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Heterocyclic Chemistry at a Glance

Second Edition

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Biography

John Arthur Joule was born in Harrogate, Yorkshire, England, but grew up and attended school in Llandudno, North Wales, going on to study for BSc, MSc, and PhD (1961; with George F. Smith) degrees at The University of Manchester. Following post-doctoral periods in Princeton (Richard K. Hill) and Stanford (Carl Djerassi) he joined the academic staff of The University of Manchester where he served for 41 years, retiring and being appointed Professor Emeritus in 2004. Sabbatical periods were spent at the University of Ibadan, Nigeria, Johns Hopkins Medical School, Department of Pharmacology and Experimental Therapeutics, and the University of Maryland, Baltimore County. He was William Evans Visiting Fellow at Otago University, New Zealand.

Dr. Joule has taught many courses on heterocyclic chemistry to industry and academe in the UK and elsewhere. He is currently Associate Editor for *Tetrahedron Letters,* Scientific Editor for *Arkivoc*, and Co-Editor of the annual *Progress in Heterocyclic Chemistry.*

Keith Mills was born in Barnsley, Yorkshire, England and attended Barnsley Grammar School, going on to study for BSc, MSc and PhD (1971; with John Joule) degrees at The University of Manchester.

Following post-doctoral periods at Columbia (Gilbert Stork) and Imperial College (Derek Barton/Philip Magnus), he joined Allen and Hanburys (part of the Glaxo Group) at Ware and later Stevenage (finally as part of GSK), working in Medicinal Chemistry and Development Chemistry departments for a total of 25 years. During this time he spent a secondment at Glaxo, Verona. Since leaving GSK he has been an independent consultant to small pharmaceutical companies.

Dr. Mills has worked in several areas of medicine and many areas of organic chemistry, but with particular emphasis on heterocyclic chemistry and the applications of transition metal-catalysed reactions.

Heterocyclic Chemistry was first published in 1972, written by George Smith and John Joule, followed by a second edition in 1978. The third edition (Joule, Mills and Smith) was written in 1995 and, after the death of George Smith, a fourth edition (Joule and Mills) appeared in 2000 and a fifth edition in 2010. The first edition of *Heterocyclic Chemistry at a Glance* was published in 2007.

Abbreviations

Ac	acetyl [$CH_3C{=}O$], thus AcOH = ethanoic (acetic) acid; Ac_2O = ethanoic anhydride (acetic anhydride)
anti	on the opposite side (antonym of *syn*)
aq	aqueous – the reaction mixture contains water
Ar	general designation for a benzenoid aromatic group
[bmim][BF_4]	1-*n*-butyl-3-methylimidazolium tetrafluoroborate (an ionic liquid)
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl – ligand for palladium(0)
Bn	benzyl [$PhCH_2$] – *N*-protecting group; removed by hydrogenolysis over Pd
Boc	*t*-butyloxycarbonyl [*t*-BuOCO] – protecting group; removed with acid
Bom	benzyloxymethyl [$PhCH_2OCH_2$] – protecting group; removed by hydrogenolysis over Pd
Bt	benzotriazol-1-yl (structure page 136)
Bz	benzoyl [PhCO] as in OBz, a benzoate
c	cyclo as in *c*-C_6H_{11} = cyclohexyl
c.	concentrated, as in c. H_2SO_4 = concentrated sulfuric acid
cat	catalyst – reagent not consumed in the reaction – usually, in the case of metal catalysts, e.g. Pd, used in sub-stoichiometric quantities – 1–5 mol%
Cbz	benzyloxycarbonyl [$PhCH_2OCO$] – protecting group; removed by hydrogenolysis
CDI	1,1′-carbonyldiimidazole [$(C_3H_3N_2)_2C{=}O$] – peptide coupling reagent
Cy	cyclohexyl [*c*-C_6H_{11}]
dba	*trans,trans*-dibenzylideneacetone [PhCH=CHCOCH=CHPh] – ligand for palladium(0)
DCC	dicyclohexylcarbodiimide [*c*-$C_6H_{11}N{=}C{=}N$*c*-C_6H_{11}] – for coupling acid and amine to give amide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone – oxidant, often used for dehydrogenation
DMAP	4-dimethylaminopyridine [4-$Me_2NC_5H_4N$] – nucleophilic catalyst
DME	1,2-dimethoxyethane [$MeO(CH_2)_2OMe$] – ethereal solvent
DMF	dimethylformamide [$Me_2NCH{=}O$] – dipolar aprotic solvent
DMFDMA	dimethylformamide dimethyl acetal [$Me_2NCH(OMe)_2$]
DMSO	dimethylsulfoxide [$Me_2S{=}O$] – dipolar aprotic solvent
dppb	1,4-bis(diphenylphosphino)butane [$Ph_2P(CH_2)_4PPh_2$] – ligand for palladium(0)
dppe	1,2-bis(diphenylphosphino)ethane [$Ph_2P(CH_2)_2PPh_2$] – ligand for palladium(0)
dppf	1,1′-bis(diphenylphosphino)ferrocene [$(Ph_2PC_5H_4)_2Fe$] – ligand for palladium(0)
dppp	1,3-bis(diphenylphosphino)propane [$Ph_2P(CH_2)_3PPh_2$] – ligand for palladium(0)
ee	enantiomeric excess – a measure of the efficiency of an asymmetric synthesis
El^+	general designation for a positively charged electrophile
Et	ethyl [CH_3CH_2]
f.	fuming, as in f. HNO_3 = fuming nitric acid
2-Fur	furan-2-yl [C_4H_3O]
GABA	γ-aminobutyric acid (4-aminobutanoic acid) [$H_2N(CH_2)_3CO_2H$]
Hal	general designation for a halogen
Het	general designation for a heteroaryl group

i-Pr	isopropyl [Me_2CH]
LDA	lithium di-isopropylamide [$LiN(i\text{-}Pr)_2$] – hindered strong base
LiTMP	lithium 2,2,6,6-tetramethylpiperidide [$LiN(C(Me)_2(CH_2)_3C(Me)_2$] – hindered non-nucleophilic strong base
Me	methyl [CH_3]
Ms	methanesulfonyl (mesyl) [$MeSO_2$] – protecting group for azole nitrogen
NaHMDS	sodium bis(trimethylsilyl)amide [sodium hexamethyldisilazide] [$NaN(SiMe_3)_2$] – hindered non-nucleophilic strong base
NBS	*N*-bromosuccinimide [$C_4H_4BrNO_2$] – brominating agent
NCS	*N*-chlorosuccinimide [$C_4H_4ClNO_2$] – chlorinating agent
NMP	*N*-methylpyrrolidin-2-one (1-methylpyrrolidin-2-one) [C_5H_9NO] – dipolar aprotic solvent
n-Bu	normal butyl [$CH_3(CH_2)_3$]
n-Pr	normal propyl [$CH_3CH_2CH_2$]
Nu^-	general designation for a negatively charged nucleophile
Ph	phenyl [C_6H_5]
PMB	*p*-methoxybenzyl [$4\text{-}MeOC_6H_4CH_2$]
Pr	see *i*-Pr and *n*-Pr
2-Py; 3-Py; 4-Py	pyridin-2-yl; pyridin-3-yl; pyridin-4-yl [C_5H_4N]
R	general designation for an alkyl group
o-Tol	*ortho*-tolyl (2-methylphenyl) [C_7H_7]
p-Tol	*para*-tolyl (4-methylphenyl) [C_7H_7]
rt	room temperature (ca. 20 °C)
Selectfluor^{TM}	1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane tetrafluoroborate – electrophilic fluorinating agent
SEM	trimethylsilylethoxymethyl [$Me_3Si(CH_2)_2OCH_2$] – protecting group; removed with fluoride
SES	trimethylsilylethanesulfonyl [$Me_3Si(CH_2)_2SO_2$] – N-protecting group; removed with fluoride
SPhos	2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl – ligand for palladium(0)
syn	on the same side (antonym of *anti*)
TBDMS	*t*-butyldimethylsilyl [$t\text{-}Bu(CH_3)_2Si$] – bulky silyl protecting group
t-Bu	tertiary butyl [$(CH_3)_3C$]
Tf	trifluoromethanesulfonyl [CF_3SO_2], thus TfO^- = triflate [$CF_3SO_3^-$] – triflate is a good leaving group
THF	tetrahydrofuran – common ethereal solvent for dry reactions at low temperature
THP	tetrahydropyran-2-yl [C_5H_9O] – protecting group; removed with aqueous acid
TIPS	tri-isopropylsilyl [$Si(i\text{-}Pr)_3$] – protecting group for nitrogen or oxygen
TIPB	1,3,5-tri-*iso*-propylbenzene – inert high-boiling solvent
TMSCl	trimethylsilyl chloride (chlorotrimethylsilane) [Me_3SiCl] – *O*- and *N*-trimethylsilylating reagent
Tol	same as *p*-Tol
TosMIC	tosylmethyl isocyanide [$TolSO_2CH_2N^+{\equiv}C^-$]
Ts	*p*-toluenesulfonyl (tosyl) [$p\text{-}TolSO_2$] – Ts is a good protecting group for azole nitrogen and Ts^- can be a leaving group (*para*-toluensulfinate)
Tr	trityl (triphenylmethyl) [Ph_3C] – *N*-protecting group; removed with acid
TTF	tetrathiafulvalene ($C_6H_4S_4$)
X	general designation for halogen (or in palladium(0) chemistry, sometimes OTf)

Introduction to Second Edition

The material in this book comprises an introduction to, and summary of, the most important ideas and principles of heterocyclic chemistry. We have attempted to encapsulate everything that a non-specialist, or beginning student, would need to know of the subject. At the same time, we believe that this book will serve as a good starting point for further, more extensive study of the subject.

This Second Edition has been expanded by 50% compared with the First Edition (2007), allowing us to include more examples and illustrations, and exercises at the ends of the chapters (with answers available online at http://booksupport.wiley.com). The other significant difference to the First Edition is the use of colour in the schemes (for details, see below).

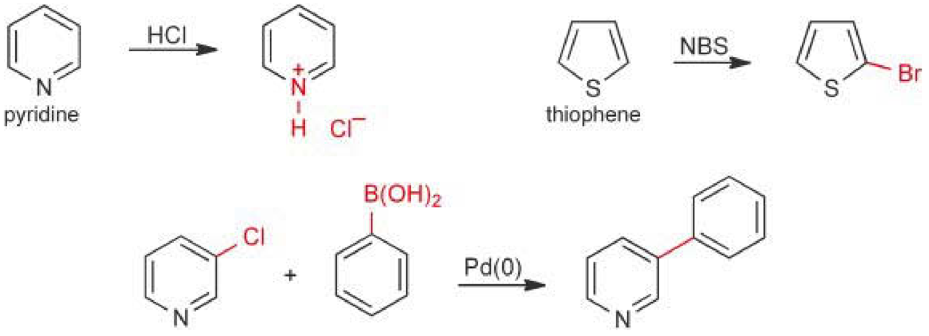
We now have three supplementary chapters dealing with the occurrence and significance of heterocycles in the world at large: Chapters 17 and 18 deal with 'Heterocycles in Nature' and 'Heterocycles in Medicine'; Chapter 19 discusses major significant heterocyclic involvements in dyes and pigments, polymers, pesticides, explosives, food and drink, and electronics.

The book is mainly concerned with aromatic heterocycles though we also include a short discussion of non-aromatic heterocycles (Chapter 16). We deal with the characteristic reactivities of the most important heteroaromatic systems and the principal routes for their ring synthesis from non-heterocyclic precursors. Thus the chemistry of pyridines, pyridazines, pyrimidines, pyrazines, quinolines, isoquinolines, pyrylium and benzopyrylium cations, pyrroles, indoles, thiophenes, furans, imidazoles, oxazoles, thiazoles, pyrazoles, isoxazoles, isothiazoles, purines, heterocycles with more than two heteroatoms in the ring (for example triazoles and triazines) and heterocycles in which a heteroatom is located at a ring junction (for example pyrrolizines and indolizines) is covered (Chapters 5–15). The book starts with a discussion of nomenclature and structures of aromatic heterocycles (Chapters 1 and 2); then follows Chapter 3, which examines in detail the typical reactions of heterocycles, except for those involving palladium-catalysis, since these are considered separately in the following Chapter 4.

The book assumes a basic knowledge of organic chemistry such as one would expect of a student at the second year level of a UK Honours Chemistry course and thus would be suitable for second/third/fourth year undergraduate and post-graduate courses in UK Universities. It is also relevant that much Inorganic Chemistry relies on maintaining metals in various (often unusual) oxidation states by surrounding them with ligands and that these are very often heterocyclic, so choosing or designing appropriate heterocyclic ligands and then being able to synthesise them, is also an integral prerequisite of Inorganic Chemistry. With this book we also target students in other disciplines – Pharmacy, Pharmacology, Medicinal Chemistry – whose subjects require them to assimilate the basics of this particular area of organic chemistry. The vital importance of a proper understanding of heterocyclic chemistry for the study of biochemistry at the molecular level and for drug design and synthesis in medicinal chemistry, is emphasised in Chapters 17 and 18, 'Heterocycles in Nature' and 'Heterocycles in Medicine'.

It is not the purpose of this book to provide guidance for the conduct of practical work: especially at the undergraduate level, all experimental work must be conducted under the supervision of an experienced teacher. For experimental details the reader must consult the original literature – many references to suitable, key papers can be found in our fuller exposition – *Heterocyclic Chemistry, 5th Edition,* Joule and Mills, Wiley, 2010. All the examples in *Heterocyclic Chemistry at a Glance* are taken from the literature and the vast majority proceed in good yields. In the reaction schemes, so that the reader can concentrate on the chemistry in question, we have simply shown that a particular compound will react with a particular reagent or reactant to give a product, and we have omitted practical details such as solvent, reaction time, yields, and most other details, except where their inclusion makes a didactical point. Where reactions were carried out at room temperature or with gentle warming or cooling, no comment is made. Where reactions were carried out with strong heating (e.g. reflux in a high-boiling solvent) the word 'heat' is used on the reaction arrow; for transformations carried out at very low temperature, this is specified on the reaction arrow. For some of the palladium-catalysed reactions we give full experimental conditions, to illustrate what is typical for cross-couplings.

In the reaction schemes, we have highlighted in red those parts of the products (or intermediates) where a change in structure or bonding has taken place. We hope that this both facilitates comprehension of the chemical processes that are occurring and quickly focuses the reader's attention on just those parts of the molecules where structural change has occurred. For example, in the first reaction below, only changes at the pyridine nitrogen are involved; in the second example, the introduced bromine resulting from the substitution, and its new bond to the heterocycle, are highlighted. The exception to this policy is in palladium-catalysed cross-coupling processes where the functional groups in each of the coupling partners, as well as the new bond formed, are coloured red, as shown in the third example below.



Finally we acknowledge the crucial advice, support and encouragement from staff at Wiley, in bringing this project to fruition, in particular Paul Deards and Sarah Tilley. Mrs Joyce Dowle is thanked for her helpful comments during the preparation of Chapter 19 and Judith Egan-Shuttler for her careful copy editing.

Further reading

This book can act only as an introduction to heterocyclic chemistry and does not include references to original literature, or to the many reviews that are available. For further study and to go more deeply into the topics covered in this book we recommend, as a first port-of-call, our textbook *Heterocyclic Chemistry* [1] in which there are a host of leading references to the original literature and appropriate reviews.

The premier sources of regular reviews in this area are *Advances in Heterocyclic Chemistry* [2] and *Progress in Heterocyclic Chemistry* [3] and the principles of heterocyclic nomenclature are set out in one review [4] in the former series. The journal, *Heterocycles,* also carries many useful reviews specifically in the heterocyclic area. As its title implies, an exhaustive coverage of the area is provided in the three parts of *Comprehensive Heterocyclic Chemistry* (CHC), original (1984), and its two updates (1996 and 2008) [5]. Note: The three parts must be read *together* – the later parts update but do not repeat the earlier material. The *Handbook of Heterocyclic Chemistry* [6] that accompanies CHC encapsulates the key information from the series in a single volume. There is a comprehensive compilation of heterocyclic data and facts: the still-continuing and still-growing series of monographs [7] dealing with particular heterocyclic systems, edited originally by Arnold Weissberger, and latterly by Edward C. Taylor and Peter Wipf, is a vital source of information and reviews for all those working with heterocyclic compounds. The '*Science of Synthesis*' series contains authoritative discussions on the synthesis of heterocycles, organized in a hierarchical system [8]; volumes 9–17, published over the period 2000–2008, discuss aromatic heterocycles.

For further reading relating in particular to Chapters 17, 18 and 19, we recommend *Heterocycles in Life and Society* [9], *Introduction to Enzyme and Coenzyme Chemistry* [10], *Nucleic Acids in Chemistry and Biology* [11], *The Alkaloids; Chemistry and Biology* [12], *Comprehensive Medicinal Chemistry II* [13], *Molecules and Medicine* [14], *Goodman and Gilman's The Pharmacological Basis of Therapeutics* [15], *The Chemistry of Explosives* [16], *Food. The Chemistry of its Components* [17], *Perfumes: the Guide* [18], *Handbook of Conducting Polymers* [19], *Handbook of Oligo- and Polythiophenes* [20], *Tetrathiafulvalenes, Oligoacenenes, and their Buckminsterfullerene Derivatives: the Bricks and Mortar of Organic Electronics* [21].

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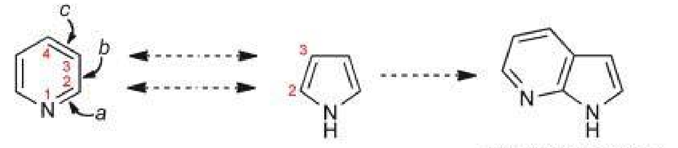
1

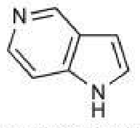
Heterocyclic Nomenclature

A selection of the structures, names and standard numbering of the more common heteroaromatic systems and some common non-aromatic heterocycles, are shown in this chapter. The aromatic heterocycles are grouped into those with six-membered rings and those with five-membered rings. The names of six-membered aromatic heterocycles that contain nitrogen generally end in ‘ine’, though note that ‘purine’ is the name for a very important bicyclic system which, has both a six- and a five-membered nitrogen-containing heterocycle. Five-membered heterocycles containing nitrogen generally end with ‘ole’. Note the use of italic ‘*H*’ in a name such as ‘9*H*-purine’ to designate the location of an *N*-hydrogen in a system in which, by tautomerism, the hydrogen could reside on another nitrogen (e.g. N-7 in the case of purine). Names such as ‘pyridine’, ‘pyrrole’ and ‘thiophene’ are the original, and now standard, names for these heterocycles; names such as ‘1,2,4-triazine’ for a six-membered ring with three nitrogens located as indicated by the numbers, are more logically systematic.

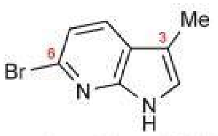
A detailed discussion of the systematic rules for naming polycyclic systems in which several aromatic or heteroaromatic rings are fused together, is beyond the scope of this book, however, two simple examples will serve to illustrate the principles. In the name ‘pyrrolo[2,3-*b*]pyridine’, the numbers signify the positions of the first named heterocycle, numbered as if it were a separate entity, which are the points of ring fusion; the italic letter, ‘*b*’ in this case, designates the *side* of the second named heterocycle to which the other ring is fused, the lettering deriving from the numbering of that heterocycle as a separate entity, that is, side *a* is between atoms 1 and 2, side *b* is that between atoms 2 and 3, and so on. Actually, this particular heterocycle is more often referred to as ‘7-azaindole’ – note the use of the prefix ‘aza’ to denote the replacement of a ring carbon by nitrogen. Similarly, ‘5-azaindole’ is systematically called ‘pyrrolo[3,2-*c*]pyridine’ – note that the order of the numbers ‘3,2-’ arises because the first atom of the pyrrole encountered in counting round from the pyridine nitrogen to determine the side of fusion, and thus the label ‘*c*’, is C-3 of the pyrrole unit. The numbering of a bi- or polycyclic system *as a whole* is generated from a series of rules concerned with the orientation of the rings and the positions of the nitrogen(s), but we do not deal with these here – the overall numbering for these two systems is shown for two substituted examples.



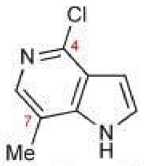
pyrrolo[2,3-*b*]pyridine
(7-azaindole)



pyrrolo[3,2-*c*]pyridine
(5-azaindole)



6-bromo-3-methylpyrrolo[2,3-*b*]pyridine

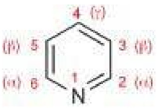


4-chloro-7-methylpyrrolo[3,2-*c*]pyridine

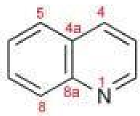
A device that is useful in discussions of reactivity is the designation of positions as ‘α’, ‘β’ or ‘γ’. For example, the 2- *and* the 6-positions in pyridine are equivalent in reactivity terms, so to make discussion of such reactivity clearer, each of these positions is referred to as an ‘α-position’. Comparable use of α and β is made in describing reactivity in five-membered systems. These useful designations are shown on some of the structures. Note that carbons at angular positions do not have a separate number but are designated using the number of the preceding atom followed by ‘a’ – as illustrated for quinoline.

Heterocyclic Chemistry at a Glance, Second Edition. John A. Joule and Keith Mills.

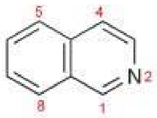
Six-membered aromatic heterocycles



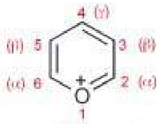
pyridine



quinoline

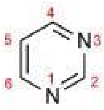


isoquinoline

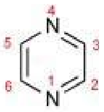


pyrylium cation

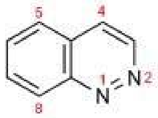
pyridazine



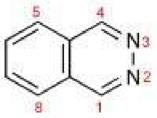
pyrimidine



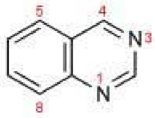
pyrazine



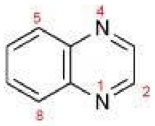
cinnoline



phthalazine

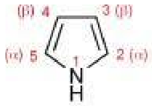


quinazoline

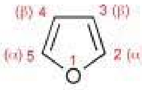


quinoxaline

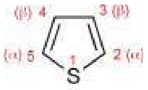
Five-membered aromatic heterocycles



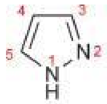
pyrrole



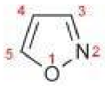
furan



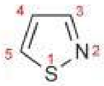
thiophene



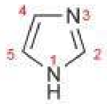
pyrazole



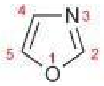
isoxazole



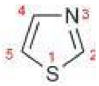
isothiazole



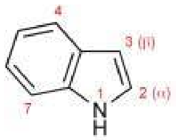
imidazole



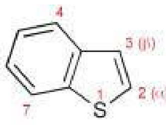
oxazole



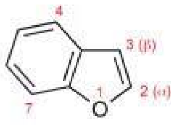
thiazole



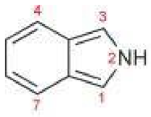
indole
[1*H*-indole]



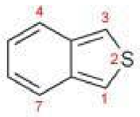
benzothiophene
[benzo[*b*]thiophene]



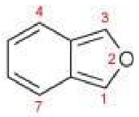
benzofuran
[benzo[*b*]furan]



isoindole

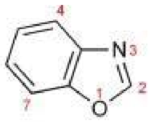


benzo[*c*]thiophene

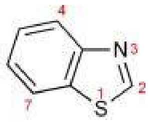


isobenzofuran

benzimidazole



benzoxazole

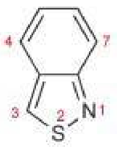


benzothiazole

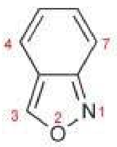
1*H*-indazole

1,2-benzisoxazole

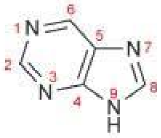
1,2-benzisothiazole



2,1-benzisothiazole

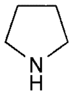


2,1-benzisoxazole
(anthranil)

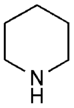


purine
[9*H*-purine]

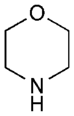
Non-aromatic heterocycles



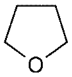
pyrrolidine



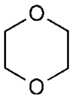
piperidine



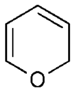
morpholine



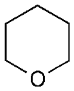
tetrahydrofuran
(THF)



dioxane
[1,4-dioxane]



2*H*-pyran

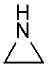


tetrahydropyran

Small-ring heterocycles

azirine
[2*H*-azirine]

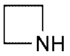
oxirane
(ethylene oxide)



aziridine
(ethylene imine)

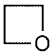
thiirane
(ethylene sulfide)

azete



azetidine

2*H*-oxete



oxetane

2*H*-thiete

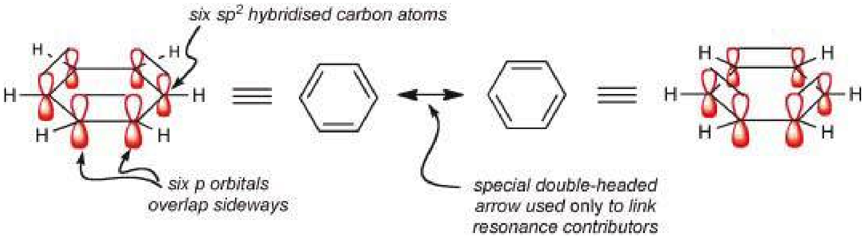
thietane

2

Structures of Heteroaromatic Compounds

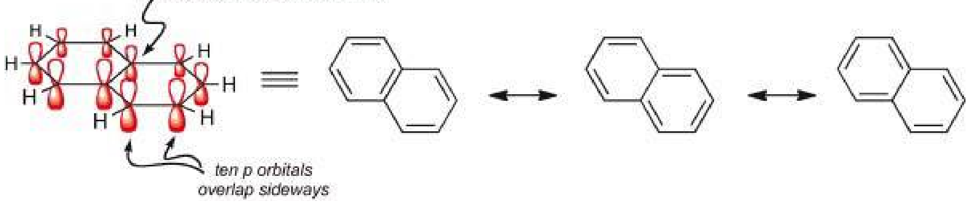
Structures of benzene and naphthalene

We start our consideration of heteroaromatic structures by recalling the prototypical structures of aromatic hydrocarbons such as benzene and naphthalene. Hückel's rule states that aromaticity is associated with fully conjugated cyclic systems of $4n+2$ π-electrons, that is with 2, 6, 10, 14 and so on, π-electrons, with 6π-electron monocyclic compounds being by far the commonest. Thus, benzene has a cyclic arrangement of six π-electrons comprising a conjugated molecular orbital system that is thermodynamically much more stable than a corresponding non-cyclically conjugated system – this additional stabilisation is called 'resonance energy' and has a value of about 152 kJ mol^{-1} for benzene. Compared with alkenes, this results in a much diminished tendency to react with electrophiles by addition and a greater tendency to react by substitution of hydrogen. Addition reactions would lead to products in which a substantial proportion of the resonance energy had been lost. As we shall remind ourselves in Chapter 3, *electrophilic substitution* is *the* prototypical reaction of benzene.



In benzene, the geometry of the ring, with angles of 120°, fits precisely 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 sideways to generate the π-molecular orbitals associated with the aromatic system.

We shall represent the stabilising delocalisation of aromatic molecules by drawing 'mesomeric structures', thus benzene is represented as a 'resonance hybrid' of the two extreme forms. These have no existence in their own right, but are 'resonance contributors' to the 'real' structure. The use of mesomeric structures is particularly useful in representing the polarisation inherent in many heterocycles and, especially, for representing the delocalisation of charge in reaction intermediates. We shall find them invaluable in helping to understand heteroaromatic reactivity and regioselectivity.



Naphthalene, with ten carbons and ten orthogonal p orbitals, has an aromatic system with ten π-electrons. Naphthalene is represented by three mesomeric structures and has a resonance energy of about 255 kJ mol^{-1}, substantially less than twice that of benzene.

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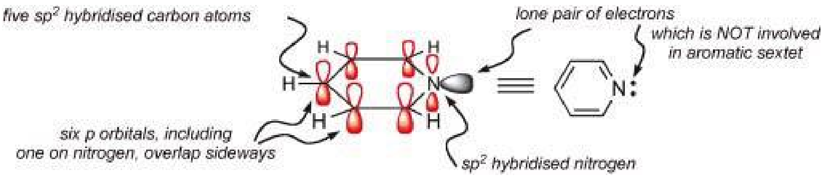
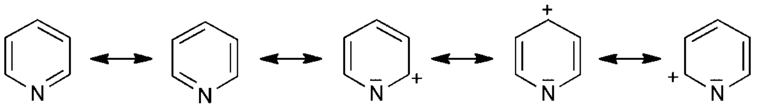
Structures of pyridines and pyridiniums

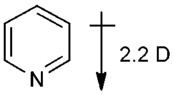
The structure of pyridine is completely analogous to that of benzene, being related through replacement of CH by N. The key differences are: (i) the departure from perfectly regular hexagonal geometry caused by the presence of the heteroatom, in particular shorter carbon–nitrogen bonds, (ii) the replacement 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*, (iii) a strong permanent dipole, traceable to the greater electronegativity of nitrogen compared with carbon and (iv) the presence of a polarised imine unit (C=N). Note: It is the nitrogen lone pair, not involved in the aromatic sextet, that is responsible for the basic and nucleophilic reactivities of pyridine that we shall discuss in Chapter 5.



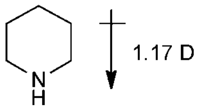
The electronegative nitrogen causes inductive polarisation, *and additionally*, stabilises polarised mesomeric structures in which nitrogen is negatively charged that, together with the two neutral contributors, represent pyridine. The polarised contributors imply a *permanent polarisation of the π-electron system*. The resonance energy of pyridine is about 117 kJ mol^{-1}.



Inductive and resonance effects work in the same direction in pyridine resulting in a permanent dipole towards the nitrogen atom. A comparison with the dipole moment of piperidine, which is due wholly to the induced polarisation of the σ-skeleton, illustrates the additional π-system polarisation. The polarisation of the π-system also means that there are fractional positive charges on the carbons of the ring, mainly at the α- and γ-positions. It is because of this general electron-deficiency at carbon that pyridine and similar heterocycles are sometimes referred to as 'π-deficient'.

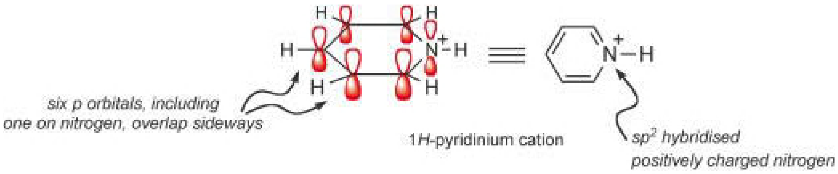


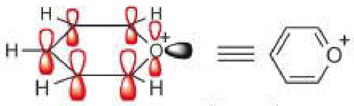
pyridine



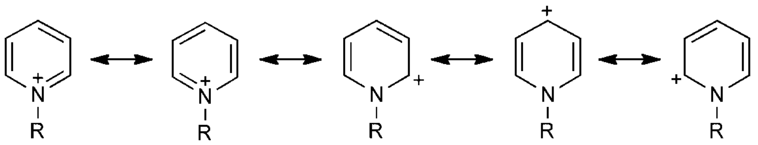
piperidine

Addition of a positively charged electrophile to the pyridine nitrogen, utilising the lone pair of electrons to make a bond, generates pyridinium ions, the simplest being 1*H*-pyridinium formed by addition of a proton. Pyridinium cations are still aromatic – 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 high fractional positive charges, as indicated by the mesomeric structures. The structure of the pyrylium cation is analogous, but without a substituent on the oxygen.





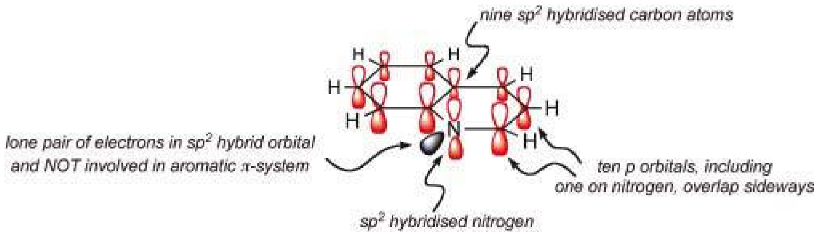
pyrylium cation

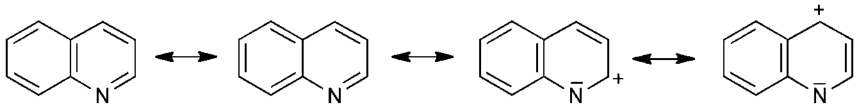


mesomeric structures of a 1-R-pyridinium cation demonstrating strong polarisation

Structures of quinolines and isoquinolines

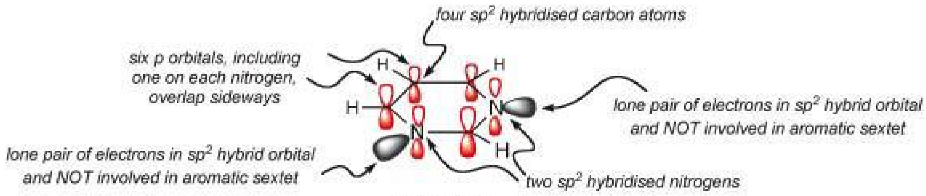
Quinoline and isoquinoline are related to pyridine exactly as naphthalene is related to benzene, that is they are 10π-electron aromatic systems. Only the heterocyclic ring is strongly polarised and, using quinoline as an example, the polarisation is represented as before by dipolar mesomeric contributors. Isoquinoline is completely analogous.



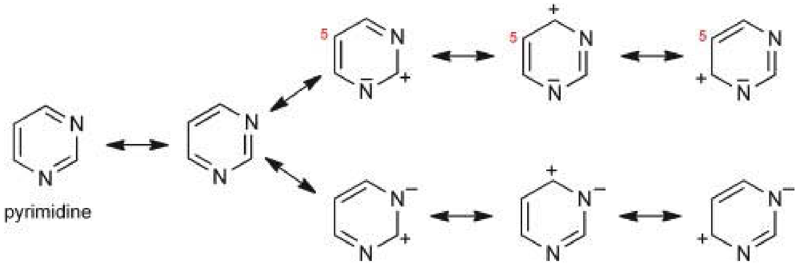


Structures of diazines (illustrated using pyrimidine)

Diazines contain two sp² hybridised nitrogens in a six-membered ring. The presence of the additional electron-withdrawing imine (C=N) has a major impact on the structure and chemical reactivity – the resonance contributors for pyrimidine illustrate the polarisation, which substantially increases the partial positive charges at all carbons, but to a lesser extent at C-5.

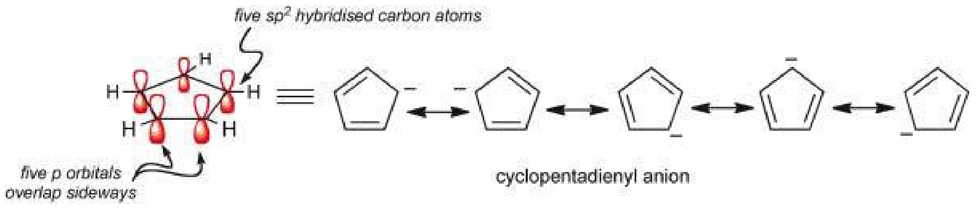


pyrimidine

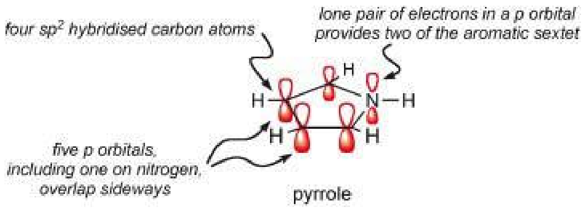


Structures of pyrroles, thiophenes and furans

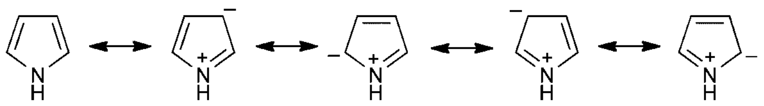
We began our discussion of the structure of pyridine by reference to that of benzene and so, with pyrrole, it is useful to recall the structure of the cyclopentadienyl anion. The cyclopentadienyl anion, produced by the removal of one proton from cyclopentadiene, is a 6π-electron aromatic system. Five equivalent contributing structures show each carbon atom to be equivalent and hence to carry one fifth of the negative charge.



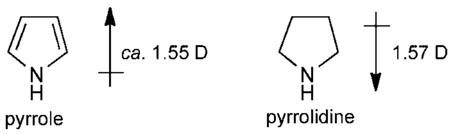
Pyrrole is related to the cyclopentadienyl anion through the replacement of a CH by an NH, thus pyrrole is isoelectronic with the cyclopentadienyl anion. It is electrically neutral because of the higher nuclear charge on nitrogen.



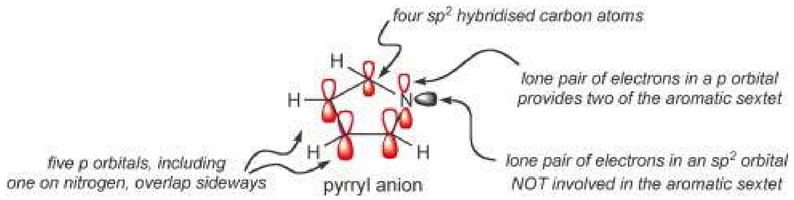
Pyrrole does not have five equivalent mesomeric forms: it has one with no charge separation, and four contributors in which there is charge separation, indicating electron density drift *away from the nitrogen*, in direct contrast with pyridine (page 5).



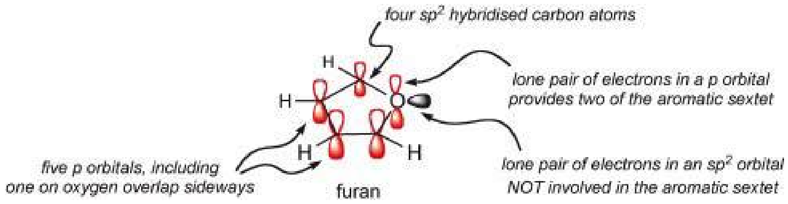
Resonance in pyrrole thus leads to the establishment of *partial negative charges on the carbons and a partial positive charge on nitrogen*. The electronic distribution in pyrrole is a balance of two opposing effects, inductive (towards the electronegative nitrogen) and mesomeric (away from nitrogen), of which the latter is the more significant. It is because of this net electronic drift away from nitrogen and towards the ring carbons that five-membered heterocycles of the pyrrole type are sometimes referred to as 'π-excessive'. The polarised contributors imply a *permanent polarisation of the π-electron system* that shows itself in the dipole moment of pyrrole, which is directed *away from the nitrogen* in spite of the intrinsic polarisation of the σ-skeleton towards the more electronegative nitrogen, as shown in pyrrolidine. The resonance energy of pyrrole is about 90 kJ mol^{-1}.



A significant aspect of pyrrole reaction chemistry is the relative acidity of the pyrrole *N*-hydrogen. Its removal as a proton, using a strong base, produces the pyrryl anion in which there are two pairs of electrons associated with the nitrogen: one pair is part of the aromatic sextet and the other, in the plane of the ring, is available for interaction with electrophiles *without* disrupting the 6π-electron aromatic system.

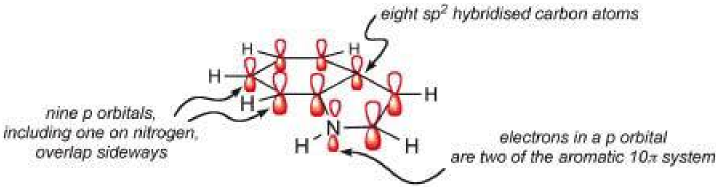


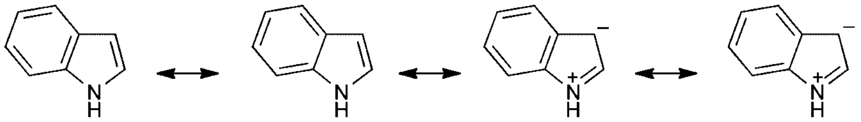
Other five-membered aromatic heterocycles have exactly comparable structures to that of pyrrole: thiophene (resonance energy ~122 kJ mol^{-1}) is the 'most aromatic' of the trio and furan (~68 kJ mol^{-1}) the 'least aromatic' and, indeed, furan does behave as a diene, rather than an aromatic molecule, in some cases. Note that in these two heterocycles, the *heteroatom has two different types of lone pair* – one involved in the aromatic sextet and the other, in the plane of the ring, in an sp^2 hybrid orbital, and NOT involved in the aromatic π-system. The electron drift away from the heteroatoms in these two heterocycles is less than that in pyrrole and as a result both have dipole moments directed towards the heteroatom.



Structure of indoles

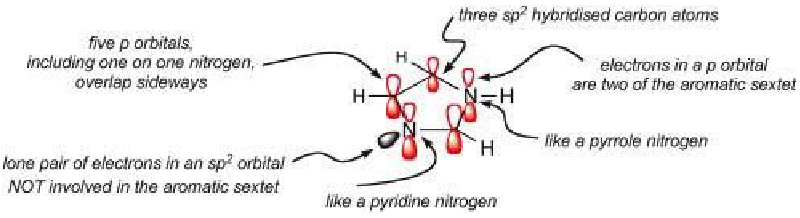
When a benzene ring is fused to a pyrrole, as in the 10π-electron indole, strong polarisation is seen only in the heterocyclic ring as implied by the resonance contributors.

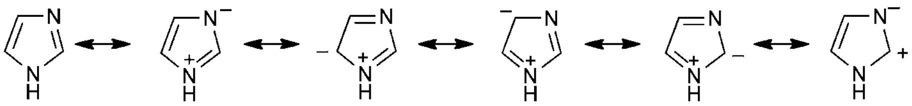




Structures of azoles (illustrated using imidazole)

Finally, we consider the azoles: five-membered heterocycles with a nitrogen and another heteroatom located either adjacent to the nitrogen (1,2-azoles) or in a 1,3-relationship (1,3-azoles). We can understand their structures by considering one typical example – imidazole.





The two nitrogen atoms are completely different – one of them is like the nitrogen in pyrrole, but the other (the imine nitrogen) is like the nitrogen in pyridine. The former donates a pair of electrons into the aromatic π-system; the latter donates just one electron into the aromatic system. The former carries an *N*-hydrogen, the latter does not. The former does not have a pair of electrons in the plane of the ring, the latter does.

3

Common Reaction Types in Heterocyclic Chemistry

Introduction

There are some ideas and reagents and reaction methodologies and reactivity patterns that turn up again and again in heterocyclic chemistry and we summarise and explain these in detail in this chapter, so that they do not have to be discussed in detail at each separate occurrence in the rest of the book. In heteroaromatic chemistry, electrophilic substitution (mainly of hydrogen) is important for the five-membered heterocycles and nucleophilic substitution (mainly of halogen) is important for six-membered heterocycles. The use of transition metal catalysis, especially palladium-catalysis, is so important in heterocyclic chemistry that we devote the whole of Chapter 4 to that topic.

Acidity and basicity

Many heterocyclic compounds contain a ring nitrogen. In some, especially five-membered heterocycles, the nitrogen may carry a hydrogen. It is vital to the understanding of the chemistry of such nitrogen-containing heterocycles to know whether, and to what extent, they are basic – will form salts with protic acids or complexes with Lewis acids, and for heterocycles with *N*-hydrogen, and to what extent they are acidic – will lose the *N*-hydrogen as a proton to an appropriately strong base. As a measure of these properties we use pK_a values to express the acidity of heterocycles with *N*-hydrogen and pK_{aH} values to express base strength. *The lower the* pK_a *value the more acidic; the higher the* pK_{aH} *value the more basic.* It may be enough to simply remember this trend; a little more detail is given below.

For an acid AH dissociating in water:

$$\mathrm{AH} + \mathrm{H_2O} \rightleftharpoons \mathrm{A^-} + \mathrm{H_3O^+}$$

$$K_a = \frac{[\mathrm{A^-}][\mathrm{H_3O^+}]}{[\mathrm{AH}]} \qquad pK_a = -\log[K_a]$$

The corresponding equation for a base involves the *dissociation of the conjugate acid* of the base, so we use pK_{aH}.

$$\mathrm{BH^+} + \mathrm{H_2O} \rightleftharpoons \mathrm{B} + \mathrm{H_3O^+}$$

$$K_{aH} = \frac{[\mathrm{B}][\mathrm{H_3O^+}]}{[\mathrm{BH^+}]} \qquad pK_{aH} = -\log[K_{aH}]$$

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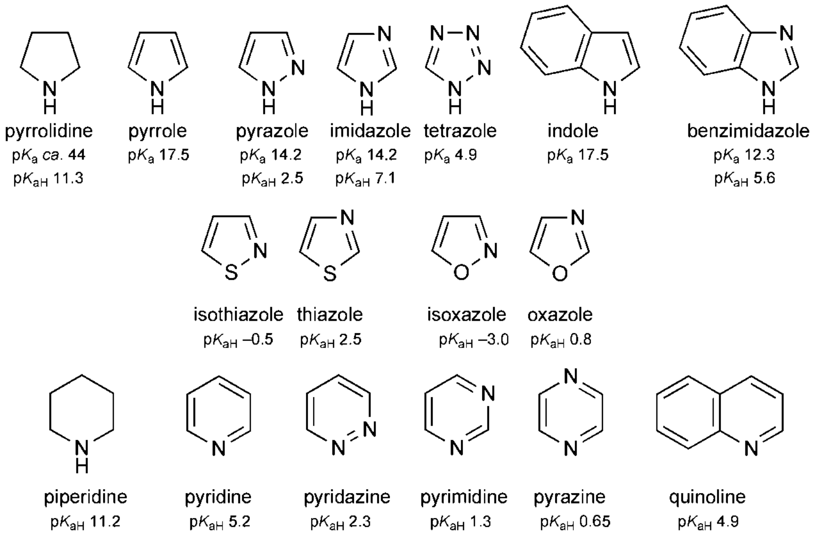
Table 3.1 Table of pK_{aH} and pK_a values of some typical heteroaromatic ring systems.

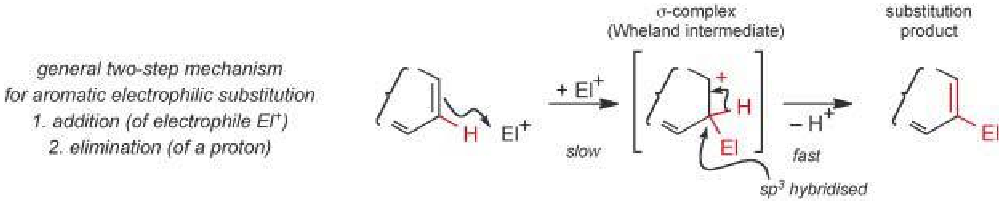


Note: The pK_a values for the aromatic *N*-hydrogen heterocycles all fall within the range where, under aqueous basic conditions, they would be partly or fully deprotonated.

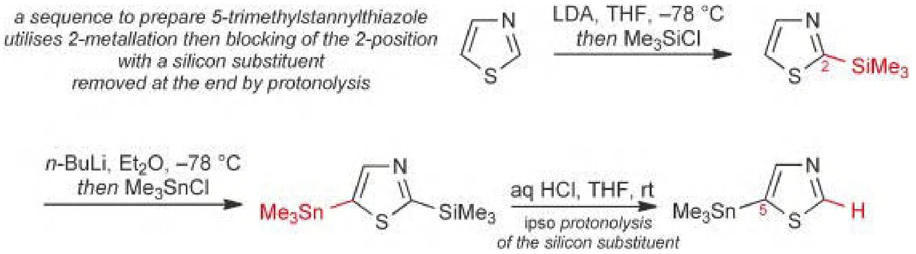
Electrophilic substitution of aromatic molecules

The majority of heterocycles dealt with in this book are aromatic and so, as in benzene chemistry, they are subject to *substitution* reactions with *electrophiles* – some less easily than benzene and some more easily. All electrophilic substitutions of aromatic molecules proceed via a two-step sequence: (i) addition of the electrophile to a favoured carbon forming a non-aromatic, though delocalised, cation, then (ii) loss of the proton attached to that carbon, returning the system to an aromatic status. This is described as *ipso* substitution – the electrophile ends up on the same carbon as the hydrogen that it displaces. Usually, the first step is the slower (rate-determining) step, because an aromatic starting molecule has to lose some delocalisation energy in forming the intermediate; the corollary is that the second step is fast because the system is regaining aromaticity.

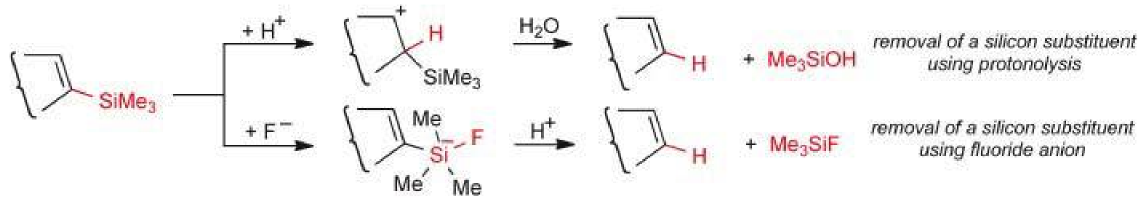
In the remaining chapters, chemical schemes that include electrophilic substitutions do not explicitly show the cationic intermediate or the aromatising loss of a proton, but the two-step nature of the process must always be kept in mind.



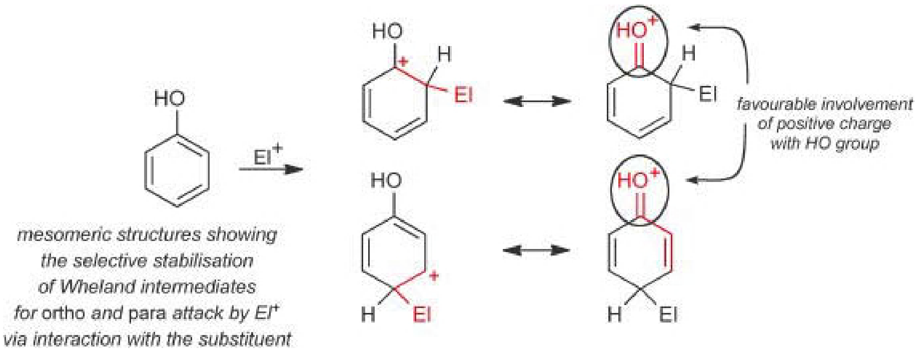
Ipso displacement of groups other than hydrogen can also occur, for example of CO_2H. In the present context the most important examples are displacements of trialkylsilyl groups – indeed electrophilic *ipso* displacement of silicon is actually favoured over substitution of hydrogen so that trialkylsilyl groups can be used as blocking groups, to be removed selectively by protonolysis ($El^+ = H^+$) when they have served their purpose, as in the scheme below (for a discussion of C-metallation see pages 16–17).

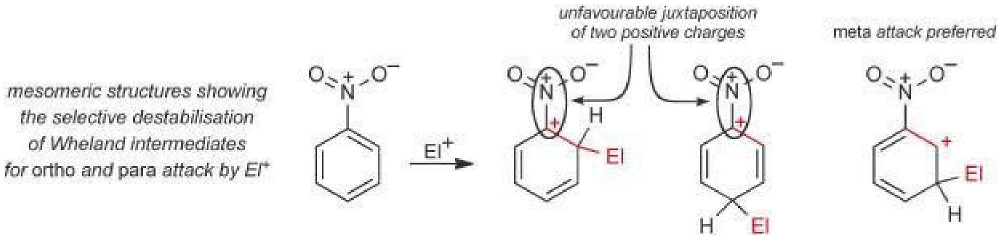


Reaction with fluoride anion, sometimes provided by TBAF (tetra-*n*-butylammonium fluoride, *n*-Bu_4NF) can alternatively be utilised to remove silicon blocking substituents, by a different mechanism.

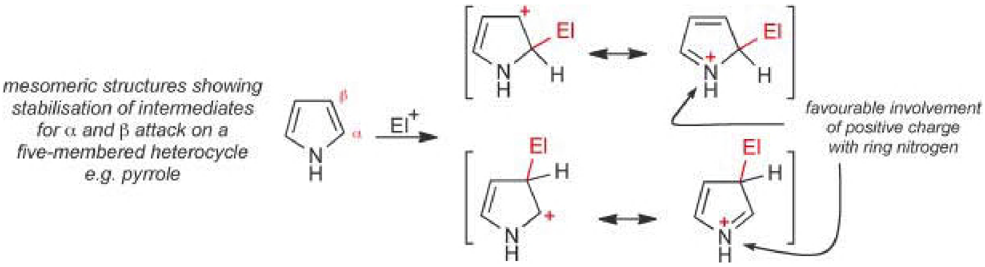


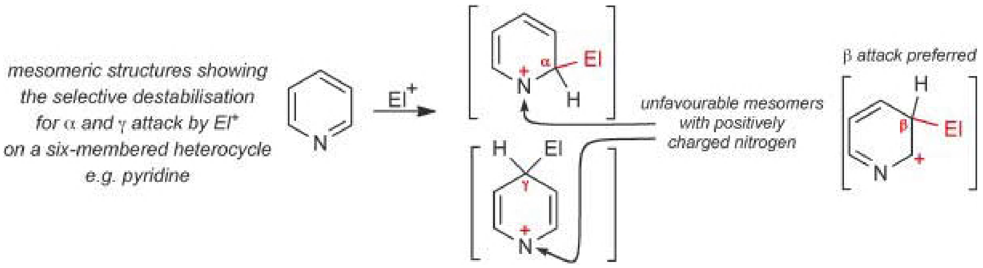
Ring substituents that release electrons favour electrophilic attack and substituents that withdraw electrons slow such processes down. For example, alkyl groups are moderately electron-releasing by an inductive mechanism; alkoxy, hydroxy and amino are more strongly electron-releasing via a mesomeric mechanism. Groups that disfavour electrophilic attack are nitro, cyano, ester and ketone, via both inductive and mesomeric effects. Further, substituents favour (or disfavour) electrophilic attack *regioselectively*. The electron-releasing groups selectively stabilise Wheland intermediates (and the transition states that lead to them) in which the electrophile has been added *ortho* or *para* to the substituent. The electron-withdrawing groups *destabilise* selectively the Wheland intermediates in which the electrophile has been added *ortho* or *para* to the substituent and thus lead to substitution at the least-deactivated position, the *meta* position. Under most circumstances, electrophilic substitutions are irreversible and the ratio of isomeric products is determined by kinetic control.





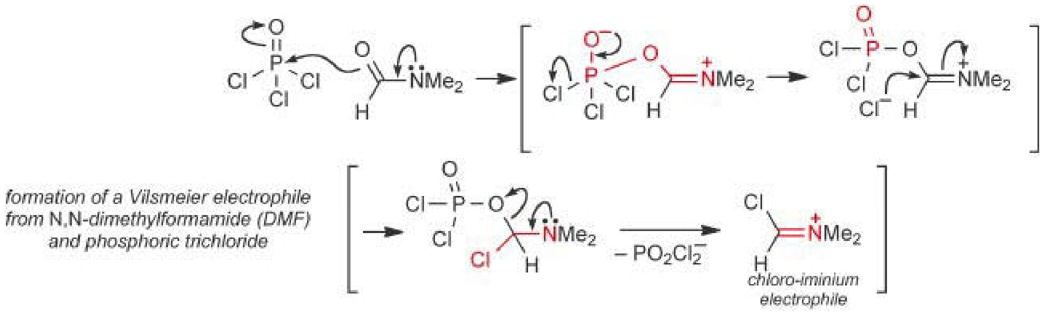
In the context of the electrophilic substitution of heterocycles, one can view the heteroatom(s) as a directing group *within* the ring, as opposed to substituents *on* the ring in benzene chemistry. The way in which the heteroatom influences the facility and regioselectivity of electrophilic attack for the six- and five-membered situations is discussed in detail on pages 34 and 78, respectively, and is summarised below for pyrrole and pyridine as prototypes. The five-membered heterocycles undergo electrophilic substitution easily; the six-membered heterocycles are only readily substituted with electrophiles if there is an activating substituent on the ring, cf. phenol above.



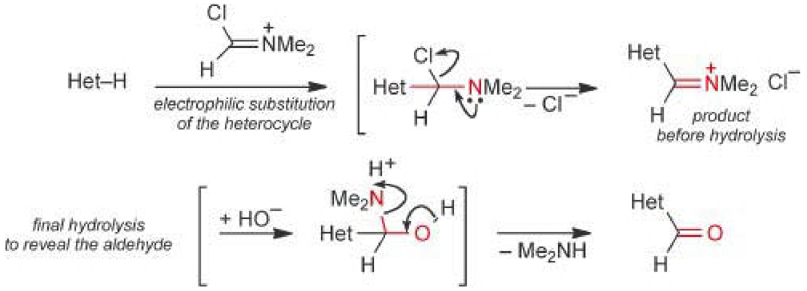

mesomeric structures showing the selective destabilisation for α and γ attack by El⁺ on a six-membered heterocycle e.g. pyridine

The Vilsmeier reaction – formylation

In the Vilsmeier reaction, a nucleophilic molecule (in this book, a five-membered aromatic heterocycle) is formylated, that is a C–H is converted into C–CHO. The reagent is made *in situ* from the interaction of a formamide (most often *N,N*-dimethylformamide (DMF)) and phosphoric trichloride (often referred to as phosphorus oxychloride, $POCl_3$). The scheme shows the long sequence of steps, which starts with the amide oxygen acting as a nucleophile towards the very electrophilic phosphorus and leads eventually to a chloro-iminium salt – this is the electrophile that attacks the nucleophilic heterocycle.

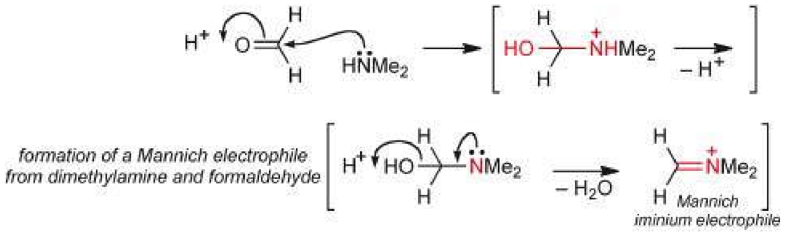

formation of a Vilsmeier electrophile from N,N-dimethylformamide (DMF) and phosphoric trichloride

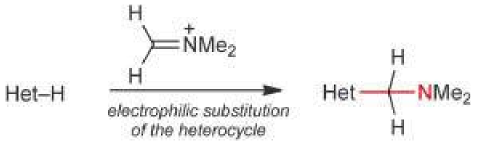
When reaction with the heterocycle is complete, the reaction mixture is exposed to aqueous alkali, which brings about a hydrolysis of the iminium product, revealing the aldehyde.



The Mannich reaction – dialkylaminomethylation

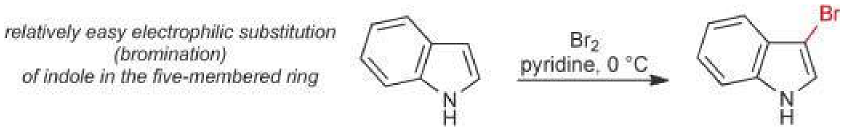
In the Mannich reaction, a nucleophilic molecule (five-membered aromatic heterocycles in this book) is dialkylaminomethylated (most often dimethylaminomethylated), thus a C–H is converted for example into C–CH_2NMe_2. The reactive electrophilic species, for example $[CH_2{=}NMe_2]^+$, is most often generated *in situ* by the interaction of an aldehyde, a secondary amine and an organic acid, thus a mixture of dimethylamine, formaldehyde and acetic acid generates $[CH_2{=}NMe_2]^+$. These reaction mixtures are partly aqueous but the anhydrous salt $[CH_2{=}NMe_2]^+$ I^- (Eschenmoser's salt) is commercially available and can be used in a dry organic solvent. It is highly reactive and will react with substrates that are resistant to the standard aqueous conditions.

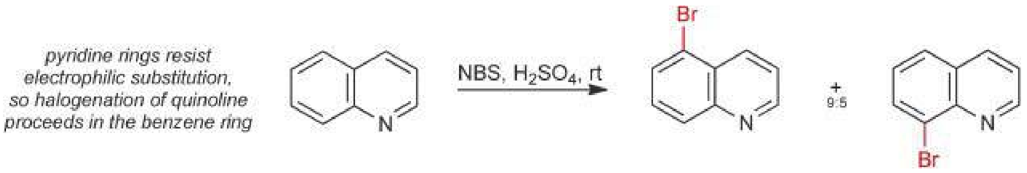

formation of a Mannich electrophile from dimethylamine and formaldehyde



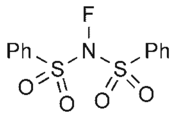
Halogenation

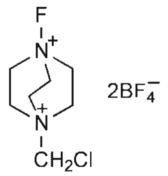
Five-membered aromatic heterocycles are sufficiently reactive that the introduction of a halogen by electrophilic substitution can often be achieved using the halogen alone, that is without the Lewis acid catalyst usually required in benzene chemistry. The indole example below illustrates both this intrinsically high reactivity towards electrophiles and also selectivity over benzene ring substitution. On the other hand, six-membered nitrogen heterocycles are relatively resistant to electrophilic substitution so halogenation of quinoline proceeds in the benzene ring.





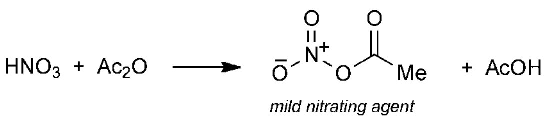
Fluorine itself is highly reactive and difficult to handle, but several mild electrophilic fluorinating agents are commercially available, the most notable being various *N*-fluoroamides (cf. *N*-bromo- and *N*-chlorosuccinimides) or *N*-fluoro-quaternary salts, for example NFSI and Selectfluor^{TM}.


NFSI
N-fluoro-*N*-(phenylsulfonyl)benzenesulfonamide


Selectfluor^{TM}
1-(chloromethyl)-4-fluoro-
1,4-diazoniabicyclo[2.2.2]octane tetrafluoroborate

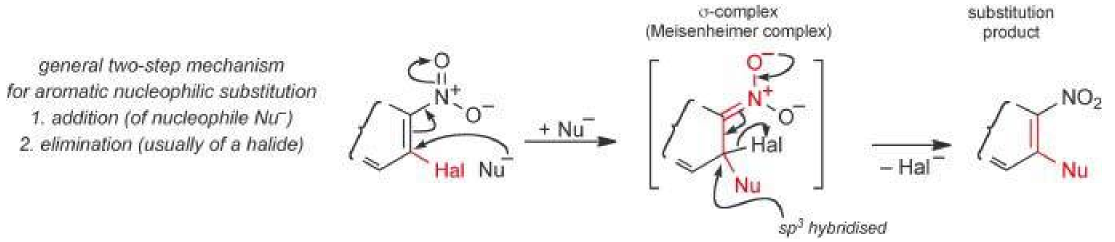
Nitration

Here again, much milder conditions suffice for the substitution of five-membered heterocycles than are required in benzene chemistry. Also, many of the five-membered heterocycles are not stable to the classical concentrated acidic conditions. A device that can be used is the formation of the mixed anhydride of nitric acid and acetic acid, generated by mixing acetic anhydride with nitric acid – this serves as a source of NO_2^+ via displacement of acetate.

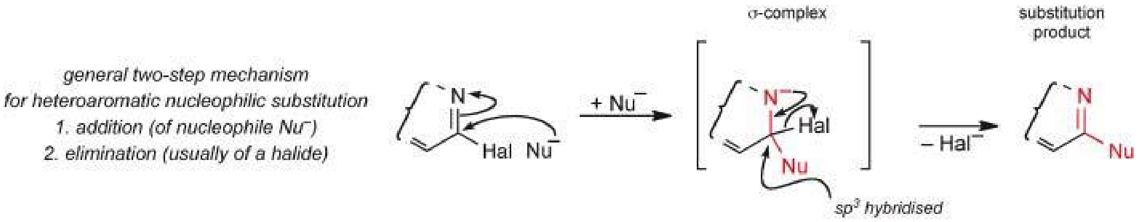


Nucleophilic substitution of aromatic molecules

In benzene chemistry, nucleophilic substitution is the exception, rather than the rule. Again, a two-step sequence is required: (i) addition of the nucleophile to a favoured carbon forming a non-aromatic, though delocalised, anion, then (ii) loss of the substituent attached to that carbon, returning the system to an aromatic status. There must be a group present to facilitate the addition of the nucleophile, that is the group must be capable of stabilising a *negatively* charged, non-aromatic intermediate; in benzene chemistry this group is usually *ortho-* or *para*-nitro. Further, the substituent that is *ipso* displaced must be capable of departing carrying a negative charge – normally halide. This type of transformation is generally referred to as an addition/elimination process.

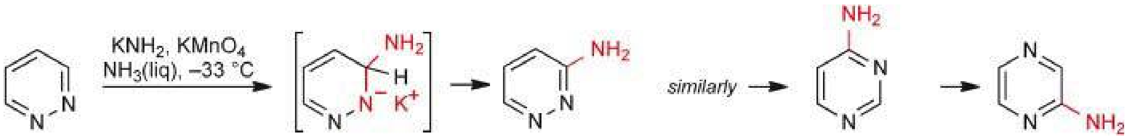


In the context of heteroaromatic reactivity, the group that both encourages addition and accepts responsibility for the negative charge in the intermediate is normally a ring imine (C=N) and halide is the group normally *ipso* displaced.



Typical conditions for replacement of halogen can be seen in the following examples.

Using strong nucleophiles, even hydrogen can be displaced in some cases. Addition to an unsubstituted imine carbon occurs, giving a relatively stable dihydro intermediate. Further reaction with an oxidising agent may be required to remove the H, leading to re-aromatisation.

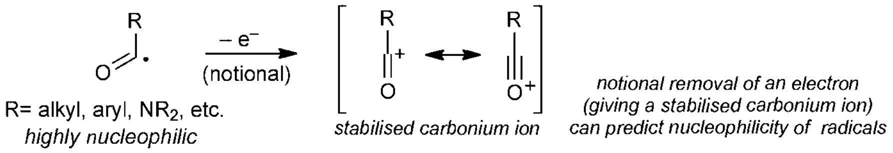


Radical substitution of heterocycles

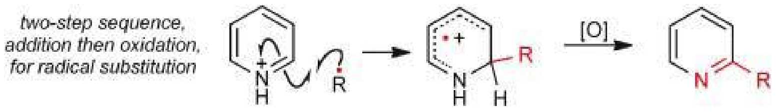
The Minisci reaction: addition of nucleophilic radicals

Although many reactions of (carbon) radicals with heterocycles are of only academic interest, one of these processes – the Minisci reaction – is of significant practical use with electron-deficient heterocycles, most prominently pyridines and quinolines, but also other systems that have an imine unit.

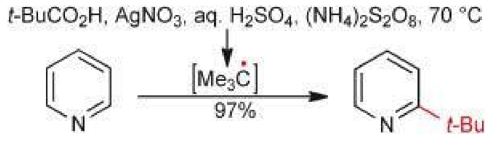
Although radicals are neutral species, they do have degrees of polarisation, and a number exhibit significant nucleophilic character and are capable of adding to heterocycles with imine units. As a ‘rule of thumb’, one can say that if the notional removal of the lone electron from a radical would generate a particularly stabilised carbonium ion, then that radical would be expected to be nucleophilic. This leads to an interesting, very useful, contrast with normal reactivity, for example acyl radicals are very good nucleophiles, whereas acyl reagents are more usually encountered as acyl cations in the Friedel–Crafts reaction. Similarly, *t*-butyl radicals are much better nucleophiles than methyl radicals, in fact methyl radicals are often used to generate other, more nucleophilic, radicals via H-abstraction.

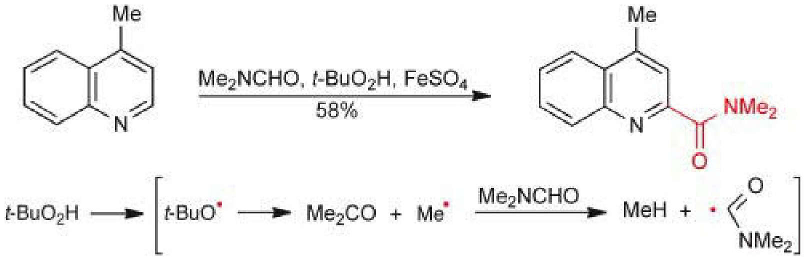


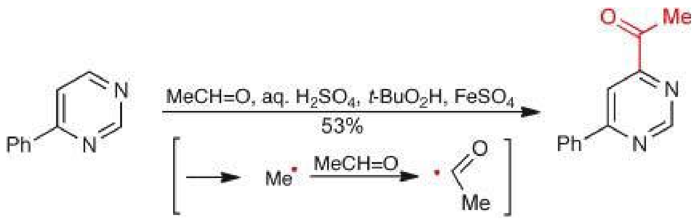
Another advantage of the Minisci reaction is that very simple conditions are used – aqueous sulfuric acid, with an oxidant and sometimes a catalyst [Fe(II) or Ag(I)]. These oxidising conditions generate the radicals and also re-aromatise the initial product of radical addition. Additionally, protonation of the imine nitrogen greatly increases the susceptibility of the heterocycle to nucleophilic radical addition, which takes place at the imine carbon.

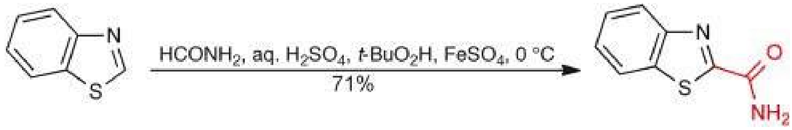


The four examples illustrate the use of the Minisci process for pyridine, a quinoline, a pyrimidine and a benzothiazole, where the imine unit is in a five-membered ring.



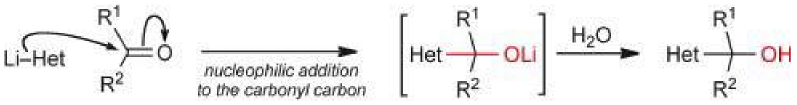






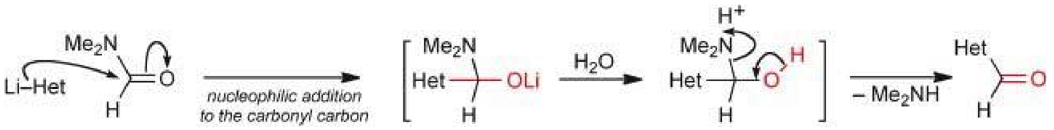
C-Metallated heterocycles as nucleophiles

Organometallics, especially organolithium intermediates, are very frequently used in heterocyclic chemistry. The generation and use of organolithium intermediates must generally be conducted at very low temperatures, typically that of an acetone–dry ice (solid CO_2) cooling bath (−78 °C). Organolithiums are nucleophiles, thus reaction with ketones and aldehydes gives alcohols following 'aqueous work-up'. In the remaining chapters, chemical schemes which include reactions of lithium derivatives do not explicitly show the intermediate, or the addition of water, but the requirement for an 'aqueous work-up' must always be kept in mind.



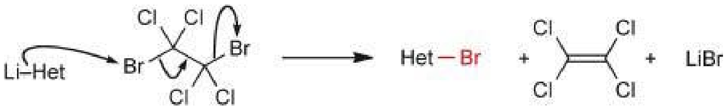
Also very useful are the reactions of organolithium nucleophiles with *N*,*N*-dimethylformamide (DMF), with disulfides (RS–SR), with halogen donors such as $BrCCl_2CCl_2Br$, with trialkyl borates (e.g. $B(OMe)_3$), and with chlorotrialkylstannanes (e.g. n-Bu_3SnCl). In the first case, an aldehyde is the product, in the second case a sulfide, in the third case a halide is the product and in the last two, heteroarylstannanes and heteroarylboronic acids result.

The organolithium species adds to the carbonyl carbon of the DMF, but it is not until aqueous work-up that loss of dimethylamine reveals the aldehyde (compare with the final step in the Vilsmeier reaction, page 12).

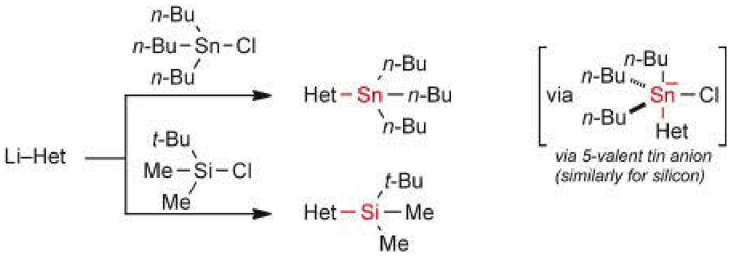


In the reaction of an organolithium reagent with a disulfide, the nucleophile attacks one sulfur and the relatively weak S—S bond is cleaved, RS^- being expelled as a leaving group.

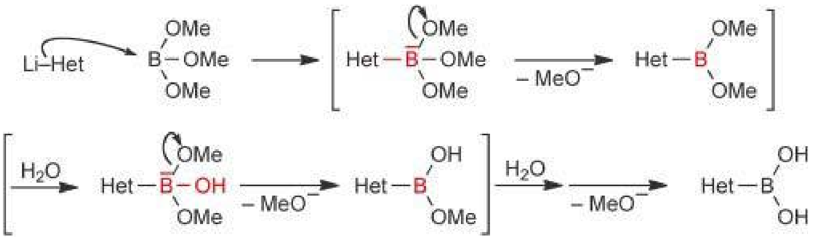
Bromination with 1,2-dibromo-1,1,2,2-tetrachloroethane involves a fragmentation process, as illustrated.



One of the important routes to prepare boronic acids and stannanes, each of which are widely used in palladium(0)-catalysed processes (Chapter 4), involves the reaction of an organolithium reagent. Thus, reaction with a halotrialkylstannane gives stannanes by displacement of the halide. Similarly, reaction with halotrialkylsilanes generates trialkylsilyl derivatives. Each of these proceeds via addition of the nucleophile giving an intermediate pentavalent anion and then elimination of the halide.

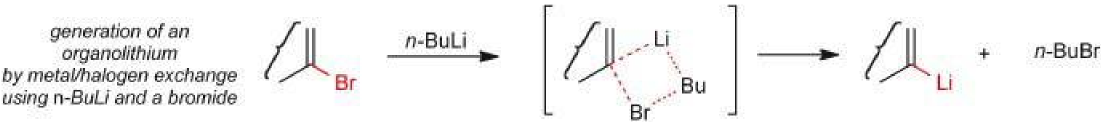


Reaction with a trialkyl borate and then hydrolysis produces boronic acids.

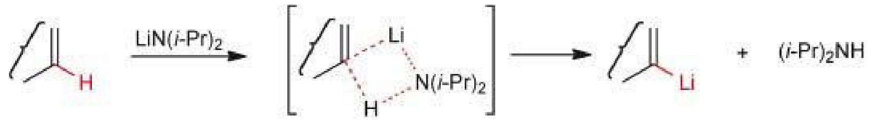


Generation of *C*-metallated heterocycles

There are two important ways in which organolithium intermediates are generated: (i) by metal/halogen exchange using a heteroaryl bromide (or iodide) and *n*-butyllithium or *t*-butyllithium; (ii) by abstraction of a proton using a strong lithium base such as *n*-butyllithium, *t*-butyllithium or lithium di-isopropylamide (LiN(*i*-Pr)$_2$; LDA), for some heterocycles directly at favoured positions but also, and importantly, via Directed *ortho* Metallation (DoM) (see below). Note: Though alkyllithiums can act in both types of process, LDA is simply a strong base – it will NOT take part in metal/halogen exchange processes.

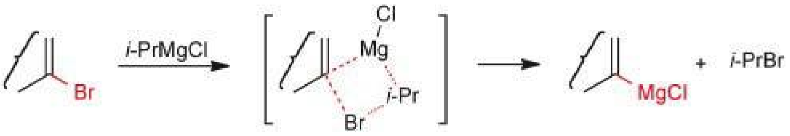


generation of an organolithium by deprotonation using LDA



The preparation of heteroaromatic Grignard reagents using the halide and magnesium metal is usually difficult, however they can be easily prepared by reacting a halide with isopropylmagnesium chloride – this is especially important for electron-deficient systems such as pyridines. Grignard reagents have some advantages over lithium nucleophiles – they can often be formed and used at room temperature and are more tolerant of functional groups.

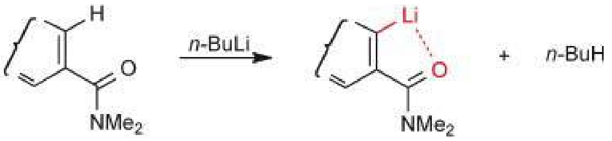
generation of a Grignard reagent by metal/halogen exchange using i-PrMgCl and a bromide



Directed *ortho* Metallation (DoM)

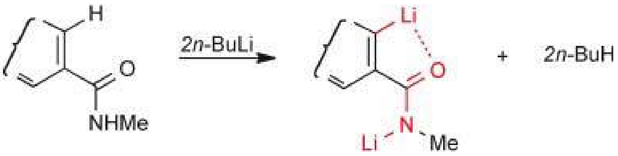
Here, a substituent on the heteroaromatic ring activates an *ortho* proton, which is not otherwise ‘acidified’, for abstraction by a strong base. This is in part due to coordination of the base to the directing group, bringing it into close proximity to the proton. Many types of substituent will achieve this effect – important ones are $CONR_2$, CONHR, NHCOR, RO and Hal.

lithiation of an aromatic compound ortho assisted by a tertiary amide (DoM)

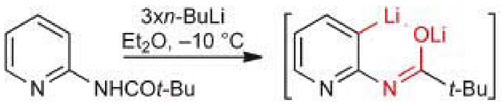


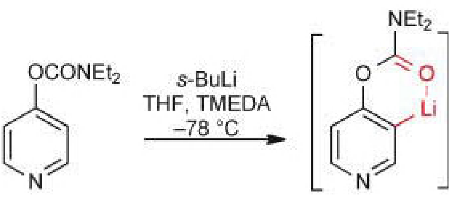
When a secondary amide is used, a second mole equivalent of the base is required to react with the *N*-hydrogen, as shown.

lithiation of an aromatic compound ortho assisted by a secondary amide



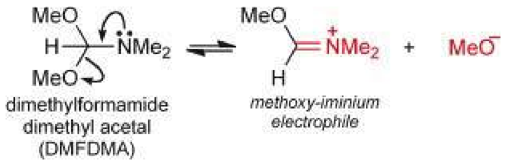
The following examples are typical of the conditions that must be used to generate organolithium intermediates, which are also typically then reacted with the electrophile at the low temperature. In the examples given in other chapters, conditions such as these should be assumed, unless otherwise stated.

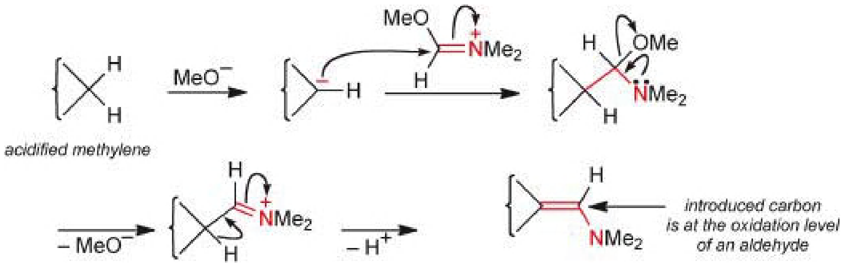


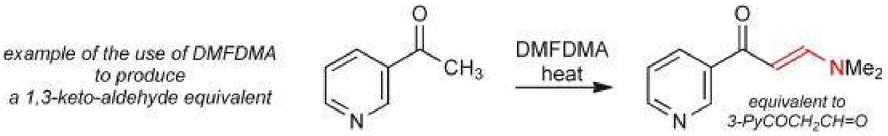


Dimethylformamide dimethyl acetal (DMFDMA)

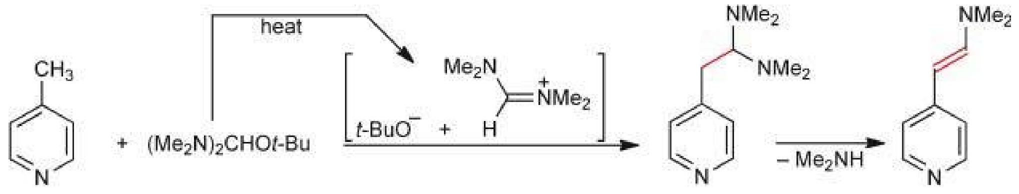
Acidified methylenes (CH_2 α to a carbonyl, for example) react with hot DMFDMA to produce dimethylaminomethylene derivatives (enamines), that is to introduce a one-carbon unit at the oxidation level of an aldehyde (see Common synthetic equivalents on page 19). The hot reagent is in equilibrium with MeO^- (which removes one of the acidified protons) and [$MeO(H)C{=}N^+Me_2$] (which reacts with the anion generated) a final loss of methanol producing the enamine.





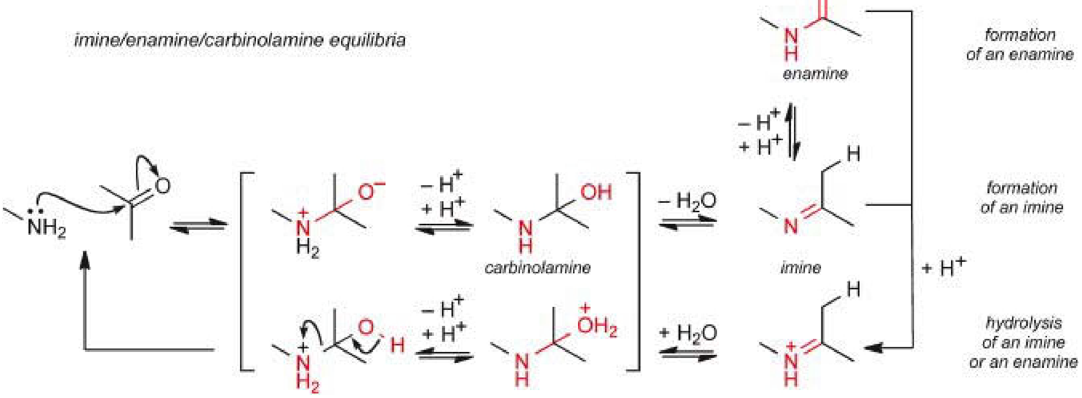


Brederick's reagent, $(Me_2N)_2CHOt\text{-}Bu$, can also be utilised for the generation of dimethylaminomethylene derivatives. Here, *t*-butoxide is the base and dimethylamine is the unit lost in the final stage. In the example below, the acidified group is a methyl at a pyridine γ-position (cf. page 40).



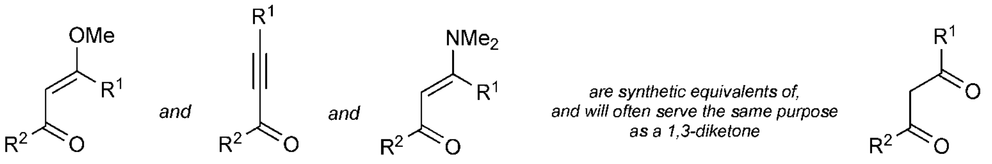
Formation and hydrolysis of imine/enamine

Very frequently in heterocyclic ring syntheses, the interaction (often acid-catalysed) of an amine with a ketone or aldehyde carbonyl group is involved. After nucleophilic addition of the amine to the carbonyl carbon, and proton transfers, a carbinolamine is generated which can lose water to form an imine then this, in turn, can tautomerise to form an enamine. Further, the reverse sequence can also easily occur – only a few simple imines are stable to hydrolysis, but *particularly*, when these are cyclic. Imines and enamines are often intermediates, whether stable or not, *en route*, via a series of equilibria, to an aromatic heterocycle.

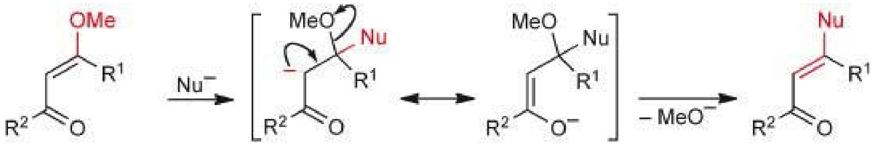


Common synthetic equivalents of carbonyl compounds in ring synthesis

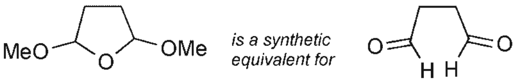
Quite frequently, and especially in heterocyclic ring synthesis, a reaction component is replaced with a molecule that reacts in the same way – serves the same purpose – as the traditional or classical component. For example, a ring synthesis might require a 1,3-diketone – a 3-alkoxy-enone would serve instead; a conjugated yne-one is also equivalent to a 1,3-diketone and so is a 3-dialkylamino-enone.



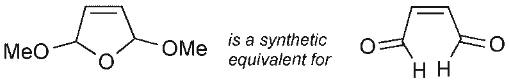
Ene-ones carrying a β-leaving group (like the 3-alkoxy-enone and the 3-dialkylamino-enone instanced above), usually react with a nucleophile at the β-carbon via an addition–elimination sequence, as shown.



2,3,4,5-Tetrahydro-2,5-dimethoxyfuran is a convenient, protected form in which to supply butane-1,4-dial; 2,5-dihydro-2,5-dimethoxyfuran similarly provides the equivalent of but-2-ene-1,4-dial.



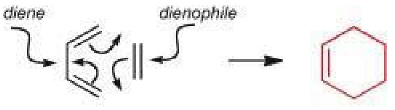
2,3,4,5-tetrahydro-2,5-dimethoxyfuran



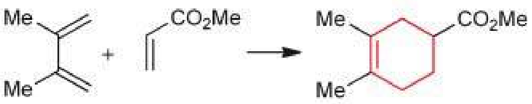
2,5-dihydro-2,5-dimethoxyfuran

Cycloaddition reactions

A very important synthetic protocol is the process known as the Diels–Alder reaction. In essence, a conjugated 1,3-diene reacts with a dienophile – an alkene or an alkyne, for example – to generate a six-membered ring containing one (or two) double bonds – a [4 + 2] cycloaddition. In the standard process, the diene is electron-rich (has electron-releasing substituents) and the dienophile is electron-deficient (has electron-withdrawing substituents). In 'inverse-electron-demand' Diels–Alder cycloadditions, the diene is electron-deficient and the dienophile electron-rich. We do not go into the subtleties of the mechanism or stereochemistry here, but it is important to recognise that six π-electrons are redistributed in the process to form two new σ-bonds and to leave one π-bond – the arrows on the general reaction below show only this distribution and do not imply a flow of electrons in the clockwise direction shown.

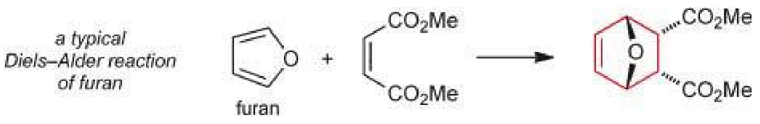


the Diels–Alder reaction

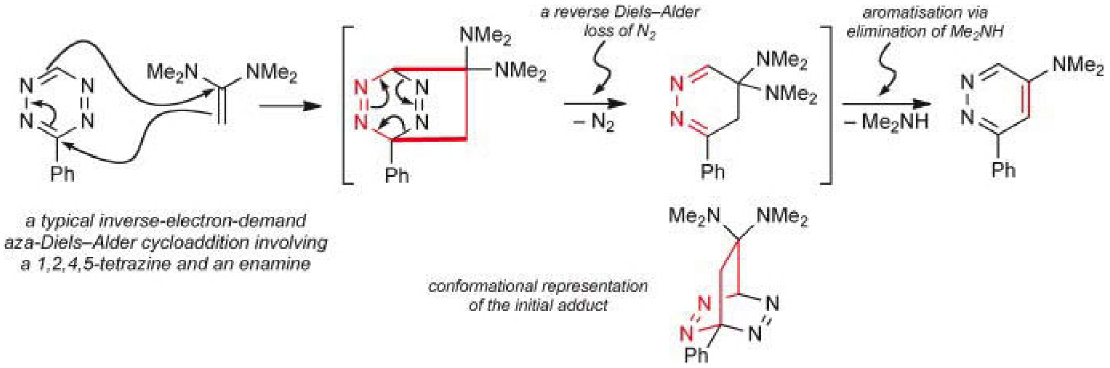


an example of the Diels–Alder reaction

In the heterocyclic context, some five-membered heterocycles – notably furans – participate as electron-rich dienes in Diels–Alder reactions.



Some six-membered heterocycles – in particular those with more than one nitrogen – participate as aza- or diazadienes in inverse-electron-demand Diels–Alder cycloadditions and final products are formed via the loss of a small stable molecule (e.g. N_2 or HCN).



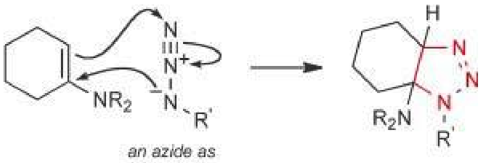
a reverse Diels–Alder loss of N_2

aromatisation via elimination of Me_2NH

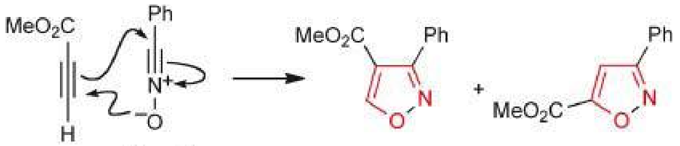
a typical inverse-electron-demand aza-Diels–Alder cycloaddition involving a 1,2,4,5-tetrazine and an enamine

conformational representation of the initial adduct

There is another category of cycloadditions important for heterocyclic chemistry, again involving redistribution of six electrons, known as dipolar cycloadditions – [3 + 2] cycloadditions. These provide unique methods for the ring synthesis of some five-membered systems. The two reacting partners are a three-atom unit – the 1,3-dipole – and a two-atom unit, the dipolarophile, with the latter having either a double or a triple bond. All 1,3-dipoles contain a heteroatom as the central atom of the trio, and in the common ones it is sp hybridised. Note: it is not possible to write a neutral resonance form for 1,3-dipoles – azides ($N{\equiv}N^+{-}N^-{-}R$) and nitrile oxides ($R{-}C{\equiv}N^+{-}O^-$) are two examples. The illustrations below show two dipolar cycloadditions, these being ring syntheses of a 4,5-dihydro-1,2,3-triazole using an azide and that of a mixture of isoxazoles, using a nitrile oxide.



an azide as 1,3-dipole



a nitrile oxide as 1,3-dipole

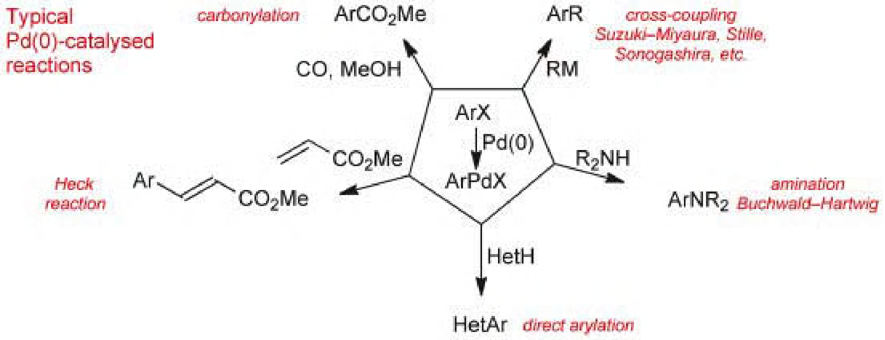
4

Palladium in Heterocyclic Chemistry

Palladium(0)-catalysed (and related) reactions

The use of palladium catalysis for the construction of new C–C and C–heteroatom bonds to aromatic molecules is one of the major advances in synthetic organic chemistry in the last 30 years or so. Such processes work equally well with carbocyclic and heterocyclic systems, are very widely used and are amongst the most important transformations of modern heterocyclic chemistry. We have gathered a range of examples of typical palladium-catalysed reactions of all heterocyclic systems together in this chapter as they can be applied generally across the whole range, with the nature of the heterocycle only being reflected in secondary effects such as rates and selectivity and, occasionally, stability of reactants. The chapters discussing particular heterocycles include further examples. Palladium-catalysed processes can also be employed in the ring synthesis of some heterocyclic systems.

By far the most important reactions involve aromatic halides, where the catalytic species is always Pd(0). A particular significance of these reactions is that these normally unreactive aromatic-type halogens can be replaced under relatively mild conditions. Another important feature is that they are generally not jeopardised by the presence of, and do not interfere with, most other functional groups.


Typical Pd(0)-catalysed reactions

R = any type of organic moiety Ar = heterocyclic or carbocyclic aryl

R$_2$NH = amine or heterocyclic ring-NH M = any metal X = often Br, but also Cl, I and OTf

These reactions of halides are carried out in the presence of a catalytic amount (usually 1–5%) of a palladium complex, with a second reactant. The second reactant is most commonly an organometallic nucleophile but other partners, such as alkenes, carbon monoxide or a range of heteroatom nucleophiles, can also be utilised. Either the halo compound, or the second reactant, or both, can be heterocyclic.

Typical examples of these transformations are shown in this chapter, illustrating the versatility of the methods; more examples are given in the chapters devoted to individual heterocyclic systems. The mechanisms and further variations are discussed in the later sections of this chapter. In a few typical examples, we give the full experimental details but apart from these we simply indicate 'Pd(0)' so as to focus attention on the transformation being achieved.

Catalysts

A number of metals can be used as catalysts in these types of reaction, for example nickel, which is closely related to palladium, but palladium is by far the most generally useful and understood. In what follows we discuss palladium-catalysed reactions, apart from a small section on copper.

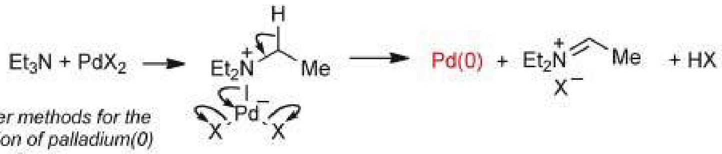
Heterocyclic Chemistry at a Glance, Second Edition. John A. Joule and Keith Mills.

Palladium in its zero oxidation state – Pd(0) – is always the active catalytic species in reactions of halides, but the metal can be added to the reaction mixture in various ways. It can be added in the zero oxidation state, for example as tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] or as a mixture of a Pd(0) complex, such as $Pd_2(dba)_3$, with a phosphine. Alternatively, a Pd(II) compound can be used, either as a mixture of a salt such as palladium acetate [$Pd(OAc)_2$] with a phosphine or other ligand, or as a pre-formed phosphine complex such as bis(tri-*o*-tolylphosphine) palladium dichloride [$PdCl_2(P(o\text{-}Tol)_3)_2$]. (Ligands are generally necessary to stabilise Pd(0), but they also may deactivate it to some degree.) The use of a Pd(II) compound is a common cause of confusion – the true catalyst is still Pd(0), which is formed *in situ* in an initiation step: in cross-couplings for example, via conversion into a diarylpalladium by reaction with RM, followed by reductive elimination.

initiation step for the formation of the true Pd(0) catalyst from a Pd(II) pre-catalyst (PdX_2 is the palladium(II) precatalyst RM is an organometallic coupling partner)

$$RM + PdX_2 \xrightarrow[-MX]{} RPdX \xrightarrow[-MX]{RM} RPdR \longrightarrow R{-}R + Pd(0)$$

A number of other agents can bring about reduction of Pd(II) to Pd(0), such as the triethylamine used in Heck reactions, or triphenylphosphine.



two other methods for the generation of palladium(0) from a palladium(II) precatalyst

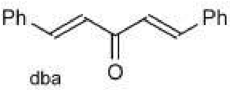
$$PdX_2 + Ph_3P + H_2O \longrightarrow Pd(0) + Ph_3PO + 2HX$$

Although there are large numbers of catalyst–ligand combinations in the literature, most reactions are carried out using one of a small range of well-established standard catalysts. However, there is an important group of newer catalysts that are particularly useful for less reactive substrates such as chloro-aromatics, and also can improve some other standard transformations. These newer catalyst combinations generally use highly hindered, electron-rich, phosphines or heterocyclic carbenes as ligands. It may seem curious that highly hindered ligands can increase the reactivity of Pd(0), but the reason is that they cannot fully 'saturate' the metal, as occurs for example with $Pd(PPh_3)_4$, because there is not enough space around the metal to accommodate four of these larger ligands. This 'unsaturated' Pd(0) is then more reactive than that in $Pd(PPh_3)_4$, which is a stable, convenient, easily handled solid, but its reactivity depends on small amounts of $Pd(PPh_3)_3$ or $Pd(PPh_3)_2$ that form in solution. Electron-rich ligands also increase the reactivity of Pd(0) by increasing electron density on the metal.

The choice of a catalyst–ligand system for a particular transformation often comes down to experience of related reactions and/or to trial and error. The particular combination of catalyst, solvent and base can be critical in some cases.

$Pd(PPh_3)_4$ $Pd_2(dba)_3$
Pd(0) sources

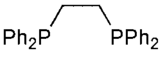
$Pd(OAc)_2$ $PdCl_2(dppe)$ $PdCl_2(PhCN)_2$
Pd(II) sources



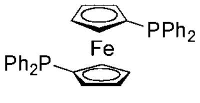
dba

Ph_3P

triphenylphosphine
the most common standard phosphine

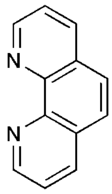


dppe

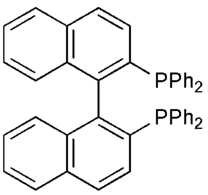


dppf

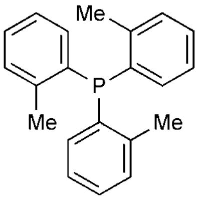
bidentate ligands



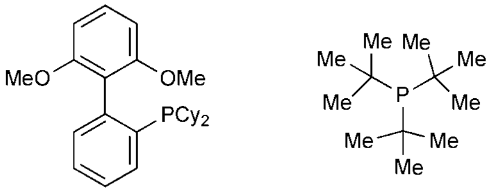
1,10-phenanthroline



BINAP



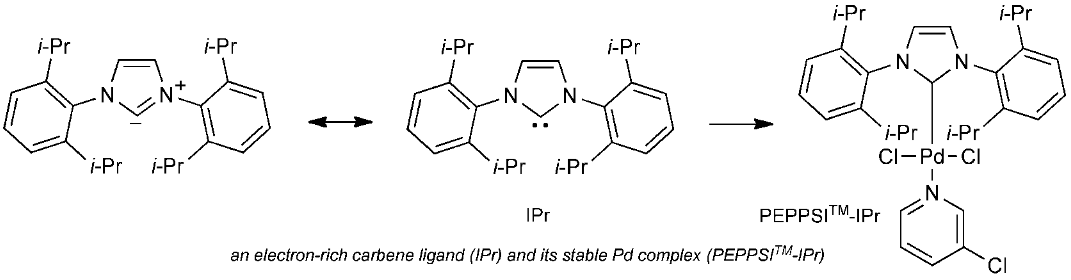
tri-o-tolylphosphine
a hindered phosphine



SPhos

tri-*t*-butylphosphine

highly hindered electron-rich ligands



IPr

PEPPSI™-IPr

an electron-rich carbene ligand (IPr) and its stable Pd complex (PEPPSI™-IPr)

Cross-coupling reactions between organometallic species and halides (sometimes triflates) – making carbon–carbon bonds

The overall conversion can be summarised as follows:

M is a 'metal',
such as boron, tin, zinc, magnesium, silicon
Ar represents an aryl group,
which can be heterocyclic or carbocyclic
R represents any organic moiety,
most commonly aryl or heteroaryl
X is often Br

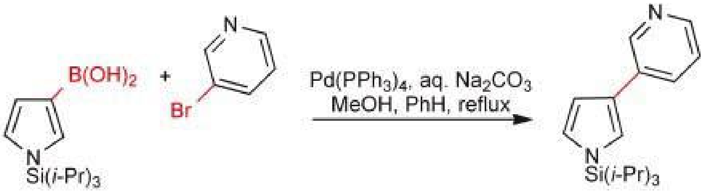
$$\mathrm{Ar{-}X} + \mathrm{RM} \longrightarrow \mathrm{Ar{-}R} + \mathrm{MX}$$

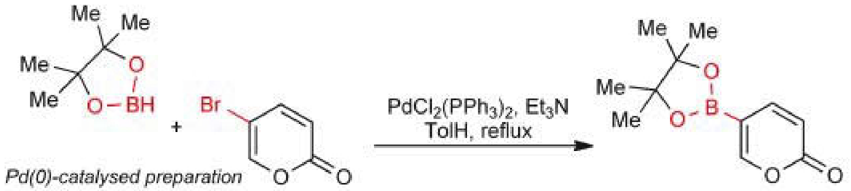
The organometallic components (RM) are often prepared by an exchange reaction with an organolithium (see individual chapters for the generation of heterocyclic lithium reagents) and also, for boron and tin, by palladium-catalysed methods, as illustrated for selected examples below. Note: Organolithium compounds do not perform well in cross-coupling reactions.

Boronic acid couplings (Suzuki–Miyaura reaction)

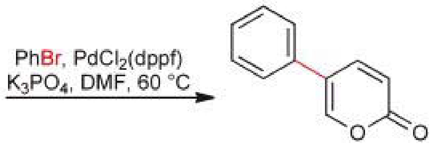
This reaction is the most important of the cross-coupling reactions and is widely used for production of fine chemicals, such as pharmaceuticals. All variations of this reaction are equally useful: $\mathrm{Het^1B(OH)_2} + \mathrm{Het^2X} \rightarrow \mathrm{Het^1{-}Het^2}$, $\mathrm{ArB(OH)_2} + \mathrm{HetX} \rightarrow \mathrm{Ar{-}Het}$ and $\mathrm{HetB(OH)_2} + \mathrm{ArX} \rightarrow \mathrm{Het{-}Ar}$. Either a free boronic acid or an ester can be used. The inclusion of a mild base is essential for these couplings.

cross-coupling
using a pyrrole-3-boronic acid

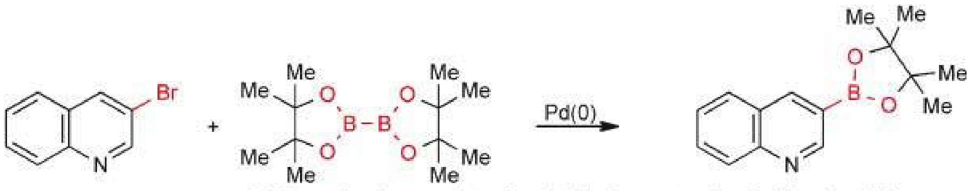




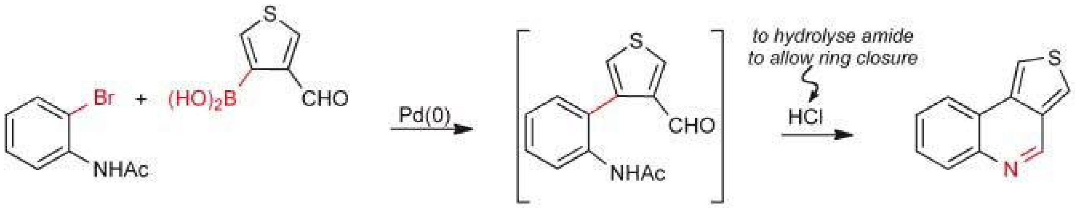
Pd(0)-catalysed preparation of a 2-pyrone-5-boronate using pinacol borane



cross-coupling using a 2-pyrone-5-boronate

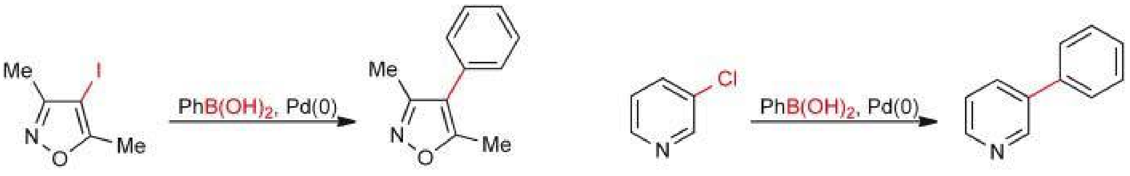


Pd(0)-catalysed preparation of a quinoline boronate using bis(pinacolato)diboron



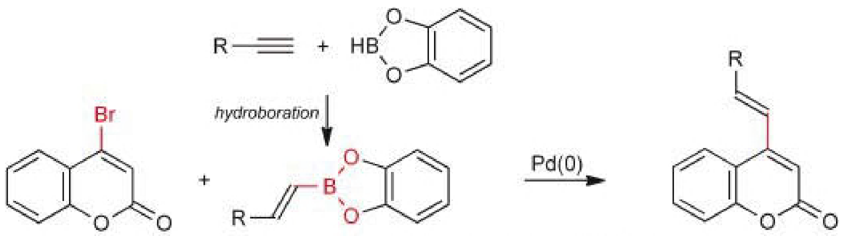
a coupling using a thiophene-3-boronic acid, with other functional groups present, in both components, which do not interfere

Bromide is the most common leaving group but iodide and chloride can also be used, but for the last a more reactive catalyst may sometimes be needed.

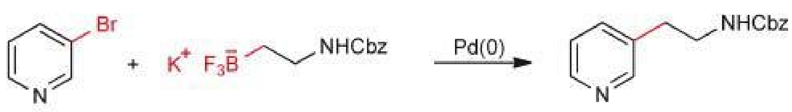


couplings of phenylboronic acid with a chloride and with an iodide

Non-aromatic (alkyl and alkenyl) boronates can also be used, but the corresponding trifluoroborates (RBF$_3$K) have the advantages of better stability with consistent reactivity. Trifluoroborates are easily prepared by reaction of boronic acids with KHF$_2$.



cross-coupling using an alkenyl boronate

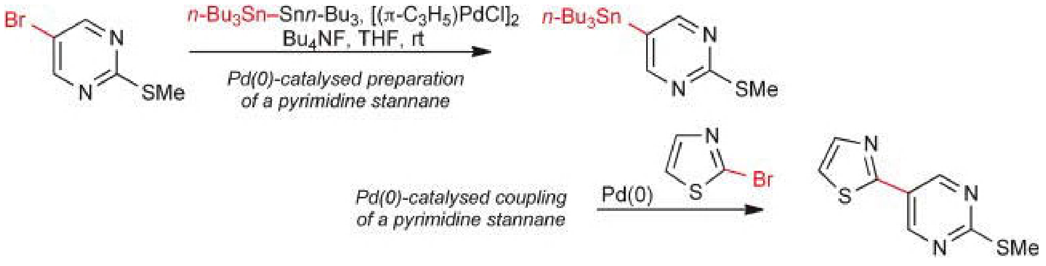


trifluoroborates are particularly useful for saturated alkyl (and alkenyl) couplings

Stannane couplings (Stille reaction)

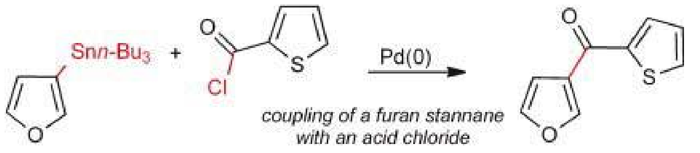
Couplings with $HetSnR_3$ are particularly useful in cases where the corresponding boronic acid would be unstable, for example some azole boronic acids. However, all of the variations equivalent to the boronic acid couplings can be used.

Stannane couplings suffer from the disadvantage that organotin compounds tend to be toxic and environmentally hazardous. In particular, trimethyltin compounds are very toxic to humans and organotin compounds generally are highly toxic to many aquatic organisms and are therefore subject to stringent regulatory control concerning aqueous effluents. Organotin compounds are lipophilic and are therefore readily absorbed through the skin.

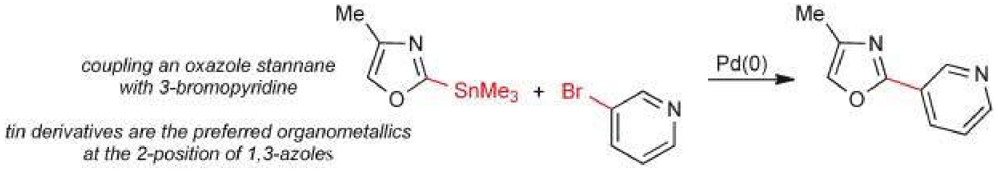


Pd(0)-catalysed preparation of a pyrimidine stannane

Pd(0)-catalysed coupling of a pyrimidine stannane



coupling of a furan stannane with an acid chloride

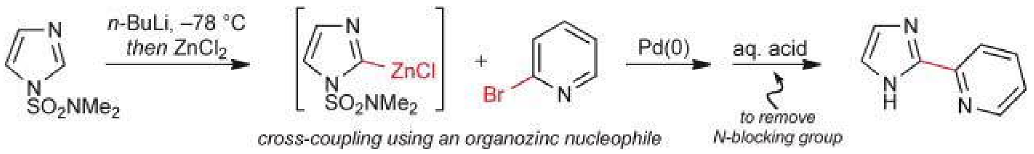


coupling an oxazole stannane with 3-bromopyridine

tin derivatives are the preferred organometallics at the 2-position of 1,3-azoles

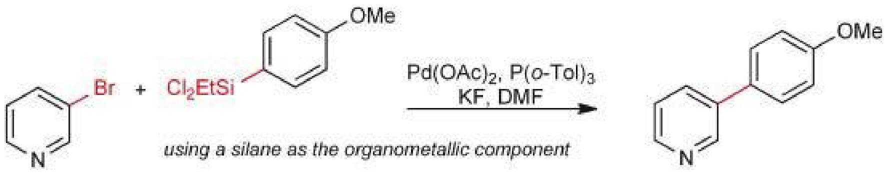
Cross-couplings using other organometallic reagents

Grignard reagents are useful partners (Kumada–Corriu reaction) when functional groups are absent but the corresponding zinc reagents (Negishi reaction) are more tolerant of functional groups and can often give better yields. Nickel is a good replacement for palladium in some reactions. Silanes can also be useful partners (Hiyama–Denmark reaction).



cross-coupling using an organozinc nucleophile

to remove N-blocking group

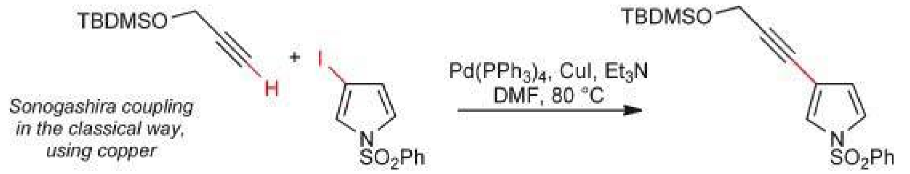


using a silane as the organometallic component

nickel catalysis can be used instead of palladium in some cases

Acetylene couplings (Sonogashira reaction)

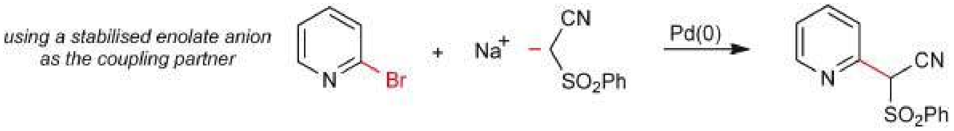
The Sonogashira reaction, which involves *in situ* formation of a copper acetylide as the reactive organometallic, is a very convenient and simple method to link an alkyne to an aromatic ring, but an equivalent standard organometallic cross-coupling (without copper), using a preformed acetylide, can also be useful on occasion. Iodide is the most common leaving group in Sonogashira reactions.


Sonogashira coupling in the classical way, using copper


coupling using a preformed acetylene organometallic, without using copper

Couplings using anions from C–H-acidic compounds

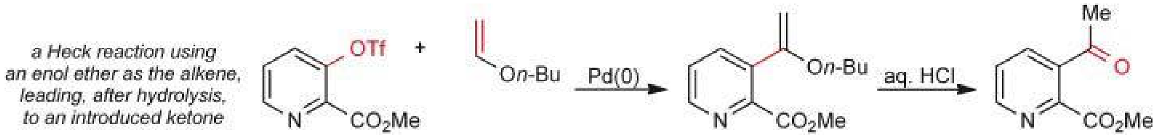
Enolates and related anions, particularly doubly stabilised, generally work well and can introduce multiple functional groups.


using a stabilised enolate anion as the coupling partner

Addition to alkenes: the Heck reaction

The Heck reaction was the first palladium-catalysed reaction to be developed and widely used, and is still very useful for the introduction of alkenyl groups onto a heterocycle in replacement of a leaving group (normally halogen). It uses conditions similar to those used for cross-coupling reactions but has the advantage of not requiring an organometallic reagent. Acrylates have been the most used alkenes; they give rise to (*E*)-ArCH=CHCO$_2$R products. A Heck reaction using an enol ether as the alkene results, after hydrolysis, in the overall introduction of an acyl group. For a different type of Heck reaction, see under electrophilic palladation (pages 29–30).


a Heck reaction using methyl acrylate as the alkene


a Heck reaction using an enol ether as the alkene, leading, after hydrolysis, to an introduced ketone

Carbonylation reactions

Reaction of a halide and palladium(0) with carbon monoxide and a nucleophile – water, amine or alcohol – gives an acid, carboxamide or ester, respectively, (the mechanism is given on page 29).


introduction of an ester group via Pd(0)-catalysed reaction of a halide with carbon monoxide and an alcohol

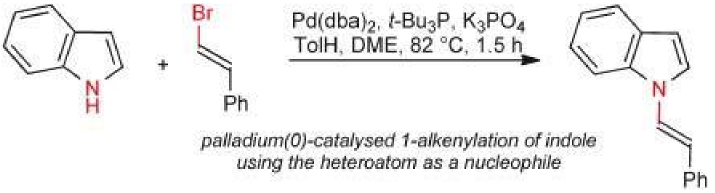
It is also possible to use an organometallic, giving a ketone, but careful choice of partner is required to avoid competitive cross coupling.

Cross-coupling reactions between heteroatom nucleophiles and halides – making carbon–heteroatom bonds

Heteroatom nucleophiles bearing an 'acidic' hydrogen, in the presence of a base, or as a preformed metal derivative, can be used in palladium(0)-catalysed processes to make carbon–heteroatom bonds. Cross-couplings with nitrogen, sulfur and oxygen nucleophiles (amine, thiol and alcohol/phenol) work well. Heterocyclic *N*-hydrogen can also be substituted using palladium catalysis, though there are many more examples using copper (page 30).

palladium(0)-catalysed formation of C–N and C–S bonds

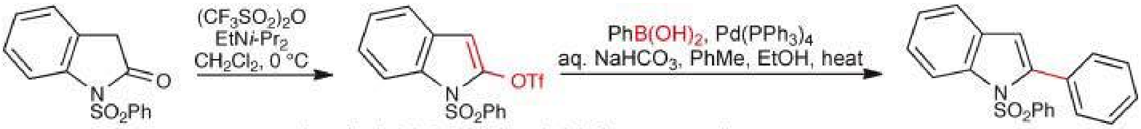
a useful preparation of aryl hydrazines, of use, for example, in Fischer indole syntheses



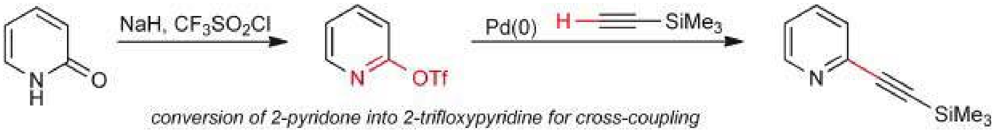
palladium(0)-catalysed 1-alkenylation of indole using the heteroatom as a nucleophile

Triflates as substrates for palladium-catalysed reactions

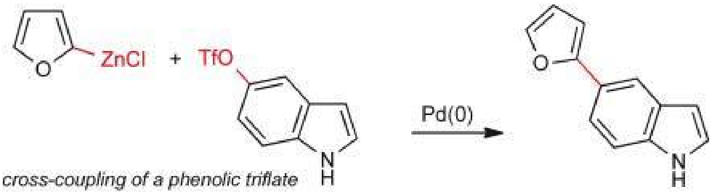
Triflates (trifluoromethanesulfonates: Ar–OSO_2CF_3) give comparable reactions to bromides and are very useful for activating phenols when the corresponding aryl halide is not available. In the context of this book, they can also be used to activate α- and γ-hydroxy-heterocycles that usually exist as carbonyl tautomers, for example oxindoles, pyridones and furanones.



conversion of oxindole into 2-trifloxyindole for cross-coupling



conversion of 2-pyridone into 2-trifloxypyridine for cross-coupling

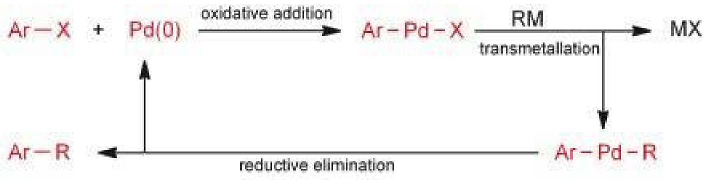


cross-coupling of a phenolic triflate

Mechanisms of palladium(0)-catalysed processes

None of the palladium(0)-catalysed transformations, exemplified above, are single-step processes but all involve three-step catalytic cycles, with changes in the oxidation state of the metal. Each starts with the reaction of Pd(0) with a halide (triflate) and finishes with the expulsion of Pd(0), allowing the cycle to continue. Note: the metal in species ArPdX and ArPdR is at the oxidation level of Pd(II).

In the scheme below, all palladium compounds are in a variable state of coordination with phosphines or other ligands, which are not shown for the sake of clarity.



general catalytic cycle for cross-couplings

Ar denotes any aromatic or heteroaromatic group; X = Hal or TfO
R denotes a general group: aryl, heteroaryl, alkyl, alkynyl, enolate, R'$_2$N, R'O

Note: The intermediate arylpalladium halides (Ar—Pd—Hal), despite an apparent resemblance to Grignard reagents, are generally fairly stable to air and water and do not react with electrophiles.

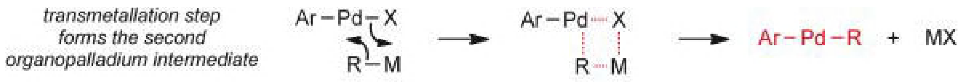
Individual steps in the cross-coupling mechanism

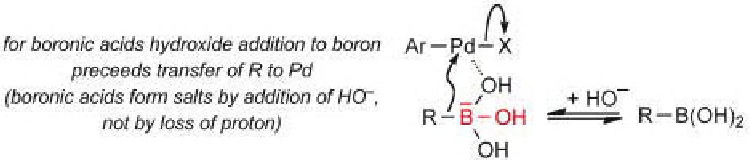
Although some seem similar to classical nucleophile/electrophile interactions, the steps shown below are generally concerted cyclic processes. Some reactions with simple nucleophiles in the transmetallation step can be regarded as classical in nature, although those of the standard organometallics (boron, tin, etc.) are concerted.

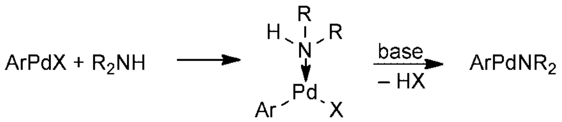
The *oxidative addition* of Pd(0) to the halide is the basis and starting point for all these reactions and as such, is the most important single palladium reaction in organic chemistry. Pd(0) has some nucleophilic character but inserts into the carbon–halogen bond directly, rather than via an addition–elimination attack at carbon. However, the reaction can be promoted by similar factors to those that favour nucleophilic substitution, for example, the reactivity of Pd(0) can be increased by electron-rich ligands, which increase the electron density on the metal.

oxidative addition step forms the first organopalladium intermediate

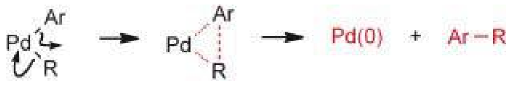
The *transmetallation* step involves transfer of the organic residue from the organometallic reactant, RM, to palladium. It can be regarded conveniently as equivalent to a nucleophilic displacement of the halide from Pd. Organometallic reagents, such as Grignards and zinc compounds can be used but the conventionally 'less reactive' boron and tin compounds are best. Acetylenes (Sonogashira reaction) react via an organocopper compound formed *in situ*. For boronic acids, a nucleophile such as hydroxide is required to generate a tetrahedral boronate, which is the species involved in transmetallation. The equivalent step with covalent derivatives of heteronucleophiles, for example R_3SnNR_2, probably involves a similar mechanism to tin reagents in the Stille reaction. However, the base-catalysed reaction with free amines occurs via a simple coordination to the palladium (much as for coordination of a simple ligand such as a phosphine), followed by reaction with base to eliminate HX.





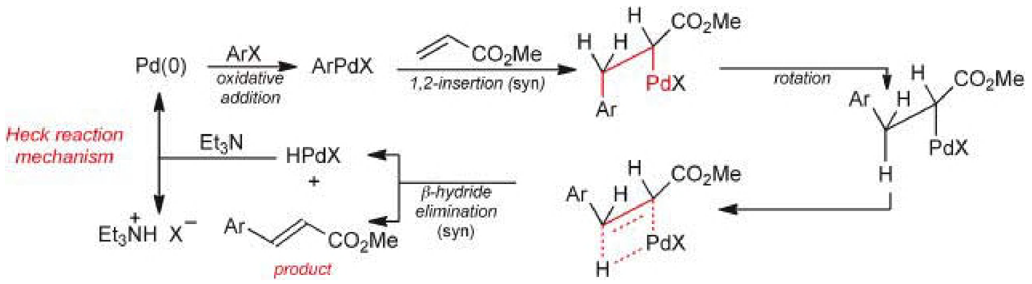


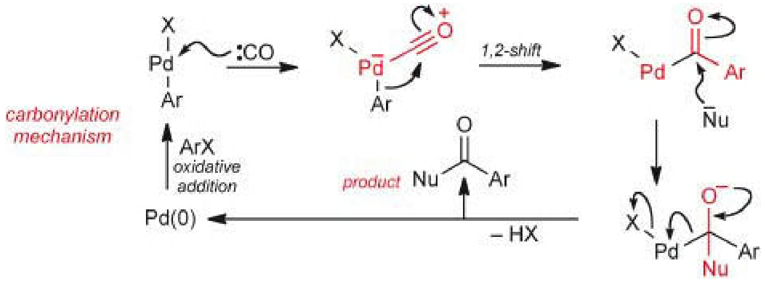
Finally, *reductive elimination* forms the carbon–carbon or carbon–heteroatom bond and eliminates Pd(0), which then returns to the oxidative addition step, completing the catalytic cycle.



Mechanisms of other reactions

The Heck reaction, and carbonylation, also proceed via an initial oxidative addition but this is followed by insertion of the palladium–carbon bond into an alkene, or carbon monoxide, followed by elimination of HPdX or nucleophilic attack at CO, respectively. HPdX breaks down in the presence of base to give back Pd(0).



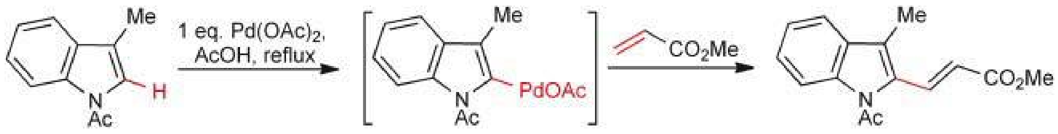


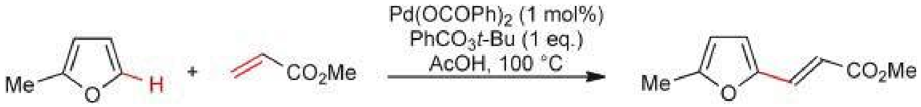
Reactions involving electrophilic palladation

Pd(II) compounds are electrophilic species that can react with electron-rich systems, such as particular five-membered heterocycles or carboaromatics, with replacement of hydrogen. These are just standard aromatic electrophilic substitutions, as occur, for example with Hg(II) compounds or bromine.

$$\mathrm{ArH} + \mathrm{PdX_2} \longrightarrow \mathrm{Ar{-}Pd{-}X} + \mathrm{HX}$$

It is immediately obvious that the product of such a substitution is exactly the same as the product of oxidative insertion of Pd(0) into ArX, and can therefore undergo the same transformations. However, although reactions using stoichiometric amounts of palladium are successful, catalytic processes using this approach cannot generally be carried out, as the conditions for electrophilic palladation are not compatible with the other coupling partners, such as boronic acids, which would react with PdX_2 much faster than would ArH. An exception is the Heck reaction, which can succeed in the presence of selective oxidants that reconvert Pd(0) into Pd(II) *in situ.*

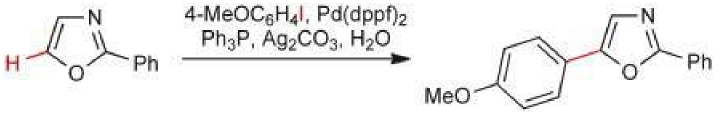




A more generally useful method (Direct Arylation), however, uses the $Ar^1{-}Pd{-}X$, produced by oxidative addition to Ar^1X, as the electrophilic reagent to palladate a second component, Ar^2H.

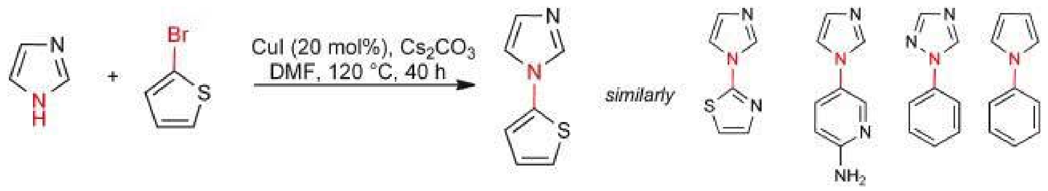
$$Ar^1X + Pd(0) \longrightarrow Ar^1{-}Pd{-}X \xrightarrow{Ar^2H} Ar^1{-}Pd{-}Ar^2$$

This can be carried out in a catalytic way under similar conditions to the other major Pd(0) reactions. Again, this is generally restricted to electron-rich five-membered rings, although pyridine *N*-oxides do react, very selectively at C-2. A major advantage is that preparation of an organometallic is not required, although a disadvantage in some cases is lack of specificity for particular positions. The mechanism is very similar to cross-coupling, but the transmetallation step is replaced by the electrophilic metallation step.

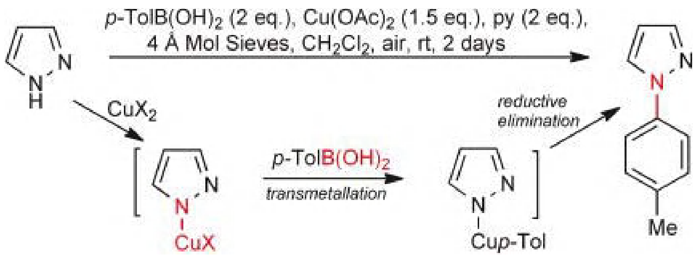


Copper-catalysed amination

Copper catalysis, under similar conditions to the palladium reactions, has been found to be particularly useful for amination of (hetero) aromatic halides, and the complementary method of *N*-arylation of heterocyclic N–H.



Another very useful *N*-arylation uses a boronic acid, rather than a halide, as the aryl partner (Chan–Lam reaction). In this reaction a stoichiometric amount of copper is used – this is not an issue, as copper is vastly cheaper than palladium!



Selectivity

Achieving a selective coupling reaction involving just one particular halogen in a polyhalo-compound can be very useful synthetically. Selectivity in polyhalo-compounds is governed by the first step – the oxidative addition, which is irreversible. Also useful, but less common, is selection between two different metals.

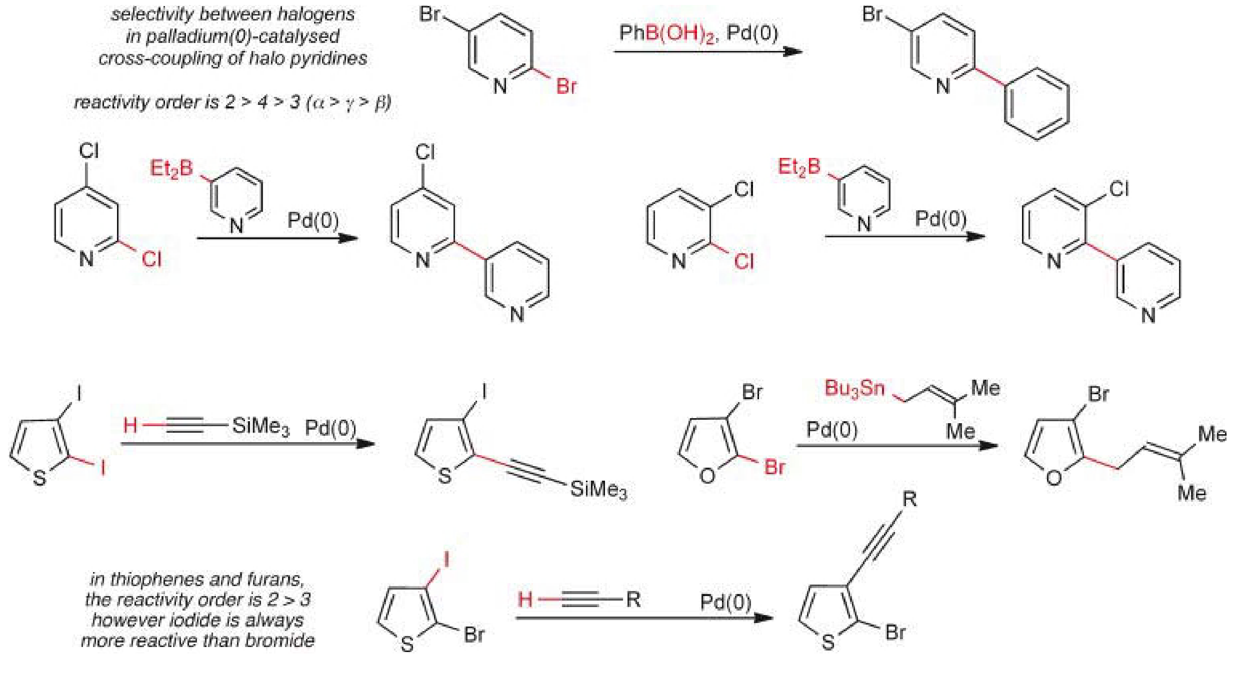
There are two main forms of halide selectivity: (i) between different leaving groups and (ii) between different carbons bearing the same leaving group (regioselectivity). Selectivity between different leaving groups almost always dominates over regioselectivity.

Leaving groups

The reactivity of different 'leaving groups' to oxidative addition is related inversely to the strength of the carbon–halogen bond, that is I > Br ~ OTf > Cl. However, although iodide is the most reactive in oxidative addition, it may not give the fastest reaction overall, as this step may not be rate-limiting. Iodides also have a tendency to give more side reactions than the other halides. Bromides are the most widely used substrates although the cheaper and more readily available chlorides are also important, due to the development of more active catalysts.

Regioselectivity (between the same halogen at different positions)

Oxidative addition involves a concerted nucleophilic-like attack by Pd(0), but differs from the standard two-step aromatic nucleophilic displacement in that direct attack at the carbon–halogen bond occurs and mesomeric stabilisation of an intermediate is not involved. That being said, those same mesomeric relationships do contribute, together with inductive effects, to the total electron density at the carbons involved. *The tendency is for oxidative addition to select the carbon with the lowest electron density*. In simple systems, there seems to be a good correlation with total electron density at carbon – pyridine, furan and thiophene show highest reactivity at C-2. In more complex (and reactive) systems such as pyrimidines, the correlation is not as clear-cut and other factors may be involved. In pyridines, for oxidative addition the order is C-2 > C-4 > C-3, whereas for nucleophilic displacement (see page 35) it is C-4 > C-2 > C-3, showing the greater effect of induction at C-2 in the former, whereas in the latter, stabilisation of an intermediate adduct is more important.

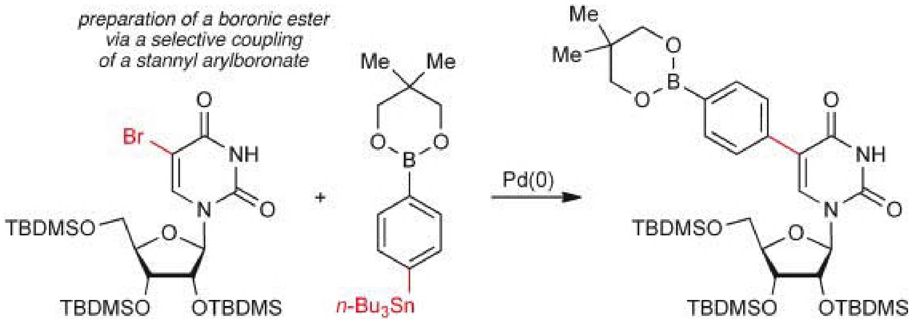

selectivity between halogens in palladium(0)-catalysed cross-coupling of halo pyridines

reactivity order is 2 > 4 > 3 ($\alpha > \gamma > \beta$)

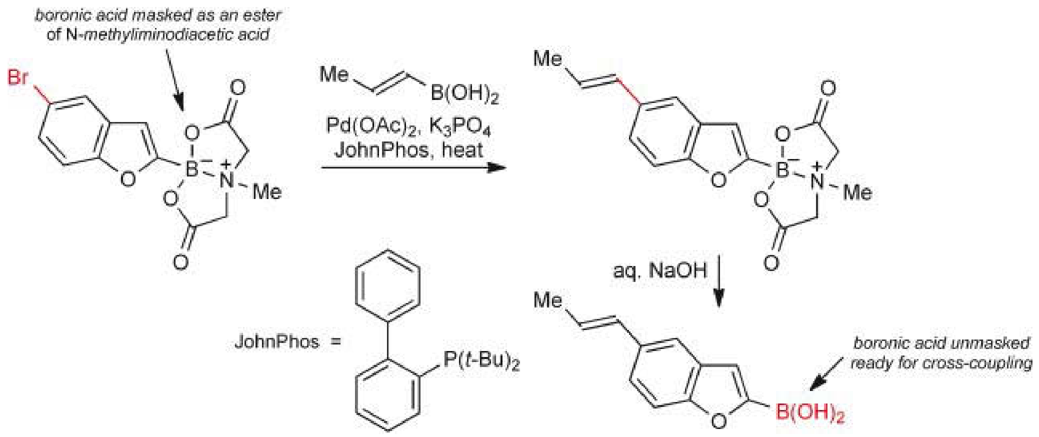
in thiophenes and furans, the reactivity order is 2 > 3 however iodide is always more reactive than bromide

Organometallic selectivity

Different classes of organometallic reagent may require very different conditions to achieve coupling. Whereas stannane couplings are usually carried out in non-polar solvents, boronic acids are usually reacted under polar conditions in the presence of a base. The difference in requirements is such that highly selective couplings can be carried out, as is clearly demonstrated by the use of a stannyl arylboronate (under neutral, non-polar conditions) to prepare a boronic acid ester.

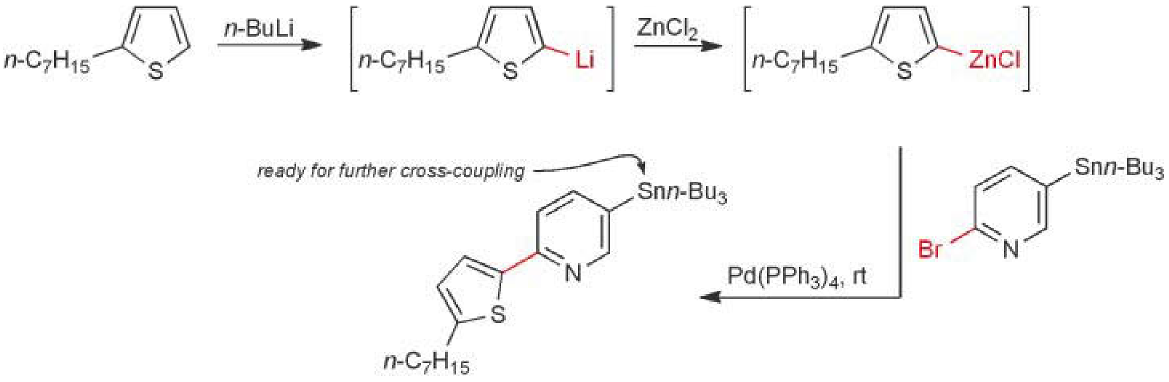

preparation of a boronic ester via a selective coupling of a stannyl arylboronate

High-yielding Suzuki-Miyaura substitutions of halogen in substrates containing both a halogen and a boronic acid are possible using *N*-methyliminodiacetic acid (MIDA) to form a protected boronate, which resists coupling under anhydrous conditions. Following the cross-coupling, the boronic acid can be released under mild conditions, ready for further reaction.


boronic acid masked as an ester of N-methyliminodiacetic acid

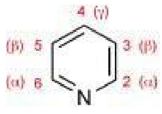
boronic acid unmasked ready for cross-coupling

Negishi cross-couplings on 2-bromo-5- and -6-tri-*n*-butylstannyl pyridines are possible due to the relatively high reactivity of α-bromopyridines, which allows a relatively low temperature to be used.

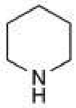

ready for further cross-coupling

5

Pyridines



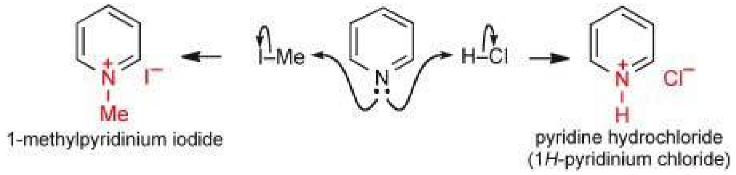
pyridine
pK_{aH} 5.2



piperidine
pK_{aH} 11.2

Electrophilic addition to nitrogen

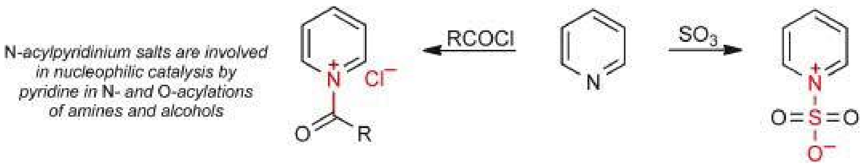
With simple pyridines, all electrophiles react, at least initially, by addition to the nitrogen, that is the electrophile accepts the nitrogen lone electron pair to form a bond in the plane of the ring. Protonation, for example, occurs easily, on nitrogen. Pyridine is a weaker base than typical aliphatic amines (pK_{aH} values of 9–11), but is nevertheless widely used in synthetic processes that require the presence of a base. Pyridines form stable crystalline, but often hygroscopic, pyridinium salts with strong acids, for example hydrochloric acid, however, salts with weaker acids, such as acetic, readily dissociate to reform the pyridine and the acid. Pyridinium salts are still aromatic, though the π-system is further polarised.



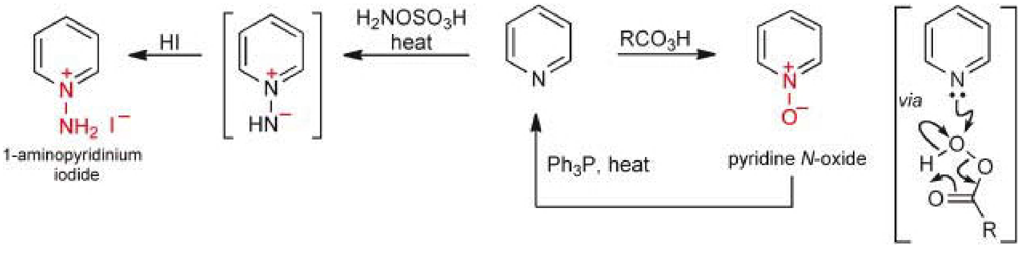
1-methylpyridinium iodide

pyridine hydrochloride
(1*H*-pyridinium chloride)

Alkyl halides react irreversibly with pyridines to give 1-alkylpyridinium salts. Both bromine and sulfur trioxide will add to the nitrogen to form crystalline complexes. Acyl halides and sulfonyl halides react at nitrogen generating readily hydrolysed N^+-acyl and N^+-sulfonyl pyridinium salts (1-acylpyridinium and 1-sulfonylpyridinium), which are the actual electrophilic agents when pyridine is used as a nucleophilic catalyst in acylations and sulfonylations of alcohols and amines.



Pyridines react easily with peracids to generate *N*-oxides and can be *N*-aminated with hydroxylamine-*O*-sulfonic acid. Pyridine *N*-oxides can be converted into pyridines in several ways, for example with a phosphine (which forms the corresponding phosphine oxide).

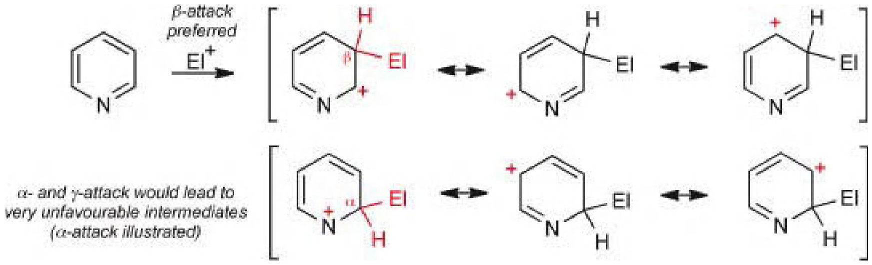


Heterocyclic Chemistry at a Glance, Second Edition. John A. Joule and Keith Mills.

Electrophilic substitution at carbon

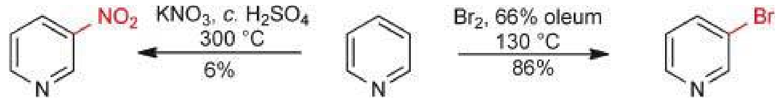
The electronic structure of pyridine (page 5) involves mesomeric transfer of electron density from C-2(6) and C-4 to the nitrogen and this, combined with inductive withdrawal of electron density by the heteroatom, results in overall electron deficiency at all carbons, but particularly at C-2(6) and C-4 (the α- and γ-positions). Thus pyridine, as an electron-deficient aromatic compound, is intrinsically *much* less susceptible to electrophilic attack at carbon than is benzene. Additionally, there is also a second, more important factor, in that attempted substitution with all electrophiles initially generates *N*-substituted pyridinium species by addition of the electrophile (or a proton in acidic conditions) to nitrogen, in which the normal polarisation is greatly enhanced, so that the possibility for electrophilic attack at carbon is suppressed even more. Thus, substitution requires *either* attack by the electrophile on a positively charged pyridinium ring *or* attack on a small concentration of the free pyridine in equilibrium with the pyridinium species.

The regiochemistry of electrophilic substitution is a reflection of the relatively *higher destabilisation* of intermediates for α- and γ-attack due to very unfavourable delocalisation of the positive charge onto nitrogen – this is avoided in the intermediate for β-attack.

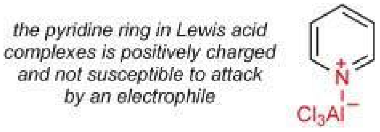

β-attack preferred

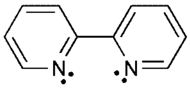
α- and γ-attack would lead to very unfavourable intermediates (α-attack illustrated)

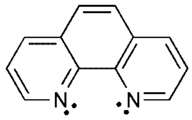
When electrophilic substitutions of simple pyridines are successful, they require very vigorous conditions and proceed only at C-3, which is the *least deactivated* position. A miniscule yield of 3-nitropyridine using the standard nitrating mixture applied at an outrageously high temperature, and the vigorous conditions necessary to produce 3-bromopyridine illustrate this well (a practical conversion of pyridines into 3-nitropyridines is described on page 37).

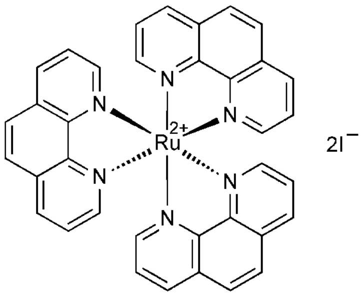


The Friedel–Crafts alkylation/acylation reaction for the introduction of carbon substituents, which is so important in benzene chemistry, is not applicable at all to pyridines – pyridines form strongly bound complexes with the typical Lewis acid catalysts (e.g. $AlCl_3$), which totally resist electrophilic *C*-substitution. This propensity for the pyridine nitrogen lone pair to interact with metal centres has been very widely exploited in coordination chemistry, particularly where two such nitrogens can be brought to bear, for example in 2,2'-bipyridine or 1,10-phenanthroline. The structure of one enantiomer of a typical complex, $Ru(phen)_3I_2$, is shown.

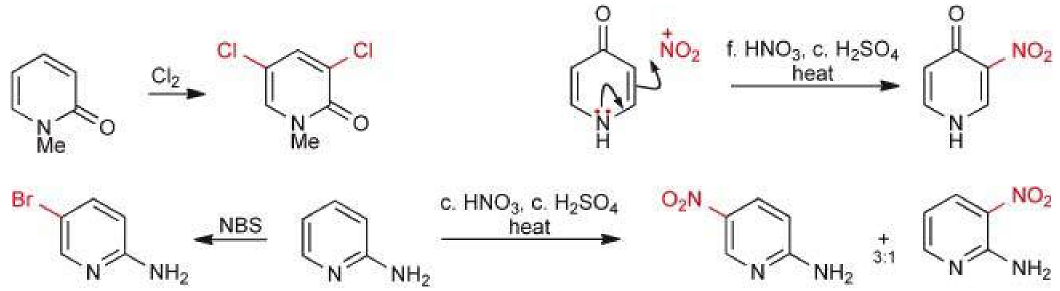

the pyridine ring in Lewis acid complexes is positively charged and not susceptible to attack by an electrophile


2,2'-bipyridine
(bipy)

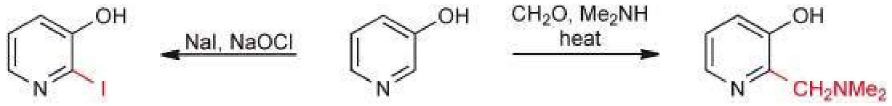

1,10-phenanthroline
(phen)



In contrast to what has been explained above, the presence of activating (electron-releasing) substituents such as amino and hydroxyl (or the tautomeric pyridones – see page 41) allows standard electrophilic substitutions in a pyridine ring to be carried out under relatively mild conditions. The usual *ortho/para* directing effects of these substituents operate so that, for example, chlorination of 1-methyl-2-pyridone proceeds at the available positions *ortho* and *para* to the oxygen. One may alternatively view electrophilic substitutions of pyridones as involving attack at the β-position of the enamine (or dienamine) units in these molecules – as suggested by the arrows on 4-pyridone below.

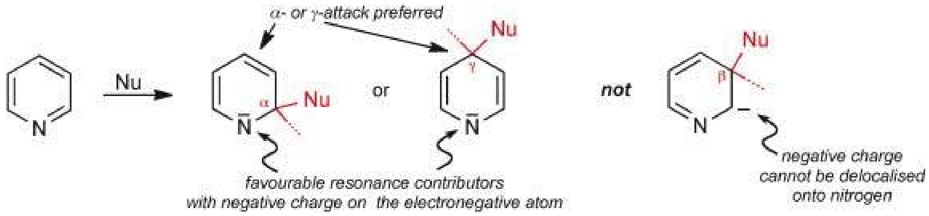


It is a curious fact, but with little theoretical rationale, that electrophilic substitutions of pyridines carrying an activating substituent at C-3, generally occur at C-2 rather than C-4/C-6, as exemplified by the iodination and Mannich substitution of 3-hydroxypyridine. This selectivity is also found in nucleophilic substitution of 3-substituted pyridines.



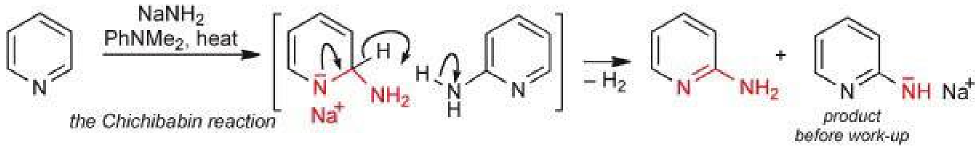
Nucleophilic substitution

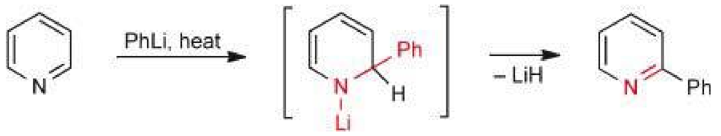
Pyridine is susceptible to addition of nucleophiles at the α- and γ-positions due to delocalisation of the negative charge onto nitrogen in the intermediate anion thus produced. This process is very similar to the addition of nucleophiles to the carbonyl carbon of a ketone or the β-position of an α, β-unsaturated (conjugated) ketone. In intermediates that would result from nucleophilic addition at a β-position, the nitrogen cannot directly assist the delocalisation.



Substitution of hydrogen

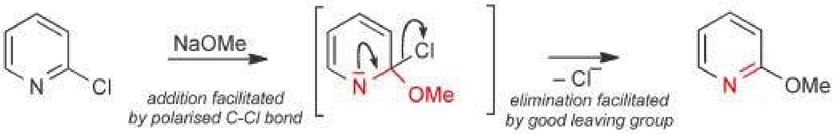
Simple pyridines react with strong nucleophiles such as sodium amide, or alkyl- or aryllithiums, under forcing conditions, with elimination of hydrogen in the former case and lithium hydride in the latter, resulting in the formation of 2-amino-, 2-alkyl- or 2-arylpyridines, respectively. The intermediate 1,2-dihydropyridines from alkyl- and aryllithiums can also be re-aromatised by oxidation – simply with air or oxygen. These nucleophilic substitutions of hydrogen usually occur at C-2, probably because the reagents coordinate with the pyridine nitrogen in the relatively non-polar conditions and then the nucleophile is delivered selectively to the α-position by an intramolecular process.





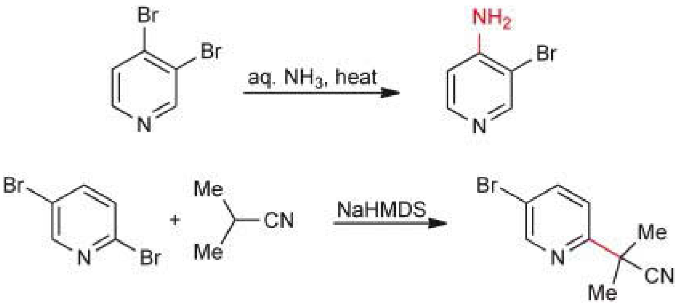
Substitution of leaving groups

Nucleophilic displacement of good leaving groups such as a halide (as opposed to hydrogen) from either the α- or γ-positions requires very much milder conditions and proceeds via a two-step mechanism – addition–elimination. The initial addition is facilitated by the polarisation of the carbon–halogen bond; the second step is also facilitated – elimination of Hal^- producing the final product is much easier than expelling 'hydride'. 4-Halopyridines are more reactive than 2-halopyridines in these nucleophilic displacement reactions.



A very important distinction from nucleophilic displacements of saturated alkyl halides must be made. In pyridines (and related systems such as diazines, Chapter 6), fluoride is a better leaving group than other halides, whereas in the alkyl fluorides, this halogen is a very poor leaving group. In the addition–elimination mechanism, the first step is rate limiting and is accelerated by the strong electron-withdrawing effect of the fluorine, whereas in the concerted one-step (S_N2) mechanism for alkyl halides, the high strength of the carbon–fluorine bond dominates.

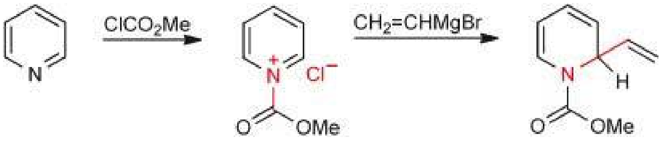
Halogen at a β-position is *much* less easily displaced, as little mesomeric stabilisation of an intermediate is available. However β-halides are still somewhat more reactive than in corresponding carbocyclic (benzene) systems, due to the inductive effect of the nitrogen.

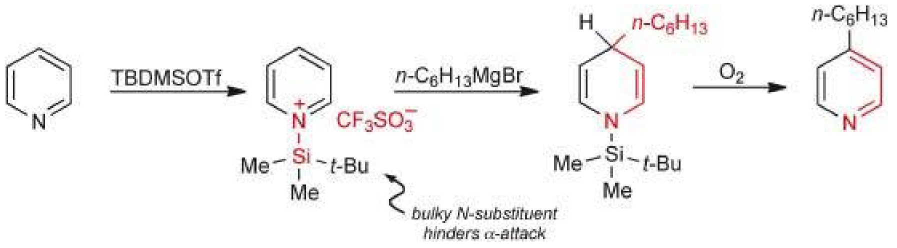


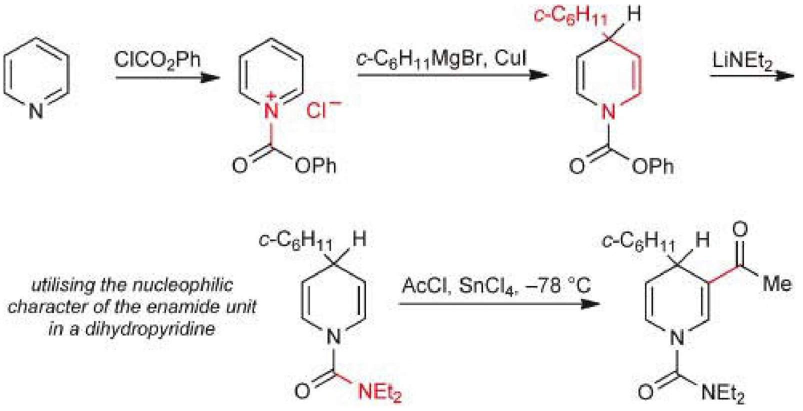
Nucleophilic addition to pyridinium salts

Owing to the full positive charge on nitrogen, 1-alkyl- and 1-acylpyridinium salts are *much* more reactive to nucleophiles than simple pyridines, and again show the same propensity for attack at C-2/C-4. Dihydropyridines are usually the products from these reactions but while the *N*-alkyl dihydropyridines are often unstable (easily oxidised back to pyridinium systems), the *N*-acyl derivatives are generally stable and easily isolated. Nucleophilic additions of organometallic nucleophiles to pyridinium salts, especially to 1-alkoxy(or 1-aryloxy)carbonylpyridinium salts ($N^+–CO_2R$), have become very important, giving synthetic intermediates that can be utilised in various ways for further transformations. The dihydro-adducts can be aromatised to give substituted pyridines or the enamide character can be employed for the introduction of substituents at C-3.

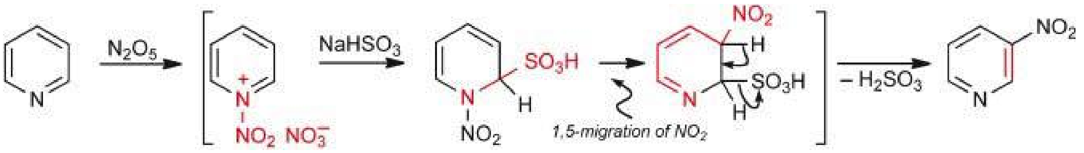
The α/γ-selectivity in these additions varies with the nucleophile and can also be controlled by the use of removable bulky *N*-blocking groups or by using cuprate nucleophiles to encourage 1,4-addition – these aspects are illustrated in the examples below.



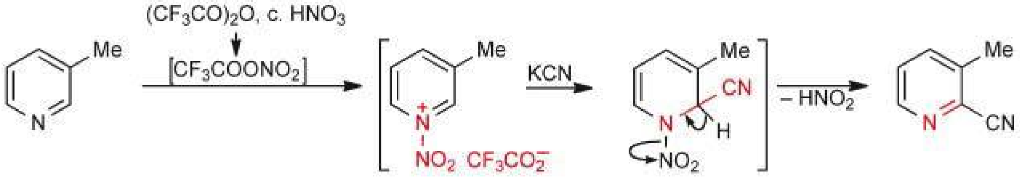




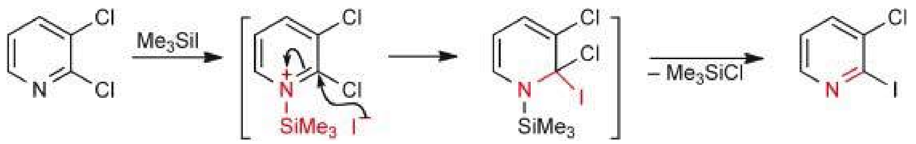
We give two more illustrations of the utility of dihydropyridines formed by nucleophilic addition to pyridinium salts. A non-isolated intermediate is involved in the only practical method for the synthesis of 3-nitropyridines from pyridines: reaction with dinitrogen pentoxide, N_2O_5 (or NO_2OCOCF_3 formed from HNO_3 and $(CF_3CO)_2O$) then hydrogen sulfite proceeds by initial formation of a 1-nitropyridinium salt followed by α-addition of hydrogen sulfite to give a dihydropyridine, in which the nitro group then migrates from nitrogen to carbon, loss of sulfurous acid completing the overall *C*-substitution.



Other nucleophiles will also react at C-2 of a 1-nitropyridinium salt leading, following loss of the nitro as nitrite, to 2-substituted pyridines, for example 2-cyanopyridines.

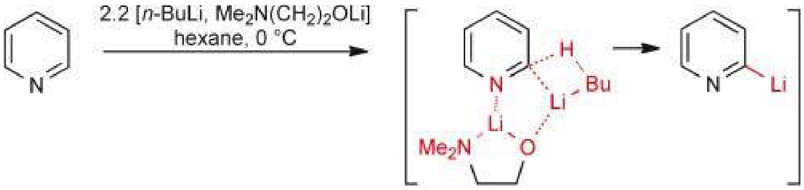


It is possible to replace an α-chlorine with bromine or iodine by reaction with the halotrimethylsilane: this involves an intermediate 1-trimethylsilylpyridinium salt.

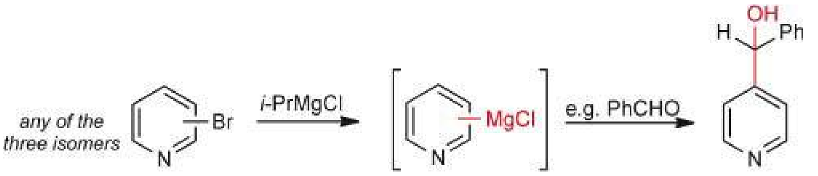


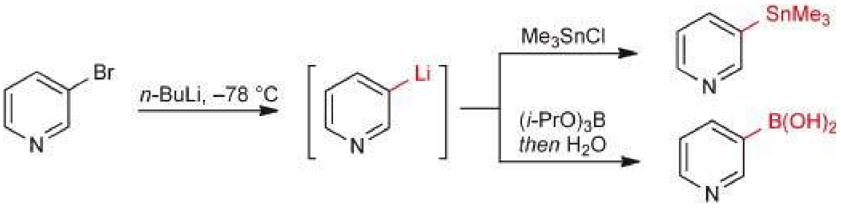
C-metallated pyridines

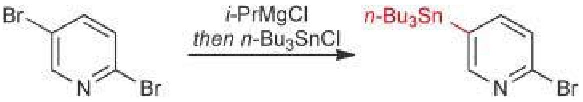
Direct deprotonation of pyridine can be carried out regioselectively at an α-position, using the mixed base produced from two mole equivalents of *n*-butyllithium with one of dimethylaminoethanol, that is a 1:1 mixture of *n*-BuLi and $Me_2N(CH_2)_2OLi$ (BuLi–LiDMAE).



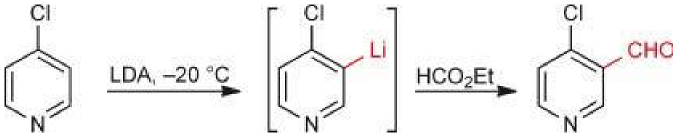
However, more use has been made of halogen exchange reactions for the generation of pyridine organometallic nucleophiles. All three isomeric bromopyridines can be converted into lithio derivatives at low temperature. Particularly significant is the conversion of halopyridines into Grignard reagents by reaction with isopropylmagnesium chloride at room temperature, avoiding the very low temperatures required for the generation of organolithium species (temperatures of around –70 °C have to be used in exchange reactions with *n*-butyllithium in order to avoid nucleophilic *addition* of the reagent to the heterocycle, cf. pages 35–36). Grignard reagents are also more tolerant of functional groups in a reaction partner than are organolithium species. Selectivity in Grignard formation and halogen–metal exchange is for a β-halogen over an α- or γ-halogen.

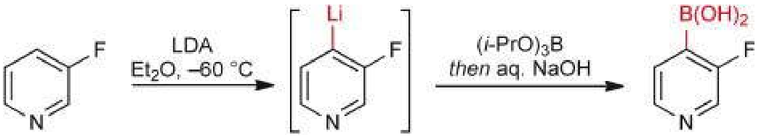


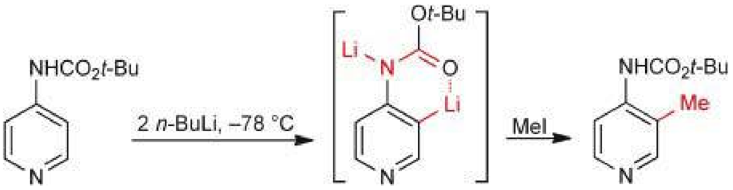




Another, very widely used protocol is metallation *ortho* to directing groups (DoM: Directed *ortho* Metallation). In the examples shown, a 4-carbamate or 4-chlorine allows lithiation at C-3 and a 3-fluorine leads to lithiation at C-4 – in general, when a directing group is located at pyridine C-3, lithiation usually takes place at C-4, not C-2. Note: Either *n*-butyllithium *or* lithium diisopropylamide can be used in these metallations/deprotonations, but only *n*-butyllithium will serve in metal–halogen exchange reactions.

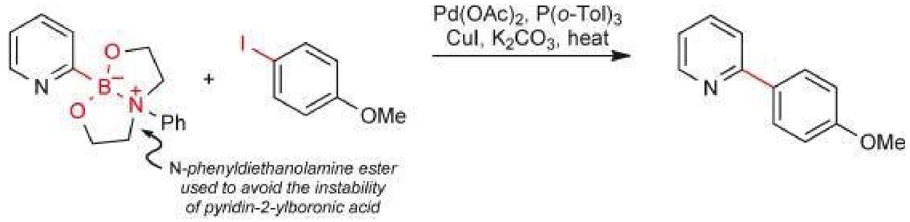




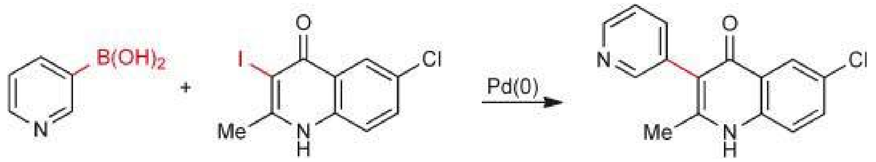


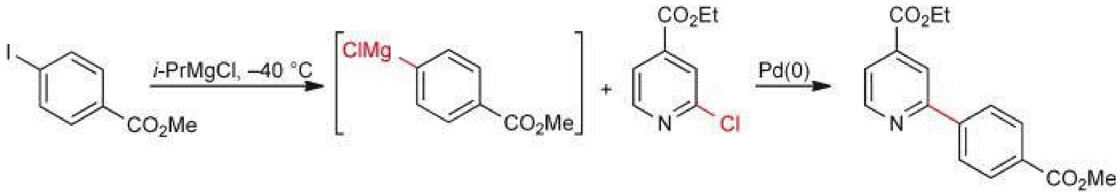
Palladium(0)-catalysed reactions

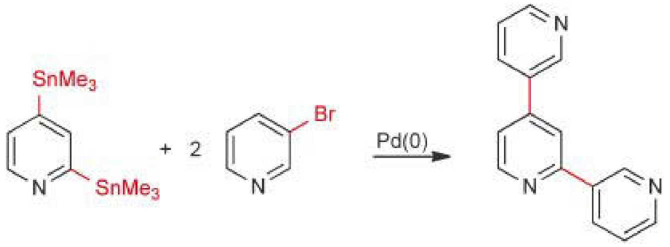
Extensive use has been made of palladium(0)-catalysed cross-couplings using halopyridines, pyridine triflates, pyridine Grignard reagents and zinc derivatives, pyridine stannanes, pyridine boranes and boronic acids. A small selection of illustrative examples is shown below. Note that pyridin-2-ylboronic acids are quite unstable (in the presence of base), but the *N*-phenyldiethanolamine ester gives the right balance between stability and reactivity for successful cross-couplings. Pyridin-3-ylboronic acids are much more stable and react normally without special precautions.

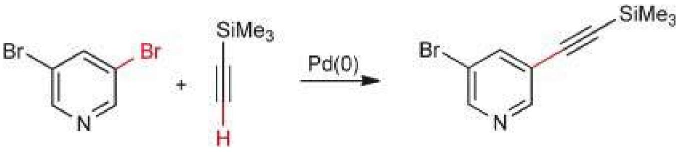


N-phenyldiethanolamine ester used to avoid the instability of pyridin-2-ylboronic acid



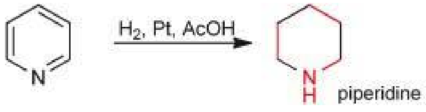


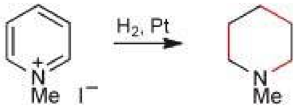




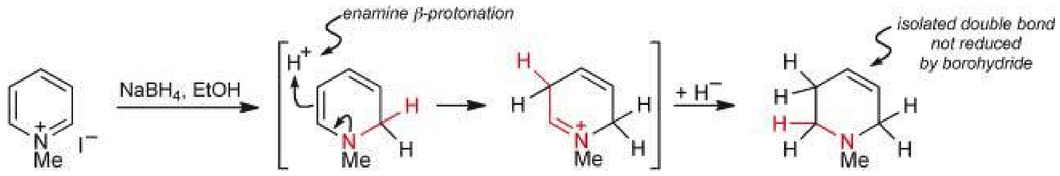
Oxidation and reduction

In contrast to the aromatic ring of benzenoid compounds, the pyridine ring is easily reduced, for example with hydrogen over a platinum catalyst in acidic solution. It is certainly the *N*-protonated pyridine that is reduced and thus *N*⁺-alkyl pyridinium salts are also easily reduced, with hydrogen and a catalyst.

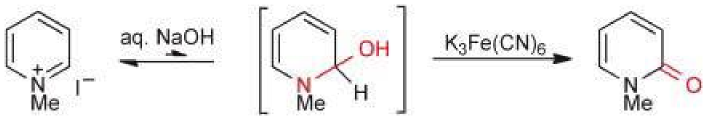




Sodium borohydride in a protic solvent reduces pyridinium salts to a tetrahydropyridine oxidation level, via an enamine protonation of a dihydro-intermediate.

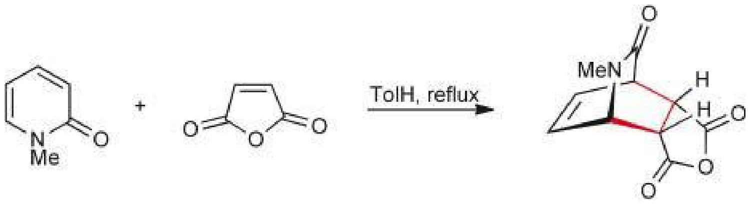


The pyridine ring is very resistant to oxidative attack, however *N*$^+$-alkyl pyridinium salts are oxidised in alkaline solution to *N*-alkyl 2-pyridones – a small concentration of an adduct, formed by addition of hydroxide, is trapped by the oxidant.

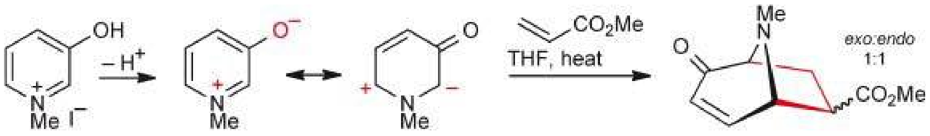


Pericyclic reactions

There are only a few specialised situations where pyridines take part in electrocyclic processes (this contrasts with six-membered heterocycles with more than one nitrogen atom, see pages 54–55 and 141) – 2-pyridones reacting as dienes in Diels–Alder reactions is one of these situations.

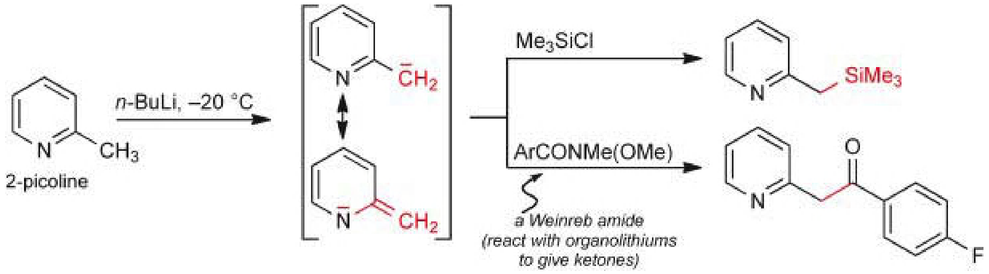


An interesting example of another type of cycloaddition – a 1,3-dipolar cycloaddition – is that of the betaines that are generated by treatment of 3-hydroxypyridinium cations with mild base. These species, for which no neutral mesomeric structure can be drawn, behave as 1,3-dipoles and add to polarised alkenes – methyl acrylate in the example shown.

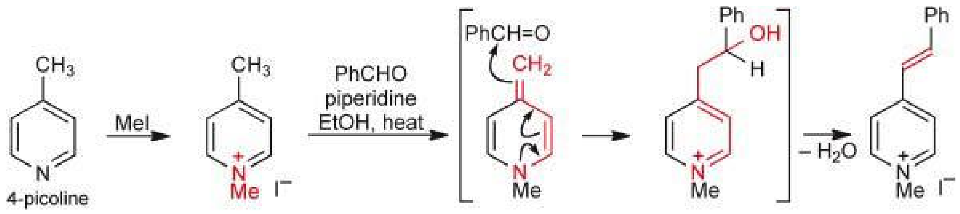


Alkyl and carboxylic acid substituents

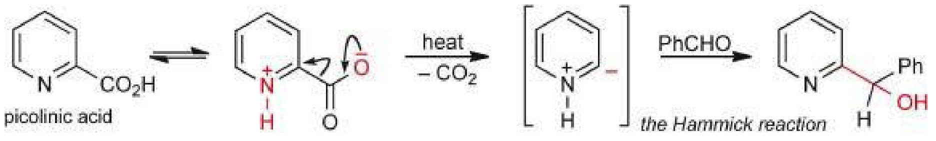
Alkyl groups at the α- and γ-positions of pyridines are 'acidic' in that they can be deprotonated using strong bases to give anions, which can then be reacted with electrophiles. The analogy to α-deprotonation of ketones (formation of enolates – although requiring somewhat milder bases) is clear, with delocalisation of the negative charge onto nitrogen. Alkyl at a β-position can be deprotonated but under much stronger conditions. The methylpyridines are often called picolines; dimethylpyridines are called lutidines, for example 2,4-lutidine.



Side-chain deprotonation (and thence reaction) of picolinium salts requires considerably milder base catalysis.

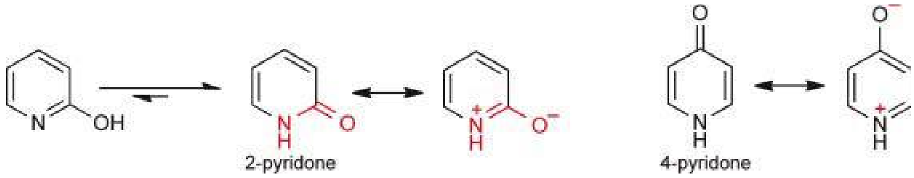


Pyridine carboxylic acids, like simple amino acids, exist mainly as zwitterions (internal salts). The zwitterion of picolinic acid decomposes on heating, with loss of carbon dioxide, to generate a transient ylide, which can be trapped if the reaction is carried out in the presence of benzaldehyde. The 3-acid is usually called nicotinic acid and the 4-acid, isonicotinic acid.

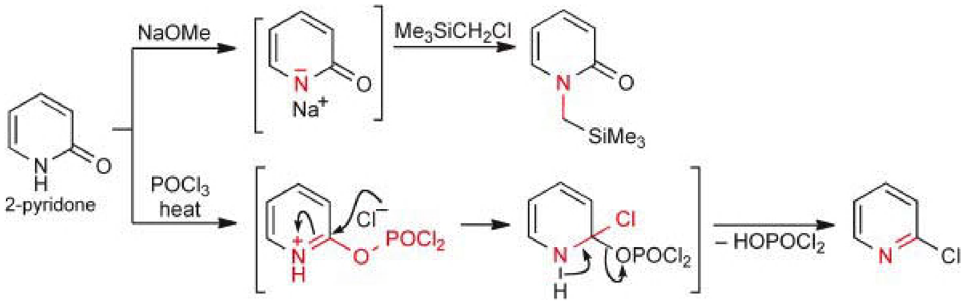


Oxygen substituents

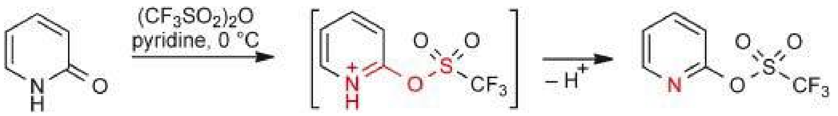
The 2- and 4-hydroxypyridines exist predominantly in the tautomeric *pyridone* form, whereas 3-hydroxypyridines exist only as the hydroxyl form.



The NH in pyridones is relatively acidic, with pK_a values of about 11, and thus can be abstracted by mild base to give anions, which alkylate mainly on nitrogen with primary halides. An important reaction of both α- and γ-pyridones, not shown at all by benzenoid phenols, is their ready conversion into halopyridines by reaction with phosphorus halides. The process proceeds because the amide-like carbonyl oxygen acts as a nucleophilic centre with the phosphorus halide generating a pyridinium salt to which halide adds, followed by 1,2-elimination (of phosphorodichloridic acid when using phosphoric trichloride).

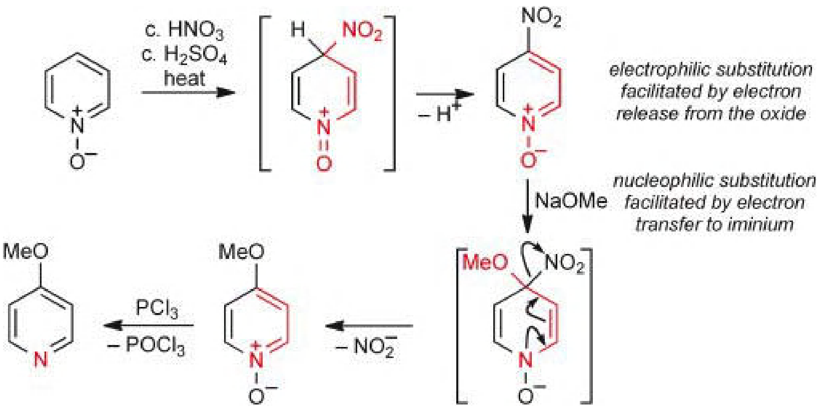


Electrophilic attack at carbonyl oxygen is also involved in the conversion of pyridones into triflates by reaction with trifluoromethanesulfonic anhydride (triflic anhydride) and a base; these derivatives are of particular interest in the context of palladium(0)-catalysed cross-couplings.

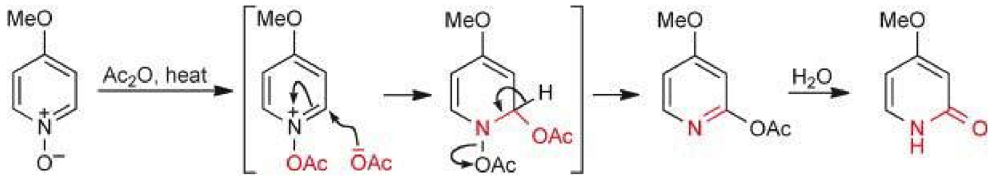


N-Oxides

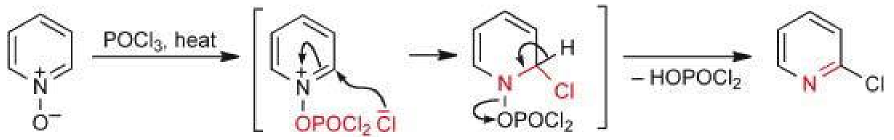
Pyridine *N*-oxides are very useful synthetic reagents, having an ambiphilic nature, that is they can react with electrophiles or nucleophiles because either the positive charge on nitrogen or the negative charge on oxygen can be delocalised to the α- or γ-positions, depending on demand from the reagent: 4-bromination and 4-nitration under standard conditions are examples of electrophilic substitution. In the sequence shown, 4-nitropyridine *N*-oxide undergoes easy nucleophilic substitution (nitrite is the leaving group). A pyridine *N*-oxide oxygen can be easily removed using a variety of reducing agents, revealing the aromatic pyridine – reaction with a trivalent phosphorus compound has often been used (see also page 33).



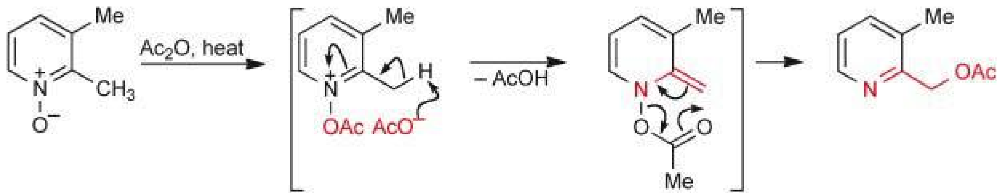
Nucleophilic additions at α-positions of pyridine *N*-oxides are often carried out under conditions where the oxygen is first acylated, enhancing the positive character of the nitrogen and the polarisation of the iminium unit. The initially formed dihydropyridine adduct undergoes re-aromatisation via a 1,2-elimination in which the oxygen substituent is lost from the nitrogen. Using 4-methoxypyridine *N*-oxide as a substrate, reaction with acetic anhydride leads to 2-acetoxy-4-methoxypyridine; such esters (of 2- and 4-hydroxypyridines) are very easily hydrolysed to reveal the corresponding pyridone – overall, an α-unsubstituted pyridine has been converted into a 2-pyridone.



Another useful process is the conversion of a pyridine, via its *N*-oxide, into a 2-halopyridine, again achieving functionalisation of an α-unsubstituted pyridine in two easy steps; the sequence shown is for pyridine *N*-oxide itself, proceeding via an adduct which finally loses phosphorodichloridic acid.

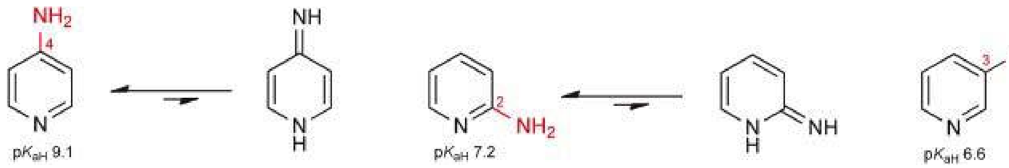


2-Methylpyridine *N*-oxides react with hot acetic anhydride and produce 2-acetoxymethylpyridines; once again electrophilic attack at the *N*-oxide oxygen initiates the sequence.

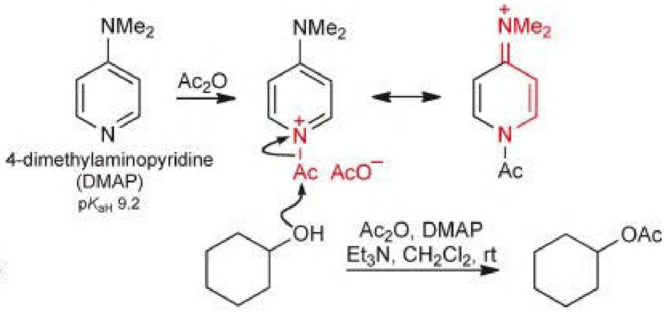


Amine substituents

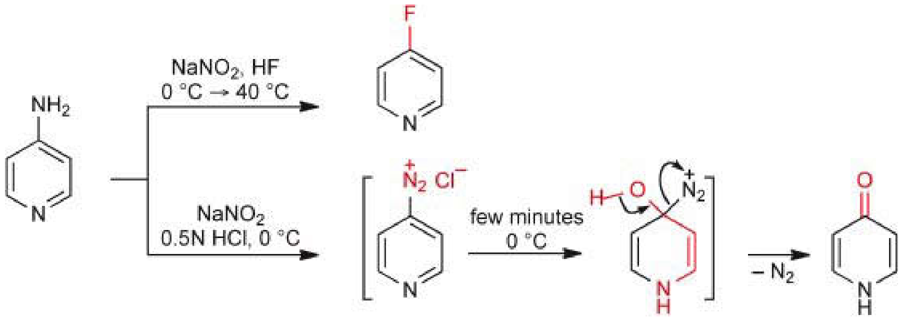
All the amino-pyridines exist in the amino tautomeric form (not the alternative imine form) and protonate on the ring nitrogen, the 2- and 4-isomers giving particularly stabilised salts due to involvement of the substituent amine lone pair in stabilising the positive charge (3-aminopyridine has a pK_{aH} of 6.6). For this reason, 4-dimethylaminopyridine (DMAP) is a very widely used nucleophilic catalyst in organic synthesis.



DMAP is used as a nucleophilic catalyst: the catalysis involves addition of an electrophile at the pyridine nitrogen, giving a pyridinium species, from where it is transferred to the nucleophile regenerating DMAP

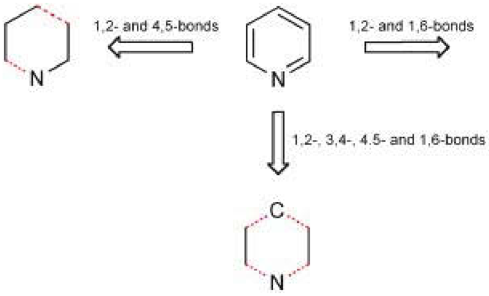


Aminopyridines undergo many standard aniline-type reactions, such as diazotisation, and the diazonium salts can be utilised for the introduction of halogen. However, care is necessary, because pyridine diazonium salts are more reactive than those from anilines, and are thus easily hydrolysed forming pyridones, as illustrated by the conversion of 4-aminopyridine, via hydrolysis of the diazonium salt, into 4-pyridone. The pyridine-2- and 4-diazonium salts are especially destabilised, having opposing electron-withdrawing systems.



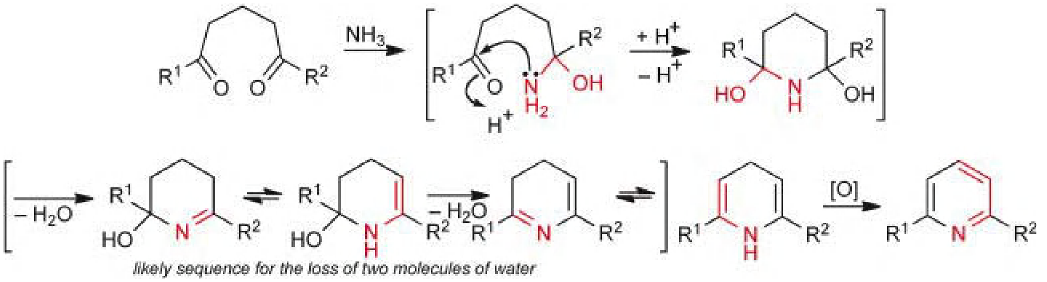
Ring synthesis – disconnections

Pyridine rings have been synthesised by many different methods, however three important disconnections for the construction of pyridines from precursors without a pyridine ring are exemplified in what follows. These are shown together with the new bonds formed in each route. Pyridine rings are also generated by various cycloaddition strategies (see pages 54, 115 and 141).



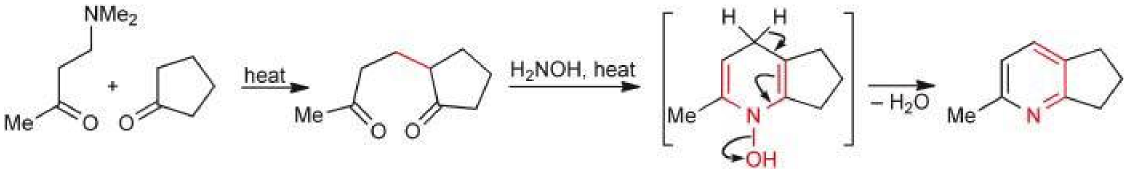
Synthesis of pyridines from 1,5-dicarbonyl compounds
(1,2- and 1,6-bonds made)

An obvious route to a pyridine involves a five-carbon unit and a source of nitrogen – in practice, the interaction of ammonia with a 1,5-dicarbonyl compound. Successive inter- and then intramolecular nucleophilic additions of ammonia/amine nitrogen to the two carbonyl groups, followed by loss of two molecules of water complete the formation of a dihydropyridine, probably a 1,4-dihydropyridine, then requiring a relatively easy oxidation to achieve the aromatic oxidation level, shown in general terms below.

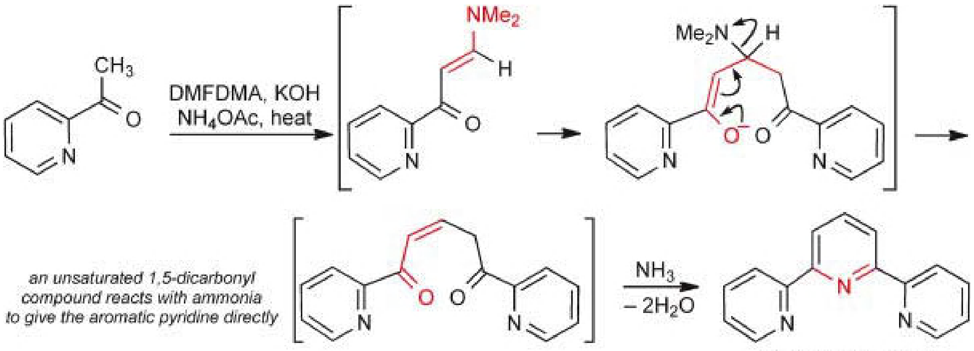


likely sequence for the loss of two molecules of water

A preferred variant of this avoids the oxidation step by the use of hydroxylamine in place of ammonia, where aromatisation of a 1,4-dihydro-1-hydroxypyridine intermediate occurs *in situ* by loss of water. 1,5-Diketones are accessible via a number of routes, for example by Michael addition of enolate to enone (or precursor Mannich base, as in the example).



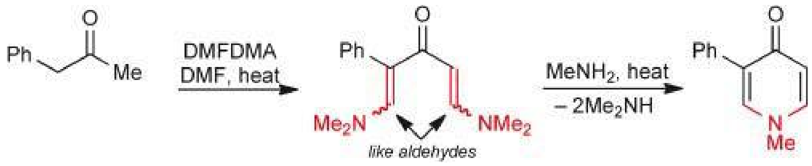
The use of an unsaturated 1,5-dicarbonyl compound will produce an aromatic pyridine directly. In a nice example, 2,2':6',2"-terpyridine can be synthesized in one pot from 2-acetylpyridine, *N,N*-dimethylformamide dimethyl acetal (DMFDMA) and ammonia; the first step is presumed to be dimethylaminomethylenation of the ketone methyl group followed then by addition/elimination by the enolate of the starting ketone.



an unsaturated 1,5-dicarbonyl compound reacts with ammonia to give the aromatic pyridine directly

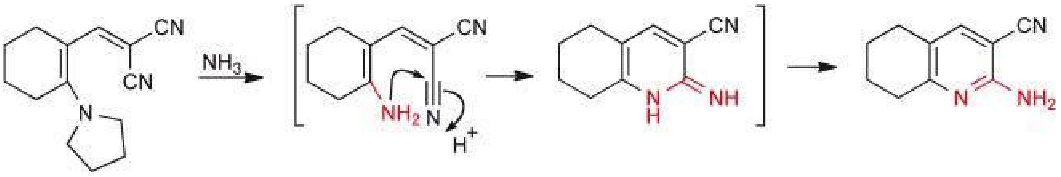
2,2':6',2"-terpyridine

Precursors with carbons at a higher oxidation level lead to a correspondingly oxidised pyridine. As an example, a dienamine, generated easily by reaction of a ketone with DMFDMA, is a synthetic equivalent of a 1,5-dialdehyde but additionally it has a high oxidation level central carbon so that when the ring closes, by reaction with methylamine, a 4-pyridone results.



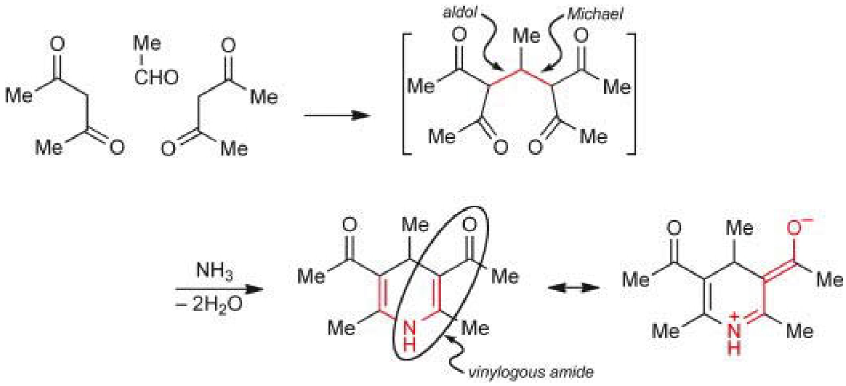
like aldehydes

When one of the 'carbonyl' groups is, instead, a nitrile, this oxidation level is reflected in the product, which will then have an amino group at an α-position. In the example shown, a pyrrolidine enamine represents the other carbonyl group and the first step is the displacement of pyrrolidine by the ammonia, via addition/elimination, ring closure then producing the 2-aminopyridine.

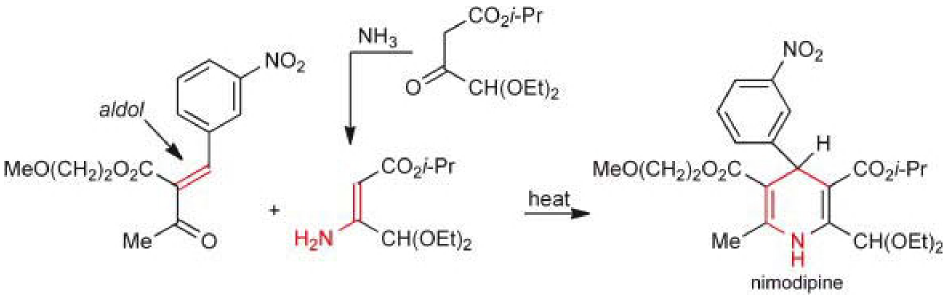


Synthesis of pyridines from an aldehyde, two equivalents of a 1,3-dicarbonyl compound and ammonia (1,2-, 3,4-, 4,5-, and 1,6-bonds made)

This is the classical *Hantzsch* pyridine *synthesis*. Two equivalents of a 1,3-dicarbonyl compound (diketone or keto-ester), and one equivalent each of an aldehyde and ammonia, are reacted together in a one-pot process. The products, which are necessarily symmetrically substituted 1,4-dihydropyridines, can be aromatised by any of a number of oxidising agents, although the dihydro-compounds themselves can be the desired products, and are stable – the conjugation of the nitrogen with the 3- and 5-carbonyl groups is responsible for the stabilisation of these dihydropyridines – they can be viewed as vinylogous amides. The exact sequence of steps involved in this synthesis is not certain, but one plausible route is that a 1,5-dicarbonyl intermediate (see above) is formed *in situ*, by successive aldol condensation and then Michael addition.

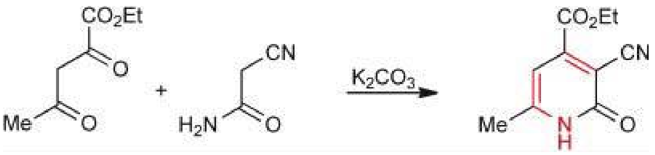


Particularly important examples of 1,4-dihydropyridines that can be prepared by this route are used as antihypertensive agents (calcium channel blockers, see page 173). The medicinal examples are not symmetrical so a modification of the sequence must be used in which an aldol condensation product from the aldehyde and one of the 1,3-dicarbonyl components is reacted with the primary enamine obtained from the other 1,3-dicarbonyl compound by its reaction with ammonia.

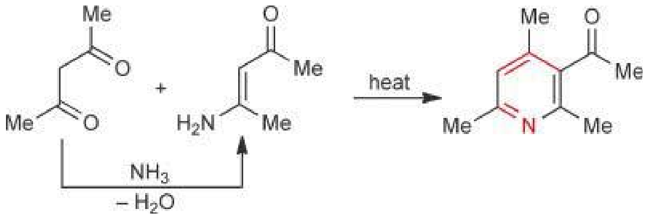


Synthesis of pyridines from 1,3-dicarbonyl compounds and a C_2N unit (3,4- and 1,6-bonds made)

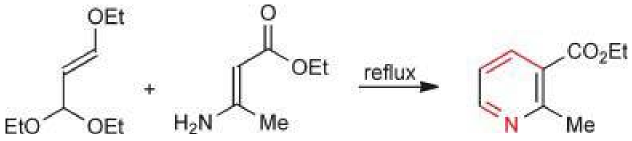
This route utilises a 1,3-diketone in reaction with a second component that provides the other two carbons *and* the nitrogen. One example of such a second component is cyanoacetamide, which leads then to a 3-cyano-2-pyridone, and this variant is referred to as the *Guareschi synthesis*. Clearly two bonds are formed, a double bond at C-3═C-4 in a formal aldol condensation, and the 1,6-bond in a formal enamine formation, though the precise order of events is not known (and may involve the enolised form of the 1,3-dicarbonyl component).



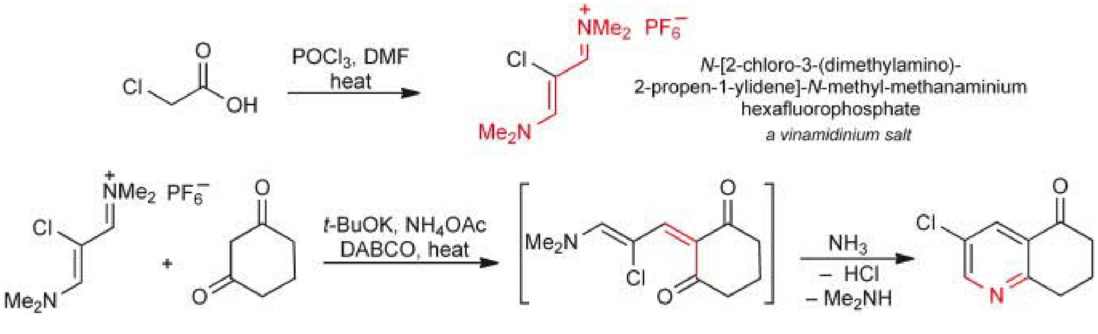
The C_2N component can also be a primary enamine derived from a 1,3-diketone; in the example, the enamine derived from pentane-2,4-dione when combined with pentane-2,4-dione gives 3-acetyl-2,4,6-trimethylpyridine.



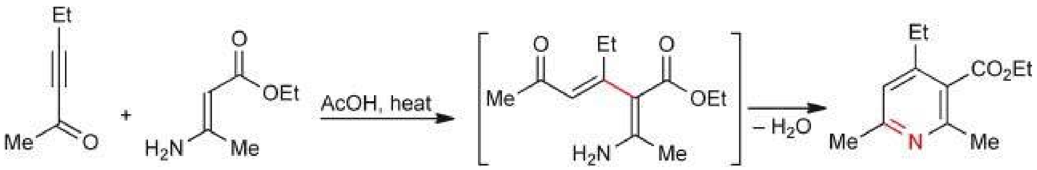
Similarly, the C_2N component can be the primary enamine derived from a 1,3-keto-ester; the next example, aimed at a 4,5,6-unsubstituted pyridine, uses 1,3,3-tri(ethoxy)prop-1-ene (the acetal enol ether of malondialdehyde) as a synthetic equivalent, because the simplest 1,3-dicarbonyl compound, malondialdehyde, is too unstable to be stored and used.



Vinamidinium salts, easily prepared from carboxylic acids RCH_2CO_2H with $POCl_3$ and DMF, serve as 2-substituted malondialdehyde equivalents.



The final variation that we deal with here is the *Bohlmann-Rahtz reaction* in which the enamino-ketone reacts with an yne-one as the 1,3-dicarbonyl equivalent. The first step is conjugate addition to the alkyne so this dictates the regiochemistry of combination.

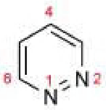


Exercises

1. What factors make it much more difficult to bring about electrophilic substitution of pyridine than benzene? At which position does electrophilic substitution take place and why?
2. Nitration of aniline is not generally possible, yet nitration of 2- and 4-aminopyridines can be achieved easily – why?
3. What are the structures of the products in the following reactions: (i) $C_7H_8N_2O_3$ produced by treating 3-ethoxypyridine with f. HNO_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 $KMnO_4$.
4. What are the structures of the compounds produced at each stage in the following sequence: 4-methylpyridine reacted with $NaNH_2 \rightarrow C_6H_8N_2$, this then 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–$(CO_2Et)_2 \rightarrow C_{11}H_{13}NO_4$?
5. Detail, with explanations, the relative reactivities of bromobenzene, 2-bromopyridine, 3-bromopyridine towards replacement of the halide with EtO on treatment with NaOEt.
6. What would result from treatment of 3-chloropyridine with LDA at low temperature?
7. What are the structures of the products in the following sequences: (i) 2-chloropyridine with LDA then iodine → C_5H_3ClNI; (ii) 3-fluoropyridine with LDA then with acetone → $C_8H_{10}FNO$; (iii) 4-(diisopropylaminocarbonyl)pyridine with LDA then with benzophenone, then with hot acid → $C_{19}H_{13}NO_2$; (iv) 2-bromopyridine with *n*-butyllithium at –78 °C then chlorotrimethylstannane (Me_3SnCl) → $C_8H_{13}NSn$.
8. What would be the result of treating a 1:1 mixture of 2- and 3-methylpyridines with 0.5 equivalents of LDA and then 0.5 equivalents of MeI?
9. A crystalline solid $C_9H_{11}BrN_2O_3$ is formed when 2-methyl-5-nitropyridine is reacted with bromoacetone. Subsequent treatment with $NaHCO_3$ gives $C_9H_8N_2O_2$ – what are the structures and what is the mechanism for the formation of the final product?
10. Suggest a structure and explanation, for the product, $C_{16}H_{22}N_2O_5$ resulting from the interaction of 4-vinylpyridine with the sodium salt of diethyl acetamidomalonate ($AcNHCNa(CO_2Et)_2$).
11. At which sites would deuterium be found when 1-butylpyridinium iodide is reduced with $NaBD_4$ in EtOH forming 1-butyl-1,2,5,6-tetrahydropyridine.
12. What pyridones would be produced from the following combinations of reactants: H_2NCOCH_2CN (cyanoacetamide) with: (i) $EtCOCH_2CO_2Et$; (ii) 2-acetylcyclohexanone; (iii) ethyl propiolate?
13. When the sodium salt of formyl acetone ($MeCOCH{=}CHO^- Na^+$) is treated with ammonia, a pyridine, C_8H_9NO is formed – what is its structure?
14. 2,3-Dihydrofuran reacts with acrolein to give an adduct $C_7H_{10}O_2$; reaction of this with aq. H_2NOH–HCl gives a pyridine, C_7H_9NO; what is its structure?

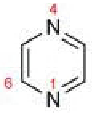
6

Diazines

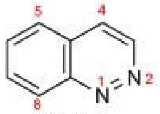


pyridazine
pK_{aH} 2.3

pyrimidine
pK_{aH} 1.3

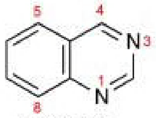


pyrazine
pK_{aH} 0.65

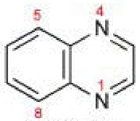


cinnoline

phthalazine



quinazoline

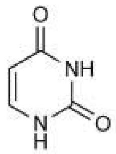


quinoxaline

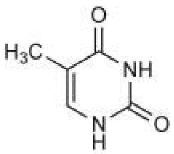
The diazines – pyridazine, pyrimidine and pyrazine – show many similarities to pyridines with respect to their reactivities, but to an exaggerated degree. In particular, the presence of two nitrogens, both as imines, results in increased electron deficiency at carbon and hence an increased susceptibility to nucleophilic addition but an increased resistance to electrophilic attack.

As is also the case for the purines (Chapter 13), there has been emphasis on the study of amino- and oxy-pyrimidines (uracil, thymine and cytosine) due to their importance as constituents of the nucleic acids DNA and RNA (see pages 163–164), where they occur in nucleotide polymers. These three pyrimidines, and their nucleosides, can be isolated from some natural sources, but they are readily available in quantity via fermentation (with or without further chemical modification) or direct chemical synthesis – uracil in particular, as would be expected for this simple compound, is very cheap.

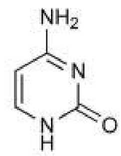
It should be noted that 2- and 4-amino-pyrimidines exist as the amino tautomers; 2- and 4-oxy-pyrimidines exist as carbonyl tautomers. These tautomeric preferences are essential for their role in DNA, where hydrogen bonding holds the two chains of the double helix together (see page 164).



uracil
RNA only



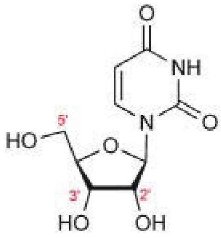
thymine
DNA only



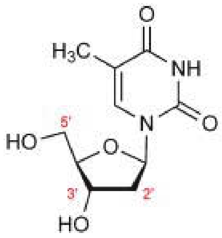
cytosine
DNA and RNA

pyrimidine nucleic acid bases
and their nucleoside derivatives:
a nucleotide is a nucleoside
carrying a phosphate on the
5' (or 3') OH

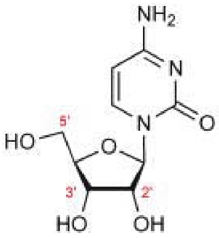
RNA contains ribosides
DNA contains deoxyribosides



uridine
a riboside



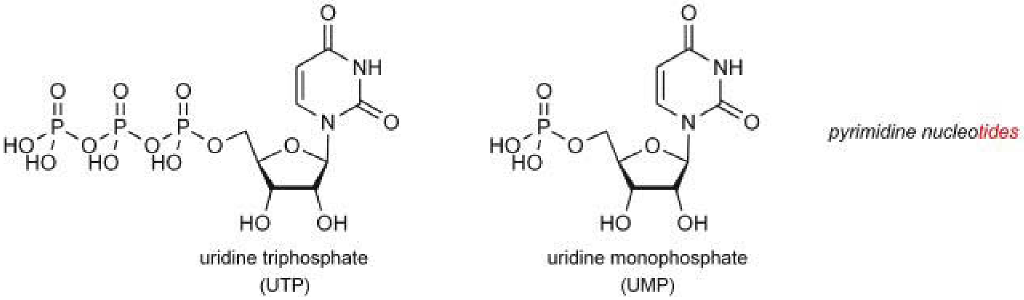
thymidine
a deoxyriboside



cytidine

pyrimidine nucleosides

Heterocyclic Chemistry at a Glance, Second Edition. John A. Joule and Keith Mills.

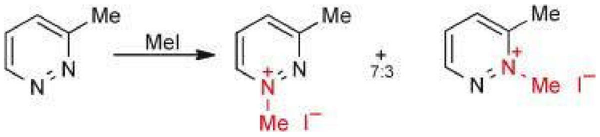


Unlike the purines, these pyrimidine bases and their nucleosides and nucleotides generally do not have a great deal of biological significance outside of their participation in nucleic acids. However, an exception is uridine di/triphosphate, which has a key role in glucose metabolism and the biosynthesis of glycogen. Pyrazines have widespread natural occurrences, in low concentrations (see Food and Drink, page 186), but pyridazines are rare in nature.

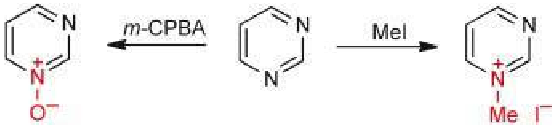
Electrophilic addition to nitrogen

The inductive and mesomeric effects of the second nitrogen lead to a considerable reduction in the basicity of the parent diazines relative to pyridine (pK_{aH} 5.2). However, secondary effects result in a different order of basicity between the individual diazines than would be predicted based simply on induction. In particular, destabilising interactions between the adjacent nitrogen lone pairs in pyridazine lead to a relatively higher basicity. Only in very strong acid can a proton be added to both nitrogens, giving doubly protonated salts.

The diazines react with alkyl halides to give quaternary salts, although somewhat less readily than does pyridine. Pyridazine is the most reactive. Steric hindrance by substituents adjacent to ring nitrogens generally governs regioselectivity.

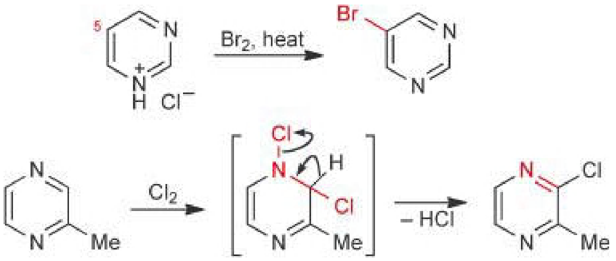


All three diazines react with peracids to give *N*-oxides, but less acidic conditions are required for pyrimidine, due to the susceptibility of pyrimidine *N*-oxide to acid-catalysed decomposition.

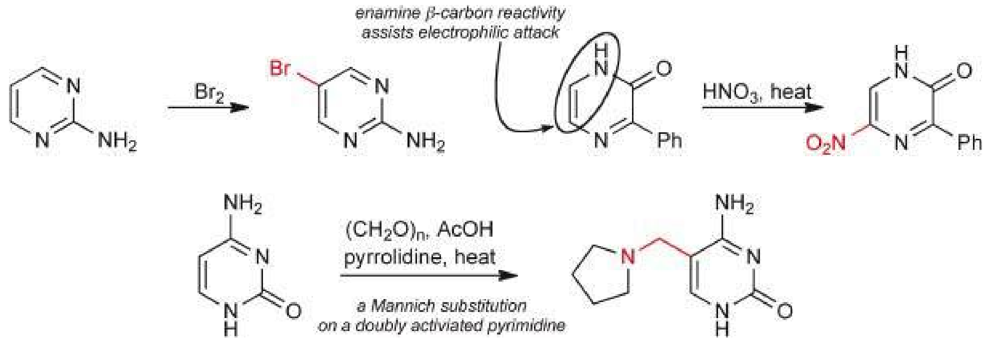


Electrophilic substitution at carbon

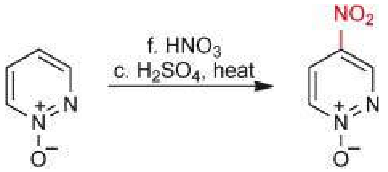
Direct electrophilic attack at carbon in simple diazines is unusual. Pyrimidine can be brominated under conditions similar to those required for pyridine, reaction occurring at the 5-position – the *only* position that is not α or γ to nitrogen and therefore equivalent to a β-position in pyridine – in fact it is the only such position in any diazine. Chlorination of 2-methylpyrazine occurs under such mild conditions that some mechanism other than a classical aromatic electrophilic substitution must be involved: addition of chlorine across the 3,4-imine unit, initiated by electrophilic attack on nitrogen, then loss of hydrogen chloride, is the most likely sequence.



The amino-diazines, benefiting from activation by the electron-releasing substituent, generally undergo electrophilic substitution under normal conditions. Oxy-diazines are similarly activated for electrophilic substitution but this probably owes more to the enamine-like system present in the keto-tautomer, which allows electron donation from the ring nitrogen. With two activating groups, even mild electrophiles can bring about substitution.

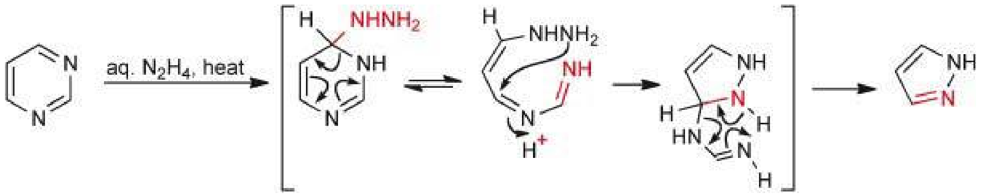


N-Oxides are also useful substrates for electrophilic substitution, another parallel to the chemistry of pyridines.



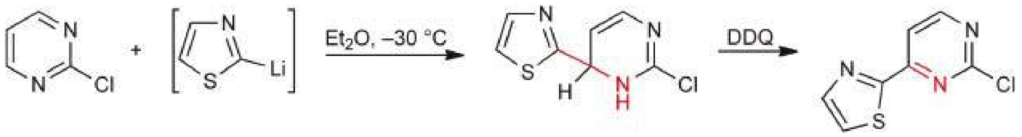
Nucleophilic substitution

The simple diazines are much more susceptible to nucleophilic attack than is pyridine. Pyrimidine, for example, is decomposed by hot aqueous alkali due to attack by hydroxide. Pyrimidine also reacts cleanly with hydrazine to give pyrazole as the result of an ANRORC sequence (Addition of Nucleophile Ring Opening Ring Closure).

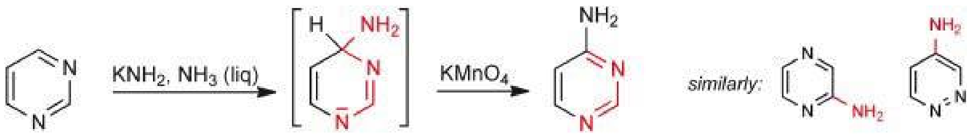


Substitution of hydrogen

All three diazines undergo ready addition of Grignard reagents and alkyl- and aryllithiums, at the carbon of one of the imine units, to give dihydro-intermediates that can be easily re-aromatised, the overall effect being nucleophilic substitution of hydrogen. This reaction is particularly useful for chlorodiazines and it is notable that attack occurs at a carbon that does *not* bear a halogen. (This should be contrasted with attack by soft nucleophiles (see below).)

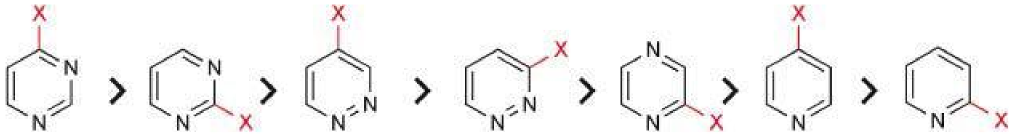


Amination can be achieved efficiently – amide anion adds easily (but reversibly) to the diazines but, in contrast to the Chichibabin reaction of pyridines, the presence of an oxidant is required for the final aromatisation.



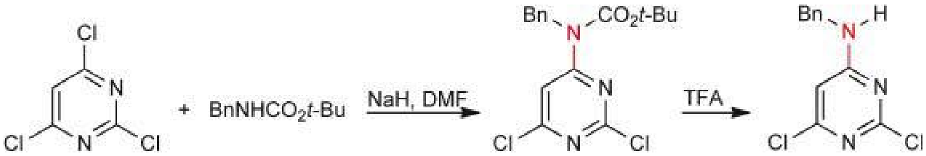
Substitution of leaving groups

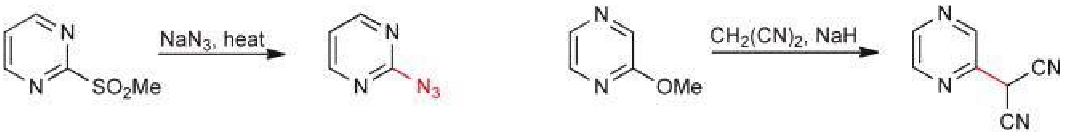
The nucleophilic displacement of halogen and other leaving groups by 'soft' nucleophiles (amines, thiols, alkoxides, enolates) is a very important method for manipulation of diazines. Only 5-halopyrimidines, in analogy to 3-halopyridines, are resistant. The relative reactivities are summarised below – all halodiazines (except 5-halopyrimidines) are more reactive than the corresponding pyridine halide.



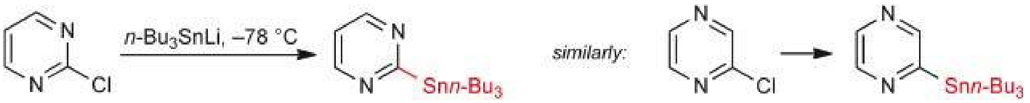
relative order of reactivity towards nucleophilic displacement (X = halogen)

Chlorine is the most commonly used leaving group but sulfones are also very useful and even methoxy groups can be displaced in these highly reactive systems. The use of the sodium salts of carbamates as nucleophiles gives good 4-selectivity in 2,4,6-trichloropyrimidines.

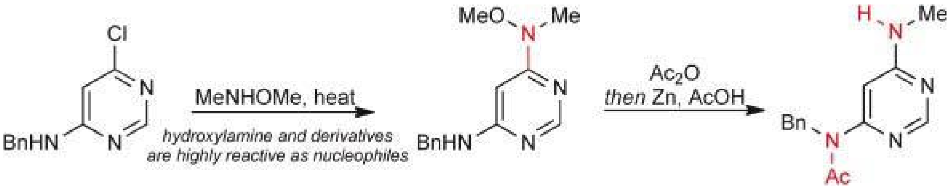




Stannanes can be prepared via nucleophilic displacements at low temperature.

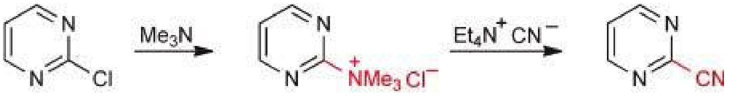


An important point to remember is that the presence on the ring of an electron-donating group, particularly an amino group, greatly reduces the reactivity of a halide. This means that clean mono-substitution in dihalo-compounds is easy if the first displacement introduces an electron-releasing group, but also that special methods may be necessary to achieve displacement of the second halide, such as the use of 'supernucleophiles'. Hydroxylamines are very reactive nucleophiles and, as the N–O bond in the products can be hydrogenolysed, nucleophilic substitution with a hydroxylamine provides a means for the introduction of (a second) amine.



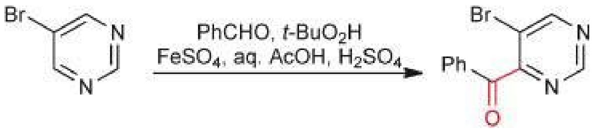
hydroxylamine and derivatives are highly reactive as nucleophiles

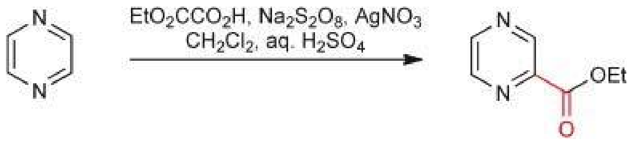
A device used to enhance reactivity, which is also used in pyridine and purine chemistry, is the initial replacement of halogen with a tertiary amine, the resulting salt, now having a better leaving group for carbon nucleophiles, undergoes substitution more easily.



Radical substitution

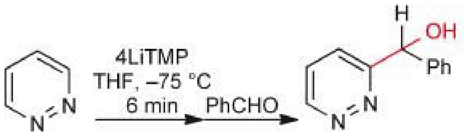
The Minisci reaction (page 14) is particularly useful in the diazines because there are many situations where good regioselectivity can be achieved.



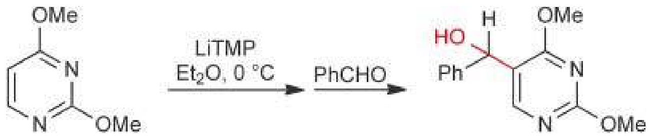


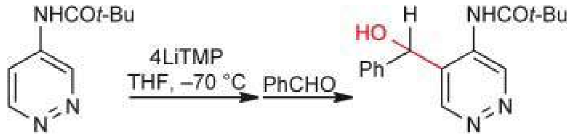
C-Metallated diazines

Diazines undergo nucleophilic *addition* with many standard lithiating agents, however metallation and metal–halogen exchange *can* be carried out, but require carefully controlled conditions, normally very low temperatures and a hindered base (lithium tetramethylpiperidide; LiTMP), for deprotonations. The three parent diazines can be lithiated adjacent to nitrogen (for pyrimidine at C-4, not C-2) and moderate to good yields of trapped products can be obtained either by using very short lithiation times or by *in situ* trapping where the electrophile is added *before* the metallating agent.

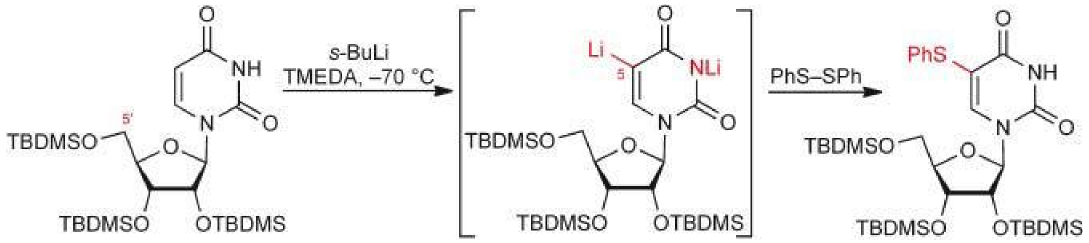


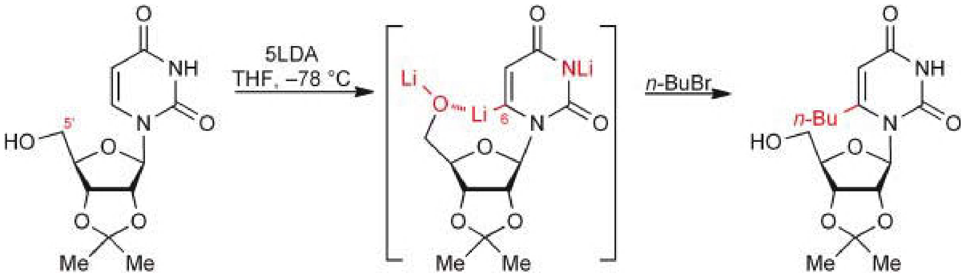
Lithiation of diazines with *ortho*-directing groups is straightforward and this strategy is used widely, for example, 2,4-dimethoxypyrimidine (a masked uracil) is lithiated at C-5 by LiTMP.



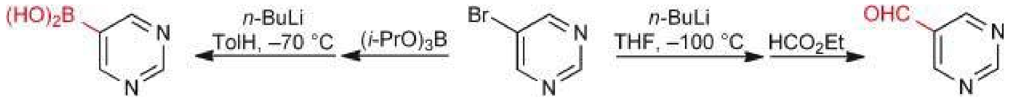


Metallation of pyrimidine-diones in nucleosides may not require protection of acidic *N*-hydrogen, the use of excess lithiating agent being sufficient. This is a particularly useful technique for ribosides, where the regioselectivity of the reaction (C-5 versus C-6) can be controlled by the presence or absence of a protecting group on the 5'-hydroxy group.

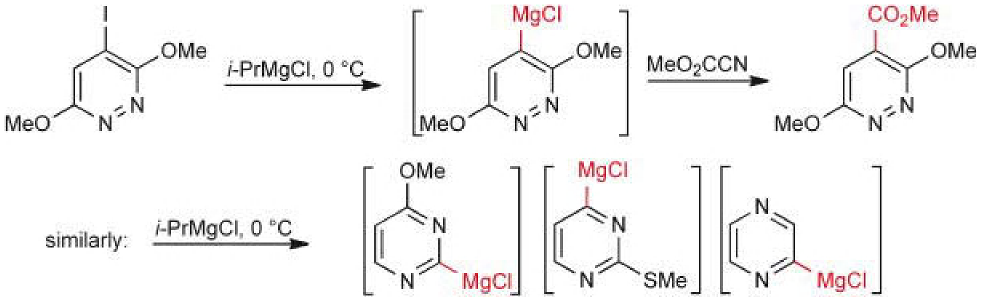




Lithiodiazines are also accessible via halogen exchange with alkyllithiums. The examples show how 5-bromopyrimidine can be converted into 5-substituted derivatives using either a very low temperature, or by adding the electrophile *before* the *n*-butyllithium so that the 5-lithiopyrimidine is trapped as soon as it is formed.

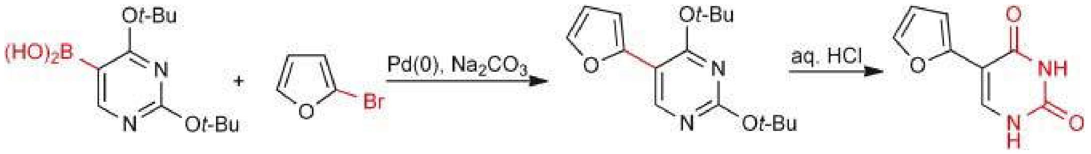


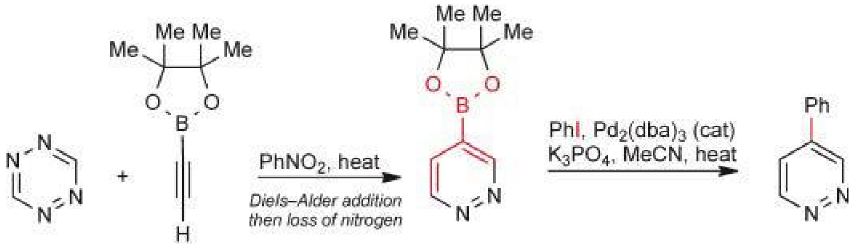
Diazine Grignard reagents can be obtained and used without the need for very low temperatures; diazine zinc compounds can be obtained by exchange of lithium compounds (see next section).

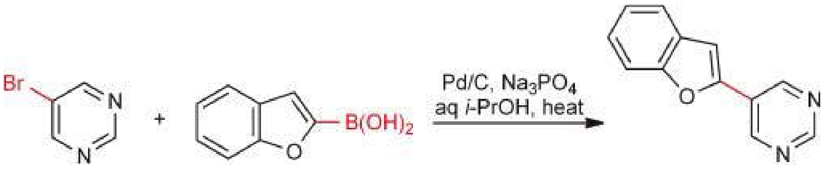


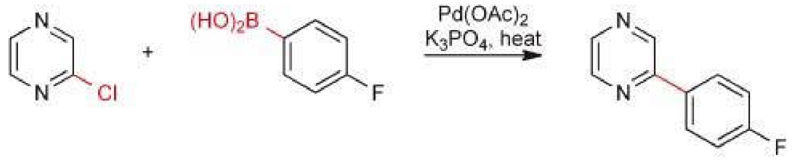
Palladium(0)-catalysed reactions

Boronic acids (or boronate esters) and stannanes of all the parent diazines and at all positions are known, pyrimidine-2- and -5-boronic acids, and pyridazine-4-boronic acids finding particular use. 2,4,6-Trichloropyrimidine can be used as a substrate for clean sequential Suzuki couplings: C-4, then C-6, then C-2. Some typical examples are given below.

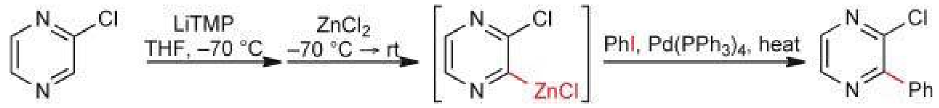


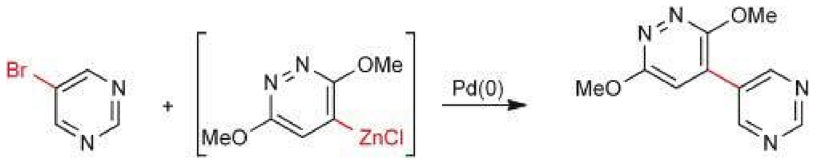


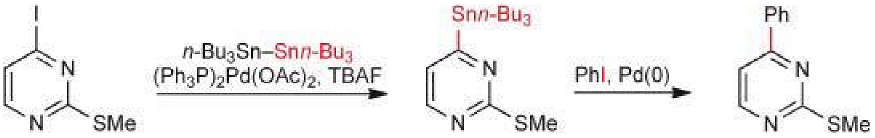




Negishi cross-couplings with organozinc reagents and Stille reactions with stannanes, prepared by various means, have been utilised in the diazine series.

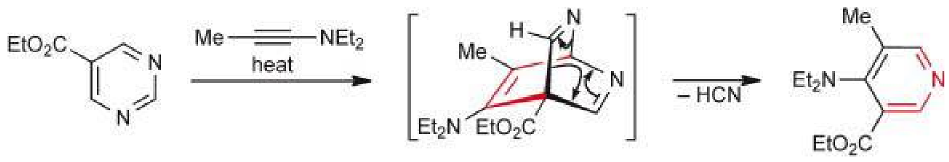


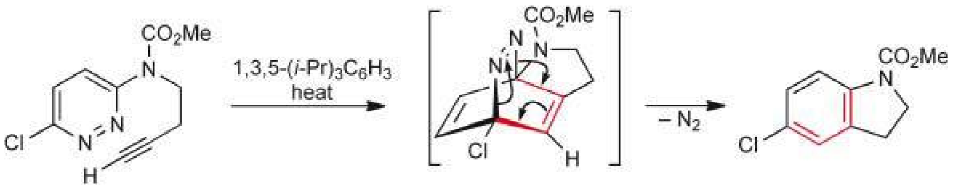




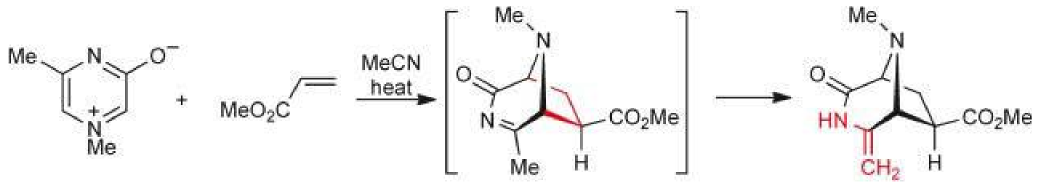
Pericyclic reactions

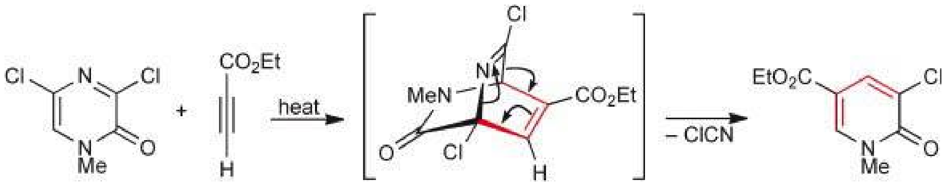
All the diazines, providing they also have electron-withdrawing substituents, undergo Inverse Electron Demand Diels–Alder (IEDDA) additions with dienophiles, the 'inverse-electron-demand' relating to the fact that in 'normal' Diels–Alder reactions the diene component is electron-rich. Intramolecular reactions occur the most readily, and even in the absence of activating substituents. The immediate products of such processes usually lose nitrogen (pyridazine adducts) or hydrogen cyanide (adducts from pyrimidines and pyrazines) to generate benzene and pyridine products, indeed this can be viewed as a means for the ring synthesis of pyridines.



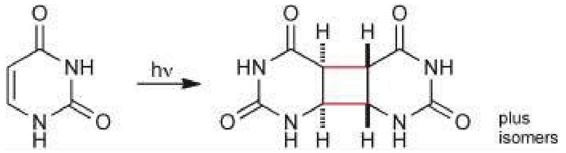


Mesoionic pyrazinium-3-olates undergo cycloadditions similar to those known for pyridinium-3-olates (page 40) and pyrylium-3-olates (page 73). 3,5-Dihalo-2(1*H*)-pyrazinones and their derivatives also undergo cycloadditions, followed by cycloreversions to give pyridones.



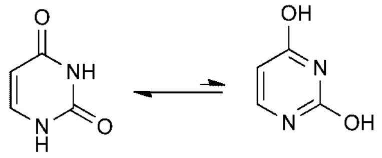


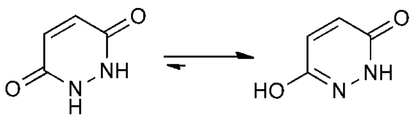
The photocatalysed dimerisation of uracil may have relevance to mutagenesis mechanisms.

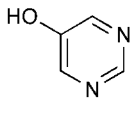


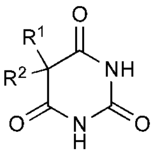
Oxygen substituents (see also pages 48 and 164)

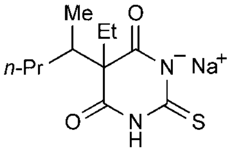
The majority of oxydiazines exist in the keto form and are named as such – diazinones. Notable exceptions are the phenol-like 5-hydroxypyrimidine and 6-hydroxypyridazin-3(2*H*)-one ('maleic hydrazide'). The latter exists as the mono-keto-mono-hydroxy form, thus avoiding the unfavourable juxtaposition of like charges on nitrogen (due to amide mesomerism) in the dicarbonyl form. The family of 5,5-dialkylated drugs known as 'barbiturates' exist necessarily as tricarbonyl structures, but so does the parent, unsubstituted barbituric acid.


uracil


6-hydroxypyridazin-3(2*H*)-one
('maleic hydrazide')

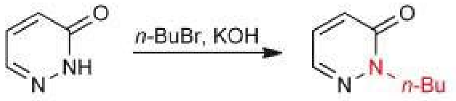

5-hydroxypyrimidine

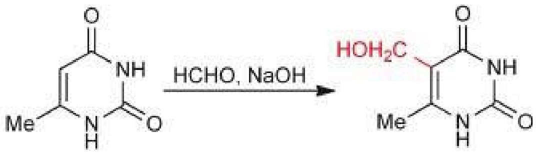

barbiturates
R^1=R^2=H = barbituric acid


sodium pentothal
short-acting anaesthetic

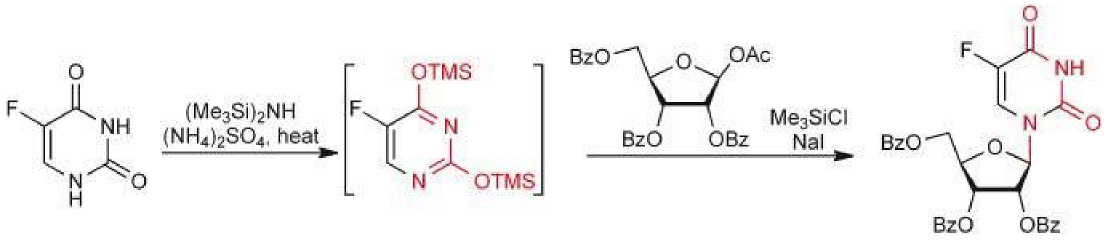
N-Deprotonation, *N*-alkylation and *N*-arylation

As with pyridones, diazinones are relatively acidic and can be N–H-deprotonated under mild conditions, the resulting anions reacting with electrophiles on either nitrogen (usually), oxygen or carbon.

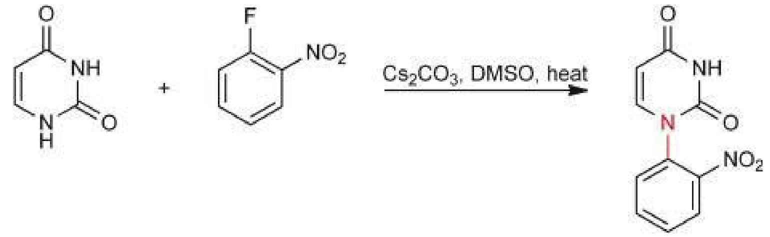


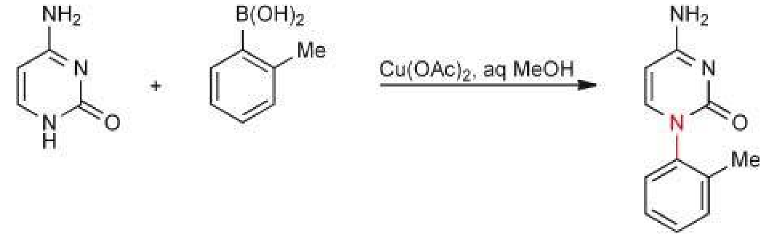


N-Alkylation of *O*-silylated derivatives is an important method for unambiguous *N*-alkylation, especially for ribosylation of uracils.



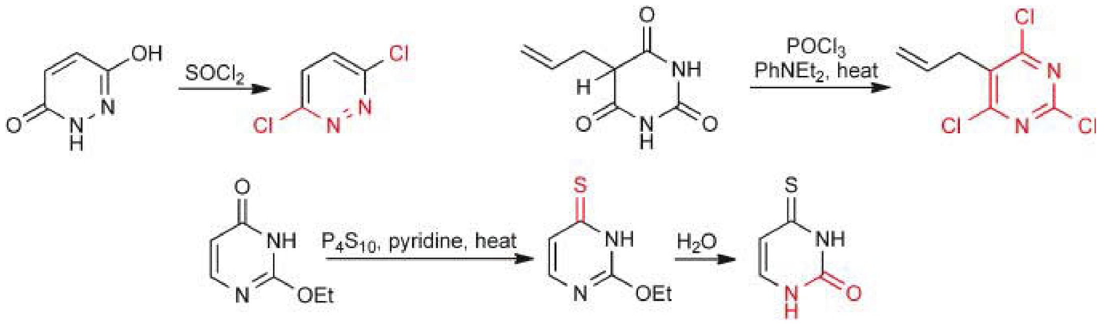
N-Arylation can be achieved either using base with a reactive aryl halide or by copper-catalysed reaction with either a boronic acid or (unactivated) aryl halide.





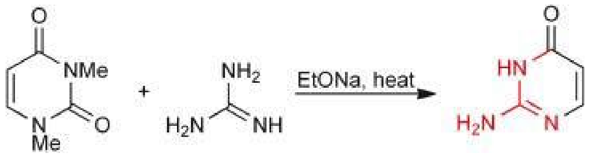
Replacement of oxygen

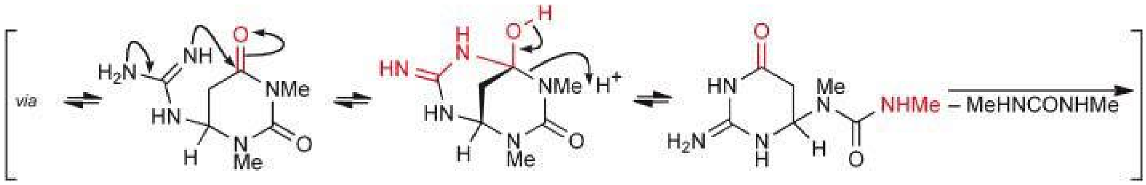
The diazinones are the best sources of the synthetically versatile halo-diazines, by reaction with thionyl choride or phosphoric trichloride ($POCl_3$). Thiones can also be prepared by direct replacement of oxygen using phosphorus sulfides.



Nucleophilic addition

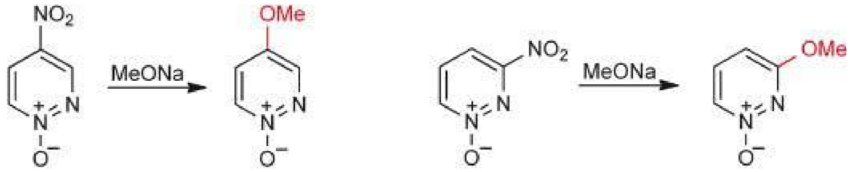
An interesting and useful example involving nucleophilic addition to the uracil ring is the reaction of 1,3-dimethyluracil with double nucleophiles such as guanidines, which results in replacement of three ring atoms (N–CO–N).



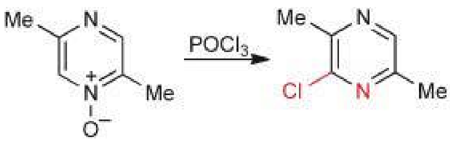


N-Oxides (see also page 49)

Nucleophilic displacement of nitro at C-3 in pyridazine *N*-oxides (i.e. β to an *N*-oxide function), occurs about as readily as that of a γ-nitro group and faster than for the corresponding base.

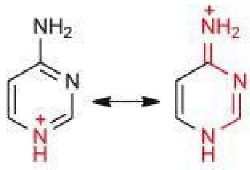


Nucleophilic substitutions by halide, cyanide and carbon nucleophiles such as enamines and acetate (by reaction with acetic anhydride), with concomitant loss of the oxide function, occur smoothly in all three systems, though the site of introduction of the nucleophile is not always that (α to the *N*-oxide) predicted by analogy with pyridine chemistry.

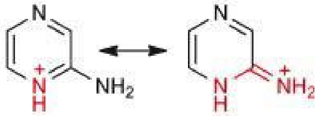


Amine substtuents (see also pages 48 and 164)

Aminodiazines show a strong analogy to aminopyridines and similarly exist in the amino tautomeric form. They are stronger bases than the parent heterocycles, protonation and quaternisation occurring on the ring nitrogen.

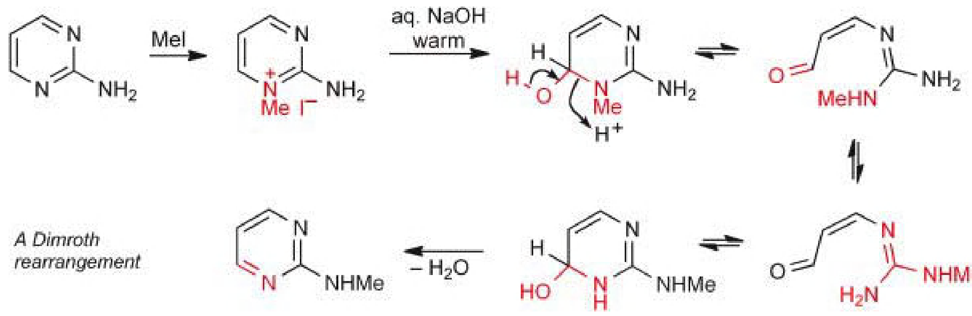


pK_{aH} 5.7



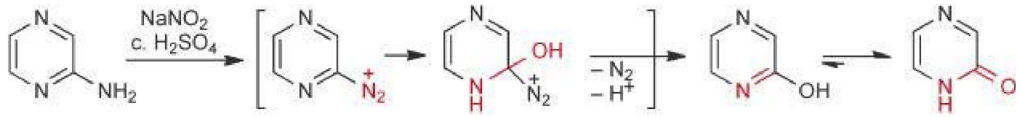
pK_{aH} 3.1

The alkali-promoted rearrangement of quaternary salts derived from 2-aminopyrimidine is an example of the *Dimroth rearrangement* – where the ring nitrogen and the side-chain nitrogen swap places (another ANRORC sequence). The larger the substituent on the positively charged ring nitrogen, the more rapidly the rearrangement proceeds, as a result of the consequent relief in strain between the substituent and the adjacent amino group.



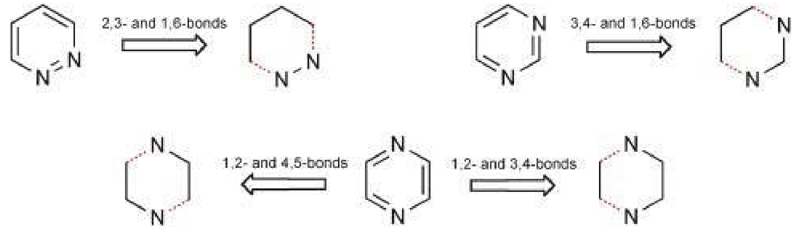
A Dimroth rearrangement

Diazine diazonium salts are even less stable than those in the pyridine series and are only synthetically useful for the conversion of amino-diazines into diazinones.



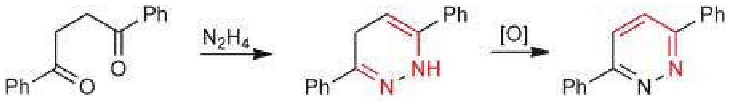
Ring synthesis – disconnections

Only the most frequently used routes are discussed here. The disconnections for pyridazines, pyrimidines and pyrazines are shown together with the new bonds formed in each route. Pyrimidines can also be prepared via cycloaddition reactions on 1,3,5-triazines (see page 141) and pyridazines via cycloaddition reactions with 1,2,4-triazines or 1,2,4,5-tetrazines (see page 141).

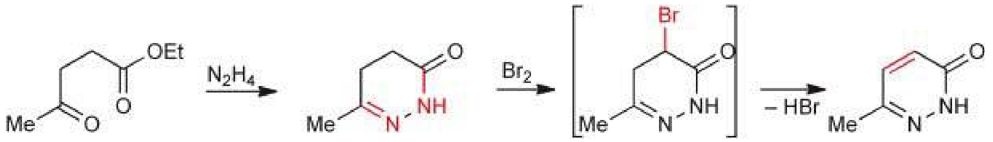


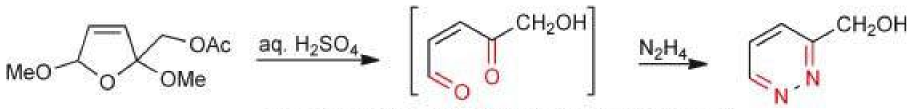
Synthesis of pyridazines from 1,4-dicarbonyl compounds
(2,3- and 1,6-bonds made)

Pyridazines are most commonly prepared by condensation of 1,4-dicarbonyl compounds with hydrazine. When a saturated 1,4-dicarbonyl component is used, there has to be a final oxidative step to bring about aromatisation. A preferred option is the use of a dicarbonyl component already having a carbon–carbon double bond located between the carbonyl groups; this leads to a fully aromatic pyridazine directly.



reaction with a 1,4-dicarbonyl compound gives a dihydropyridazine, requiring dehydrogenation

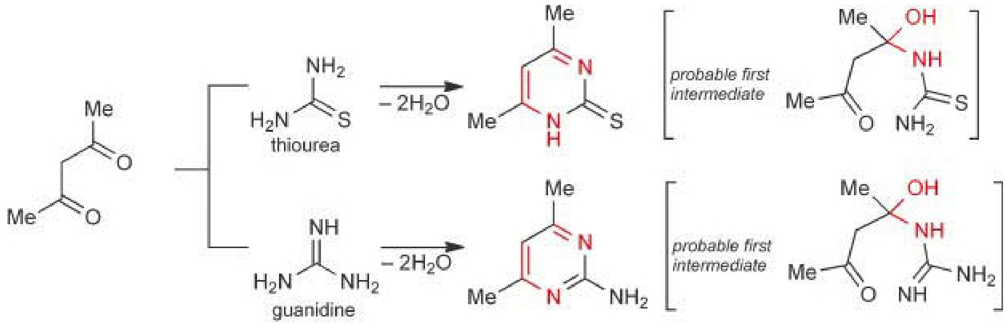




use of an ene-dione leads directly to aromatic oxidation level

Synthesis of pyrimidines from 1,3-dicarbonyl compounds
(3,4- and 1,6-bonds made)

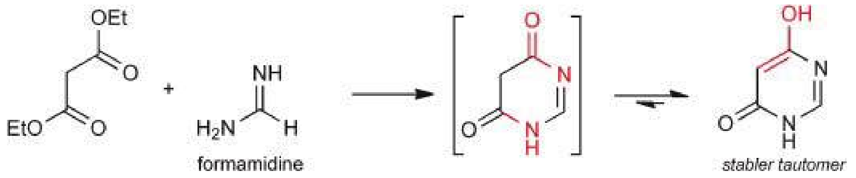
Pyrimidines can be prepared by condensation of a 1,3-dicarbonyl compound with an N–C–N unit, usually a urea, thiourea, amidine RC(=NH)NH$_2$, or guanidine RHNC(=NH)NH$_2$. The urea products have a 2-carbonyl (thiocarbonyl), the amidine products have a 2-R substitutent and the guanidine products have a 2-RHN substituent. These cyclocondensations must start with an amino-to-carbonyl addition (or amino-to-carbon of the enolised form of the 1,3-dicarbonyl system) but one cannot say in which order the subsequent bonds are made and eliminations of water occur.



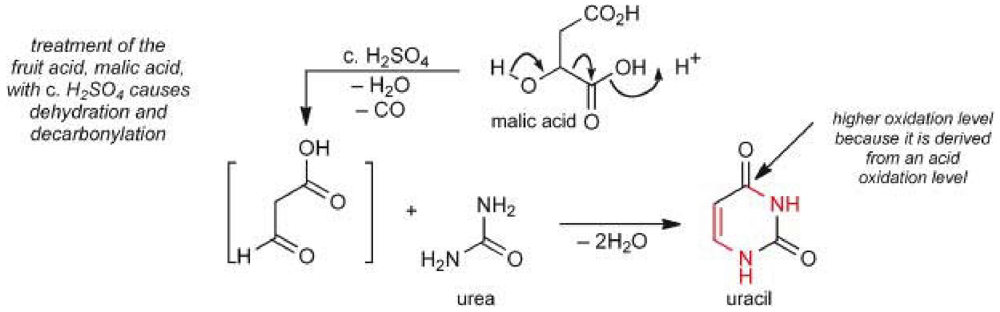
probable first intermediate

probable first intermediate

With regard to the 1,3-dicarbonyl unit, when a carbonyl is at the acid/ester oxidation level, oxygenated pyrimidines result. The use of a nitrile in lieu of a carbonyl leads to amino-pyrimidines.

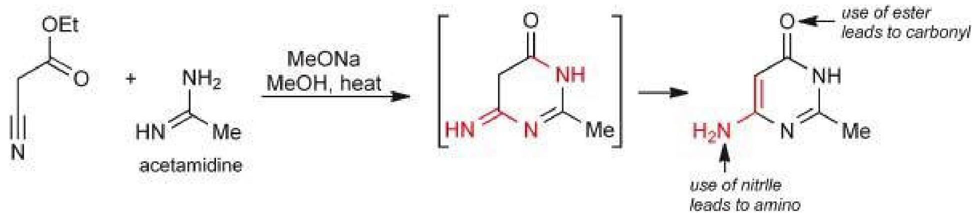


stabler tautomer



treatment of the fruit acid, malic acid, with c. H_2SO_4 causes dehydration and decarbonylation

higher oxidation level because it is derived from an acid oxidation level



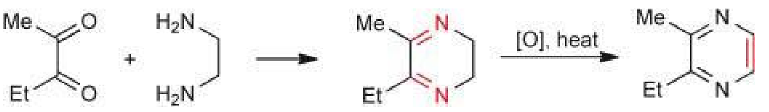
use of ester leads to carbonyl

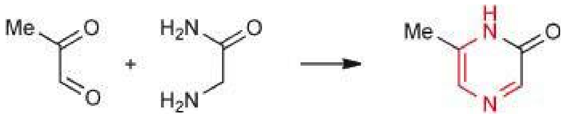
use of nitrile leads to amino

Synthesis of pyrazines from 1,2-dicarbonyl compounds

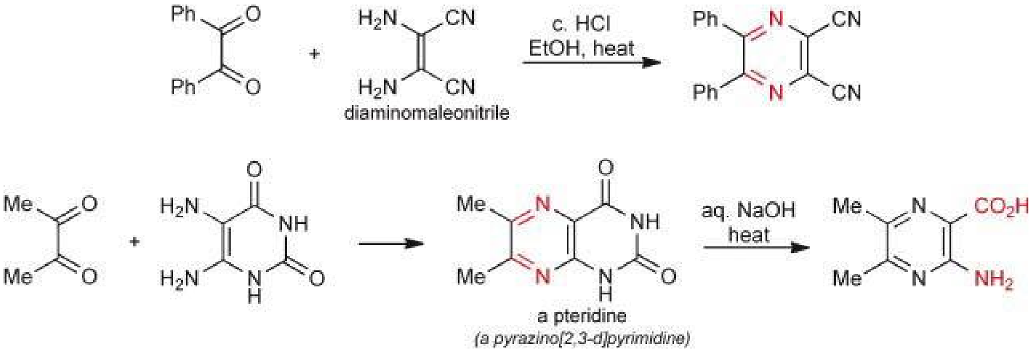
(4,5- and 1,6-bonds made)

Pyrazines are usually prepared via condensation reactions of 1,2-dicarbonyl compounds with 1,2-diamines. When saturated diamines are used, an additional oxidation (aromatisation) step is required. Aromatisation is not necessary when one of the amines is an amide, the resulting product being a pyrazinone.





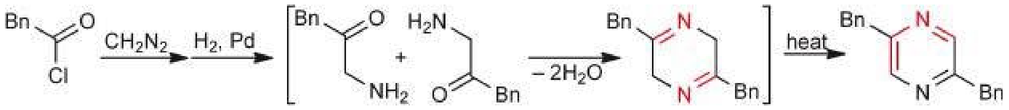
Unsaturated 1,2-diamines (ene-diamines), where an aromatisation step would not be needed, are generally not stable, one exception being diaminomaleonitrile. 5,6-Diaminouracil can be used as a stable masked ene-diamine, a final hydrolysis revealing a 3-aminopyrazine-2-carboxylic acid. (Note: The intermediate bicyclic compound is a 'pteridine' – the pteridine ring system is present in a number of important natural products (pages 159–160). Pteridines show the expected reactivity for the individual diazine rings and can be prepared using standard pyrazine or pyrimidine ring syntheses, as in the example.)



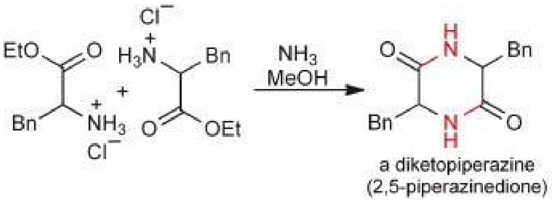
Synthesis of pyrazines from α-amino-carbonyl compounds

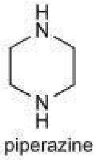
(1,2- and 4,5-bonds made)

α-Amino-ketones, which are stable only as their salts, are usually prepared *in situ* by the reduction of 2-diazo-, -oximino- or -azido-ketones. Self-condensations of such amino-ketones give symmetrically substituted dihydropyrazines that are very easily aromatised, sometimes just by heating. (Similar processes also occur in nature and during cooking (see pages 186–187).)



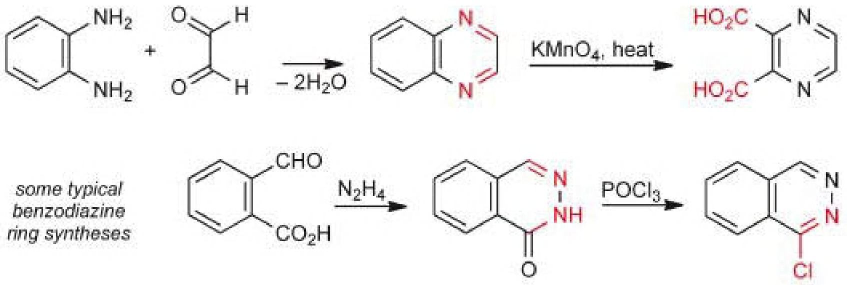
α-Amino-esters are more stable than α-amino-ketones but nonetheless easily self-condense to give stable heterocycles, generally known as 2,5-diketopiperazines (a misleading name as the carbonyl groups are amide not ketone carbonyls). Hexahydropyrazine is called piperazine.

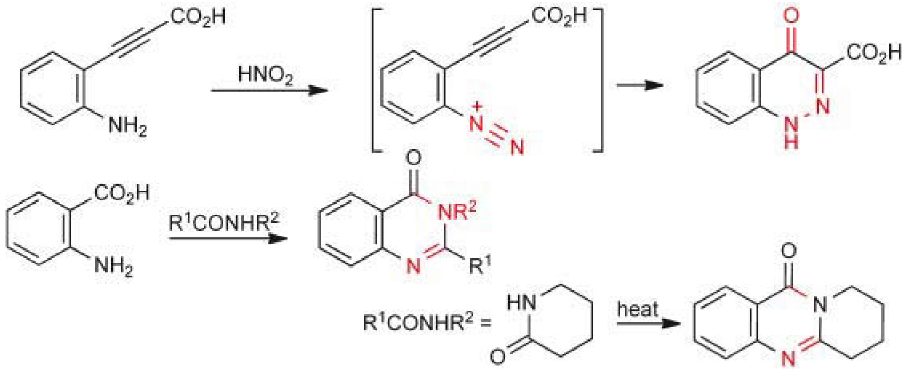




Benzodiazines

Reactions in the heterocyclic ring are principally electrophilic additions on nitrogen and nucleophilic addition to carbon (there are no pyridine-like β-carbon positions), with an increase in reactivity comparable to the pyridine–quinoline/isoquinoline relationship. The heterocyclic rings are resistant to oxidation and the heterocyclic core is retained on strong oxidation.



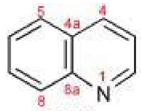


Exercises

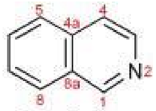
1. How could one convert an oxydiazine, where the oxygen is α to a nitrogen, into (i) a corresponding chlorodiazine and (ii) efficiently into a corresponding *N*-methyldiazin-2-one?
2. How could one transform pyrimidine, in two steps, into pyrimidin-4-one?
3. How could one transform pyrimidine-2-thione, in three steps, into 2-azidopyrimidine?
4. What are the structures of the compounds formed: (i) $C_6H_9IN_2S$ from 3-methylthiopyridazine with MeI; (ii) $C_6H_8ClIN_2$ from 3-chloro-6-methylpyridazine, with MeI; and (iii) $C_5H_2Cl_2N_2O$ from treatment of 2,6-dichloropyrazine with LiTMP then HCO_2Et?
5. What are products in the following ring syntheses:
   - (i) chlorobenzene reacted with succinic anhydride–$AlCl_3$ ($\rightarrow C_{10}H_9ClO_3$), then this product reacted 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 product firstly treated with aqueous acid and then hydrazine ($\rightarrow C_6H_8N_2$);
   - (iii) 4,4-dimethoxybutan-2-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) $PhCOCH_2CO_2Et$ with $EtC(=NH)NH_2$ ($\rightarrow C_{12}H_{12}N_2O$);
   - (ix) PhCOCHO with $MeCH(NH_2)CONH_2$ ($\rightarrow C_{11}H_{10}N_2O$).

7

Quinolines and Isoquinolines



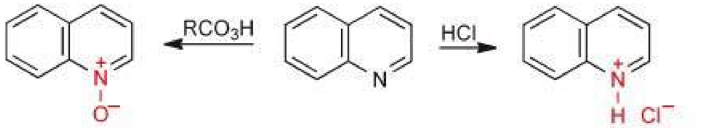
quinoline
pK_{aH} 4.9



isoquinoline
pK_{aH} 5.4

Electrophilic addition to nitrogen

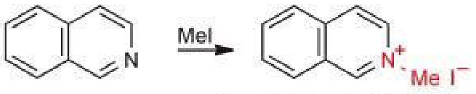
Most of the chemistry of quinoline parallels that of isoquinoline so in this chapter we use examples from each series, more or less randomly. The benzene rings and the pyridine rings of quinoline and isoquinoline each display the reactivity typical of these monocyclic systems, but modified, in some cases, by the presence of the other ring. Thus, in processes exactly like those for pyridine, electrophiles *add* to the heterocyclic nitrogen – reaction with acids or electrophilic halides gives quinolinium and isoquinolinium salts, or with peracids, *N*-oxides.



quinoline *N*-oxide

1*H*-quinolinium chloride
(quinoline hydrochloride)

addition of electrophiles
to the ring nitrogen
of quinolines and isoquinolines
is very easy



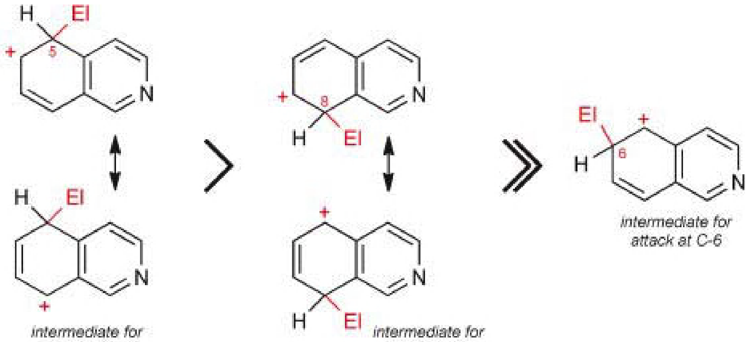
2-methylisoquinolinium iodide

Electrophilic substitution at carbon

As we reminded ourselves (pages 10–11), electrophilic substitution is *the* typical reaction of benzene compounds. We also learnt that pyridines, without activating substituents, are *very* resistant to electrophilic *C*-substitution (pages 12 and 34). In quinolines and isoquinolines, then, it is no surprise that standard electrophilic substitutions occur exclusively on the benzene ring. Further, and recalling the propensity for naphthalene to be attacked most rapidly at the 1-position, such electrophilic substitutions of quinolines and isoquinolines take place only at the 5- and 8-positions. It is important to realise that these substitutions probably involve attack on quinolinium and isoquinolinium cations.

electrophilic substitution
of quinolines and isoquinolines
proceeds in the benzene ring

positional selectivity in
electrophilic substitution
of isoquinoline can be
rationalised by the relative
stabilities of intermediates



intermediate for attack at C-5

intermediate for attack at C-8

intermediate for attack at C-6

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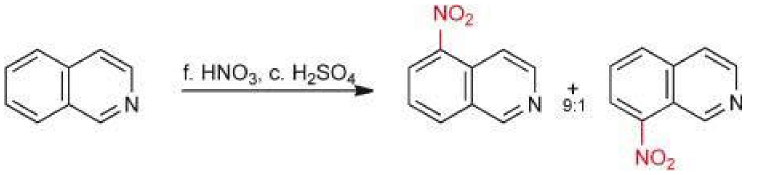
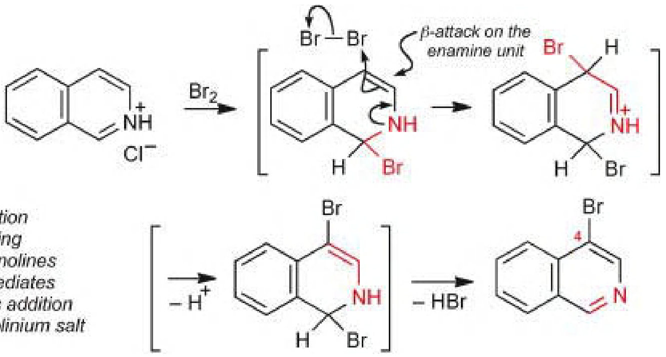
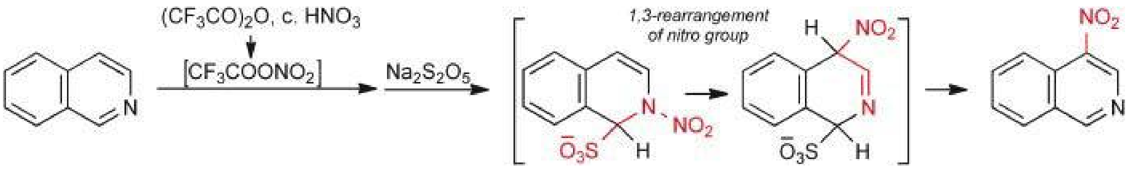


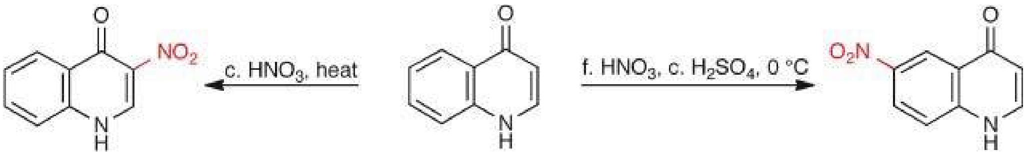
Exceptionally, and via a different mechanism, some substitutions in the *pyridine* ring of quinoline and isoquinoline are known, notably bromination and nitration. These rest on the ability of the bicyclic systems (in contrast to monocyclic pyridine) to add successively an electrophile at the nitrogen and then a nucleophile, forming an adduct; the adduct contains an enamine unit and the electrophilic step involves attack at the β-position of the enamine unit.



electrophilic substitution in the heterocyclic ring of quinolines and isoquinolines involves dihydro-intermediates resulting from nucleophilic addition to a quinolinium or isoquinolinium salt



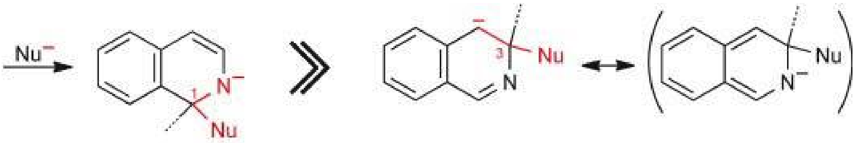
Electron-releasing substituents on the heterocyclic ring can permit substitution in that ring: an interesting case is the nitration of quinolin-4-one where, depending on the strength of acid used, substitution of the heterocyclic ring occurs on the neutral molecule but nitration in the benzene ring must involve the *O*-protonated species, that is, the 4-hydroxy-1*H*-quinolinium cation.



Nucleophilic substitution

Recalling that pyridine is susceptible to addition of nucleophiles at the α- and γ-positions and that benzene compounds are *not* normally attacked by nucleophiles, it follows that it is *only* the heterocyclic ring in quinoline/isoquinoline which is subject to nucleophilic substitution. In quinoline, there is one α- and one γ-type position, C-2 and C-4; of the two α-type positions in isoquinoline, reaction at the 1-position is *much* the more favoured one.

positional selectivity in nucleophilic substitution of isoquinoline rationalised by relative stabilities of intermediates



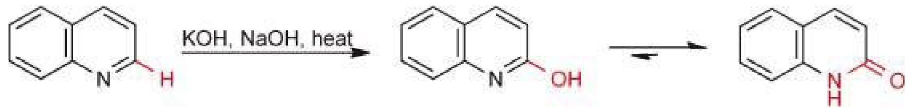
intermediate for attack at C-1

intermediate for attack at C-3

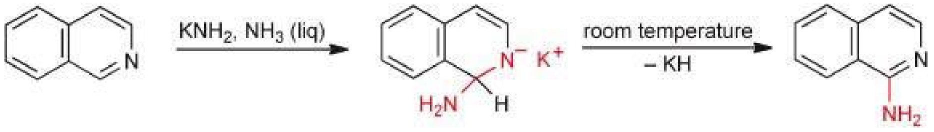
negative charge cannot be delocalised onto nitrogen without disrupting benzenoid resonance

Substitution of hydrogen

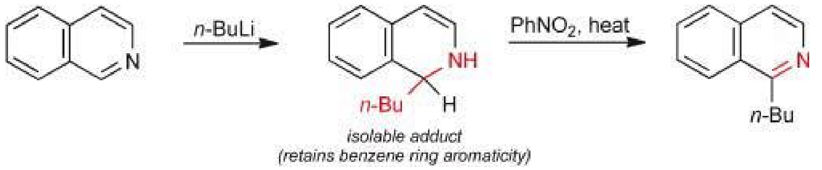
As the intermediates for nucleophilic addition to the heterocyclic ring *still contain a complete benzene ring, with its associated resonance stabilisation, nucleophilic addition is easier in* these *bicyclic systems* than in pyridines – less resonance stabilisation is lost in proceeding to the intermediate (strictly, the transition state which leads to it). Some examples serve to illustrate this point: both quinoline and isoquinoline can be hydroxylated (at C-2 and C-1, respectively) by heating with potassium hydroxide – no such transformation is possible with pyridines. The products exist in the carbonyl tautomeric forms in an exact parallel to the hydroxypyridine–pyridone situation (page 41).



A second example of the ease of nucleophilic addition is the reaction of amide anion with isoquinoline, which takes place even at –65 °C, re-aromatisation occurring *in situ* by reaction at room temperature (amination of pyridine needs strong heating).

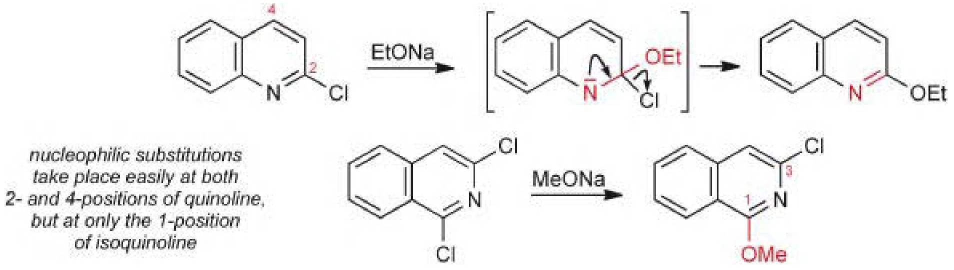


It is a corollary of the easier addition of a nucleophile to the heterocyclic ring of the bicyclic systems, and the relative stability of the adduct, that such adducts can be sometimes isolated, but then require more effort for re-aromatisation.



Substitution of leaving groups

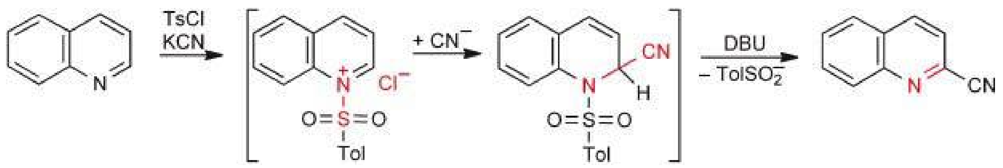
Nucleophilic displacement of leaving groups from the quinoline-2- and -4-positions and the isoquinoline-1-position occurs under quite mild conditions via the two-step, addition–elimination mechanism. Halogens at other positions are best regarded as being exactly like those in benzene compounds, though an isoquinoline 3-halide *can* be displaced under more vigorous conditions.



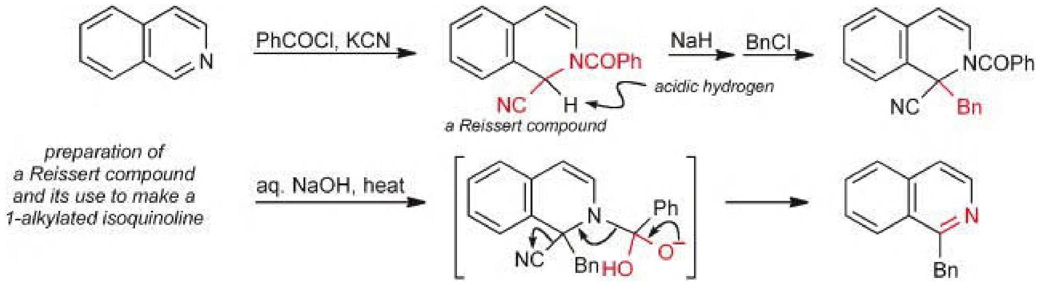
nucleophilic substitutions take place easily at both 2- and 4-positions of quinoline, but at only the 1-position of isoquinoline

Nucleophilic addition to quinolinium/isoquinolinium salts

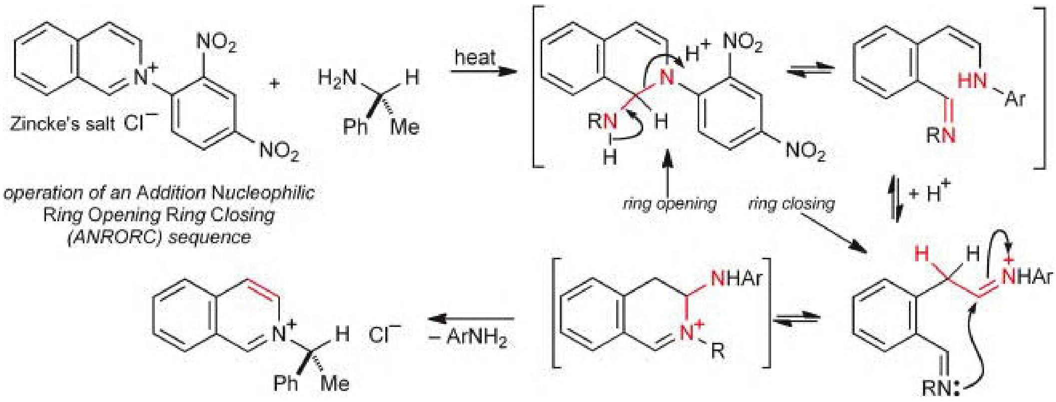
Addition of nucleophiles to quinolinium and isoquinolinium salts is a very easy process; the point made earlier, that in such products there still remains a complete aromatic ring, is again relevant. Such processes are sufficiently important that we give three examples as illustrations. In the first, an *N*-tosylquinolinium salt is prepared and used *in situ* for the addition of cyanide at C-2; additionally, base-catalysed elimination of *p*-toluenesulfinate then produces 2-cyanoquinoline – an overall nucleophilic substitution of hydrogen.



'Reissert compounds' are formed when quinoline or isoquinoline is reacted with an acid chloride, usually benzoyl chloride, in the presence of cyanide – here, it is the cyanide that adds as a nucleophile, generating isolable and stable adducts. Various uses have been devised for Reissert compounds: our example shows that the nitrile-bearing carbon carries an acidified *C*-hydrogen, which can be removed with a strong base, the resulting carbanion alkylated, hydrolytic conditions then producing overall a *C*-1-alkylated heterocycle.

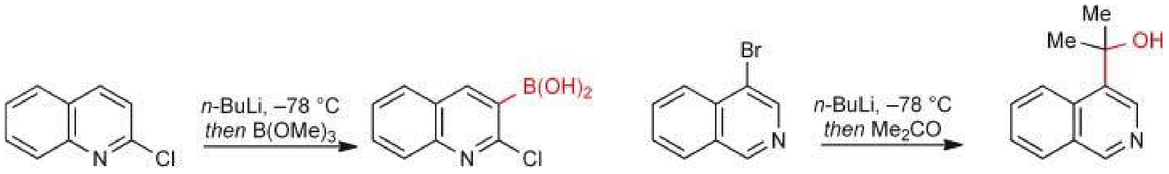


The salt that results from *N*-arylation of isoquinoline with 2,4-dinitrochlorobenzene (cf. pages 13–14), and is known as Zincke's salt, easily adds primary amines at C-1. These adducts undergo a ring-opening–ring-closing sequence – the acronym 'ANRORC' (Addition Nucleophilic Ring Opening Ring Closing) is usually used for such sequences – to regenerate an isoquinolinium salt, but in which the attacking primary amine nitrogen is now the isoquinolinium nitrogen and 2,4-dinitroaniline has been expelled.



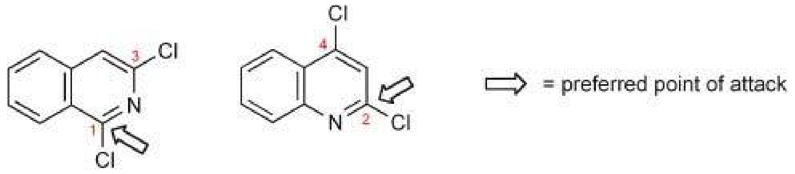
C-Metallated quinolines and isoquinolines

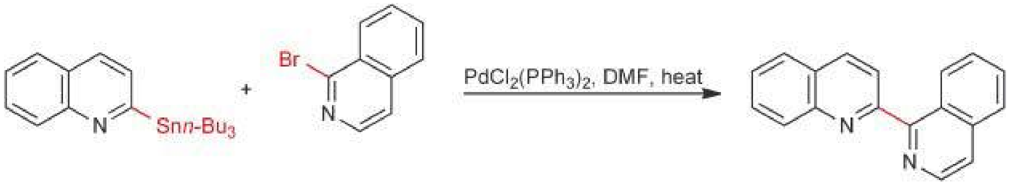
Direct deprotonation of quinolines/isoquinolines has only been carried out with *ortho* assistance (DoM). Quinolines with a directing group at C-3 are lithiated at C-4, not C-2. Metal–halogen exchange processes can be used to produce organometallic nucleophiles from halides located on either the benzene ring or on the heterocyclic ring, but the maintenance of a low temperature is essential to avoid the type of facilitated nucleophilic addition discussed above.

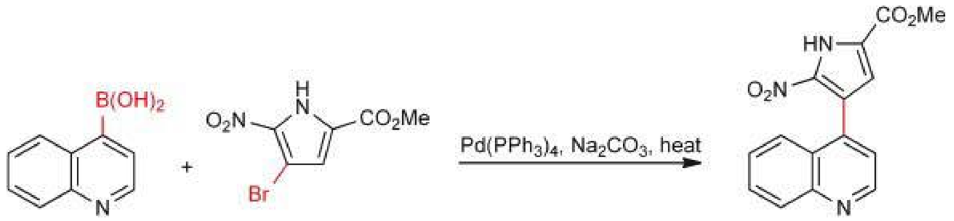


Palladium(0)-catalysed reactions

Boronic acid and stannane derivatives at all positions of the heterocyclic ring of quinoline and isoquinoline are known and take part in cross-coupling reactions. Two typical examples are shown. Positional selectivity can be seen when a dihalide is used for the coupling, for example, in 1,3-dichloroisoquinoline, reaction takes place at C-1. Similarly, 2,4-dichloroquinoline reacts first at C-2.

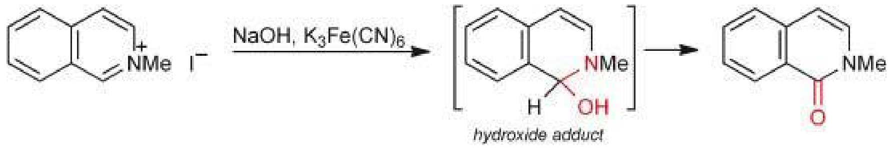




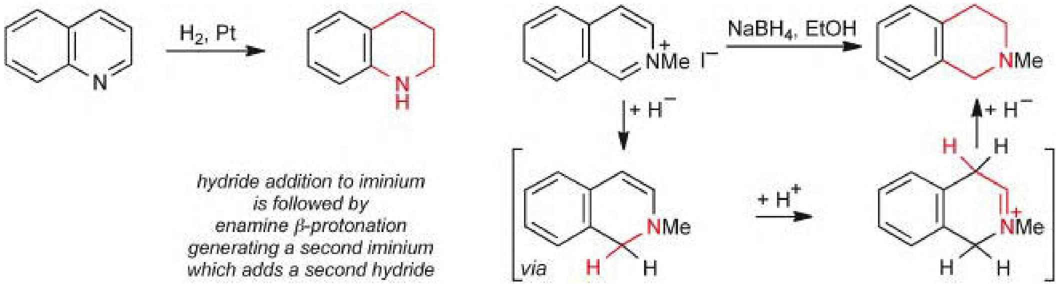


Oxidation and reduction

N$^+$-Alkylquinolinium and -isoquinolinium salts are oxidised in alkaline solution to *N*-alkyl-quinolin-2-ones and - isoquinolin-1-ones, respectively – the adduct formed by the ready addition of hydroxide is oxidised.

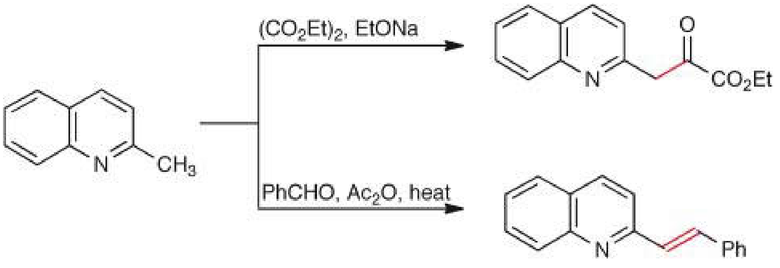


The heterocyclic ring is more easily reduced than the benzene ring. Hydride reagents bring about selective reductions of the heterocyclic ring of *N*$^+$-alkylquinolinium or -isoquinolinium salts.



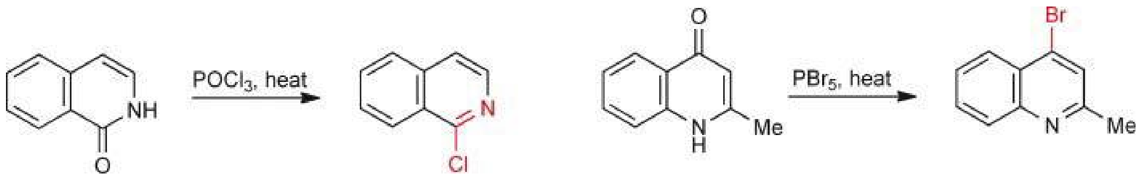
Alkyl substituents

The particular acidity of the protons of pyridine α- and γ-alkyl groups is echoed by quinoline-2- and 4-alkyl groups and by alkyl at the isoquinoline 1-position. Condensation reactions with alkyl groups at these activated positions can be achieved with either basic or acidic catalysis.



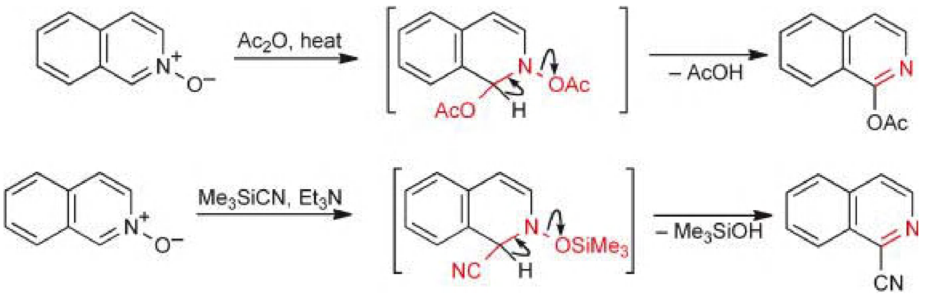
Oxygen substituents

Quinolines and isoquinolines with hydroxyl groups on the benzene rings are normal phenols. Oxygen at the isoquinoline-1-position and the quinoline-2- or -4-positions takes the carbonyl tautomeric form; the reactions of isoquinolin-1-one and the quinolones strictly parallel those of pyridones, for example conversion into halides by reaction with phosphorus halides.



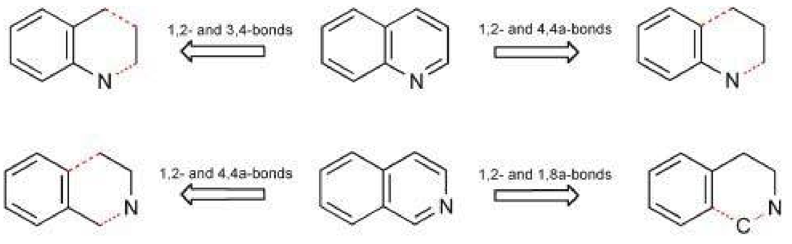
N-Oxides

Like the *N*-oxide of pyridine, those of quinoline and isoquinoline are versatile synthetic reagents, their reactivity being closely similar to that of their monocyclic counterpart, and for this reason we give just a couple of typical examples using isoquinoline *N*-oxide. Each transformation involves initial interaction of an electrophile with the oxygen to give an isoquinolinium salt, which adds a nucleophile, at C-1, the final product resulting from a 1,2-elimination and thus re-formation of the aromatic system.



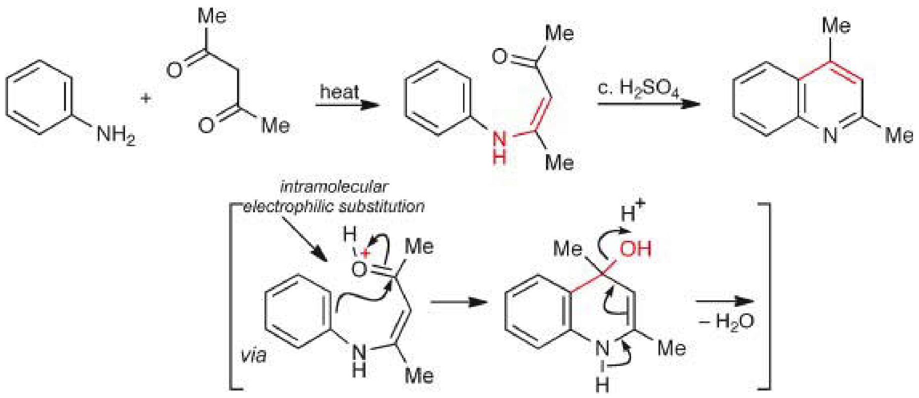
Ring synthesis – disconnections

In order to discuss ring synthesis, we need to consider quinoline and isoquinoline separately. The important routes to quinolines all start with an aniline. Isoquinolines can be made from 2-arylethanamines or from aryl aldehydes. The new bonds formed in the processes are shown.

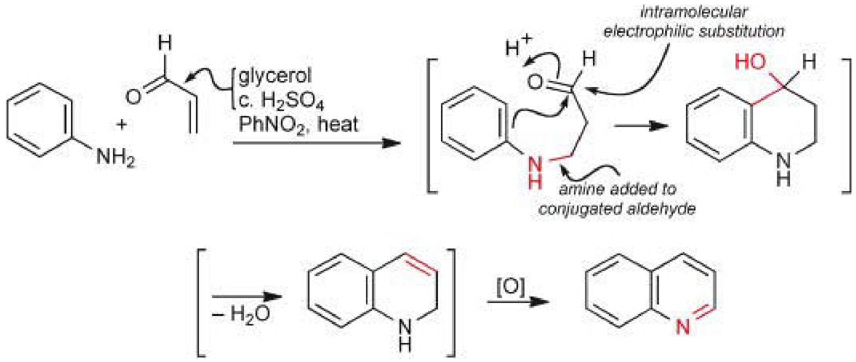


Synthesis of quinolines from anilines
(1,2- and 4,4a-bonds made)

Anilines react with 1,3-dicarbonyl compounds very efficiently to give β-arylamino-enones; these can be cyclised with acid involving electrophilic attack on the benzene ring; final loss of water produces the aromatic quinoline – the *Combes synthesis*. If one of the carbonyl groups is that of an ester, then a quinolone results.



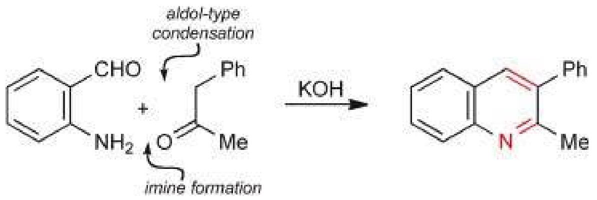
In a very similar approach, an α, β-unsaturated ketone or aldehyde can be employed, though, as the scheme makes clear, an oxidant is now required and is incorporated into the reaction mixture – *Skraup reactions* are the classical examples. The aniline, an oxidant (sometimes simply the aromatic nitro-compound corresponding to the aniline), concentrated sulfuric acid and glycerol are heated together. From this 'witches brew', and often via a very exothermic and hazardous process, comes a quinoline, unsubstituted on the heterocyclic ring. The glycerol is doubly dehydrated to produce acrolein, *in situ*, to which the aniline adds in a conjugate fashion. Acid-catalysed ring closure – another intramolecular electrophilic attack on a benzene ring – and dehydration, produce a dihydroquinoline, which is oxidised to the aromatic product. The use of a preformed aniline–acrolein adduct with a milder oxidant (chloranil (2,3,5,6-tetrachloro-1,4-benzoquinone)) offers greater control and safety.



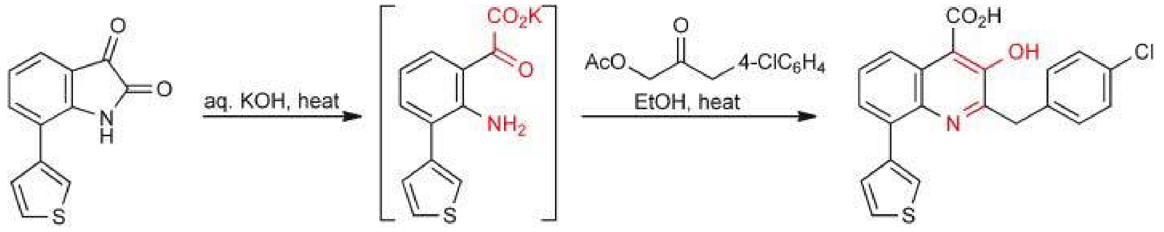
Synthesis of quinolines from *ortho*-aminoaryl ketones or aldehydes

(1,2- and 4,4a-bonds made)

Perhaps the most obvious disconnection for a quinoline is to envisage forming the two double bonds of the heterocyclic ring – the 1,2-double bond is an imine and the 3,4-carbon–carbon double bond by an aldol-type condensation. An *ortho*-amino aryl-aldehyde or -ketone is reacted with a ketone (to form the imine) carrying an α-methylene (CH_2 α to the ketone for the aldol-type condensation), though the exact order of steps is not known in the *Friedländer synthesis*.

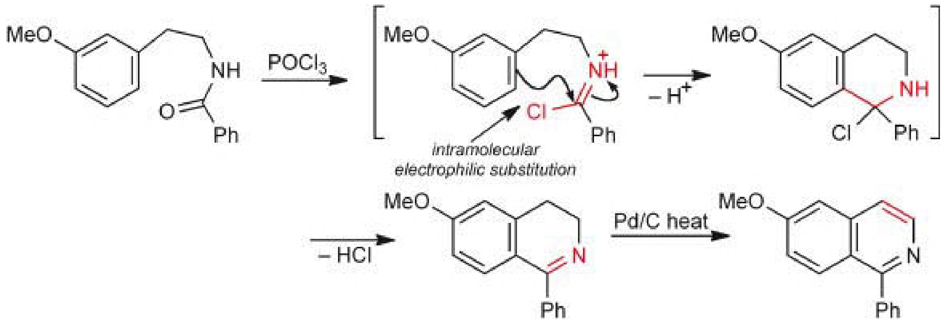


An extension of this route, known as the *Pfitzinger synthesis*, employs the *ortho*-aminoaryl-ketone-acids that are readily available via hydrolysis of an isatin (see page 97 for isatin synthesis), as illustrated below.



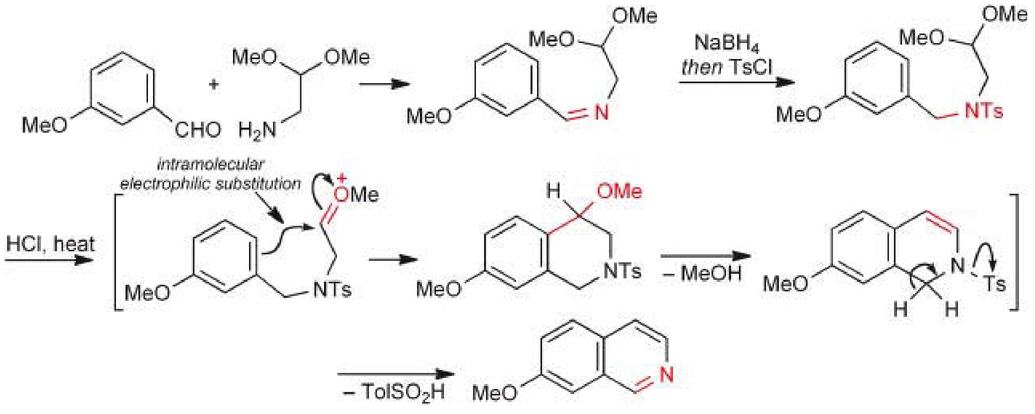
Synthesis of isoquinolines from 2-arylethamines
(1,2- and 1,8a-bonds made)

The trivial conversion of a 2-arylethanamine into an amide provides a substrate that will undergo ring closure to a 3,4-dihydroisoquinoline; these can be easily dehydrogenated to the aromatic species; the approach is known as the *Bischler–Napieralski reaction*, which was first described in 1893 and is still the most popular route to isoquinolines. The ring closure – another intramolecular electrophilic attack on a benzene ring – is usually effected with a phosphorus halide, the electrophilic species being exactly of the type involved in Vilsmeier reactions – a chloro-iminium ion (page 12). Because of the nature of the ring-closing step, electron-releasing substituents on the benzene ring improve the efficiency; the ring closure occurs *para* to the activating group where that is possible, as in the example shown.



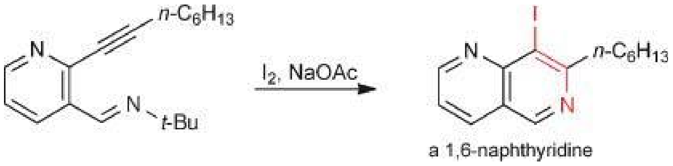
Synthesis of isoquinolines from aryl-aldehydes and an aminoacetaldehyde acetal (1,2- and 4,4a-bonds made)

A quite different route to isoquinolines – the *Pomeranz–Fritsch synthesis* – begins with an aryl-aldehyde which is condensed with aminoacetaldehyde dimethyl acetal ($H_2NCH_2CH(OMe)_2$) a bifunctional component with the aldehyde masked. Although the product imines can be ring closed directly, it is much more efficient to reduce the imine and protect the resulting amine as a tosylamide before the acid-catalysed ring closure, which also causes elimination of *para*-toluenesulfinic acid (Note: the sulfur has changed oxidation level) leading directly to the aromatic isoquinoline, unsubstituted on the heterocyclic ring.

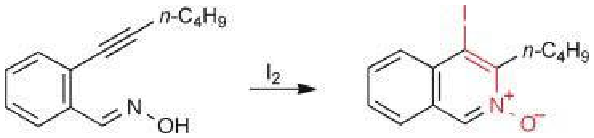


Synthesis of isoquinolines from *ortho*-alkynyl aryl-aldehydes or corresponding imines (2,3-bond made)

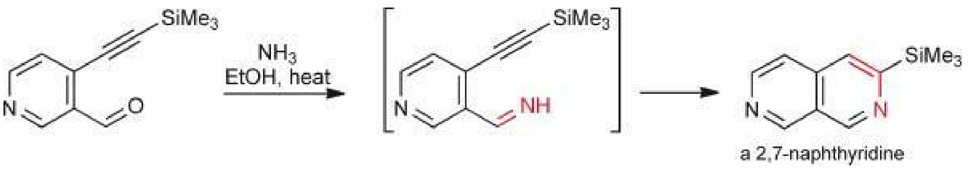
Electrophile-promoted closure of *ortho*-alkynyl arylaldehyde *t*-butylimines, with loss of the *N*-substituent, generates isoquinolines carrying the electrophile at C-4. The example below shows how this approach can also be used to produce naphthyridines, in the case shown, a 1,6-naphthyridine.



If, instead of an imine, the aldehyde oxime is used, the result is formation of an isoquinoline *N*-oxide.



Even simpler, and also for the synthesis of naphthyridines, each of the isomeric *ortho*-alkynyl pyridinyl aldehydes will react with ammonia to produce a naphthyridine (or with hydroxylamine to give a naphthyridine *N*-oxide), possibly, but not necessarily, via the imine, as shown.



Exercises

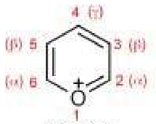
1. What are the structures of the high-yield mono-nitration products: (i) $C_{10}H_8N_2O_3$ from 6-methoxyquinoline; (ii) $C_{10}H_8N_2O_3$ from 7-methoxyisoquinoline; and (iii) $C_{16}H_{12}N_2O_2$ from 1-benzylisoquinoline?
2. What is the structure of the product $C_{16}H_{16}ClNO_4$ from 1,3-dichloroisoquinoline and $NaCH(CO_2Et)_2$?
3. Deduce a structure for the product $C_{15}H_{18}N_2OS$, formed on treatment of 2-(*t*-BuCONH)-quinoline successively with three equivalents of *n*-BuLi and then dimethyl disulfide (MeSSMe).
4. What reactants would combine to produce: (i) 6-methoxyquinoline; (ii) 6-methoxy-2,4-diethylquinoline; and (iii) 7-methoxyisoquinoline?
5. Deduce the structure of the quinoline that is formed by the following sequence: isatin (page 94) is hydrolysed with NaOH to give $C_8H_6NNaO_3$. This is then reacted with dimedone (5,5-dimethylcyclohexane-1,3-dione) to produce $C_{16}H_{15}NO_3$.

8

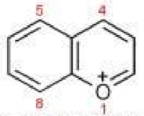
Pyryliums, Benzopyryliums, Pyrones and Benzopyrones

Pyrylium salts

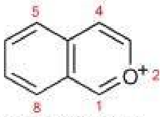
Pyrylium salts, especially perchlorates (ClO_4^-), tetrafluoroborates (BF_4^-) or hexachloroantimonates(V) ($SbCl_6^-$), are stable but reactive aromatic compounds. Historically, perchlorate salts have been used, but tetrafluoroborates or hexachloroantimonates are preferred. (CAUTION: all perchlorates, particularly when dry, are potentially explosive and should be handled with great care.) Alternatively, trifluoromethanesulfonates have a particular advantage in that they are more soluble in organic solvents than the other salts mentioned above.



pyrylium



1-benzopyrylium
(chromylium)



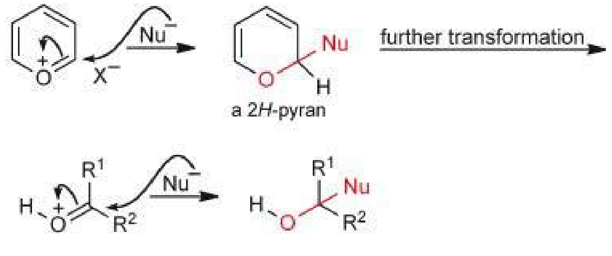
2-benzopyrylium
(isochromylium)

Electrophiles

Pyrylium cations *do not react* with electrophiles. There are no examples of electrophilic substitutions of pyryliums or, indeed, on the benzene ring of benzopyryliums.

Nucleophilic addition

Addition of nucleophiles, especially negatively charged nucleophiles, to pyrylium cations is extremely easy, as one would anticipate for the interaction of a positively charged substrate with a negatively charged reagent. The normal position of attack is an α-position – the analogy with nucleophilic addition to an *O*-protonated carbonyl group is clear. Such additions produce neutral 1,2-dihydro-products (2*H*-pyrans) and it is the further chemistry of these adducts which comprises the bulk of pyrylium chemistry.



nucleophilic addition to a pyrylium cation is analogous to addition to an O-protonated ketone or aldehyde

Substituents at the α-positions stabilise pyryliums towards nucleophilic addition to an extent – for example, while the pyrylium cation itself is attacked even by neutral water, at 0 °C, 2,4,6-trimethylpyrylium is stable in water at 100 °C. Hydroxide, as a negatively charged nucleophile, is more reactive, adding to all pyrylium cations at low temperature.

Ring-opening reactions of 2*H*-pyrans

Hydroxide adds reversibly, for example to 2,4,6-trimethylpyrylium cation, giving a cyclic hemiacetal, which is in equilibrium with various ring-opened isomers. On heating, an intramolecular aldol reaction involving an enolate anion leads, after loss of water and tautomerism, to 3,5-dimethylphenol.

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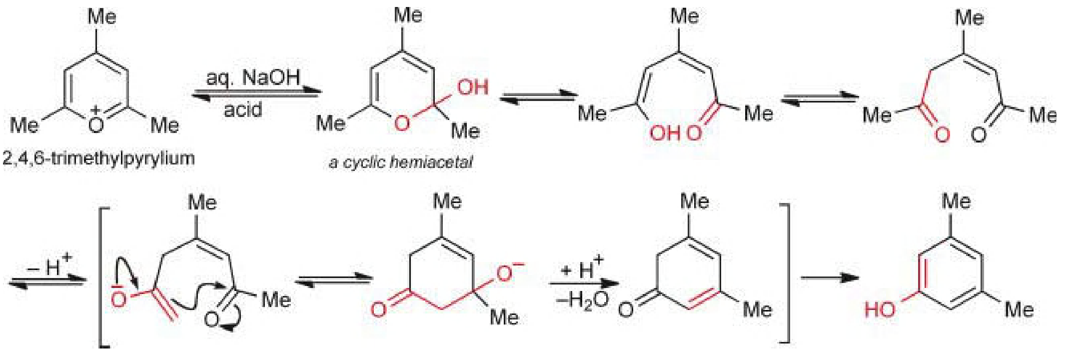
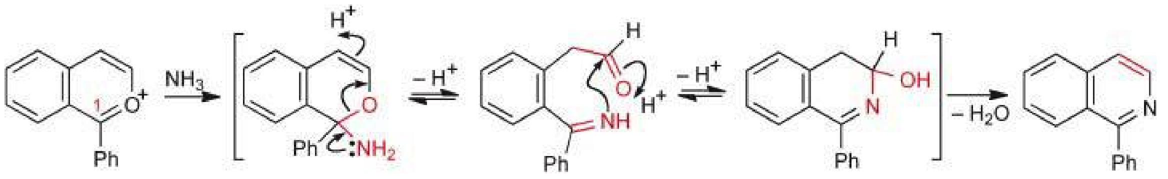
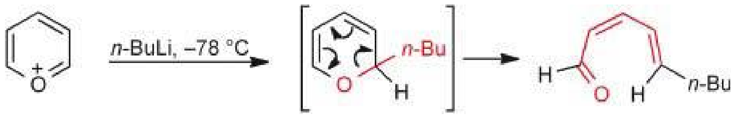


The reaction of pyrylium salts with ammonia (or primary amines) produces pyridines (or pyridinium salts). Here, after ring opening of the initial hemi-aminal adduct, cyclocondensation of the amino aldehyde generates the nitrogen heterocycle.

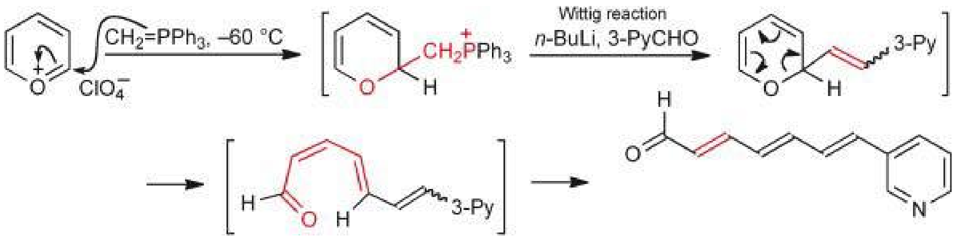
2-Benzopyrylium salts are equally susceptible to nucleophilic additions, at C-1 on the heterocyclic ring. In the case of ammonia, the adduct from a 2-benzopyrylium ring opens and eventually an isoquinoline is formed; ammonia adducts from 1-benzopyryliums do not have an option to give the corresponding quinolines.



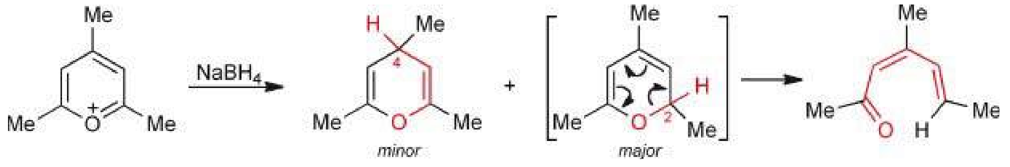
Organometallic reagents add rapidly to pyrylium salts, and the 2*H*-pyran adducts thus produced ring open: diene-als or diene-ones are the isolated products, retaining the geometry of the original 4,5-bond, thus pyrylium perchlorate reacts with *n*-BuLi to give (*Z*,*E*)-nona-2,4-dienal.



In another example, addition of triphenylphosphonium methylide as the nucleophile, then a Wittig condensation, electrocyclic ring opening and double-bond equilibration produces all-*trans* 7-substituted 2,4,6-heptatrienals as shown in the example below.

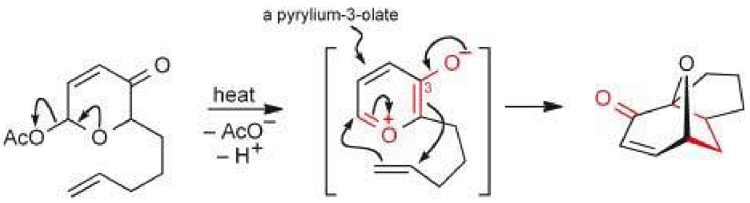


In reductions of pyryliums, for example 2,4,6-trimethylpyrylium perchlorate as shown, hydride adds easily and predominantly at an α-position. This produces a 2*H*-pyran that is not isolated but undergoes ring opening to the final product, a (*Z*,*E*)-dienone. Note that the minor reduction product, a 4*H*-pyran, is stable.



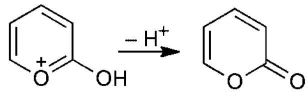
Oxygen substituents – pyrones and benzopyrones

The deprotonation of a hydroxyl group at a pyrylium 3-position generates pyrylium-3-olates; these take part in cycloadditions as 1,3-dipoles, across the 2- and 6-positions (cf. pyridinium-3-olates, page 40 and pyrazinium-3-olates, page 55). Most often, such zwitterions are generated by elimination of acetic acid from a 6-acetoxy-2*H*-pyran-3(6*H*)-one, in the presence of an external dipolarophile or, in the case illustrated, having a tethered double bond to serve as an intramolecular dipolarophile.

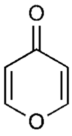


generation of a pyrylium-3-olate and its 1,3-dipolar cycloaddition, in this case, in an intramolecular sense

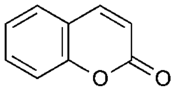
The *O*-deprotonated forms of α- and γ-hydroxypyryliums are neutral pyrones and their properties are like those of pyridones (pages 35, 40 and 41), their benzanellated analogues, chromones, coumarins and isocoumarins being analogous to quinolones and isoquinolones (pages 63 and 67). It follows that the pyrones and benzopyrones protonate, reluctantly, on the carbonyl oxygen giving hydroxypyrylium or hydroxybenzopyrylium salts. Highly reactive alkylating agents, such as Meerwein salts, will alkylate the carbonyl oxygen, giving alkoxy-pyryliums.



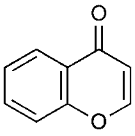
2-hydroxypyrylium 2-pyrone



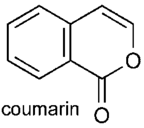
4-pyrone



coumarin

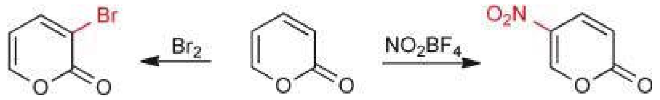


chromone

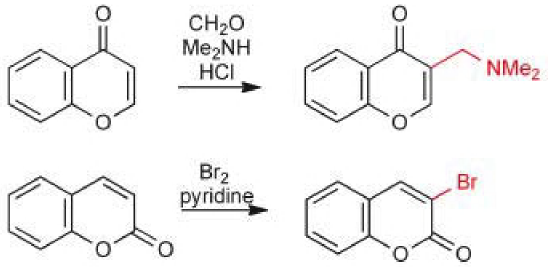


isocoumarin

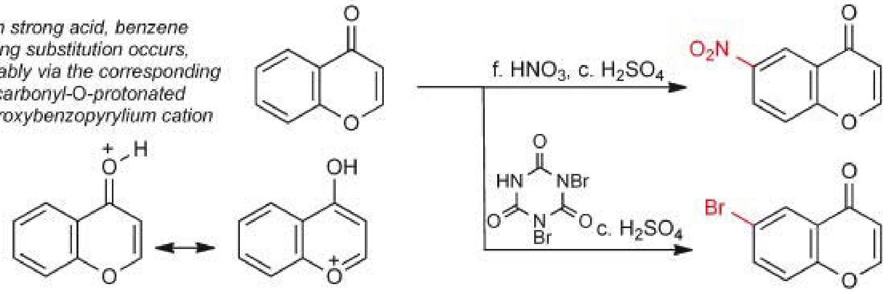
There are only a few examples of electrophilic substitution of pyrones, at C-3/C-5, nitration and bromination being two. Chromones and coumarins are attacked by electrophiles at C-3 in neutral solution.



electrophilic substitution of pyrones is selective for C-3/C-5

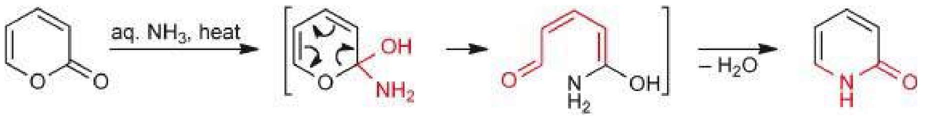


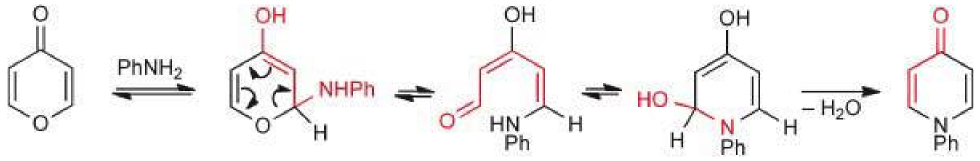
electrophilic substitution of chromone and coumarin is selective for the pyrone ring in neutral solution



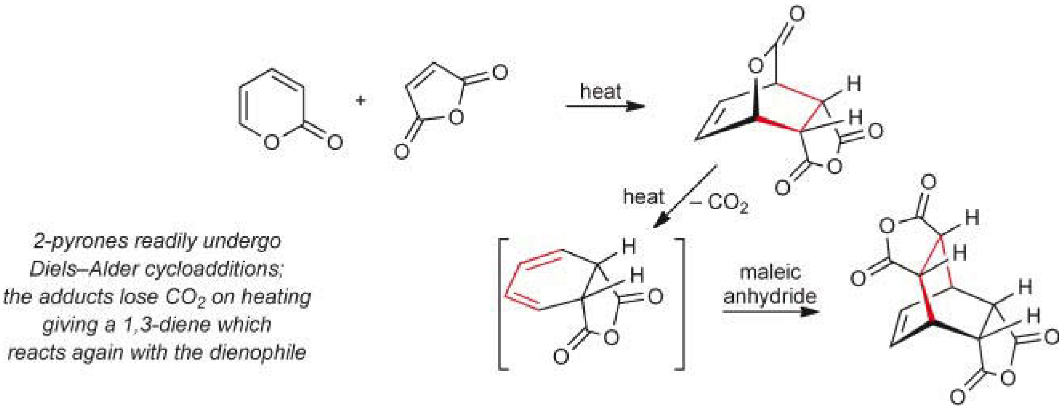
in strong acid, benzene ring substitution occurs, probably via the corresponding carbonyl-O-protonated hydroxybenzopyrylium cation

Much of the remainder of the chemistry of the pyrones and benzopyrones can be summarised by saying that they behave like unsaturated ketones and lactones. 2-Pyrones can in principle add nucleophilic reactants either at C-2 (carbonyl carbon), C-4, or C-6: their reactions with ammonia/amines are examples, 2-pyrones are converted into 2-pyridones, probably via initial attack at C-2. 4-Pyrones are similarly converted into 4-pyridones on reaction with ammonia or amines – clearly, in these transformations the ammonia/amine must attack initially at C-2, not at the carbonyl carbon.



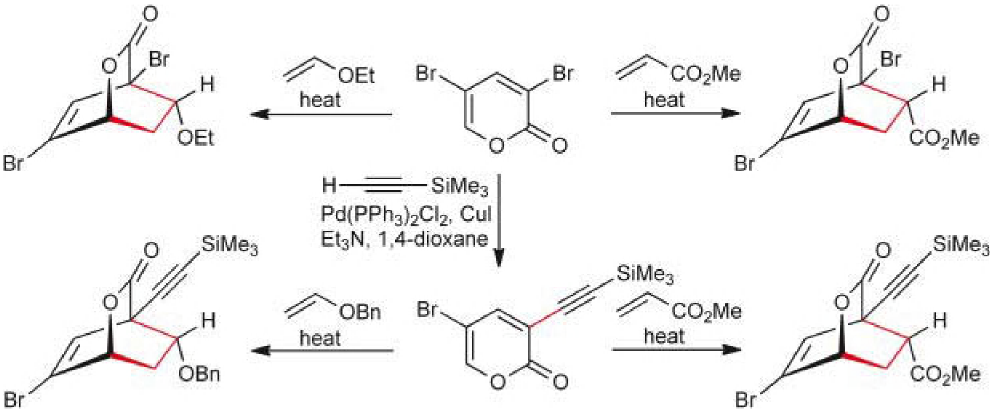


The reactivity of 2-pyrones as dienes in Diels–Alder reactions is notable and is a measure of the diene, (rather than aromatic) character of 2-pyrones. There is a tendency for the cycloadducts to lose carbon dioxide in a cycloreversion on stronger heating. The elimination of carbon dioxide can be discouraged by operating at a lower temperature and using very high pressure, or by using a catalyst.



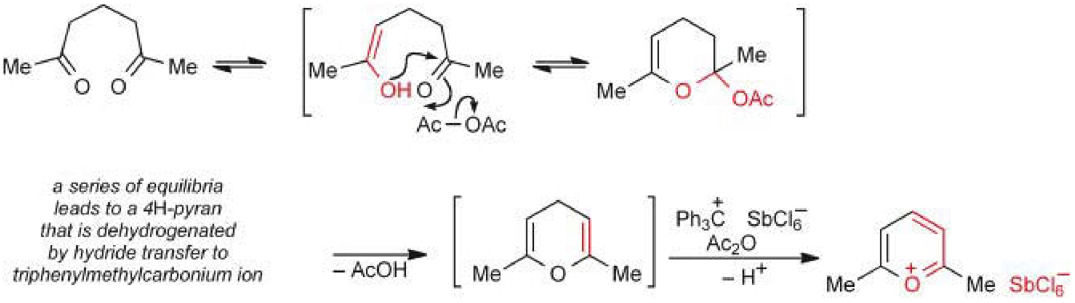
2-pyrones readily undergo Diels–Alder cycloadditions; the adducts lose CO_2 on heating giving a 1,3-diene which reacts again with the dienophile

The pericyclic reactivity of 3- and 5-bromo- and 3,5-dibromo-2-pyrones is special since they act as efficient dienes towards *both* electron-poor dienophiles (normal electron demand) *and* electron-rich dienophiles (inverse electron demand). 3,5-Dibromo-2-pyrone undergoes palladium(0)-catalysed cross-coupling selectively at C-3 and the resulting C-3-substituted 5-bromo-2-pyrones can also be used with both types of dienophile, as the scheme illustrates (only the major *endo* isomer shown in each case).



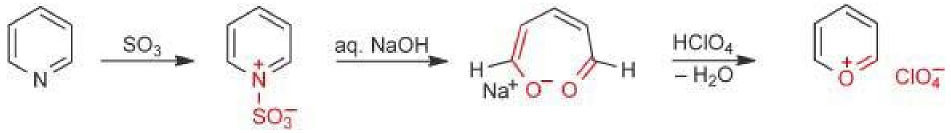
Ring synthesis of pyryliums from 1,5-diketones (1,2-bond made)

The synthesis of pyrylium cations centres on the use of a 1,5-dicarbonyl compound (or its synthesis *in situ*). As an example, mono-enolisation of heptane-2,6-dione, intramolecular hemi-acetal formation, loss of water and finally an oxidation produces the six-membered aromatic salt. Various oxidants can be used – in the example shown, the species that abstracts hydride from the intermediate 4*H*-pyran is the triphenylmethyl carbonium ion (Ph_3C^+), and acetic anhydride facilitates formation of the 4*H*-pyran.



A suitable 1,5-diketone can be prepared and utilised *in situ* via the addition of an enol or enolate to a chalcone (a 'chalcone' is an α,β-unsaturated ketone formed by aldol condensation of an aryl-aldehyde with an aryl methyl ketone). The excess chalcone is the oxidant of the intermediate 4*H*-pyran.

The oxidative step is unnecessary if a 1,5-dicarbonyl compound already containing a C–C double bond is used as starting material. A synthesis of pyrylium perchlorate itself (CAUTION: potentially explosive) illustrates this – the sodium salt of glutaconaldehyde (pent-2-ene-1,5-dial), available via hydrolysis of the pyridine–sulfur trioxide complex, is ring closed using perchloric acid.

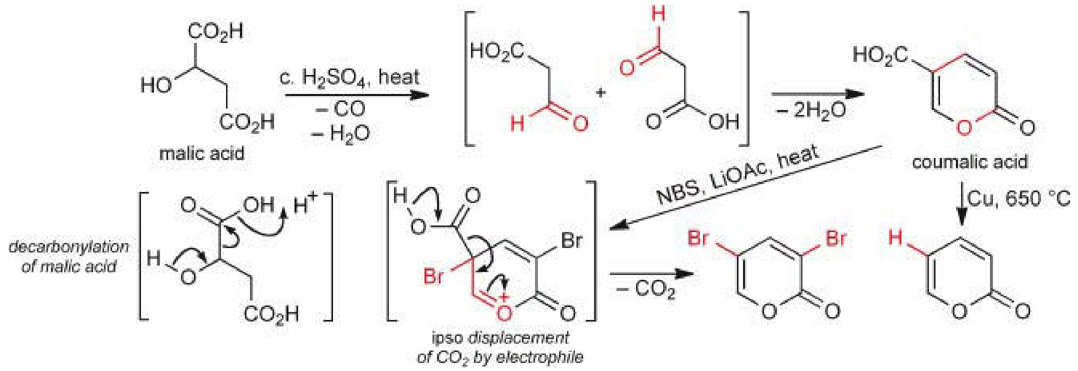


Ring synthesis of 4-pyrones from 1,3,5-triketones (1,2-bond made)

A synthesis of 4-pyrone also involves formation of a 1,2-bond. The 1,3,5-tricarbonyl compound, which is easily prepared by a double Claisen condensation of acetone with diethyl oxalate, closes to a 4-pyrone di-acid on mineral acid treatment, the presence of the central carbonyl group of the starting material being reflected by its presence in the ring closed heterocycle.

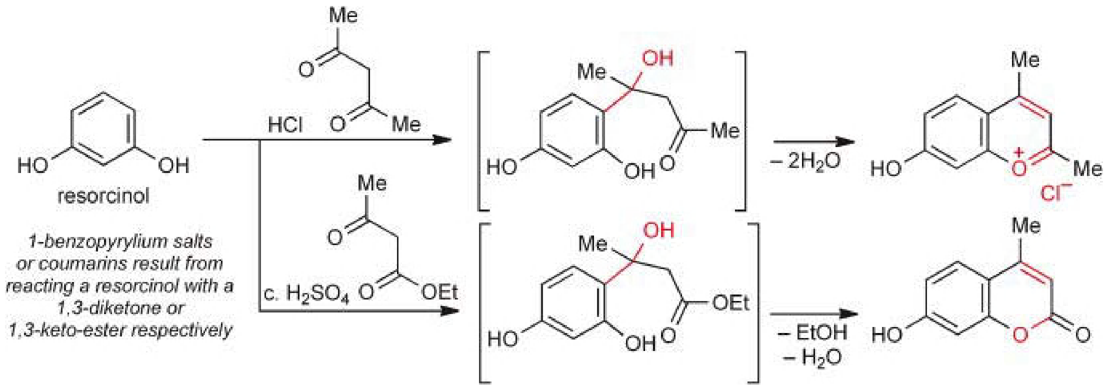
Ring synthesis of 2-pyrones from 1,3-keto-aldehydes (1,2- and 4,5-bonds made)

The classical synthesis of 2-pyrone involves the decarbonylation of malic acid (the tart component of apples and other fruits, first isolated from apple juice in 1785 by Scheele) and then the double condensation of two molecules of the resulting formylacetic acid to give coumalic acid (2-pyrone-5-carboxylic acid). Decarboxylation of coumalic acid produces 2-pyrone and bromination gives 3,5-dibromo-2-pyrone. (Note the easy *ipso* replacement of carbon dioxide by bromine: the intermediate is highly activated for decarboxylation.)

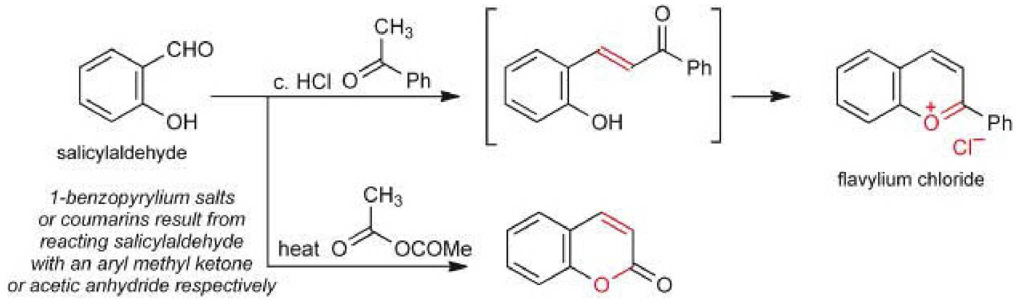


Ring synthesis of 1-benzopyryliums, coumarins and chromones

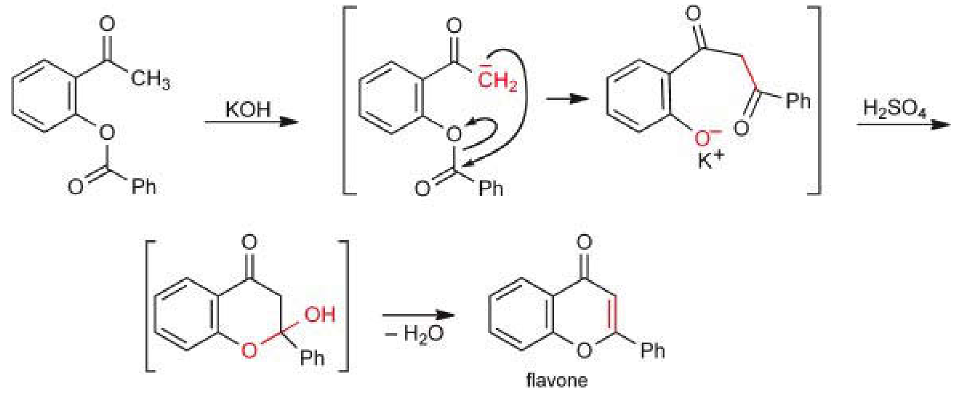
All practical syntheses of benzene ring-fused-pyryliums and benzopyrones start from phenols. For example, resorcinol reacts with 1,3-diketones in acidic solution to give 1-benzopyrylium salts. Changing the oxidation level of one of the carbonyl groups to that of an ester, that is reaction of resorcinol with a β-keto-ester, allows the synthesis of coumarins. The initiating step in these syntheses is electrophilic attack on the aromatic ring by the *O*-protonated 1,3-dicarbonyl compound, the presence of an activating hydroxyl *para* to the point of attack facilitating the sequence.



Salicylaldehyde reacts with aryl methyl ketones in acid to produce flavylium salts (2-aryl-1-benzopyrylium salts): aldol condensation is followed by ring closure and then dehydration. Once again, changing the oxidation level of the second component – condensing a salicylaldehyde with acetic anhydride – produces a coumarin (the Perkin reaction - see page 191).



ortho-Hydroxyaryl methyl ketones can be simply *O*-acylated giving phenolic esters. Carrying out a base-induced rearrangement on these (arrows) leads to a 1,3-diketone phenolate anion that closes to a chromone when acidified. 2-Arylchromones are generally known as 'flavones'.

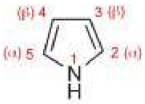


Exercises

1. Devise a mechanism to explain the formation of 1,3,5-triphenylbenzene from 2,4,6-triphenylpyrylium perchlorate on reaction with two mole equivalents of $Ph_3P{=}CH_2$.
2. 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 then this with acrylonitrile → $C_{10}H_{11}NO_3$.
3. Draw a mechanism for the conversion of 4-pyrone into 1-methylpyridin-4-one on reaction with methylamine.
4. Deduce structures for the pyrylium salt formed by the following sequence: pinacolone (Me_3CCOMe) condensed with pivaldehyde ($Me_3CCH{=}O$) giving $C_{11}H_{20}O$, which is 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 giving a pyrylium salt.
5. Deduce structures for the pyrones formed by the following sequences: (i) $PhCOCH_3$ with $PhC{\equiv}CCO_2Et$ in the presence of NaOEt; (ii) $PhCOCH_2COCH_3$ with two mole equivalents of NaH then with methyl 4-chlorobenzoate.
6. 'Dehydroacetic acid' (ethyl 2-hydroxy-4-pyrone-3-carboxylate) was first synthesised in 1866 by reacting ethyl acetoacetate ($MeCOCH_2CO_2Et$) with hot $NaHCO_3$. Recalling the synthesis of coumalic acid by condensation of two three-carbon units, suggest a mechanism for the formation of dehydroacetic acid.
7. Deduce the structures of the intermediate and the final product in the sequence: salicylaldehyde heated with $MeOCH_2CO_2Na$ and Ac_2O → $C_{10}H_8O_3$, this then with one mole equivalent of PhMgBr → $C_{16}H_{14}O_3$ and finally this with HCl → $C_{16}H_{13}O_2^+$ Cl^-.

9

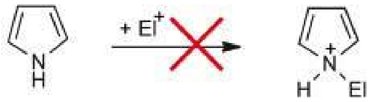
Pyrroles



pyrrole

Electrophilic substitution at carbon

Pyrroles do not react with electrophiles by addition at nitrogen (a direct contrast with pyridines) – the nitrogen electron pair is involved in the aromatic sextet and addition of an electrophile to the nitrogen would produce a high-energy non-aromatic species.

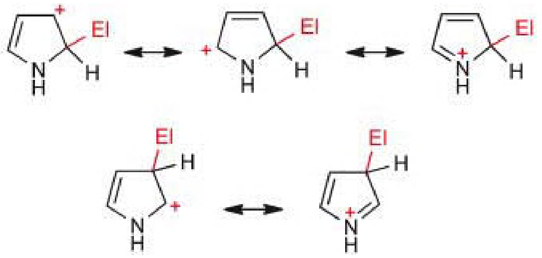


*pyrroles do **not** add electrophiles (or protons) at the nitrogen*

Pyrroles readily undergo electrophilic *C*-substitution, preferentially at an α-position but also, and only slightly less rapidly, at a β-position. Pyrroles are attacked by electrophiles *much* more easily than benzene – about 10^5 times more rapidly. Both of these aspects are nicely illustrated by the nitration of pyrrole, which requires only a weakly electrophilic nitrating agent ($AcONO_2$) and a low temperature to produce a mixture of 2- and 3-nitropyrroles, favouring the former. The tetra-iodination of pyrrole, again under mild conditions, is another good illustration of the high reactivity of pyrrole towards even weak electrophiles.

easy nitration and iodination of pyrrole

Positional selectivity and the high reactivity can both be explained by a consideration of the mesomeric contributors to the intermediates (and, by implication, the transition states that lead to them) for electrophilic substitution. Intermediate cations from both α- and β-attack are well stabilised, however the delocalisation, involving donation of electron density from the heteroatom, is greater in the intermediate from α-attack, as illustrated by the number of low energy resonance contributors (three) compared with the β-intermediate (two). Note that the carbon-carbon double bond in the intermediate for β-attack is not, and cannot become, involved in delocalisation of the charge.



α-attack by El$^+$ gives more stable intermediate

β-attack by El$^+$ gives less stable intermediate

positional selectivity in electrophilic substitution of pyrrole rationalised by relative stabilities of intermediates

The balance in positional selectivity can be tipped to β by the presence of bulky groups on nitrogen, which sterically impede reaction at α-positions. For example, 1-(tri-isopropylsilyl)pyrrole (TIPS-pyrrole) is attacked exclusively at a

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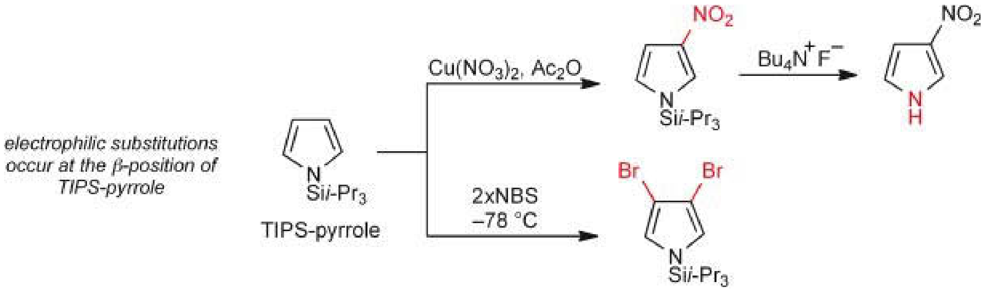
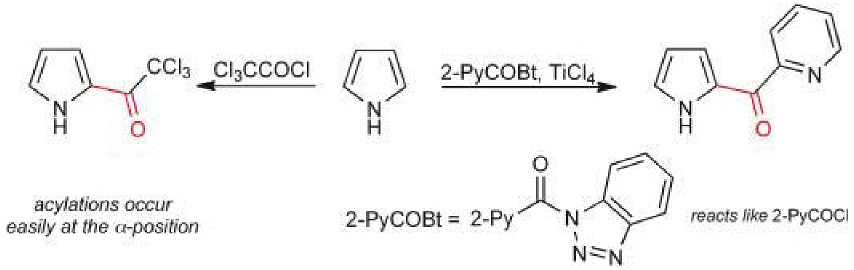
Heterocyclic Chemistry at a Glance, Second Edition. John A. Joule and Keith Mills.

β-position. An *N*-trialkylsilyl substituent can be subsequently easily removed using fluoride, to provide an *N*-hydrogen β-substituted pyrrole.



electrophilic substitutions occur at the β-position of TIPS-pyrrole

Electrophilic substitutions of pyrroles are very useful, though strong protic or Lewis acidic conditions must be avoided. The high reactivity of the heterocycle means that such conditions would lead to rapid degradation or polymerisation. Fortunately, this very same high reactivity means that acylations of pyrrole do not require a strong Lewis acid catalyst: reaction with trichloroacetyl chloride, for example, requires no catalyst at all. 1-Aroylbenzotriazoles (preferred to acid chlorides) can be used to introduce aroyl groups and require only titanium(IV) chloride as a catalyst.

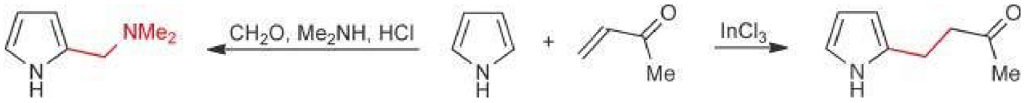


acylations occur easily at the α-position

A frequently used substitution is the Vilsmeier reaction, which efficiently forms pyrrole aldehydes.

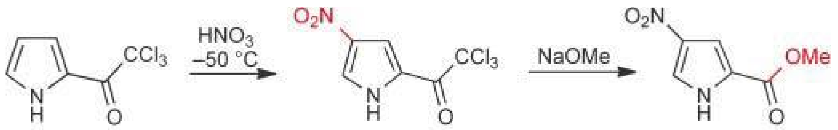
Vilsmeier formylation of pyrrole proceeds at the α-position

C-Alkylation of pyrroles proceeds easily with α, β-conjugated ketones. Using the Mannich reaction, dialkylaminoalkylpyrroles are formed (the electrophile is an iminium ion, e.g., $CH_2=N^+Me_2$, conveniently formed *in situ*). Pyrroles also react readily with *O*-protonated aldehydes and ketones, though simple hydroxyalkyl substitution products cannot usually be obtained, as such compounds react further in the presence of acid (see pages 82–83).



It can sometimes be of benefit to moderate the high reactivity of pyrrole while at the same time requiring (allowing) the use of slightly more vigorous reagents. The presence of electron-withdrawing groups on the nitrogen or on a carbon achieves this end. For example, clean 2,5-dibromination of 1-(*t*-butoxycarbonyl)pyrrole (Boc-pyrrole) can be achieved with *N*-bromosuccinimide. *N*-Tosylpyrrole can also be dibrominated, but at the 3- and 4-positions. Incidentally, halopyrroles are intrinsically rather unstable but the presence of electron-withdrawing groups on nitrogen considerably stabilises them and thus facilitates subsequent manipulations.

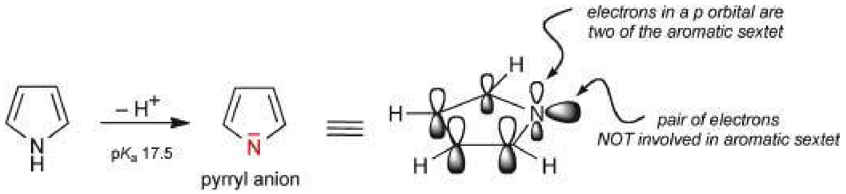
Strong electron-withdrawing groups on carbon can, additionally, modify the regioselectivity of electrophilic attack. For example, a synthesis of methyl 4-nitropyrrol-2-ylcarboxylate involves nitration of 2-trichloroacetylpyrrole. The acyl group selectively deactivates the C-3 and C-5 positions and this influence overrides the intrinsic pyrrole tendency for α-substitution and attack takes place *meta* to the chloroacetyl group. Methanolysis of the trichloroacetyl substituent produces the ester.



in electrophilic substitution of a 2-acylpyrrole intrinsic pyrrole α-selectivity is overcome by the meta-directing acyl influence

N-Deprotonation and *N*-metallated pyrroles

The *N*-hydrogen of pyrrole can be quantitatively removed with strong bases giving a pyrryl anion. The pK_a for this process is 17.5, which, contrasted with the value for pyrrolidine of ~44, shows pyrrole to be appreciably more acidic than an amine. Pyrryl anions are still aromatic species, with two lone pairs associated with the nitrogen, one orthogonal to the ring and participating in the aromatic sextet, and the second in the plane of the ring and available for reaction with electrophiles *without* disrupting the aromaticity, thus allowing *N*-substitution.



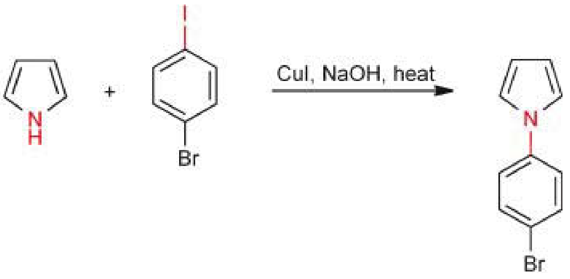
electrons in a p orbital are two of the aromatic sextet

pair of electrons NOT involved in aromatic sextet

N-Substitution can also be achieved via small concentrations of the pyrryl anion generated by weaker bases, such as 4-dimethylaminopyridine (DMAP). Syntheses of *N*-Boc-pyrrole and *N*-TIPS-pyrrole illustrate the synthetically important electrophilic trapping of pyrryl anions. *N*-Alkylation similarly employs alkyl halides with a pyrryl anion.

N-*substitution of pyrroles using the nucleophilic reactivity of the pyrryl anion*

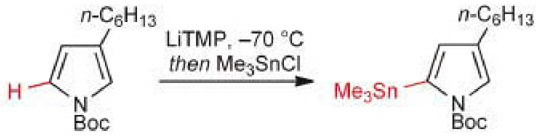
N-Arylation of pyrroles can be achieved with the assistance of a catalyst – copper has been used most frequently.



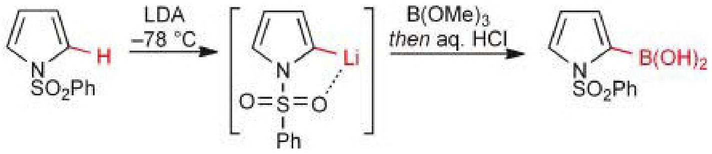
N-*arylation of pyrroles requires a catalyst and involves a different mechanism from pyrryl anion alkylation*

C-Metallated pyrroles

N-Substituted pyrroles can be deprotonated with strong bases, *selectively at an* α*-position*, producing organometallic intermediates that react even with weak electrophiles, for example aldehydes and ketones, giving α-substituted products. If appropriately chosen, the *N*-(blocking) substituent can then be removed to give *N*-hydrogen products. Some *N*-substituents also facilitate the α-metallation by induction and/or coordination to the lithium.

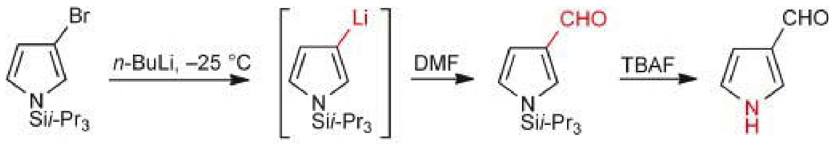


lithiation by deprotonation occurs at the α-position



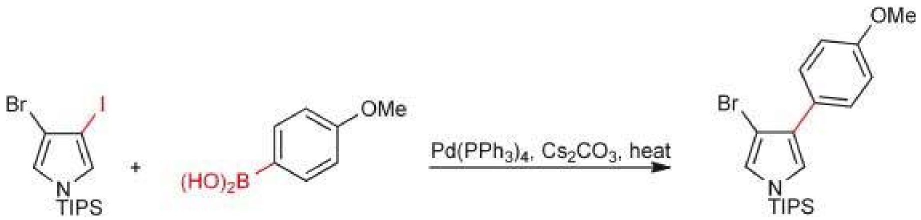
electron-withdrawing groups on nitrogen facilitate α-lithiation by inductive withdrawal and also, in some cases, by coordinating the lithium

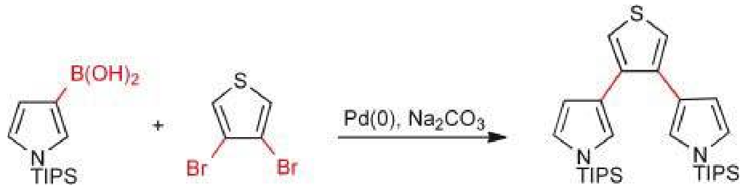
Pyrrolyllithiums can also be generated via metal–halogen exchange processes.

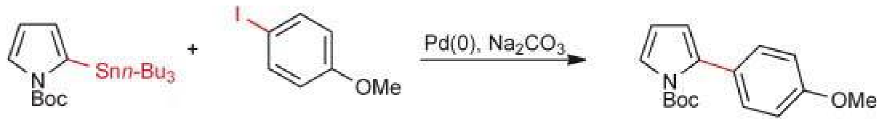


Palladium(0)-catalysed reactions

Pyrrole halides, boronic acids and stannanes have been employed in palladium(0)-catalysed cross-couplings, as illustrated by the synthesis of some 2- and 3-substituted pyrroles shown below.





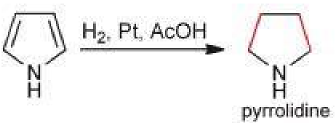


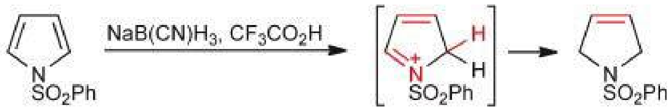
Oxidation and reduction

Simple pyrroles are rather easily oxidised, usually with degradation of the ring, although sometimes maleimides can be isolated.

An important area where technology and heterocyclic chemistry overlap is that of electroactive organic materials. Pyrrole can be oxidatively polymerised either electrochemically or chemically (e.g., using iron(III) chloride), to give (mainly) 2,5-coupled polymers. The initial neutral polymers are non-conducting but on further oxidation are converted partially into cation radicals or dications, with incorporation of counterions from the reaction medium – a process known as 'doping' – giving conducting materials (see page 193).

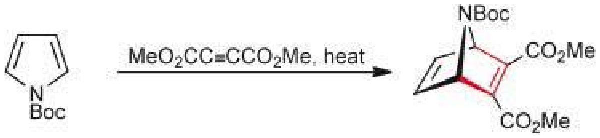
Reduction of pyrroles to pyrrolidines with hydrogen can be effected using various catalysts. Partial reduction using a hydride reagent in the presence of acid, gives a 2,5-dihydropyrrole, via an α-protonated intermediate. This is better carried out using 1-phenylsulfonylpyrrole, as shown.





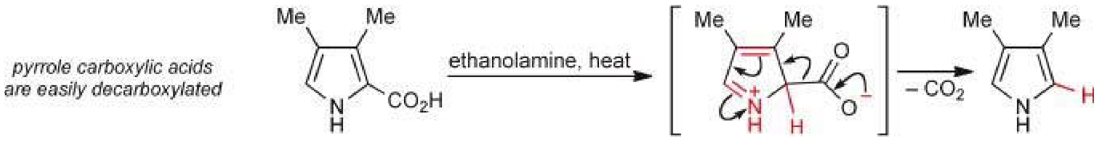
Pericyclic reactions

Pyrroles, as aromatic molecules, do not generally behave as dienes. However, when an electron-withdrawing substituent is located on the nitrogen, its effect, both inductive and mesomeric, reduces the aromatic character to the extent that such molecules will take part in Diels–Alder processes as the diene component. The reactions of *N*-Boc-pyrrole have been widely exploited: its reaction with dimethyl acetylenedicarboxylate is illustrative.

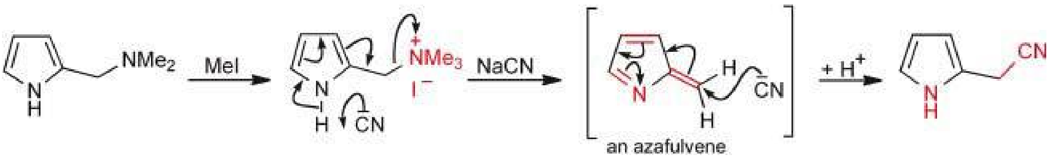


Reactivity of side-chain substituents

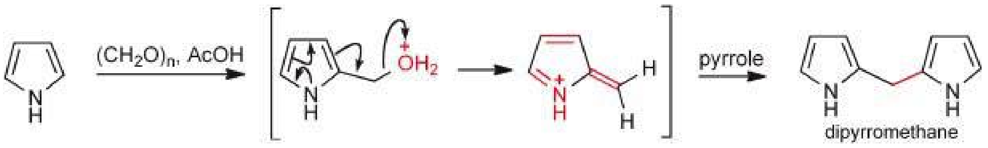
The electron-rich character of the pyrrole ring gives rise to some important properties of side-chain substituents. Pyrrole carboxylic acids readily decarboxylate, reflecting *C*-protonation to cations from which carbon dioxide is lost, as indicated. Several methods for the ring synthesis of pyrroles produce pyrrole-esters and these can be readily hydrolysed and decarboxylated, if the ester is not required.



Dialkylaminomethyl-pyrroles, easily produced in Mannich substitutions, can be utilised in further elaborations, as the amine group (or an ammonium group derived from the amine by quaternisation) can be easily displaced by nucleophiles such as cyanide, as in the example shown. These are not direct displacements but involve ring-*N*-hydrogen deprotonation and an intermediate azafulvene, to which the nucleophile adds, as shown, in an extended aza-Michael-type addition.

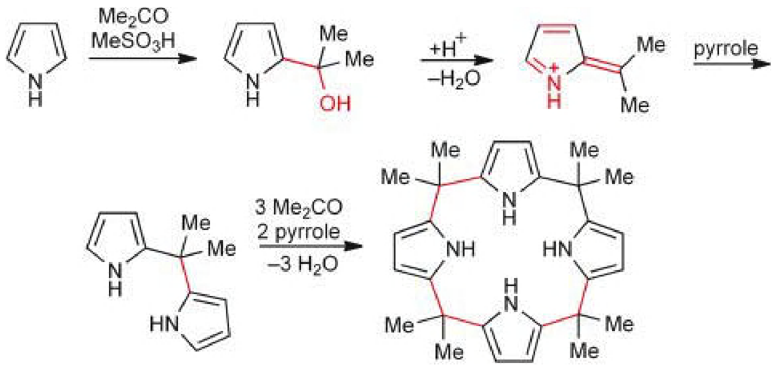


The 2-(hydroxyalkyl)-pyrroles, which result from reaction with an aldehyde or ketone with acid catalysis, readily lose water generating an electrophilic azafulvenium species. In some cases these can be trapped, for example by a second equivalent of the pyrrole; dipyrromethane can be made in this way.



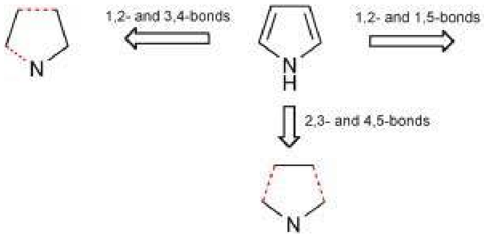
The 'pigments of life'

Not even a brief description of pyrrole chemistry can ignore the biological significance of the two pigments – heme and chlorophyll – which are central to all life (see page 162). It is amazing how easy it is to construct such apparently complex macrocycles, the reactions involved all being understandable with just the discussions above. For example, reaction of pyrrole and acetone, with acid catalysis, gives rise to a macrocycle in high yield, the intermediates shown illustrating: (i) selective α electrophilic substitution, (ii) easy elimination of benzylic side-chain hydroxyl, then (iii) attack by the azafulvenium cation as an electrophile on a second pyrrole at its α-position. The process then continues in a similar vein.



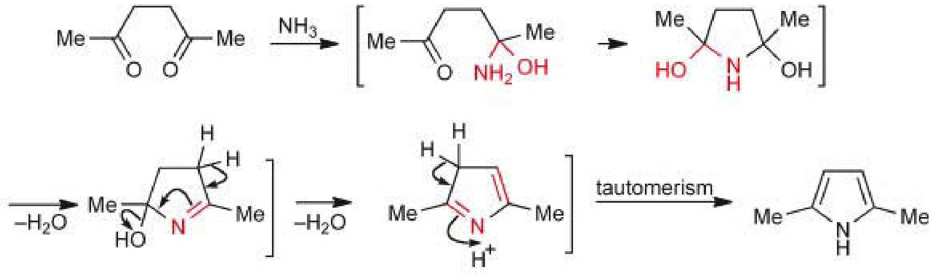
Ring synthesis – disconnections

There are three important disconnections for the construction of pyrroles, summarised below, with the new bonds made in the processes shown.



Synthesis of pyrroles from 1,4-dicarbonyl compounds
(1,2- and 1,5-bonds made)

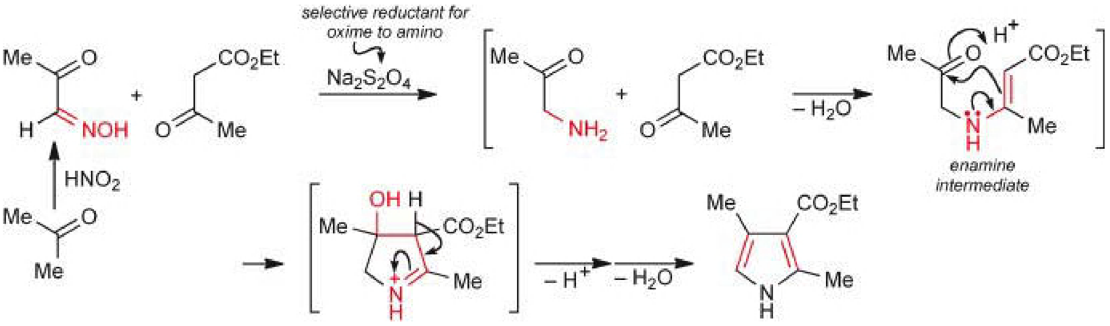
The most obvious route to pyrroles involves the interaction of ammonia, or a primary amine, with a 1,4-dicarbonyl compound – the *Paal-Knorr synthesis*. Successive intermolecular then intramolecular nucleophilic additions of ammonia/amine nitrogen to the two carbonyl groups, followed by loss of two molecules of water and finally tautomerism, leads to the aromatic molecule.



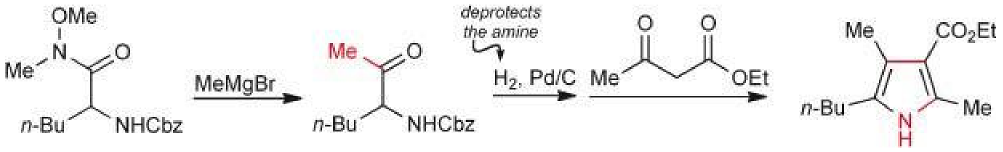
2,3,4,5-tetrahydro-2,5-dimethoxyfuran as an equivalent of butane-1,4-dial for synthesis of C-unsubstituted pyrroles

Synthesis of pyrroles from α-amino-ketones (1,2- and 3,4-bonds made)

This route, often referred to as the *Knorr synthesis*, rests on the one-pot, sequential condensations of an α-amino-ketone with a 1,3-diketone or 1,3-keto-ester, which contain the relatively acidified central methylene (CH_2) necessary for the reaction to proceed. Clearly, aldol-type condensation to form the C-3–C-4 bond and amine-to-ketone-carbonyl nucleophilic addition to generate the N-1–C-2 bond are involved, though the exact order of events is not certain – probably the N–C bond is formed first, giving an enamine. Note: α-Amino-ketones are unstable in that they self-condense to form dihydropyrazines (cf. page 60). Two strategies are available to avoid this problem. The amino-ketone can be provided in *N*-protected form, as a protonic salt for example, the amine being liberated by base *in the presence of* the other synthesis component. Alternatively, the amino-ketone can be *formed* in the presence of the other component, for example by reduction of a precursor α-keto-oxime. The synthesis of the ethyl 2,4-dimethylpyrrole-3-carboxylate shown involves pyruvaldehyde oxime and ethyl acetoacetate. The amino-ketone is produced by reduction of the oxime *in situ*.



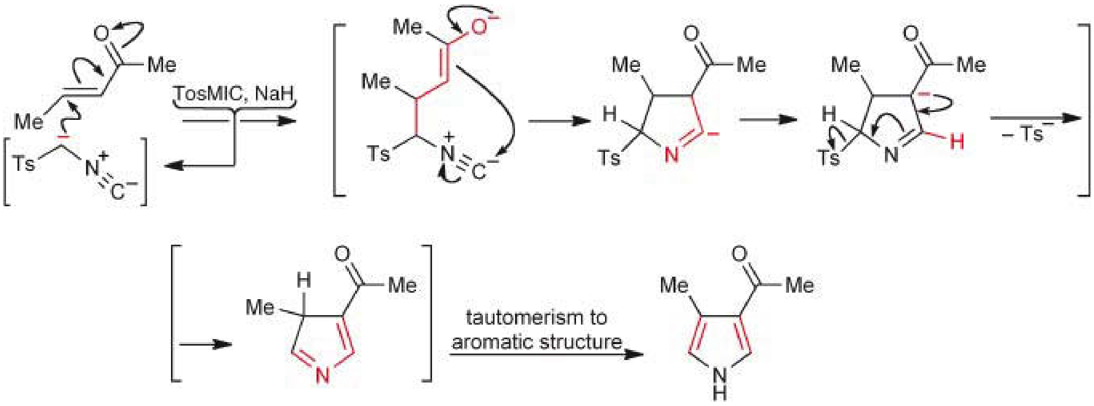
A useful route to *N*-protected α-amino-ketones is the reaction between the 'Weinreb amide' [RCON(OMe)Me] of an *N*-Cbz-protected α-amino acid and an alkyl- or aryllithium or Grignard reagent, to give the ketone. In this situation, the α-amino-ketone is released by hydrogenolysis of the Cbz protecting group, in the presence of the other ring synthesis component, as illustrated for a reaction with ethyl acetoacetate.



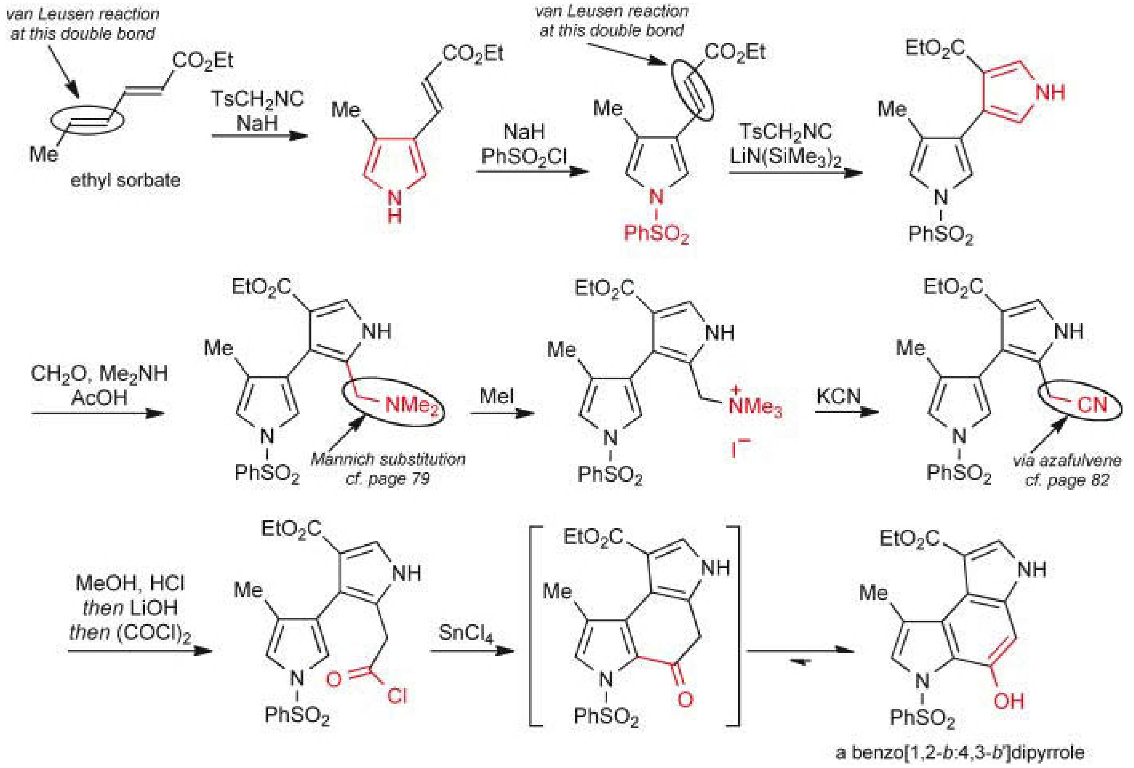
The Knorr synthesis often produces pyrrole esters and it is relevant to recall (page 82) their hydrolysis and easy decarboxylation, if the ester is not required.

Synthesis of pyrroles using isocyanides (2,3- and 4,5-bonds made)

An important disconnection for pyrrole ring synthesis leads back to a two-carbon fragment and a C–N–C fragment – it is this latter unit which includes an isocyanide – tosylmethyl isocyanide (TolSO$_2$CH$_2$NC, TosMIC) has been the most frequently used – the *van Leusen synthesis*. The anion of TosMIC, easily generated, is reacted with an alkene conjugated with an ester or ketone; we represent the sequence (again a one-pot process in which several mechanistic steps occur) as starting with a Michael-type addition. The next step, perhaps strange looking at first sight, is intramolecular nucleophilic addition of the enolate α-carbon to the carbon of the isocyanide, formally negative in the resonance form shown (the other contributor is RN=C:). Proton transfers and finally loss of *p*-toluenesulfinate (Note: the sulfur has changed oxidation level from sulfonate to sulfinate) gives a species requiring only tautomerism to arrive at the aromatic pyrrole.



Benzo[1,2-*b*:4,3-*b*']dipyrroles can be constructed using the pyrrole chemistry described earlier in this chapter in combination with two van Leusen syntheses. For the first van Leusen reaction, the substrate is ethyl sorbate. After masking the pyrrole nitrogen in the product by *N*-phenylsulfonylation via the pyrryl anion, a second use of TosMIC generates a second pyrrole unit. This intermediate has two pyrrole rings, but that with phenylsulfonyl on nitrogen is more deactivated than the other, so Mannich substitution selects the other ring and, of the two available α-positions on that ring, that which is not *ortho* (deactivated by) to the ester. Quaternisation of the side-chain amine allows cyanide to displace the dimethylamine unit (cf. page 82) and the product nitrile is converted into an acid chloride. Finally an intramolecular Friedel–Crafts acylation of the second pyrrole ring, catalysed by tin(IV) chloride, generates the six-membered ring, initially as a ketone, but this immediately tautomerises to the phenolic structure.



Exercises

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. Starting from pyrrole, how would one prepare: (i) 2-bromopyrrole and (ii) 3-bromopyrrole (more than one step may be necessary)?
3. What would be the structures of the products from the following reactions: (i) pyrrole with CH_2O–pyrrolidine–AcOH and (ii) pyrrole with NaH–MeI?
4. How could pyrrole be converted into pyrrol-2-yl-$CH_2CH(CO_2Me)_2$ (more than one step is required)?
5. How could pyrrole be converted into 2-phenylpyrrole (several steps are required)?
6. Which ring synthesis method and what reactants would be appropriate for the synthesis of a pyrrole, unsubstituted on the ring carbons but carrying $CH(Me)(CO_2Me)$ on nitrogen?
7. With what reactant would pentane-2,4-dione ($MeCOCH_2COMe$) need to be reacted to produce 3-acetyl-2-methyl-4,5-diphenylpyrrole?
8. With what reactant would TosMIC ($TsCH_2NC$) need to be reacted to produce methyl 4-ethylpyrrol-3-carboxylate?

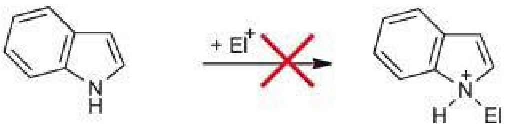
10

Indoles

indole

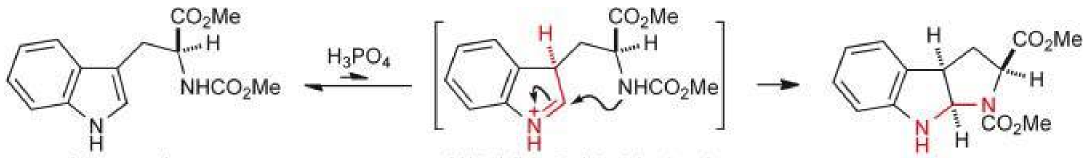
Electrophilic substitution at carbon

Indoles are not basic – they do not form salts by protonation on the nitrogen – this would destroy the aromaticity of the pyrrole ring and produce a localised (non-resonance-stabilised) ammonium ion.



*Indoles do **not** add electrophiles (or protons) at the nitrogen*

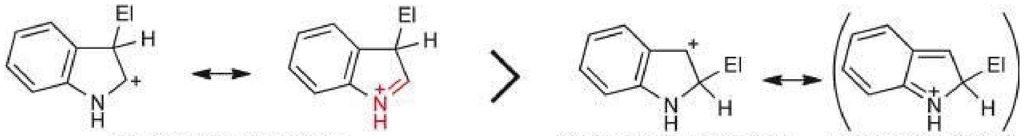
Electrophilic addition of a proton to an indole β-position does occur, to a minor degree, however if the small equilibrium concentration of the resulting cation can be trapped, products resulting from that 3-protonated species (known as a 3*H*-indolium cation or indoleninium cation) can be isolated. Thus, an *N*-protected tryptophan ester can be converted into a tricyclic product via a small concentration of the indoleninium cation, as shown.



an *N*-protected tryptophan methyl ester

a 3*H*-indolium (indoleninium) cation

Similarly, indole does not add electrophiles at the nitrogen, but does readily undergo electrophilic *C*-substitution in the much more electron-rich pyrrole ring. Indoles are attacked by electrophiles *much* more easily than benzene. Attack is preferentially at the β-position but will also, and only slightly less rapidly, take place at an α-position when the β-position is blocked. Positional selectivity and the high reactivity are both well explained by a consideration of the resonance contributors to the intermediates for electrophilic substitution. Intermediate cations from both α- and β-attack are stabilised (and both retain a complete benzene ring), however delocalisation, involving donation of electron density from the heteroatom, is greater in the intermediate from β-attack compared with the α-intermediate, but note that the latter is only slightly less stabilised, being a benzylic cation.



intermediate for β-attack by El⁺

intermediate for α-attack by El⁺

mesomer with disrupted benzene ring is much less important

The high reactivity of indole towards electrophiles is demonstrated by the several substitution reactions illustrated below. Thus, the bromination of indole uses bromine alone; its acylation with a reactive acid chloride does not require

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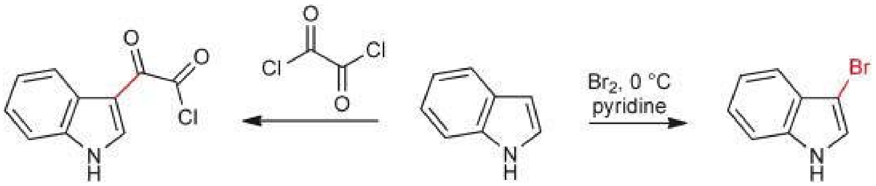
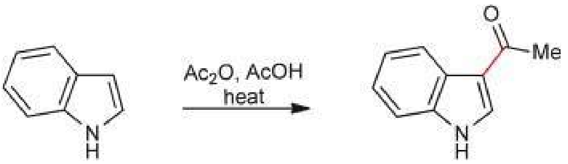
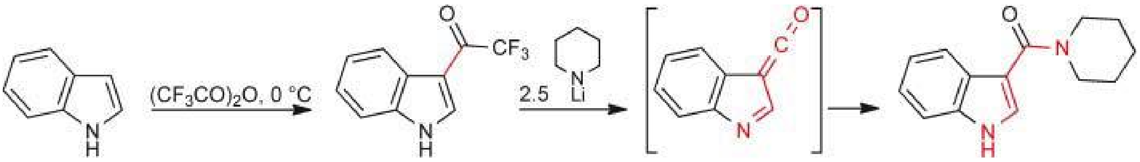
Heterocyclic Chemistry at a Glance, Second Edition. John A. Joule and Keith Mills.

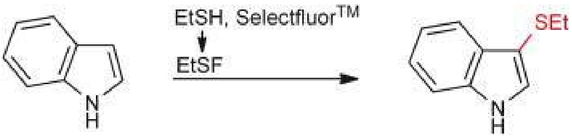
a Friedel–Crafts catalyst: 3-acetylation simply requires heating with acetic anhydride; trifluoroacetylation proceeds even at 0 °C and this product can be simply hydrolysed to the corresponding acid, or converted into a 3-carboxamide, as indicated.



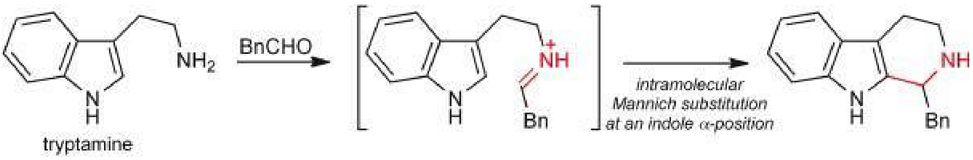




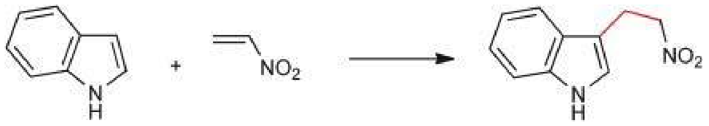
Sulfur substituents can also be introduced via electrophilic substitution: sulfonation uses the pyridine-sulfur trioxide complex; sulfenylation is achieved with a sulfenyl halide (often conveniently generated *in situ*).

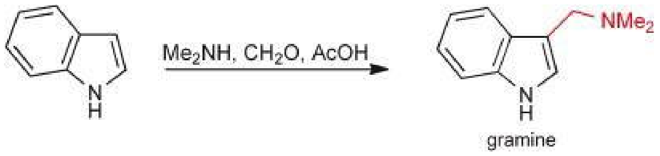


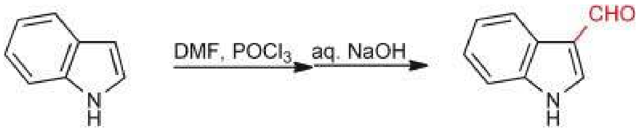
Easy substitution at the α-position is illustrated by the mild intramolecular Mannich reaction involved in the conversion of tryptamine, via an electrophilic iminium intermediate, into a 1,2,3,4-tetrahydro-β-carboline (β-carboline is the widely used, trivial name for pyrido[3,4-*b*]indole).



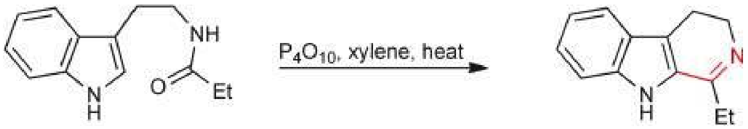
Electrophilic substitutions of indoles are widely used – three other illustrative examples, from many, are: (i) alkylation with nitroethene, again without any acid or other catalyst being required, (ii) conversion into a 3-aldehyde via the Vilsmeier reaction, and (iii) Mannich substitution forming a 3-dialkylaminomethylindole ('gramine' from indole itself, formaldehyde and dimethylamine), involving attack by a mild iminium electrophile, $[H_2C{=}NR_2]^+$, all illustrating again selectivity for the β-position.



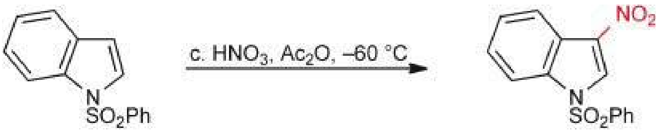


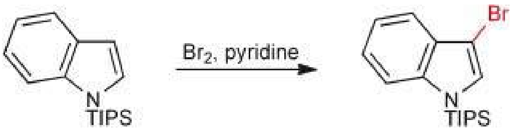


Vilsmeier reactions in an intramolecular sense, at an indole α-position, generate 3,4-dihydro-β-carbolines.

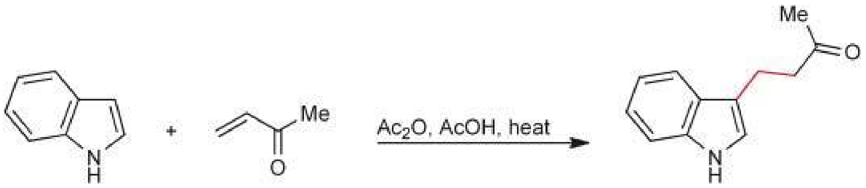


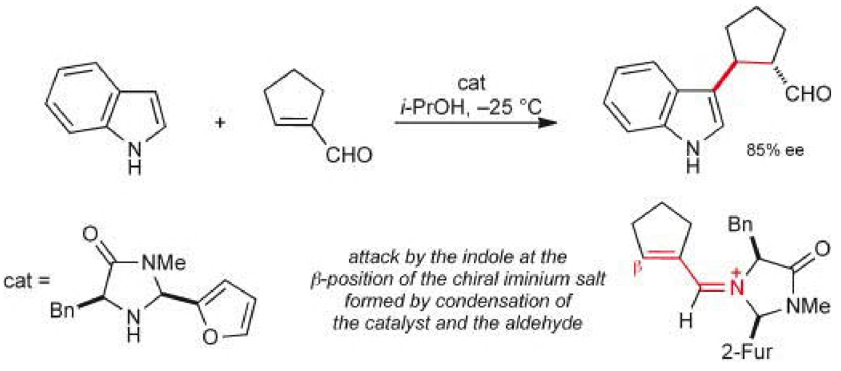
Even indoles carrying electron-withdrawing (and therefore deactivating) groups on nitrogen will undergo β-electrophilic substitution, the 3-nitration of 1-phenylsulfonylindole being an example. Actually, it can be of benefit to stability if an indole is *N*-substituted, with a temporary protecting group if required – this applies particularly to halo-indoles – so the product of bromination of 1-tri-isopropylsilylindole is more easily handled than 3-bromoindole itself.



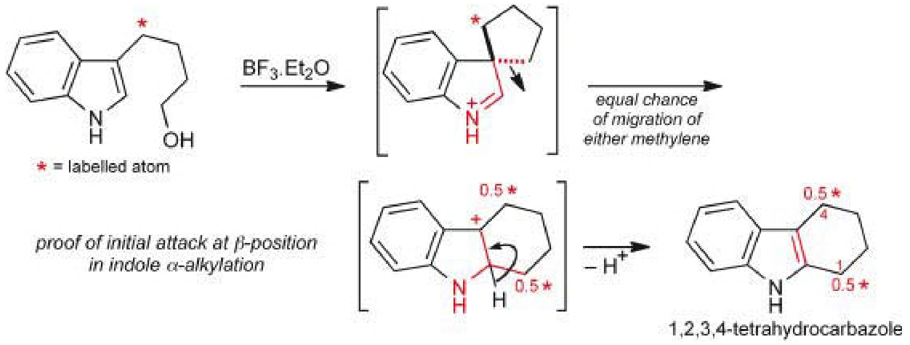


Alkylation of indoles can be achieved with α, β-unsaturated ketones or aldehydes via conjugate addition, usually using acidic conditions. The second example shows how the alternative use of a chiral organo-catalyst can induce optical activity in the product.



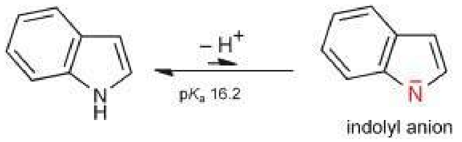


α-Alkylation of 3-alkyl-substituted indoles by cationic reagents involves a rearrangement of a first-formed 3,3-dialkylated-3*H*-indolium cation, verified in the formation of 1,2,3,4-tetrahydrocarbazole by boron trifluoride catalysed cyclisation of 4-(indol-3-yl)butan-1-ol using an isotopically labelled substrate. The consequence of the rearrangement of the symmetrical spirocyclic intermediate, produced by initial preferred electrophilic attack at the β-position, is the equal distribution of the label between the C-1 and C-4 carbons of the product.

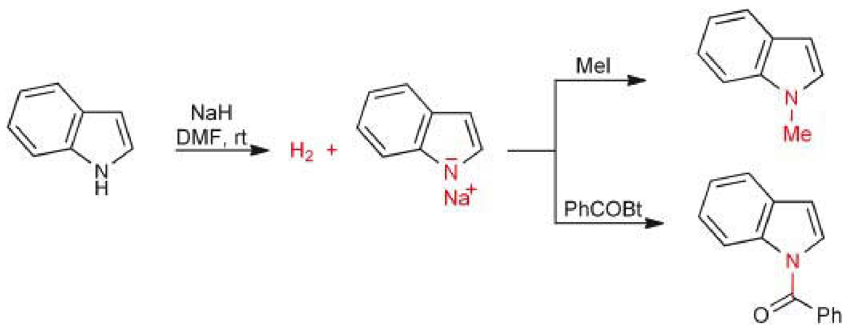


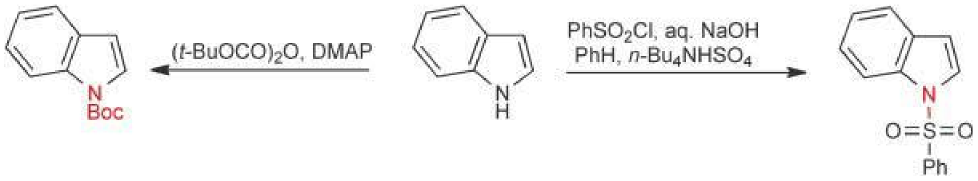
N-Deprotonation and *N*-metallated indoles

The *N*-hydrogen of indole can be quantitatively removed with strong bases giving an indolyl anion. The pK_a of 16.2 for this process is similar to that for pyrrole, 17.5, and much lower than that of an aromatic amine, such as aniline (pK_a 30.7). Indolyl anions are still aromatic species, with two lone pairs associated with the nitrogen, one in the plane of the ring, is available for reaction with electrophiles *without* disrupting the aromaticity, thus allowing *N*-substitution. *N*-Substitution can also be achieved via small concentrations of the indolyl anion generated by weaker bases or in phase-transfer situations.

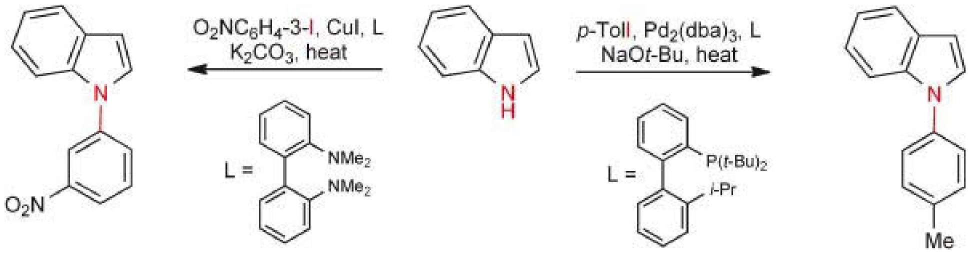


The synthetically-important electrophilic trapping of indolyl anions is illustrated below by the preparation of *N*-benzoylindole and *N*-methylindole, via the indolyl anion (produced quantitatively with a strong base – sodium hydride), and *N*-phenylsulfonylindole and *N*-Boc-indole, via small concentrations of the anion.



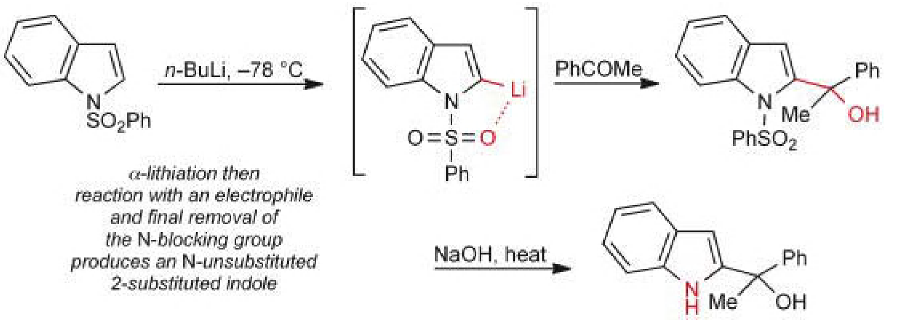


N-Arylation of indoles can be carried out efficiently using palladium or copper catalysis; various ligands have been utilised and two sets of conditions, from several that are known, are shown below.

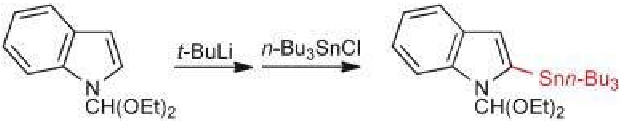


C-Metallated indoles

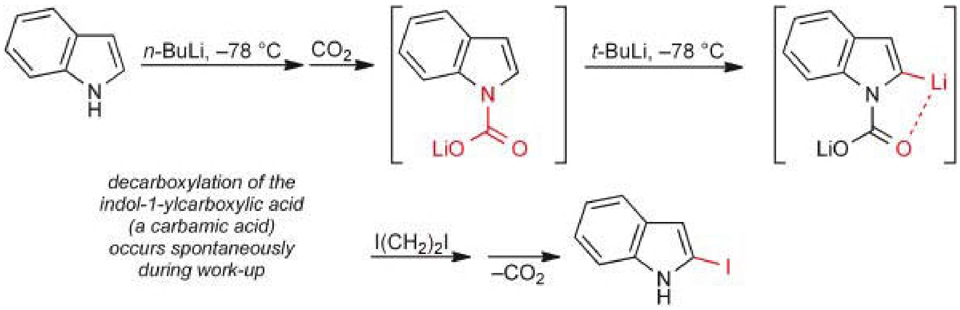
N-Substituted indoles can be *C*-deprotonated, with very strong bases, *selectively at the* α*-position* (2-position), producing organometallic intermediates, which can react with even weak electrophiles, for example carbonyl compounds, giving α-substituted products. This can be carried out using appropriate removable *N*-protecting groups. Several of the common *N*-protecting groups also assist the regioselective α-lithiation via intramolecular co-ordination and electron withdrawal, for example phenylsulfonyl. Amongst other useful removable indole-*N*-protecting groups are *t*-butoxycarbonyl and diethoxymethyl. The examples below illustrate the importance of this lithiation methodology in indole chemistry.



α-lithiation then reaction with an electrophile and final removal of the N-blocking group produces an N-unsubstituted 2-substituted indole

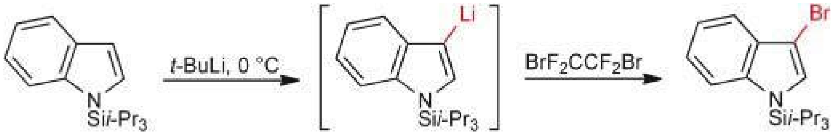


Another elegant device for *N*-protection involves indole-*N*-carboxylation (base and CO_2) before α-lithiation, that is, formation of the lithium salt of a carbamic acid. (A carbamic acid has the general formula $R^1R^2NCO_2H$; a carbamate ester is $R^1R^2NCO_2R^3$.) *N*-Lithiation, addition of CO_2, then reaction with an electrophile at C-2 and *N*-deprotection are carried out all in one pot, without isolation of intermediates – the scheme shows how this works for a synthesis of 2-iodoindole.

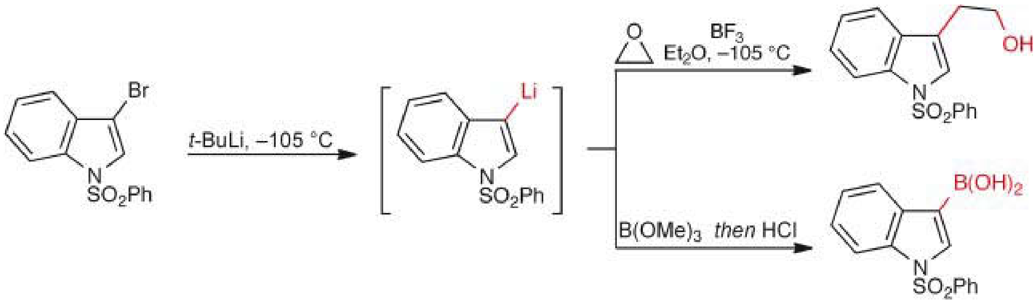


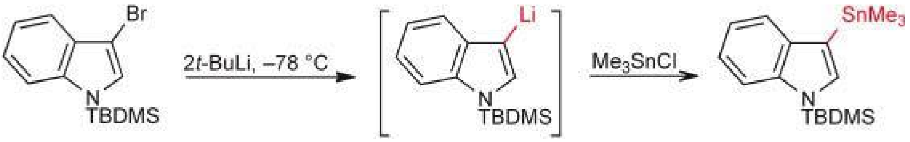
decarboxylation of the indol-1-ylcarboxylic acid (a carbamic acid) occurs spontaneously during work-up

3-Lithio-indoles are usually generated via metal-halogen exchange processes, however direct 3-lithiation of indoles with bulky *N*-trialkylsilyl substituents can also be used.



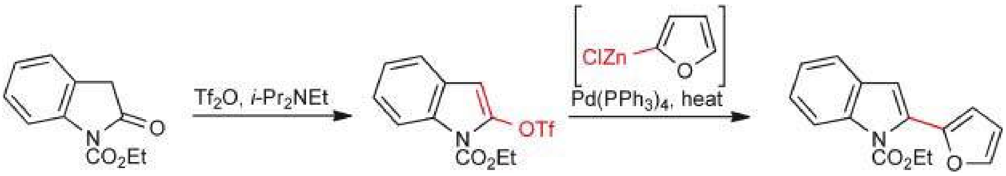
Metal–halogen exchange reactions for the preparation of indol-3-yl-lithiums necessarily require the absence of the acidic *N*-hydrogen. Very-low temperatures must be maintained to prevent isomerisation to the more stable 2-lithiated indole (an *N*-*t*-butyldimethylsilyl 3-lithio derivative is regiostable, even at 0 °C).

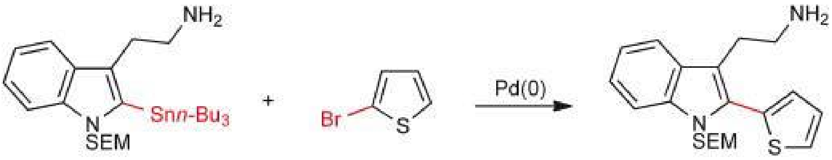


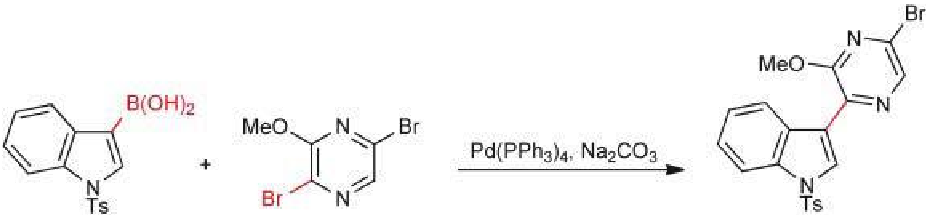


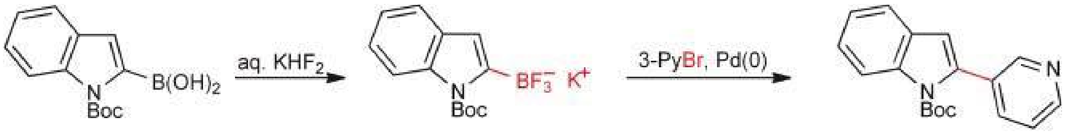
Palladium(0)-catalysed reactions

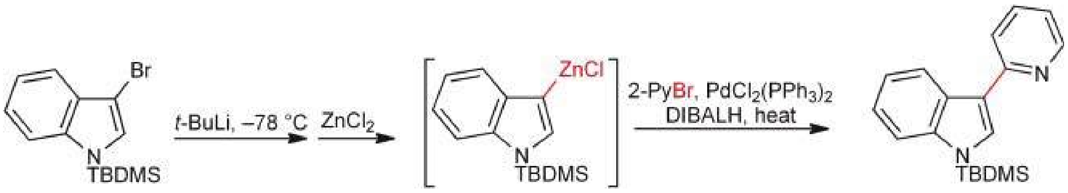
Extensive use of transition metal-catalysed cross-coupling chemistry has been made in the manipulation of indoles. Boronic acids, stannanes and halides can all be utilised, as can triflates formed from 2- or 3-oxygenated indoles. Some typical examples are shown below.





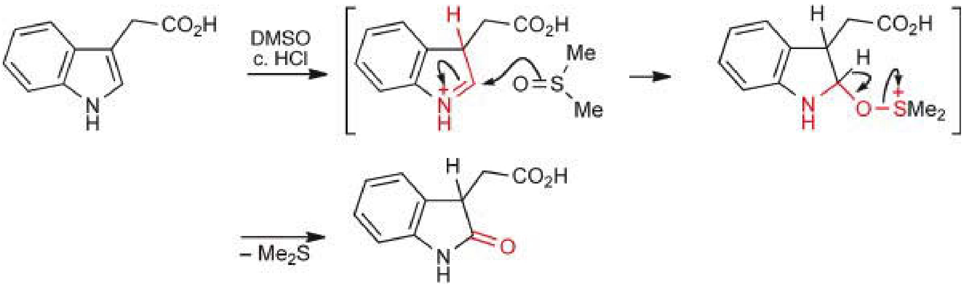




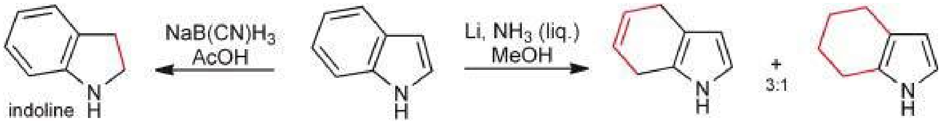


Oxidation and reduction

Indoles are easily autoxidised in the reactive heterocyclic ring. Conversion of 3-substituted indoles into their corresponding oxindoles (page 94) can be brought about using dimethylsulfoxide in acid – a small concentration of β-protonated indole is the key to the sequence (compare with page 86).

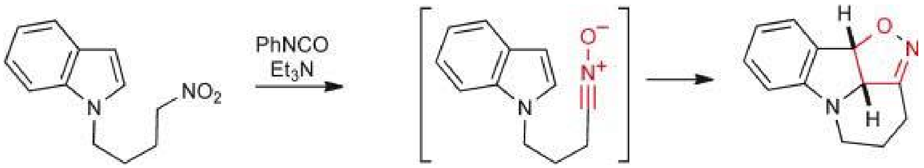


Treatment of indole with sodium in liquid ammonia (Birch reduction) causes reduction of the benzene ring only; it is significant that the products are now dialkyl-pyrroles. Metal (or metal hydride)-acid combinations reduce only the heterocyclic ring; the process involves attack on a small amount of 3*H*-indolium salt. The 2,3-dihydroindole products are known as indolines but, chemically speaking, behave as anilines.

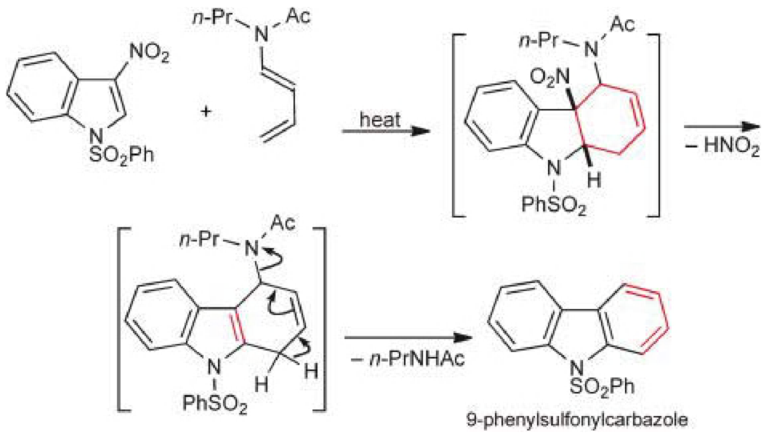


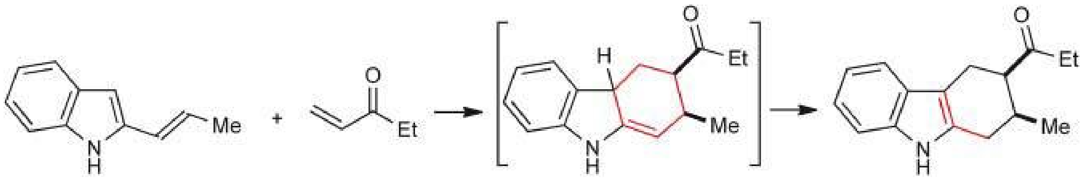
Pericyclic reactions

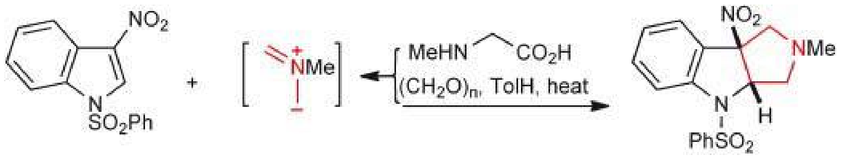
Indoles, as aromatic molecules, only rarely act as partners in electrocyclic processes – special situations are needed to force the 2,3-double bond to participate in cycloadditions. The 2,3-double bond in simple indoles will take part in cycloaddition reactions with dipolar 4π components, and with electron-deficient dienes (i.e. inverse electron demand), especially when the two reacting components are tethered together.



When electron-withdrawing substituents are present on nitrogen and/or at C-3, even electron-rich dienes react, for example 3-nitro-1-phenylsulfonylindole takes part in dipolar cycloaddition with azomethine ylides and undergoes Diels–Alder addition across the 2,3-double bond with 1-acylaminobuta-1,3-dienes (the final product is formed via successive losses of nitrous acid and then the amine giving a carbazole). Both 2- and 3-vinylindoles will act as dienes in Diels–Alder additions.

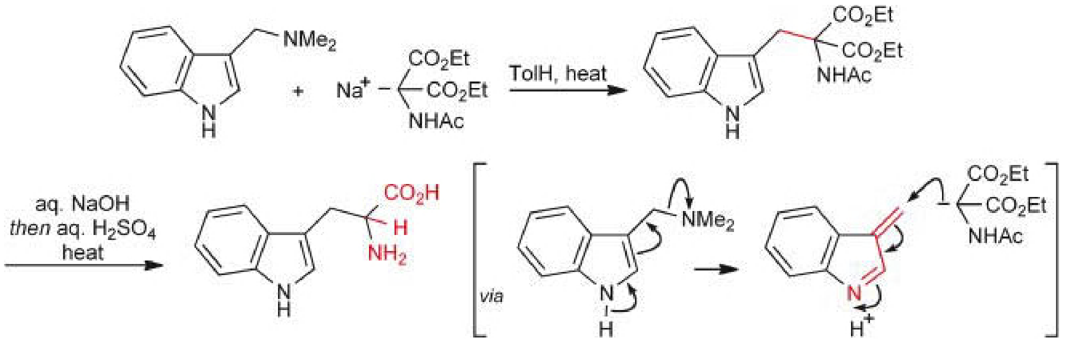




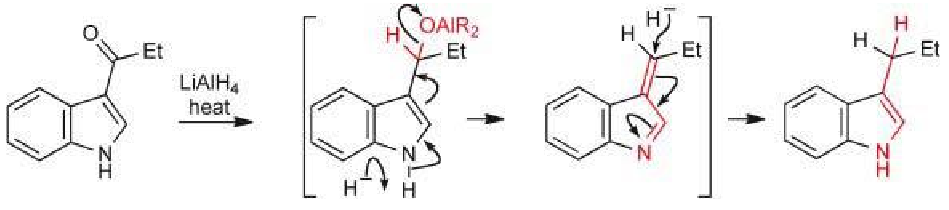


Reactivity of side-chain substituents

The electron-rich character of indoles gives rise to some special properties of side-chain substituents. 3-Dialkylaminomethyl-indoles, easily produced in Mannich substitutions (page 88), can be utilised in further elaborations, because the amine group (or an ammonium group derived by selective side-chain amine quaternisation) can be easily displaced by nucleophiles. These are not direct displacements but involve ring-*N*-hydrogen deprotonation by the nucleophile, acting as a base, leading to elimination of the side-chain nitrogen and an intermediate 3-alkylidene-indolenine; the nucleophile then adds, in a conjugate fashion.

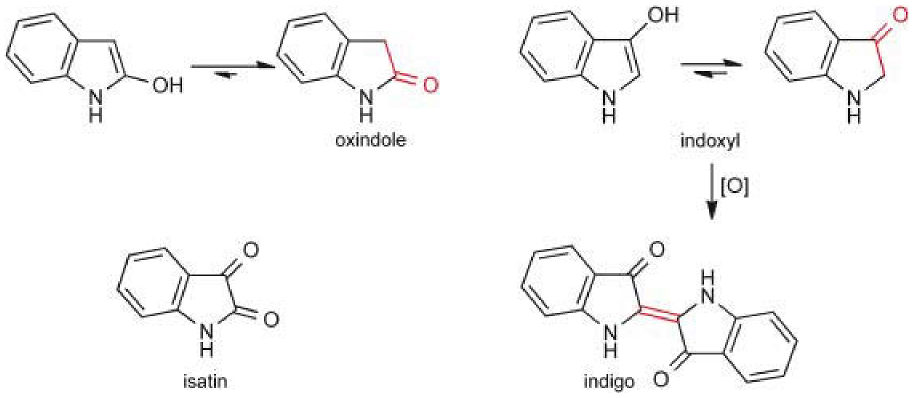


A related sequence is involved in the lithium aluminium hydride reduction of indol-3-ylcarbinols (or the corresponding ketones) constituting a useful synthesis of 3-alkylindoles.



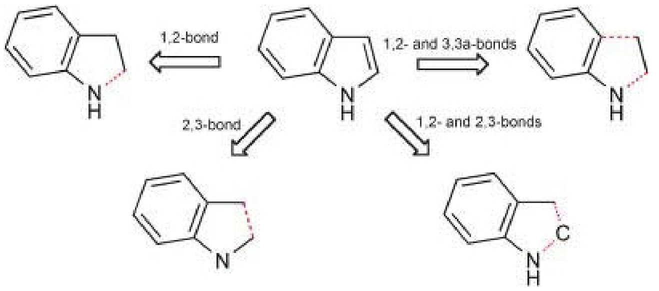
Oxygen substituents

Indoles with a hydroxyl group on the benzene ring behave as normal phenols. '2-Hydroxyindole' exists entirely in the carbonyl tautomeric form and is known as oxindole. The properties of oxindole are generally those of a five-membered lactam but with somewhat enhanced acidity of the methylene at C-3. 3-Hydroxyindole is the minor component in tautomeric equilibrium with the ketone form, and this mixture is usually known as indoxyl. It is easily oxidised and transformed into the ancient dye, indigo. Isatin is best viewed simply as an α-keto-amide. Isatins undergo straightforward electrophilic substitution in the benzene ring, at C-5, and this, coupled with reaction chemistry of the ketone and amide groups, can be used to advantage for the synthesis of indoles and quinolines (see page 69).



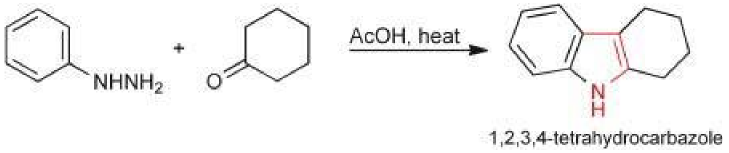
Ring synthesis – disconnections

There are many, many ways to synthesise indoles but here we will discuss six important routes for the construction of indoles from precursors without a pyrrole ring, based on the disconnections summarised below. Indoles can also be obtained readily by dehydrogenation of indolines (2,3-dihydroindoles) with various oxidants.

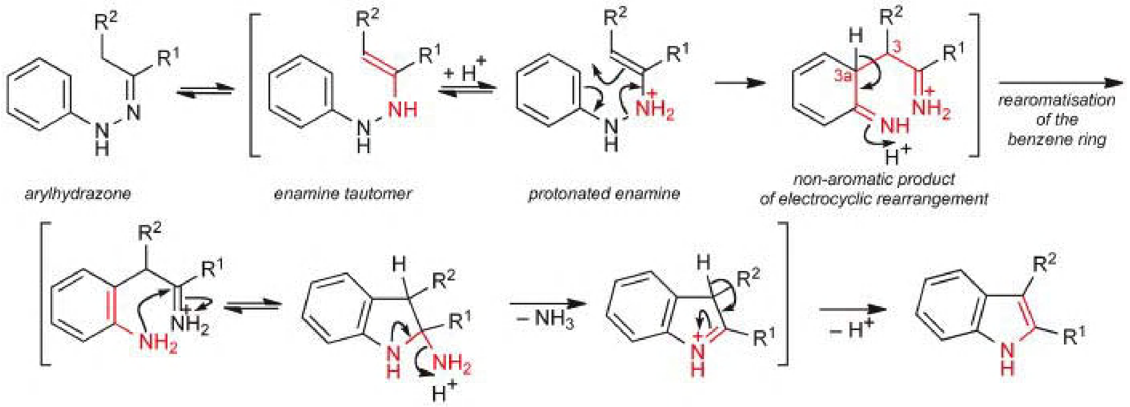


Synthesis of indoles from arylhydrazones (1,2- and 3,3a-bonds made)

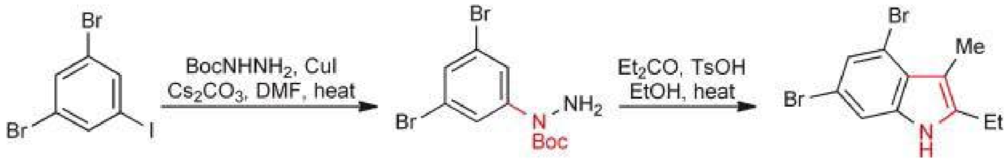
The *Fischer synthesis*, the classic route to indoles, was discovered by Emil Fischer in 1883. It is still one of most widely used routes to indoles. In essence, an arylhydrazone of a ketone or aldehyde is heated with acid, ammonia is lost and an indole is formed. Often it is convenient to make the arylhydrazone *and* carry out the ring synthesis in one pot without isolation of the arylhydrazone, for example the reaction between cyclohexanone and phenylhydrazine producing tetrahydrocarbazole.



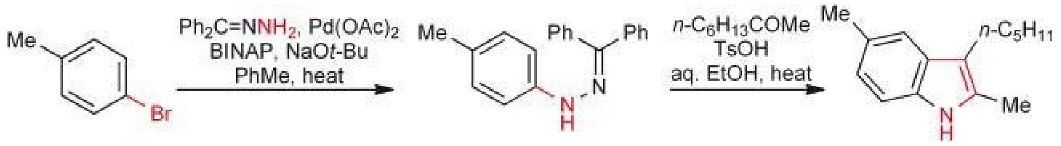
The scheme shows the sequence of steps for a general ketone with phenylhydrazine. The phenylhydrazone is in equilibrium with a small amount of its enamine tautomer, which is *N*-protonated, and it is this species that undergoes an *irreversible* electrocyclic rearrangement in which the 3–3a bond is made and the N–N bond is broken. Re-aromatisation of the benzene ring, then intramolecular amine→iminium addition, and finally loss of ammonia produces the indole.



Alternative routes to arylhydrazines for Fischer cyclisations are useful, for example aryl halides can be substrates using transition metal-catalysed *N*-arylation. *N*-Boc-hydrazine aminates various aryl iodides forming *N*-aryl-*N*-Boc-hydrazines for use directly in the Fischer sequence (the Boc is lost during the reaction).

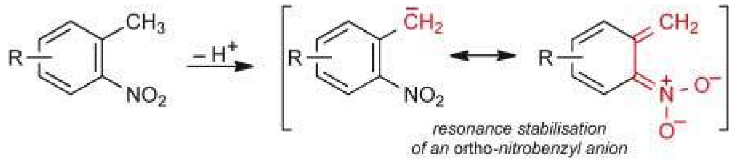


Benzophenone hydrazone can be similarly used to produce arylhydrazones of benzophenone from aryl halides, and these can be utilised directly, acid-catalysed exchange with the desired ketone *in situ* being followed by the Fischer sequence.

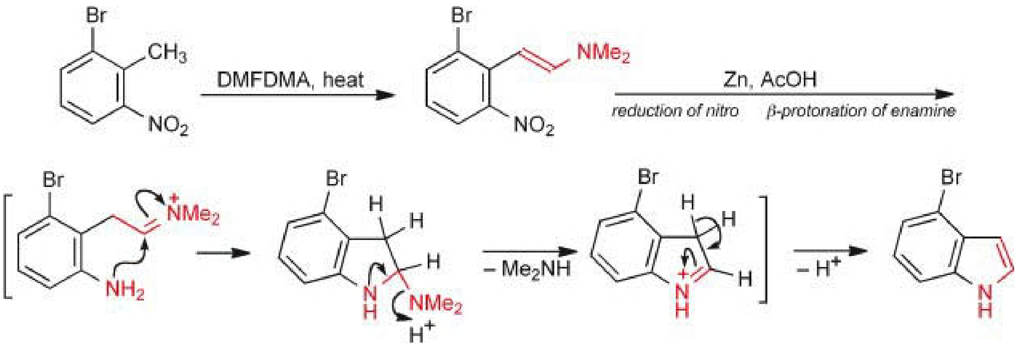


Synthesis of indoles from *ortho*-nitrotoluenes (1,2- and 2,3-bonds made)

The hydrogens of the methyl group of *ortho*-nitrotoluenes are acidified because the anion produced is stabilised by resonance interaction with the nitro group. The *Leimgruber–Batcho synthesis* takes advantage of this acidity.

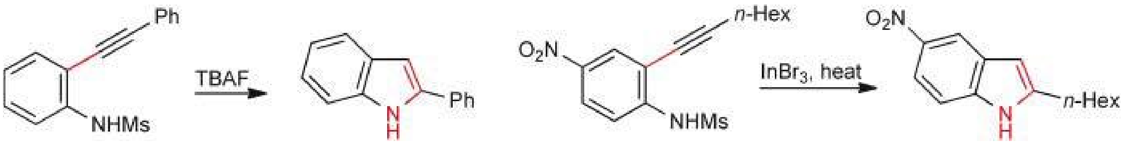


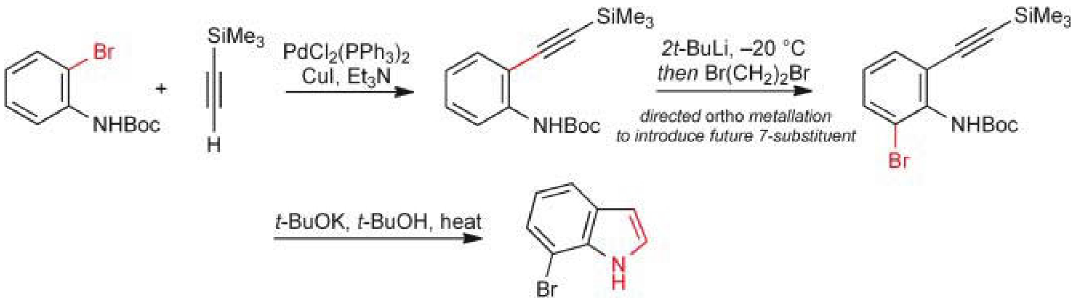
An *ortho*-nitrotoluene is simply heated with dimethylformamide dimethyl acetal (DMFDMA) giving an isolable enamine, reduction of which, in acidic conditions, then leads to the indole. The final stages in the sequence are closely similar to the final steps in the Fischer sequence.



Synthesis of indoles from *ortho*-aminoaryl alkynes (1,2-bond made)

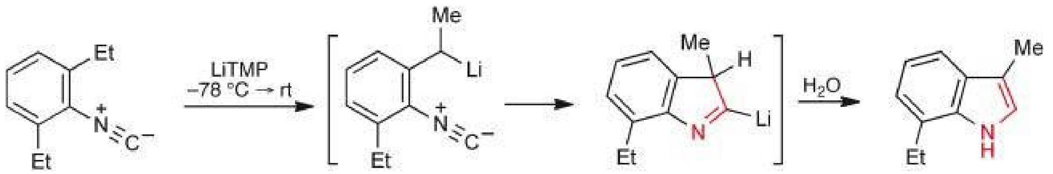
With the advent of palladium-catalysed cross-coupling methodology, indoles can be synthesised starting from arenes in which a halide is *ortho* to a nitrogen function – a nitro or amine group or a protected amine. The palladium-catalysed step involves displacement of the halide with an alkyne with concurrent or later ring closure. When an *ortho*-nitroaryl halide is employed for the cross-coupling, ring closure cannot take place until a subsequent reductive step takes the nitro group down to an amine. Three examples of the several available variants of this theme are shown below.





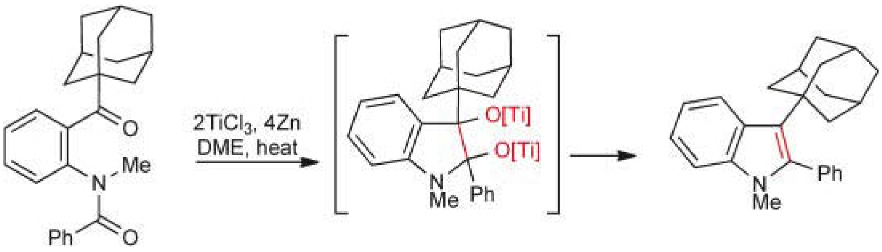
Synthesis of indoles from *ortho*-alkylaryl isocyanides (2,3-bond made)

Cyclisation of benzylic anions derived from *ortho*-alkylaryl isocyanides, formed at low temperature and allowed to come to room temperature, produces 2-unsubstituted indoles. The synthesis is shown in a simple form in the scheme, however it is flexible, for example the initial benzylic anion from *ortho*-isocyanotoluene can be alkylated with halides or epoxides, before the ring closure thus providing 3-substituted indoles.



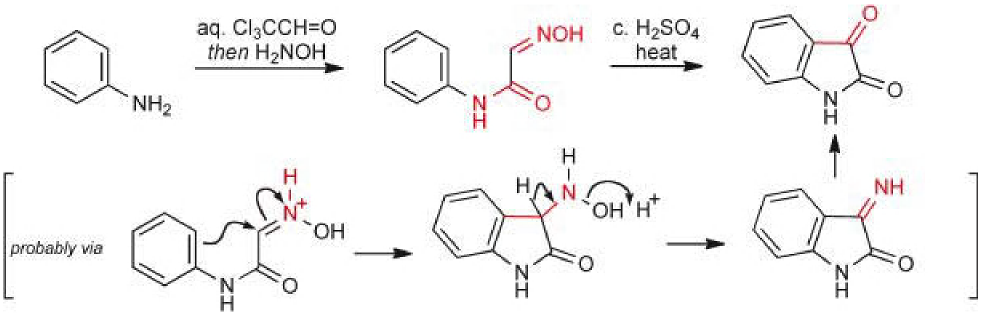
Synthesis of indoles from *ortho*-acyl anilides (2,3-bond made)

The flexible *Fürstner synthesis* depends on the reductive cyclisation of *ortho*-acylanilides with low valent titanium – the conditions used for the McMurray coupling of ketones to produce alkenes. Indoles carrying two bulky substituents on the heterocyclic ring can be assembled in this way.



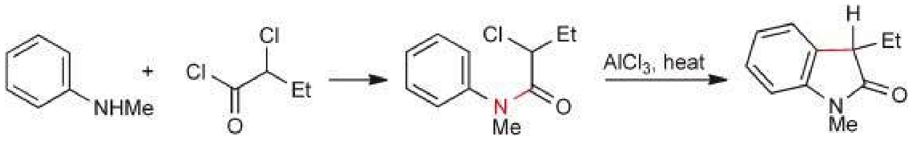
Synthesis of isatins from anilines (1,2- and 3,3a-bonds made)

Isatins can be readily prepared via the reaction of an aniline with chloral, the resulting product being converted into an oxime, which is then cyclised in strong acid.



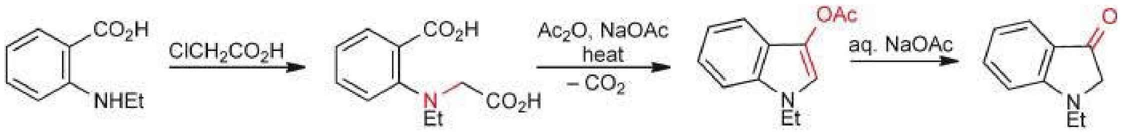
Synthesis of oxindoles from anilines (1,2- and 3,3a-bonds made)

The main synthesis of oxindoles is simple and direct and involves an intramolecular Friedel–Crafts alkylation reaction as the cyclising step.

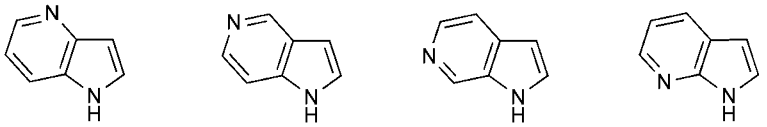


Synthesis of indoxyls from anthranilic acids (1,2- and 2,3-bonds made)

Indoxyls are normally prepared from anthranilic acids; first, the nitrogen is alkylated with a 2-haloacetic acid and then cyclisation is achieved with loss of carbon dioxide; the resulting acetate of the indoxyl is easily hydrolysed.

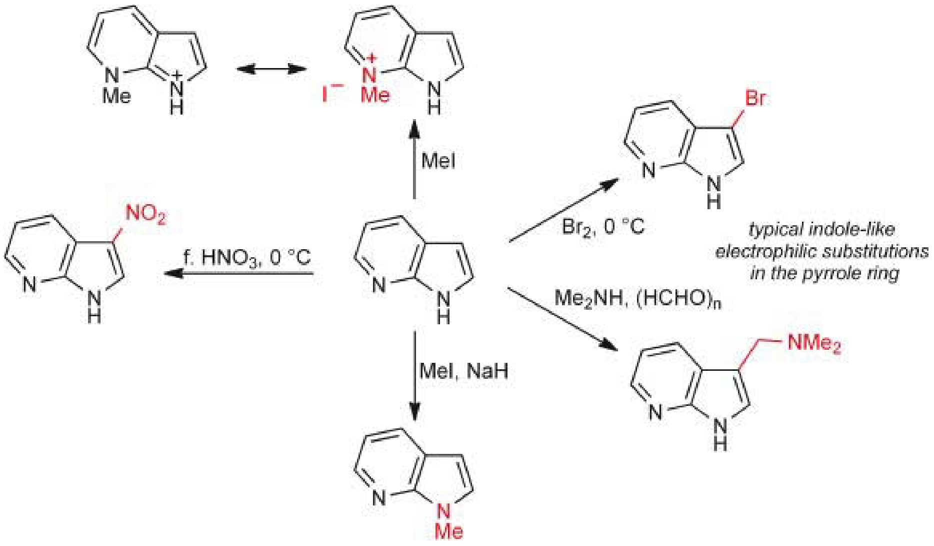


Azaindoles

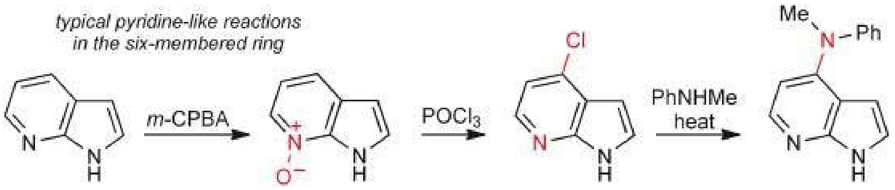


	4-azaindole [pyrrolo[3,2-*b*]pyridine]	5-azaindole [pyrrolo[3,2-*c*]pyridine]	6-azaindole [pyrrolo[2,3-*c*]pyridine]	7-azaindole [pyrrolo[2,3-*b*]pyridine]
pK_{aH}	6.94	8.26	7.95	4.59

The (mono) azaindoles (more correctly pyrrolopyridines), where one of the carbons of the six-membered ring of indole has been notionally replaced by nitrogen, are of chemical interest as typical bicyclic systems comprising an electron-rich fused to an electron-poor system. Although they do not occur in nature, they have a number of potential applications, including in medicinal chemistry, as isosteres or substitutes for various indole-based moieties. The pyrrole enamine system and the pyridine imine system can interact mesomerically in all four isomers.



Like indole, they undergo electrophilic substitution in the five-membered ring but have the advantage of not being as acid-sensitive as indole. Nucleophilic substitution can be carried out in the six-membered ring, with a reactivity similar to the corresponding chloropyridines (much less reactive than chloro-(iso)quinolines).



Exercises

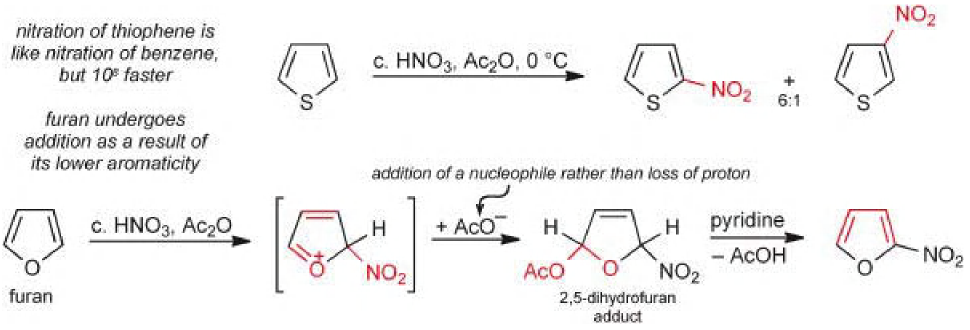
1. What are the structures of the intermediates and final product in the following sequence: indole with $(COCl)_2 \rightarrow C_{10}H_6ClNO_2$ then this with ammonia $\rightarrow C_{10}H_8N_2O_2$ then this with $LiAlH_4 \rightarrow C_{10}H_{12}N_2$?
2. Deduce a structure, and write out the mechanism for the conversion of 2-formylindole into a tricyclic compound, $C_{11}H_9N$, on treatment with a combination of NaH and $Ph_3P^+CH{=}CH_2\,Br^-$.
3. What are the products formed in the following sequence: 3-iodoindole with LDA, then $PhSO_2Cl \rightarrow C_{14}H_{10}INO_2S$, then this product with LDA, then $I_2 \rightarrow C_{14}H_9I_2NO_2S$.
4. When 3-dimethylaminomethylindole is heated with NaCN, 3-cyanomethylindole (indol-3-yl-CH_2CN) is formed. What is the mechanism?
5. When indol-3-yl-CH_2OH is heated with acid, di(indol-3-yl)methane is formed: suggest a mechanism for this transformation.
6. Which phenylhydrazones would be required for the Fischer indole synthesis of: (i) 3-*n*-propylindole; (ii) 1,2,3,4-tetrahydro-6-methoxycarbazole; (iii) 2-ethyl-3-methylindole; and (iv) 3-ethyl-2-phenylindole?
7. What product, $C_{10}H_{11}NO$, would be obtained from refluxing a mixture of phenylhydrazine and 2,3-dihydrofuran in acetic acid?
8. 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; and (iv) 2,3-dinitro-1,4-dimethylbenzene then H_2–Pd gave $C_{10}H_8N_2$.
9. How could one convert 2-bromoaniline into 2-phenylindole (more than one step is required)?

11

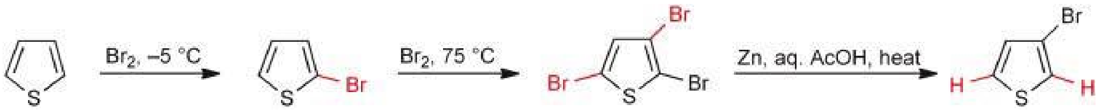
Furans and Thiophenes

Electrophilic substitution at carbon

Furan and thiophene can usefully be examined in parallel, comparing one with the other and with pyrrole. Each of them, like pyrrole, is very much more reactive towards electrophiles than benzene. In this trio of heteroaromatic systems, thiophene is the 'most aromatic' – the most like benzene – and furan is the 'least aromatic' – the most like a 1,3-diene. For example, thiophene undergoes normal nitration, with α-selectivity (like pyrrole – see the discussion on page 78) but furan tends to produce 2,5-dihydrofuran *adducts* in which the elements of the attacking agent ($AcONO_2$ in the case of nitration) have *added* to the heterocycle with a consequent loss of aromaticity. The aromatic substitution product can be easily obtained from the adduct by base-induced loss of acetic acid.

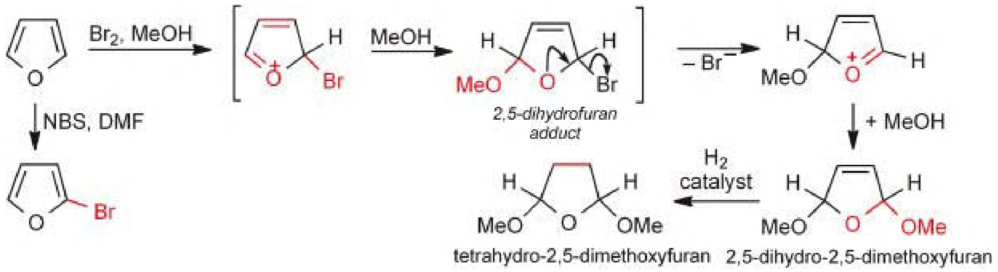


Another example is bromination – 2-bromothiophene is obtained from thiophene, even at –5 °C, using bromine alone, no catalyst is required – thiophene is more reactive than benzene and furan more reactive than thiophene. Under slightly more vigorous conditions, it is easy to 2,5-di-, 2,3,5-tri- and 2,3,4,5-tetra-brominate thiophene and 2,3,5-tribromothiophene and 2,3,4,5-tetrabromothiophene can be used to access 3- or 3,4-dibromothiophenes because zinc–acetic acid specifically reduces out α-bromines.

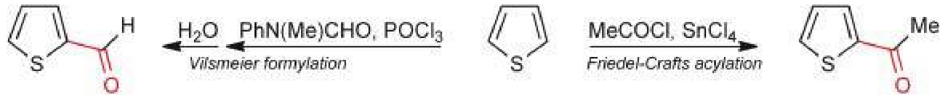


Furan also reacts rapidly with bromine, but in a nucleophilic solvent, such as methanol, the initial cationic intermediate is trapped by *addition* of solvent. The final product, 2,5-dihydro-2,5-dimethoxyfuran results from a nucleophilic displacement of the bromine from its reactive position in the first adduct, the bromine being both allylic and α to oxygen. 2,5-Dihydro-2,5-dimethoxyfuran is a synthetic equivalent of but-2-ene-1,4-dial, and its dihydro-derivative, of butane-1,4-dial, and both of these are valuable in heterocyclic ring synthesis (see pages 58 and 83).

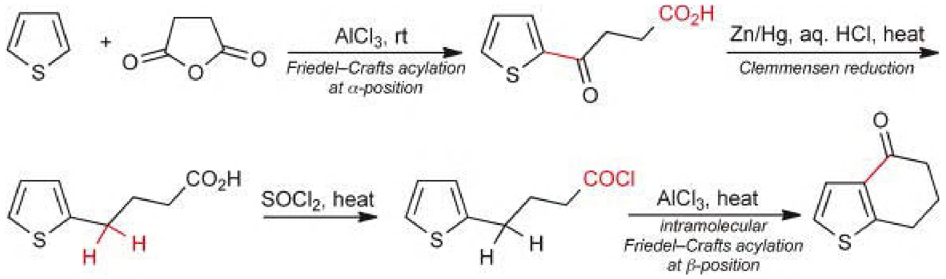
Heterocyclic Chemistry at a Glance, Second Edition. John A. Joule and Keith Mills.



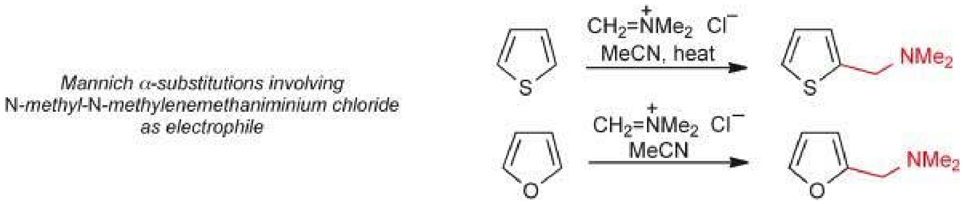
Vilsmeier formylation and Friedel–Crafts acylations proceed efficiently with thiophene and furan, using $SnCl_4$ as the catalyst for thiophenes and BF_3 for furans.

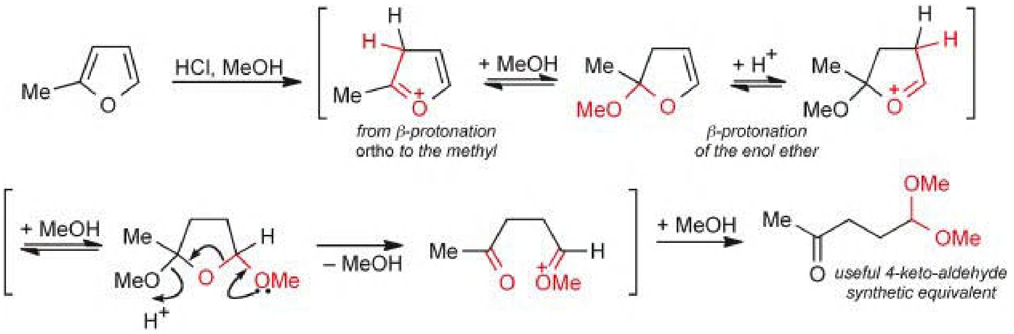


Though α-selectivity is the rule, β-substitution also occurs easily when the 2- and 5-positions cannot be accessed. This can be illustrated by the synthesis of 4-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene from thiophene, involving two acylations, the first at an α-position and the second at a β-position.



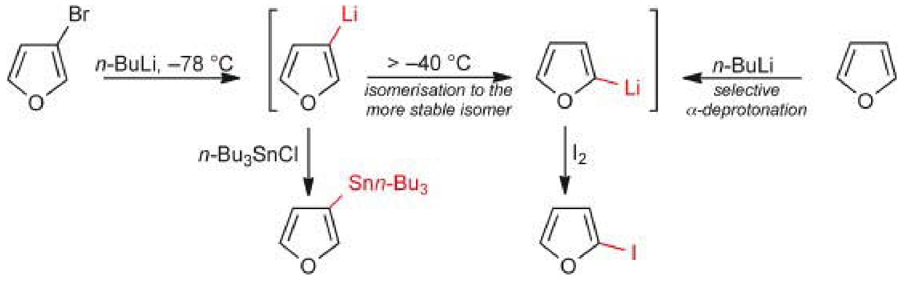
The Mannich dimethylaminomethylation of thiophene and furan is conducted using the preformed iminium salt. This is especially important in the case of furan as this heterocycle is sensitive to acid; indeed, under the appropriate conditions, furans can be converted, using acid, into useful non-cyclic derivatives of 1,4-dicarbonyl compounds. It is not possible to be sure of the exact sequence of events, but a series of protonations and additions of methanol are involved.



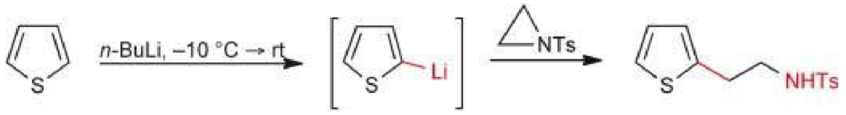


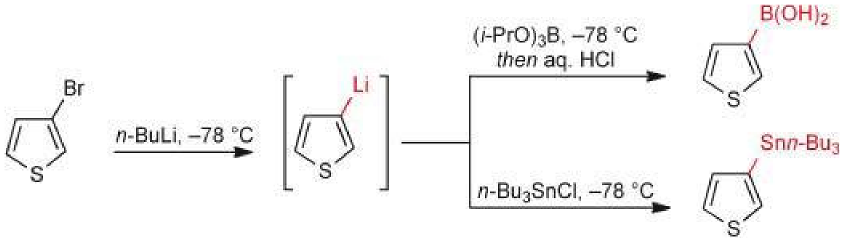
C-Metallated thiophenes and furans

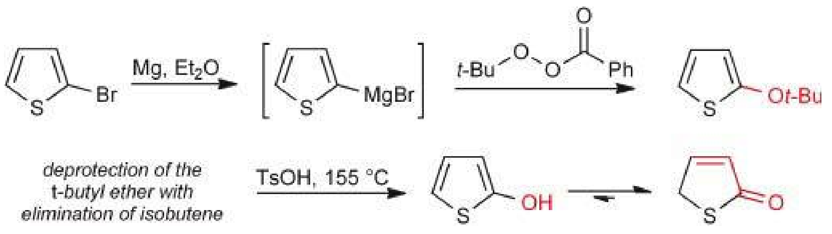
In thiophene and furan chemistry, there is, of course, no equivalent to the acidic *N*-hydrogen of pyrrole. Thus, we can compare strong base metallation of thiophene or furan to the deprotonation of *N*-substituted pyrroles, and in the absence of other influences, exactly comparable selectivity is observed – *exclusive deprotonation at the* α*-position*, adjacent to the heteroatom. The selectivity is further illustrated by the isomerisation of the 3-lithiated heterocycles (generated from the 3-halides by exchange reactions), to the 2-lithio-heterocycles at temperatures above about −40 °C.



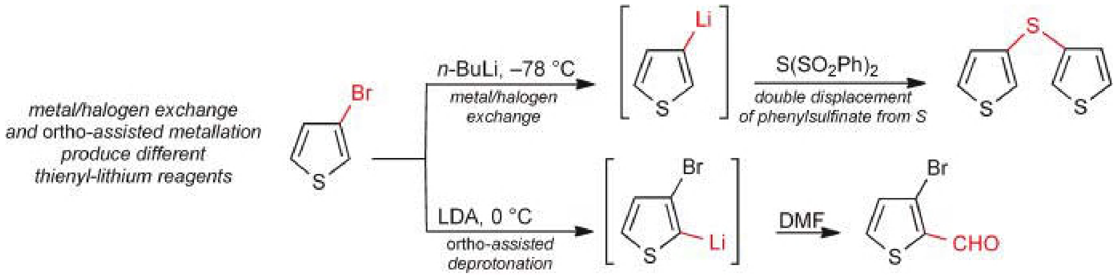
The 2-lithio- and the 3-lithio-species (at low temperature) behave as normal carbon organometallic nucleophiles and will react with the full range of electrophilic reagents. Grignard reagents can be formed easily from bromo- and iodothiophenes and, significantly, the 3-isomer does not isomerise to its 2-isomer, even at room temperature.





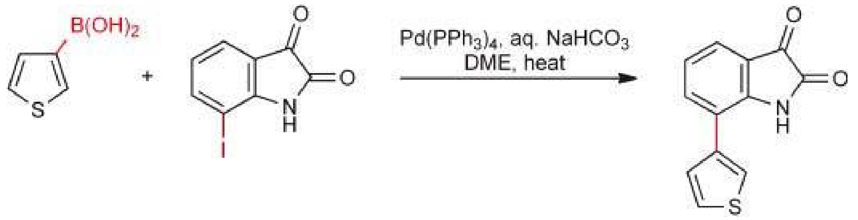


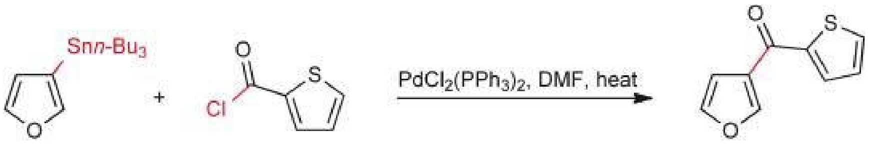
Lithio-reagents formed by deprotonations under the influence of an *ortho*-directing group (DOM) also feature widely in the chemistry of thiophene and furan. A nice and illustrative example is the deprotonation of 3-bromothiophene with LDA: *ortho*-assistance from the electronegative halogen substituent guides deprotonation to the 2-position, rather than the other α-position (C-5). In contrast, reaction with *n*-butyllithium brings about a metal–halogen exchange process and gives 3-lithiothiophene.

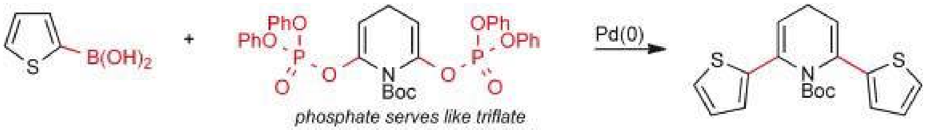


Palladium(0)-catalysed reactions

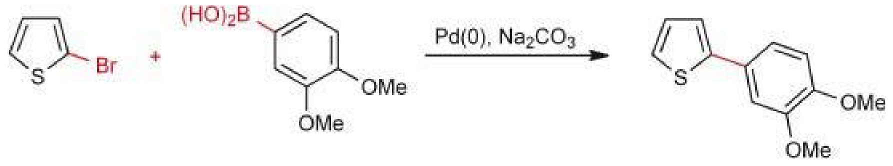
Boron and tin derivatives are known at α- and β-positions of furan and thiophene and are extensively used in cross-couplings and other reactions, but the α-boronic acids have a tendency to protodeboronation under strongly basic conditions. Halides at either position of either heterocycle have also been widely employed in this context. The small selection of such carbon–carbon bonding reactions shown illustrates the wide applicability of palladium(0)-catalysed processes in thiophene and furan chemistry.

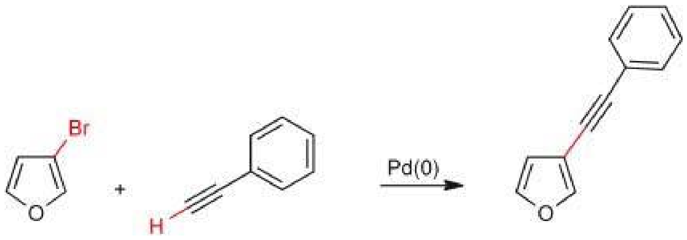






phosphate serves like triflate (but is somewhat less reactive)

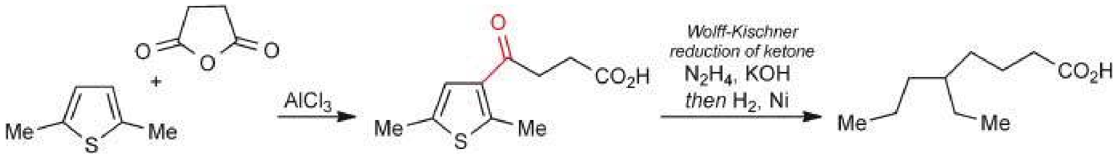




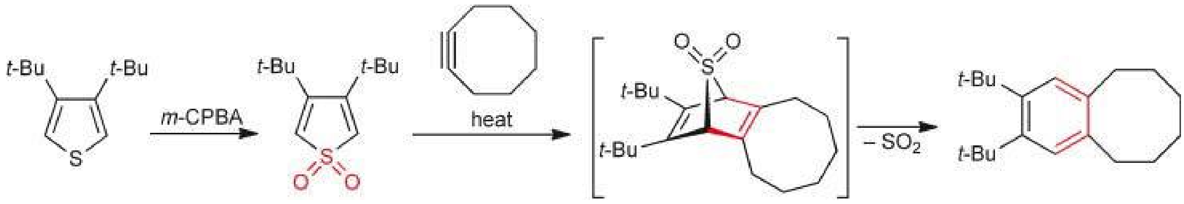
Oxidation and reduction

Exhaustive reduction and *S*-oxidation of thiophenes

There are two aspects of thiophene chemistry that are not mirrored by furan or pyrrole. Firstly, Raney nickel and hydrogen bring about complete reduction, including removal of the sulfur. Thus thiophene can be used as a framework to build up a branched carbon skeleton with a final removal of the sulfur and reduction. For example, Friedel–Crafts acylation of 2,5-dimethylthiophene (only β-positions available) using succinic anhydride, followed by Wolff–Kischner reductive removal of the resulting ketone and finally Raney nickel hydrogenation/hydrogenolysis, produces 5-ethyloctanoic acid.

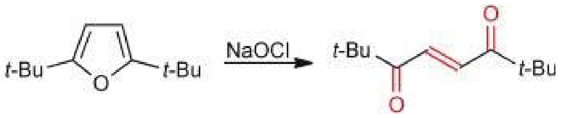


Peracids convert thiophenes into *S*,*S*-dioxides that are no longer aromatic (no electrons on the sulfur to make up an aromatic sextet) and which react as dienes in Diels–Alder reactions. Generally sulfur dioxide is extruded from the initial adducts, leading to aromatisation, as in the example shown (see also page 104).

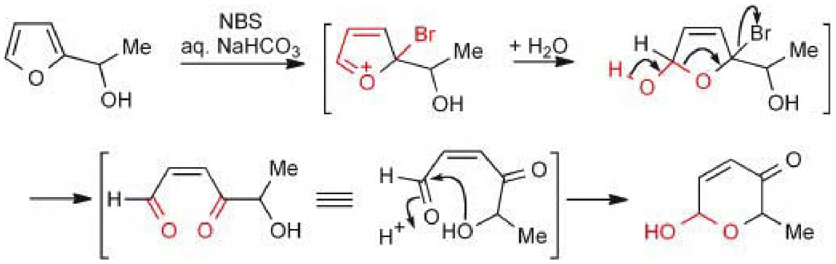


Controlled oxidation of furans

The conversion of furans into 2,5-dihydro-2,5-dimethoxyfurans (synthetic equivalents of unsaturated 1,4-dicarbonyl compounds, see page 100) via halogenation in methanol is effectively an oxidation. There are other ways in which desirable unsaturated 1,4-diketones can be accessed from furans. Clearly, oxidative cleavage of the ring must produce *Z*-isomers initially and these can be the isolated products using *m*-chloroperbenzoic acid or hydrogen peroxide catalysed by methyltrioxorhenium. Acid catalyses isomerisation to the more stable *E*-isomers.

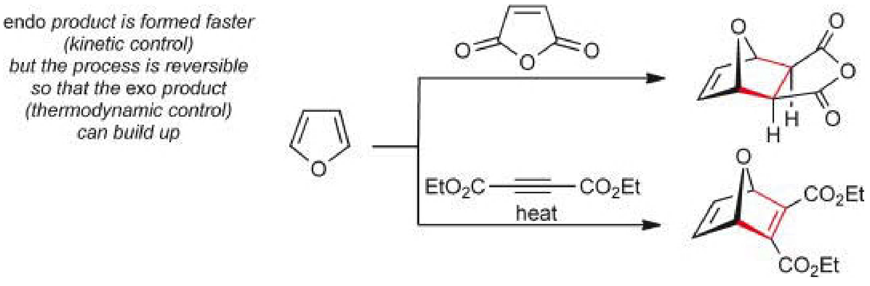


The oxidation of furyl-2-carbinols can produce 6-hydroxy-2*H*-pyran-3(6*H*)-ones, which can be used for the formation of pyrylium-3-olates (page 73).

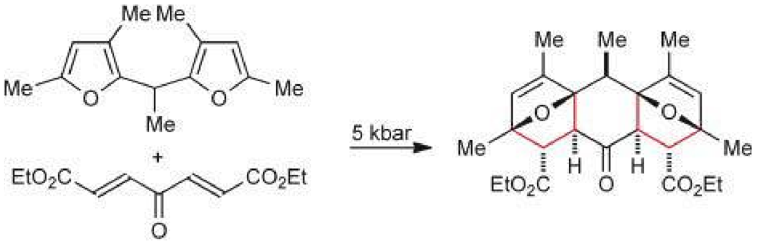


Pericyclic reactions

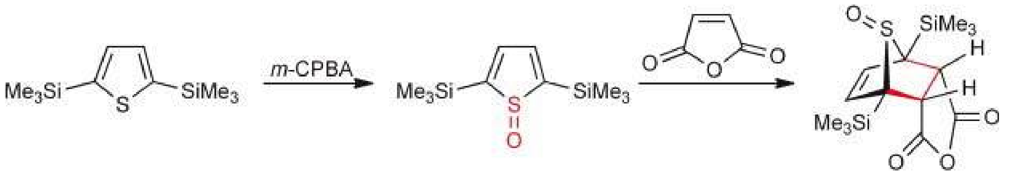
Furan, the 'least aromatic' of the trio furan/thiophene/pyrrole, reacts readily with electron-deficient dienophiles; the *exo* structure of its product using maleic anhydride is the result of a readily reversible cycloaddition that allows the kinetic *endo* product to be converted into the more stable *exo* isomer. At higher reaction temperatures or under very high pressures, alkynes and even electron-rich alkenes will cycloadd to furan. Pyrroles will only act as 4π components in Diels–Alder reactions when an electron-withdrawing substituent is present on the nitrogen to make them 'less aromatic' – more like a diene (page 82).



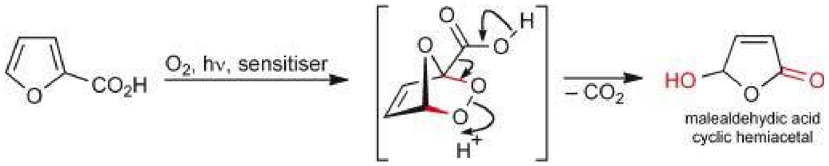
There are many examples of intramolecular furan cycloadditions and of the construction of complex polycycles using this furan reactivity. Illustrated below is a process in which the second of the two cycloadditions is intramolecular – the overall conversion proceeds in 95% yield!



Thiophene takes part in a cycloaddition with maleic anhydride only under extreme conditions. However, there is a way in which thiophenes can be made 'more like a diene', by *S*-oxidation to thiophene *S*-oxides or *S*,*S*-oxides, which enter into Diels–Alder cycloadditions readily.

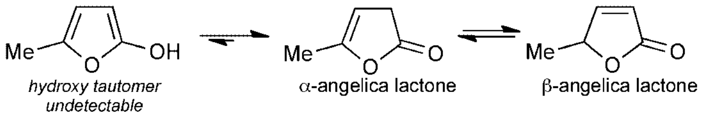


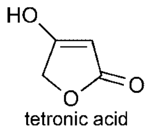
The cycloaddition of furans with singlet oxygen gives cyclic peroxides (effectively ozonides of cyclobutadiene!). These are important because they can be further utilised. A nice example is the reaction of furoic acid with singlet oxygen. The adduct undergoes decarboxylation (as illustrated) leading to 5-hydroxy-2(5*H*)-furanone ('malealdehydic acid'). Furoic acid (furan-2-carboxylic acid) is readily available by oxidation of the 2-aldehyde (furfural), in turn available in large amounts by acid treatment of residues from the manufacture of porridge oats and cornflakes. The adduct breaks down via loss of carbon dioxide, breaking the O—O bond, and revealing the cyclic hemiacetal of malealdehydic acid (i.e. 5-hydroxy-2(5*H*)-furanone).



Oxygen substituents

3-Hydroxyfuran is entirely in the carbonyl tautomeric form and 3-hydroxythiophene is the minor tautomer in a mixture (1:3) with the carbonyl form. 2-Hydroxythiophenes and 2-hydroxyfurans exist in carbonyl tautomeric forms, with the remaining C—C double bond at C-3—C-4 or C-4—C-5 or as a mixture, depending on the substituents. In some cases the tautomers are separable, for example the α- and β-angelica lactones. Generally, in the context of their occurrence in natural products, these furan lactones are referred to as butenolides. A 4-hydroxybutenolide is known as a tetronic acid.



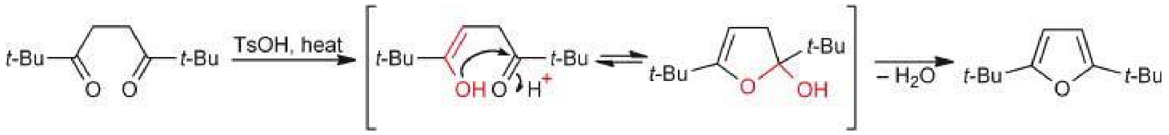


Ring synthesis – disconnections

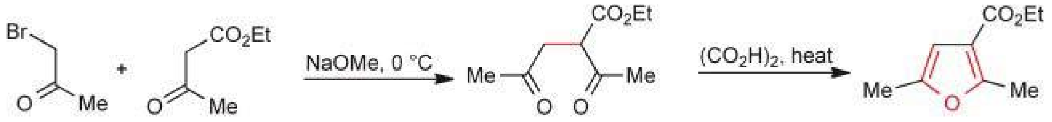
Various routes for the ring synthesis of furans and thiophenes have been devised; interest in furan construction has been particularly popular. Here we deal only with the most straightforward strategy, which involves 1,4-di-functionalised four-carbon precursors; the new bonds made are shown.

Synthesis of furans and thiophenes from 1,4-dicarbonyl compounds (1,2-bond made)

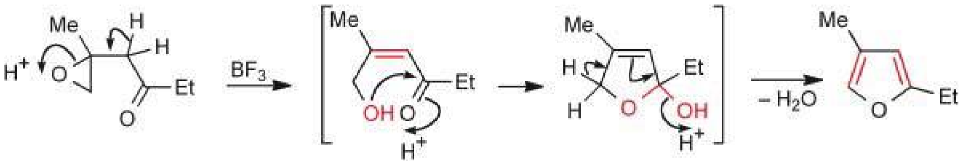
The conversion of a 1,4-diketone into a furan is simply a dehydration (it is the converse of the hydrolytic ring opening discussed on page 100) and is known as the *Paal–Knorr synthesis*. The most likely sequence has intramolecular addition of enolic oxygen to the other carbonyl group requiring then, simply loss of water.



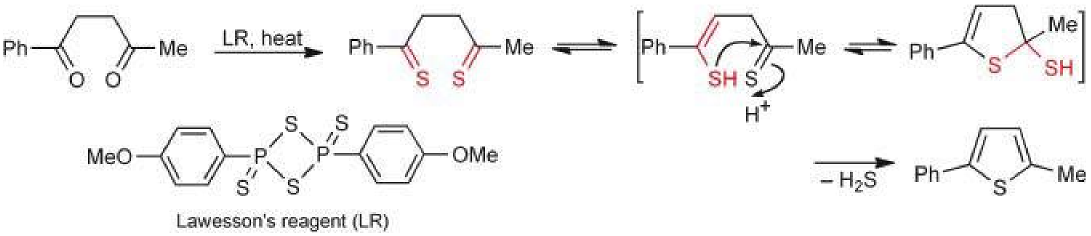
1,4-Diketones can be obtained in several ways: the alkylation of a 1,3-keto-ester with an α-halo-ketone is one such and is illustrated below.



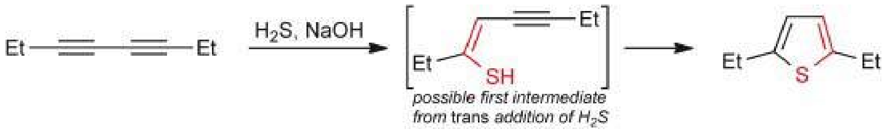
Variants on this route require only a C_4-unit with an oxygen at a terminus, and two degrees of unsaturation located somewhere in the five-atom sequence. For example, γ-hydroxy-enones are isomeric and at the same oxidation level as 1,4-diketones. There are various ways in which to produce such compounds, one of which is the acid (Lewis acid) promoted eliminative opening of an epoxide. The acid then catalyses the ring closure and conversion into the aromatic furan via the 1,4-elimination of water (for simplicity, the scheme shows a proton in lieu of the Lewis acid).



To change this strategy into a thiophene synthesis, all that is necessary is to expose a 1,4-dicarbonyl precursor to conditions that convert carbonyl into thiocarbonyl. It is generally not known whether both carbonyl groups are converted, but exactly comparable sequences lead to the aromatic thiophene, with loss of H_2S (if both have been thionated) or H_2O (if only one has been thionated). Traditionally, the thionation reagent was P_4S_{10}, but Lawesson's reagent is more soluble in organic solvents and is now the reagent of choice.



A route to thiophenes, which certainly mirrors the biosynthesis of naturally occurring thiophenes, is the very simple and effective reaction between a 1,3-diyne and sulfide or hydrogen sulfide. The diyne is, of course, at the same oxidation level as a 1,4-diketone; the first step may be direct formation of a thioenolate by nucleophilic addition of hydrogen sulfide to one of the alkynes.

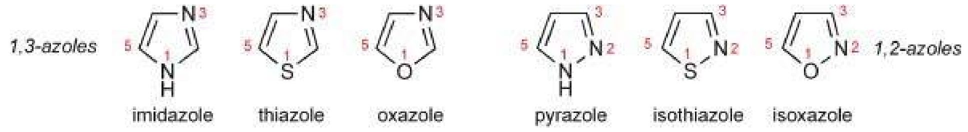


Exercises

1. What would be the structures of the products of carrying out Vilsmeier reactions with 2-methyl- and 3-methylthiophenes?
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 would be the principal site of deprotonation on treatment of 2- and 3-methoxythiophenes with *n*-BuLi?
4. How could one prepare *n*-decane from thiophene?
5. Write structures for the products of reaction of:
   (i) furfuryl alcohol with $H_2C{=}C{=}CHCN \rightarrow C_9H_9NO_2$; and
   (ii) 2,5-dimethylfuran with $CH_2{=}CHCOMe$/15 kbar.
6. How could one prepare:
   (i) 2,5-diethylthiophene; and
   (ii) 2,5-diphenylfuran?
7. What is the structure of the thiophene $C_{11}H_{16}S$ obtained from 3-acetylcyclononanone with P_4S_{10}?
8. 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 of one of the esters in this product with $LiAlH_4$ then gave $C_6H_{11}NO_3$, which, with acid, cyclised → $C_5H_7NO_2$, aqueous acidic hydrolysis of which produced tetronic acid.

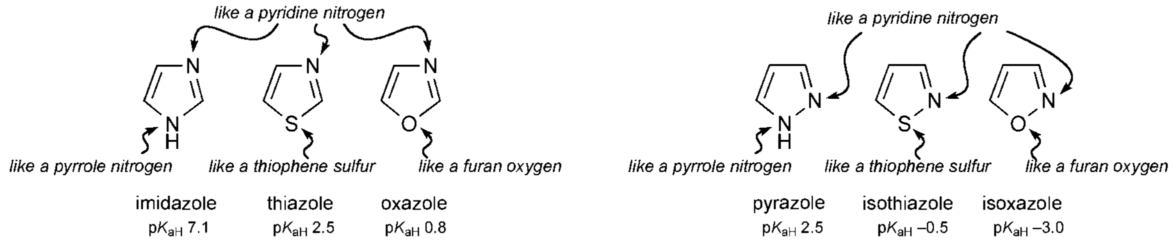
12

1,2-Azoles and 1,3-Azoles



Introduction

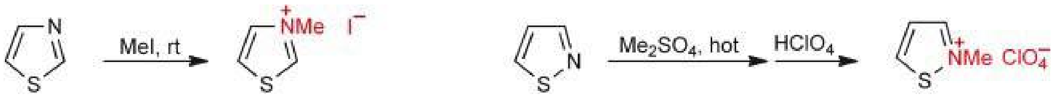
The 1,2- and 1,3-azoles each contain a nitrogen in an environment analogous to that in pyridine, that is, an imine nitrogen with a lone pair of electrons in an sp^2 orbital in the plane of the ring and not involved in the aromatic sextet. Each also has another heteroatom in the environment of the nitrogen in pyrrole, the sulfur in thiophene, or the oxygen in furan, with a pair of electrons in a p orbital orthogonal to the ring and part of the aromatic sextet. Consequently, the chemical reactions of the azoles present a combination and mutual interaction of the types of reactivity typical of pyridine on the one hand and of pyrrole, thiophene and furan on the other.



Electrophilic addition to N

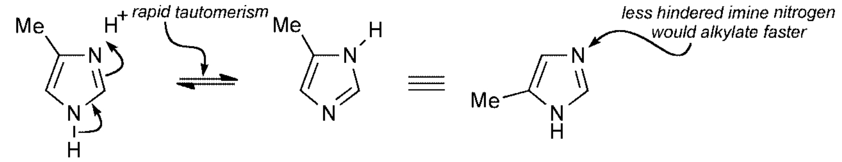
The imine (pyridine-like) nitrogen has first call on electrophiles. The azoles are basic and react with acids to form azolium salts. The second heteroatom has a substantial effect on the basicities. Considering first imidazole and pyrazole, addition of a proton produces species in which the positive charge is shared *equally* between the two nitrogens – there are two exactly equivalent resonance structures. Consequently, imidazole and pyrazole are the strongest bases in their respective trios. Inductive withdrawal means that replacing the NH of imidazole and pyrazole with the more electronegative sulfur or oxygen reduces the basicity of the imine nitrogen. Additionally, the linking of one electronegative atom directly to another further reduces basic strength, cf. NH_3 (pK_{aH} 9.3) versus NH_2NH_2 (7.9) versus NH_2OH (5.8), thus each 1,3-azole is a stronger base than its 1,2-counterpart.

The azoles react at the imine nitrogen with alkyl halides, pyrazole and imidazole the fastest in their trios, the sulfur-containing heterocycles faster than the oxygen-containing heterocycles and the 1,3-azoles much faster than the 1,2-azoles, that is, the relative nucleophilicities are similar to the relative basicities.



Heterocyclic Chemistry at a Glance, Second Edition. John A. Joule and Keith Mills.

To understand the *N*-alkylation of imidazole and pyrazole, we need firstly to be aware of the tautomerism that rapidly transfers the *N*-hydrogen between the two nitrogens but only becomes evident in unsymmetrically substituted compounds. The two tautomers of an imidazole or pyrazole are in rapid equilibrium and are inseparable so we write, for example, '4(5)-methylimidazole' to designate the tautomerism in such molecules. So, in 4(5)-substituted imidazoles, the alkylating electrophile reacts at a different rate with the two alternative imine nitrogens, on the basis of steric hindrance, and the mixture of salts produced reflects that rate difference.

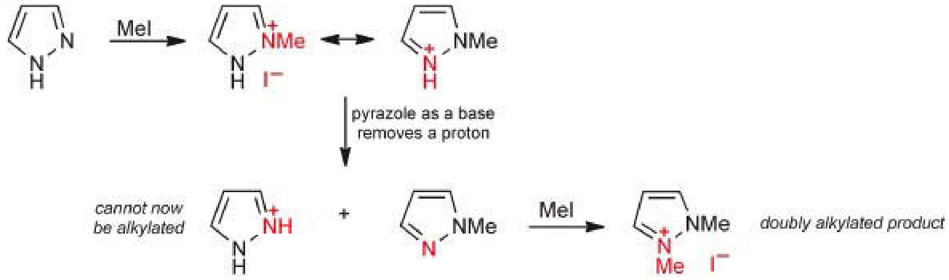


very rapid transfer of a proton between the two nitrogens of a pyrazole or an imidazole

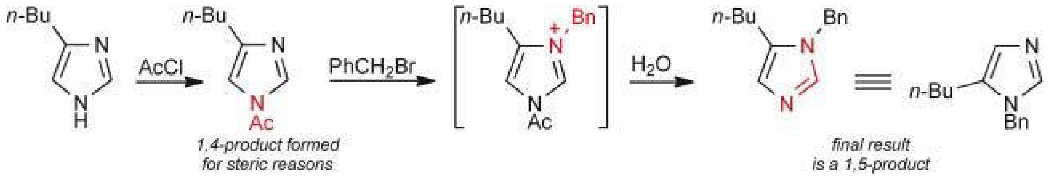
4-methylimidazole

5-methylimidazole

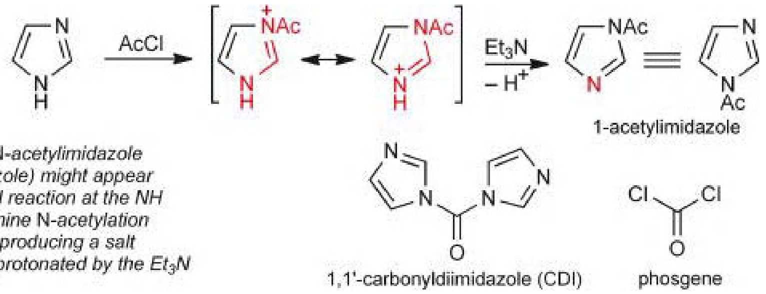
There is a further aspect of alkylations of imidazoles and pyrazoles that we illustrate with pyrazole: the first formed salt is an *N*-alkylpyrazolium salt but it is also the protonic salt of an *N*-alkylpyrazole. This salt can lose an *N*-proton in an equilibrium with unreacted pyrazole, generating the protonic salt of the starting material, which *cannot* then alkylate, and a neutral *N*-alkylpyrazole, which *can* alkylate but gives an *N*-1,*N*-2-dialkylpyrazolium salt. The consequence of this interplay can be the formation of three-component *mixtures* of starting material with mono- and di-alkylated products.



One way to avoid such difficulties is to alkylate the *N*-anion of the heterocycles (pages 110–111). Another strategy is to use an *N*-acyl or *N*-sulfonyl derivative from which, although the derivative is less nucleophilic, only one salt is obtained, an easy hydrolysis of the *N*-blocking group then giving the desired mono-*N*-alkylated product. Note also, that in the formation of an *N*-acylimidazole from a 4(5)-R-imidazole, a 1,4-disubstituted product is obtained (as a consequence of reaction at the least hindered nitrogen), so after *N*-alkylation of this and hydrolysis of the *N*-acyl, the more hindered 1,5-disubstitution pattern is achieved.



N-Acylimidazoles are best prepared using the acylating agent together with a tertiary amine base that removes an *N*-proton from the first formed *N*-acylimidazolium salt. The carbonyl group in *N*-acylimidazoles is very easily attacked by nucleophiles and advantage is taken of this property in the use of 1,1′-carbonyldiimidazole (CDI) as a safe synthetic equivalent for the highly toxic phosgene, that is, it is a synthetic equivalent for O=C^{2+}.



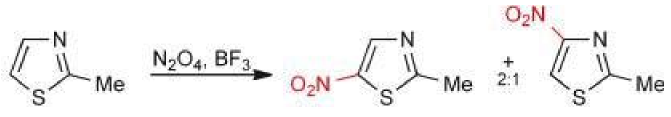
formation of N*-acetylimidazole (1-acetylimidazole) might appear to have involved reaction at the NH but actually, imine* N*-acetylation takes place, producing a salt which is then* N*-deprotonated by the Et$_3$N*

Electrophilic substitution at C

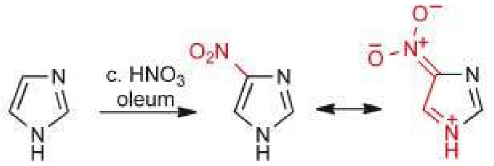
In the sense that the azoles have a five-membered heteroaromatic system, one might anticipate easy electrophilic *C*-substitution, as in pyrrole, for example. However, the imine nitrogen inductively withdraws electrons and reduces markedly the ability of these heterocycles to undergo electrophilic *C*-substitution compared with pyrrole, thiophene and furan. A second important generalisation is that the 1,2-azoles are substantially less reactive than their 1,3-counterparts, to the extent that some simple substitutions do not occur at all. Overall, the utility of electrophilic *C*-substitutions in azole manipulation is distinctly less than for pyrrole, thiophene and furan.

The gradation of reactivity is well illustrated by nitrations. Imidazole undergoes normal nitration at room temperature whereas thiazole itself is untouched by nitric acid–oleum at 160 °C. 2-Methylthiazole can however be nitrated, though requiring a higher reaction temperature than does imidazole. Oxazoles do not undergo nitration. The orientation of attack on 2-methylthiazole is significant: both 4- and 5-substituted products are formed but with the latter predominating. Note that the isolation of 4-nitroimidazole from nitration of imidazole does not necessarily imply that attack is at C-4 since in 4(5)-nitroimidazole the tautomeric equilibrium lies almost completely on the side of the 4-isomer. Each of the 1,2-azoles can be nitrated, at C-4. It is important to remember, in making comparisons, that although pyrazole and imidazole are more reactive than other azoles, they are also more basic, and in the strongly acidic media of typical nitrating mixtures, there is a much smaller concentration of the neutral heterocycle available for attack and, depending on conditions, the substitution may actually take place on the salt.

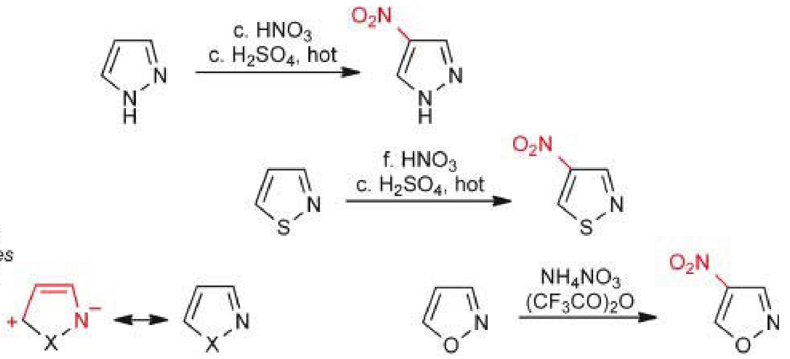
electrophilic substitution is selective for the 5-position of 1,3-azoles – the position that is 'like' the α-position of pyrrole



4(5)-nitroimidazole exists largely as the 4-nitro isomer however initial attack is probably mainly at C-5

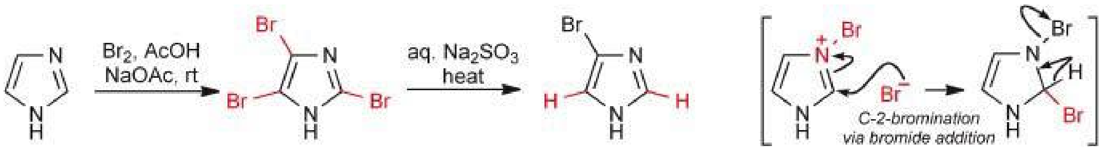


push-pull interaction favours 4-isomer

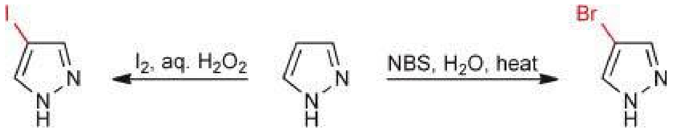


selectivity for electrophilic attack at C-4 in the 1,2-azoles can be ascribed to specific deactivation of C-5 by electron withdrawal by the imine nitrogen

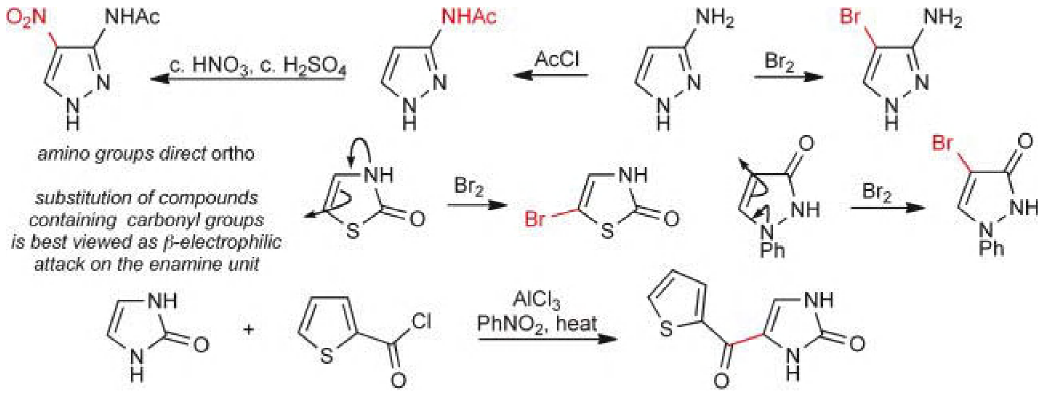
A comparable pattern of reactivity applies in halogenations: imidazole is brominated so easily that 2,4,5-tribromoimidazole is formed without a catalyst and probably by a special mechanism in which the 2-bromine is introduced as bromide anion. The 2- and 5-halogens can be easily reductively removed. The thiazole system requires the activation of a 2-methyl to permit formation of 5-bromo-2-methylthiazole; oxazole has not been directly halogenated.



4-Halopyrazoles are accessible directly from the heterocycle, as are 4-bromoisothiazole and 4-bromoisoxazole, though less efficiently.



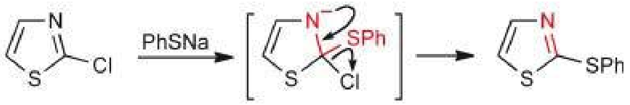
Electrophilic substitutions with carbon electrophiles, as in Friedel–Crafts processes, are virtually unknown in azole chemistry except where there is a strong activating group already present. Electrophilic substitution takes place *ortho* to an amino- or acylamino-substitutent.


amino groups direct ortho

substitution of compounds containing carbonyl groups is best viewed as β-electrophilic attack on the enamine unit

Nucleophilic substitution of halogen

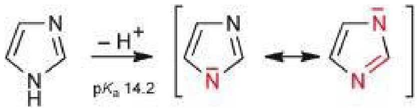
The 2-position in 1,3-azoles is formally analogous to the α-positions of a pyridine and thus nucleophilic substitutions of halide take place relatively easily, though most of the imidazole examples have N-1 blocked, that is, they do not have an acidic hydrogen.

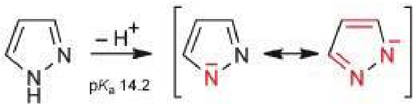

nucleophilic displacement of halogen from a thiazole 2-position proceeds via the usual addition/elimination two-step sequence

In principle, both 3- and 5-positions of an isothiazole are positions at which nucleophilic substitution is facilitated by conjugation to the imine. In an interesting example, selective displacement of a 5-chloride occurs with the further activation of an *ortho* nitrile substituent.

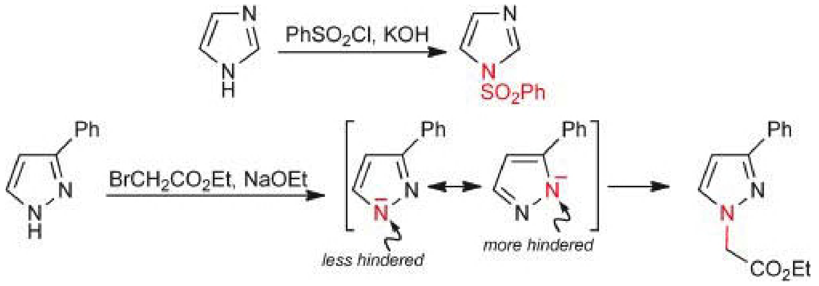
N-Deprotonation and *N*-metallated imidazoles and pyrazoles

Just as addition of a proton to pyrazole and imidazole generates symmetrical cations, and is therefore relatively favoured, so the removal of an *N*-hydrogen generates symmetrical anions with two equivalent mesomeric forms, and thus both imidazolyl and pyrazolyl anions are more stabilised than the pyrryl anion, that is, imidazole and pyrazole are more acidic than pyrrole: imidazole pK_a 14.2, pyrazole 14.2 and pyrrole 17.5.

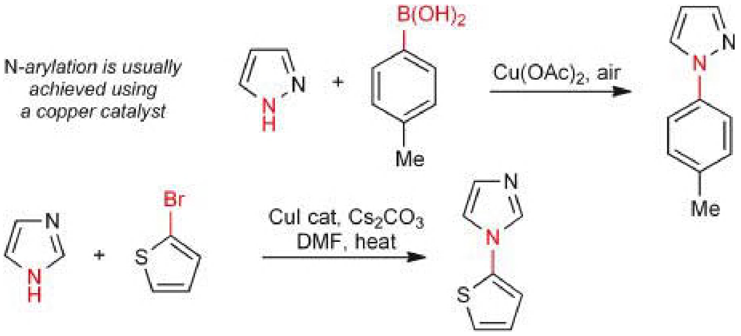




These *N*-anions provide the means for the controlled introduction of substituents onto the nitrogen of pyrazoles and imidazoles by reaction with electrophiles. It is important to remember that, as the resonance structures imply, the anions are ambident, that is, can react at either nitrogen, and the product or product mixture obtained from substituted pyrazoles or imidazoles may reflect a difference in steric hindrance to reaction at the two different nitrogen sites.

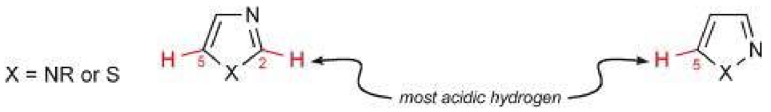


N-Arylation can be achieved; most often a copper-catalysed reaction is used and the aryl donor is either an aryl halide or an aryl boronic acid. *N*-Alkenylation with vinyl halides similarly requires copper catalysis.

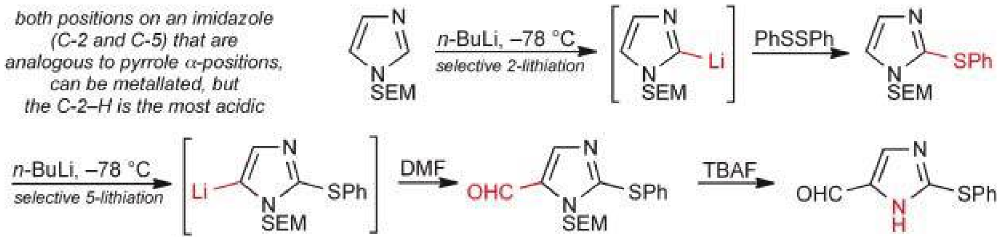


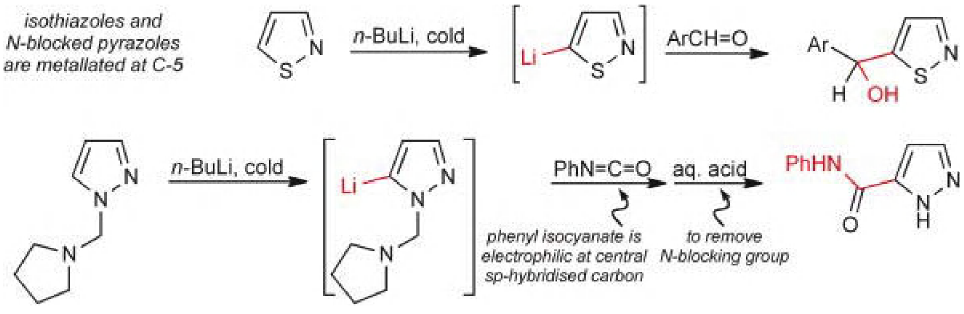
C-Metallated *N*-substituted imidazoles and pyrazoles, and *C*-metallated thiazoles and isothiazoles

Without the complication of an acidic *N*-hydrogen, strong base deprotonation of these azoles follows the principle that the most acidic *C*-proton is on a carbon adjacent to the pyrrole/thiophene-like heteroatom. This is unambiguously the 5-hydrogen in isothiazoles and *N*-substituted pyrazoles; two hydrogens fulfil this criterion in thiazoles and *N*-substituted imidazoles, but the 2-hydrogen is further acidified by electron withdrawal by the imine unit and is the most acidic. Various removable protecting groups have been used to mask the nitrogen of pyrazoles and imidazoles prior to *C*-metallation (and may also provide assistance by coordination to the lithiating agent) and three are illustrated in the examples below.

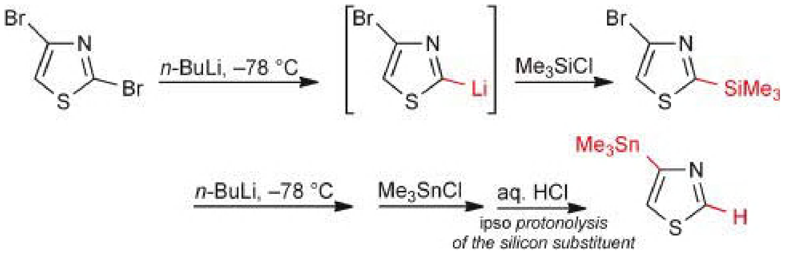


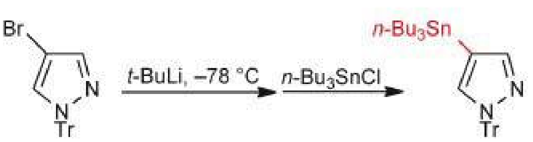
When the 2-position is blocked, the 5-position is readily metallated, as the following sequence illustrates: lithiation of *N*-SEM-imidazole, at C-2, is followed by the introduction of a substituent at that position. Now, lithiation proceeds easily at C-5. Lithiated azoles react with the full range of electrophilic reagents: PhSSPh, DMF, an aldehyde and an isocyanate are the examples in the following sequences.

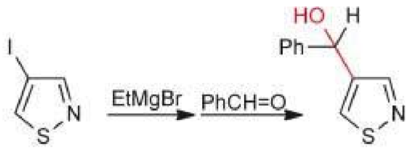




Organolithium, and in some cases Grignard, reagents are available from azole halides. The relative reactivities to metal–halogen exchange, of halides at different positions, mirrors the C─H acidities discussed above. For example, 2,4-dibromothiazole gives the 2-lithio-derivative.

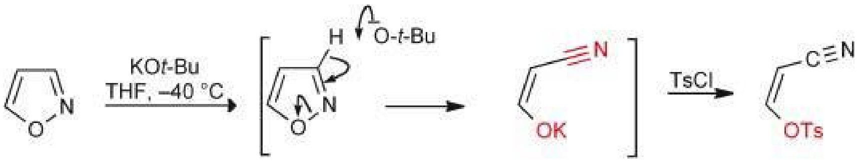




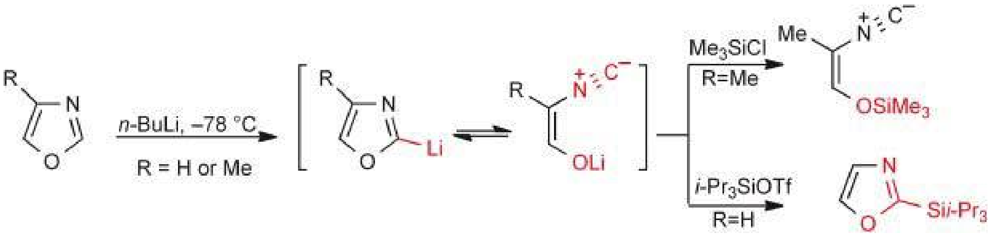


C-Deprotonation of oxazoles and isoxazoles

The deprotonation of oxazoles or isoxazoles needs to be considered separately. The complication is that the carbanions produced can undergo ring-opening processes, the driving force for which can be traced to the greater electronegativity of oxygen. Thus base treatment of isoxazoles that have a hydrogen at C-3 leads inevitably to ring opening, with the oxygen as the anionic leaving group, indeed this type of cleavage was first recognised as long ago as 1891, when Claisen found that 5-phenylisoxazole was cleaved by sodium ethoxide.

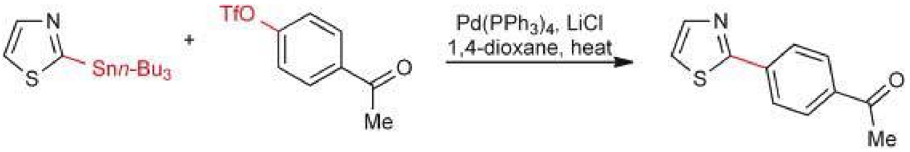


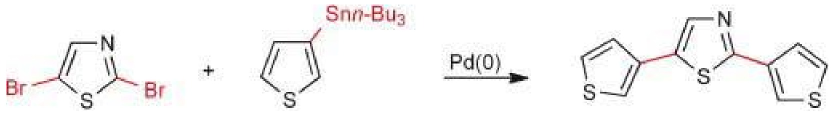
2-Lithiation of oxazoles can lead to open isonitrile-enolates, the existence of which can be demonstrated by trapping with electrophiles. Significantly, trapping the equilibrating mixture from isoxazole itself with triisopropylsilyl triflate produces 2-triisopropylsilyloxazole exclusively and this can then be utilised, via lithiation at C-5, the blocking 2-substituent being finally removed with acid. 2-Zinc and 2-magnesium oxazoles exist in ring-closed form.

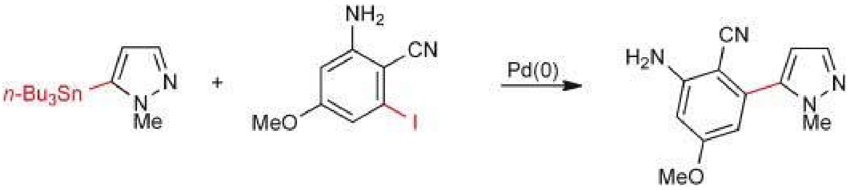


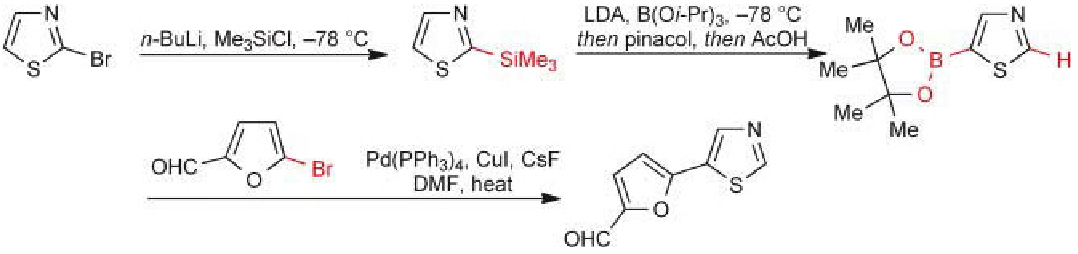
Palladium(0)-catalysed reactions

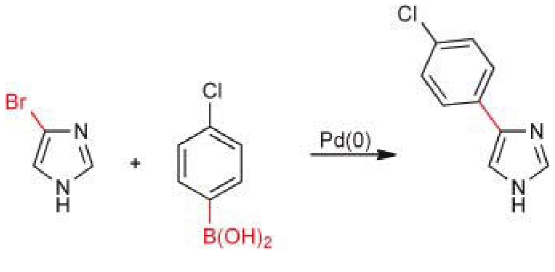
Extensive use has been made of palladium(0)-catalysed cross-couplings of the azoles, particularly involving halogen, boron and tin derivatives of thiazole, imidazole and pyrazole, but stannanes are particularly useful at the 2-position of 1,3-azoles due to their much greater stability compared with boronic acids. The selection below is illustrative of this.





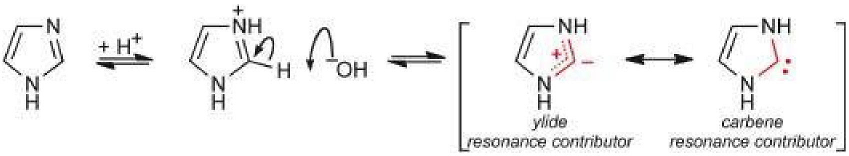




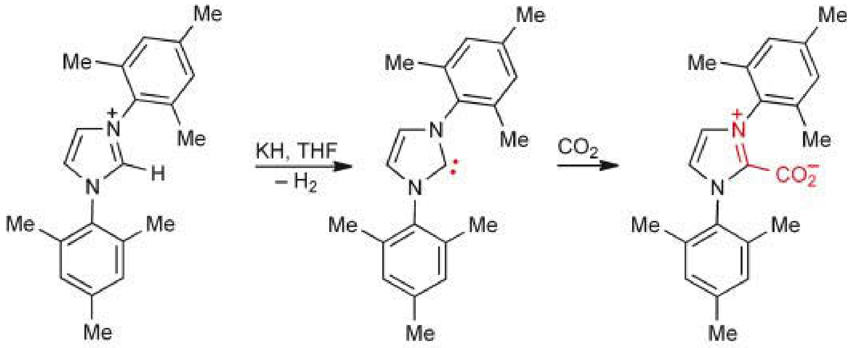


1,3-Azolium ylides

One special aspect of 1,3-azole chemistry is the acidity of the C-2–hydrogen of 1,3-azolium salts. At room temperature, in neutral or weakly basic solution, all three 1,3-azoles undergo a rapid C-2–H exchange, the relative rates being in the order: imidazole > oxazole > thiazole. The mechanism for this special process involves, firstly, formation of a concentration of protonic salt, then C-2–H deprotonation of the salt, producing an ylide, to the structure of which a carbene form is an important resonance contributor. Note that these species are overall neutral. It follows that quaternary salts of 1-alkylimidazoles and of oxazole and thiazole also undergo regioselective C-2–H exchange. For the azolium salts, the relative rates of exchange via this ylide mechanism, are: oxazolium > thiazolium > *N*-methylimidazolium, in a ratio of about 10^5:10^3:1 (see pages 161–162 for the involvement of thiazolium ylides in the mechanism of action of thiamine (vitamin B_1)).



Highly hindered analogues of these products, which have become known as '*N*-heterocyclic carbenes' (NHCs), are important ligands for transition metals, especially in catalytic processes. Isolable, crystalline carbenes can be derived, via C-2–H deprotonation, even from a salt as simple as 1,3,4,5-tetramethylimidazolium. The NHC that has been most utilized, in stabilizing both high and low valency states of metals, is the 1,3-bis(2,4,6-trimethylphenyl)-substituted imidazole carbene (1,3-dimesitylimidazol-2-ylidene, usually represented as IMes). The pK_{aH} values for NHCs, in the range of 22–24, show them to be amongst the most basic, non-ionic compounds; they are strongly nucleophilic.

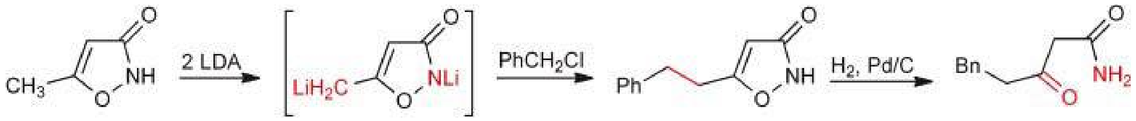


1,3-dimesitylimidazol-2-ylidene
(IMes)

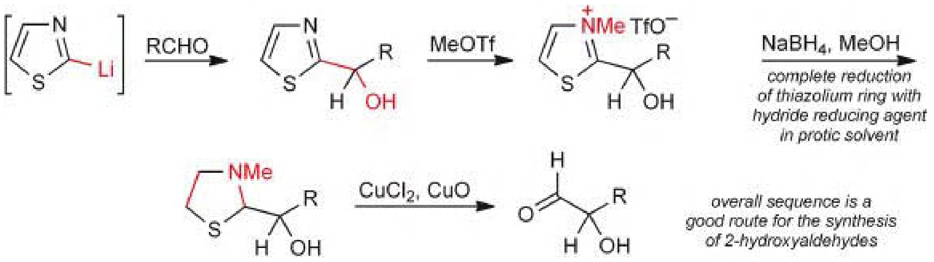
NHC–metal complexes for catalysis are usually generated *in situ* from the imidazolium salt and a base, but can be prepared separately.

Reductions

There is little to say about oxidative manipulations of azoles, however there are some significant reductive processes. The N–O bond of isoxazoles, or isoxazolones is, like all N–O bonds, subject to hydrogenolysis over a noble metal catalyst; this reveals 1,3-difunctionalised compounds that can find various uses, not the least, in the synthesis of other heterocyclic compounds.

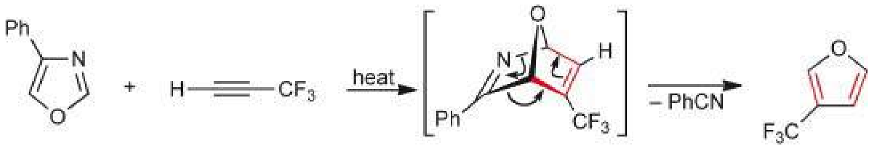


A thiazolium ring can be fully reduced (*without* hydrogenolysis of sulfur) using a hydride reagent. This is central to a general route for the synthesis of 2-hydroxyaldehydes, which is illustrated below.

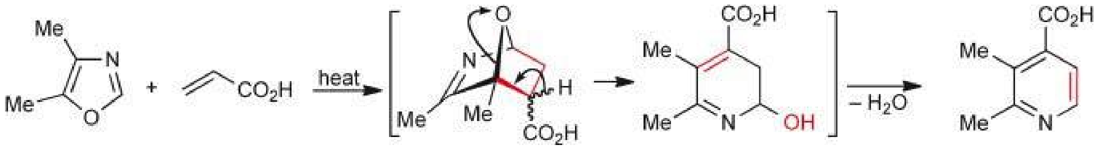


Pericyclic reactions

Cycloaddition reactions of azoles as 4π components are important only for the 1,3-azoles, and amongst these, oxazole reactions have been the most studied, for example reactions with alkynes, benzyne, singlet oxygen and with typical alkene dienophiles are known. One use that can be made of alkyne adducts is to carry out the reaction at such a temperature that a subsequent retro-Diels–Alder loss of a nitrile produces a furan.

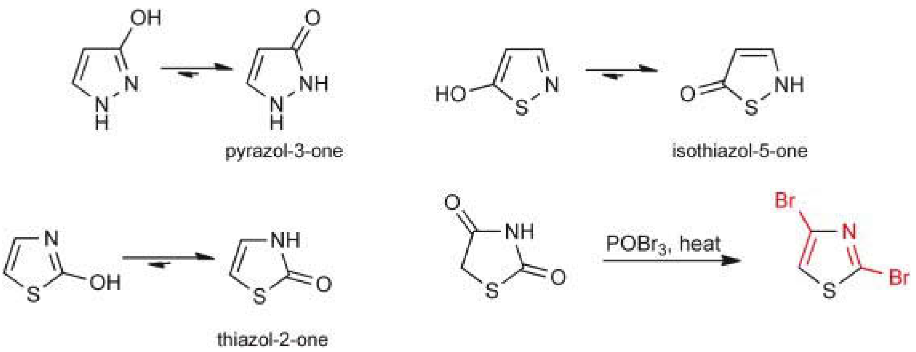


Oxazoles can be converted into pyridines by reaction with, for example, acrylic acid, the initial adduct losing water to form the pyridine.

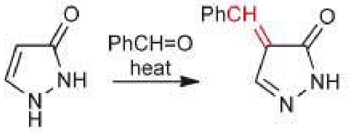


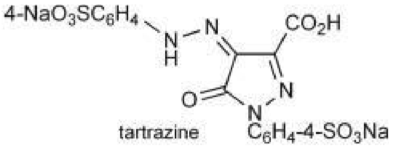
Oxygen and amine substituents

The oxygen-substituted 1,3-azoles exist in their carbonyl tautomeric forms and are essentially non-aromatic. Similarly, 3- and 5-hydroxy-1,2-azoles are very much the minor tautomeric forms. 1,3-Azol-2-ones react, like 2-pyridones, with phosphorus halides and thus can be converted into the 2-haloazoles. 2,4-Dibromothiazole can be accessed from thiazolidine-2,4-dione.

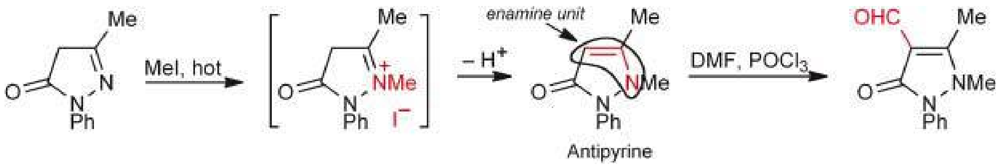


Azolones will undergo aldol-type condensations with aldehydes α to the carbonyl and will also couple at that position with aryldiazonium cations giving coloured compounds that have been used as dyestuffs – tartrazine, a food and drink colorant, is an example.

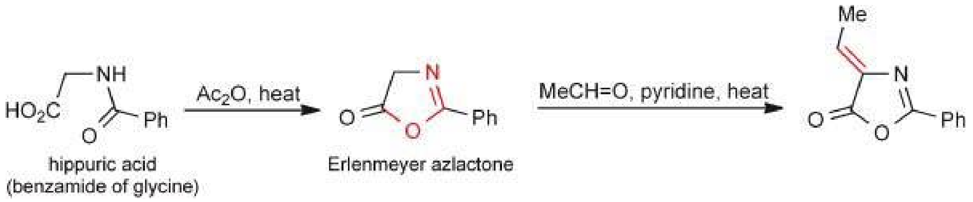




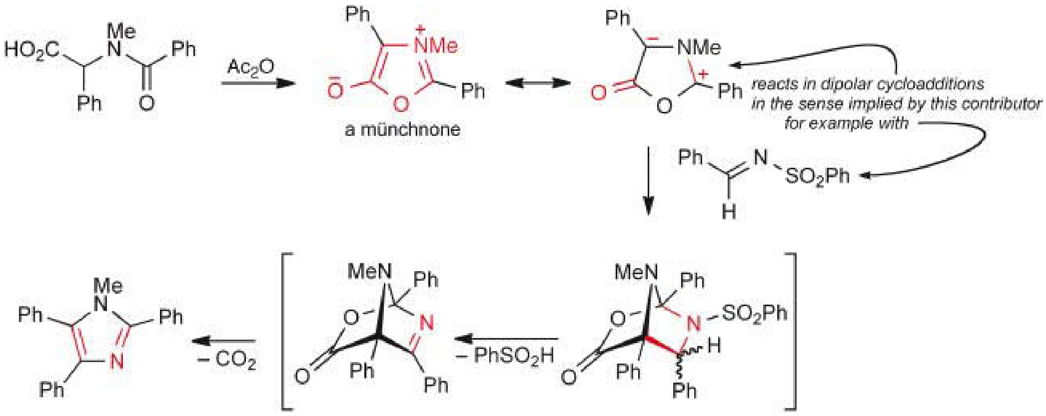
The Vilsmeier formylation of 'Antipyrine', once used as an analgesic, is again best understood as electrophilic substitution at the β-position of the enamine unit.



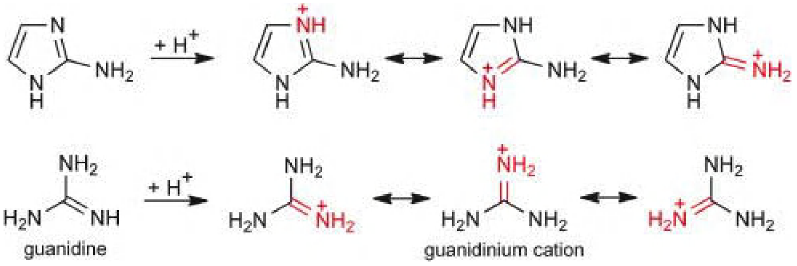
Oxazol-5-ones are simply cyclic anhydrides of *N*-acyl α-amino acids, and are constructed in the way that this implies; they have been known for many years and are usually called 'azlactones'. Azlactones undergo ready condensation with aldehydes, and the products can be converted into α-amino acids via double-bond reduction followed by hydrolysis.



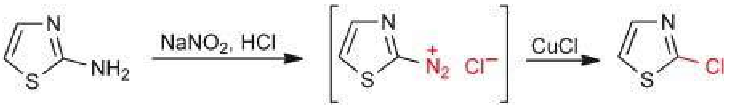
If the nitrogen of the starting amide also carries an alkyl group, cyclisation can only lead to an overall neutral product by adopting a zwitterionic structure, for which no neutral resonance form can be written – a mesoionic structure. Mesoionic oxazolones (named 'münchnones' after their discovery at the University of München, Germany; strictly called 1,3-oxazolium-5-olates) undergo ready dipolar cycloadditions, with loss of carbon dioxide from the initial adduct.



Amino-azoles exist as the amino tautomers and all protonate on the ring nitrogen. The pK_{aH} of 2-aminoimidazole, at 8.46 the most basic isomer, reflects the symmetry of the resonating guanidinium system within its cation.

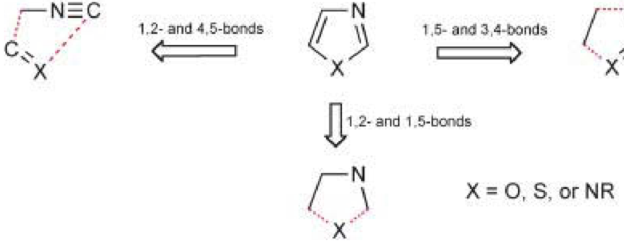


The amino-azoles behave as typical arylamines, for example they can be diazotised, thus providing routes to halo-azoles.



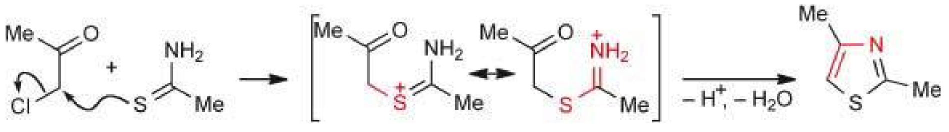
1,3-Azoles ring synthesis – disconnections

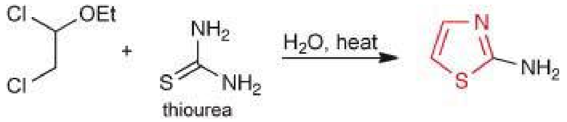
There are three important disconnections for the construction of 1,3-azoles, summarised below with the new bonds made in the processes shown.



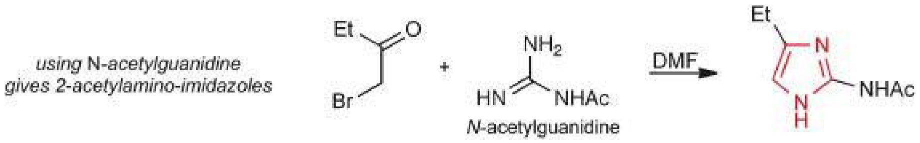
Synthesis of thiazoles and imidazoles from α-halo-ketones
(1,5- and 3,4-bonds made)

This disconnection is most important for the synthesis of thiazoles. A thioamide is reacted with an α-halo-ketone, with the first bond made being between sulfur and carbon – the 1,5-bond. Shown below are the syntheses of 2,4-dimethylthiazole where the heteroatoms are provided by thioacetamide, and of 2-aminothiazole, in which 1,2-dichloroethyl ethyl ether is utilised in lieu of chloroethanal and the heteroatoms derive from thiourea; these are typical examples of the *Hantzsch synthesis* (note there is an important pyridine ring synthesis also named a Hantzsch synthesis – page 45).



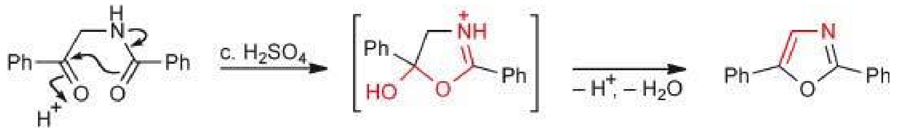


This route can also be utilised to prepare imidazoles, for example using amidines ($RC(=NH)NH_2$) gives 2-substituted (alkyl or aryl) imidazoles and using *N*-acetylguanidine produces 2-acetylamino-imidazoles.

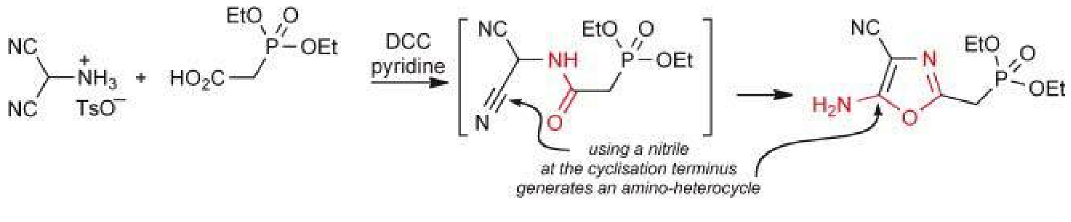


Synthesis of 1,3-azoles from 1,4-dicarbonyl compounds
(1,2- and 1,5-bonds made)

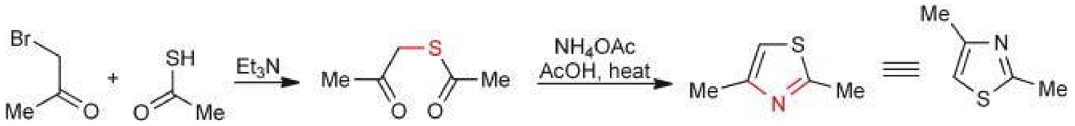
This route is of most importance for the synthesis of oxazoles, but thiazoles and imidazoles can also be accessed via this strategy. The amides of α-amino-ketones produce oxazoles when exposed to acidic dehydrating conditions – note the analogy to the ring closure of 1,4-diketones to give furans (page 105).

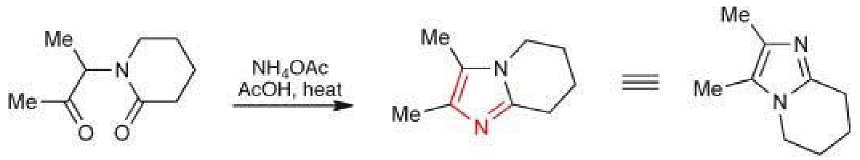


The synthesis of the 5-amino-oxazole shown below illustrates the general principal that if a nitrile is utilised instead of a ketone/aldehyde, the result is an amino-heterocycle: the ring closure substrate is prepared in this case from aminomalononitrile by a dicyclohexylcarbodiimide (DCC) mediated amide bond formation with a carboxylic acid.

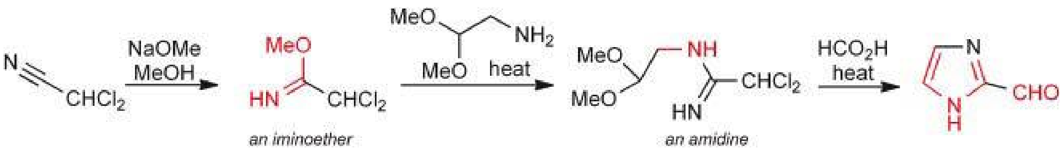


The introduction of ammonia to an α-acylthio-ketone will generate a thiazole, and similarly ammonia with an α-acylamino-ketone will produce an imidazole, as shown.



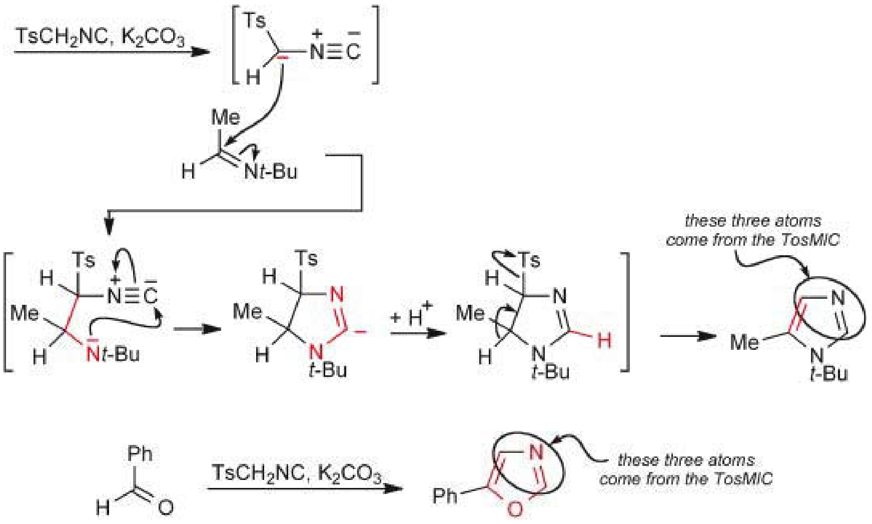


As a final example in this category we show the synthesis of 2-formylimidazole. An imino-ether (normally formed by treating a nitrile with HCl gas and an alcohol) is, in this case, prepared from dichloroacetonitrile under basic conditions. The methoxyl group is displaced by reaction with aminoethanal dimethyl acetal giving an amidine; so in the context of this section, one of the 'carbonyl' groups is an imine and one is, at this stage, masked as an acetal. Ring closure is efficient, the dichloromethyl group being concurrently hydrolysed to reveal the aldehyde group.



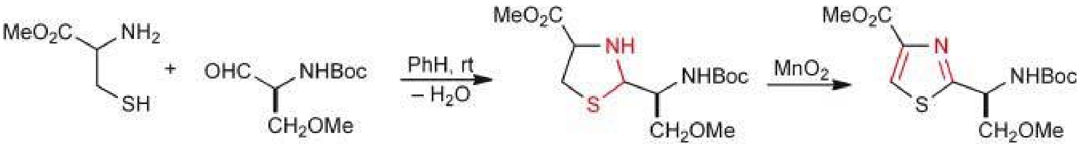
Synthesis of 1,3-azoles using tosylmethyl isocyanide
(1,2- and 4,5-bonds made)

All three types of 1,3-azole can be constructed using tosylmethyl isocyanide (TosMIC; $TsCH_2NC$). Illustrated below are imidazole and oxazole examples. The anion of TosMIC can be generated using mild base, though often a stronger base is employed. Addition of this anion to a carbonyl or imine unit, then ring closure of the heteroatom onto the isonitrile carbon and finally loss of *p*-toluenesulfinic acid produces the aromatic azole (compare with the use of TosMIC for the synthesis of pyrroles, on page 84).

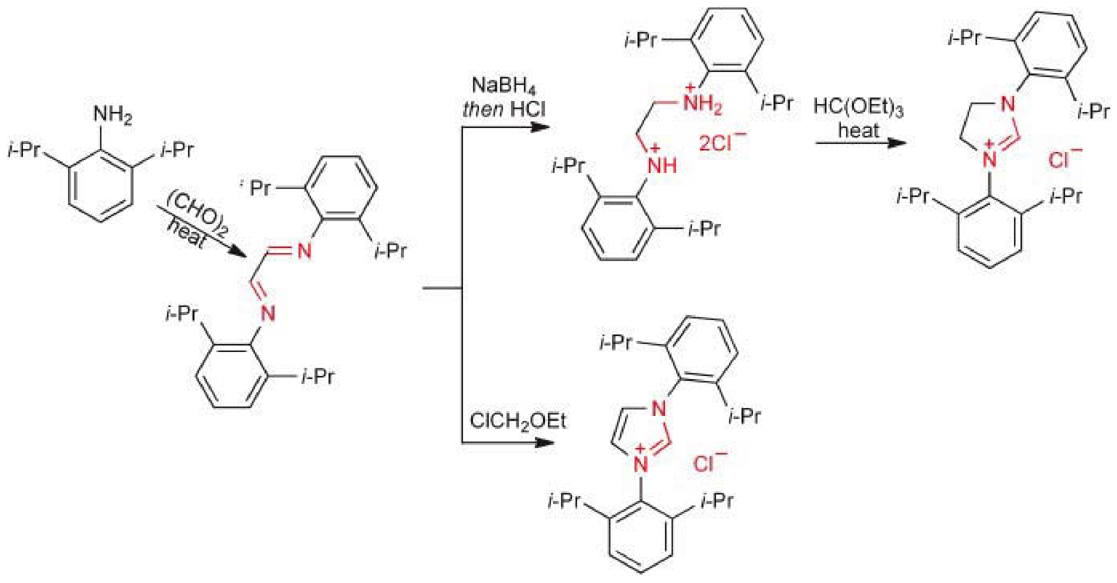


Synthesis of 1,3-azoles via dehydrogenation

The ring synthesis of tetrahydro-1,3-azoles is simply the formation of *N*,*N*-, *N*,*O*- or *N*,*S*-analogues of aldehyde ethylene glycol cyclic acetals, that is, the reaction of an aldehyde with $HXCHR^1CHR^2NH_2$ with removal of water. They can be dehydrogenated to produce the aromatic azoles using various oxidants – manganese(IV) oxide in the example below. Note that the mildness of the conditions allows retention of the integrity of the asymmetric centre.

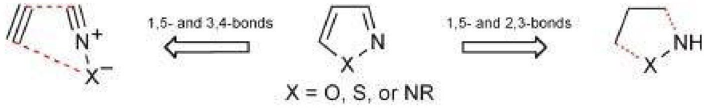


The construction of 1,3-diaryl 4,5-dihydroimidazolium cations can be achieved by the reaction of 1,2-diamines with triethyl orthoformate ($HC(OEt)_3$). 1,3-Diarylimidazolium salts, as precursors for *N*-heterocyclic carbenes such as 1,3-di(2,6-diisopropylphenyl)imidazol-2-ylidene, can be made from a glyoxal bis-imine, the remaining carbon being provided by ethyl chloromethyl ether.



1,2-Azoles ring synthesis – disconnections

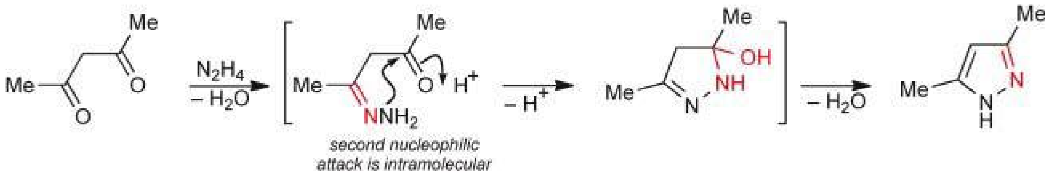
There are two important disconnections for the construction of 1,2-azoles, summarised below with the new bonds made in the processes shown.

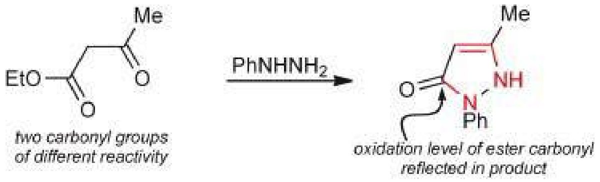


Synthesis of pyrazoles and isoxazoles from 1,3-dicarbonyl compounds

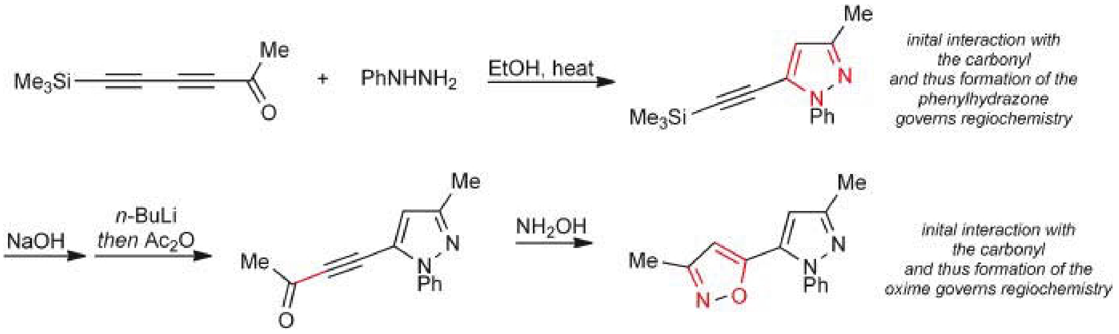
(1,5- and 2,3-bonds made)

This is the most obvious route to the 1,2-azoles and is of major relevance for the synthesis of pyrazoles and isoxazoles. Condensation of a 1,3-diketone, or synthetic equivalent, with a hydrazine or with hydroxylamine (each is doubly nucleophilic) initially intermolecularly and then intramolecularly using the second heteroatom, produces the aromatic 1,2-azole directly. Substituted hydrazines generally give mixtures of regioisomers, unless a 1,3-dicarbonyl component (or an equivalent) having markedly different reactivities at the two carbonyl groups is used. For example phenylhydrazine reacts with ethyl acetoacetate to produce only one pyrazolone (note also that the higher oxidation level of one of the carbonyl groups is reflected in the oxidation level of that carbon in the product).

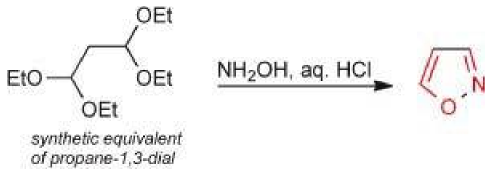




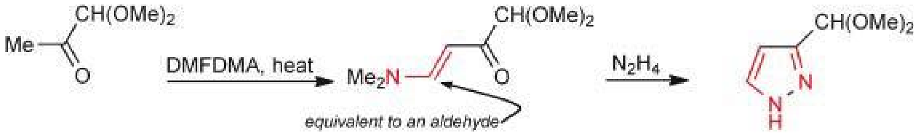
Regiocontrol can also be achieved by using a 1,3-dicarbonyl equivalent, for example an alkynyl-ketone – the terminal alkyne carbon is at the oxidation level of a carbonyl group. In a nice example of this, 5-(isoxazol-5-yl)pyrazoles can be constructed, as shown.



Isoxazoles are similarly efficiently produced from 1,3-dicarbonyl compounds or synthetic equivalents thereof, using hydroxylamine.



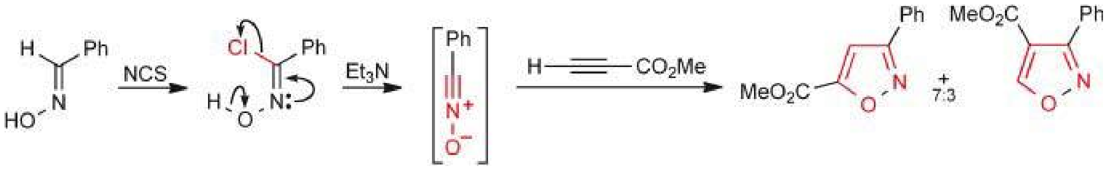
There are of course many ways to produce 1,3-dicarbonyl compounds; a neat and efficient route when one of the carbonyl groups is to be an aldehyde utilises an enamine as aldehyde equivalent, obtained by a condensation reaction of dimethylformamide dimethyl acetal (DMFDMA) α to a ketone.



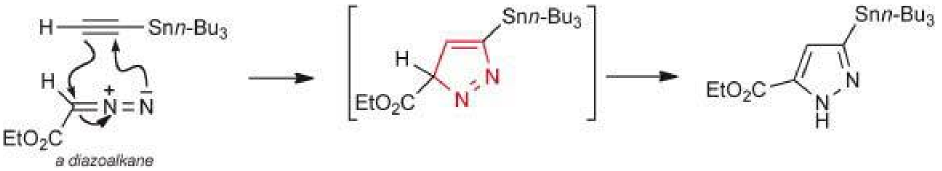
Synthesis of isoxazoles and pyrazoles from alkynes
(1,5- and 3, 4-bonds made)

This method is of most relevance to the synthesis of isoxazoles, though pyrazoles can also be produced. Nitrile oxides (R–C≡N⁺–O⁻) readily take part in 1,3-dipolar cycloadditions with alkenes or alkynes generating five-membered heterocycles. Addition to alkynes produces isoxazoles, directly. Addition to alkenes gives 4,5-dihydroisoxazoles (isoxazolines), but these can be easily dehydrogenated. Though less frequently used, a nitrile imine will add to an alkyne producing a pyrazole.

Nitrile oxides are usually generated *in situ*, in the presence of the other reactant, either by dehydration of a nitro compound (RCH_2NO_2) using phenyl isocyanate or by base-catalysed elimination of hydrogen halide from a halo-oxime (RC(Hal)=NOH), as illustrated. Nitrile imines can be similarly accessed by dehydrohalogenation of hydrazonoyl halides themselves prepared by NBS or NCS treatment of the corresponding hydrazones.

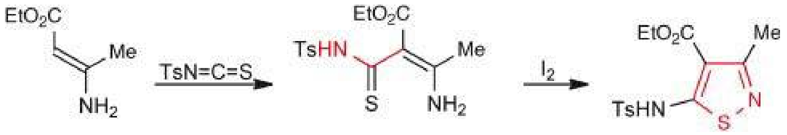


Diazoalkanes will also add to alkynes.



Synthesis of isothiazoles from β-amino α,β-unsaturated carbonyl compounds (1,2-bond made)

Because unsubstituted thiohydroxylamine is not available, ring-closing N–S bond formation is the most common method of synthesis of isothiazoles. The ring closure of β-amino α, β-unsaturated thioketones (usually generated *in situ* by reaction with P_4S_{10}) or β-amino α, β-unsaturated thioamides, in the presence of an oxidising agent (iodine in the example shown below), leads to isothiazoles.



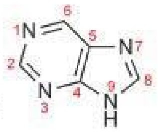
Exercises

1. What are the structures of the halogen-containing compounds formed in the following ways:
   - (i) imidazole reacted with NaOCl → $C_3H_2Cl_2N_2$;
   - (ii) 1-methylimidazole reacted with excess Br_2 in AcOH → $C_4H_3Br_3N_2$ then this reacted with EtMgBr followed by water → $C_4H_4Br_2N_2$ and this in turn with *n*-BuLi then $(MeO)_2CO$ giving $C_6H_7BrN_2O_2$.
2. What are the 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 sets of conditions.
3. When the methyl ester of histidine is reacted with carbonyl diimidazole, a product $C_8H_9N_3O_3$ is formed – what is its structure? Reaction of this substance with iodomethane takes place easily producing a salt $C_9H_{12}N_3O_3^+ I^-$, which on simple treatment with methanol leads to $C_{10}H_{15}N_3O_4$ – what is the structure of this product?
4. What are the structures of the intermediates and final products that are formed when:
   - (i) 4-phenyloxazole is heated with but-3-yn-2-one → $C_6H_6O_2$; and
   - (ii) 5-ethoxyoxazole is heated with dimethyl acetylenedicarboxylate → $C_{10}H_{12}O_6$.
5. Draw all the important resonance contributors to the münchnone, 3-methyl-2,4-diphenyl-1,3-oxazolium-5-olate. Predict the structure of the product of its reaction with methyl propiolate ($HC{\equiv}CCO_2Me$).
6. 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).
7. Deduce structures for each of the products formed in the following sequence: 1-methylimidazole/*n*-BuLi at –30 °C then TMSCl (Me_3SiCl) → $C_7H_{14}N_2Si$ then this with *n*-BuLi at –30 °C then TMSCl → $C_{10}H_{22}N_2Si_2$, then this with MeOH–rt → $C_7H_{14}N_2Si$, which is different to the first product.
8. What are the structures of the 1,3-azoles that are produced from the following reactant combinations:
   - (i) 1-chlorobutan-2-one and thiourea;
   - (ii) thiobenzamide and chloroacetaldehyde;
   - (iii) thioformamide and ethyl bromoacetate; and
   - (iv) 2-amino-1,2-diphenylethanone and cyanamide ($H_2NC{\equiv}N$).
9. Draw the structures of the two products that are formed when hydroxylamine reacts with $PhCOCH_2CH{=}O$. Suggest an unambiguous route for the preparation of 5-phenylisoxazole.
10. Devise a mechanism to explain the generation of a nitrile oxide ($RC{\equiv}N^+{-}O^-$) ready for 1,3-dipolar cycloadditions, by treatment of a nitroalkane (RCH_2NO_2) with phenyl isocyanate ($PhN{=}C{=}O$).

13

Purines

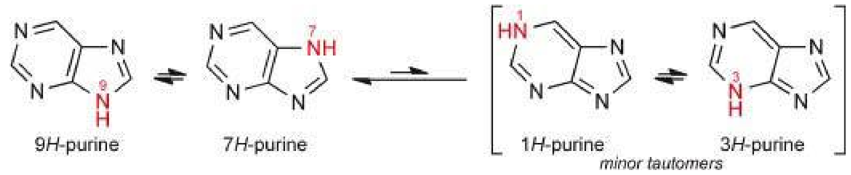
purine
[9*H*-purine]



the standard numbering of the purine ring system is anomalous for historical reasons

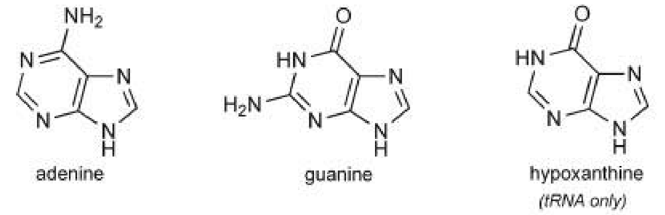
Purines are of great interest for several reasons, but in particular, together with certain pyrimidines, they are components of DNA and RNA, the genetic templates of all life (pages 163–164), and also serve in a range of other biological roles. A corollary of this central biological role is the significance of purines and their analogues in a number of areas of medicinal chemistry.

Chemically, there are significant lessons to be learnt from the study of purines since their reactions exemplify the interplay of the constituent imidazole and pyrimidine rings, just as the reactions of indole show modified pyrrole and modified benzene chemistry. The pyrimidine contributes an electron-poor and the imidazole an electron-rich unit to the structure and chemistry. Although purines can theoretically exist as four tautomers, only the 7*H*- and 9*H*-forms are of significance.

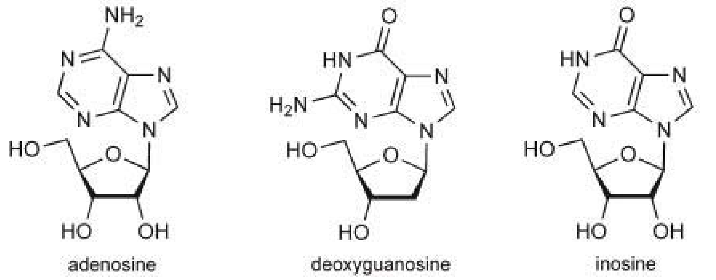


In their biological roles, purines (and pyrimidines) occur mainly as oxy- and amino-derivatives, with a ribose or 2-deoxyribose residue attached to N-9. When the ribose residue is a simple sugar, the compounds are referred to as 'nucleo*sides*', and when a phosphate is also attached to the sugar, they are called 'nucleo*tides*'. (Note: The nucleosides and nucleotides are drawn with the purine above the ribose to save space. In reality it would normally be rotated away from the ribose.)

Other than their occurrence in the polymers DNA and RNA, their other biological roles are fulfilled as monomers. The nucleoside adenosine is an important hormone and neurotransmitter, and is of medical use for the treatment of some cardiovascular conditions. Adenine/adenosine and guanine/guanosine are constituents of DNA and RNA, while hypoxanthine/inosine is present in tRNA and is also the biosynthetic precursor for the other purine nucleosides.



purine bases in DNA and RNA

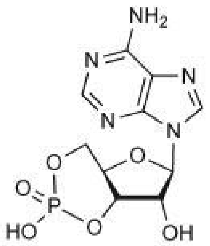


RNA contains ribosides
DNA contains deoxyribosides

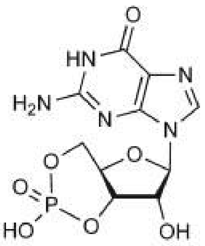
purine nucleosides

Heterocyclic Chemistry at a Glance, Second Edition. John A. Joule and Keith Mills.

Adenosine nucleotides are at the heart of energy transfer in many metabolic systems, via the interconversion of adenosine triphosphate (ATP), diphosphate (ADP) and monophosphate (AMP). The cyclic monophosphates cAMP and cGMP are particularly important as 'second messengers', which transfer signals from neurotransmitters such as adrenaline, and peptide hormones (e.g. glucagon) acting at receptors on the outer surface of cells. The nucleotides are released from the inner surface of the cell wall to activate systems within the main body of the cell. Inhibitors of enzymes (phosphodiesterases: PDEs) that catalyse the breakdown of these cyclic phosphates can prolong activity and are a very important class of drugs, for example sildenafil (page 175). Adenosine is also a component of a number of co-enzymes (pages 160–161).

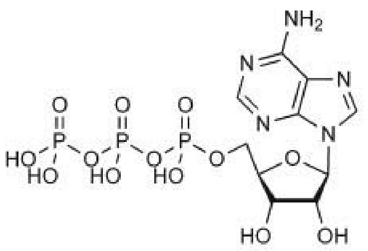


cyclic adenosine monophosphate (cAMP)

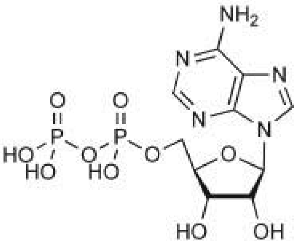


cyclic guanosine monophosphate (cGMP)

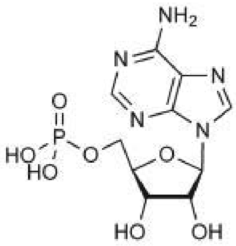
purine nucleotides are phosphorylated purine nucleosides



adenosine triphosphate (ATP)

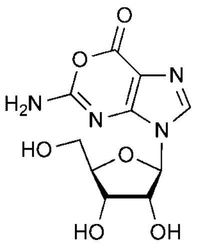


adenosine diphosphate (ADP)

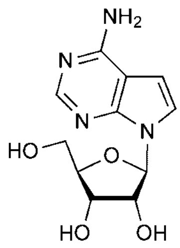


adenosine monophosphate (AMP)

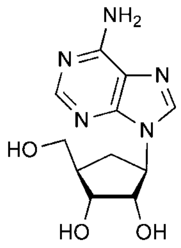
A number of purine nucleoside analogues occur naturally. Some of these involve modification of the purine nucleus, where a nitrogen is notionally replaced by another atom, for example oxanosine, where N-1 is replaced by oxygen, and tubercidin, where N-7 is replaced by carbon (this latter system is often referred to informally as a '7-de-azapurine'). Other natural products contain modified ribose moieties, the best-known example probably being aristeromycin, where the cyclic oxygen is replaced by CH_2. This compound, isolated from a *Streptomyces* species, can be produced by fermentation, and is a useful starting material for the synthesis of 'carba' nucleosides. Other purine analogues have been prepared for medicinal chemistry, where further nitrogens replace carbons.



oxanosine



tubercidin

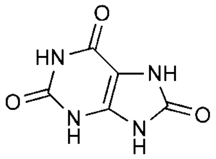


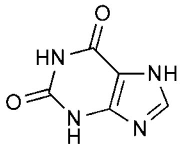
aristeromycin

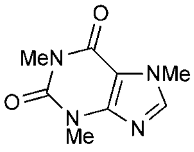
some naturally occurring nucleoside analogues

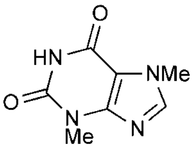
Much of the chemistry of purines, as for pyrimidines, centres on oxy- and amino-compounds (or related derivatives such as halides) because of the biological importance of these compounds and also their ready availability as starting materials. This is particularly true of the nucleic acid bases adenine, guanine and hypoxanthine and their corresponding ribosides, adenosine, guanosine and inosine, which are all readily available in quantity, being produced mainly by fermentation or partial synthesis from fermentation products.

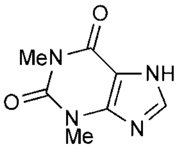
The polyoxy-purine uric acid is also readily available and is easily converted into 2,6,8-trichloropurine, which is a very useful starting material in which all the free carbons of purine can be manipulated by nucleophilic substitution. Uric acid, the end product of nucleic acid metabolism in animals, birds and reptiles, was one of the first (heterocyclic) compounds to be isolated as a pure substance – by the Swedish chemist Carl Scheele in 1776. When there is excess uric acid in the blood, crystals of uric acid can be deposited leading to the joint pain known as gout, typically initially in the big toe and usually in males. The dioxy-purine xanthine is an important structural type present in caffeine, theobromine (in chocolate) and theophylline, a drug sometimes used for asthma.


uric acid


xanthine

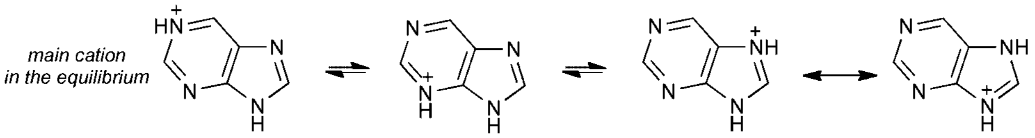

caffeine


theobromine
in chocolate


theophylline
used to treat asthma

Electrophilic addition to nitrogen

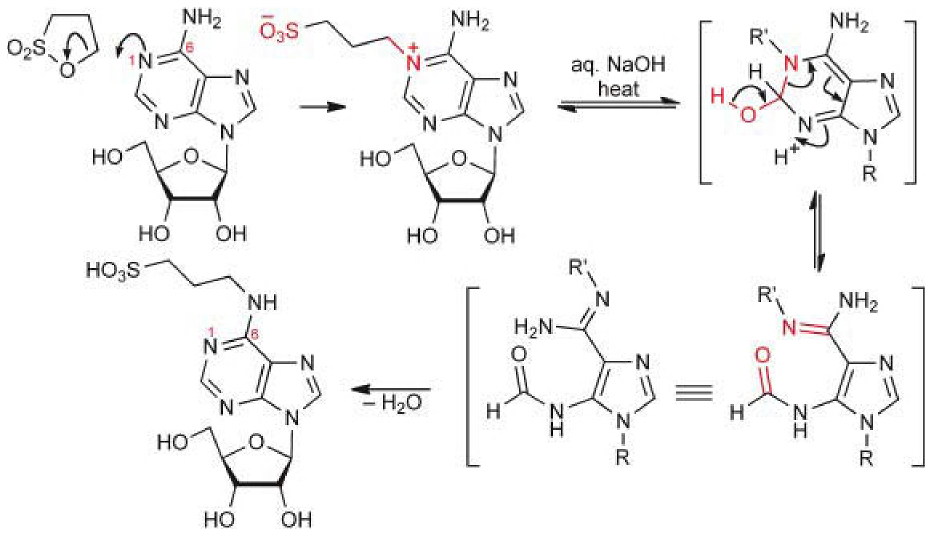
Purine itself is a relatively weak base, pK_{aH} 2.5, with protonation taking place to give three mono-cations but with the N-1—H^+ form predominant. Amino derivatives are stronger bases, for example adenine (pK_{aH} 4.0), which protonates only at N-1. Hypoxanthine, which has a 6-oxo group and therefore an 'amidic' N-1, protonates on the imidazole ring. As an acid, purine has a pK_a of 8.9.



N-Alkylation (see also under N-deprotonation and N-metallation)

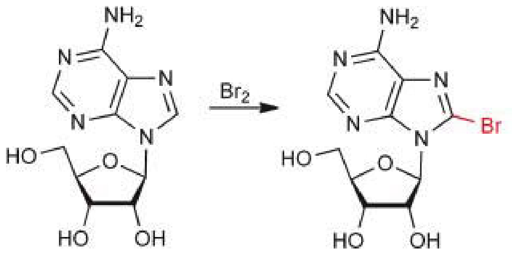
N-Alkylation follows similar (but not always the same) patterns to protonation, for example adenine reacts on the pyrimidine ring, but at N-3. However, when N-3 is subject to steric hindrance, as in adenosine derivatives, alkylation reverts to N-1.

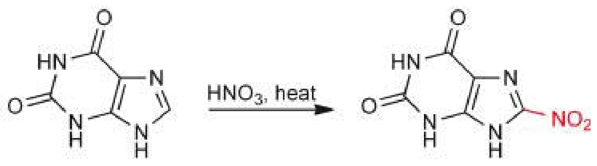
The salts from N-1–alkylation of (9-blocked) adenine derivatives undergo the Dimroth rearrangement on treatment with base (for another example of the Dimroth rearrangement see page 57). This reaction results in interchange of N-1 with the 6-amino group, giving a 6-*N*-alkylamino adenine. This outcome is the result of a ring opening and recyclisation via an ANRORC sequence and is quite common in purinium salts and some other ring systems, and is of significant synthetic utility for the preparation of 6-*N*–monoalkylated adenines. In the example shown, the initial alkylation at N-1 is carried out with 1,2-oxathiolane 2,2-dioxide, which contains an internal sulfonate leaving group that is retained in the product as the sulfonic acid.



Electrophilic substitution at carbon

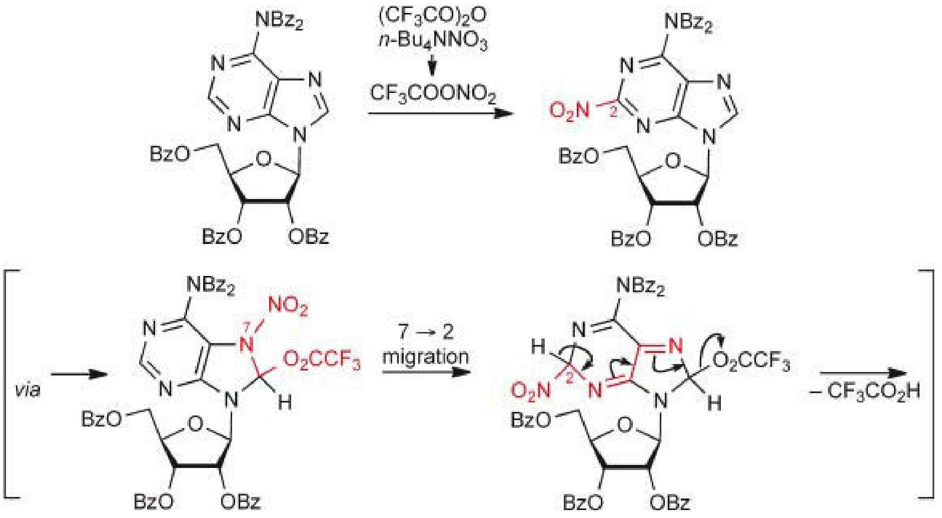
Simple purines are generally resistant to electrophilic substitution at carbon but oxo- and amino-compounds will react, under fairly normal conditions, in the electron-rich imidazole ring at C-8.





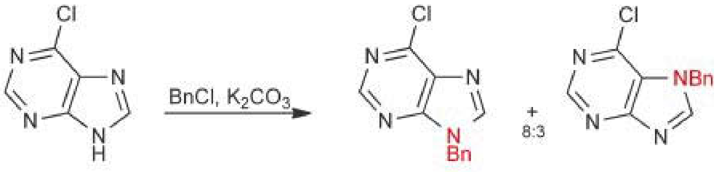
electrophilic substitution of purines proceeds at C-8

Diverse 6-substituted purines can be 'nitrated' at C-2, although the mechanism is not direct electrophilic substitution. The transformation is brought about using the mixed anhydride of trifluoroacetic acid and nitric acid, generated *in situ*, and is initiated by electrophilic attack on N-7. Addition of trifluoroacetoxy to C-8 follows, then migration of the nitro group to C-2, and finally re-aromatisation. This is a particularly useful reaction as nitro is a good leaving group for subsequent nucleophilic substitution.

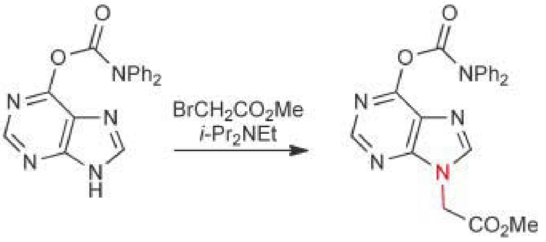


N-Deprotonation and *N*-metallated purines

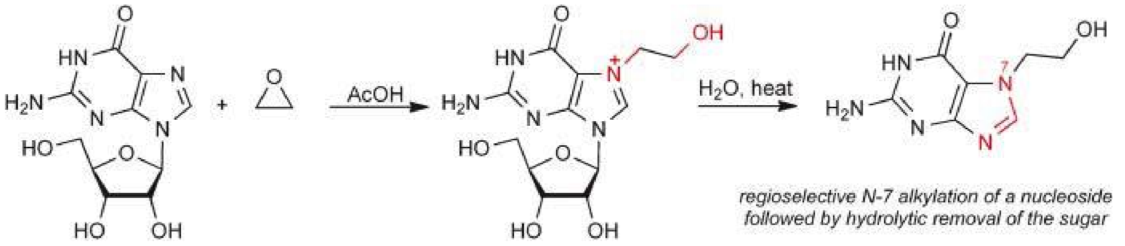
N-Alkylation of purines that have a free imidazole NH is most commonly carried out under basic conditions, when reaction occurs in the imidazole ring via an *N*-anion. This often results in a mixture of N-7/N-9 isomers, but such reactions can be driven towards N-9 by the presence of bulky substituents at C-6.



steric hindrance of N-7 by a C-6-substituent leads to selective N-9 alkylation

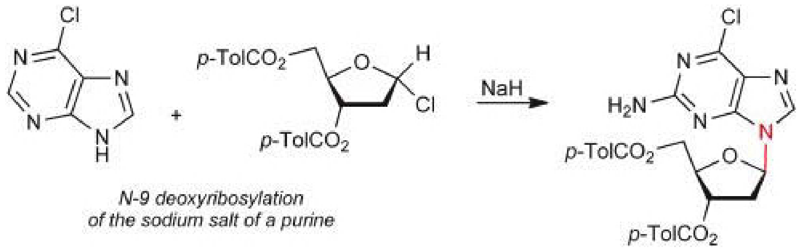


Regiospecific 7-alkylations can be achieved via the quaternisation of a 9-riboside followed by hydrolytic removal of the sugar unit.



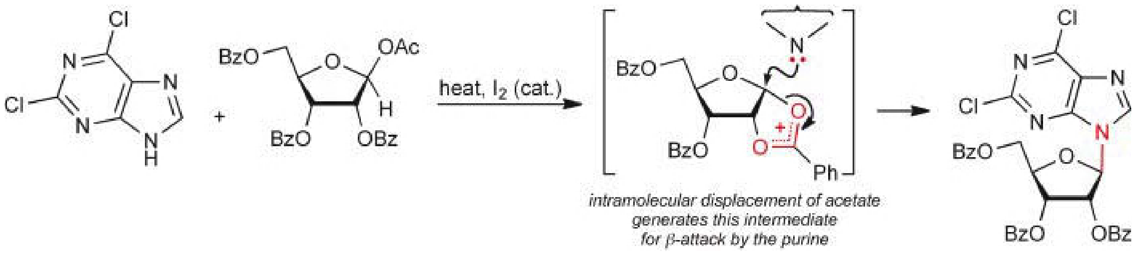
regioselective N-7 alkylation of a nucleoside followed by hydrolytic removal of the sugar

In the context of synthesis of nucleosides and analogous compounds, the *N*-ribosylation (and *N*-deoxyribosylation) of purines has been much studied. Such 'alkylations' must address not only regioselectivity (N-7/N-9) on the purine, but also the formation of the required epimer at the linking C-1′ of the sugar. Each case must be taken on its merits because there are no conditions that are universally effective. These alkylations often employ halo-ribosides in conjunction with a purine derivative of mercury, silicon or sodium, and stereoselective displacements of halide can sometimes be achieved.



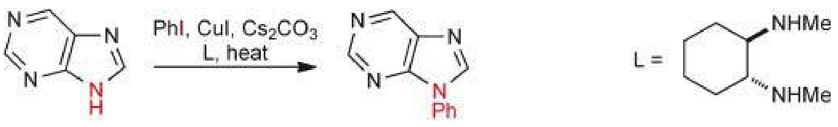
N-9 deoxyribosylation of the sodium salt of a purine

Another useful method, which gives very high stereoselectivity, involves anchimeric assistance by a 2-benzoate.



intramolecular displacement of acetate generates this intermediate for β-attack by the purine

N-9 Arylation of purine can be achieved with copper catalysis.



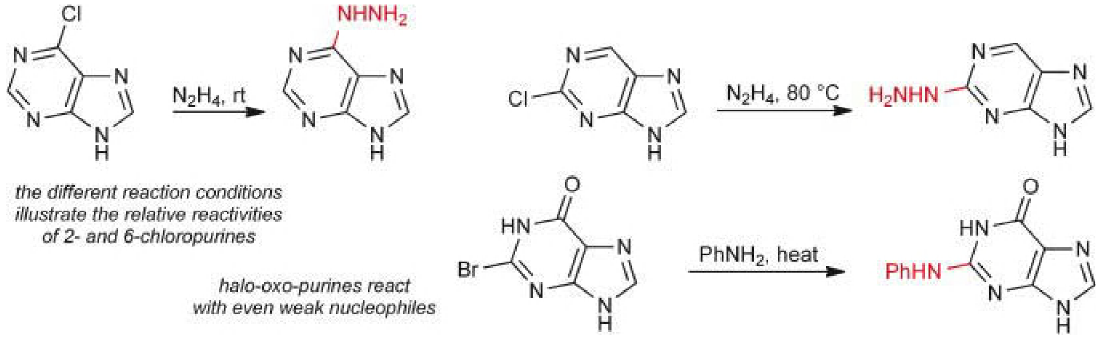
Oxidation

Chemical oxidation of purines usually gives *N*-oxides but C-8-oxidation is an important biological process mediated, for example, by the oxo-transferase enzyme, xanthine oxidase, which converts hypoxanthine and xanthine into uric acid (see page 159).

Nucleophilic substitution

Purines are susceptible to nucleophilic substitution, which is of particular relevance in the displacement of a halide, and this is probably the most widely used reaction for manipulation of purines. A wide range of nitrogen, oxygen, sulfur and carbon nucleophiles can be employed, and the reaction occurs via an addition–elimination mechanism as in similar displacements in pyridines. Many different leaving groups have been used on purines, and the interplay (regarding reactivity, rates and selectivity) between different permutations of leaving group and nucleophile is very complex.

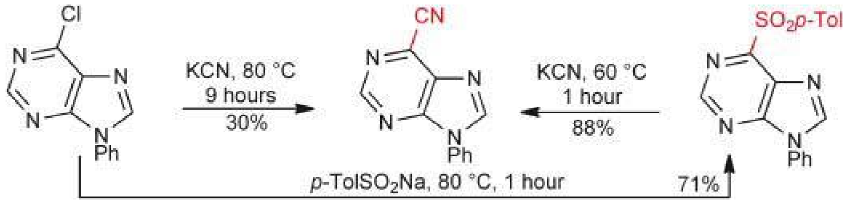
Halide located at any of the three available carbons – C-2, C-6 and C-8 – is readily displaced. In a 9-substituted purine, which cannot form an *N*-anion, the relative reactivity is 8>6>2. However, in a 9*H*-purine, this is modified to 6>8>2, the demotion of the 8-position being associated with anion formation in the five-membered ring. The presence of an amino group reduces the reactivity of a purine halide but it is enhanced by electron-withdrawing oxo groups. One illustration of relative reactivity is the conditions required for the reactions of 2- and 6-chloropurines with hydrazine. Halo-oxo-purines react easily, even with poor nucleophiles.



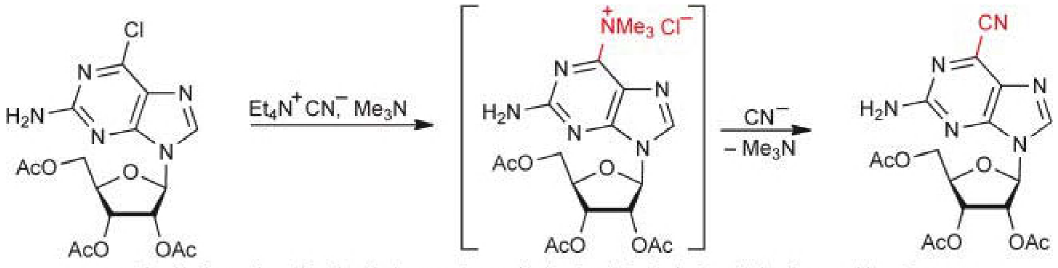
the different reaction conditions illustrate the relative reactivities of 2- and 6-chloropurines

halo-oxo-purines react with even weak nucleophiles

Other useful leaving groups include triflate, alkylthio and arylthio, and sulfone, the last also being involved in the sulfinate-catalysed displacement of halide. Significantly, in this process, sulfinate is more reactive than cyanide as a nucleophile for the displacement of chloride but is *also* more reactive than chloride as a leaving group, as illustrated by the stoichiometric reactions shown below.

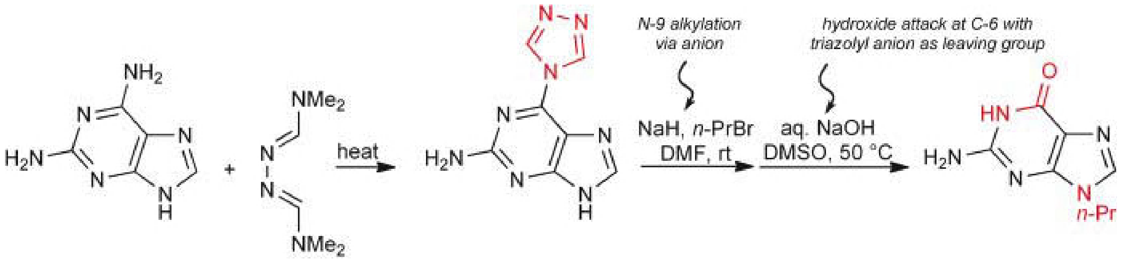


A similar device commonly used to activate purine chlorides is reaction with a tertiary amine, such as trimethylamine, giving a quaternary salt that has greatly enhanced reactivity. This can also be carried out as separate steps or *in situ.*



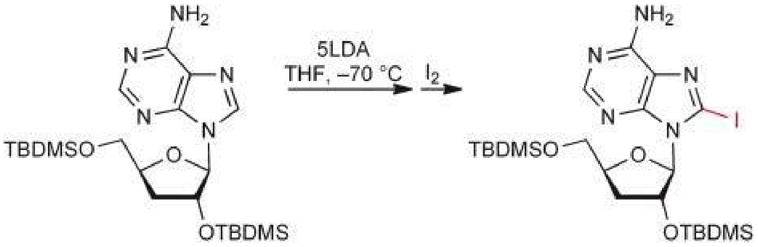
an in situ *formation of a trimethylammonium salt allowing trimethylamine to be the good leaving group*

Even primary amino groups can be easily converted into leaving groups by conversion into a 1,2,4-triazole.

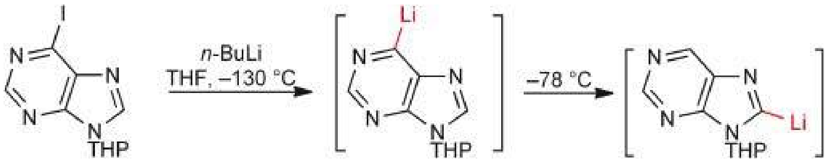


C-Metallated purines by direct deprotonation or halogen–metal exchange

After protection of the 9-position, purines can be directly lithiated at C-8, the lithio compounds then reacting with a variety of electrophiles under normal conditions. Even an adenine derivative containing a free NH_2 can be directly metallated if a large excess of base is used.

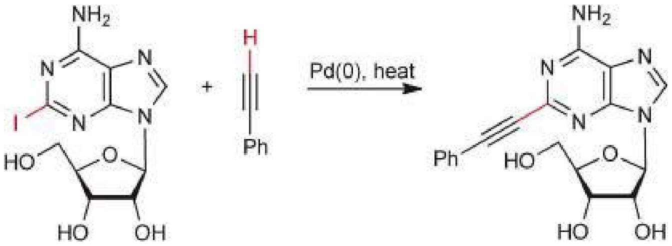


Compounds metallated in the six-membered ring are available via halogen–lithium exchange, but if C-8 is unsubstituted, very low temperatures must be maintained to avoid a rapid equilibration to the much more stable 8-lithio compounds.



Palladium(0)-catalysed reactions

Most commonly, palladium-catalysed substitutions on purines are carried out on a halopurine. Cross-couplings on 6,8-dichloropurines are highly selective for C-6.



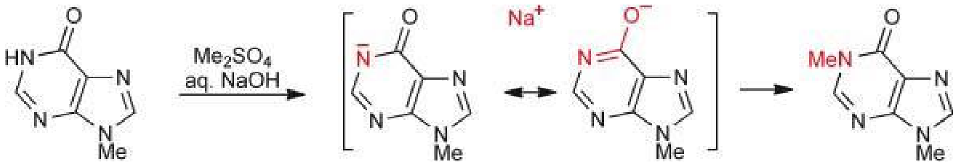
Purines with oxygen and amine substituents

Oxy- and amino-purines are potentially tautomeric compounds that exist predominantly as carbonyl and amino structures, respectively, as indicated at the beginning of this chapter and in line with the situation in simpler heterocycles, such as pyridines.

Oxypurines

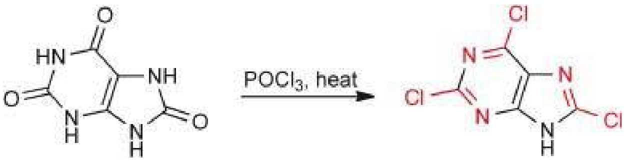
Alkylation

The 'amide' *N*-hydrogen in oxypurines is relatively acidic and these compounds can be readily alkylated under basic conditions, substitution occurring only on nitrogen. This acidity can be readily understood in terms of the phenolate-like resonance contributor to the anion. Conversely, acylation, sulfonation and silylation occur on the oxygen.



Conversion of oxygen into leaving groups

As discussed previously, nucleophilic displacement of leaving groups is a very important reaction of purines. Oxopurines are the prime sources for preparation of the substrates for these reactions, being readily converted into chloro-compounds by replacement of the oxygen, including even the fully oxygenated purine, uric acid. Alternatively, an oxygen can be activated by conversion into an acyloxy or sulfonyloxy derivative.



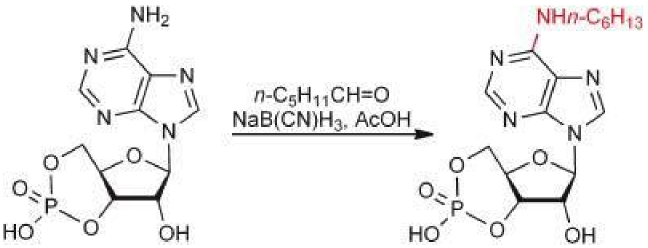
Replacement by sulfur

Replacement of oxygen by sulfur can be achieved directly using a phosphorus sulfide, or by nucleophilic substitution after conversion into a leaving group. The thiopurines are of interest in their own right but are also a potential precursor to sulfones, which are highly reactive towards nucleophilic displacement (page 127).

Aminopurines

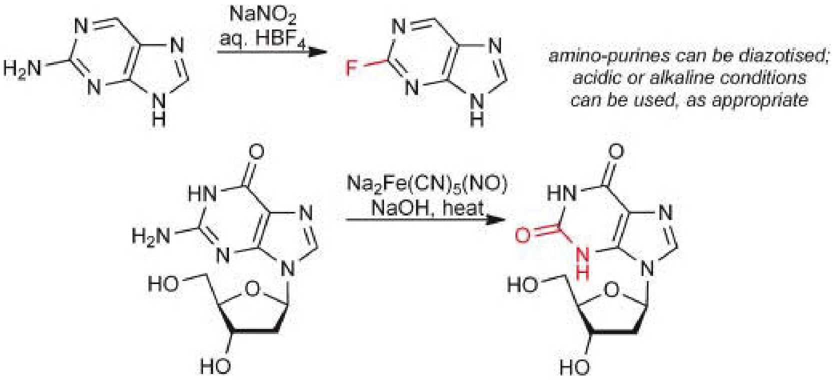
Alkylation

As discussed previously, alkylation under neutral conditions results in reaction at nuclear nitrogen and the product can then be converted into a side-chain alkylamino purine by means of the Dimroth rearrangement (see page 127). An alternative direct method for mono-alkylation of an amino group is by reductive alkylation using an aldehyde and a reducing agent.



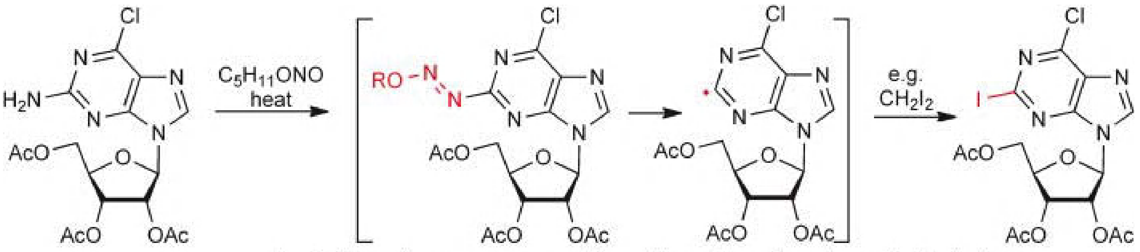
Diazotisation

The reaction of purine 2- and 6-amino groups with nitrous acid is similar to that of 2-aminopyridines, in that the diazonium salts are relatively unstable when compared with phenyl diazonium salts but can, nevertheless, be utilised for the introduction of groups such as halide. 8-Diazonium salts are considerably more stable due to mesomeric interaction with the electron-rich ring. Diazotisation can also be carried out under basic conditions when acid-sensitive groups such as (deoxy)ribosides are present.



amino-purines can be diazotised; acidic or alkaline conditions can be used, as appropriate

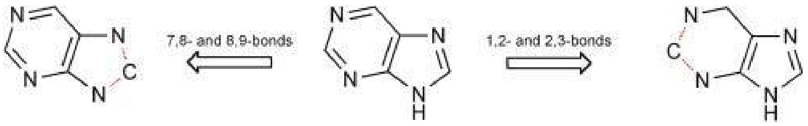
A related reaction with an alkyl nitrite produces purinyl radicals, which are efficiently converted into halopurines by abstraction of halogen from poly-halogenated solvents.



diazotisation under non-aqueous conditions; intermediacy of a carbon-centred radical

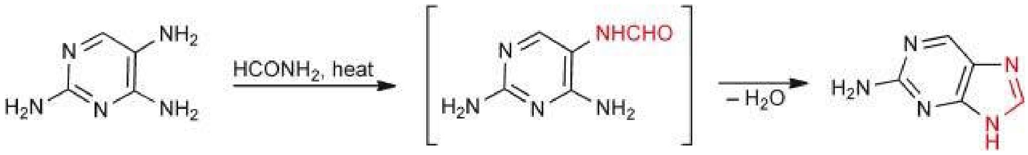
Ring synthesis – disconnections

Most purine syntheses involve cyclisation reactions of 4,5-diaminopyrimidines or of derivatives of 5-aminoimidazole-4-carboxylic acid.



Synthesis of purines from 4,5-diaminopyrimidines
(7,8- and 8,9-bonds made)

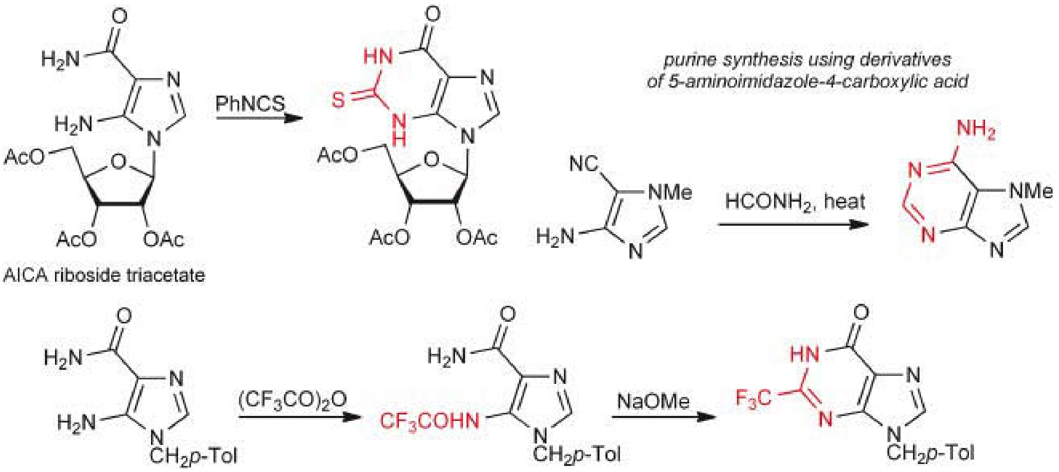
8-Unsubstituted purines can be prepared simply by heating 4,5-diaminopyrimidines with a formylating agent, usually formamide. The reaction involves firstly *N*-formylation of the amine and then *in situ* dehydration–cyclisation of the resulting formamide. This is the classical *Traube synthesis* of purines.



8-Substituted purines can be prepared via *N*-acylation with higher acids. In some simple cases, *in situ* cyclisation occurs but usually a two-step sequence is required in which an amide is formed first.

Synthesis of purines from 5-aminoimidazole-4-carboxamide
(1,2- and 2,3-bonds made)

5-Aminoimidazole-4-carboxamide (usually known by the acronym AICA) and its riboside are commercially available and are the best starting materials for the preparation of 2-substituted hypoxanthines and inosines, respectively. Adenine derivatives can also be prepared by a very similar route, employing the corresponding aminoimidazole-carbonitriles. (AICA riboside is the biosynthetic precursor to inosine.)

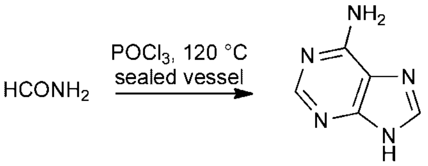


AICA riboside triacetate

purine synthesis using derivatives of 5-aminoimidazole-4-carboxylic acid

'One-step syntheses'

The formation of purines, such as adenine, in the 'primordial soup' was probably a pre-condition for the evolution of life! Amazingly, relatively complex molecules such as adenine can be formed by the sequential condensation of very simple, fundamental molecules such as ammonia and hydrogen cyanide. Adenine, $C_5H_5N_5$, is formally a pentamer of hydrogen cyanide and indeed can be prepared in the laboratory by reaction of ammonia with hydrogen cyanide, although not with great efficiency. An equivalent, but more practical, method involves dehydration of formamide.



Exercises

1. What are the structures of the intermediates and final product of the following sequence: guanosine 2′,3′,5′-triacetate reacted with $POCl_3 \rightarrow C_{16}H_{18}ClN_5O_7$ then this with *t*-BuONO–$CH_2I_2 \rightarrow C_{16}H_{16}ClIN_4O_7$, this product with NH_3–MeOH $\rightarrow C_{10}H_{12}IN_5O_4$ 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 $Me_2SO_4 \rightarrow C_{11}H_{15}N_5O_4$, 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).

14

Heterocycles with More than Two Heteroatoms: Higher Azoles (5-Membered) and Higher Azines (6-Membered)

Higher Azoles

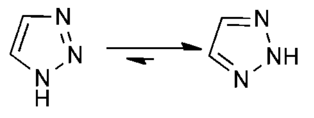
Introduction

Any or all of the carbon atoms in all the five-membered heterocyclic systems described in previous chapters could, in theory, be replaced by nitrogen. Using nitrogen, oxygen and sulfur, there are 18 possible azoles with three or more heteroatoms, of which 13 are known. (Three of the unknown parents are those that contain no carbon.) However, the tautomers of the three systems containing only nitrogen as the heteroatom could also be considered as individual azoles and do show differences in aromaticity and reactivity when fixed by substitution on nitrogen. Of course, the more heteroatoms there are present, the less opportunity there is for chemistry at carbon!

When a ring contains several heteroatom–heteroatom and heteroatom–carbon bonds, there is the probability of thermodynamic instability and the possibility of kinetic instability, and the latter particularly if the juxtaposition of these atoms could allow facile extrusion of stable molecules such as nitrogen (gas) or even elemental carbon or sulfur. In fact, some of this class of compounds do find use as commercial explosives (see pages 184–186) but, on the other hand, many are quite docile. Amongst tetrazoles, in particular, there are examples of both aspects – some are exceptionally dangerous compounds and others are used as building blocks of medicines (for examples see pages 133 and 168). Indeed many of the higher azoles are of great importance in medicinal chemistry and in industry.

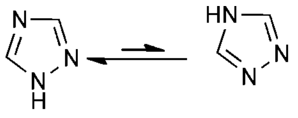
Higher azoles containing nitrogen as the only ring heteroatom: triazoles, tetrazole and pentazole

There are four higher azoles containing only nitrogen as the heteroatom – two triazoles, tetrazole and pentazole. The triazoles and tetrazole each exist as mixtures of two tautomers. Of the parent compounds, only pentazole has not been isolated, indeed only a few unstable derivatives have been prepared. The other three systems have very extensive chemistry.



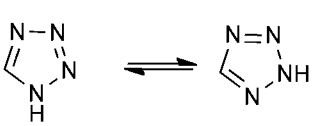
1*H*-1,2,3-triazole 2*H*-1,2,3-triazole

pK_{aH} 1.2 pK_a 9.4



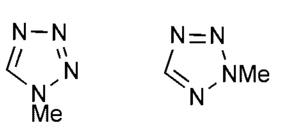
1*H*-1,2,4-triazole 4*H*-1,2,4-triazole

pK_{aH} 2.2 pK_a 10.3

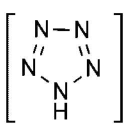


1*H*-tetrazole 2*H*-tetrazole

pK_a 4.9



tautomers can be fixed by N-*substitution and then often have very different properties*

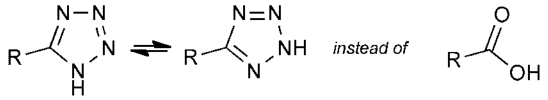


pentazole

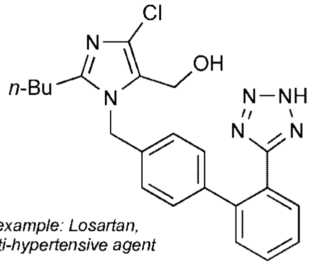
parent unknown and the few known derivatives are very unstable

The triazoles are weak bases but relatively acidic – about the same as phenol. Tetrazoles are even weaker bases but more acidic – about the same as a carboxylic acid, and they are used as isosteric replacements for carboxylic acids in a number of drugs.

Heterocyclic Chemistry at a Glance, Second Edition. John A. Joule and Keith Mills.



tetrazoles are used in drugs as equivalents of carboxylic acids



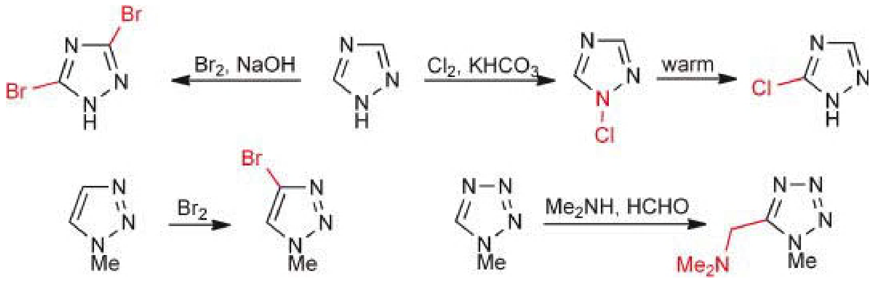
for example: Losartan, an anti-hypertensive agent

1,2,3-Triazoles are remarkably stable, considering that they contain three directly-linked nitrogens, and will generally withstand temperatures greater than 150 °C. Tetrazoles usually are also surprisingly stable although tetrazole itself (mp 158 °C, decomposes above180 °C) is classified as an explosive, at least for shipping. The ring systems of these azoles are very resistant to reduction.

Most of the relatively few known pentazoles (*N*-aryl derivatives) are unstable at room temperature – some are even said to explode on reaching −10 °C.

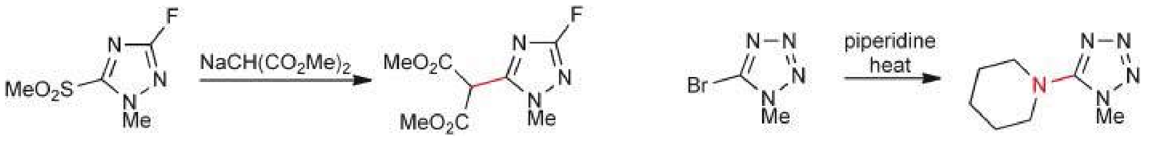
Electrophilic substitution at carbon

The triazoles and tetrazole undergo electrophilic substitution under surprisingly mild conditions, considering the electron-deficient nature of the rings. Although some of these reactions on NH substrates are base-catalysed, and therefore may proceed via the anion, *N*-alkyl compounds react similarly, so some mechanism other than that for standard aromatic electrophilic substitution may be involved.



Nucleophilic substitution at carbon

Nucleophilic displacements occur with reasonable ease in *N*-alkylated compounds, that is, those lacking the acidic NH. Sulfones are particularly good leaving groups for carbon nucleophiles.



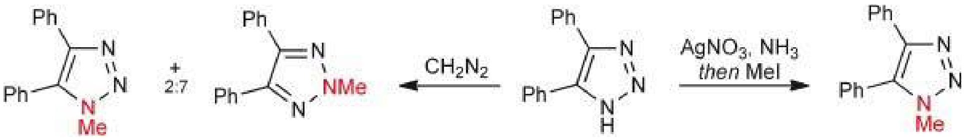
N-Deprotonation and *N*-metallated triazoles and tetrazoles

N-Alkylation is one of the most important reactions of NH triazoles and tetrazoles, with control of regioselectivity being a significant problem, the proportions of regioisomers depending on substituents in the heterocyclic ring, the bulk of the alkylating agent, and reaction conditions. The preparation of the pure regioisomers can be a significant challenge.

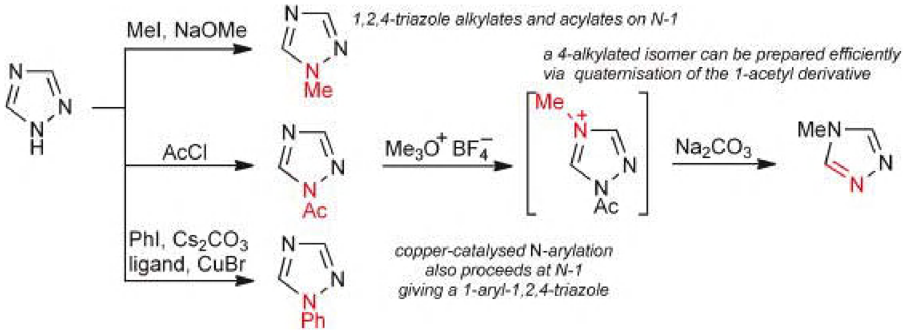
Owing to their relatively high acidity, all these azoles can be readily alkylated in the presence of weak bases.

(Note: Many 1-substituted 1,2,3-triazoles and tetrazoles are actually readily available by direct ring synthesis, but the 2-substituted isomers are usually not accessible in this way and often depend on preparation via *N*-alkylation.)

1,2,3-Triazoles have some tendency to alkylate on N-2 but there is considerable variation in selectivity, although this can often be controlled (by trial and error!) by choice of conditions, as exemplified below.



1,2,4-Triazoles alkylate very predominantly on one of the two adjacent nitrogens and the minor regioisomer (on the lone nitrogen) is eliminated during a simple isolation. (Note: The 1- and 2-nitrogens of the parent heterocycle are equivalent before alkylation.) Selective alkylation on the lone (4-) nitrogen requires a more complex method: selective acylation at N-1 allows the product to be quaternised selectively at N-4. Easy hydrolysis of the acyl group during work-up permits isolation of the pure 4-alkyl derivative. However, this method has limited scope, as only a few highly reactive alkylating agents can quaternise triazoles.



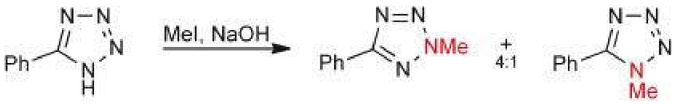
1,2,4-triazole alkylates and acylates on N-1

a 4-alkylated isomer can be prepared efficiently via quaternisation of the 1-acetyl derivative

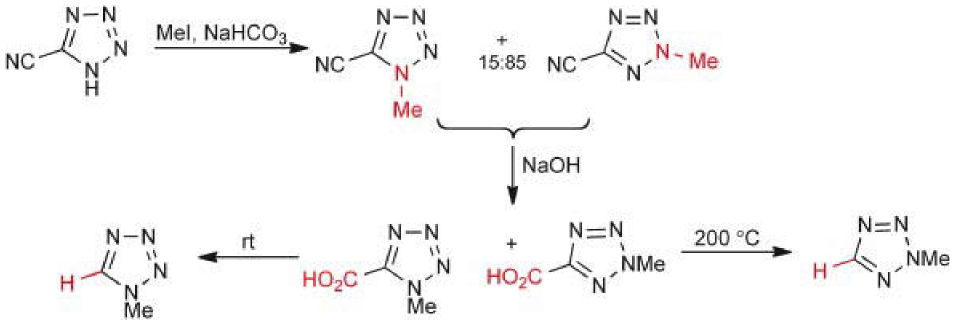
copper-catalysed N-arylation also proceeds at N-1 giving a 1-aryl-1,2,4-triazole

Copper-catalysed *N*-arylation is also known: 1,2,3-triazole reacts at N-1; 1,3,4-triazole is arylated, as for alkylation, at one of the adjacent nitrogens.

The regioselectivity of *N*-alkylation of tetrazoles is also affected by the steric and polar properties of the 5-substituent, thus electron-withdrawing or bulky groups at C-5 favour 2-alkylation, as exemplified by *N*-methylation of 5-phenyltetrazole, as shown below.

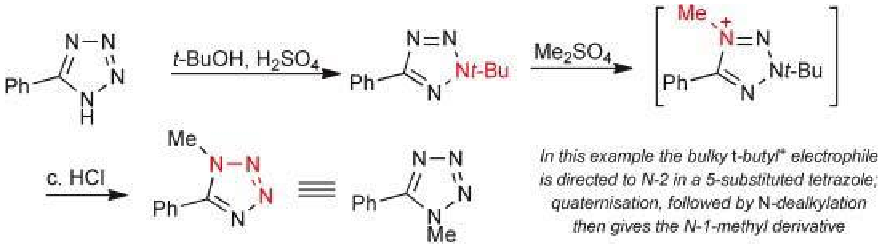


The reaction of 5-cyanotetrazole with iodomethane also proceeds selectively, 85:15, N-2:N-1, despite the low steric requirements of the cyano group.



As mentioned previously, the reactivity of 'fixed' tautomers can be very different and this is nicely demonstrated by the further transformations of the mixture of methyl cyanotetrazoles shown above. 1-Methyltetrazole-5-carboxylic acid decarboxylates spontaneously at room temperature, whereas its 2-methyl isomer requires heating to 200 °C to achieve the same result. Thus hydrolysis of the mixture of nitriles gives a mixture of 1-methyltetrazole and 2-methyltetrazole-5-carboxylic acid, which can be easily separated; decarboxylation of the 2-methyl-5-acid at 200 °C then gives pure 2-methyltetrazole.

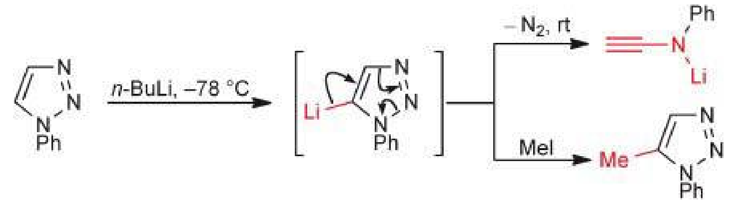
Selective 1-alkylation of some tetrazoles can be achieved by a two step method similar to that used for the 4-alkylation of 1,2,4-triazole shown above, but again it is limited by the availability of sufficiently reactive alkylating agents.

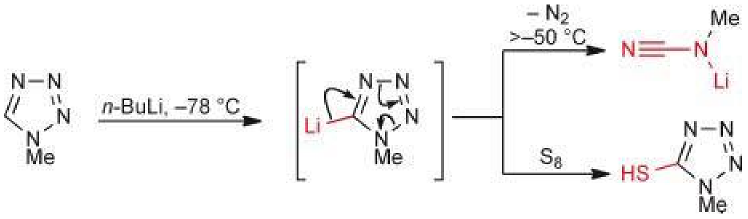


In this example the bulky t-butyl⁺ electrophile is directed to N-2 in a 5-substituted tetrazole; quaternisation, followed by N-dealkylation then gives the N-1-methyl derivative

C-Metallation

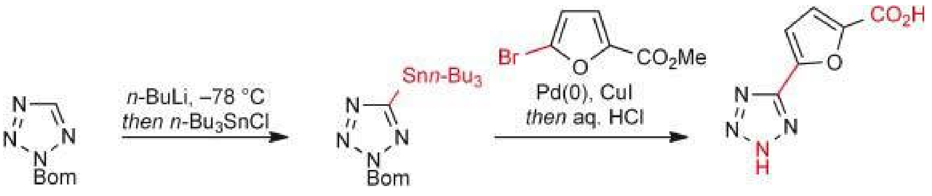
1-Alkylated 1,2,3- and 1,2,4-triazoles lithiate readily at C-5, but the lithio-compound from the 1,2,3-isomer decomposes on warming to room temperature; the lithiated 1,2,4-isomer is significantly more stable. The lithio-compound from a 1-substituted tetrazole decomposes above −50 °C. However, all react normally with electrophiles while low temperatures are maintained.

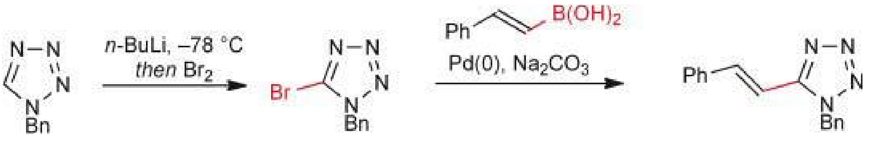




Palladium(0)-catalysed reactions

There are only a few examples of organometallics derived from higher azoles being used in cross-coupling reactions, particularly zinc and tin derivatives; the reverse coupling using the haloazole as substrate is more generally applicable.

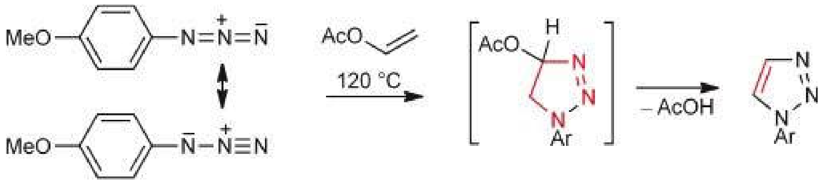




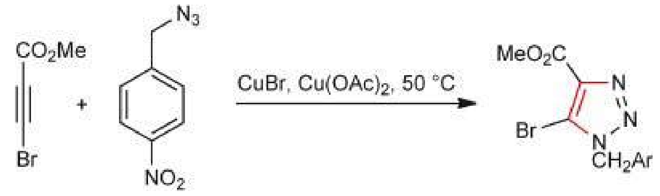
Ring synthesis

1,2,3-Triazoles are usually prepared via a cycloaddition of an azide to an alkyne or its equivalent; for example, in the example below vinyl acetate is used as a higher boiling equivalent of ethyne. (**Caution:** All azides are potentially explosive but the risk varies greatly – low molecular weight alkyl azides and hydrazoic acid are particularly dangerous. Trimethylsilyl azide and aryl azides are safer.)

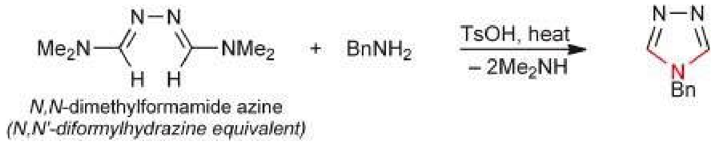
This triazole ring synthesis is often referred to as a 'Click reaction' on account of its efficiency, reliability and general applicability, especially for the purpose of linking (clicking together) two moieties. (The term 'Click reaction' originally referred to any highly efficient and reliable general reaction that can be used for linking moieties.)

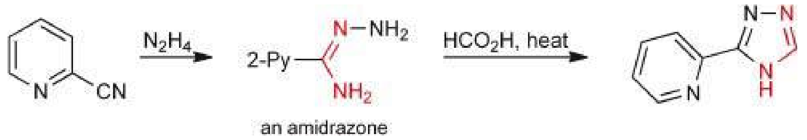


Copper catalysis is often used, allowing a wider application under milder conditions.

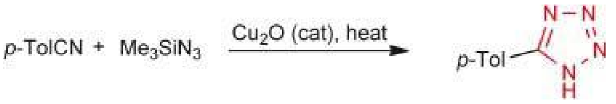


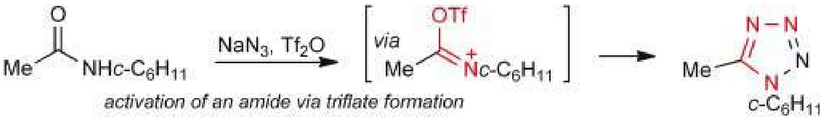
4-Substituted 1,2,4-triazoles are accessible from the reaction between *N*,*N'*-diacylhydrazines and primary amines, but this requires vigorous conditions so more reactive equivalents of the diacylhydrazines, such as *N*,*N*-dimethylformamide azine, are usually preferred. 3-Substituted 1,2,4-triazoles result from the condensation of amidrazones (available from reaction of hydrazine with a nitrile) with formic acid, esters or nitriles.





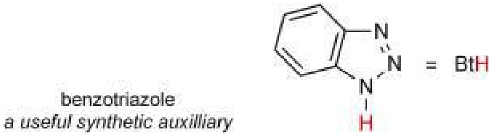
Tetrazoles are usually prepared by the reaction of azide anion, or an azide, with a nitrile or activated amide. Trimethylsilyl azide is more convenient and safer; the silyl group is lost during the process.



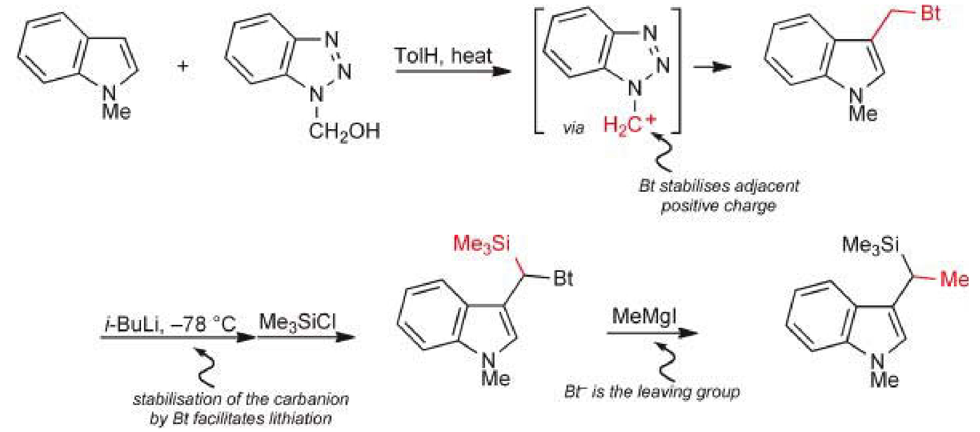


Benzotriazole

Benzotriazole has significant uses as an auxiliary for general organic synthesis. It has the properties of being an activating group for stabilisation of α-carbocations *and* α-carbanions and can also act as a leaving group.



The sequence below illustrates the stabilisation of a cation (Mannich reaction), the stabilisation of an anion to allow lithiation and action as a leaving group for displacement with a Grignard nucleophile.

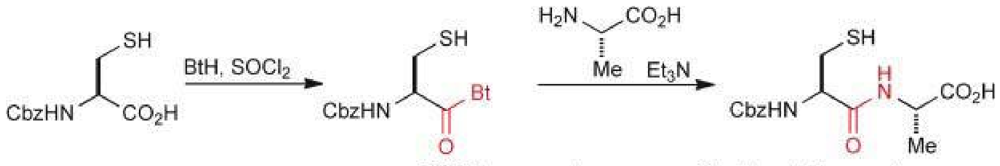


Bt stabilises adjacent positive charge

stabilisation of the carbanion by Bt facilitates lithiation

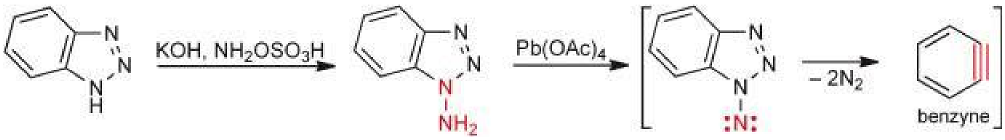
Bt⁻ is the leaving group

N-Acylbenzotriazoles, which are stable, more easily handled and milder electrophiles than acid chlorides or anhydrides, can be prepared from a large variety of acids, including *N*-protected α-amino acids, by simple reaction of benzotriazole with an acid chloride, generated *in situ* using thionyl chloride. *N*-Acylbenzotriazoles have been widely used as *N*-, *O*-, *S*- and *C*-acylating agents. In particular they can be used to form amide bonds in the synthesis of peptides, that is, as *N*-acylating agents. An illustrative example is shown below.



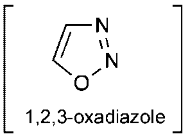
BtCOR compounds are very useful mild acylating agents

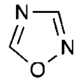
In addition to the important role of benzotriazole as a synthetic auxiliary, there are other ways in which the ring system can be utilised. Perhaps the most important of these is the relatively mild, neutral oxidative degradation of 1-aminobenzotriazoles, used to generate benzynes.

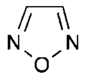


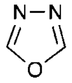
Higher azoles also containing ring sulfur or oxygen: oxa- and thiadiazoles

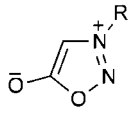
There are eight possible oxa- and thiadiazoles and all are known, stable compounds apart from 1,2,3-oxadiazole, which is unstable with respect to a ring-open tautomer. However, mesoionic derivatives of 1,2,3-oxadiazole – sydnones – are useful stable intermediates. Only one divalent heteroatom can be incorporated into a simple five-membered, aromatic heterocycle, unless a carbonyl is also present. 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.

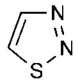

1,2,3-oxadiazole

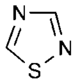

1,2,4-oxadiazole

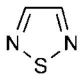

1,2,5-oxadiazole

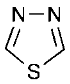

1,3,4-oxadiazole


sydnones


1,2,3-thiadiazole


1,2,4-thiadiazole

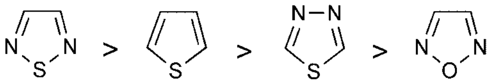

1,2,5-thiadiazole


1,3,4-thiadiazole

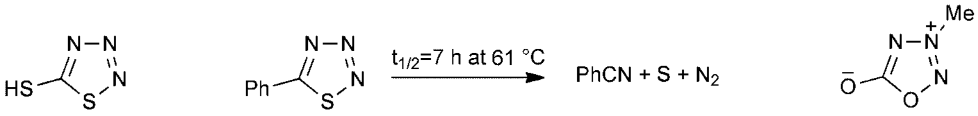
Relative aromaticities and stabilities

Predicting precise interactions between the heteroatoms in these systems is not easy but the general stability/reactivity can be implied from their relative aromaticities, based on bond lengths and NMR (nuclear magnetic resonance) data.

approximate order of aromaticity



Of the oxa- and thia-compounds with more than two nitrogens, only derivatives of 1,2,3,4-thiatriazoles are well defined, but even here only 5-aryl and 5-amino compounds are reasonably stable; some compounds, such as the 5-chloro and the 5-thiol, are dangerously explosive. The source of this instability is an easy loss of sulfur and molecular nitrogen as can be seen by inspection of the structure. Mesoionic 1,2,3,4-oxatriazoles (azasydnones) are relatively stable, and indeed are the only stable 1,2,3,4-oxatriazoles, probably because there is no low energy possibility for these isomers to lose nitrogen. (The presence of two contiguous unsubstituted nitrogen atoms can allow easy extrusion of nitrogen gas, however in the azasydnone this direct elimination of N_2 is blocked by the presence of methyl on the central nitrogen.)

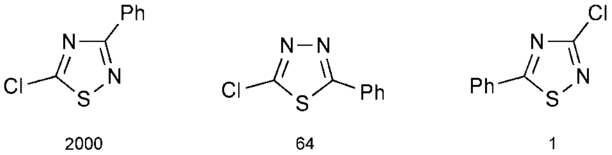


explodes at 50 °C　*controlled decomposition*　*stable in refluxing EtOH for >3 h*

Nucleophilic substitution at carbon

Owing to the highly electron-deficient nature of these rings, electrophilic substitution on carbon is rare but, conversely, nucleophilic displacements proceed readily. There are large differences in relative reactivity, which are rather difficult to predict on simple examination, but some experimental data are available.

relative rates of reaction of chlorothiadiazoles with piperidine in ethanol



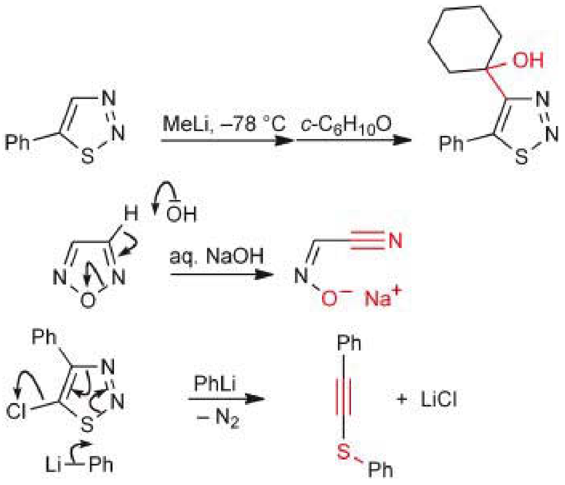
C-Metallation of higher azoles (containing O/S)

Lithiation occurs readily and can be used for manipulation of substituents, but ring-opening and other side reactions are common. Some systems, such as 1,2,5-oxadiazole, are decomposed even by weak bases. In the thia-compounds, direct attack on S can also occur, particularly with organolithium reagents, leading to fragmentation of the ring.

normal lithiations are possible in some systems

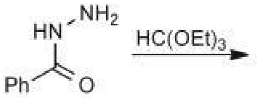
1,2,5-oxadiazole is very sensitive to base

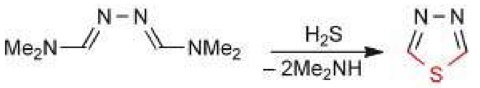
attack at sulfur by organolithiums can occur

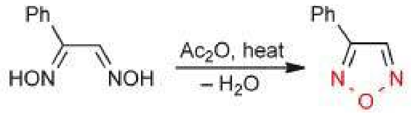


Ring synthesis

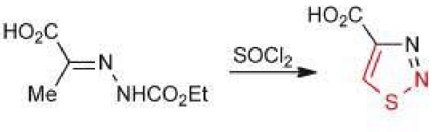
Some syntheses of oxa- and thiadiazoles follow the condensation–cyclisation approaches used for simpler azoles, but oxidative cyclisations may be required when a sulfur–nitrogen bond is required.

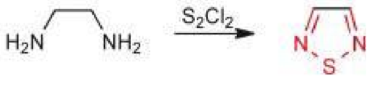






cyclocondensation reactions can be used to prepare oxa- and thiadiazoles

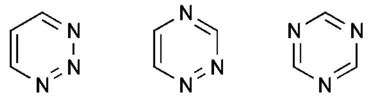




oxidising conditions are usually required when a sulfur–nitrogen bond is to be formed

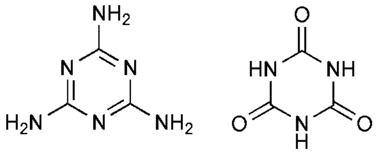
Higher Azines

Any or all of the carbon atoms in all the six-membered nitrogen-containing heterocyclic systems described in previous chapters could, in theory, be replaced by nitrogen. All three possible triazine parent systems are stable and have an extensive chemistry but of the five possible azines with four or more nitrogens, only 1,2,4,5-tetrazines are known as monocyclic compounds. 1,2,3,5-Tetrazine rings can be prepared in fused systems, such as temozolomide (see below and page 178), although this has the benefit of pyridone-like stabilisation. Known 1,2,3,4-tetrazines are limited to *N*-oxides in fused systems. Pentazines and hexazines are unknown.



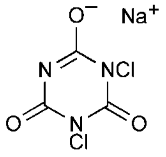
1,2,3-triazine 1,2,4-triazine 1,3,5-triazine

all three possible triazines are stable



melamine cyanuric acid

1,3,5-triazines used on industrial scale



sodium dichloroisocyanurate

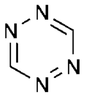
a widely-used disinfectant

Triazines are found in some drugs (cf. Chapter 18) but probably the best-known triazine is melamine (2,4,6-triamino-1,3,5-triazine), which is used industrially to make plastics. 'Cyanuric acid' (1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione) was first prepared in 1776 by Scheele by the pyrolysis of uric acid. Sodium dichloroisocyanurate is a very widely used bleach-type disinfectant.

1,2,3,4-tetrazine 1,2,3,5-tetrazine pentazine hexazine

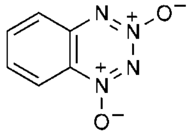
unknown systems

Replacement of carbon in an azine by oxygen or sulfur would not give a neutral aromatic compound, although a divalent heteroatom can be accommodated when a carbonyl group is present – the equivalent of an azapyrone. Oxa- and thia-diazinones are stable compounds and are useful in Diels–Alder reactions, as illustrated later.

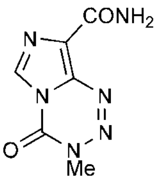


1,2,4,5-tetrazine

the only known stable monocyclic tetrazine system

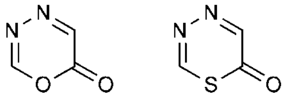


one of the very few known fused 1,2,3,4-tetrazines



temozolomide

ring fusion stabilises, hence this example of a 1,2,3,5-tetrazine

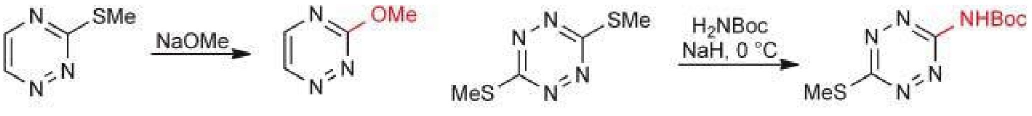


two examples of neutral azines containing ring O or S only possible in pyridone-like systems

The thermal stabilities of the known 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.

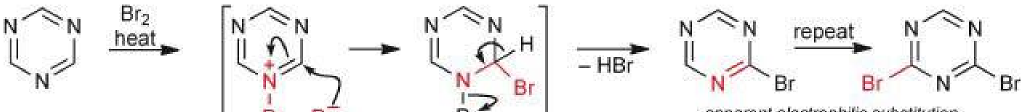
Nucleophilic substitution at carbon

Nucleophilic substitutions and additions are the most important reactions of the higher azines, electrophilic substitutions on carbon being unknown. They are generally more reactive in these nucleophilic reactions than the diazines, due to the inductive effect of the extra nitrogen(s), for example the parent systems and many derivatives react with water in acidic or basic solution.



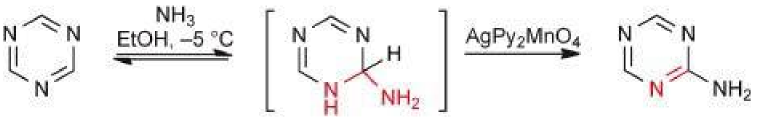
nucleophilic substitutions are very easy

There are some substitutions on carbon that might appear to be electrophilic, for example bromination of 1,3,5-triazine, but this almost certainly proceeds via electrophilic attack on nitrogen, followed by nucleophilic addition of bromide on carbon, as indicated below.



apparent electrophilic substitution initiated by electrophilic addition to nitrogen

1,3,5-Triazine readily but reversibly adds ammonia and simple amines (contrast the requirement for hot sodamide in the Chichibabin reaction for pyridine, page 35) but the aromatised amino- and alkylamino-derivatives can be obtained by trapping the adduct using a permanganate oxidant.

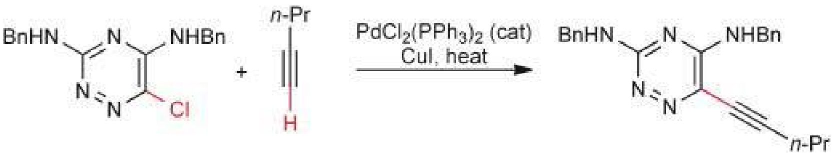


The susceptibility of 1,3,5-triazine to nucleophilic attack with ring opening makes it a synthetically useful equivalent of formate or formamide for the synthesis of other heterocycles, for example imidazoles and benzimidazoles.

1,3,5-triazine used to supply a one-carbon unit at the oxidation level of formic acid

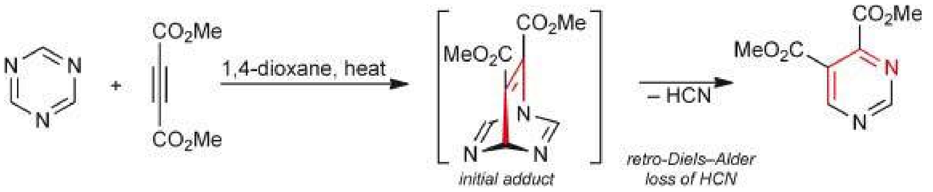
Palladium(0)-catalysed reactions

There are relatively few examples of cross-couplings with the higher azines but the halo-derivatives are good substrates. A Sonogashira example is given below.

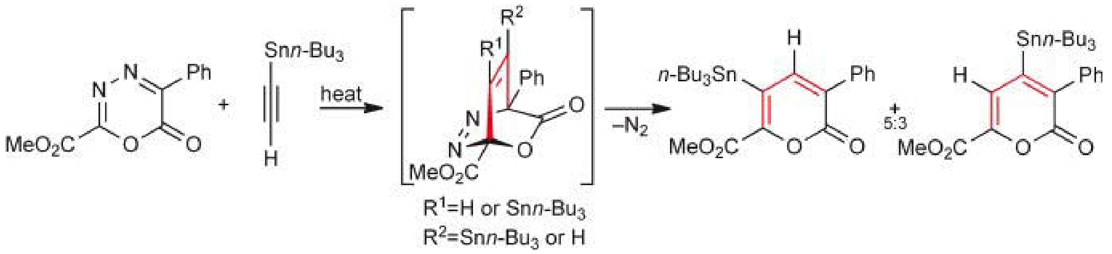


Pericyclic reactions

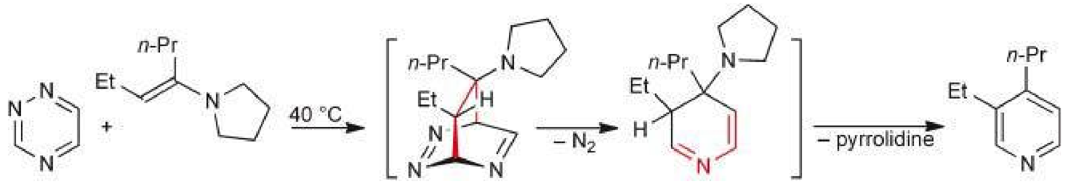
A principal chemical application of triazines and tetrazines is as electron-deficient 'dienes' in Inverse Electron Demand Diels–Alder (IEDDA) cycloadditions. These processes produce either pyridines or diazines via reverse Diels–Alder elimination of hydrogen cyanide, a nitrile, or nitrogen from the initial adduct.



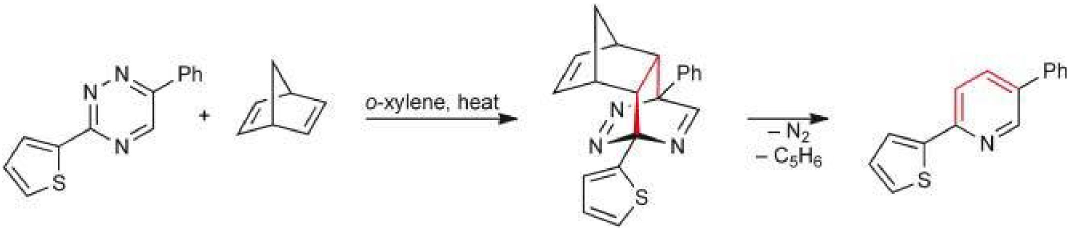
Oxadiazinones are good ‘dienes’ for Diels–Alder reactions, as shown below. It is interesting that nitrogen rather than carbon dioxide is eliminated from the initial adduct.

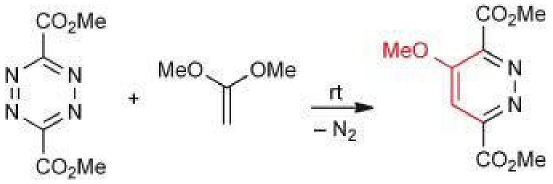


Enamines are often used as acetylene equivalents, the amine fragment being lost at a late stage to generate the aromatic heterocycle.



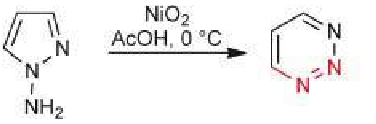
The best equivalent of ethyne itself for these reactions is norbornadiene, cyclopentadiene as well as nitrogen being lost in the final stages.

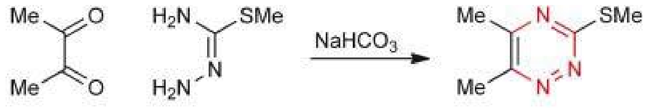


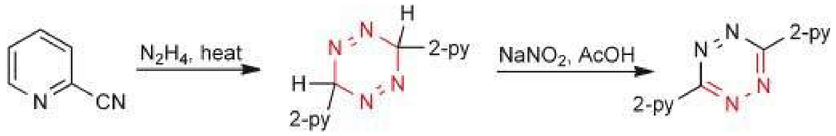


Ring synthesis of higher azines

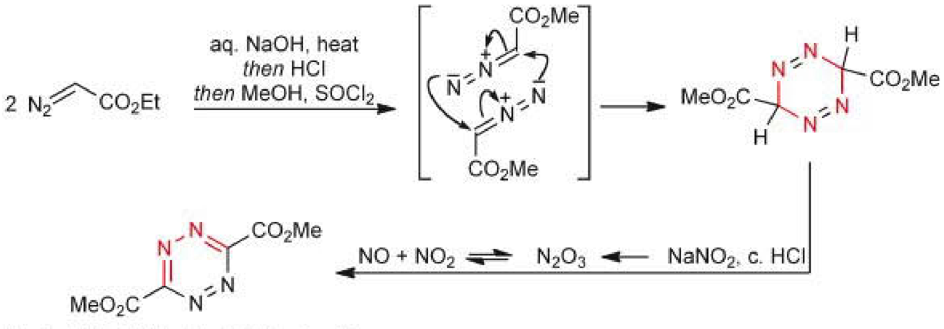
1,2,3-Triazine is prepared by oxidation of 1-aminopyrazole. Other triazines are usually prepared by cyclocondensation reactions. Symmetrically substituted 1,2,4,5-tetrazines are prepared by dimerisation–condensation reactions, followed by oxidative aromatisation. Most unsymmetrically-substituted tetrazines are prepared by manipulation of the substituents of symmetrical compounds.







Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate, which is much used in Diels–Alder reactions, is prepared by the base-catalysed dimerisation of ethyl diazoacetate, then oxidation of the resulting dihydro-tetrazine (after re-esterification).



dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate

Exercises

1. What are the products of the following (Diels–Alder) reactions:
   (i) 1-pyrrolidinylcyclopentene with (a) 1,3,5-triazine and (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 that contains no azide group; on subsequent reaction with methylamine this compound is converted into $C_2H_4N_4S$ – what are the structures?
3. What are the products of the reaction of PhCONH$_2$ with DMFDMA to give $C_{10}H_{12}N_2O$ and then this with (a) N_2H_4 or (b) H_2NOH?
4. 1,3,5-Triazine reacts with
   (i) aminoguanidine [$H_2NN{=}C(NH_2)_2$] to give 2-amino-1,3,4-triazole and with
   (ii) diethyl malonate to give ethyl 4-hydroxypyrimidine 5-carboxylate. What reasonable mechanistic sequences will rationalise these transformations?

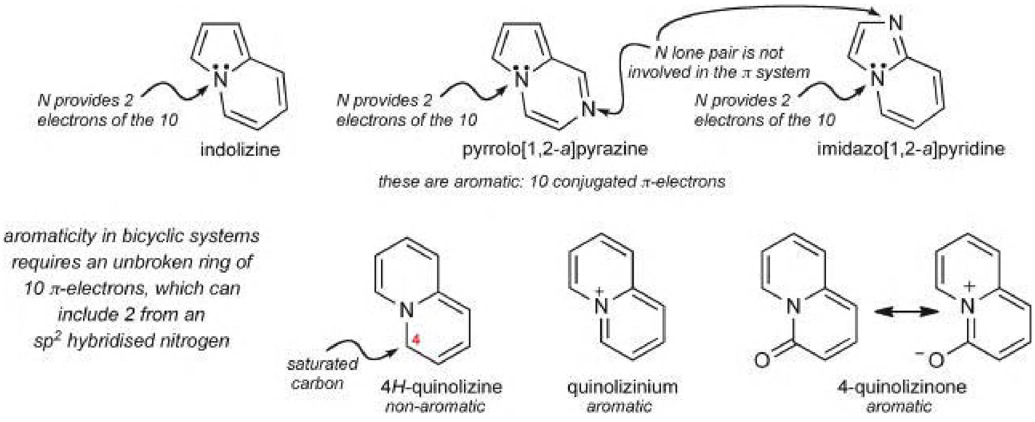
15

Heterocycles with Ring-Junction Nitrogen (Bridgehead Nitrogen)

Introduction

In addition to the biologically important purines and major benzo-fused heterocycles such as indole, many other aromatic bicyclic and polycyclic fused heterocyclic ring systems are known. The most important of these other ring systems are those containing a ring-junction nitrogen (a bridgehead nitrogen) – that is, where a nitrogen is common to both rings. These compounds, although rare in nature, have great significance in applied chemistry, particularly medicines. Only bicyclic combinations of five- and six-membered rings are considered here, although other combinations are possible and known.

Of the parent systems that have a ring-junction nitrogen as the only heteroatom, only indolizine has a neutral, fully conjugated aromatic ten-electron π-system, comprising four pairs of electrons from the four double bonds and the lone pair from the nitrogen, much as in indole. 4*H*-Quinolizine is not aromatic because there is a saturated carbon interrupting the conjugation, but the cation, quinolizinium, derived formally by loss of hydride from quinolizine, does have an aromatic ten-electron π-system. 4-Quinolizinone is similarly a ten-electron π-system as illustrated by the polarised resonance contributor.



N provides 2 electrons of the 10

N provides 2 electrons of the 10

N lone pair is not involved in the π system

N provides 2 electrons of the 10

these are aromatic: 10 conjugated π-electrons

aromaticity in bicyclic systems requires an unbroken ring of 10 π-electrons, which can include 2 from an sp² hybridised nitrogen

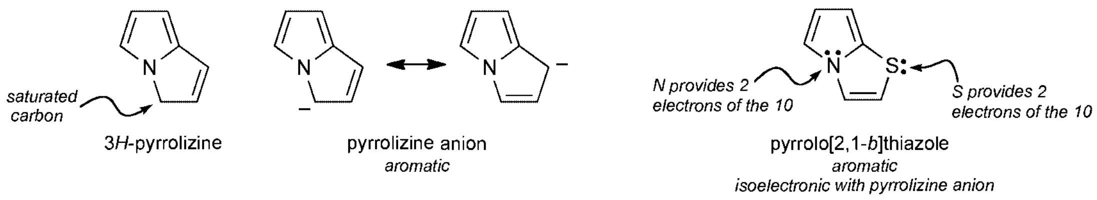
saturated carbon

non-aromatic

aromatic

aromatic

Pyrrolizine, which is already aromatic as a pyrrole, can only achieve a bicyclic aromatic ten-electron π-system by conversion into its conjugate anion. However, and more interestingly, replacing the saturated carbon by a heteroatom, which contributes a lone pair to the π-system, gives stable aromatic compounds *isoelectronic* with the anion.



saturated carbon

aromatic

N provides 2 electrons of the 10

S provides 2 electrons of the 10

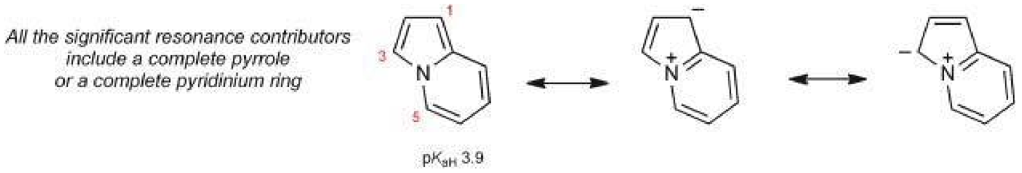
aromatic

isoelectronic with pyrrolizine anion

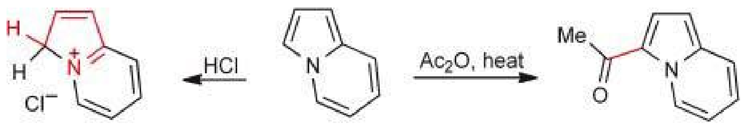
In all these systems, replacement of carbon by nitrogen does not disrupt the aromaticity, as can be seen in the benzene–pyridine relationship. This feature leads to a wide range of interesting heterocyclic systems (the azaindolizines), illustrated above by pyrrolo[1,2-*a*]pyrazine and imidazo[1,2-*a*]pyridine.

Heterocyclic Chemistry at a Glance, Second Edition. John A. Joule and Keith Mills.

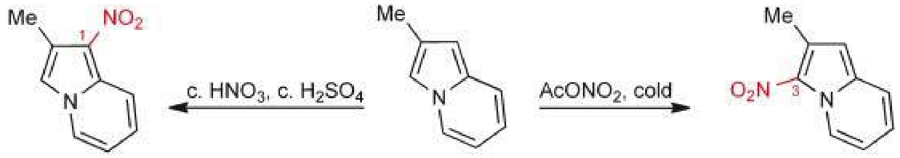
Indolizine



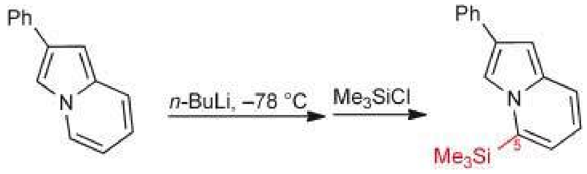
Indolizine is an electron-rich system with a reactivity similar to that of indole. However, it is significantly more basic than indole (pK_{aH} –3.5). As for indole, protonation occurs on carbon – usually C-3 – not on the nitrogen because this would produce a non-aromatic π-system. The six-membered ring of indolizine is not very pyridine-like, because it does not contain an imine so nucleophilic additions therefore are rare, however when protonated it has an iminium.

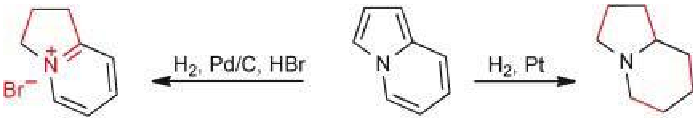


Standard electrophilic substitutions take place at C-3, but under strongly acidic conditions, reaction occurs at C-1, presumably via attack on the indolizinium cation.

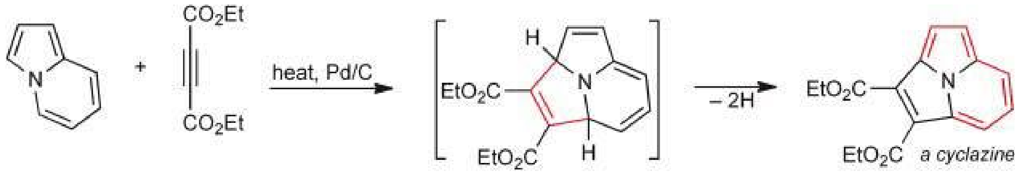


Lithiation occurs readily in the pyridine ring at C-5. Reduction in acidic solution can give either the dihydro or fully saturated derivatives.





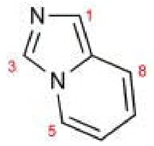
Despite its ten-electron aromatic π-system, indolizine participates as an eight-electron π-system in its reaction with diethyl acetylene dicarboxylate, although details of the mechanism are not clear. The reaction is carried out in the presence of a catalyst to convert the unstable intermediate adduct into the stable, aromatic cyclazine product (see pages 148–149).



Azaindolizines

(Note: The numbering of azaindolizines is complex and varies with the number and disposition of nitrogens.)

imidazo[1,2-*a*]pyridine

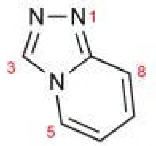


imidazo[1,5-*a*]pyridine

pyrazolo[1,5-*a*]pyridine

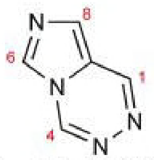
1,2,3-triazolo[1,5-*a*]pyridine

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

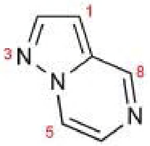


1,2,4-triazolo[4,3-*a*]pyridine

imidazo[1,5-*c*]pyrimidine



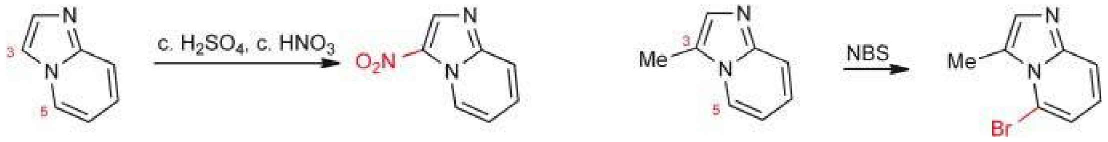
imidazo[1,5-*d*][1,2,4]triazine



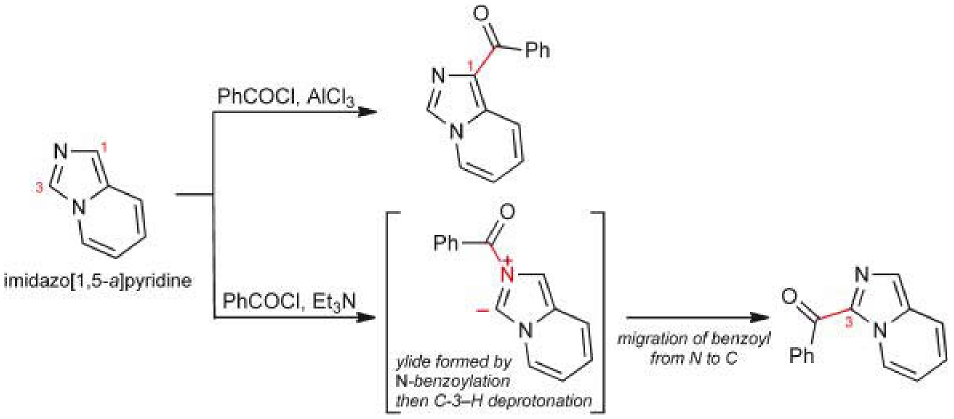
pyrazolo[1,5-*a*]pyrazine

'Azaindolizines' – indolizines containing additional nitrogen(s) replacing carbons – are common. Compounds with extra nitrogen(s) in the six-membered ring now contain imine systems and are much more susceptible to nucleophilic attack in that ring. Compounds with extra nitrogens in the five-membered ring show the expected relationships to the other azoles – imidazole, pyrazole, triazoles and tetrazole.

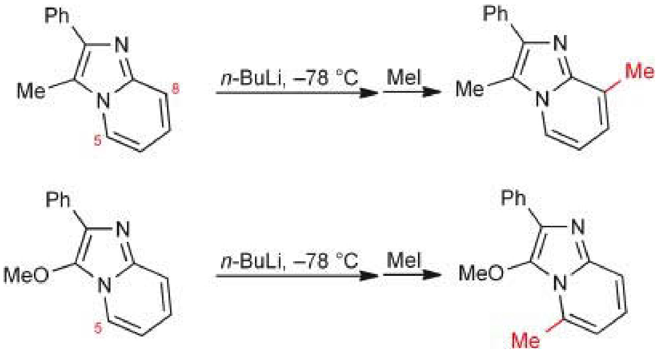
Imidazo[1,2-a]pyridine undergoes electrophilic substitution, under mild conditions, at C-3 but if this position is blocked, substitution at C-5 occurs.



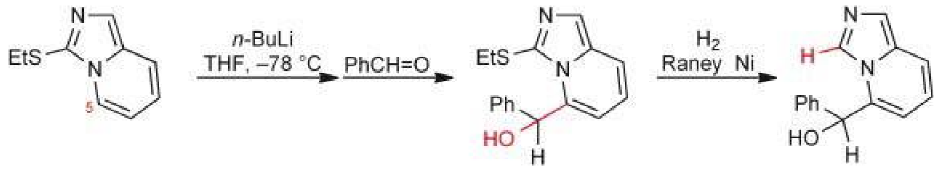
Imidazo[1,5-a]pyridine undergoes electrophilic substitution at C-1 but, in contrast to its isomer, the alternative position C-3 in the five-membered ring is next most favoured. However, a variation allows direct C-3–benzoylation via the intermediacy of an ylide formed by deprotonation of an *N*-benzoyl cation.



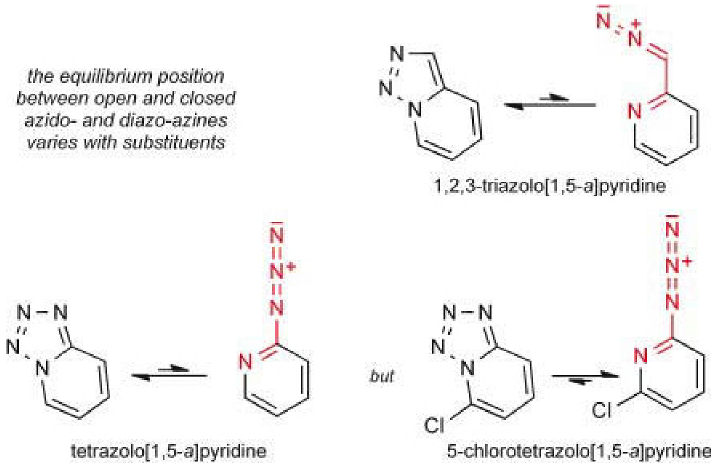
The preferred position for lithiation of both imidazopyridines is C-3, but when this is blocked, reaction occurs at either C-5 or C-8. In the examples shown below, a methyl group in a *peri*-position hinders reaction at C-5 but a methoxy at the same position directs the lithiation by coordination to the reagent (DoM).



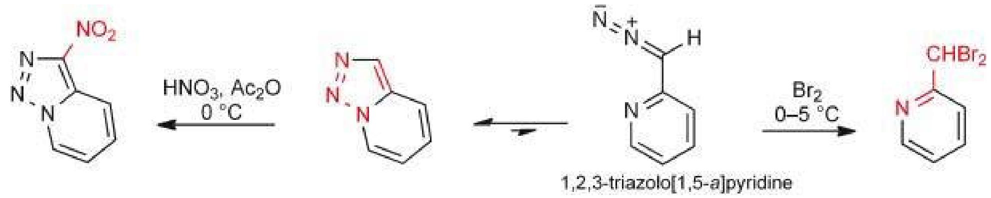
Imidazo[1,5-*a*]pyridines similarly undergo preferential lithiation at C-3, but when this is blocked by an ethylthio-group, reaction is directed to C-5. This blocking/directing group is particularly useful as it is easily removed, revealing the C-3–H.



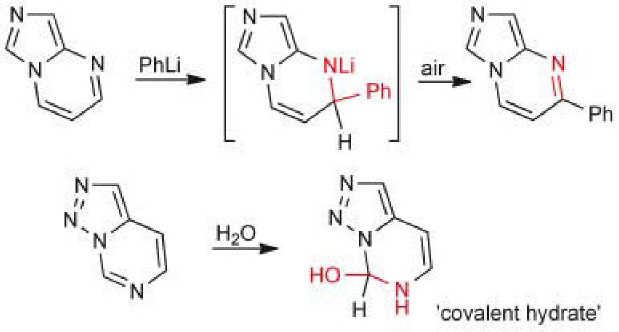
1,2,3-Triazolo[1,5-a]pyridine and *tetrazolo[1,5-a]pyridine* can both exist in equilibrium with ring-open forms. For the former, the ring-closed version is very dominant. *Tetrazolopyridines* can exist predominantly in either form, depending on substituents – the parent is mainly the closed form but the 5-chloro-derivative is open.



Reaction of 1,2,3-triazolo[1,5-*a*]pyridines with electrophiles can take two courses, which may reflect the reactivity of the two tautomers: bromine and aqueous acid give 2-substituted pyridines, whereas acylation and nitration lead to simple substitution of the bicyclic system.

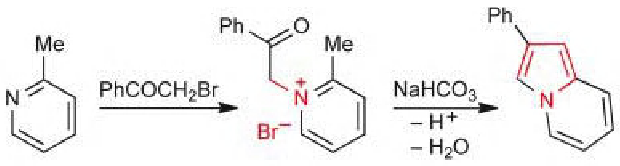


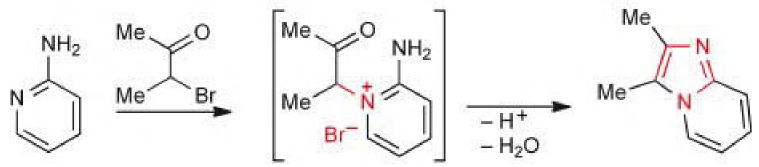
Systems with extra nitrogen(s) in the six-membered ring have as a common feature ease of nucleophilic addition to the six-membered ring, indeed some are so reactive that even exposure to moist air results in formation of a 'covalent hydrate'.

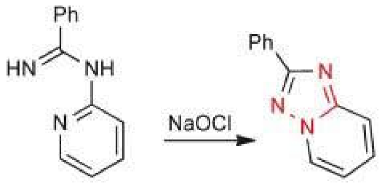


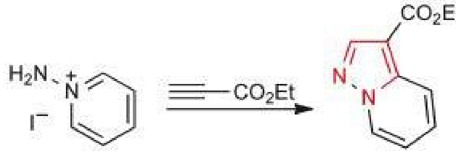
Synthesis of indolizines and azaindolizines

Syntheses of imidazopyridines and some triazolopyridines are carried out mainly by two modes: cyclocondensation or dipolar cycloaddition. The majority of routes start from pyridines or the higher azines.

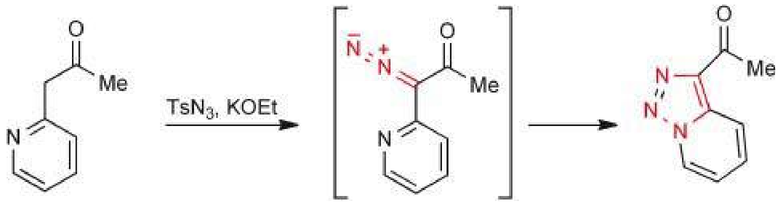




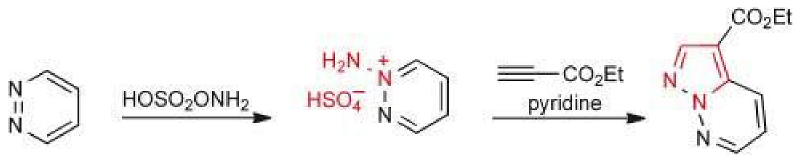


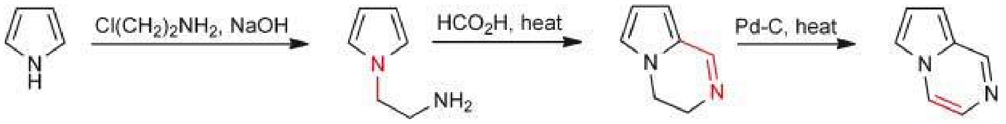


1,2,3-Triazolo[1,5-a]pyridines and tetrazolopyridines are usually synthesised via generation of their ring-open forms. (**Caution:** TsN_3 (tosyl azide) is a widely used reagent but is potentially explosive. Safer diazo-transfer reagents, for example 4-acetamidobenzenesulfonyl azide, are available and serve the same purpose.)



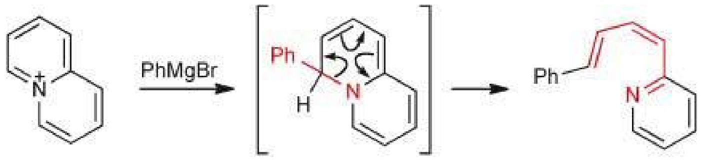
Compounds with additional nitrogens in the six-membered ring are again formed by cyclocondensations or cycloadditions starting with a higher azine, often with exact analogy to the pyridine-derived systems. However, sometimes a route starting with the five-membered component is preferred.

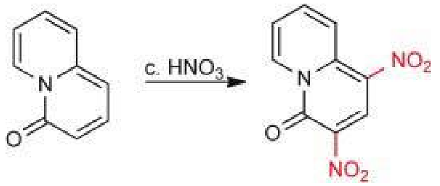




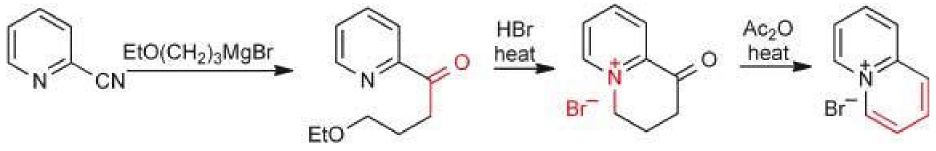
Quinoliziniums and quinolizinones

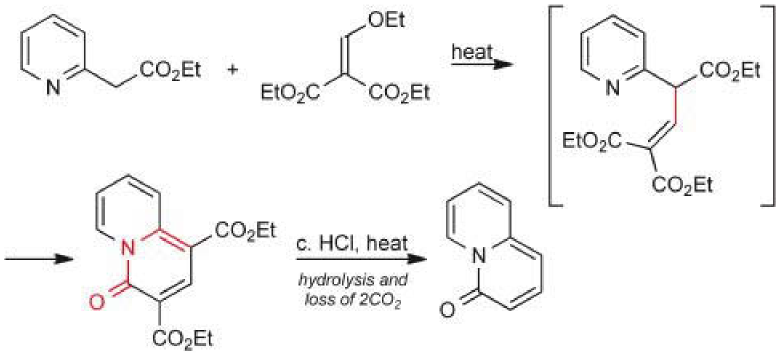
Quinoliziniums are about as reactive to nucleophilic addition as are pyridiniums, the quinazoline products undergoing spontaneous electrocyclic ring opening to give 2-substituted pyridines. Quinolizinones are susceptible to electrophilic attack in the ring bearing the carbonyl function, there being a clear analogy to the reactivity of pyridones.





Quinolizines are usually prepared via cyclisations of 2-substituted pyridines.

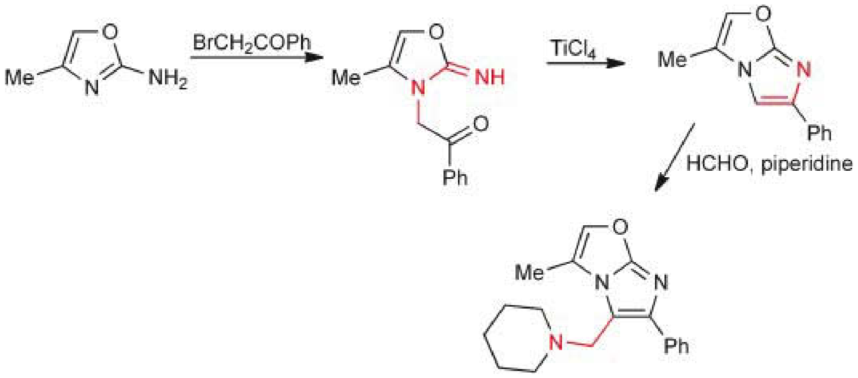




Heteropyrrolizines (Pyrrolizines containing additional heteroatoms)

In these systems, electrophilic substitution in either of the rings is the most common reactivity, with fairly general susceptibility to lithiation and with occasional examples of nucleophilic displacement.

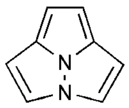
Syntheses are usually cyclisations starting with a monocyclic compound and bear close analogy to methods used in the other systems discussed above.



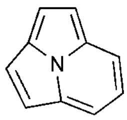
Cyclazines

The cyclazines are fused tricyclic systems containing a central nitrogen atom and a peripheral π-system. Unlike the bicyclic systems, the central nitrogen does not appear to have much influence and, on a simplistic view, the aromaticity seems to follow the 4n+2 rule for the peripheral π-system. Hence, the (peripheral) ten-electron (3.2.2)cyclazine and its isoelectronic analogue (2.2.2)azacyclazine both behave as aromatic molecules, whereas (3.3.3)cyclazine (12 electrons) is unstable and highly reactive. The hexaaza(3.3.3)cyclazine is very stable (due to perturbation of the orbitals).

(A synthesis of a (3,2,2)cyclazine from indolizine is shown above on page 144.)

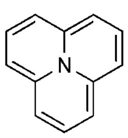


(2.2.2)azacyclazine



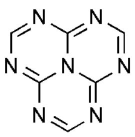
(3.2.2)cyclazine

10-π-electron sytems – aromatic and stable



(3.3.3)cyclazine

12-π-electron system
not aromatic and not stable



a hexa-aza-analogue of (3.3.3)cyclazine

1,3,4,5,7,9,9b-heptaazaphenalene

Exercises

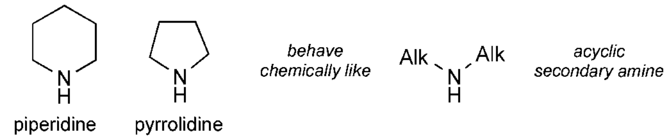
1. Which indolizines would be formed from the following combinations: (i) 2-picoline with (a) $BrCH_2COMe$–$NaHCO_3$ and (b) $MeCHBrCHO$–$NaHCO_3$? (ii) What would be the products if the 2-picoline was replaced by 2-aminopyridine?
2. Deduce the structures of intermediates and final product in the following 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) → $C_8H_8N_2O$.
3. 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?
4. Give the structures of the bicyclic compounds formed by the following reactions: (i) 2-hydrazinothiazole with nitrous acid ($C_3H_2N_4S$; and (ii) 2-aminothiazole with $BrCH_2COPh$ → $C_{11}H_8N_2S$.
5. Suggest a structure for the final, monocyclic product of the following sequence: quinolizinium bromide with $LiAlH_4$ and then H_2–Pd giving $C_9H_{13}N$.
6. What are 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 (→ $C_9H_{12}NO^+ I^-$); this salt was then heated with Ac_2O (→ $C_9H_{10}N^+ I^-$) and this finally heated with Pd–C to afford quinolizinium iodide.

16

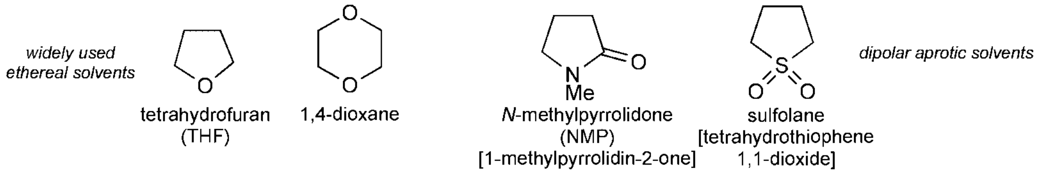
Non-Aromatic Heterocycles

Introduction

This book is principally concerned with the chemistry of aromatic heterocycles, but there are many other heterocycles, including those with three- and four-membered rings, that are not aromatic. We devote comparatively little space to these because their reactions are very similar to those of acyclic analogues – the reactions of piperidine or pyrrolidine, for example, are exactly like those of any secondary dialkylamine. Small-ring heterocycles (three- and four-membered) have reactivities associated with relief of the strain inherent in their structures, when the ring is opened.

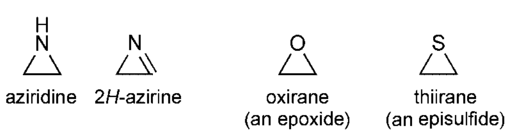


Some saturated heterocycles are widely used as solvents for organic reactions, notably tetrahydrofuran (THF) and 1,4-dioxane (often referred to simply as ‘dioxane’), which are inert, ethereal-type solvents. *N*-Methylpyrrolidone (NMP) and sulfolane are useful dipolar aprotic solvents, with characteristics like those of dimethylformamide (DMF) and dimethyl sulfoxide (DMSO). Saturated and partially unsaturated heterocycles occur widely as components of natural product structures.



Three-membered rings

Aziridines, oxiranes and thiiranes are well-known stable compounds. Oxiranes (epoxides) and aziridines are widely-used intermediates in general synthesis. 1*H*-Azirines only occur as reactive intermediates but 2*H*-azirines, by contrast, are well-known stable compounds.

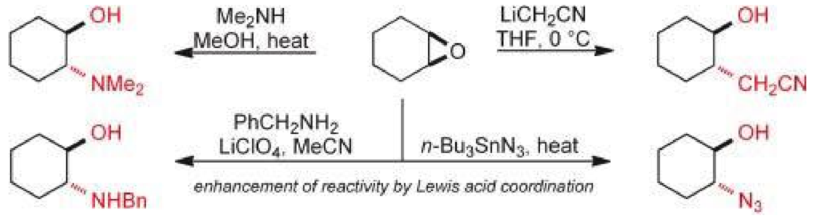


The pK_{aH} of aziridine (7.98) shows it to be an appreciably weaker base than the four-membered azetidine (11.29). The explanation is probably associated with the strain in the three-membered compound, meaning that the lone pair is in an orbital with less p-character than a ‘normal’ sp^3 nitrogen orbital, and is therefore held more tightly. The rate of pyramidal inversion of the saturated nitrogen in aziridines 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 main 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 heteroatom 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 heteroatom nucleophiles have been shown to react in this way, including amines,

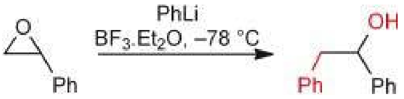
Heterocyclic Chemistry at a Glance, Second Edition. John A. Joule and Keith Mills.

alcohols, thiols, hydride ($LiAlH_4$), malonate anions, and so on. The regiochemistry of nucleophilic attack is determined mainly by steric effects. Assistance by protic solvents or *O*-coordinating metal cations (Lewis acids) further weaken the C–O bond and can dramatically increase the rate of ring-opening reactions. Reagents such as tributyltin azide, which is itself a Lewis acid (coordination to 'Bu_3Sn^+'), but also contains a nucleophilic function (N_3^-), are useful in this respect.

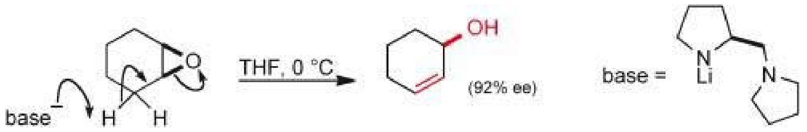


Under pure nucleophilic attack, steric effects dominate and nucleophilic opening of an epoxide takes place at the least hindered position. Under acidic conditions, incipient carbonium ion formation tends to direct attack to the most hindered position – it is often a fine balance.

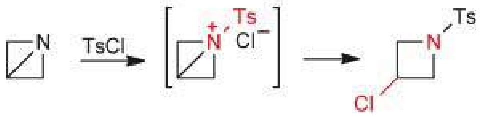
'Harder' organometallic nucleophiles such as alkyllithiums can give rise to side reactions but their combination (at −78 °C) with boron trifluoride gives very clean and efficient reactions.

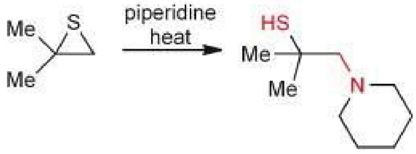


Ring-opening of epoxides by β-elimination, on reaction with strong bases such as lithium amides, is a useful method for the preparation of allylic alcohols, particularly as it can be carried out enantioselectively using a chiral base.

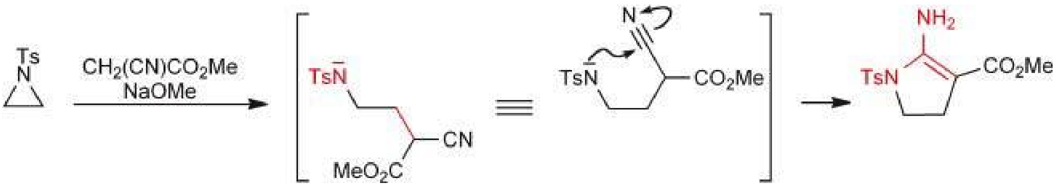


Acid-catalysed opening of aziridines is usually fairly rapid, but simple nucleophilic reactions, without acid catalysis, are very slow due to the much poorer leaving ability of negatively charged nitrogen. However, *N*-acyl and *N*-sulfonyl aziridines have similar reactivities to epoxides. Thiiranes similarly undergo ring-opening reactions with nucleophiles, such as amines.

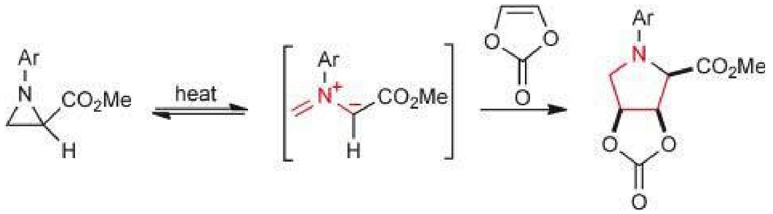




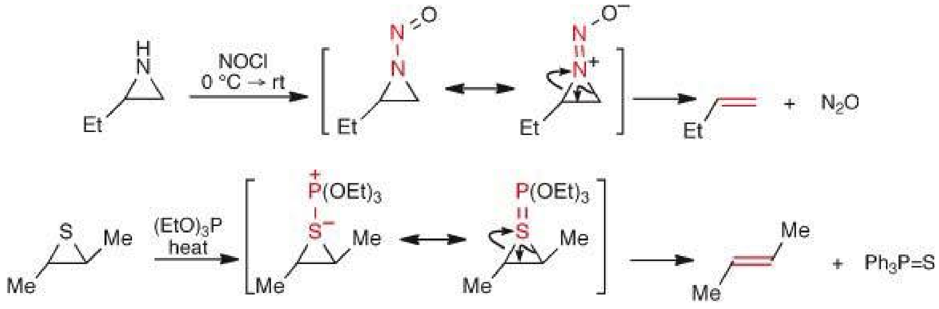
In the opening of *N*-tosylaziridine with the anion of cyanoacetate, a second step, ring closure, produces a 2-amino-4,5-dihydropyrrole.



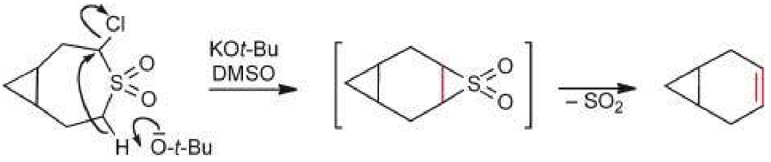
Substituted derivatives of all three systems are able to undergo concerted thermal ring opening, generating ylides that can be trapped in 3+2 cycloaddition reactions, for example providing a route to pyrrolidines (from aziridines).



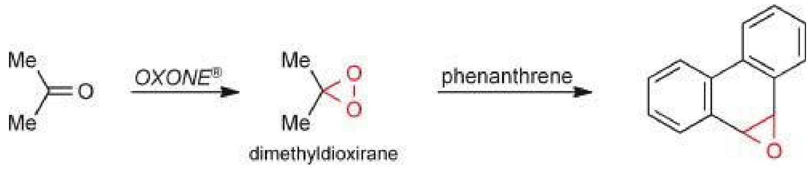
The heteroatom in aziridines and thiiranes can be eliminated via various cycloreversion reactions, for example via *N*-nitrosation of aziridines leading to loss of nitrous oxide (N_2O), or by the reaction of thiiranes with trivalent phosphorus compounds, when a phosphorus sulfide is eliminated.



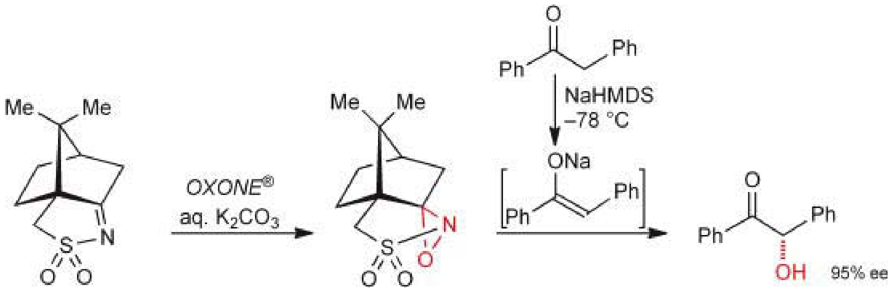
A related elimination of sulfur dioxide occurs during the Ramberg–Bäcklund synthesis of alkenes, which generates an episulfone as a transient intermediate.



Diaziridines and dioxiranes are relatively stable isolable systems, although dioxiranes can be explosive and should be handled in dilute solution. Dimethyldioxirane is a relatively strong oxidant but can show good selectivity: its reactivity is similar to that of a peracid but it has the advantage of producing a neutral, volatile by-product (acetone). Dioxiranes are obtained by reaction of ketones with *OXONE*® ($2KHSO_5.KHSO_4.K_2SO_4$) the active ingredient being potassium peroxymonosulfate.

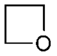


Oxaziridines, prepared by *OXONE*® oxidation of imines, are selective oxygen-transfer reagents; in particular, the camphor-derived reagent is widely used for enantioselective oxygenation of enolates and other nucleophiles.

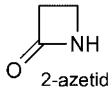


Four-membered rings

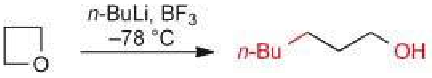

azetidine


oxetane

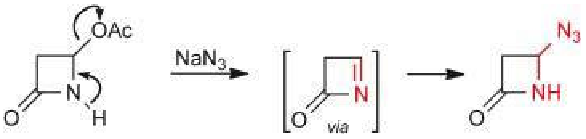

thietane


2-azetidinone
(a β-lactam)

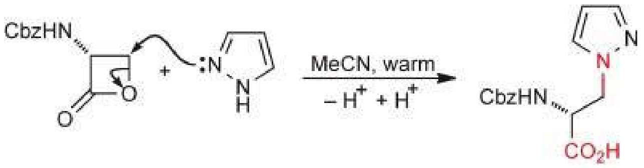
Oxetane and azetidine are considerably less reactive towards ring-opening (strain-relieving) nucleophilic processes than their three-membered counterparts (oxetane reacts with hydroxide anion 10^3 times more slowly than does oxirane). However, oxetane will react, for example, with organolithium reagents in the presence of boron trifluoride, and azetidine is opened, for example, on heating with concentrated hydrochloric acid.



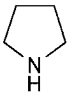
The most important four-membered system is undoubtedly the β-lactam ring, which is present in, and essential for the biological activity of, the penicillin and cephalosporin antibiotics (see page 177). β-Lactams are very susceptible to ring-opening via nucleophilic attack at the carbonyl carbon – in stark contrast to five-membered analogues (pyrrolidones) or acyclic amides, which are 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. Substitution of the acetoxy group in a 4-acetoxyazetidinone by nucleophiles is an important synthetic method: the reaction proceeds via addition to an intermediate imine, rather than by direct displacement.

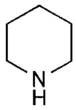


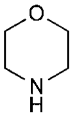
β-Lactones (propiolactones) are also readily attacked at the carbonyl carbon, for example they are particularly easily hydrolysed compared with simple esters, or five- or six-membered lactones. However, a second mode of nucleophilic attack – S_N2 displacement of carboxylate via attack at C-4 – occurs with many nucleophiles; the example of this given below shows the use of a homochiral β-lactone, available from serine.



Five- and six-membered rings

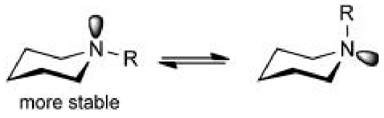

pyrrolidine
pK_{aH} 11.27


piperidine
pK_{aH} 11.29

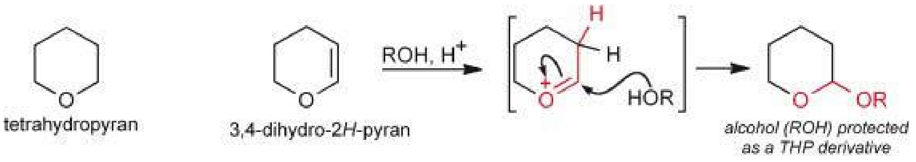

morpholine
pK_{aH} 8.3

Pyrrolidine and piperidine are somewhat better nucleophiles than diethylamine, principally because the nitrogen is less hindered – in the heterocycles the two alkyl 'substituents', that is, the ring carbons, are constrained back and away from the nitrogen, and approach by an electrophile is thus rendered easier. The pK_{aH} values of pyrrolidine (11.27) and piperidine (11.29) are typical of amine bases (diethylamine, 10.98); morpholine (8.3) is a somewhat weaker base.

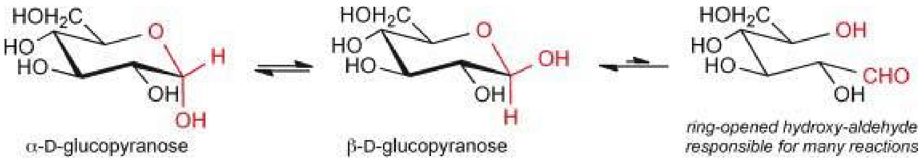
Piperidines, like cyclohexanes, adopt a preferred chair conformation. Both an *N*-hydrogen and an *N*-alkyl substituent take up an equatorial orientation, though in the former case the equatorial isomer is favoured by only a small margin.

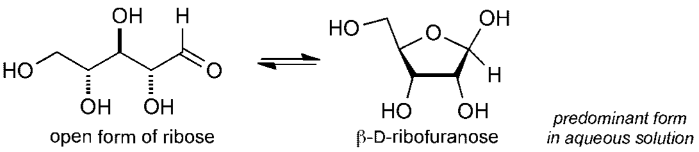


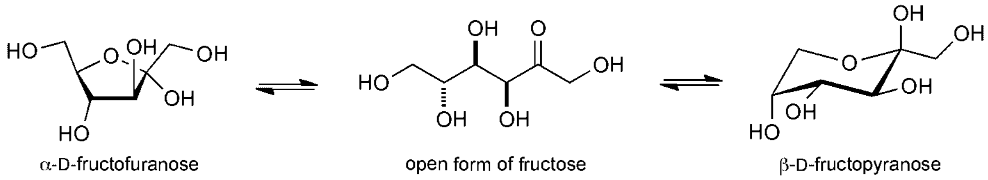
3,4-Dihydro-2*H*-pyran is an enol ether. It is widely used to protect alcohols, with which it reacts readily under acidic catalysis, producing acetals known as THP derivatives, which are stable to even strongly basic conditions but easily hydrolysed back to the alcohol under mildly acidic aqueous conditions.



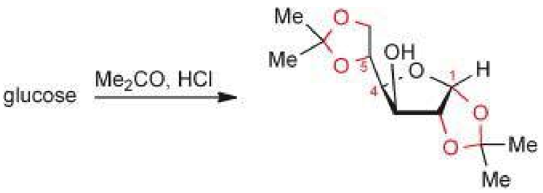
A great deal is known about hydroxylated tetrahydrofurans and tetrahydropyrans because such ring systems occur in sugars. Glucose has two cyclic forms (α-D-glucopyranose and β-D-glucopyranose), hemiacetals containing a tetrahydropyran. However, in solution many sugars, including glucose, exist in equilibrium with a small concentration of ring-opened hydroxy aldehydes, which are involved in many of the important chemical reactions of sugars. Sugars such as glucose, which form these aldehydes, are known as 'reducing sugars' due to the typical reactivity of the aldehyde functional group, whereas sugars that cannot form aldehydes, for example fructose, are 'non-reducing'. All 5-hydroxy-aldehydes, 5-hydroxy-ketones and 5-hydroxy-acids easily close to 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, that is, based on tetrahydrofuran.

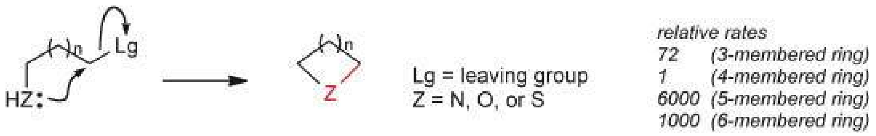


Tetrahydropyran, like piperidine, adopts a chair conformation. 2-Alkoxy-tetrahydropyrans prefer a conformation in which the alkoxy group is axial – this is referred to as the 'anomeric effect'.

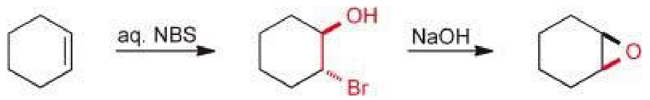
Ring synthesis

From bifunctional acyclic precursors

Five- and six-membered saturated rings can be prepared by reduction of the corresponding heteroaromatic 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 – an '*exo-tet*' ring closure. 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.

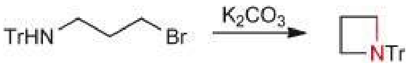


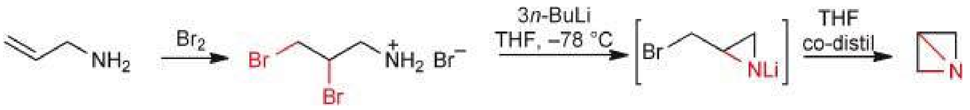
As examples of this strategy, oxetanes and oxiranes can be prepared by cyclisation of 1,3-halo-alcohols or of 1,2-halo-alcohols ('halohydrins'), respectively.



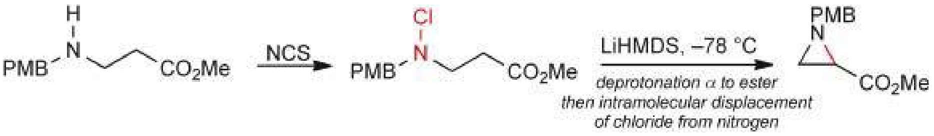
Aziridines can be prepared by alkali-promoted cyclisation of 2-halo-amines or of a 2-hydroxy-amine hydrogen sulfate ester.

Azetidines can be obtained by cyclisations of 3-halo-amines. Even the highly strained 1-azabicyclo[1.1.0]butane can be made by this strategy.



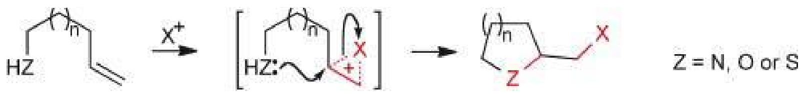


Reversing the sense of cyclisation, *N*-chloroamines, with a suitable C–H-acidifying substituent, can be ring closed efficiently producing *N*-alkylaziridines.

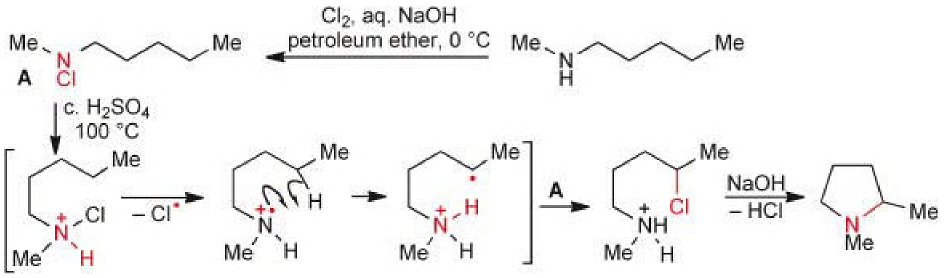


Thietanes, tetrahydrothiophenes and tetrahydrothiapyrans can all be prepared by the reaction of the appropriate 1,ω-dihalide with sulfide anion: the sodium salt of a 1,ω-halo-hydrosulfide is the intermediate.

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 – such closures are nominally '*exo-trig*'.

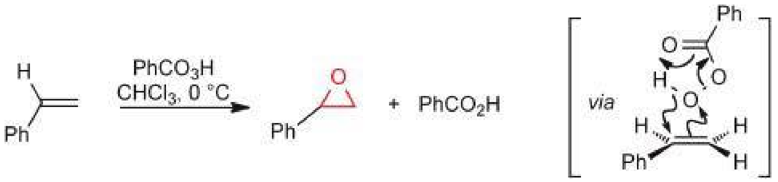


The *Hofmann–Löffler–Freytag reaction* is a neat method for the synthesis of pyrrolidines and does not require a difunctionalised starting material – a radical process is used to introduce the second functional group. The six-membered size of the cyclic transition state leads selectively to a 1,4-halo-amine, and thence to pyrrolidines.

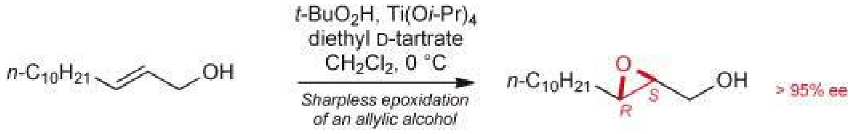


Three-membered heterocycles from alkenes

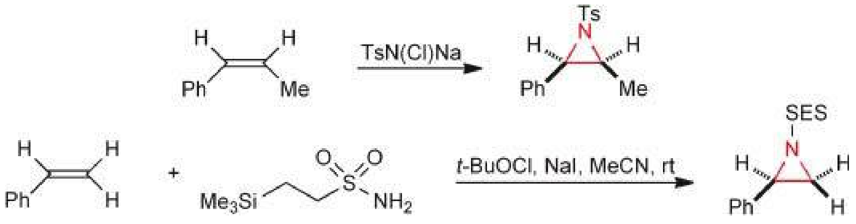
By far the most widely used method for the preparation of oxiranes (epoxides) involves oxidation of an alkene by a peracid, via a direct one-step transfer of an oxygen atom. More highly substituted alkenes react fastest showing that electronic effects are more important than steric effects in this reaction. Steric effects do, however, control the facial selectivity of epoxidation.



Several other direct oxygen-transfer reagents have been developed of which by far the most important is the Sharpless reagent – a mixture of a hydroperoxide with titanium isopropoxide and a dialkyl tartrate. 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 enantio-pure tartrate esters are used, a highly ordered asymmetric reactive site results, leading in turn to high optical induction in the product.

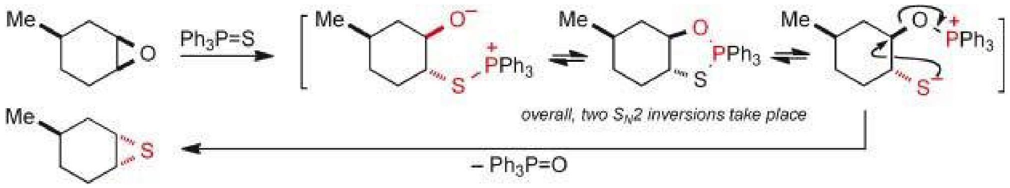


N-Sulfonylaziridines can be obtained directly from alkenes by reaction with 'Chloramine T' (TsN(Cl)Na) or from other sulfonamides by generating an *N*-halo-compound *in situ*, via reaction with *t*-butyl hypochlorite and sodium iodide.



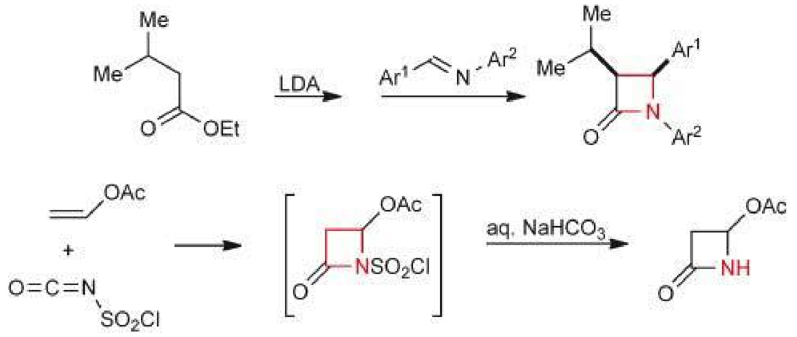
Thiiranes via interchange of heteroatoms

The most common method for the preparation of thiiranes is via reaction of an epoxide with thiocyanate, thiourea, or a phosphine sulfide. As a consequence of the mechanism, the stereochemistry of the thiirane is opposite to that of the starting epoxide – two S_N2 inversions take place.

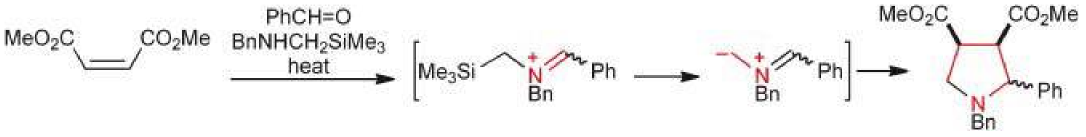


Cycloaddition reactions

Many methods have been developed for β-lactam synthesis, the most widely used methods being two-component couplings that occur either via concerted cycloaddition or two-step mechanisms.

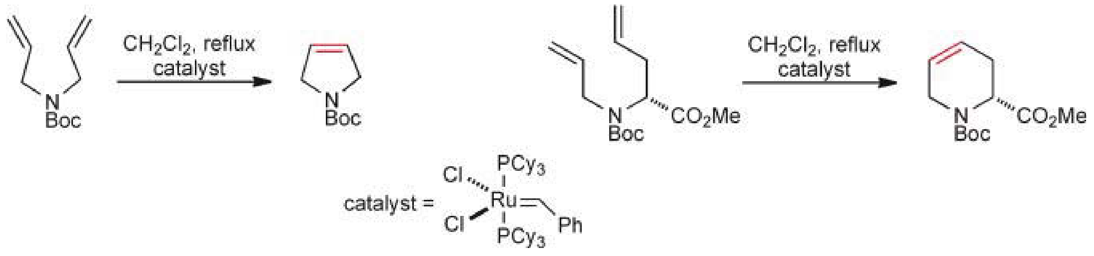


The cycloaddition of azomethine ylides to alkenes is an elegant entry to pyrrolidines. The required 1,3-dipoles can be produced in a number of ways; the example below is one of the simplest wherein a trimethylsilylmethylamine, an aldehyde and the alkene are simply heated together.



Metathesis

A very useful general method for the synthesis of five- to seven-membered, and higher, partially unsaturated heterocycles is Grubbs' olefin metathesis applied to acyclic bis(alkenyl)-amines, -ethers and so on, as illustrated below by dihydropyrrole and tetrahydropyridine syntheses.



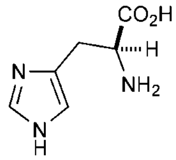
17

Heterocycles in Nature

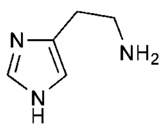
Heterocyclic α-amino acids and related substances

There are four α-amino acids, amongst the 22 that make up proteins, that have an aromatic side-chain and, of these, two have a heteroaromatic side-chain – histidine with an imidazole and tryptophan with an indole. Both of these are amongst the 'essential amino acids', that is they need to be part of the diet as they cannot be biosynthesised by human beings (cf. proline below). Decarboxylation of histidine produces the hormone histamine, a vasodilator and a major factor in allergic reactions such as hay fever. Decarboxylated tryptophan is called tryptamine. The phenol 5-hydroxytryptamine (5-HT or serotonin) is a very important neurotransmitter substance in the central nervous system and also in the cardiovascular and gastrointestinal systems.

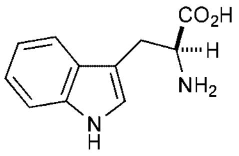
The acetamide of 5-methoxytryptamine, known as melatonin, is produced by the pineal gland, a pea-sized gland at the base of the brain. It is involved in controlling the natural daily cycle of hormone release in the body – the circadian rhythm. The secretion of melatonin is triggered by the dark and is suppressed by natural daylight, therefore controlling periods of sleepiness and wakefulness. It is used as a supplement to treat disruption of circadian rhythm, including jet lag.



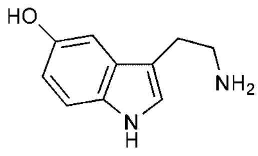
histidine



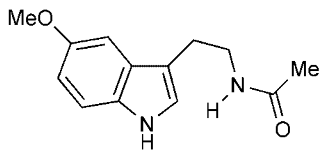
histamine



tryptophan



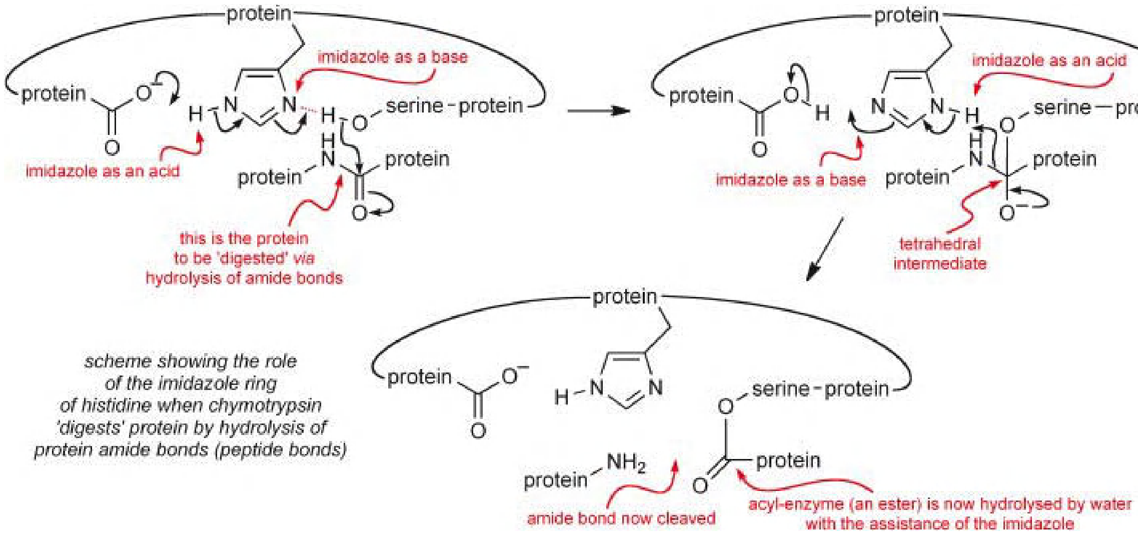
5-hydroxytryptamine
(5-HT) (serotonin)



melatonin

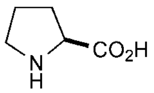
The ability of imidazole to act both as an acid (*N*-hydrogen) and as a base (the imine nitrogen) is put to good use in the active sites of several enzymes. The imidazole rings of appropriately placed histidines effectively 'shuffle' protons from one place to another. One example is the digestive enzyme chymotrypsin, which brings about the hydrolysis of protein amide groups ('peptide bonds') 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. Effectively, the imidazole activates the serine alcoholic hydroxyl by removing the proton as the oxygen attacks the amide bond. Subsequently, that same proton is delivered to the cleaving amide nitrogen as the tetrahedral intermediate breaks down.

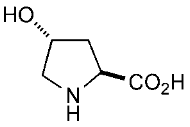
Heterocyclic Chemistry at a Glance, Second Edition. John A. Joule and Keith Mills.



scheme showing the role of the imidazole ring of histidine when chymotrypsin 'digests' protein by hydrolysis of protein amide bonds (peptide bonds)

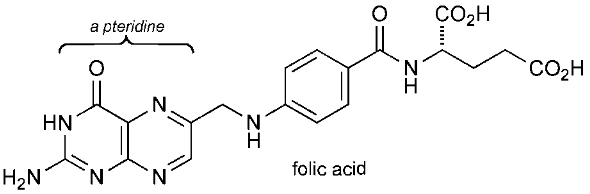
The (non-essential) amino acid proline is based on pyrrolidine. Hydroxyproline, which is synthesised (after incorporation into a protein) from proline units in the body, is a major component of collagen, the fibrous structural protein that supports tissues and is the main component of cartilage and the most abundant protein in the human body.


proline

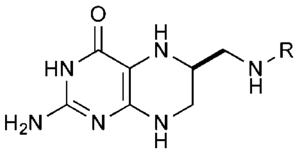

hydroxyproline

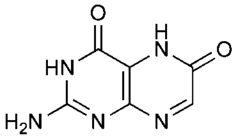
Heterocyclic vitamins – co-enzymes

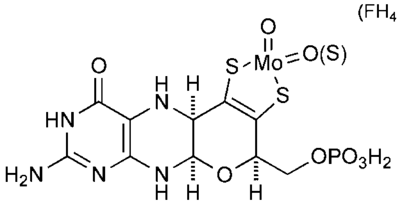
Vitamins are substances essential for a healthy life; humans must ingest vitamins via their diet because there is no mechanism for their biosynthesis in the body. There are 14 vitamins – absolutely essential dietary components, indeed the name was coined when the first vitamin chemically identified (vitamin B_1 in 1910) turned out to be an amine – a *vit*al *amin*e. A typical vitamin is folic acid, a complex molecule in which the functionally important section is the bicyclic pyrazino-pyrimidine ring, known as a pteridine and its aminomethyl substituent. The name 'pteridine' was coined when the first natural substances shown to involve this ring system were the wing pigments of butterflies (*Lepidoptera*). This vitamin is converted in the body into a tetrahydrofolic acid (FH_4), which is crucial in carrying one-carbon units, at various oxidation levels, for example in the biosynthesis of purines, and is mandatory for healthy development of the fetus during pregnancy. Other essential cofactors that contain pteridine units must and can be biosynthesised in humans – without them we cannot survive – these are oxygen-transfer enzymes based on molybdenum in which the metal is liganded by a complex ene-dithiolate in a ubiquitous cofactor. Xanthine oxidase is an example.



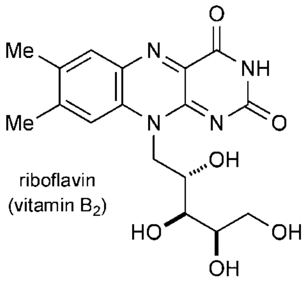
folic acid

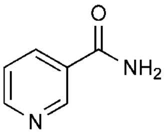

tetrahydrofolic acid (FH_4)

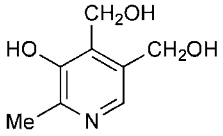

xanthopterin
yellow butterfly pigment


molybdenum cofactor
of oxo-transferases

Several highly significant vitamins are water-soluble and heterocyclic in nature and, further, their utility in the enzyme cofactors into which they are incorporated can only be understood on the basis of their intrinsic heterocyclic reactivity. We deal in detail first with the two important pyridine-containing vitamins – vitamin B_3 (niacin or nicotinamide) and vitamin B_6 (pyridoxine) and then with the thiazole-containing thiamin (vitamin B_1).

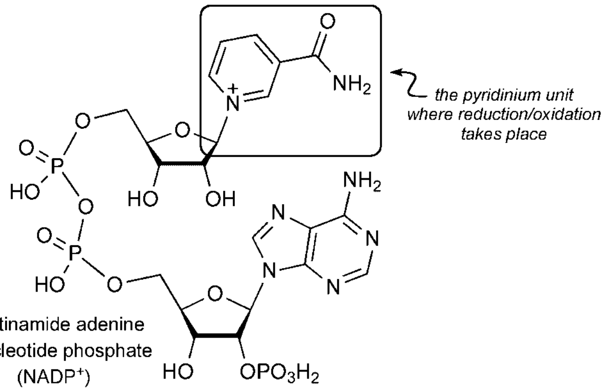

riboflavin
(vitamin B_2)


niacin (nicotinamide)
(vitamin B_3)

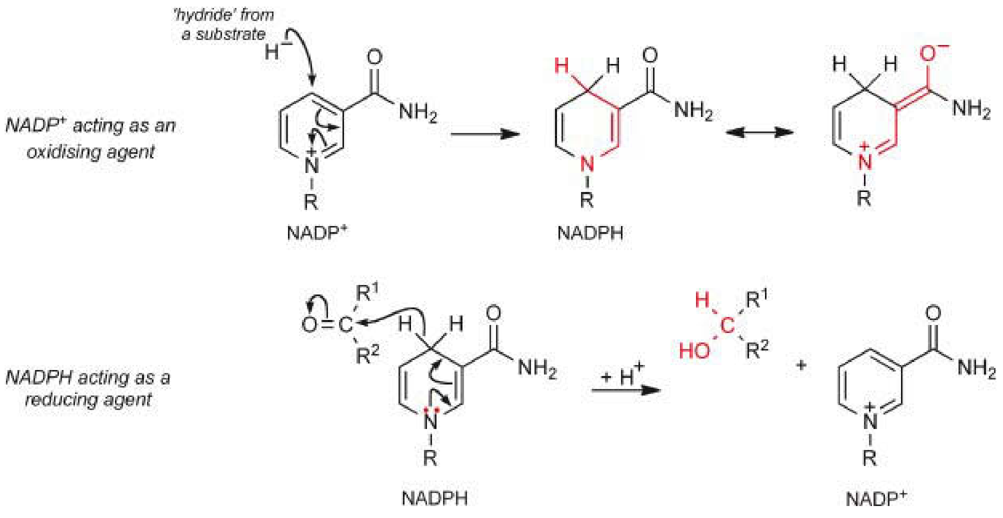

pyridoxine
(vitamin B_6)

Niacin (vitamin B_3) and nicotinamide adenine dinucleotide phosphate ($NADP^+$)

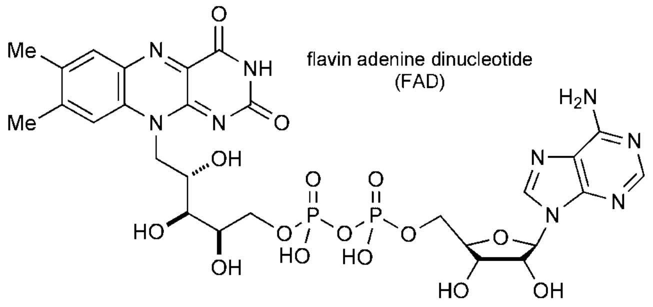
Nicotinamide adenine dinucleotide phosphate ($NADP^+$) is a large complicated co-enzyme, but the significant part, for its role in oxidation/reduction processes, is the pyridinium ring – think of it as simply an *N*-alkylpyridinium salt of nicotinamide. The positively charged nitrogen acts as an electron sink and allows this co-enzyme to accept two electrons and a hydrogen (proton), that is, effectively, hydride. In line with typical pyridinium reactivity, the hydride adds at a γ-position thus producing a 1,4-dihydropyridine (NADPH), the process being facilitated because it is a stabilised 1,4-dihydropyridine, in which the ring nitrogen is conjugated to the carbonyl of the 3-substitutent, as in the products of a Hantzsch pyridine synthesis (page 45). In the reverse sense, NADPH is a vital reducing agent in biosynthesis – it is Nature's $NaBH_4$. The rationale for the reverse process is the regaining of the aromaticity in the co-enzyme product – a pyridinium ion.

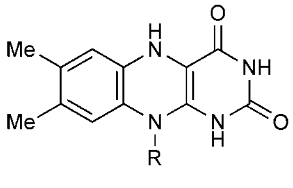

the pyridinium unit where reduction/oxidation takes place

nicotinamide adenine dinucleotide phosphate ($NADP^+$)



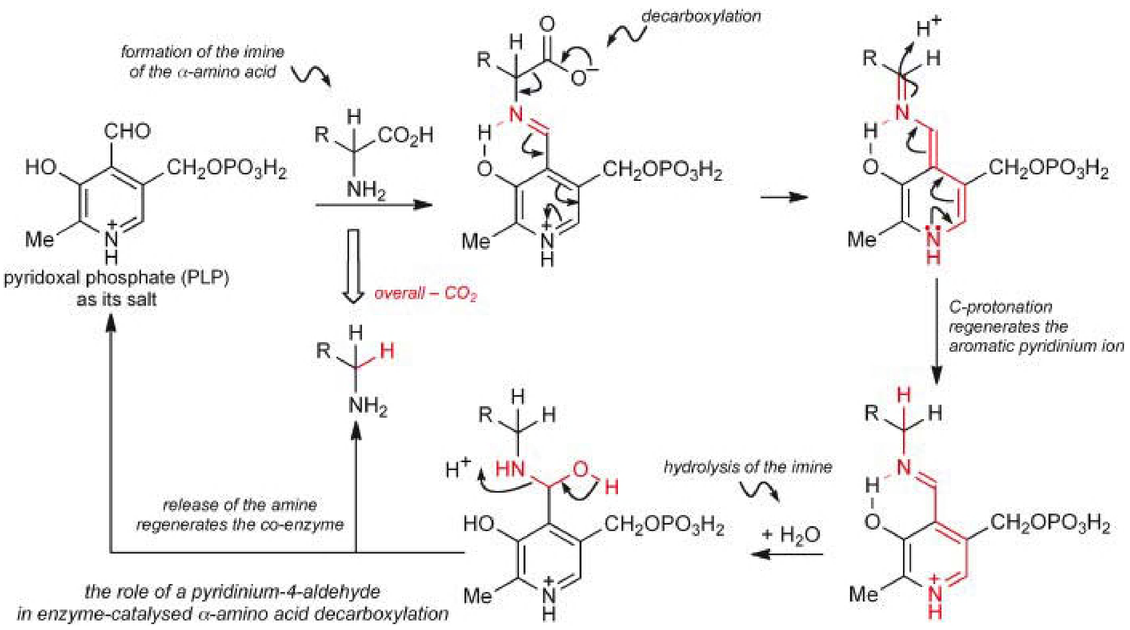
Riboflavin is incorporated into another complex co-enzyme, flavin adenine dinucleotide (FAD). This is involved in enzyme-catalysed reductions of carbon–carbon double bonds, and the reverse. After accepting two hydrogens, the co-enzyme is converted into a dihydro-derivative ($FADH_2$), the driving force being the relief of the unfavoured interaction between the polarised, opposed C=N bonds.


flavin adenine dinucleotide (FAD)


$FADH_2$

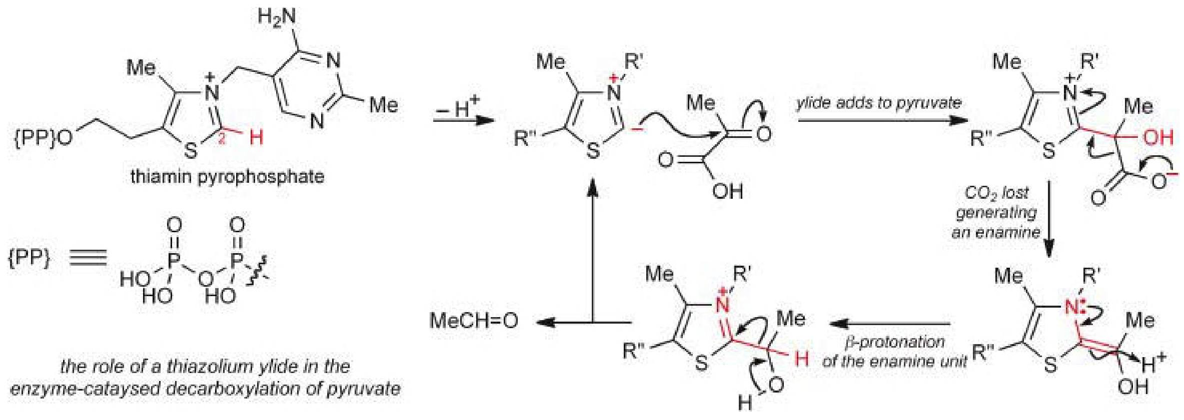
Pyridoxine (vitamin B_6) and pyridoxal phosphate (PLP)

Vitamin B_6 is transformed into pyridoxal phosphate (PLP), which, as a pyridine, is basic at the ring nitrogen, and in the active form, is *N*-protonated. Enzymes containing PLP have various functions, all connected with α-amino acids. Amongst other activities, PLP-containing enzymes can: (i) effect transfer of an amino group from an α-amino acid to an α-keto-acid, (ii) bring about decarboxylation of an α-amino acid, or (iii) bring about de-amination of an α-amino acid. In each case, the chemistry of the process depends critically on the intrinsic chemical reactivity of the pyridine. Consider decarboxylation: condensation of the pyridine-4-aldehyde with the amino group of an α-amino acid generates an imine, which is stabilised by hydrogen bonding with the adjacent phenolic hydroxyl group. The decarboxylation is promoted by the flow of electrons from the breaking C–C bond through to the positively charged pyridine nitrogen, generating an extensively conjugated enamine–imine system, which regains the aromaticity of the pyridine ring by *C*-protonation. Finally, a standard hydrolysis of the new imine link produces the amine corresponding to the original α-amino acid, together with the regenerated co-enzyme.


the role of a pyridinium-4-aldehyde in enzyme-catalysed α-amino acid decarboxylation

Thiamin (vitamin B_1) and thiamine pyrophosphate

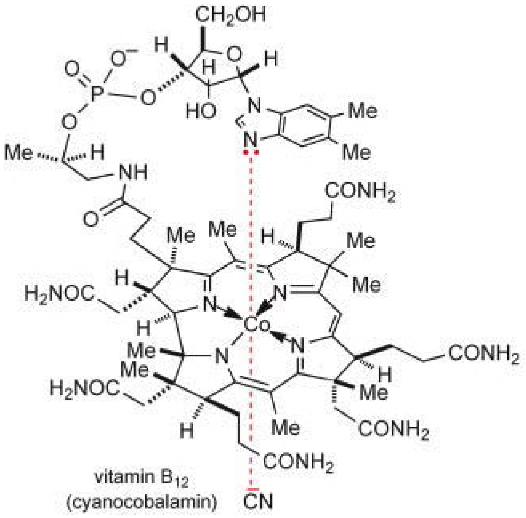
Thiamin pyrophosphate acts as a co-enzyme in several biochemical processes and, in each case, its mode of action depends on the intermediacy of a 2-deprotonated species – an ylide (see pages 113–114 for a discussion). For example, in the later stages of alcoholic fermentation, which converts glucose into ethanol and carbon dioxide, the enzyme pyruvate decarboxylase catalyses the conversion of pyruvate into ethanal (acetaldehyde) and carbon dioxide, the former then being converted into ethanol by the enzyme alcohol dehydrogenase. Thiamin pyrophosphate, in the form of its ylide, adds 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 ylide as a leaving group, to continue the cycle. In the laboratory, thiazolium salts will act as nucleophilic catalysts by utilising this ability to form an ylide by C-2-deprotonation.



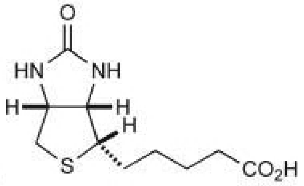
the role of a thiazolium ylide in the enzyme-cataysed decarboxylation of pyruvate

Aromatic thiophenes play no part in animal metabolism, however they do occur in some plants, in association with polyacetylenes with which they are biogenetically linked. Biotin (vitamin H) is a tetrahydrothiophene.

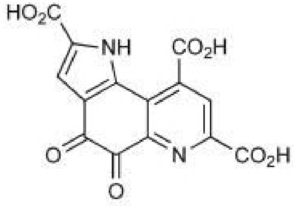
After the identification of the thirteenth vitamin, vitamin B_{12}, in 1948, there was a gap of 55 years before the fourteenth, a pyrroloquinoline quinone (PQQ), previously known and named methoxatin as a redox enzyme cofactor in bacteria, was shown, in 2003, to be a human dietary requirement.



vitamin B_{12}
(cyanocobalamin)



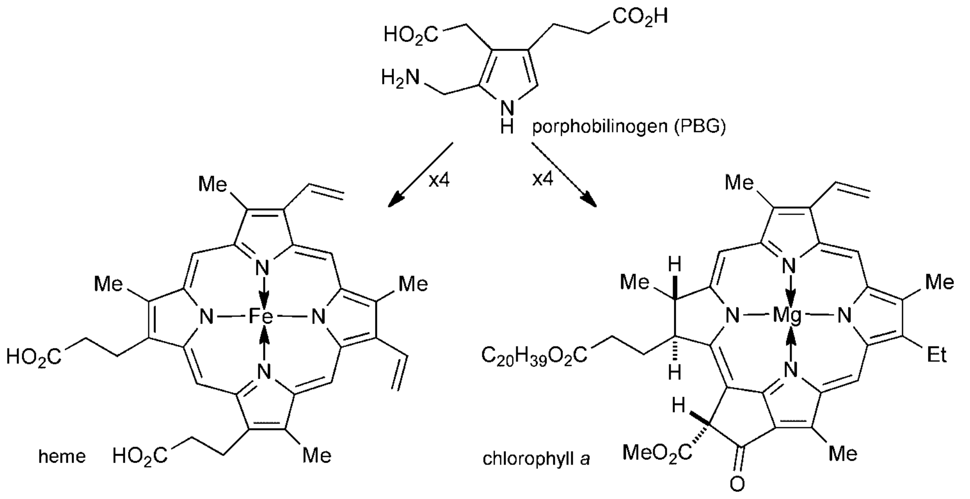
(+)-biotin
(vitamin H)

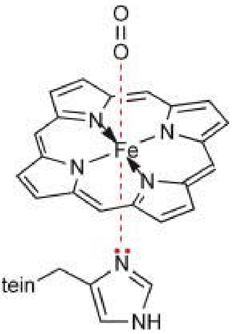


methoxatin
a pyrroloquinoline quinone
(PPQ)

Porphobilinogen and the 'Pigments of Life'

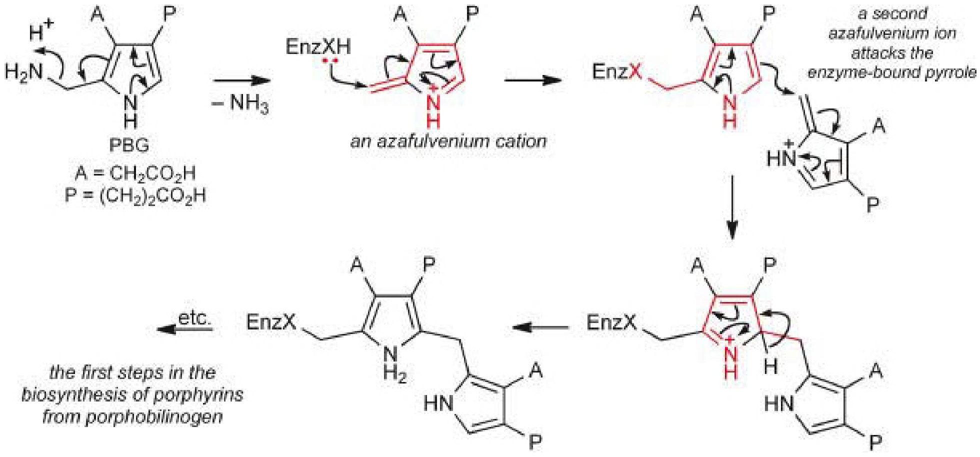
Two other macrocycles crucial to all life are based on pyrroles. Chlorophyll *a* is the green pigment in plants that harvests sunlight and so is at the commencement of the life cycle. Heme, the red pigment in blood, transports oxygen around the body; the oxygen is attached to the iron as shown below.





central portion of oxygenated haemoglobin

All the tetrapyrrole pigments are biosynthesised by the combination of four molecules of porphobilinogen (PBG), this in turn is made from δ-aminolevulinic acid (5-aminolevulinic acid, $H_2NCH_2CO(CH_2)_2CO_2H$) and this from glycine and succinic acid. There are complexities late in the tetramerisation sequence which we do not go into here, but the essence of the process can be easily understood on the basis of the pyrrole chemistry described in Chapter 9: consider the first step as typical. Protonation of the amino group of PBG converts it into a leaving group generating an electrophilic azafulvene (compare with page 82) for attachment via a nucleophilic atom, X, on the enzyme. This first enzyme-bound pyrrole is now attacked, as is typical for all pyrroles, at an α-position, by a second molecule of electrophilic azafulvenium ion.



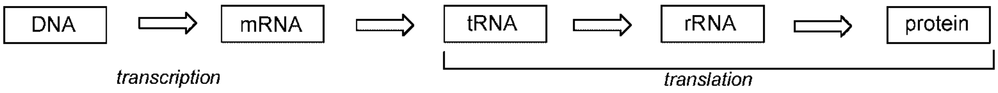
the first steps in the biosynthesis of porphyrins from porphobilinogen

Deoxyribonucleic acid (DNA), the store of genetic information, and ribonucleic acid (RNA), its deliverer

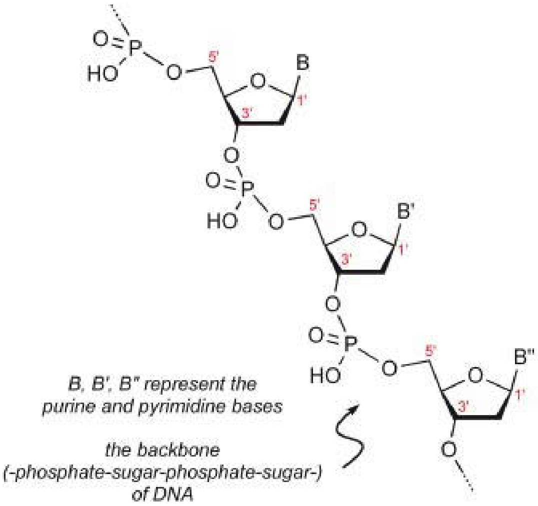
(The information on pyrimidine and purine bases and their nucleosides and nucleotides, in Chapters 6 and 13, is required reading prior to this section. Particular note should be taken of the tautomeric forms of the nucleic acid bases, which are critical in the formation of specific hydrogen bonds: *N*-hydrogens of pendant amino groups and the *N*-hydrogens of ring 'amides' form hydrogen bonds to the oxygens of carbonyl groups and the nitrogens of ring imine units.)

The genetic information of all life is stored in DNA*. This information is used for protein synthesis and its delivery to the 'production site' for these proteins requires the intervention of three types of RNA: messenger RNA (mRNA), transfer RNA (tRNA) and ribosomal RNA (rRNA). A simplified explanation of the functions of these types of RNA is that mRNA reads the information on (a single strand of) DNA and passes this information to tRNA, which transfers a specific amino acid to rRNA for assembly into the protein.

*Some viruses use RNA to carry genetic information, but this raises a philosophical question about what is life. RNA viruses include the retroviruses, of which the most notorious is HIV. Retroviruses are so-named because they induce *reverse transcription*, which uses the RNA template of the virus to generate DNA, which is then incorporated into the host's genome.

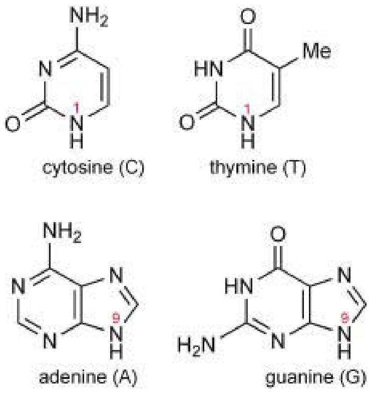


DNA consists of two intertwining helices, each being a mixed polymer of nucleotides. Each of these polymeric intertwining strands has a backbone on the outside, consisting of alternating sugars (deoxyribose) and phosphate (‘phosphodiester’) bridges. From each sugar, pointing inwards, there is one of four heterocyclic bases: two purines (adenine (A) and guanine (G)) and two pyrimidines (thymine (T) and cytosine (C)), linked from C-1' of the sugar to N-1 of the pyrimidine bases or N-9 of the purine bases.



B, B', B" represent the purine and pyrimidine bases

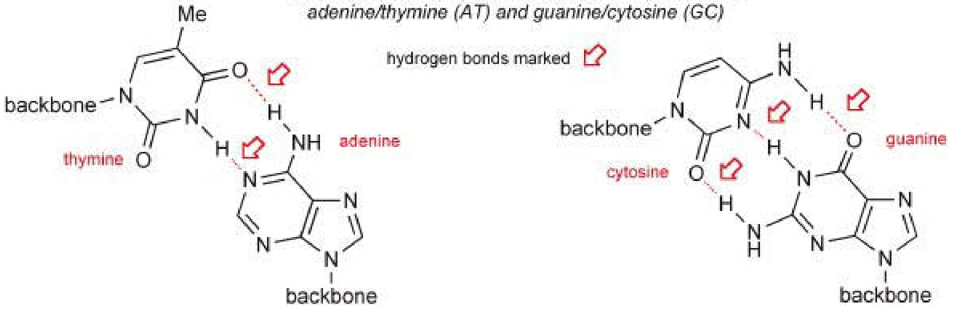
the backbone (-phosphate-sugar-phosphate-sugar-) of DNA



the four heterocyclic bases found in DNA

The close association of the two strands is based on very specific hydrogen bonding between an A residue of one strand and a T residue in the precisely opposite section of the other strand, and between a C residue on one strand and a 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 the *sequence of the bases* along the chain that carries the information – particular sets of three bases code for a particular amino acid – the genetic information content comes down simply to heterocyclic chemistry! The hydrogen bonding serves not only to hold the two strands together *but also* to transfer information since, when the strands separate, these same types of hydrogen bond allow it to act as a template for both mRNA and self-replication. Both the *replication* of DNA and *transcription* to mRNA are enzymatic processes using the nucleic acid as a template.

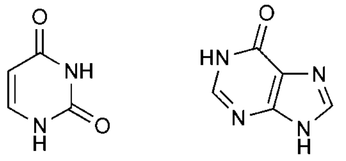
the only effective hydrogen bonding pairings in DNA: adenine/thymine (AT) and guanine/cytosine (GC)



The basic chemical differences between the two nucleic acids is the presence in RNA of the extra 2'-hydroxy in the sugar and uracil (which occurs *only* in RNA) replacing the closely related thymine (which occurs *only* in DNA).

Although DNA and RNA are closely related and can bind with one another by the same type of hydrogen bonds, there are significant differences. DNA is a very large molecule, containing up to about a billion nucleotide units in animals. The length of such a molecule, if extended, would be more than 30 cm; considerable folding is required to fit into a cell! On the other hand, RNA is much smaller, the smallest being tRNA with only around 80 nucleotides. Also, RNA exists mainly as single strands, although substructures such as ‘hairpins’ are common, where the strand folds back along itself with H-bonding between bases.

tRNA also contains hypoxanthine (inosine) residues, which are less selective in hydrogen bonding to specific complementary bases and thus can lead to some loss of selectivity in identifying codes for specific amino acids, a flexibility referred to as ‘wobble’.



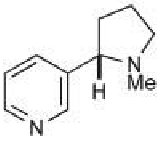
uracil hypoxanthine

additional bases in RNA

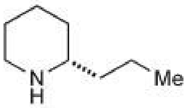
Heterocyclic secondary metabolites

An enormous structural variety of secondary metabolites, that is substances not involved in primary metabolism, have been isolated from many types of organisms. Often, these compounds have no obvious purpose and do not appear to convey any benefit to the organism. However, many do have very considerable biological effects on mammals, notably on man, and plant extracts containing them were used in ancient medicine. We give here just a small selection to illustrate the enormous range and variety of structures.

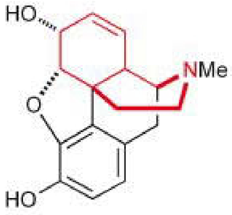
Plants of many genera produce alkaloids – many thousands are known. The name 'alkaloid' was coined because these natural substances are basic (amines), that is alkali-like, although the name is often used now to refer to nitrogenous natural compounds generally, whether basic or not. A structurally simple example is nicotine, a highly toxic substance, the major active component in tobacco (*Nicotiana* sp.). Coniine, the active ingredient of hemlock (*Conium maculatum*), is another toxic example, famously used to put Socrates to death. Alkaloids that have been of benefit to mankind include morphine from the opium poppy (*Papaver somniferum*) and quinine (*Cinchona officinalis*). Although not immediately obvious, morphine is a 1-benzyl-isoquinoline alkaloid (of which there are many); the modified isoquinoline unit is highlighted in red.



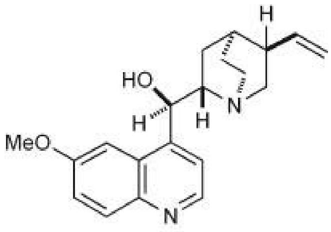
nicotine



coniine



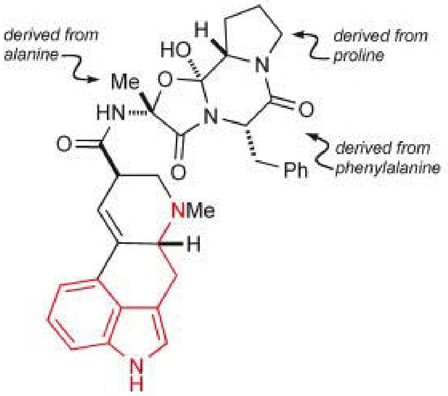
morphine



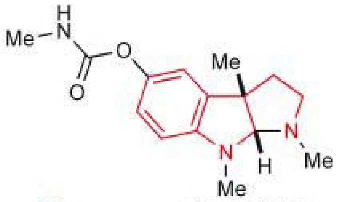
quinine

Alkaloids derived biosynthetically from tryptophan/tryptamine are amongst the most prolific: in the structures shown, for ergotamine (the ergot fungus, *Claviceps purpurea*), physostigmine (*Physostigma venenosum*) and strychnine (*Strychnos nux vomica*), the residual tryptamine unit is coloured.

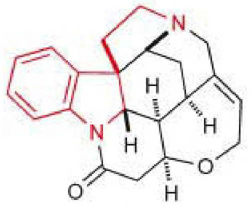
(These three compounds are also highly toxic and all have been used in both medicine and in less benign circumstances. Ergotamine is a toxic contaminant found in certain foods (page 192) and a medicine for migraine; physostigmine is the active component of Calabar beans, which were used in 'trial by ordeal' in West Africa, and is a medicine for glaucoma and other diseases; strychnine was used as a vermin poison and for murder (possibly many undetected, as the symptoms of poisoning resemble those of tetanus), but was also used (in low doses!) as a stimulant.)



ergotamine

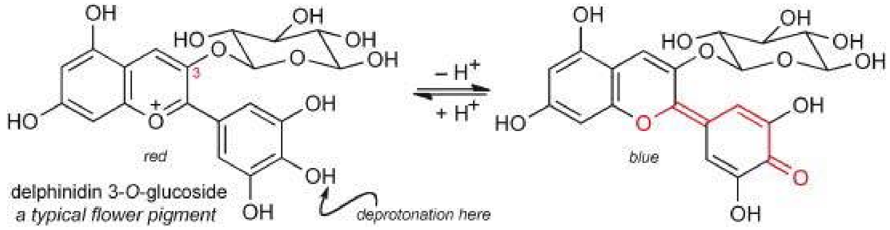


physostigmine



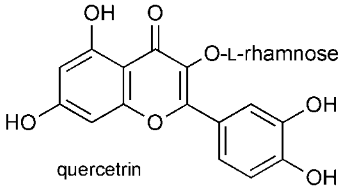
strychnine

1-Benzopyryliums (chromyliums) occur as pigments in flower petals, in substances known as anthocyanins – most blue, purple and red flower colours are due to anthocyanins. The actual colour shown by a particular anthocyanin depends on pH and upon the presence of co-pigments – the pH is important because deprotonation of phenolic hydroxyl groups markedly affects the UV–Vis absorption. The petals of hydrangeas, which can exhibit any colour from blue to red, contain delphinidin 3-*O*-glucoside, shown below in protonated and *O*-deprotonated forms.

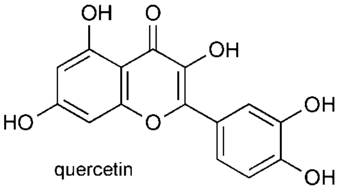


delphinidin 3-*O*-glucoside
a typical flower pigment

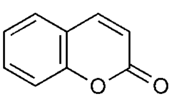
The naturally occurring flavones (page 77) are yellow and are very widely distributed in plants. They accumulate in almost any part of a plant, from the roots to the flower petals. Flavones are stable and have, from time immemorial, been used as dyes, because they impart various shades of yellow to wool, for example the commercial 'quercitron bark' from a North American oak, *Quercus velutina*, 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. Coumarin has the sweet scent of newly-mown hay, and is used in perfumes (see pages 76, 191, 192).



quercetrin

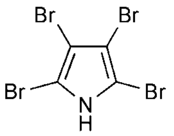


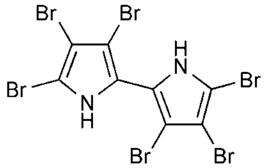
quercetin

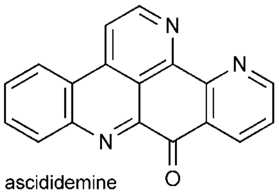


coumarin

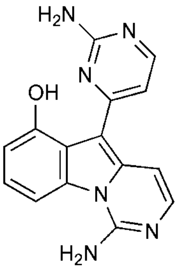
In recent years explorations of sea animals have thrown up a staggering variety of heterocyclic substances, and we present just a few structures here, as illustrations. Many contain halogen(s), as one might anticipate from creatures living in the marine environment – tetrabromopyrrole and hexabromo-2,2'-bipyrrole are amongst the structurally simplest. Ascididemine (tunicate, *Didemnum* sp.), variolin B (sponge, *Kirkpatrickia varialosa*), lamellarin B (mollusc, *Lamellaria* sp.), diazonamide A (ascidian, *Diazona chinensis*) and telomestatin (*Streptomyces anulatus*) all have multi-heterocycle structures, which challenge the ingenuity of synthetic chemists who might seek to achieve their total synthesis.



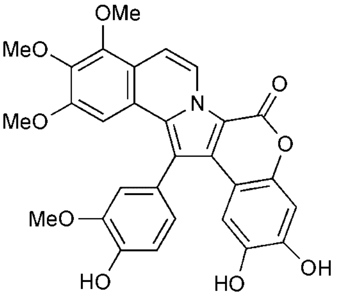




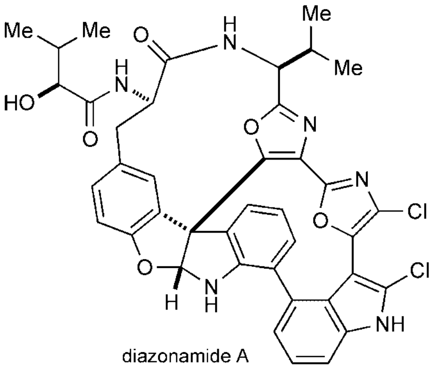
ascididemine



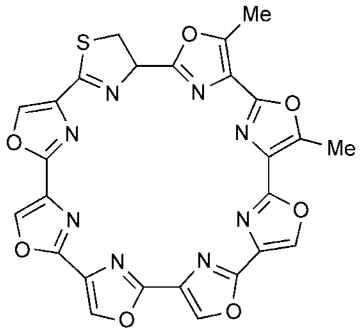
variolin B



lamellarin B



diazonamide A



telomestatin

18

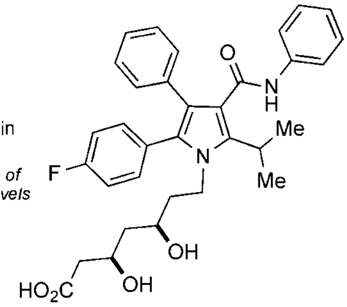
Heterocycles in Medicine

Medicinal chemistry – how drugs function

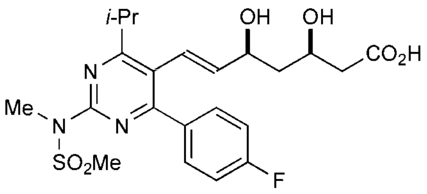
Heterocycles are extremely important building blocks for (medicinal) drugs and they have dominated the area for many years. Heterocyclic alkaloids were the active ingredients in many natural remedies long before the development of modern chemistry and some are still used today, for example morphine derivatives and quinine. Despite the current hot area of biologics, such as monoclonal antibodies, heterocyclic substances still represent about half of the top 20 best selling (by value) drugs, as illustrated by the compounds shown below, for 2009.

Rather than using complex systematic chemical names, drugs are given 'trivial' generic names and drugs acting on the same pharmacological basis often have related names, particularly by the word ending, for example ondansetron and granisetron (both used to relieve nausea), losartan and candesartan (both used to treat hypertension). The manufacturer will also give a proprietary (trade) name to a drug, which is treated as a proper noun and capitalised. In this chapter, we give first the generic name with, where appropriate, a proprietary name in parentheses. Note that proprietary names may be different in different countries or when marketed by different companies.

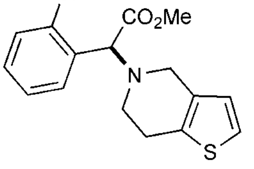
atorvastatin
(Lipitor)
for reduction of chlolesterol levels



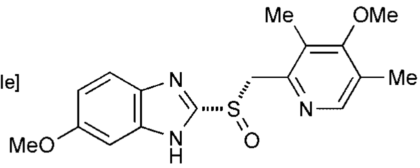
rosuvastatin
(Crestor)
for reduction of chlolesterol levels



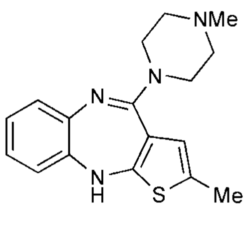
clopidogrel
(Plavix)
antiplatelet agent to prevent blood clots



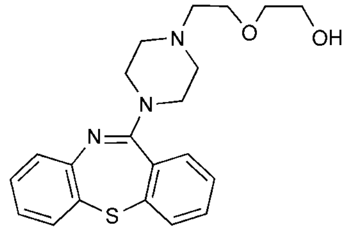
esomeprazole [(*S*)-omeprazole]
(Nexium)
for treatment of gastric ulcers and acid reflux



olanzapine
(Zyprexa)
for treatment of schizophrenia

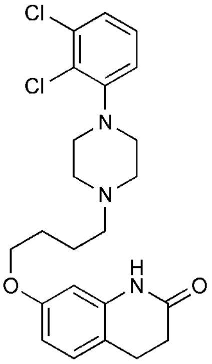


quetiapine
(Seroquel)
for treatment of schizophrenia and bipolar disorder

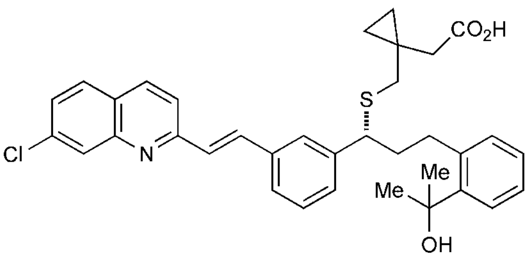


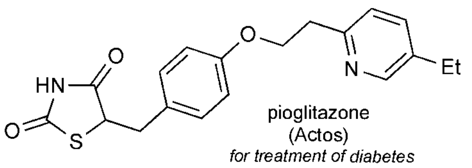
Heterocyclic Chemistry at a Glance, Second Edition. John A. Joule and Keith Mills.

aripiprazole
(Abilify)
an antipsychotic and antidepressant



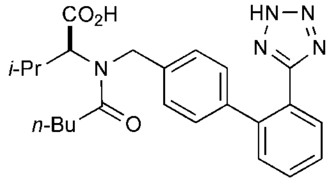
montelukast
(Singulair)
a leucotriene antagonist for treatment of asthma and allergies





pioglitazone
(Actos)
for treatment of diabetes

valsartan
(Diovan)
an angiotensin II antagonist for treatment of high blood pressure and heart disease



Drugs exert their effects by a number of mechanisms, the most important being:

(a) Mimicking or opposing the effects of physiological hormones or neurotransmitters. Compounds that mimic the effect of the natural agent are known as *agonists*, those that oppose are known as *antagonists*. These drugs act by binding at a receptor – the site where the natural physiological agent binds. This receptor is usually a specific domain of a protein molecule comprising part of a cell.
(b) Interaction with enzymes, usually by inhibition. This generally occurs by binding at the active site of the enzyme (where the substrate binds), in a very similar manner to receptor binding – the comments shown below, concerning receptors, can equally be applied to enzyme interactions with drugs.
(c) Modifying natural macromolecules such as DNA and RNA either by direct interaction or by the incorporation of synthetic analogues of structural components (e.g. one of the heterocyclic bases) into the polymer.

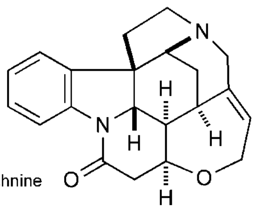
- Binding at the receptor may be *competitive* (i.e. the drug is in equilibrium/exchange with the natural agent) or, in others, it can be *non-competitive* – firmly bound with no exchange.
- Receptors usually exist as a number of subtypes, often with further subdivisions, which mediate different physiological effects *by interaction with the single natural agent.* The key to a successful drug very often depends on devising a molecule that has a selective interaction with just one subtype.
- Sometimes, binding at a site other than at the normal receptor (*allosteric binding*) can be the mechanism of action – the remote binding alters the shape of the protein as a whole and hence influences the receptor.
- Binding/action at the receptor is often only the start of a complex cascade of actions within the cell.
- The mechanisms of binding to the receptor can be essentially physical (H-bonding, or attractions via ionic or Van der Waals forces, etc.), with several points of interaction, or it may be covalent (e.g. *N*-alkylation) and thus irreversible.

In this book we are concerned with heterocycles, so the coverage in what follows does not necessarily reflect the relative medical importance of different areas. Complete coverage of all areas of significance is obviously impossible but the aim is to give an appreciation of the wide-ranging importance of heterocycles in medicine.

Drug discovery

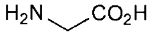
There are a number of stages in the 'invention' and commercialisation of a drug, and chemistry is very heavily involved in the early stages of discovery, design and process development. Also, later chemical investigations are concerned with the absorption and metabolism of the drug in the body. After the drug is marketed there is also a significant role to play in the detection of fraud and 'forgery', which, unfortunately, are not uncommon in today's international medicines market.

A traditional logical approach to drug design involves the synthesis of compounds that are structurally similar to the natural agent, with alterations of substituents or variations in the electronic nature or precise shape of any aromatic rings (a key asset of heterocycles!). Modifications using heterocycles can also be used to give favourable physical properties, for example replacing a benzene ring by a pyridine ring may improve aqueous solubility. However, a surprising number of biologically active substances bear only a tenuous (or no!) structural similarity to the natural agent/transmitter. An excellent illustration is the well-known indole alkaloid strychnine, which is a competitive antagonist of the Central Nervous System (CNS) neurotransmitter glycine!



strychnine

competitive antagonist of



glycine

Other routes to drug discovery include isolation and screening of compounds ('natural products') from natural sources that may have been reported in folklore to have medicinal properties, the fortuitous discovery of unexpected activity in a compound being investigated in another disease area (Viagra is an example) and the crude but reasonably effective method of screening large numbers of random compounds synthesised by combinatorial chemistry (the rapid synthesis of a large number of different but structurally related molecules by varying substituents at 'points of diversity' on a template). When a 'lead compound' has been obtained by one of these methods, more rational optimisation can be carried out.

Drug development

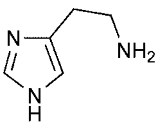
One key to commercialising a drug is a good chemical synthesis, which is highly reproducible in chemistry and product purity. It must also be produced to a target price – this varies greatly depending on a number of factors, including potency, that is, it relates to the amount of the chemical substance used in the final formulation, such as in tablets. This is the most demanding area for the chemist. Yields for steps in a process are very frequently increased dramatically by intensive process research – improving literature reactions with reported yields of 20–30% up to a usable 80–90% is not uncommon.

The neurotransmitters

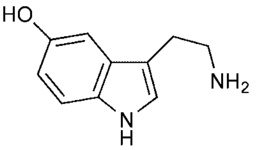
The major neurotransmitters shown below act in both the *peripheral system* (the muscles, blood vessels and organs) and *central nervous system* (CNS), which comprises the brain and spinal cord. These neurotransmitters include heterocyclic (histamine, 5-hydroxytryptamine) and non-heterocyclic substances (catecholamines: adrenaline, noradrenaline, and dopamine; acetyl choline). The CNS also has other important neurotransmitters, including the amino acids glycine, glutamic acid, and GABA (γ-aminobutyric acid, $H_2N(CH_2)_3CO_2H$).

The CNS and peripheral systems are separated by the *blood–brain barrier*, which stands between the blood stream and the brain tissue – it is essentially the walls of the brain's blood vessels, which are different to those in the periphery. A complex combination of physical factors, such as lipophilicity/polarity, molecular weight and active transport systems, determines the ability of molecules to cross the blood–brain barrier and thus gain access to the CNS. The consideration as to whether a drug can or cannot reach the brain is always an important design consideration – drugs acting on the CNS obviously need to reach it but for peripherally-acting drugs, the opposite is required – keeping them out may be essential to avoid side-effects.

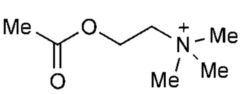
the two heterocyclic neurotramsmitters



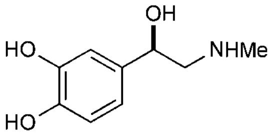
histamine



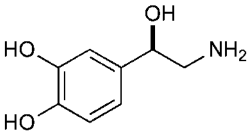
5-hydroxytryptamine
(5-HT; serotonin)



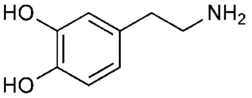
acetylcholine (ACh)



adrenaline
(epinephrine)



noradrenaline



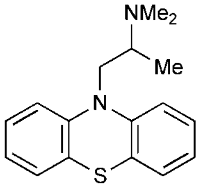
dopamine

For convenience, the following sections on receptor-based drugs are grouped, where possible, according to the natural neurotransmitter or enzyme to which the drugs relate and may include central and peripheral actions. A separate section on CNS-specific drugs with more complex mechanisms is included later. Subsequent major sections (infection and cancer) are, of necessity, related to disease areas.

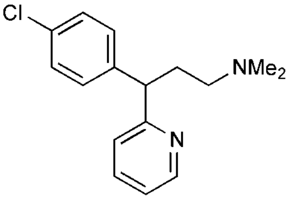
Histamine

There are two main histamine receptors and action at the H_1 receptor is mainly known for producing allergic responses, for example hay fever and skin reactions such as urticaria ('nettle rash'). Antagonists at this receptor, which suppress these actions of histamine, are well known to the layman, under the loose description 'antihistamines', as hay fever remedies. The allergic response is quite complex and other mediators, such as leukotrienes, may also be released, hence the use of leukotriene antagonists, such as montelucast (page 168), for the treatment of asthma and allergies.

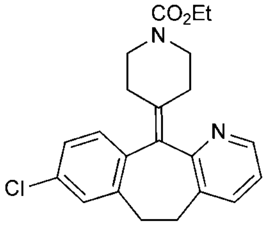
Typical H_1 antagonists are not particularly structurally reminiscent of histamine. Early compounds often had side-effects caused by actions at other receptors, such as that for acetylcholine, but their main drawback is antagonism of H_1 receptors in the CNS, leading to drowsiness. Promethazine has such strong effects in the CNS that it has found use as a sedative and is also of use for treatment of motion sickness. Others, such as chlorpheniramine, show only moderate sedative effects. More recently, compounds such as loratidine have been devised that do not enter the CNS and are therefore free from sedative effects.



promethazine
(Sominex)

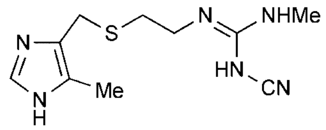


chlorpheniramine
(Piriton)

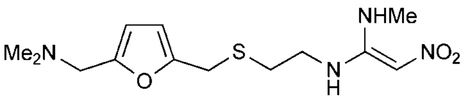


loratidine
(Clarityn)

The H_2 receptor is part of a complex system involved in mediating release of acid into the stomach. Although this is an essential part of digestion, excessive amounts of acid can lead to simple indigestion or acid reflux (heartburn) but can also cause or aggravate the more serious medical problem of peptic ulcers. The development, in the 1970s, of selective H_2 antagonists that inhibit the release of gastric acid was a major advance in medicine, as they are very effective in treating ulcers and have almost eliminated the need for surgery. They were an enormous financial success because of this. The first compound developed was cimetidine, which is obviously closely structurally related to histamine and, as such, a more 'logically' designed compound than the H_1 antagonists. Other H_2 antagonists, particularly ranitidine followed, which had an even more favourable side-effect profile. The dimethylaminomethyl-furan unit in ranitidine can be visualised as replacing the imidazole ring at the receptor. A closer imidazole-substitute is the thiazole ring found in famotidine.

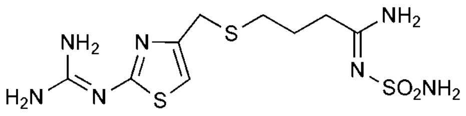


cimetidine
(Tagamet)



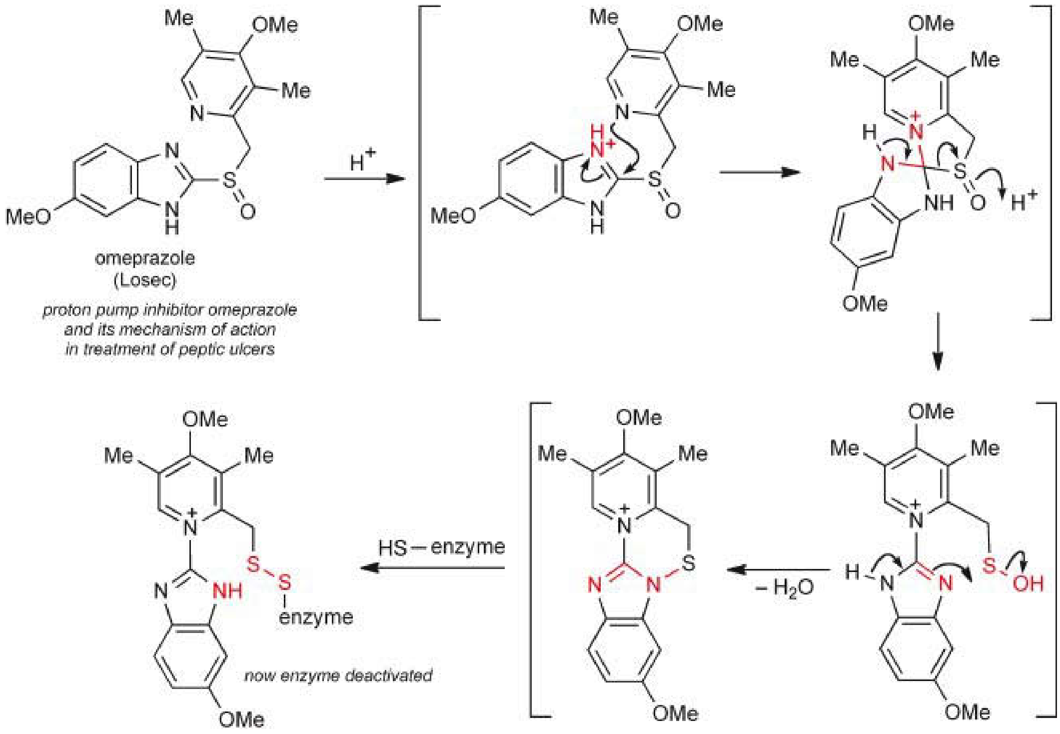
ranitidine
(Zantac)

the development of selective H_2 antagonists that inhibit the release of gastric acid, was a major advance in medicine



famotidine
(Pepcid)

Another type of antacid is the *proton pump inhibitor*. As mentioned above, H_2 receptors initiate a complex cascade resulting in the production of gastric acid, but the actual final release of the acid from the cell is via an enzyme – H^+,K^+-ATPase, the 'proton pump' – which exchanges protons from inside the cell with potassium ions from outside. Omeprazole was designed to deactivate this enzyme and is even more effective than the H_2 antagonists, almost completely stopping the production of acid. The mechanism of action of omeprazole is very different from competitive H_2 antagonism, it being a highly selective sulfenylating agent for the SH of a specific cysteine residue in the enzyme. This disulfide formation irreversibly deactivates the enzyme so effectively that recovery of acid production requires the biosynthesis of new enzyme.



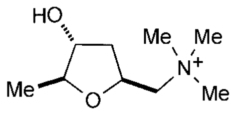
omeprazole
(Losec)

proton pump inhibitor omeprazole and its mechanism of action in treatment of peptic ulcers

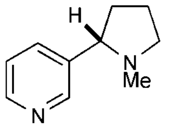
Acetylcholine (ACh)

Acetylcholine mediates two different types of activity at corresponding receptors – *muscarinic* and *nicotinic*, which are related to the pharmacological activities of two natural products, muscarine and nicotine. The first type of action occurs in nerve synapses and the latter at neuromuscular junctions and peripheral ganglia. The term *cholinergic* is used for the general effects of acetylcholine.

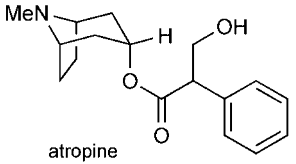
Some clinically useful muscarinic agents are simple choline derivatives although the alkaloid pilocarpine is a muscarinic agonist used in the treatment of glaucoma. The muscarinic antagonist pirenzepine is an alternative to the H_2 antagonists for the treatment of peptic ulcers and some cholinergic side-effects caused by radiotherapy. The best-known nicotinic agonist is nicotine! Nicotinic antagonists include the natural quaternary bis-tetrahydroisoquinoline alkaloid tubocurarine, the paralytic agent from curare (South American Indian arrow poison), which is used in surgery as a muscle-relaxant. Other muscarinic antagonists include the saturated heterocyclic alkaloid atropine, which has a number of medical applications, including dilation of the pupil of the eye, but the shorter acting and less toxic analogue tropicamide is preferred for this purpose in routine ophthalmological examinations.



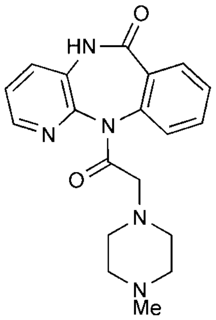
muscarine



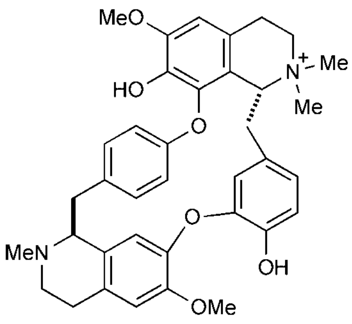
nicotine



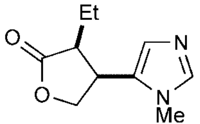
atropine
muscarinic antagonist



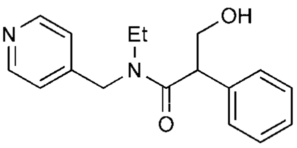
pirenzepine
(Gastrozepin)
muscarinic antagonist



tubocurarine
muscle relaxant during surgery



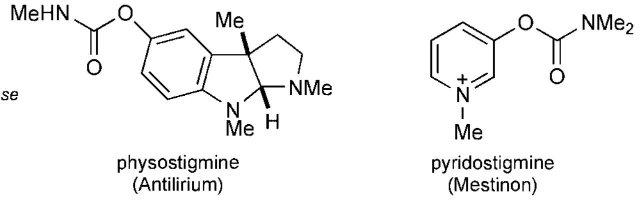
pilocarpine
muscarinic agonist



tropicamide
(Mydriacyl)
for ophthalmological examinations

Anticholinesterase agents

The physiological activity of acetylcholine relies on local release, stimulation of the receptor then rapid hydrolysis by acetylcholinesterase, which results in deactivation. The indole alkaloid physostigmine, from the West African Calabar bean, and the relatively simple synthetic compound pyridostigmine, which has a more obvious relationship to choline, are reversible inhibitors of acetylcholinesterase. Controlled inhibition of the enzyme by such drugs, which results in a build-up of ACh, is useful in conditions such as myasthenia gravis, a muscle weakness that is caused by insufficient production of ACh.

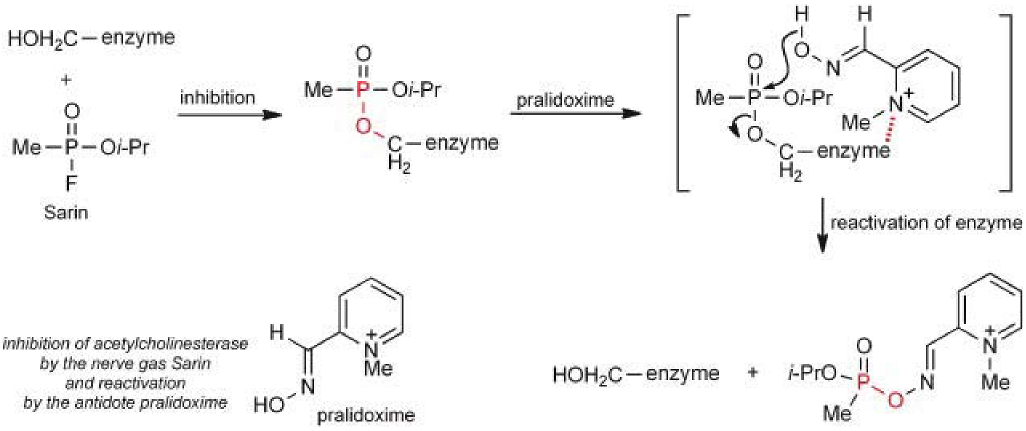


reversible inhibitors of acetylcholinesterase for treatment of myasthenia gravis

physostigmine
(Antilirium)

pyridostigmine
(Mestinon)

Irreversible inhibition of acetylcholinesterase is the mechanism of action of poisoning by nerve gases such as Sarin and to a lesser degree by other organophosphates such as those used as insecticides, leading to persistent and widespread excessive cholinergic effects. The inhibition is due to phosphorylation of a serine hydroxyl group at the active site of the enzyme – this OH is the nucleophile that attacks the acetyl group during physiological functioning of the enzyme. It is possible to reactivate the enzyme, provided treatment is given promptly, by use of pralidoxime. Here, the *N*-methylpyridinium binds via electrostatic forces to the same site as the choline trimethylammonium grouping, bringing the very nucleophilic oxime oxygen close enough to attack the phosphoryl group, releasing the serine OH. Atropine would also be given concurrently to antagonise the effects of the excess ACh.

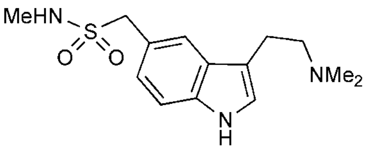


inhibition of acetylcholinesterase by the nerve gas Sarin and reactivation by the antidote pralidoxime

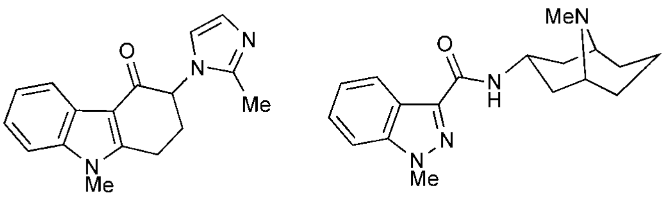
5-Hydroxytryptamine (5-HT) (serotonin)

5-Hydroxytryptamine has at least 14 receptors and sub-types. Compounds acting on these receptors are drugs for the treatment of cardiovascular, gastrointestinal and central nervous systems. Sumatriptan, a 5-HT$_{1D}$ agonist acts, at least in part, by causing vasoconstriction selectively in intracranial blood vessels, opposing the vasodilation that is a component of the pathological basis of migraine. The discovery of the triptan class of drugs was a major advance in the treatment of migraine.

The 5-HT$_3$ antagonists ondansetron and granisetron are effective in relieving the nausea and vomiting that are side-effects of radiotherapy and treatment with cytotoxic drugs. They probably function by a combination of central and peripheral actions.



sumatriptan
(Imigran)
a 5-HT$_{1D}$ agonist for treatment of migraine



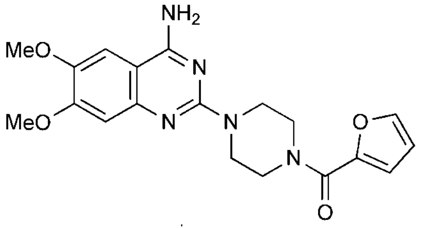
ondansetron
(Zofran)

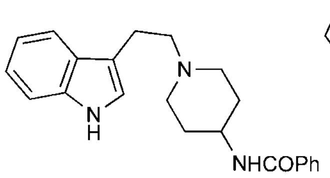
granisetron
(Kytril)

5-HT$_3$ antagonists for relief of nausea and vomiting due to cancer therapy

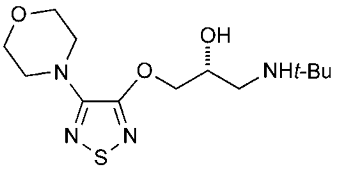
Adrenaline and noradrenaline

Adrenaline and noradrenaline are prominent in the cardiovascular system, acting through α- and β-adrenergic receptors, which exist as a number of subtypes. The interplay of effects from these receptors is quite complex. Many common drugs are simple carbocyclic analogues of adrenaline but a few of the important compounds are heterocyclic.


prazosin
(Minipress)


indoramin
(Baratol)

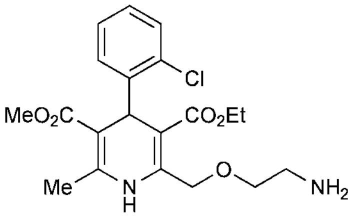
adrenergic α-antagonists for treatment of hypertension and benign prostatic hypertrophy


timolol
(Timoptic)

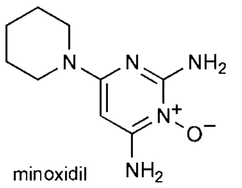
an adrenergic β-antagonist for treatment of hypertension, angina, and arrythmia

Other significant cardiovascular drugs

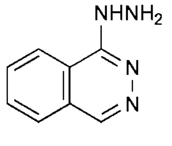
Amlodipine is one of a number of 1,4-dihydropyridines, the mechanism of action of which involves blocking calcium channels (they are said to be 'calcium antagonists'), resulting in a relaxation of vascular smooth muscle. They are useful for hypertension and angina. Diazoxide is a vasodilator used for intravenous administration in hypertensive emergency. Hydralazine and minoxidil are vasodilators used for chronic hypertension, the latter being particularly useful for cases resistant to other drugs. Minoxidil is also of proven value for the treatment of baldness (alopecia).


amlodipine
(Norvasc)

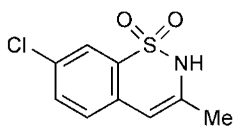
treatment of hypertension and angina


minoxidil
(Rogaine)

treatment of hypertension and alopecia


hydralazine
(Apresoline)

treatment of hypertension

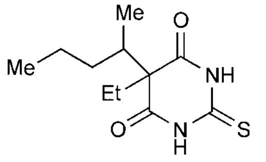

diazoxide
(Proglycem)

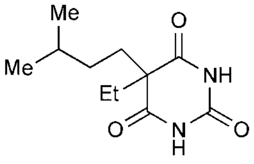
treatment of hypertension

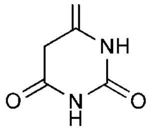
Drugs acting specifically on the CNS

The CNS contains a wide variety of neurotransmitters and high concentrations of receptors. Mechanisms of action of many drugs are often complex combinations of receptor-based actions. Some of the most widely used (and abused) drugs are hypnotics/sedatives, for treatment of insomnia. Barbiturates such as amylobarbitone have been used for many years but suffer from side-effects and are addictive. Thiopentone, however, is very useful as a short-acting intravenous anaesthetic. The benzodiazepines are safer drugs for insomnia and also can be used for treatment of anxiety and muscle spasms. Zolpidem is a newer more selective hypnotic.

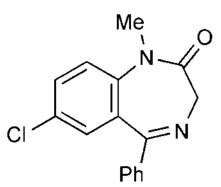
barbiturates (based on barbituric acid) have been in use for many years e.g. thiopentone as a short-acting anaesthetic and amylobarbitone as a hypnotic and sedative

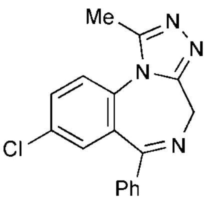

thiopentone (as sodium salt)
(Sodium Pentothal)

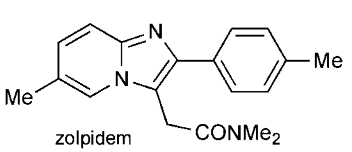

amylobarbitone


barbituric acid

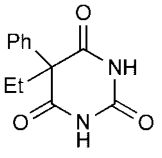
benzodiazepines e.g. diazepam and alprazolam are safer drugs for treatment of insomnia

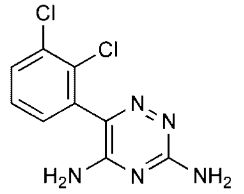

diazepam
(Valium)


alprazolam
(Xanax)

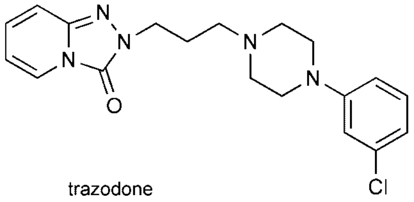

zolpidem
(Ambien)
hypnotic

Phenobarbitone (another barbiturate, also known as phenobarbital) and a newer drug lamotrigine are used to treat epilepsy. Trazodone is a useful antidepressant with fewer side effects than some of the older drugs.

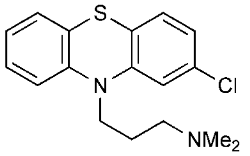

phenobarbitone
(Luminal)

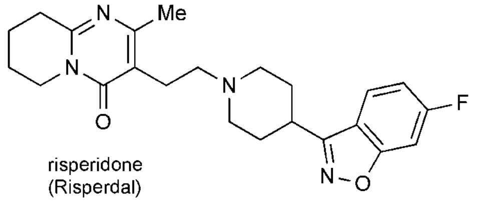

lamotrigine
(Lamictal)

treatment of epilepsy


trazodone
(Molipaxin)
antidepressant

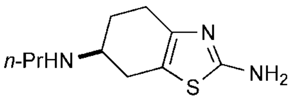
Antipsychotic agents, acting primarily as dopamine and 5-HT antagonists, are used mainly to treat schizophrenia. Newer agents such as olanzapine (page 167) and risperidone have fewer side effects than the traditional phenothiazines such as chlorpromazine.

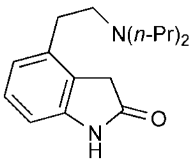

chlorpromazine
(Largactil)
a traditional phenothiazine for treatment of schizophrenia

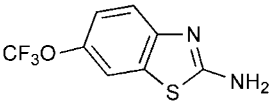

risperidone
(Risperdal)
treatment of schizophrenia

The neurodegenerative states present a challenge for medicinal chemistry. Parkinson's disease is caused primarily by a deficiency of dopamine and so dopamine agonists are effective in alleviating some of the symptoms. Riluzole is the only drug so far developed to have a significant effect in treatment of motor neurone disease.

the dopamine agonists pramipexole and ropinirole are used for treatment of Parkinson's disease

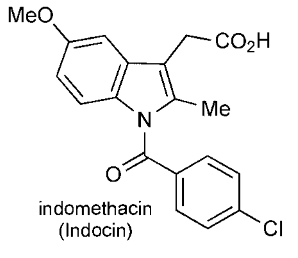

pramipexole
(Mirapex)

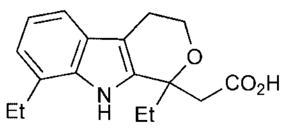

ropinirole
(Requip)

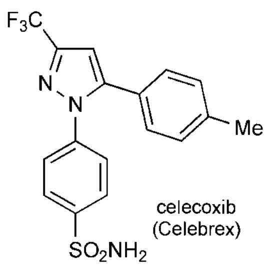

riluzole
(Rilutek)
treatment of motor neurone disease

Other enzyme inhibitors

COX (*cyclooxygenase*) *enzymes* are involved in the first stage of prostoglandin synthesis and their inhibition is the basis of action of the Non-Steroidal Anti-Inflammatory Drugs (NSAIDS). There are two types of enzyme, COX-1 and COX-2 – inhibition of the latter results in anti-inflammatory and analgesic effects while inhibition of the former is responsible for side-effects, particularly gastric bleeding. Most older NSAIDS have both COX-1 and COX-2 activity (indomethacin is an example), but etodolac shows very good selectivity for COX-2. Highly selective COX-2 inhibitors such as celecoxib are now at the forefront. Ketorolac has a different balance of analgesic and anti-inflammatory properties and is particularly useful for topical administration to the eye.

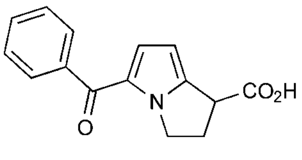

indomethacin
(Indocin)


etodolac
(Eccoxolac)


celecoxib
(Celebrex)

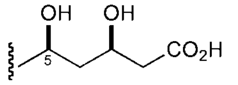
Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) target COX (cyclooxygenase) enzymes

ketorolac
(Acular)
topical administration to the eye

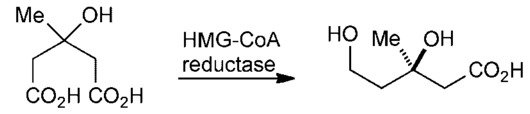


Statins reduce the amount of cholesterol in the blood by inhibition of one of the enzymes (HMG CoA reductase) involved in its biosynthesis and are therefore very useful for prevention of heart disease. The original statins are complex aliphatic fungal metabolites but a number of synthetic heterocyclic drugs, carrying only a small portion of the original structures, are now available, for example atorvastatin and rosuvastatin (page 167). The relationship of the inhibitory portion of the statins to the product, mevalonic acid, can clearly be seen.

(or the corresponding lactone with the 5-OH)



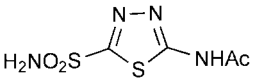
key component of statins: inhibitors of HMG-CoA reductase



3-hydroxy-3-methylglutaric acid mevalonic acid

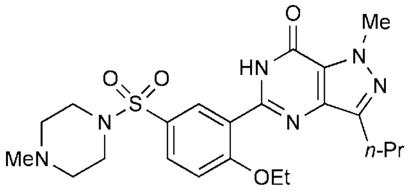
vital step in cholesterol biosynthesis

Other useful enzyme inhibitors include acetazolamide (carbonic anhydrase) for the treatment of glaucoma, congestive heart failure, epilepsy and motion sickness (a very useful drug!). Sildenafil (Viagra), famous for the effective treatment of impotence, inhibits a phosphodiesterase enzyme (PDE5) that is involved in the breakdown of adenosine triphosphate (ATP).



acetazolamide
(Diamox)

enzyme inhibitor for treatment of glaucoma, congestive heart failure, epilepsy and motion sickness

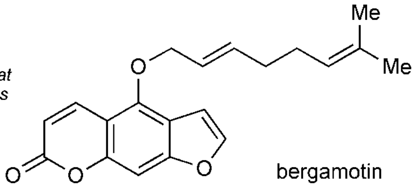


sildenafil
(Viagra)

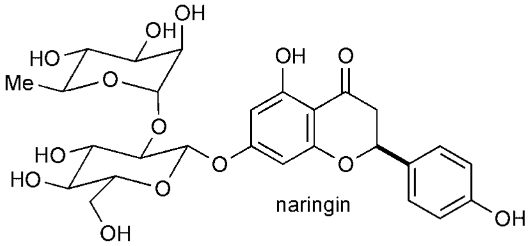
phosphodiesterase inhibitor for treatment of impotence

As an aside, but particularly of relevance to statins, some foods contain enzyme inhibitors that may have important effects. A notable example is grapefruit (juice), containing substances such as bergamotin and naringin, which inhibit the enzymes involved in breaking down a number of drugs. Because drug doses are based on standard rates of metabolisim, inhibition of the enzymes involved can result in much higher, often toxic, blood levels of the drug.

natural inhibitors of the enzymes that break down statins and other drugs



bergamotin



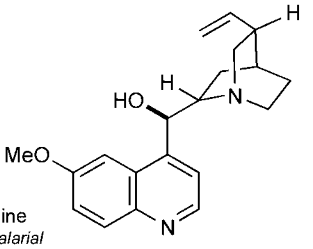
naringin

Anti-infective agents

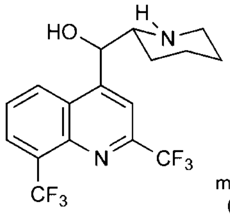
The next three sections cover drugs against parasitic (protozoa and helminths ('worms')), bacterial and viral diseases. The mechanisms of action of many of these agents are complex and diverse and, in some cases, not fully understood, but enzyme inhibition is common to many.

Antiparasitic drugs

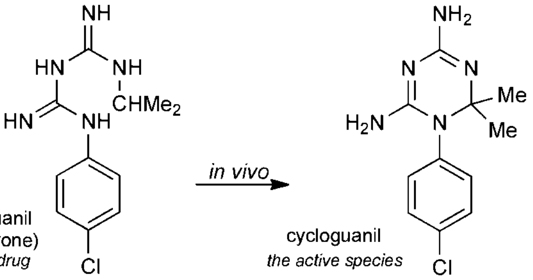
The most important protozoan infection is malaria and this was an early target for medicinal chemical research. The traditional treatment was an extract of the bark of the cinchona tree, which contained the quinoline alkaloid quinine. Current emphasis is on prevention by continuous dosing during exposure using synthetic antimalarial drugs, which must be under constant review as resistance eventually develops. Many of these drugs are quinolines with obvious similarities to quinine. Proguanil is of particular interest because the active species, formed *in vivo*, is a triazine (cycloguanil).



quinine
antimalarial



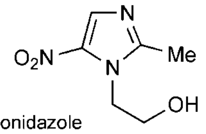
mefloquine
(Lariam)
antimalarial



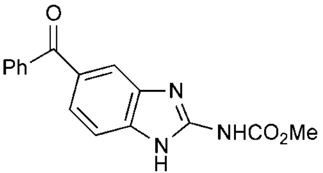
proguanil
(Malarone)
a pro-drug

cycloguanil
the active species

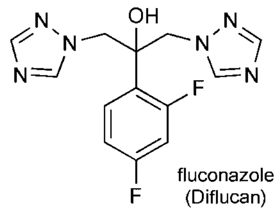
Metronidazole is used for both bacterial (commonly for dental infections) and some protozoan infections such as amoebic dysentery. Benzimidazoles, such as mebendazole, are an important group of anthelmintics. The most common antifungal agents are triazoles such as fluconazole.



metronidazole
(Flagyl)
antiprotazoan/antibacterial



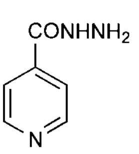
mebendazole
(Vermox)
anthelmintic agent



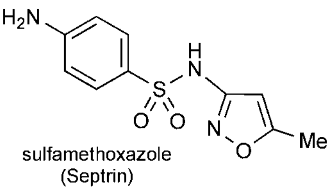
fluconazole
(Diflucan)
antifungal agent

Antibacterial drugs

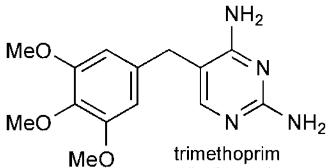
Among antibacterial agents, the simplest must be the pyridine-hydrazide, isoniazid, an important antituberculosis drug. Heterocyclic contributions to mainstream antibiotics include a group of quinolones, such as the broad spectrum antibacterial ciprofloxacin (perhaps best known in connection with recent terrorist use of anthrax), and the diamino-pyrimidine trimethoprim. Many of the sulfonamides, the first synthetic antibiotics, contain heterocyclic residues. Of course, penicillins and cephalosporins are saturated heterocycles and many aromatic heterocycles are included in a multitude of side-chain variants. Co-trimoxazole is a well-known combination of a sulfonamide (sulfamethoxazole) with trimethoprim. This combination inhibits enzymes at two points of folic acid utilisation – the sulfonamide inhibits incorporation of *p*-aminobenzoic acid during bacterial folic acid synthesis, and trimethoprim inhibits its conversion into tetrahydrofolate. The overall result is *synergistic*, that is, there is a greater activity than the sum of the two components.



isoniazid
(Laniazid)
antituberculosis drug



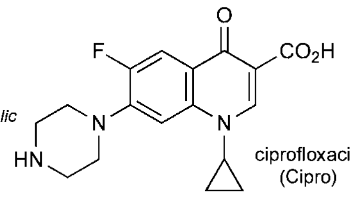
sulfamethoxazole
(Septrin)



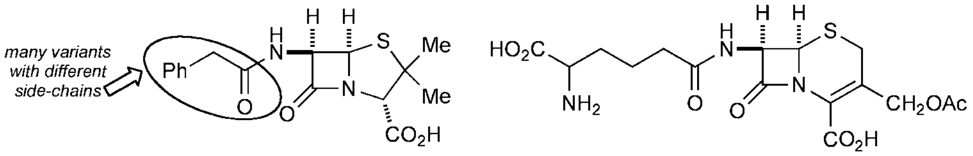
trimethoprim
(Proloprim)

sulfamethoxazole and trimethoprim are frequently used in combination as Co-trimoxazole

broad spectrum antibacterial agent well-known to the public for its action against anthrax



ciprofloxacin
(Cipro)


many variants with different side-chains

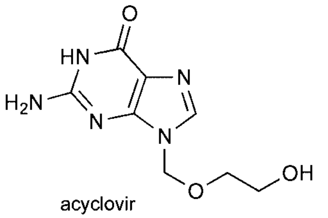
penicillin-G

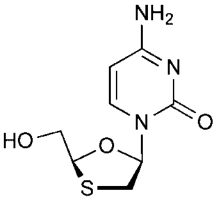
cephalosporin-C

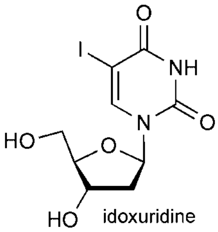
two typical β-lactam-containing antibacterial drugs

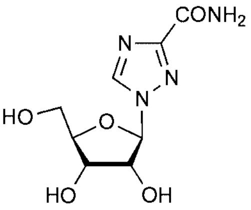
Antiviral drugs

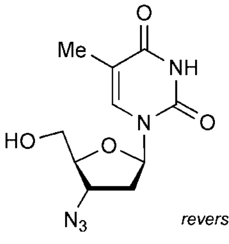
Many antiviral agents are modified (often quite simply) nucleosides or fairly closely related structures, for example ribavirin. These generally work by disrupting the synthesis of viral DNA following incorporation, in competition with natural nucleosides, at an early stage. Non-nucleoside compounds, such as delavirdine and saquinavir, act by binding close to the active site of an enzyme, altering its conformation and thereby deactivating it.

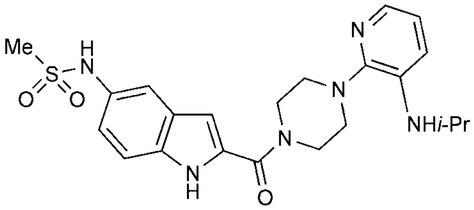

acyclovir
(Zovirax)
antiherpes

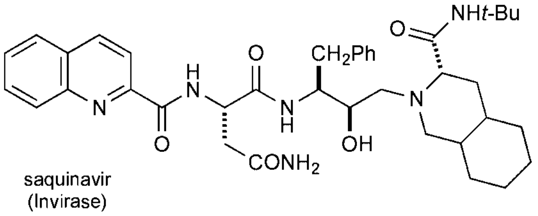

3-TC
(Lamivudine)
antihepatitis B and antiHIV


idoxuridine
antiherpes


ribavirin
(Copegus)
general antiviral

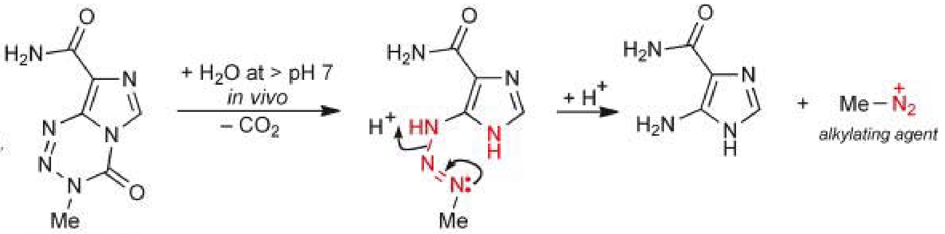

AZT
(Zidovudine)
antiHIV
reverse transcriptase inhibitor


delavirdine
(Rescriptor)
antiHIV
reverse transcriptase inhibitor


saquinavir
(Invirase)
antiHIV
protease inhibitor

Anticancer drugs

Anticancer drugs generally act by disrupting the growth of cells and therefore oppose the excessive and abnormal growth that is the basis of cancer pathology. They are often referred to as cytotoxic or antimetabolites. One of several mechanisms can be operative: disrupting the synthesis of DNA either by *N*-alkylating one of the bases (adenine, guanine, cytosine or thymine) or by incorporation of a modified base or nucleoside by competition with the natural bases for the DNA-synthesising enzymes. Alkylating agents are usually simple chemical 'reagents' or their precursors, an example of the latter being temozolomide, a prodrug, which breaks down when hydrolysed *in vivo* to give the powerful alkylating agent, methyl diazonium cation. Possibly the resemblance of temozolomide to a nucleic acid base allows it to come into close contact with its target.

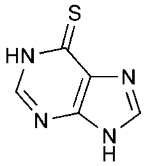


temozolomide is used to treat glioblastoma multiforme, an aggresive brain tumour

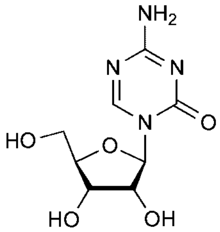
temozolomide
(Temodar)

Some cytotoxic agents are used as immunosuppressive drugs rather than for treating cancer, acting by similar mechanisms but with different balances of effects. These drugs would typically be used to prevent organ rejection following transplantation or to treat severe inflammatory diseases due to autoimmune reactions.

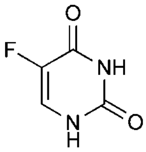
Other mechanisms include interference with the function of folic acid, an important growth factor. Methotrexate is a well-established and widely-used anticancer and immunosuppressive agent that acts in this manner.



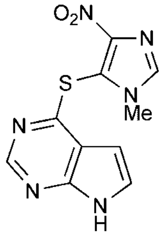
6-mercaptopurine
(Purinethol)
treatment of leukemia



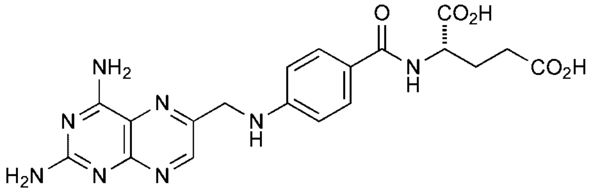
azacitidine
(Vidaza)
treatment of leukemia



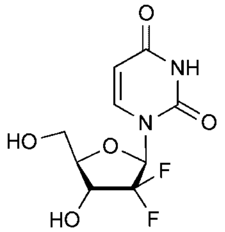
5-fluorouracil
(5-FU) (Carac)
treatment of solid tumours



azathioprine
(Imuran)
an immunosuppressive agent

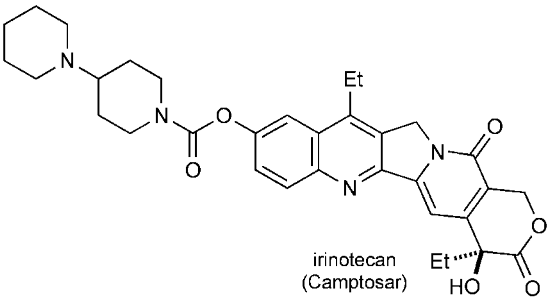


methotrexate
(Trexall)
an immunosuppressive and anticancer agent

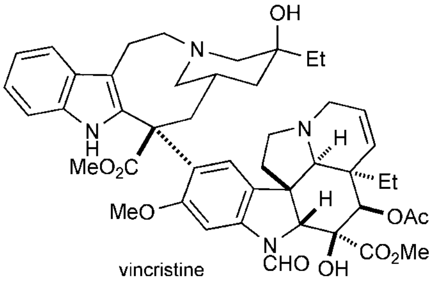


gemcitabine
(Gemzar)
treatment of pancreas and lung tumours

Irinotecan, a more selective synthetic analogue of camptothecin (a natural but toxic anticancer alkaloid), acts by inhibiting topoisomerase I, an enzyme involved in ordering the strands of DNA. Some compounds act by physical binding with secondary structures of vital natural polymers – the complex indole alkaloid vincristine is a classic example – it binds to tubulin, a protein essential to cell division.



irinotecan
(Camptosar)



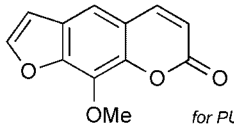
vincristine

Photochemotherapy

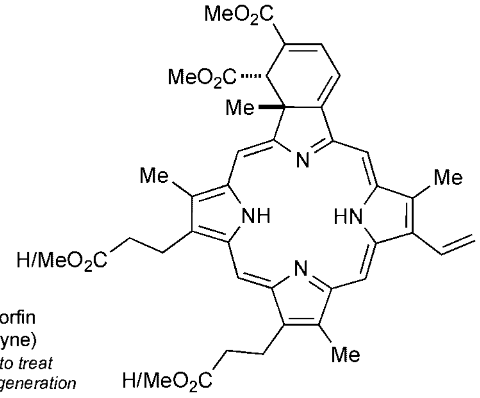
Photochemotherapy is used for the treatment of a number of diseases, predominantly, for obvious reasons, of the skin (and some mucous membranes) and other areas of the body that are accessible to light, such as the eyes.

The process involves administering (systemically or topically) a photoactive substance, then irradiating (with visible or ultraviolet light) to activate the compound so as to generate cytotoxic substances – particularly singlet oxygen, although direct interaction of the drug with DNA may also occur. Selectivity can be achieved by, for example, application of the drug to a defined area of the skin or by selective area irradiation. In some cases lasers may be used. These are not burning lasers, but just high intensity sources of the appropriate activating wavelength.

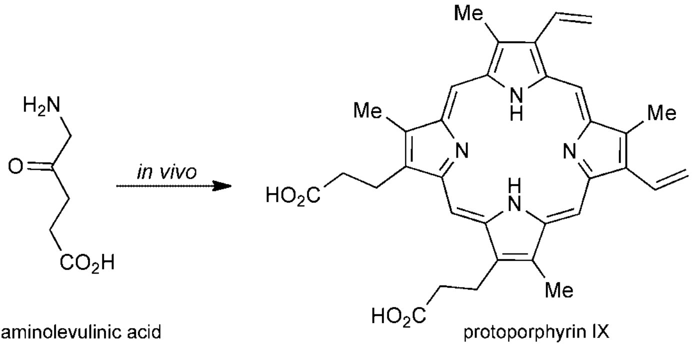
Two significant forms of photochemotherapy are PUVA (Psoralen-UltraViolet A) for skin diseases such as psoriasis, and PDT (PhotoDynamic Therapy), which can be used to treat tumours and macular degeneration. For the PDT, porphins are often used but in an ingenious modification, 5-aminolevulinic acid (a natural porphin biosynthetic precursor) can be applied to skin lesions so as to allow the body to make the required local high concentration of the sensitiser! (Psoralen is the name given to a class of furocoumarins, such as methoxsalen.)



methoxsalen
for PUVA to treat psoriasis



verteporfin
(Visudyne)
for PDT to treat macular degeneration



5-aminolevulinic acid
(ALA)
for in situ generation of protoporphyrin IX for PDT

protoporphyrin IX

19

Applications and Occurrences of Heterocycles in Everyday Life

Introduction

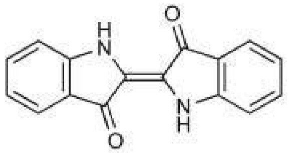
Heterocycles have great importance outside 'pure' chemistry and are of significance, both as natural and synthetic compounds, in many aspects of daily life and industry. The major areas of medicines and 'natural products'/biomolecules have been covered in their own chapters (18 and 17) but here we give an overview of some other important areas.

Classical aromatic chemistry – that is the chemistry of benzene derivatives – gives rise to many important industrial and fine chemical applications. However there is only one neutral monocarbocyclic aromatic ring – benzene – but there are 32 known monocyclic aromatic 5- and 6-membered heterocyclic rings (containing only N, O and S) and these are great sources of diversity. As in medicine, the varied nature of these heterocyclic ring systems allows fine-tuning of many chemical and physical properties for a variety of purposes.

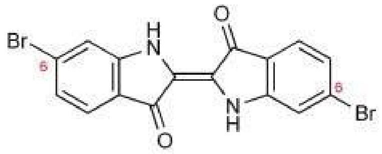
Dyes and pigments (see also page 190)

The general term 'colorants' is used to describe pigments and dyes, the latter being soluble materials used for dying cloth and so on. Many dyes are also used as stains for microscopy and analysis.

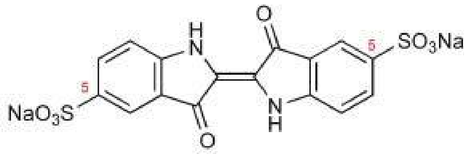
Natural dyes, mainly plant-based, have been used for centuries and many of these are heterocyclic, particularly anthocyanins and flavonoids (see pages 165–166). Indigo is an important ancient plant-based dye, but is now produced synthetically on a large scale to colour blue jeans (ca. 6–10 g per pair). Tyrian purple, an extremely expensive ancient dye used in Roman times, is the 6,6′-dibromo derivative of indigo, and was extracted from a sea snail. Indigo carmine, a food colorant, is the disodium salt of the 5,5′-disulfonic acid and also has a number of medical uses, such as the ability to selectively identify tissue during endoscopy.


indigo

blue dye, originally from plants used for blue jeans

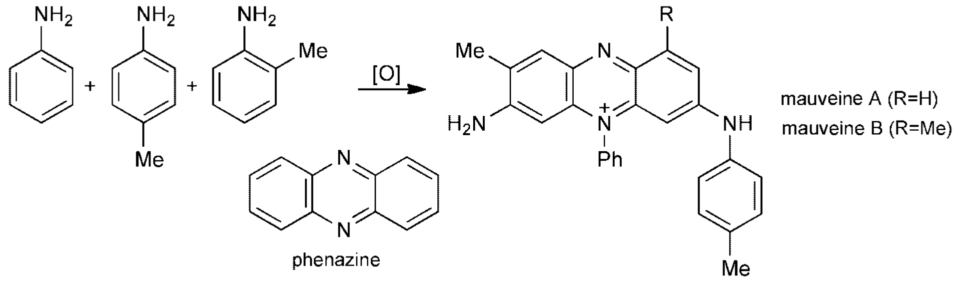

Tyrian purple

from a sea snail


indigo carmine

synthetic food colorant and medical dye

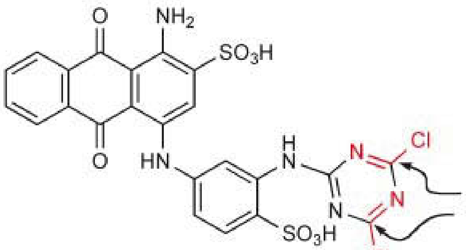
The first (1857) mass-produced synthetic dye – W.H. Perkin's mauve (mauveine) (a bright purple) – was an accidentally-prepared heterocycle, from the oxidation of a mixture of substituted anilines. This is generally held to be the start of the Fine Chemicals industry. This process was developed before the structural theory of aromatic and heterocyclic chemistry was established, but later mauveine was shown to be a mixture of several closely related compounds, dominantly mauveines A and B (phenazinium salts), the final detail being established only in 1994.



Heterocyclic Chemistry at a Glance, Second Edition. John A. Joule and Keith Mills.

Modern synthetic dyes and pigments include the phthalocyanines, which are reminiscent of natural porphins and are commonly used as metal complexes, particularly with copper: such metal derivatives have a cation complexed at the centre, much like the iron atom in heme (see pages 162–163). Many variations, including solubilised (sulfonated) forms, are used in shades of blue and green, the latter being chlorinated derivatives. The phthalocyanines comprise about one quarter of all colorants sold, with copper phthalocyanine being the single largest volume colorant. These compounds have a multitude of applications, including artists' pigments, inkjet inks, industrial paints, plastics and in the manufacture of CDs.

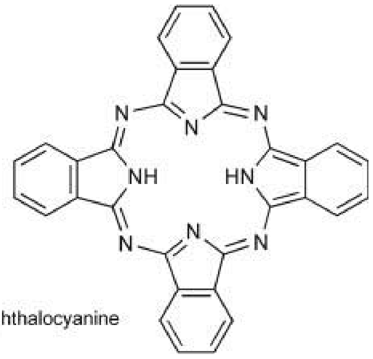
Reactive dyes, which bind very strongly (and therefore do not 'wash out'), usually contain halo-heterocycles that react with nucleophilic centres, such as OH and NH, in the fabric (cotton, wool, nylon), to give covalent bonds by displacement of the halogen.



halogens displaceable by nucleophilic centres in the cloth

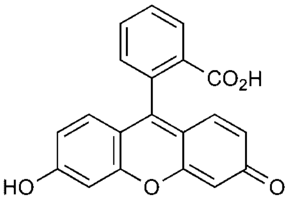
Reactive Blue 4

reactive dye forms covalent bond with substrate

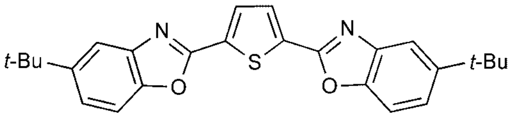


phthalocyanine

Related to the coloured appearance (reflected light) of dyed fabrics is fluorescence (the absorption of UV light, followed by emission of visible light), which has important practical uses. The intensity of the colour means that low concentrations can be easily detected, such as the use of fluorescein to trace water courses. Fluorescein is also the molecular core for many fluorescent metal and biomolecule sensors. Optical brighteners, which emit blue light, are very prominent in everyday substances such as washing powders – the addition of more blue results in a whiter appearance.



fluorescein



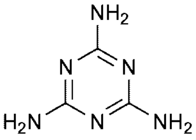
Benetex OB

an optical brightener absorbs UV, emits blue

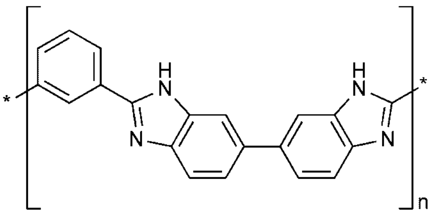
Polymers

Most polymer plastics and fibres are composed of aliphatic or carbocyclic aromatic compounds, but a few are heterocyclic, one of the prime properties of which being resistance to heat.

Melamine–formaldehyde polymers are widely-used, relatively cheap plastics for housewares and in laminates such as Formica. At the other end of the scale, polybenzimidazole is used to make expensive high performance fibres, for example for fireproof clothing, and high performance engineering plastics (e.g. Celazole-PBI), which are suitable for constant use at over 300 °C. The fibre is also under investigation for use in high temperature membranes.

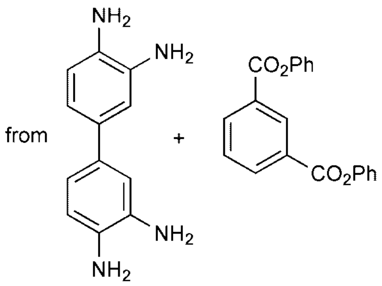


melamine

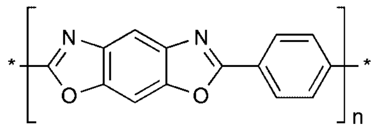


polybenzimidazole

used in high temperature fibres and engineering plastics

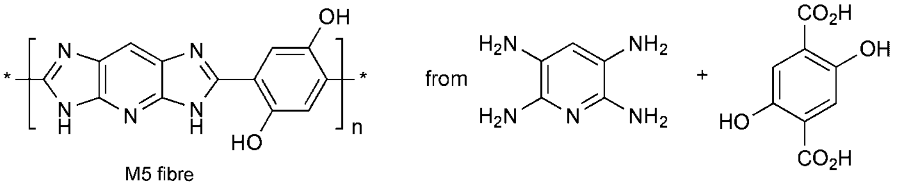


Polybenzoxazoles (e.g. Zylon-PBO) form very strong lightweight fibres, used, for example, in racing yacht rigging, but a disadvantage is that this polymer degrades in light and therefore must have a protective coating. M5 fibre has very high strength and heat resistance, and is being developed for use in body armour.



a polybenzoxazole (Zylon-PBO)

very high strength fibres



M5 fibre

very high strength and heat resistance used in body armour

Pesticides

Pesticides are designed to kill living organisms that are harmful to human interests. The ‘pests’ are mainly insects, weeds, fungi and animals (particularly rats). Many of these pesticides are restricted to agricultural use under close control, although a few are available for use by domestic consumers, and some others in professional public health applications.

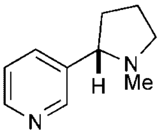
These substances are essential to modern agriculture and very useful in general life, but will always be controversial, particularly the herbicides and insecticides, because of their ability to damage beneficial organisms. There is also the potential to leave trace residues in foods, which have been claimed to have adverse health effects in humans.

There is a certain amount of confusion, and constant change, in the usage of pesticides in various regions of the world, with some widely used compounds being banned or severely restricted in certain countries, quite often in the EU and the USA.

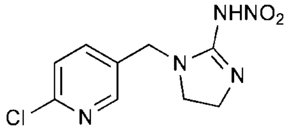
Insecticides

Most insecticides for domestic use are (non-heterocyclic) pyrethroids, which have very low toxicity to humans, although some of those used by professionals for use in public hygiene situations are heterocycles. A much larger range, including many heterocycles, is used in agriculture under rigorously controlled circumstances, to avoid adverse effects, for example on pollinating insects such as bees.

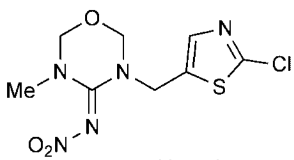
The cholinergic system, which is similar to that in humans, is one of the main targets. Nicotine was widely used as an insecticide, but is extremely toxic to humans (similar to hydrogen cyanide – lethal dose about 60 mg) and readily absorbed through the skin. A number of compounds – ‘neonicotinoid insecticides’ – have been developed that have the same mechanism of toxicity (acetylcholine agonists) but are much more selective for insects. Not surprisingly, many are 3-substituted pyridines (e.g. imidacloprid), together with some thiazoles (e.g. thiamethoxam).



nicotine



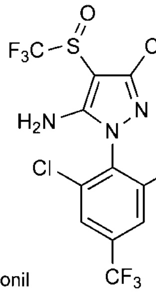
imidacloprid



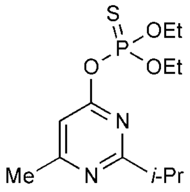
thiamethoxam

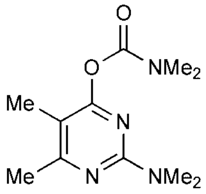
neonicotinoids

Other substances are choline esterase inhibitors, either reversible, such as the carbamates, for example pirimicarb, or irreversible (mainly organophosphates). A number of organophosphates have been modified by the addition of heterocyclic rings, for example diazinon. The organophosphates are close relatives of nerve gases such as Sarin (page 172), but are somewhat less toxic to humans, but still cause considerable concern. (The nerve gases were discovered during research on insecticides in the 1930s.) Insecticides acting by non-cholinergic mechanisms include Fipronil (which acts at GABA receptors in the CNS).


fipronil

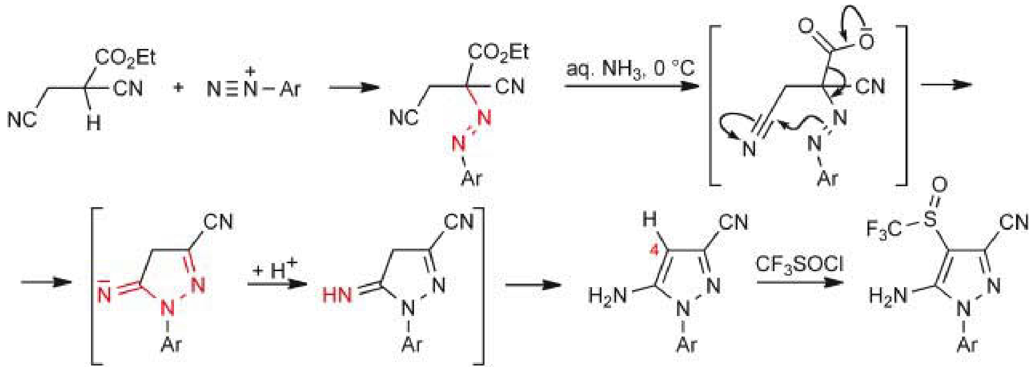
acts at GABA receptor


dazinon


pirimicarb

choline esterase inhibitors

The key steps in an elegant synthesis of Fipronil are the condensation of the enolate of ethyl 2,3-dicyanopropanoate with 2,6-dichloro-4-trifluoromethylphenyl diazonium ion. Aqueous ammonia treatment of the product then initiates a sequence leading directly to a pyrazole: hydrolysis of the ester induces ring closure, as shown. The sulfur substituent can then be introduced via electrophilic attack at pyrazole C-4.

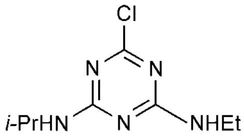


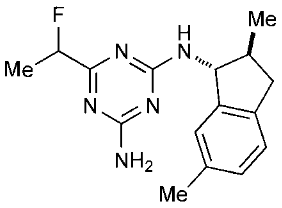
Some of these compounds are also used to treat animals, such as in sheep dips and 'flea drops' for cats and dogs. (Note that cats are particularly sensitive to organophosphates and should only be given products designed for them in the specified dose; poisoning of cats is not uncommon if this is disregarded.)

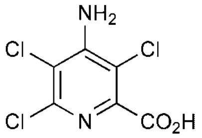
Herbicides

Herbicides can be made selective for different classes of plants – broadleaf, grasses, and so on, but control of the mode of use is also important. Herbicides can be divided into two classes – systemic, in which the compound is taken up by the roots, and contact (e.g. paraquat), in which only the exposed portions of the plant are affected.

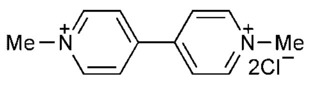
Atrazine is a controversial selective herbicide, very widely used in the world but banned in the EU. It has very low acute toxicity to animals and humans but there are claims of longer term adverse endocrine effects and possible carcinogenesis. Its mechanism of action is interference with photosynthesis. Its selectivity in corn crops is achieved because the compound is rapidly deactivated by endogenous compounds in the corn plant. A structurally related, but biologically different, analogue, indaziflam, acts by inhibition of cellulose biosynthesis.


atrazine

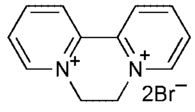

indaziflam


picloram

Picloram is a selective systemic herbicide, which kills broad-leaved weeds but not grasses. Paraquat is a non-selective very fast-acting contact herbicide that is also highly toxic to humans. It has the advantage that it is deactivated on contact with soil, which reduces collateral damage. Its mechanism is inhibition of photosynthesis, by generation of reactive oxygen species, which damage porphins. It is one of the most widely used herbicides throughout the world, but banned in the EU and restricted in the USA. The related diquat is less toxic.



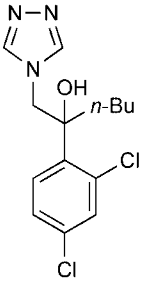
paraquat



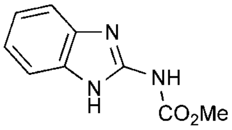
diquat

Fungicides

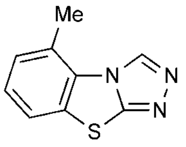
Agricultural fungicides are often triazoles, such as hexaconazole, similar to those used in medicine, or benzimidazoles, such as carbendazim. There are also some more chemically interesting heterocycles, such as tricyclazole.



hexaconazole



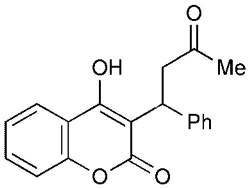
carbendazim



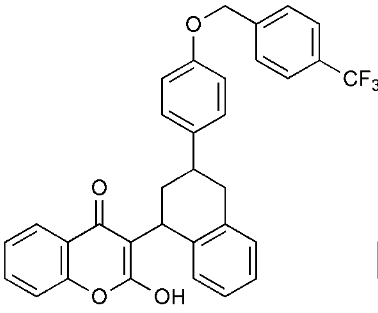
tricyclazole

Rodenticides

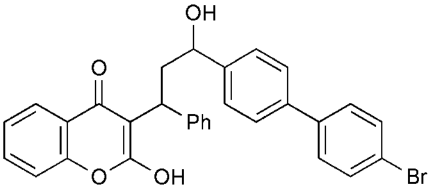
The most well-known rodenticide is warfarin, the action of which against rats is the same as for its medicinal use in humans, that is, inhibition of blood coagulation. The development of resistance to its effects (in rats!) led to the development of much more potent second-generation analogues such as flocoumafen and bromadiolone.



warfarin



flocoumafen



bromadiolone

Explosives

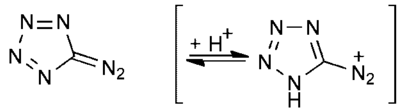
Many compounds are explosive but relatively few of them are suitable as practical explosives. The most important requirements are that they are stable and not easy to initiate accidentally! Friction, static electricity and impact are the main dangers.

Much research has been carried out to develop 'insensitive explosives', which are almost impossible to detonate without a proper detonator – the least sensitive will burn quietly and not react even if a bullet is fired into them.

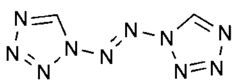
Commercial explosives are often mixtures, designed to have perfect oxygen balance or modified properties for specific purposes, such as quarry blasting, munitions or propellants (for cartridges or rockets). Solid rocket fuels are basically explosives, modified so that burning does not progress to explosion.

In a chemical explosion, it is assumed that CHNO compounds are converted into carbon monoxide or dioxide (depending on the oxygen balance), water and nitrogen. The formation of these very stable molecules results in the release of a considerable amount of energy and gas. It follows that many heterocycles, particularly high nitrogen compounds, are highly energetic compounds, with the potential to be used as explosives.

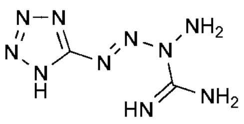
Tetrazoles have the highest proportion of nitrogen and tetrazole itself is classified as an explosive for transportation purposes, although not used as such. Diazotetrazole (or the equivalent diazonium salt) has the requisite energy but is exceptionally dangerous due to facile spontaneous detonation. 1,1′-Azobistetrazole, which has a chain of ten nitrogen atoms, is slightly more stable and can be isolated as a solid, but 'attempts to manipulate the dry solid inevitably led to extremely loud explosions and the destruction of labware'! However 'Tetrazene' is a safe commercial explosive, used in detonators. 5-Aminotetrazole, which is not explosive in its own right, can release much energy (and large volumes of gas) on decomposition as a component of mixtures, and is used in this way in vehicle air bag inflators. Combining the potential of a tetrazole with a suitable metal can produce a less polluting firework colorant, the example below producing a red colour.



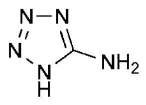
diazotetrazole
extremely dangerous
due to spontaneous detonation



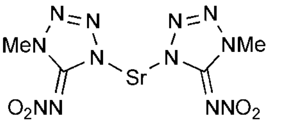
1,1'-azobistetrazole
chain of 10 nitrogens
highly sensitive



Tetrazene
an important primary explosive
used in detonators

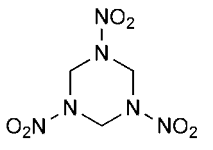


5-aminotetrazole
a component in
air bag inflators

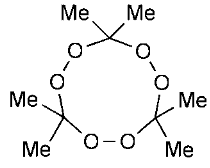


strontium *bis*-(1-methyl-5-nitriminotetrazolate)
a pyrotechnic colorant (red colour)

The saturated heterocycle RDX, a very widely used high explosive, is a component of Semtex and was used as a replacement for TNT in the Second World War. The dangerously unstable acetone peroxide, which has been used by terrorists, is 'trimeric' and contains a nine-membered ring, although dimers and tetramers can also be formed from acetone and hydrogen peroxide. Acetone peroxides (and many other peroxides) are notorious amongst chemists as unwanted by-products from hydrogen peroxide reactions, being extremely sensitive and prone to detonation.

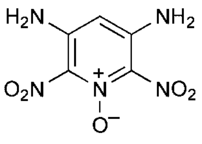


RDX
a widely used military explosive
a component of Semtex

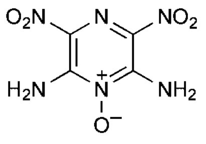


acetone peroxide
infamous for use in
terrorist bombs

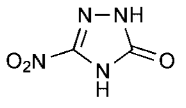
3,5-Diamino-2,6-dinitropyridine *N*-oxide (DADNPO) has a high heat tolerance (up to 300 °C) and is therefore particularly suitable for use in oil wells. The related LLM-105, a pyrazine *N*-oxide, is a quite insensitive high explosive. 5-Nitro-1,2,4-triazol-3-one, which also has low sensitivity, has a wide range of explosive applications. Even a seemingly innocuous compound such as 3,4-diaminofurazan (DAF; 3,4-diamino-1,2,5-oxadiazole) is under development.



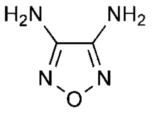
DADNPO
high temperature
tolerance



LLM-105
an insensitive
explosive



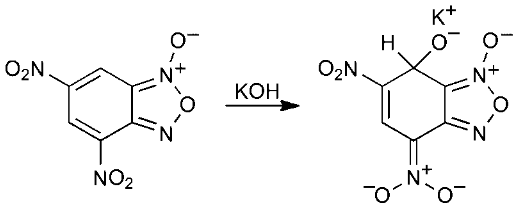
NTO
a general purpose
explosive



DAF

A primary explosive is one that is used (in a small quantity) to initiate the detonation of the main (secondary) explosive, which is usually difficult to detonate directly. The primary explosive is usually contained in a detonator or ignition cap.

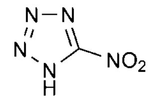
Classical primary explosives are often heavy metal salts, such as lead azide ($Pb(N_3)_2$) or lead styphnate (the lead salt of 2,4,6-trinitroresorcinol (2,4,6-trinitrobenzene-1,3-diol)), which can cause pollution problems, particularly on firing ranges. A number of heterocyclic compounds are being developed to avoid this 'heavy metal problem'. 4,6-Dinitrobenzofuroxan (DNBF; 4,6-dinitro-2,1,3-benzoxadiazole) is a widely used primary explosive and it is notable that it is used for this purpose as its potassium salt, which is actually a Meisenheimer complex (KDNBF). It is a replacement for lead styphnate. Amine salts of 5-nitrotetrazole have also been proposed as 'Green' alternatives for detonators.



DNBF

KDNBF

heavy metal-free explosive for detonators



5-nitrotetrazole (as amine salt)

a promising 'Green' substitute for heavy metal salts in detonators

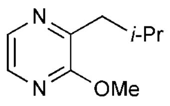
Food and drink

Heterocycles are significant components of foods, as nutritionally important constituents, as colouring agents and as flavours and aromas. Many of these are present in raw foods but some are 'additives' (natural or synthetic) or are formed during cooking – the kitchen is a site of extensive heterocyclic synthesis!

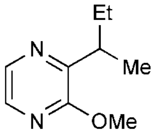
We also consume, in all foods, large numbers of other compounds of no nutritional benefit, which just happen to be there naturally. Most of these are relatively innocuous but some can produce adverse effects in certain circumstances (see page 192, divicine). Other compounds can be pleasingly psychoactive: caffeine is a well-known component of tea and coffee but the less well-known, closely-related theobromine is a major constituent of chocolate.

Food flavour and aroma components include many pyrazines and furans, with significant contributions from thiazoles (which can have similar aromas to pyrazines) and thiophenes. Many of these simple aroma compounds can be detected (smelt) down to very low levels (ppb or even less). Also, depending on concentration, the same compound may show a range of aromas. The overall flavours and aromas are generally the sum of the effects of complex mixtures.

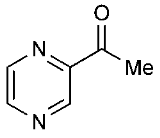
The most important natural aroma compounds in raw foods are probably pyrazines, which tend to be simple alkyl and methoxy derivatives. They occur in fresh vegetables such as peas and capsicum peppers, and in many grape and wine aromas. Amongst other important products, furfuryl mercaptan is the main aroma compound in coffee. Significant non-aromatic furanones include sotolone, a naturally-occurring compound, which is also used to flavour artificial maple syrup (it has a maple aroma at low concentration and fenugreek at higher concentrations) and furaneol, whose alternative name 'strawberry furanone' explains everything.



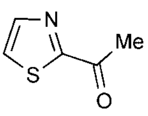
from bell pepper



from green peas and coffee

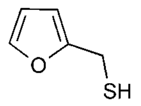


from coffee



popcorn aroma

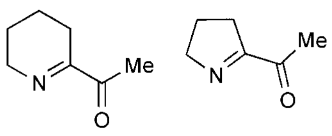
occurs in asparagus, potatoes, bread



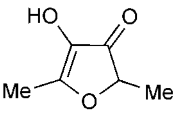
furfuryl mercaptan

major aroma component of coffee

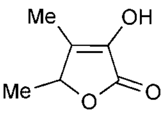
typical food flavour and aroma components



baked bread aromas



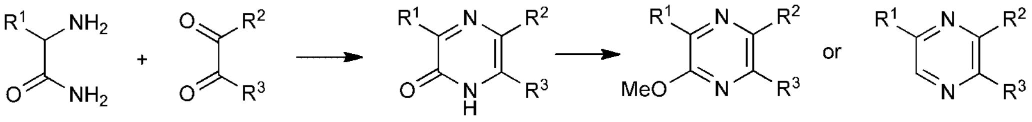
furaneol (strawberry furanone)



sotolone

aroma of raw cane sugar and maple syrup

The biosynthesis of these 'raw' pyrazines probably involves condensation of α-amino acid amides with 1,2-dicarbonyl compounds, such as glyoxal, and/or are the products of dimerisation of α-amino acids. The amino acid side-chains are retained, unlike in the products of the Maillard reaction (see page 188).



probable biosynthetic route to pyrazines in plants

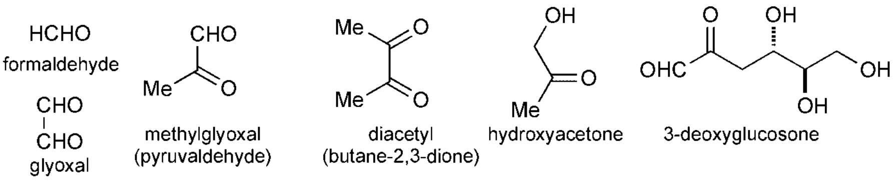
Heterocyclic chemistry of cooking

The heterocycles produced during cooking include more pyrazines and also many furans and a range of sulfur-containing compounds.

The details of chemical processes in cooking are very complex but the examples below will give an idea of the general types of reaction.

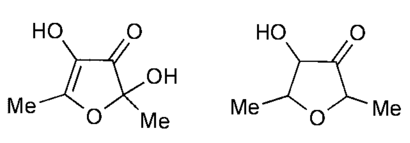
The main components of food, apart from water, are carbohydrates, proteins, amino acids and fats, and all of these can undergo considerable chemical change on heating. Some of the products may be formed from one of the class types and others from combinations. Analytically, raw meat does not contain carbohydrates, but they can be formed from glycogen and nucleotides, or they can be added in marinades and so on. The amino acid cysteine is the major source of sulfur.

The most significant processes are those that occur during baking or frying. Normal frying and baking temperatures vary between about 170 and 250 °C, but, of course, this mainly affects the outer layer (of the food), with the inner part being much cooler. The crust is where the interesting chemistry occurs! Two- to four-carbon α-dicarbonyl or α-hydroxy-carbonyl compounds, which are important in the Maillard reaction (see page 188), can arise from the breakdown of sugars or fats. These fragmentations can also occur slowly in water and can be found in unexpected situations, such as heat sterilisation of glucose solutions for intravenous administrations, but fortunately only at low levels (<0.1%).

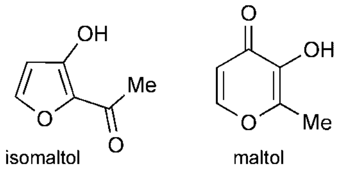


fragmentation and degradation products from glucose
(important in the Maillard reaction)

Caramelisation



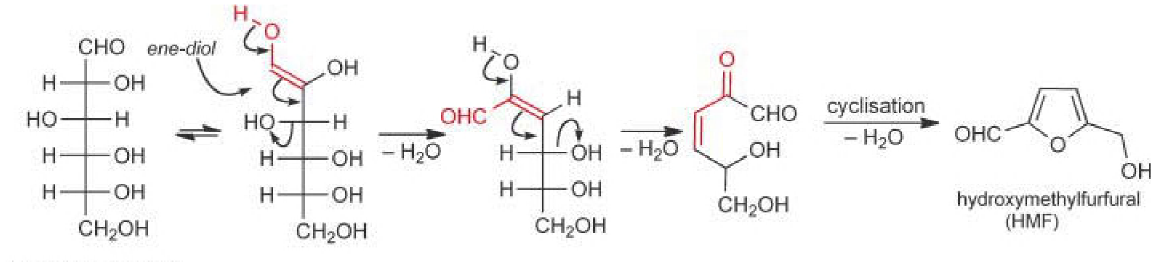
main caramel flavours



toasty and baked aromas formed via Maillard reaction

When sugars are heated they turn to caramel, which shows shades of gold–brown due to the formation of polymeric material of uncertain structure. In addition, various volatile monomeric aroma molecules are produced, including hydroxymethylfurfural (HMF), and various furanones, and also a number of chain-cleavage products, such as those shown above. The formation of the oxygen heterocycles is easily rationalized by invoking the open chain form of the sugars, with reference to the standard ring syntheses of furans (page 105), via cyclocondensations of 1,4-diketones or 4-hydroxy-ketones.

The key to the conversions of these open sugars is the equilibrium of α-hydroxy-carbonyl compounds with ene-1,2-diols. The ene-diols can then form the reverse α-hydroxy-carbonyl system by tautomerism, or initiate further reactions, such as loss of adjacent hydroxyls, resulting in formation of α-dicarbonyl (1,2-dicarbonyl) compounds. These, in turn, can then undergo cyclisation giving furans, but are also, together with smaller fragmentation products, important in reactions with amino acids in the Maillard reaction (see below).

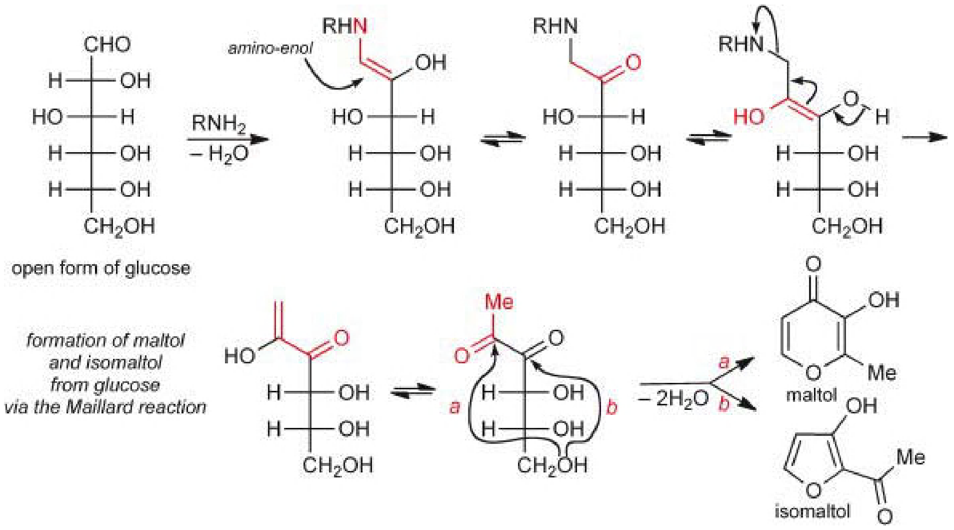


formation of hydroxymethyl furfural from glucose

(Commercial caramel is made by heating sugars in the presence of a catalyst (acid or sulfite), with or without ammonia, those with ammonia showing darker colours. Being a type of product formed by normal cooking processes, it is considered a natural substance and therefore can be added to various food and drinks. It is by far the most common food colour additive. The 'ammoniated' dark caramels are used especially for beers and cola-type drinks.)

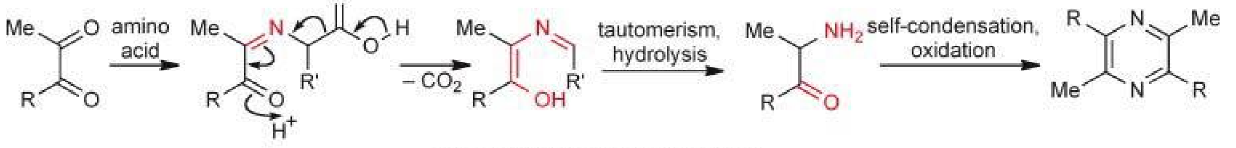
Maillard reaction

The Maillard reaction can be considered as an extension of caramelisation. This reaction occurs when sugars and amino compounds are heated together and results in a much more rapid and intense browning than simple caramelisation. The basic mechanism (and often the outcome) is similar to that shown above except that an amino-enol intermediate, rather than an ene-diol is involved. Alternatively, later loss of the amino group (rather than an internal hydroxy) results in formation of a methyl ketone and thence to compounds such as maltol and isomaltol.

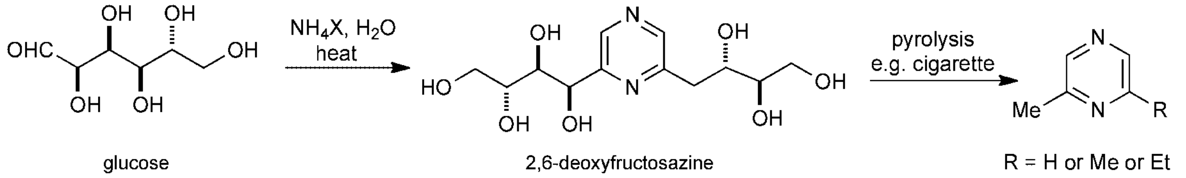


formation of maltol and isomaltol from glucose via the Maillard reaction

When the amino compound is an α-amino acid (an extremely common occurrence!), the process results in the cleavage of the amino acid side-chain and formation of a primary amino sugar. This type of reaction can also occur with the smaller dicarbonyl fragments. Self-condensations of the amino-ketones lead to pyrazines: non-volatile (such as 2,6-Deoxyfructosazine) from sugars, and volatile, from the smaller fragments. (Note: 2,6-Deoxyfructosazine can be prepared quite efficiently by heating glucose with ammonium salts in water. It has been shown to produce volatile simple alkyl pyrazines on heating above 220 °C.)

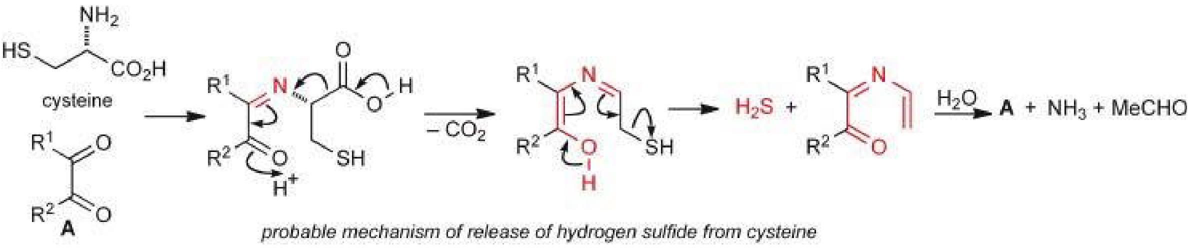


example of Maillard route to pyrazines

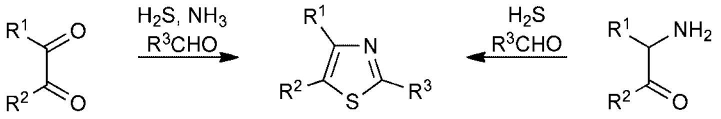


It is not only sugars that are the basis for heterocycle production, hot cooking oils also generate decomposition products that can react with amino acids. An analysis of the volatile products from heating peanut oil with cysteine showed many thiazoles and thiophenes, together with a few pyridines and pyrroles.

Cysteine is the main source of sulfur for many of these products. Its decomposition to produce hydrogen sulfide can be explained by the decarboxylation of its condensation product with an α-dicarbonyl compound, and it is also possible that the sulfur could already be attached to another reactant before cleavage.



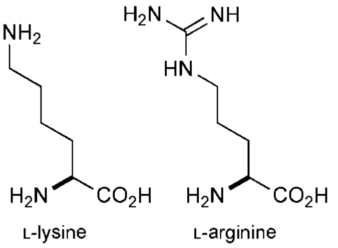
probable mechanism of release of hydrogen sulfide from cysteine

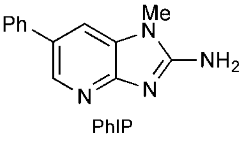


potential condensations to give thiazoles

A number of other flavour components are also the results of Maillard-type reactions, such as the baked bread aroma acetyl pyrroline, although in this case, the product retains the 'side-chain' from the starting proline.

More complex heterocyclic compounds can also be produced (particularly on prolonged cooking at high temperatures), including the potentially carcinogenic (and vaguely named) 'heterocyclic amines', such as PhIP.





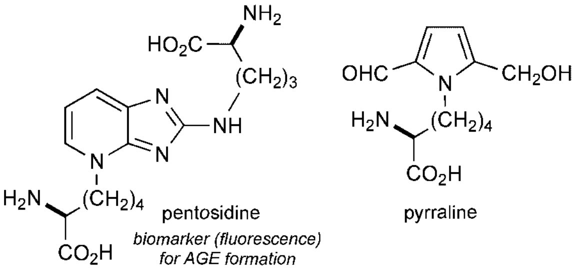
potential food carcinogen formed via Maillard reaction

Physiological aspects of the Maillard reaction

In addition to reactions during cooking, Maillard-type reactions can also occur after food is eaten, that is, in the body. In this situation, reactions involving two basic amino acids (those with an additional ω-NH_2: lysine and arginine) are particularly important.

In addition to the normal Maillard reaction involving the α-amino group, with decarboxylation and loss of the side-chain, reaction at the ω-amino group retains the side-chain and further transformations lead to another group of heterocycles, known as Advanced Glycation End products (AGEs). These end products can be free small molecules, or the equivalent products involving lysine or arginine residues in proteins, leading to cross-linking or other modifications, thus damaging the physiological function of the protein. These occur normally and are not usually a problem, but excessive formation has been implicated in a number of diseases such as cataracts and the serious sequelae of diabetes, possibly related to the excess (blood) sugar and oxidative stress. The quantity of AGEs has been shown to correlate with the seriousness of the disease. They are also thought to have a general role in aging.

monomeric AGEs, which can also be components of proteins: pyrraline as a simple modifier, pentosidine as a cross-link



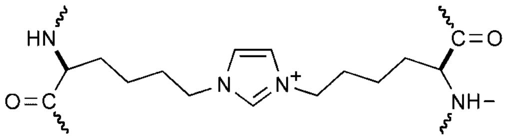
pentosidine

biomarker (fluorescence) for AGE formation

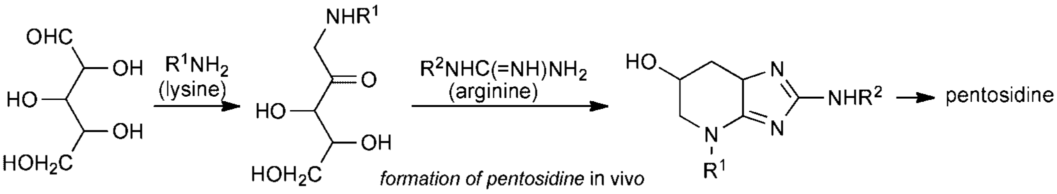
pyrraline

A number of heterocycles have been identified, such as the simple pyrrole, pyrraline, but also in cross-linking by imidazoles and more complex systems, exemplified by pentosidine (which is derived by cyclisation involving the sugar residue). Pentosidine-type cross-linking is significant, but free pentosidine (which is fluorescent) is used as a convenient marker for AGE formation.

an imidazolium salt as a cross-link in proteins



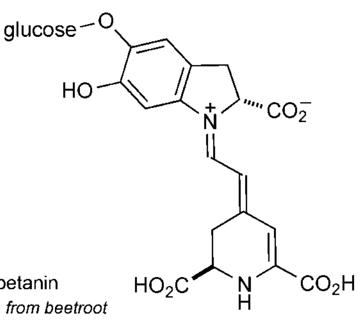
Pentosidine, as its name implies, is mainly derived from pentoses, such as ribose, although it can form from glucose and fructose.



formation of pentosidine in vivo

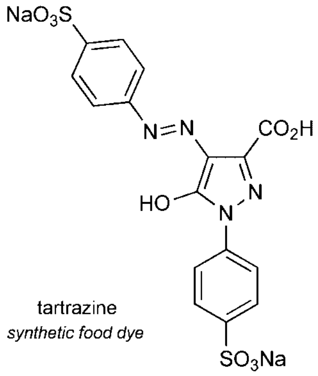
Natural and synthetic food colours

Natural food colours include the large general class of anthocyanins and flavonoids (see pages 165–166), and also substances specific to small groups of plants, such as betanin, the red substance in beetroot. This, being natural, requires no safety testing and is used as a colour additive in other foods, in preference to synthetic dyes. Many synthetic dyes permitted in foods are azo dyes, including the heterocycle tartrazine, but development of new synthetic food dyes is now much more difficult and expensive, due to the requirement for rigorous safety testing, almost like that required for new drugs.



betanin

red dye from beetroot



tartrazine

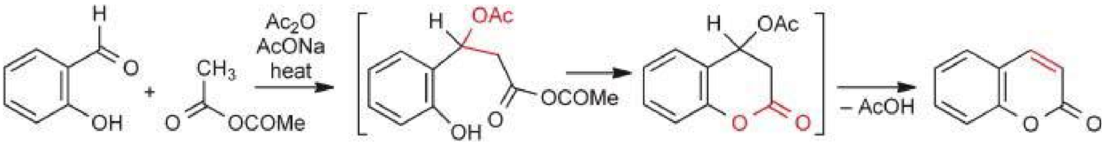
synthetic food dye

Flavours and fragrances (F&F)

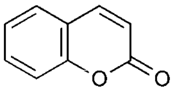
Flavours and fragrances are very closely linked commercially and suppliers generally sell components for use in both areas. There is often crossover between applications. The final products, particularly fragrances, are usually complex blends of components. Whilst most F&F constituents are aliphatic or carbocyclic, a large number of heterocycles are listed by the F&F suppliers, including many furans and pyrazines, together with thiazoles and some quinolines, indoles and thiophenes.

Flavours have applications, not only in food products, but also in cosmetics and medicinal products (e.g. toothpastes, cough syrups, lipsticks). Fragrances also have a range of uses: 'fine' perfumes and other cosmetics, and household products such as detergents, soap, cleansing agents, washing powders and air fresheners. Many of the F&F components occur naturally and the commercial materials can be natural, fully 'artificial' or 'nature identical synthetics'. The natural materials often contain trace components most of which are potent heterocyclics, which make them more 'rounded' or 'fuller'. (The natural occurrence, formation and use of some of the heterocycles (particularly pyrazines and furans), in relation to food, are discussed in the previous section.)

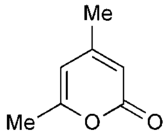
While most fragrance materials are not heterocyclic, the official birth date of the synthetic fragrance industry is held to be the development of a route to coumarin by W.H. Perkin in 1868, using a reaction that we now call the *Perkin condensation.*



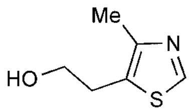
Some other significant commercial heterocyclic F&F components are also shown below. Sulfurol occurs naturally (a breakdown product of thiamine) and is used (meaty smell) in food products, and a number of its (non-natural) esters have wider applications. Even skatole and indole, which in bulk have sickly faecal aromas, are used at very low concentrations in fragrances to give jasmine or 'masculine/animalic' notes. Indolall is a mixture of citronellal and indole, which contains the bis-indolyl 'aminal' (it is also referred to as indole/hydroxycitronellal Schiff base). A number of closely related quinolines are also used, particularly *sec*-butyl derivatives, and their *iso*-propyl and *iso*-butyl analogues, which allow the fine-tuning of the basic leather/woody notes.



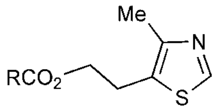
coumarin
first mass-produced perfume component
aroma: new mown hay



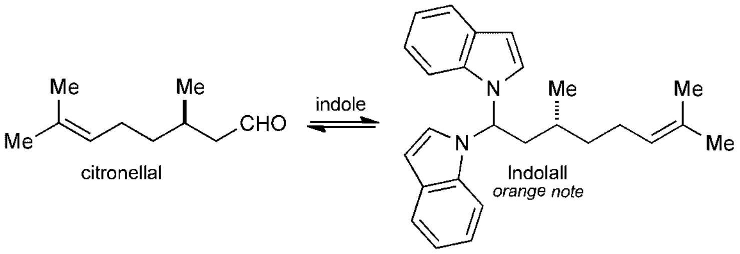
levistamel
caramel, balsamic notes



sulfurol
used in food flavours: roast/ nutty/ meaty
naturally-occurring degradation product of thiamin: in cooked meat, beer, brandy, roast peanuts

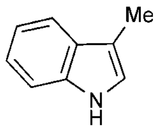


sulfurol esters
non-natural used in flavours and in some fragrances

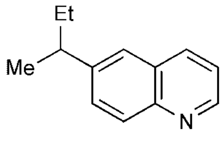


citronellal

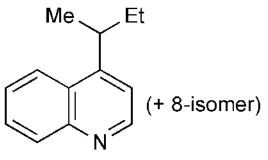
Indolall
orange note



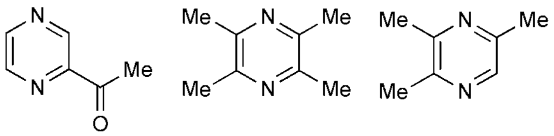
skatole
unpleasant at high concentration but at very low concentration gives a jasmine note in perfume



pyralone
leather, woody notes



'butyl quinoline secondaire'
leather, woody, earthy notes



major commercial pyrazine flavouring agents

These F&F components are regulated by government agencies, such as the Food and Drug Administration (FDA) in the USA. Safety testing is more limited and less onerous than that for new drugs, but the associated costs are high in comparison to product value. Also, these regulations are being further tightened in some parts of the world, and this represents a significant threat to the industry. Most compounds are used only at low concentrations and this fact, together with the known natural occurrence (or close analogy to naturals) of many, is considered when carrying out a risk assessment. Taking the permitted levels of consumption of flavours, and consideration of specific circumstances of use in cosmetics and household goods and so on, and the results of some genotoxicity and general toxicity tests, approved compounds are classified as G.R.A.S. (Generally Regarded As Safe).

For flavours, permitted levels (sometimes only a few ppm) of flavouring additives are set by considering the consumption of such compound types as natural components of food and setting a level for the additive that is a minor part of the total. For example, in the USA (1999) the annual consumption of pyrazines naturally contained in food was about 350 000 kg, and synthetic 2000 kg.

For fragrances, the levels are set as concentrations (usually significantly higher than food additives) in the final compositions, and are based on an estimate of how much could be absorbed by skin contact, or cause significant irritation.

F&Fs act at receptors (similarly to some drugs) and likewise show structure–activity relationships (SARs), where relatively minor structural changes (including chirality) can produce very large changes in odour, intensity or 'side effects'. The potential hazards of using close structural analogy for safety prediction are demonstrated by phototoxicity caused by a (cosmetic) mixture of coumarins where, eventually, coumarin itself was shown to be the only innocent party. The phototoxic analogues were 6- and 7-methylcoumarins and 3,4-dihydrocoumarin. (Coumarin is not allowed as a food additive as there is a potential for hepatotoxicity, although some foods contain significant quantities naturally.)

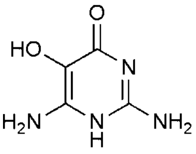
Toxins

Non-nutritional natural constituents present in food plants that do not cause any problem for the normal population can cause severe problems in susceptible sub-groups. An important example of this is favism, a serious haemolytic disease, which results from the consumption of broad (fava) beans. It is caused by divicine, which is a direct haemolytic agent in a group of people, primarily of Mediterranean origin, who have genetically determined low levels of a particular enzyme.

A much more general problem is the contamination by toxins (mycotoxins) due to fungi growing on food, which can lead to acute poisoning or longer term effects such as carcinogenesis. The oldest known example of this is ergotism, caused by a fungus that affects growing grains (particularly rye), and is incorporated into the flour during milling. The causal agent is ergotamine, a lysergic acid amide, which leads to severe vasoconstriction in the limbs, resulting in gangrene and death. The disease can be avoided by use of fungicides and careful inspection of the grain before milling.

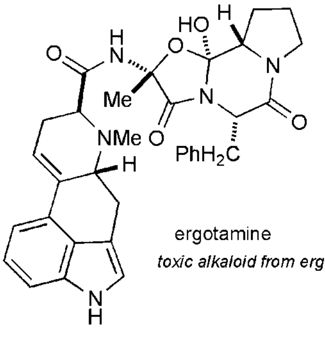
The most important mycotoxin is aflatoxin B_1 (the most toxic of the group), formed by a number of *Aspergillus* species, which affect a number of foodstuffs but most famously peanuts and derived products such as peanut butter. Growth of the fungus is favoured by warm, damp climates. Acute toxicity (severe liver damage) can occur, usually in animals, but from a human viewpoint low dose chronic ingestion is a major cause of liver cancer in the developing world.

A very different toxin, ochratoxin A, is produced by other *Aspergillus* species affecting badly stored foods, which has caused occasional outbreaks of severe kidney disease in humans and is also thought to have wider long term carcinogenic potential.



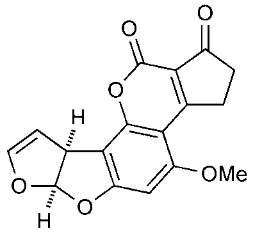
divicine

from broad beans causes favism



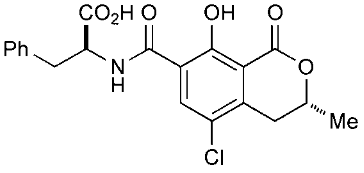
ergotamine

toxic alkaloid from ergot



aflatoxin B$_1$

fungal carcinogen



ochratoxin A

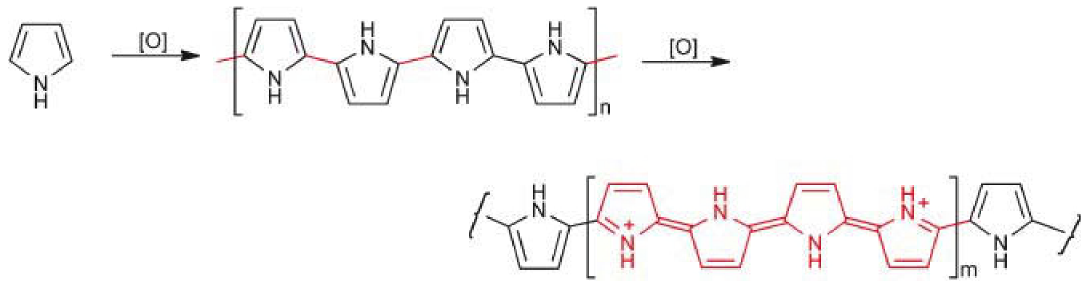
fungal toxin

Electrical and electronic

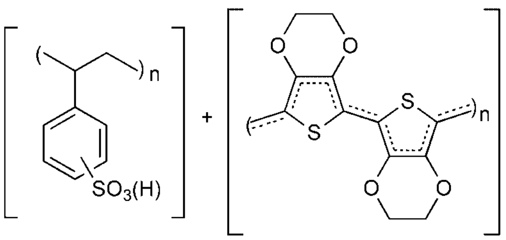
There are many possible applications for heterocycles in electronics, for example as organic conductors and semiconductors, and in electrochromic devices and Organic Light Emitting Diodes (OLEDs). The use of such organic materials offers a potential escape from limitations of supply and cost of classical materials, that is, metals. They also offer a probable major reduction of dimensions and weight. Extensive research is being carried out in this area, but large-scale applications have been progressing more slowly than expected. The promise (and expectation) is still there though.

The most useful materials are conducting polymers that consist of a cationic heterocyclic polymer or oligomer, with a counter anionic component (monomeric or polymeric). (Note: These polymers are not continuous chains, but overlapping chains, with electron transfer between chains.)

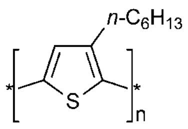
Poly(pyrrole), made via the oxidative polymerisation of pyrrole, was the first heterocyclic conducting polymer and has found applications in, for example, electronic shielding, capacitors and sensors. The initial neutral polymer is non-conducting but on further oxidation is converted partially into cation radicals or dications, with incorporation of counterions from the reaction medium – a process known as 'doping' – giving conducting materials.



The closely related poly(thiophene)s, which can be made in a much wider variety than poly(pyrrole), are currently the more prominent, and have seen significant commercialization as anti-static films, and probably as components of OLEDs. They form flexible films and can be formed by polymerisation of the monomers *in situ*, and also applied as inks. Two prominent commercial examples are Clevios™ and Plexcore™.

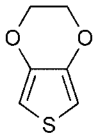


Clevios™ P



Plexcore®

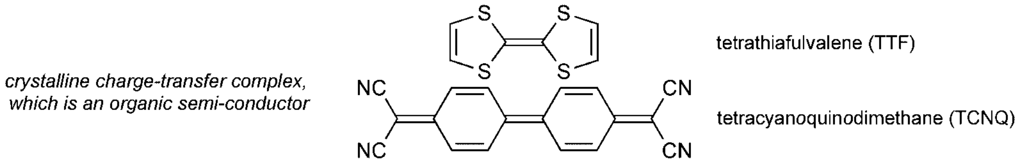
poly(thiophenes): organic conductors for use in a variety of electronic applications



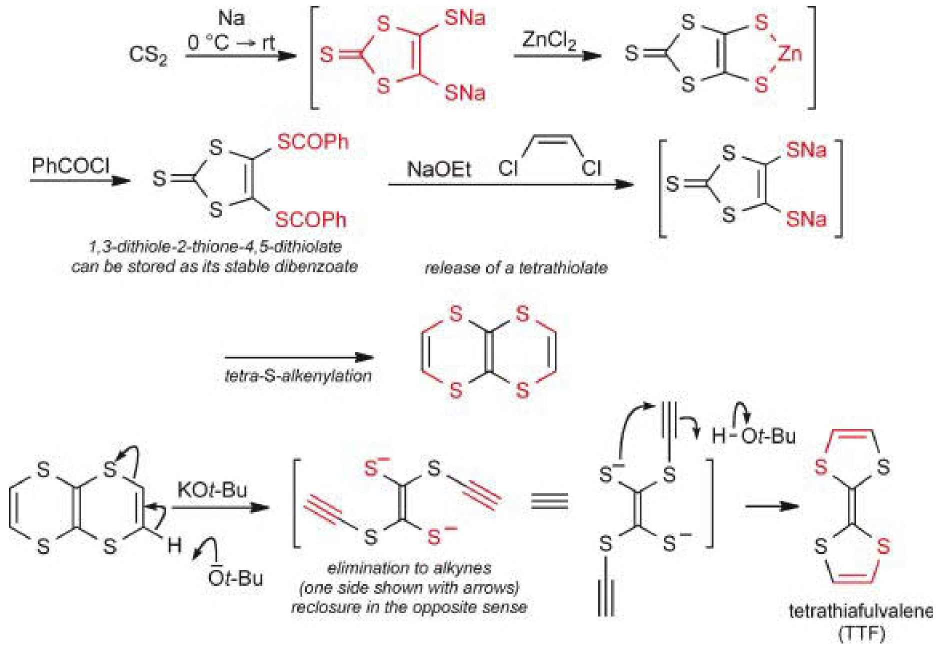
Clevios™ M V2

monomer used to generate Clevios™ P in situ

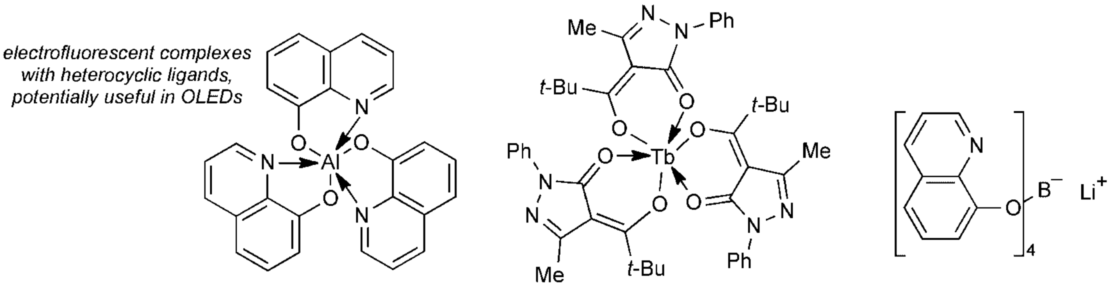
The tetrathiafulvalene (TTF)–TCNQ complex shown below, and a number of its analogues, have been used as the basis for much research into conducting organic materials, and depend on the crystal structure for alignment of the components for a charge transfer process to occur. These complexes can have directionally dependent semi-conducting properties.



Tetrathiafulvalenes can be prepared in a number of ways, for example using 1,3-dithiole-2-thione-4,5-dithiolate, itself prepared by reductive trimerisation of carbon disulfide.



A number of electrofluorescent materials, which emit light on application of an electric current, with potential for use in OLEDs, are metal complexes with heterocyclic ligands. A well-established (and cheap) ligand, 8-hydroxyquinoline, is popular but a number of purpose-designed ligands are also used.



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Items are listed alphabetically and ignoring prefix numbers, hyphens, and Greek letters [however, e.g. 'Pyridine, 2-lithio-' will be found before 'Pyridine, 3-lithio-'] . In some cases the 'correct' order of substituents is not used, in order to emphasise the important functional group, e.g. '3-lithio-1-tri-isopropylsilylindole'. To find, e.g. 4-methylpyridine see 'Pyridine, 4-methyl-'. Names containing, e.g. 'dimethyl…' and 'tribromo…' are listed under 'd' and 't' respectively. Names such as '2-Pyridone' are so listed and not as 'pyridin-2-one'.

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