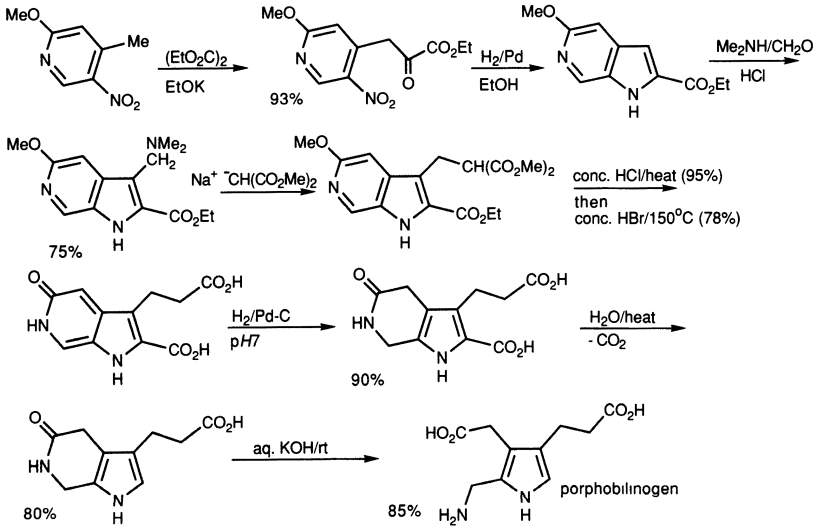
Dehydration of *N*-acylamino acids generates azlactones; these are in equilibrium with mesoionic species which can be trapped by reaction with alkynes.



13.18.2 Examples of notable synthesis of pyrroles

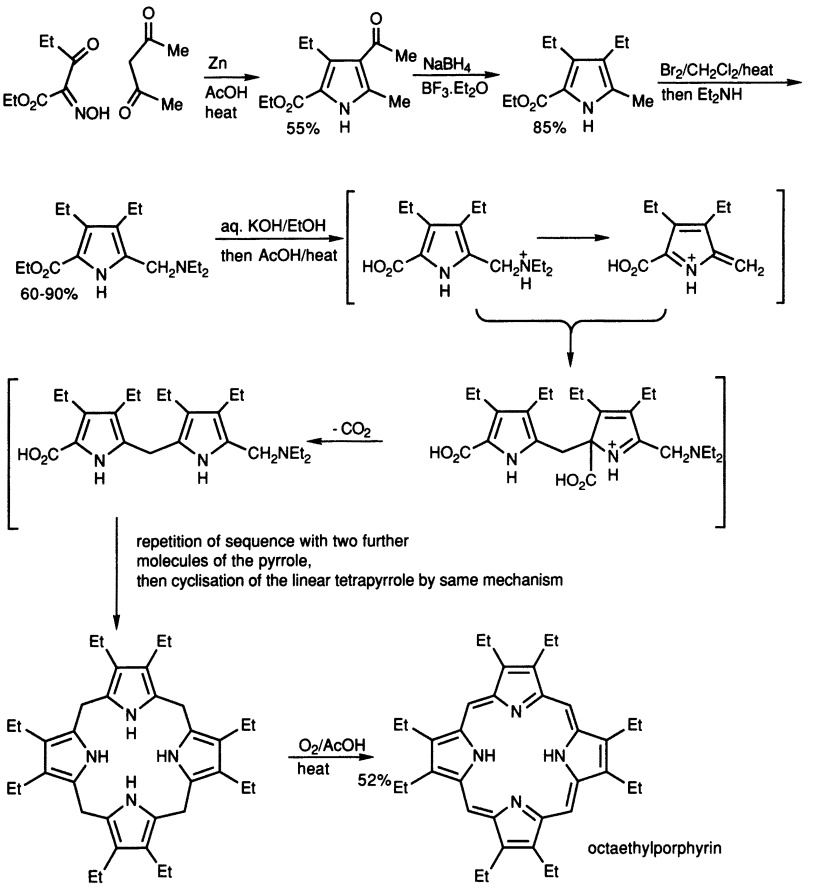
13.18.2.1 *Porphobilinogen*

The synthesis of porphobilinogen[100] from 2-methoxy-4-methyl-5-nitropyridine (section 5.15.2.3) is an example of a Reissert-type synthesis (section 17.16.1.2) affording, in this case, a 6-azaindole as an intermediate for the pyrrole.



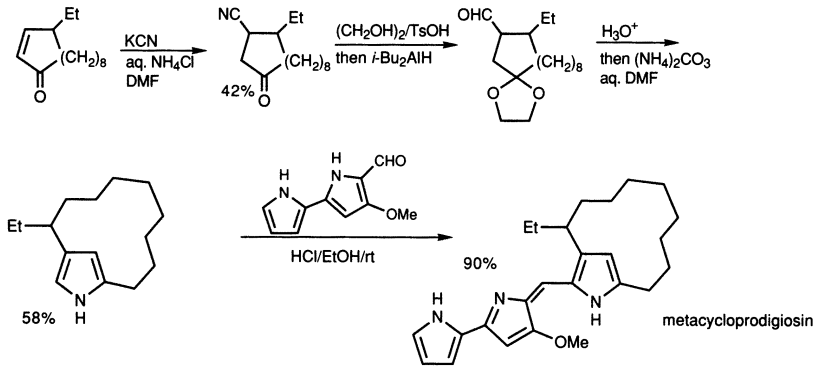
13.18.2.2 *Octaethylporphyrin*[101]

This synthesis of this widely used model compound uses a Knorr sequence as the first step; the oligomerisation steps and the final cyclisation rest on side-chain reactivity of pyrrolylammonium salts (section 13.12) and the easy decarboxylation of pyrrole acids (section 13.14).



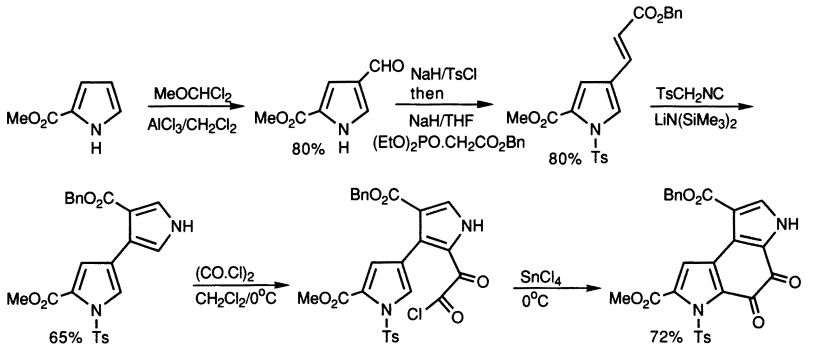
13.18.2.3 *Metacycloprodigiosin*

Metacycloprodigiosin[102] is a red pigment from *Streptomyces longisporus ruber.*



13.18.2.4 *Benzo[1,2-b:4,3-b]dipyrroles*

Several ingenious approaches have been described for the elaboration of the pyrrolo-indole unit (strictly a benzo[1,2-*b*:4,3-*b'*]dipyrrole), three of which are present in the potent anti-tumour agent CC-1065;[103] the approach shown here employs the method described in section 13.18.1.4 for the construction of the pyrrole nuclei.[104]



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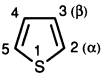
EXERCISES FOR CHAPTER 13

1. Two isomeric mono-nitro-derivatives, $C_5H_6N_2O_2$, are formed in a ratio of 6 : 1, by treating 2-methylpyrrole with Ac_2O/HNO_3. What are their structures and which would you predict to be the major product?
2. Write structures for the products of the following sequences: (i) pyrrole treated with $Cl_3CCO.Cl$, then the product with Br_2, then this product with MeONa/MeOH → $C_6H_6BrNO_2$ (ii) pyrrole treated with DMF/$POCl_3$, then with MeCO.Cl/$AlCl_3$, then finally with aq. NaOH → $C_7H_7NO_2$ (iii) 2-chloropyrrole treated with DMF/$POCl_3$, then aq. NaOH, then the product with $LiAlH_4$ → C_5H_6ClN.
3. Write structures for the products formed by the reaction of pyrrole with $POCl_3$ in combination with (i) *N*,*N*-dimethylbenzamide; (ii) pyrrole-2-carboxylic acid *N*,*N*-dimethylamide; (iii) 2-pyrrolidone → $C_8H_{10}N_2$, in each case followed by aq. NaOH.
4. Treatment of 2-methylpyrrole with HCl produces a dimer, not a trimer as does pyrrole itself (section 13.1.8). Suggest a structure for the dimer, $C_{10}H_{14}N_2$, and explain the non-formation of a trimer.
5. Treatment of 2,5-dimethylpyrrole with Zn/HCl gave a mixture of two isomeric products $C_6H_{11}N$: suggest structures.
6. (i) Heating 1-methoxycarbonylpyrrole with diethyl acetylenedicarboxylate at 160°C produced diethyl 1-methoxycarbonylpyrole-3,4-dicarboxylate; suggest a mechanism and a key intermediate; (ii) deduce the structure of the product, $C_{11}H_{12}N_2O_2$, resulting from successive treatment of 1-methoxycarbonylpyrrole with singlet oxygen, then a mixture of 1-methylpyrrole and $SnCl_2$.
7. Deduce structures for the products formed at each stage by treating pyrrole successively with (i) Me_2NH/HCHO/AcOH; (ii) CH_3I; (iii) piperidine in hot EtOH → $C_{10}H_{16}N_2$.
8. From a precursor which does not contain a pyrrole ring how might one synthesise (i) 1-propylpyrrole; (ii) 1-(thien-2-yl)pyrrole; (iii) 1-benzenesulfonylpyrrole?

9. Reaction of $MeCO.CH_2CO_2Et$ with HNO_2, then a combination of Zn/AcOH and pentane-2,4-dione gave a pyrrole, $C_{11}H_{15}NO_3$. Deduce the structure of the pyrrole, write out a sequence for its formation, and suggest a route whereby it could then be converted into 2,4-dimethyl-3-ethylpyrrole.
10. How might one prepare (i) diethyl 4-methylpyrrole-2,3-dicarboxylate; (ii) ethyl 2,4,5-trimethylpyrrole-3-carboxylate; (iii) ethyl 4-amino-2-methylpyrrole-3-carboxylate; (iv) ethyl 3,4,5-trimethylpyrrole-2-carboxylate?

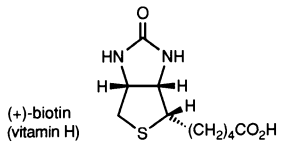
Thiophenes: reactions and synthesis

14

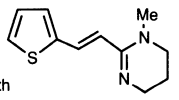


thiophene

The simple thiophenes[1] are stable liquids which closely resemble the corresponding benzene compounds in boiling points and even in smell. They occur in coal tar distillates – the discovery of thiophene in coal tar benzene provides one of the classic anecdotes of organic chemistry. In the early days, colour reactions were of great value in diagnosis: an important one for benzene involved the production of a blue colour on heating with isatin (section 14.1.1.7) and concentrated sulfuric acid. In 1882, during a lecture-demonstration by Viktor Meyer before an undergraduate audience, this test failed, no doubt to the delight of everybody except the professor, and especially except the professor's lecture assistant. An inquiry revealed that the lecture assistant had run out of commercial benzene and had provided a sample of benzene which he had prepared by decarboxylation of pure benzoic acid. It was thus clear that commercial benzene contained an impurity and that it was this, not benzene, which was responsible for the colour reaction. In subsequent investigations, Meyer isolated the impurity *via* its sulfonic acid derivative and showed it to be the first representative of a then new ring system, which was named thiophene from *theion*, the Greek word for sulfur, and another Greek word *phaino* which means shining, a root first used in phenic acid (phenol) because of its occurrence in coal tar, a by-product of the manufacture of illuminating gas.



(+)-biotin
(vitamin H)



Banminth

Aromatic thiophenes play no part in animal metabolism; biotin, one of the vitamins, is a tetrahydrothiophene, however aromatic thiophenes do occur in some plants, in association with polyacetylenes with which they are biogenetically linked. Banminth (Pyrantel), a valuable anthelminth used in animal husbandry, is one of the few thiophene compounds in chemotherapy.

14.1 REACTIONS WITH ELECTROPHILIC REAGENTS

14.1.1 Substitution at carbon

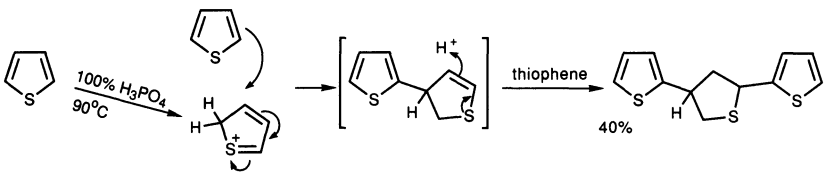
14.1.1.1 *Protonation*

Thiophene is stable to all but very strongly acidic conditions, so many reagent combinations which lead to acid-catalysed decomposition or polymerisation of furans and pyrroles are able to be applied successfully with thiophenes.

Measurements of acid-catalysed exchange, or of protonolysis of other groups, for example silicon,[2] or mercury,[3] show the rate of proton attack at C-2 to be about 1000 times faster than at C-3.[4] The pK_a for 2,5-di-*t*-butylthiophene forming a salt by protonation at C-2 is -10.2.[5]

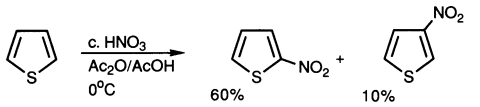
Reactions of protonated thiophenes

The action of hot phosphoric acid on thiophene leads to a trimer;[6] its structure suggests that, in contrast with pyrrole (section 13.1.8), the electrophile involved in the first C–C bonding step is the α-protonated cation.



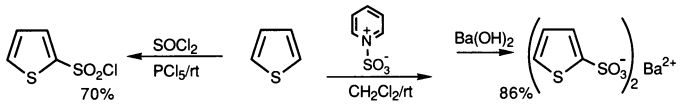
14.1.1.2 *Nitration*

Nitration of thiophene needs to be conducted in the absence of nitrous acid, which can lead to an explosive reaction;[7] the use of acetyl nitrate[8] or nitronium tetrafluoroborate[9] are satisfactory. Invariably, the major 2-nitro-product is accompanied by approximately 10% of the 3-isomer.[10] Further nitration of either 2- or 3-nitrothiophenes[11] also leads to mixtures – equal amounts of 2,4- and 2,5-dinitrothiophenes from the 2-isomer, and mainly the former from 3-nitrothiophene.[12] Similar, predictable isomer mixtures are produced in other nitrations of substituted thiophenes, for example 2-methylthiophene gives rise to 2-methyl-5- and 2-methyl-3-nitrothiophenes,[13] and 3-methylthiophene gives 4-methyl-2-nitro- and 3-methyl-2-nitrothiophenes,[14] in each case in ratios of 4 : 1.



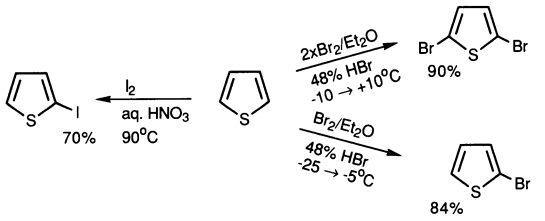
14.1.1.3 *Sulfonation*

As discussed in the introduction, the production of thiophene-2-sulfonic acid by sulfuric acid sulfonation of the heterocycle has been long known;[15] use of the pyridine–sulfur trioxide complex is probably the best method.[16] 2-Chlorosulfonation[17] and 2-thiocyanation[18] are similarly efficient.



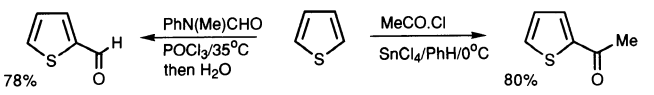
14.1.1.4 *Halogenation*

Halogenation of thiophene occurs very readily at room temperature and is rapid even at −30°C in the dark; higher temperatures give rise to polysubstitution and even addition products. The rate of halogenation of thiophene, at 25°C, is about 10^8 times that of benzene.[19] 2-Bromo-[20] and 2-iodothiophene[21] can be produced cleanly under various controlled conditions, free from 2,5-disubstituted product which is always present in chlorinations.



14.1.1.5 *Acylation*

The Friedel-Crafts acylation of thiophenes is a much-used reaction and proceeds generally to give good yields under controlled conditions, despite the fact that aluminium chloride reacts with thiophene to generate tars: this problem can be avoided by adding catalyst to the thiophene and the acylating agent;[22] tin tetrachloride has been used most frequently. Almost exclusive α-substitution is observed, but where both α-positions are substituted, β-substitution occurs easily.



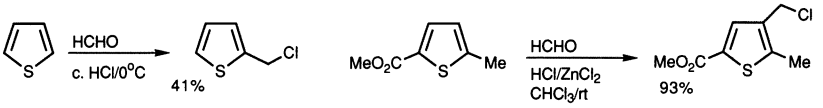
Acylation with anhydrides, catalysed by phosphoric acid,[23] is an efficient method; reaction with acetyl *p*-toluenesulfonate, in the absence of any catalyst, produces 2-acetylthiophene in high yield.[24] Vilsmeier formylation leads efficiently to 2-formylthiophene.[25]

14.1.1.6 *Alkylation*

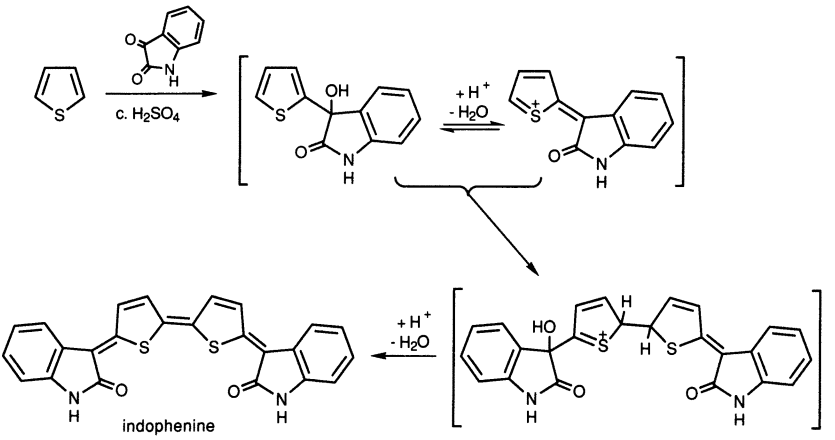
Alkylation occurs readily, but is rarely of preparative use; the efficient 2,5-di-*t*-butylation of thiophene is one such example.[26]

14.1.1.7 *Condensation with aldehydes and ketones*

Acid-catalysed reaction of thiophene with aldehydes and ketones is not a viable route to hydroxyalkylthiophenes, for these are unstable under the reaction conditions. Chloroalkylation can however be achieved[27] and, with the use of zinc chloride, even thiophenes carrying electron-withdrawing groups react.[28] Care is needed in choosing conditions; there is a tendency for formation of either di-2-thienylmethanes[29] or 2,5-bis(chloromethyl)thiophene.[30]



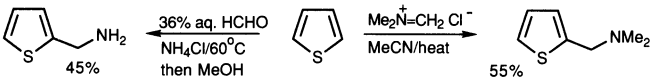
A reaction of special historical interest, mentioned in the introduction to this chapter, is the condensation of thiophene with isatin in concentrated sulfuric acid, to give the deep blue indophenine[31] as a mixture of geometrical isomers.[32]



14.1.1.8 *Condensation with imines and immonium ions*

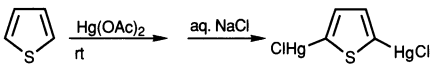
Aminomethylation of thiophene[33] was reported long before the more common Mannich reaction – dimethylaminomethylation, which, although it can be achieved under routine conditions with methoxythiophenes,[34] requires the use

of $Me_2N^+=CH_2\ Cl^-$ ('Eschenmoser's salt' is the iodide) for thiophene and alkylthiophenes .[35]



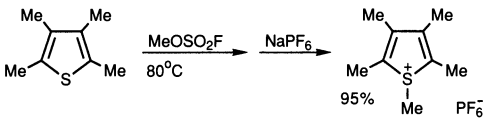
14.1.1.9 *Mercuration*

Mercuration of thiophenes occurs with great ease; mercuric acetate is more reactive than the chloride;[36] tetrasubstitution and easy substitution of halothiophenes can also be achieved.[37]

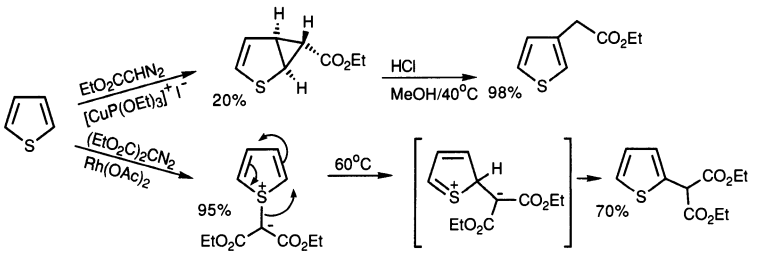


14.1.2 Addition at sulfur

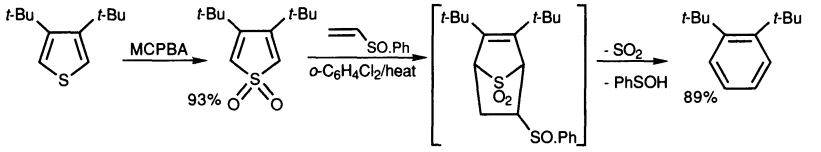
In reactions not possible with the second row element-containing pyrrole and furan, thiophene sulfur can add electrophilic species. Thiophenium salts,[38] though not formed efficiently from thiophene itself, are produced in high yields with polyalkyl-substituted thiophenes.[39] The sulfur in such salts is probably tetrahedral,[40] i.e. the sulfur is sp^3 hybridised.



Even thiophene itself will react with carbenes, at sulfur, to produce isolable thiophenium ylids, and in these the sulfur is definitely tetrahedral.[41] The rearrangement[42] of thiophenium bis(methoxycarbonyl)methylide to the 2-substituted thiophene provides a rationalisation for the long known[43] reaction of thiophene with ethyl diazoacetate, which produces what appears to be the product of carbene addition to the 2,3-double bond, but which can now be viewed as being produced *via* initial attack at sulfur followed by S → C-2 rearrangement, then collapse to the cyclopropane. Acid catalyses conversion of the cyclopropanated compound into a thiophene-3-acetic ester.[44] 2,5-Dichlorothiophenium bis(methoxycarbonyl)methylide has been used as an efficient source of the carbene: simply heating it in an alkene results in the transfer to the alkene.[45]



S-Oxidation of a thiophene leads to a dioxide, which in the case of thiophene itself dimerises in low yield,[46] but with substituted thiophenes can be isolated; peracids[47] or 2,2-dimethyloxirane, which improves yields from 2,5-disubstituted thiophenes, can be used.[48] The *S,S*-dioxides are no longer aromatic thiophenes and react as dienes in Diels-Alder reactions; generally sulfur dioxide is extruded from the initial adduct, leading to further reaction[49] – eventual aromatisation in the example shown.[50]

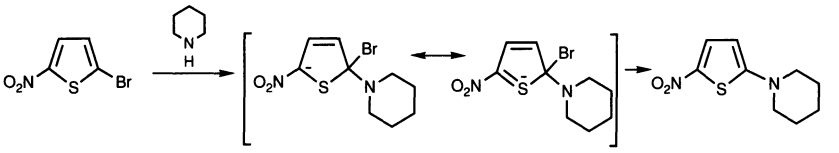


14.2 REACTIONS WITH OXIDISING AGENTS

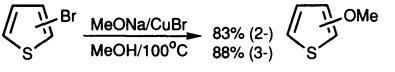
Apart from the *S*-oxidations discussed above, the thiophene ring system, unless carrying electron-releasing substituents, is relatively stable to oxidants; side-chains can be oxidised to carboxylic acid groups, though not usually in synthetically useful yields.

14.3 REACTIONS WITH NUCLEOPHILIC REAGENTS

Simple thiophenes do not react with nucleophiles by addition or by substitution, though nitro-substituents activate the displacement of leaving groups like halide, as in benzene chemistry, and extensive use of this has been made in thiophene chemistry. It has been shown that such nucleophilic displacements proceed at least 10^2 times faster than for benzenoid counterparts, and this may be accounted for by invoking participation of the sulfur in the delocalisation of charge in the Meisenheimer intermediate.



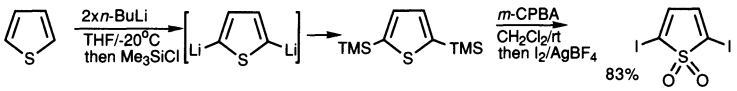
Copper has been used extensively to catalyse displacement of bromine and iodine, but not chlorine, in simpler halo-thiophenes.[51]



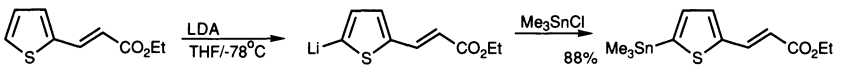
14.4 REACTIONS WITH BASES

14.4.1 Deprotonation of *C*-hydrogen

Monolithiation of thiophene takes place at C-2; two mol equivalents of lithiating agent easily produces 2,5-dilithiothiophene.[52]



Lithiation at a thiophene β-position, in the presence of a free α-position, has been achieved with the assistance of an *ortho*-directing substituent at C-2.[53] A surprising degree of functionality can be tolerated in some lithiations.[54]

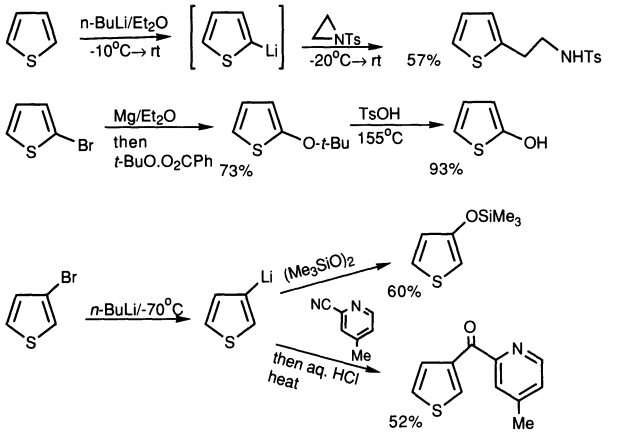


Thiophene-2-carboxylic acid lithiates at C-3, *via ortho* assistance, using butyllithium,[55] but at C-5 using lithium diisopropylamide.[56] The lithiation of 2-chloro-5-methoxythiophene at C-4 and C-3, in a ratio of 2 : 1, is instructive.[57] 2- and 3-Bromothiophenes undergo lithium–halogen exchange with *n*-butyllithium, but α-deprotonation with LDA.[58]

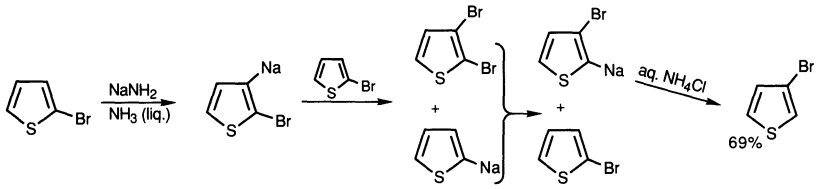
14.5 REACTIONS OF *C*-METALLATED THIOPHENES

14.5.1 Lithio and magnesio derivatives

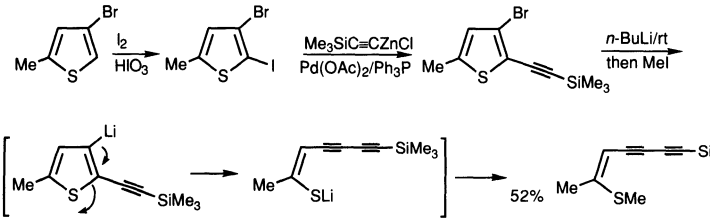
2-Bromo- and -iodothiophenes readily form thienyl Grignard reagents,[59] as do 3-iodothiophenes, though 3-bromothiophenes require the use of the entrainment method; however bromine and iodine at either α- or β-positions undergoes exchange with alkyllithiums. The use of thienyl Grignard reagents, and more recently lithiated thiophenes, has been extensive and is illustrated in this section by citing formation of oxythiophenes, either by reaction of the former with *t*-butyl perbenzoate[60] or the latter directly with bis(trimethylsilyl) peroxide[61] or *via* the boronic acid,[62] the synthesis of thiophene carboxylic acids by reaction of the organometallic with carbon dioxide,[63] the synthesis of ketones, by reaction with a nitrile,[64] and the reaction of 2-lithiothiophene with *N*-tosylaziridine.[65]



There are two complications which can arise in the formation and the use of lithiated thiophenes: the occurence of a 'base-catalysed halogen dance',[66] and the ring opening of 3-lithiated thiophenes. As an example of the first of these, and one in which the phenomenon is put to good use, consider the transformation of 2-bromothiophene into 3-bromothiophene by reaction with sodamide in ammonia.[67] The final result is governed, in a set of equilibrations, by the stability of the final anion: the system settles to an anion in which the charge is both adjacent to halogen and at an α-position.

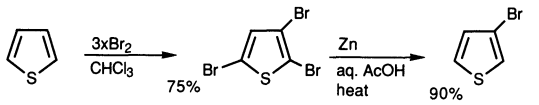


If 3-lithiothiophenes are allowed to warm, a ring opening occurs, and subsequent trapping at sulfur produces 1-thio-ene-3-ynes, though the 3-lithiothiophene can be utilised straightforwardly at low temperature. The ring opening can be used to advantage in the synthesis of Z-ene-ynes.[68]



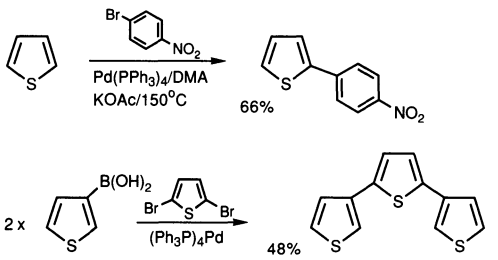
It has long been known that treatment of polyhalogenothiophenes with zinc and acid brings about selective removal of α-halogen;[69] one interpretation of

this is that it involves first electron transfer to the bromine, then transient 'anions'; thus halogen can be selectively removed from that position where such an anion is best stabilised – normally an α position. Conversion to a Grignard species then quenching with water can also be used for the stepwise removal of α-bromines.[70]



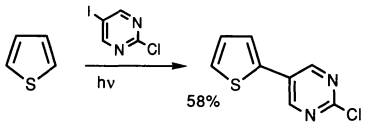
14.5.2 Palladium-catalysed reactions

Arylthiophenes have been produced by palladium-catalysed couplings of both thiophene-2- and -3-boronic[71] acids and directly from the heterocycle in an alternative palladium-catalysed process.[72]



14.6 REACTIONS WITH RADICAL REAGENTS

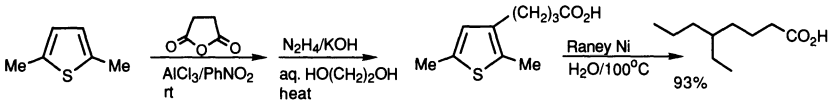
The production of arylthiophenes by radical substitution was never a particularly efficient procedure and has now been superseded by palladium-catalysed coupling processes. Aryl radicals generated by a variety of methods,[73] the most effective of which are aprotic diazotisation[74] and photolysis of iodoarenes, particularly iodoheterenes,[75] give 2-substituted thiophenes.



14.7 REACTIONS WITH REDUCING AGENTS

Catalytic reductions of the thiophene ring, or of substituents attached to it, are complicated by two factors: poisoning of the catalyst, and the possibility of competing hydrogenolysis – reductive removal of sulfur, particularly with Raney nickel – indeed the use of thiophenes as templates on which to elaborate a structure, followed finally by desulfurisation, is an important synthetic strategy

(for another example see section 14.13.2.3). This has been developed extensively for thiophene acids, where the desulfurisation can be achieved very simply by dissolving Raney alloy in an alkaline aqueous solution of the acid,[76] and for long chain hydrocarbons,[77] and large-ring ketones.[78]

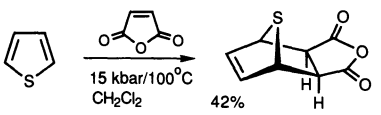


Sodium/ammonia[79] treatment also causes disruption of the ring in thiophene and simple thiophenes, however thiophene-2-carboxylic acid and 2-acylthiophenes can be converted into the 2,5-dihydro-derivatives using lithium in ammonia.[80] Side-chain reductions can be achieved selectively with reagents such as metal hydrides, which do not affect the ring.

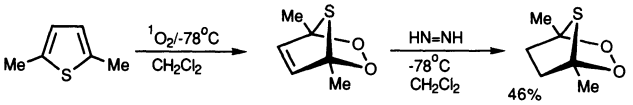
Simple saturation of the ring can be achieved using 'ionic hydrogenation',[81] i.e. a combination of a trialkylsilane and acid, usually trifluoroacetic; the reduction proceeds *via* a sequence of proton then 'hydride' additions[82] and consequently requires electron-releasing susbstituents to facilitate the first step. 2,5-Dihydro-products accompany tetrahydrothiophenes as products of reductions with zinc and trifluoroacetic acid.[83]

14.8 ELECTROCYCLIC REACTIONS (GROUND STATE)[84]

Thiophenes show little tendency to react as 4π components in the Diels-Alder sense; for example, even at 15 kbar only maleic anhydride, of the common, electron-deficient dienophilic partners, gives an adduct.[85] Electrophilic alkynes will react with thiophenes under vigorous conditions,[86] though the initial adduct extrudes sulfur and substituted benzenes are obtained as products.



Singlet oxygen adds across the 2- and 5-positions of alkyl- and phenyl-substituted thiophenes; the further decomposition of the adducts is complex,[87] but their existence has been neatly demonstrated *via* trapping by diimide reduction.[88]

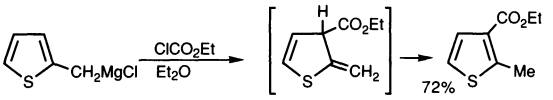


14.9 PHOTOCHEMICAL REACTIONS

The best known photochemical reaction involving thiophenes is the isomerisation of 2-arylthiophenes to 3-arylthiophenes;[89] the aromatic substituent remains attached to the same carbon and the net effect has been shown to involve interchange of C-2 and C-3, with C-4 and C-5 remaining in the same relative positions; scrambling of deuterium labelling is however observed and the detailed mechanism for the rearrangement is still a matter for discussion.

14.10 THIOPHENE-C-X COMPOUNDS: THENYL DERIVATIVES

The unit – thiophene linked to a carbon – is termed thenyl, hence thenyl chloride is the product of chloromethylation (section 14.1.1.7); thenyl bromides are usually made by side-chain radical substitution.[90] Relatively straightforward benzene-analogue reactivity is found with thenyl halides, alcohols (conveniently preparable by reducing aldehydes) and amines, from, for example, reduction of oximes. One exception is that 2-thenyl Grignard reagents usually react to give 3-substituted derivatives, presumably *via* a non-aromatic intermediate.[91]



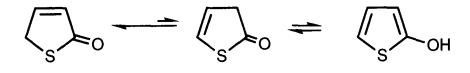
14.11 THIOPHENE ALDEHYDES AND KETONES, AND CARBOXYLIC ACIDS AND ESTERS

Here, the parallels with benzenoid counterparts continue, for these compounds have no special properties – their reactivities are those typical of benzenoid aldehydes, ketones, acids, and esters. For example, in contrast to the easy decarboxylation of α-acids observed for pyrrole and furan, thiophene-2-acids do not easily decarboxylate. Just as in benzene chemistry, Wolff-Kischner or Clemmensen reduction of ketones is a much-used route to alkylthiophenes, hypochlorite oxidation of acetylthiophenes a good route to thiophene acids, Beckmann rearrangement of thiophene oximes is a useful route to acylaminothiophenes and hence aminothiophenes, and esters and acids are interconvertible with no complications.

14.12 OXY- AND AMINOTHIOPHENES

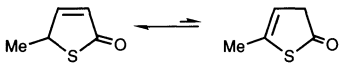
14.12.1 Oxythiophenes

These compounds are much more difficult to handle and much less accessible than phenols. Neither 2-hydroxythiophene nor its 4-thiolen-2-one tautomer are detectable, the compound existing as the conjugated enone isomer.[92]



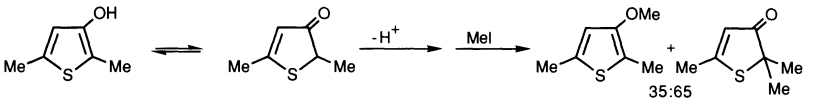
3-thiolen-2-one 4-thiolen-2-one (not detectable) 2-hydroxythiophene (not detectable)

The inclusion of alkyl groups stabilises both the compound and the double bond to which they are attached. In these more stable compounds alternative tautomers are found, thus 5-methyl-2-hydroxythiophene exists as a mixture (actually separable by fractional distillation!) of the two enone tautomers.[93]

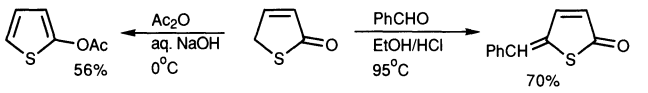


85% 15%

β-Hydroxythiophenes are even more unstable than α-hydroxythiophenes; 3-hydroxy-2-methylthiophene exists as a mixture of hydroxyl and carbonyl tautomeric forms, with the former predominating.[94]



The acidities of the thiolenones are comparable with those of phenols, with pK_as of about 10. Oxythiophene anions can react at oxygen or carbon and products from reaction of electrophiles at both centres can be obtained.[95]



14.12.2 Aminothiophenes

Here again, these thiophene derivatives are much less stable than their benzenoid counterparts, unless the ring is provided with other substitution. The unsubstituted aminothiophenes (thiophenamines) can be obtained by reduction of the nitrothiophenes,[96] but in such a way as to isolate them as salts – usually hexachlorostannates – or *via* Beckmann rearrangements[97] or Hofmann degradation,[98] as acyl derivatives which are stable. Many substituted amines have been prepared by nucleophilic displacement of halogen in nitro-halo-thiophenes. In

so far as it can be studied, in simple cases, and certainly in substituted thiophenamines, the amino form is the only detectable tautomer.[99]

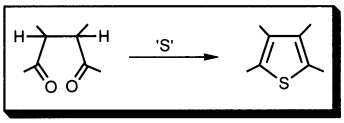
14.13 SYNTHESIS OF THIOPHENES[100]

Thiophene is manufactured by the gas-phase interaction of C_4 hydrocarbons and elementary sulfur at 600°C. Using *n*-butane, the sulfur first effects dehydrogenation and then interacts with the unsaturated hydrocarbon by addition, further dehydrogenation generating the aromatic system.

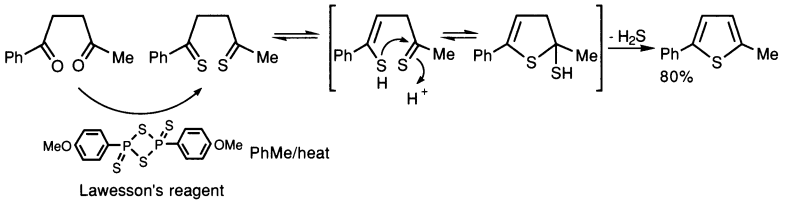
14.13.1 Ring synthesis

14.13.1.1 *From 1,4-dicarbonyl compounds and a source of sulfur*

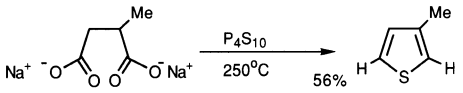
1,4-Dicarbonyl compounds can be reacted with a source of sulfur to give thiophenes.



The reaction of a 1,4-dicarbonyl compound with a source of sulfur, traditionally phosphorus sulfides, but Lawesson's reagent has been recommended for improved yields,[101] gives thiophenes, presumably, but not necessarily, *via* the bis(thioketone).

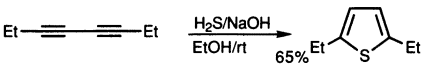


When the process is employed with 1,4-dicarboxylic acids a reduction must occur at some stage, for thiophenes, and not 2-/5-oxygenated thiophenes, result.[102]



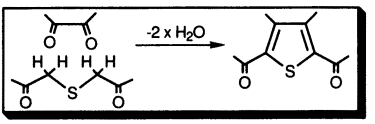
Conjugated diynes, also at the oxidation level of 1,4-dicarbonyl compounds, react smoothly with hydrosulfide, under mild conditions, to give thiophenes; unsymmetrical 2,5-disubstituted thiophenes can be produced in this way too.[103] Since nearly all naturally occurring thiophenes are found in plant genera, and

co-occur with polyynes, this laboratory ring synthesis may be mechanistically related to their biosynthesis.



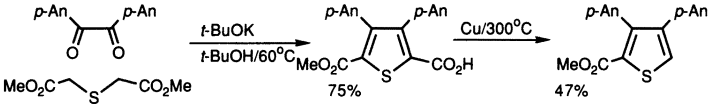
14.13.1.2 *From thiodiacetates and 1,2-dicarbonyl compounds*

1,2-Dicarbonyl compounds condense with thiodiacetates (or thiobis-methyleneketones) to give thiophene-2,5-diacids (-diketones).



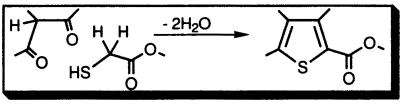
The Hinsberg synthesis

Two consecutive aldol condensations between a 1,2-dicarbonyl compound and diethyl thiodiacetate give thiophenes. The immediate product is an ester-acid, produced[104] by a Stobbe-type mechanism, but the reactions are often worked up *via* hydrolysis to afford an isolated diacid.

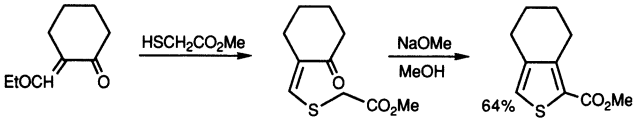


14.13.1.3 *From thioglycolates and 1,3-dicarbonyl compounds*

Thioglycolates react with 1,3-dicarbonyl compounds (or equivalents) to give thiophene-2-carboxylic esters.

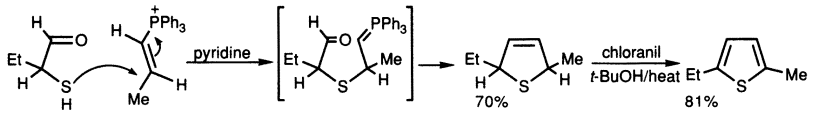


Thioglycolates, as donors of an S–C unit, react with 1,3-keto-aldehydes, to give intermediates which can be ring closed to give thiophenes; a variant utilises β-chlorovinylketones, as a synthon for the dicarbonyl component.[105]



14.13.1.4 *From α-thiocarbonyl compounds*

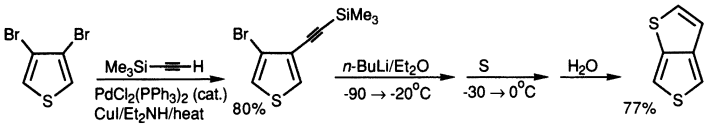
2-Keto-thiols add to alkenylphosphonium ions, affording ylids which then ring close by Wittig reaction and give 2,5-dihydrothiophenes, which can be dehydrogenated.[106]



14.13.2 Examples of notable syntheses of thiophene compounds

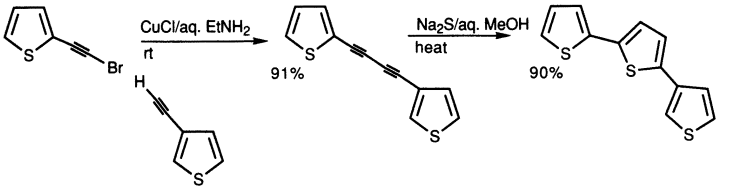
14.13.2.1 *Thieno[3,4-b]thiophene*

Thieno[3,4-*b*]thiophene was prepared from 3,4-dibromothiophene utilising the two halogens in separate steps: palladium-catalysed coupling and lithiation by transmetallation.[107]



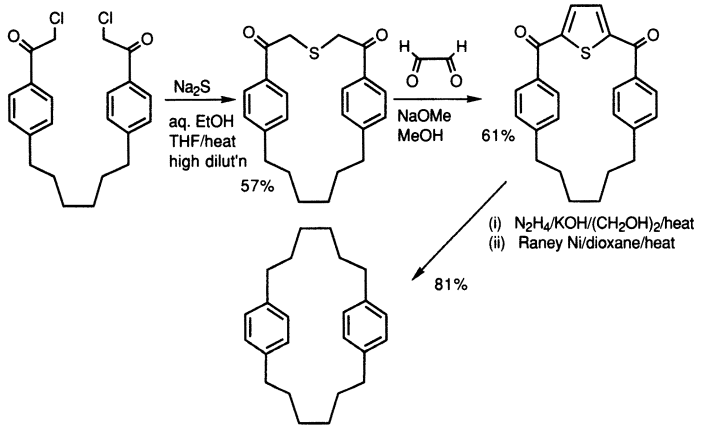
14.13.2.2 *2,2′:5′,3′′-Terthiophene*

This sequence, for the regioselective synthesis of 2,2′:5′,3′′-terthiophene, uses the reaction of a diyne with sulfide to make the central ring.[108]



14.13.2.3 *[6.6]Paracyclophane*

Here the thiophene rings were produced using the Hinsberg approach; hydrogenolytic removal of sulfur, having served its purpose to allow construction of the large ring, gave the cyclophane.[109]



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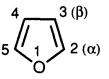
EXERCISES FOR CHAPTER 14

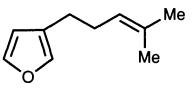
1. Deduce the structure of the compound, $C_4H_3NO_2S$, produced from thiophene by the following sequence: $ClSO_3H$, then f. HNO_3, then H_2O/heat; the product is isomeric with that obtained by reacting thiophene with acetyl nitrate.
2. Suggest structures for the major and minor isomeric products, $C_5H_5NO_3S$, from 2-methoxythiophene with HNO_3/AcOH at $-20°C$.
3. What compounds would be formed by the reaction of (i) thiophene with propionic anhydride/H_3PO_4; (ii) 3-*t*-butylthiophene with PhN(Me)CHO/$POCl_3$ then aq. NaOH; (iii) thiophene with $Tl(O_2CCF_3)_3$, then aq. KI $\rightarrow$ C_4H_2IS; (iv) thiophene/succinic anhydride/$AlCl_3$ $\rightarrow$ $C_8H_8O_3S$, then N_2H_4/KOH/heat $\rightarrow$ $C_8H_{10}O_2S$, then $SOCl_2$, then $AlCl_3$ $\rightarrow$ C_8H_8OS.
4. Predict the principal site of deprotonation on treatment of 2- and 3-methoxythiophenes with *n*-BuLi.
5. Deduce structures for the compounds, C_4HBr_3S and $C_4H_2Br_2S$, produced successively by treating 2,3,4,5-tetrabromothiophene with Mg then H_2O, and then the product again with Mg then H_2O.
6. Deduce the structure of the compound, $C_9H_6OS_2$, produced by the sequence: thiophene with BuLi, then CO_2 $\rightarrow$ $C_5H_4O_2S$, then this with thiophene in the presence of P_4O_{10}.
7. Deduce the structure of the thiophenes: (i) $C_6H_4N_4S$, produced by reacting $(NC)_2C{=}C(CN)_2$ with H_2S; (ii) $C_8H_8O_6S$ from diethyl oxalate, $(EtO_2CCH_2)_2S$/NaOMe, aq. NaOH, then Me_2SO_4; (iii) $C_{11}H_{16}S$ from 3-acetylcyclononanone with P_4S_{10}.

15 Furans: reactions and synthesis

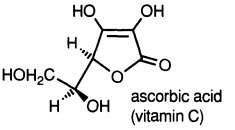


furan

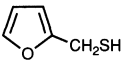
Furans[1] are volatile, fairly stable compounds with pleasant odours. Furan itself is slightly soluble in water. It is readily available, and its commercial importance is mainly due to its role as the precursor of the very widely used solvent tetrahydrofuran (THF). Furan is produced by the gas-phase decarbonylation of furfural (2-formylfuran, furan-2-carboxaldehyde), which in turn is prepared in very large quantities by the action of acids on vegetable residues, mainly from the manufacture of porridge oats and cornflakes. Furfural was first prepared in this way as far back as 1831 and its name is derived from *furfur*, which is the latin word for bran; in due course, in 1870, the word furan was coined from the same root.



perillene

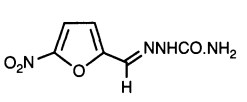


ascorbic acid (vitamin C)

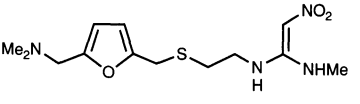


furfuryl thiol

The aromatic furan ring system, though not found in animal metabolism, occurs widely in secondary plant metabolites, especially in terpenoids: perillene is a simple example. Vitamin C, ascorbic acid, is at the oxidation level of a trihydroxyfuran, though it assumes an unsaturated lactone tautomeric form. Though one normally associates thiols with unpleasant odours, furfuryl thiol is present in the aroma of roasted coffee. Some 5-nitrofurfural derivatives are important in medicine; Nitrofurazone, a bactericide, is a simple example. Ranitidine is one of the most commercially successful medicines ever developed; it is used for the treatment of stomach ulcers.



Nitrofurazone



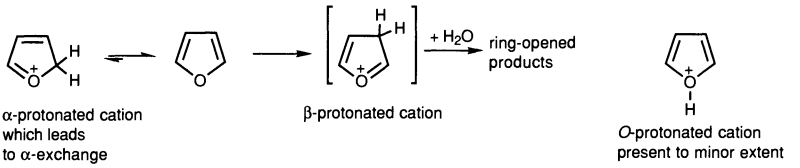
Ranitidine

15.1 REACTIONS WITH ELECTROPHILIC REAGENTS

Of the three five-membered systems with one hetero atom considered in this book, furan is the 'least aromatic' and as such has the greatest tendency to react in such a way as to give addition products – this is true in the context of its interaction with the usual electrophilic substitution reagents, considered in this section, as well as in Diels-Alder type processes (section 15.8).

15.1.1 Protonation

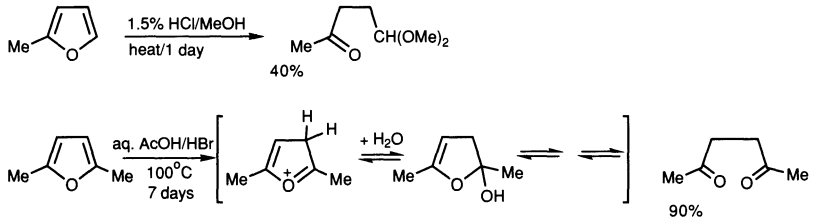
Furan and the simple alkyl furans are relatively stable to aqueous mineral acids, though furan is instantly decomposed by concentrated sulfuric acid or by Lewis acids such as aluminium chloride. Furan reacts only slowly with hydrogen chloride, either as the concentrated aqueous acid or in a non-hydroxylic organic solvent. Hot dilute aqueous mineral acids cause hydrolytic ring opening.



No pK_a value is available for *O*-protonation of furan but it is probably much less basic at oxygen than an aliphatic ether. Acid-catalysed deuteration occurs at an α-position;[2] 3/4-deuteriofurans are not obtained because, although β-protonation probably occurs, the cation produced is more susceptible to water, leading to hydrolytic ring opening. An estimate of pK_a −10.0 was made for the 2-protonation of 2,5-di-*t*-butylfuran, which implies a value of about −13 for furan itself.[3] An α-protonated cation, stable in solution, is produced on treatment of 2,5-di-*t*-butylfuran with concentrated sulfuric acid.[3,4]

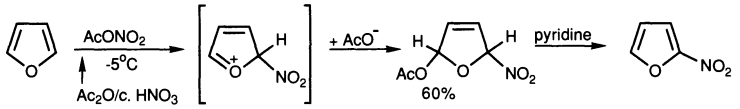
Reactions of protonated furans

The hydrolysis (or alcoholysis) of furans involves nucleophilic addition of water (or alcohol) to an initially formed cation, giving rise to open-chain 1,4-dicarbonyl compounds or derivatives thereof. This is in effect the reverse of one of the general methods for the construction of furan rings (section 15.13.1.1). Succindialdehyde cannot be obtained from furan itself, presumably because the dialdehyde is too reactive under conditions for hydrolysis, but some alkylfurans can be converted into 1,4-dicarbonyl products quite efficiently; however, a more general route to these involves hydrolysis of 2,5-dialkoxytetrahydrofurans (section 15.1.4).



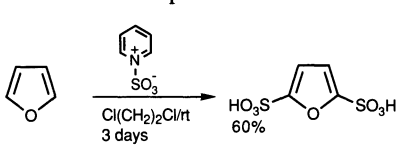
15.1.2 Nitration

Sensitivity precludes the use of concentrated acid nitrating mixtures. Reaction of furan, or substituted furans,[5] with acetyl nitrate produces non-aromatic adducts, in which progress to a substitution product has been interrupted by nucleophilic addition of acetate to the cationic intermediate, usually[6] at C-5.[7] Aromatisation, by loss of acetic acid, to give the nitro-substitution product, will take place under solvolytic conditions, but is better effected by treatment with a weak base like pyridine.[8] Further nitration of 2-nitrofuran gives 2,5-dinitrofuran as the main product.[9]



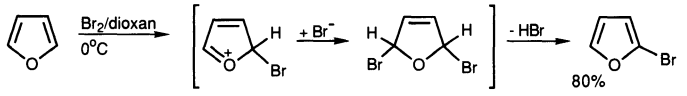
15.1.3 Sulfonation

Furan and its simple alkyl derivatives are decomposed by the usual strong acid reagents, but the pyridine–sulfur trioxide complex can be used, disubstitution of furan being observed even at room temperature.[10]



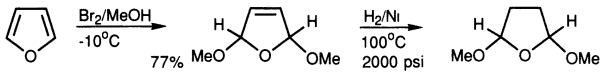
15.1.4 Halogenation

Furan reacts vigorously with chlorine and bromine at room temperature to give polyhalogenated products, but does not react at all with iodine. More controlled conditions can give 2-bromofuran[11] in a process which probably proceeds *via* a 1,4-dibromo-1,4-dihydro-adduct; indeed such species have been observed at low temperature using ^{1}H NMR spectroscopy.[12]



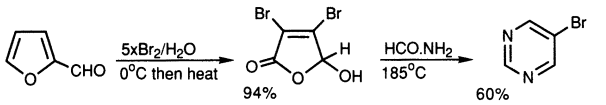
If the bromination is conducted in an alcoholic solvent, trapping of intermediate by C-5 addition of methanol, then methanolysis of C-2-bromide, produces

2,5-dialkoxy-2,5-dihydrofurans, as mixtures of *cis* and *trans* isomers;[13] hydrogenation of these species affords 2,5-dialkoxytetrahydrofurans, extremely useful as 1,4-dicarbonyl synthons – the unsubstituted example is equivalent to succindialdehyde.[14] 2,5-Dialkoxy-2,5-dihydrofurans can also be obtained by electrochemical oxidation in alcohol solvents.[13,15]



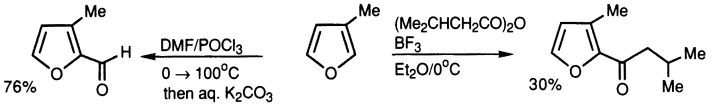
In related chemistry, the actual ring-opened, Δ-2-unsaturated 1,4-diones can be obtained in *E*- or *Z*-form using bromine in aqueous acetone[16a] or *m*-CPBA respectively.[16b]

The intrinsically high reactivity of the furan nucleus can be further exemplified by the reaction of furfural with excess halogen to produce 'mucohalic acids'; incidentally, mucobromic acid reacts with formamide to provide a useful synthesis of 5-bromopyrimidine.[17] On the other hand, with control, methyl furoate can be cleanly converted into its 5-monobromo- or 4,5-dibromo-derivatives, hydrolysis and decarboxylation of the latter then affording 2,3-dibromofuran.[18]



15.1.5 Acylation

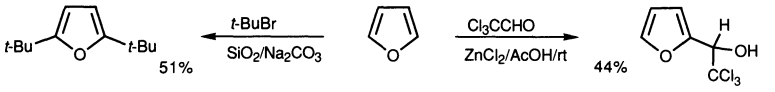
Carboxylic acid anhydrides or halides normally require the presence of Lewis acid (often boron trifluoride) for Friedel-Crafts acylation of furans, though trifluoroacetic anhydride will react alone. The rate of aluminium chloride-catalysed acetylation of furan shows the α-position to be 7×10^4 times more reactive than the β-position.[19] 3-Alkylfurans substitute mainly at C-2;[20] 2,5-dialkylfurans can be acylated at a β-position, but generally with more difficulty.



Vilsmeier formylation of furan is a good route to formylfurans,[21] though the ready availability of furfural as a starting material, and methods involving lithiated furans (section 15.4.1), are important. Formylation of substituted furans follows the rule that the strong tendency for α-substitution overrides other factors, thus both 2-methylfuran[22] and methyl furan-3-carboxylate[23] give the 5-aldehyde; 3-methylfuran gives mainly the 2-aldehyde.[24]

15.1.6 Alkylation

Traditional Friedel-Crafts alkylation is not generally practicable in the furan series, partly because of catalyst-caused polymerisation and partly because of polyalkylation. Instances of preparatively useful reactions include production of 2,5-di-*t*-butylfuran[25] from furan and the isopropylation of methyl furoate with double substitution, at 3- and 4-positions.[24]

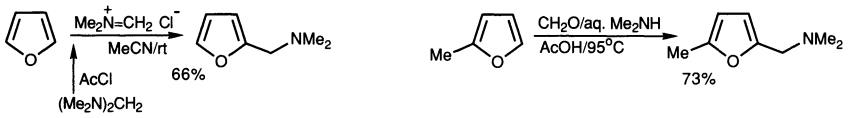


15.1.7 Condensation with aldehydes and ketones

This occurs by acid catalysis, but generally the immediate product, a furfuryl alcohol, reacts further; 2-(3,3,3-trichloro-1-hydroxy)ethylfuran can however be isolated.[26] A macrocycle can be obtained by condensation with acetone[27] *via* a sequence exactly comparable to that described for pyrrole (section 13.1.7).

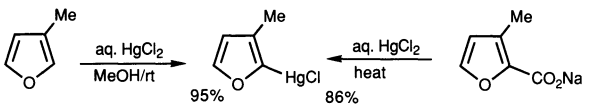
15.1.8 Condensation with imines and immonium ions

Early attempts to effect Mannich reactions with furan itself failed, though mono-alkylfurans undergo the reaction normally,[28] but by reaction with pre-formed immonium salt, normal 2-substitution of furan itself occurs at room temperature.[29]



15.1.9 Mercuration

Mercuration takes place very readily with replacement of hydrogen, or carbon dioxide, from an acid.[30]



15.2 REACTIONS WITH OXIDISING AGENTS

The electrochemical or bromine/methanol oxidations of furans to give 2,5-dialkoxy-2,5-dihydrofurans (section 15.1.4), and the cycloaddition of singlet oxygen (section 15.8), are discussed elsewhere. The ring-opened ketonic equiv-

alents, even but-2-en-1,4-dial itself, can be produced by oxidation with dimethyldioxirane.[31]

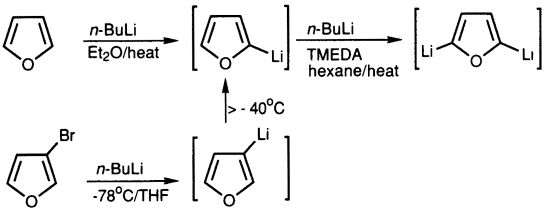
15.3 REACTIONS WITH NUCLEOPHILIC REAGENTS

Simple furans do not react with nucleophiles by addition or by substitution. Nitro substituents activate the displacement of halogen, as in benzene chemistry.

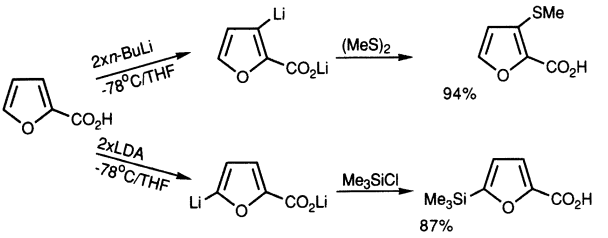
15.4 REACTIONS WITH BASES

15.4.1 Deprotonation of *C*-hydrogen

Metallation with alkyllithiums proceeds selectively at an α-position, indeed metallation of furan is one of the earliest examples[32] of the now familiar practice of aromatic ring-metallation. The preference for α-deprotonation is nicely illustrated by the demonstration that 3-lithiofuran, produced from 3-bromofuran by metal/halogen exchange at −78°C, equilibrates to the more stable 2-lithiofuran if the temperature rises to > −40°C;[33] more forcing conditions can bring about 2,5-dilithiation of furan.[34]



Lithium diisopropylamide can effect C-2-deprotonation of 3-halofurans.[35] With furoic acid and two equivalents of lithium diisopropylamide, selective formation of the carboxylate/5-carbanion is found,[36] whereas *n*-butyllithium, *via* *ortho*-assistance, produces the lithium carboxylate/3-carbanion.[37]

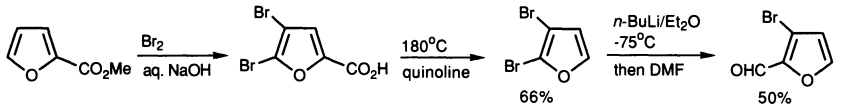


Ortho direction of metallation to C-3 by 2-bisdimethylaminophosphate[38] and 2-oxazolidine[39] groups, and to C-2 by 3-hydroxymethyl,[40] have also been described.

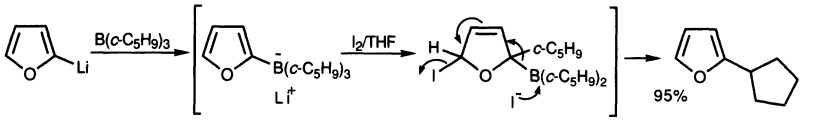
15.5 REACTIONS OF *C*-METALLATED FURANS

15.5.1 Lithio derivatives

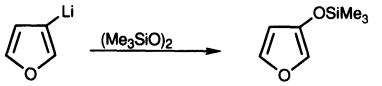
Metallation at C-3 can be achieved *via* metal–halogen exchange. The greater stability of carbanion at an α-position shows up again in a mono-exchange of 2,3-dibromofuran with selective replacement of the α-bromine.[24,41]



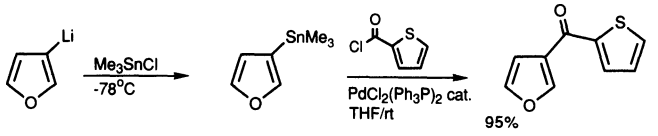
There are many examples of the use of 2- and 3-lithiofurans in reactions with various electrophilic species, such as aldehydes, ketones[32,42] and halides.[43] It has been shown that treatment of 2-lithiofuran with cupric chloride leads to 2,2′-bifuran,[44] and with trialkylboranes to borates, subsequent treatment of which with halogen provides an excellent method for the overall introduction of alkyl groups at the furan α-position.[45]



3-Lithiofuran, earlier usually prepared from 3-iodofuran but now best obtained[46] from 3-bromofuran, can be oxygenated to provide the TMS ether of 3-hydroxyfuran directly.[47]



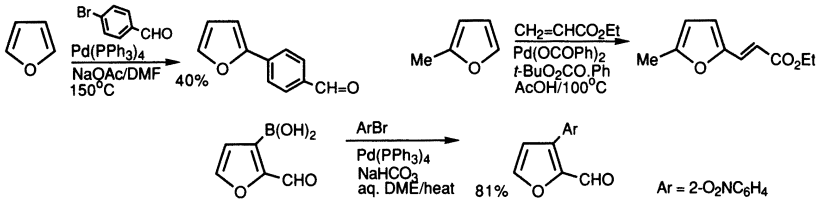
3-Trimethylstannylfuran can be utilised in palladium-catalysed acylation and arylation.[48]



Furan-2- and 3-boronic acids have been made by reaction of the lithiated species with tributyl borate;[49] they are very useful for palladium-catalysed coupling reactions. Oxidation of a 2-boronate ester is a means for the synthesis of butenolides (section 15.12.1).[50]

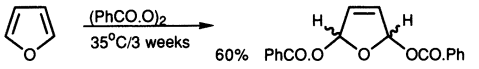
15.5.2 Palladium-catalysed couplings

Palladium chemistry has been utilised to introduce aryl groups to a furan α-position[51] by substitution of hydrogen, and *via* boronic acids,[52] and in Heck-type alkenylations, again at C-2,[53] *via* 'oxidative' type palladation (cf. section 2.7.2.1).



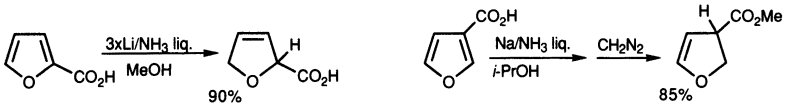
15.6 REACTIONS WITH RADICAL REAGENTS

Reactions of furans with radical species (cf. section 2.4.2) as synthetically useful processes have been little developed; arylation[54] and alkylation[55] are selective for α-positions. Exposed to dibenzoyl peroxide, furan produces a stereoisomeric mixture of 1,4-addition products.



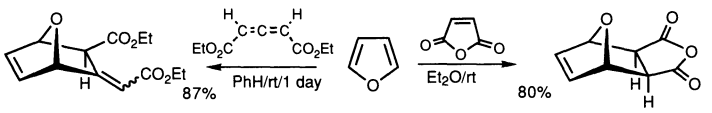
15.7 REACTIONS WITH REDUCING AGENTS

The best way to reduce a furan to a tetrahydrofuran is using Raney nickel catalysis, though ring opening, *via* hydrogenolysis of C–O bonds, can be a complication. Most furans are not reduced simply by metal/ammonia combinations, however furoic acids give dihydro-derivatives.[56]

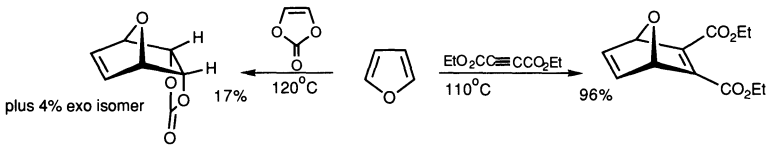


15.8 ELECTROCYCLIC REACTIONS (GROUND STATE)

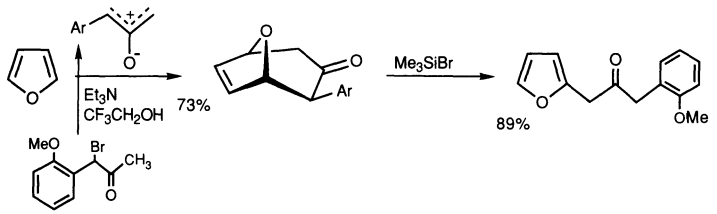
The 4 + 2 cycloaddition of furan to reactive dienophiles such as maleic anhydride[57] was one of the earliest described examples of the Diels-Alder reaction;[58] the isolated product is the *exo* isomer,[59] though this has been shown to be the thermodynamic product, the *endo* isomer being the kinetic product and the cycloaddition being easily reversible.[60]



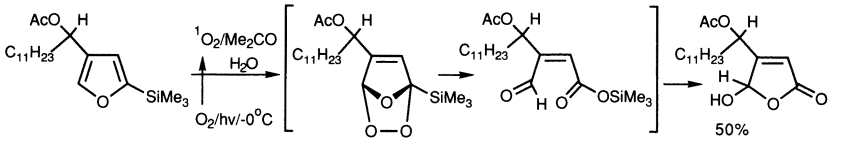
Furan also undergoes cycloadditions with allenes[61] and even with simpler dienophiles, like acrylonitrile and acrylate (specifically enhanced by the presence of zinc iodide),[62] and with maleate and fumarate esters, if the addition is conducted under high pressure.[63] This device can also be used to increase markedly the reactivity of 2-methoxy- and 2-acetoxyfuran towards dienophiles.[64] Lewis acid catalysis can also been used to accelerate furan Diels-Alder additions.[65] At higher reaction temperatures alkynes[66] and even electron-rich alkenes[67] will add to furan.



Although, as one would anticipate for the electron-rich component of a normal Diels-Alder pairing, 2-formylfuran is a poor diene, its dimethylhydrazone is a good one, though only ring-opened benzenoid products, derived subsequently from the adducts, are isolated.[68] The cycloaddition of 2-oxyallyl cations[69] is interesting in its own right and also can be made the means for the introduction of acylmethyl groups at the furan 2-position.[70] Many examples of furans participating in intramolecular Diels-Alder addition have been described.[71]

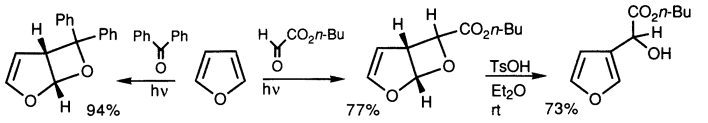


Furans also undergo cycloaddition with singlet oxygen;[72] this can be made the basis for the synthesis of 5-hydroxy-2(5*H*)-furanones (4-hydroxybut-2-enolides, see section 15.12), a structural unit which occurs in several natural products. For example, addition to a 3-substituted furan in the presence of a hindered base[73] or addition[74] to 2-trialkylsilyl-4-substituted furans[75] leads through, as shown, to 4-substituted 5-hydroxy-2(5*H*)-furanones. A particularly neat example is the reaction of 2-furoic acid, which is converted in quantitative yield, with decarboxylation, into malaldehydic acid (the cyclic hemiacetal of *Z*-4-oxobut-2-enoic acid).[76]



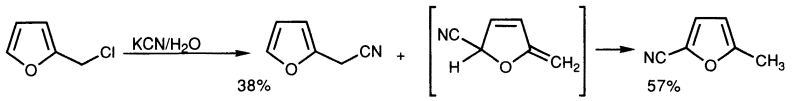
15.9 PHOTOCHEMICAL REACTIONS

The cycloaddition of diarylketones and some aldehydes across the furan 2,3-double bond proceeds regioselectively to afford oxetanodihydrofurans; proton-catalysed cleavage of the acetal linkage produces 3-substituted furans.[77]

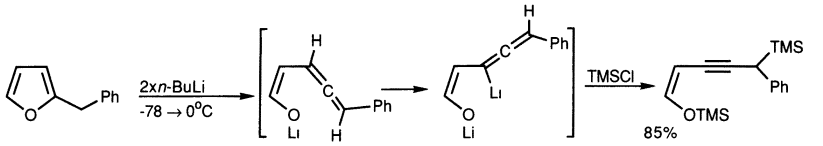


15.10 FURYL-C-X COMPOUNDS; SIDE-CHAIN PROPERTIES

The nucleophilic displacement of halide from furfuryl halides often produces mixtures of products resulting from straightforward displacement on the one hand and displacement with nucleophilic addition to C-5 on the other;[78] the second mode proceeds through a non-aromatic intermediate which then isomerises to aromatic product.

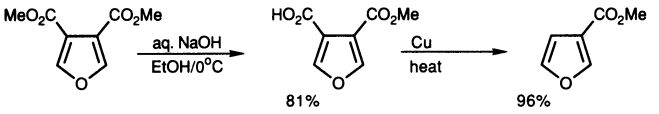


With anion-stabilising groups present it is possible to deprotonate furan α-alkyl groups; these side-chain anions promote ring opening to allene-enolates which, in the presence of excess lithiating agent, undergo a second lithiation.[79]



15.11 FURAN CARBOXYLIC ACIDS AND ESTERS

Save for their easy decarboxylation, furan acids (and their esters) are unexceptional. Carbon dioxide is easily lost[80] from either α- or β-acids and presumably involves ring-protonated intermediates and a decarboxylation analogous to that of β-keto-acids, at least in those examples where copper is not utilised.



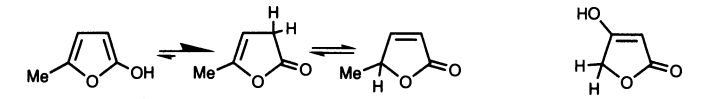
Nitration of 3-furoic acid takes place normally, and at C-5;[81] α-acids sometimes undergo *ipso*-substitution with decarboxylation,[82] for example 2-furoic acid gives mainly the 5-nitro-derivative but accompanied by some 2,5-dinitrofuran.[83]

15.12 OXY- AND AMINOFURANS

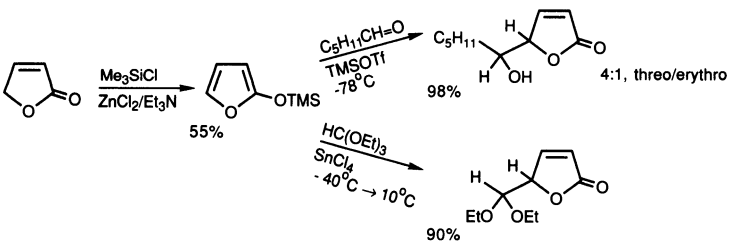
15.12.1 Oxyfurans

2-Hydroxyfurans exist, if at all, at undetectably low concentrations in tautomeric equilibria involving 2(5*H*)-furanone and 2(3*H*)-furanone forms; for example, the angelica lactones can be equilibrated *via* treatment with an organic base, the more stable being the β-isomer; the chemistry of 2-oxyfurans, then, is that of unsaturated lactones. Less is known of 3-hydroxyfurans, save again that the carbonyl tautomeric form predominates.

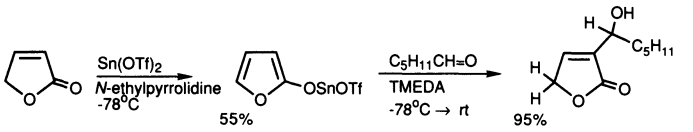
Many natural products[84] and natural aroma components[85] contain 2-furanone units and considerable synthetic work has thereby been engendered.[86] In the context of these natural products, the name 'butenolide' is generally employed and compounds are therefore numbered as derivatives of 4-hydroxybutenoic acid and not as a furan; for example, a tetronic acid is a 3-hydroxybut-2-enolide.



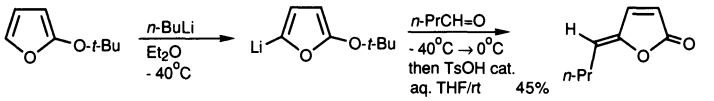
Butenolides can be converted into furans by partial reduction of the lactone, then dehydration.[87]



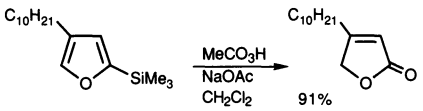
Synthons which have been developed for butenolide construction include 2-trimethylsilyloxyfuran,[88] which reacts with electrophiles at (furan) C-5,[89] and, complimentarily, furan carrying an oxy-tin (or oxy-boron) substituents, which, *via* chelation control, react with electrophiles at C-3.[90]



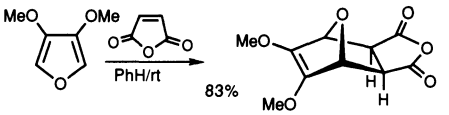
2-*t*-Butoxyfuran, available from the reaction of 2-lithiofuran with *t*-butyl perbenzoate,[91] can be lithiated at C-5, reaction with a carbonyl component, then hydrolysis with dehydration, furnishing alkylidene-butenolides.[92]



2-Trimethylsilylfurans are converted into the butenolide by oxidation with peracid.[93]



2-Methoxy- and 2-acetoxyfurans are available from 2,5-dimethoxy- and 2,5-diacetoxy-2,5-dihydrofurans (section 15.1.4) *via* acid-catalysed elimination.[94] They undergo Diels-Alder cycloadditions; the adducts can be further transformed into benzenoid compounds by acid-catalysed opening. 3,4-Dihydroxyfuran is undetectable in tautomeric equilibria between mono-enol and dicarbonyl forms; the dimethyl ether behaves as a normal furan, undergoing easy α-electrophilic substitution, mono- or dilithiation at the α-positions,[95] and Diels-Alder cycloadditions.[96] 2,5-Bis(trimethylsilyloxy)furan is synthesised from succinic anhydride; it too undergoes Diels Alder additions readily.[97]



Both 2- and 3-thiols can be obtained by reaction of lithiated furans with sulfur; in each case the predominant tautomer is the thiol form.[98]

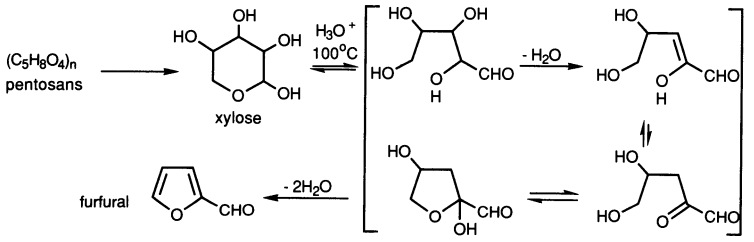
15.12.2 Aminofurans

So little has been described of the chemistry of aminofurans that general comment on their reactivity is difficult to make; it seems likely that 2-aminofurans

are too unstable to be isolable, though 2-acylaminofurans have been described. 3-Amino-2-methylfuran is relatively stable and behaves like an aromatic amine.[99]

15.13 SYNTHESIS OF FURANS

Furfural and thence, by vapour phase decarbonylation, furan are available in bulk and represent the starting points for many furan syntheses. The aldehyde is manufactured[100] from xylose, obtained in turn from pentosans, which are polysaccharides extracted from many plants, e.g. corn cobs and rice husks. Acid catalyses the overall loss of three moles of water in very good yield. The precise order of events in the multistep process is not known for certain, however a reasonable sequence[101] is shown. Comparable dehydrative ring closure of fructose produces 5-hydroxymethylfurfural.[102]

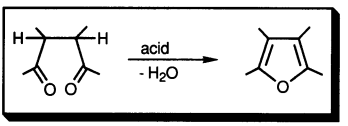


15.13.1 Ring syntheses

Many routes to furans have been described, but the majority are variants on the first general method – the dehydrating ring closure of a 1,4-dicarbonyl substrate.

15.13.1.1 *From 1,4-dicarbonyl compounds*

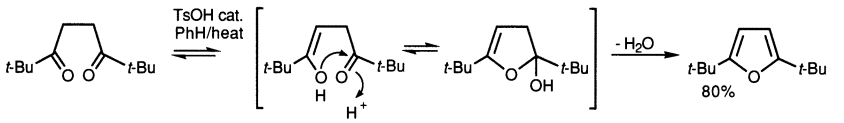
1,4-Dicarbonyl compounds can be dehydrated, with acids, to form furans.



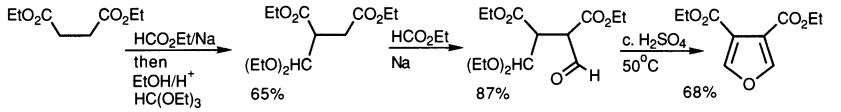
The Paal-Knorr synthesis

The most widely used approach to furans is the cyclising dehydration of 1,4-dicarbonyl compounds, which provide all of the carbon atoms and the oxygen necessary for the nucleus. Usually, non-aqueous acidic conditions[103] are employed to encourage the loss of water. The process involves addition of the

enol oxygen of one carbonyl group to the other carbonyl group, then elimination of water.

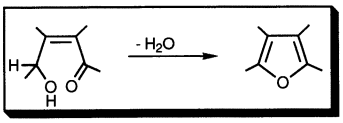


Access to a 1,4-dicarbonyl substrate has been realised in several ways: alkylation of imines with 2-alkoxy-allyl halides (equivalents of 2-haloketones),[104] addition of β-ketoester anions to nitroalkenes, followed by Nef reaction,[105] and rhodium-catalysed carbonylation of 2-substituted acrolein acetals[106] are just three routes by which such precursors can be obtained. The dialdehyde (as a mono-acetal) necessary for a synthesis of diethyl furan-3,4-dicarboxylate was obtained by two successive Claisen condensations between diethyl succinate and ethyl formate.[107]

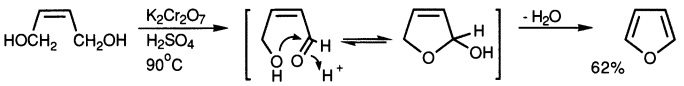


15.13.1.2 *From γ-hydroxy-α,β-unsaturated carbonyl compounds*

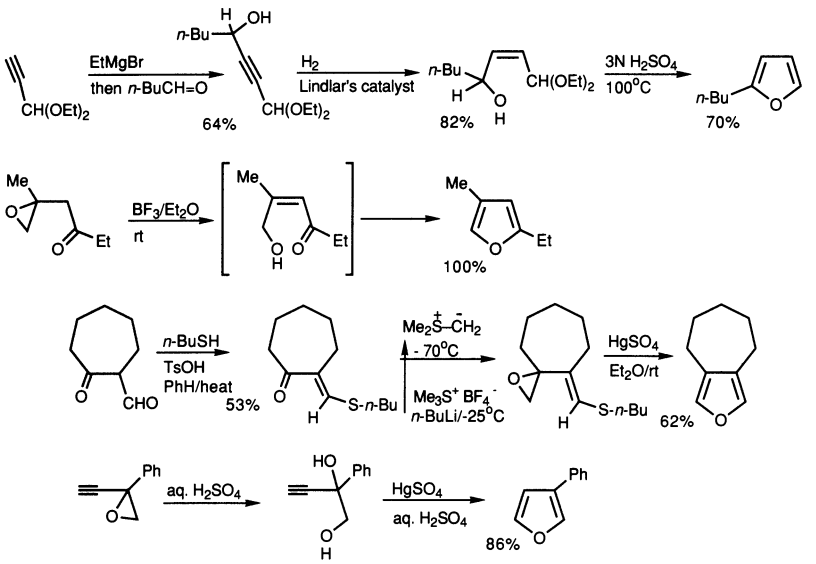
γ-Hydroxy-α,β-unsaturated carbonyl compounds can be dehydrated, using mineral or Lewis acids, to form furans.



The simplest example here is the oxidation of *cis*-but-2-ene-1,4-diol, which gives furan *via* the hydroxy-aldehyde.[108]

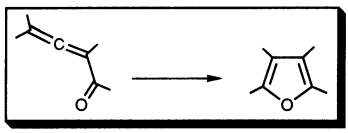


More elaborate 4-hydroxy-ene-als and -ene-ones have been generated in a variety of ways, for example *via* alkynes[109] or often *via* epoxides,[110] it being sometimes unnecessary to isolate the hydroxy-ene-one.[111] Acetal[112], thioenolether[113] or terminal alkyne[114] can be employed as surrogate for the carbonyl group.

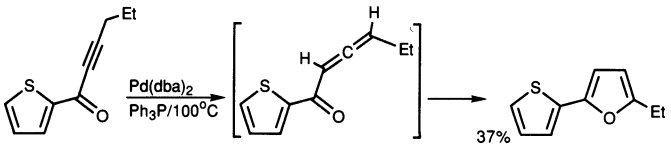


15.13.1.3 *From allenyl ketones*

Allenyl ketones cyclise to furans with metal ion or metal(0) catalysis.

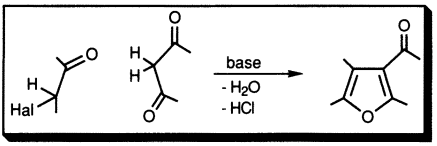


Allenyl ketones, presynthesised,[115] or generated *in situ* by acylation of silylallenes,[116] or by palladium(0)-catalysed isomerisation of conjugated[117] or non-conjugated[118] alkynyl ketones, can be cyclised to furans. The ring closure has been effected with silver[112] or palladium[117,118] catalysis; acylation of silylallenes leads to the furan directly.[112] In the presence of water, palladium(2)-catalysed closure of β,γ-alkynyl ketones is believed to proceed *via* the enol, not the allene.[119] 1,2,3-Trienyl-4-ols have also been shown to cyclise to give furans.[120]



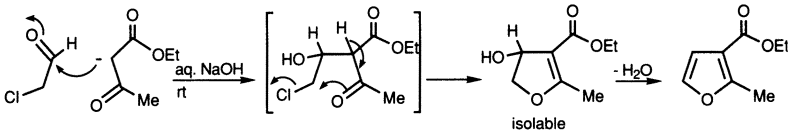
15.13.1.4 *From α-halocarbonyl and 1,3-dicarbonyl compounds*

α-Halocarbonyl compounds react with 1,3-dicarbonyl compounds in the presence of a base (not ammonia, cf. section 13.18.1.3) to give furans.

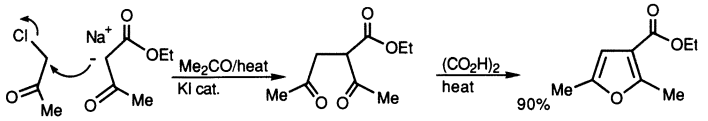


The Feist-Benary synthesis

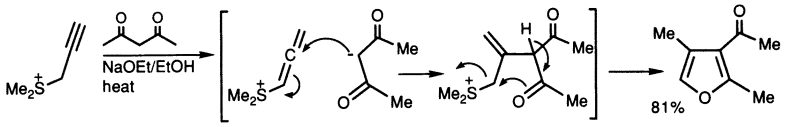
This synthesis rests on an initial aldol condensation at the carbonyl carbon of a 2-halocarbonyl component; ring closure is achieved *via* intramolecular displacement of halide by enolate oxygen; intermediates supporting this mechanistic sequence have been isolated in some cases.[121]



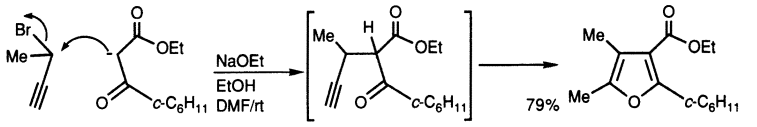
It is important to distinguish this synthesis from the alkylation of a 1,3-dicarbonyl enolate with an 2-haloketone, with displacement of halide, producing a 1,4-dicarbonyl unit for subsequent ring closure;[122] presumably the difference lies in the greater reactivity of the aldehyde group in the Feist-Benary sequence.



In a pair of comparably contrasting modern variants on the Feist-Benary *versus* 1,4-dicarbonyl-forming theme, alkynes are utilised as carbonyl equivalents; an allene is implicated in the first.[123]



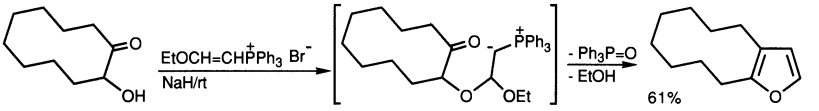
Contrasting is the alkylation, with halide displacement, of 1,3-dicarbonyl compounds with propargyl halides, followed by ring closure.[124]



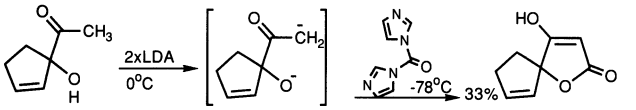
15.13.1.5 *Miscellaneous methods.*

Considerable ingenuity has been exercised in the development of alternative

routes to furans. For example, acyloins react with 'acetylene-transfer' reagents,[125] in one of the few furan syntheses which begins with formation of the ether unit; the cyclising step is a Wittig reaction.



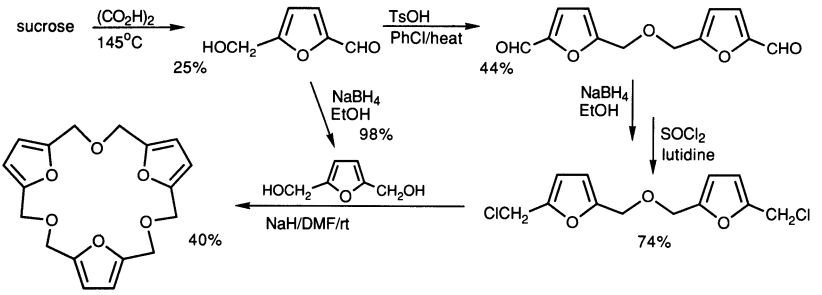
Tetronic acids can be constructed using the dianion of an acyloin, this time with the phosgene equivalent, 1,1′-carbonyldiimidazole.[126]



15.13.2 Examples of notable syntheses of furans

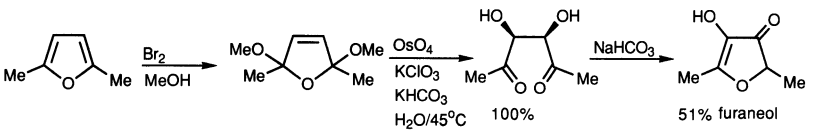
15.13.2.1 *Tris(furanyl)-18-crown-6*

Tris(furanyl)-18-crown-6 was prepared utilising the reactivity of furfuryl alcohols and chlorides.[127]



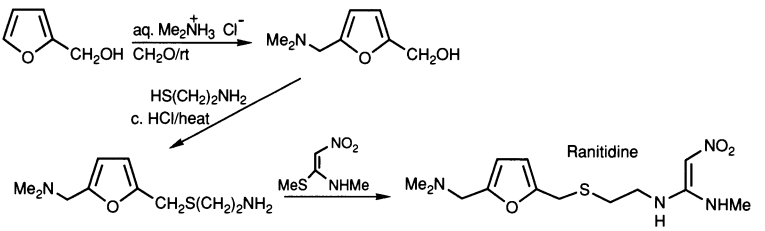
15.13.2.2 *Furaneol*

Furaneol is a natural flavour principle, isolated from pineapple and strawberry, and used in the food and beverage industries.[128]



15.13.2.3 *Ranitidine*

Ranitidine has been synthesised from furfuryl alcohol.



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EXERCISES FOR CHAPTER 15

1. Hydrolysis of 2-methoxyfuran with aqueous acid produces 4-hydroxybut-2-enoic acid lactone and $MeO_2C(CH_2)_2CH{=}O$: write sequences involving protonation and reaction with water to rationalise formation of each of these.
2. Suggest structures for the products: (i) $C_{11}H_8O$ produced by treating 2-phenylfuran with the combination DMF/$POCl_3$ then aqueous base; (ii) $C_9H_{10}O_4$ from ethyl furoate/Ac_2O/$SnCl_4$; (iii) $C_5H_2N_2O_3$ from 3-cyanofuran with Ac_2O/HNO_3; (iv) $C_{14}H_{11}Cl_3O_6$ from methyl furoate, CCl_3CHO/H_2SO_4.
3. Electrochemical oxidation of 5-methylfurfuryl alcohol in methanol solvent afforded $C_8H_{14}O_4$, hydrogenation of which produced $C_8H_{16}O_4$ acid treatment of this gave a cyclic 1,2-dione, $C_6H_8O_2$. What are the structures of these compounds?
4. Trace the course of the following synthesis by writing structures for all intermediates: ethyl 2-methylfuran-3-carboxylate with $LiAlH_4$, then $SOCl_2$, then $LiAlH_4$ → C_6H_8O, treatment of which with Br_2/MeOH, then H_2O/60°C, then aq. $NaBH_4$ gave $C_6H_{12}O_2$.
5. Write structures for the products of reacting 2-lithiofuran with (i) cyclohexanone, (ii) $Br(CH_2)_7Cl$.
6. Suggest structures for the (main) product from the following combinations: (i) 3-methylfuran/DMF/$POCl_3$ then aq. NaOH; (ii) 2,3-dibromofuran/*n*-BuLi then H_2O; (iii) 3-bromofuran/LDA, then CH_2O → $C_5H_5BrO_2$; (iv) furfural with EtOH/H^+ → $C_9H_{14}O_3$, then this with BuLi, followed by $B(OBu)_3$ and aqueous acid → $C_5H_5BO_3$; (v) 3-bromofuran/BuLi/−78°C, then Bu_3SnCl → $C_{16}H_{30}OSn$ and this with MeCO.Cl/$PdCl_2$ → $C_6H_6O_2$.
7. Write structures for the products of reaction of (i) furfuryl alcohol with $H_2C{=}C{=}CHCN$ → $C_9H_9NO_2$; (ii) 2,5-dimethylfuran with $CH_2{=}CHCO$-Me/15 kbar; (iii) furan with 2-chlorocyclopentanone/Et_3N/$LiClO_4$ → $C_9H_{10}O_2$.
8. (i) How could one prepare 2-trimethylsilyloxyfuran? (ii) What product, $C_6H_5NO_2$, would be formed from this with ICH_2CN/$AgOCO.CF_3$?
9. What is the product, $C_{11}H_8O_2$, formed from the following sequence: 2-*t*-BuO-furan/*n*-BuLi, then PhCH=O, then TsOH?
10. Decide the structures of the furans produced by the ring syntheses summarised as follows: (i) $CH_2{=}CHCH_2MgBr$/EtCH=O, then *m*-CPBA, then

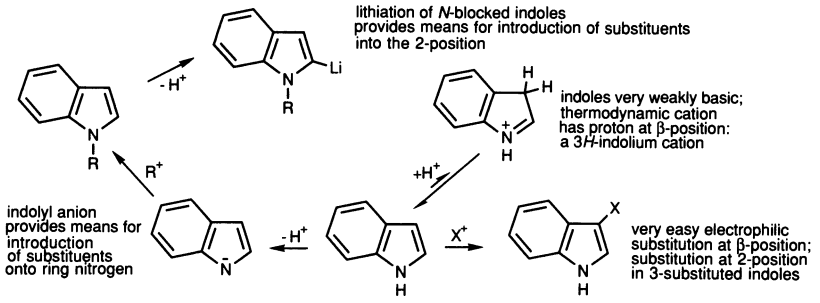
CrO_3/pyridine then BF_3; (ii) CH_2=C(Me)CH_2MgCl/$HC(OEt)_3$, then *m*-CPBA, then aq. H^+; (iii) $(MeO)_2CH_2CO.Me$/$ClCH_2CO_2Me$/NaOMe then heat.

11. For the synthesis of tetronic acid summarised as follows, suggest structures for the intermediates: methylamine was added to dimethyl acetylenedicarboxylate (DMAD) → $C_7H_{11}NO_4$, selective reduction with $LiAlH_4$ then giving $C_6H_{11}NO_3$, which with acid cyclised → $C_5H_7NO_2$, aqueous acidic hydrolysis of which produced tetronic acid.

Reactivity of indoles, benzo[*b*]thiophenes, benzo[*b*]furans, isoindoles, benzo[*c*]thiophenes and isobenzofurans

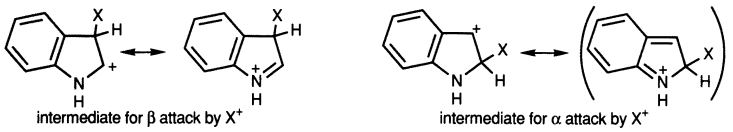
16

The fusion of a benzene ring to the 2,3-positions of a pyrrole generates one of the most important heterocyclic ring systems – indole. This chapter develops a description of the chemistry of indole, then discusses modifications necessary to rationalise the chemistry of the benzo[*b*]furan and benzo[*b*]thiophene analogues. Finally, the trio of heterocycles in which the benzene ring is fused at the five-membered ring 3,4-positions are considered.



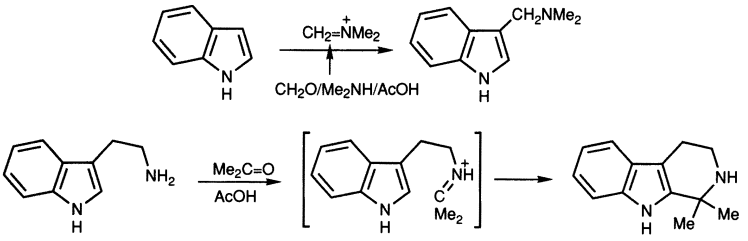
The chemistry of indole is dominated by its very easy electrophilic substitution. Of the two rings, the heterocyclic ring is very electron-rich, by comparison with a benzene ring, so **attack by electrophiles always takes place in the five-membered ring**, except in special circumstances. Of the three positions on the heterocyclic ring, attack at nitrogen would destroy the aromaticity of the five-membered ring, and produce a localised cation; both of the remaining positions can be attacked by electrophiles, leading to *C*-substituted products, but the β-position is preferred by a considerable margin. This contrasts with the

regiochemistry shown by pyrrole but again can be well rationalised by a consideration of the Wheland intermediates for the two alternative sites of attack.

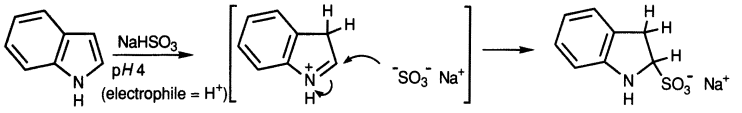


The intermediate for attack at C-2 is stabilised – it is a benzylic cation – but it cannot derive assistance from the nitrogen without disrupting the benzenoid resonance (resonance contributor, which makes a limited contribution, shown in parentheses). The more stable intermediate from attack at C-3 has charge located adjacent to nitrogen and is able to derive the very considerable stabilisation attendant upon interaction with its lone pair of electrons.

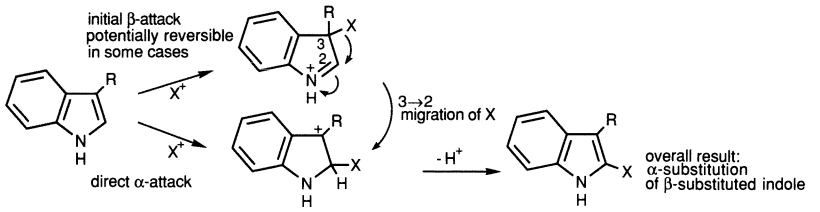
The facility with which indoles undergo substitution, and the possibility for substitution at C-2, can both be illustrated using Mannich reactions – the electrophilic species in such reactions ($C{=}N^{+}R_2$) is generally considered to be a 'weak' electrophile, yet substitution occurs easily under mild conditions.



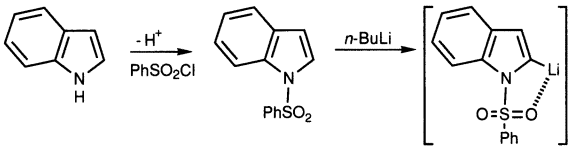
There is a **strong preference for attack at C-3**, even when that position carries a substituent, and this is nicely shown by examples in which there is the possibility for nucleophilic trapping of the Wheland intermediate: the reaction of indole with sodium hydrogen sulfite is a simple example.



2-Electrophilic substitution of 3-substituted indoles could proceed in three ways: (i) initial attack at a 3-position, followed by 1,2-migration to the 2-position; (ii) initial attack at the 3-position, followed by reversal (when possible), then (iii); or (iii) direct attack at the 2-position. It has been definitely demonstrated, in the case of some irreversible substitutions, that the migration route operates, but equally it has been demonstrated that direct attack at an α-position can occur.



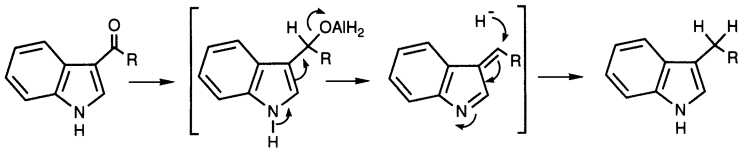
Indoles react with strong bases, losing the *N*-hydrogen and forming indolyl anions. When the counterion is an alkali metal these salts have considerable ionic character and react with electrophiles at the nitrogen, affording a practical route for *N*-alkylation (or acylation) of indole nitrogen. Indolyl anions are used, for example, for the synthesis of indoles carrying *N*-blocking substituents. From *N*-blocked indoles, deprotonation (lithiation) can be effected at C-2, often with the additional chelating assistance of the *N*-substituent, though this last is not essential, for even *N*-methylindole lithiates at C-2, where the acidifying effect of the electronegative hetero atom is felt most strongly.



The reactivity of *N*-magnesioindoles, which result from displacement of the active *N*-hydrogen with a Grignard reagent, or the analogous zinc derivatives, are rather different from that of the sodium, potassium and lithium salts. The greater covalent character of the *N*-metal bond means that electrophiles tend to react at C-3, rather than at nitrogen.

The ready electron availability in the heterocyclic ring means that indoles are rather easily (aut)oxidised in the five-membered ring. Reductions can be made selective for either ring: in acid solution dissolving metals attack the hetero-ring, and the benzenoid ring can be selectively reduced by Birch reduction.

Apart from commenting that substituents on the homocyclic ring of indoles are 'normal', i.e. they behave as they would on simpler benzene compounds, the last major aspect of note is the reactivity of indoles which carry leaving groups at benzylic positions, especially C-3, on the heterocyclic ring. Such compounds undergo displacement processes extremely easily, encouraged by stabilisation of positive charge by the nitrogen or, alternatively, in basic conditions, by loss of the indole hydrogen. This last occurs in lithium aluminium hydride reduction of 3-acylindoles which produces 3-alkylindoles.

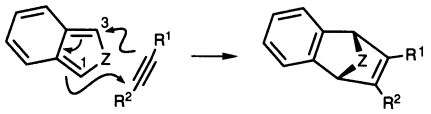


In a sense, 3-ketones behave like vinylogous amides, and reduction intermediates are able to lose oxygen to give species which, on addition of a second hydride, produce the indolyl anion of the 3-alkylindole, converted into the indole during aqueous work up.

In comparison with indoles, benzo[*b*]furans and benzo[*b*]thiophenes have been studied much less fully; however similarities and some differences have been noted. Each system undergoes electrophilic substitution but the 3-regioselectivity is much lower than for indole, even to the extent that some attack takes place in the benzene ring of benz[*b*]thiophene and that 2-substitution is favoured for benzo[*b*]furan. These changes are consequent upon the much poorer electron-donating ability of oxygen and sulfur – the nitrogen of indole is able to make a much bigger contribution to stabilising intermediates, particularly, as was shown above, for β-attack, and consequently to have a larger influence on regioselectivity. In the case of benzo[*b*]furan, it appears that simple benzylic resonance stabilisation in an intermediate from 2-attack outweighs the ability that oxygen might have on stabilising an adjacent positive charge.

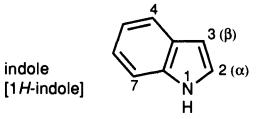
Oxygen and sulfur systems undergo lithiation at their 2-positions, consistent with the behaviour of furans, thiophenes, and of *N*-blocked pyrroles and indoles.

The chemical behaviour of isoindole, benzo[*c*]thiophene and isobenzofuran is dominated by their lack of a 'complete' benzene ring: these three heterocycles undergo cycloaddition processes across the 1,3-positions with great facility, because the products do now have a regular benzene ring. Often, these systems are only generated in the presence of the dienophile with which it is desired that they react. As a result of this strong tendency, few of the classical electrophilic and nucleophilic processes have been much studied.



Indoles: reactions and synthesis

17

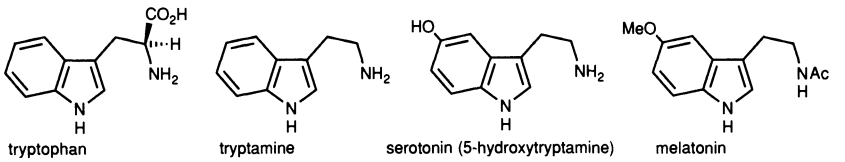


Indole[1] and the simple alkylindoles are colourless crystalline solids, with a range of odours from naphthalene-like, in the case of indole itself, to faecal in the case of skatole (3-methylindole). Many simple indoles are available commercially and all of these are produced by synthesis: indole, for example, is made by the high-temperature vapour-phase cyclising dehydrogenation of 2-ethylaniline.

Most indoles are quite stable in air, with the exception of those which carry a simple alkyl group at C-2: 2-methylindole autoxidises easily even in a dark brown bottle.

The word indole is derived from the word India: a blue dye imported from India was known as indigo in the sixteenth century. Chemical degradation of the dye gave rise to oxygenated indoles (section 17.14) which were named indoxyl and oxindole; indole itself was first prepared in 1866 by zinc dust distillation of oxindole.

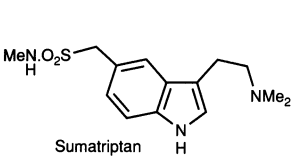
Indoles are probably the most widely distributed heterocyclic compounds in nature. Tryptophan is an essential amino acid and as such is a constituent of most proteins; it also serves as a biosynthetic precursor for a wide variety of tryptamine- and indole-containing secondary metabolites.



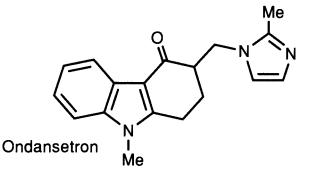
In animals, serotonin (5-hydroxytryptamine) is a very important neurotransmitter in the central nervous system, and also in the cardiovascular and

gastrointestinal systems. The structurally similar hormone melatonin is thought to control the diurnal rhythm of physiological functions.

Study and classification of serotonin receptors has resulted in the design and synthesis of highly selective medicines such as Sumatriptan, for the treatment of migraine, and Ondansetron for the suppression of the nausea and vomiting caused by cancer chemotherapy and radiotherapy.

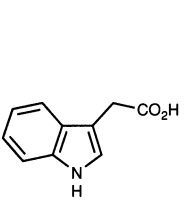


Sumatriptan

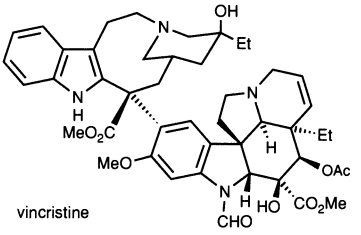


Ondansetron

Tryptophan-derived substances in the plant kingdom include indol-3-ylacetic acid, a plant growth-regulating hormone, and a huge number and structural variety of secondary metabolites – the indole alkaloids.[2] In the past, the potent physiological properties of many of these led to their use in medicine, but in most instances these have now be supplanted by synthetic substances, although vincristine, a 'dimeric' indole alkaloid, is still extremely important in the treatment of leukemia. The physiological activity of lysergic acid diethylamide (LSD) is notorious.

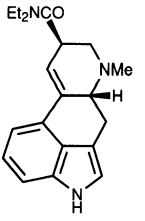


indol-3-ylacetic acid

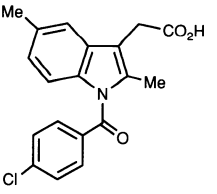


vincristine

The synthetic indol-3-ylacetic acid derivative Indomethacin is still, after many years, one of the major medicines for the treatment of rheumatoid arthritis.



lysergic acid diethylamide (LSD)

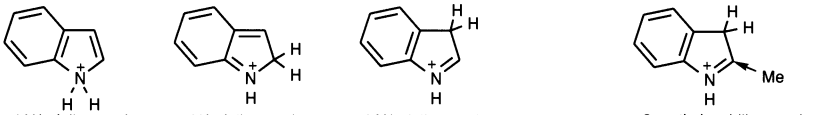


Indomethacin

17.1 REACTIONS WITH ELECTROPHILIC REAGENTS

17.1.1 Protonation

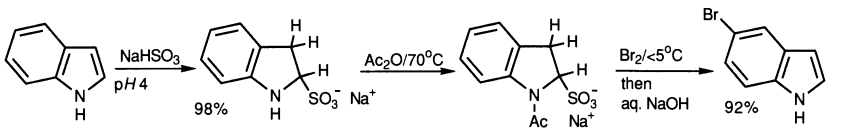
Indoles, like pyrroles, are very weak bases: typical pK_a values are indole, −3.5; 3-methylindole, −4.6; 2-methylindole. −0.3.[3] This means, for example, that in 6M sulfuric acid two molecules of indole are protonated for every one unprotonated, whereas 2-methylindole is almost completely protonated under the same conditions. By NMR and UV examination, only the 3-protonated cation (3*H*-indolium cation) is detectable;[4] it is the thermodynamically stablest cation, retaining full benzene aromaticity (in contrast to the 2-protonated cation) with delocalisation of charge over the nitrogen and α-carbon. The spectroscopically undetectable *N*-protonated cation must be formed, and formed very rapidly, for acid-catalysed deuterium exchange at nitrogen is 400 times faster than at C-3;[5] indeed the *N*-hydrogen exchanges rapidly even at p*H* 7, when no exchange at C-3 occurs: clean conversion of indole into 3-deuterioindole can be achieved by successive deuterio-acid then water treatments.[6] Base-catalysed exchange, *via* the indolyl anion (section 17.4) likewise takes place at C-3.[7]



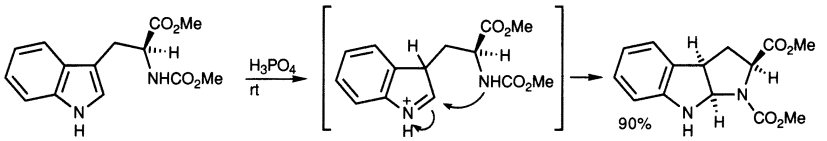
That 2-methylindole is a stronger base than indole can be understood on the basis of stabilisation of the cation by electron release from the methyl group; 3-methylindole is a somewhat weaker base than indole.

Reactions of β-protonated indoles (see also sections 17.1.6 and 17.1.9)

3*H*-Indolium cations are of course electrophilic species, in direct contrast with neutral indoles, and under favourable conditions will react as such. For example, the 3*H*-indolium cation itself will add bisulfite at p*H* 4, under conditions which lead to the crystallisation of the product, the sodium salt of indoline-2-sulfonic acid (indoline is the widely used, trivial name for 2,3-dihydroindole). The salt reverts to indole on dissolution in water; however it can be *N*-acetylated and the resulting acetamide used for halogenation or nitration at C-5, final hydrolysis with loss of bisulfite affording the 5-substituted indole.[8]

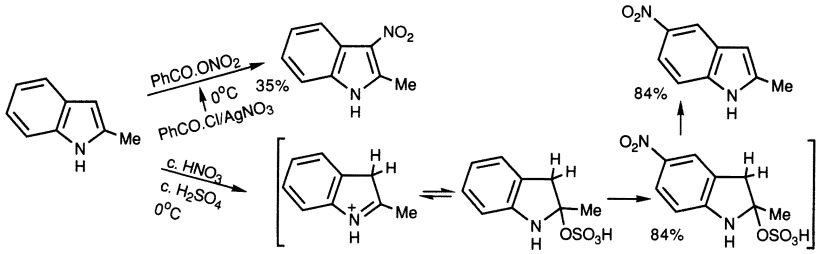


When *N*-protected tryptophans are exposed to strong acid, the 3-protonated indolium cation is trapped by intramolecular cyclisation of the side-chain nitrogen.[9]



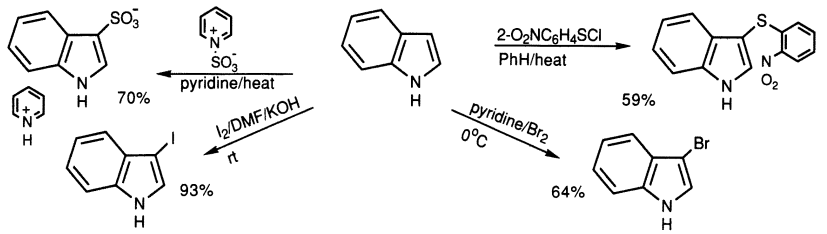
17.1.2 Nitration

Indole itself can be nitrated using benzoyl nitrate as a non-acidic nitrating agent; the usual mixed acid nitrating mixture leads to intractable products, probably because of acid-catalysed polymerisation. 2-Methylindole likewise gives a 3-nitro-derivative with benzoyl nitrate,[10] but can also be nitrated successfully with concentrated nitric/sulfuric acids, but with attack at C-5. The absence of attack on the heterocyclic ring is explained by the complete protonation of 2-methylindole under these conditions; the regioselectivity of attack, *para* to the nitrogen, may mean that the actual moiety attacked is a bisulfate adduct of the initial 3*H*-indolium cation. 5-Nitration of 3*H*-indolium cations has been independently demonstrated using an authentic 3,3-disubstituted 3*H*-indolium cation.[11]



17.1.3 Sulfonation; reactions with other sulfur electrophiles

Sulfonation of indole,[12] at C-3, is achieved using the pyridine–sulfur trioxide complex in pyridine as solvent. Sulfenylation also occurs readily, at C-3.[13]



17.1.4 Halogenation

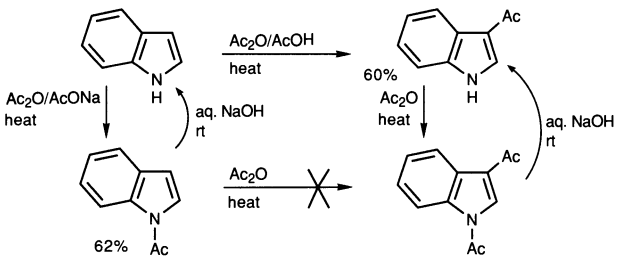
3- and, even more so, 2-haloindoles are unstable and must be utilised as soon as they are prepared. A variety of methods are available for the β-halogenation of indoles: bromine or iodine (the latter with potassium hydroxide) in DMF[14a] give very high yields; pyridinium bromide perbromide[15b] works efficiently;

iodination[15c] and chlorination[15d] tend to be carried out in alkaline solution and, at least in the latter case, is believed to involve initial *N*-chlorination, then rearrangement. Reaction of 3-substituted indoles with halogens is more complex; initial 3-halogenation occurs,[15] but the actual products obtained then depend upon the reaction conditions, solvent, etc.; for example in aqueous solvents, water addition at C-2 and loss of hydrogen halide produces oxindoles (section 17.14).

2-Bromo and -iodoindoles can be prepared very efficiently *via* α-lithiation (section 17.6.1);[16] 2-haloindoles are also available from the reaction of oxindoles with phosphorus oxyhalides.[17]

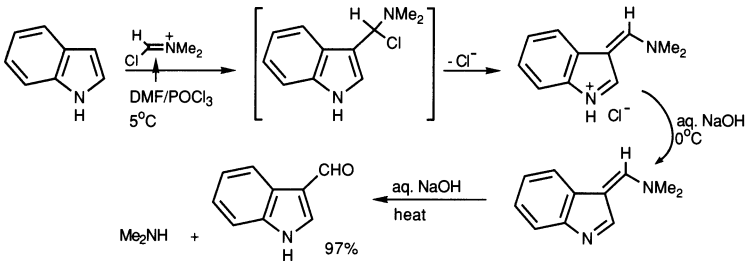
17.1.5 Acylation

Indole only reacts with acetic anhydride at an appreciable rate above 140°C, giving 1,3-diacetylindole predominantly, together with smaller amounts of *N*- and 3-acetylindoles; 3-acetylindole is prepared by alkaline hydrolysis of product mixtures.[18] That β-attack occurs first is shown by the resistance of 1-acetylindole to *C*-acetylation, but the easy conversion of the 3-acetylindole into 1,3-diacetylindole. In contrast, acetylation in the presence of sodium acetate, or 4-dimethylaminopyridine,[19] affords exclusively *N*-acetylindole, probably *via* the indolyl anion (section 17.4). Trifluoroacetic anhydride, being much more reactive, acylates at room temperature, in DMF at C-3, but in dichloromethane at nitrogen.[20]

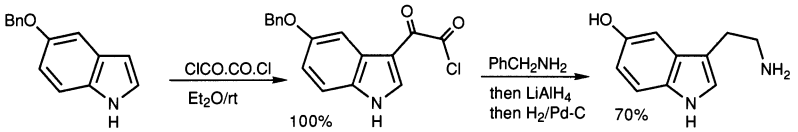


N-Acylindoles are much more readily hydrolysed that ordinary amides, aqueous sodium hydroxide at room temperature being sufficient: this lability is due in part to a much weaker mesomeric interaction of the nitrogen and carbonyl groups, making the latter more electrophilic, and in part to the relative stability of the indolyl anion, which makes it a better leaving group than amide anion.

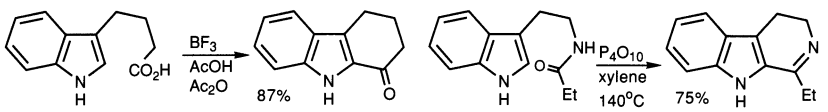
The Vilsmeier reaction is the most efficient route to 3-formylindoles[21] and to other 3-acylindoles using other amides in place of dimethylformamide.[22] Even indoles carrying an electron-withdrawing group at the 2-position, for example ethyl indole-2-carboxylate, undergo smooth Vilsmeier β-formylation.[23]



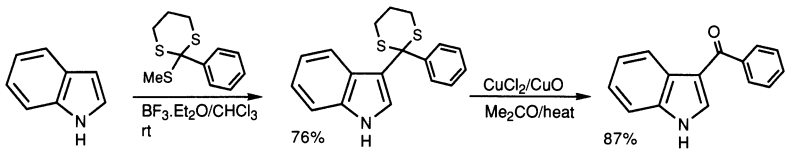
A particularly useful and high-yielding reaction is that between indole and oxalyl chloride, which gives a ketone-acid chloride convertible into a range of compounds, for example tryptamines; a synthesis of serotonin utilised this reaction.[24]



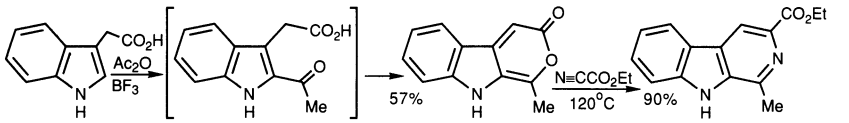
Indoles, with a side-chain acid located at C-3, undergo cyclising acylation forming indole α-ketones.[25] Interestingly, intramolecular Vilsmeier processes lead to the imine, rather than a ketone, as the final product; the cyclic nature of the imine favours its retention rather than hydrolysis to amine plus ketone.[26]



The employment of 1,1-dialkoxycarbenium salts[27] or 1,1,1-trialkylthioalkanes with boron trifluoride[28] are alternative means for increasing the reactivity of 'acylating' agents.

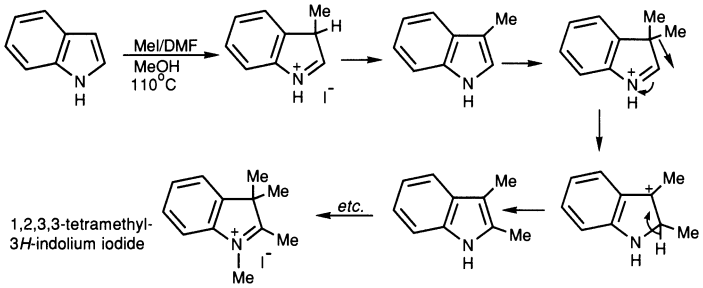


Acylation of 3-substituted indoles is more difficult: 2-acetylation can be effected with the aid of boron trifluoride catalysis.[25] When the 3-substituent is an acetic acid moiety, a subsequent enol-lactonisation produces an indole fused to a 2-pyrone; these can be hydrolysed to the keto-acid, or the diene character of the 2-pyrone (section 8.2.2.4) utilised.[29]

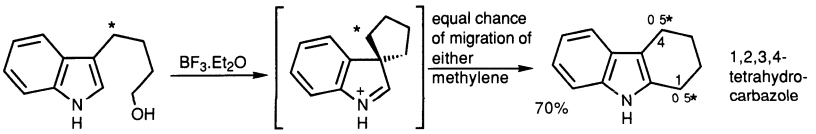


17.1.6 Alkylation

Indoles do not react with alkyl halides at room temperature. Indole itself begins to react with iodomethane in DMF at about 80°C, when the main product is skatole (3-methylindole). As the temperature is raised, further methylation occurs until eventually 1,2,3,3-tetramethyl-3*H*-indolium iodide is formed. More reactive alkylating electrophiles react at correspondingly lower temperature, dimethylallyl bromide, for example, at room temperature.[30]

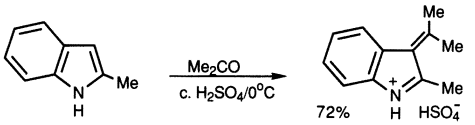


The rearrangement of 3,3-dialkyl-3*H*-indolium ions by alkyl migration to give 2,3-dialkylindoles, as shown in the sequence above, is related mechanistically to the Wagner-Meerwein rearrangement, and is known as the Plancher rearrangement.[31] It is likely that most instances of 2-alkylation of 3-substituted-indoles by cationic reagents proceed by this route, and this was neatly verified in the formation of 1,2,3,4-tetrahydrocarbazole by boron trifluoride-catalysed cyclisation of 4-(indol-3-yl)butan-1-ol. The experiment was conducted with material labelled at the benzylic carbon. The consequence of the rearrangement of the symmetrical spirocyclic intermediate, which results from attack at C-3, was the equal distribution of the label betweeen the C-1 and C-4 carbons of the product.[32] It is important to note that further experiments demonstrated that direct attack at C-2 can and does occur,[33] especially when this position is further activated by a 6-methoxyl group.[34]

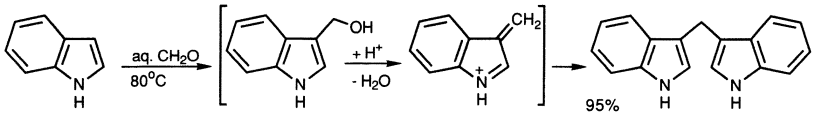


17.1.7 Reactions with aldehydes and ketones

Indoles react with aldehydes and ketones under acid catalysis – the initial products, indol-3-ylcarbinols are never isolated, for in the acidic conditions they dehydrate to 3-alkylidene-3*H*-indolium cations; those from aromatic aldehydes have been isolated in some cases;[35] reaction of 2-methylindole with acetone under anhydrous conditions gives the simplest isolable salt of this class.[36] Reaction with 4-dimethylaminobenzaldehyde (the Ehrlich reaction, see section 13.1.7) gives a mesomeric and highly coloured cation.

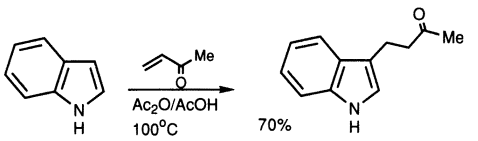


3-Alkylidene-3*H*-indolium cations are themselves electrophiles and react with more of the indole, as illustrated for reaction with formaldehyde.[37] Cyclic ketones react with 1,2-dimethylindole producing 3-cycloalkenylindoles.[38]

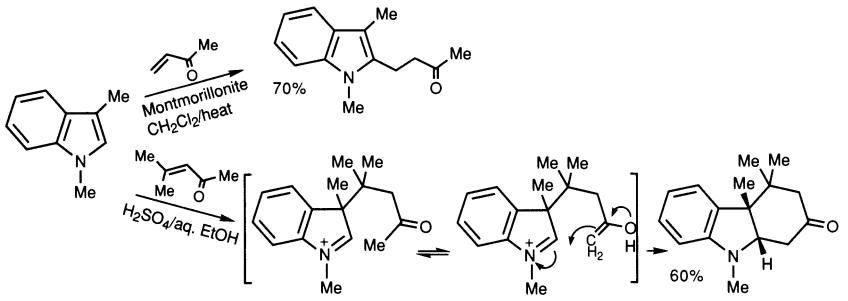


17.1.8 Reactions with α,β-unsaturated ketones, -nitriles and -nitro-compounds

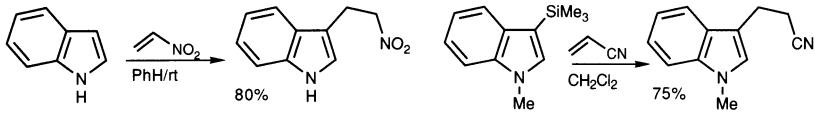
Such reactions are usually effected using acid, for catalysis, and can be looked on as an extension of the reactions discussed in 17.1.7 above. In the simplest example indole reacts with methyl vinyl ketone in a conjugate fashion.[39]



The use of montmorillonite clay, a very efficient 'acidic' catalyst, allows α-alkylation of β-substituted indoles.[40] This efficient catalysis contrasts with the different, but very instructive, reaction pathway followed when mesityl oxide and 1,3-dimethylindole are combined in the presence of sulfuric acid.[41]

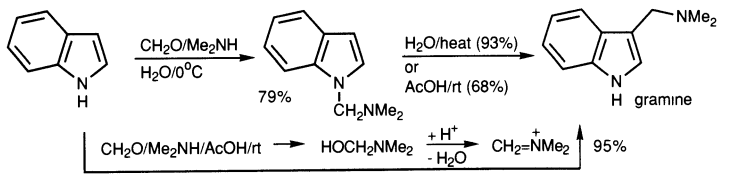


Nitroethene is sufficiently electrophilic to substitute indole without the need for acid catalysis;[42] the employment of 2-dimethylamino-1-nitroethene in trifluoroacetic acid leads to an indol-3-ylnitroethene – the reactive species is the protonated enamine and the process is similar to a Mannich condensation (section 17.1.9).[43] The use of 3-trimethylsilylindoles, with *ipso* substitution of the silane,[44] is an alternative means for effecting alkylation avoiding the need for acid catalysis.



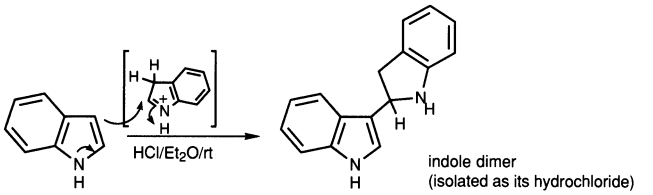
17.1.9 Reactions with immonium ions: the Mannich reaction[45]

Under neutral conditions and at low temperature indole reacts with a mixture of formaldehyde and dimethylamine by substitution at the indole nitrogen;[46] it seems likely that this reaction involves a low equilibrium concentration of the indolyl anion. In neutral solution at higher temperature or in acetic acid, conversion into the thermodynamically more stable, 3-substituted product, gramine, takes place. Gramine is formed directly, smoothly and in high yield, by reaction in acetic acid.[47] The Mannich reaction is very useful in synthesis because not only can the electrophilic immonium ion be varied widely, but the product gramines are themselves intermediates for further manipulation (section 17.12).



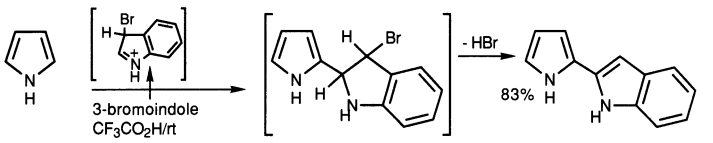
The immonium ion electrophile can be synthesised separately, as a crystalline solid known as 'Eschenmoser's salt' ($Me_2N^+{=}CH_2\ I^-$).[48] With this extremely reactive electrophile the reaction is normally carried out in a non-polar solvent. Examples which illustrate the variation in immonium ion structure that can be

tolerated include the reaction of indole with pyrimidine,[49] and the acid-catalysed dimerisation of indole.[50] In the former example protonated pyrimidine is the electrophile, in the latter indole is attacked by *protonated* indole!

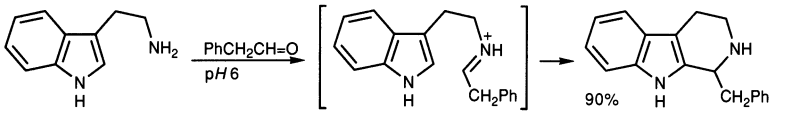


Skatole is converted into an α,α′-linked dimer in acid; 2-methylindole, in contrast, is not susceptible to acid-catalysed dimerisation, reflecting the lower electrophilic character of the 3-protonated 2-substituted 3*H*-indolium cation, much as ketones are less reactive than aldehydes.

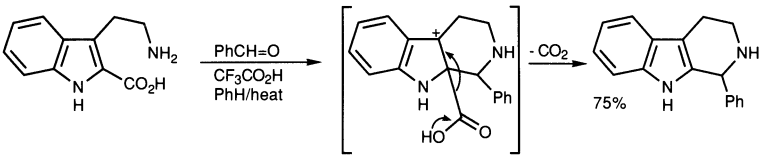
When protonated 3-bromoindole is employed as electrophile, a final elimination of hydrogen bromide gives rise to rearomatised 2-substituted indoles; pyrrole (illustrated) or indoles will take part in this type of process.[51]



Conducted in an intramolecular sense, both Mannich and Vilsmeier reactions have been much used for the construction of tetrahydro-β-carbolines[52] (dihydro-β-carbolines), such as are found in many indole alkaloids (β-carboline is the widely used, trivial name for the pyrido[3,4-*b*]indole nucleus).



There is still controversy as to whether such cyclisations proceed by direct electrophilic attack at the α-position, or whether by way of β-attack then rearrangement. It may be significant that Mannich processes, as opposed to the alkylations discussed in section 17.1.6, are reversible, which would allow a slower, direct α-substitution to provide the principal route to the α-substituted structure. It has been shown that tryptamines carrying a 2-carboxylic acid group, which can be conveniently prepared (section 17.16.2) but are not easily decarboxylated, undergo cyclising Mannich condensation with aldehydes and ketones, with loss of the carbon dioxide in a final step and under much milder conditions.[53]



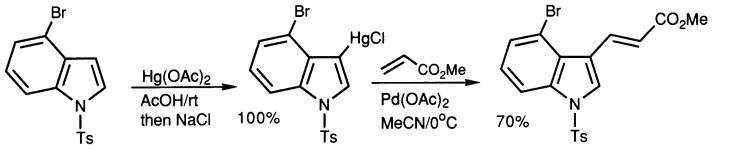
17.1.10 Diazo-coupling and nitrosation

The high reactivity of indole is shown up well by the ease with which it undergoes substitution with weakly electrophilic reagents such as benzenediazonium chloride and nitrosating agents. Indoles react rapidly with nitrous acid; indole itself reacts in a complex manner, but 2-methylindole gives a 3-nitroso-product cleanly. This can also be obtained by a base-catalysed process using amyl nitrite as a source of the nitroso group; these basic conditions also allow clean 3-nitrosation of indole itself. 3-Nitrosoindoles exist predominantly in the oximino tautomeric form.[54] Skatole and other 3-substituted indoles give relatively stable *N*-nitroso products with nitrous acid,[55] consistent with kinetic studies on 2-methylindole which show that *N*-substitution precedes *C*-substitution. *N*-Nitrosoindoles may be produced from indoles, following ingestion – such compounds may be mutagenic.

17.1.11 Electrophilic metallation

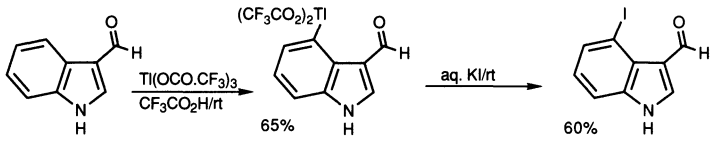
17.1.11.1 *Mercuration*

Indole reacts readily with mercuric acetate at room temperature to give a 1,3-disubstituted product.[56] Even *N*-acylindoles are substituted under mild conditions; the 3-mercurated compounds thus produced are useful in palladium-catalysed couplings.[57]



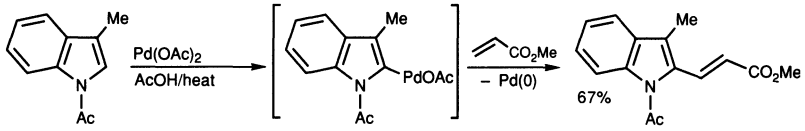
17.1.11.2 *Thallation*

Thallium trifluoroacetate reacts rapidly with simple indoles, but well-defined products cannot be isolated. 3-Acylindoles, however, undergo a very selective substitution at C-4, due to chelation and protection of the heterocyclic ring by the electron-withdrawing 3-substituent.[58] The products are good intermediates for the preparation of 4-substituted indoles, for example 4-iodo- and thence 4-alkoxy-, alkenyl[59] and methoxycarbonyl,[60] *via* palladium-mediated couplings. The regiochemistry is neatly complemented by thallation of *N*-acetylindoline, which goes to C-7, allowing introduction of substituents at this carbon[61] (cf. sections 17.16.1.8 and 17.8).



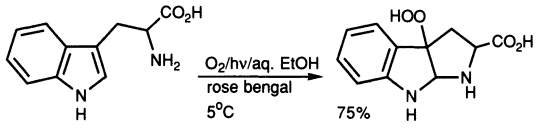
17.1.11.3 *Palladation*

Even indoles bearing acyl or phenylsulfonyl substituents on nitrogen are easily palladated at moderate temperatures, substitution occuring at C-3, or at the 2-position if C-3 is occupied. The metallated products are seldom isolated but allowed to react with acrylates, other alkenes (Heck reaction) or carbon monoxide[62] *in situ*.[63] Although electrophilic palladation normally requires one equivalent of palladium(2), the incorporation of reoxidants selective for Pd(0), such as *t*-butyl perbenzoate or copper(2), allows a catalytic conversion to be carried out.[64]

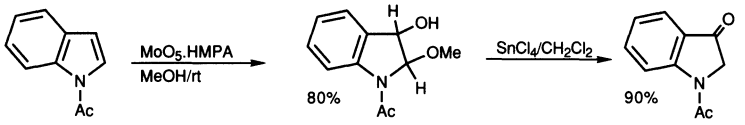


17.2 REACTIONS WITH OXIDISING AGENTS

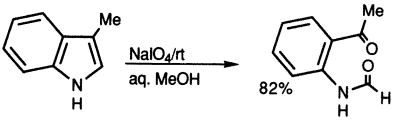
Autoxidation occurs readily with alkyl indoles; thus for example, 2,3-diethylindole gives an isolable 3-hydroperoxy-3*H*-indole. Generally such processes give more complex product mixtures resulting from further breakdown of the hydroperoxide; singlet oxygen also produces hydroperoxides, but by a different mechanism. If the indole carries a side-chain capable of trapping the indolenine by intramolecular nucleophilic addition, then tricyclic hydroperoxides can be isolated.[65]



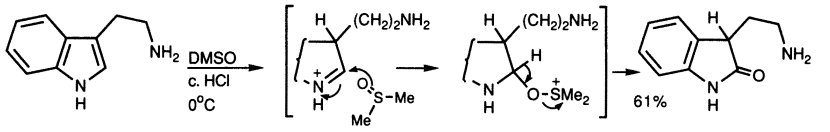
The reagent MoO_5.HMPA, known as 'MoOPH', in methanol, brings about addition of the elements of methyl hydrogen peroxide to an *N*-acylindole, and these adducts in turn can be utilised: one application is to induce loss of methanol, and thus the overall transformation of an indole into an indoxyl.[66]



Oxidative cleavage of the indole 2,3-double bond has been achieved with ozone, sodium periodate,[67] potassium superoxide,[68] with oxygen in the presence of cuprous chloride,[69] and with oxygen photochemically in ethanolic solution;[70] irradiation in an organic acid as solvent leads to oxidation at 2- and 3-alkyl groups.[70,71]

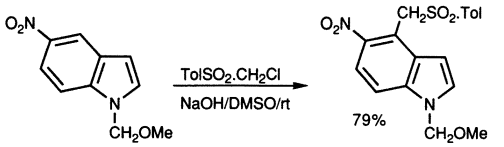


The conversion of 3-substituted indoles into their corresponding oxindoles can be brought about by reaction with DMSO in acid.[72]

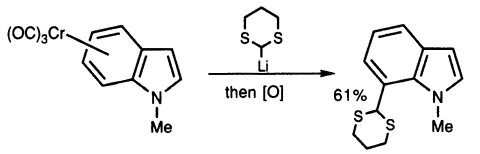


17.3 REACTIONS WITH NUCLEOPHILIC REAGENTS

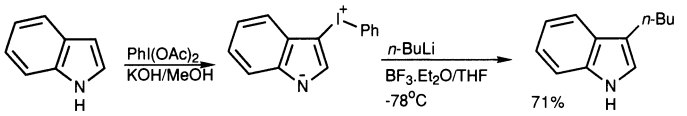
As with pyrroles and furans, indoles undergo very few nucleophilic substitution processes. Those that are known involve special situations: benzene-ring-nitro-indoles, in which the *N*-hydrogen has been removed as well, undergo the process known as **V**icarious **N**ucleophilic **S**ubstitution (VNS).[73]



In chromium carbonyl complexes of indole, the metal is associated with the benzene ring, hence nucleophilic additions take place in that ring, usually at C-4; in the example shown the relatively unusual attack at C-7 can be induced to revert to the usual C-4 if an indole with a bulky *N*-protecting group is utilised.[74]



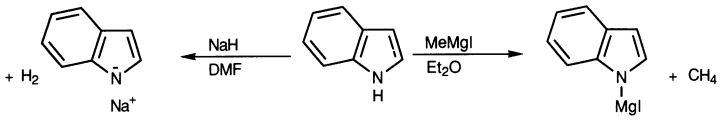
The overall nucleophilic displacement reactions of indole-3-iodonium salts (**CAUTION**: explosive) probably proceed by initial addition of the nucleophile to the iodine.[75]



17.4 REACTIONS WITH BASES

17.4.1 Deprotonation of *N*-hydrogen

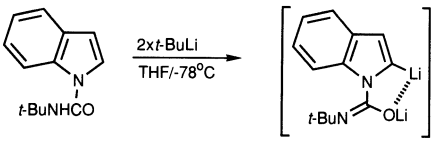
As in pyrroles, the *N*-hydrogen in indoles is much more acidic (pK_a 16.2) than that of an aromatic amine, say aniline (pK_a 30.7). Any very strong base will effect complete conversion of an *N*-unsubstituted indole into the corresponding indolyl anion, amongst the most convenient being sodium hydride, *n*-butyllithium, or an alkyl Grignard reagent.



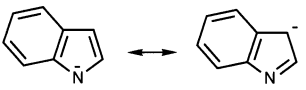
Electron-withdrawing substituents, particularly at the β-position, increase the acidity markedly, for example 3-formylindole is about 5 pK_a units more acidic than indole and the α-isomer is some 3 units more acidic.[76]

17.4.2 Deprotonation of *C*-hydrogen

Deprotonation of *C*-hydrogen in indoles requires the absence of the much more acidic *N*-hydrogen, i.e. the presence of an *N*-substituent like methyl[77] or if required, a removable group: phenylsulfonyl,[78] lithium carboxylate[79] and *t*-butoxycarbonyl[80] have been used widely; dialkylaminomethyl,[81] trimethylsilylethoxymethyl[82] and methoxymethoxy[83] have also been recommended; clearly, in the last case, the *N*-substituent cannot be introduced into an indole – it requires a preformed 1-hydroxyindole – but it is possible to reduce it off to leave an *N*-hydrogen-indole. *t*-Butylaminocarbonyl[84] and methoxymethoxy are said to be the optimal protecting/activating groups. Each of these removable substituents assists lithiation by intramolecular chelation and in some cases by electron withdrawal, reinforcing the intrinsic tendency for metallation to proceed at the α-position.

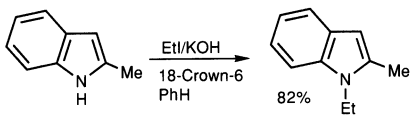


17.5 REACTIONS OF *N*-METALLATED INDOLES

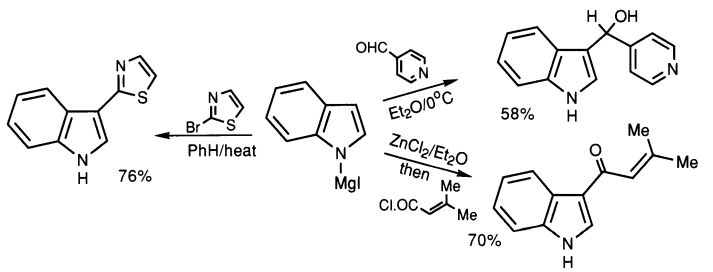


The indolyl anion has two main mesomeric structures showing the negative charge to reside mainly on nitrogen and the β-carbon. In its reactions, then, this anion behaves as an ambident nucleophile; the ratio of *N*- to β-substitution with electrophiles depends on the associated metal, the polarity of the solvent, and the nature of the electrophile. Generally, the more ionic sodio- and potassio-derivatives tend to react at nitrogen, whereas magnesio-derivatives have a greater tendency to react at C-3.[85] However, reaction of indolyl Grignards in HMPA leads to more attack at nitrogen, whereas non-polar solvents favour attack at carbon.[86] Complimentarily, more reactive electrophiles show a greater tendency to react at nitrogen than less electrophilic species.

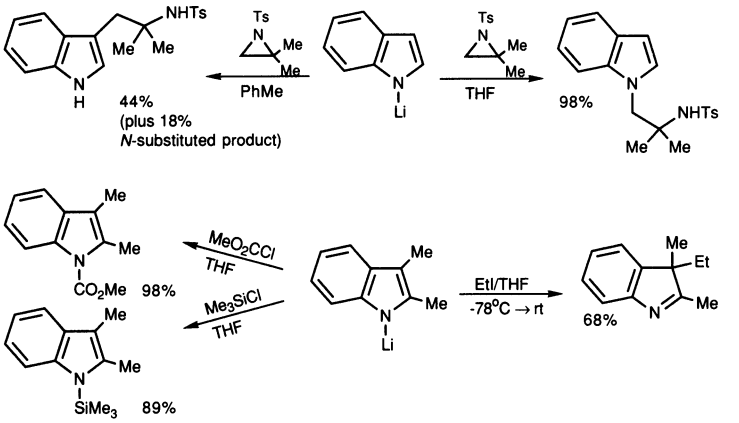
N-Alkylation of indoles can utilise indol-1-ylsodiums,[87] generated quantitatively as above, or it can involve a small concentration of an indolyl anion, produced by phase-transfer methods;[88] indole *N*-acylation[89] and -arylsulfonylation[90] can also be achieved efficiently using phase-transfer methodology (see also section 17.1.4).



Indolyl *N*-Grignards[91] or, even better, their zinc equivalents[92] undergo reaction predominantly at C-3 with a variety of carbon electrophiles such as aldehydes, ketones and acid halides, and even 2-bromothiazole.[93]



1-Lithioindoles are equally useful; again, the position of attack depends on both solvent and the nature of the electrophile, as illustrated below.[94]

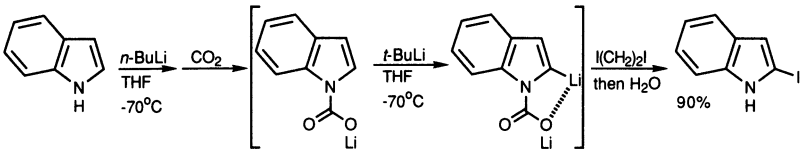


It is important to note that when an *N*-metallated 3-substituted indole alkylates at carbon, necessarily a 3,3-disubstituted-3*H*-indole (an indolenine) is formed, which cannot rearomatise to form an indole (see section 17.1.6 for rearrangements of 3,3-disubstituted indolenines).

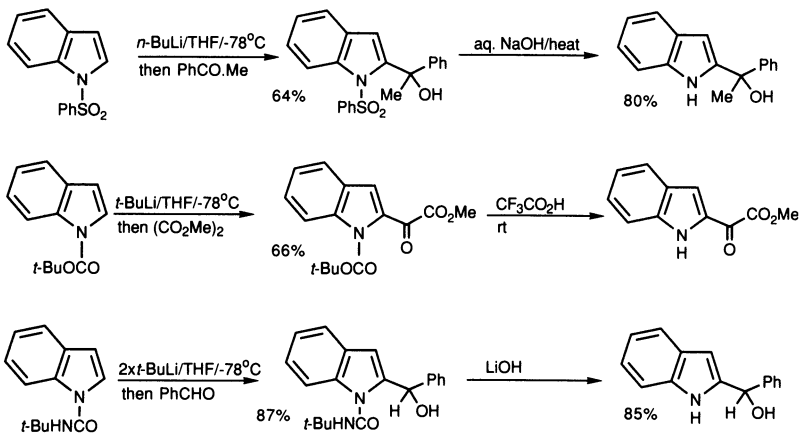
17.6 REACTIONS OF *C*-METALLATED INDOLES

17.6.1 Lithio derivatives

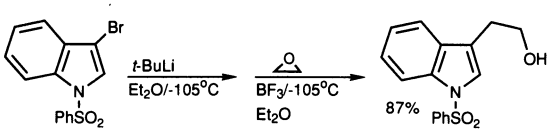
One of the most convenient *N*-protecting groups to be used in indole α-lithiations is carbon dioxide[79] because the *N*-protecting group is installed *in situ* and, further, falls off during normal work-up. This technique has been used to prepare 2-haloindoles[16] and to introduce a variety of substituents by reaction with appropriate electrophiles – aldehydes, ketones, chloroformates, etc.



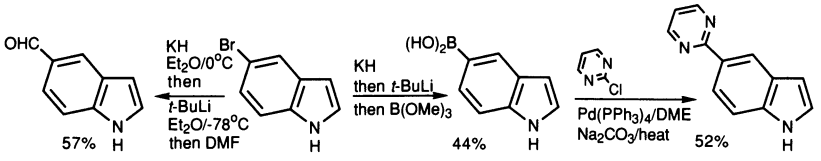
Given below is a selection of α-substitutions achieved with various *N*-blocking/activating groups.[77–84,95]



3-Lithioindoles can be prepared by halogen exchange[96] of 3-halo-*N*-phenylsulfonylindoles; the temperature must be kept low to prevent isomerisation to the more stable 2-lithio species; hetero-ring opening and production of an alkyne, with the nitrogen anion acting as a leaving group, surprisingly is not a problem at the temperatures normally utilised[97,98] (cf. section 18.3). 3-Lithiation with replacement of a 3-hydrogen has also been accomplished with '*ortho*' assistance from a 2-(2-pyridyl)[98] or a 2-carboxyl group.[99]

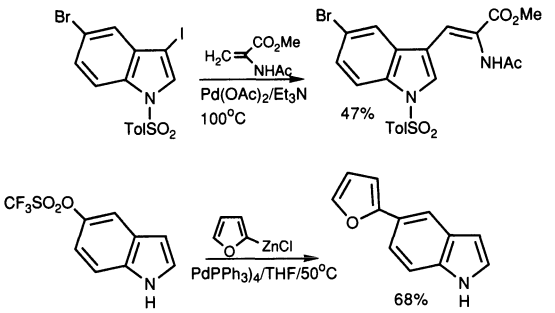


Amazingly, metal–halogen exchange can be achieved with 5-bromoindole without *N*-protection; the indole is first converted into its *N*-potassio-salt.[100]



17.6.2 Palladium-catalysed reactions

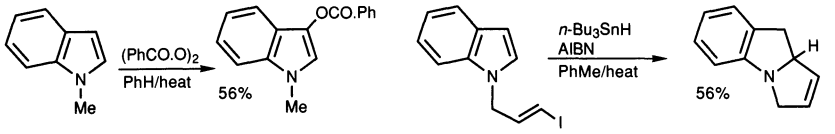
Bromo- and iodoindoles, and the similarly reactive triflates, undergo palladium-catalysed couplings as normal aryl halides. Since 2- and 3-haloindoles are unstable it is expedient to employ their *N*-acyl derivatives.[101]



When an organometallic derivative of indole is required for a coupling reaction, boronic acids are to be preferred,[102] although some zinc derivatives can be used.

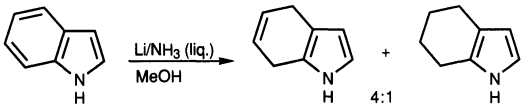
17.7 REACTIONS WITH RADICALS

The small amount of work reported on the reactions of radicals with indoles makes clear that they are not regioselective, and consequently of little synthetic value. For example, exposure to benzyl radicals gives a complex mixture resulting from attack on the heterocyclic ring, whereas hydroxylation gives mixtures resulting from attack on the benzene ring. However, benzoyloxylation of indoles having no *N*-hydrogen gives benzoates of indoxyl,[103] i.e. it effectively oxidises the indole heterocyclic ring. Some selective, intramolecular reactions have been carried out[104] and hetero-ring methyls can be halogenated.[105]

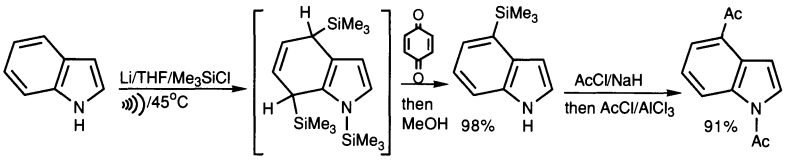


17.8 REACTIONS WITH REDUCING AGENTS

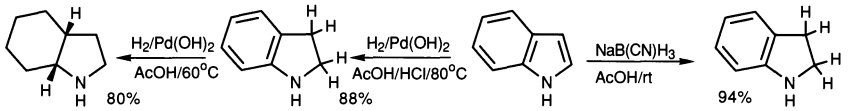
The indole ring system is not reduced by nucleophilic reducing agents such as lithium aluminium hydride and sodium borohydride; lithium/liquid ammonia does however reduce the benzene ring; 4,7-dihydroindole is the main product.[106]



Reduction with lithium in the presence of trimethylsilyl chloride, followed by rearomatisation, produces 4-trimethylsilylindole, an intermediate useful for the synthesis of 4-substituted indoles *via* electrophilic *ipso* replacement of silicon.[107]

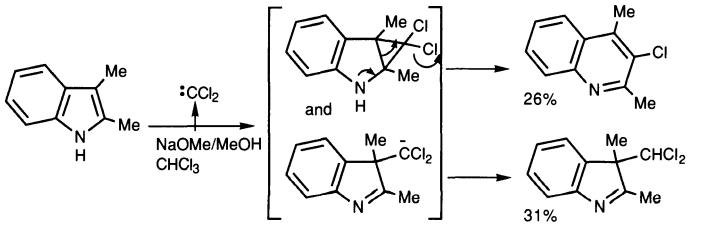


Reduction of the heterocyclic ring is readily achieved under acidic conditions; formerly, metal–acid combinations[108] were used, but now much milder conditions employ relatively acid-stable metal hydrides such as sodium cyanoborohydride. Triethylsilane in trifluoroacetic acid is another convenient combination; 2,3-disubstituted indoles give *cis* indolines by this method.[109] Such reductions proceed by hydride attack on the β-protonated indole – the 3*H*-indolium cation.[110] Catalytic reduction of indole, again in acid solution, produces indoline initially, further slower reduction completing the saturation.[111]

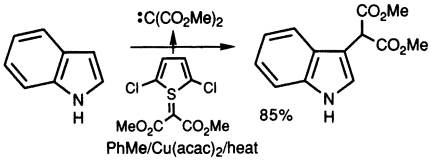


17.9 REACTIONS WITH CARBENES

No isolable cyclopropane-containing products have been obtained by the reaction of indoles with carbenes (cf. section 13.10) but a dichlorocyclopropane is believed to be an intermediate in the pathway which leads from 2,3-dimethylindole to 3-chloro-2,4-dimethylquinoline; the second product arises *via* nucleophilic attack by the indolyl anion on the electrophilic dichlorocarbene.[112] In the comparable reaction of indole itself, only the second pathway operates and 3-formylindole, the hydrolysis product of the 3-dichloromethyl-substituted heterocycle, is isolated.

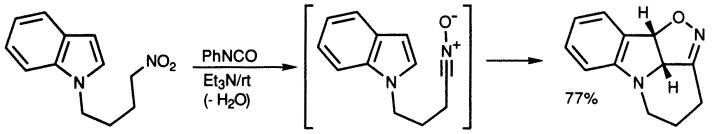


Methoxycarbonyl-substituted carbenes also give rise only to a substitution product.[113]

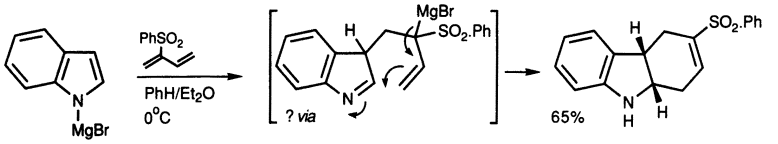


17.10 ELECTROCYCLIC AND PHOTOCHEMICAL REACTIONS

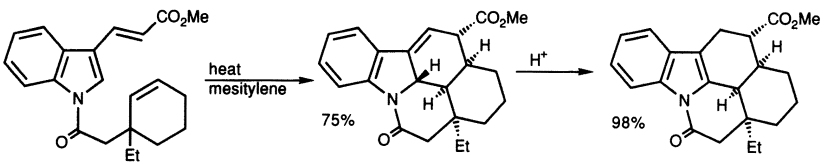
The heterocyclic double bond in simple indoles will take part in cycloaddition reactions with dipolar 4π components,[114] and with electron-deficient dienes (i.e. inverse electron demand), in most reported cases, held close using a tether;[115] a comparable effect is seen in the intermolecular cycloaddition of 2,3-cycloalkyl indoles to *ortho*-quinone generating a 1,4-dioxan.[116] The introduction of electron-withdrawing substituents enhances the tendency for cycloaddition to electron-rich dienes: 3-acetyl-1-phenylsulfonylindole, for example, undergoes aluminium chloride-catalysed cycloaddition with isoprene.[117]



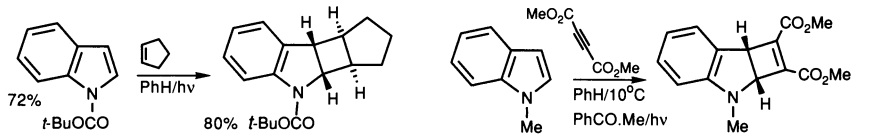
Some other apparent cycloadditions probably proceed by non-concerted pathways; for example, addition of 1,3-cyclohexadiene in the presence of light and 2,4,6-triphenylpyrylium probably involves radical intermediates,[118] and reactions of 2-phenylsulfonyl-dienes with indolyl Grignard reagents probably proceed in stepwise fashion.[119]



Both 2- and 3-vinylindoles take part quite readily as 4π components in Diels-Alder cycloadditions; often, but not always,[120] these employ *N*-acyl- or *N*-arylsulfonylindoles, in which the interaction between nitrogen lone pair and π-system has been reduced.[121] The example below shows how this process can be utilised in the rapid construction of a complex pentacyclic indole.[122]

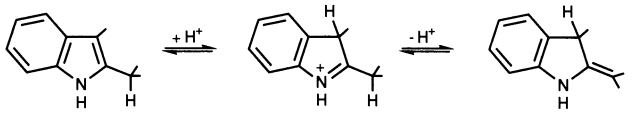


N-Methylindoles add dimethyl acetylenedicarboxylate, generating cyclobutenofused products,[123] and even simple alkenes add in an apparent 2 + 2 fashion to *N*-acylindoles, but the mechanism probably involves radical intermediates.[124] Other photochemical additions, to form *N*-benzoylindolines fused to four-membered rings, include addition to the carbonyl group in benzophenone, and to the double bond in methyl acrylate.[125]

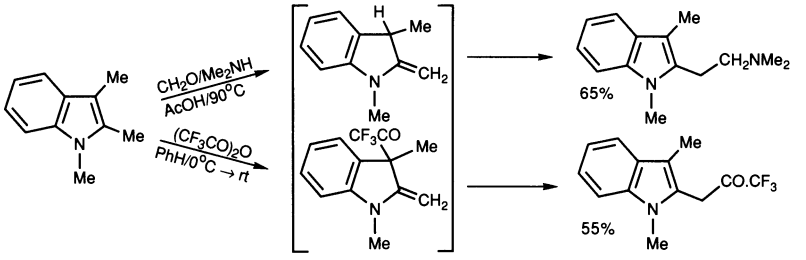


17.11 ALKYLINDOLES

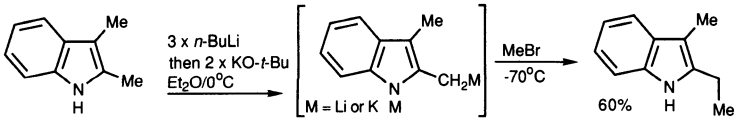
Only alkyl groups at indole α-positions show any special reactions. Many related observations confirm that, in a series of equilibria, β-protonation can lead to 2-alkylidene-indolines, and hence reactivity towards electrophiles at an α-, but not a β-alkyl group; for example, in DCl at 100°C 2,3-dimethylindole exchanges H for D only at the 2-methyl.



This same phenomenon is seen in Mannich condensation[126] and trifluoroacetylation[127] of 1,2,3-trimethylindole at the α-methyl.

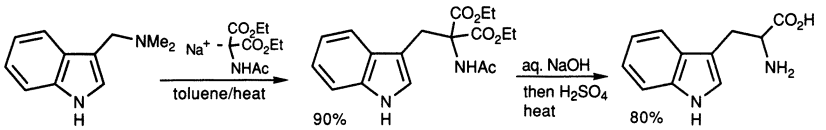


Side-chain lithiation is again specific for an α-substituent, first achieved *via* an *N*-lithium carboxylate[128] and subsequently even without *N*-protection.[129]

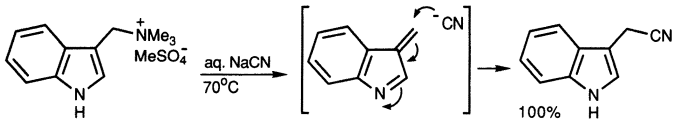


17.12 REACTIONS OF INDOLYL-C-X COMPOUNDS

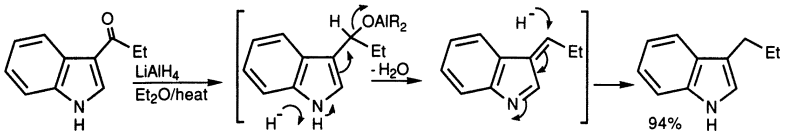
Gramine and, especially, its quaternary salts are very useful synthetic intermediates in that they are easily prepared and the dimethylamino group is easily displaced by nucleophiles – reactions with cyanide[130] and acetamidomalonate[131] anions are typical.



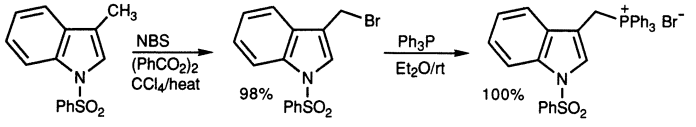
The easy displacement of the amine (ammonium) group proceeds by way of an elimination, involving loss of the indole hydrogen, and thus the intermediacy of a β-alkylidene-indolenine which then readily adds the nucleophile, regenerating the indole. This mechanism has been verified by observing (i) very much slower displacement with a corresponding 1-methylgramine, and (ii) racemisation on displacement using a substituted gramine in which the nitrogen-bearing carbon was a chiral centre.[132]



A related sequence is involved in the lithium aluminium hydride reduction of indol-3-ylcarbinols (which can be obtained from the corresponding ketones using milder reducing agents) with formation of the alkylindole. This constitutes a useful synthesis of 3-alkylindoles.[133]



Although haloalkylindoles are generally unstable and not synthetically useful, *N*-acylated derivatives are much more stable, can be prepared by side-chain radical substitution, and can be utilised in nucleophilic substitution processes.[134]



17.13 INDOLE CARBOXYLIC ACIDS

Both indole-3-carboxylic[135] and indol-2-ylacetic acids are easily decarboxylated in boiling water. In each case carbon dioxide is lost from a small concentration of β-protonated 3*H*-indolium cation, the loss, in each case, being analogous to the decarboxylation of a β-keto-acid.

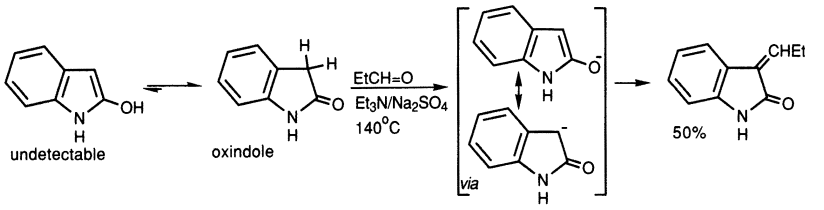
Indole-2-carboxylic acids can only be decarboxylated by heating in mineral acid or in the presence of copper salts.[136]

17.14 OXYINDOLES

Indoles with a hydroxy group on the benzene ring behave like normal phenols; indoles with an oxygen at either of the heterocyclic ring positions are quite different.

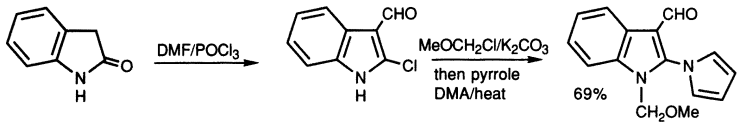
17.14.1 Oxindole

2-Hydroxyindole does not exist as such: the stable form is the carbonyl tautomer; the hydroxy tautomer cannot be detected. There is nothing remarkable about the reactions of oxindole: for the most part it is a typical 5-membered lactam, except that deprotonation at the β-carbon (pK_a ~ 18) occurs more readily than with simple amides, because the resulting anion is stabilised by an aromatic indole canonical contributor. This anion will react with electrophiles like alkyl halides and aldehydes[137] at the β-carbon, the last with dehydration and the production of aldol condensation products. It is interesting that the 3-position is three times more reactive than the 1-position.[138] Oxindoles can be effectively oxidised to isatins (section 17.14.3) *via* easy 3,3-dibromination, then hydrolysis.[139]



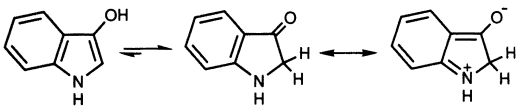
The interaction of oxindole with the Vilsmeier reagent produces 2-chloro-3-formylindole efficiently;[140] this difunctional indole has considerable potential

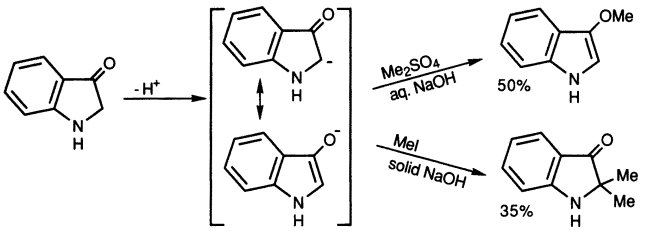
for elaboration; for example, nucleophilic displacement of the halogen, activated by the *ortho* aldehyde, can produce indoles carrying a nitrogen substituent at C-2.[141]



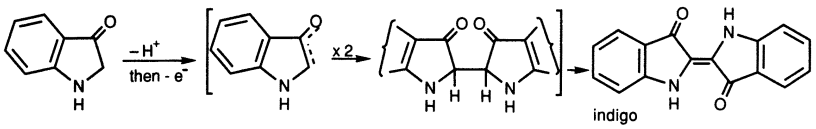
17.14.2 Indoxyl[142]

3-Hydroxyindole certainly contributes in the tautomeric equilibrium with the carbonyl form, though it is the minor component. Indoxyl, pK_a 10.46,[143] is more acidic than oxindole, the anion produced is ambident; reactions with electrophiles at both oxygen and carbon are known.[144]

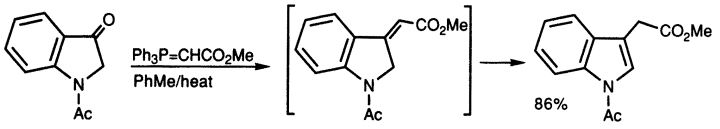




The indoxyl anion is particularly easily autoxidised producing the ancient blue dye, indigo. The mechanism probably involves dimerisation of a radical formed by loss of an electron from the anion.

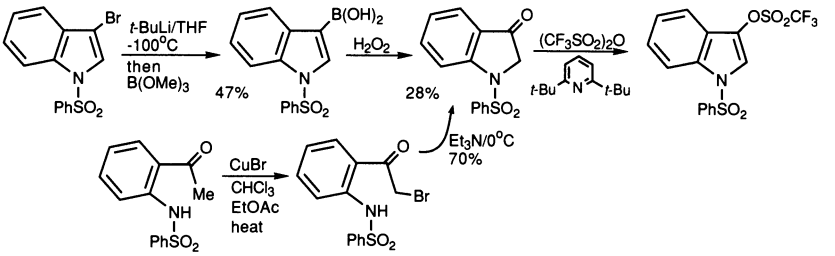


O-Acetylindoxyl[145] and *N*-acylindoxyls are more stable substances; the latter undergo normal ketone–carbonyl reactions, such as the Wittig reaction.[146]



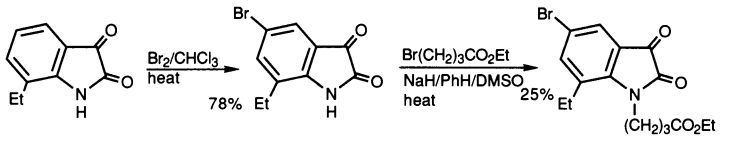
Mirroring oxindoles, aldol-type condensation at the 2-position in indoxyls can be accomplished either using the acetate of the enol form and base catalysis,[147] or with indoxyl itself, in either acid or basic conditions.[148] Borohydride reduction and dehydration allows these alkylidene condensation products to be converted into 2-substituted indoles.

Peroxide oxidation of *N*-phenylsulfonylindole-3-boronic acid gives *N*-phenylsulfonylindoxyl, which can be converted into the triflate of the 3-hydroxyindole tautomer,[149] and this in turn utilised in palladium-catalysed cross-coupling processes.[150] The same *N*-protected indoxyl can be prepared by ring synthesis.



17.14.3 Isatin[151]

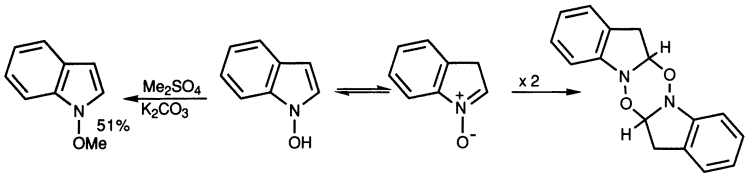
Isatin is a stable, bright orange solid which is commercially available in large quantities. Because it readily undergoes clean aromatic substitution reactions at C-5, *N*-alkylation *via* an anion, and ketonic reactions at the C-3-carbonyl group, it is a very useful intermediate for the synthesis of indoles and other heterocycles.



Reduction of isatins to afford oxindoles can be achieved by catalytic reduction in acid,[152] or by the Wolff-Kischner process.[153] 3-Substituted indoles result from Grignard addition at the ketone carbonyl, followed by lithium aluminium hydride reduction of the residual amide, then dehydration.[154]

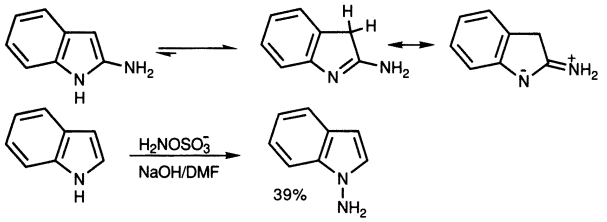
17.14.4 1-Hydroxyindole

1-Hydroxyindole can be prepared in solution, but attempted purification leads to dimerisation *via* its nitrone tautomer; however, *O*-alkyl derivatives can be formed easily and are stable.[155]



17.15 AMINOINDOLES

2-Aminoindole exists mainly as the 3*H*-tautomer, presumably because of the advantages conveyed by amidine-type resonance. 3-Aminoindole is very unstable, and easily autoxidised.[156] 1-Aminoindoles can be prepared by direct amination.[157]



17.16 SYNTHESIS OF INDOLES

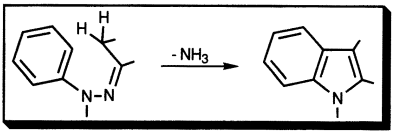
17.16.1 Ring synthesis

Indoles are usually prepared from non-heterocyclic precursors by cyclisation reactions on suitably substituted benzenes; they can also be prepared from pyrroles by construction of the homocyclic aromatic ring, and from indolines by dehydrogenation.

Because of the importance of indoles in natural products synthesis and pharmaceuticals, a large number of new routes to indoles and improvements of older reactions have been developed since the last edition of this book. This section discusses the most important methods, often those which have been used most frequently and are the most adaptable.[158] Five generally important approaches to indoles are summarised in this section.

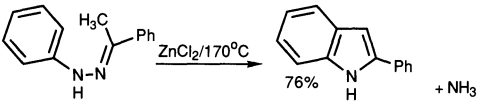
17.16.1.1 *From phenylhydrazones of aldehydes and ketones*

Still the most widely used route, the Fischer synthesis consists of heating a phenylhydrazone, usually with acid, sometimes in an inert solvent; ammonia is lost and an indole formed.



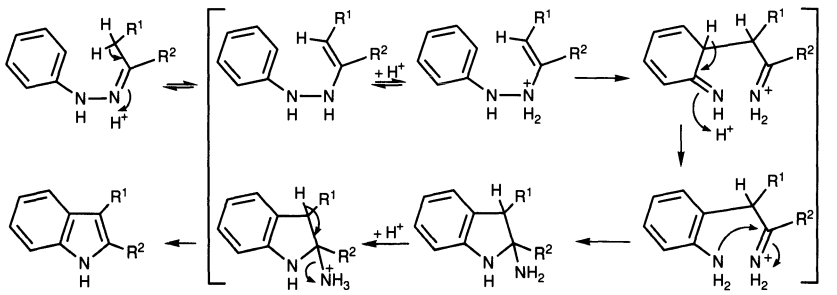
The Fischer synthesis

The Fischer synthesis,[159] first discovered in 1883, involves the acid- or Lewis acid-catalysed rearrangement of a phenylhydrazone with the elimination of ammonia. The preparation of 2-phenylindole illustrates the process in its simplest form.[160]



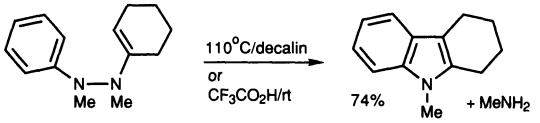
In many instances the reaction can be carried out simply by heating together the aldehyde or ketone and phenylhydrazine in acetic acid;[161] the formation of the phenylhydrazone and its subsequent rearrangement take place without the necessity for isolation of the phenylhydrazone. Toluenesulfonic acid, cation exchange resins, and phosphorus trichloride have each been recommended for efficient cyclisations, sometimes even at or below room temperature.[162] Electron-releasing substituents on the benzene ring increase the rate of Fischer cyclisation whereas electron-withdrawing substituents slow the process down,[163] though even phenylhydrazones carrying nitro-groups can be indolised satisfactorily with appropriate choice of acid and conditions, for example a two-phase mixture of toluene and phosphoric acid,[164] or boron trifluoride in acetic acid.[165] Electron-withdrawing substituents *meta* to the nitrogen give rise to roughly equal amounts of 4- and 6-substituted indoles; electron-releasing groups similarly oriented produce mainly the 6-substituted indole.[165]

The full mechanistic details of the multi-step Fischer sequence are still not completely sure, but there is considerable evidence that the sequence shown below operates; for example, labelling studies proved the loss of the β-nitrogen as ammonia, and in some cases intermediates have been detected by ^{13}C and ^{15}N NMR spectroscopy.[166] The most important step – the one in which a carbon–carbon bond is made – is electrocyclic in character and analogous to the Claisen rearrangement of phenyl allyl ethers.

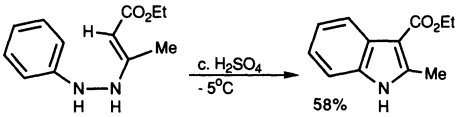


Support for this sequence also comes from the observation that in many cases indolisation can be achieved thermally, at a temperature as low as 110°C, in the special case of preformed ene-hydrazines, i.e. in which the first step of the nor-

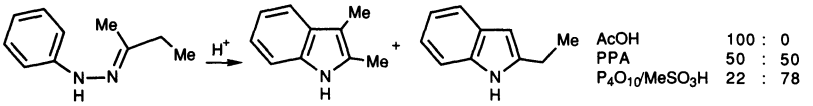
mal sequence – acid-catalysed tautomerisation of imine to enamine – has already been accomplished.[167] The reaction does however still occur more rapidly in the presence of acid and this is interpreted as protonation of the β-nitrogen, as shown, facilitating the electrocyclic step. Some normal Fischer cyclisations have been achieved thermally, but much higher temperatures are required and proton transfer from solvent (typically a glycol) is certainly involved.



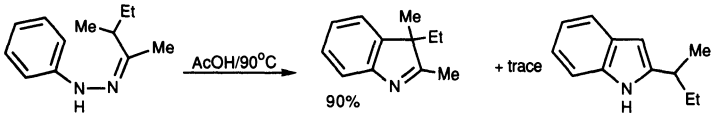
An extreme case of acid catalysis is the indolisation of phenylhydrazones of β-dicarbonyl compounds in concentrated sulfuric acid;[168] in milder acid only pyrazolones are produced from the interaction of β-keto-esters with hydrazines (section 22.12.1.1).



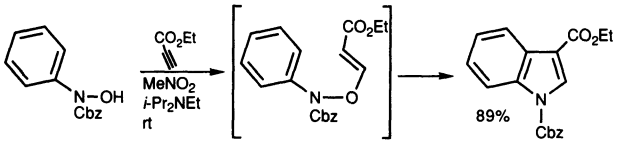
An aspect of the Fischer reaction which is of considerable practical importance is the ratio of the two possible indoles formed from unsymmetrical ketones; in many instances mixtures result because ene-hydrazine formation occurs in both directions. It appears that strongly acidic conditions favour the least substituted ene-hydrazine.[169]



Indolenines (3*H*-indoles) are formed efficiently on Fischer cyclisation of the phenylhydrazones of branched ketones; note, again, the use of a weaker acid medium to promote formation of the more substituted ene-hydrazine required for indolenine formation.[170]

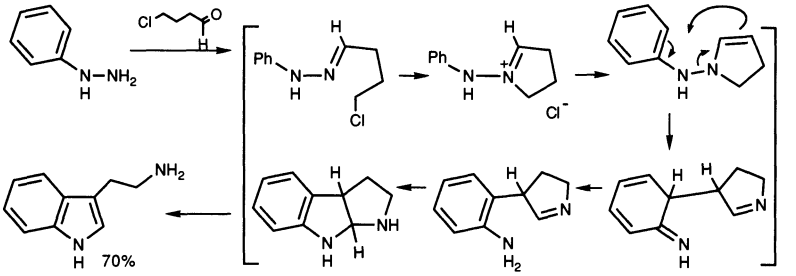


Transformations which are mechanistically analogous to the Fischer, and also produce indoles, use phenylhydroxylamines instead of phenylhydrazines.[171]



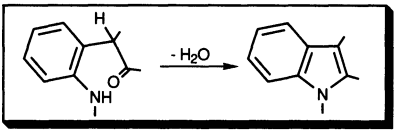
The Grandberg synthesis

An exceptionally useful adaptation is the Grandberg synthesis of tryptamines from 4-halobutanals, in which the nitrogen usually lost during the Fischer process is incorporated as the nitrogen of the aminoethyl side-chain.[172]



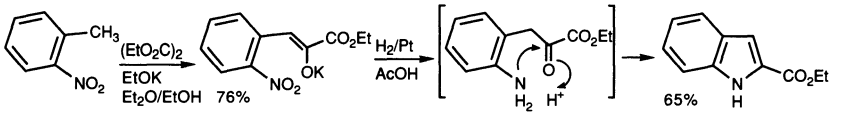
17.16.1.2 *From ortho-(2-oxoalkyl)anilines*

Cyclisation of *ortho*-(2-oxoalkyl)anilines, by simple intramolecular condensation with loss of water, occurs spontaneously. Several new ways of generating the intermediate amino-ketone have been developed; the prototype was the Reissert synthesis.



The Reissert synthesis

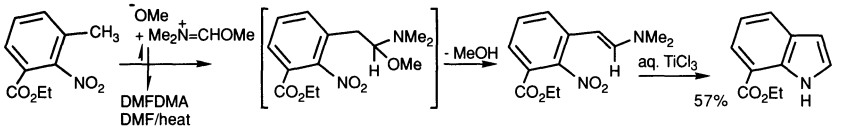
In the classical Reissert synthesis the acidity of a methyl group *ortho* to nitro on a benzene ring is the means for condensation with oxalate; the nitro group is then reduced to amino.[173]



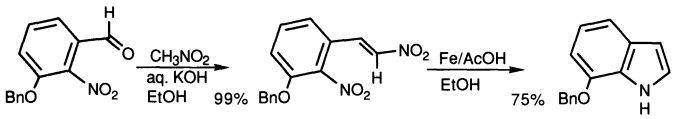
Leimgruber-Batcho synthesis

The Leimgruber-Batcho synthesis[174] is one of the most widely used new variations, which also depends on the acidity of methyl groups *ortho* to aromatic nitro (or at α or γ positions on a pyridine[175]) to allow introduction of the future indole α-carbon as an enamine. Condensation with hot dimethylformamide dimethyl acetal (DMFDMA) (no added base being necessary) leads to an enamine; subsequent reduction of the nitro group, usually in acid conditions, leads directly to the hetero-ring-unsubstituted indole. Mechanistically this, at first sight extraordinary, process is believed to involve ionisation of the reagent producing methoxide (which deprotonates the aromatic methyl) and an electrophilic component,

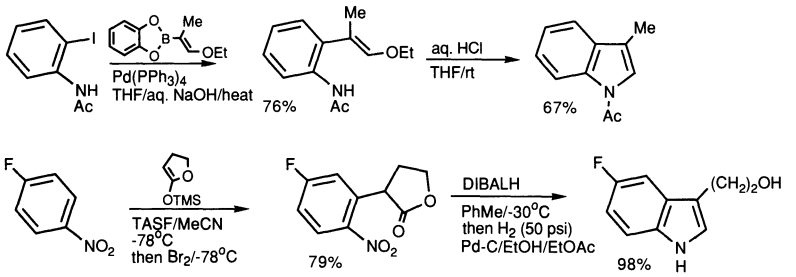
$MeOCH{=}N^{+}Me_2$, which combines with the deprotonated aromatic. Both tris(piperidin-1-yl)methane and bis(dimethylamino)-*t*-butoxymethane are said to function even better than the commercially available DMFDMA.[176] A variety of benzene substituents are tolerated and the approach has been utilised for syntheses of, amongst others, 4- and 7-indole-carboxylic esters.[177]



An intermediate at the same oxidation level can be produced in a totally different manner *via* the ready condensation of an *ortho*-nitrobenzaldehyde with nitromethane; reduction to an anilino-enamine has been achieved traditionally with metal/acid combinations, and more recently by catalytic transfer hydrogenation.[178]

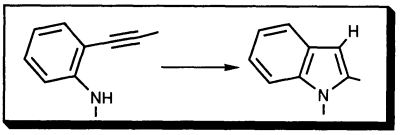


Coupling reactions using *ortho*-haloanilines have been widely used; in these instances no reductive step is required, though the carbonyl unit is sometimes incorporated in masked form requiring deprotection; the examples shown are a palladium-catalysed coupling and a silyl ether/nitroarene condensation.[179]

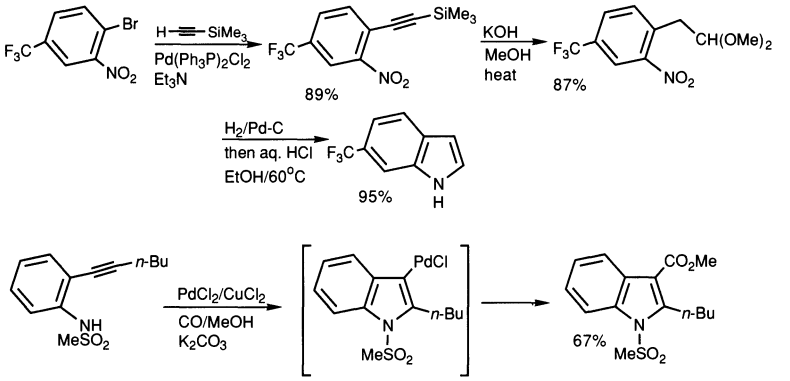


17.16.1.3 *From ortho-alkynylanilines*

Cyclisation of *ortho*-alkynylanilines can be achieved in various ways; palladium-catalysed couplings provide the starting alkynylanilines.

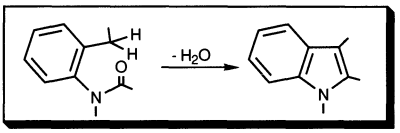


Palladium-catalysed coupling methodology now allows easy access to arenes with an alkynyl substituent *ortho-* to nitrogen, from *ortho*-iodo- and -bromonitrobenzenes,[180] or *ortho*-iodo- and -bromo-*N*-acyl (or -sulfonyl) anilines,[181] or even by coupling acetylenes with 2-iodoaniline itself.[182] Conversion of *ortho* alkynyl-nitrobenzenes and -anilines into indoles has been achieved in two ways. The former react with alkoxides *via* addition to the triple bond and form nitroacetals, reduction and hydrolysis of which allows ring closure. Alternatively, direct cyclisation of *ortho*-alkynylanilines can be effected, using palladium or copper salts, and in the former cases the organopalladium intermediate can be either protonolysed, or trapped out with consequent insertion of a substituent at the indole β-position.[183]



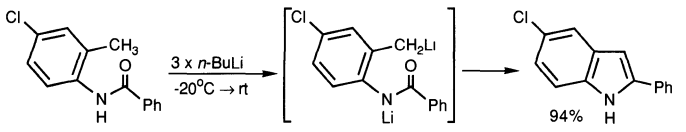
17.16.1.4 *From ortho-toluidides*

Base-catalysed cyclo-condensation of an *ortho*-alkylanilide gives an indole.

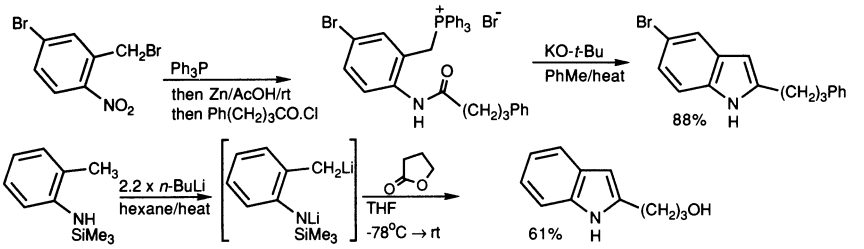


The Madelung synthesis

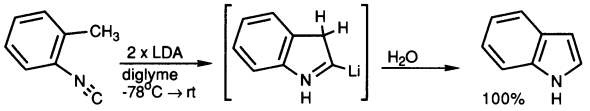
In its original form, this route employed very harsh conditions (typically[184] sodium amide or potassium *t*-butoxide at 250–350°C) to effect base-catalysed intramolecular condensation between an unactivated aromatic methyl and an *ortho* acylamino-substituent, and was consequently limited to situations having no other sensitive groups. With the advent of the widespread use of alkyllithiums as bases, these cyclocondensations can now be brought about under much milder conditions.[185]



Modifications in which the benzylic hydrogens are acidified also allow the use of mild conditions; one example is the generation of a phosphonium ylid and then an intramolecular Wittig-like reaction, involving the amide carbonyl;[186] another variant uses a benzylsilane.[187] The use of an amino-silane permits reaction at both nitrogen and benzylic carbon to take place in one pot.[188]

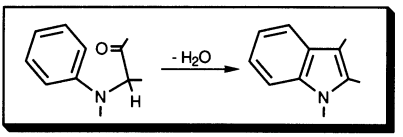


Finally, in this category there must be included cyclisations of the benzylic anions derived from *ortho*-isocyanotoluenes.[189]



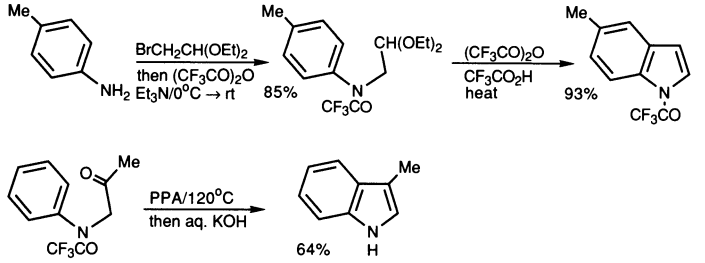
17.16.1.5 *From α-arylaminoarbonyl compounds*

An α-arylaminoketone is cyclised by electrophilic attack onto the aromatic ring.



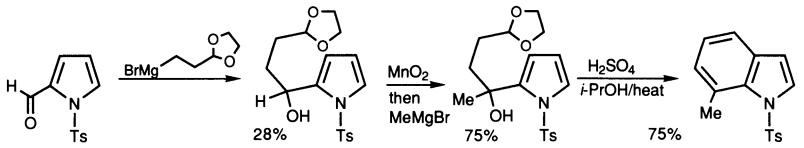
The Bischler synthesis

In the original method, the Bischler synthesis, harsh acidic treatment of α-arylaminoketones (produced from the 2-haloketone and an arylamine) was used to bring about electrophilic cyclisation onto the aromatic ring; these conditions often resulted in mixtures of products *via* rearrangements.[190] It is now known that *N*-acylated α-arylamino ketones can be cyclised under much more controlled conditions and, in contrast to early work, this approach to indoles can even be used to produce hetero-ring-unsubstituted indoles.[191]



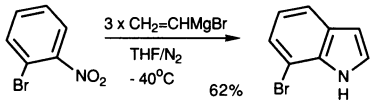
17.16.1.6 *From pyrroles*

Several unrelated strategies have been utilised for the fusion of a benzene ring onto a pyrrole to generate an indole;[192] most follow a route in which a pyrrole, carrying a four-carbon side chain at the α-carbon, is cyclised *via* an electrophilic attack at the adjacent pyrrole β-position; one of these is shown.[193]

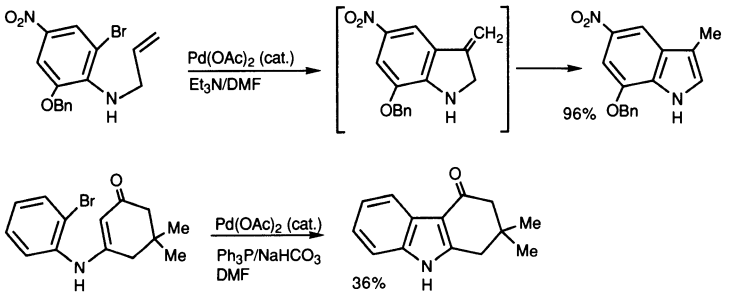


17.16.1.7 *Miscellaneous indole ring-forming methods*

In an extraordinary but nonetheless efficient and extremely practically simple process, *ortho*-substituted-nitrobenzenes treated with three mol equivalents of vinyl magnesium bromide give 7-substituted indoles; the mechanism is not fully understood.[194]

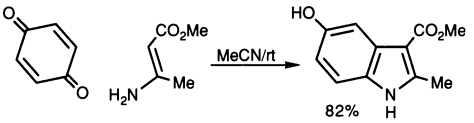


Intramolecular Heck-type reactions can be used to synthesise indoles,[195] but it is not clear whether the palladium-mediated cyclisations of anilino-acrylates and related sytems[60] operate by this mechanism or *via* an electrophilic palladation.



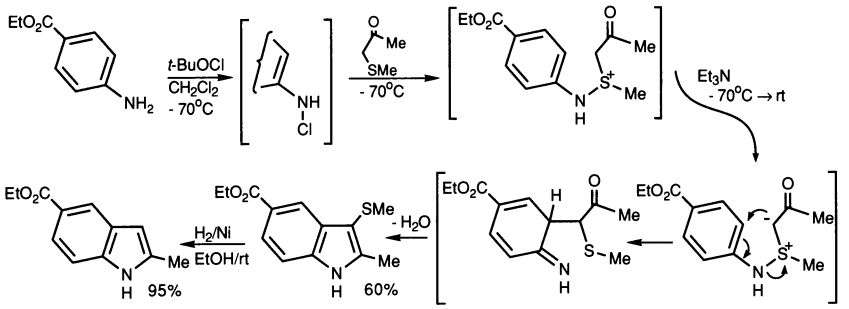
The Nenitzescu synthesis

The Nenitzescu synthesis[197] is another process about which some of the mechanistic details remain unclear,[198] but which can be used for the efficient synthesis of certain 5-hydroxyindoles.[199]



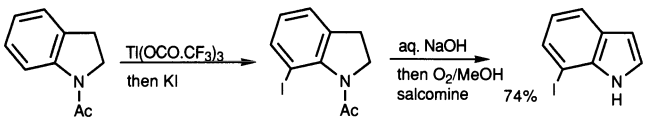
The Gassman synthesis

The Gassman synthesis[200] produces sulfur-substituted indoles, but these can easily be hydrogenolysed if required.

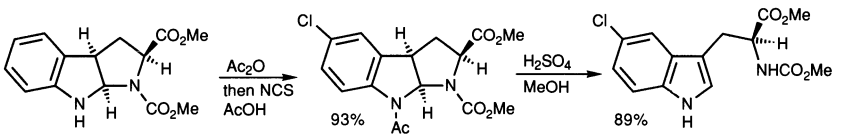


17.16.1.8 *From indolines*

Indolines are useful intermediates for the synthesis of indoles with substituents in the carbocyclic ring. In electrophilic substitutions, they behave like anilines; the example shows *N*-acetylindoline undergoing regioselective 7-thallation. Indolines can be obtained easily from indoles by reduction (see section 17.8) and can be cleanly oxidised back to indoles using a variety of methods, including oxygen with cobalt catalysis (salcomine),[201] hypochlorite/dimethylsulfide,[202] Mn(3),[203] and Au(3)[204].

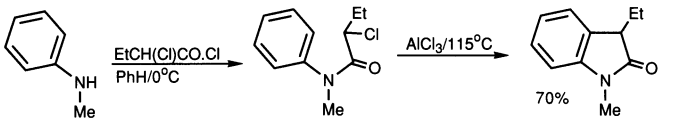


An attractive variant is to utilise certain products of reversible addition to 3*H*-indolium cations, such as the the indole bisulfite adduct (section 17.1.1), or where there has been an intramolecular nucleophilic addition: such compounds, though they are indolines, are still at the oxidation level of indoles, needing only mild acid treatment to regenerate the aromatic system.[205]

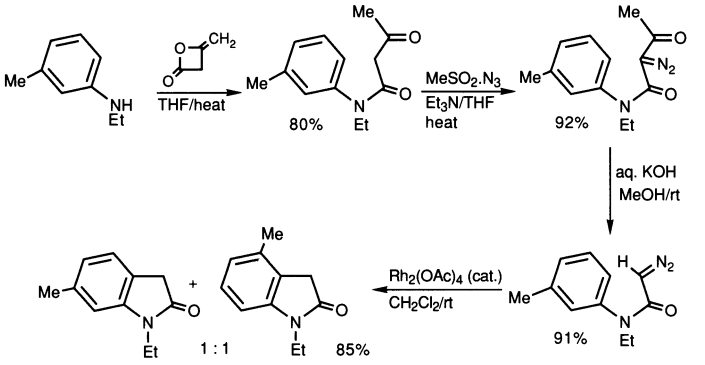


17.16.2 Synthesis of oxindoles

The main synthesis of oxindoles is simple and direct and involves an intramolecular Friedel-Crafts alkylation reaction as the cyclising step.[206]

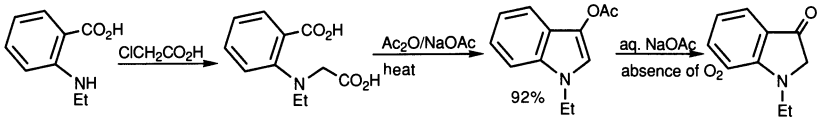


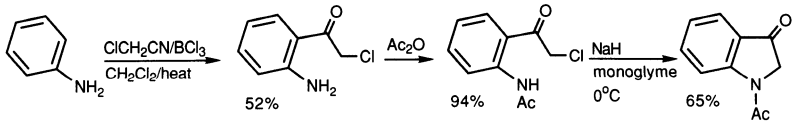
An entirely different route to oxindoles depends on the intramolecular insertion of a rhodium carbenoid into an adjacent aromatic C–H bond.[207]



17.16.3 Synthesis of indoxyls

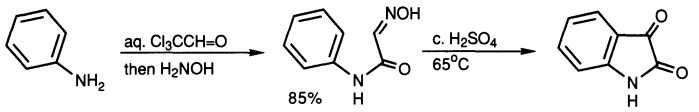
Indoxyls are normally prepared from anthranilic acids *via* alkylation with a haloacetic acid, followed by a cyclising Perkin condensation.[208] It is also possible to directly chloroacylate an aniline, *ortho* to the nitrogen.[209]





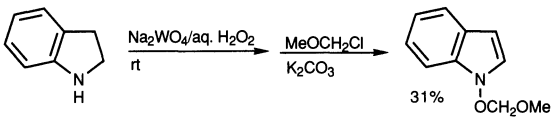
17.16.4 Synthesis of isatins

Isatins are readily prepared *via* the reaction of an aniline with chloral, the resulting product converted into an oxime, and this cyclised in strong acid.[210]



17.16.5 Synthesis of 1-hydroxyindoles

The oxidation of indolines with sodium tungstate/hydrogen peroxide both aromatises and also oxidises the nitrogen, resulting in 1-hydroxyindoles.[83]

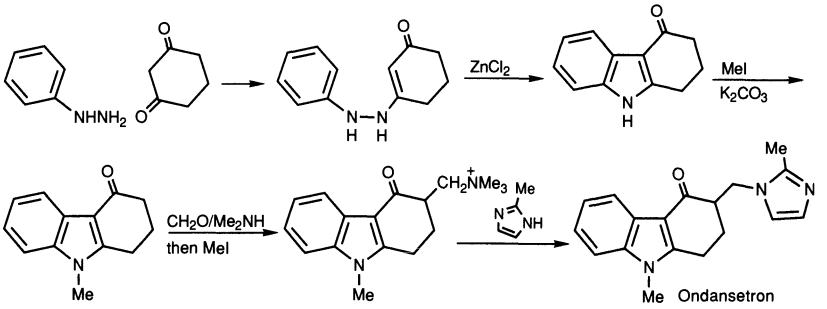


1-Hydroxyindoles can be obtained by reduction of Leimgruber-Batcho intermediate nitro-enamines (section 17.16.2) with zinc.[211]

17.16.6 Examples of notable indole syntheses

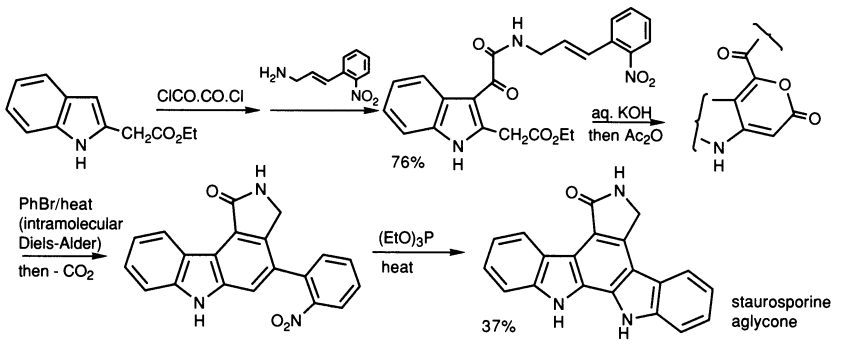
17.16.6.1 *Ondansetron*

Ondansetron is a selective, 5-hydroxytryptamine antagonist, used to prevent vomiting during cancer chemotherapy and radiotherapy.



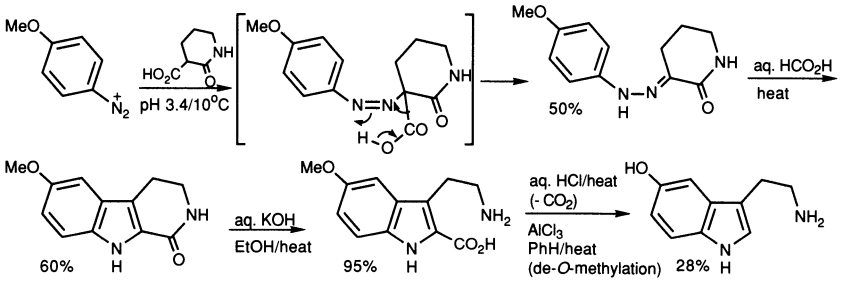
17.16.6.2 *Staurosporine aglycone*[212]

Staurosporine and related molecules are under active investigation as potential antitumour agents. The synthesis illustrates several aspects of heterocyclic chemistry, including a 2-pyrone acting as a diene in an intramolecular Diels-Alder reaction, and the use of nitrene insertion for the formation of 5-membered nitrogen rings.



17.16.6.3 *Serotonin*

Serotonin has been synthesised by several routes; the method shown relies on a Fischer indole synthesis, the requisite phenylhydrazone being constructed by a process known as the Japp-Klingemann reaction, in which the enol of a 1,3-dicarbonyl compound is reacted with an aryldiazonium salt, with subsequent cleavage of the 1,3-dicarbonyl unit.



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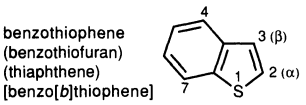
EXERCISES FOR CHAPTER 17

1. Indole reacts with a mixture of *N*-methyl-2-piperidone and $POCl_3$, followed by NaOH work-up to give $C_{14}H_{18}N_2O$. What is its structure?
2. Suggest a structure for the tetracyclic product, $C_{18}H_{19}NO$, formed when 3-methylindole is treated with 2-hydroxy-3,5-dimethylbenzyl chloride.
3. When indole dimer (section 17.1.9) is subjected to acid treatment in the presence of indole, 'indole trimer', $C_{24}H_{21}N_3$, is produced. Suggest a structure for the 'trimer' (hint: consider which of the two reactants would be most easily protonated, and at which atom).
4. Starting from indole, and using a common intermediate, how could one prepare (i) indol-3-ylacetic acid and (ii) tryptamine?
5. What would be the products from the reactions of 5-bromo-3-iodo-1-phenylsulfonylindole with (i) $PhB(OH)_2/Pd(PPh_3)_4$/aq. Na_2CO_3; (ii) ethyl acrylate/$Pd(OAc)_2/Ph_3P/Et_3N$?
6. Deduce a structure, and write out the mechanism for the conversion of 2-formylindole into a tricyclic compound, $C_{11}H_9N$, on treatment with a combination of NaH and $Ph_3P^+CH{=}CH_2\,Br^-$.
7. When 3-ethyl-3-methyl-3*H*-indole is treated with acid, two products, each isomeric with the starting material, are formed – deduce their structures and explain the formation of two products.
8. Suggest a structure for the salt $C_{15}H_{13}N_2^+\,Br^-$ formed by the following sequence: 2-(2-pyridyl)indole reacted first with *n*-BuLi, then $PhSO_2Cl$ ($\rightarrow C_{19}H_{14}N_2O_2S$), then this sequentially with *t*-BuLi at $-100°C$, then ethylene oxide ($\rightarrow C_{21}H_{18}N_2O_3S$), aq. NaOH ($\rightarrow C_{15}H_{14}N_2O$), and this, finally reacted with PBr_3.
9. What are the products formed in the following sequence: indole/*n*-BuLi, then I_2, then LDA, then $PhSO_2Cl \rightarrow C_{14}H_{10}INO_2S$, then this with LDA, then $I_2 \rightarrow C_{14}H_9I_2NO_2S$.
10. When indol-3-yl-CH_2OH is heated with acid, diindol-3-ylmethane is formed: suggest a mechanism for this transformation.
11. Which phenylhydrazones would be required for the Fischer indole synthesis of (i) 3-methylindole; (ii) 1,2,3,4-tetrahydrocarbazole; (iii) 2-ethyl-3-methylindole; (iv) 3-ethyl-2-phenylindole?
12. What product, $C_{10}H_{11}NO$, would be obtained from refluxing a mixture of phenylhydrazine and 2,3-dihydrofuran in acetic acid?
13. Draw structures for the azaindoles resulting from treatment of 2-methyl-3-nitro- and 4-methyl-3-nitropyridines, respectively, with $(EtO_2C)_2$/EtONa,

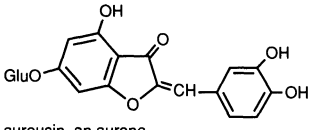
followed by H_2/Pd-C. Both products have the molecular formula $C_{10}H_{10}N_2O_2$.

14. Heating DMFDMA with the following aromatic compounds led to condensation products; subsequent reduction with the reagent shown gave indoles. Draw the structures of the condensation products and the indoles: (i) 2,6-dinitrotoluene then $TiCl_3$ gave $C_8H_8N_2$; (ii) 2-benzyloxy-6-nitrotoluene then H_2/Pt gave $C_{15}H_{13}NO$; (iii) 4-methoxy-2-nitrotoluene then H_2/Pd gave C_9H_9NO; (iv) 2,3-dinitro-1,4-dimethylbenzene then H_2/Pd gave $C_{10}H_8N_2$.

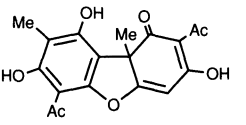
18 Benzo[*b*]thiophenes and benzo[*b*]furans: reactions and synthesis



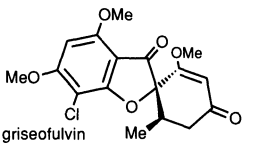
Benzo[*b*]thiophene[1] and benzo[*b*]furan,[2] frequently (and in the rest of this chapter) referred to simply as benzothiophene and benzofuran, are the sulfur and oxygen analogues of indole, respectively, but have been much less fully studied. The oxygen system occurs in a range of plant- and microbial-derived natural products, ranging in complexity from 5-methoxybenzofuran, through the orange 'aurones', a group of plant pigments isomeric with co-occurring flavones (section 9.2.3.10), usnic acid, a yellow pigment found in many lichens, to griseofulvin, from *Penicillium griseofulvum*, used in medicine as an antifungal agent.



aureusin, an aurone



usnic acid



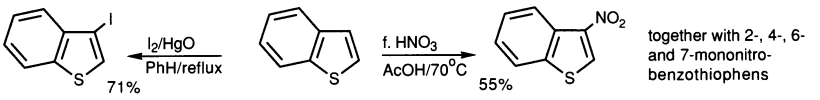
griseofulvin

18.1 REACTIONS WITH ELECTROPHILIC REAGENTS

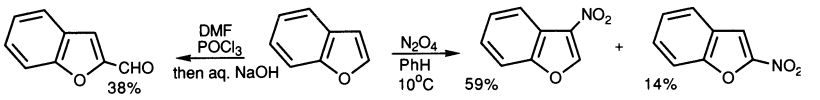
18.1.1 Substitution at carbon

The electrophilic substitution of these systems is much less regioselective than that of indole (effectively complete selectivity for attack at C-3), even to the extent that the hetero-ring positions are only a little more reactive than some of the benzene ring positions. For example, nitration of benzothiophene gives a mixture in which, although more than half the product is the 3-nitro-derivative, 2-nitro-, 4-nitro-, 6-nitro- and 7-nitrobenzothiophenes are also all produced, each representing about 10% of the product mixture.[3] Measurements of detritiation of

2- and 3-tritiobenzothiophene in trifluoroacetic acid showed rates which were effectively the same for both hetero-ring positions.[4] Friedel-Crafts alkylation[5] of benzothiophene gives mixtures in which the 3-isomer predominates over the 2-isomer; however, in other substitutions the 3-isomer is said to be the only product – iodination[6] falls into this category, as does controlled bromination;[7] the 2,3-dibromide can be selectively reduced to the 3-monobromo derivative with zinc in acetic acid, which must relate to the greater stability of a 2- *versus* a 3-anion.



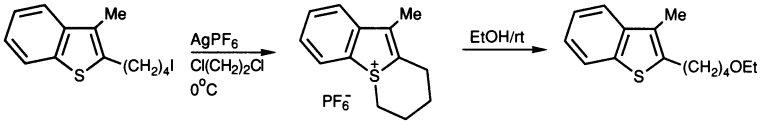
Benzofuran displays a lesser tendency for 3-substitution: formylation of benzofuran reportedly gives only the 2-formyl derivative,[8] and nitric acid nitration[9] produces 2-nitrobenzofuran, though in all studies where the isolation of a major product is described, particularly those conducted before the advent of modern analytical techniques, one must be aware that the presence of other minor isomers may have gone undetected; a later study using dinitrogen tetroxide found 3-nitrobenzofuran as a major product together with a smaller percentage of the 2-isomer.[10] Treatment of benzofuran with halogens results in 2,3-addition products,[11] with the initial electrophilic attack taking place at C-2; from these addition products, by base-promoted hydrogen halide elimination, 3-monohalo benzofurans can be obtained in high yields.[12] Friedel-Crafts substitution is difficult for hetero-ring unsubstituted benzofurans because typical catalysts tend to cause resinification, but 3-acylations[13] have been reported using ferric chloride.



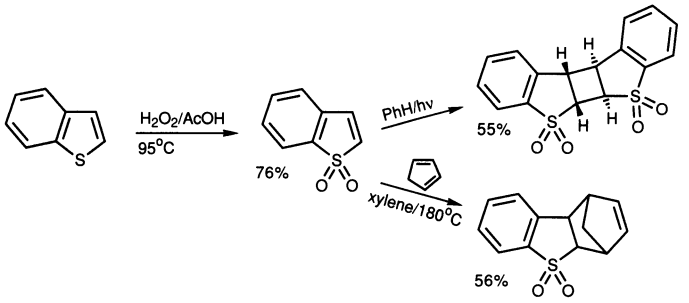
With substituents already present, the pattern of substitution is even more complex: some examples serve to illustrate this. Nitration of 2-bromobenzothiophene results in *ipso* substitution and thus the formation of 2-nitrobenzothiophene, whereas 2-chlorobenzothiophene gives the 3-nitro-substitution product;[14] on the other hand, 3-carboxy- or 3-acylbenzothiophenes nitrate mainly in the benzene ring.[15] Bromination[16] and Friedel-Crafts substitution[17] of 3-methyl- and 2-methylbenzothiophenes takes place cleanly at the vacant hetero-ring position; similarly 2-bromobenzothiophene undergoes formylation at C-3.[18] 3-Methoxybenzothiophene gives the corresponding 2-aldehyde under Vilsmeier conditions at moderate temperatures, but at 95°C 3-chlorobenzothiophene-2-carboxaldehyde is obtained;[19] 6-ethoxybenzothiophene formylates at C-2.[20]

18.1.2 Addition to sulfur in benzothiophenes

Benzothiophenium salts are produced by the reaction of the sulfur heterocycle with more powerful alkylating combinations such as Meerwein salts;[21] benzothiophenium salts can themselves act as powerful alkylating agents with fission of the C–S^+ bond.[22]

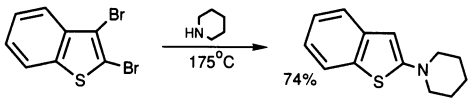


S-Oxidation produces 1,1-dioxides which readily undergo cycloadditions as dienophiles,[23] or photodimerisation, the head-to-head dimer (shown) being the major product.[24]



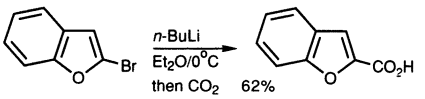
18.2 REACTIONS WITH NUCLEOPHILIC REAGENTS

Halogen at a benzothiophene 2-position is subject to displacement with amine nucleophiles,[25] and, surprisingly, rather more easily than halogen at the 3-position, even though an intermediate for 3-attack carries negative charge at C-2, adjacent to the hetero atom. Equally surprising are reactions in which secondary amine anions add to benzothiophene to give 2-dialkylamino-2,3-dihydrobenzothiophenes;[26] with irradiation, addition of primary amines gives 3-alkylamino-2,3-dihydrobenzothiophenes.[27]

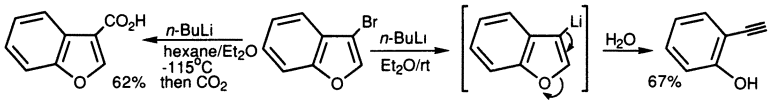


18.3 REACTIONS WITH BASES; REACTIONS OF *C*-METALLATED BENZO[*b*]THIOPHENES AND BENZO[*b*]FURANS

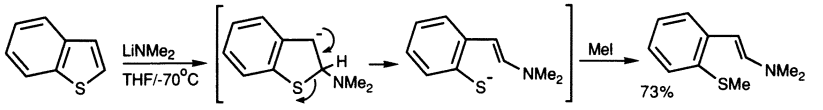
In some of the earliest uses of *n*-butyllithium, 2-lithiobenzofuran was obtained by metal–halogen exchange between a 2-bromo-heterocycle and *n*-butyllithium,[28] or by deprotonation of benzofuran.[29]



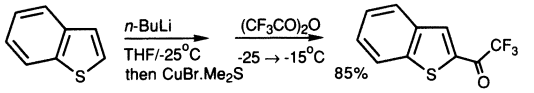
The generation of 3-metallated benzofurans generally results in fragmentation with the production of 2-hydroxyphenylacetylene at room temperature,[28,30] though the 3-lithio-derivative can be utilised at very low temperature.[31]

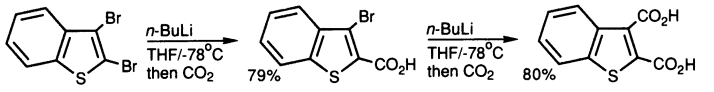


Ring opening in a rather different manner results from exposure of the heterocycle to lithium dimethylamide, followed by trapping with iodomethane, producing an enamine which must result from initial addition at C-2, perhaps by a minor pathway, but one which then leads to ring-opening elimination.[32]



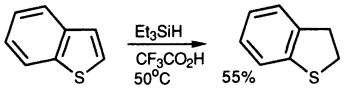
3-Lithiobenzothiophenes can be generated, and reacted with electrophiles, if the temperature is kept low.[33] Direct deprotonation of benzothiophenes follows the usual pattern for five-membered heterocycles and takes place adjacent to the hetero atom,[34] and in concord with this pattern, metal–halogen exchange processes favour a 2- over a 3-halogen.[35] 2-Trialkylstannylbenzofurans are useful for palladium-catalysed coupling with aromatic halides.[36]





18.4 REACTIONS WITH REDUCING AGENTS

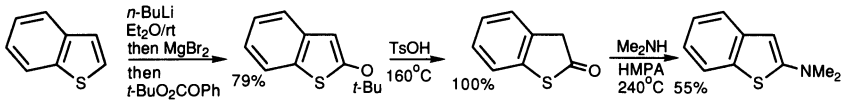
Hydrodesulfurisation of benzothiophenes is conveniently achieved using Raney nickel,[37] and before the advent of modern spectroscopic methods was utilised in the determination of structure of substituted benzothiophenes by conversion to a recognisable derivative.



Reduction of the hetero-rings of both benzofuran and benzothiophene, in the latter case with retention of the sulfur, can be achieved using triethylsilane in acidic solution giving 2,3-dihydro-derivatives.[38]

18.5 OXY-[39] AND AMINO-BENZOTHIOPHENES AND -BENZOFURANS

Thiooxindoles (benzo[*b*]thiophene-2(3*H*)-ones) can be conveniently accessed by oxidation of 2-lithiobenzothiophenes.[40] Thiooxindole will condense at the 3-position with aromatic aldehydes;[41] thioindoxyl (benzo[*b*]thiophene-3(2*H*)-one) reacts comparably at its 2-position.[42]



Both 2-(3*H*)-benzofuranone, known trivially in the older literature as coumaranone, and best viewed as a lactone, and the isomeric 3-(2*H*)-benzofuranone, form ambident anions by deprotonation at the methylene group, the former[43] requiring a stronger base than the latter.[44]

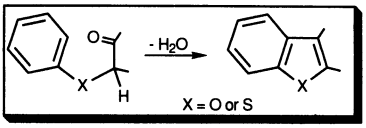
Little is known of simple 2- and 3-amino-derivatives; 2-dialkylaminobenzothiophenes can be obtained by reaction of thiooxindole with secondary amines.[40] Diazotisation of 2-aminobenzothiophene leads to thiooxindole, but in other ways the amine behaves like a normal aromatic amine.[45]

18.6 SYNTHESIS OF BENZO[*b*]THIOPHENES AND BENZO[*b*]FURANS

18.6.1 Ring synthesis

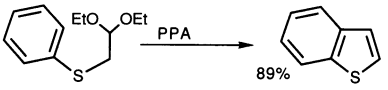
18.6.1.1 *From 2-arylthio- or 2-aryloxyaldehydes, -ketones or -acids*

Cyclisation of 2-arylthio- or 2-aryloxyaldehydes, -ketones or -acids *via* intramolecular electrophilic attack on the aromatic ring, with loss of water, creates the heterocyclic ring; this route is the commonest method for benzothiophenes.

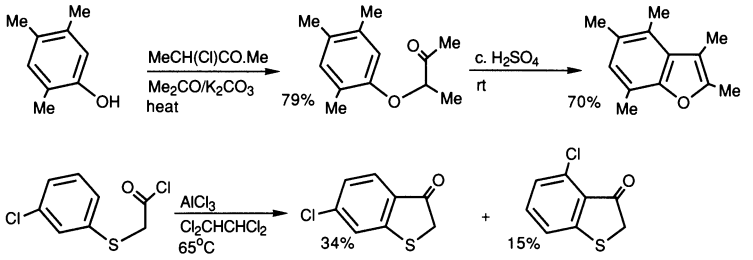


In order to produce hetero-ring unsubstituted benzothiophenes[46] an arylthioacetaldehyde acetal is generally employed prepared, in turn, from

bromoacetaldehyde acetal and the thiophenol. An exactly parallel sequence produces 2,3-unsubstituted benzofurans.[47]

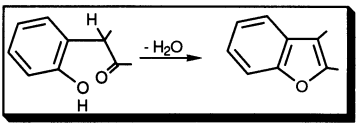


Comparable acid-catalysed ring closures of 2-arylthio-[48] and 2-aryloxy-[49] -ketones, and -2-arylthio-[50] and 2-aryloxyacetyl[51] chlorides lead to 3-substituted heterocycles and 3-oxygenated heterocycles respectively. Attempted formation of 3-arylbenzothiophenes by this route is always accompanied by partial or complete isomerisation to the 2-aryl-heterocycle.[52]

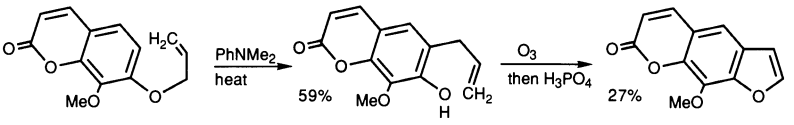


18.6.1.2 *From 2-(ortho-hydroxyaryl)-acetaldehydes, -ketones or -acids*

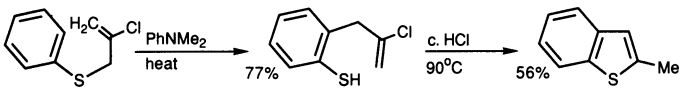
Cyclising dehydration of 2-(*ortho*-hydroxyaryl)-acetaldehydes, -ketones or -acids gives the heterocycles; this route is important for benzofurans.



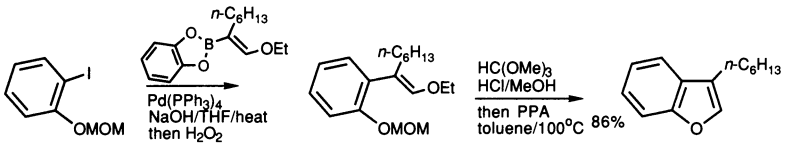
Claisen rearrangement of allyl phenolic ethers, followed by oxidation of the alkene generates *ortho*-hydroxyarylacetaldehydes, which close to give benzofurans under acid catalysis.[53] The formation of 2-substituted benzofurans from 2-(*ortho*-hydroxyaryl)-ketones is also very easy.[54]



The employment of aryl 2-chloroprop-2-enyl sulfides (or ethers) as thio-Claisen rearrangment substrates neatly eliminates the necessity for an oxidative step, thus providing a route to 2-methylbenzothiophenes (-benzofurans).[55]

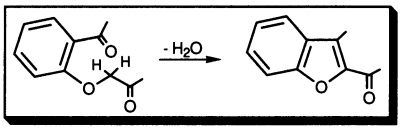


Another route to compounds of the same oxidation level involves palladium-catalysed coupling of enol ethers.[56]

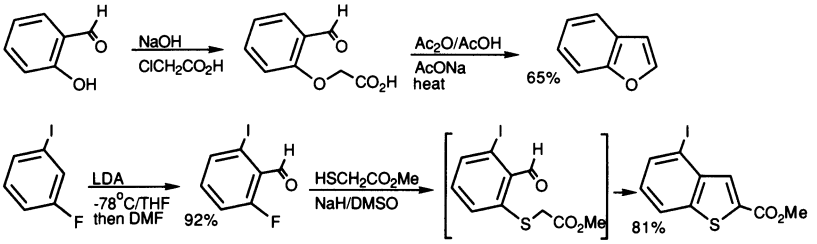


18.6.1.3 *From ortho-acylaryloxy- or -arylthioacetic acids (esters) (ketones)*

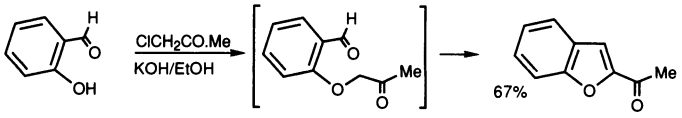
Cyclising dehydration of *ortho*-acylaryloxy- or -arylthioacetic acids (esters) or ketones gives the bicyclic heterocycles.



Intramolecular aldol/Perkin type condensation of aryloxyacetic acids and arylthioacetic esters produces benzofuran[57] and benzothiophene-2-esters[58] respectively. The examples shown illustrate contrasting methods – classical and modern – for the preparation of the required starting materials.

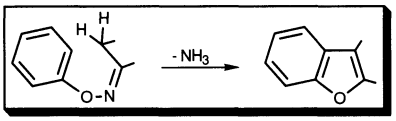


ortho-Hydroxyaromatic ketones, after *O*-alkylation with α-haloketones, afford substrates which on intramolecular aldol condensation produce 2-acyl-3-substituted benzofurans.[59]

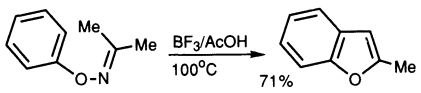


18.6.1.4 *From O-aryl ketoximes*

The electrocyclic rearrangement of *O*-aryl ketoximes produces benzofurans.



The acid-catalysed rearrangement of *O*-aryl ketoximes,[60] which produces benzofuran, exactly parallels the rearrangement of phenylhydrazones, which gives indoles (section 17.16.1).



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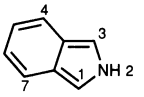
EXERCISES FOR CHAPTER 18

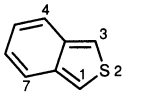
1. Suggest structures for the compounds formed at each stage in the following sequence: PhSH with $ClCH_2CO.CH_2CO_2Et$ ($\rightarrow C_{12}H_{14}SO_3$), then PPA/heat ($\rightarrow C_{12}H_{12}SO_2$), then NH_3 ($\rightarrow C_{10}H_9NSO$), then $LiAlH_4$ ($\rightarrow C_{10}H_{11}NS$), then HCO_2H/heat ($\rightarrow C_{11}H_{11}NSO$), then $POCl_3$/heat giving finally a tricylic substance, $C_{11}H_9NS$.
2. Draw structures for the heterocycles formed from the following combinations: (i) $C_{13}H_{16}O$ from 2,4,5-trimethylphenol with 3-chloro-2-butanone, then the product with c. H_2SO_4; (ii) $C_{12}H_8O_4$ from 7-hydroxy-8-methoxycoumarin with $CH_2{=}CHCH_2Br/K_2CO_3$, then the product heated strongly giving an isomer, then reacted successively with O_3 then H^+; (iii) 4-trifluoromethylfluorobenzene with LDA then DMF ($\rightarrow C_7H_4F_4O$), then with $HSCH_2CO_2Me$/NaH giving $C_{10}H_7F_3O_2$; (iv) $C_9H_7NO_3$ from 4-fluoronitrobenzene with $Me_2C{=}NONa$, then c. HCl/heat.
3. Deduce structures for the bi- and tetracyclic heterocycles formed in the following two steps, respectively: 4-chlorophenylthioacetic acid with PCl_3 then $AlCl_3$ ($\rightarrow C_8H_5ClOS$), then this with phenylhydrazine in hot AcOH $\rightarrow$ $C_{14}H_8ClNS$.

19 Isoindoles, benzo[*c*]thiophenes and isobenzofurans: reactions and synthesis

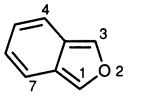
3,4-benzopyrrole
isoindole
[2*H*-isoindole]



3,4-benzothiophene
isobenzothiophene
[benzo[*c*]thiophene]

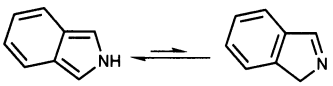


3,4-benzofuran
benzo[*c*]furan
[isobenzofuran]



Isoindole,[1] benzo[*c*]thiophene[2] and isobenzofuran[3] are much less stable than their isomers, indole, and benzo[*b*]thiophene and benzo[*b*]furan. This is undoubtedly associated with their lower aromaticity, which can be appreciated qualitatively by noting that in these [*c*]-systems the six-membered ring is not a complete benzenoid unit. Of the three unsubstituted heterocycles, benzo[*c*]thiophene is the most stable – it survives as a solid for a few days at −30°C – but most chemistry has been carried out with substituted derivatives. The instability manifests itself in a **strong tendency to add reagents so as to generate products which do have a complete benzene ring**, in particular these heterocycles are susceptible to cycloaddition of dienophiles. In this context, then, it is not surprising that for isoindole, for which an alternative tautomer (1*H*-isoindole, sometimes called 'isoindolenine') is possible, which does have a complete benzenoid unit, an appreciable percentage of that alternative exists in equilibrium.[4] Indeed, some isoindoles exist largely as the tautomer with a C–N double bond – 1,3,4,7-tetramethylisoindole is an example[5] – but 1-phenylisoindole favours the 2*H*-tautomer to the extent of 91%.[6] Substituents on the benzenoid ring can also influence both the stability of the isoindole and the position of tautomeric equilibrium; for example, 4,5,6,7-tetrabromoisoindole is a stable crystalline isolable solid which exists wholly as the 2*H*-tautomer;[7] a pivaloyl substituent at C-5, though remote from the sensitive heterocyclic ring, can also stabilise an isoindole.[8] The position of such tautomeric equilibria can be altered by changing solvent – solvents such as DMSO tend to favour the *N*-hydrogen tautomer, where protic solvents like alcohols favour the imine tautomer.

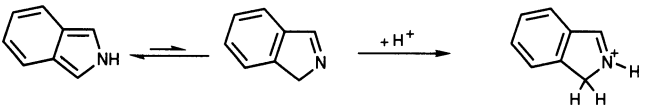
[2*H*-isoindole]



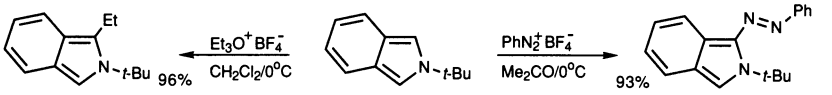
[1*H*-isoindole]

19.1 REACTIONS WITH ELECTROPHILIC REAGENTS

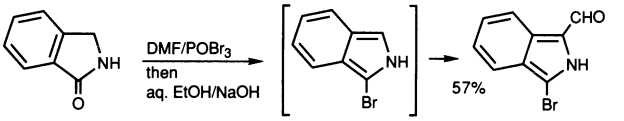
Isoindoles protonate to generate only one cation;[5] this electrophilic addition of protons sets the pattern for substitution in these systems, but there are relatively few clear cut examples, no doubt partly because of the instability of less substituted isoindoles, isobenzofurans and benzo[*c*]thiophenes. Detritiation studies showed the intrinsic reactivity of 2-methylisoindole in this electrophilic substitution to be 10^4 greater than that of 1-methylindole.[9]



2-*t*-Butylisoindole is much more stable than the unsubstituted heterocycle or other 2-substituted isoindoles, thus its reactions can be used as a measure of intrinsic reactivity, set aside from instability: even weak electrophiles such as aryldiazonium ions attack it and it undergoes alkylation, in each case at the hetero-ring 1-position.[10]



An interesting example of electrophilic substitution is the conversion of phthalimidine (2,3-dihydro-1*H*-isoindol-1-one) into 1-bromo-3-formylisoindole under Vilsmeier conditions (formation of 1-bromo-2*H*-isoindole must be the first step).[11] Mannich condensation of 2-methyl-1-phenylisoindole is another straightforward example.[12]

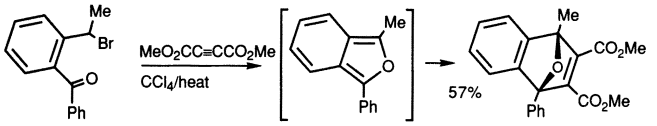


19.2 ELECTROCYCLIC REACTIONS (GROUND STATE)

Each of the three systems has a strong tendency for cycloaddition with dienophiles across the 1- and 3-positions, thereby gaining the stabilising contribution of a complete benzene ring; isobenzofuran itself, for example, reacts instantly at 0°C with maleic anhydride.[13]

Reactions of 1,3-diphenylisobenzofuran are typical: it undergoes Diels-Alder cycloaddition with diethyl acetylenedicarboxylate[14] and adds singlet oxygen;[15] indeed this commercially available isobenzofuran is often used as a trapping reagent for transient alkenes and alkynes. Less stable isobenzofurans are traditionally generated and reacted *in situ*: 1-methyl-3-phenylisobenzofuran is typical.[16] More modern methods for the production of isobenzofurans in solu-

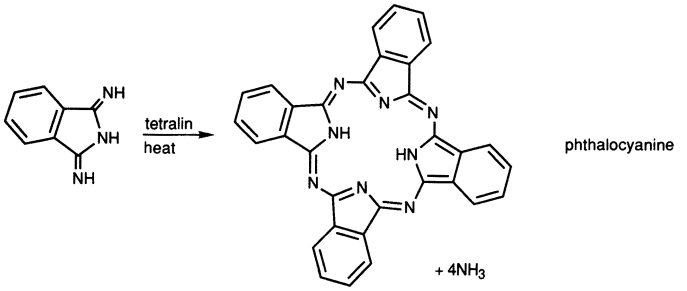
tion have allowed detailed study of the rates of various substituted derivatives with *N*-methylmaleimide.[17]



Diels-Alder additions are also known for benzo[*c*]thiophene[18,19] and isoindoles.[4]

19.3 PHTHALOCYANINES[20]

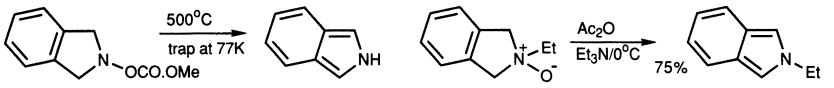
The phthalocyanine macrocyclic system, formally derived from four isoindoles, is the basis for many blue dyestuffs. Metal derivatives have a cation complexed at the centre, much as the iron atom in haem. Phthalocyanine can be produced by the reductive cyclisation of 2-cyanobenzamide or, in a route which makes its relationship to isoindole more obvious, by the combination of four molecules of 1,3-diiminoisoindoline with the elimination of ammonia.[21]



19.4 SYNTHESIS OF ISOINDOLES, BENZO[*c*]THIOPHENES AND ISOBENZOFURANS

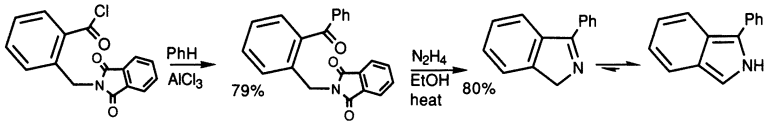
19.4.1 Isoindoles

Isoindoles can be produced by eliminations from *N*-substituted isoindolines (1,3-dihydroisoindoles), themselves readily produced by the reaction of a nitrogen nucleophile and a 1,2-bis(bromomethyl)benzene:[22] examples are the pyrolytic elimination of the elements of methyl hydrogen carbonate from the cyclic hydroxylamine carbonate,[4] or, at a much lower temperature, of benzyl alcohol from an *N*-hydroxyisoindoline benzyl ether,[23] or of methanesulfonate from a corresponding mesylate.[24]

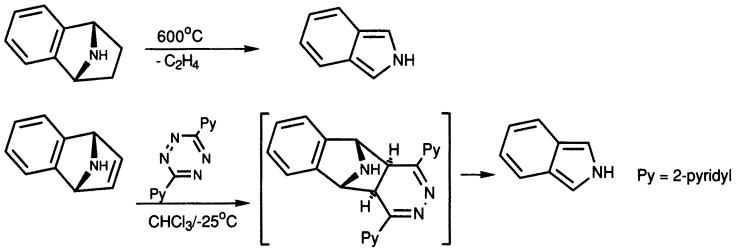


N-Substituted isoindoles, too, have generally been made from an isoindoline by elimination processes, thus *N*-oxides can be made to lose water by pyrolysis[25] or better, by treatment with acetic anhydride.[26]

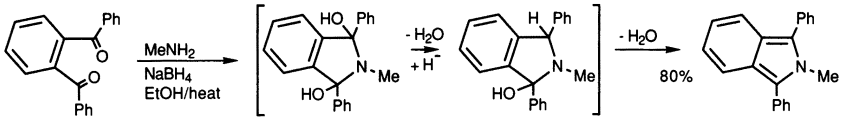
A synthesis of 1-phenylisoindole represents a classical approach to the construction of a heterocycle: a precursor is assembled in which there is an amino group (initially protected in the form of a phthalimide) five atoms away from a carbonyl group with which it must interact and form a cyclic imine.[6]



More recently developed routes involve cycloreversions as final steps;[27] each of the starting materials shown below is available from the cycloadduct (cf. section 13.9) of benzyne and 1-methoxycarbonylpyrrole.



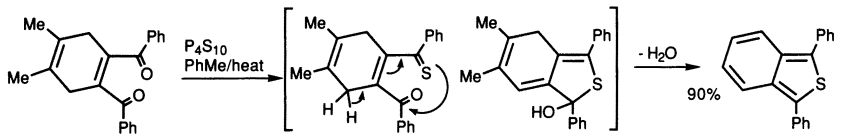
1,3-Diarylisoindoles can be constructed from 1,2-diaroylbenzenes by reaction with an amine and a reducing agent.[28]



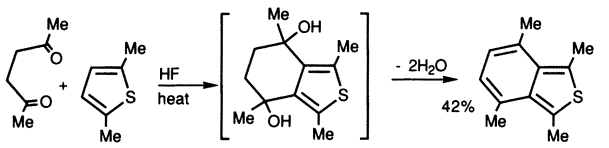
19.4.2 Benzo[*c*]thiophenes

Elimination from dihydrobenzo[*c*]thiophene *S*-oxides has been successfully applied, as for isoindoles, for the preparation of benzo[*c*]thiophenes.[19,29]

In a neat manipulation of oxidation levels, the reaction of a 1,4-dihydro-1,2-diaroylbenzenes, such as are available from Diels-Alder additions of buta-1,3-dienes with 1,2-diaroylalkynes, with a sulfur source, produces benzo[*c*]thiophenes;[30] note that no reductant is required as would be necessary if a 1,2-aroylbenzene were utilised. These same Diels-Alder adducts react with primary amines to give 2-substituted isoindoles.

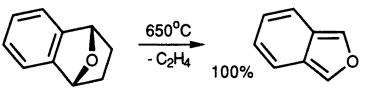


It is comparatively rare for the construction of a benzanellated heterocycle to involve formation of the benzene ring last; however, benzo[*c*]thiophenes can be made by this strategy, utilising a double Friedel-Crafts type alkylation of a 2,5-disubstituted (to prevent attack at α-positions) thiophene with a 1,4-diketone.[31]

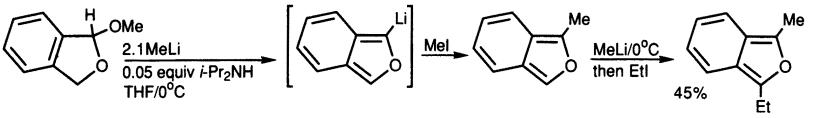


19.4.3 Isobenzofurans

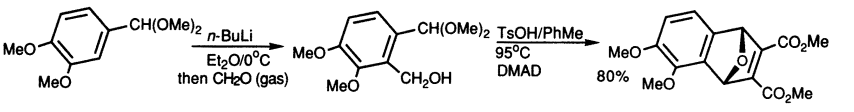
Isobenzofuran can be isolated by trapping on a cold finger, following thermolysis of a suitable precursor such as 1,4-epoxy-1,2,3,4-tetrahydronaphthalene.[13,32]



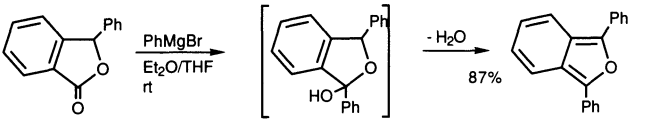
Partial oxidation of 1,2-bishydroxymethylbenzene produces 1-methoxy-1,3-dihydroisobenzofuran, from which methanol can be eliminated, using LDA, giving isobenzofuran.[33] Subsequently, conditions have been defined whereby this elimination can be run in such a way as to allow immediate ring lithiation; this species then can be further reacted.[34]



This same oxidation level situation – an *ortho* disubstituted benzene with aldehyde (ketone) vicinal to carbinol ready for cyclisation and dehydration to an isobenzofuran – can be achieved in alternative ways: phthalaldehyde can be mono-acetalised, then the remaining aldehyde reduced,[35] or lithiation methodology can be utilised, as shown below.[36]



Most of the stable isobenzofurans are 1,3-diaryl substituted, which are deep yellow. Such compounds are available *via* the partial reduction and dehydrating cyclisation of 1,2-diaroylbenzenes.[37] Both 1-mono- and 1,3-disubstituted isobenzofurans are available from phthalides by Grignard addition then elimination of water.[38]



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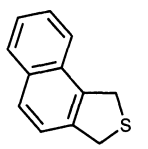
EXERCISES FOR CHAPTER 19

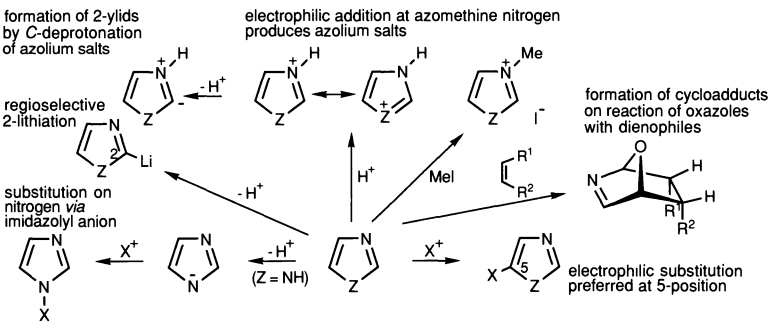
1. Deduce structures for the compounds formed at each stage in the following sequences: (i) 1,2-bis(bromomethyl)-4-pivaloylbenzene with $H_2NCH_2C{\equiv}CH/Et_3N \rightarrow C_{16}H_{19}NO$, which was then heated at 500°C producing $C_{13}H_{15}NO$, which was trapped with *N*-phenylmaleimide $\rightarrow C_{23}H_{22}N_2O_3$ (what is the mechanism of the high temperature reaction?); (ii) phthalaldehyde reacted, in sequence, with 2 × $NaHSO_3$, then $MeNH_2$, then 2 × KCN $\rightarrow C_{10}H_8N_2$; (iii) benzoic acid *N,N*-diethylamide with *n*-BuLi, then PhCH=O, then acid $\rightarrow C_{14}H_{10}O_2$, then this with PhMgBr, then acid $\rightarrow C_{20}H_{14}O$, and finally this with O_2/methylene blue/hν/−50°C $\rightarrow C_{20}H_{14}O_3$; (iv) phthalaldehyde with $HO(CH_2)_2OH/CuSO_4 \rightarrow C_{10}H_{10}O_3$, then this with $NaBH_4$, followed by TsOH with $MeO_2CC{\equiv}CCO_2Me$ in hot toluene $\rightarrow C_{14}H_{12}O_5$; (v) the naphthalene compound A with $Ac_2O/Al_2O_3 \rightarrow C_{12}H_8S$, then this with *N*-phenylmaleimide $\rightarrow C_{22}H_{15}NO_2S$; (vi) benzo[*c*]thiophene with maleic anhydride, then hot NaOH, then acid $\rightarrow C_{12}H_8O_4$.

A 

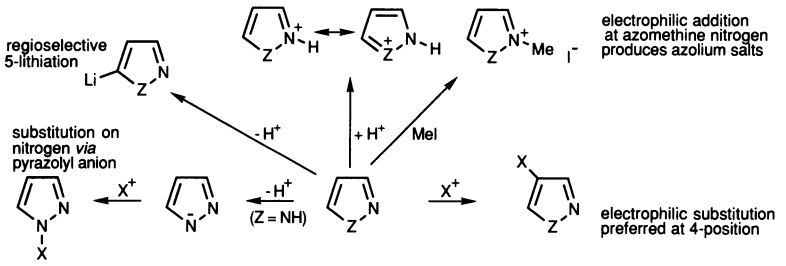
Typical reactivity of 1,3- and 1,2-azoles

20

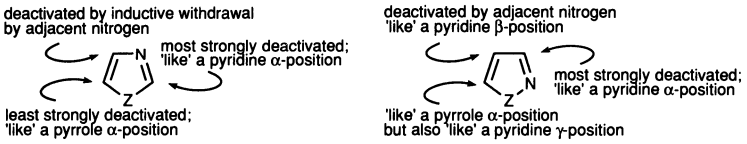
The 1,3- and 1,2-azoles each contain one hetero atom in an environment analogous to that of the nitrogen in pyridine – an azomethine nitrogen – and one hetero atom in the environment of the nitrogen in pyrrole, the sulfur in thiophene, or the oxygen in furan, respectively. Consequently, their chemical reactions present a fascinating combination and mutual interaction of the types of reactivity which have been described earlier in this book for pyridines on the one hand and for pyrrole, thiophene and furan on the other, with the variation in electronegativity of the five-membered-type hetero atom having a substantial differentiating effect.



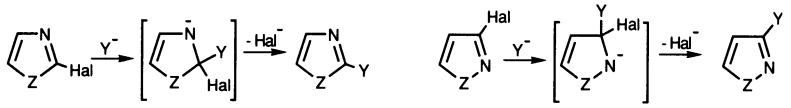
Many of the lessons to be learnt apply to both 1,3- and 1,2-azoles, though the direct linking of the two hetero atoms in the latter has a substantial inductive influence, altering properties in degree. The 1,2-azoles tend to be less nucleophilic and less basic at the azomethine nitrogen than their 1,3-isomers. That such additions occur again illustrates that the azomethine nitrogen lone pair is not involved in the aromatic sextet of electrons.



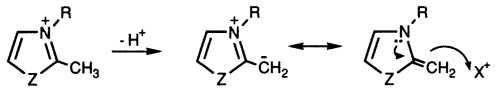
Electrophilic substitution in the azoles is intermediate in facility between pyridine and pyrroles, thiophene and furans: the presence of the electron-withdrawing azomethine unit has an effect on the five-membered aromatic heterocycles just as it does when incorporated into a six-membered aromatic framework, i.e. the comparison is like that between benzene and pyridine (chapter 4). The order of reactivity – pyrrole > furan > thiophene – is echoed in the azoles, though the presence of the basic nitrogen complicates such comparisons. The regiochemistry of electrophilic attack can be seen nicely by comparing the 'character' of the various ring positions – those that are activated in being five-membered in character and those that are deactivated by their similarity to α– and γ-positions in pyridine.



The converse of electrophilic substitution following the five-membered pattern is that nucleophilic substitution of halogen follows the pyridine pattern, i.e. it is much faster at the 2-position of 1,3-azoles, and at the 3-position of 1,2-azoles, than at other ring positions. Resonance contributors to the intermediates for such substitutions make the reason for this plain: the azomethine nitrogen can act as an electron sink for attack only at these positions.

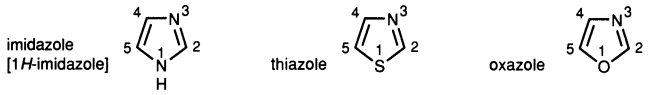


Continuing the analogy with pyridine reactivity, methyl groups at the 2-positions of 1,3-azoles and the 3-positions of 1,2-azoles carry acidified hydrogen atoms and can be deprotonated with strong bases. In further analogy with pyridines, the quaternisation of the azomethine nitrogen makes such deprotonations even easier; the resulting enamines react with electrophiles at the side-chain carbon.

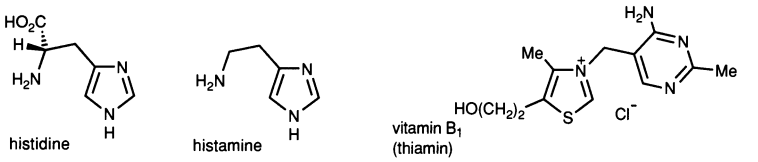


The facility with which 1,3-diazolium cations form ylids (carbenes) by 2-deprotonation is at the heart of the biological activity of thiamine pyrophosphate. Lithiation of the azoles is regioselective for the 2-position in the 1,3-isomers and for 5-position in the 1,2-isomers.

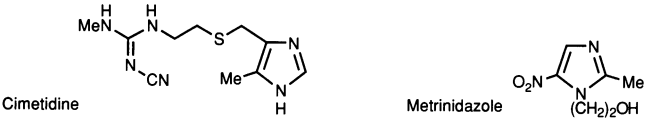
21 1,3-Azoles: imidazoles, thiazoles and oxazoles: reactions and synthesis



The three 1,3-azoles, imidazole,[1] thiazole and oxazole,[2] are all very stable compounds which do not autoxidise. Oxazole and thiazole are water-miscible liquids with pyridine-like odours. Imidazole, which is a solid at room temperature, and 1-methylimidazole are also water-soluble but are odourless. They boil at much higher temperatures (256°C and 199°C) than oxazole (69°C) and thiazole (117°C); this can be attributed to stronger dipolar association resulting from the very marked permanent charge separation in imidazoles (the dipole moment of imidazole is 5.6 D; cf. oxazole, 1.4 D; thiazole, 1.6 D), and for imidazole itself, in addition, from extensive intermolecular hydrogen bonding.



Only oxazole, of the trio, does not play any part in normal biochemical processes, though there are secondary metabolites which incorporate oxazole units.[3] Imidazole occurs in the essential amino acid histidine; histidines within enzymes are intimately involved in catalysis requiring proton transfers. The related hormone, histamine, is a vasodilator and a major factor in allergic reactions such as hay fever. The thiazolium ring is the chemically active centre in the coenzyme derived from thiamin (vitamin B_1).



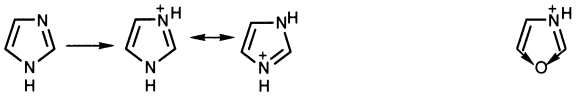
Amongst synthetic substances in use as therapeutic agents are Cimetidine, for the treatment of peptic ulcers, and Metrinidazole, an antiprotozoal, for example in the treatment of amoebic dysentry.

21.1 REACTIONS WITH ELECTROPHILIC REAGENTS

21.1.1 Addition at nitrogen

21.1.1.1 *Protonation*

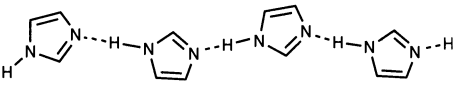
Imidazole, thiazole and alkyloxazoles, though not oxazole itself, form stable crystalline salts with strong acids, by protonation of the imine nitrogen, N-3, known as imidazolium, thiazolium and oxazolium salts.



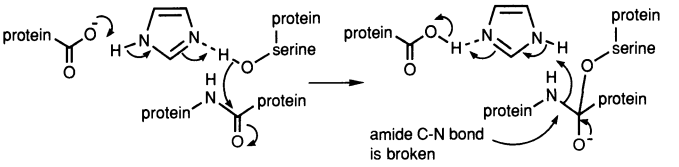
Imidazole, with a pK_a of 7.1, is a very much stronger base than thiazole (pK_a 2.5) or oxazole (pK_a 0.8). That it is also stronger than pyridine (pK_a 5.2) is due to the amidine-like resonance which allows both nitrogens to participate equally in carrying the charge. The particularly low basicity of oxazole can be understood as a combination of inductive withdrawal by the oxygen and weaker mesomeric electron release from it. The 1,3-azoles are stable in hot strong acid.

Hydrogen bonding in imidazoles

Imidazole, like water, is both a good donor and a good acceptor of hydrogen bonds; the imine nitrogen donates an electron pair and the *N*-hydrogen, being appreciably acidic (section 21.4.1), is an acceptor.

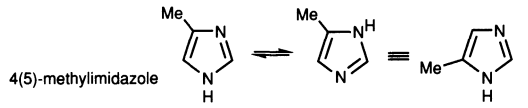


This property is central to the mode of action of several enzymes which utilise the imidazole ring of a histidine. These include the digestive enzyme chymotrypsin, which brings about amide hydrolysis of peptides in the small intestine: the enzyme provides a 'proton' at one site, while it accepts a 'proton' at another, making use of the ambivalent character of the imidazole ring to achieve this. The illustration shows how the heterocycle allows a proton to 'shuttle' from one site to another *via* the heterocycle.



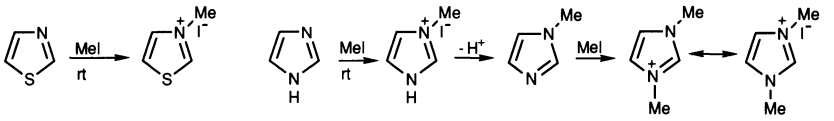
Tautomerism in imidazoles

Imidazoles with a ring *N*-hydrogen are subject to tautomerism, which becomes evident in unsymmetrically substituted compounds such as the methylimidazole shown. This special feature of imidazole chemistry means that to write simply '4-methylimidazole' would be misleading, for this molecule is in tautomeric equilibrium with 5-methylimidazole, and quite inseparable from it. All such tautomeric pairs are inseparable and the convention used to cover this phenomenon is to write '4(5)-methylimidazole'. In some pairs, one tautomer predominates, for example 4(5)-nitroimidazole favours the 4-nitro-tautomer by 400 : 1.

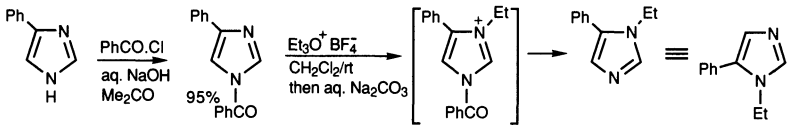


21.1.1.2 *Alkylation at nitrogen*

The 1,3-azoles are quaternised easily at the imine nitrogen with alkyl halides; the relative rates are 1-methylimidazole : thiazole : oxazole, 900 : 15 : 1.[4] In the case of imidazoles which have an *N*-hydrogen, the immediate product is a protonated *N*-alkylimidazole; this can lose its proton to unreacted imidazole and react a second time, meaning that reactions with alkyl halides give a mixture of imidazolium, 1-alkylimidazolium and 1,3-dialkylimidazolium salts. Furthermore, an unsymmetrically-substituted imidazole can give two isomeric 1-alkyl derivatives. The use of a limited amount of the alkylating agent, or reaction in basic solution,[5] when it is the imidazolyl anion (section 21.4.1) which is alkylated, can minimise these complications.



Alkylation of oxazoles,[6] or imidazoles carrying, for example, a phenylsulfonyl group on nitrogen, is more difficult, requiring methyl triflate or a Meerwein salt for smooth reaction. Subsequent simple alcoholysis of the imidazolium-sulfonamide releases the *N*-substituted imidazole.[7] Moreover, since acylation of 4(5)-substituted imidazoles gives the sterically less crowded 1-acyl-4-substituted imidazoles, subsequent alkylation, then hydrolytic removal of the acyl group, produces 1,5-disubstituted imidazoles.[8]

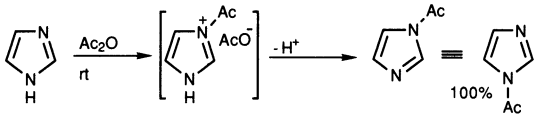


Exposure of imidazole to 'normal' Mannich conditions leads to *N*-dimethylaminomethylimidazole, presumably *via* attack at the imine nitrogen, followed by loss of proton from the other nitrogen.[9]

21.1.1.3 *Acylation at nitrogen*

By the same token, acylation of imidazole produces *N*-acylimidazoles *via* loss of proton from the initially formed *N*-3-acylimidazolium salt.[10] A device which has been employed frequently for the synthesis of 1-acylimidazoles is to use two mol equivalents of the heterocycle for one of the acylating agent, the second mole of imidazole serving to deprotonate the first-formed *N*-acylimidazolium salt.

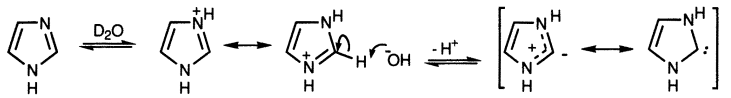
N-Acylimidazoles are even more easily hydrolysed than *N*-acylpyrroles, moist air is sufficient. The ready susceptibility to nucleophilic attack at carbonyl carbon has been capitalised upon: commercially available 1,1′-carbonyldiimidazole (CDI), prepared from imidazole and phosgene, can be used as a safe phosgene-equivalent, i.e. a synthon for $O{=}C^{2+}$, and also in the activation of acids for formation of amides and esters *via* the *N*-acylimidazole.[11] In another application, *N*-acylimidazoles react with lithium aluminium hydride at 0°C to give aldehydes, providing a route from the acid oxidation level.[12]



21.1.2 Substitution at carbon

21.1.2.1 *Protonation*

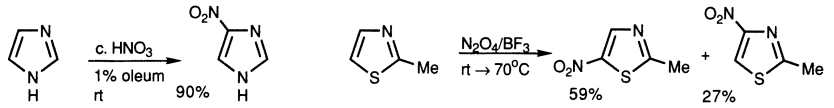
In acid solution, *via* a proton-addition/proton-loss sequence, hydrogen at the imidazole 5-position exchanges about twice as rapidly as at C-4 and > 100 times faster than at C-2.[13] An altogether faster exchange, which takes place at room temperature in neutral or weakly basic solution, but not in acidic solution, brings about C-2-exchange;[14] oxazole and thiazole also undergo this regioselective C-2–H-exchange, the relative rates being in the order: imidazole > oxazole > thiazole.[15] The mechanism for this special process involves first, formation of a concentration of protonic salt, then C-2-deprotonation of the salt, producing a transient ylid, to which a carbene form is an important resonance contributor. It follows from this mechanism that quaternary salts of 1-alkylimidazoles and of oxazole and thiazole will also undergo regioselective C-2-exchange, and this is indeed the case. Most attention[16] has been paid to thiazolium salts (section 21.10) because of the involvement of exactly such an ylid in the mode of action of thiamin in its role as a component of a coenzyme in several biochemical processes.[17] The relative rates of exhange, *via* the ylid mechanism, are in the order: oxazolium > thiazolium > *N*-methylimidazolium, in a ratio of about $10^5 : 10^3 : 1$.[18]



Ylids at C-5 are thought to intervene in the decarboxylation of 5-acids, where again the order of ease of loss of carbon dioxide is oxazole- > thiazole- > *N*-methylimidazole-5-acids; however, comparison with the decarboxylations of the 2-acids shows the 5-isomers to lose carbon dioxide 10^6 more slowly, implying a much lower stability for the 5-ylids.[19]

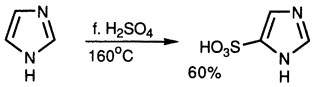
21.1.2.2 *Nitration*

Imidazole is much more reactive towards nitration than thiazole, substitution taking place *via* the salt,[20] as does nitration of alkylthiazoles.[21] Thiazole itself is untouched by nitric acid/oleum at 160°C but methylthiazoles are sufficiently activated to undergo substitution, the typical regioselectivity being for formation of more 5-nitro- than 4-nitro derivative;[22] the 2-position is not attacked: 4,5-dimethylimidazole is resistant to nitration. The much less reactive oxazoles do not undergo nitration.



21.1.2.3 *Sulfonation*

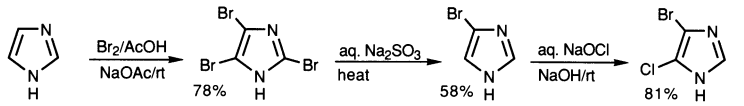
Here again, thiazoles are much less reactive than imidazoles,[23] generally requiring high temperatures and mercuric sulfate as catalyst for any reaction to take place;[24] oxazole sulfonations are unknown.



21.1.2.4 *Halogenation*

Imidazole,[25] and 1-alkyl imidazoles,[26] are brominated with remarkable ease at all free nuclear positions. 4(5)-Bromoimidazole can be obtained by reduction of tribromoimidazole,[27] *via* regioselective exchange of the 2-and 5-halogens then water quenching,[28] or by bromination with 4,4-dibromocyclohexa-2,5-dienone.[29] Chlorination with hypochlorite in alkaline solution effects substitution only at the 4- and 5-positions.[30] Iodination of imidazoles which have a free *N*-hydrogen, in alkaline solution and therefore *via* the imidazolyl anion, can also give fully halogenated products;[31] 4,5-diiodination of imidazole takes place in cold alkaline solution.[32]

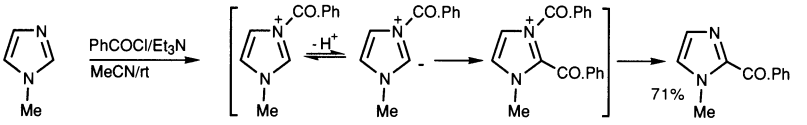
It is, at first sight, somewhat surprising that such relatively mild conditions allow bromination at C-2, but it must be remembered that the neutral imidazole, not its protonic salt (cf. nitration and sulfonation), is available for attack.



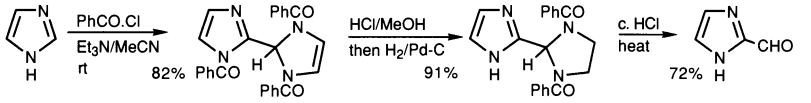
Thiazole does not undergo bromination easily, though 2-methylthiazole brominates at C-5; when the 5-position is not free no substitution occurs, thus 2,5-dimethylthiazole, despite its two activating substituents, is not attacked.[33] Halogenation of simple oxazoles has not been reported.

21.1.2.5 *Acylation*

Friedel-Crafts acylations are unknown for the azoles, clearly because of interaction between the basic nitrogen and the Lewis acid catalyst. It is, however, possible to 2-aroylate 1-alkylimidazoles,[34] or indeed imidazole itself,[35] by reaction with the acid chloride in the presence of triethylamine, the substitution proceeding *via* an *N*-acylimidazolium ylid; it is similarly possible to introduce cyano to the 2-position by reaction with *N*-cyano-4-dimethylaminopyridinium chloride.[36] In the reverse sense, 2-acyl substituents can be cleaved by methanolysis, the mechanism again involving the imidazolium ylid.[37]



Another fascinating example of the utility of *N*-acylimidazolium ylids provides a means for efficiently synthesising 2-formylimidazole: the electrophile which attacks the ylid is in this case an *N*-benzoylimidazolium cation.[38]



21.1.2.6 *Reactions with immonium ions*

The standard, acidic Mannich conditions do not allow simple substitutions of the imidazole and thiazole systems; with the much less basic oxazole an intramolecular Mannich cyclisation has been described.[39]

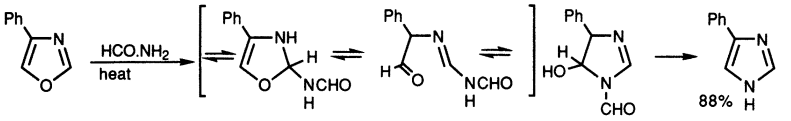
21.2 REACTIONS WITH OXIDISING AGENTS

Resistance to oxidative breakdown falls off in the order thiazoles > imidazoles > oxazoles. 2-Substituted thiazoles can be converted into *N*-oxides,[40] however peracids bring about degradation of imidazoles; oxazole *N*-oxides can only be prepared by ring synthesis.

21.3 REACTIONS WITH NUCLEOPHILIC REAGENTS

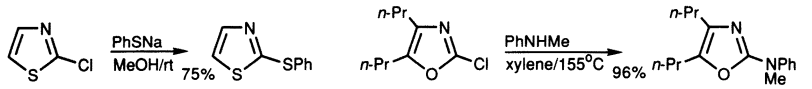
21.3.1 With ring opening

Generally speaking, the 1,3-azoles do not show the pyridine-type reactions in which hydrogen is displaced, although a Chichibabin substitution on 4-methylthiazole has been reported.[41] There are however reactions in which the heterocyclic ring is opened, for example phenylhydrazine attacks oxazoles leading to osazones.[42] Reaction of an oxazole with hot formamide also leads to a ring opening; a re-closure results in the formation of imidazoles; the example shows a reasonable intermediate.



21.3.2 With replacement of halogen

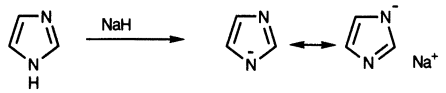
There are many examples of halogen at a 2-position undergoing nucleophilic displacement, for example 2-halothiazoles with sulfur nucleophiles[43] (indeed, more rapidly than for 2-halopyridines), 2-halo-1-substituted imidazoles,[44] and 2-chlorooxazoles[45] with nitrogen nucleophiles.



21.4 REACTIONS WITH BASES

21.4.1 Deprotonation of *N*-hydrogen

The pK_a for loss of the *N*-hydrogen of imidazole is 14.2; it is thus an appreciably stronger acid than pyrrole (pK_a 17.5) because of the enhanced delocalisation of charge, especially onto the second nitrogen, in the imidazolyl anion.

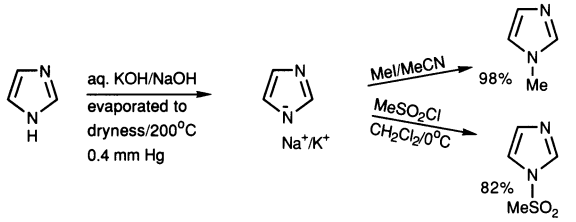


21.4.2 Deprotonation of *C*-hydrogen

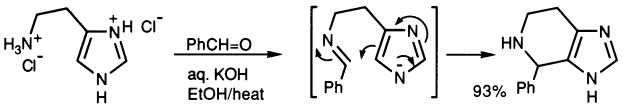
The specific exchange at C-2 in the azoles in neutral solution, *via* an ylid, has already been discussed (section 21.1.2.1). In strongly basic solution, deprotonation takes place by direct abstraction of proton from the neutral heterocycle at the positions adjacent to the oxygen and the sulfur in oxazole and thiazole[46] and, less easily, at C-5 in *N*-methylimidazole.[47]

21.5 REACTIONS OF *N*-METALLATED IMIDAZOLES

Salts of imidazoles can be alkylated or acylated on nitrogen. One convenient method is to use the dry sodium/potassium salt obtained by evaporation of an aqueous alkaline solution;[48] sodium hydride in dimethylformamide also serves very well for this purpose. When there is a route for the entering group to be lost again, as in the addition to a carbonyl-conjugated alkene, a 2,4(5)-substituted imidazole will give the less hindered 1,2,4-trisubstituted product rather than the 1,2,5-isomer.[49]



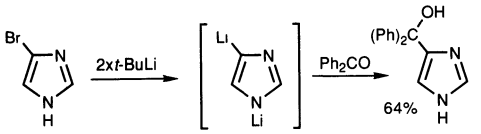
Imidazoles react with Mannich electrophiles at nitrogen, however the overall effect of Mannich *C*-substitution has been found in base-catalysed cyclisation of histamine Schiff bases; closure does not take place in the absence of base and it must be the imidazolyl anion which reacts intramolecularly with the side-chain imine.[50]

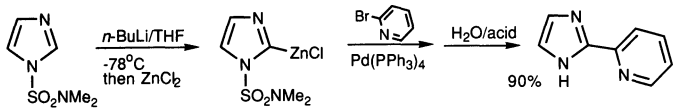


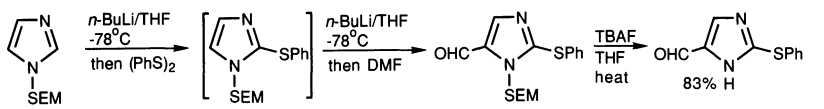
21.6 REACTIONS OF *C*-METALLATED 1,3-AZOLES

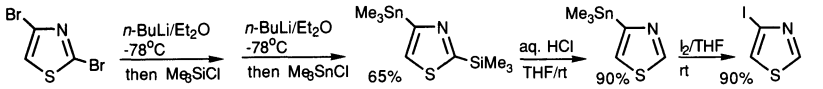
In line with the exchange processes discussed above, preparative strong-base deprotonation of oxazoles,[51] thiazoles[52] and *N*-methylimidazole[53] takes place preferentially at C-2, or at C-5 if the former position is blocked,[54] and the lithiated derivatives can then be utilised in reactions with electrophiles. A variety of removable *N*-protecting groups have been used to achieve comparable transformations for *N*-unsubstituted imidazoles, including phenylsulfonyl,[55] dimethylaminosulfonyl,[56] dimethylaminomethyl,[9] trimethylsilylethoxymethyl (SEM),[57] diethoxymethyl,[58] 1-ethoxyethyl[59] and trityl.[60] The intrinsic tendency to lithiate at C-2, then C-5, taken with metal–halogen exchange processes for the 4-position, are a powerful combination for elaborations of the 1,3-azoles; for example, all three isomeric trimethylsilyl- and all three trimethylstannylthiazoles have been made in this way and provide means for subsequent regiospecific *ipso* displacement with electrophiles under mild conditions.[61] Given below is a selection of transformations which have been achieved using

lithiated azoles. Conditions for the metal–halogen exchange of 4-bromoimidazole, without protection, have been defined.[62]

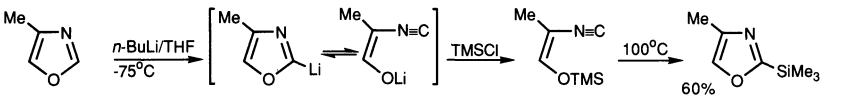








Although oxazoles follow the pattern and lithiate at C-2, 4-substituted products can be produced with some electrophiles; this is interpreted by a ring opening of the anion, to produce an enolate which after *C*-electrophilic attack, recloses. The open enolates can be trapped by reaction with chlorotrimethylsilane; the open, enol trimethylsilyl ether will undergo a thermal rearrangement to form a 2-trimethylsilyloxazole.[63]

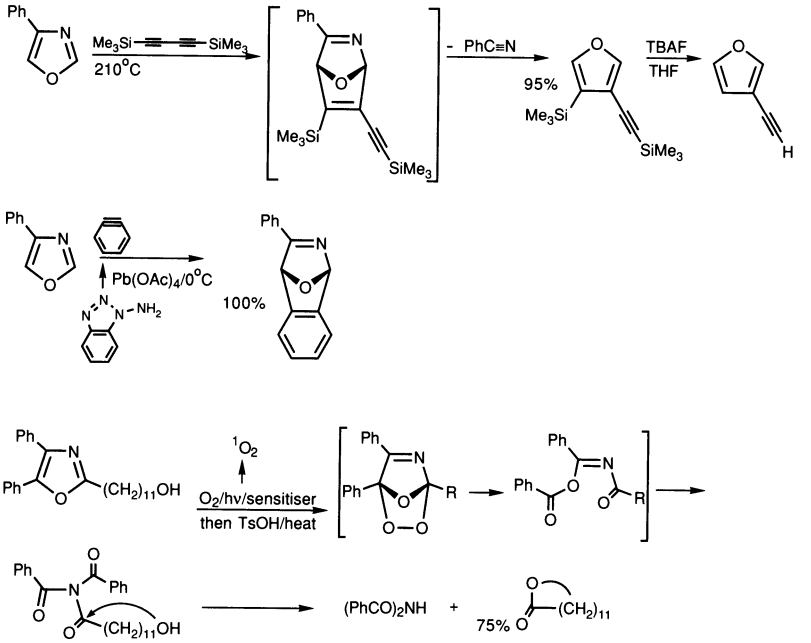


21.7 REACTIONS WITH REDUCING AGENTS

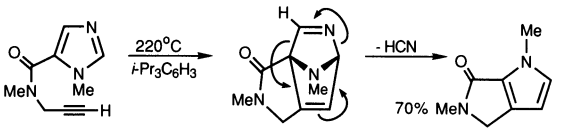
Oxazoles are the most easily reduced, catalytic sequences allowing C–O bond cleavage. 1,3-Azolium salts are of course more easily attacked by hydride reducing agents: thiazolium salts produce tetrahydro-derivatives.[64]

21.8 ELECTROCYCLIC AND PHOTOCHEMICAL REACTIONS

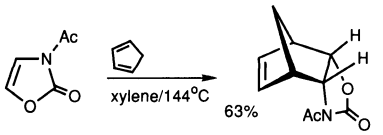
Oxazoles readily undergo cycloaddition across the 2,5-positions, in parallel with the behaviour of furans (section 15.8); thiazoles do not show this reactivity and there is only one example in imidazole chemistry. The last two do react with highly electrophilic alkynes, but *via* initial electrophilic addition to the nitrogen, then nucleophilic intramolecular cyclising addition.[65]



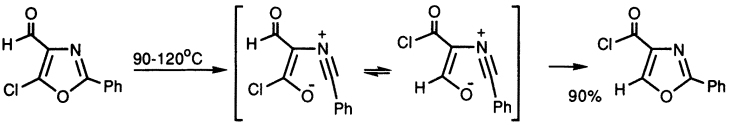
Oxazole cycloadditions have been reported with alkyne dienophiles[66] (tandem Diels-Alder addition and retro Diels-Alder loss of a nitrile leads on to furans), benzyne (the primary adduct can be isolated),[67] and with typical alkene dienophiles. The primary adducts from addition of singlet oxygen rearrange, by a mechanism which is not definitely established, to form triamides, themselves useful synthetic intermediates.[68] The only example of this sort of process with an imidazole is an intramolecular example, the product in this case being a pyrrole.[69]



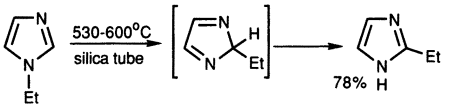
Considerable attention has been paid to the reactions of oxazoles with typical Diels-Alder alkene dienophiles; much of the early work is relatively inaccessible, being described in Russian and patent literature.[70] The adducts are transformed into pyridines by different routes (section 5.15.1.4). Electron-releasing substituents on the oxazoles increase the rate of reaction: 5-alkoxyoxazoles are comparable in reactivity to typical all-carbon dienes. Particularly useful dienophiles are the *N*-acyl-oxazolones: these are synthons for *cis*-1,2-amino-alcohols.[71]



Thermally induced equilibration of oxazole-4-aldehydes and -ketones[72] and 5-ethoxy-4-amides[73] takes place at remarkably low temperatures (90–120°C) giving the more stable, isomeric carbonyl compound. The intermediates are believed to be nitrilium-enolates.

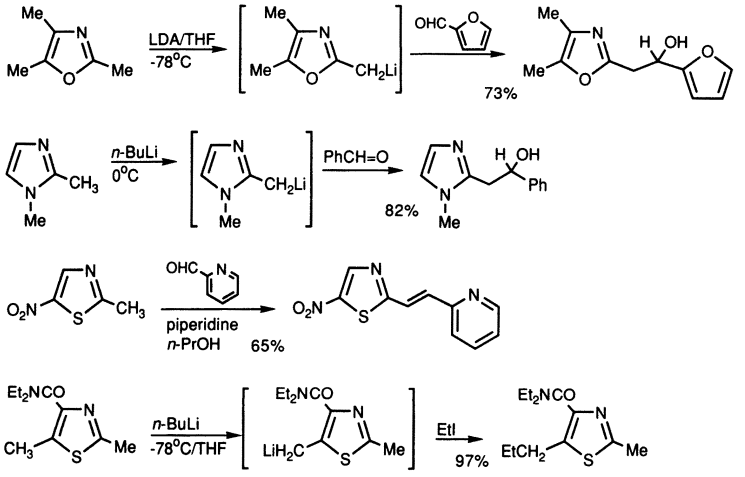


Another thermally induced rearrangement takes place when 1-alkylimidazoles are heated strongly.[74]

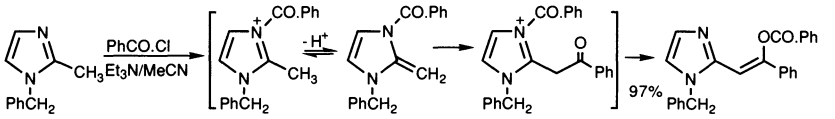


21.9 ALKYL-1,3-AZOLES

Protons on alkyl groups at the 1,3-azole 2-positions are sufficiently acidic for strong base deprotonation,[75] and are more acidic than methyl groups at other positions; even the assistance of an *ortho*-related carboxylate is usually insufficient to overcome the intrinsic tendency for 2-methyl-lithiation, though an adjacent tertiary amide can do this.[76] The side-chain metallated derivatives can be utilised in reactions with electrophiles. The presence of a 5-nitro group allows much milder, base-catalysed condensations to occur.[22]

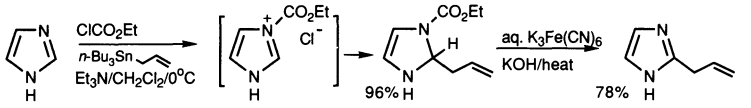


N-Acylation also increases the acidity of 2-methyl groups, allowing acylation *via* a non-isolable enamide.[77]

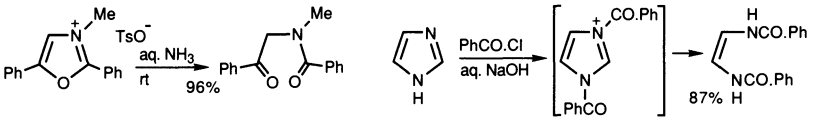


21.10 QUATERNARY 1,3-AZOLIUM SALTS

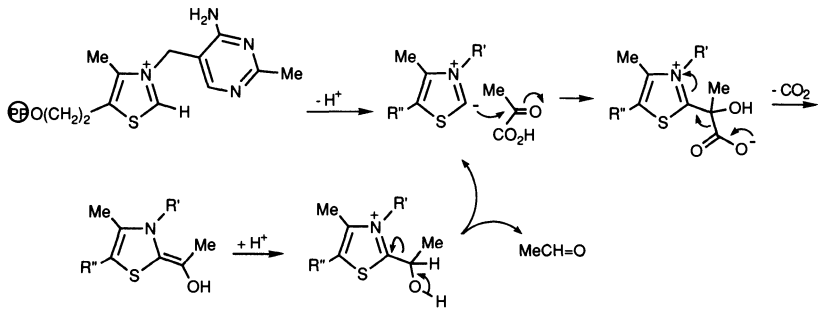
N-acylimidazolium salts will react with allylstannanes, by addition of the equivalent of an allyl anion.[78]



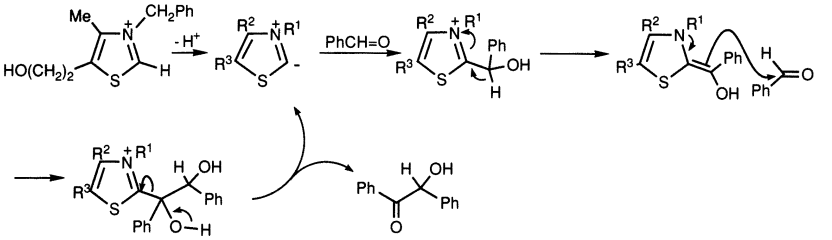
Azolium salts are readily attacked by nucleophiles; for example, with hydroxide, addition at C-2 is followed by ring opening.[79]



The C-2-exchange of azolium salts *via* an ylid mechanism has already been discussed (section 21.1.2.1). Thiamin pyrophosphate acts as a coenzyme in several biochemical processes and in these its mode of action also depends on the intermediacy of a 2-deprotonated species. For example, in the later stages of alcoholic fermentation, which converts glucose into ethanol and carbon dioxide, the enzyme pyruvate decarboxylase converts pyruvate into ethanal and carbon dioxide, the former then being converted into ethanol by the enzyme alcohol dehydrogenase. It is believed that, in the operation of the former enzyme, the coenzyme, thiamin pyrophosphate, adds as its ylid to the ketonic carbonyl group of pyruvate; this is followed by loss of carbon dioxide, then the release of ethanal by expulsion of the original ylid.

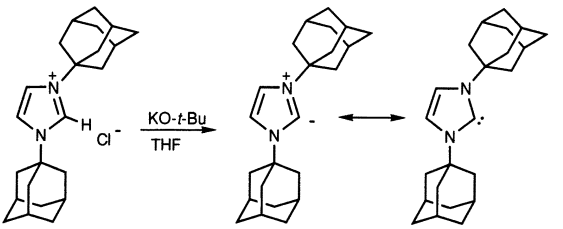


In the laboratory, thiazolium salts (3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride is commercially available) will act as catalysts for the benzoin condensation, and in contrast to cyanide, the classical catalyst, allow such reactions to proceed with alkanals, as opposed to aryl aldehydes; the key steps in thiazolium ion catalysis for the synthesis of 2-hydroxyketones are shown below. Such catalysis, which also finds other applications, provides acyl anions, in effect.



It is very interesting that replacing a thiazolium ring with an oxazolium ring gives a thiamin analogue in which there is complete loss of catalytic activity;[80] similarly, 3,4-dimethyloxazolium iodide has no activity to catalyse a benzoin condensation.[81] Nature has chosen the heterocyclic system with the correct balance – oxazolium ylids are formed faster but, because of the greater stability that this reflects, do not then add to carbonyl groups as is required for catalytic activity. In keeping with the carbenoid character of thiazolium ylids, they dimerise; the dimers, either in their own right, or by reversion to monomer, are also catalysts for the benzoin condensation.[82]

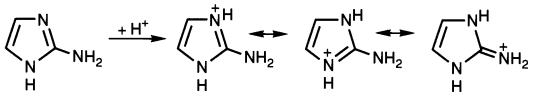
The 1,3-dimethylimidazolium ylid, generated using sodium hydride, allows the introduction of electrophiles to C-2,[83] and the first reported isolable, recrystallisable carbene is an imidazolium ylid: it was prepared by C-2-deprotonation of the highly hindered 1,3-diadamantylimidazolium chloride.[84]



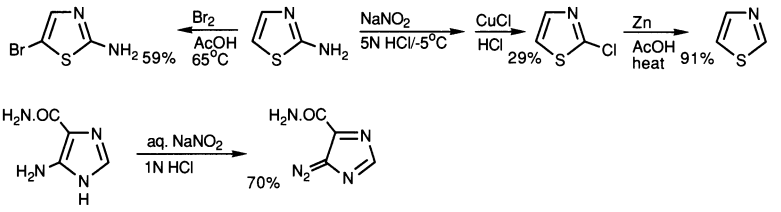
21.11 OXY-[85,86] AND AMINO-1,3-AZOLES

Amino-1,3-azoles exist as the amino tautomers, though 2-arylsulfonylaminothiazoles have been shown to exist as the imino tautomers.[87] 2-Amino-1,3-azoles tend to be more stable than other isomers. All amino-1,3-azoles protonate on the ring nitrogen. 2-Aminothiazole has a pK_a of 5.39 which compares with the

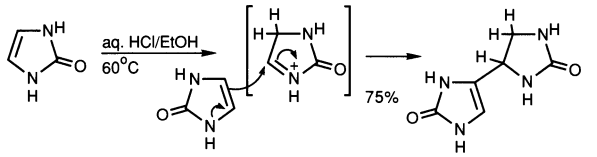
value for 2-aminoimidazole of 8.46, reflecting the symmetry of the resonating guanidinium-type system in the latter.



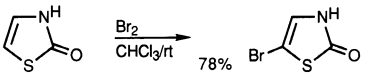
The amino-1,3-azoles behave as normal arylamines, for example undergoing carbonyl condensation reactions, easy electrophilic substitutions,[88] and diazotisation,[89] though 2-aminooxazoles cannot be diazotised,[90] presumably due to the greater electron-withdrawal by the oxygen. In appropriate cases, good yields of diazoazoles,[91] as opposed to azole-diazoniums salts, can be obtained from aminoimidazoles.[92]



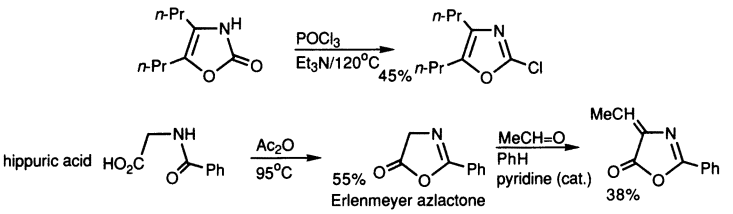
The oxygen-substituted 1,3-azoles exist in their carbonyl tautomeric forms. That there is little aromatic character left in such systems is nicely illustrated by the acid-catalysed dimerisation of imidazol-2-one, which acts as an enamide in the process.[93]



The bromination of thiazol-2-one, at C-5, is also a nice demonstration of relative reactivity: here the double bond carries both sulfur and nitrogen, and it is the latter, i.e. the enamide rather than the thioenol ester character, which dictates the site of electrophilic attack.[94]

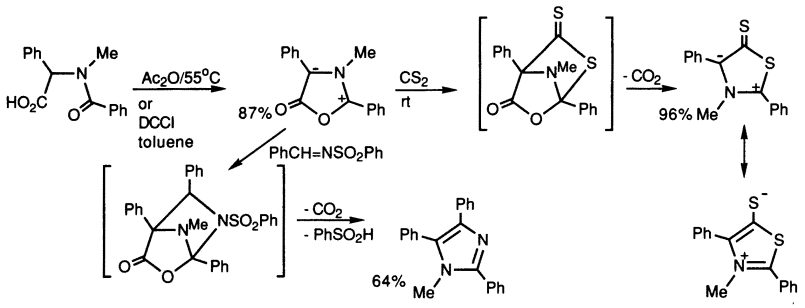


1,3-Azol-2-ones can be converted into the 2-haloazoles by reaction with phosphorus halides.[45] The 5-ones condense in an aldol fashion at C-4.[95]



Alkylation of the 1,3-azolones can take place either on the oxygen, giving alkyloxyazoles, or on nitrogen; for example, thiazol-2-one reacts with diazomethane giving 2-methoxythiazole, but with methyl iodide/methoxide, to give 3-methylthiazol-2-one.[94]

4(5)-Oxazolones are simply cyclic anhydrides of *N*-acyl-α-amino acids, and are constructed in the way that this implies. If the nitrogen also carries an alkyl group, cyclisation[96] can only lead to an overall neutral product by its adopting a zwitterionic structure, for which no neutral canonical form can be written – a mesoionic structure. Mesoionic oxazolones undergo ready dipolar cycloadditions, with loss of carbon dioxide from initial adduct; the examples[97] show the conversion of a mesoionic oxazolone into a mesoionic thiazolone and into an imidazole.



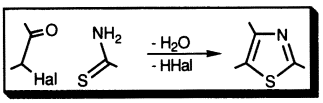
21.12 SYNTHESIS OF 1,3-AZOLES[98]

21.12.1 Ring synthesis

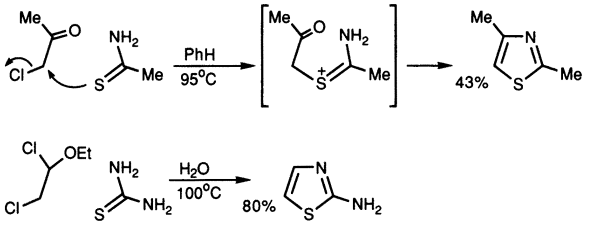
Considerable parallelism emerges from an examination of the major methods for the construction of oxazole, thiazole and imidazole ring systems.

21.12.1.1 *From an α-halocarbonyl component (or an equivalent) and a three-atom unit supplying C-2 and the hetero atoms*

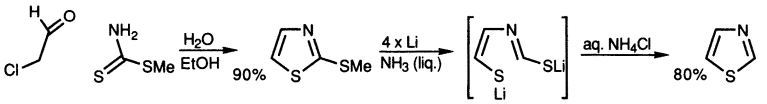
Reaction of an α-halocarbonyl component and a three-atom unit supplying C-2 and the hetero atoms gives the five-membered heterocycle; this route is particularly important for thiazoles.



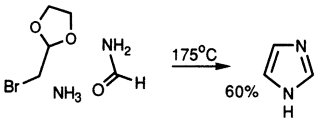
Simple examples of this strategy, which for the synthesis of thiazoles is known as the *Hantzsch synthesis*, are provided by the syntheses of 2,4-dimethylthiazole, where the hetero atoms are provided by thioacetamide,[99] and of 2-aminothiazole, in which 1,2-dichloroethyl ethyl ether is utilised as a synthon for chloroethanal and the hetero atoms derive from thiourea.[100] The first step in such ring syntheses is *S*-alkylation.[101]



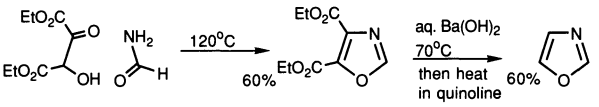
The interaction of ammonia with carbon disulfide produces ammonium dithiocarbamate in solution, which reacts with 2-haloketones to produce thiazol-2-thiones;[102] similarly, methyl dithiocarbamate serves as a component for the construction of 2-methylthiothiazole, reducable to thiazole itself, thus providing a good route to the unsubstituted heterocycle.[103]



Imidazole itself can be prepared efficiently from bromoethanal ethylene acetal, formamide and ammonia; by analogy it is likely that displacement of halogen by ammonia occurs at an early stage.[104]

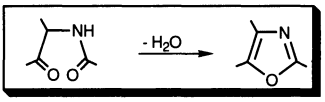


Oxazole itself has been prepared from its 4,5-diester, by hydrolysis then decarboxylation; though this formally falls into the same category of synthesis, it is probable that the ring oxygen derives from the 2-hydroxy-ketone, and not from the formamide;[105] the reaction of acyloins with formamide can be looked on as a general approach to oxazoles.[106] The use of cyanamide gives 2-amino-oxazoles.[107]

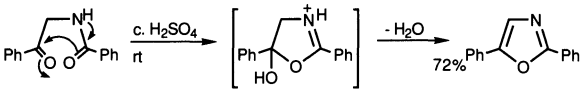


21.12.1.2 *By cyclising dehydration of α-acylaminocarbonyl compounds*

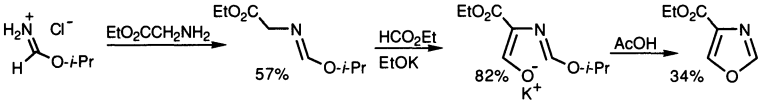
Cyclising dehydration of an α-acylaminocarbonyl compound is particularly important for oxazoles, and can be adapted for thiazole formation.



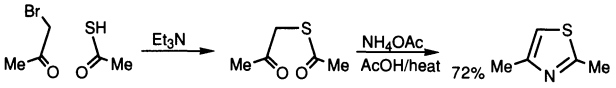
The classical method for making oxazoles, the *Robinson-Gabriel synthesis*, which is formally analogous to the cyclising dehydration of 1,4-dicarbonyl compounds to furans (section 15.13.1.1), is the acid-catalysed closure of α-acylaminocarbonyl compounds.[108]



A synthesis of ethyl oxazole-4-carboxylate illustrates a sophisticated use of this strategy.[109]

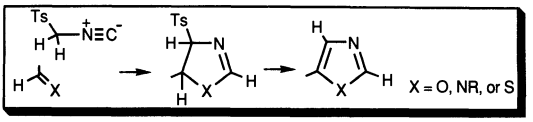


α-Acylthioketones close with ammonia to give thiazoles.[110]



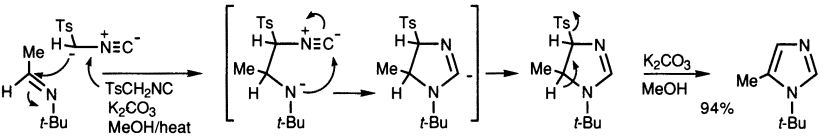
21.12.1.3 *From isocyanides*

Isocyanides, for example tosylmethylisocyanide (TOSMIC), can be converted into 1,3-azoles.

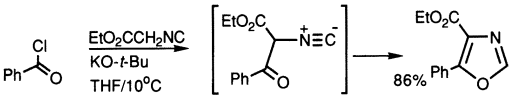


Tosylmethylisocyanide has been used in the synthesis of all three 1,3-azole types. It reacts with aldehydes affording adducts, which lose toluenesulfinate on heating giving oxazoles;[111] with carbon disulfide it produces 4-tosyl-5-

alkylthiothiazoles (following a subsequent *S*-alkylation)[112] and, in analogy to its interaction with aldehydes, it adds to imines when, following elimination of toluenesulfinate, imidazoles are formed.[113]



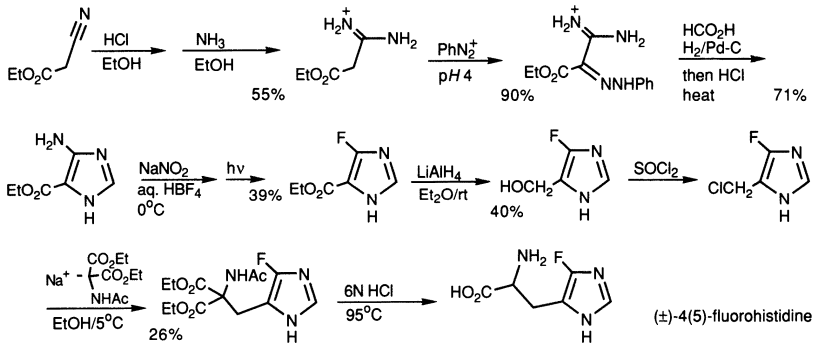
Anions derived from other isocyanides have been acylated (and thioformylated[114]), the products spontaneously closing to oxazoles[115] (thiazoles).



21.12.2 Examples of notable syntheses involving 1,3-azoles

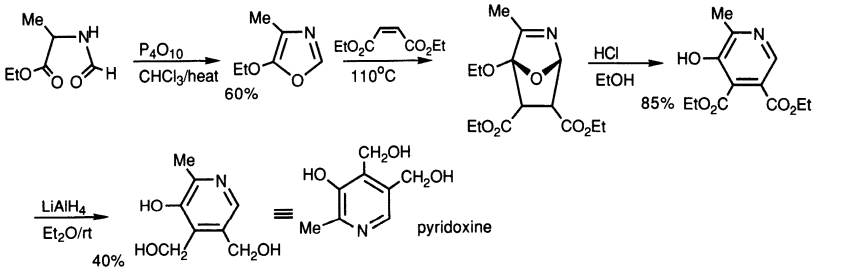
21.12.2.1 *4(5)-Fluorohistamine*

4(5)-Fluorohistamine[116] was synthesised *via* nucleophilic displacement of a side-chain leaving group (cf. pyrroles, section 13.12).



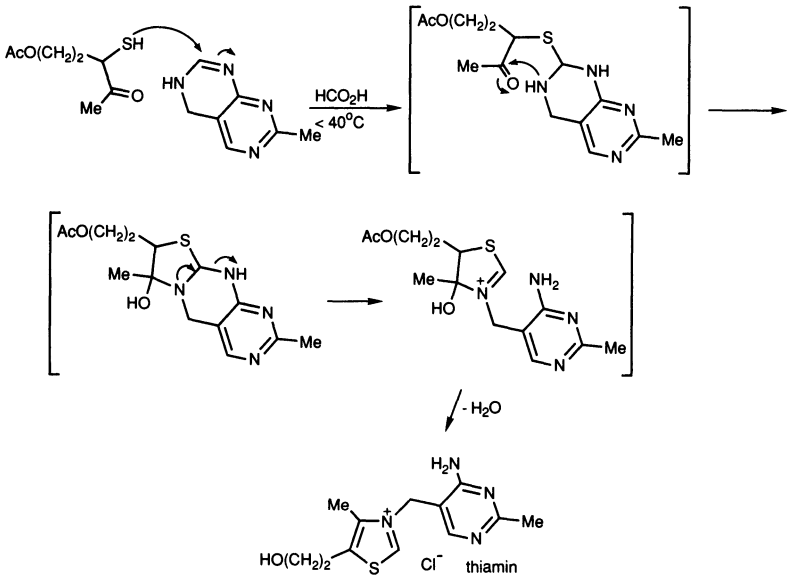
21.12.2.2 *Pyridoxine*[117]

This synthesis illustrates the use of an oxazole undergoing a Diels-Alder addition, leading on to a pyridine.



21.12.2.3 *Thiamin*

Thiamin was first synthesised in 1937.[118] It is widely used as a feed/food additive and in pharmaceutical preparations. A recent synthesis[119] of thiamin utilised an α-keto-thiol; the C-2-carbon was neatly delivered as the carbon of an amidine, one of the nitrogens providing the thiazole ring nitrogen and the other being the eventual amino group of the substituent pyrimidine.



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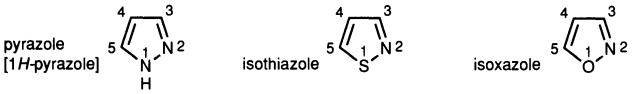
EXERCISES FOR CHAPTER 21

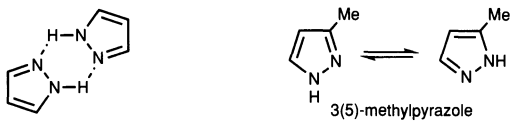
1. Suggest structures for the halo compounds formed in the following ways: (i) imidazole with NaOCl → $C_3H_2Cl_2N$; (ii) 1-methylimidazole with excess Br_2 in AcOH → $C_4H_3Br_3N_2$, then this with EtMgBr followed by water → $C_4H_4Br_2N_2$, and this in turn with *n*-BuLi, then $(MeO)_2CO$ gave $C_6H_7BrNO_2$.
2. Draw structures for the intermediates and final products which are formed when (i) 4-phenyloxazole is heated with but-1-yn-3-one → $C_6H_6O_2$; (ii) 5-ethoxyoxazole is heated with dimethyl acetylenedicarboxylate → $C_{10}H_{12}O_6$.
3. When the cyclic acyloin, $(CH_9)_{10}CO.CH(OH)$ was heated with formamide, in the presence of acid, a bicyclic oxazole, $C_{13}H_{21}NO$, was formed; draw its structure. This bicyclic oxazole was converted by exposure to $^1O_2$, then heating, into the acyclic cyano-acid, $HO_2C(CH_2)_{10}CN$; draw a mechanism for the transformation.
4. Deduce structures for the products formed at each stage of the following syntheses: 1,2-dimethyl-5-nitroimidazole heated with $Me_2NCH(O\text{-}t\text{-}Bu)_2$ → $C_8H_{12}N_4O_2$; this then heated with Ac_2O → $C_{10}H_{14}N_4O_3$. This product reacted (i) with guanidine, $H_2NC(NH_2)=NH$ → $C_9H_{10}N_6O_2$, and (ii) with $MeNHNH_2$ → $C_8H_9N_5O_2$.
5. Deduce structures for the products formed in the following sequences: 1-methylimidazole/*n*-BuLi/−30°C, then TMSCl → $C_7H_{14}NSi$, then *n*-BuLi/−30°C, then TMSCl → $C_{10}H_{22}N_2Si_2$, then this with MeOH/rt → $C_7H_{14}NSi$, which was different to the first product.

6. Explain the following: 4-bromo-1-methylimidazole treated with *n*-BuLi/−78°C then DMF gave $C_5H_6N_2O$. Carrying out the same sequence but allowing the solution to warm to 0°C before addition of DMF gave an isomeric product.
7. Thiazole-2-thione reacted with $Br(CH_2)_3Br$ to give, mainly, a salt $C_6H_8NS_2^+ Br^-$; suggest a structure and a mechanism for its formation.
8. Deduce structures for the 1,3-azoles which are produced from the following reactant combinations: (i) 1-chlorobutan-2-one and thiourea; (ii) thiobenzamide and chloroethanal; (iii) thioformamide and ethyl bromoacetate.
9. Write structures for the intermediates in the following synthesis of 3,4-bisacetoxymethylfuran: phenacyl bromide/$NH_4^+ HCO_2^- \rightarrow C_9N_7NO$; this then heated with $AcOH_2CC{\equiv}CCH_2OAc$.
10. What imidazoles would be formed from the following reactant combination: (i) $MeN{\equiv}C$/*n*-BuLi and $PhC{\equiv}N$; (ii) 2-amino-1,2-diphenylethanone and $H_2NC{\equiv}N$?

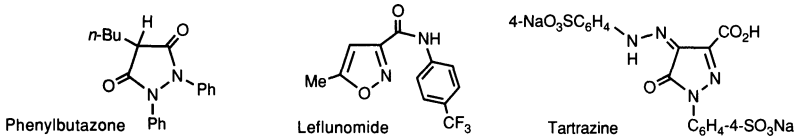
22 1,2-Azoles: pyrazoles, isothiazoles and isoxazoles: reactions and synthesis



The properties of the three 1,2-azoles, pyrazole,[1] isothiazole[2] and isoxazole[3] can be usefully compared and contrasted with those of their 1,3-isomeric counterparts. Echoing the higher boiling point of imidazole, pyrazole, which is the only one of the trio to be solid at room temperature, also has a much higher boiling point (187°C) than isothiazole or isoxazole (114°C and 95°C), again reflecting the intermolecular hydrogen bonding available only to the former. This association probably takes the form of dimers, trimers and oligomers; dimeric forms are of course not available to imidazole. Each 1,2-azole has a pyridine-like odour but is only partially soluble in water. Rapid tautomerism, involving switching of hydrogen from one nitrogen to the other, as in imidazoles, means that substituted pyrazoles are inevitably mixtures, and a nomenclature analogous to that used for imidazoles is employed to signify this: 3(5)-methylpyrazole, for example.



Phenylbutazone has been utilised for some time in the treatment of severe arthritis, which, incidentally, afflicted such notables as Casanova, Goethe and Luther. Leflunomide is in development for the therapy of autoimmune diseases, such as rheumatoid arthritis. There are many pyrazole dyestuffs – the food colourant tartrazine is one such substance.

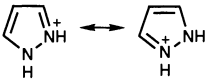


22.1 REACTIONS WITH ELECTROPHILIC REAGENTS

22.1.1 Addition at nitrogen

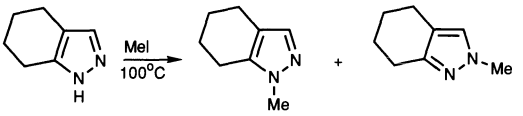
22.1.1.1 *Protonation*

Direct linking of two hetero atoms has a very marked base-weakening effect, as in hydrazine and hydroxylamine (pK_avalues: NH_3, 9.3; H_2NNH_2, 7.9; $HONH_2$, 5.8), and this is mirrored in the 1,2-azoles: pyrazole with a pK_a of 2.5 is some 4.5 pK_a units weaker than imidazole; isothiazole (−0.5) and isoxazole (−3.0) are some 3 pK_a units weaker than their 1,3-isomers. The higher basicity of pyrazole reflects the symmetry of the cation with its two equivalent contributing resonance structures. Clearly, again, oxygen has a larger electron-withdrawing effect than sulfur.



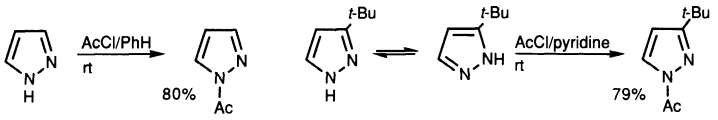
22.1.1.2 *Alkylation at nitrogen*

The 1,2-azoles are more difficult to quaternise than their 1,3-analogues: isothiazoles, for example, require reactive reagents such as benzyl halides and Meerwein salts.[4] Additionally, isoxazolium salts are particularly susceptible to ring cleavage (see section 22.10). 3(5)-Substituted pyrazoles, which have an *N*-hydrogen, can in principle give rise to two isomeric *N*-alkyl pyrazoles, after loss of proton from nitrogen, and there is the further complication that this initial product can undergo further reaction producing an *N,N'*-disubstituted quaternary salt.[5] However, the quaternisation of a 1-substituted pyrazole generally requires more vigorous conditions, no doubt because of steric impediment to reaction due to the substituent on the adjacent nitrogen.



22.1.1.3 *Acylation at nitrogen*

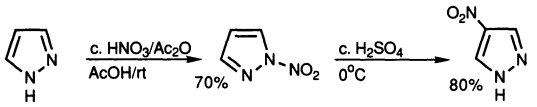
The introduction of an acyl[6] or phenylsulfonyl[7] group onto a pyrazole nitrogen is usually achieved in the presence of a weak base such as pyridine; such processes proceed *via* azomethine nitrogen acylation, then deprotonation. Since acylation, unlike alkylation, is reversible, the more stable product is obtained.



22.1.2 Substitution at carbon

22.1.2.1 *Nitration*

Pyrazole[8] and isothiazole[9] undergo straightforward nitration, at C-4, but the less reactive isoxazole nitrates in only minute yield; 3-methylisoxazole, however, has sufficient extra reactivity that it can be satisfactorily nitrated, at C-4.[10] With the mild nitrating agent, acetyl nitrate, 1-nitropyrazole is formed in good yield; this can be rearranged to 4-nitropyrazole in acid at low temperature.[11]



22.1.2.2 Sulfonation

Electrophilic sulfonation of isoxazole is of no preparative value; the substitution of only the phenyl substituent of 5-phenylisoxazole with chlorosulfonic acid makes the same point.[12] Both isothiazole[9,13] and pyrazole[14] can be satisfactorily sulfonated.

22.1.2.3 *Halogenation*

Halogenation of pyrazole gives 4-monohalopyrazoles, for example 4-iodo-,[15] or 4-bromopyrazole[16] under controlled conditions. Poor yields are obtained on bromination of isothiazole[17] and isoxazole[18] with bromine, again with attack at C-4, but with activating groups present, halogenation proceeds better.[19]

22.1.2.4 *Acylation*

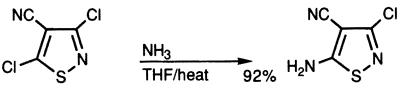
Only for pyrazole, of the trio, have any useful electrophilic substitutions involving carbon electrophiles been described,[7,20] and even here only *N*-substituted pyrazoles react well, perhaps because of inhibition of N^+-salt formation.

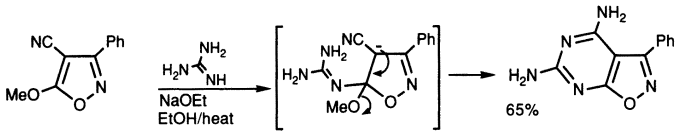
22.2 REACTIONS WITH OXIDISING AGENTS

The 1,2-azole ring systems are relatively stable to oxidative conditions, allowing substituent alkyl, or more efficiently, acyl groups to be oxidised up to carboxylic acid.[21]

22.3 REACTIONS WITH NUCLEOPHILIC REAGENTS

The 1,2-azoles do not generally react with nucleophiles with replacement of hydrogen; there is a limited range of examples of displacements of leaving groups from the 5-position[22] when it is activated by a 4-keto or similar group, but interestingly, 3-halo groups are less easily displaced; 4-halides behave like halobenzenes.

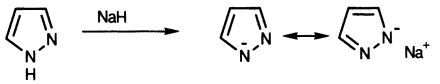




22.4 REACTIONS WITH BASES

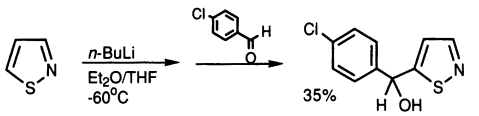
22.4.1 Deprotonation of pyrazole *N*-hydrogen

The pK_a for loss of the *N*-hydrogen of pyrazole is 14.2, compared with 17.5 for pyrrole; for the pyrazolyl anion, there are again two equally contributing resonance forms.

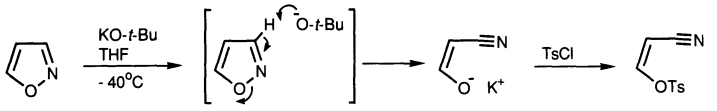


22.4.2 Deprotonation of *C*-hydrogen

The C-5-deprotonation of pyrazoles requires the absence of the *N*-hydrogen; removable *N*-protecting groups which have been used include phenylsulfonyl,[23] trimethylsilylethoxymethyl,[24] hydroxymethyl,[25] methylsulfonyl[26] and pyrrolidin-1-ylmethyl.[27] Isothiazole undergoes rapid exchange at C-5 with sodium deuteroxide in DMSO[28] and can be preparatively 5-lithiated in the usual way.[29]

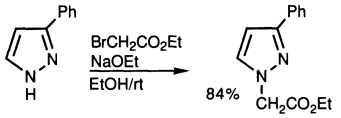


Attempted *C*-deprotonation of isoxazoles with hydrogen at C-3 leads inevitably to ring opening, with the oxygen as anionic leaving group[30] indeed this type of cleavage was first recognised as long ago as 1891, when Claisen found that 5-phenylisoxazole was cleaved by sodium ethoxide[31] (see section 22.10 for ring cleavage of isoxazolium salts). Comparable cleavages of isothiazoles can also be a problem.

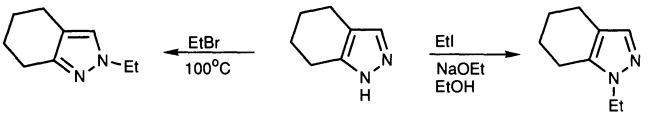


22.5 REACTIONS OF *N*-METALLATED PYRAZOLES

Alkylation of pyrazoles in basic solution involves an *N*-anion, and proceeds straightforwardly.[32]

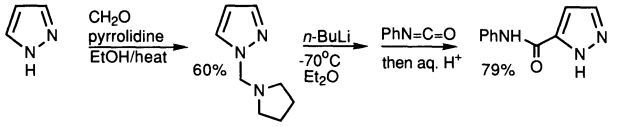


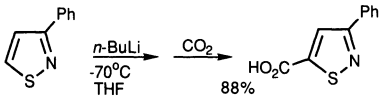
3(5)-Substituted pyrazoles may give a product isomeric with that which is obtained by reaction in neutral solution.[5]



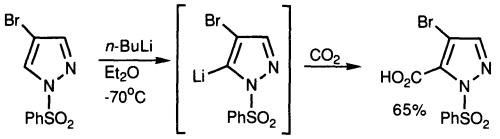
22.6 REACTIONS OF *C*-METALLATED 1,2-AZOLES

The reactions of 5-lithiated isothiazoles and of 5-lithiated-1-substituted pyrazoles allow the introduction of substituents at that position by reaction with a range of electrophiles; two examples are shown below.[27,33]



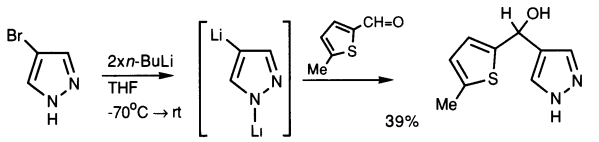


It is significant that treatment of 4-bromo-1-phenylsulfonylpyrazole with *n*-butyllithium results in 5-deprotonation and not metal–halogen exchange.[23]



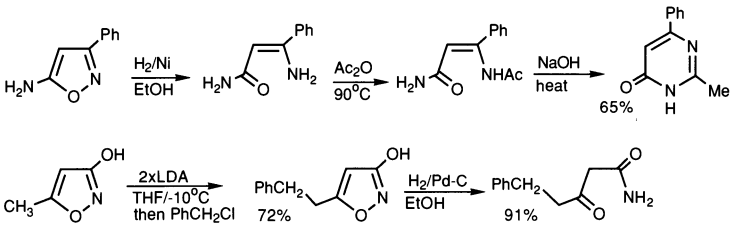
Metal–halogen exchange has been achieved in the formation of 3-lithio-1-methylpyrazole from the bromopyrazole,[34] and reaction of 4-bromopyrazole

with two equivalents of *n*-butyllithium produced a 1,4-dilithiopyrazole which reacted normally with electrophiles at C-4.[35]



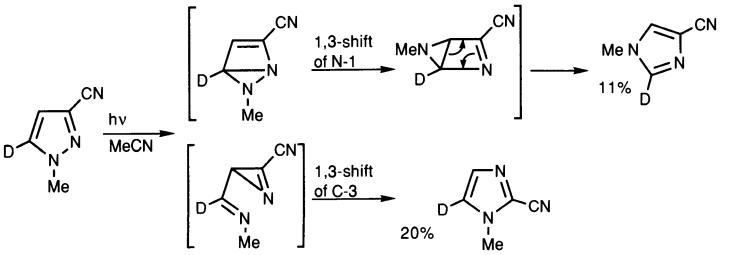
22.7 REACTIONS WITH REDUCING AGENTS

Pyrazoles are relatively stable to catalytic and chemical reductive conditions, particularly when there is no substituent on nitrogen, though catalytic reduction can be achieved in acid solution.[36] Isothiazoles are reductively desulfurised using Raney nickel, with loss of the ring.[37] Catalytic hydrogenolysis of the N–O bond in isoxazoles takes place readily over the usual noble metal catalysts,[38] and this process is central to the stratagem in which isoxazoles are employed as masked 1,3-dicarbonyl compounds. The immediate products of N–O hydrogenolysis, β-aminoenones, can often be isolated as such, or further processed. The use of this ring cleavage to provide routes to pyrimidinones[39] and 3-keto-carboxamides is illustrated below.[40]



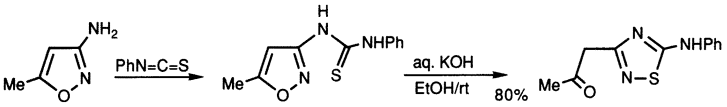
22.8 ELECTROCYCLIC AND PHOTOCHEMICAL REACTIONS

There are examples of 1,2-azoles being converted into their 1,3-isomers by irradiation; for example, the conversion of cyanopyrazoles into cyanoimidazoles was studied using 3-cyano-5-deuterio-1-methylpyrazole, the resulting mixture of products requiring a duality of mechanism.[41]



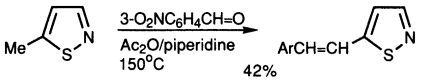
In a similar way, many simpler pyrazoles were converted into imidazoles,[42] phenylisothiazoles partially converted into phenylthiazoles,[43] and 3,5-diarylisoxazoles converted into 2,5-diaryloxazoles by irradiation.[44]

The transformation of 1,2-azoles carrying, at C-3, a side-chain of three atoms terminating in a doubly bonded hetero atom, into isomeric systems with a new five-membered ring is a general process,[45] though there is no definitive view as to the details of its mechanism.

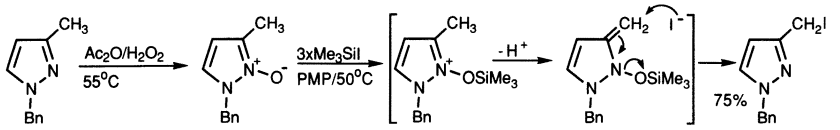


22.9 ALKYL-1,2-AZOLES

4-Methylisothiazoles are not especially acidic, but it is rather surprising that 3-methylisothiazoles are also not reactive, whereas 5-methyl substituents will undergo condensation reactions.[46]



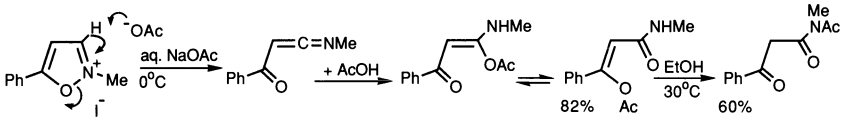
This same effect is also found in isoxazoles. In order to study methyl group acidity in isoxazoles, the 3-position was blocked to prevent ring degradation (section 22.4.2); thus 3,5-dimethylisoxazole was shown to exchange, with methoxide in methanol, 280 times faster at the 5- than at the 3-methyl group. Preparative deprotonations of this same isoxazole proceed exclusively at the 5-methyl substituent, allowing subsequent reactions with electrophiles at that position. So strong is this tendency, that reaction of 3,5-dimethylisoxazole with three equivalents of base and three equivalents of iodomethane produces only 5-*t*-butyl-3-methylisoxazole, no alkylation of the 3-methyl being observed, even in competition with the 5-isopropyl group which is present in a penultimate intermediate.[47] By working at low temperature, thus avoiding ring degradation, 5-methylisoxazole can be deprotonated at the methyl, without the 3-deprotonation which would cause ring degradation.[48] Conversion to *N*-oxide[49] activates adjacent methyl groups, for example subsequent reaction with trimethylsilyl iodide permits side-chain iodination.[50]



22.10 QUATERNARY 1,2-AZOLIUM SALTS

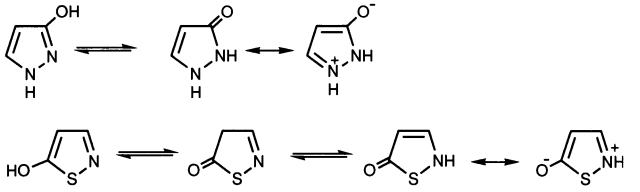
The base-catalysed degradation of the ring of isoxazolium salts is particularly easy, requiring only alkali metal carboxylates to achieve it. The mechanism,[51]

illustrated for the acetate-initiated degradation of 2-methyl-5-phenylisoxazolium iodide, involves initial 3-deprotonation with cleavage of the N–O bond; subsequent rearrangements lead to an enol acetate which rearranges to a final keto-imide.

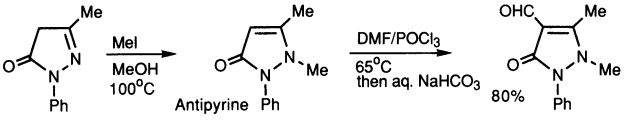


22.11 OXY- AND AMINO-1,2-AZOLES

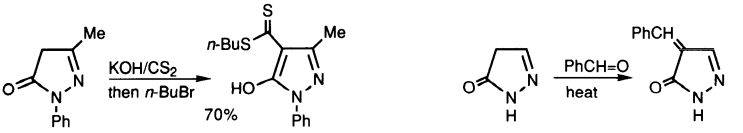
Only 4-hydroxy-1,2-azoles can be regarded as being phenol-like.[52] 3- and 5-Hydroxy-1,2-azoles exist mainly in carbonyl tautomeric forms, encouraged by resonance involving donation from a ring hetero atom, and are therefore known as pyrazolones, isothiazolones and isoxazolones, though for all three systems, and depending on the nature of other substituents, an appreciable percentage of hydroxy tautomer exists in solution.



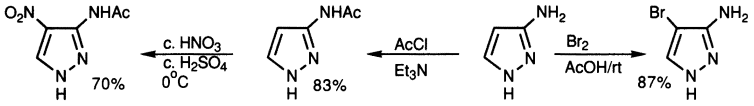
The reactivity of the 3- and 5-azolones centres mainly on their ability to react with electrophiles such as halogens[53] (giving 4,4-dihalo-derivatives with excess reagent), or to nitrate,[54] or undergo Vilsmeier formylation;[55] the example shown below is the formylation of 'Antipyrine', once used as an analgesic. Many dyestuffs have been synthesised *via* coupling of aryldiazonium cations with 5-pyrazolones at C-4 – tartrazine is such an example.



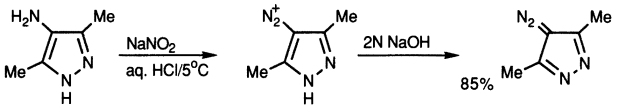
Pyrazolones also condense with aldehydes[56] in aldol-type processes, or react with other electrophiles such as carbon disulfide,[57] in each case reaction presumably proceeding *via* the enol tautomer, or its anion.



Amino-1,2-azoles exist as the amino tautomers. Aminopyrazoles and aminoisothiazoles are relatively well-behaved aromatic amines, for example 3(5)-aminopyrazole undergoes substituent-*N*-acetylation and easy electrophilic bromination at C-4.[58] Diazotisation and a subsequent Sandmeyer reaction provides routes to halo-isothiazoles[59] and azidopyrazoles.[60]



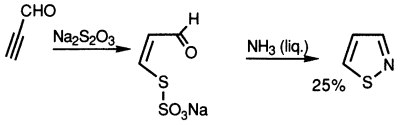
Diazotisation of 4-aminopyrazoles, then deprotonation, yields stable diazopyrazoles.[61]



22.12 SYNTHESIS OF 1,2-AZOLES

22.12.1 Ring synthesis

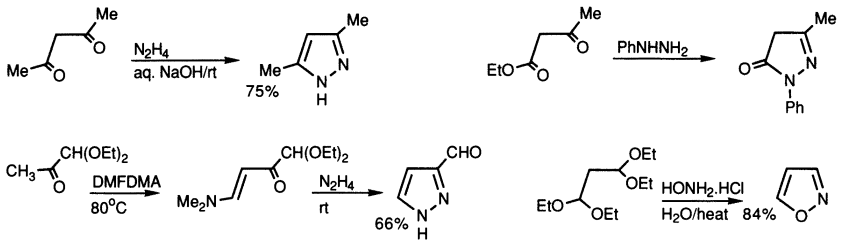
There are parallels, but also methods unique to particular 1,2-azoles, in the principal methods available for the construction of pyrazoles, isothiazoles and isoxazoles: neither the reaction of propene with sulfur dioxide and ammonia at 350°C, which gives isothiazole itself[62] in 65% yield, nor a convenient laboratory synthesis[63] from propargyl aldehyde and thiosulfate have direct counterparts for the other 1,2-azoles.



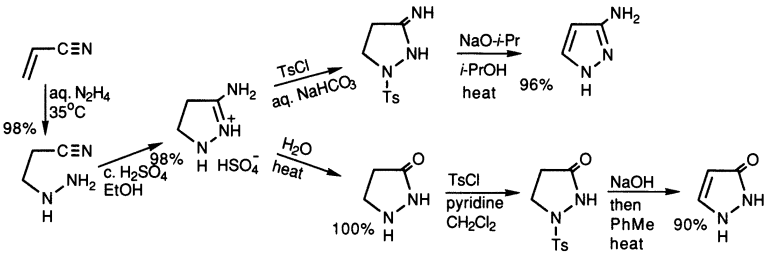
22.12.1.1 *From 1,3-dicarbonyl compounds and hydrazines or hydroxylamine*

Pyrazoles and isoxazoles can be made from a 1,3-dicarbonyl component and a hydrazine or hydroxylamine respectively.

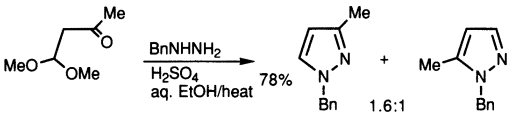
This, the most widely used route to pyrazoles and isoxazoles rests on the doubly nucleophilic character of hydrazines and hydroxylamines, allowing them to react in turn with each carbonyl group of a 1,3-diketone,[64] keto-aldehyde (usually with the aldehyde masked[65] as enol ether, acetal or enamine[66]), β-keto-ester, or an equivalent of one of these.



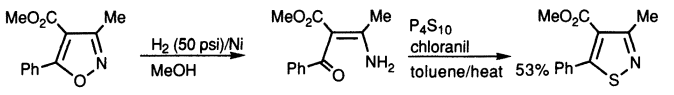
When β-keto-esters are used, the products are pyrazolones[67] or isoxazolones;[68] similarly, β-ketonitriles with hydrazines give aminopyrazoles.[69] 3(5)-Aminopyrazole itself is prepared *via* a dihydro-precursor formed by addition of hydrazine to acrylonitrile then cyclisation;[70] hydrolysis of the first cyclic intermediate in this sequence and dehydrogenation *via* elimination of *p*-toluenesulfinate allows preparation of 3-pyrazolone.[71]



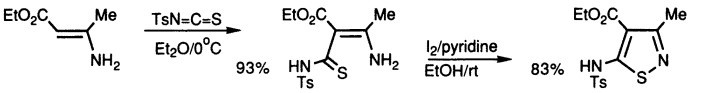
Generally speaking, unsymmetrical 1,3-dicarbonyl components produce mixtures of 1,2-azole products.[50] Sometimes this difficulty can be circumvented by the use of acetylenic-aldehydes or -ketones, for here a hydrazone or oxime can be formed first by reaction at the carbonyl group and this can then be cyclised in a separate, second step.[72] Pyrazole itself can be formed by the reaction of hydrazine with propargyl aldehyde.[8] Using β-chloro-[73] or -alkoxy-enones[74] as 1,3-dicarbonyl synthons also allows control over the regiochemistry of attack.



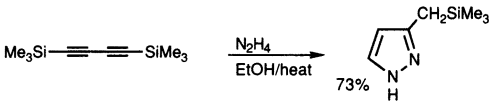
When a β-aminoenethione, which can be produced from an isoxazole *via* hydrogenolysis, then reaction of the β-aminoenone with a thionating agent, is treated with a dehydrogenating agent such as chloranil[75] or sulfur,[76] ring closure to an isothiazole results.



The ring closure of β-aminoene-thioamides (N–C=C–C(=S)N) comparably leads to 5-aminoisothiazoles.[77]

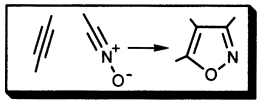


In an interesting variant, isoxazoles and pyrazoles can be constructed from diynes.[78]

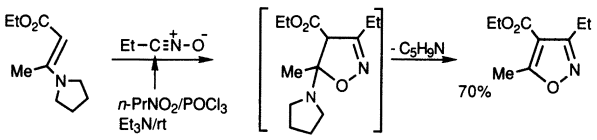


22.12.1.2 *Dipolar cycloadditions of nitrile oxides*

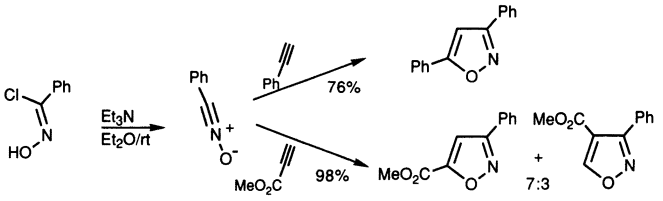
Isoxazoles are produced by the dipolar cycloaddition of nitrile oxides to alkynes.



Nitrile oxides (R–C≡N⁺–O⁻),[79] which can be generated by elimination of hydrogen chloride from chlorooximes (RC(Cl)=NOH), or by dehydration of nitro compounds (RCH_2NO_2), readily add to alkenes and to alkynes generating five-membered heterocycles. Addition to an alkene produces a dihydroisoxazole (isoxazoline), unless the alkene also incorporates a group capable of being eliminated in a step after the cycloaddition;[80] isoxazolines can sometimes be dehydrogenated to the aromatic system.[81]

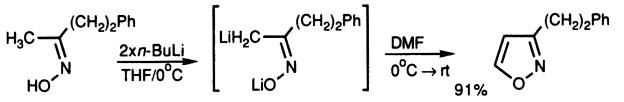


Cycloaddition of a nitrile oxide to an alkyne generates an aromatic isoxazole directly. Mono-alkyl or -aryl-substituted alkynes lead to 5-substituted isoxazoles;[82] with other mono-substituted alkynes mixtures are obtained.[83] The use of tin- and boron-substituted alkynes produces the metal-substituted heterocycle which can then be used, for example, in coupling processes.

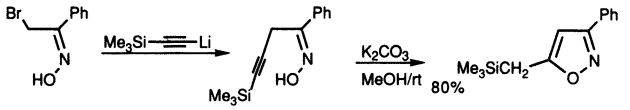


22.12.1.3 *From oximes and hydrazones*

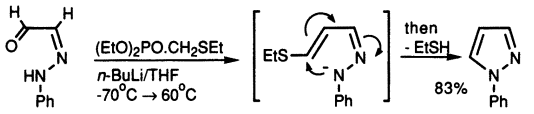
Exposure of ketone oximes which have an α-hydrogen, to two mol equivalents of butyllithium leads to *C*-lithiation *syn* to the oxygen; reaction with dimethylformamide as electrophile then allows *C*-formylation and ring closure *in situ* to an isoxazole.[84]



Displacement of the halogen of an α-bromoketone oxime with an alkyne leads to an intermediate which closes to an isoxazole simply on treatment with mild base.[85]



Introduction of the future C-5 into a 1,2-diketone monohydrazone, at the correct oxidation level and *via* a Wittig reaction, leads to pyrazoles.[86]



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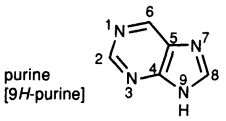
EXERCISES FOR CHAPTER 22

1. Suggest structures for the isomeric products, $C_9H_7N_3O_2$, formed when 1-phenylpyrazole is reacted with (i) c. H_2SO_4/c. HNO_3 or (ii) Ac_2O/HNO_3. Explain the formation of different products under the two conditions.

2. Draw structures for the products obtained by reacting 3,5-dimethylisoxazole with $NaNH_2$ then (i) *n*-PrBr; (ii) CO_2; or (iii) $PhCO_2Me$.
3. Deduce structures for the products obtained by treating 5-methylisoxazole with SO_2Cl_2 → C_4H_4ClNO, and this with aqueous sodium hydroxide → C_4H_4ClNO (which contains no rings).
4. Draw the structures of the products which would be formed from the reaction of $BnNHNH_2$ with $MeCO.CH_2CO.CO_2Me$.
5. Draw the structures of the two products which are formed when hydroxylamine reacts with $PhCO.CH_2CH{=}O$; suggest an unambiguous route for the preparation of 5-phenylisoxazole.
6. Deduce structures for the products formed in the following sequence: pyrazole/Me_2NSO_2Cl/Et_3N → $C_5H_9N_3O_2S$, then this with *n*-BuLi/−70°C, then TMSCl → $C_8H_{17}N_3O_2SSi$, then this with PhCH=O/CsF → $C_{12}H_{15}N_3SO_3$.
7. Deduce the structures of the heterocyclic substances produced: (i) C_7H_9NO, from cyclohexanone oxime with 2 mol equivalents of *n*-BuLi then dimethyl formamide; (ii) $C_{11}H_{15}NOSSi$ from thien-3-ylC(=NOH)CH_2Br and $Me_3SiC{\equiv}CLi$, then K_2CO_3/MeOH; (iii) $C_{11}H_{12}N_2$ from $MeCO.C(=NNHPh)Me$ with $(EtO)_2PO.CH_2SEt$/*n*-BuLi.
8. Suggest a structure for the heterocyclic product, $C_7H_{13}NOSi$, formed by reaction of $Me_3SiC{\equiv}CC{\equiv}CSiMe_3$ and hydroxylamine.

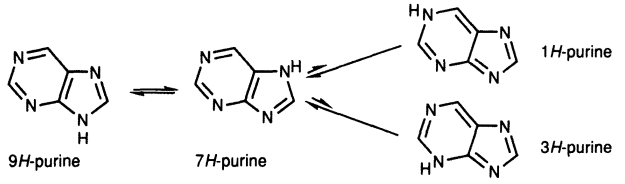
Purines: reactions and synthesis

23



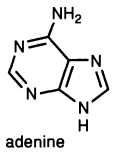
Purines are of great interest for several reasons, but in particular, together with certain pyrimidine bases, they are constituents of DNA and RNA and consequently of fundamental importance in life processes. Additionally, as nucleosides and nucleotides (see below) they act as hormones and neurotransmitters and are present in some co-enzymes. The interconversion of mono-, di-, and triphosphate esters of nucleosides is at the heart of energy-transfer in many metabolic systems and is also involved in intracellular signalling. This central biological importance, together with medicinal chemists' search for anti-tumour and anti-viral (particularly anti-AIDS) agents, have resulted in a rapid expansion of purine chemistry in recent years.

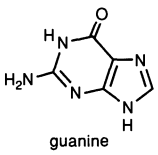
There are significant lessons to be learnt from the chemistry of purines, since their reactions exemplify the interplay of its constituent imidazole and pyrimidine rings just as the properties of indole show modified pyrrole and modified benzene chemistry. Thus purines can undergo both electrophilic and nucleophilic attack at carbon in the five-membered ring, but only nucleophilic reactions at carbon in the six-membered ring.

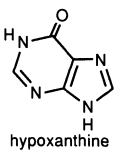


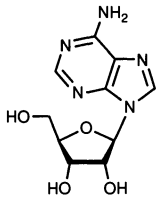
The numbering of the purine ring system is anomolous and reads as if purine were a pyrimidine derivative. There are in principle four possible tautomers of purine containing an *N*-hydrogen; in the crystalline state purine exists as the

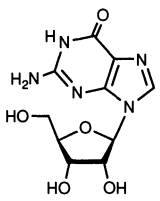
7*H*-tautomer, however in solution both 7*H*- and 9*H*-tautomers are present in approximately equal proportions; the 1*H*- and 3*H*- tautomers are not significant.[1]

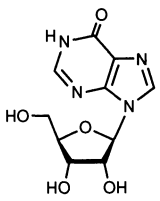

adenine

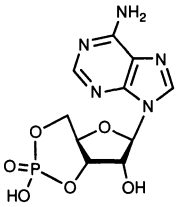

guanine


hypoxanthine

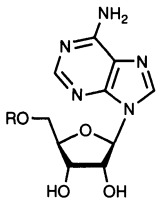

adenosine

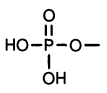

guanosine

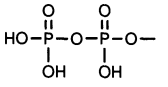

inosine

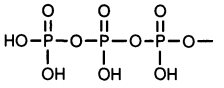

cyclic AMP

Not surprisingly, because the naturally occurring purines are amino and/or oxygenated substances, the majority of reported purine chemistry pertains to such derivatives and, as a consequence, reactions of the simpler examples, such as in other chapters are given as typical, have received limited attention. Since the study of purines stems from interest in the naturally occurring derivatives, a 'trivial' nomenclature has evolved which is in general usage. A **nucleoside** is a sugar (generally 9-(riboside) or 9-(2′-deoxyriboside)) derivative of a purine base (or pyrimidine base); for example, adenosine is the 9-(riboside) of adenine, itself the generally used trivial name for 6-aminopurine. A **nucleotide** is a 5′-phosphate (or di- or tri-phosphate) of a nucleoside – adenosine 5′-triphosphate (ATP) is an example.

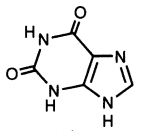


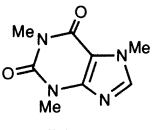
adenosine-5′-monophosphate (AMP) R = 

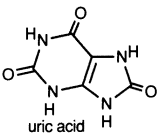
adenosine-5′-diphosphate (ADP) R = 

adenosine-5′-triphosphate (ATP) R = 

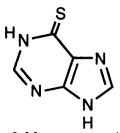
Caffeine (1,3,7-trimethylxanthine) is the well-known stimulant present in tea and coffee. In mammals the end-product of metabolic breakdown of nucleic acids is urea, but in birds and reptiles it is uric acid; uric acid was one of the first heterocyclic compounds to be isolated as a pure substance, for it was obtained from gallstones by Scheele in 1776.

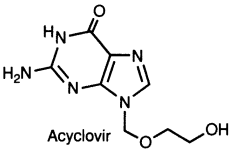

xanthine

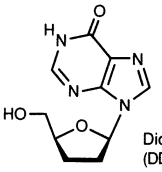

caffeine


uric acid

6-Mercaptopurine is used in the treatment of leukemia and other cancers, Acyclovir is an antiviral agent used in the treatment of *Herpes* infections, and DDI is used in the treatment of AIDS.

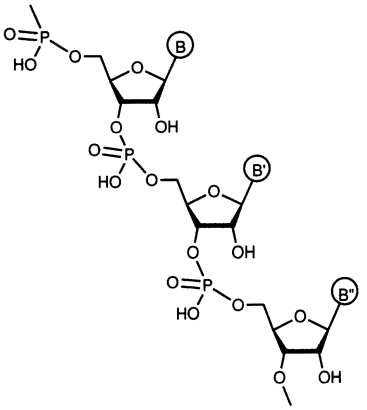

6-Mercaptopurine


Acyclovir


Dideoxyinosine (DDI)

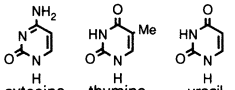
23.1 NUCLEIC ACIDS, NUCLEOSIDES AND NUCLEOTIDES[2]

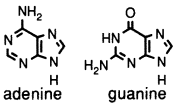
Nucleic acids are high-molecular-weight, mixed polymers of mononucleotides, in which chains are formed by monophosphate links between the 5′-position of one nucleoside and the 3′-position of the next. The 'backbone' of the chain is thus composed of alternating phosphates and sugars, to which purine and pyrimidine bases are attached at regular intervals. The polymer is known as **r**ibo**n**ucleic **a**cid (RNA) when the sugar is ribose, and **d**eoxyribo**n**ucleic **a**cid (DNA) when the sugar is 2-deoxyribose.



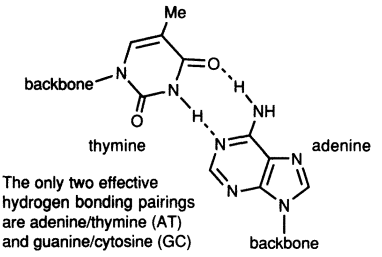
The (-phosphate-sugar-phosphate-sugar-) 'backbone' of RNA

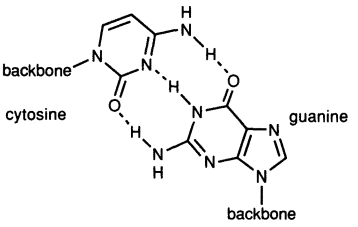
B, B', B" represent the purine and pyrimidine bases


cytosine thymine (DNA only) uracil


adenine guanine

DNA contains two purine bases, guanine and adenine, and two pyrimidine bases, cytosine and thymine. In RNA, thymine is replaced by uracil and in another form, *t*-RNA, other bases including small amounts of *N*-alkylated derivatives are present.





Nucleic acids occur in every living cell. DNA carries genetic information and transfers this information, *via* RNA, thus directing protein synthesis. The genetic information embodied in DNA is connected with the close association of two nucleic acid strands, which is based on very specific hydrogen bonding between an adenine (A) residue of one strand and a thymine (T) residue in the precisely opposite section of the other strand, and between a cytosine (C) residue on one strand and a guanine (G) residue on the other. This pairing is absolutely specific – adenine cannot form multiple hydrogen bonds with guanine or cytosine and cytosine cannot form multiple hydrogen bonds with thymine or adenine. It is amazing that all heredity and evolution depend on two sets of hydrogen bonds! The genetic code for the synthesis of a particular amino acid is a sequence of three bases attached to the backbone, read in the 5′ → 3′ direction; for example, the triplet which codes for the synthesis of tryptophan is UGG, however most amino acids can be coded for by more than one triplet, some having as many as four, the variation coming in the third nucleotide, thus both UAU and UAC code for tyrosine. The genetic information is transmitted when the strands of the DNA separate, replication then being governed by the establishment of the AT and GC sets of hydrogen bonds to a newly developing strand.

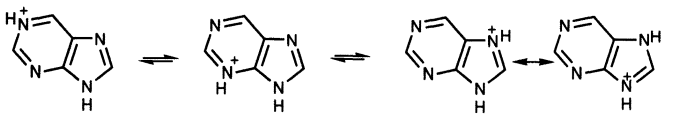
23.2 REACTIONS WITH ELECTROPHILIC REAGENTS

23.2.1 Addition at nitrogen

23.2.1.1 *Protonation*

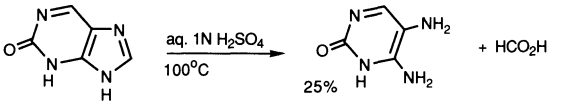
Purine is a weak base, pK_a 2.5. ^{13}C NMR studies suggest that all three protonated forms are present in solution but the predominant cation is formed by N-1-protonation.[3] In strong acid solution a dication is formed by protonation at N-1 and on the five-membered ring.[4]

The presence of oxygen functions does not seem to affect purine basicity to



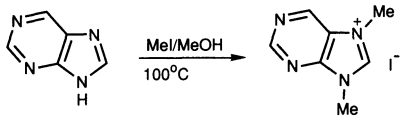
any great extent, thus hypoxanthine has a pK_a of 2.0. Amino groups increase the basicity, as illustrated by the pK_a of adenine, 4.2, and oxo groups reduce the basicity of amino-purines, thus guanine has a pK_a of 3.3; the position of protonation of the latter in the solid state has been established, by X-ray analysis, as on the five-membered ring – this nicely illustrates the extremely subtle interplay of substituents and ring hetero atoms, for although the 2-amino substituent increases the basicity of the purine to which it is attached, this does not necessarily mean that it is the associated N-3 which is protonated.

Purine itself slowly decomposes in aqueous acid, to the extent of about 10% in 1N sulfuric acid at 100°C. The stability of oxypurines to aqueous acid varies greatly; for example, xanthine is stable to aqueous 1N sulfuric acid at 100°C whereas 2-oxypurine is completely converted into a pyrimidine in 2 hours under the same conditions.



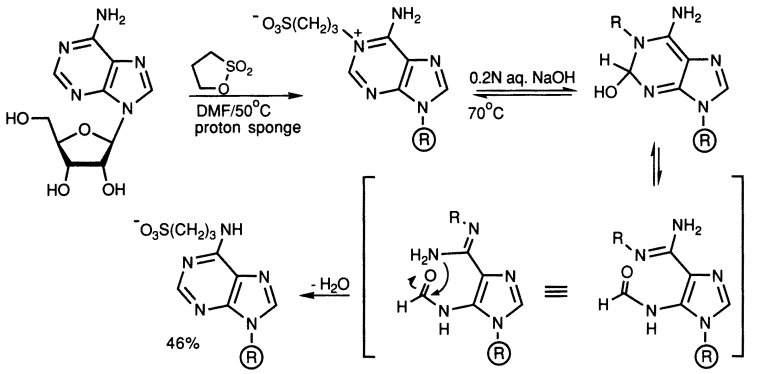
23.2.1.2 *Alkylation at nitrogen*

As would be expected from systems containing four nitrogen atoms, *N*-alkylation of purines is complex and can take place on the neutral molecule or *via* an *N*-anion. Purine reacts with iodomethane to give a 7,9-dimethylpurinium salt.[5]

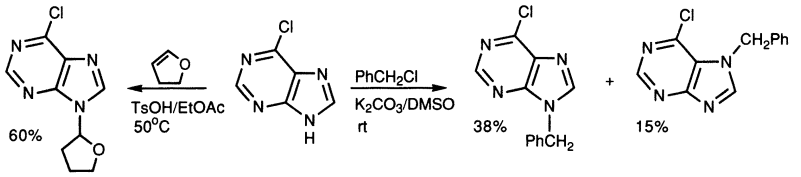


Adenine gives mainly 3-alkylated products under neutral conditions but 7/9-substitution when there is a base present. Adenosine derivatives on the other hand usually give 1-alkylated products, presumably due to hindrance to *N*-3-attack by the *peri* 9-ribose substituent. That attack can still occur at N-3 is shown by the intramolecular quaternisation, which is an important side- reaction when 5′-halides are subjected to displacement conditions.

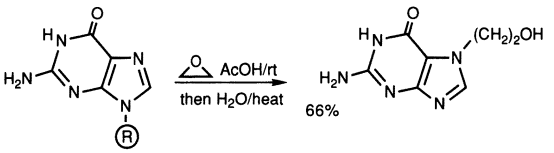
An effective method for alkylating the 6-amino group of adenosine is to effect rearrangement of a 1-alkyladenosinium salt; this involves an ANRORC sequence, another example of a Dimroth rearrangement.[6]



Alkylation of oxygenated purines in alkaline media, for example hypoxanthine, tends to occur both at amidic nitrogen and also at a five-membered ring nitrogen, making selectivity a problem. Under neutral conditions xanthines give 7,9-dialkylated quaternary salts. The alkylation of 6-chloropurine illustrates the complexity: in basic solution both 7- and 9-substitution occurs,[7] whereas reaction with a carbocation is selective for N-9.[8]

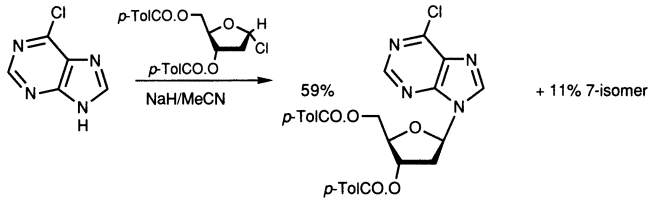


Regiospecific 7-alkylations can be achieved *via* the quaternisation of a 9-riboside followed by hydrolytic removal of the sugar residue.[9] The ratio of N-9 to N-7 alkylation is also influenced by the size of a 6-substituent, larger groups at C-6 lead to increased percentages of 9- *versus* 7-alkylation.[10] The N-9 : N-7 ratio of products varies with time when alkylations employ a Michael acceptor like methyl acrylate, for here the alkylation is reversible and the concentration of thermodynamic product can build up.[11]

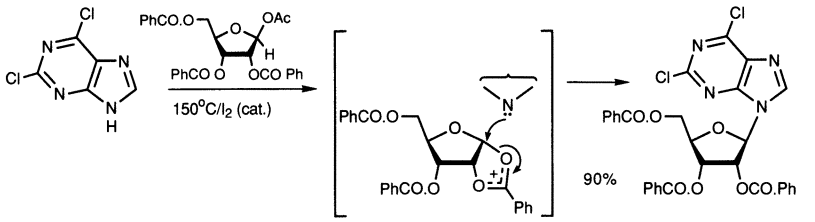


In the ribosylation of purines, in addition to the question of regioselectivity on the purine, there is the possibility of forming epimeric products at the linking C-1′ of the ribose, and this is often the more difficult to control. A great deal of work has been done and many different conditions shown to be effective in specific cases, but conditions which are generally effective have not been defined.[12]

These alkylations usually employ acylated or halo ribosides in conjunction with a purine derivative of mercury,[13] silicon[12] or sodium,[14] and stereoselective displacements of halide can sometimes be achieved.

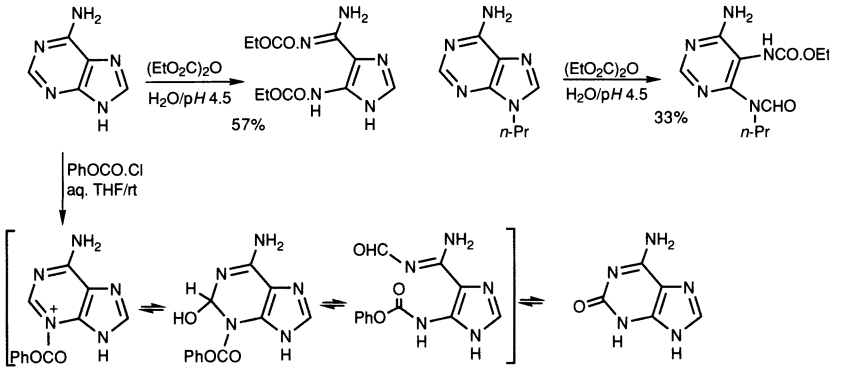


Other methods of controlling stereochemistry include the use of the size of an isopropylidene protecting group to shield one face of the sugar[15] or, as shown, achimeric assistance from a 2′-benzoate.[16]



23.2.1.3 *Acylation at nitrogen*

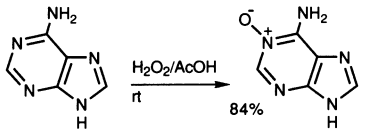
Purines react with acylating agents such as chloroformates or ethyl pyrocarbonate[17] to give non-isolable N^+-acyl salts, which can suffer various fates following nucleophilic addition; products of cleavage of either ring have been observed, as have recyclisation products.[18]



23.2.1.4 *Oxidation at nitrogen*

Peracid *N*-oxidation of purines gives 1- and/or 3-oxides, depending on exact conditions.[19] Adenine and adenosine give 1-oxides whereas guanine affords the 3-oxide.[20] The 3-oxide of purine itself has been obtained *via* oxidation of 6-

cyanopurine (at N-3), then hydrolysis and decarboxylation,[19] the relatively easy loss of carbon dioxide echoing the analogous process discussed for pyridine-α-acids (section 5.12).

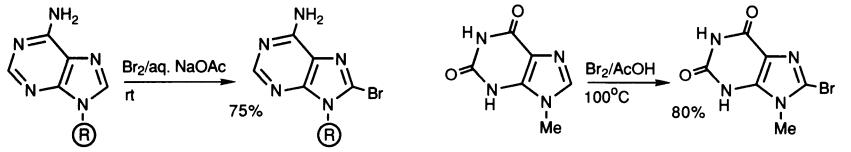


23.2.2 Substitution at carbon

Typical electrophilic aromatic substitution reactions have not been reported for purine or simple alkyl derivatives.

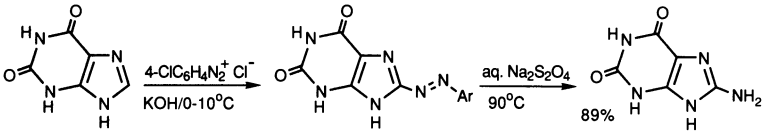
23.2.2.1 *Halogenation*

Purine itself simply forms an N^+-halogen complex but does not undergo *C*-substitution, however adenosine,[21] hypoxanthine and xanthine derivatives[22] undergo chlorination and bromination at C-8. There is the possibility that these substitution products arise *via* *N*-halopurinium salts, nucleophilic addition of bromide anion to these at C-8, then elimination of hydrogen halide.



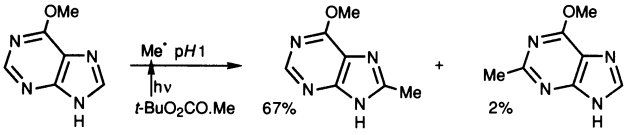
23.2.2.2 *Coupling with diazonium salts*

Amino and oxypurines couple at their 8-position; a weakly alkaline medium is necessary, so it seems likely that the reactive entity is an anion.[23]



23.3 REACTIONS WITH RADICAL REAGENTS

Purines react readily with hydroxyl, alkyl, aryl and acyl radicals, usually at C-6, or at C-8 (or C-2) if the 6-position is blocked. Both reactivity and selectivity for C-8 are increased when the substitution is conducted at lower p*H*.[24]

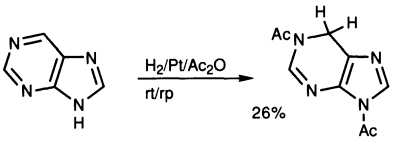


23.4 REACTIONS WITH OXIDISING AGENTS

There are no significant oxidations of purines, apart from *N*-oxidations (section 23.1.1.4), though *C*-oxidation is an important process *in vivo*, for example with the enzyme xanthine oxidase, where oxygen is introduced at C-8.

23.5 REACTIONS WITH REDUCING AGENTS

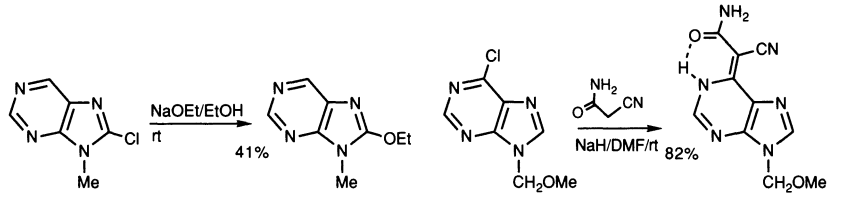
The reduction of substituted purines is very complex and ring-opened products are often obtained. 1,6-Dihydropurine is formed by catalytic or electrochemical[25] reduction of purine, but this is unstable. More stable compounds can be obtained by reduction in the presence of acylating agents.[26] 7/9-Quaternary salts are easily reduced by borohydride in the five-membered ring to dihydro-derivatives.[27]



23.6 REACTIONS WITH NUCLEOPHILIC REAGENTS

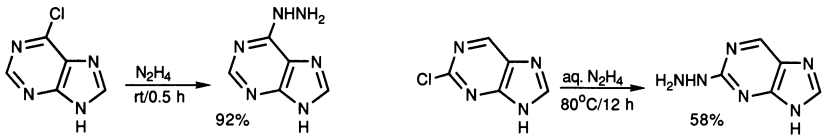
The reactions of the 2-, 6- and 8-halopurines are very important in purine synthesis. Halo-purines can be prepared from oxy-, amino- or thiopurines and the 8-isomers are also available by direct halogenation or *via* lithiated intermediates. Chloro compounds have been the most commonly used, but bromo and iodo purines react similarly, though without any great operational advantage, fluorides however, are more reactive.

Relatively easy nucleophilic displacement takes place at all three positions with a wide range of nucleophiles such as alkoxides,[28] sulfides, amines, azide, cyanide, and malonate and related carbanions.[29]

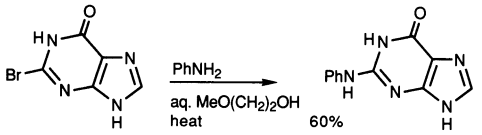


Mechanistically, such nucleophilic displacements proceed by the same type of addition/elimination sequence discussed previously (chapter 4). In 9-substituted purines, the relative reactivity is 8 > 6 > 2, but in 9*H*-purines this is modified to 6 > 8 > 2, the demotion of the 8-position being associated with anion formation in the five-membered ring. Conversely, in acidic media the

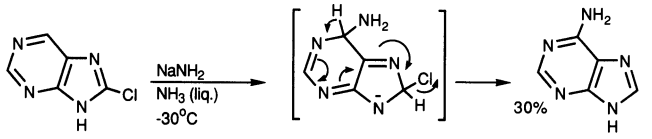
reactivity to nucleophilic displacement at C-8 is enhanced: protonation of the five-membered ring facilitates the nucleophilic addition step.[28] The relative reactivities of 2- and 6-positions is nicely illustrated by the conditions required for the reaction of the respective chlorides with hydrazine, a relatively good nucleophile.[30] It is worth noting the parallelism between the relative positional reactivity here with that in halopyrimidines (4 > 2).



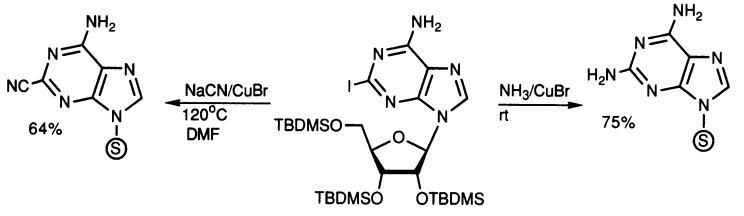
In 2,6-dichloropurine, reactivity at C-6 is enhanced relative to 6-chloropurine by the inductive effect of the second halogen; thus the dihalide will react with simple amines at room temperature where the monochloride would require heating, for example in isopropanol. The presence of electron-releasing substituents, such as amino, somewhat deactivate halogen to displacement, but conversely, oxygenated purines, probably because of their carbonyl tautomeric structures, react easily.[31]



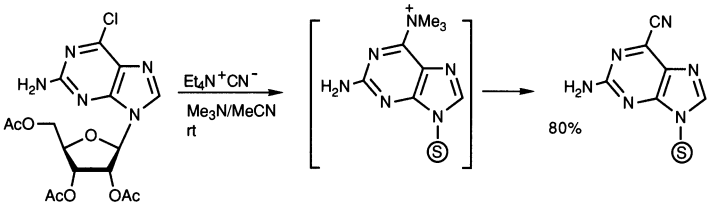
The generation of an *N*-anion by deprotonation in the five-membered ring is given as the reason why 8-chloropurine reacts with sodamide to give adenine (6-aminopurine): inhibition of attack at C-8 allows the alternative addition to C-6 to lead eventually to the observed major product.[32]



Displacement of iodide can be catalysed by copper salts, allowing milder reaction conditions, though it is not clear by what mechanism the metal salt brings about its effect.[33]



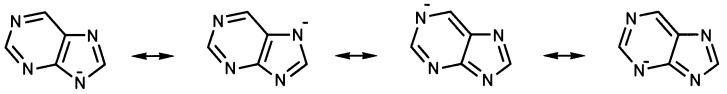
The role of trimethylamine in catalysing displacement (by cyanide) is to displace the halide, giving a quaternary salt which is now more reactive for reaction with cyanide;[34] the same device has been used to allow preparation of fluoropurines.[35]



23.7 REACTIONS WITH BASES

23.7.1 Deprotonation of *N*-hydrogen

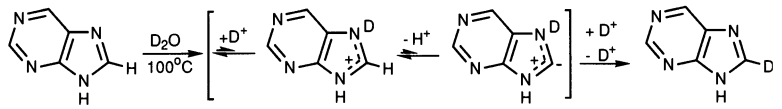
Purine, with a pK_a of 8.9, is slightly more acidic than phenol and much more acidic than imidazole or benzimidazole (pK_a values 14.2 and 12.3 respectively). This relatively high acidity is probably a consequence of extensive delocalisation of the negative charge over four nitrogens; however, alkylation of the anion (section 23.2.1.2) takes place in the five-membered ring since attack at N-1 or N-3 would generate less aromatic products.



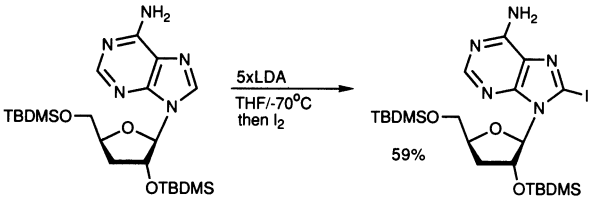
Oxypurines are even more acidic, due to more extensive delocalisation involving the carbonyl groups: xanthine has a pK_a of 7.5 and uric acid, 5.75.

23.7.2 Deprotonation of *C*-hydrogen

The rapid deuteration of purine at C-8[36] in neutral water at 100°C probably involves 8-deprotonation of a concentration of purinium cation to give a transient ylid (cf. 1,3-azole 2-exchange, section 21.1.2.1). 9-Alkylated purines undergo a quite rapid exchange in basic solution involving direct deprotonation of the free heterocycle.



9-Blocked purines can be deprotonated at C-8 with strong bases such as LDA, even in the presence of *N*-hydrogen in the other ring.[37]



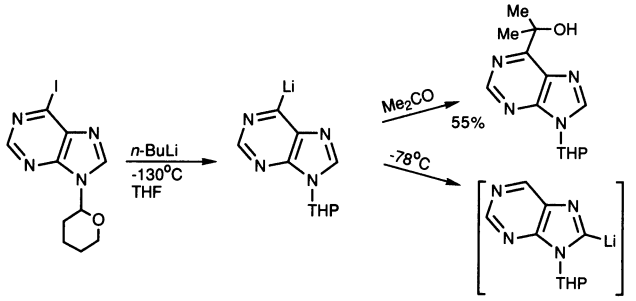
23.8 REACTIONS OF *N*-METALLATED PURINES

These have been dealt with in section 23.2.1.2.

23.9 REACTIONS OF *C*-METALLATED PURINES

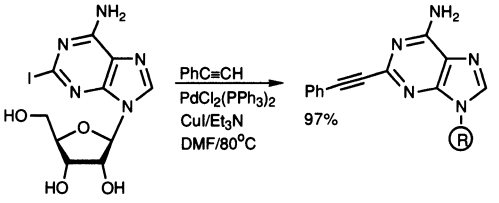
23.9.1 Lithio derivatives

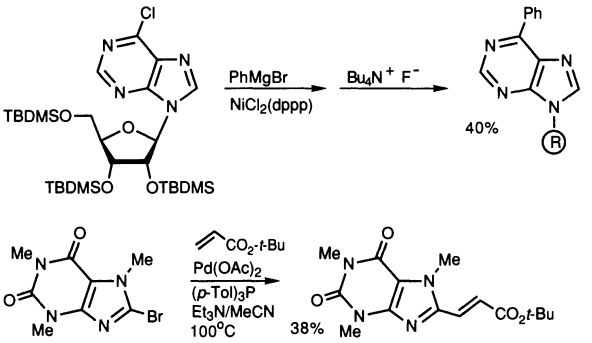
Preparative lithiation of purines requires the protection of the 7/9-position; lithiation then takes place at C-8.[38] Purines lithiated at C-2 or C-6 can be generated by way of halogen exchange with alkyllithiums, but it is important to maintain a very low temperature in order to avoid subsequent equilibration to the more stable 8-lithiated species.[39]



23.9.2 Palladium-catalysed reactions

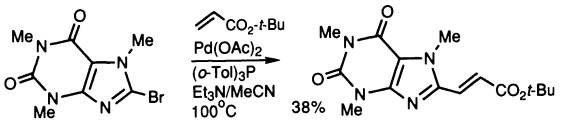
Iodo- and bromopurines undergo the usual palladium-[40] and nickel-catalysed reactions under standard conditions. As with other halo-azines, chloro compounds are usually sufficiently activated to use palladium, though nickel may be the preferred catalyst in certain cases.[41]





23.10 OXY- AND AMINOPURINES

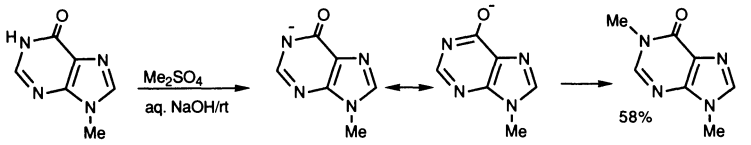
These are tautomeric compounds which exist predominantly as carbonyl and amino structures, thus falling in line with the analogous pyrimidines and imidazoles.



23.10.1 Oxypurines

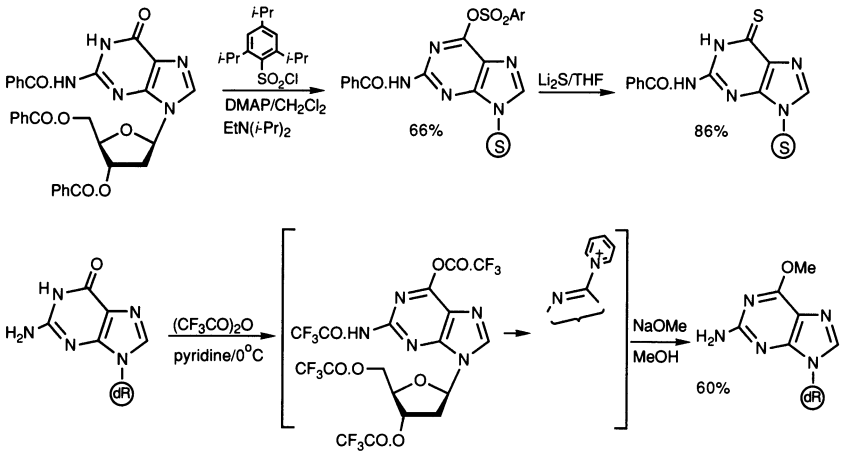
23.10.1.1 *Alkylation*

The amide-like *N*-hydrogen in oxypurines is relatively acidic; the acidity is readily understood in terms of the phenolate-like resonance contributor to the anion. Alkylation takes place at nitrogen, not oxygen.[42]

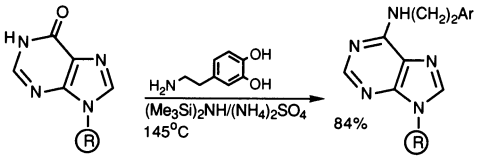


23.10.1.2 *Acylation*

In contrast to alkylation, acylation and sulfonylation frequently occur at oxygen; the resulting *O*-acylated products are relatively unstable but can be utilised, for example conducting the acylation in pyridine, as solvent, produces a pyridinium salt resulting from displacement of acyloxy by pyridine. Both *O*-acylated purines and the corresponding pyridinium salts can in turn be reacted with a range of nucleophiles[43] to allow the overall replacement of the amide-like oxygen; this is an important alternative to activation of the carbonyl by conversion into halogen (below).

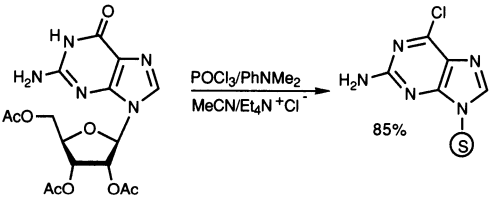


A closely related conversion utilises a silylating agent, in the presence of the desired nucleophile, and presumably involves *O*-silylation then displacement of silyloxy.[44]

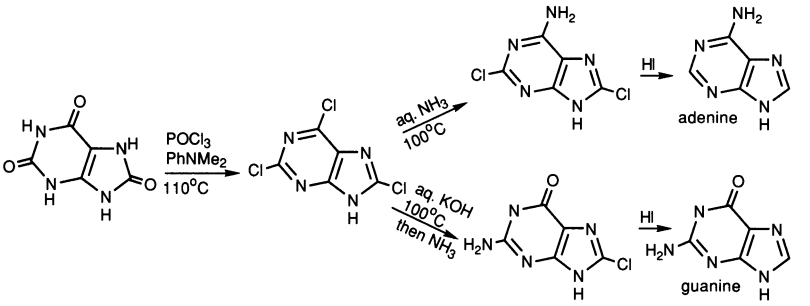


23.10.1.3 *Replacement by chlorine*[45]

This is a very important reaction in purine chemistry and has been widely utilised to allow subsequent introduction of nucleophiles (section 23.5), including replacement with hydrogen by chemical (HI) or catalytic hydrogenolysis. Most commonly, phosphoryl chloride is used, neat, or in solution, especially when there is a ribose present; thionyl chloride is an alternative reagent.

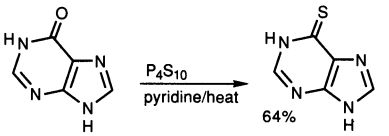


Syntheses of adenine and guanine from uric acid illustrate well the selective transformations to which the halopurines, prepared from a precursor oxypurine,[46] can be put.



23.10.1.4 *Replacement by sulfur*

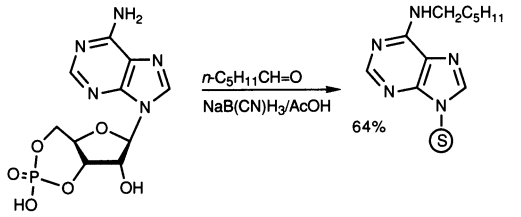
Replacement by sulfur[47] can be achieved *via* a halopurine, or directly using a phosphorus sulfide.



23.10.2 Aminopurines

23.10.2.1 *Alkylation*

Alkylation under neutral conditions involves attack at a nuclear nitrogen; Dimroth rearrangement (23.2.1.2) of these salts affords side-chain-alkylated purines. Direct introduction of substituents onto a side-chain nitrogen can be achieved by reductive alkylation.[48]



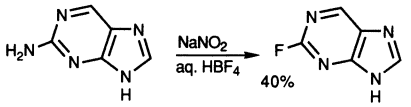
23.10.2.2 *Acylation*

Aminopurines behave just like anilines with anhydrides and acid chlorides, though the resulting amides are somewhat more easily hydrolysed. Both mono- and diacylation can be utilised as a protecting-group strategy.

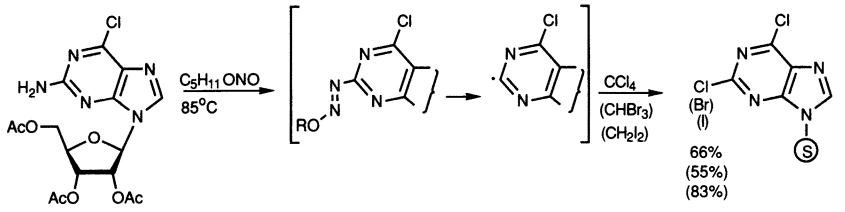
23.10.2.3 *Diazotisation*

The reaction of 2- and 6-amino groups with nitrous acid is similar to that of 2-aminopyridines, in that diazonium salts are produced, but relative to

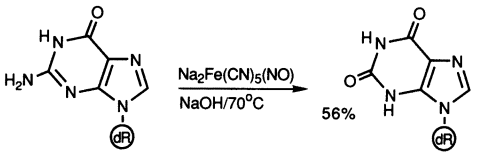
phenyldiazonium salts, these are unstable. Despite this, they can be utilised for the introduction of groups such as halide[49] or hydroxyl, with loss of nitrogen. 8-Diazonium salts are considerably more stable.[50]



The related reaction with alkyl nitrites generates purinyl radicals which efficiently abstract halogen from halogenated solvents and this procedure is generally to be preferred for the transformation of aminopurine into halopurine.[51] Comparably, the use of dimethyl disulfide produces methylthiopurines.[52]

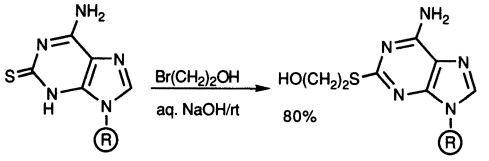


Diazotisation can also be carried out in basic solution and in this way acid-sensitive ribosides can be tolerated.[53] A nucleophilic displacement of amino by hydroxy can be effected enzymatically using adenosine deaminase; this is a useful practical method because it is a very selective transformation under mild conditions.[54] Chemical hydrolysis requires more vigorous conditions.

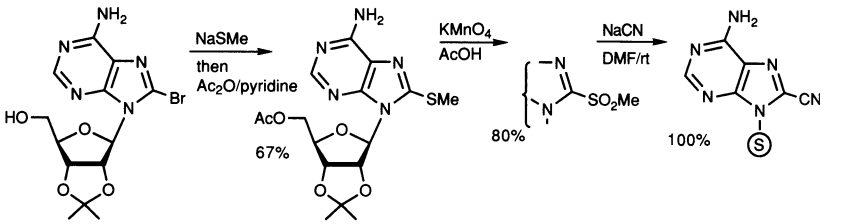


23.10.3 Thiopurines

Thiopurines are prepared from halo- or oxypurines or by ring synthesis. In contrast with oxypurines, in alkaline solution they readily alkylate on sulfur, rather than nitrogen.[55]

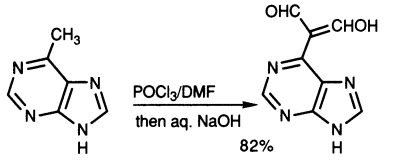


Alkylthio substituents can be displaced by the usual range of nucleophiles, but the corresponding sulfones are more reactive.[52,56]



23.11 ALKYLPURINES

Comparitively little information is available concerning any special reactivity associated with purine alkyl groups, but what is available[57] suggests that their reactivity is comparable to pyridine α-alkyl substituents.



23.12 PURINE CARBOXYLIC ACIDS

Here again, comparatively little systematic information is available, but a parallel with pyridine α-acids can again be implied in that purine acids undergo decarboxylation on heating.[58]

23.13 SYNTHESIS OF PURINES

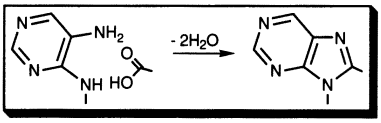
Because of the ready availability of nucleosides from natural sources, a frequently used route to substituted purines is *via* the manipulation of one of these.

23.13.1 Ring synthesis

There are two general approaches to the construction of the purine ring system. Additionally, a third category can be defined as 'one pot' methods, which are adaptations of the type of process which probably took place in prebiotic times, when simple molecules, such as hydrogen cyanide and ammonia, are believed to have combined to give the first purines.

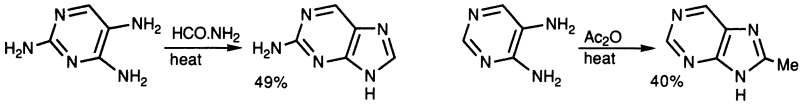
23.13.1.1 *From 4,5-diaminopyrimidines*

4,5-Diaminopyrimidines react with carboxylic acids or derivatives to give purines, the 'carboxyl' carbon corresponding to C-8.

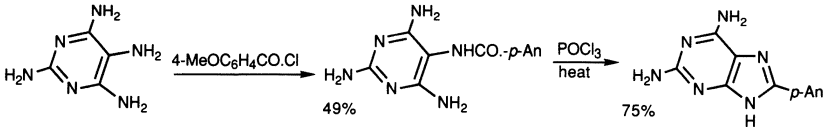


Traube synthesis

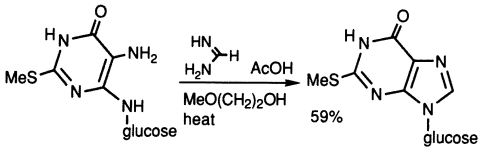
8-Unsubstituted purines can be prepared simply by heating 4,5-diaminopyrimidines with formic acid,[59] but formamide[60] (or formamidine[61]) are better. The reaction proceeds *via* cyclising dehydration of an intermediate formamide; this usually takes place *in situ* using formamide but generally requires a second, more forcing step when formic acid is employed initially. Purine itself can be prepared by this route.[62]

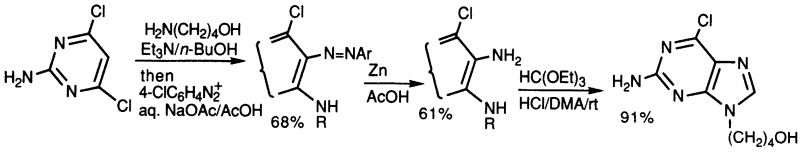


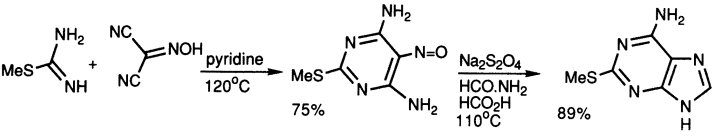
8-Substituted purines are comparably prepared using acylating agents corresponding to higher acids; in most cases the amide is isolated and separately cyclised.[63] The diaminopyrimidines required are usually prepared by the coupling of a monoaminopyrimidine with an aryl diazonium ion, then reduction, or by ring synthesis.[64]



Precursors to 9-substituted purines, requiring a substituent on the pyrimidine-4-amino group, are available from the reaction of a 4-chloropyrimidine with the amine.

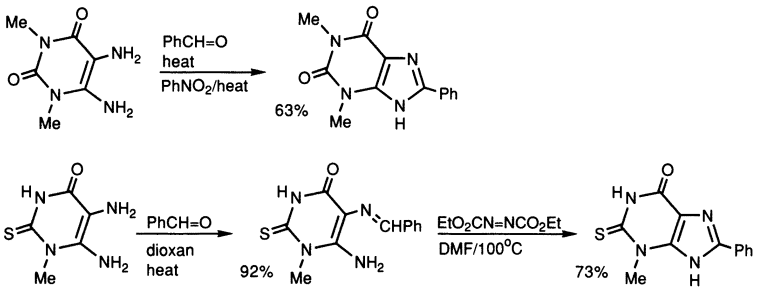






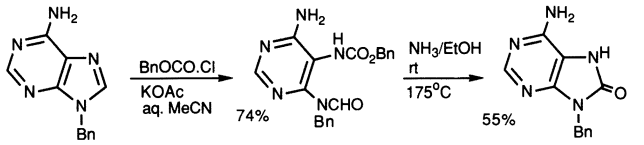
When milder conditions are required for the cyclisation, perhaps because of the presence of a sugar residue, an ortho ester (often activated[65] with acetic anhydride) can be used.[66]

A related reaction is the oxidative cyclisation of anils, originally under vigorous conditions such as heating in nitrobenzene,[67] but now achievable at much lower temperatures using diethyl azodicarboxylate.[68]



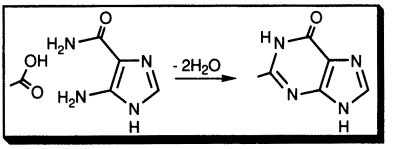
Amino nitrosopyrimidines can also be converted directly into purines, without the need for reduction to diamine, by reaction with Wittig reagents.[69]

The formation of 8-oxo- or 8-thiopurines require one-carbon components at a higher oxidation level: urea and thiourea are appropriate. The products of chloroformate five-membered cleavage of purine (section 23.2.1.3) can be recyclised to produce 8-oxopurines.[70]



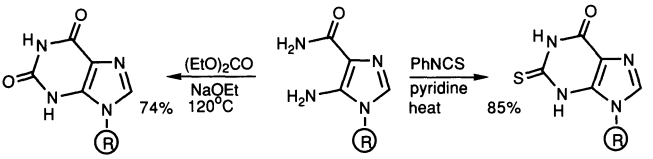
23.13.1.2 *From 5-aminoimidazole-4-carboxamide, or -nitrile*[71]

5-Aminoimidazole-4-carboxamides (or -nitriles) similarly interact with components at the carboxylic acid oxidation level giving purines, the 'carboxyl' carbon becoming C-2.

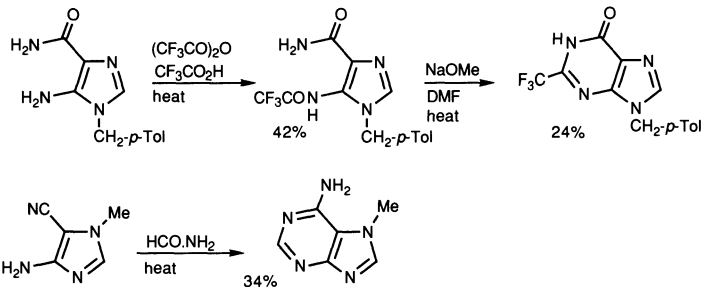


Biosynthetically, purines are built up *via* formation of the imidazole ring first, from glycine and formate, and thence to hypoxanthine and then the other natural purines. In the laboratory, most imidazole-based purine syntheses start with derivatives of 5-aminoimidazole-4-carboxylic acid, particularly its amide (known by the acronym AICA) which together with its riboside are commercially

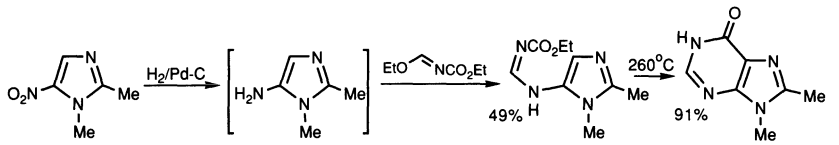
available from biological sources. The use of 5-aminoimidazole-4-carbonitrile in this approach results in the formation of 6-aminopurines, as in a synthesis of adenine itself.[72]



Conversion into 2-alkyl- or -arylpurines requires the insertion of one carbon to create the six-membered ring and this is usually effected by condensation with esters in the presence of base,[73] although amides[74] are occasionally utilised. The use of an isothiocyanate leads to a 2-thiopurine.[75]



There are a few examples of purine ring syntheses which start from simpler imidazoles, for example a 5-aminoimidazole, generally prepared and utilised *in situ*.[76]

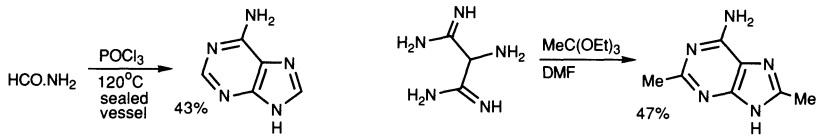


23.13.1.3 *'One-step' syntheses*

It is amazing that relatively complex molecules such as purines can be formed by the sequential condensation of very simple molecules such as ammonia and hydrogen cyanide. That the intrinsic reactivity embodied in these simple molecules leads 'naturally' to purines must surely be relevant to the evolution of a natural system which relies on these 'complex' molecules. In other words it seems highly likely that purines existed before the evolution of life and were incorporated into its mechanism because they were there and, of course, because they have appropriate chemical properties.

Adenine, $C_5H_5N_5$, is formally a pentamer of hydrogen cyanide and indeed can be produced in the laboratory by the reaction of ammonia and hydrogen

cyanide, although not with great efficiency. A related and more practical method involves the dehydration of formamide.[77] Purine itself can also be obtained from formamide.[78]

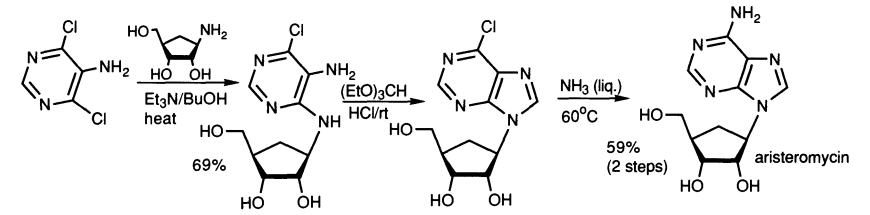


Methods derived from this fundamental process involve the condensation of one-, two- and three-carbon units such as amidines, aminonitriles and carboxamides, which represent intermediate stages of the ammonia/hydrogen cyanide reaction. Pyrimidines or imidazoles are usually intermediates.[79]

23.13.2 Examples of notable syntheses involving purines

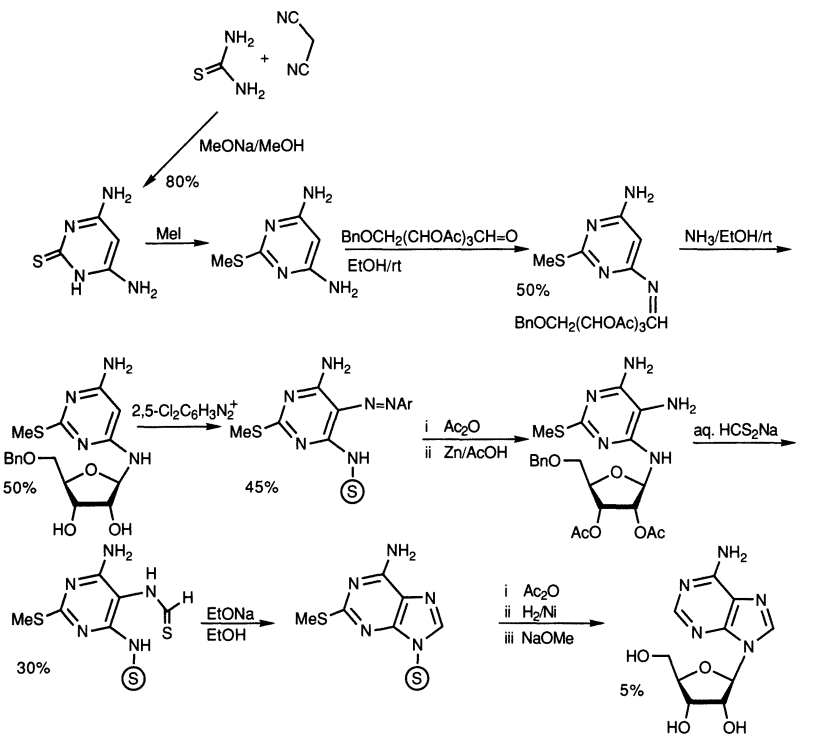
23.13.2.1 *Aristeromycin*

A synthesis of aristeromycin[80] makes use of the displacement of a pyrimidine 4-chloride, to allow introduction of the amine and the generation of the 4,5-diaminopyrimidine for subsequent closure of the five-membered ring.



23.13.2.2 *Adenosine*

Adenosine[81] has also been synthesised using the pyrimidine → purine strategy. In this synthesis the sugar was also introduced at an early stage, but here *via* condensation with a 4-amino group.



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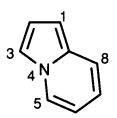
EXERCISES FOR CHAPTER 23

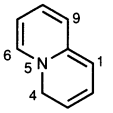
1. What are the structures of the intermediates and final product of the following sequence: guanosine 2′,3′,5′-triacetate reacted with $POCl_3$ → $C_{16}H_{18}ClN_5O_7$ then this with *t*-BuONO/CH_2I_2 → $C_{16}H_{16}ClIN_4O_7$, this product with NH_3/MeOH → $C_{10}H_{12}IN_5O_4$ and finally this compound with $PhB(OH)_2/Pd(PPh_3)_4/Na_2CO_3$ giving $C_{16}H_{17}N_5O_4$. How could this same purine be prepared from AICA-riboside in four steps?
2. Suggest a sequence for the transformation of adenosine into 8-phenyladenosine.
3. Give structures and explain the following: adenosine with Me_2SO_4 → $C_{11}H_{15}N_5O_4$, this with aq. HCl produces $C_6H_7N_5$, and finally aq. NH_3 on this last compound gives an isomer, $C_6H_7N_5$.
4. Write structures for the purines produced by the following reactions: (i) heating 4,5,6-triaminopyrimidine with formamide; (ii) treating 2-methyl-4,5-diaminopyrimidin-6-one with sodium dithioformate, then heating in quinoline.

24 Heterocycles containing a ring-junction nitrogen

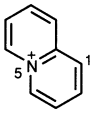
In addition to the biologically important purines and pteridines and the major benzo-fused heterocycles such as indole, many other aromatic, fused heterocyclic ring systems are known, and of these, the most important are those containing a ring-junction nitrogen – that is, where a nitrogen is common to two rings.[1] The vast majority of these systems do not occur naturally, but they have been the subject of many studies from the theoretical viewpoint, for the preparation of potentially biologically active analogues, and for other industrial uses. For reasons of space, only combinations of five- and six-membered rings are considered here, though other combinations are possible and are known.



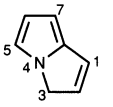
indolizine



4*H*-quinolizine



quinolizinium



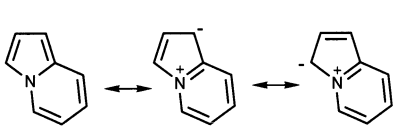
3*H*-pyrrolizine

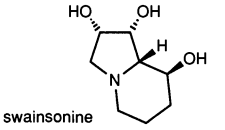
pyrrolizine anion

Of the parent systems which have the ring-junction nitrogen as the only hetero atom, only indolizine (often 'pyrrocoline' in the older literature) has a neutral, fully conjugated 10-electron π-system, comprising four pairs of electrons from the four double bonds and a pair from nitrogen, much as in indole. 4*H*-Quinolizine is not aromatic – there is a saturated atom interrupting the conjugation – but the cation, quinolizinium, formed formally by loss of hydride from quinolizine, does have an aromatic 10-electron system: it is completely isoelectronic with naphthalene, the positive charge resulting from the higher nuclear charge of nitrogen *versus* carbon. Similarly, pyrrolizine, which is already aromatic in being a pyrrole (with an α-vinyl substituent), on conversion to its conjugate anion, attains a 10-electron π-system.

24.1 INDOLIZINES[2]

The aromatic character of indolizine is expressed by three main mesomeric contributors, two of which incorporate a pyridinium moiety; other structures (not shown), incorporating neither a complete pyrrole nor a pyridinium, are less important.



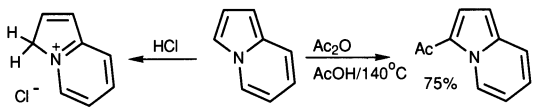


Aromatic indolizines are very rare in nature, but the fully reduced (indolizidine) nucleus is widespread, particularly in alkaloids, of which swainsonine is a typical example. Synthetic indolizines have found use in photographic dyes.

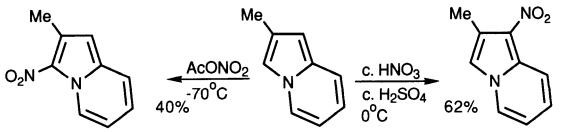
24.1.1 Reactions of indolizines

Indolizine is an electron-rich system and its reactions are mainly electrophilic substitutions, which occur about as readily as for indole, and go preferentially at C-3, but may also take place at C-1. Consistent with their similarity to pyrroles, rather than pyridines, indolizines are not attacked by nucleophiles, nor are there examples of nucleophilic displacement of halide.

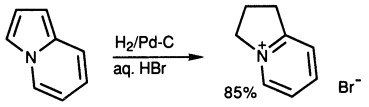
Indolizine, pK_a 3.9,[3] is much more basic than indole (pK_a −3.5) and the implied relative stability of the cation makes it less reactive, and thus indolizines resistant to acid-catalysed polymerisation (cf. section 17.1.9). Indolizine protonates at C-3, but 3-methylindolizine protonates mainly (79%) at C-1; the delicacy of the balance is further illustrated by 1,2,3-trimethyl- and 3,5-dimethylindolizines, each of which protonate exclusively at C-3. Electrophilic substitutions such as acylation,[4] Vilsmeier formylation,[5] and diazo-coupling[6] all take place at C-3.



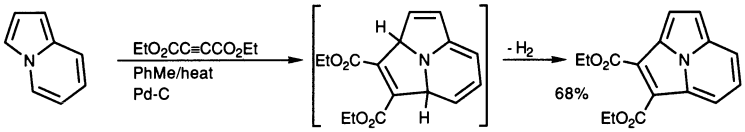
Nitration of 2-methylindolizine under mild conditions results in substitution at C-3,[7] but under strongly acidic conditions it takes place at C-1,[8] presumably *via* attack on the indolizinium cation.



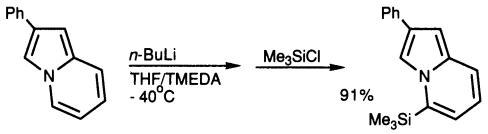
Indolizine and its simple alkyl derivatives are sensitive to light and to aerial oxidation, which lead to destruction of the ring system. Catalytic reduction in acidic solution – reduction of the indolizinium cation – gives a pyridinium salt;[9] complete saturation, affording 'indolizidines', results from reductions over platinum.[10]



Despite its 10-electron aromatic π-system, indolizine apparently participates as an 8-electron system in its reaction with diethyl acetylenedicarboxylate, though the process may be stepwise and not concerted. By carrying out the reaction in the presence of a noble metal as catalyst, the initial adduct is converted into an aromatic cyclazine (section 24.5).[11]



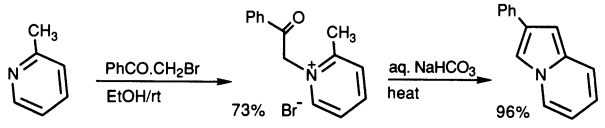
5-Methylindolizine undergoes lithiation at the side-chain methyl;[12] 2-phenylindolizine lithiates at C-5.[13]



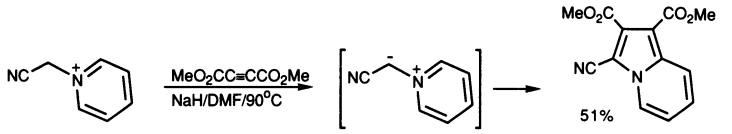
Of its functional derivatives, worth noting is the easy cleavage of carboxyl and acyl groups on heating with aqueous acid, and the instability of amino-derivatives, which cannot be diazotised, but which can be converted into stable acetamides.

24.1.2 Synthesis of indolizines[14]

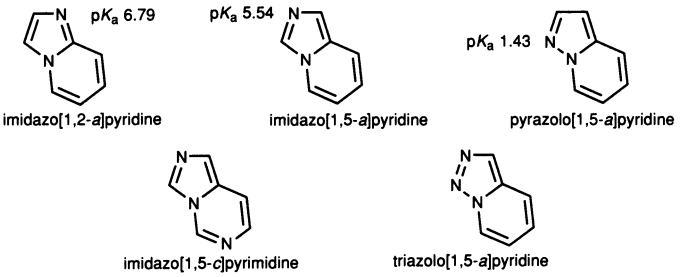
The most general approach to indolizines is the *Chichibabin synthesis*,[15] which involves quaternisation of a 2-alkylpyridine with an α-haloketone, followed by base-catalysed cyclisation *via* deprotonation of the pyridinium α-methyl.[16]



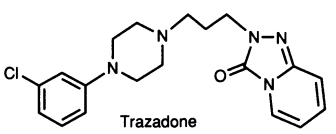
Another useful method involves the intermediacy of a pyridinium ylid as a 1,3-dipole in a cycloaddition.[17]

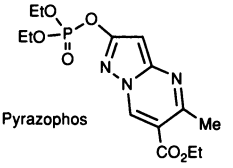


24.2 AZA-INDOLIZINES



Seven monoaza- and many more polyaza-indolizines (some are shown above) are possible, indeed compounds with up to six nitrogen atoms have been frequently reported. Despite the great rarity of such systems in nature, there has been much interest in aza-indolizines stemming from their structural similarity to both indoles and purines. The imidazopyrazine ring occurs in *Cypridina* luciferin (chapter 11). The antidepressant Trazadone is an example of the large number of aza-indolizines which have been prepared for assessment of their pharmacological activity. Compounds of use in other areas include the plant antifungal agent Pyrazophos.

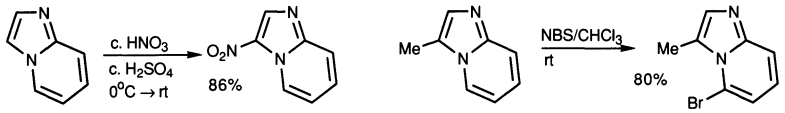




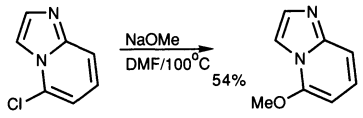
Apart from pyrrolo[1,2-*b*]pyridazine, all the monoaza-indolizines protonate on the second (non-ring-junction) nitrogen, rather than on carbon.[3,18] Alkylation similarly goes on nitrogen; however, other electrophilic reagents attack with regioselectivity similar to indolizine itself – they effect substitution of the five-membered ring at positions 1 and 3 (where these are carbon).

24.2.1 Imidazo[1,2-*a*]pyridine

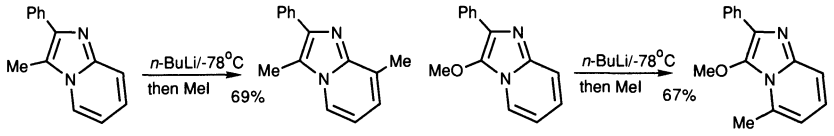
Electrophilic substitutions such as halogenation, nitration, etc. go at C-3, or at C-5 if position 3 is blocked.[19]



Of all the positional chloro-isomers, nucleophilic displacement reactions are only known for the 5-isomer; the 7-chloro isomer, where one might have anticipated similar activation, is not reactive in this sense.[20]

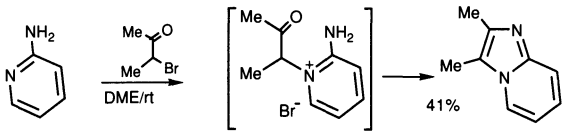


Base-catalysed deuterium exchange goes at C-3 and C-5;[21] preparative lithiation occurs at C-3, or if C-3 is blocked, at C-5 or C-8 depending on other substituents.[22]



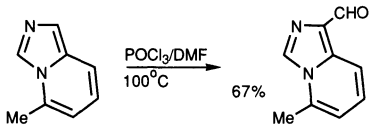
Amino-imidazo[1,2-*a*]pyridines are even more unstable than aminoindolizines; they exist as amino tautomers, but 2- and 5-oxygenated derivatives are in the keto form. These last react as usual with phosphoryl chloride yielding chloro-compounds.[20]

The ring synthesis of imidazo[1,2-*a*]pyridines is based on the Chichibabin route to indolizines (section 24.1.2), but using 2-aminopyridines instead of 2-alkylpyridines. The initial reaction with the halo-ketone is regioselective for the ring nitrogen, so isomerically pure products are obtained.[23] 2-Oxoimidazo[1,2-*a*]pyridines are the products when an α-bromo-ester is used instead of a ketone.[24]

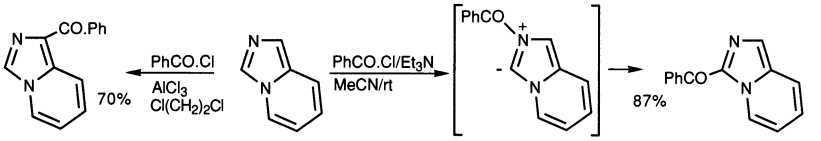


24.2.2 Imidazo[1,5-*a*]pyridines

Electrophilic substitution in this system again occurs in the five-membered ring, at C-1, or at C-3 if the former position is occupied.[25,26] Reaction with bromine gives a 1,3-dibromo-product.[27]

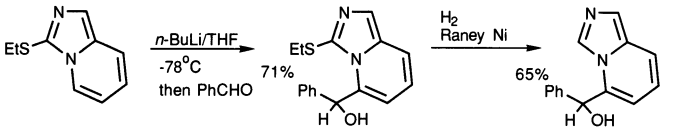


Benzoylation provides an instructive example: under normal conditions *C*-substitution occurs at C-1, however in the presence of triethylamine, 3-benzoylimidazo[1,5-*a*]pyridine is the product.[28] This can be explained by assuming the intermediacy of an ylid formed by deprotonation of an initial N^+-benzoylated salt (cf. section 21.1.2.5).

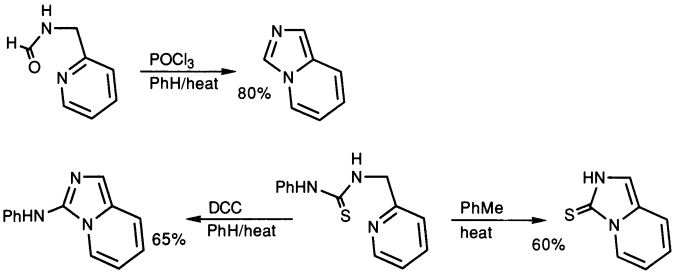


Five-membered ring cleavage occurs relatively easily: hot aqueous acid converts these heterocycles into 2-aminomethylpyridines.

Lithiation, by direct analogy with imidazole, results in loss of the 3-proton,[5] but 5-lithiation occurs on comparable treatment of 3-ethylthio-derivative, the substituent both blocking attack at C-3 and assisting lithiation at the *peri* position; the ethylthio group can of course be subsequently easily removed.[29]

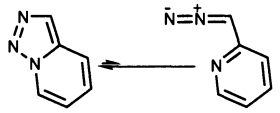


Imidazo[1,5-*a*]pyridines are synthesised by the dehydrative cyclisation of *N*-acyl-2-aminomethylpyridines.[26] 3-Amino-,[30] oxy-[31] and thio-[32] -derivatives are available *via* related cyclisations.



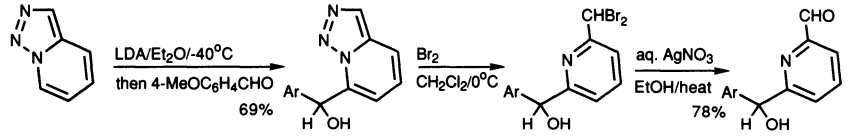
24.2.3 Triazolo[1,5-*a*]pyridine and other compounds with N–N bonds

Triazol[1,5-*a*]pyridine can be, in theory, in equilibrium with its ring-opened diazo tautomer;[33] although it actually exists in the closed form, its reactions tend to reflect this potential equilibrium: reaction with electrophiles can take two courses. Acylation and nitration occur normally, at C-1, but reagents such as bromine lead to a very easy ring cleavage.[34] Aqueous acid similarly brings about ring cleavage and the formation in this case of 2-hydroxymethylpyridine.

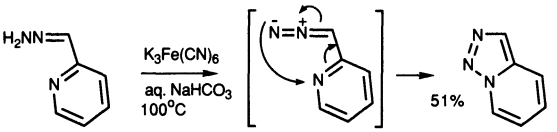


2-Azido-azines are in equilibrium with fused tetrazoles, the position of the equilibrium being very sensitive to substituent influence; for example, in the unsubstituted case the equilibrium lies predominantly towards the closed form whereas the analogous 6-chloro-compound is predominantly open.[35]

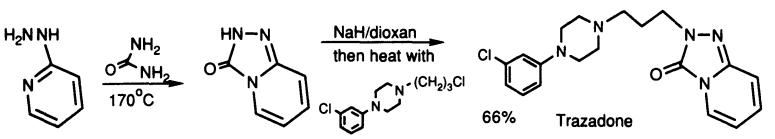
Direct lithiation of triazolo[1,5-*a*]pyridines occurs with ease, at C-5, subsequent reaction with electrophiles being unexceptional; for example, conversion into the 5-bromo-derivative then allows nucleophiles to be introduced *via* displacement of halide, thus providing, overall, a route to 2,6-disubstituted pyridines.[36]



The ring system can be synthesised by oxidation of pyridine 2-carboxaldehyde hydrazone, presumably by way of the diazo-species.[37]



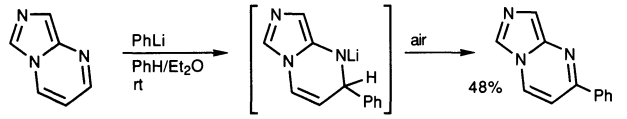
In the preparation of Trazadone, the heterocyclic nucleus is synthesised by cyclisation of 2-hydrazinopyridine with urea.[38]



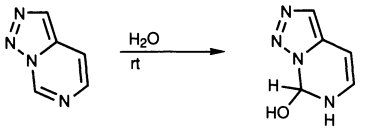
24.2.4 Compounds with an additional nitrogen in the six-membered ring

In addition to the propensity for electrophilic substitution at C-1/C-3 (see above), the main feature of this class of heterocycle is that they undergo relatively easy nucleophilic attack in the six-membered ring,[39] which is now

considerably electron-deficient – the analogy with the ease of nucleophilic addition to diazines is obvious.



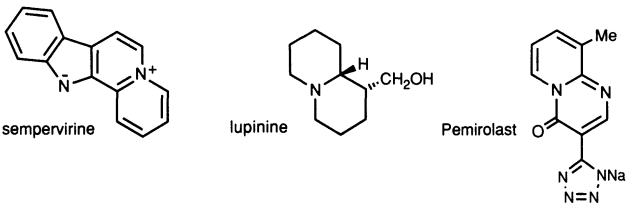
Some are so susceptible to nucleophilic addition that they form 'hydrates' even on exposure to moist air.[33]



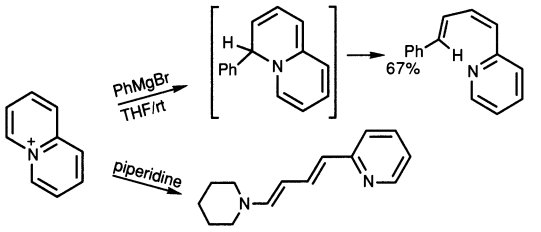
Ring synthesis of such molecules can proceed from diazines using methods analogous to those described for the synthesis of azolopyridines from pyridines, but generally they are more easily obtained from a five-membered precursor.

24.3 QUINOLIZINIUMS[40] AND RELATED SYSTEMS

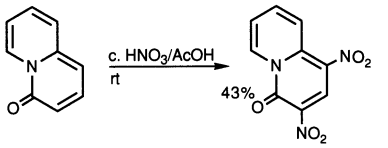
The quinolizinium ion occurs naturally only rarely, for example as a fused ylid in the alkaloid sempervirine; however, there are hundreds of indole alkaloids which have the same tetracyclic system, but with the quinolizine at an octahydro-level; in addition, many simpler quinolizidine alkaloids, such as lupinine, are known. Amongst synthetic compounds, the anti-asthma drug Pemirolast is an aza-analogue.



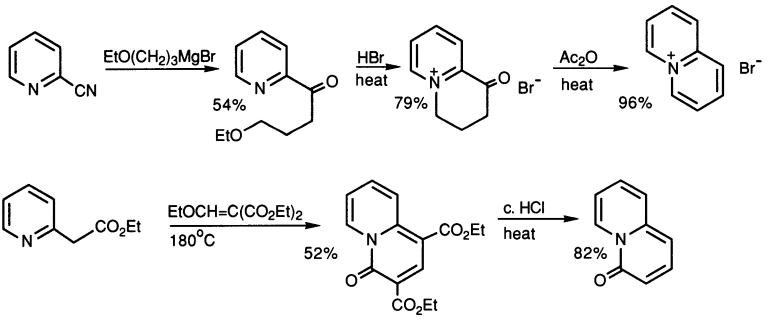
Practically all the reactions of quinolizinium ion are similar to those of pyridinium salts, thus it is resistant to electrophilic attack but readily undergoes nucleophilic addition, the initial adducts undergoing spontaneous electrocyclic ring opening to afford, finally, 2-substituted pyridines;[41] however, the susceptibility of the cation to nucleophiles is not extreme – like simpler pyridinium salts it is stable to boiling water.



Quinazolones can be made to undergo electrophilic substitution, at C-1/C-3,[42] there being a clear analogy with the reactivity of pyridones.



Quinolizine derivatives are usually prepared by cyclisations onto the nitrogen in a precursor pyridine.[43]

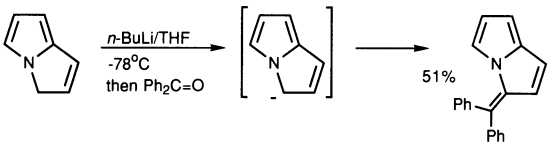


24.4 PYRROLIZINES AND RELATED SYSTEMS

The saturated or partially saturated pyrrolizidine alkaloids are the main naturally occurring pyrrolizines; senecionine is an example.

The relatively high pK_a of 29 for deprotonation of 3*H*-pyrrolizine (cf. indene, pK_a 18.5) indicates that formation of the 10-electron pyrrolizine anion adds only minor stabilisation relative to the simple pyrrole originally present. Its reactions

are those of a highly reactive carbanion, for example benzophenone condenses to generate a fulvene-like product.[44]

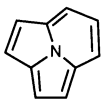


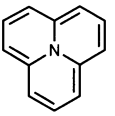
Isoelectronic replacement of a carbanionic carbon by a hetero atom gives much more stable compounds; such 5,5-bicyclic aromatic systems have received considerable attention; pyrrolo[2,1-*b*]thiazole is one such example. Although we have not had sufficient space to describe these in this short chapter, their properties and synthesis follow the general principles discussed; for example, imidazothiazoles are prepared from substituted thiazoles in a way analogous to the preparation of imidazopyridines, from substituted pyridines.

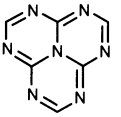
pyrrolo[2,1-*b*]thiazole 

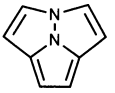
24.5 CYCLAZINES

The cyclazines (a trivial name) are tricyclic fused molecules containing a central bridgehead nitrogen and a peripheral π-system. The definition of aromaticity in these compounds is not as straightforward as for the simple bicyclic molecules discussed above, and a more detailed analysis of the molecular orbitals may be required.


(3.2.2)cyclazine


(3.3.3)cyclazine


hexa-aza-analogue of (3.3.3)cyclazine

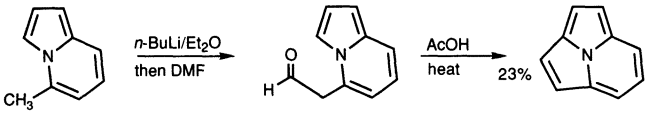

(2.2.2)azacyclazine

(3.2.2)Cyclazine is a stable aromatic system with a ring current, has a 10-electron annular π-system (excluding nitrogen), and is stable to light and air but, unlike its close analogue indolizine, is non-basic indicating the much weaker interaction between the nitrogen lone pair and the peripheral π-system. It does however react as an electron-rich aromatic, undergoing electrophilic substitution readily.

In contrast, (3.3.3)cyclazine has no aromatic resonance stabilisation and is unstable and highly reactive, displaying some diradical character. However, its hexa-aza-analogue is extremely stable, this stabilisation being attributed to perturbation of the molecular orbitals by the electronegative atoms leading to a

much larger separation of the HOMO and LUMO.[45] The double bridgehead nitrogen system, (2.2.2)azacyclazine, is isoelectronic with (3.2.2)cyclazine and is similarly a stable system.

Cyclazines can be prepared by cyclisation of bicyclics, for example (3.2.2)cyclazine is prepared *via* a cycloaddition reaction on indolizine (section 24.1.1), or by cyclocondensation, as shown.



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EXERCISES FOR CHAPTER 24

1. Suggest a structure for the final, monocyclic product of the following sequence: quinolizinium bromide with $LiAlH_4$ and then H_2/Pd giving $C_9H_{13}N$.
2. Write down the structures of the intermediates in the following synthesis of the quinolizinium cation: 2-methylpyridine was reacted with LDA, then $EtO(CH_2)_2CH{=}O$ to give $C_{11}H_{17}NO_2$, which was heated with HI ($\rightarrow C_9H_{12}NO^+ I^-$); this salt was then heated with Ac_2O ($\rightarrow C_9H_{10}N^+ I^-$) and this finally heated with Pd–C to afford quinolizinium iodide.
3. Which indolizines would be formed from the following combinations: (i) 2-picoline with (a) $BrCH_2CO.Me/NaHCO_3$, (b) $MeCHBrCHO/NaHCO_3$? (ii) What would be the products if the 2-picoline was replaced by 2-aminopyridine?
4. Deduce the structures of intermediates and final product in the following

sequence: 5-methoxy-2-methylpyridine reacted with KNH_2/*i*-AmONO → $C_7H_8N_2O_2$, then this with Zn/AcOH → $C_7H_{10}N_2O$, and finally this with HCO_2Me/PPE (polyphosphate ester) → $C_8H_8N_2O$.

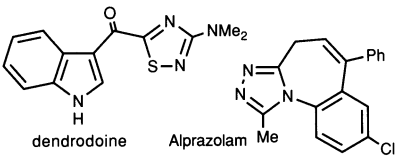
5. Imidazo[1,5-*a*]pyridine, on reaction with aqueous HNO_2, gave 3-(pyridin-2-yl)-1,2,4-oxadiazole. Suggest a mechanism. What product would be obtained by reaction of indolizine with nitrous acid?
6. Give the structures of the bicyclic compounds formed by the following reactions: (i) 2-hydrazinothiazole with nitrous acid → $C_3H_2N_4S$; (ii) 2-aminothiazole with $BrCH_2CO.Ph$ → $C_{11}H_8N_2S$.

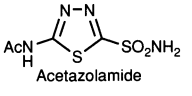
Heterocycles containing more than two hetero atoms

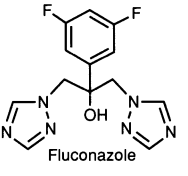
25

In systems which contain more than two hetero atoms in the same ring we find the trends in properties, which this book has described, taken to further extremes. In particular, the additional hetero atoms, in both six- and five-membered systems, lead to a suppression of electrophilic substitution and a slowing of electrophilic addition to nitrogen. On the other hand, further increases in tendencies for nucleophilic substitution and addition, and in the five-membered compounds, further increases in acidities of *N*-hydrogen are shown.

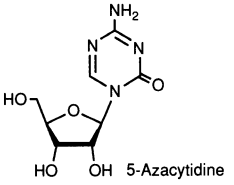
Multihetero atom heterocycles are comparitively rare in nature, dendrodoine, a cytotoxic substance from a marine tunicate, is an example; however in medicinal chemistry they are of considerable significance: Alprazolam is a major drug for the treatment of anxiety, Acetazolamide is an inhibitor of the enzyme carbonic anhydrase and is used principally for the treatment of glaucoma, and Fluconazole is an antifungal agent.

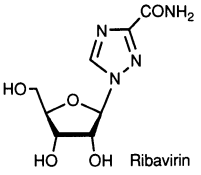


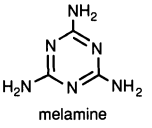




Analogues of the pyrimidine nucleosides have been extensively studied: 5-Azacytidine is antileukemic and Ribavirin, an antiviral agent, is used in the treatment of lung infections in infants. Melamine, which on condensation with formaldehyde produces the melamine resins well known in kitchen utensils, is an important industrial intermediate.





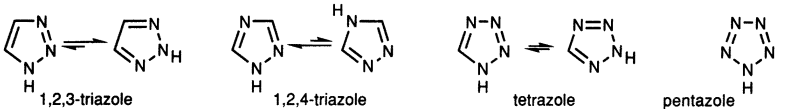


25.1 FIVE-MEMBERED RINGS

25.1.1 Azoles

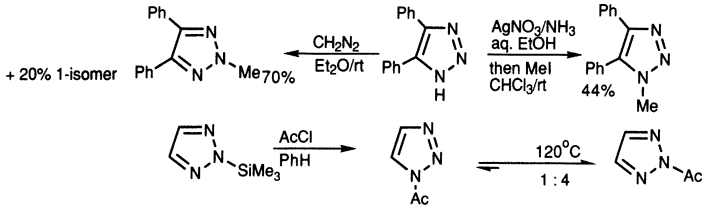
The triazoles are named to indicate the relative positions of the nitrogen atoms; tetrazole and pentazole are unambiguous names. 1,2,3-Triazoles are surprisingly stable, when one considers that they contain three directly-linked nitrogen atoms, but on FVP at 500°C they do lose nitrogen to give 2*H*-azirines, probably *via* the 1*H*-isomer.[1] Benzotriazole is similarly relatively stable and has been distilled *in vacuo* at 200°C, though explosions have been reported during this process. Simple tetrazoles are also relatively stable, but the pentazole ring system is only known in a few aryl derivatives which generally decompose (possibly explosively) at or below room temperature.[2]

The additional hetero atoms make these systems less basic but more acidic than comparable 1,2- and 1,3-azoles. Each is subject to the same kind of tautomerism as discussed for the 1,2- and 1,3-azoles (section 21.1.1.1), in which the tautomers are equivalent (not shown) but also, in these systems, to tautomerism which generates different arrangements.

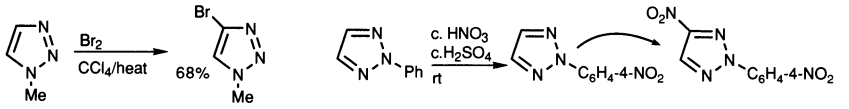


25.1.1.1 *1,2,3-Triazole*[3]

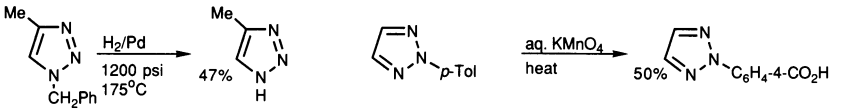
1,2,3-Triazole is fairly resistant to *N*-alkylation under neutral conditions; however, both acylations and alkylations involving *N*-anions occur readily, but mixtures of 1- and 2-substituted products are often obtained.[1,4] An equilibrium mixture of *N*-acetyl-1,2,3-triazoles contains predominantly the 2-acetyl-isomer,[5] as in the parent: this may reflect unfavourable *ortho* lone-pair/lone-pair interactions in the 1-isomer and is in agreement with calculations which suggest that the 2*H*-isomer is more aromatic.[6]



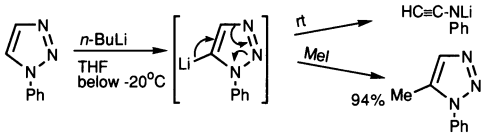
1-Methyl-1,2,3-triazole can be brominated at C-4, but the 2-methyl isomer is less reactive, requiring the use of an iron catalyst;[7] the lower reactivity of the latter is probably related to the presence of two azomethine units. Nitration of 2-phenyl-1,2,3-triazole proceeds first on the benzene ring, but then does bring about hetero-ring substitution.[8]



The ring system is relatively resistant to both oxidation and reduction.[9]

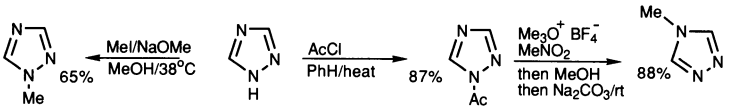


N-Substituted 1,2,3-triazoles can be lithiated directly at carbon, but low temperatures must be maintained to avoid ring cleavage by cycloreversion.[10,11]

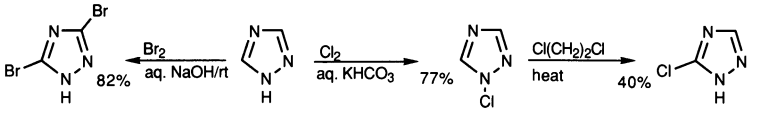


25.1.1.2 *1,2,4-Triazole*

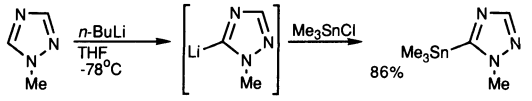
Alkylations and acylations generally occur at N-1, reflecting the higher nucleophilicity of N–N systems (cf. section 11.1.1.2); however, 4-alkyl derivatives can be prepared *via* quaternisation of 1-acetyl-1,2,4-triazole[12] (Note that N-1 and N-2 are equivalent until substitution occurs).



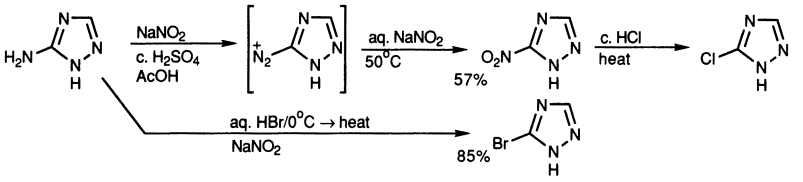
Bromination occurs readily in alkaline solution giving 3,5-dibromo-1,2,4-triazole;[13] the 3-monochloro-derivative can be obtained by thermal rearrangement of the *N*-chloro isomer;[14] an analogous N → C 1,5-sigmatropic shift converts the 1- into the 3-nitro-compound.[15]



C-Lithiations can be easily effected on N-1-protected 1,2,4-triazoles, the resulting 5-lithio-derivatives being much more stable than lithiated-1,2,3-triazoles.[16]

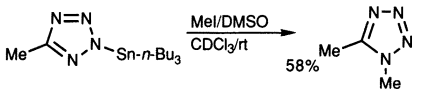


3-Amino-1,2,4-triazole can be diazotised normally: the resulting diazonium salt has been used for the production of azo dyes, and also loses nitrogen with easy replacement by nucleophiles. The bromo- and nitrotriazoles which can be thus prepared are themselves substrates for nucleophilic displacement reactions.[12,17]

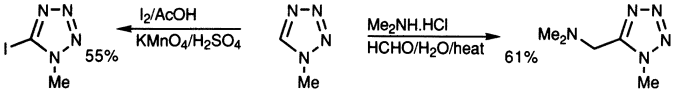


25.1.1.3 *Tetrazole*[18]

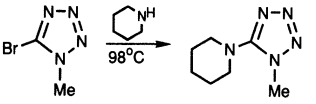
Noting the similarity of tetrazole pK_a values to those of carboxylic acids, tetrazoles have often been used as bioisosteric replacements for CO_2H in pharmacologically active compounds. Tetrazoles alkylate and acylate on N-1 or N-2 depending on substituents at C-5, however selective 1-alkylations by quaternisation of 2-tri-*n*-butylstannyl derivatives have been reported.[19]



Remarkably, some *C*-electrophilic substitutions such as bromination,[20] mercuration[21] and even Mannich reactions[22] (but not nitration) have been achieved, though the mechanisms for these substitutions may not be of the conventional type.

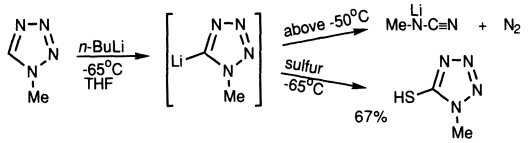


As would be expected from inductive effects, 5-bromo-1-methyltetrazole is more reactive in nucleophilic substitution than are the corresponding halo-1,2,4- and -1,2,3-triazoles, which in turn are more reactive than the corresponding haloimidazoles. 5-Bromo-2-methyltetrazole is significantly less reactive than its 1-methyl isomer, due to less effective delocalisation of the negative charge in the intermediate adduct.[23]

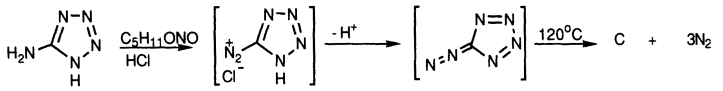


C-Lithiation occurs readily and the resulting lithio-derivatives can be trapped

with electrophiles, despite a strong tendency for cycloreversion. Tetrazole can also act as an *ortho*-directing group, as in the lithiation of 5-phenyltetrazole.[24,25]



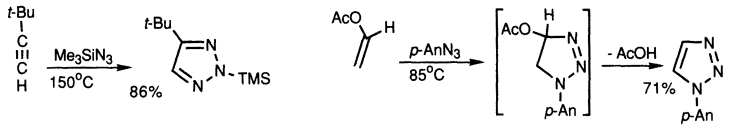
5-Aminotetrazole gives a diazonium salt (with the formula $CN_6.HCl$!) (**CAUTION**: EXPLOSIVE) which has been used to generate atomic carbon![26] 1-Substituted-5-aminotetrazoles seem to give relatively stable *N*-nitroso derivatives.



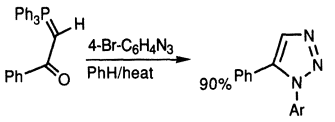
25.1.1.4 *Ring synthesis of azoles*

1,2,3-Triazoles

1,2,3-Triazoles are generally prepared by the cycloaddition of an alkyne with an azide, but the hazardous nature of some alkyl azides limits the method in these cases. A convenient synthesis which leads to *N*-hydrogen 1,2,3-triazoles utilises the stable (and relatively safe) trimethylsilyl azide.[27] For *C*-unsubstituted 1,2,3-triazoles, ethyne itself would be required but it is much more convenient to use as starting material, vinyl acetate instead of the gaseous ethyne or, in general, an enamine or an enol ether as alkyne equivalents.[28,29]

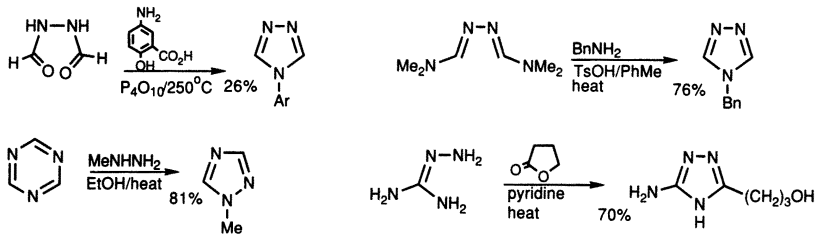


The condensation of azides with acyl-Wittig reagents offers a regiospecific synthesis of 1,5-disubstituted 1,2,3-triazoles.[30]



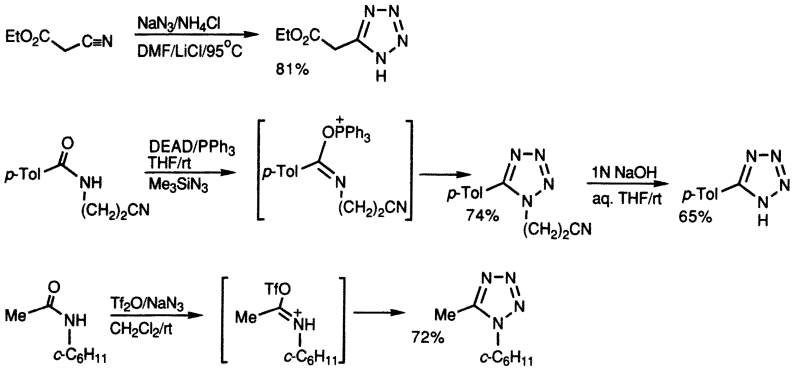
1,2,4-Triazoles

1,2,4-Triazoles are available *via* cyclodehydration reactions of *N,N'*-diacylhydrazine with amines, although the conditions are often quite vigorous.[31] An interesting variant utilises *sym*-triazine as an equivalent of $HN(CHO)_2$.[32] Condensations of aminoguanidine with esters give the versatile 3-amino compounds.[33]



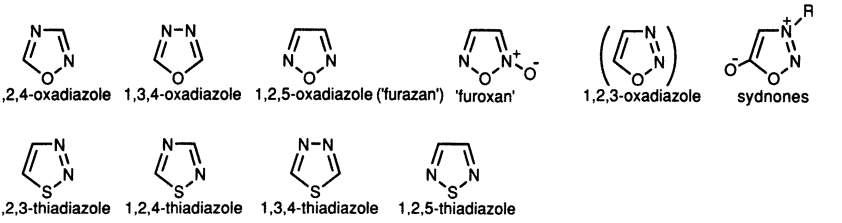
Tetrazoles

Tetrazoles are usually prepared by the reaction of an azide with a nitrile, or an activated amide; tri-*n*-butyltin azide and trimethylsilyl azide are more convenient and safer reagents than azide anion in some cases. The example shown illustrates the use of a cyanoethyl group as a removable protecting group for amide nitrogen.[34]



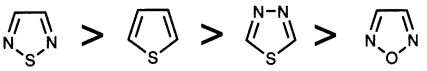
25.1.2 Oxadiazoles and thiadiazoles

Only one divalent hetero atom can be incorporated into a simple five-membered, aromatic heterocycle. These systems are named with the non-nitrogen atom numbered as 1, and the positions of the nitrogen atoms shown with reference to the divalent atom.

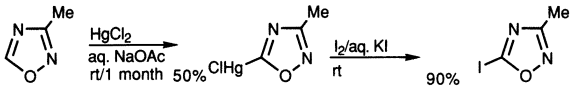


1,2,4-Oxadiazoles,[35] 1,3,4-oxadiazoles[36] and 1,2,5-oxadiazoles are well known, but the 1,2,3-oxadiazole system, which calculations indicate to be unstable relative to its ring-opened diazoketone tautomer,[37] is known only as a benzo-fused derivative (in solution) and in mesoionic substances, known as 'sydnones',[38] which have been well investigated. 'Furoxans',[39] which are

formed by the dimerisation of nitrile oxides, have also been extensively studied. 1,2,3-Thiadiazoles, 1,2,4-thiadiazoles,[40] 1,3,4-thiadiazoles[41] and 1,2,5-thiadiazoles[42] are all represented by well-characterised compounds. Estimates of aromaticity, based on bonds lengths and NMR data produced the following relative order:[43]

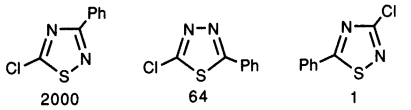


As with the azoles, oxa- and thiadiazoles are very weak bases due to the inductive effects of the extra hetero atoms, although *N*-quaternisation reactions can be carried out. For similar reasons, electrophilic substitutions on carbon are practically unknown, apart from a few halogenations and mercurations[44] – it is an intriguing paradox that mercurations, with what is generally thought of as a weak electrophile, are often successful in electron-poor heterocycles. Another important difference from the azoles is of course the absence of *N*-hydrogen, so that *N*-anion-mediated reactions are not possible.

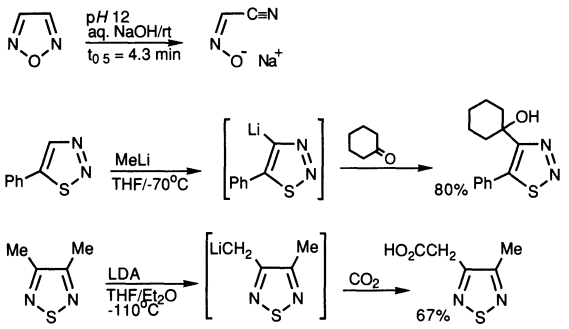


All these systems are susceptible to nucleophilic attack, particularly the oxadiazoles, which often undergo ring cleavage with aqueous acid or base unless both (carbon) positions are substituted. Similarly, leaving groups are generally displaced easily; there is substantial differential positional reactivity: in both 1,2,4-oxa- and -thiadiazoles a 5-chlorine is displaced much more easily that a 3-chlorine, no doubt due to the more effective stabilisation of the intermediate anionic adduct in the former situation. There is a far from complete set of comparisons of relative reactivities, but some data is available.[45]

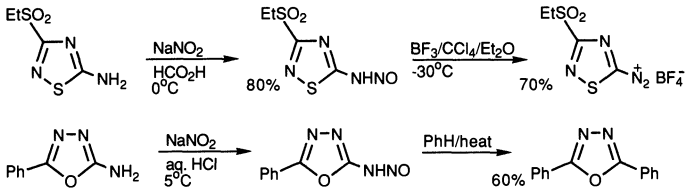
Relative rates of reaction with piperidine in ethanol



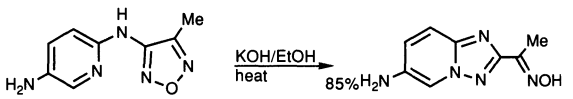
Base-catalysed proton exchange occurs readily, but decomposition *via* cycloreversion or β-elimination in the intermediate anion often competes.[46] Direct lithiations at carbon are generally easy,[47] but the resulting lithio derivatives vary greatly in stability, some being of no use synthetically.[48] Hydrogens on side-chain alkyl groups are 'acidified' by delocalisation of the charge in the deprotonated species onto ring nitrogens. There is an interesting difference between 1,2,5-oxa- and thiadiazoles in this context: in the former, smooth metallation of a 3-methyl occurs with *n*-butyllithium, but for the latter, LDA must be used to avoid competing nucleophilic addition to the sulfur, leading then to ring decomposition.[49]



Generally, amines can be diazotised and converted, for example, into halides, but in some cases the intermediate, *N*-nitroso compound is stable, and only then subsequently converted into a diazonium salt by treatment with strong acid – this may reflect the lower stability of a positively charged group attached to an electron-deficient ring.[50]

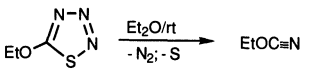


An interesting and fairly general type of reaction in ring systems such as these is ring interconversion *via* intramolecular attack on nitrogen.[51]

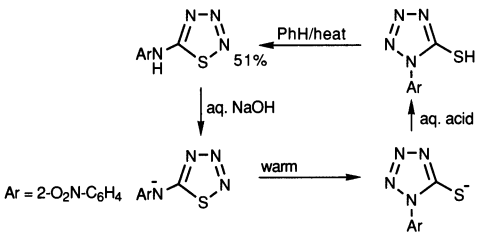


25.1.3 Other systems

Of the higher aza-compounds, only derivatives of 1,2,3,4-thiatriazole[52] are well defined, but even here alkyl derivatives decompose at or below 0°C, though 5-aryl- and amino derivatives are generally fairly stable. Many other derivatives are, however, dangerously explosive, for example the 5-chloro and thiolate derivatives. The controlled decomposition of 5-alkoxy-1,2,3,4-thiatriazoles (for example the 5-ethoxy-derivative in ether at 20°C) has been recommended as the best preparation of pure alkyl cyanates; thermal decomposition of 5-aryl compounds gives the corresponding nitrile.[53]



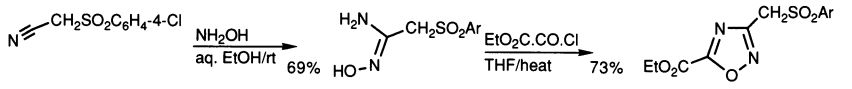
An interesting isomerisation cycle interconverts aminothiatriazoles and tetrazole thiols.[54]

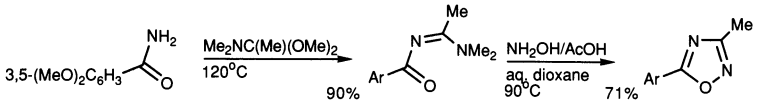


25.1.4 Ring synthesis

25.1.4.1 *1,2,4-Oxadiazoles*

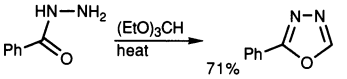
1,2,4-Oxadiazoles can be prepared by acylation of amidoximes[55] or from amides *via* acylamidines.[56]





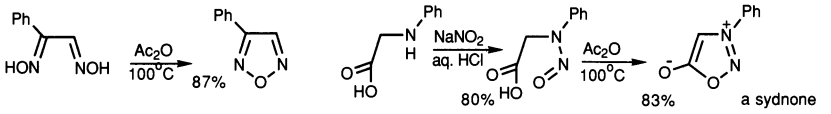
25.1.4.2 *1,3,4-Oxadiazoles*

1,3,4-Oxadiazoles are available by cyclodehydration of *N,N'*-diacylhydrazines or their equivalents.[57]



25.1.4.3 *1,2,5-Oxadiazoles*

1,2,5-Oxadiazoles result from the dehydration of 1,2-bisoximes.[46]

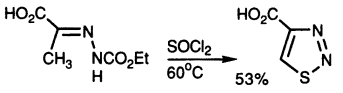


25.1.4.4 *Sydnones*

Sydnones are normally prepared by the dehydration of *N*-nitrosamino acids.[58]

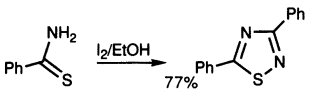
25.1.4.5 *1,2,3-Thiadiazoles*

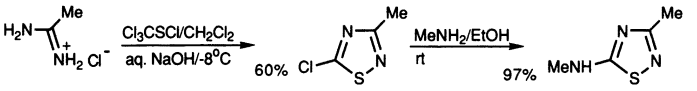
1,2,3-Thiadiazoles are prepared by reaction of a hydrazone, containing an acidic methylene group, with thionyl chloride.[59]



25.1.4.6 *1,2,4-Thiadiazoles*

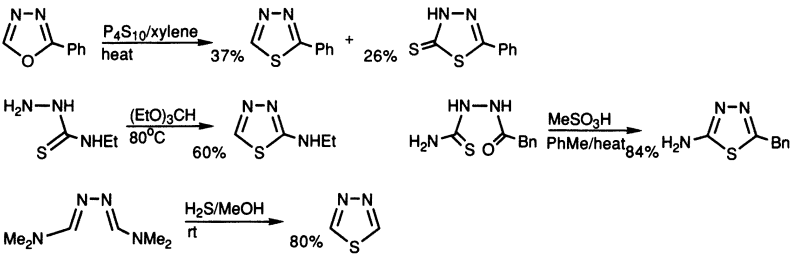
1,2,4-Thiadiazoles carrying identical groups at the 3- and 5-positions are obtained by the oxidation of thioamides; [60] 5-chloro-1,2,4-thiadiazoles result from the reaction of amidines with perchloromethyl mercaptan.[61]





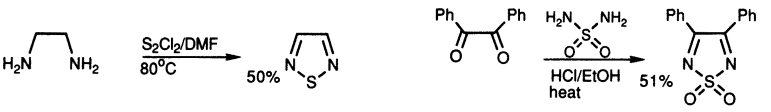
25.1.4.7 *1,3,4-Thiadiazoles*

1,3,4-Thiadiazoles are available by a number of convenient general routes including cyclisation of *N,N'*-diacylhydrazines, or 1,3,4-oxadiazoles, with phosphorus sulfides.[62] 3-Amino-1,3,4-thiadiazoles are prepared *via* acylation of thiosemicarbazides[63] and the parent compound is easily obtained from hydrogen sulfide and dimethylformamide azine.[64]



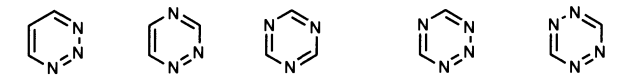
25.1.4.8 *1,2,5-Thiadiazoles*

1,2,5-Thiadiazoles can be prepared by the oxidative cyclisation of 1,2-diamines or aminocarboxamides.[65] Condensation of sulfamide ($SO_2(NH_2)_2$) with 1,2-diketones gives 1,2,5-thiadiazole 1,1-dioxides.[66]



25.2 SIX-MEMBERED RINGS

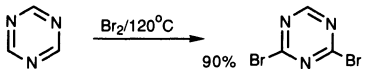
25.2.1 Azines



Neutral six-membered aromatic heterocycles cannot contain a divalent hetero atom. The azines are numbered to indicate the relative positions of the nitrogen atoms. 1,2,3,4-Tetrazine, pentazine and hexazine are unknown. Of the other systems, very little information is available on 1,2,3,5-tetrazine but, on the other hand, derivatives of 1,3,5-triazine are very well known and available in large quantities, indeed they are amongst the oldest known heterocycles: the trioxy-compound ('cyanuric acid') was first prepared in 1776 by Scheele by the pyrolysis of uric acid.

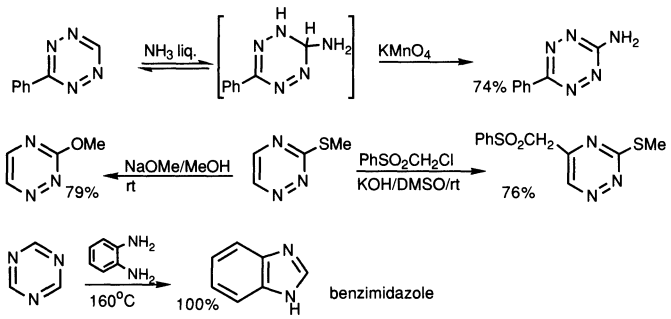
The thermal stabilities of the parent systems vary from 1,2,3-triazine, which decomposes at about 200°C, to 1,3,5-triazine, which is stable to over 600°C – at this temperature it decomposes to give hydrogen cyanide, of which it is formally a trimer.

In comparison with the diazines, the inductive effects of the 'extra' nitrogen(s) leads to an even greater susceptibility to nucleophilic attack and as a result, all the parent systems and many derivatives react with water, in acidic or basic solution. Similarly, simple electrophilic substitutions do not occur; some apparent electrophilic substitutions, such as the bromination of 1,3,5-triazine, probably take place *via* bromide nucleophilic addition to an N^+–Br complex.[67]

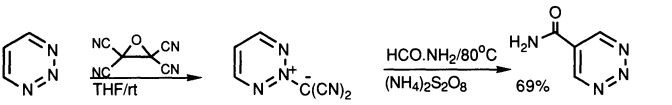


The examples shown below are illustrative of the many easy nucleophilic additions to the polyaza-azines: the reaction of 1,2,4,5-tetrazine with simple amines[68] can be contrasted with the requirement for sodamide (Chichibabin reaction) for the diazines and pyridine. The easy addition at C-5 of 1,2,4-triazines[69] is shown by the VNS reaction of the 3-methylthio-derivatives in the absence of activating groups: the ready displacement of methylthio from the same compound is also indicative.[70]

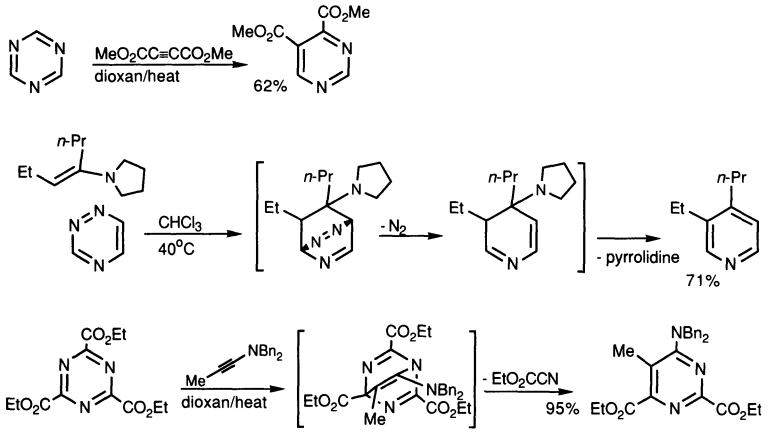
The susceptibility of 1,3,5-triazine to nucleophilic attack with ring opening makes it a synthetically useful equivalent of formate, or formamide, particularly for the synthesis of other heterocycles such as imidazoles and triazoles[71] (section 25.1.1.4; 1,2,4-triazoles).



An interesting variant of the Minisci reaction has been reported for 1,2,3-triazine, which is unstable to the usual acidic conditions: here, activation of the heterocycle to attack by the nucleophilic radical is brought about by the agency of a dicyanomethine ylid.[72]



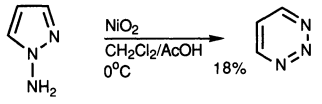
Probably the most useful and general reaction of all these systems is the inverse-electron demand Diels-Alder reaction with acetylenes (or equivalents) to produce either pyridines or diazines *via* elimination of hydrogen cyanide or nitrogen.[73]



25.2.2 Ring syntheses

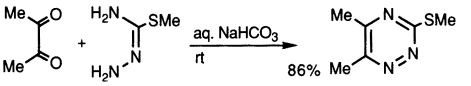
25.2.2.1 *1,2,3-Triazine*

1,2,3-Triazine has been prepared by the oxidation of 1-aminopyrazole.[74]



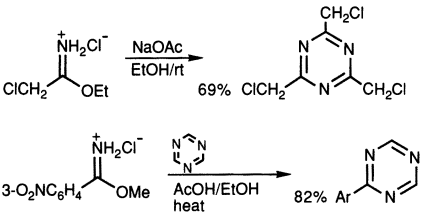
25.2.2.2 *1,2,4-Triazines*

1,2,4-Triazines have been prepared by the condensation of amidrazones with diketones or halo-ketones.[75]



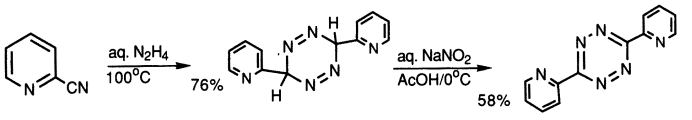
25.2.2.3 *1,3,5-Triazines*

1,3,5-Triazines are usually most easily obtained by substitution reactions on 2,4,6-trichloro-1,3,5-triazine, but the ring system can also be synthesised by cyclocondensation reactions. Trimerisation of nitriles (a common industrial method) or imidates[76] gives symmetrically substituted compounds; mono-substituted-1,3,5-triazines can be obtained *via* reaction of imidates with 1,3,5-triazine itself.[77]



25.2.2.4 *1,2,4,5-Tetrazines*

1,2,4,5-Tetrazines can be produced by condensation of hydrazine with carbonyl compounds at acid oxidation level, followed by oxidation of the dihydroproducts: this generally produces 3,6-identically-substituted derivatives, crossed condensation reactions being inefficient.[64,78]



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EXERCISES FOR CHAPTER 25

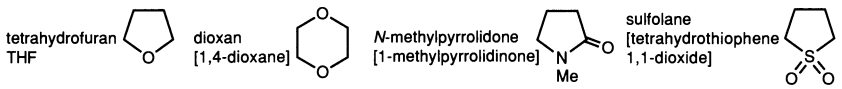
1. What are the products of the following (Diels-Alder) reactions: (i) 1-pyrrolidinylcyclopentene with (a) 1,3,5-triazine, (b) 1,2,4-triazine; (ii) 3-phenyl-1,2,4,5-tetrazine with 1,1-diethoxyethene?
2. Thiophosgene ($S{=}CCl_2$) reacts at low temperature with sodium azide to give a product which contains no azide group; on subsequent reaction with methylamine this compound is converted into $C_2H_4N_4S$ – suggest structures.
3. What are the products of the reaction of $PhCO.NH_2$ with DMFDMA then (a) N_2H_4 and (b) H_2NOH?
4. 1,3,5-Triazine reacts with (i) aminoguanidine to give 4-amino-1,3,4-triazole and with (ii) diethyl malonate to give ethyl 4-hydroxypyrimidine 5-carboxylate. Write mechanisms for these transformations.

Saturated and partially unsaturated heterocyclic compounds: reactions and synthesis

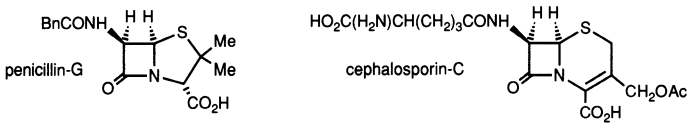
26

This book is principally concerned with the chemistry of aromatic heterocycles, however mention must be made of the large body of remaining heterocycles, including those with small rings[1] (3- and 4-membered). Most of the reactions of saturated and partially unsaturated heterocyclic compounds are so closely similar to those of acyclic or non-heterocyclic analogues that a full discussion is not appropriate in this book; however, in this chapter we discuss briefly those aspects in which they do differ – perhaps the most obvious aspect in which they differ from aromatic heterocycles is in having sp^3 hybridised atoms, i.e. in the exhibition of stereochemistry.[2]

Saturated and partially unsaturated heterocycles are widely distributed as natural products. Some are used as solvents for organic reactions, notably tetrahydrofuran (THF) and dioxan, where diethyl ether is unsuitable. *N*-Methylpyrrolidone and sulfolane are useful dipolar aprotic solvents, with characteristics like those of dimethylformamide (DMF) and dimethyl sulfoxide (DMSO).

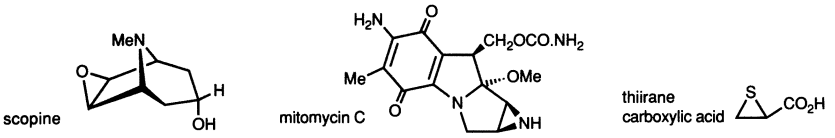


The four-membered β-lactam ring is the essential component of the penicillin and cephalosporin antibiotics.



Epoxides (three-membered saturated oxygen-containing rings) are components of epoxy resins and occur in some natural products, such as the alkaloid scopine. Epoxides, because of their alkylating properties, can be carcinogenic –

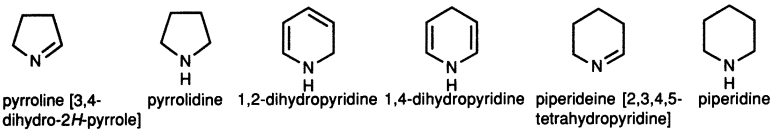
the biologically active metabolites of carcinogenic hydrocarbons are examples – however they are also found in some anti-tumour agents.



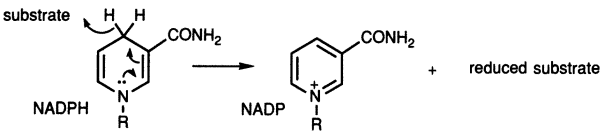
Aziridines (three-membered saturated nitrogen-containing rings) are also found in anti-tumour agents, such as the mitomycins. Thiiranes also occur naturally, as plant products such as thiirane-2-carboxylic acid, isolated from asparagus.

26.1 FIVE- AND SIX-MEMBERED RINGS

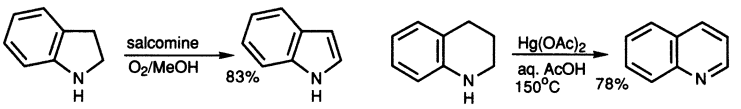
26.1.1 Pyrrolidines and piperidines



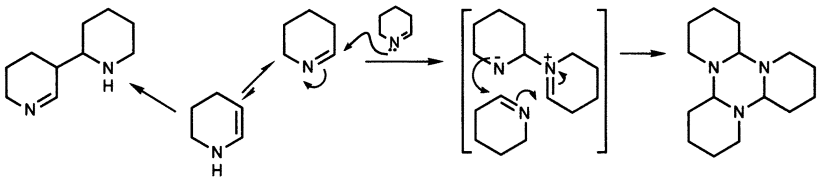
The main chemical aspect in which compounds with a nitrogen in a five- or six-membered ring differ from their acyclic counterparts is in the possibility open to them to be dehydrogenated to the corresponding aromatic system. Dihydroaromatic systems naturally show the greatest tendency to aromatise, indeed one of the important reducing coenzymes, NADPH, makes use of this tendency, as indicated below.



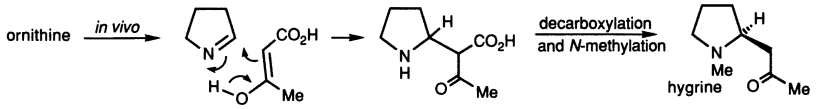
Dihydro-compounds are often useful synthetic intermediates showing different reactivity patterns to the parent, aromatic heterocycle. For example, indolines (2,3-dihydroindoles) can be used to prepare indoles[3] with substituents in the carbocyclic ring, *via* electrophilic substitution then rearomatisation (section 17.16.8), and similarly, electrophilic substitutions of dihydropyridines, impossible in pyridines themselves, followed by rearomatisation can give substituted pyridines. Dehydrogenation of tetra- and hexahydro-derivatives requires much more vigorous conditions.



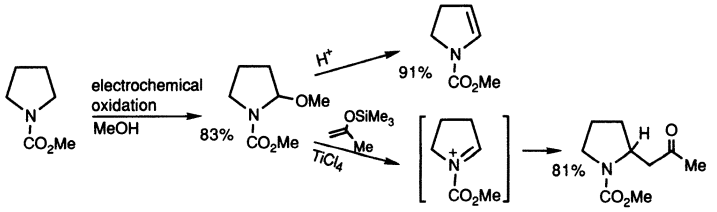
Generally speaking, piperideines and pyrrolines exist predominantly in the imine form and not in the tautomeric enamine form; *N*-alkyl analogues have no alternative but to exist as enamines. These cyclic imines are resistant to hydrolytic fission of the C=N bond, in strong contrast with acyclic imines, but nonetheless they are very susceptible to nucleophilic addition at the azomethine carbon. An example of this is that both piperideine and pyrroline exist as trimers formed by the nucleophilic addition of nitrogen of one molecule to the azomethine carbon of a second molecule, etc.



The presence of some enamine, at equilibrium, is demonstrated by the conversion of piperideine into a dimer; indeed, the ability of these two systems to serve as both imines and enamines in such aldol-like condensations is at the basis of their roles in alkaloid biosynthesis. Formed in nature by the oxidative deamination and decarboxylation of ornithine and lysine, they become incorporated into alkaloid structures by condensation with other precursor units.[4] Hygrine is a simple example in which the 1-pyrroline, as an imine, has condensed with acetoacetate, or its equivalent.



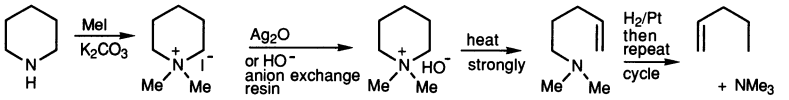
Controlled oxidation of *N*-acylpiperidines and -pyrrolidines can be used to prepare 2-alkoxy-derivatives or the equivalent enamides, which are useful general synthetic intermediates.[5] The former are susceptible to nucleophilic substitution under Lewis acid catalysis, *via* Mannich-type intermediates, and the latter can undergo electrophilic substitution at C-3 or addition to the double bond.



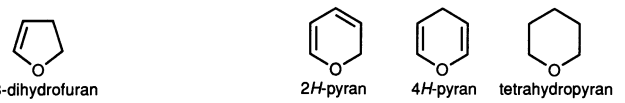
Pyrrolidine and piperidine are better nucleophiles than diethylamine, principally because the lone pair is less hindered – in the heterocycles the two alkyl 'substituents', i.e. the ring carbons, are constrained back and away from the nitrogen lone pair, and approach by an electrophile is thus rendered easier than in diethylamine where rotations of the C–N and C–C bonds hinder approach. The pK_a values of pyrrolidine (11.27) and piperidine (11.29) are typical of amine bases; they are slightly stronger bases than diethylamine (10.98).

Piperidines, like cyclohexanes, adopt a preferred chair conformation. Much controversy centred over the years on the question as to whether in piperidines it is the *N*-substituent (or *N*-hydrogen) or the *N*-lone pair which adopts an equatorial or axial orientation; some confusion arose because of the results from *N*-alkylation reactions, the products from which do not necessarily reflect ground state conformational populations. Both an *N*-hydrogen and an *N*-alkyl substituent adopt an equatorial orientation, though in the former case the equatorial isomer is favoured by only a small margin.[6]

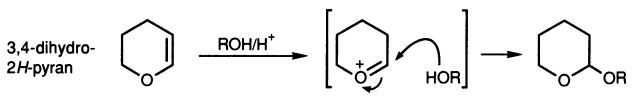
In early days, structure determination of natural products involved degradative methods. Many alkaloids incorporate saturated nitrogen rings, so degradations were used which gave information about the environment of the basic nitrogen atom. The classical method for doing this was the 'Hofmann exhaustive methylation' procedure. This is illustrated as it would be applied to piperidine. What the method does is to cleave N–C bonds and eventually remove the nitrogen; one repetition of the cycle, as in the example, removes the nitrogen – it was originally part of a ring; a third cycle would be necessary if the nitrogen had been originally a component of two rings. At the end of the process a nitrogen-free fragment is left for study to determine the original carbon skeleton.



26.1.2 Pyrans and reduced furans

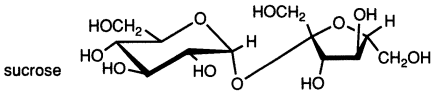


3,4-Dihydro-2*H*-pyran and 2,3-dihydrofuran behave as enol ethers, the former being widely used to protect alcohols[7] with which it reacts readily under acidic catalysis, producing acetals which are stable to even strongly basic conditions but easily hydrolysed back to the alcohol under mildly acidic aqueous conditions.

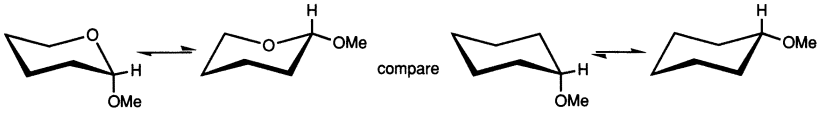


4*H*-Pyran appears to be somewhat less stable than dihydropyran but reacts similarly; for example, it lithiates at C-2 and undergoes Diels-Alder reactions as an enol ether.[8]

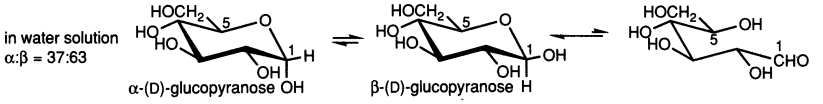
A great deal is known about hydroxylated tetrahydrofurans and tetrahydropyrans because such ring systems occur in sugars and sugar-containing compounds – sucrose and RNA (section 23.1) are examples.[9]



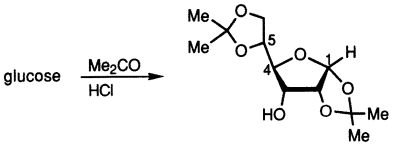
Tetrahydropyran, like piperidine, adopts a chair conformation. One of the interesting aspects to emerge from studies of alkoxy-substituted tetrahydropyrans is that when located at C-2, alkoxyl groups prefer an axial orientation (the 'anomeric effect'[10]). The reason for this is that in an equatorial orientation there are unfavourable dipole–dipole interactions between lone pairs on the two oxygen atoms, and the energy gain, when these are relieved in a conformation with the C-2-substituent axial, more than offsets the unfavourable 1,3-diaxial interactions which are introduced at the same time.



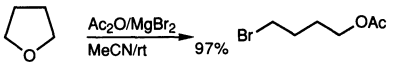
Glucose, of which many of the chemical reactions actually involve the small concentration of acyclic polyhydroxyaldehyde in equilibrium with the cyclic forms, hemiacetals containing a tetrahydropyran: this illustrates the inherent stability of chair conformers of saturated six-membered systems. The propensity for cyclisation is a general one: 5-hydroxyaldehydes, -ketones and -acids all easily form six-membered oxygen-containing rings – lactols and lactones respectively.



Five-membered rings, too, are relatively easy to form: depending on conditions, glucose derivatives can easily be formed in the furanose form, i.e. based on tetrahydrofuran.

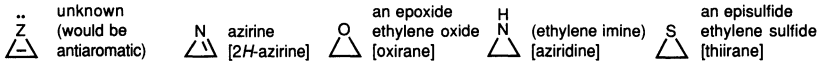


Saturated cyclic ethers are inert like acyclic ethers, requiring strong conditions for C–O bond cleavage;[11] this contrasts with heterocycles having smaller ring sizes (sections 26.2 and 26.3).



26.2 THREE-MEMBERED RINGS

Δ-2-Unsaturated three-membered systems are unknown as stable molecules because they would have a 4-electron π-system, and thus be antiaromatic.[12] 1*H*-Azirines occur as reactive intermediates and there is evidence for the existence of 2-thiirene in a low temperature matrix.[13] Azirines,[14] by contrast, are well-known stable compounds. Thiirene *S*,*S*-dioxides are also stable molecules, probably best likened to cyclopropenones.[15] The chemistry of saturated three-membered heterocycles is, however, very extensive, in particular, epoxides (oxiranes) are vital intermediates in general synthesis.

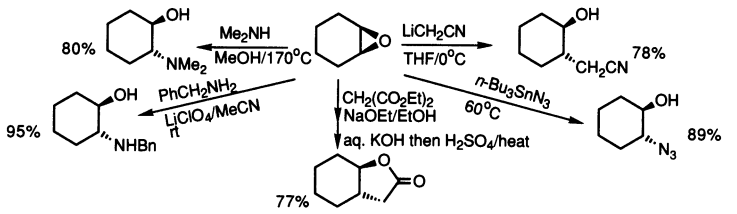


A major advance has been the development of an efficient synthesis of epoxides of high optical purity from allylic alcohols and related systems (the *Sharpless epoxidation*) (below); such epoxides have been used extensively for the synthesis of complex natural products in homochiral form.

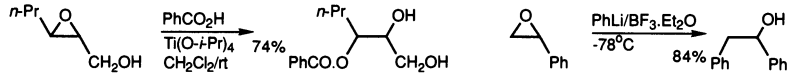
The pK_a of aziridine (7.98) shows it to be an appreciably weaker base than azetidine (11.29), the four-membered analogue, which is 'normal' for acyclic amines and for five- and six-membered saturated amines. The low basicity is mirrored in the oxygen series, as measured by the ability of oxiranes to form hydrogen bonds. The explanation is probably associated with the strain in the three-membered compounds, meaning that the lone pair is in an orbital with less p-character than a 'normal' sp^3 nitrogen or oxygen orbital, and is therefore held more tightly. The rate of pyramidal inversion of the 'saturated' nitrogen in azirines is very slow compared with simpler amines. This is because there is a further increase in angle strain when the nitrogen rehybridises (→ sp^2) in the transition state for inversion.

The chemical reactions of three-membered heterocycles are a direct consequence of the strain inherent in such small rings, which, combined with the ability of the hetero atom to act as a leaving group, means that most of the chemical properties involve ring-opening reactions. Most epoxide ring openings occur by S_N2 nucleophilic displacements at carbon and a very wide range of carbanion and hetero atom nucleophiles have been shown to react in this way, including amines,[16] alcohols, thiols, hydride ($LiAlH_4$), malonate anions,[17] etc. Assistance by protic solvents or *O*-coordinating metal cations (Lewis acids), which help to further weaken the C–O bond, can dramatically increase the rate

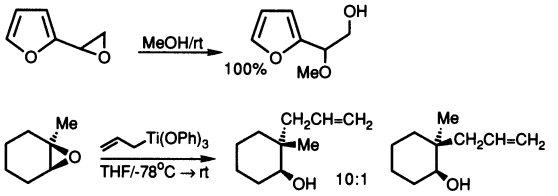
of reaction. Additives such as alumina,[18] titanium alkoxides,[19] and lithium perchlorate,[20] and reagents such as tributyltin azide,[21] which is itself a Lewis acid (coordination to 'Bu_3Sn^+'), but also contains a nucleophilic function (N_3^-), are useful in this respect.



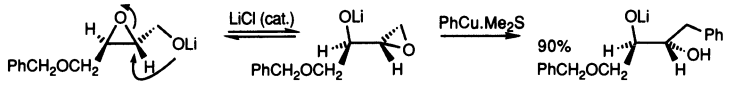
'Harder' organometallic nucleophiles such as alkyllithiums often give rise to side reactions but their combination (at −78°C) with boron trifluoride gives very clean and efficient reactions.[22]



The regiochemistry of ring opening is determined mainly by steric and to a lesser extent by inductive and electronic effects. Where strong Lewis acids are used or where a highly stabilised (incipient) carbonium ion can be formed, such as when an α-aryl substituent is present, reaction can occur mainly at the most substituted position, an extreme case being the solvolysis of 2-furyloxirane in neutral methanol;[23] however, selective substitution at the most highly substituted position of even simple, alkyl epoxides has been achieved with an allyltitanium reagent.[24]

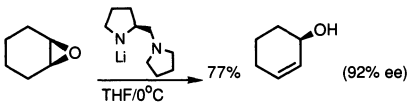


The Payne rearrangement of epoxy-alcohols is a special case of an intramolecular nucleophilic opening of epoxides and is of synthetic significance due to its application to Sharpless epoxides.[25]

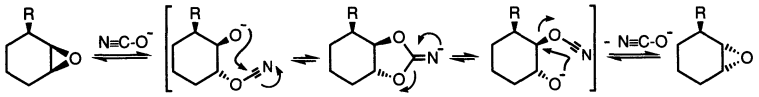


Ring opening of epoxides by β-elimination, on reaction with strong bases such as lithium amides, or combinations of TMSOTf with DBU,[26] is a useful

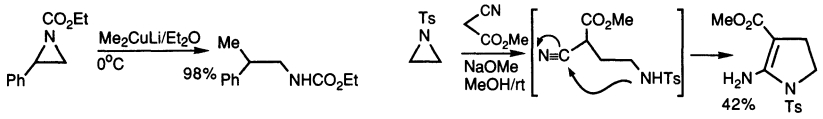
synthetic method for allylic alcohols, particularly as it can be carried out enantioselectively.[27]



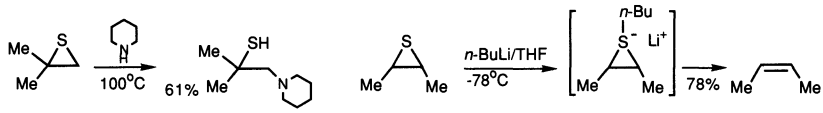
The relative stereochemistry of epoxides can be inverted by equilibration with cyanate anion.[28]



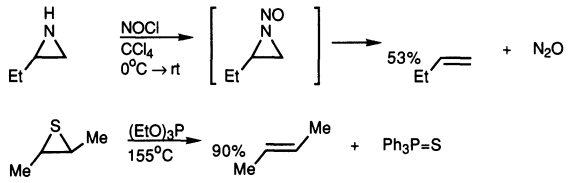
Acid-catalysed opening of aziridines is usually quite rapid, but simple nucleophilic reactions, without acid catalysis, are very slow due to the much poorer leaving ability of negatively charged nitrogen; however, *N*-acyl or *N*-sulfonyl aziridines have reactivity similar to epoxides.[29]



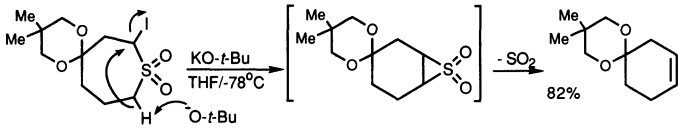
Thiiranes similarly undergo ring-opening reactions with nucleophiles such as amines,[30] but attack at sulfur can also occur with lithium reagents.[31]



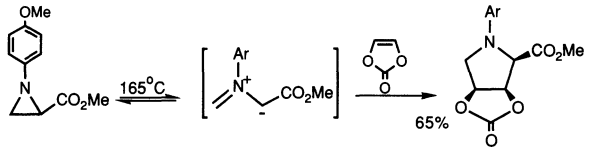
The hetero atom in a three-membered heterocycle can be eliminated *via* various cycloreversion reactions, for example by nitrosation of aziridines,[32] or by the reaction of thiiranes with trivalent phosphorus compounds.



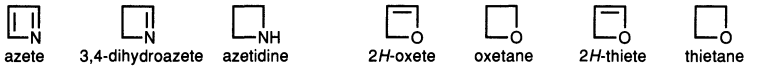
A related elimination of sulfur dioxide occurs during the Ramburg-Backlung synthesis of alkenes, which generates an episulfone as a transient intermediate, although episulfones are isolable under controlled conditions.[33]



Substituted derivatives of all three systems are able to undergo a highly stereospecific concerted thermal ring opening, generating ylides which can be utilised (trapped) in 3 + 2 cycloaddition reactions.[34]

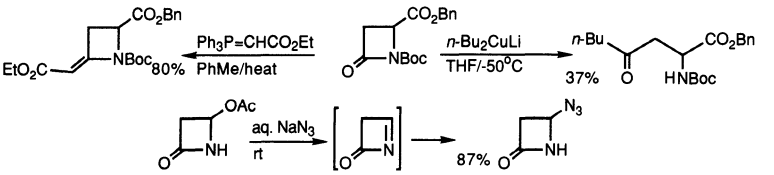


26.3 FOUR-MEMBERED RINGS

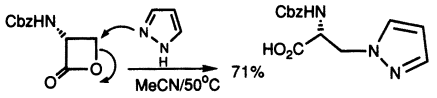


Derivatives of azete are only known as unstable reaction intermediates. Oxetane and azetidine are considerably less reactive than their three-membered counterparts (oxetane reacts with hydroxide anion 10^3 times more slowly than does oxirane), but nonetheless do undergo similar ring opening reactions; for example, oxetane reacts with organolithium reagents,[22] in the presence of boron trifluoride, or with cuprates,[35] and azetidine is opened on heating with concentrated hydrochloric acid.

The most important four-membered system is undoubtedly the β-lactam ring[36] which is present in, and essential for the biological activity of, the penicillin and cephalosporin antibiotics. β-Lactams are very susceptible to ring opening *via* attack at the carbonyl carbon – in stark contrast to the five-membered analogues (pyrrolidones) or acyclic amides, which are relatively resistant to nucleophilic attack at carbonyl carbon. In addition, β-lactams are hydrolysed by a specific enzyme, β-lactamase, the production of which is a mechanism by which bacteria become resistant to such antibiotics. Although the β-lactam ring is easily cleaved by nucleophiles, both *N*- and *C*-alkylation (α to carbonyl) can be achieved using bases to deprotonate; it is even possible to carry out Wittig reactions at the 'amide' carbonyl without ring opening.[37] Substitution of the acetoxy group in a 4-acetoxyazetidinone by nucleophiles is an important synthetic method; the reaction proceeds *via* an imine or an immonium intermediate rather than by direct displacement.[38]

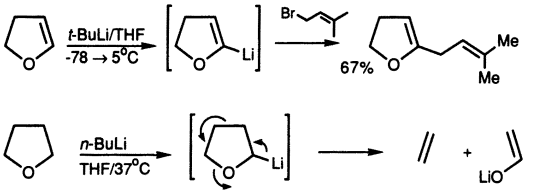


β-Lactones (propiolactones)[39] too are readily attacked at the carbonyl carbon, for example they are particularly easily hydrolysed, but a second mode of nucleophilic attack – S_N2 displacement of carboxylate *via* attack at C-4 – occurs with many nucleophiles.[40] The example shows the use of a homochiral lactone, available from serine.

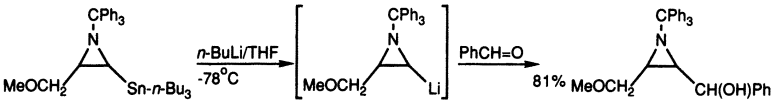


26.4 METALLATION

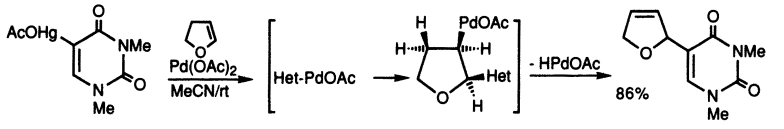
Saturated and mono-unsaturated 5-[41] and 6-membered rings can be metallated in the same way as their acyclic analogues. In the case of tetrahydrofuran, however, warming with *n*-butyllithium produces a lithio-derivative which undergoes a cycloreversion, generating ethene and the lithium enolate of ethanal.[42] This process represents the most convenient preparation of this enolate but can also be a significant, unwanted side-reaction during lithiation reactions using THF as solvent.



Three-membered rings have not been metallated directly in the absence of anion-stabilising substituents but simple lithio-derivatives or aziridines have been prepared by exchange from the corresponding stannane.[43]

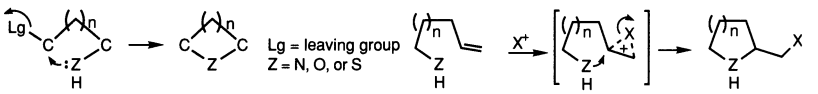


The conformationally restrained, cyclic nature of dihydrofuran (and dihydropyran) leads to an abnormal sequence during a Heck reaction. The addition of the arylpalladium halide occurs normally but rotation cannot occur so, instead of syn β-hydride elimination towards the aryl substituent, elimination takes place towards C-4.[44] In some cases, particularly at higher temperatures, further migration of the double bond occurs.



26.5 RING SYNTHESIS

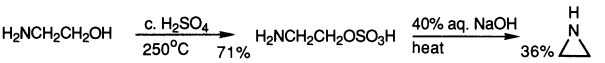
Five- and six-membered saturated rings can be prepared by reduction of the corresponding aromatic compound, but the most general method for making all ring sizes is by cyclisation of an ω-substituted amine, alcohol or thiol *via* an intramolecular nucleophilic displacement. As an illustration, the rate of cyclisation of ω-halo-amines goes through a minimum at the four-membered ring size; the five and six-membered rings are by far the easiest to make (relative rates: 72 (3-membered ring) : 1 (4) : 6000 (5) : 1000 (6)).[45] A factor which influences the rate of 3-*exo-tet* cyclisations is the degree of substitution at the carbon carrying the hetero atom: increasing substitution increases the rate of cyclisation, because in the small ring product there is some degree of relief of steric crowding for the substituents compared with acyclic starting material.[46]



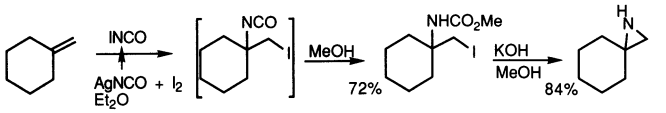
Related cyclisations involving hetero atom attachment to an alkene *via* π-complexes with cations such as Br^+, I^+, Hg^+ and Pd^+ are useful methods because they give products with functionalised side-chains for further transformations.

26.5.1 Saturated nitrogen heterocycles

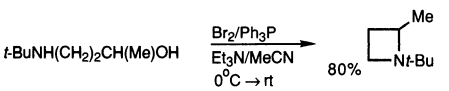
Aziridines can be prepared by alkali-catalysed cyclisation of 2-haloamines or of a 2-hydroxyamine sulfonate ester.[47]



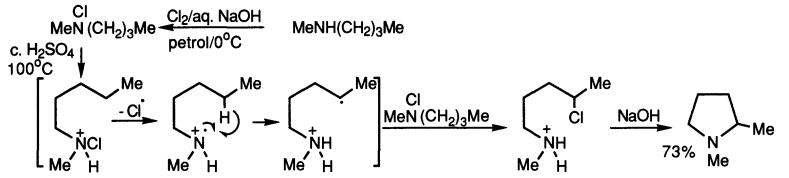
Related methods include reaction of an alkene with INCO[48] or IN_3.[49] The product from the latter reaction can be converted into the aziridine *via* reduction, or into an azirine *via* elimination of hydrogen iodide and pyrolysis.[50]



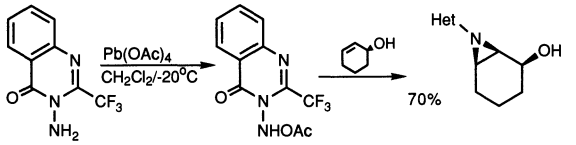
Azetidines can be obtained by cyclisations of 3-halo-amines, but yields are generally not as good as those for the formation of aziridines. The generation of the bifunctional precursors for cyclisation to azetidines has been achieved in a number of ways.[51]



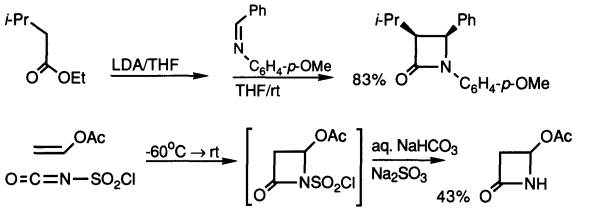
A very neat method for the synthesis of pyrrolidines does not require a difunctionalised starting material, but relies on the Hofmann-Löffler-Freytag reaction[52] – which is a radical process – to introduce the second functional group. The six-membered size of the cyclic transition state leads selectively to a 1,4-halo-amine, and thence to pyrrolidines.



Aziridines can also be prepared by addition of nitrenes to alkenes,[53] or by the use of nitrogen-transfer agents analogous to epoxidising agents.[54]

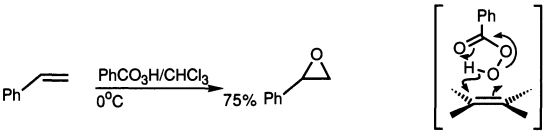


Many methods have been developed for β-lactam synthesis,[36,55] including cyclisation of the corresponding amino acids. The most widely used methods are two-component couplings[38,56] which occur *via* concerted cycloaddition or two-step mechanisms.

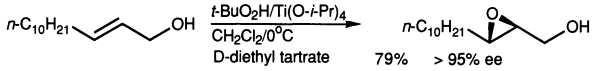


26.5.2 Saturated oxygen heterocycles

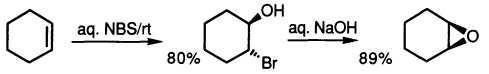
The most widely used method for the preparation of epoxides involves oxidation of an alkene by a peracid,[57] *via* a direct one-step transfer of an oxygen atom. More highly (alkyl) substituted alkenes react fastest, showing that electronic effects are more important than steric effects in this reaction. Steric effects do, however, control the facial selectivity of epoxidation; conversely hydrogen-bonding groups such as OH and NH can direct the reaction to the *syn* face.

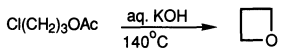


Several other direct oxygen-transfer reagents have been developed, of which by far the most important is Sharpless' reagent – a mixture of a hydroperoxide with titanium isopropoxide and an alkyl tartrate.[58] The structure of the reagent is complex but it reacts readily with alkenes containing polar groups, for example allylic alcohols, which can coordinate the metal. The most important feature of this process is that when homochiral tartrate esters are used, a highly ordered asymmetric reactive site results, leading in turn to high optical induction in the product.

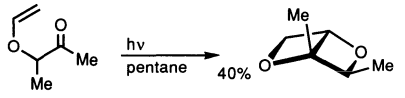


Epoxides and oxetanes can also be prepared by cyclisation of 1,2- (halohydrins) and 1,3-halo-alcohols.[59]



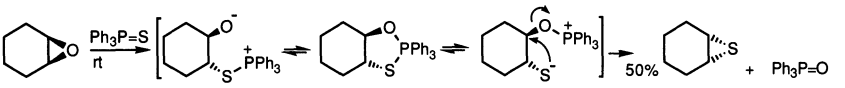


Oxetanes have often been prepared by the *Paterno-Büchi reaction*,[60] in which a compound containing a carbon–carbon double bond cycloadds to an aldehyde or ketone under the influence of light.[61]

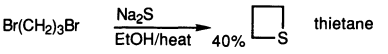


26.5.3 Saturated sulfur heterocycles

Thiiranes can be prepared by cyclisation of 2-halo-thiols but the most common method is *via* reaction of an epoxide with thiocyanate (cf. section 26.2), a phosphine sulfide, or with dimethylthioformamide.[62]



Thietanes, tetrahydrothiophenes and tetrahydrothiapyrans can all be prepared by the reaction of the appropriate 1,ω-dihalide with sulfide anion.



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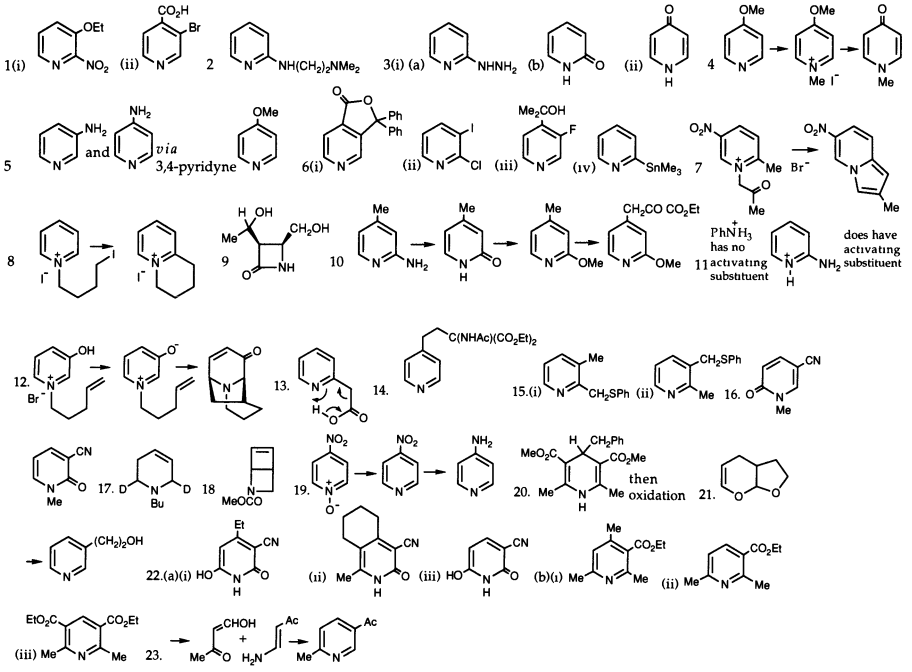
Appendix: answers to exercises

27

CHAPTER 5



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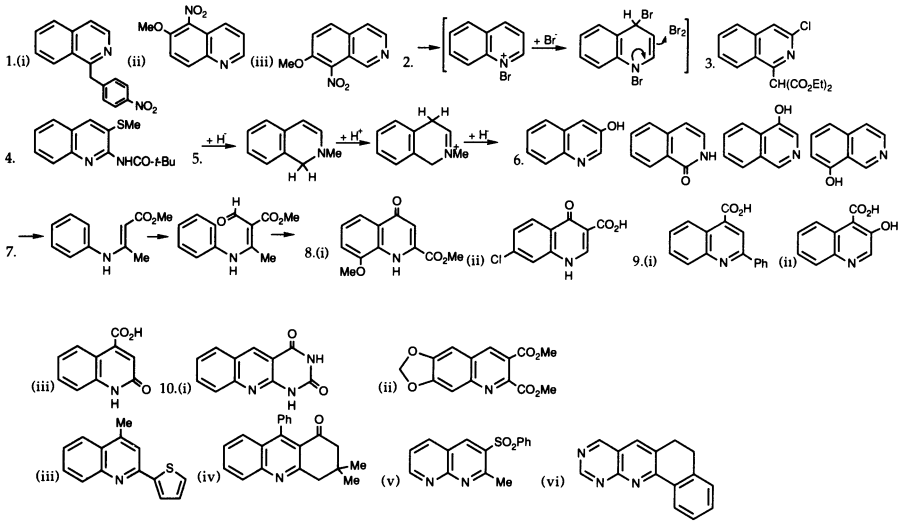

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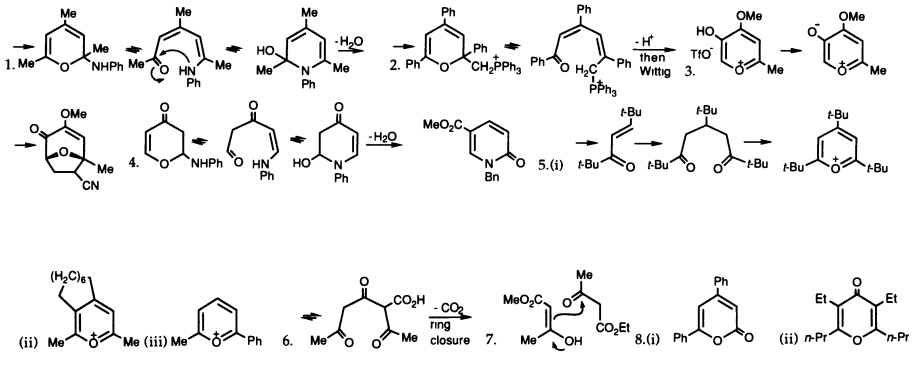

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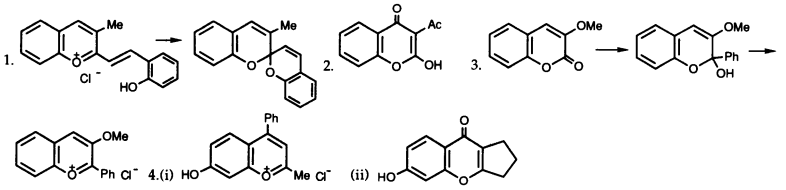

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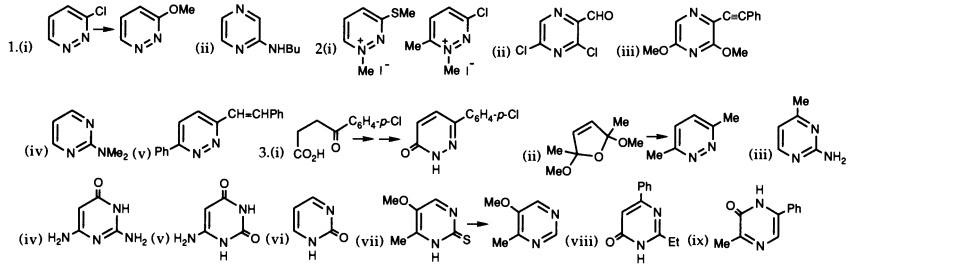

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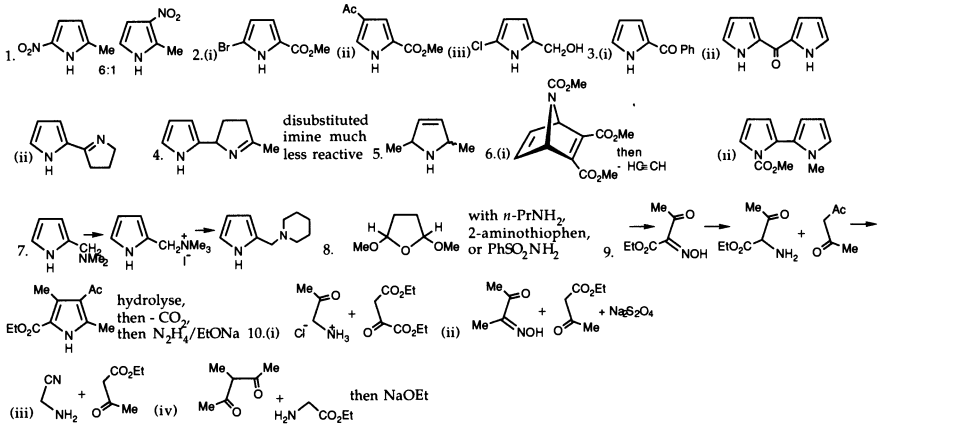

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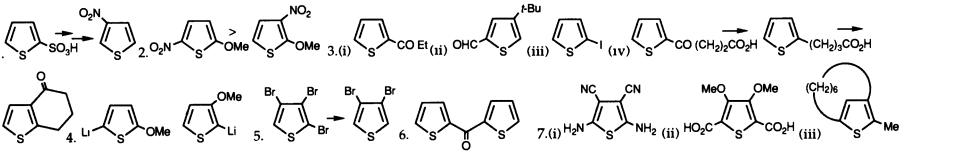

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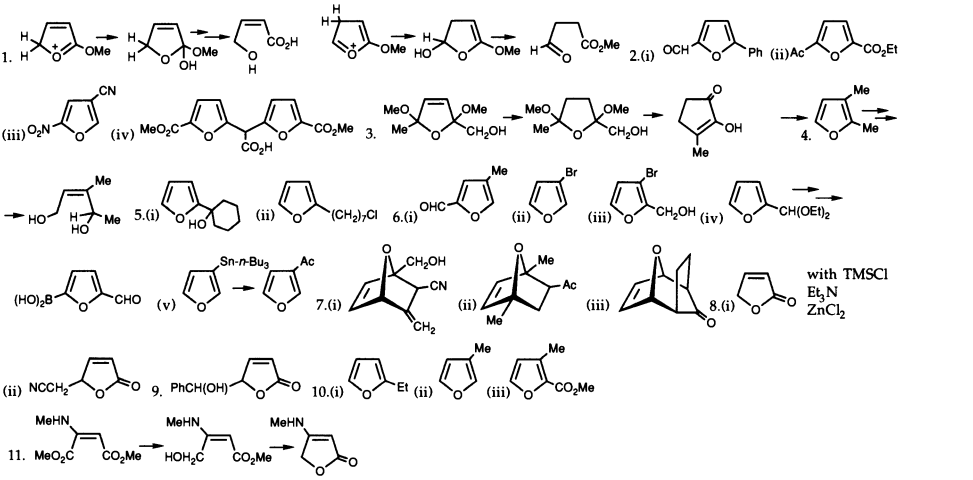

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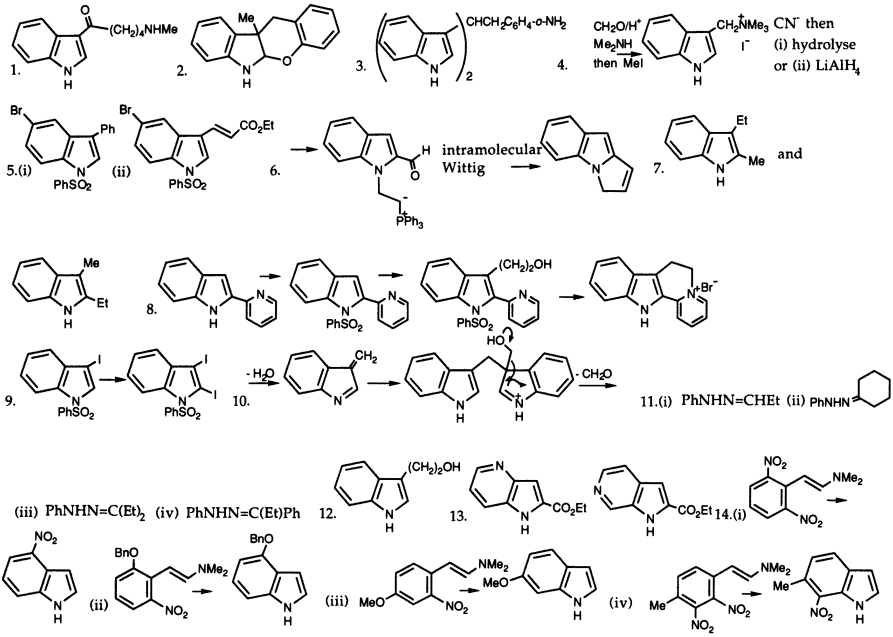

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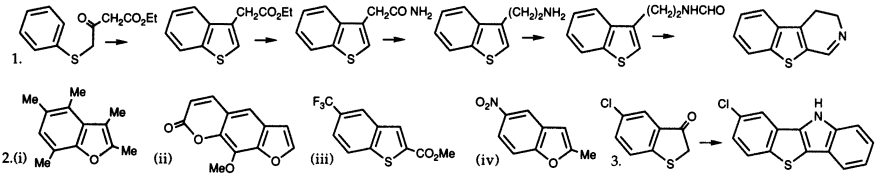

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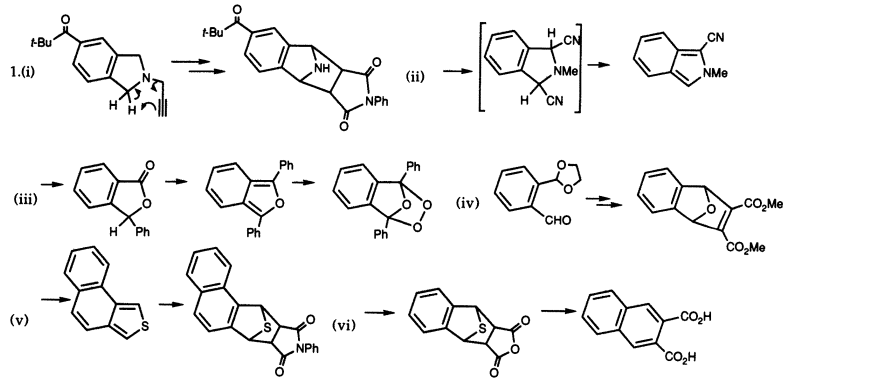

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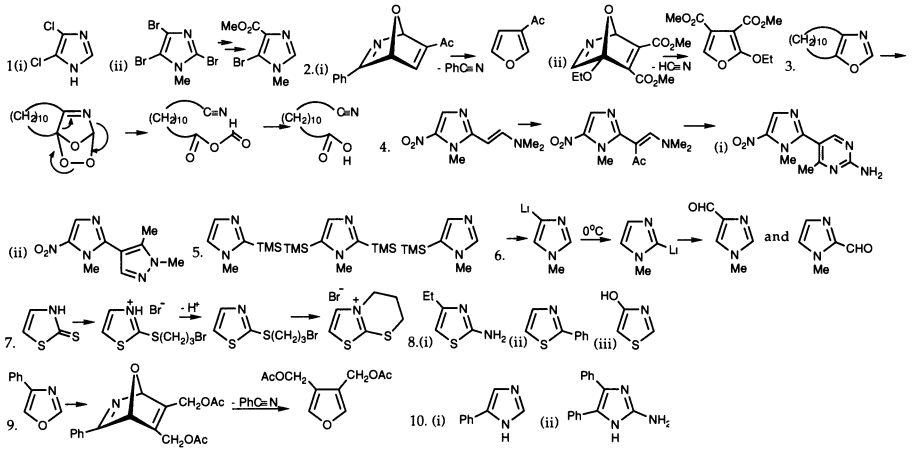

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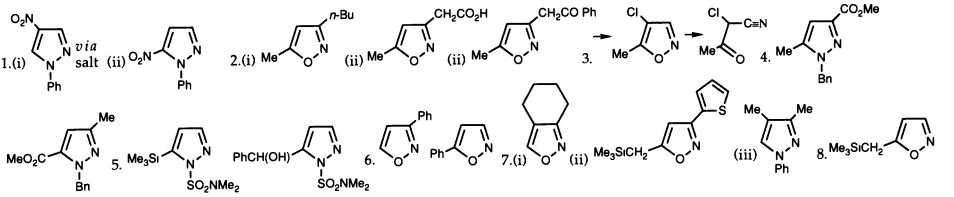

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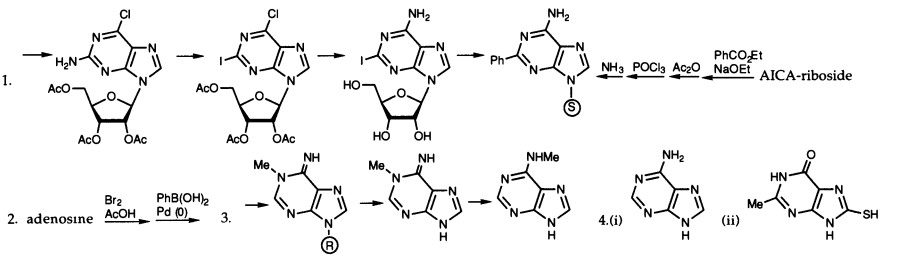

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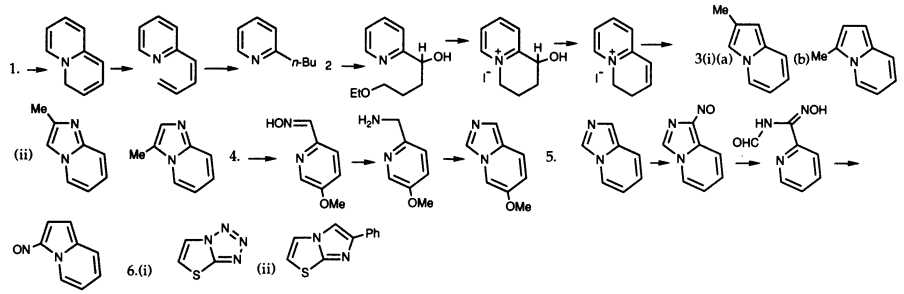

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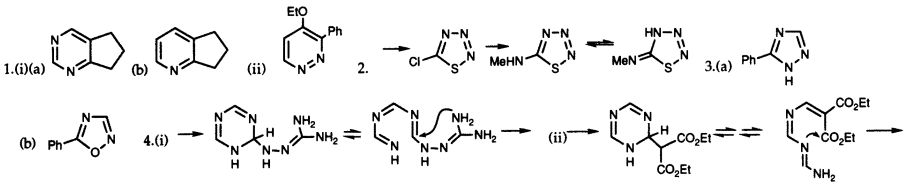

Index

Individual compounds are listed by name, ONLY when the text gives a ring synthesis, or total synthesis, or where a particular aspect of reactivity is also noted; metallated species are however listed because of their importance in synthesis – products derived from these intermediates are not listed. Some liberties have been taken with chemical names, with the aim of helping the Reader seeking chemical information, for example the Index gives 'Indole, 2-lithio-1-phenylsulfonyl-' but also (incorrectly) 'indole, 2-lithio-1-*t*-butoxycarbonyl'. Also, names emphasize the heterocyclic aspect e.g. 'furan, 2-ethoxycarbonyl' is used rather than 'ethyl furan-2-carboxylate'. The (inorganic) counteranions to heterocyclic cations are omitted e.g. 'Pyrylium' not 'Pyrylium perchlorate'; pyridinium salts are listed as 'Pyridiniums' *etc.*