Heterocyclic Chemistry at a Glance
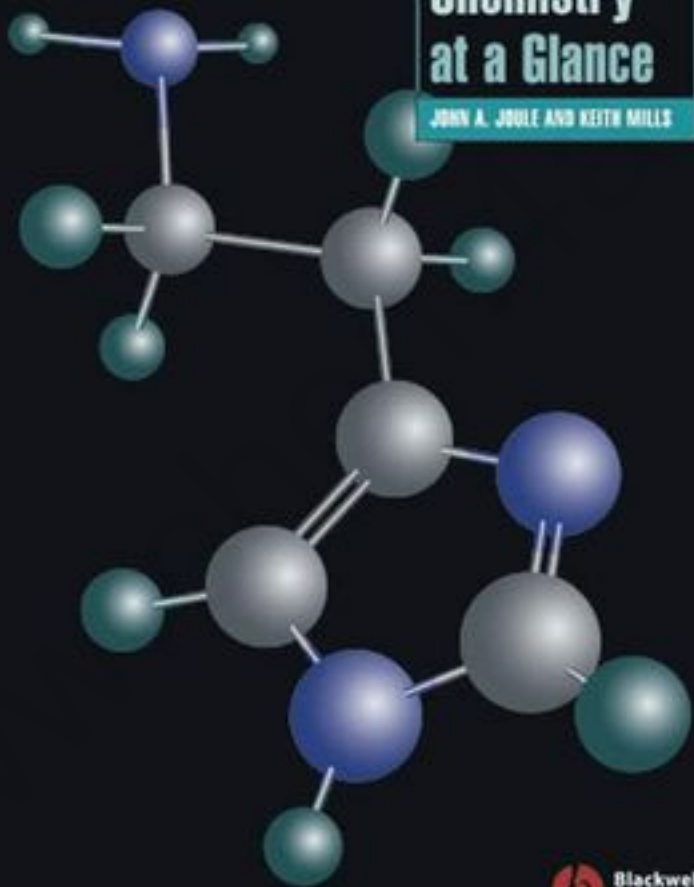
JOHN A. JOULE AND KEITH MILLS

Heterocyclic Chemistry at a Glance

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and

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Contents

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*)
Ar	general designation for a benzenoid aromatic group
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
Bt	benzotriazol-1-yl (structure page 95)
c	cyclo as in *c*-C_6H_{11} = cyclohexyl
c.	concentrated, as in concentrated sulfuric acid: c. H_2SO_4
cat	catalytic – 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	CO_2CH_2Ph – *N*-protecting group removed by hydrogenolysis
Cy	cyclohexyl (*c*-C_6H_{11})
dba	*trans, trans*-dibenzylideneacetone ($PhCH{=}CHCOCH{=}CHPh$)
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone – oxidant, often used for dehydrogenation
DME	1,2-dimethoxyethane ($MeO(CH_2)_2OMe$) – ethereal solvent
DMF	dimethylformamide ($Me_2NCH{=}O$) – dipolar aprotic solvent
dppb	1,4-bis(diphenylphosphino)butane ($Ph_2P(CH_2)_4PPh_2$) – ligand for palladium(0)
dppf	1,1′-bis(diphenylphosphino)ferrocene – ligand for palladium(0)
dppp	1,3-bis(diphenylphosphino)propane ($Ph_2P(CH_2)_3PPh_2$) – ligand for palladium(0)
El^+	general designation for a positively charged electrophile
f.	fuming, as in fuming nitric acid: f. HNO_3
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 [$LiN(C(Me)_2(CH_2)_3C(Me)_2)$] – very hindered strong base
Me	methyl (CH_3)
Ms	mesyl [$MeSO_2$] – protecting group for azole nitrogen
NBS	*N*-bromosuccinimide – brominating agent
NCS	*N*-chlorosuccinimide – chlorinating agent
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)
2-py; 3-py; 4-py	pyridin-2-yl; pyridin-3-yl; pyridin-4-yl
R	general designation for an alkyl group
o-Tol	*ortho*-tolyl (2-methylphenyl)
p-Tol	*para*-tolyl (4-methylphenyl)
rt	room temperature (*ca.* 20 °C)
SEM	trimethylsilylethoxymethyl [$Me_3Si(CH_2)_2OCH_2$] – protecting group; removed with fluoride
syn	on the same side (antonym of *anti*)
TBAF	tetrabutylammonium fluoride (*n*-Bu_4NF) – reagent for deprotection of *O*- or *N*-silyl groups
TBDMS	*t*-butyldimethylsilyl (*t*-$Bu(Me)_2Si$)
t-Bu	tertiary butyl (($CH_3)_3C$)
Tf	trifluoromethylsulfonyl (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
TIPS	tri-isopropylsilyl ($Si(i\text{-}Pr)_3$) – protecting group for nitrogen or oxygen
Tosmic	tosylmethyl isocyanide [$TolSO_2CH_2N{\equiv}C$]
Ts	tosyl [*p*-$TolSO_2$] – Ts is a good protecting group for azole nitrogen and Ts^- can be a leaving group
Tr	trityl (triphenylmethyl) (Ph_3C) – good *N*-protecting group; removed with acid

Introduction

The material in this book comprises an introduction to, and summary of, all 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 can serve either as a revision summary for students who have studied the subject in depth, perhaps at a post-graduate level, or as a starting point for further, more extensive study of the subject.

The book is mainly concerned with aromatic heterocycles though we also include a short discussion of saturated heterocycles. We deal with the characteristic reactivities of all the most important hetero-aromatic systems and the principal routes for their ring synthesis from non-heterocyclic precursors. Thus the chemistry of pyridines, quinolines, isoquinolines, pyridazines, pyrimidines, pyrazines, pyrylium and benzopyrylium cations, pyrroles, thiophenes, furans, indoles, imidazoles, oxazoles, thiazoles, pyrazoles, isoxazoles, isothiazoles, purines, heterocycles with more than two hetero-atoms in the ring (for example triazoles and triazines) and heterocycles in which a hetero-atoms is located at a ring junction (for example pyrrolizines and indolizines) are covered.

The book assumes a basic knowledge of organic chemistry such as one would expect of a student at the 2nd year level of a UK bachelors degree in chemistry and thus would be suitable for 2nd/3rd/4th year level organic chemistry courses in UK universities. It is important to realise that much modern inorganic chemistry relies on maintaining metals in various (often unusual) oxidation states by surrounding them with ligands which are very often heterocyclic, so choosing or designing appropriate heterocyclic ligands and then being able to synthesise them is then an integral prerequisite of modern inorganic chemistry too. However, 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, medicinal chemistry, and drug design and synthesis, is emphasised in the final two chapters of the book, 'Heterocycles in Biochemistry' and 'Heterocycles in Medicine'. Even in what one may describe as 'materials science', the role and importance of heterocyclic compounds cannot be underestimated – heterocycles are intrinsic components in various electroactive devices, in conducting polymers, in electrochromic molecules. It is a fair wager that the first 'organic computer' will depend for its operation on heterocyclic components!

It is not the purpose of this book to provide guidance for the conduct of practical work: for such experimental details the reader must consult the original literature. Many references to suitable key papers can be found in our fuller exposition – *Heterocyclic Chemistry* (Joule and Mills, 2000, published by Blackwell Science). Accordingly, in the reaction schemes in *Heterocyclic Chemistry at a Glance*, we have simply shown that a particular compound will react with a particular reagent, and we have omitted practical details like solvent, reaction time, yields and most other details, except in so far as these make a didactical point, so that the reader can concentrate on the chemistry in question. All the examples in this book are taken from the literature and the vast majority proceed in good yields. 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) or at very low temperature (dry ice temperatures), the words 'heat' or 'cold' are used on the reaction arrow.

Heterocyclic Nomenclature

A selection of the structures, names and standard numbering of the more common heteroaromatic systems and some common non-aromatic heterocycles is shown below and opposite. The aromatic heterocycles have been 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 that 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, thiophene, originally trivial, are now the standard, systematic 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, a simple example will serve to illustrate the principle. 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, i.e. 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, i.e. of the C-7–H of indole by N.

Naming a system in which two heterocycles are fused together.

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, and 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 (only) for quinoline.

pyrrolidine   piperidine   morpholine   tetrahydrofuran   dioxane   2*H*-pyran   tetrahydropyran
THF   [1,4-dioxane]

Some non-aromatic heterocycles.

azirine   oxirane   aziridine   thiirane
[2*H*-azirine]   (ethylene oxide)   (ethylene imine)   (ethylene sulfide)

azete   azetidine   2*H*-oxete   oxetane   2*H*-thiete   thietane

Small-ring heterocycles.

pyrrole

furan

thiophene

pyrazole

isoxazole

isothiazole

imidazole

oxazole

thiazole

indole

benzothiophene
[benzo[*b*]thiophene]

benzofuran
[benzo[*b*]furan]

isoindole

benzo[*c*]thiophene

isobenzofuran

1*H*-benzimidazole

benzoxazole

benzothiazole

1*H*-indazole

1,2-benzisoxazole

1,2-benzisothiazole

2,1-benzisothiazole

2,1-benzisoxazole
(anthranil)

purine
[9*H*-purine]

Five-membered aromatic heterocycles.

pyridine

quinoline

isoquinoline

pyrylium cation

pyridazine

pyrimidine

pyrazine

cinnoline

phthalazine

quinazoline

quinoxaline

Six-membered aromatic heterocycles.

3

Structures of Heteroaromatic Compounds

2.1 Structure of Benzene and Typical Reactivity

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, etc., π-electrons, with 6-π-electron monocyclic compounds being by far the commonest. Thus, benzene has a cyclic arrangement of 6 π-electrons comprising a conjugated molecular orbital system which 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. As we shall remind ourselves later, *electrophilic substitution* is *the* prototypical reaction of benzene.
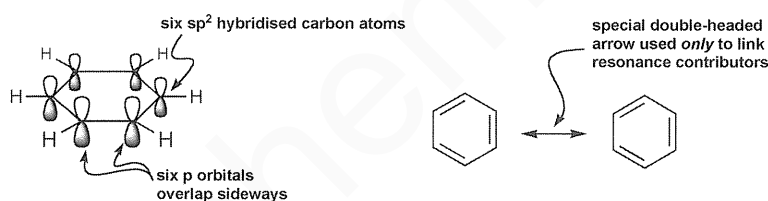
Structure of benzene; mesomeric structures (resonance contributors).

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 that 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 mesomeric structures are particularly useful in representing the polarisation inherent in many heterocycles and especially, by representing the delocalisation of charge in reaction intermediates, in helping to understand the heteroaromatic reactivity and regioselectivity.
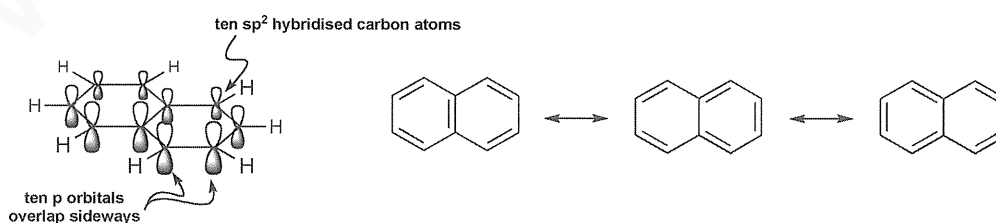
Structure of naphthalene; mesomeric structures (resonance contributors).

Naphthalene, with 10 carbons and 10 orthogonal p orbitals, has an aromatic system with 10 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.

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 resonance stabilised, cation, and 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 which 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. Ring substituents that release electrons favour electrophilic attack and substituents that withdraw electrons slow down such processes.

In the remaining sections, 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.
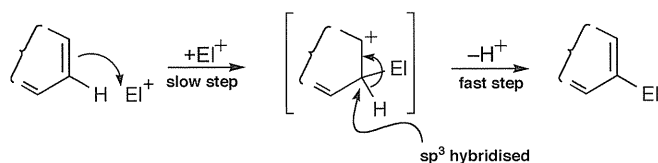
General two-step mechanism of aromatic electrophilic substitution of hydrogen.

Ipso-displacement of groups other than hydrogen can also occur – in the present context the most important examples are displacements of trialkylsilicon 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 ($X^+ = H^+$) when they have served their purpose.

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 resonance stabilised, anion, and 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; i.e. 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 which is *ipso*-displaced must be capable of departing, carrying a negative charge – normally halide.
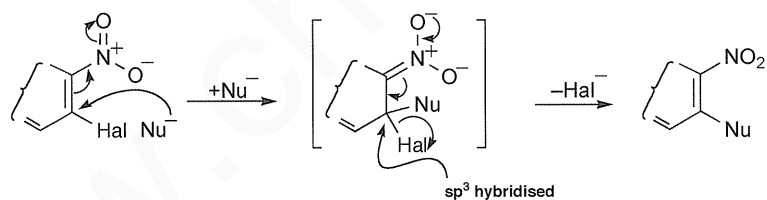
General two-step mechanism of aromatic nucleophilic substitution of halide.

2.2 Structures of Six-Membered Aromatic Heterocycles

2.2.1 Pyridines and pyridiniums

The structure of pyridine is completely analogous to that of benzene, being related by replacement of CH by N. The key differences are (i) the departure from perfectly regular hexagonal geometry caused by the presence of the 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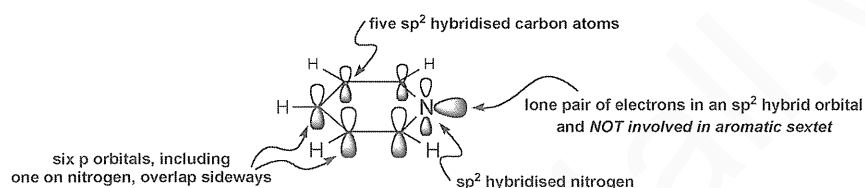 the aromatic sextet, which is responsible for the basic and nucleophilic reactivities of pyridine, as we shall discuss in Section 4.

Structure of pyridine – orbitals.

The electronegative nitrogen causes inductive polarisation *and, additionally,* stabilises polarised mesomeric structures in which nitrogen is negatively charged, which, 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}.
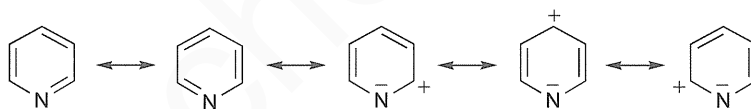
Structure of pyridine – resonance contributors include neutral and polarised forms.

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 referred to as 'electron-poor', or sometimes 'π-deficient'.

Dipole moments of pyridine and 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 1H-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 intact, 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.
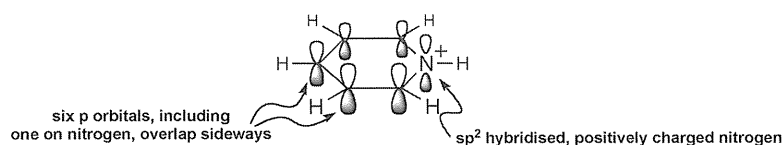
Structure of 1*H*-pyridinium cation – orbitals.
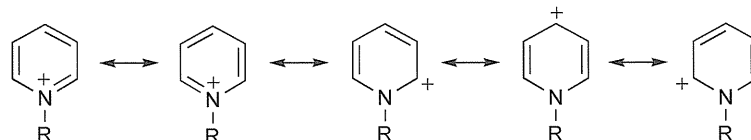
Structure of a pyridinium cation – resonance contributors.

2.2.2 Quinolines and isoquinolines

Quinoline and isoquinoline are related to pyridine exactly as is naphthalene related to benzene; i.e. they are $10\text{-}\pi$-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.
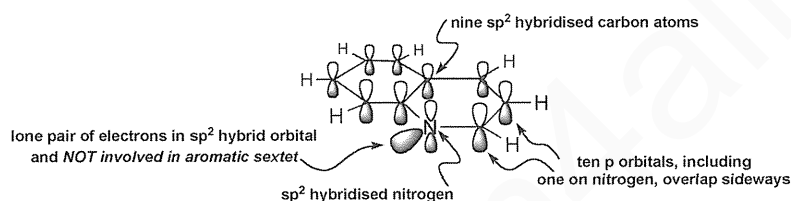
Structure of quinoline – orbitals.
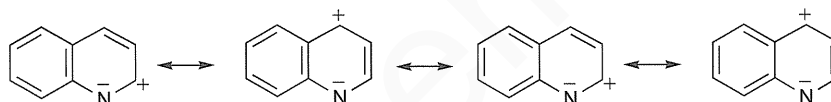
Structure of quinoline – polarised resonance contributors.

2.2.3 Diazines

The presence of an additional electron-withdrawing imine (C=N) unit in the six-membered ring of the diazines has a major impact on the structure and chemical reactivity – the resonance contributors for pyrimidine illustrate the polarisation that substantially increases the partial positive charges at the α-carbons.
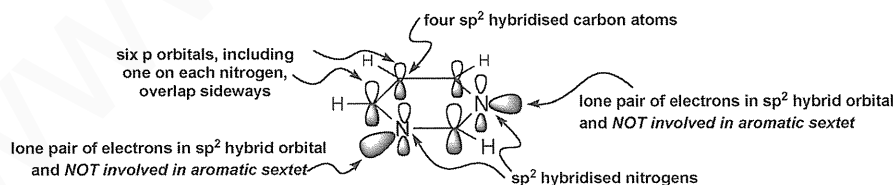
Structure of pyrimidine – orbitals.
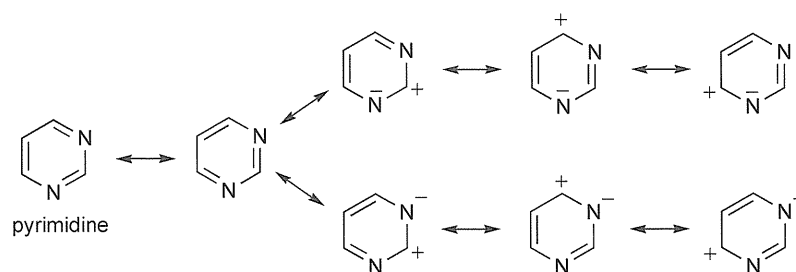
Structure of pyrimidine – resonance contributors.

2.3 Structures of Five-Membered Aromatic Heterocycles

2.3.1 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 6-π-electron aromatic system. Five equivalent contributing structures show each carbon atom to be equivalent and hence to carry one fifth of the negative charge.
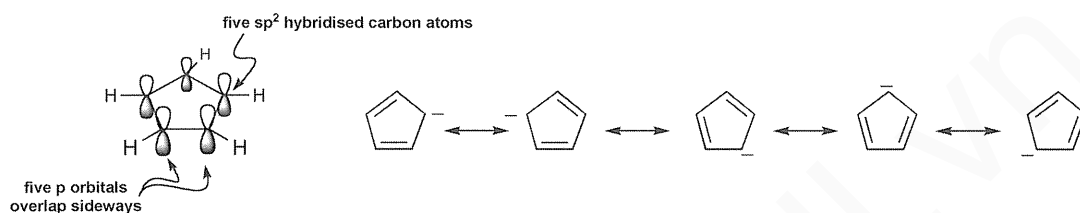
Structure of cyclopentadienyl anion – resonance contributors.

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

Structure of pyrrole – orbitals.

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*.
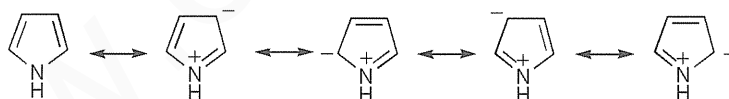
Structure of pyrrole – resonance contributors show electron movement *away* from nitrogen.

Resonance in pyrrole then 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 mesom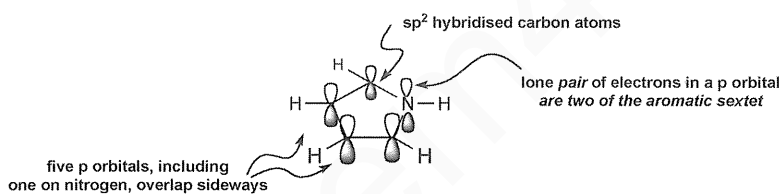eric (away from nitrogen), of which the latter is the more significant. It is because of this net electronic drift away from nitrogen and towards the ring carbons that five-membered heterocycles of the pyrrole type are referred to as 'electron-rich', or sometimes 'π-excessive'. The polarised contributors imply a *permanent polarisation of the π-electron system* which 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}.
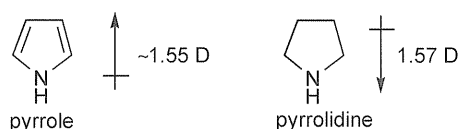
Dipole moments of pyrrole and pyrrolidine.

Other five-membered aromatic heterocycles have exactly comparable structures to that of pyrrole: thiophene (resonance energy $\sim$122 kJ mol^{-1}) is the 'most aromatic' of the trio and furan ($\sim$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 kinds 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.
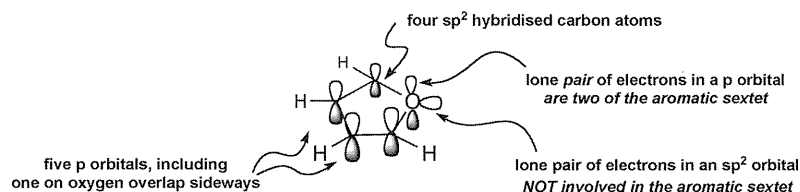
Structure of furan – orbitals.

2.3.2 Indoles

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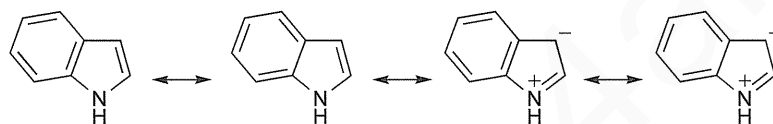
Structure of indole – resonance contributors.

2.3.3 Azoles

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.
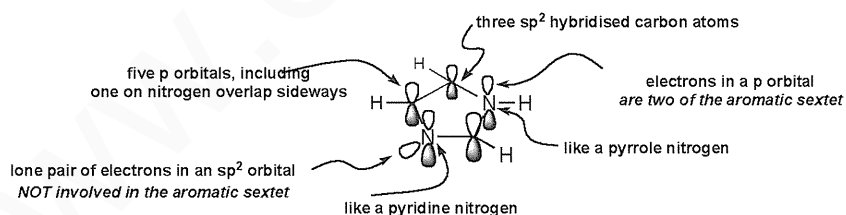
Structure of imidazole – orbitals.
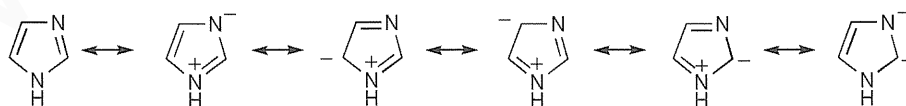
Structure of imidazole – resonance contributors.

The two nitrogen atoms are completely different – one of them is like the nitrogen in pyrrole, and 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 reactivity patterns that turn up again and again in heterocyclic chemistry and we summarise and explain these in detail in this section, so that they do not have to be discussed on each separate occurrence in the rest of the book. In heterocyclic 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 Pd(0)-catalysis is so important in heterocyclic chemistry that we devote the whole of Section 16 to that topic.

3.1 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, 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:

$$AH \; + \; H_2O \; \rightleftharpoons \; A^- \; + \; H_3O^+$$

$$K_a \; = \; \frac{[A^-][H_3O^+]}{[AH]} \qquad pK_a \; = \; -\log[K_a]$$
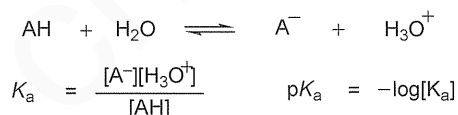
The corresponding equation for a base involves the *dissociation of the conjugate acid* of the base, and so we use pK_{aH}.

$$BH^+ \; + \; H_2O \; \rightleftharpoons \; B \; + \; H_3O^+$$

3.2 Important Electrophilic Substitutions

3.2.1   The Vilsmeier reaction – formylation

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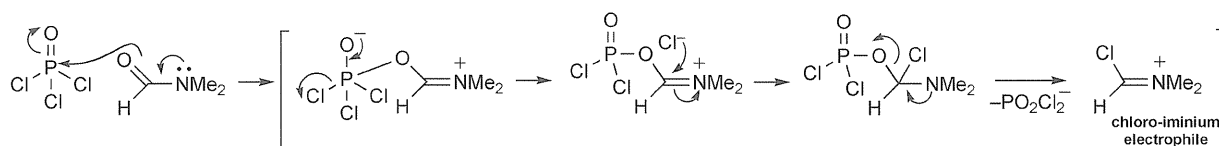
Formation of a Vilsmeier electrophile from dimethylformamide and phosphoryl chloride (phosphorus oxychloride).

Subsequently, the reaction mixture is exposed to aqueous alkali, which brings about a hydrolysis, revealing the aldehyde.
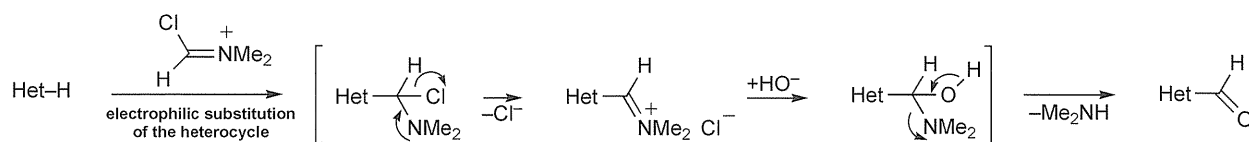
Reaction of the Vilsmeier electrophile with an electron-rich heterocycle, giving an aldehyde after base treatment.

3.2.2 The Mannich reaction – dialkylaminomethylation

In the Mannich reaction, a nucleophilic molecule (five-membered heterocycles in this book) is dialkylaminomethylated – most often dimethylaminomethylated – a C—H is converted, e.g., into C—CH$_2$NMe$_2$. The reactive electrophilic species, e.g. [CH$_2$=NMe$_2$]$^+$, is most often generated *in situ* by the interaction of an aldehyde, a secondary amine and an organic acid – 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, can be used in a dry organic solvent, and is highly reactive and will react with substrates that are resistant to the standard aqueous conditions.
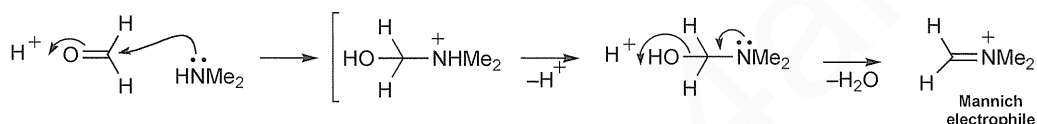
Formation of a Mannich electrophile from dimethylamine, formaldehyde and acetic acid.
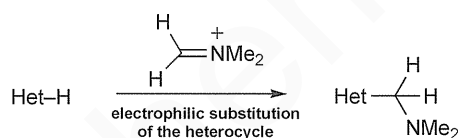
Reaction of the Mannich electrophile with an electron-rich heterocycle, giving a dimethylaminomethylated product.

3.3 Nucleophilic Substitution of Aromatic Molecules

In benzene chemistry (*cf.* page 5) nucleophilic substitution of good leaving groups only occurs when an *ortho* or *para* strong electron-withdrawing group allows the first, nucleophilic addition to occur. In the context of heterocyclic reactivity, the group which both encourages addition and accepts responsibility for the negative charge in the intermediate, is normally a ring imine (C=N). Halide is the group normally *ipso* displaced, however even hydrogen can be displaced by nucleophiles in some cases – the formal loss of hydride (H$^-$) in the rearomatising second step is then required.
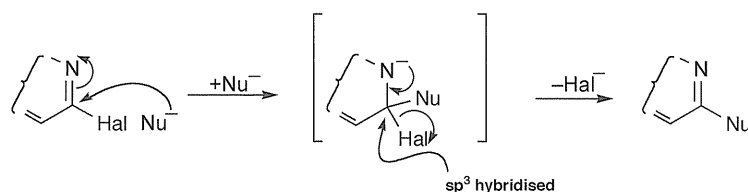
General two-step mechanism of heteroaromatic nucleophilic substitution of halide.

3.4 C-Metallated Heterocycles

3.4.1 As nucleophiles

Organolithium intermediates are frequently used in heterocyclic chemistry. They are nucleophiles. For example, reaction with ketones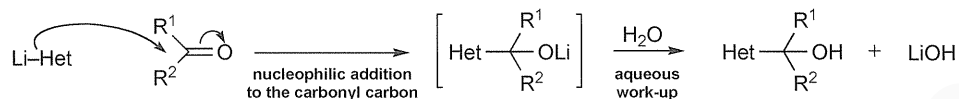 and aldehydes gives alcohols following 'aqueous work-up'. In the remaining sections, chemical schemes that include reactions of lithium derivatives do not explicitly show the intermediate, or the addition of water, but the requirement for an 'aqueous work-up' must always be kept in mind.

Reaction of an organolithium nucleophile with a ketone or aldehyde, giving an alcohol.

Perhaps less familiar, but very useful, is the reaction of organolithium nucleophiles with DMF or with disulfides (RS—SR). In the first case, an aldehyde is the product; in the second case a sulfide is the product. 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.
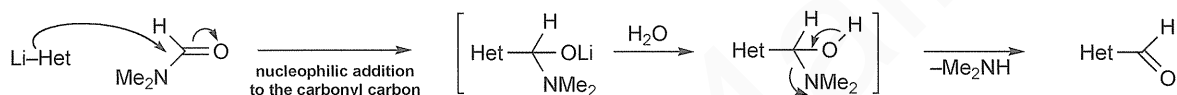
Reaction of an organolithium nucleophile with dimethylformamide, giving an aldehyde.

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.

Reaction of an organolithium nucleophile with a disulfide, giving a sulfide.

3.4.2 Preparation of heteroaryllithiums

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 diisopropylamide ($LiN(i\text{-}Pr)_2$) (LDA), for some heterocycles directly at favoured positions but also, and importantly, via directed *ortho*-metallation (DoM).

Note: Although alkyllithiums can act in both types of process, LDA is simply a strong base – it will *not* take part in metal/halogen exchange processes.
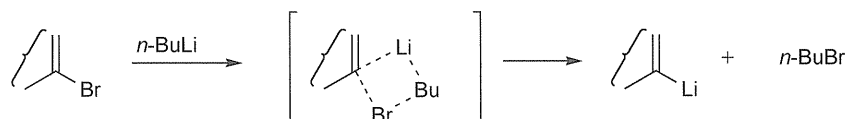
Generation of an organolithium nucleophile via halogen/metal exchange.
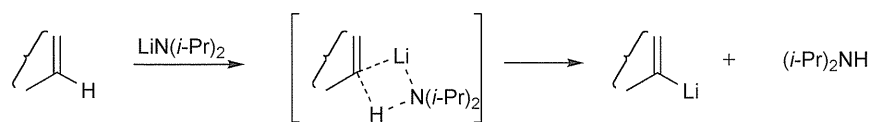
Generation of an organolithium nucleophile by deprotonation using lithium di-isopropylamide.

In directed *ortho* metallation, a substituent on the heteroaromatic ring activates an *ortho* proton, which is not otherwise 'acidified', for abstracti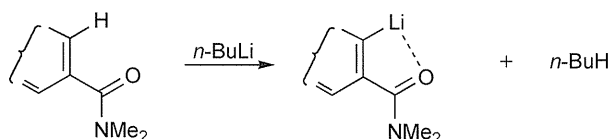on by a strong base. This is in part due to coordination of the base to the directing group, bringing it into close proximity to the proton. Many types of substituents will achieve this effect – the most important are $CONR_2$, $CONHR$, $NHCO_2R$, RO and Hal.

Metallation of an aromatic compound *ortho* assisted by a tertiary amide (DoM).

3.4.3 Preparation of heteroaryl Grignard reagents

Grignard reagents can be easily prepared from a halide and isopropylmagnesium chloride; this is especially important for electron-deficient systems – pyridines, etc. The preparation of heteroaromatic Grignard reagents using the halide and magnesium metal is usually difficult. Grignard reagents have some advantages over the lithium nucleophiles: they can often be formed and used at room temperature (formation and reactions of heteroaromatic lithiums usually need very low temperatures) and are more tolerant of functional groups.
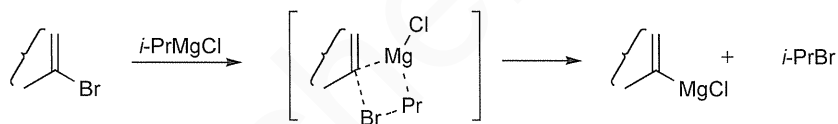
Generation of heteroaromatic Grignard nucleophiles by halogen/metal exchange.

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3.5 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, which, in turn, can tautomerise to form an enamine. Further, the reverse sequence can also occur easily – 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.
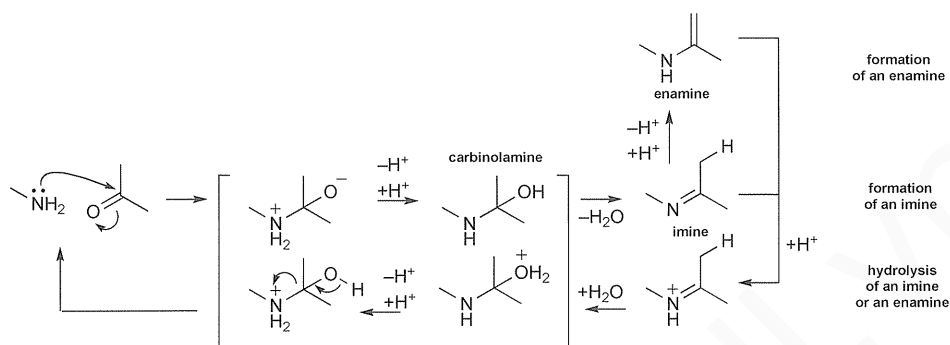
**Formation and hydrolysis of an imine or an enamine.**

3.6 Common Synthetic Equivalents of Carbonyl Compounds in Ring Synthesis

Frequently, 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. 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 is an the equivalent of but-2-ene-1,4-dial.
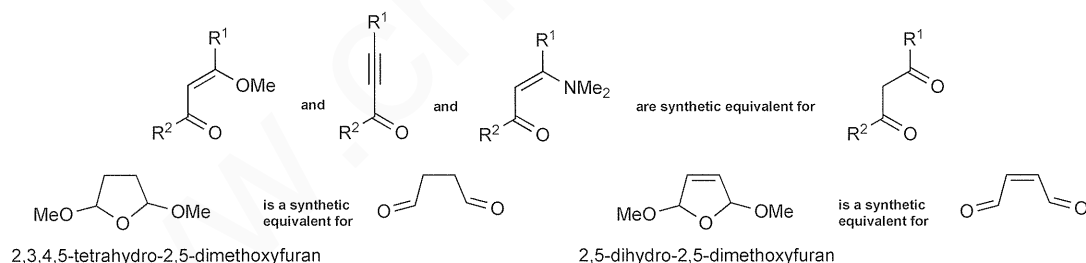
Synthetic equivalents; often referred to as 'synthons for'.

Acidified methylenes (CH_2 α to a carbonyl, for example) react with hot DMFDMA to produce dimethylaminomethylene-derivatives (enamines), i.e. to introduce a one-carbon unit at the oxidation level of an aldehyde and thus useful synthetic equivalents. The hot reagent is in equilibrium with MeO^- (which removes one of the acidified protons) and $[Me_2N{=}CHOMe]^+$ which reacts with the anion generated.
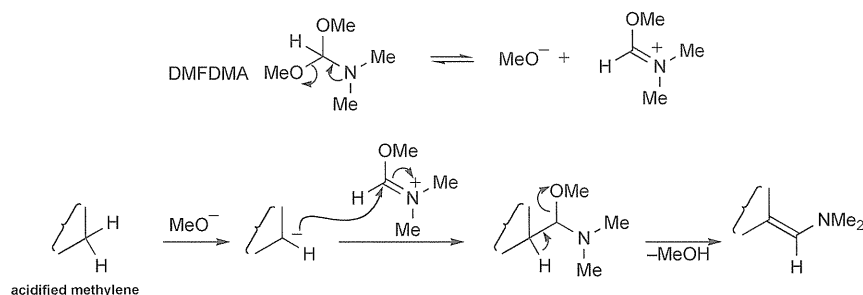
**The reaction of DMFDMA with acidified methylene groups.**

3.7 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 alkyne), to generate a six-membered ring containing one (or two) double bond(s) – 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 in essence and an example.

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-dienes 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).
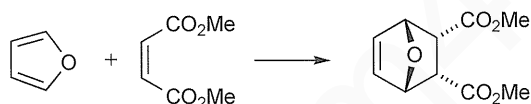

A typical Diels–Alder cycloaddition with furan.
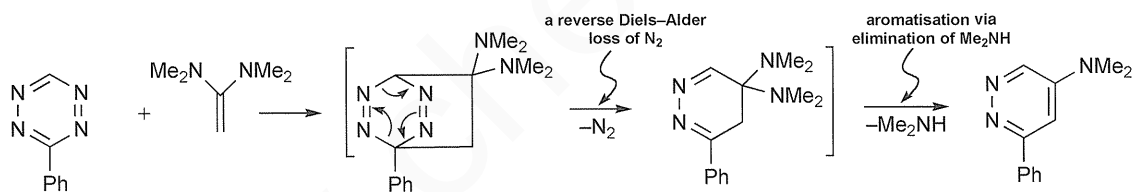
A typical inverse-electron-demand aza-Diels–Alder cycloaddition: 1,2,3,4-tetrazine and an enamine.

There is another category of cycloadditions important for heterocyclic chemistry, again involving redistribution of six electrons – dipolar cycloadditions or [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 being ring syntheses of a 4,5-dihydro-1,2,3-triazole and of a mixture of isoxazoles.
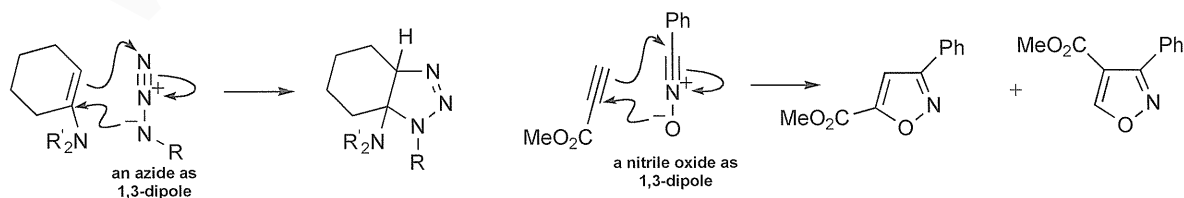

Two ring syntheses involving 1,3-dipolar cycloadditions.

Pyridines

4.1 Pyridines and Electrophiles – Addition to N and Substitution at C

4.1.1 Electrophilic addition to nitrogen

With simple pyridines, all electrophiles react, at least initially, by addition to the nitrogen; i.e. 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}s 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, e.g. hydrochloric acid; however, salts with weaker acids, such as acetic acid, readily dissociate to re-form the pyridine and the acid.
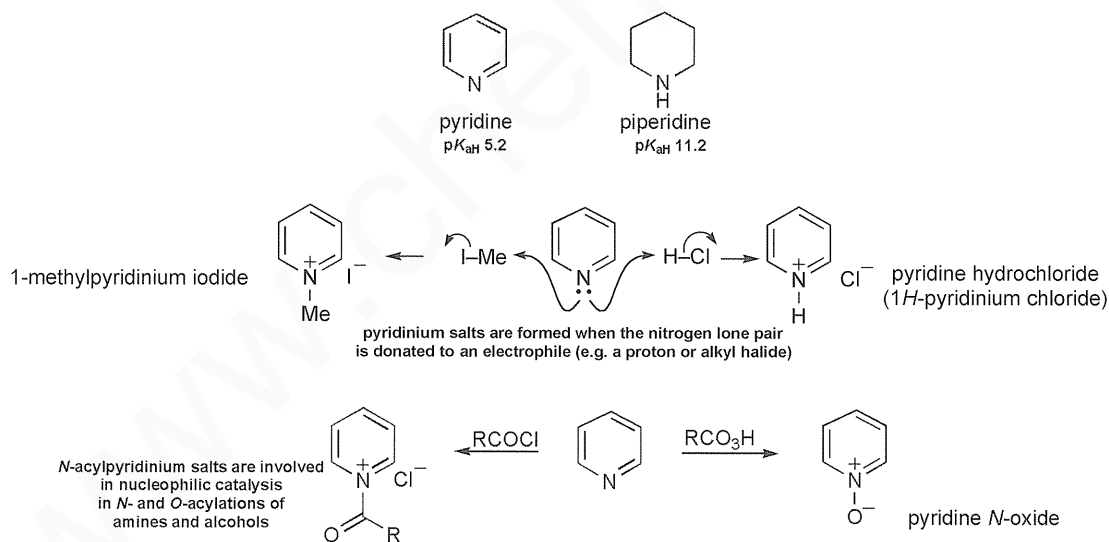

Addition of electrophiles to pyridine nitrogen.

Alkyl halides react irreversibly with pyridines to give quaternary ammonium pyridinium salts; both bromine and sulfur trioxide 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, which are the actual electrophilic agents when pyridine is used as a nucleophilic catalyst in acylations/sulfonylations of alcohols and amines. Pyridines react with peracids to generate N-oxides.
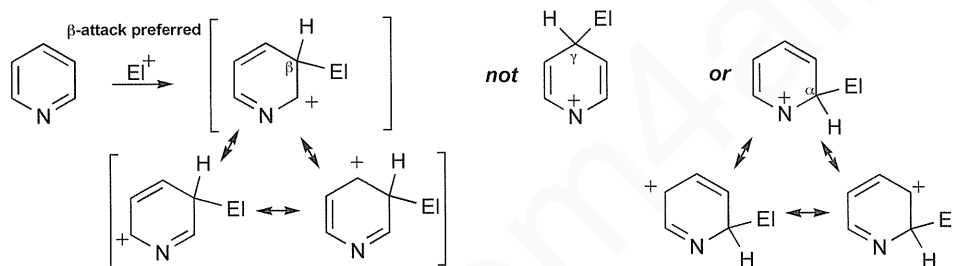
4.1.2 Electrophilic substitution at carbon

The electronic structure of pyridine (page 6) involves mesomeric transfer of electron density from C-2(6) and C-4 to the nitrogen, and this, combined with a general inductive withdrawal, 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 electrophilic attack at carbon is suppressed even more. When electrophilic substitutions 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 outrageously high temperature and the vigorous conditions necessary to produce 3-bromopyridine illustrate this well [a practical synthesis of 3-nitropyridines is described on page 19].
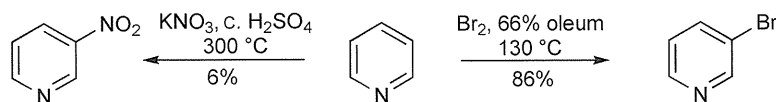
Strong conditions required to achieve any β-electrophilic substitution.

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.


Positional selectivity in electrophilic C-substitution of pyridines rationalised by consideration of possible intermediates.

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. AlCl₃), which totally resist electrophilic C-substitution.

4.1.3 Electrophilic substitution in activated pyridines

The presence of activating (electron-releasing) substituents such as amino and hydroxyl (or their tautomeric pyridones – see pages 20 and 22) allows standard electrophilic substitutions in the ring to be carried out under relatively mild conditions. The usual *ortho/para*-directing effects of these substituents operate so that chlorination of 1-methyl-2-pyridone proceeds at the available *ortho* and *para* positions. It is a curious fact – but with little theoretical rationale – that electrophilic substitutions in 3-substituted pyridines generally occur at C-2 rather than C-4/C-6 as exemplified by the Mannich substitution of 3-hydroxypyridine.
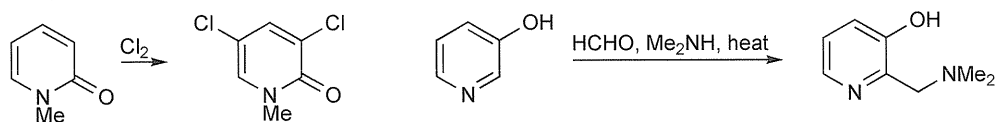

Electrophilic substitutions of a 2-pyridone and of 3-hydroxypyridine.
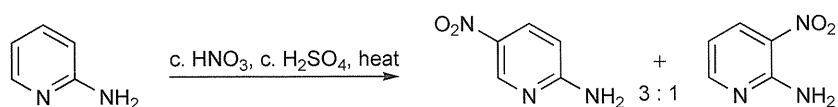
Nitration of 2-aminopyridine – *ortho* and *para* to the activating substituent.

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4.2 Pyridines and Nucleophiles

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.
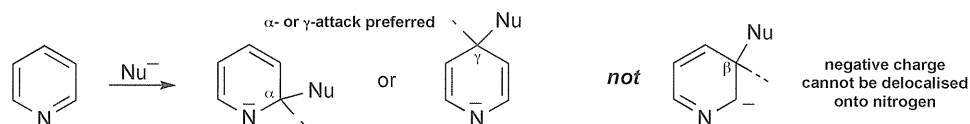

Positional selectivity in nucleophilic addition to pyridines rationalised by consideration of possible intermediates.

4.2.1 Substitution of hydrogen

Simple pyridines react with strong nucleophiles such as sodium amide or alkyl- or aryllithiums with elimination of hydrogen in the former case and lithium hydride in the latter, resulting in the formation of 2-amino- or 2-alkyl(aryl)pyridines. These reactions 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.
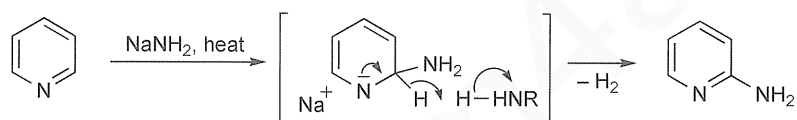

Nucleophilic 2-amination of pyridine.
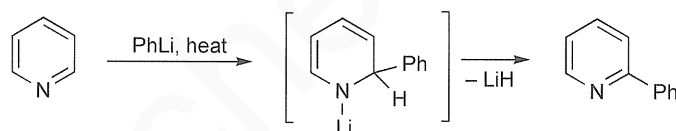
Nucleophilic 2-arylation of pyridine.

4.2.2 Displacement of leaving groups

Nucleophilic displacement of leaving groups such as halide from either α- or γ-positions occurs under quite mild conditions and proceeds via a two-step mechanism – addition–elimination – firstly addition of the nucleophile to the carbon bearing the halogen, followed by elimination of halide producing the final product. 4-Halopyridines are more reactive than 2-halopyridines in these nucleophilic displacement reactions.
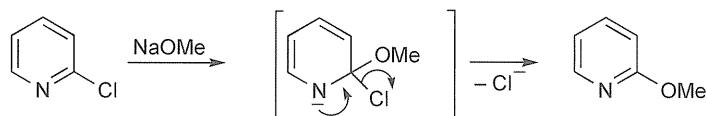
Nucleophilic displacement of an α-halogen – two-step addition–elimination sequence.
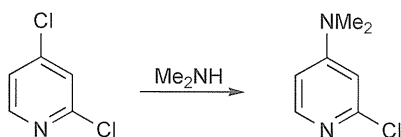
A C-4 halide is more reactive than a C-2 halide in nucleophilic substitution.

A very important distinction from nucleophilic displacements of saturated alkyl halides must be made. In pyridines (and related systems such as diazines; Section 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, they are still somewhat more reactive than in corresponding carbocyclic (benzene) systems, due to the inductive effect of the nitrogen.

Fluoride, but not bromide, is easily displaced by aryllithium nucleophiles. However, 'soft' anions, such as enolates, react readily with bromides.

**Fluoride is a very good leaving group; various types of carbanion can be used as nucleophiles.**

4.2.3   Addition to pyridinium salts

Due to the full positive charge on nitrogen, N^+-alkyl- and N^+-acylpyridinium salts are *much* more reactive to nucleophiles than simple pyridines, but 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. These salts, especially N-CO$_2$R salts, have become very important synthetic intermediates, which are utilised by reaction with a wide variety of nucleophiles, the adducts thus formed then being subjected to further transformations. The α/γ-selectivity varies with the nucleophile and can also be controlled by the use of removable blocking groups.
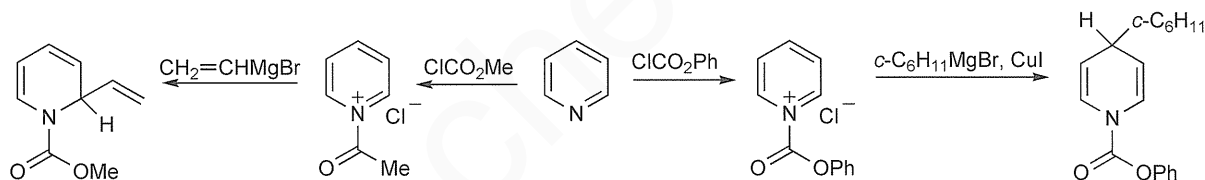
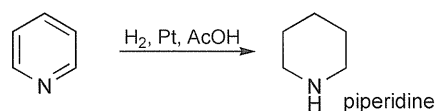**Nucleophilic addition to *N*-acylpyridinium salts.**

A dihydropyridine is involved as a non-isolated intermediate in the best practical method for the synthesis of 3-nitropyridines, which involves reaction of the pyridine with dinitrogen pentoxide and then with hydrogensulfite. An initial formation of an N^+-nitro pyridinium salt is followed by α-addition of hydrogensulfite to give a dihydropyridine, in which the nitro group migrates from nitrogen to carbon, with loss of sulfurous acid completing the overall substitution.
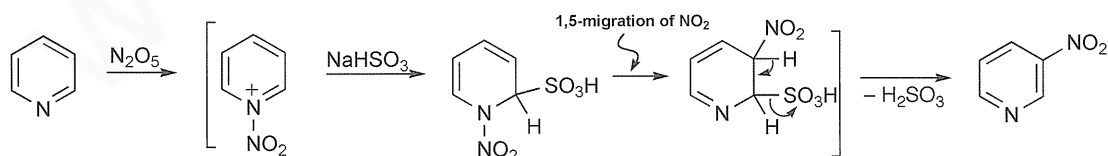
**A practical β-nitration of pyridine.**

4.3 Oxidation and Reduction of Pyridines

The pyridine ring is easily reduced, for example over a platinum catalyst in acidic solution. It is certainly the protonated pyridine which is reduced, and thus N^+-alkyl pyridinium salts are also easily reduced, with hydrogen and a catalyst or by hydride reducing agents.


Reduction of pyridine.

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 equilibrium concentration of an adduct formed by nucleophilic addition of hydroxide is trapped by the oxidant.
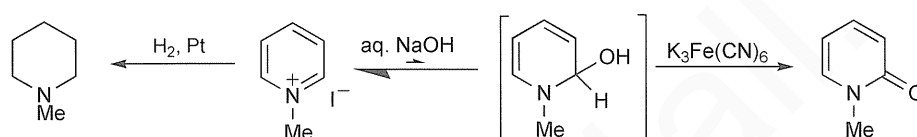
Reduction and oxidation of pyridinium salts.

# 4.4 Pyridines with 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 and can be deprotonated under mild conditions to give anions that are alkylated mainly on nitrogen. An important reaction of both α- and γ-pyridones, not shown at all by aromatic phenols, is their ready conversion into halopyridines by reaction with phosphorus halides. The process proceeds because the amide-like carbonyl oxygen interacts as a nucleophilic centre, with the phosphorus halide generating a pyridinium salt to which nucleophilic halide adds, followed by 1,2-elimination of dichlorophosphoric acid – the standard addition–elimination sequence (see page 18).
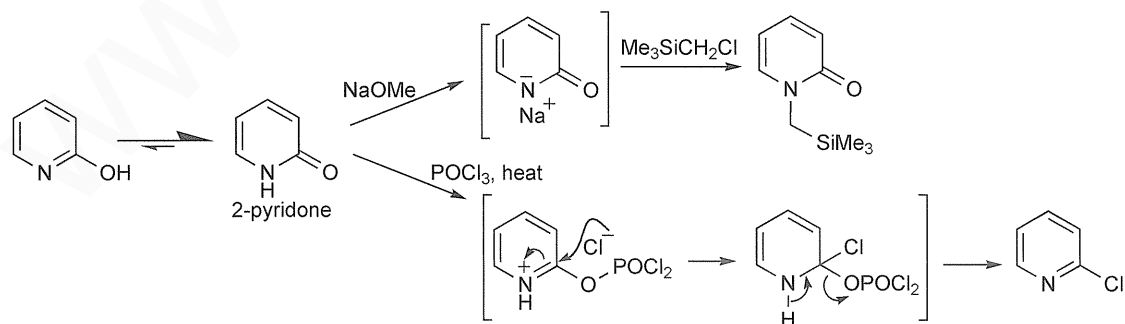
**Tautomerism in and reactions of 2-pyridone.**

4.5 Pyridine *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 nitration under standard conditions are examples of electrophilic substitution. In the sequence shown below, 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 been often used.
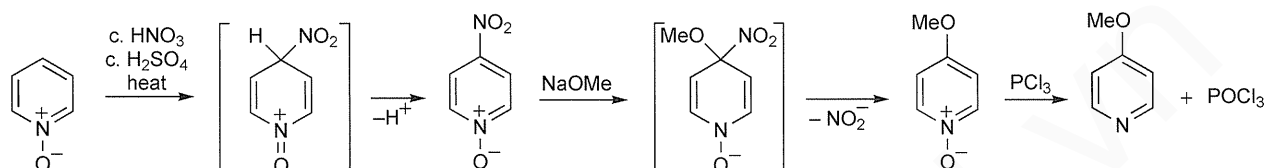
Electrophilic and nucleophilic substitutions of pyridine *N*-oxides.

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 nitrogen substituent is lost. 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 trivially hydrolysed to reveal the corresponding pyridone – overall, an α-unsubstituted pyridine has been converted into a 2-pyridone.
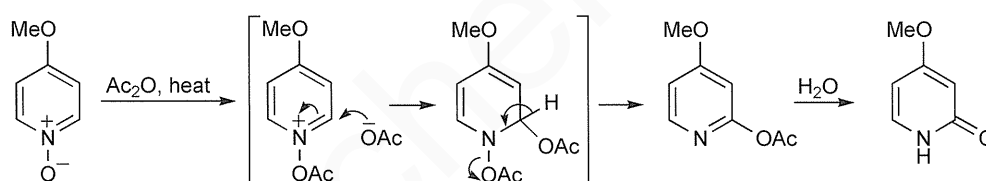
**Introduction of α-substituents via nucleophilic addition to *N*-oxides and then 1,2-elimination.**

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 below is for pyridine *N*-oxide itself, proceeding via an adduct, which finally loses dichlorophosphate.
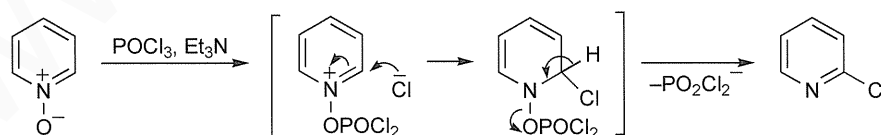

The use of pyridine *N*-oxides to form 2-halopyridines.

4.6 Pyridines with Amine Substituents

All the aminopyridines 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. For this reason, 4-dimethylaminopyridine is a very widely used nucleophilic catalyst in organic synthesis.
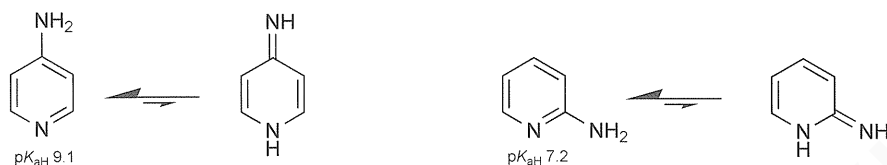

Pyridine amines are wholly in the amine tautomeric form.
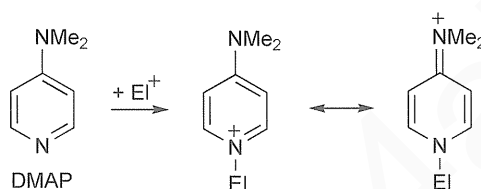
Delocalisation of charge in cations from 4-dimethylaminopyridine.

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.
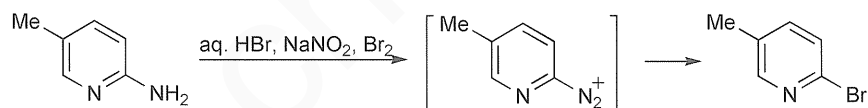

Diazotisation of a 2-aminopyridine and then Sandmeyer reaction.
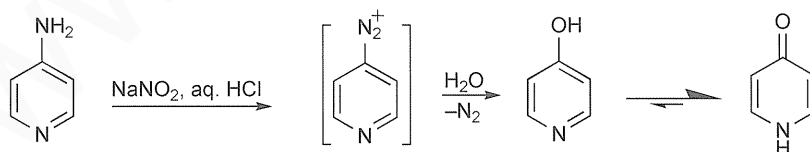
**Conversion of an 4-aminopyridine into a 4-pyridone via diazotisation.**

4.7 Alkyl Pyridines and Pyridine Carboxylic Acids

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.
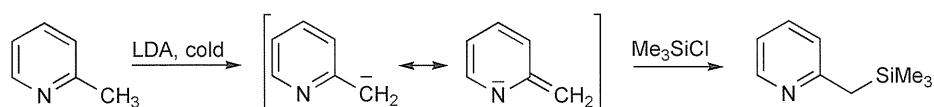

Deprotonation of a pyridine α-methyl to give a delocalised anion.

Pyridine carboxylic acids, like simple α-amino acids, exist mainly as zwitterions (internal salts). The zwitterion of picolinic acid decomposes, with loss of carbon dioxide, on heating 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.
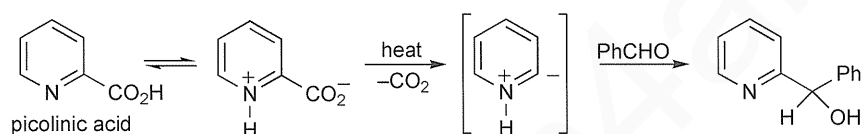
Decarboxylation of picolinic acid to a transient ylide.

4.8 Pyridines in Electrocyclic 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 – page 99) – 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, which 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 cycloadd to polarised alkenes, methyl acrylate in the example shown below.
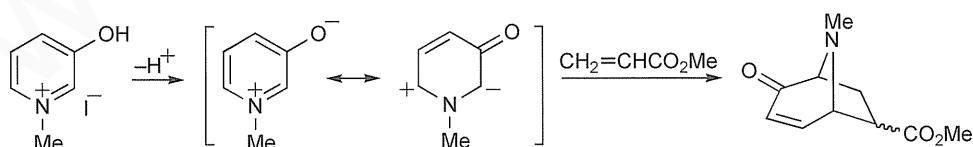

Dipolar cycloaddition reaction of a 3-oxidopyridinium zwitterion generated by *O*-deprotonation of a 3-hydroxypyridinium salt.

4.9 C-Metallated Pyridines by Direct Deprotonation or by Halogen/Metal Exchange

Direct deprotonation of pyridine itself can be carried out at the α-position, but more use has been made of halogen exchange reactions for the generation of pyridine organometallic nucleophiles. 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 $-70\,^\circ$C have to be used in exchange reactions with n-butyllithium in order to avoid nucleophilic *addition* of the reagent to the heterocycle). Grignard reagents are also more tolerant of functional groups in the reaction partner than are organolithium species.
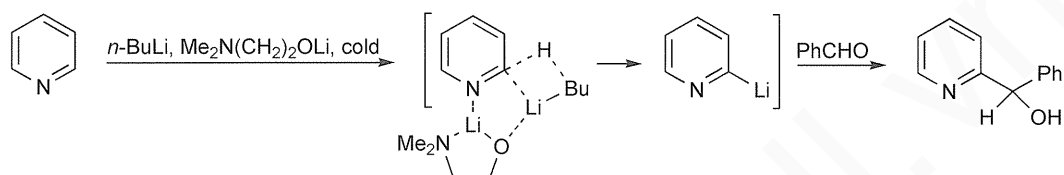
Regioselective α-lithiation of pyridines by deprotonation.
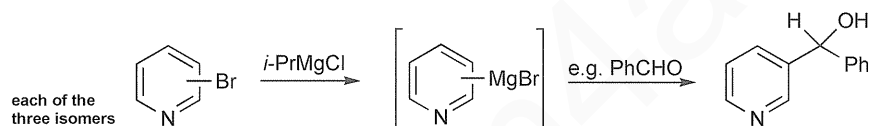
Formation of pyridine Grignard reagents.

Another, very widely used protocol is deprotonation *ortho* to a directing group (DoM; directed *ortho*-metallation). In the example shown below, a 4-carbamate allows lithiation at C-3. When a DoM group is located at C-3, lithiation usually takes place at C-4, not C-2.
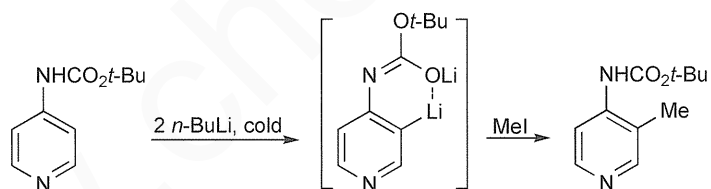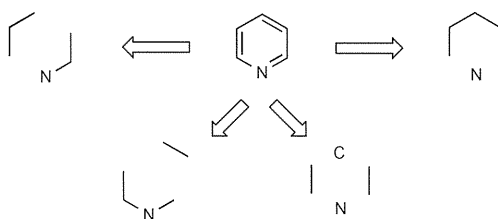

Directed *ortho*-metallation of a pyridine 4-carbamate.

# 4.10 Pyridine Ring Synthesis

4.10.1 Disconnections

Pyridine rings have been synthesised by many different methods; however, four important disconnections for the construction of pyridines are exemplified in this subsection.

**Principal disconnections for ring synthesis of pyridines.**

4.10.2 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.
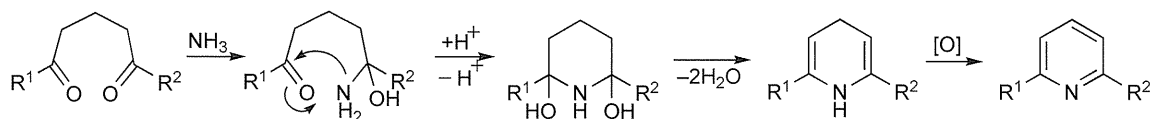
General scheme for the interaction of a 1,5-dicarbonyl compound with ammonia.

A preferred variant of this avoids the oxidation step by the use of hydroxylamine in place of ammonia, where aromatisation of the 1,4-dihydro-1-hydroxypyridine intermediate occurs *in situ* by loss of water.
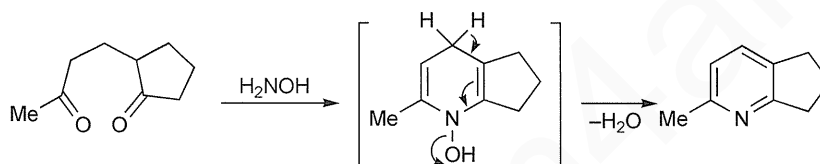
Reaction of hydroxylamine with a 1,5-diketone to produce a pyridine.

Precursors with carbons at a higher oxidation level lead to a correspondingly oxidised pyridine. As an example, a di-enamine, generated easily by reaction of a ketone with dimethylformamide dimethyl acetal, is a synthetic equivalent to a 1,5-dialdehyde but additionally it has a high oxidation level central carbon so that when ring closed, by reaction with methylamine, a 4-pyridone results.
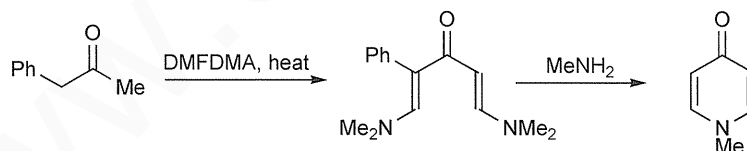
Using a synthetic equivalent to a 1,5-dialdehyde (also having a 3-ketone) gives a 2,6-unsubstituted 4-pyridone.

When one of the 'carbonyl' groups is, instead, a nitrile, this oxidation level is reflected in the product which will carry an amino group at an α-position. In the example shown below, 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.
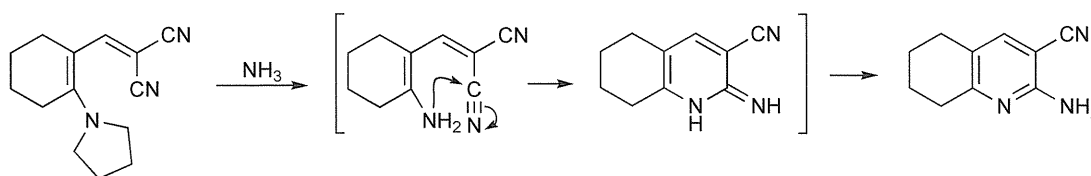
When a 'carbonyl' group is in fact a nitrile, an amino-heterocycle results.

4.10.3 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 a classical pyridine synthesis. In the Hantzsch synthesis, 2 equivalents of a 1,3-dicarbonyl compound (diketone or ketoester) and 1 equivalent each of an aldehyde and ammonia are reacted together in a one-pot process. The products, symmetrically substituted 1,4-dihydropyridines, can be aromatised by any of a number of oxidising agents, although the dihydro compounds themselves may 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 aldol condensation and then Michael addition.
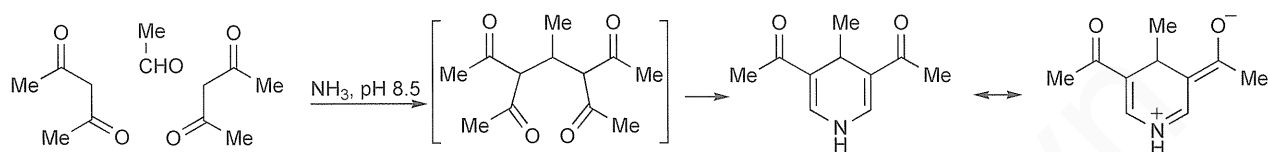
Four-component, one-pot reaction (the Hantzsch synthesis) producing a 1,4-dihydropyridine.

Particularly important examples of 1,4-dihydropyridines preparable by this route are used as anti-hypertensive agents (calcium channel blockers). The medicinal examples are not symmetrical and 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.
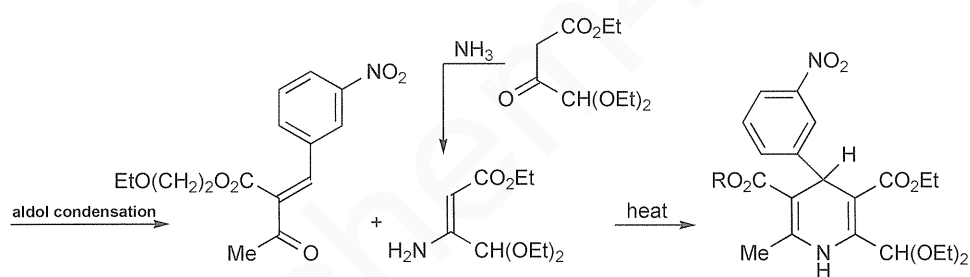
**Formation of unsymmetrically substituted 1,4-dihydropyridines.**

4.10.4 Synthesis of pyridines from 1,3-dicarbonyl compounds and a C₂N 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 then leads to a 2-pyridone. 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. As an example of a 1,3-dicarbonyl equivalent, EtOCH=CHCH(OEt)$_2$ can be used instead of malondialdehyde where a 4,5,6-unsubstituted pyridine is required.
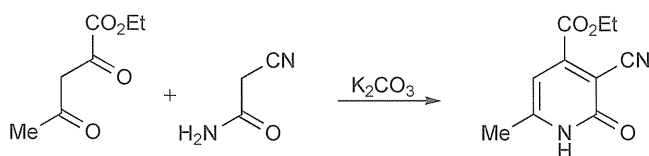

Using cyanoacetamide leads to 2-pyridones.

The C_2N component can also be a primary enamine derived from a 1,3-diketone. In the example shown below, the enamine derived from pentane-2,4-dione when combined with pentane-2,4-dione gives 3-acetyl-2,4,6-trimethylpyridine.
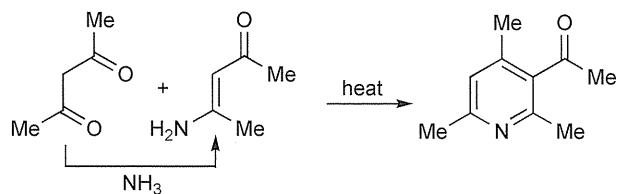
Pyridines from 1,3-diketones and β-amino-enones.

4.10.5 Synthesis of pyridines via cycloadditions (3,4- and 1,6-bonds made)

A number of cycloaddition reactions of alkenes with other heterocycles have been used to prepare pyridines, the longest established being the use of oxazoles, where the immediate product of cycloaddition from an oxazole with acrylic acid loses water (under the reaction conditions) to give the final pyridine. An inverse-electron-demand Diels–Alder addition involving a triazine, again with the expulsion of a small fragment to achieve aromaticity, is described on page 99.
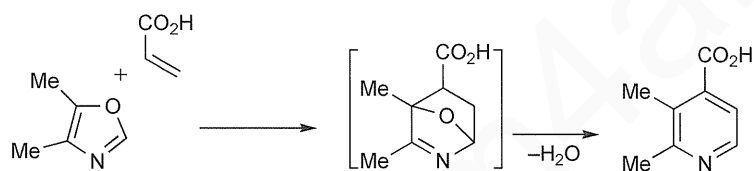
Pyridines from cycloadditions with oxazoles.

5.1 Quinolines/Isoquinolines and Electrophiles – Addition to N and Substitution at C

5.1.1 Electrophilic addition to nitrogen

Most of the chemistry of quinoline parallels that of isoquinoline, and so in this section 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. In processes exactly like those for pyridine, electrophiles *add* to the heterocyclic nitrogen – reaction with acids or electrophilic halides gives quinolinium/isoquinolinium salts, or with peracids, *N*-oxides.

quinoline
pK_{aH} **4.9**

isoquinoline
pK_{aH} **5.4**
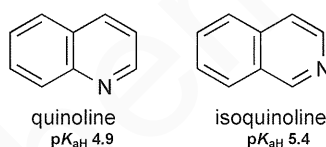
Basicities of quinoline and isoquinoline.

quinoline *N*-oxide

1*H*-quinolinium chloride
(quinoline hydrochloride)

2-methylisoquinolinium iodide
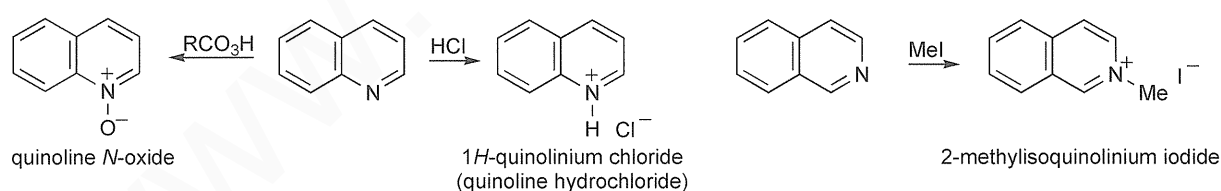
Products of electrophilic additions to quinoline/isoquinoline nitrogen.

5.1.2 Electrophilic substitution at carbon

As we reminded ourselves, electrophilic substitution is *the* typical reaction of benzene compounds; we also learnt that pyridines, without activating substituents, are *very* resistant to electrophilic C-substitution. In these bicycles, then, it is no surprise that standard electrophilic substitution is 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/isoquinolinium cations. However, *C*-electrophilic substitution has been relatively little used for the preparation of benzene-ring-substituted quinolines/isoquinolines – ring syntheses are preferred.
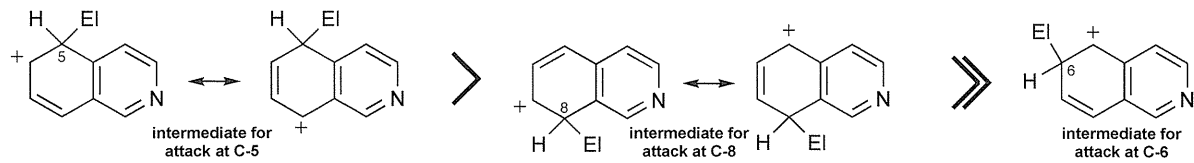
Positional selectivity in electrophilic substitution of isoquinoline rationalised by relative stabilities of intermediates.
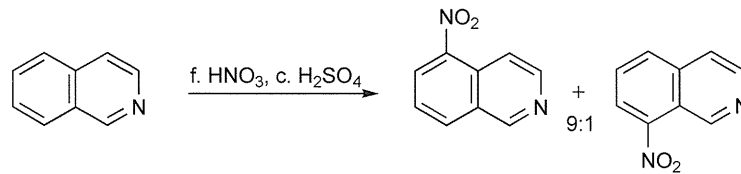

Nitration of isoquinoline – mixture of 5- and 8-substituted products.

Exceptionally, and via a different mechanism, there are some substitutions in the pyridine ring of quinoline and isoquinoline, notably bromination. These rest on the ability of the bicyclic systems to *add* a nucleophile much more easily (see page 30) than does pyridine, the electrophilic step then actually involving attack on an intermediate enamine.
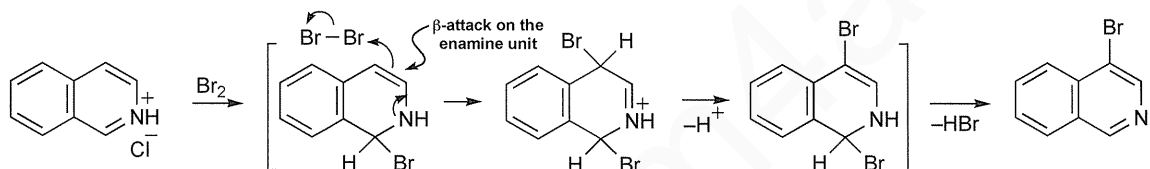
C-4-Bromination of isoquinoline.
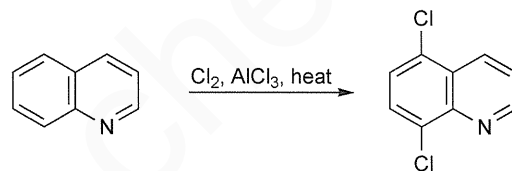
Chlorination of quinoline.

Electron-releasing substituents on the heterocyclic ring can also permit substitution in that ring; thus isoquinolin-1-ones can be brought into reaction with some carbon electrophiles, attack taking place at C-4, *para* to the oxygen, which is equivalent to saying, at the β-position of the enamine unit.

Vilsmeier formylation of 2-methylisoquinolin-1-one.

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5.2 Quinolines/Isoquinolines and Nucleophiles

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-1 and C-4; of the two α-type positions in isoquinoline, reaction at the 1-position is *much* more favoured.

attack at C-1 preferred

attack at C-3 much less favourable

negative charge cannot be delocalised onto nitrogen without disrupting benzenoid resonance
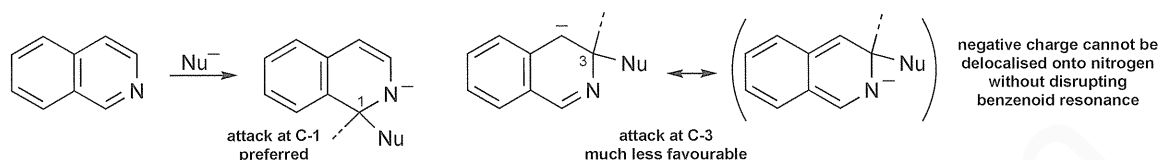
Positional selectivity in nucleophilic attack on isoquinolines rationalised by relative stabilities of intermediates.

5.2.1 Substitution of hydrogen

Since 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* – 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 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 20).

KOH, NaOH, heat
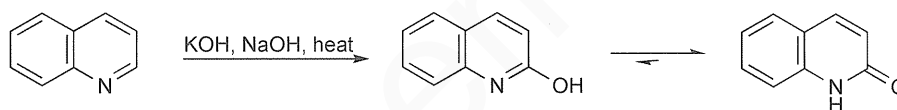
Nucleophilic substitution of quinoline by hydroxide.

A second example of the ease of nucleophilic addition is the reaction of amide anion with isoquinoline, which takes place even at $-65\,^{\circ}$C (to aminate pyridine needs strong heating), re-aromatisation occurring *in situ*.

KNH_2, NH_3 (liq)
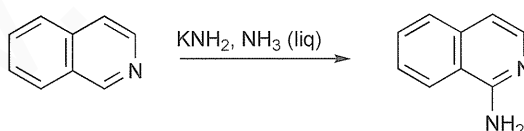
Nucleophilic 1-amination of isoquinoline.

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.


n-BuLi

$PhNO_2$, heat

n-Bu   H

n-Bu
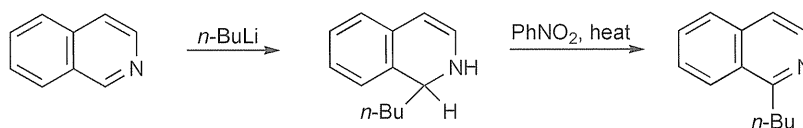
Nucleophilic 1-alkylation of isoquinoline; isolable 1,2-dihydro-adduct.

5.2.2 Displacement 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 (cf. pages 11 and 18). 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.
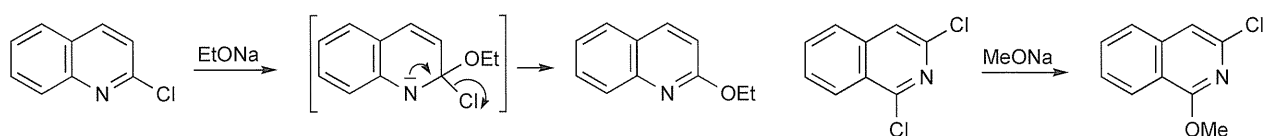
Nucleophilic displacements on 2-chloroquinoline and (selectively) on 1,3-dichloroisoquinoline.

5.2.3   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 to illustrate. In the first, an *N*-phenoxycarbonylquinolinium salt is prepared and used *in situ* for the addition of an alkyne at C-2.
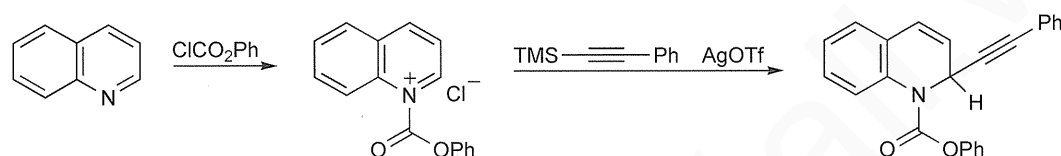
Nucleophilic addition to an *N*-phenoxycarbonylquinolinium salt.

'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 that can be removed with a strong base, and the resulting carbanion alkylated, hydrolytic conditions then producing overall a C-1-alkylated heterocycle.
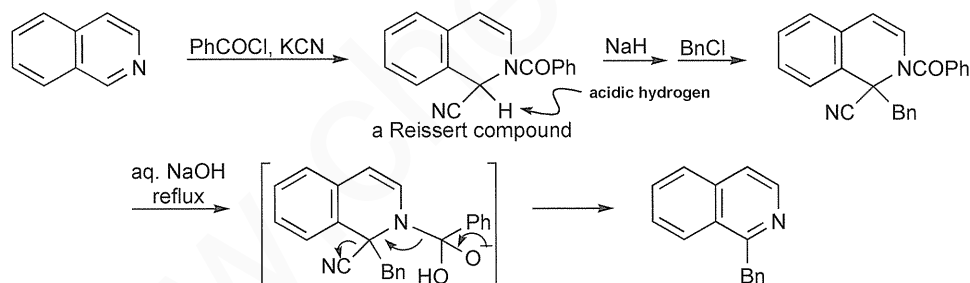
Synthesis and use of a Reissert compound – alkylation at C-1.

The salt that results from *N*-arylation of isoquinoline with 2,4-dinitrochlorobenzene (cf. page 5), 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 (*a*ddition *n*ucleophilic *r*ing *o*pening *r*ing *c*losing) 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.
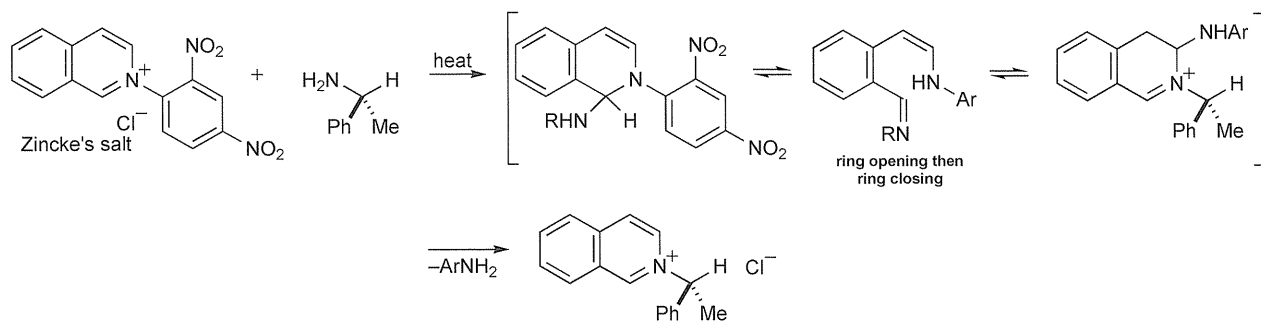
Use of Zincke's salt to prepare isoquinolinium salts from primary amines.

5.3 Quinolines/Isoquinolines with Oxygen Substituents

Quinolines/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 to 1-halides by reaction with phosphorus halides.
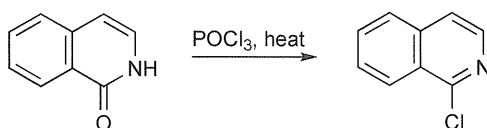
Conversion of isoquinolin-1-one into 1-chloroisoquinoline.
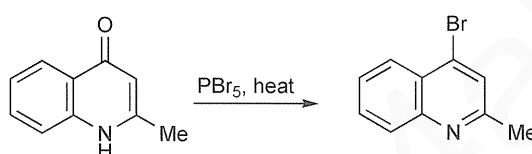
Conversion of a quinolin-4-one into the corresponding bromide.

5.4 Quinoline/Isoquinoline *N*-Oxides

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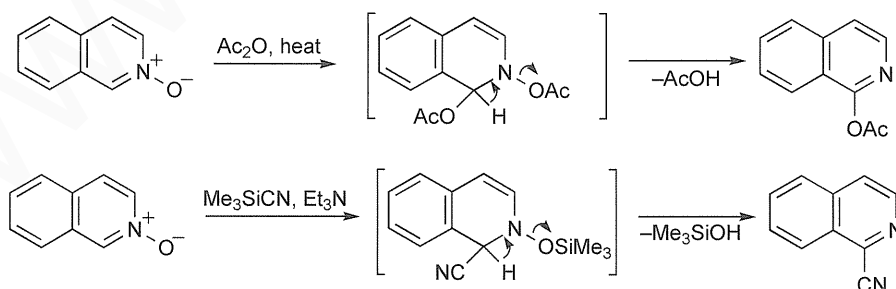
The use of isoquinoline *N*-oxide to introduce substituents at C-1.

5.5 C-Metallated Quinolines/ Isoquinolines by Direct Deprotonation or by Halogen/Metal Exchange

Direct deprotonation of quinolines/isoquinolines has only been carried out with *ortho* assistance (directed *ortho*-metallation). Quinolines with a directing group at C-3 are lithiated at C-4. Metal/halogen exchange processes can be used to produce organometallic nucleophiles from halides located either on 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.

Generation and use of lithio-quinolines and – isoquinolines.
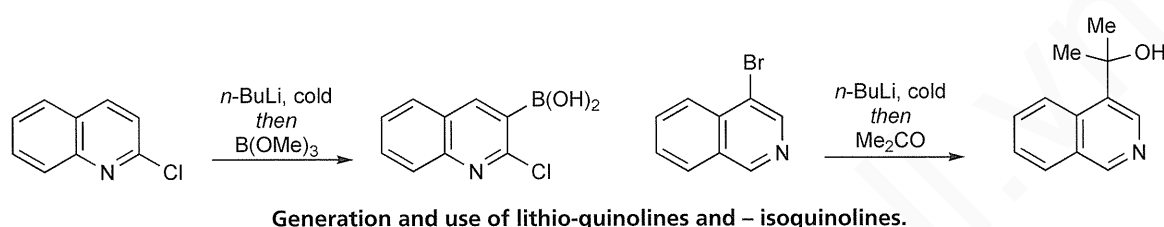
5.6 Oxidation and Reduction of Quinolines/Isoquinolines

The heterocyclic ring is more easily reduced than the benzene ring; regioselective addition of four hydrogens is easy. Hydride reagents bring about exactly comparable reductions of the heterocyclic ring of N^+-alkylquinolinium or -isoquinolinium salts.
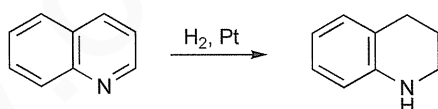
Reduction of quinoline.

N^+-Alkylquinolinium or -isoquinolinium salts are oxidised in alkaline solution to N-alkyl quinolones/isoquinolones – the adduct formed by nucleophilic addition of hydroxide is oxidised.
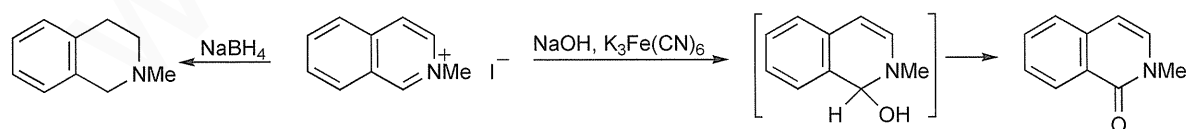
Reduction and oxidation of 1-methylisoquinolinium iodide.

5.7 Ring Synthesis

5.7.1 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.
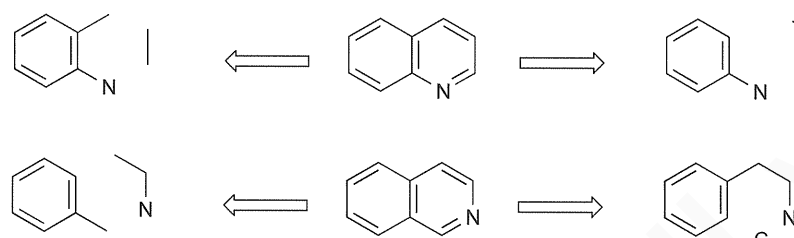
Principal disconnections for ring synthesis of quinolines and isoquinolines.

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

Anilines react with 1,3-dicarbonyl compounds very efficiently to give enamino-ketones; these can be ring closed in an acid-catalysed cyclisation involving electrophilic attack on the benzene ring; final loss of water produces the aromatic quinoline. If one of the carbonyl groups is that of an ester, then a quinolone results.
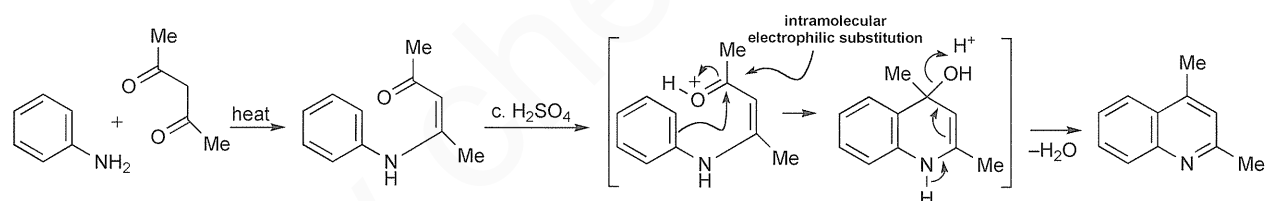
Synthesis of quinolines from anilines and 1,3-dicarbonyl compounds.

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) and glycerol are heated together. From this 'witches brew' and often via a very exothermic and potentially dangerous 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 – again, an electrophilic attack on the benzene ring – and dehydration produce a dihydroquinoline which is oxidised to the aromatic product.
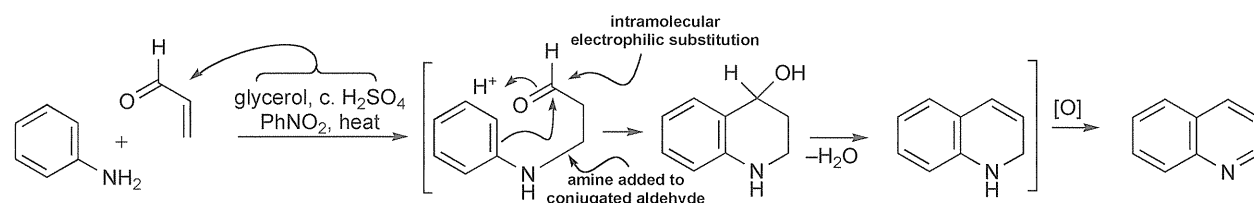
Skraup synthesis of pyridine-ring-unsubstituted quinolines from anilines and acrolein.

5.7.3 Synthesis of quinolines from ortho-aminoaryl ketones or aldehydes (1,2- and 4,4a-bonds made)

Perhaps the most obvious disconnection for a qunoline is to envisage forming the two double bonds of the heterocyclic ring – the 1,2-double bond is an imine and the 3,4-double bond might be formed by an aldol-type condensation. An ortho-aminoaryl aldehyde is reacted with a ketone (to form the imine) carrying an α-methylene (CH$_2$ α to the ketone for the aldol-type condensation); the exact order of steps is not known.
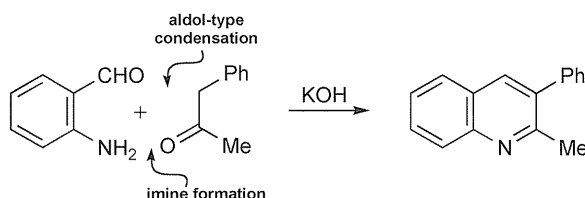
Friedländer synthesis of quinolines from an *ortho*-aminoaryl carbonyl compound and a ketone with an α-methylene.

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

The trivial conversion of a 2-arylethanamine into an amide provides a substrate which will undergo ring closure to a 3,4-dihydroisoquinoline, which can be easily dehydrogenated to the aromatic species. This 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. 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.
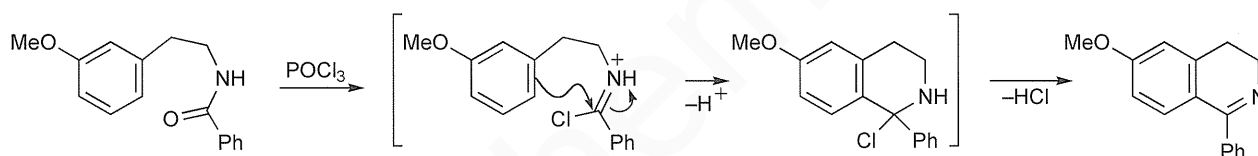
Bischler–Napieralski synthesis of a 3,4-dihydroisoquinoline.

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

A quite different route to isoquinolines begins with an aryl aldehyde which is condensed with aminoethanal dimethyl acetal (H$_2$NCH$_2$CH(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, and neatly, causes elimination of *para*-toluenesulfinate (*Note*: the sulfur has changed oxidation level), leading directly to the aromatic isoquinoline.
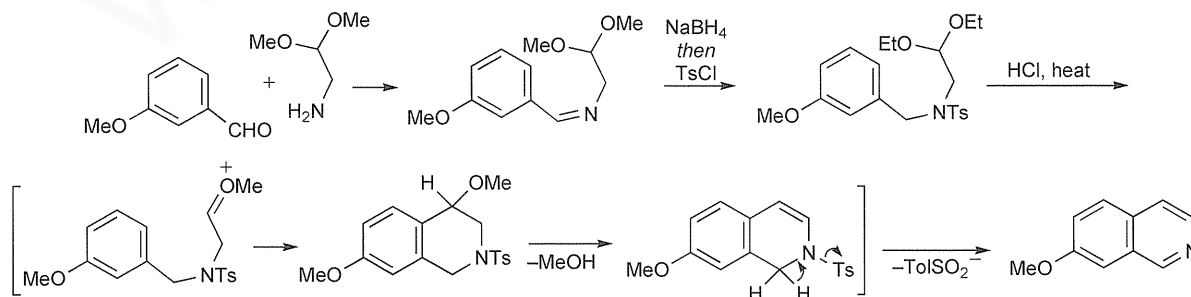
Synthesis of isoquinolines from aryl aldehydes and aminoethanal dimethyl acetal.

Introduction

The diazines – pyridazine, pyrimidine and pyrazine – show many similarities in their reactivities to pyridines, 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 with purines (Section 12), there has been much more emphasis on the amino- and oxypyrimidines as intermediates and starting materials, due to their presence, as ribosides, in nucleic acids and hence ready availability as starting materials via degradation of these natural materials.

pyridazine
pK_{aH} 2.3

pyrimidine
pK_{aH} 1.3

pyrazine
pK_{aH} 0.65

uracil
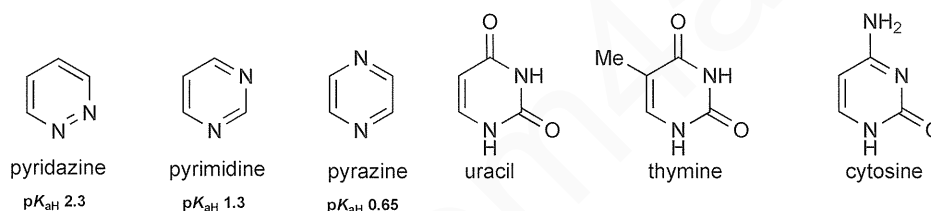
thymine

cytosine

Uracil, thymine and cytosine are readily available via degradation of DNA/RNA.

6.1 Diazines and Electrophiles – Addition to N and Substitution at C

6.1.1 Electrophilic addition to nitrogen

The inductive effect of the second nitrogen leads to a reduction in the basicity of the parent diazines relative to pyridine (pK_a 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.

The diazines react with alkyl halides to give quaternary salts, although somewhat less readily than pyridine. Again, 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 mild conditions are required for pyrimidine, due to the susceptibility of pyrimidine N-oxide to acid-catalysed decomposition.
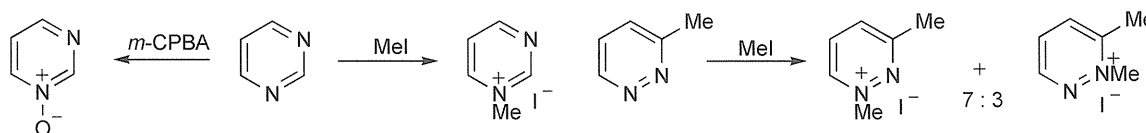
Typical electrophilic additions to nitrogen in diazines.

6.1.2 Electrophilic substitution at carbon

Electrophilic substitution at carbon in diazines is uncommon and requires special circumstances. Pyrimidine can be brominated under conditions similar to those required for pyridine, reaction occurring at the 5-position – the *only* position which 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 an imine is the most likely. The amino- and oxydiazines, benefiting from the extra activation of the electron-releasing substituent(s), generally undergo electrophilic substitution under normal conditions. *N*-Oxides are also useful substrates for electrophilic substitution, another parallel to the chemistry of pyridines.
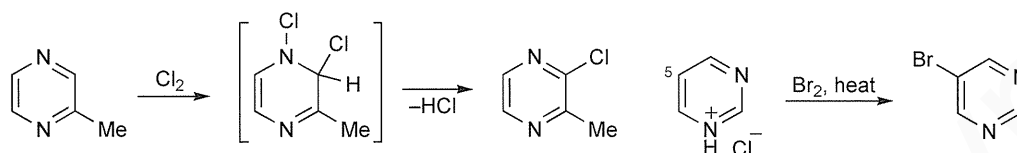
The efficient room temperature chlorination of 2-methylpyrazine pyridazine implies a special mechanism. C-5 in pyrimidine is like C-3 in pyridine, the only position *not* deactivated by conjugation to an imine unit.

Simple pyridazines are very resistant to electrophilic substitution.
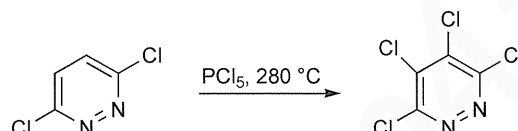
Electrophilic substitution of unactivated pyridazines requires vigorous condition.
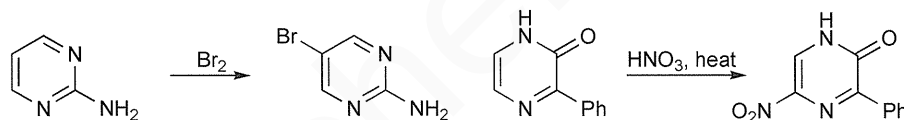
Electrophilic substitution of amino- and oxydiazines proceeds readily, *ortho* or *para* to the substituent.
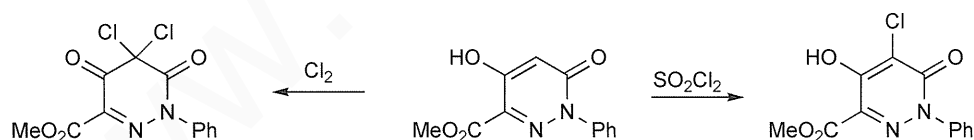
Electrophilic substitution of hydroxy-pyridazinones sometimes gives non-aromatic products.
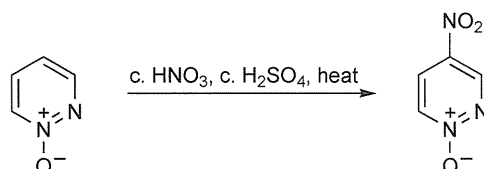
The *N*-oxide group is a good activating substituent for electrophilic substitution.

6.2 Diazines and Nucleophiles

The simple diazines are much more susceptible to nucleophilic attack than is pyridine. Pyrimidine, for example, is decomposed by hot aqueous alkali.

6.2.1 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 which are 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).]
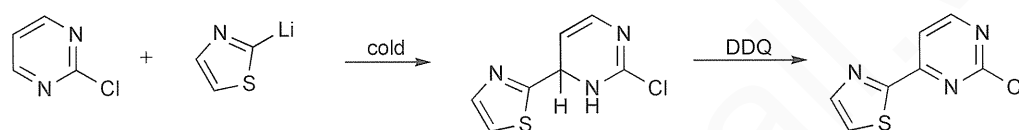
Easy nucleophilic addition to 2-chloropyrimidine and then dehydrogenation – overall nucleophilic substitution of hydrogen.

6.2.2 Displacement 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 relatively resistant. The relative reactivities are summarised in this scheme:
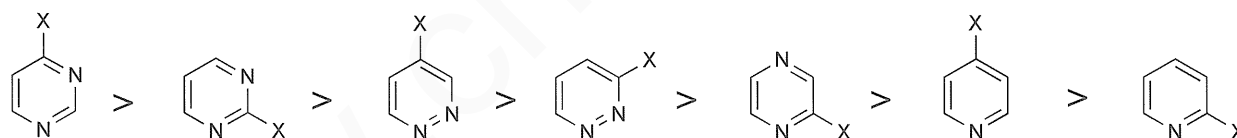
Order of reactivity in nucleophilic displacements of leaving groups – e.g. X = halogen.

   Chlorine is the most common leaving group but sulfones are also very useful and even methoxy can be displaced in these highly reactive systems.
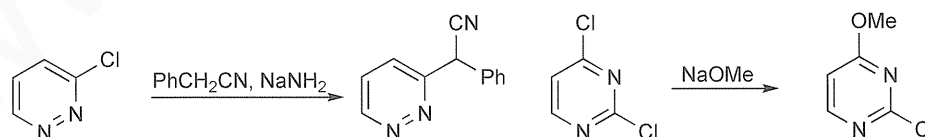
Typical nucleophilic displacements of chlorine.
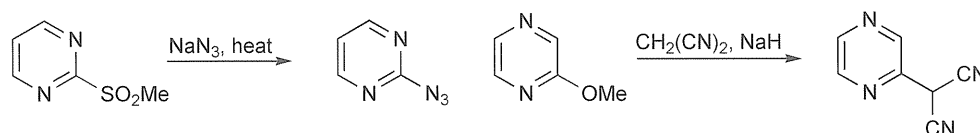
Sulfone and even methoxy can act as good leaving groups in diazine chemistry.

An important point to remember is that the presence on the ring of an electron-donating group, particularly an amino group, will greatly reduce the reactivity of a halide. Although this means that clean mono-substitution in dihalo compounds is easy, special methods may be necessary to achieve displacement of the second halide, such as the use of 'supernucleophiles'. Hydroxylamines are very reactive nucleophiles and, since 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.
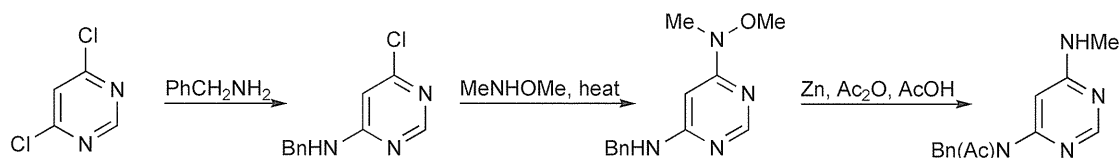
The use of a hydroxylamine as a 'supernucleophile' to displace a relatively unreactive chlorine.

The oxydiazines can also undergo nucleophilic addition or displacement of halide. Uracil and its riboside (uridine) are particularly prone to Michael-type additions to the double bond leading to *cine*-substitution rather than the usual *ipso*-substitution, for example from a 5-bromouridine to the 6-cyano-uridine shown in this scheme:
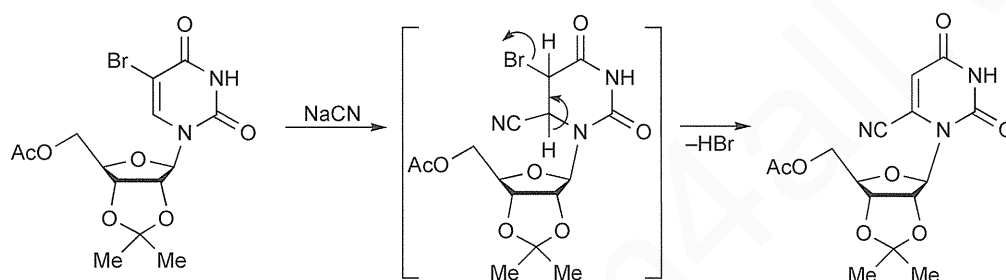
Cine-substitution of a 5-bromouridine derivative.

6.3 Diazines with amine substituents

Aminodiazines show a strong analogy to aminopyridines. They are stronger bases than the parent heterocycles, protonation and quaternisation occurring on the ring nitrogen. The derived diazonium salts are even less stable than those in the pyridine series and are only synthetically useful for the conversion of aminodiazines into diazinones.

Aminodiazines can be diazotised and the diazonium salts converted into the corresponding diazinones.

6.4 Diazines with Oxygen Substituents

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(2H)-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 diketo form.

Uracil, like most oxy-diazines, exists predominantly in the fully keto form. 'Maleic hydrazide' exists in the mono-hydroxy-mono-keto form to minimise unfavourable interactions between the nitrogens. 5-Hydroxypyrimidine is the *only* phenolic mono-oxy-diazine.

6.4.1 N-Deprotonation and N-alkylation

Like pyridones, diazinones are relatively acidic and can be N-H-deprotonated under mild conditions, the resulting anions reacting with electrophiles on either nitrogen or carbon. In some circumstances, particularly intramolecular reactions of ribosides, O-alkylation of the anion can occur.

A simple N-alkylation of pyridazin-2(1H)-one. A C-5-hydroxymethylation of a uracil via the ambident/delocalised anion formed by deprotonation at N-1.

6.4.2 Replacement of oxygen

The diazinones are the best sources of the versatile halo-diazines, by reaction with thionyl chloride or phosphoryl chloride. Thiones can also be prepared by direct replacement of oxygen using phosphorus sulfides.

Conversion of 'maleic hydrazide' into 3,6-dichloropyridazine using a standard $SOCl_2$ reaction. Preparation of uracil monothione using a selectively mono-protected starting material.

6.4.3 Electrocyclic reactions

Uracils undergo photochemical $2 + 2$ additions; these are of particular significance for the mutagenic effects of ultraviolet irradiation when dimeric bridges are formed, distorting the DNA chain.

Photochemical dimerisation also occurs in DNA and is an important mechanism of mutagenesis.

6.5 C-Metallated Diazines by Direct Deprotonation or by Halogen/Metal Exchange

Diazines will readily undergo nucleophilic *addition* with many standard lithiating agents; however, metallation and halogen exchange *can* be carried out, but require carefully controlled conditions, normally very low temperatures.

(a) A very non-nucleophilic base is often used to avoid addition to the ring when lithiating a diazine. (b) A very low temperature is used to avoid side reactions in the preparation of 5-lithiopyrimidine by halide exchange.

The lithiation of substituted diazines is a very useful synthetic method. Chloro- and alkoxy-derivatives, the synthetic equivalents of diazinones, are commonly used.
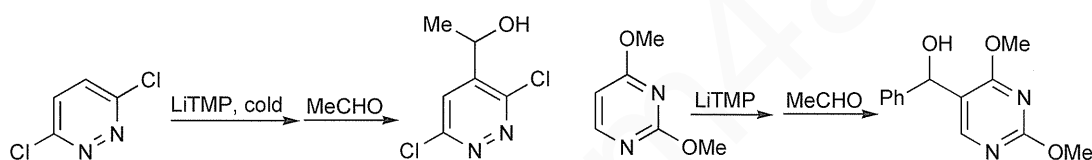
Lithiation of substituted diazines (directed *ortho*-metallation) is easier, though LiTMP is still utilised.

Metallation of pyrimidine-diones in nucleosides may not require complete 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 can be controlled by the presence or absence of a protecting group for the 5′-hydroxy group.
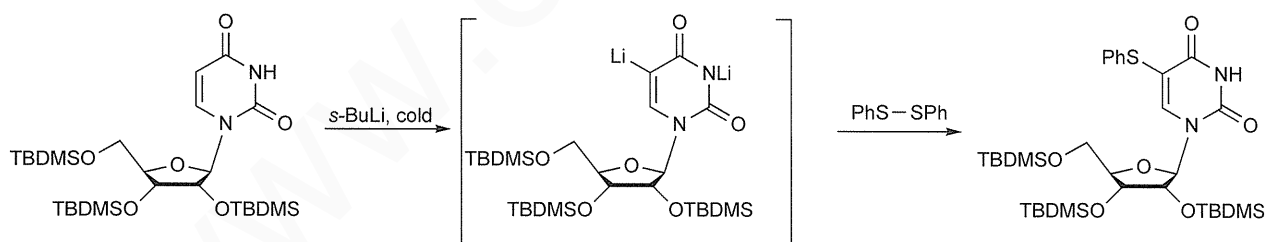
A uridine, with a fully protected ribose, reacts with excess lithiating agent to give the *N*,5-dilithio compound.
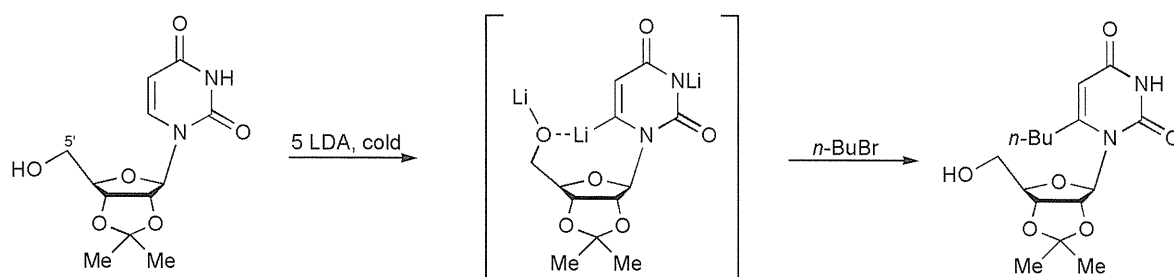
The presence of a free C-5′-OH in the ribose directs lithiation to C-6 via chelation.

41

6.6 Diazine Ring Synthesis

6.6.1 Disconnections

Only the most frequently used routes are discussed here. Pyridazines are made from 1,4-dicarbonyl compounds and hydrazine; pyrimidines result from the condensation of a 1,3-dicarbonyl compound and an N–C–N unit; pyrazines are produced from 1,2-dicarbonyl compounds and 1,2-diamines.
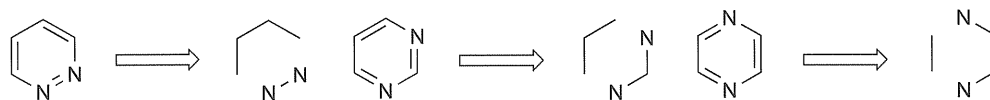
6.6.2 Synthesis of pyridazines from 1,4-dicarbonyl compounds (2,3- and 1,6-bonds made)

Pyridazines are most commonly prepared by condensation of 1,4-dicarbonyl compounds with hydrazine. The dicarbonyl component can be saturated when a final oxidative aromatisation is required, or better, already at the higher oxidation level.
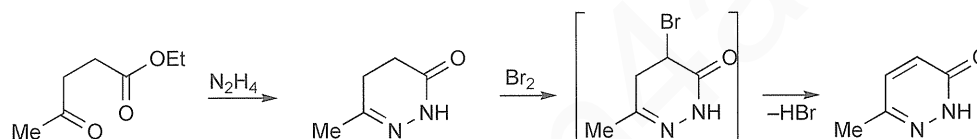
Condensation using a saturated 1,4-dicarbonyl compound requires a final aromatisation.
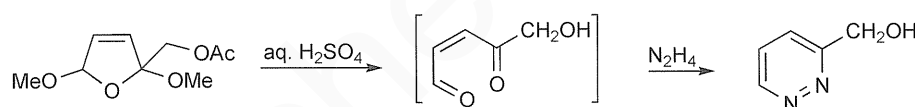
Condensation using an unsaturated 1,4-dicarbonyl compound leads directly to the aromatic pyridazine.

6.6.3 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, often a urea or amidine.
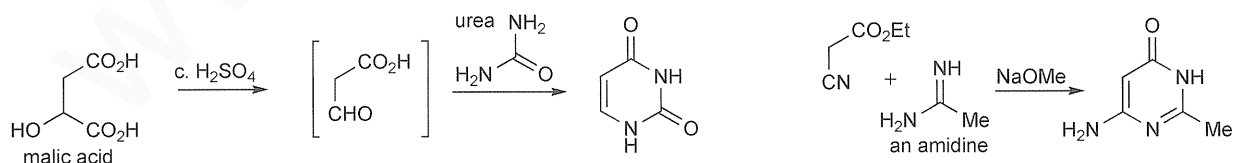
An early synthesis of uracil involved the *in situ* formation of a 1,3-aldehydo-acid and its condensation with urea. The condensation of acetamidine with ethyl cyanoacetate produces 6-aminopyrimidin-4(3H)-one.

Ketones can be easily converted into chloroenals, which are synthetic equivalents of 1,3-ketoaldehydes. Reactions of 1,3-dicarbonyl compounds with formamide give 2-unsubstituted pyrimidines.
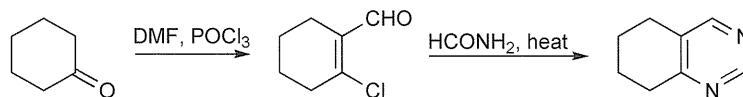
Chloroenals are easily prepared, 1,3-dicarbonyl synthetic equivalents for pyridimine synthesis.

Pyrimidines can also be prepared by cycloaddition reactions on 1,3,5-triazines (see page 99).

6.6.4 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.
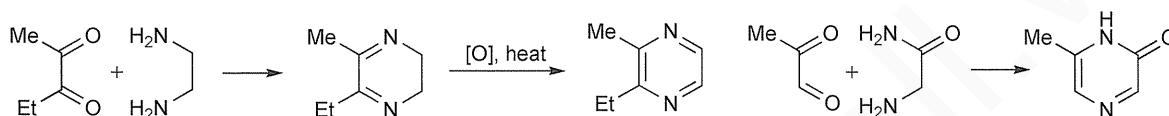
Typical pyrazine and pyrazinone syntheses.

Unsaturated 1,2-diamines (enediamines), where an aromatisation step would not be needed, are generally not stable, but the use of another diazine – 5,6-diaminouracil – as a stable masked enediamine is amusing! [Note that the intermediate bicyclic compound is a pteridine.]
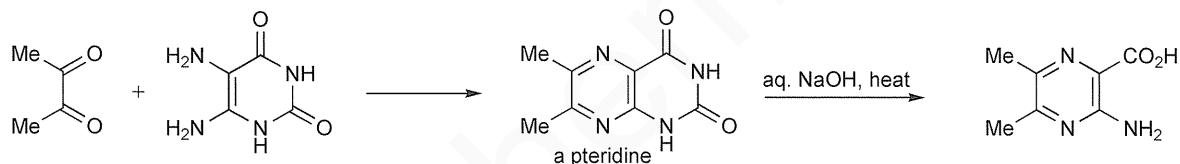
The use of 5,6-diaminouracil as a masked enediamine for the synthesis of a functionalised pyrazine.

Pyryliums and Benzopyryliums

7.1 Pyrylium Salts

Pyrylium salts, especially perchlorates (ClO_4^-), tetrafluoroborates (BF_4^-) or hexachloroantimonates(V) ($SbCl_6^-$), are stable but reactive aromatic compounds. [*Caution*: All perchlorates, particularly when dry, are potentially explosive and should be handled with great care.]

pyrylium cation   1-benzopyrylium cation   2-benzopyrylium cation
                        (chromylium)   (isochromylium)
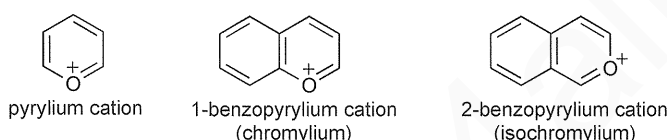
1-Benzopyryliums (chromyliums) occur as pigments in flower petals in substances known as anthocyanins; most blue, purple and red flower colours are due to anthocyanins. The actual colour shown by a particular anthocyanin depends on pH and upon the presence of co-pigments; the pH is important because 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 in protonated and *O*-deprotonated forms.
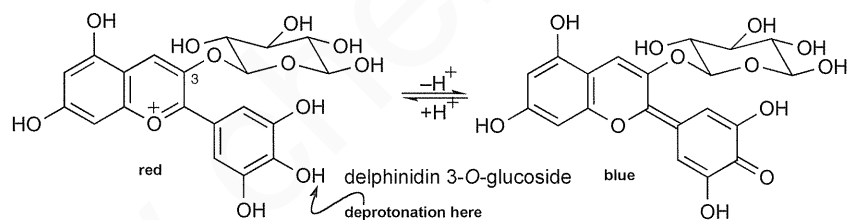
A typical flower petal pigment.

There are *no examples* of electrophilic substitutions of pyryliums or, indeed, of the benzene ring of benzopyryliums.

7.2 Pyryliums and Nucleophiles

Addition of nucleophiles, especially negatively charged nucleophiles, to pyrylium cations is easy. The normal position of attack is an α-position – the analogy to nucleophilic addition to a pyridinium salt or an *O*-protonated carbonyl group is obvious. Such additions produce neutral 1,2-dihydro products (2*H*-pyrans), and it is the further chemistry of these adducts that comprises the bulk of pyrylium chemistry.

a 2*H*-pyran   nucleophilic addition to
                                           O-protonated carbonyl
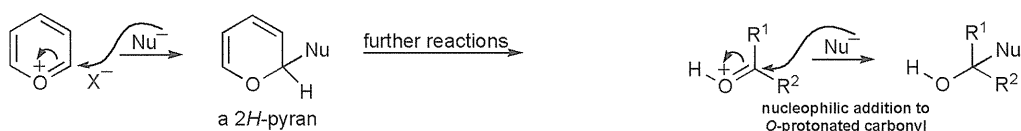
Nucleophilic addition at C-2 is *the* typical reaction of a pyrylium salt.

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 $0\,^\circ C$, 2,4,6-trimethylpyrylium is stable in water at $100\,^\circ C$. Hydroxide, as a negatively charged nucleophile, is more reactive, adding to all pyrylium cations at low temperature.

7.3 Ring-Opening Reactions of 2*H*-Pyrans

Hydroxide adds reversibly, for example to 2,4,6-trimethylpyrylium cation, giving an adduct. This cyclic hemiacetal 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.

2,4,6-trimethypyrylium
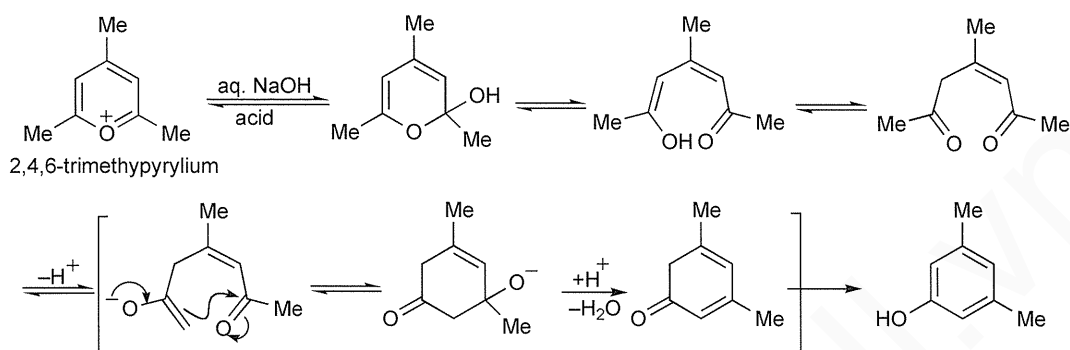
Conversion of a pyrylium salt into a benzenoid compound.

The reaction of pyrylium salts with ammonia (or primary amines) produces pyridines (or pyridinium salts). Here, after ring opening of the initial adduct, intramolecular imine formation generates the nitrogen heterocycle.
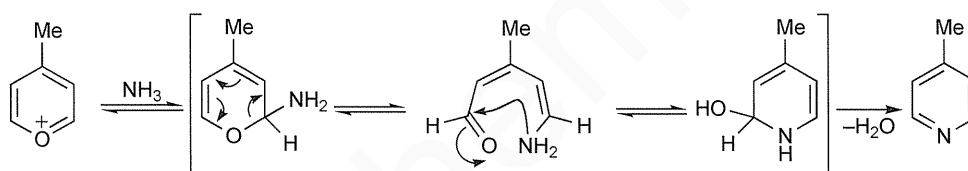
Conversion of a pyrylium salt into a pyridine.

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.
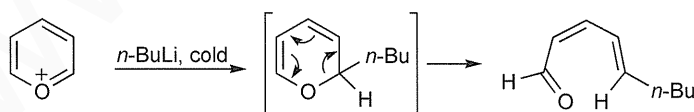
An organometallic nucleophile adding to a pyrylium salt, with subsequent ring opening.

As a final example, hydride adds predominantly at the α-position of 2,4,6-trimethylpyrylium perchlorate, the immediate 2*H*-pyran undergoing ring opening to give the isolated dienone product. Note that the minor reduction product, a 4*H*-pyran, is stable.
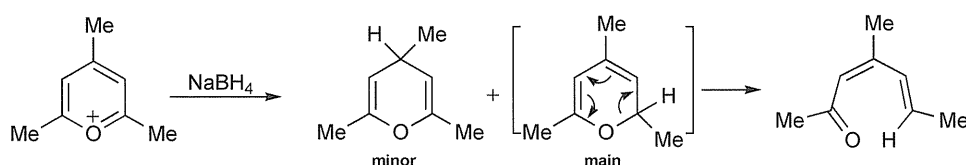
Addition of hydride to a pyrylium salt with subsequent ring opening.

7.4 Pyryliums and Benzopyryliums with Oxygen Substituents – Pyrones and Benzopyrones

The formal deprotonation of hydroxyl groups at the pyrylium 3-position generates 3-oxidopyrylium ylides; these undergo dipolar cycloadditions across the 2- and 6-positions (cf. 3-oxidopyridiniums on page 23). Most often, such zwitterions are generated by elimination of acetic acid from a 6-acetoxy-enone in the presence of an external dipolarophile or, in the case illustrated below, having a tethered double bond to serve as an intramolecular dipolarophile.
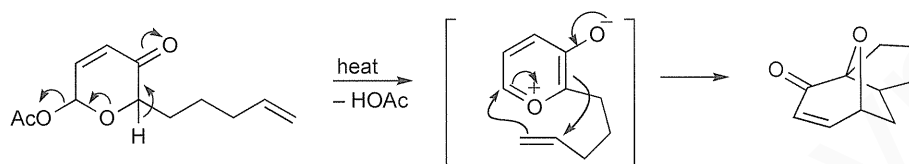
Dipolar cycloaddition of a 3-oxidopyrylium to an alkene.

The O-deprotonated forms of α- and γ-hydroxypyryliums are neutral pyrones and their properties are like those of pyridones (see page 20), their benzanellated analogues, chromones, coumarins and isocoumarins being analogous to quinolones and isoquinolones.

2-hydroxypyrylium   2-pyrone   4-pyrone   coumarin   chromone   isocoumarin
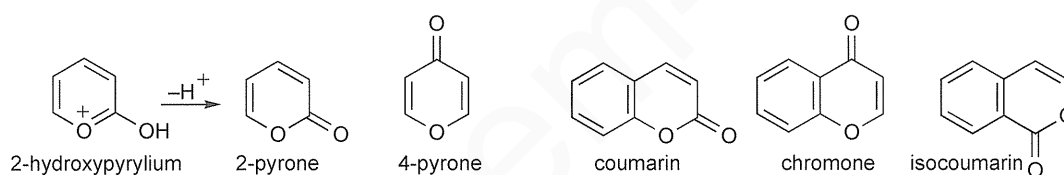
Structures of pyrones and benzopyrones.

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 at C-3.
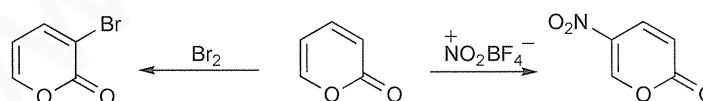
Electrophilic substitutions of 2-pyrone.
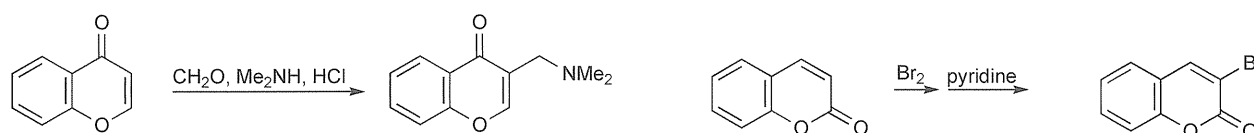
Electrophilic substitution of chromone and coumarin.

The remainder of the chemistry of the pyrones and benzopyrones can be summarised by saying that they behave like unsaturated ketones and lactones. However, the reactivity of 2-pyrones, especially 3- or 5-halo-2-pyrones, as dienes in

Diels–Alder reactions is notable. There is a tendency for such products to lose carbon dioxide on stronger heating.
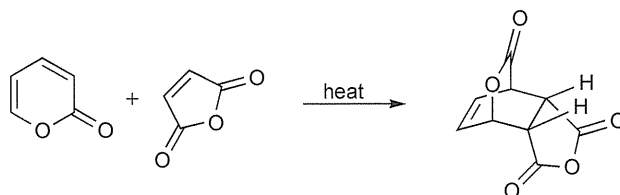
2-Pyrone acting as a 4π component in a Diels–Alder reaction.

4-Pyrone is a weak base, pK_a −0.3 which is protonated on the carbonyl oxygen to afford 4-hydroxypyrylium salts which are often crystalline; 2-pyrones are much weaker bases and though they are likewise protonated on carbonyl oxygen in strong acids, salts cannot be isolated.
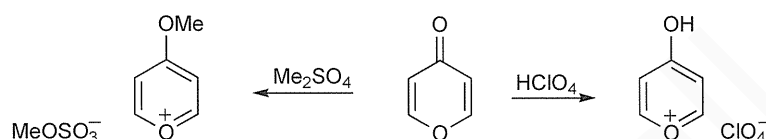
O-Protonation and O-methylation of 4-pyrone.

Ammonia and primary amines convert pyrones into pyridones; for 2-pyrones this is simply the conversion of ester (lactone) into amide; in the case of 4-pyrone, it must involve initial attack at an α-position in an aza-Michael reaction, then ring opening and reclosure.
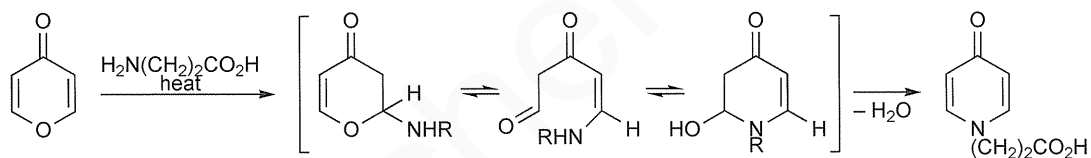
Conversion of 4-pyrone into a 4-pyridone.

2-Pyrone undergoes remarkable and efficient photochemical transformations on irradiation – a bicyclic β-lactone is formed on irradiation in a non-hydroxylic solvent and an acyclic unsaturated ester-aldehyde, via a ketene, on irradiation in the presence of methanol.
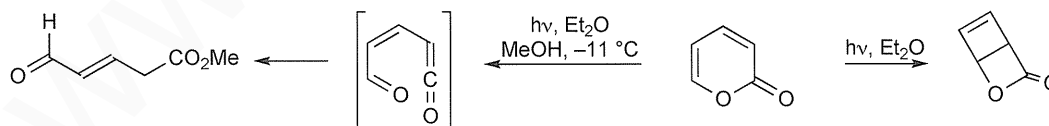
Photochemical transformations of 2-pyrone.

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7.5 Pyrylium and Benzopyrylium Ring Synthesis

7.5.1   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 hemiacetal formation, loss of water and finally an oxidation produce the six-membered aromatic salt. Various oxidants can be used; in the example shown below, the species that abstracts hydride from the intermediate $4H$-pyran is the triphenylmethyl carbonium ion (Ph_3C^+).
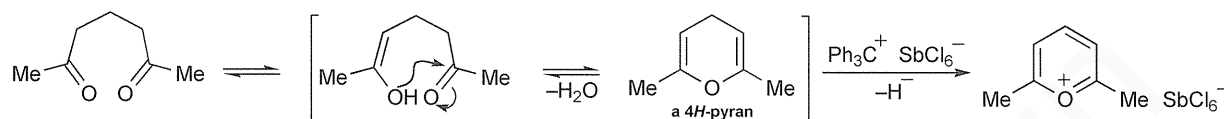
Synthesis of a pyrylium cation from a 1,5-diketone via dehydrogenation of a 4H-pyran.

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.
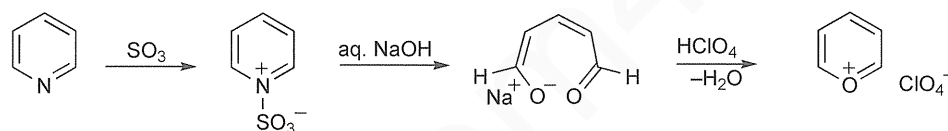
Conversion of pyridine–sulfur trioxide adduct into pyrylium perchlorate.

A synthesis of 4-pyrone is a further example of this approach. 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 diacid on mineral acid treatment, the presence of the central carbonyl group of the starting material being reflected in its presence in the ring-closed heterocycle.
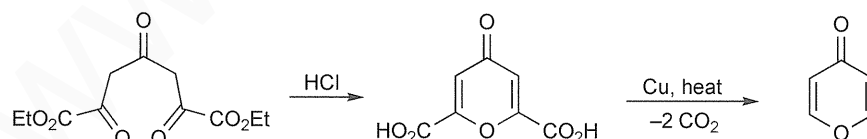
Synthesis of 4-pyrone from a 1,3-5-tricarbonyl compound.

7.5.2   Synthesis of 1-benzopyryliums, coumarins and chromones

All practical syntheses of benzene ring-fused pyryliums and pyrones 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, i.e. reaction of resorcinol with a β-ketoester, 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 the activating hydroxyl *para* to the point of attack being crucial to the success of the sequence.
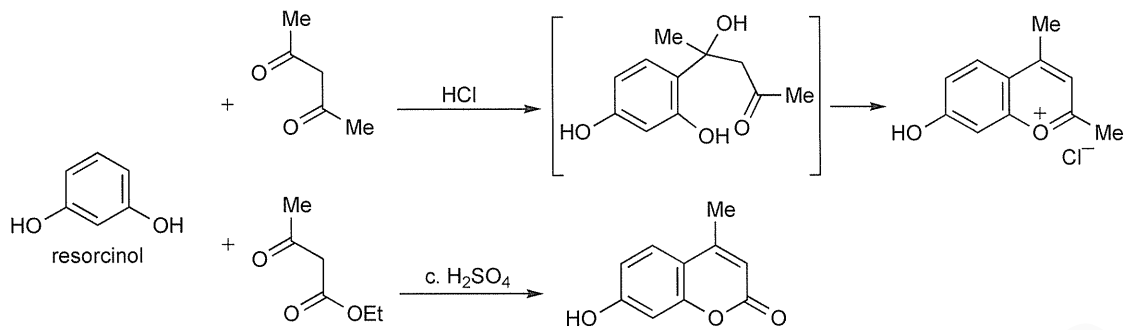
Syntheses of a coumarin and a 1-benzopyrylium salt from resorcinol.

Salicylaldehyde reacts with aryl methyl ketones in acid to produce 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 salicylaldehyde with acetic anhydride – produces coumarin.
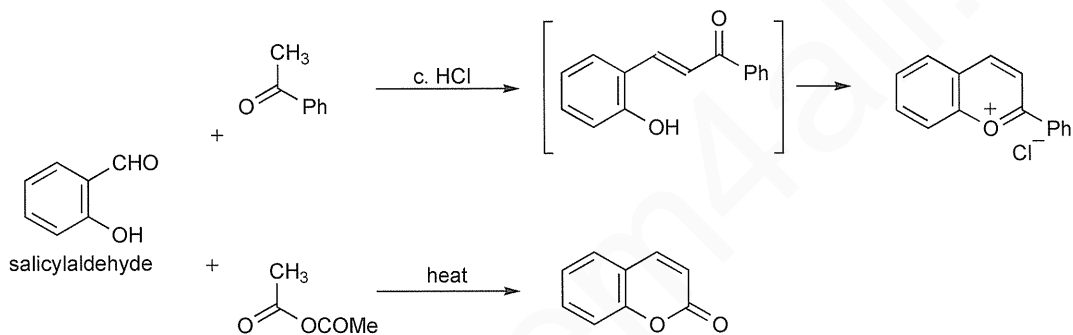
Syntheses of a coumarin and a 1-benzopyrylium salt from salicylaldehyde.

ortho-Hydroxyaryl methyl ketones can be simply *O*-acylated, giving phenolic esters. Carrying out a rearrangement (arrows) leads to a 1,3-diketone phenolate anion, which closes to a chromone when acidified.
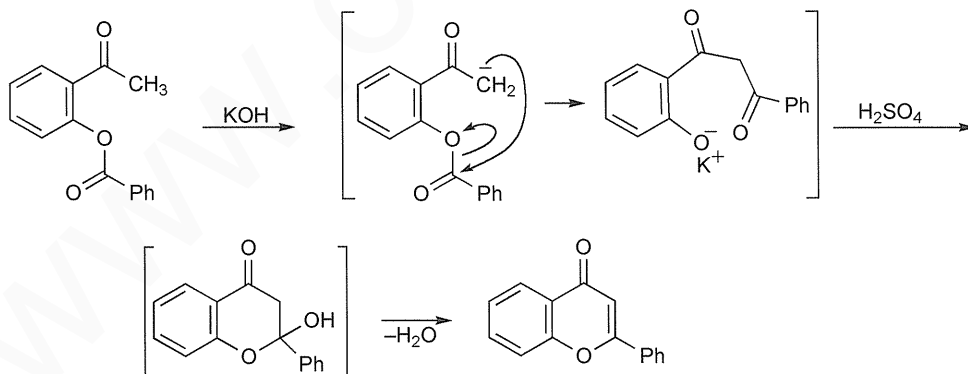
Synthesis of a 2-arylchromone (a 'flavone') from an *ortho*-hydroxyphenyl methyl ketone benzoate.

8.1 Pyrroles and Electrophiles – Substitution at C

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 – addition of an electrophile to the nitrogen would produce a high-energy non-aromatic species.
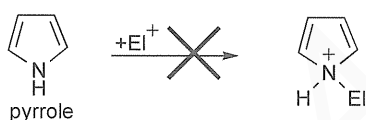
Pyrroles do *not* add electrophiles (or protons) at the nitrogen.

Pyrrole readily undergoes 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 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.
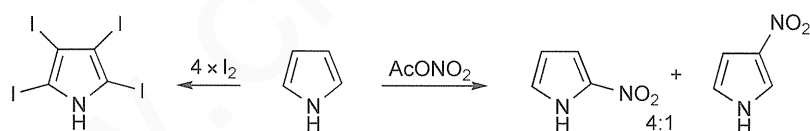
Nitration and iodination of pyrrole.

Positional selectivity and the high reactivity are both well explained by a consideration of the resonance contributors to the intermediates (and by implication, the transition states which 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 (3) compared with the β-intermediate (2). Note that the C=C double bond in the intermediate for β-attack is not, and cannot become, involved in delocalisation of the charge.
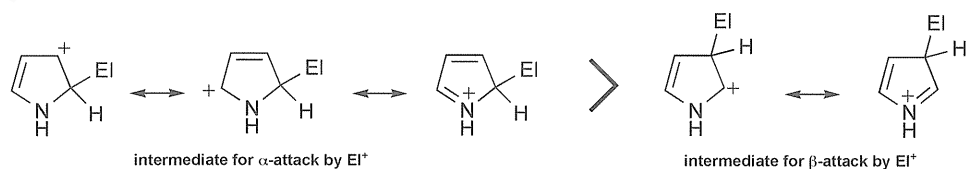
Positional selectivity in electrophilic substitution of pyrrole rationalised by relative stabilities of intermediates.

The balance in positional selectivity is tipped by the presence of bulky groups on nitrogen, which sterically impede reaction at α-positions. For example, 1-(triisopropylsilyl)pyrrole (N-TIPS-pyrrole) is attacked exclusively at a β-position. The N-substitutent can be subsequently easily removed using fluoride to provide the N-hydrogen β-substituted pyrrole.
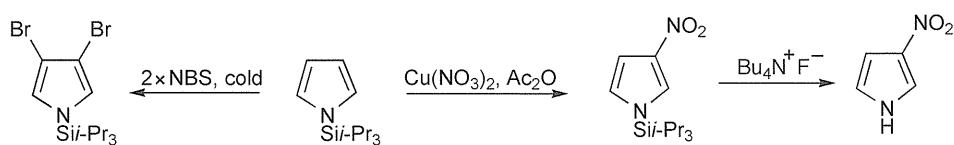
Electrophilic β-substitutions of 1-(triisopropylsilyl)pyrrole.

Electrophilic substitutions of pyrroles are very useful in synthesis, though strong protic or Lewis acidic conditions must be avoided, the high reactivity of the heterocycle meaning that such conditions lead to rapid degradation or polymerisation. Fortunately, this very same high reactivity means that Friedel–Crafts-type acylations of pyrrole do not require Lewis acid catalysis. Two of the most frequently used electrophilic substitutions involving C—C bond formation are the Vilsmeier reaction, forming an aldehyde, and the Mannich reaction, substitution being exclusively at the pyrrole α-position in each case (*cf.* pages 10 and 11).
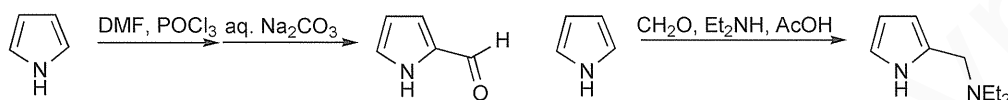
Vilsmeier formylation of pyrrole and Mannich diethylaminomethylation of pyrrole.

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 (*N*-Boc-pyrrole) can be achieved with NBS (*N*-bromosuccinimide); *N*-tosylpyrrole can also be dibrominated, but at the 3- and 4-positions. Incidentally, halo-pyrroles are generally rather unstable and the presence of electron-withdrawing groups on nitrogen considerably stabilises them and facilitates subsequent manipulations.
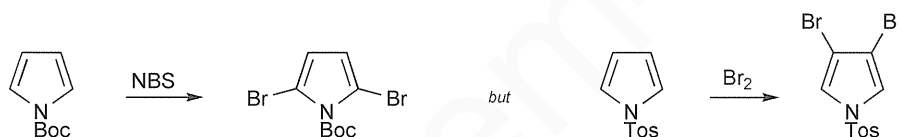
Electrophilic substitutions of 1-substituted pyrroles.

Strong electron-withdrawing groups on carbon can, additionally, modify the regioselectivity of electrophilic attack. One nice example of this is in a sequence for the synthesis of methyl 4-nitropyrrol-2-ylcarboxylate that begins with acylation of pyrrole, as usual at the α-position, with trichloroacetyl chloride and then nitration of this product ketone, in which the influence of the α-acyl substituent overrides the intrinsic tendency for α-substitution and β-substitution (*meta* to the chloroacetyl group) takes place; methanolysis of the trichloroacetyl substitutent then produces the ester.
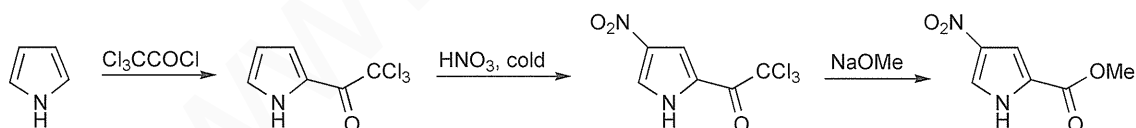
Electrophilic substitution at C-4 of a pyrrole with an electron-withdrawing group at C-2.

8.1.1 Oxidation of Pyrroles – Polypyrrole

Simple pyrroles are rather easily oxidised, usually with degradation of the ring; sometimes maleimides can be isolated. An important area where technology and heterocyclic chemistry combine is that of electroactive organic materials. The mechanism of conduction often involves long chains of conjugated molecules, thus organic conductors include poly(acetylene), poly(aniline), poly(thiophene) and poly(pyrrole). Pyrrole can be oxidatively polymerised either electrochemically or chemically, for example 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.
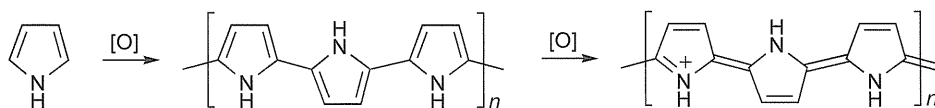
Formation of polypyrrole and its 'doping'.

8.2 *N*-Metallated Pyrroles by Deprotonation

The *N*-hydrogen of pyrrole can be quantitatively removed with strong bases, giving a pyrrolyl anion. The pK_a for this process is 17.5, which, contrasted with the value for pyrrolidine, ~44, shows pyrrole to be appreciably more acidic than an amine. Pyrrolyl 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.
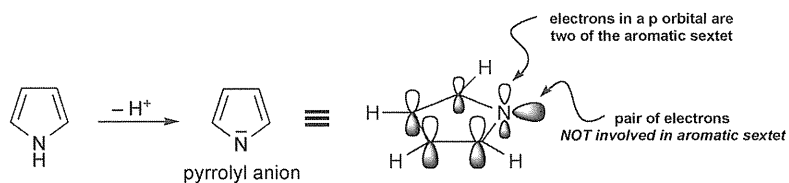
Structure of the pyrrolyl anion.

N-Substitution can also be achieved via small concentrations of the pyrrolyl anion generated by weaker bases, such as DMAP (4-dimethylaminopyridine). The syntheses of *N*-Boc-pyrrole and *N*-TIPS-pyrrole illustrate the synthetically important electrophilic trapping of pyrrolyl anions.
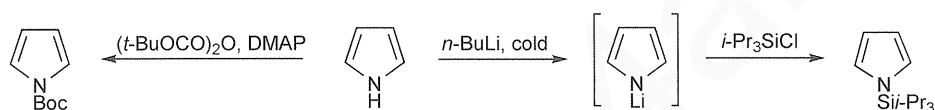
N-Substitution of pyrroles via pyrryl anions.

8.3 C-Metallated Pyrroles by Direct Deprotonation or by Halogen/Metal Exchange

N-Substituted pyrroles can also be deprotonated with strong bases, but *at carbon* and *selectively at an α-position*, producing organometallic intermediates which react with weak electrophiles, e.g. aldehydes and ketones, giving α-substituted products. If appropriately chosen, the *N*-(blocking)substitutent can then be removed. The conversion of pyrrole into 1-(trimethylsilylethoxymethyl)pyrrole (*N*-SEM-pyrrole) and thence by reaction with phthalide, a lactone, as electrophile, with final *N*-deprotection illustrate the importance of such methodology.
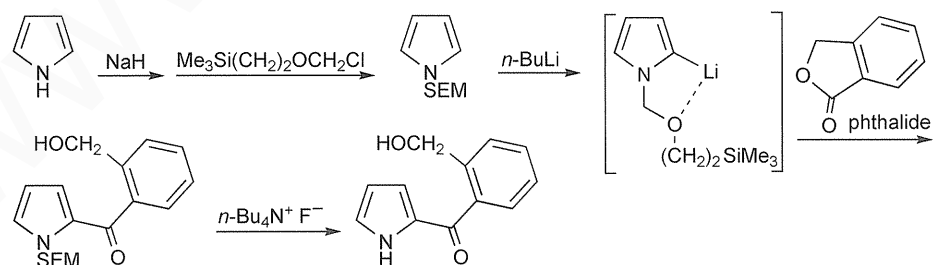
α-Substitution of a pyrrole *via* an α-lithiated intermediate.

Pyrrolyllithiums can be generated via metal/halogen exchange processes.
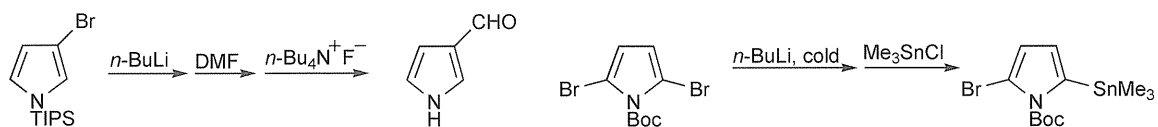
Metal/halogen exchange processes to generate pyrrolyllithiums.

8.4   Reactivity of Side-Chain Substituents

The electron-rich character of the pyrrole ring gives rise to some important, special properties of side-chain substituents. Pyrrole carboxylic acids readily decarboxylate, reflecting *C*-protonation to cations that are analogous to γ-carboxy-α,β-unsaturated ketones. 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.
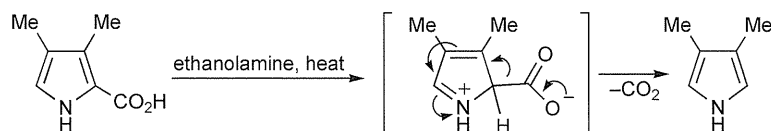
Easy decarboxylation of pyrrole acids.

Dialkylaminomethyl pyrroles, easily produced in Mannich substitutions, can be utilised in further elaborations, since the amine group (or an ammonium group derived from these by quaternisation can be easily displaced by nucleophiles, cyanide in the example shown below. 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.
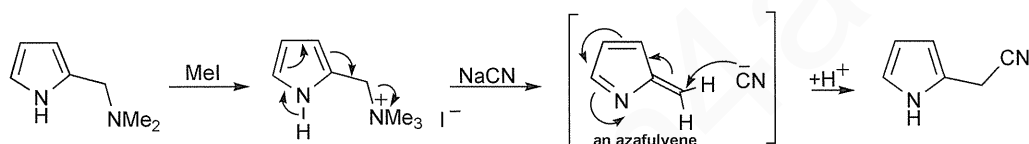
Utilising Mannich substitution products.

8.5   Pyrroles in Electrocyclic 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 reaction of *N*-Boc-pyrrole has been widely exploited: its reaction with dimethyl acetylenedicarboxylate is illustrative.
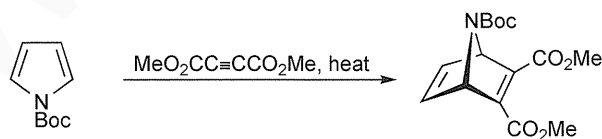
***N*-Boc-pyrrole reacting as a diene in a Diels–Alder reaction.**

By the same token, 1-phenylsulfonyl vinylpyrroles will take part in Diels–Alder cyclisations as the diene component utilising the side-chain double bond and one of the double bonds of the ring. The reaction of 1-phenylsulfonyl-3-vinylpyrrole with maleic anhydride produces an initial adduct which tautomerises to give the more stable, aromatic pyrrole-containing product.
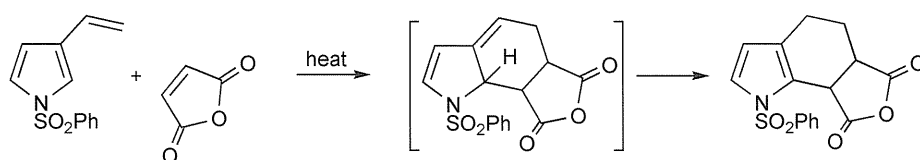
1-Phenylsulfonyl-3-vinylpyrrole reacting as a diene in a Diels–Alder reaction.

8.6 Pyrrole Ring Synthesis

8.6.1 Disconnections

There are three important disconnections for the construction of pyrroles from precursors without a pyrrole ring; these are summarised below.
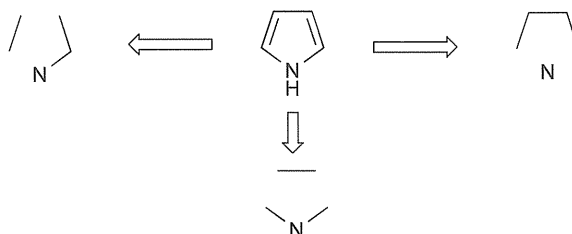
Principal disconnections for ring synthesis of pyrroles.

8.6.2 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. Successive inter- then intramolecular nucleophilic additions of ammonia/amine nitrogen to the two carbonyl groups, followed by loss of two molecules of water and finally tautomerism, lead to the aromatic molecule. The use of 2,5-dimethoxy-2,3,4,5-tetrahydrofuran, as a convenient equivalent for butane-1,4-dial, provides a useful route to N-substituted-2,3,4,5-tetra-unsubstituted pyrroles.
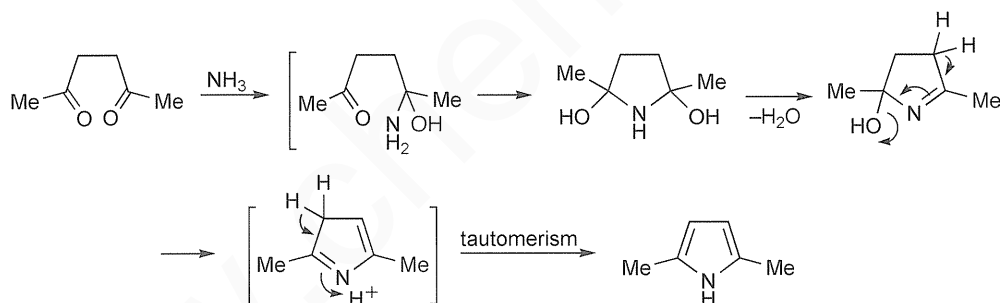
Ring synthesis of a pyrrole from a 1,4-diketone.
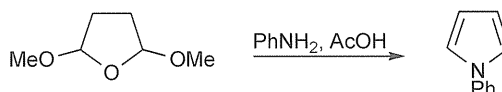
Ring synthesis of a pyrrole from 2,5-dimethoxy-2,3,4,5-tetrahydrofuran (equivalent to butane-1,4-dial).

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

This route, often referred to as the Knorr pyrrole synthesis, rests on the one-pot, sequential condensations of an α-aminoketone with a 1,3-diketone or 1,3-ketoester, 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 sure – probably the N—C bond is formed first, giving an enamine. Note that α-aminoketones are unstable as they readily self-condense to form dihydropyrazines and so must be *either* synthesised in the presence of the other reactant *or* incorporated into the reaction mixture in protected form. The simplest way to do this is to use a salt of the amine, and then add an inorganic base to liberate the amine *in situ*. The synthesis of ethyl 2,4-dimethylpyrrole-3-carboxylate

shown involves pyruvaldehyde oxime and ethyl acetoacetate. The aminoketone is produced by reduction of the oxime *in situ*.
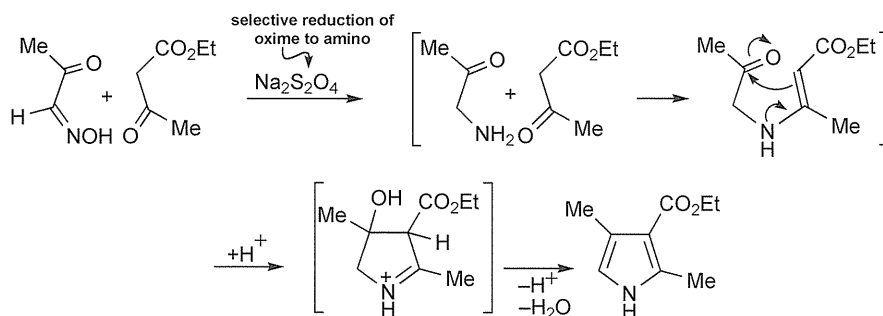
Ring synthesis of a pyrrole from an α-aminoketone.

A useful route to *N*-protected α-aminoketones is the reaction between a 'Weinreb amide' [RCON(OMe)Me] of an *N*-Cbz-protected α-amino acid; Weinreb amides react with alkyl- or aryllithiums or Grignard reagents to give ketones. In this situation, the α-aminoketone is released by hydrogenolysis of the Cbz protecting group in the presence of the other synthesis component, as illustrated for a reaction with ethyl acetoacetate.
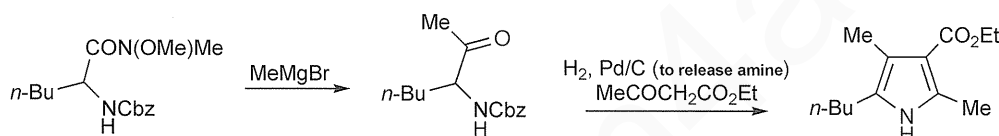
The use of Weinreb amides of protected α-amino acids to prepare protected α-aminoketones for pyrrole ring synthesis.

The Knorr synthesis often produces pyrrole esters and it is relevant to recall (page 53) their hydrolysis and easy decarboxylation, if the ester is not required.

8.6.4 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 that includes an isonitrile. Tosylmethyl isocyanide (TolSO$_2$CH$_2$NC, Tosmic) has been the most frequently used. 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.
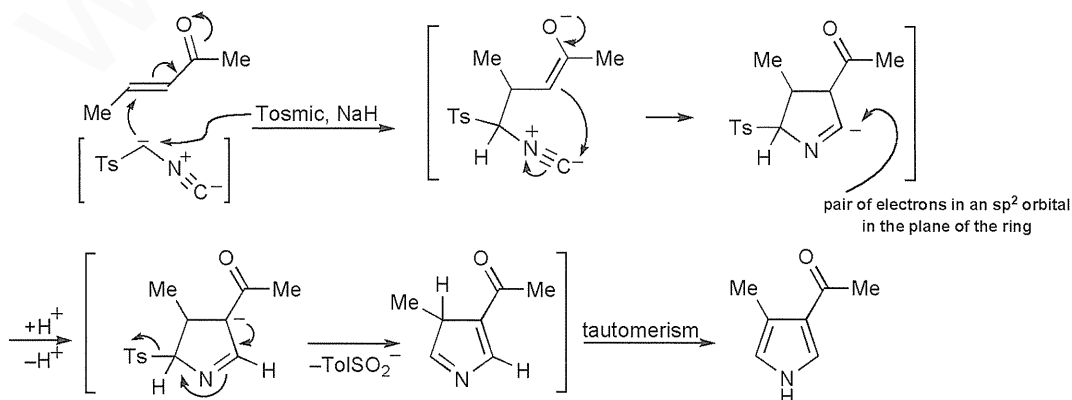
Ring synthesis of a pyrrole using tosylmethyl isocyanide (Tosmic).

Indoles

9.1 Indoles and Electrophiles – Substitution at C

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. Electrophilic addition of a proton to an indole β-position does occur, to a *very* minor degree; however, if 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.
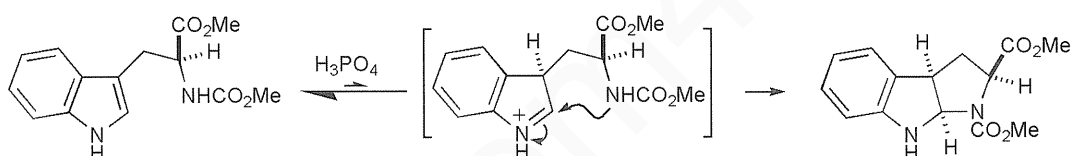
Trapping a 3H-indolium cation with a nucleophile.

Similarly, indole does not add electrophiles at the nitrogen, but does readily undergo electrophilic C-substitution in the much more electron-rich pyrrole ring. 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. Indoles are attacked by electrophiles *much* more easily than benzene. This high reactivity is demonstrated by the bromination of indole using bromine alone, and its acylation with an acid chloride, without the need for a Friedel–Crafts catalyst.
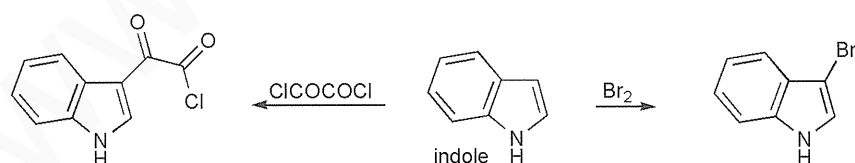
Bromination and an acylation of indole.

Easy substitution at the α-position is illustrated by the mild intramolecular Mannich reaction involved in the conversion of tryptamine, via the electrophilic iminium intermediate into a tetrahydro-β-carboline.
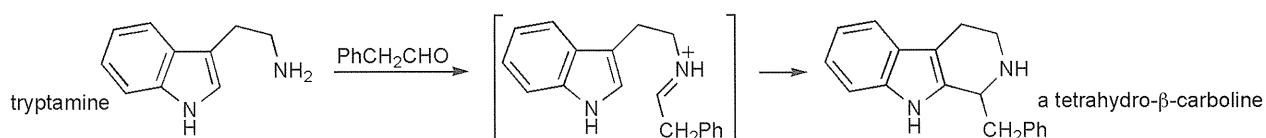
Intramolecular Mannich substitution at an indole α-position.

Positional selectivity and 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

56

retain a complete benzene ring); however, delocalisation involving donation of electron density from the hetero-atom, is greater in the intermediate from β-attack, compared with the α-intermediate, but note that it is only slightly less stabilised, being a benzylic cation.

intermediate for β-attack by El⁺   intermediate for α-attack by El⁺
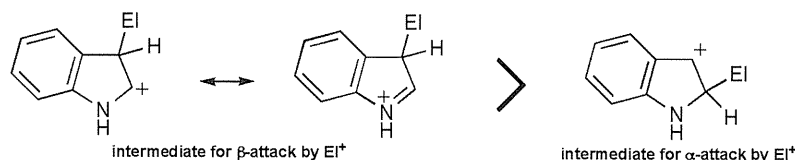
Positional selectivity in electrophilic substitution of indole rationalised by relative stabilities of intermediates.

Electrophilic substitutions of indoles are widely used. Three other illustrative examples from many are its alkylation with nitroethene again without any acid or other catalyst being required; its conversion into the 3-aldehyde via the Vilsmeier reaction; and Mannich substitution forming gramine (see also above), involving attack by a mild iminium electrophile, e.g. $[H_2C{=}NR_2]^+$, illustrating again selectivity for the β-position.
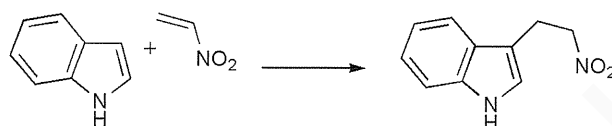
3-Alkylation of indole with nitroethene.
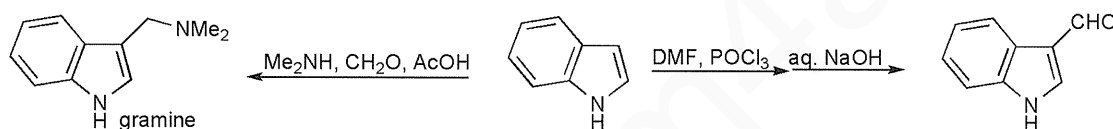
Mannich dimethylaminomethylation and Vilsmeier formylation of indole (*cf.* pages 10 and 11).

Even indoles carrying electron-withdrawing (and therefore deactivating) groups on nitrogen will undergo β-electrophilic substitution; the 3-nitration of 1-phenylsulfonylindole is 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-(triisopropylsilyl)indole is more stable than 3-bromoindole itself.
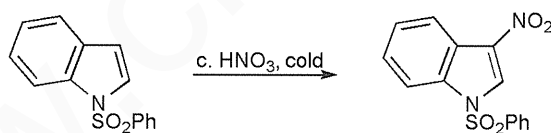
Nitration of 1-phenylsulfonylindole.
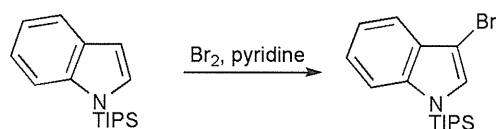
Bromination of 1-(triisopropylsilyl)indole.

9.2 *N*-Metallated Indoles by Deprotonation

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, say 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.
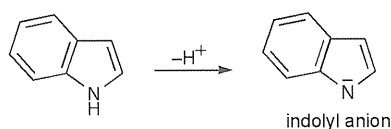
N-Deprotonation of indole generates the indolyl anion.

The synthetically important electrophilic trapping of indolyl anions is illustrated by the preparation of *N*-methylindole (1-methylindole) and *N*-Boc-indole.
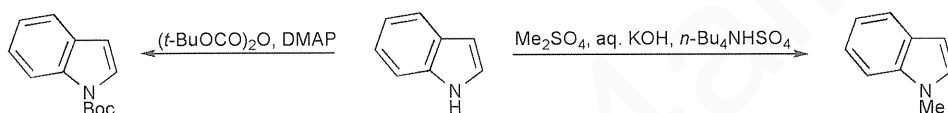
N-Substitution of indoles via indolyl anions.

9.3 C-Metallated Indoles by Direct Deprotonation

N-Substituted indoles can also be deprotonated, but only with very strong bases, *at carbon* and *selectively at the α-position*, producing organometallic intermediates which react with weak electrophiles, e.g. carbonyl compounds, giving α-substituted products. If appropriately chosen, the *N*-(blocking)substituent can then be removed. Several of the common *N*-blocking groups also assist the regioselective α-lithiation via intramolecular coordination and electron withdrawal, for example PhSO$_2$. The use of 1-phenylsulfonylindole illustrates the importance of this lithiation methodology in indole chemistry.
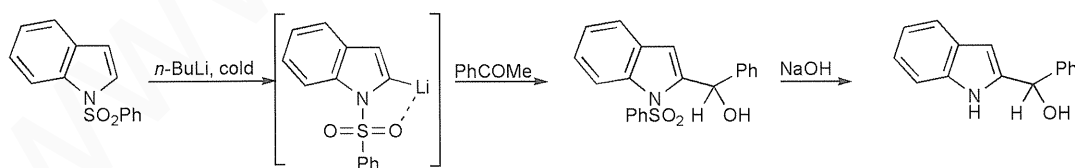
α-Alkylation of indole via α-lithiation of 1-phenylsulfonylindole.

A very elegant device for *N*-protection involves *in situ* *N*-carboxylation (base and CO$_2$) before α-lithiation. 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-bromoindole.
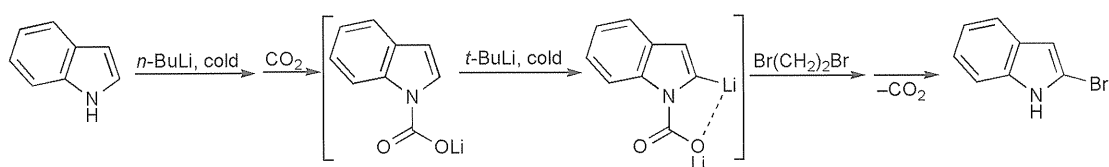
α-Bromination of indole via α-lithiation of indole-1-carboxylic acid lithium salt.

9.4 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, can be utilised in further elaborations, since the amine group (or an ammonium group derived from these by selective side-chain amine quaternisation) can be easily displaced by nucleophiles. These are not direct displacements but involve ring-*N*-hydrogen deprotonation, leading to elimination of the side-chain nitrogen and an intermediate azafulvene, to which the nucleophile adds, in a conjugate addition. The nucleophile in the example shown is the anion of a substituted malonate.
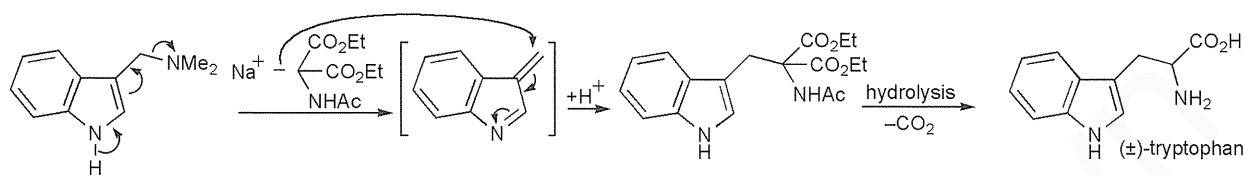
Utilising gramine to make 3-substituted indoles.

9.5 Reduction of Indoles

Treatment of indole with sodium in liquid ammonia (Birch reduction) causes reduction of the benzene ring only. Metal–acid or borohydride–acid combinations cause reduction of the heterocyclic ring only, and thus the formation of 2,3-dihydroindoles, commonly known as indolines.
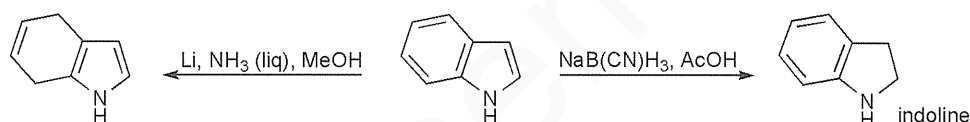
Reduction of indole.

9.6 Indoles with Oxygen Substituents

Hydroxyl groups on the benzene ring of indoles 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. 3-Hydroxyindole is the minor component in tautomeric equilibrium with the ketone form, usually, but trivially, known as indoxyl. It is easily oxidised and transformed into the ancient dye, indigo. Isatin is best viewed simply as an α-ketoamide. 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 indolic compounds.
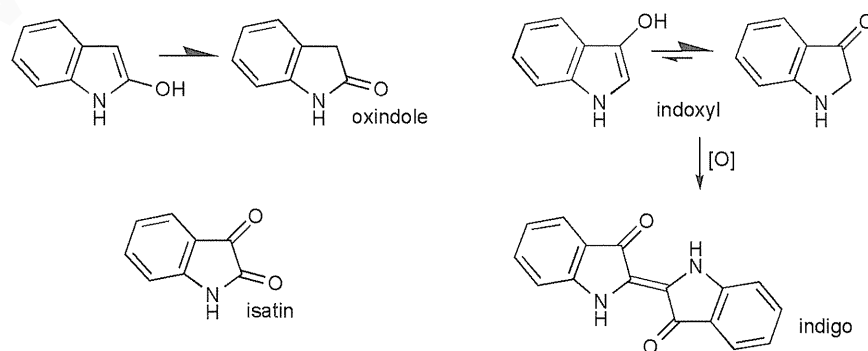
Oxygenated indoles.

9.7 Indole Ring Synthesis

9.7.1 Disconnections

There are many, many ways to synthesise indoles but here we will discuss three important routes for the construction of indoles from precursors without a pyrrole ring, based on the disconnections summarised below.
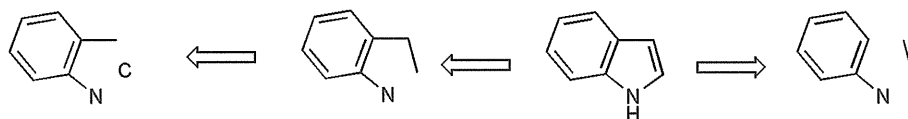
Principal disconnections for ring synthesis of indoles.

9.7.2 Synthesis of indoles from phenylhydrazones – the Fischer indole synthesis (1,2- and 3,3a-bonds made)

This, the classic synthesis of indoles, discovered by Emil Fischer in 1883, is still one of the 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 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.
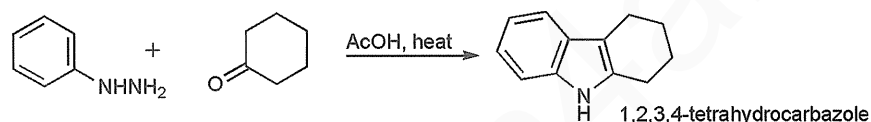
Example of a Fischer indole synthesis.

The scheme below shows the sequence of steps in general form: the phenylhydrazone is in equilibrium with a small quantity of its enamine tautomer which is *N*-protonated and it is this species which 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 to iminium addition, and finally loss of ammonia produce the indole.
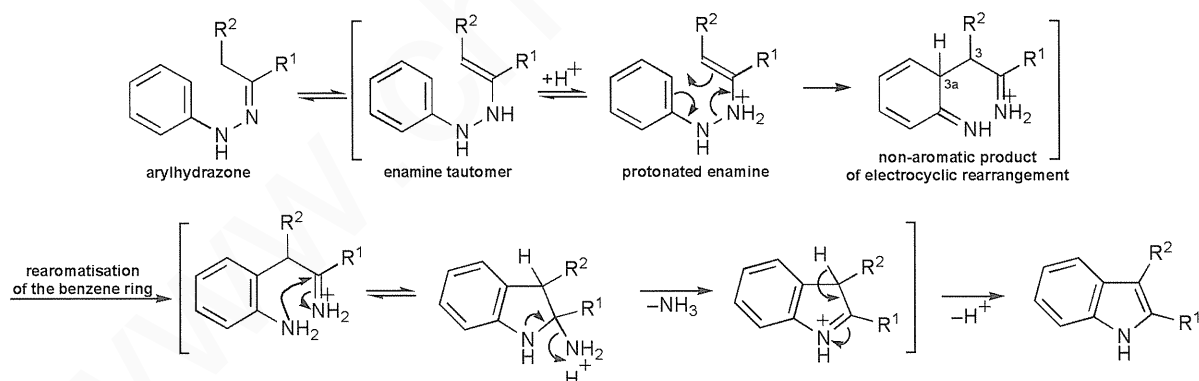
Mechanism of the Fischer indole synthesis.

9.7.3 Synthesis of indoles from ortho-nitrotoluenes (2,3- then 1,2-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. A sequence that takes advantage of this acidity is the Leimgruber–Batcho indole synthesis.
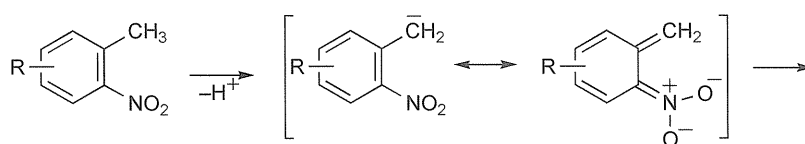
Acidity of *ortho*-nitrotoluenes.

An *ortho*-nitrotoluene is simply heated with dimethylformamide dimethylacetal (DMFDMA) (cf. page 14), 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.
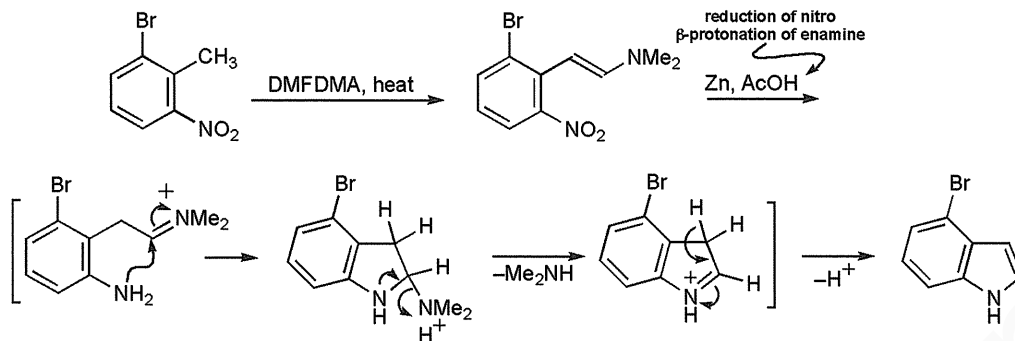
Synthesis of 4-bromoindole using a Leimgruber-Batcho synthesis.

9.7.4 Synthesis of indoles from ortho-nitroaryl halides or ortho-aminoaryl halides (3,3a- then 1,2-bonds made)

With the advent of palladium-catalysed coupling technology, indoles can be synthesised 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 coupling, ring closure cannot take place until a subsequent reductive step takes the nitro group down to amine. Note that there are several other indole syntheses which converge on the formation of an amino-carbonyl intermediate, which rapidly closes and loses water to achieve the fully aromatic status.
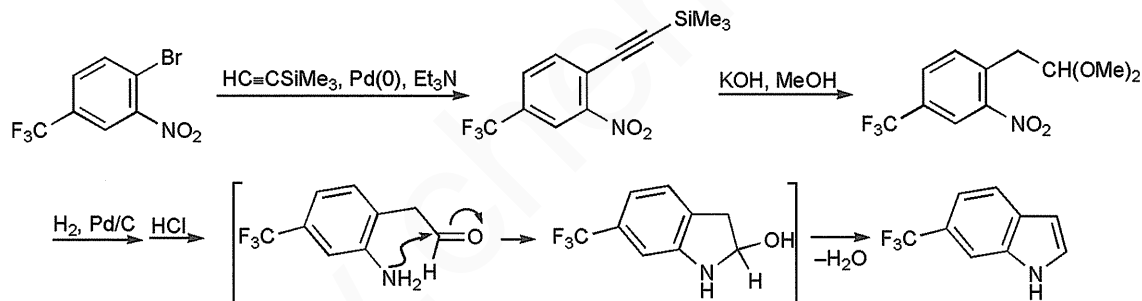
Synthesis of 2,3-unsubstituted indoles from an *ortho*-bromoaniline and trimethylsilylacetylene.

10.1 Furans and Thiophenes and Electrophiles – Substitution at C

The reactivities of furan and thiophene can usefully be examined in parallel, comparing one with the other and with pyrrole. 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 conjugated diene. For example, thiophene undergoes normal nitration, with α-selectivity (like pyrrole – see the discussion on page 50) but furan tends to produce 1,4-dihydrofuran *adducts* in which the elements of the nitrating agent ($AcONO_2$) 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.
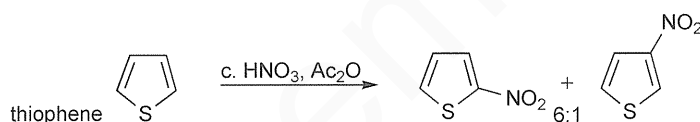
Nitration of thiophene.
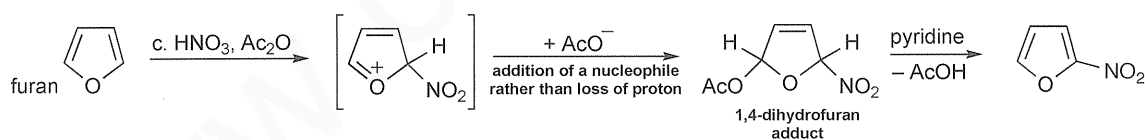
Adduct formation in nitration of furan.

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 tetrabrominate thiophene and the last two can be used to access 3- or 3,4-dibromothiophenes because zinc–acetic acid specifically reduces out α-bromines.
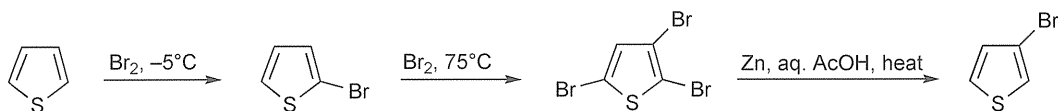
Bromination of thiophene.

Furan also reacts rapidly with bromine, but in a nucleophilic solvent like methanol, the initial cationic intermediate is trapped by *addition* of solvent, the isolated product, 1,4-dihydro-1,4-dimethoxyfuran, resulting from a final nucleophilic displacement of the bromine from its reactive position in the first adduct, the bromine being both allylic and α to oxygen.

1,4-Dihydro-1,4-dimethoxyfuran is a synthetic equivalent of but-2-ene-1,4-dial and its dihydro derivative for butane-1,4-dial, both of which are valuable in heterocyclic ring synthesis.
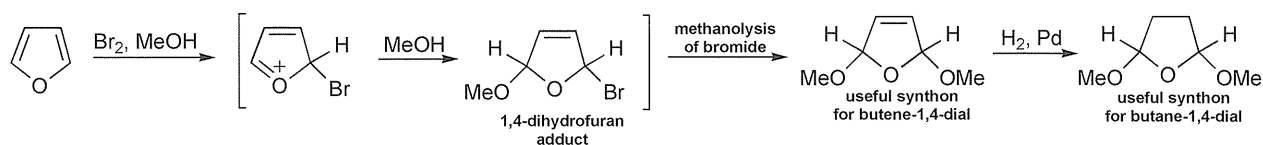
Adduct formation in 'bromination' of furan.

Vilsmeier formylation and Friedel–Crafts acylations proceed efficiently with thiophene and furan, in the former case using $SnCl_4$ as the Friedel–Crafts catalyst and in the latter, BF_3.
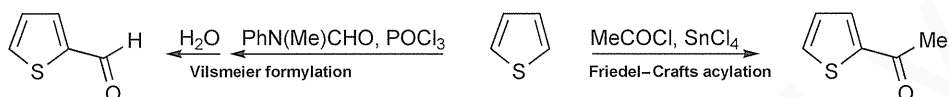
Friedel–Crafts and Vilsmeier acylations of thiophene.

The Mannich dimethylaminomethylation of thiophene and furan is conducted using the preformed iminium salt. This is especially important in the case of furan since 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.

Mannich substitutions of thiophene and furan.
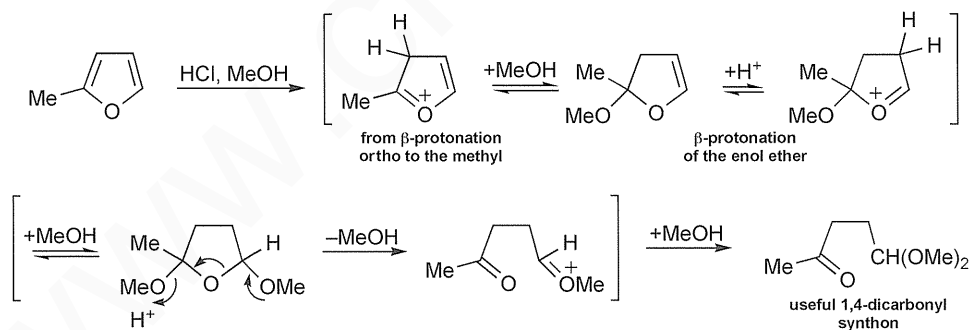
Methanolytic ring opening of a furan.

10.2 C-Metallated Thiophenes and Furans by Direct Deprotonation or Halogen/Metal Exchange

In thiophene and furan chemistry, there is, of course, no equivalent to the acidic *N*-hydrogen of pyrrole. Thus, we can compare strong base deprotonations of thiophene/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 thermodynamically controlled equilibration 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.
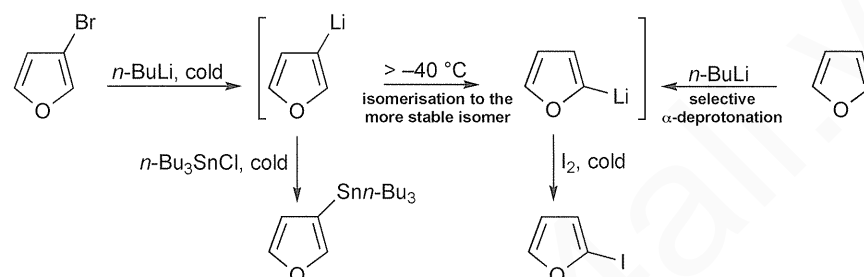
Lithiated furans – reactions with electrophiles.

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 (lithium diisopropylamide): *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 the metal/halogen exchange process and gives 3-lithiothiophene.
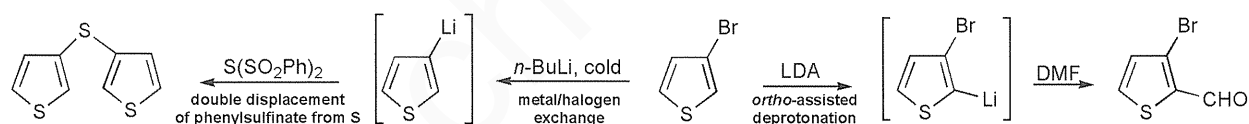
3-Bromothiophene – DoM at C-2 versus exchange to give 3-lithiothiophene.

10.3 Furans (and Thiophenes) in Electrocyclic Reactions

Furan, the 'least aromatic' of the trio furan/thiophene/pyrrole, reacts readily with electron-deficient dienophiles; the *exo* structure of its product with maleic anhydride is the result of a readily reversible cycloaddition, which allows the kinetic *endo* product to be converted into the thermodynamic *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 (as dienes) in Diels–Alder reactions when an electron-withdrawing substituent is present on the nitrogen to make them 'less aromatic' – more like a diene.
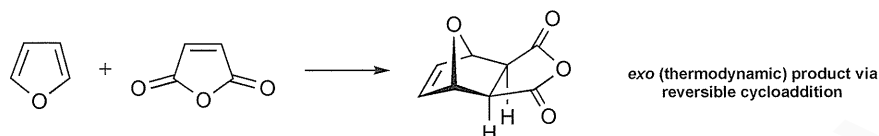
Diels–Alder reaction of furan with maleic anhydride.

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' and that is an oxidative process, not possible with furan or pyrrole. Reaction of substituted thiophenes with peracids can give isolable sulfoxides or sulfones, which, being less aromatic than the parent thiophenes, *do* take part in Diels–Alder cycloadditions readily.
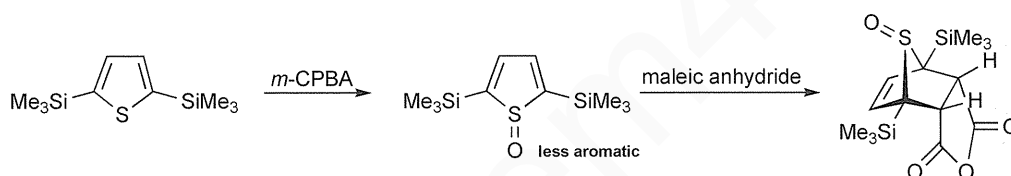
Diels–Alder reaction of a thiophene-1-oxide.

An important cycloaddition of furans is that with singlet oxygen, which gives cyclic peroxides (effectively ozonides of cyclobutadiene!) that can then be further utilised. A nice example is the reaction of furoic acid (furan-2-carboxylic acid, which is readily available by oxidation of the 2-aldehyde, furfural, in turn available in large quantities 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 malaldehydic acid (as its cyclic hemiacetal).
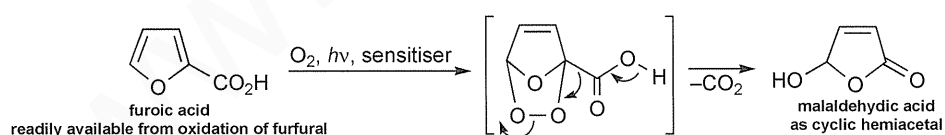
Cycloaddition of singlet oxygen with furoic acid.

10.4 Oxidation and Reduction of Furans and Thiophenes

10.4.1 Exhaustive reduction of thiophenes

There is another aspect of thiophene chemistry not mirrored by furan or pyrrole – 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 functionalised 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.
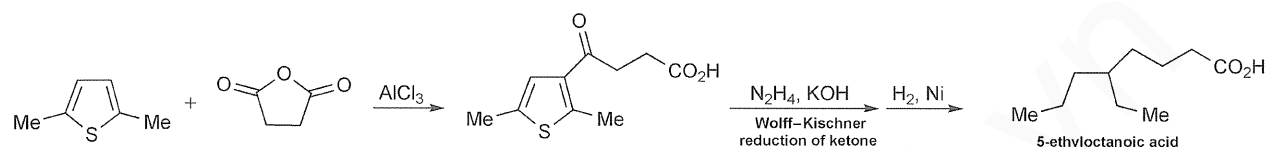
Use of a thiophene to construct a carbon skeleton with a final reduction and hydrogenolysis of the sulfur.

10.4.2 Controlled oxidation of furans

The conversion of furans into 1,4-dihydro-1,4-dimethoxyfurans (synthetic equivalents of unsaturated 1,4-dicarbonyl compounds; see page 63) via halogenation in methanol is effectively an oxidation. There are other ways in which such 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-catalysed work-up causes isomerisation to the more stable E-isomers.

Oxidative opening of furans to produce ene-1,4-diones.

10.5 Furans and Thiophenes with 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.
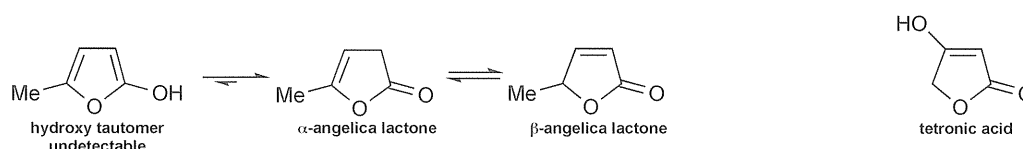
Tautomerism in oxygenated furans.

10.6 Furan and Thiophene Ring Synthesis

10.6.1 *Disconnections*

Various routes for the synthesis of these heterocycles have been devised, and interest in furan construction has been particularly popular. Here we deal only with the most straightforward processes that involve 1,4-di-functionalised four-carbon precursors.
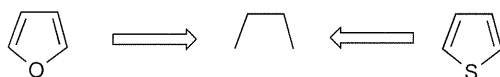
Principal disconnections for ring synthesis of furans and thiophenes.

10.6.2 *Synthesis of furans and thiophenes from 1,4-dicarbonyl compounds*
(1,2- and 1,5-bonds made)

The conversion of a 1,4-diketone into a furan is essentially a dehydration (it is the converse of the hydrolytic ring opening discussed on page 63). The most likely sequence has intramolecular addition of enolic oxygen to the other carbonyl group requiring, then, simply loss of water.
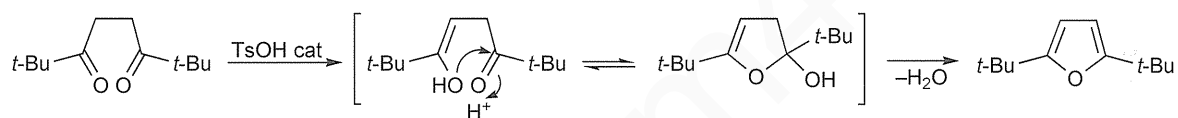
Synthesis of furans from 1,4-dicarbonyl compounds.

To change this strategy into a thiophene synthesis, all that is necessary is to expose the 1,4-dicarbonyl precursor to conditions that convert carbonyl into thiocarbonyl after which an exactly comparable sequence leads to the aromatic thiophene, with loss of H_2S. 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.
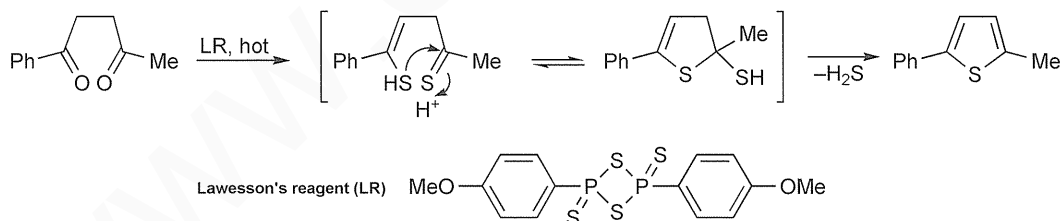
Synthesis of thiophenes from 1,4-dicarbonyl compounds.

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 H_2S to one of the alkynes.
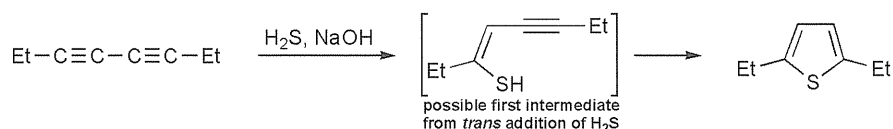
Synthesis of thiophenes from 1,3-diynes.

1,3-Azoles and 1,2-Azoles

Introduction

The 1,3- and 1,2-azoles each contain a nitrogen in an environment analogous to that in pyridine – 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 – and one 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.

imidazole	thiazole	oxazole		pyrazole	isothiazole isoxazole
pK_{aH} 7.1	pK_{aH} 2.5	pK_{aH} 0.8		pK_{aH} 2.5	pK_{aH} −0.5 pK_{aH} −3.0
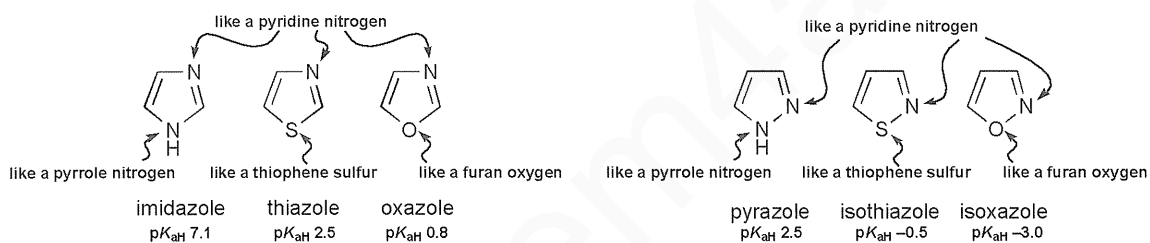
Basicities of azoles.

11.1 Azoles and Electrophiles – Addition at N and Substitution at C

11.1.1 Reactions at nitrogen

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), NH$_2$NH$_2$ (7.9), NH$_2$OH (5.8); thus, each 1,3-azole is a stronger base than its 1,2-counterpart.
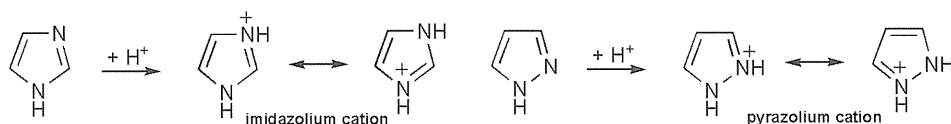
1*H*-Imidazolium and 1*H*-pyrazolium cations – resonance stabilisation.

The azoles react at the imine nitrogen with alkyl halides, pyrazole/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 (i.e. the relative nucleophilicities are similar to the relative basicities).
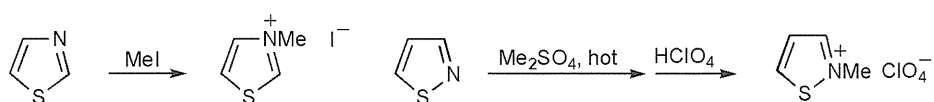
N-Methylation of thiazole and isothiazole.

To understand the *N*-alkylation of imidazole and pyrazole, we need firstly to be aware of the tautomerism, which 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. We write for example '4(5)-methylimidazole' to designate the tautomerism in such molecules. So, the alkylating electrophile reacts at a different rate with the two alternative imine nitrogens, on the basis of steric hindance, and the mixture of salts produced reflects that rate difference.
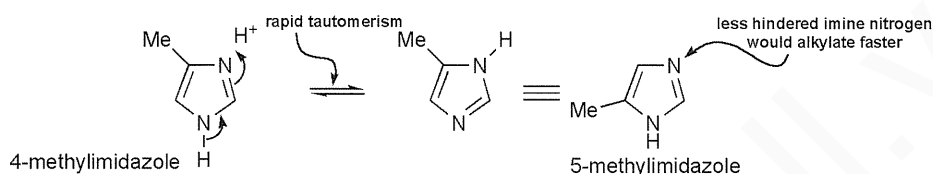
Tautomerism in 4(5)-methylimidazole.

There is a further aspect of alkylations of imidazoles and pyrazoles which we can illustrate with pyrazole: the first formed salt is both 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 starting material, which *cannot* then alkylate, and a neutral *N*-alkylpyrazole, which *can* alkylate but gives an *N,N′*-dialkylpyrazolium salt. The consequences of this interplay can be the formation of *mixtures* of starting material with mono- and dialkylated products.
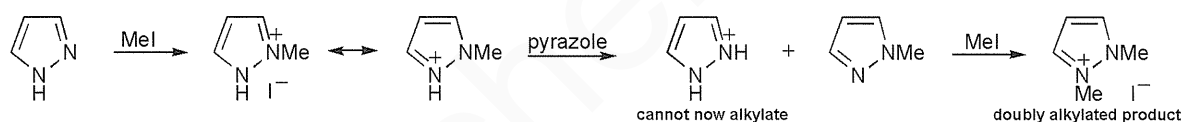
Reaction of pyrazole with iodomethane.

N-Acylimidazoles can be prepared using the acylating agent together with a tertiary amine base which 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.
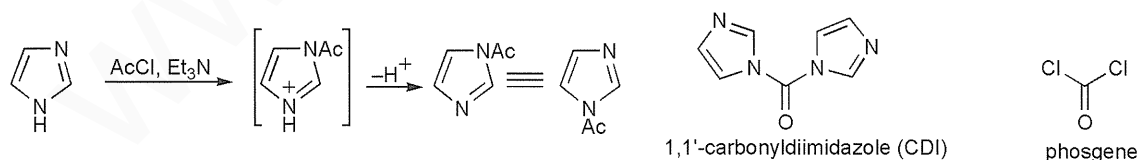
N-Acetylation of imidazole.

11.1.2 Reactions at carbon

In the sense that the azoles have a five-membered heteroaromatic system, one might anticipate easy electrophilic *C*-substitution, as in pyrrole, etc. However, the other heteroatom inductively withdraws electrons and reduces markedly the ability of these heterocycles to undergo electrophilic *C*-substitution compared with pyrrole/thiophene/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 the azoles is distinctly less than for pyrrole/thiophene/furan.

The gradation of reactivity is well illustrated by nitrations. Imidazole undergoes normal nitration at room temperature where 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*: The isolation of 4-nitroimidazole 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, this implies that there is much smaller concentration of the neutral heterocycle available for attack.
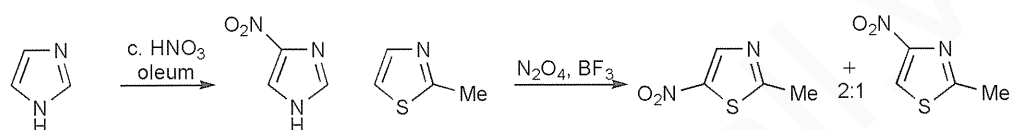
Nitration of imidazole and 2-methylthiazole.
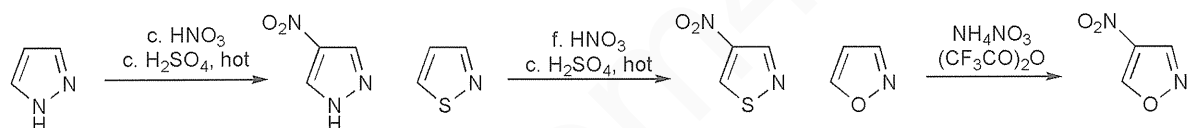
Nitration of pyrazole, isothiazole and isoxazole.

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. The thiazole system requires the activation of a 2-methyl to permit formation of 5-bromo-2-methylthiazole; oxazole has not been directly halogenated. The easily formed tribromoimidazole can be converted by reduction into 4(5)-bromoimidazole. 4-Halopyrazoles are accessible directly from the heterocycle, as are 4-bromoisothiazole and 4-bromoisoxazole, though less efficiently.
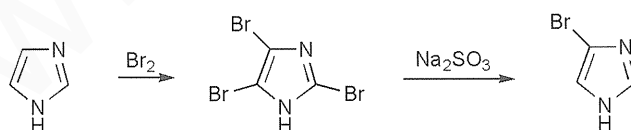
Bromination of imidazole.

Electrophilic substitutions with carbon electrophiles, as in Friedel–Crafts processes, are virtually unknown in azole chemistry.

11.1.3 Electrophilic substitution in activated ozoles

Electrophilic substitution takes place normally *ortho* to an amino- or acylamino substitutent.
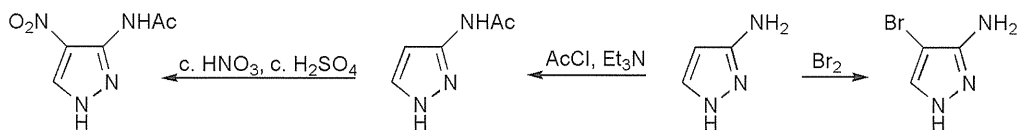
Electrophilic bromination of 3-aminopyrazole; electrophilic nitration of 3-acetylaminopyrazole.
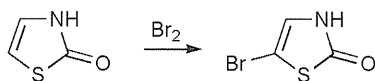
C-Bromination of thiazol-2-one.

11.2 Azoles in Nucleophilic Substitutions 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; the intermediates have a resonance contributor with negative charge on the nitrogen.

negative charge in intermediate
stabilised by nitrogen
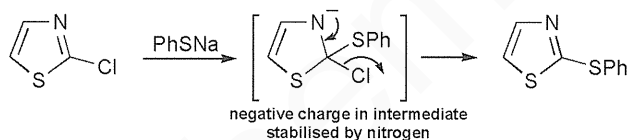
Nucleophilic substitution of a 2-halothiazole.

11.3 *N*-Metallated Azoles by Deprotonation

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; i.e., imidazole and pyrazole are more acidic than pyrrole: imidazole pK_a 14.2, pyrazole 14.2, pyrrole 17.5.
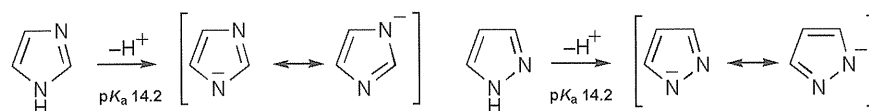
Acidity of *N*-hydrogen in imidazole and pyrazole – resonance stabilisation of imidazolyl and pyrazolyl anions.

These *N*-anions provide the means for the controlled introduction of substitutents onto the nitrogen of pyrazoles and imidazoles. It is important to remember that, as the resonance structures imply, the anions are ambident, i.e. 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 nitrogens.
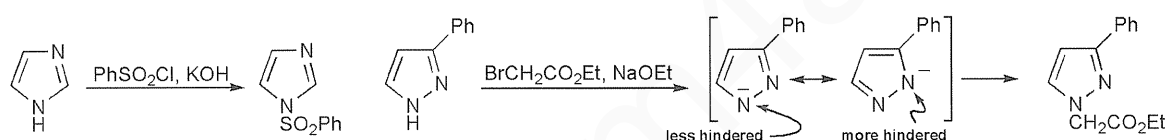
N-Substitutions of imidazoles and pyrazoles.

11.4 C-Metallated Azoles

11.4.1   Thiazoles, isothiazoles and N-substituted imidazoles and pyrazoles

11.4.1.1 By direct deprotonation

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.
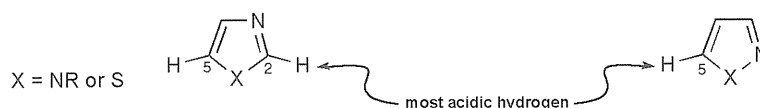
C-Hydrogen acidities in *N*-substituted-imidazoles, and -pyrazoles, thiazoles and isothiazoles.

Removal of an imidazole 5-hydrogen is perfectly possible however, with 2-substituted imidazoles, 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 and DMF are the examples in the following sequence.
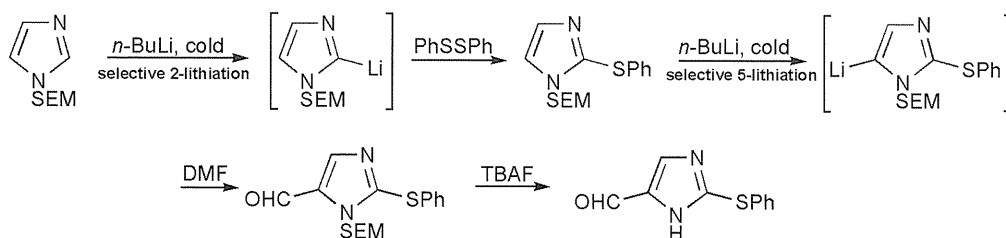
Lithiation of an *N*-blocked imidazole, exclusively at C-2, and of an *N*- *and* 2-blocked imidazole exclusively at C-5.
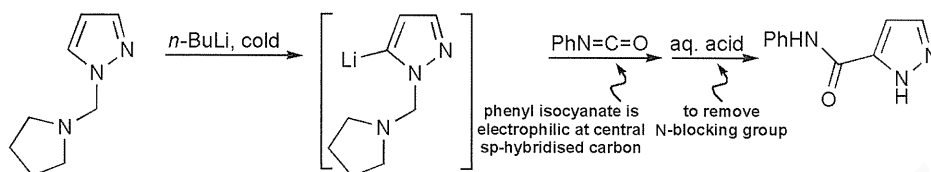
Lithiation of an *N*-blocked pyrazole exclusively at C-5.
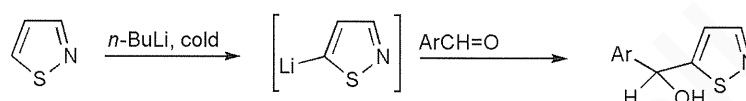
Lithiation of isothiazole exclusively at C-5.

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

11.4.1.2 By halogen/metal exchange
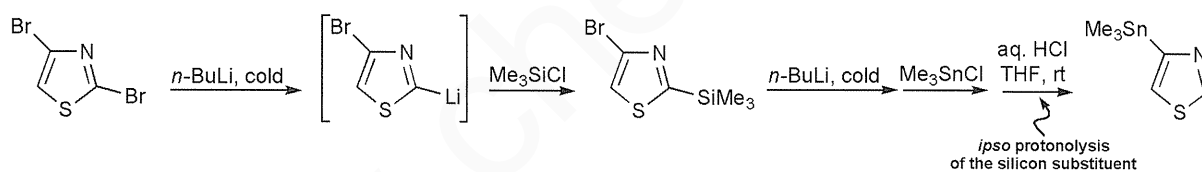
Selective metal/halogen exchange on 2,4-dibromothiazole; synthesis of 4-trimethylstannylthiazole.

Usually, when pyrazole and imidazole halides are used for these exchange reactions, an *N*-blocking group is installed.
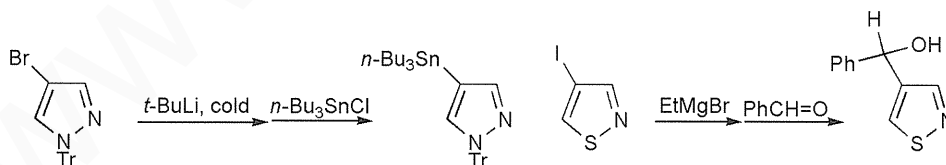
Metal/halogen exchange to generate a pyrazol-4-yllithium and an isothiazol-4-yl Grignard reagent.

73

11.4.2   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, 2-lithiation of oxazoles can lead to isonitrile-enolates. Attempted 5-lithiation of isoxazoles, which also have a hydrogen at C-3, leads inevitably to ring opening to a nitrile-enolate via removal of the 3-proton. The existence of such enolates can be demonstrated by trapping with electrophiles. Significantly, trapping the equilibrating mixture with triisopropyl 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.
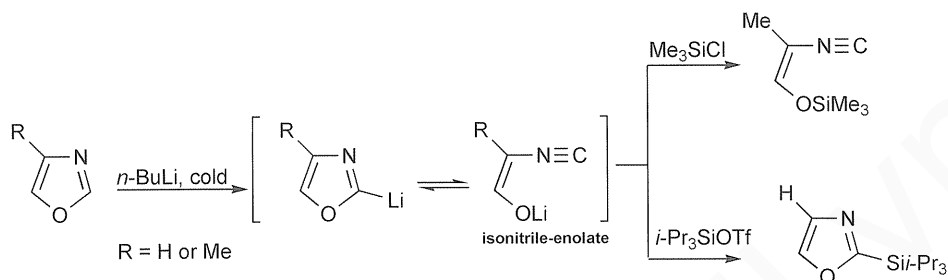
Reversible ring opening of a 2-lithio-oxazole and its trapping.
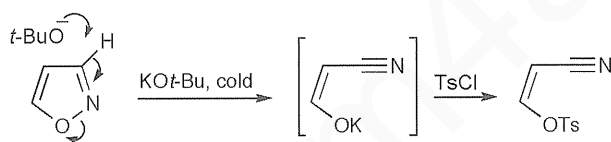
Ring opening via 3-deprotonation of an isoxazole.

11.5 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 first the formation of a concentration of protonic salt, and then C-2–H deprotonation of the salt, producing a transient ylide, to which a carbene form is an important resonance contributor. 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 $10^5{:}10^3{:}1$.
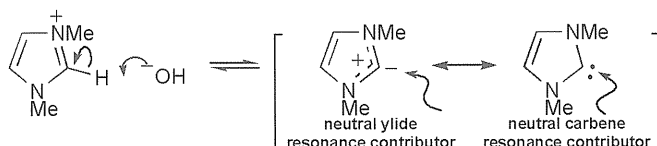
C-2-Hydrogen exchange of a 1,3-imidazolium salt via an ylide mechanism.

11.6 1,3-Azoles in Electrocyclic Reactions

Cycloaddition reactions of azoles as 4π components are important only for the 1,3-azoles, and amongst these, oxazole reactions have been most studied: 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. In other applications, oxazoles can be converted into pyridines by reaction with an electron-deficient alkene, the initial adduct losing water to form the aromatic pyridine (see page 27).
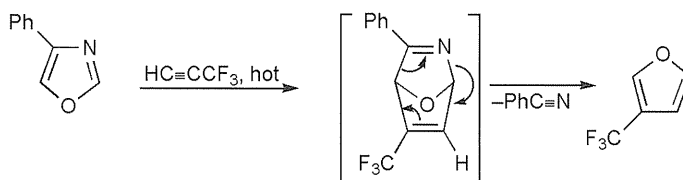
Synthesis of a furan via Diels–Alder addition of an alkyne to an oxazole.

11.7 Some Important Reductions of Azoles

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-dicarbonyl compounds that can find various uses, not the least, in the synthesis of other heterocyclic compounds.
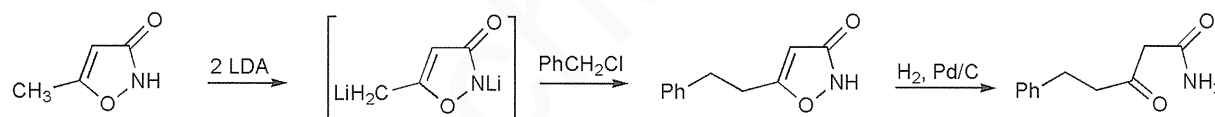
Hydrogenolysis of an isoxazol-3-one to reveal a 1,3-dicarbonyl compound.

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

complete reduction of thiazolium ring with
hydride reducing agent in protic solvent
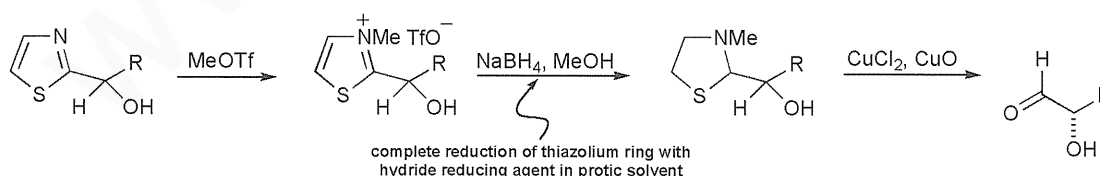
Complete reduction of a thiazolium ring with sodium borohydride, followed by hydrolysis of the resulting cyclic thioaminal.

11.8 Azoles with 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. 5-Bromination of thiazol-2-one is best viewed as β-electrophilic attack on the enamine unit. 1,3-Azol-2-ones react, like 2-pyridones, with phosphorus halides and thus can be converted into the 2-haloazoles.
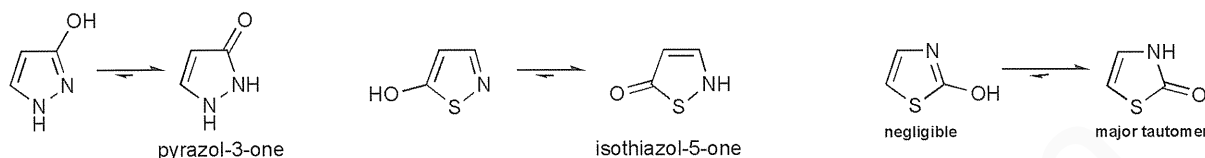
Structures of oxyazoles.

Azolones which have a methylene (CH_2) group α to the carbonyl will undergo aldol-type condensations with aldehydes at that centre and will couple at that position with aryldiazonium cations, giving coloured compounds that have been used as dyestuffs – tartrazine, used as a food or drink colourant, 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.
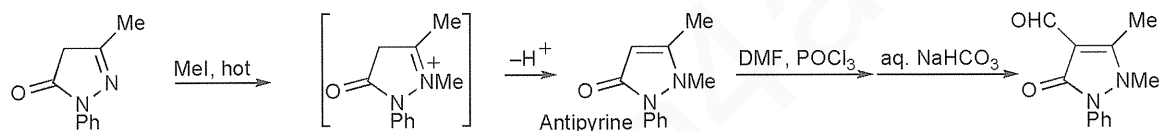
Electrophilic formylation of a pyrazol-5-one.
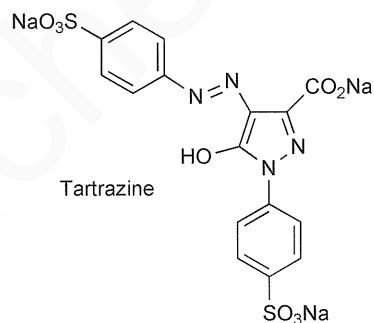
Tartrazine (E102) is a lemon yellow dye commonly used as a food colouring in the UK and the USA.

5-Oxazolones 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 called 'azlactones'. 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) undergo ready dipolar cycloadditions, with loss of carbon dioxide from the initial adduct.
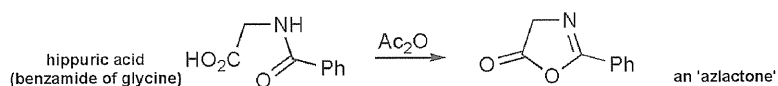
Synthesis of an azlactone (a 5-oxazolone).

The synthetically useful 2,4-dibromothiazole can be accessed from commercially available 2,4-thiazolidinedione.
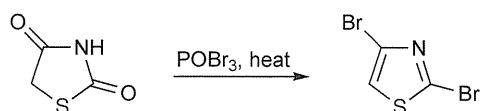
Synthesis of 2,4-dibromothiazole from commercially available dione.
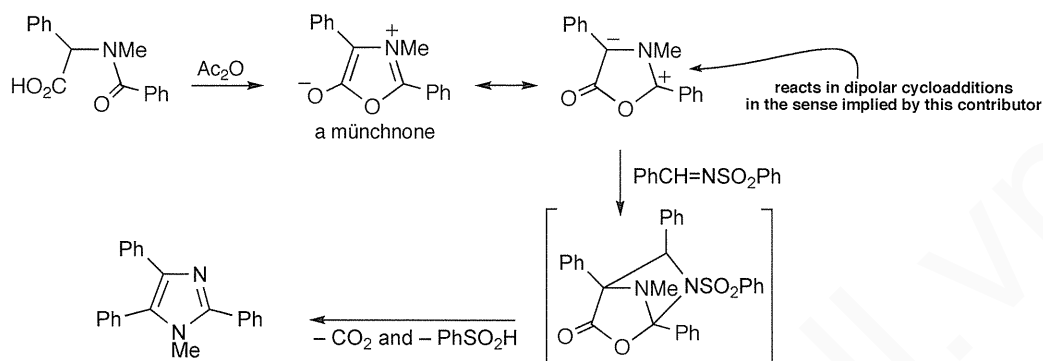
Synthesis of a münchnone and its reactivity in a dipolar cycloaddition.

Aminoazoles exist as the amino tautomers and all protonate on the ring nitrogen. The pK_{aH} of 2-aminoimidazole, the most basic isomer at 8.46, reflects the symmetry of the resonating guanidinium system in its cation. The aminoazoles behave as typical arylamines; for example they can be diazotised, thus providing routes to halo-azoles.
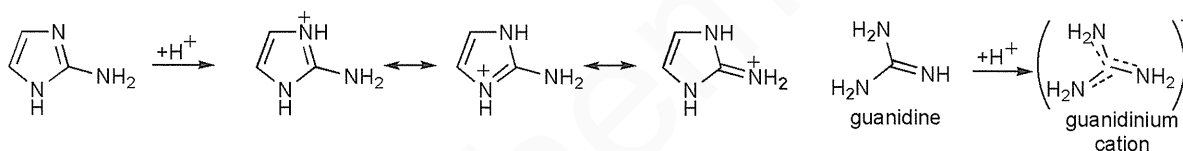
Strong basicity of 2-aminoimidazole due to guanidinium-like reasonance.
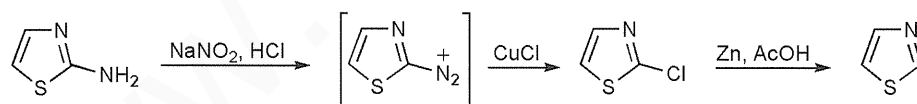
Diazotisation of 2-aminothiazole; reductive removal of a 2-halogen.

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-bromide occurs with the further activation of the *ortho* nitrile.
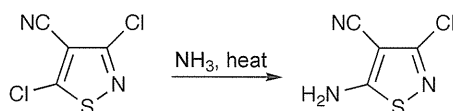
Selective displacement of bromine in an isothiazole.

11.9 1,3-Azoles Ring Synthesis

11.9.1 Disconnections
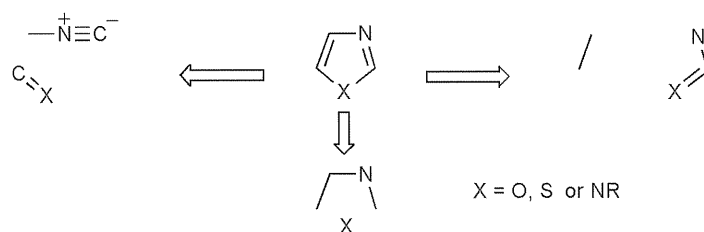
Principal disconnections for ring synthesis of 1,3-azoles.

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

This disconnection is most important for the synthesis of thiazoles. A thioamide is reacted with an α-haloketone, with the first bond made being between sulfur and carbon – the 1,5-bond. 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, are typical.
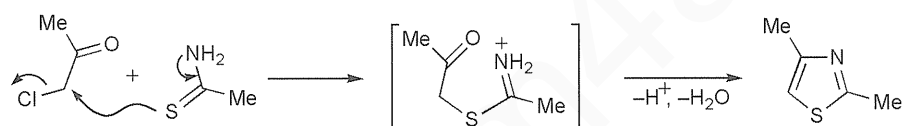
Synthesis of 2,4-dimethylthiazole – classical Hantzsch synthesis.
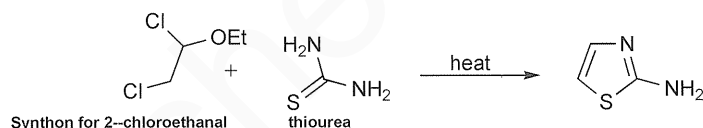
Synthesis of 2-aminothiazole.

This route can also be utilised to prepare imidazoles and oxazoles; for example using *N*-acetylguanidine produces 2-acetylaminoimidazoles.
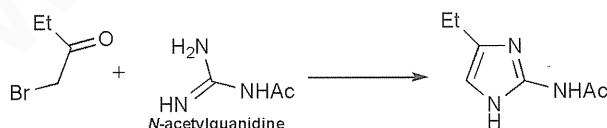
Synthesis of a 2-acetylaminoimidazole.

11.9.3 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-aminoketones produce oxazoles when exposed to acidic dehydrating conditions – the analogy to the ring closure of 1,4-diketones to give furans (page 67) is obvious.
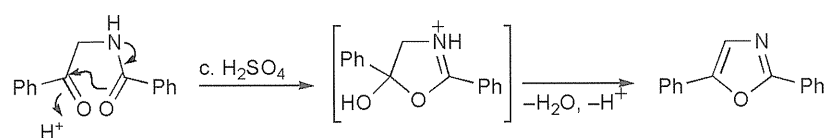
Synthesis of 2,5-diphenyloxazole.

An α-acylthio-ketone will react with a source of ammonia to generate a thiazole, the 1,4-dicarbonyl starting material being easily available from an α-bromoketone and a thioacid.
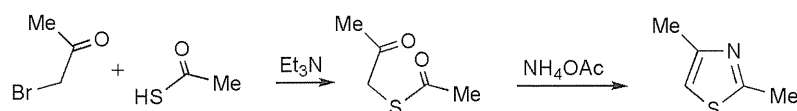
Synthesis of a thiazole from an α-acylthio-ketone.

A final example in this category is the synthesis of 2-formylimidazole. An imino-ether (normally formed by treating a nitrile with HCl and an alcohol) is 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.
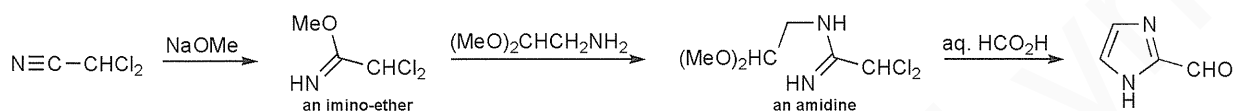
Synthesis of imidazole-2-carboxaldehyde.

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

All three 1,3-azoles 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-toluenesulfinate produces the aromatic azole (compare the use of Tosmic for the synthesis of pyrroles, on page 55).
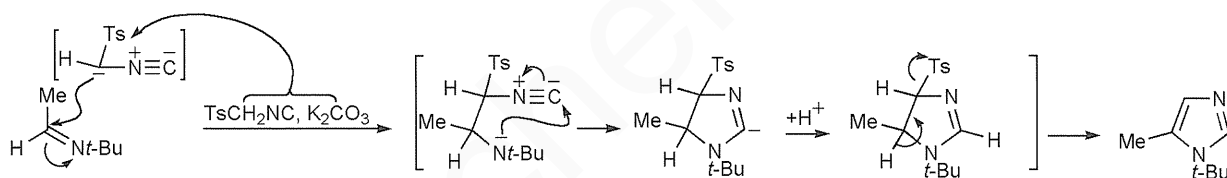
Synthesis of an imidazole utilising tosylmethyl isocyanide with an imine.
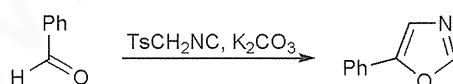
Synthesis of 5-phenyloxazole utilising tosylmethyl isocyanide with an aldehyde.

11.10 1,2-Azoles Ring Synthesis

11.10.1 Disconnections
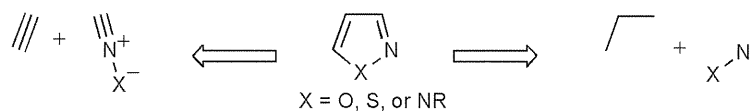
Principal disconnections for ring synthesis of 1,2-azoles.

11.10.2 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. Quite simply, double condensation of a 1,3-diketone, or synthetic equivalent, with a hydrazine or with hydroxylamine, each 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).
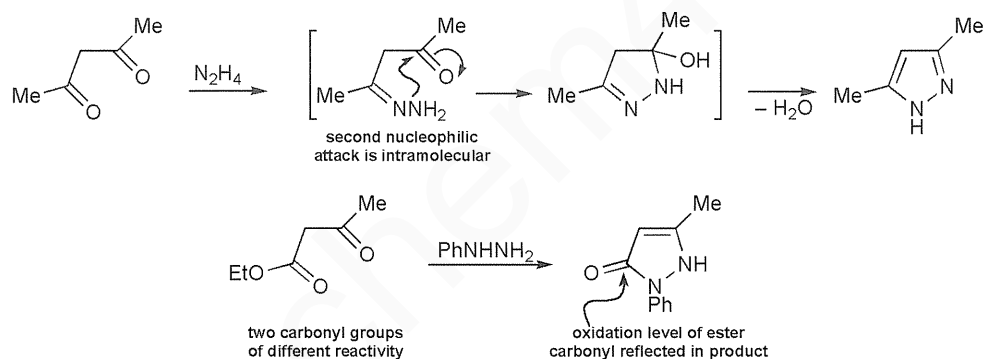
Synthesis of pyrazoles from 1,3-dicarbonyl compounds.

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.
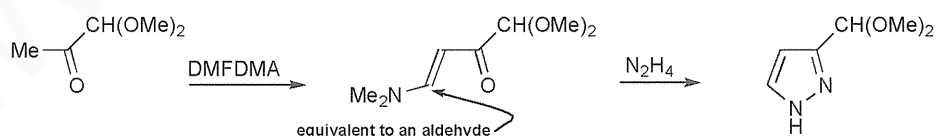
Use of an enamine as a synthetic equivalent of an aldehyde; synthesis of 3(5)-formylpyrazole dimethyl acetal.

Isoxazoles are similarly efficiently produced from 1,3-dicarbonyl compounds, using hydroxylamine as the doubly nucleophilic reactant.
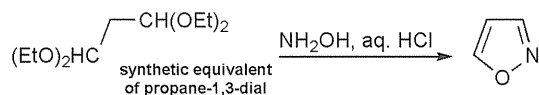
Synthesis of isoxazole.

11.10.3 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 $(R-C\equiv N^+-O^-)$ readily add to alkenes or to alkynes, generating five-membered heterocycles. Addition to alkynes produces isoxazoles, directly, and addition to alkenes gives 4,5-dihydroisoxazoles (isoxazolines), but these can be readily dehydrogenated. Similarly, though less frequently used, a nitrile imine will add to an alkyne, giving a pyrazole. Nitrile oxides are usually generated *in situ*, in the presence of the other reactant, either by base-catalysed elimination of hydrogen halide from a halo-oxime $(RC(Hal)=NOH$; strictly called an oximinoyl chloride) or by dehydration of a nitro compound (RCH_2NO_2) using phenyl isocyanate.
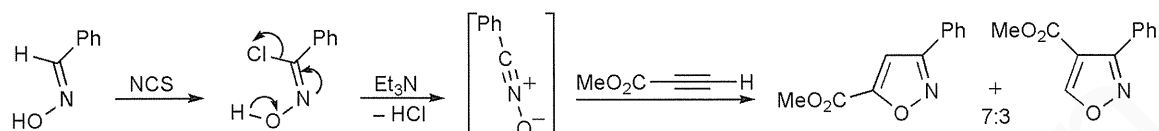
Generation of a nitrile oxide from a chloro-oxime and its dipolar cycloaddition to an alkyne.

Diazoalkanes will also add to alkynes.
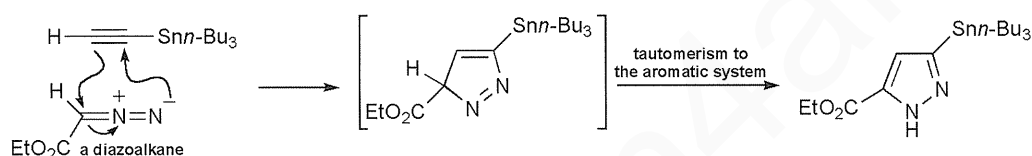
Dipolar cycloaddition of a diazoalkane to an alkyne to give a pyrazole.

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

The ring closure of β-amino α,β-unsaturated thioketones (usually generated *in situ* by reaction with P_2S_5) or β-amino α,β-unsaturated thioamides, in the presence of an oxidising agent (iodine in the example shown below), leads to isothiazoles.
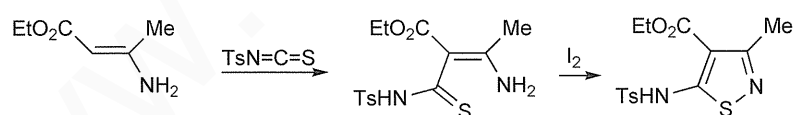
Synthesis of a 5-aminoisothiazole starting from the enamine of ethyl acetoacetate.

Introduction

Purines are of great interest for several reasons, but in particular, together with certain pyrimidines, when combined with ribose or deoxyribose as nucleosides or nucleotides (phosphate esters of nucleosides), they are constituents of the polymers DNA and RNA. Additionally, monomeric nucleosides and nucleotides act as hormones and neurotransmitters and are present in some coenzymes. Nucleotides are at the heart of energy transfer in many metabolic systems and are also involved in intracellular signalling. Some of these biochemical aspects of purines are discussed further in Topic 17.4. This central biological role also leads to the great significance of purines in a number of areas of medicinal chemistry (see Section 18).
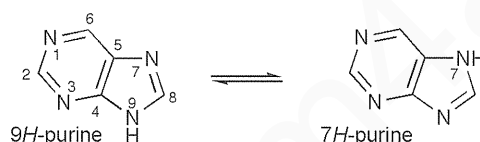
Tautomerism in purine.

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. (*Note*: The standard numbering of the purine ring system is anomalous for historical reasons.)
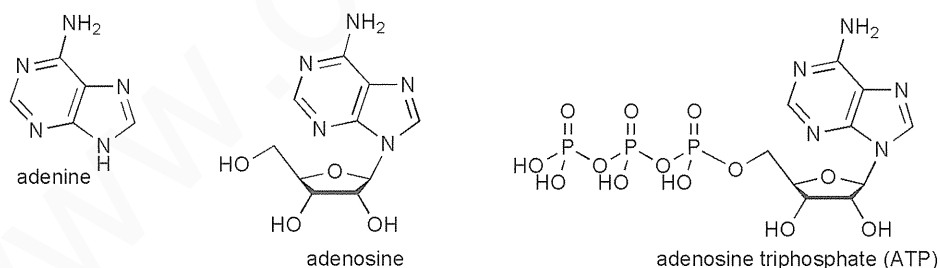
Adenine and a corresponding nucleoside (adenosine) and a corresponding nucleotide (ATP).

Much of the chemistry of purines 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 9-ribosides adenosine, guanosine and inosine, which are all readily available in large quantities. The polyoxy-purines, xanthine and uric acid, are also readily available as starting materials.
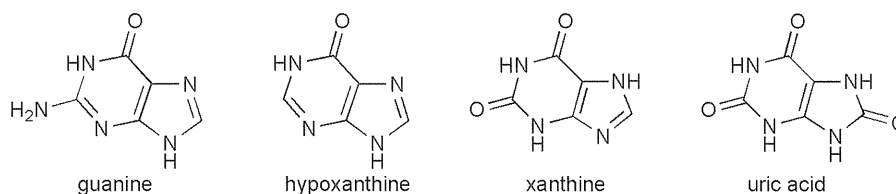
Structures of some important oxy-purines.

82

A number of purine analogues, particularly of nucleosides, also occur naturally. These notionally represent replacement of one of the purine nitrogens by other atoms, for example oxanosine, where N-1 is replaced by oxygen and tubercidin, where N-7 is replaced by carbon. The latter system can be referred to informally as a '7-de-aza purine'.

Other natural products contain modified ribose moieties, for example aristeromycin, where the ring oxygen of adenosine is replaced by a methylene.
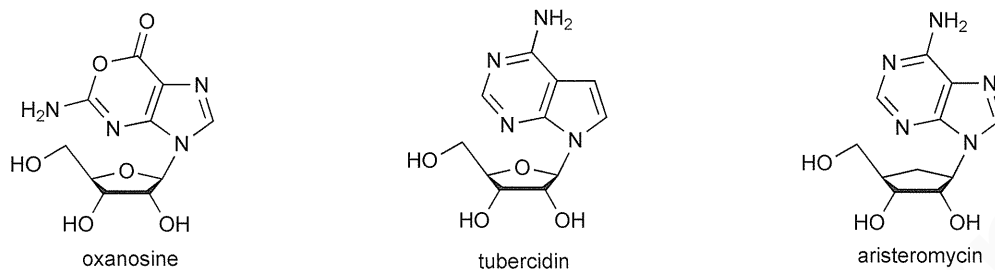
Naturally-occurring nucleoside analogues.

Nucleic acids are high-molecular-weight, mixed polymers of mononucleotides, in which chains are formed by monophosphate links between the 5′-position of one nucleoside and the 3′-position of the next (see also pages 130 and 131). The 'backbone' of the chain is thus composed of alternating phosphates and sugars, to which purine and pyrimidine bases are attached at regular intervals. The polymer is known as ribonucleic acid (RNA) when the sugar is ribose, and deoxyribonucleic acid (DNA) when the sugar is 2-deoxyribose.
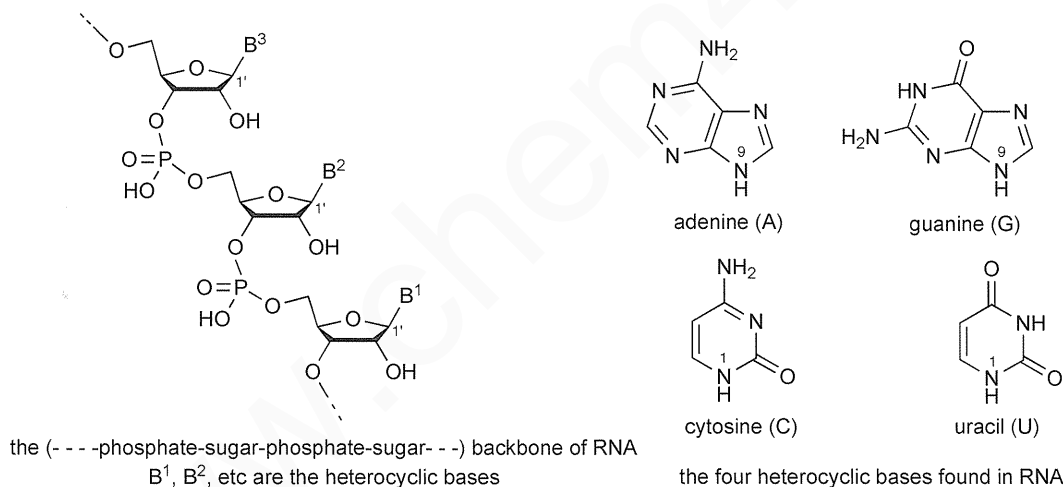
the (- - - -phosphate-sugar-phosphate-sugar- - -) backbone of RNA
B^1, B^2, etc are the heterocyclic bases

the four heterocyclic bases found in RNA

12.1 Purines and Electrophiles – Addition to N and Substitution at C

12.1.1 Electrophilic addition to nitrogen

Purine itself is a relatively weak base, pK_{aH} 2.5, with protonation taking place to give three monocations 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.
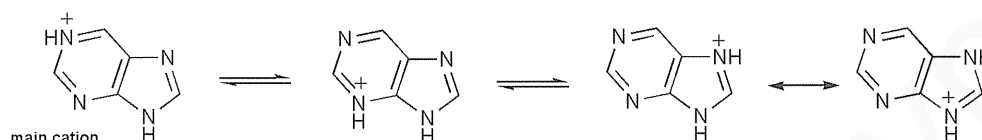
Sites of protonation of purine.

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 adenine undergo a very interesting reaction, the Dimroth rearrangement, on treatment with base. This reaction results in interchange of N-1 with the 6-amino group, giving a 6-*N*-alkylamino adenine. This seemingly unlikely outcome is the result of a ring opening and recyclisation via an ANRORC sequence (*a*ddition of *n*ucleophile *r*ing *o*pening *r*ing *c*losure) and is quite common in purinium salts and some other ring systems and is of significant synthetic utility.
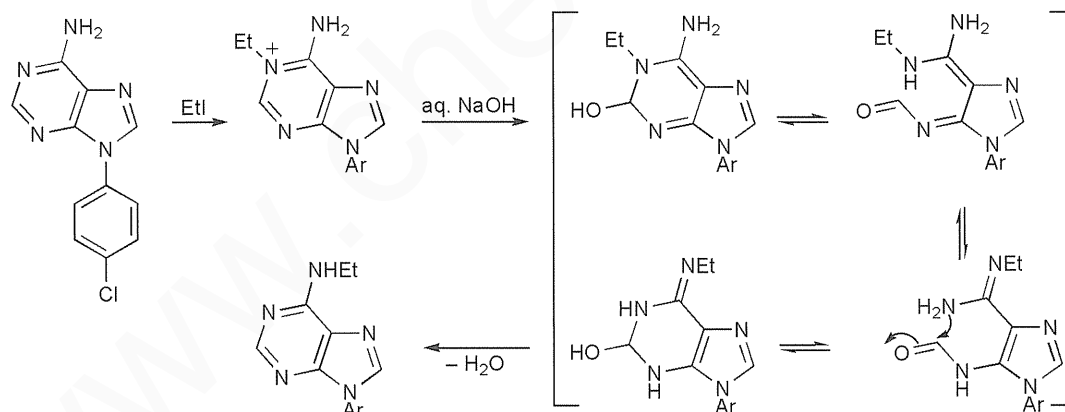
A Dimroth rearrangement of a purinium salt.

N-Alkylation of purines that have a free NH is more 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.

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

In the context of synthesis of nucleosides and analogous compounds, the *N*-ribosylation (*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.
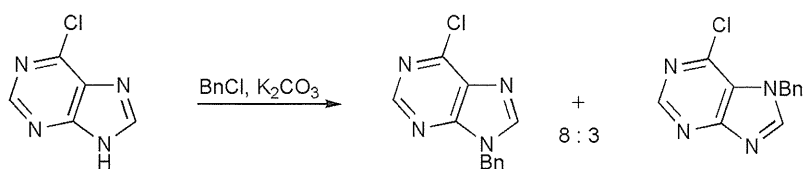
A poorly selective alkylation of a purine.
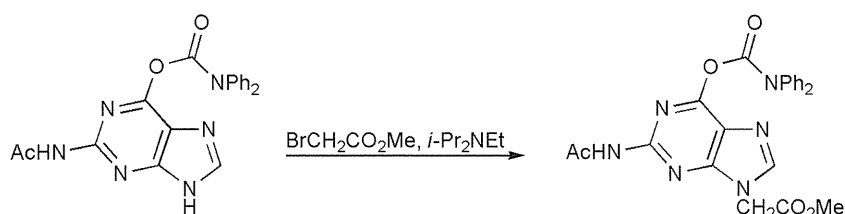
Steric hindrance of N-7 by a C-6-substituent leads to selective N-9-alkylation.
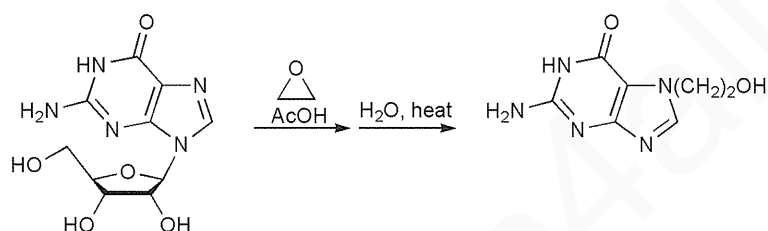
N-7-Alkylation of a nucleoside, followed by hydrolytic removal of the sugar.
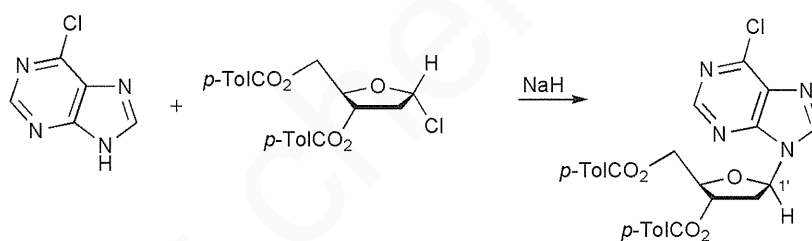
N-9-Deoxyribosylation of the sodium salt of a purine.

12.1.2 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.
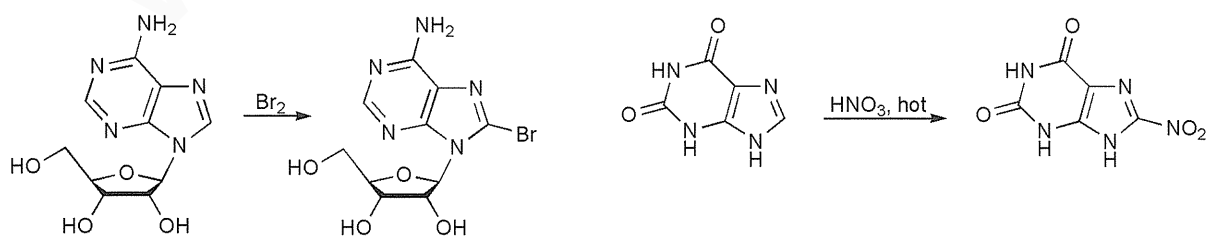
Electrophilic substitutions of purines in the imidazole ring, at C-8.

12.2 Purines and Nucleophiles

Purines are susceptible to nucleophilic substitution, this being of particular relevance in the displacement of a halide, which is probably the most widely used reaction for manipulation of purines. A wide range of nucleophiles – nitrogen, oxygen, sulfur and carbon – can be employed. The reaction occurs via an addition–elimination mechanism as in similar displacements in pyridines (page 18).

Halide located at any of the three available carbons – C-2, C-6 and C-8 – is readily displaced. In 9-substituted purines, which cannot form an N-anion, the relative reactivity is 8 > 6 > 2. However, in 9H-purines, 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.
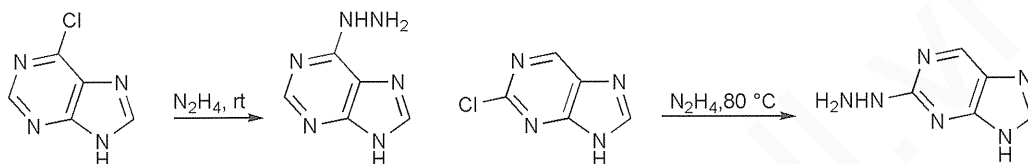
Reaction conditions illustrate the relative reactivities of 2- and 6-chloropurines.
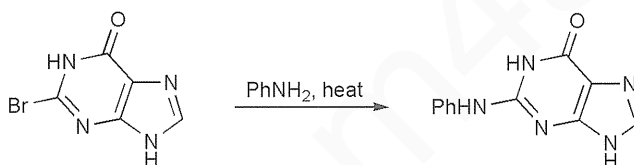
Halo-oxo-purines react easily, even with poor nucleophiles.

Other useful leaving groups include triflate, alkyl- or 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.
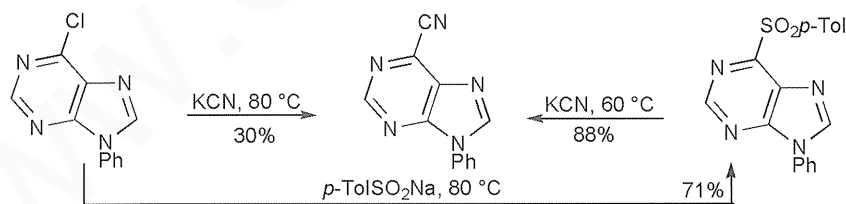
The two-step method via the sulfone is faster and gives a higher overall yield than the direct approach.

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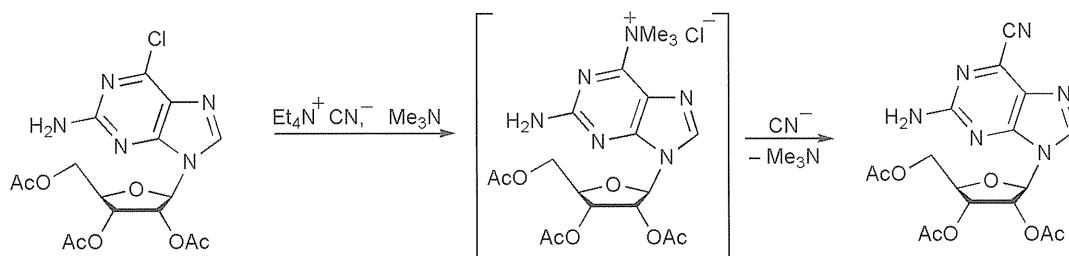
An *in situ* formation of a trimethylammonium salt allowing trimethylamine to be the good leaving group.

12.3 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 reagent is used.
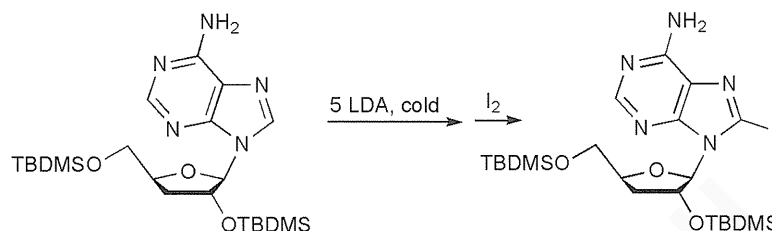
Lithiation at C-8 of a partially protected adenine derivative followed by reaction with iodine.

Lithiation occurs at C-2 if C-8 is substituted. A silyl blocking group can be easily removed later to give 8-unsubstituted purines.

the (- - - -phosphate-sugar-phosphate-sugar- - -) backbone of RNA
B^1, B^2, etc are the heterocyclic bases

adenine (A)   guanine (G)

cytosine (C)   uracil (U)

the four heterocyclic bases found in RNA
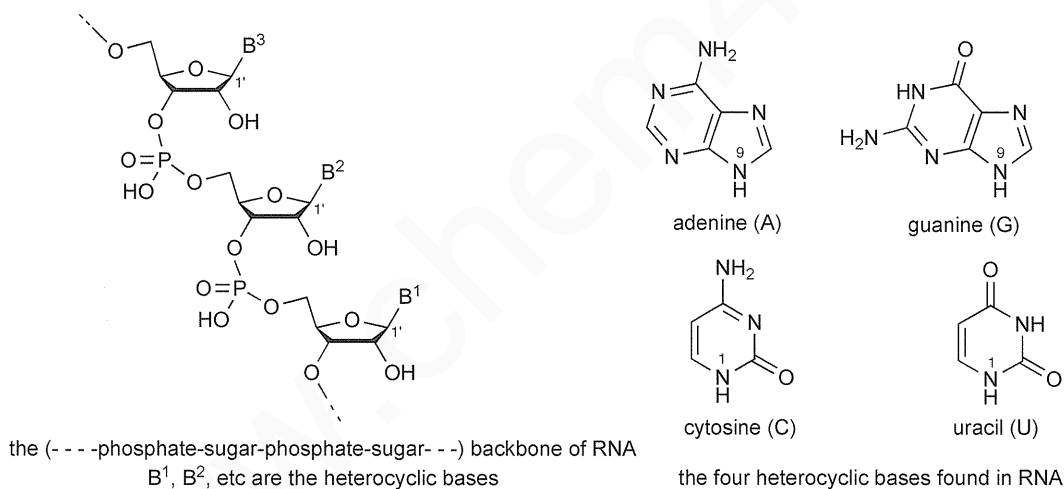
Lithiation of purines occurs at C-2 when C-8 is blocked.

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.
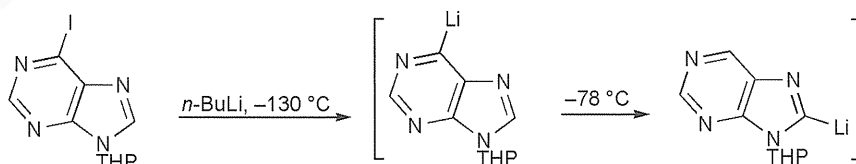
Generation of a 4-lithiopurine and its isomerisation to a 6-lithiopurine.

12.4 Purines with Oxygen Substituents

These are potentially tautomeric compounds that exist predominantly as carbonyl and amino structures respectively, as indicated at the beginning of this section and in line with the situation in simpler heterocycles, like pyridines (pages 20 and 22).

12.4.1 Alkylation

The 'amide' *N*-hydrogen in oxopurines is relatively acidic and oxopurines 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.

N-Alkylation via N-anions.
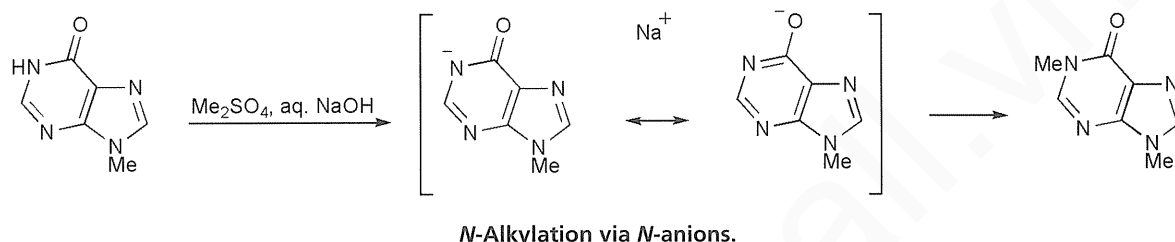
12.4.2 Conversion of oxygen into leaving groups

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. They are readily converted into chloro compounds by replacement of the oxygen, including polyoxo-purines. Alternatively, an oxygen can be activated by *O*-acylation.
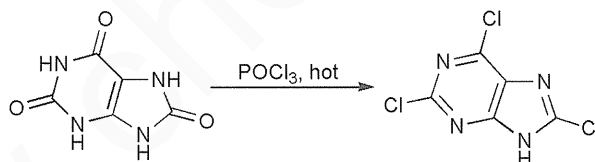
Replacement of oxygen with chlorine (for relative positional reactivities of chlorides see page 86).

12.4.3 Replacement by sulfur

Replacement by sulfur can be achieved via a nucleophilic displacement on a halo purine or directly using a phosphorus sulfide. The thiopurines may be of interest in their own right but are also a potential source for the highly reactive sulfones (page 86).
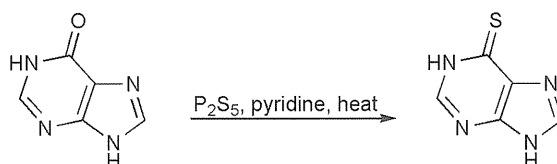
Replacement of oxygen with sulfur.

12.5 Purines with Amine Substituents

12.5.1 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 (page 84). An alternative direct method for monoalkylation of the amino group is by reductive alkylation.
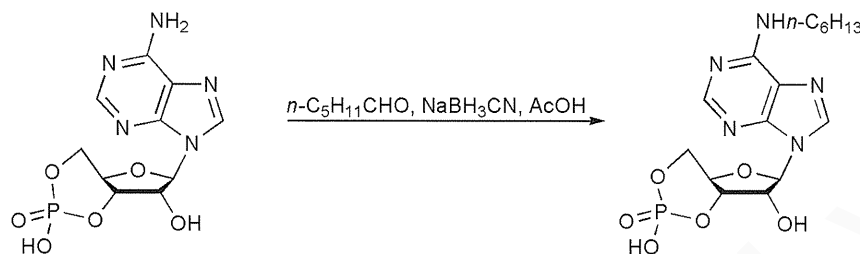
Reductive *N*-alkylation of cyclic-AMP.

12.5.2 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 to 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.
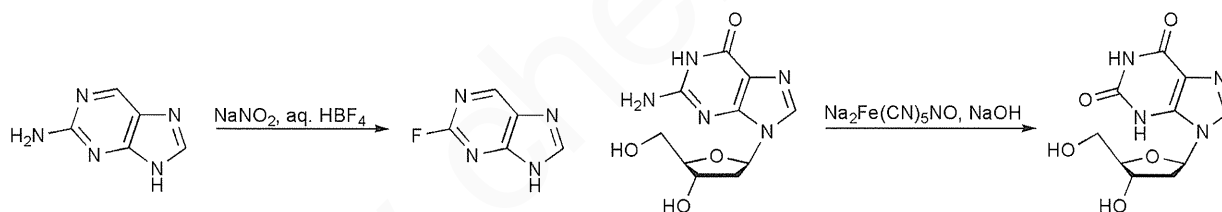
Diazotisations under acidic and alkaline conditions.

A related reaction with alkyl nitrite produces purinyl radicals, which are efficiently converted into halo purines by abstraction of halogen from polyhalogenated solvents.
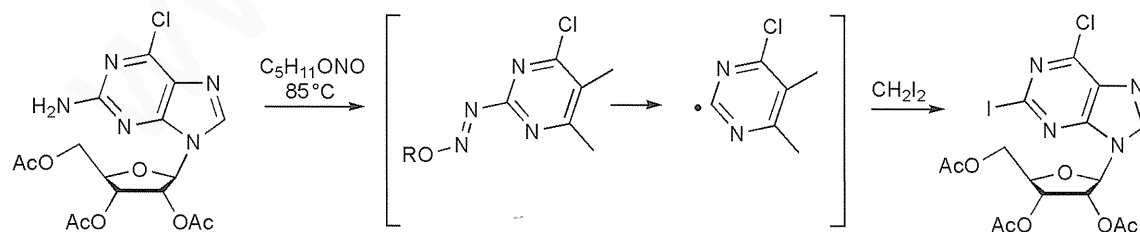
Diazotisation under non-aqueous conditions.

12.6 Purines Ring Synthesis

12.6.1 Disconnections

Most purine syntheses involve cyclisation reactions of 4,5-diaminopyrimidines or of derivatives of 5-aminoimidazole-4-carboxylic acid.
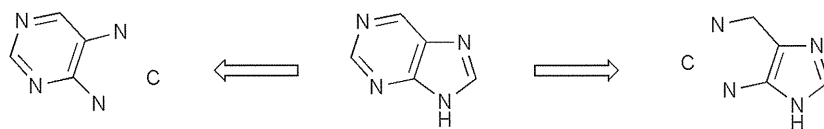
Principal disconnections for the ring synthesis of purines.

12.6.2 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.
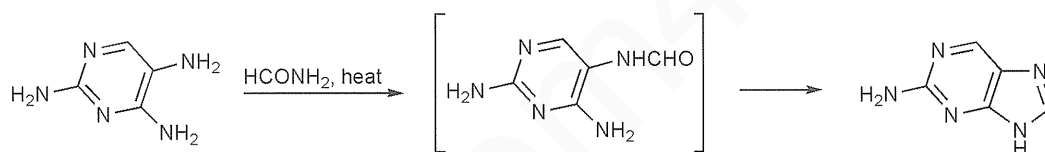
A typical synthesis forming an 8-unsubstituted purine.

8-Substituted purines can be prepared via acylation with higher acids. In some simple cases, *in situ* cyclisation occurs but usually a two-step sequence is required.
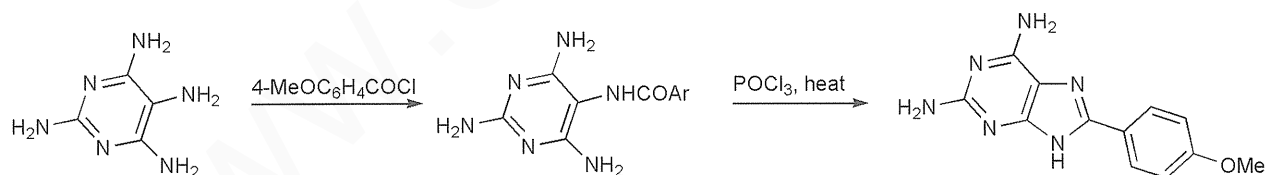
A two-stage Traube synthesis to prepare an 8-arylpurine.

12.6.3 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 purines (hypoxanthines and inosines). Adenine derivatives can also be prepared by this route by employing the corresponding aminoimidazole carbonitriles.
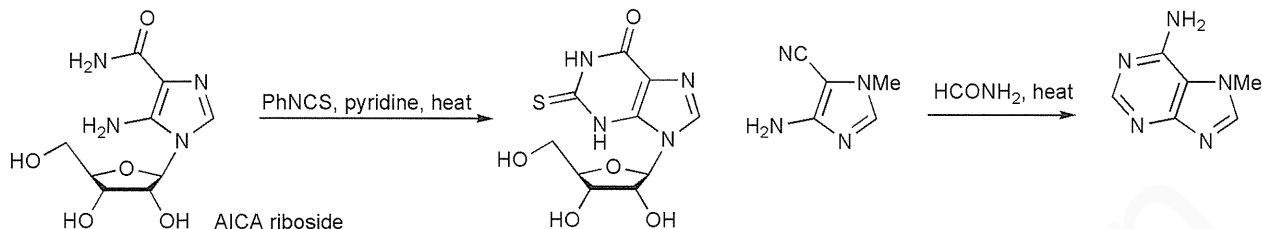
Synthesis of an amino-purine using AICA-nitrile.
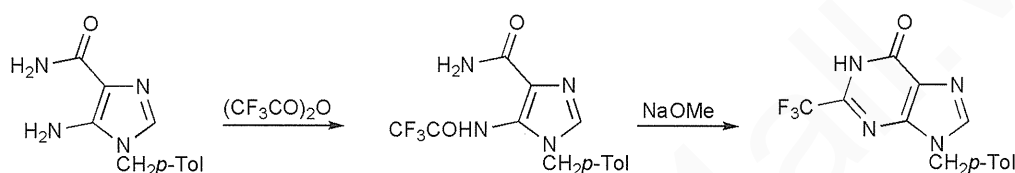
Synthesis of a purinone using an *N*-protected AICA.

12.6.4 'One-step' syntheses

The formation of purines, such as adenine, in the 'primordial soup' was probably a precondition 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.
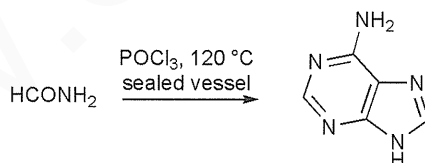
One-step synthesis of adenine.

Heterocycles with More Than Two Heteroatoms

Introduction

Any or all of the carbon atoms in all the five- and six-membered heterocyclic systems described in previous sections could, in theory, be replaced by nitrogen. In practice, replacement of all the carbons has only been achieved in a five-membered ring. Using nitrogen, oxygen and sulfur, there are 18 possible azoles with three or more heteroatoms, of which 13 are known. Only 4 of the 8 possible azines with three or more heteroatoms are known.

The presence of multiple N–N bonds, with a potential for such molecules to break down to produce molecular nitrogen, is probably at the root of the instability of some of these systems. Of course, the more heteroatoms there are present, the less opportunity there is for chemistry at carbon! Nevertheless, there is great interest in these 'higher' azoles and azines, several of which are important as components of drug molecules (see Section 18) and as industrial chemicals.

13.1 Higher Azoles Containing Nitrogen as the Only Heteroatom

Introduction

There are four higher azoles containing only nitrogen as the heteroatoms – two triazoles, tetrazole and pentazole. The triazoles and tetrazole exist as mixtures of two tautomers.
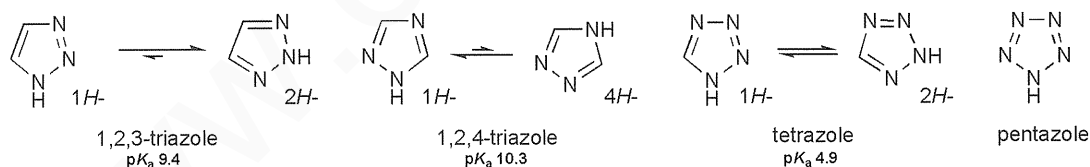
Tautomerism and *N*-hydrogen acidity in the higher azoles.

13.1.1 Stability

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 generally are also surprisingly stable although tetrazole itself (mp 158 °C, decomposes >180 °C) and is classified as an explosive, at least for shipping purposes. Tetrazole and 5-aminotetrazole are components of mixtures (with oxidants) used in car air bags as high-speed inflators with a controlled explosive liberation of nitrogen and other gases. The ring systems of these azoles are very resistant to reduction.

Other tetrazole derivatives are definitely explosives – 'Tetrazene' (a commercial name, not to be confused with the tetrazine ring) has been used as a primer for percussion caps and the highly dangerous diazotetrazole (CN_6) is a source of atomic carbon! 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.
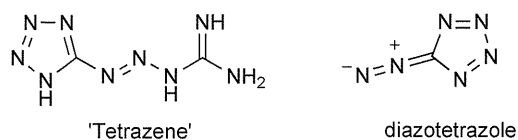
Explosive tetrazoles.
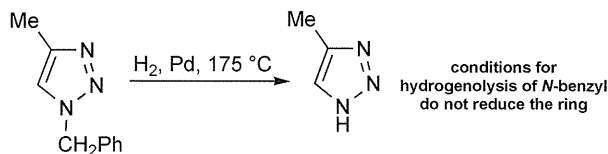
1,2,3-Triazoles (and tetrazoles) are surprisingly stable to heat and reduction.

13.1.2 Reaction with Electrophiles – Substitution at C

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.
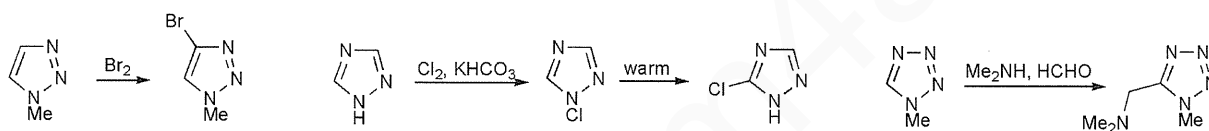
Triazoles and tetrazoles undergo surprisingly easy electrophilic substitution.

13.1.3 Reaction with Nucleophiles – Substitution at C

Nucleophilic displacements occur with reasonable ease. Sulfones are particularly good leaving groups for carbon nucleophiles.
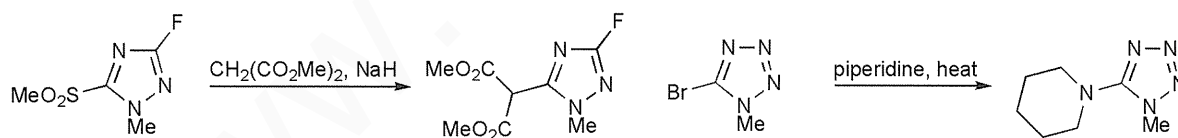
Triazoles and tetrazoles are equally susceptible to nucleophilic displacements.

13.1.4   N-Metallated Derivatives by Deprotonation

The triazoles are weak bases but moderately acidic – about as acidic as phenol. Tetrazole is as acidic as a carboxylic acid; it is also not dissimilar in shape and size to a carboxylic acid unit and, because of this, has found use in drugs as a replacement for the carboxyl group but having superior pharmacological properties.
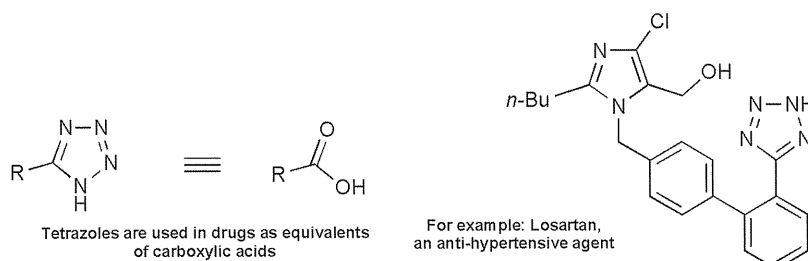
Application of the _N_-hydrogen acidity of tetrazoles.

1,2,3-Triazoles and tetrazoles tend to give mixtures of regioisomers on _N_-alkylation, the proportions depending on substituents in the heterocyclic ring, the bulk of the alkylating agent, and reaction conditions. The preparation of the pure regioisomers is a significant challenge! 1,2,4-Triazole undergoes selective alkylation on one of the adjacent nitrogens.
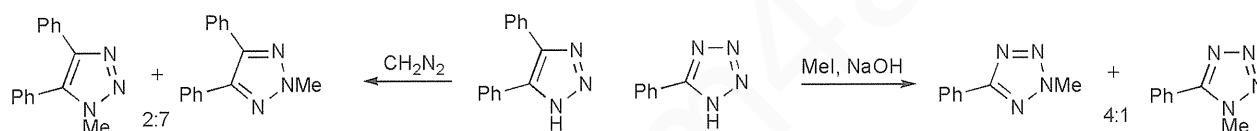
1,2,3-Triazoles and tetrazoles usually give mixtures on _N_-alkylation.

Certain devices can be used to control the regioselectivity of _N_-alkylations, particularly by placing a temporary protecting group onto the most reactive nitrogen, followed by quaternisation and then removal of the protecting group. However, only a limited number of highly reactive alkylating agents will quaternise triazoles.
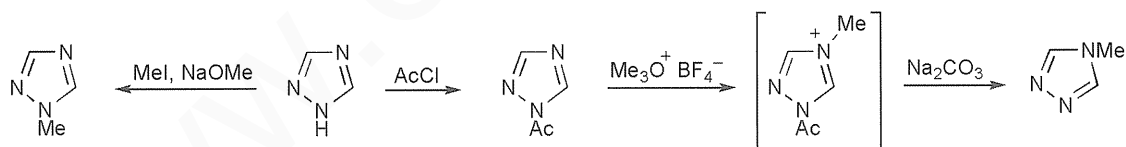
1,2,4-Triazole alkylates on N-1 but the 4-isomer can be prepared efficiently via quaternisation of the 1-acetyl derivative.
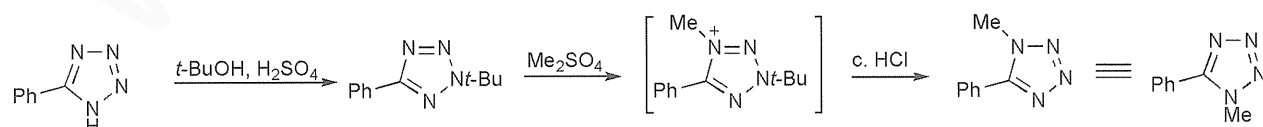
The bulky _t_-butyl group is directed to N-2 in 5-substituted tetrazoles. Quaternisation followed by _N_-dealkylation then gives the N-1-methyl derivative.

13.1.5 C-Metallated Derivatives by Direct Deprotonation

Both 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.
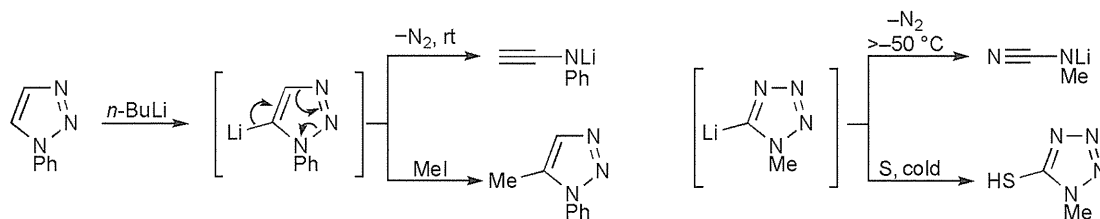
Lithiated 1,2,3-triazoles and tetrazoles decompose below room temperature but react normally if low temperatures are maintained.

13.1.6 Benzotriazole

Benzotriazole has significant uses as an auxiliary for general organic synthesis. It has the properties of being an activating group for stabilisation of cations *and* anions and can also act as a leaving group.
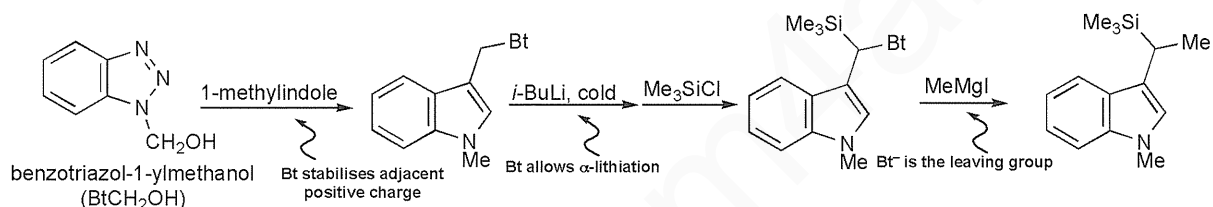
A sequence illustrating the varied reactivities of benzotriazole: stabilising a cation (Mannich reaction); stabilising an anion to allow lithiation; acting as a leaving group for a nucleophilic displacement.

In addition to the important role of benzotriazole as a synthetic auxiliary as illustrated above, there are other roles in which the ring system can be utilised. Perhaps the most important of these is the relatively mild oxidative degradation of 1-aminobenzotriazoles generating benzynes. The sequence below is a relatively elaborate example.
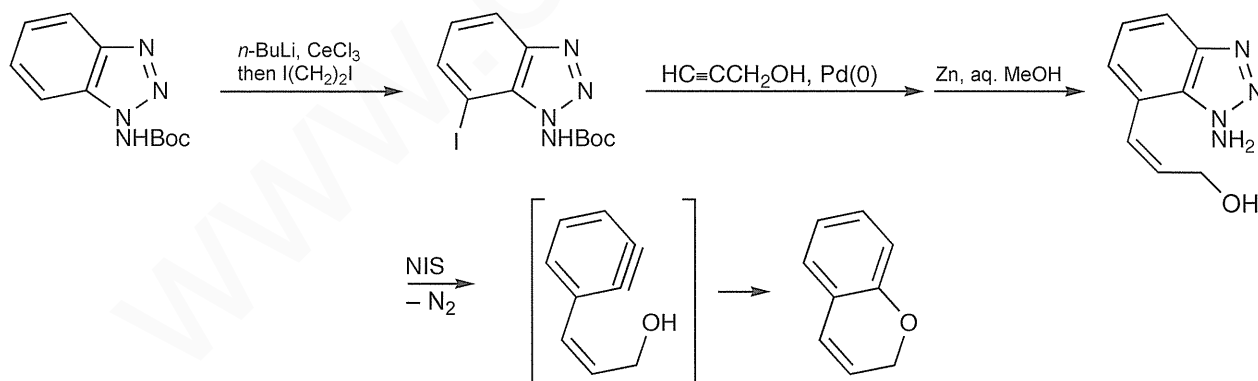
Utilising a 1-aminobenzotriazole as a means to generate a benzyme.

13.2 Higher Azoles Containing Sulfur or Oxygen

Introduction

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.

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

Structures of oxa- and thiadiazoles.
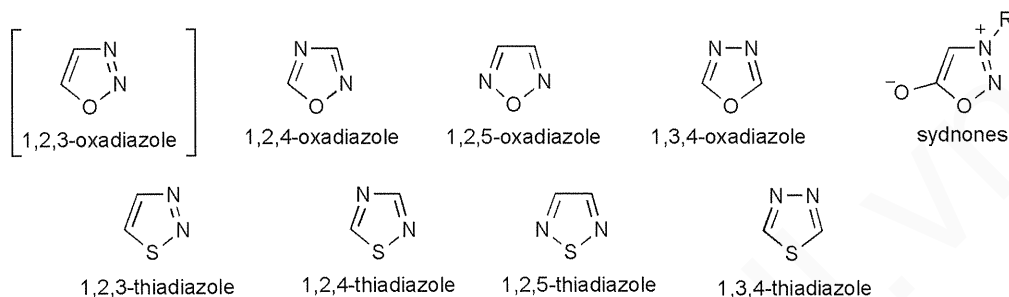
Predicting precise interactions between the heteroatoms in these systems is not easy but the general stability/reactivity can be implied from their relative aromaticity, based on bond lengths and NMR data.

Relative aromaticities.

13.2.1   Stability

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 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; this probably results from the absence of the possibility of losing nitrogen.

Explodes at 50 °C   Controlled decomposition   Stable in refluxing EtOH for >3 h

$t_{1/2}$ 7 h at 61 °C (in PhBr) → PhCN + S + N$_2$
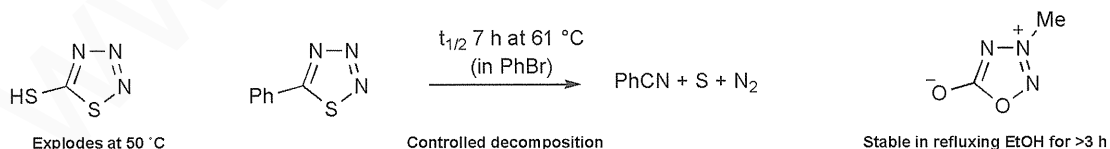
Few 1,2,3,4-thiatriazoles are stable; many undergo controlled decomposition but some are dangerously explosive. Mesoionic compounds are the only stable 1,2,3,4-oxatriazoles.

13.2.2 Reaction with Nucleophiles – Substitution at C

Due to the highly electron-deficient nature of these rings, electrophilic substitution is rare but, conversely, nucleophilic displacements proceed readily.
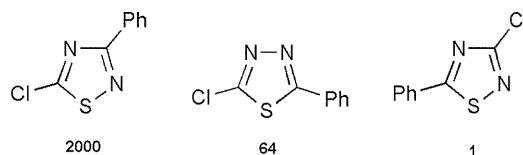
Relative rates of reaction of chlorothiadiazoles with piperidine in ethanol.

13.2.3 C-Metallated O/S-Containing Higher Azoles by Direct Deprotonation

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 by much weaker bases.
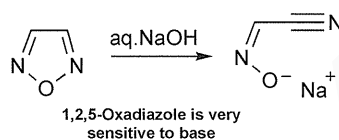
Base sensitivity of 1,2,5-oxadiazole.
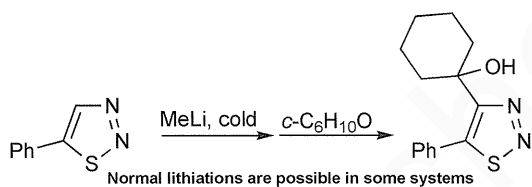
Thiadiazoles with organolithiums.
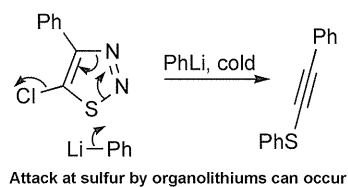
13.3 Higher Azines

Introduction

Hexazine, pentazine, 1,2,3,4- and 1,2,3,5-tetrazines are unknown, although some partially reduced 1,2,3,4-tetrazines have been prepared.

1,2,3-triazine 1,2,4-triazine 1,3,5-triazine 1,2,3,4-tetrazine 1,2,3,5-tetrazine 1,2,4,5-tetrazine pentazine hexazine
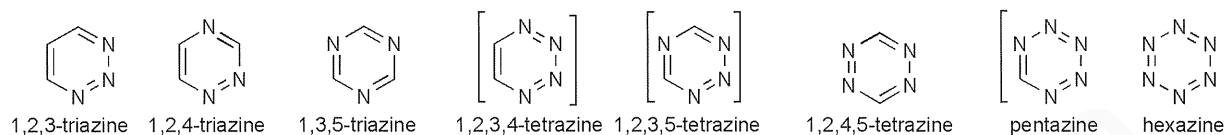
Structures of higher azines (known and unknown).

Triazines are found in some drugs (cf. Section 18) but probably the best known triazine is melamine (triamino-1,3,5-triazine), which is used industrially to make plastics.

13.3.1 Stability

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.

13.3.2 Reaction with Nucleophiles – Substitution at C

Nucleophilic additions and displacements are the most common reactions of the azines, some of these being quite easy, more so than the diazines due to the inductive effect of the extra nitrogen. 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.

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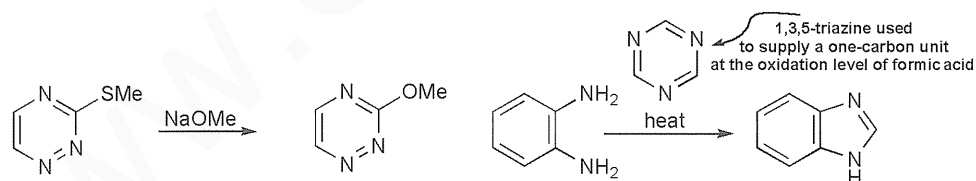
Easy nucleophilic reactions of triazines.

Tetrazines are so reactive in nucleophilic substitutions that cooling may be required to control such reactions.
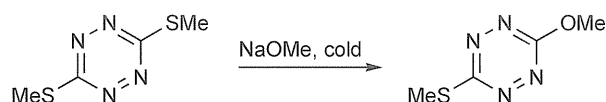
Tetrazines are very reactive in nucleophilic displacements.

13.3.3 Electrocyclic Reactions

The main chemical application of triazines and tetrazines is as electron-deficient 'dienes' in inverse-electron-demand Diels–Alder reactions, the 'inverse-electron-demand' relating to the fact that in 'normal' Diels–Alder reactions the diene component is usually electron-rich.

Replacement of carbon in an azine by oxygen or sulfur would not give a neutral aromatic compound, although they may be accommodated when a carbonyl group is present – the equivalent of an azapyrone. An example is the oxadiazinone shown below, which is also used in Diels–Alder reactions; it is interesting that nitrogen rather than carbon dioxide is eliminated in this case.
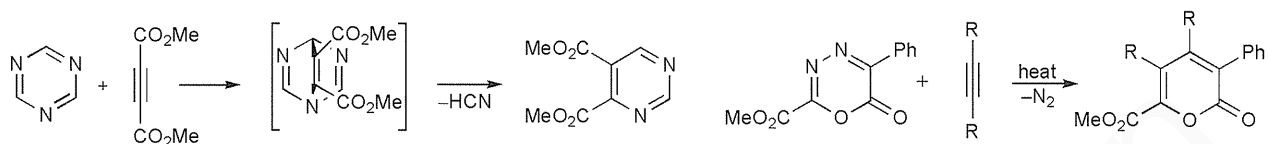
1,3,5-Triazine in an inverse-electron-demand Diels–Alder reaction (aromatisation via elimination of HCN).
An oxadiazinone in a Diels-Alder reaction (aromatisation via elimination of N_2 rather than CO_2).
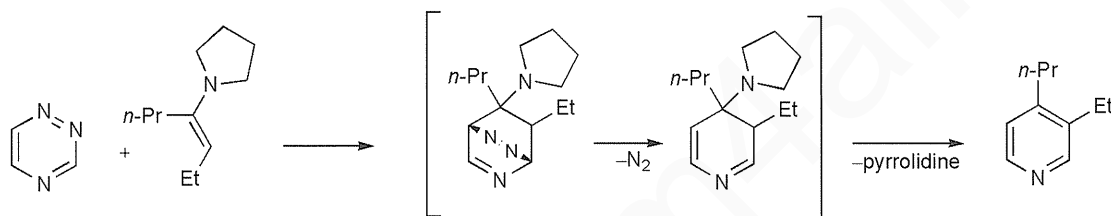
An inverse-electron-demand Diels–Alder reaction using an enamine as an acetylene equivalent
(aromatisation via elimination of N_2 and pyrrolidine).

Tetrazines are easily converted into pyridazines by these reactions. Stannyl alkynes are particularly useful dienophiles because the tin-containing product is reactive and is easily converted into other useful derivatives, such as halides, or used in palladium-catalysed coupling reactions (page 117).
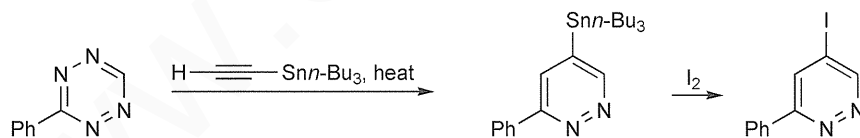
Inverse-electron-demand Diels-Alder reactions of tetrazines provide food ways to make pyridazines.

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13.4 Ring Synthesis of Higher Azoles

Some syntheses of oxa- and thiadiazoles follow the condensation–cyclisation approach used for simpler azoles, but oxidative cyclisations may be required when a sulfur–nitrogen bond is required.
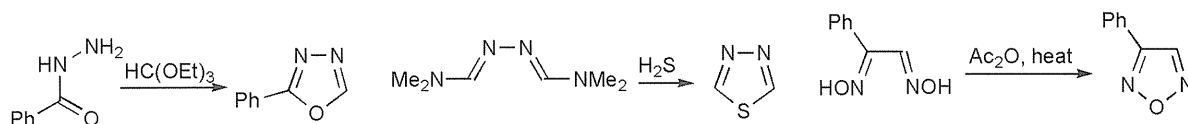
Cyclocondensation reactions used to prepare oxa- and thiadiazoles.
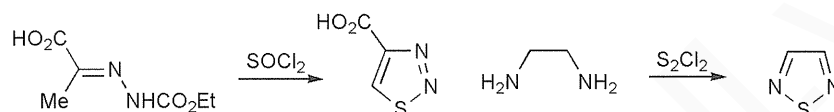
Oxidising conditions are usually required when a sulfur–nitrogen bond is to be formed.

1,2,3-Triazoles are usually prepared via a cycloaddition of an azide to an alkyne or its equivalent. [*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.] 1,2,4-Triazoles are prepared by cyclocondensation reactions.
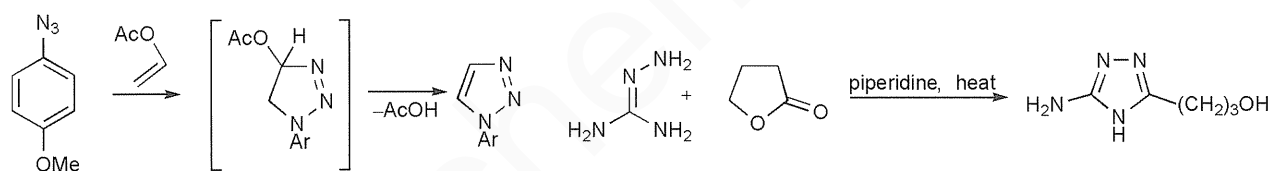
Use of vinyl acetate as a higher-boiling equivalent of acetylene in a cycloaddition with an aryl azide to give a 1,2,3-triazole
Synthesis of a 1,2,4-triazole by a cyclocondensation reaction.

Tetrazoles are usually prepared by reaction of azide with a nitrile or activated amide. A number of related partners, such as aryl isothiocyanates, can also be employed.
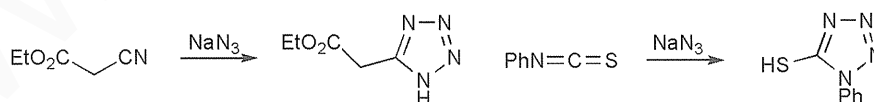
The synthesis of tetrazoles involves the reaction of azide anion with a nitrile or an equivalent.

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13.5 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.
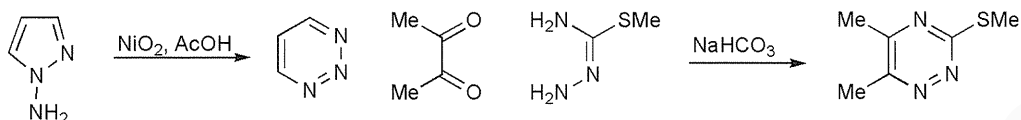
Typical syntheses of 1,2,3- and 1,2,4-triazines.
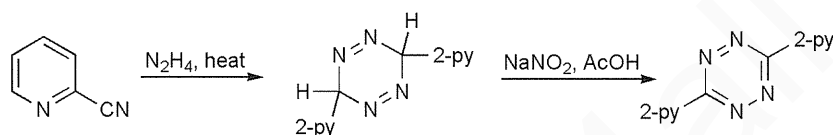
Most directly synthesised 1,2,4,5-tetrazines are symmetrical.

As seen earlier, 1,3,5-triazine itself is a useful, commercially available, reagent for the synthesis of other heterocyclic systems. It can also be used to prepare monosubstituted 1,3,5-triazines by reaction with amidines.
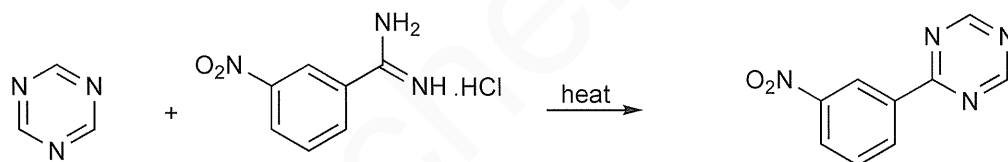
Preparation of a 1,3,5-triazine from 1,3,5-triazine itself.

Unsymmetrical trisubstituted 1,3,5-triazines can be prepared from *N*-acylamidines and amidines; the former component is prepared from an amidine.
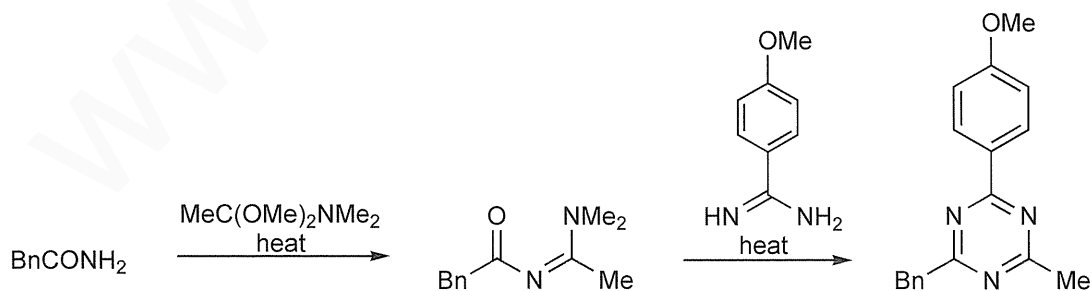
Synthesis of an unsymmetrically substituted 1,3,5-triazine from an *N*-acylamidine and an amidine.

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 (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 (see examples in Section 18). Only bicyclic combinations of five- and six-membered rings are considered here, although other combinations are possible and known.

indolizine
aromatic: 10 conjugated π-electrons

azaindolizines

saturated carbon

4H-quinolizine
non-aromatic

quinolizinium
aromatic

4-quinolizinone
(isoelectronic with quinolizinium)
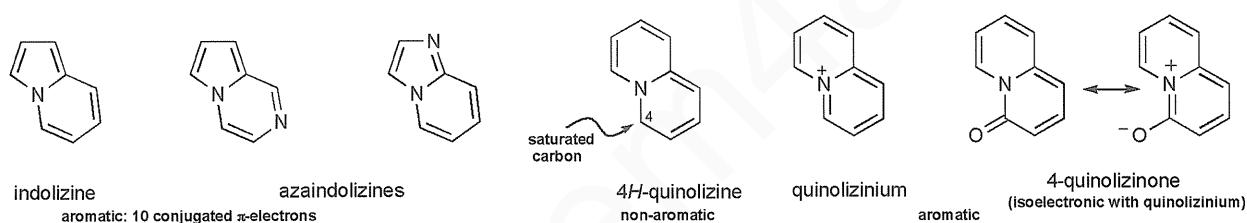
Aromaticity of bicyclic systems depends on an unbroken ring of 10 π-electrons.

Of the parent systems that have a ring-junction nitrogen as the only heteroatom, only indolizine has a neutral, fully conjugated aromatic 10-π-electron system, comprising four pairs of electrons from the four double bonds and a pair from the nitrogen, much as in indole. 4H-Quinolizine is not aromatic because there is a saturated carbon interrupting the conjugation, but the cation, quinolizinium, formed formally by loss of hydride from quinolizine, does have an aromatic 10-π-electron system. 4-Quinolizinone is similarly a 10-electron π-system as illustrated by the polarised resonance contributor.

saturated carbon a vinyl-pyrrole

3H-pyrrolizine (6π)

pyrrolizine anion (10π)

pyrrolo[2,1-b]thiazole (10π)
(isoelectronic with pyrrolizine anion)
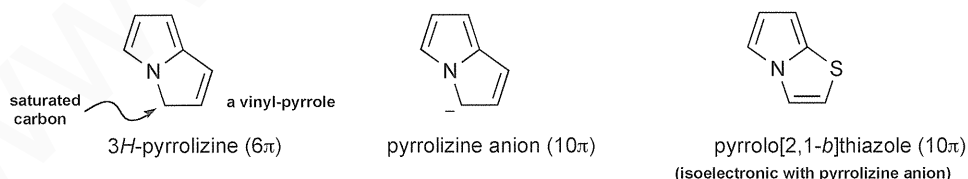
Aromaticity of 5,5-bicyclic systems – 10-π-electron systems.

Pyrrolizine, which is already aromatic as a pyrrole, can only achieve the bicyclic aromatic 10-π- electron system by conversion into its conjugate anion. However, 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.

In all these systems, replacement of carbons by nitrogen does not disrupt the aromaticity (as is true for benzene → pyridine) and gives rise to many interesting heterocycles – the 'azaindolizines' are examples.

14.1 Indolizines

14.1.1 Reaction with electrophiles

Indolizine is an electron-rich system with a similar reactivity to that of indole. However, it is significantly more basic than indole (–3.5). As for indole, protonation occurs on carbon – usually C-3 – not on the nitrogen as this would disrupt the aromatic π-system. The six-membered ring of indolizine is not very pyridine-like, because it does not contain an imine and so nucleophilic additions 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.
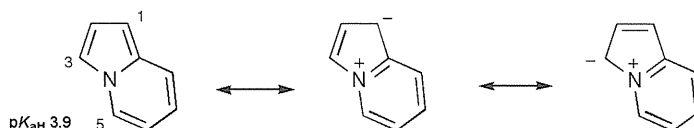
All the significant resonance contributors include a complete pyrrole or a complete pyridinium ring.
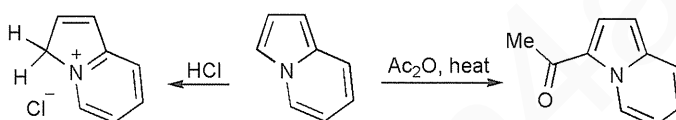
Electrophilic attack on indolizine.
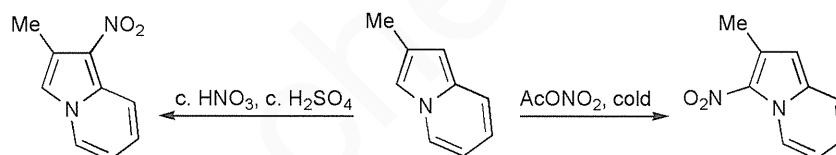
Nitration of 2-methylindolizine in neutral and acidic media.

14.1.2 Other reactions

Lithiation occurs readily in the pyridine ring at C-5. Reduction in acidic solution can give either the dihydro or fully saturated derivatives.
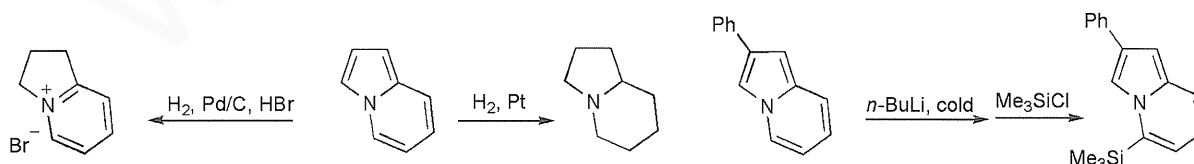
Partial or complete reduction of indolizine depends on the catalyst. **Lithiation of indolizines occurs at C-5.**

14.2 Azaindolizines and Heteropyrrolizines

14.2.1 Azaindolizines

[*Note*: The numbering of azaindolizines is complex and varies with the number and disposition of nitrogens.]

'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.
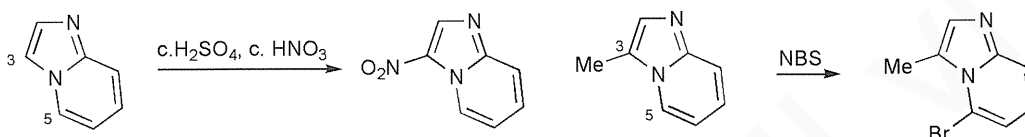
Imidazol[1,2-a]pyridines react with electrophiles at C-3 or at C-5 if C-3 is blocked.

Imidazo[1,5-a]pyridine undergoes electrophilic substitution at C-1 but, in contrast to its isomer, the alternative position 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 species.
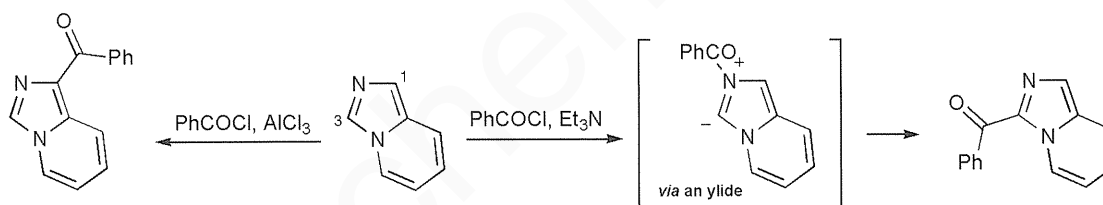
**Normal electrophilic substitution goes at C-1 in imidazol[1,5-a]pyridines.
Conditions that allow formation of an ylide lead directly to C-3 substitution.**

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, the methyl group (in a *peri*-position) hinders reaction at C-5 but the methoxy at the same position directs the lithiation by coordination to the reagent.
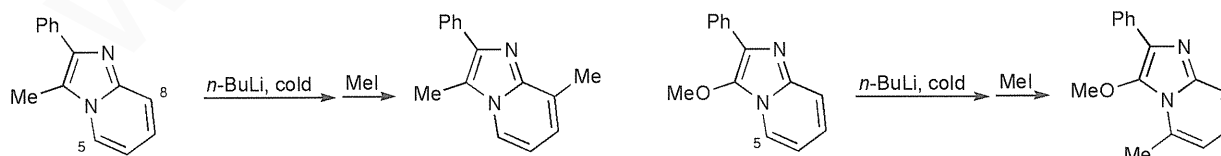
Lithiation of imidazo[1,2-a]pyridines with no free C–H in the five-membered ring proceeds at C-5 or C-8 depending on the substituents.

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.
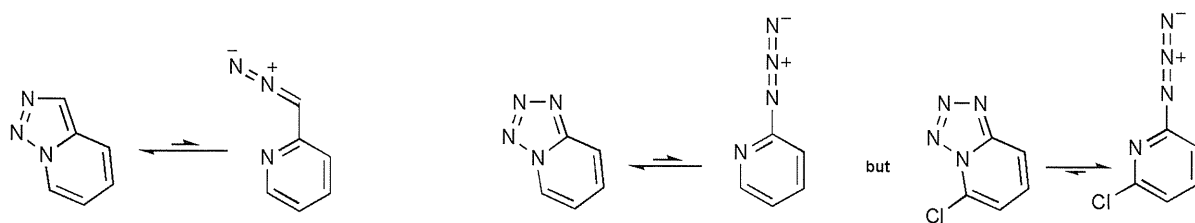
1,2,3-Triazolo[1,5-*a*]pyridine exists in the ring-closed form but tetrazolo[1,5-*a*]pyridines can exist as either the bicycle or the ring-open azidopyridine depending on substituents.

Reactivities of systems with extra nitrogen(s) in the six-membered ring are varied but a common feature is 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 'hydrate'.
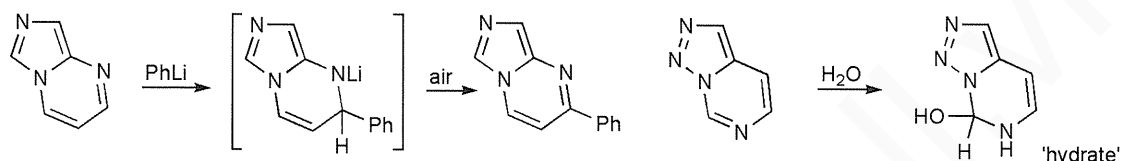
Easy addition of nucleophiles is the dominant reactivity of azaindolizines with extra nitrogens in the six-membered ring.

14.2.2 Heteropyrrolizines

In these systems, electrophilic susbstitution in either of the rings is the most common reactivity, with occasional nucleophilic displacements. Lithiations are quite general.

Syntheses are usually cyclisations starting with a monocyclic compound and bear close analogy to methods used in the other systems discussed above.
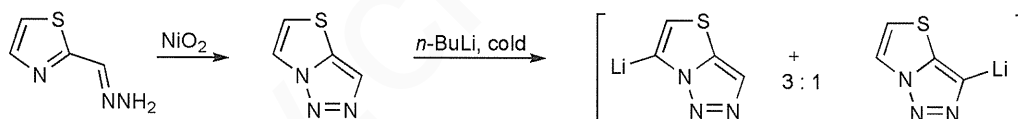
Preparation of a thiazolo[3,2-*c*][1,2,3] triazole and its lithiation.
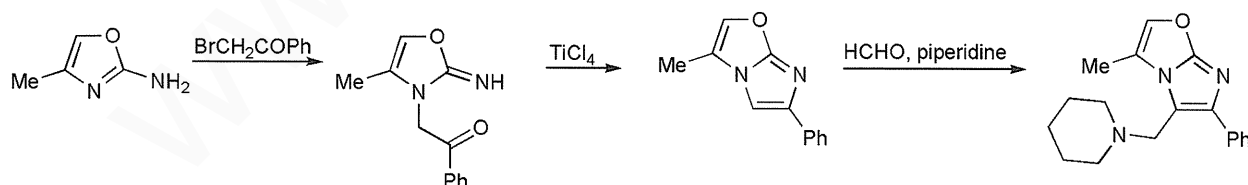
Preparation of an imidazol[2,1-*b*]oxazole followed by an electrophilic substitution – a Mannich reaction.

14.3 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 one of the higher azines.
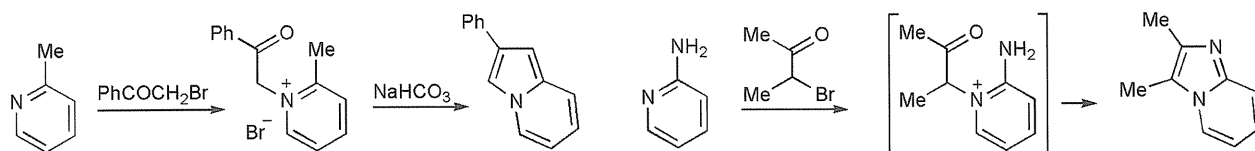
Preparation of an indolizine and an imidazol[1,2-*a*]pyridine by analogous cyclocondensations.
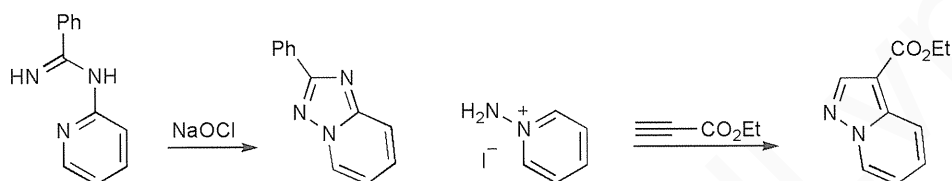
Preparation of a 1,2,4-triazolo[1,5-*a*]pyridine via an oxidative cyclisation and of a pyrazolo[1,5-*a*]pyridine via cycloaddition.

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 ArN$_3$ compounds are now available and serve the same purpose.]
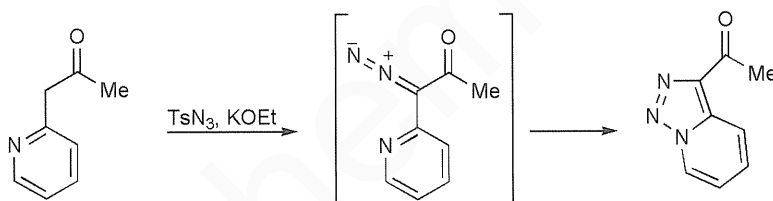
Synthesis of a 1,2,3-triazolo[1,5-*a*]pyridine via initial formation of the isomeric diazo compounds.

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, but sometimes a route starting with the five-membered component is preferred.
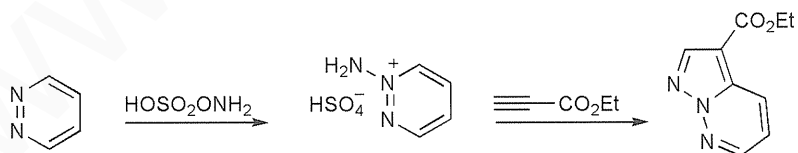
Synthesis of a pyrazolo[1,5-*b*]pyridazine via a dipolar cycloaddition reaction.
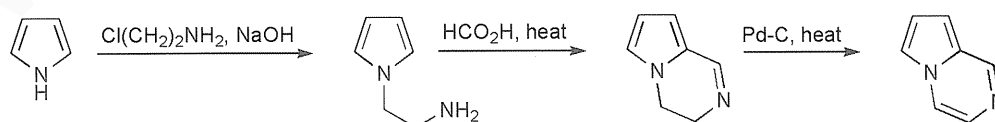
Synthesis of a pyrrolo[1,2-*a*]pyrazine from pyrrole via a dehydrogenation of a dihydro compound.

14.4 Quinoliziniums and Quinolizinones

Quinoliziniums resist electrophilic substitution and 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 with the reactivity of pyridones.
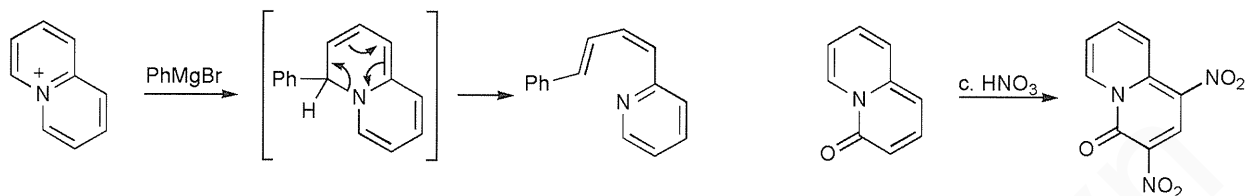
Quinoliziniums react mainly via addition of nucleophiles but quinolizinones by electrophilic substitution.

Quinolizines are usually prepared via cyclisations of 2-substituted pyridines.
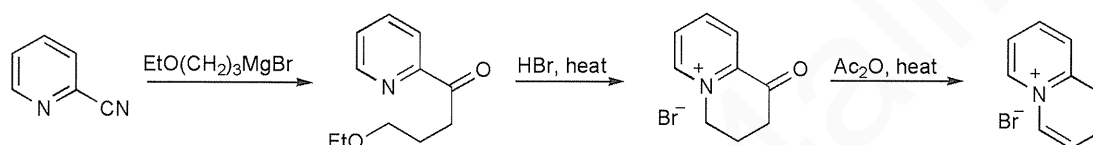
Efficient synthesis of the parent quinolizinium bromide.
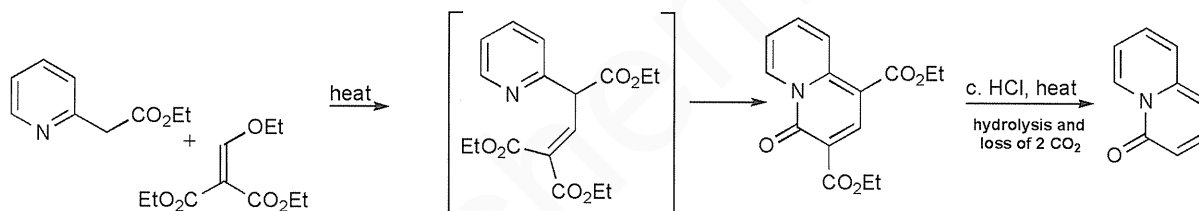
Synthesis of 4-quinolizinone via double decarboalkoxylation of a diester.

Introduction

This book is principally concerned with the chemistry of aromatic heterocycles, but there are a large number of 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 the 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 dioxane (1,4-dioxane) are inert, ethereal-type solvents.

piperidine   pyrrolidine   behave chemically like   Alk–N–Alk   secondary amine   tetrahydrofuran (THF)   dioxane   widely used ethereal solvents
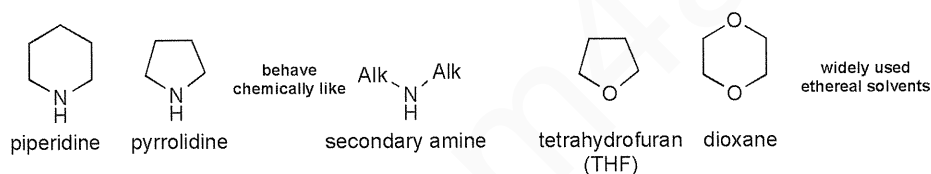
Simple saturated heterocyclic ethers and amines.

15.1 Three-Membered Rings

Aziridines, oxiranes and thiiranes are well-known stable compounds. Oxiranes (epoxides) and aziridines are widely used intermediates in general synthesis.

aziridine   oxirane (an epoxide)   thiirane (an episulfide)

Small-ring saturated heterocycles.

The pK_{aH} of aziridine (7.98) shows it to be an appreciably weaker base than azetidine (11.29). The explanation is probably associated with the strain in the three-membered compound, with the result 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 azirines is very slow compared with simpler amines. This is because there is a further increase in angle strain when the nitrogen rehybridises ($\rightarrow sp^2$) 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, alcohols, thiols, hydride (LiAlH$_4$), malonate anions, etc. 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.
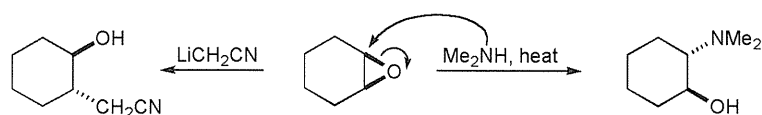
Ring opening of epoxides via nucleophilic attack.

'Harder' organometallic nucleophiles such as alkyllithiums often give rise to side reactions but their combination (at –78 °C) with boron trifluoride gives very clean and efficient reactions. The regiochemistry of nucleophilic attack is determined mainly by steric effects. Ring opening of epoxides by β-elimination, on reaction with strong bases such as lithium amides, is a useful synthetic method to make allylic alcohols.
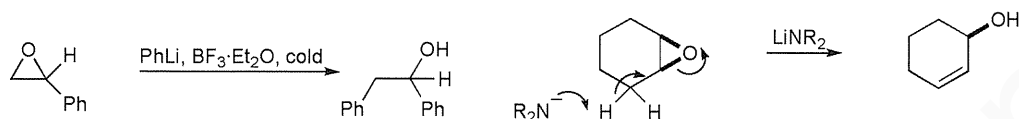
Typical epoxide reactions.

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

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, providing a route to pyrrolidines (from aziridines). Other methods are also available to generate such ylides for pyrrolidine ring synthesis.
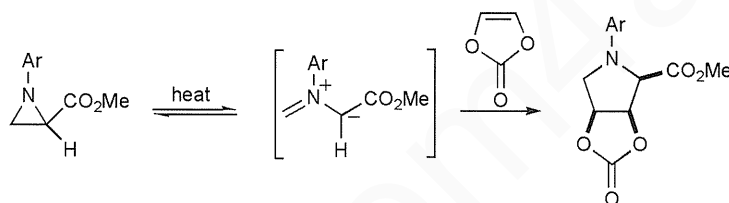
Formation of 1,3-dipoles by ring opening of aziridines.

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 $OXONE^®$ (potassium peroxymonosulfate, $KHSO_5$).

diaziridine   dioxirane   oxaziridine

Small-ring saturated heterocycles with heteroatom–heteroatom bonds.
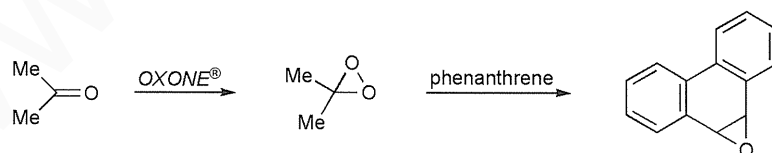
Epoxidation using a dioxirane.

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.
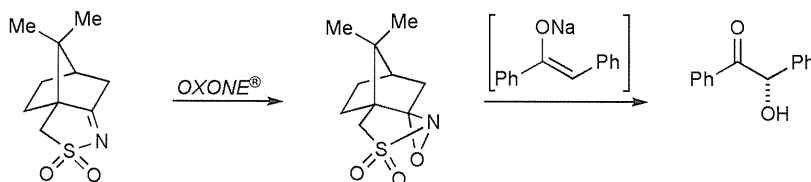
Enantioselective oxygenation of an enolate.

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15.2 Four-Membered Rings

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), but oxetane will react, for example, with organolithium reagents in the presence of boron trifluoride, and azetidine is opened on heating with concentrated hydrochloric acid.

Ring opening of four-membered heterocycles.

Two typical β-lactam-containing antibiotics.

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. β-Lactams are very susceptible to ring opening via attack at the carbonyl carbon – in stark contrast to the five-membered analogues (pyrrolidones) or acyclic amides, which are 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) too are readily attacked at the carbonyl carbon; for example, they are particularly easily hydrolysed compared with simple esters or five- or six-membered lactones.

Synthesis of 4-substituted azetidinones.

15.3 Five- and Six-Membered Rings

Pyrrolidine and piperidine are somewhat better nucleophiles than diethylamine, principally because the nitrogen is less hindered – in the heterocycles the two alkyl 'substituents', i.e. 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). Piperidines, like cyclohexanes, adopt a preferred chair conformation. Both an N-hydrogen and an N-alkyl substituent adopt an equatorial orientation, though in the former case the equatorial isomer is favoured by only a small margin.
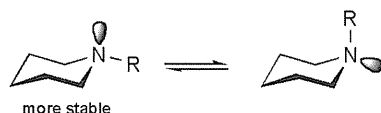
Preferred conformation of piperidines.

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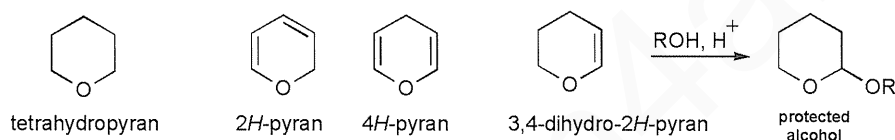
Reduced pyrans.

A great deal is known about hydroxylated tetrahydrofurans and tetrahydropyrans because such ring systems occur in sugars. Glucose has two cyclic forms, hemiacetals containing a tetrahydropyran. However, many of the reactions of sugars (glucose) involve a small equilibrium concentration of ring-opened hydroxyaldehyde. All 5-hydroxyaldehydes, 5-hydroxyketones and 5-hydroxyacids easily close to form six-membered oxygen-containing rings – lactols and lactones respectively.
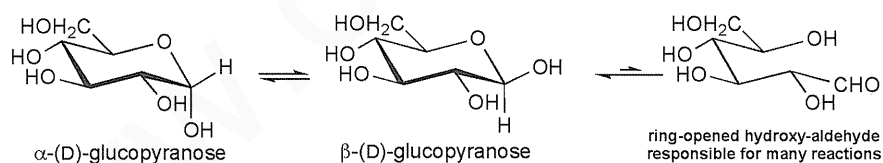
The three forms of glucose.

Tetrahydropyran, like piperidine, adopts a preferred chair conformation. 2-Alkoxy-tetrahydropyrans prefer a conformation in which the alkoxy group is axial – this is referred to as the 'anomeric effect'.
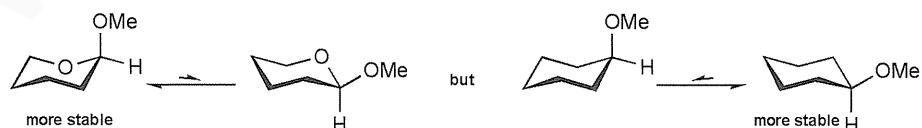
Alkoxy groups adjacent to ring oxygen in tetrahydropyrans prefer to be axial, in contrast to alkoxy-cyclohexanes.

15.4 Ring Synthesis

15.4.1 From bifunctional acyclic precursors

Five- and six-membered saturated rings can be prepared by reduction of the corresponding aromatic compound, but the most general method for making all ring sizes is by cyclisation of an ω-substituted amine, alcohol or thiol via an intramolecular nucleophilic displacement – 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.

Lg = leaving group
Z = N, O or S

relative rates
72 (three-membered ring) : 1 (4) : 6000 (5) : 1000 (6)
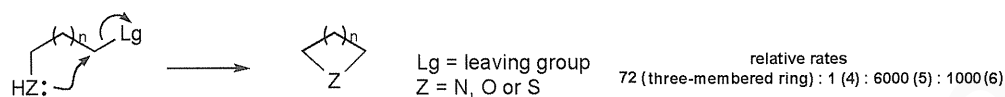
General scheme for synthesis of saturated heterocyclic rings by intramolecular nucleophilic substitution.

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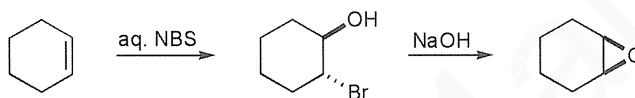
Synthesis of epoxides from halohydrins.

Aziridines can be prepared by alkali-catalysed cyclisation of 2-halo-amines or of a 2-hydroxy-amine sulfonate ester. Azetidines can be obtained by cyclisations of 3-halo-amines.

Synthesis of aziridine and an azetidine.

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.
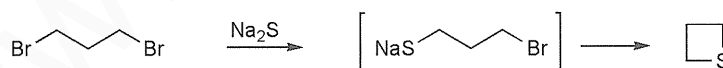
Synthesis of thietane.

Cyclisations involving heteroatom 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*'.

Z = N, O or S

General scheme for synthesis of saturated heterocyclic rings by electrophile-promoted cyclisation onto an alkene.

15.4.2 Three-membered heterocycles from alkenes

By far the most widely used method for the preparation of 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.
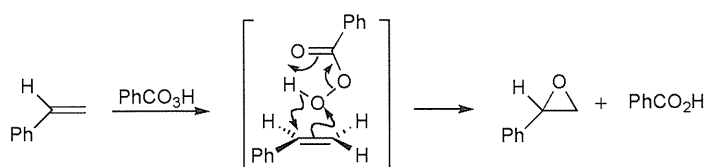
Synthesis of epoxides using a peracid.

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 enantiopure tartrate esters are used, a highly ordered asymmetric reactive site results, leading in turn to high optical induction in the product.
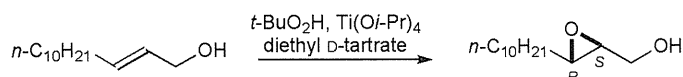
Enantioselective (Sharpless) epoxidation.

N-Tosylaziridines can be obtained directly from alkenes by reaction with 'Chloramine T' (TsN(Cl)Na).
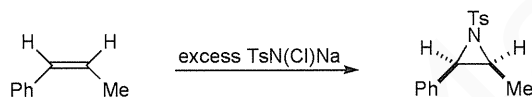
Aziridination of an alkene.

15.4.3   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.
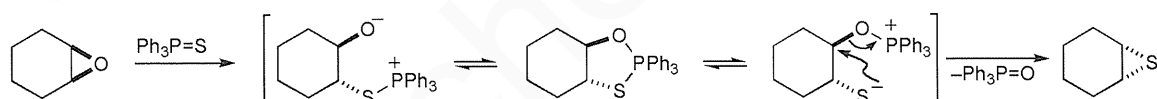
Conversion of an epoxide into a thiirane.

15.4.4   Cycloaddition reactions

Many methods have been developed for β-lactam synthesis, the most widely used methods being two-component couplings which occur either via concerted cycloaddition or via two-step mechanisms.
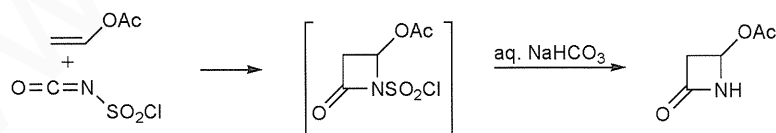
Synthesis of an azetidinone by addition to an isocyanate.

15.4.5   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 dialkenyl-amines, -ethers, etc., as illustrated below by a tetrahydropyridine synthesis.
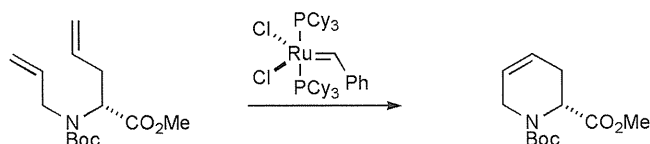
Synthesis of a tetrahydropyridine using Grubbs' olefin metathesis.

16.1 Palladium(0) (Transition Metal)-Catalysed Reactions

The use of palladium(0) catalysis for the construction of new C–C and C–hetero bonds to aromatic molecules is one of the major advances in synthetic chemistry in the last quarter of the twentieth century. 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 typical palladium-catalysed reactions of all heterocyclic systems together in this section, rather than including examples in the discussions of particular heterocycles, 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. Pd(0)-catalysed processes can also be employed in the ring synthesis of some heterocyclic systems. A particular significance of these reactions is that 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.
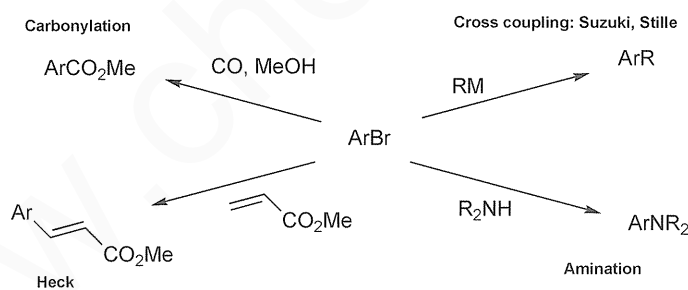
Typical palladium-catalysed reactions.

The most important methods involve the reaction of a halo compound, 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 but other partners, such as alkenes, carbon monoxide or a range of heteroatom nucleophiles, can also be utilised. Either the halo compound or the organometallic component or both can be heterocyclic.

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

Although a range of transition metal catalysts can be used, palladium is very dominant and we restrict the following discussion almost entirely to it. Nickel is the main alternative catalyst and benefits from a much lower price, but is more restricted in scope. Mechanistically, reactions catalysed by palladium and nickel are quite similar.

16.2 Cross-Coupling Reactions Between Organometallic Species and Halides: Making Carbon–Carbon Bonds

Introduction

These cross-coupling reactions are the most common use of palladium catalysis. The overall conversion is:

$$ArHal \ + \ RM \ \longrightarrow \ Ar–R \ + \ MHal$$
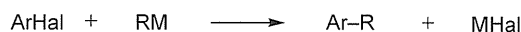
Overall conversion in cross-coupling reactions

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

The organometallic components are often prepared by an exchange reaction with an organolithium (see individual sections for the generation of heterocyclic lithium reagents) and also, for boron and tin, by palladium-catalysed methods, as illustrated for selected examples below.

Catalysts

Palladium in its zero oxidation state (Pd(0)) is always the active catalytic species 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(triphenyl-phosphine)palladium(0) (Pd(PPh$_3$)$_4$) or as a mixture of a Pd(0) complex, such as Pd(0)(dba)$_2$, 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 preformed phosphine complex such as bis(tri-o-tolylphosphine)palladium dichloride (PdCl$_2$(P(o-Tol)$_3$)$_2$). 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 via conversion into a diarylpalladium by reaction with RM, followed by reductive elimination.

$$RM \ + \ PdX_2 \ \longrightarrow \ RPdX \ \xrightarrow{RM} \ RPdR \ \longrightarrow \ R_2 \ + \ Pd(0)$$

Initiation step for the formation of the true Pd(0) catalyst from a Pd(II) precatalyst.

A wide variety of phosphines or sometimes other types of ligands can be used. The choice of the particular 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.

16.2.1 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.
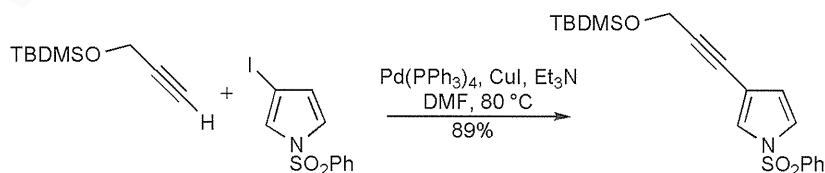
A classical Sonogashira reaction employing copper.
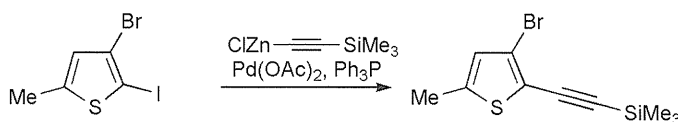
Coupling of an alkyne but without the use of copper.

16.2.2 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: $HetB(OH)_2 + Het'Hal$, $ArB(OH)_2 + HetHal$ and $HetB(OH)_2 + ArHal$. Either a free boronic acid or an ester can be used. The inclusion of a mild base is essential for these couplings.
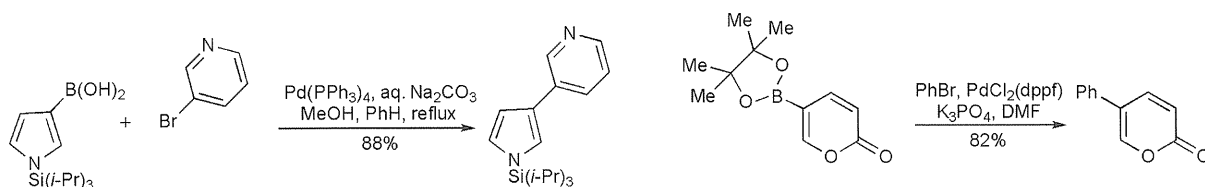
Pd(0)-catalysed couplings of a boronic acid and a boronate ester.
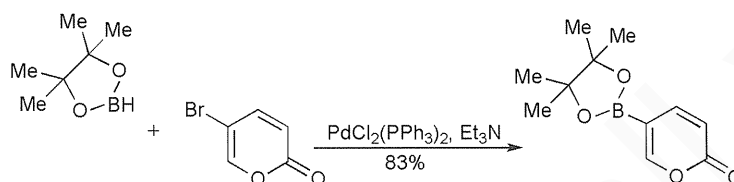
Pd(0)-catalysed synthesis of a boronate ester using a dialkoxyborane.
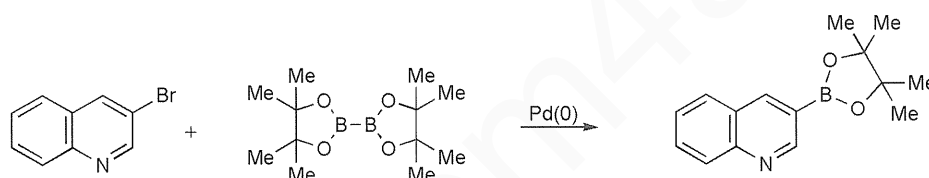
Pd(0)-catalysed synthesis of a boronate ester using a diboron compound.
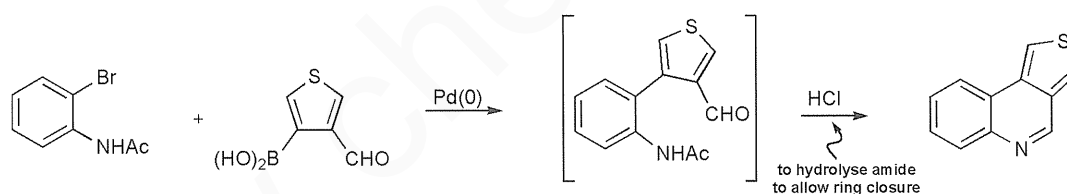
Boronic acid couplings are very tolerant of functional groups.

Bromide is the most common leaving group but iodide and chloride can also be used, although for the latter a more reactive catalyst may sometimes be needed.
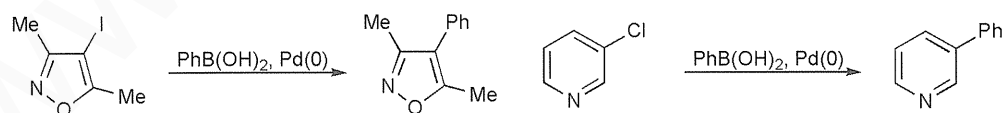
Boronic acid couplings with an iodide and a chloride.

Non-aromatic (alkenyl and alkyl) boronic acids are also useful.
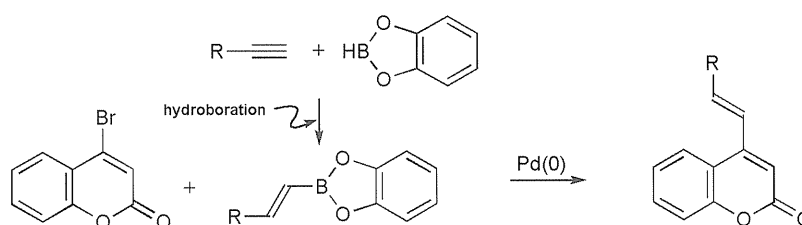
Preparation and coupling of an alkenyl boronate.

16.2.3 Stannane couplings (Stille reaction)

Couplings with HetSnR$_3$ are particularly useful in cases where the corresponding boronic acid would be unstable, for example azole boronic acids. However, all of the variations equivalent to the boronic acid couplings can be used.

Stannane couplings suffer from the disadvantage that tin 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 therefore readily absorbed through the skin.
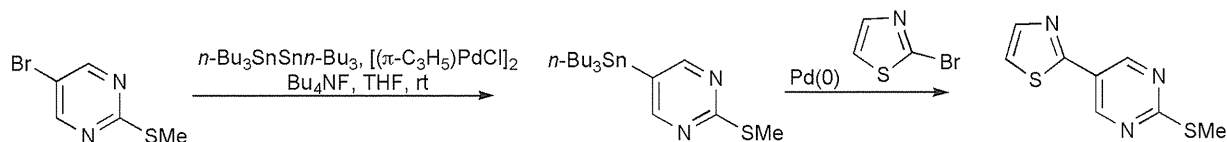
A ditin compound used for the Pd(0)-catalysed preparation of a stannyl pyrimidine and its coupling with a bromide.
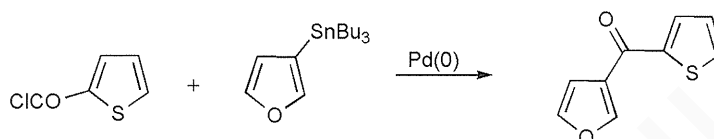
Coupling of an acid chloride with a stannylfuran.
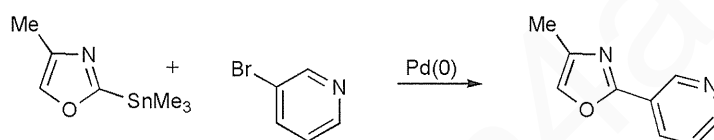
Tin derivatives of azoles are particularly useful in cross couplings. [*Caution:* Trimethyltin compounds are very toxic.]

16.2.4 Couplings using other organometallic reagents

Grignard reagents are useful partners when functional groups are absent but the corresponding zinc reagents are more tolerant of functional groups and can often give better yields. Silane couplings are becoming increasingly useful. Nickel is a good replacement for palladium in some reactions.
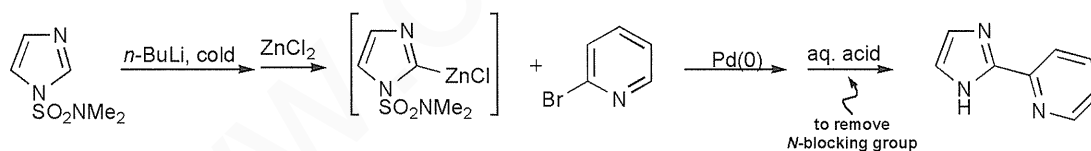
Preparation of an imidazol-2-ylzinc chloride, *in situ*, and its coupling with a bromide.
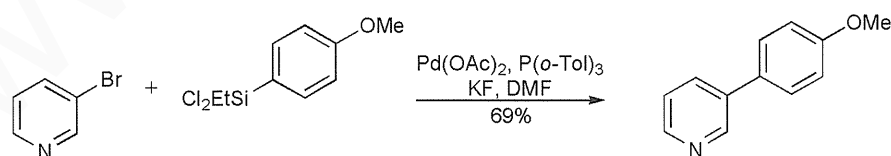
A silane coupling with a bromide.
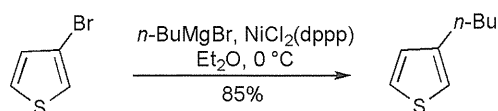
A nickel(0)-catalysed coupling with a Grignard reagent.

16.3 Other Carbon–Carbon Bond-forming Reactions

16.3.1 Couplings using anions from C–H-acidic compounds
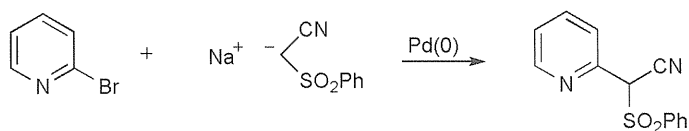
Coupling using a stabilised carbanion.

16.3.2 Reactions with 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. It uses conditions similar to those used for the other (cross) coupling reactions but has the advantage of not requiring an organometallic intermediate. A Heck reaction using an enol ether as the alkene results, after hydrolysis, in the overall introduction of an acyl group.
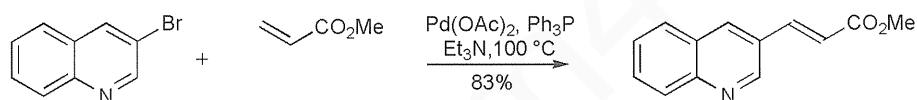
A Heck reaction using methyl acrylate as the alkene.
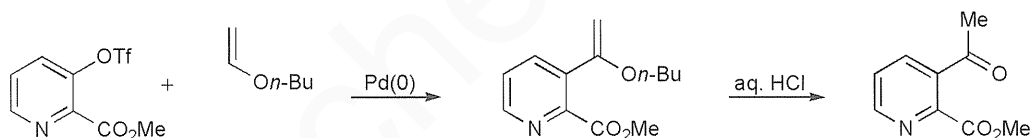
A Heck reaction using an enol ether to introduce an acetyl group.

16.3.3 Carbonylation reactions

Reaction of a halide and palladium with carbon monoxide and a nucleophile – water, amine or alcohol – gives an acid, carboxamide or ester respectively.
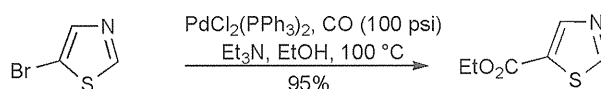
Palladium(0)-catalysed introduction of an ester group via reaction with carbon monoxide.

16.4 Cross-Coupling Reactions Between Heteroatom Nucleophiles and Halides: Making Carbon–Heteroatom Bonds

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. Nitrogen, sulfur and oxygen nucleophile (amine, thiol and alcohol/phenol) couplings all work well.
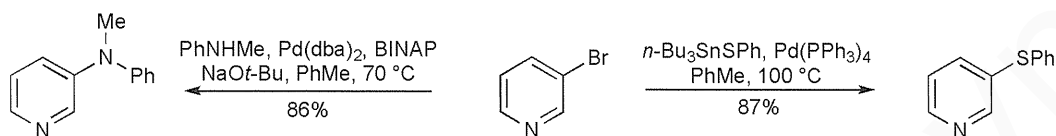
Palladium(0)-catalysed formation of C—N and C—S bonds.

16.5 Triflates as Substrates for Palladium-Catalysed Reactions

Triflates (trifluoromethanesulfonates: –OSO₂CF₃) give comparable reactions to bromides and are very useful for activating phenols when the corresponding aryl halide is not available. They can also be used to activate heterocyclic compounds which usually exist as carbonyl tautomers, for example oxindoles, pyridones, and furanones.
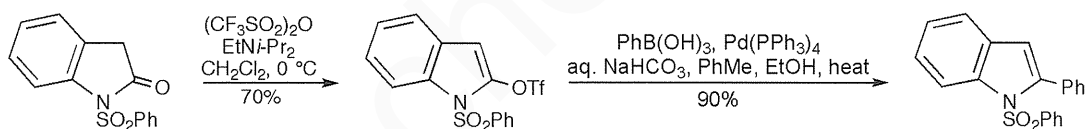
Conversion of an oxindole into a triflate and its coupling.
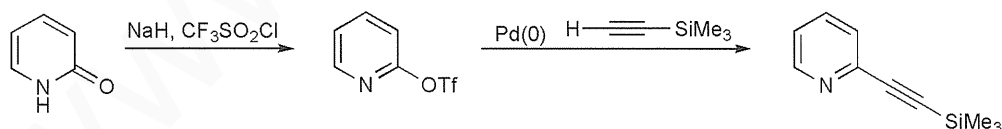
Conversion of a 2-pyridone into a triflate and its coupling.
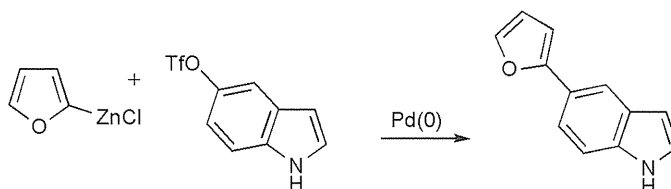
Coupling of a phenolic triflate.

16.6 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 ArPdHal and ArPdR is regarded as being Pd(II).]

In the scheme shown 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.

Cross-coupling reactions – mechanism.
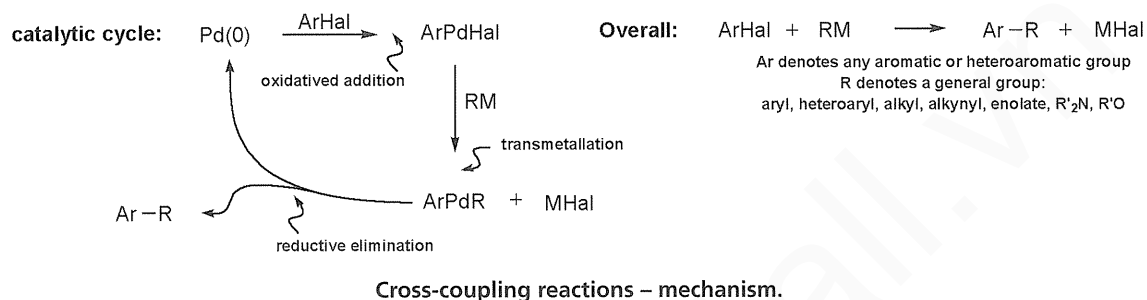
Note: The intermediate arylpalladium halides (ArPdHal), despite an apparent resemblance to Grignard reagents, are generally fairly stable to air and water and do not react with electrophiles.

16.6.1 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 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.
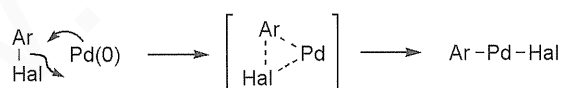
Oxidative addition step.

The *transmetallation step* involves transfer of the organic residue from the metal 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*. Simple enolates and hetero-nucleophiles such as amines react similarly. For boronic acids, a nucleophilic base such as hydroxide is required for the transmetallation step.
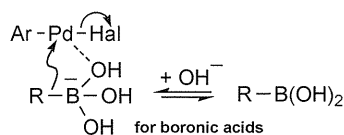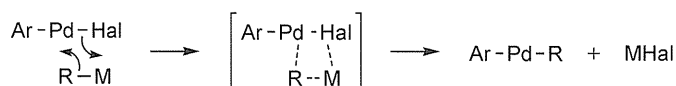
Transmetallation step.

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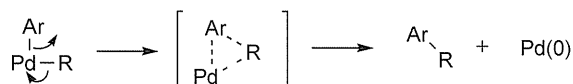
Reductive elimination step.

16.6.2   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 HPdHal or nucleophilic attack at CO respectively. HPdHal breaks down in the presence of base to give back Pd(0).
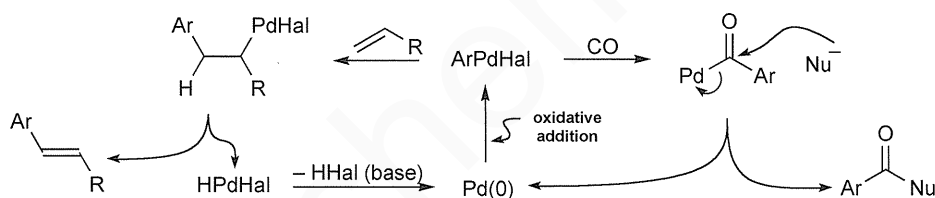
The mechanisms of Heck reactions and carbonylation reactions.

16.7 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: (1) between different leaving groups; (2) between different carbons bearing the same leaving group (regioselectivity). Selectivity between different leaving groups almost always dominates over regioselectivity.

16.7.1 Leaving groups

The reactivity of different 'leaving groups' to oxidative addition is related inversely to the strength of the carbon–halogen bond, i.e. 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 becoming important as new catalysts are developed.

16.7.2 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 18) it is C-4 > C-2 > C-3, showing the greater effect of induction at C-2 in the former.
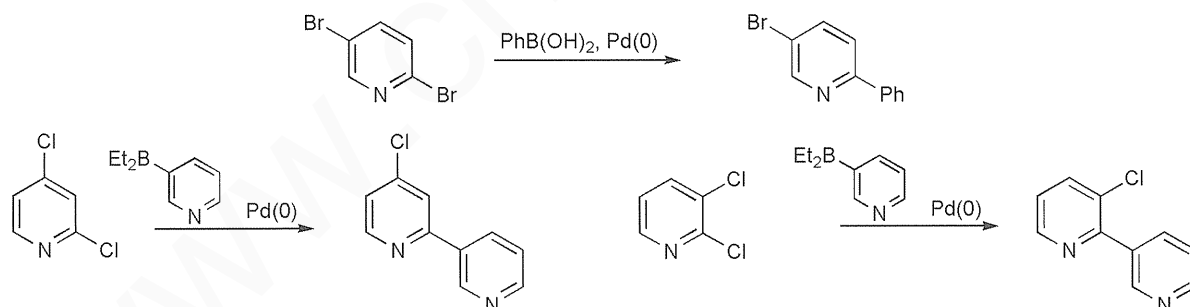
Selectivity between halogens in palladium(0)-catalysed coupling of halo-pyridines. Reactivity order is 2 > 4 > 3.
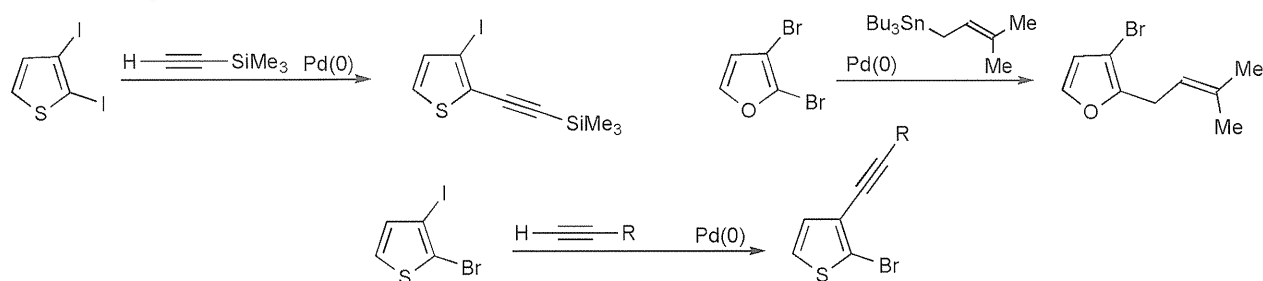
In thiophenes and furans, the reactivity order is 2 > 3; however, iodide is always more reactive than bromide.

16.7.3 Organometallic selectivity

Different classes of organometallic reagent may require very different conditions to achieve coupling – boronic acids usually react under polar conditions in the presence of a base whereas stannanes do not require the addition of a base, and reactions of these reagents are usually carried out in non-polar solvents. The difference in requirements is such that highly selective couplings can be carried out, as is clearly demonstrated by the use of stannyl boronates (under neutral, non-polar conditions) to prepare boronic acid esters.
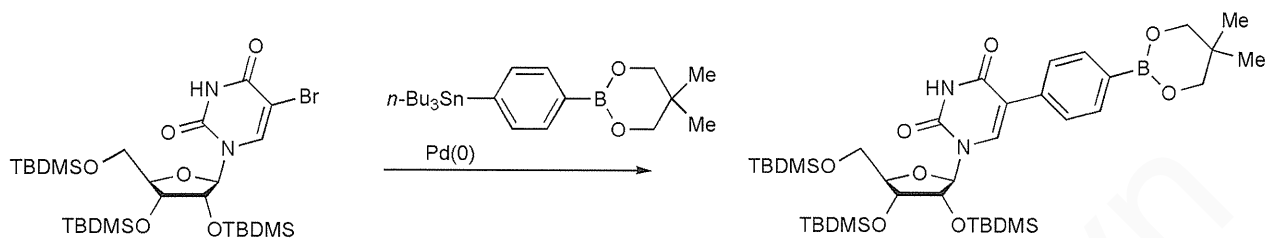
Preparation of a boronic acid ester via a selective coupling of a stannyl boronate.

Heterocycles in Biochemistry

17.1 Heterocyclic Amino Acids and Related Substances

There are four amino acids, amongst the twenty which 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'; i.e. they need to be part of the diet since they cannot be biosynthesised by human beings. 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.
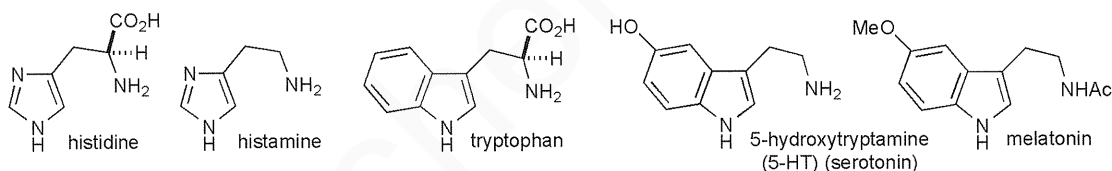
The heterocyclic amino acids and related amines.

The ability of imidazole (pages 68 and 72) to act as both an acid (*N*-hydrogen) and a base (the imine nitrogen) is put to good use in the active sites of several enzymes in which 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 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.
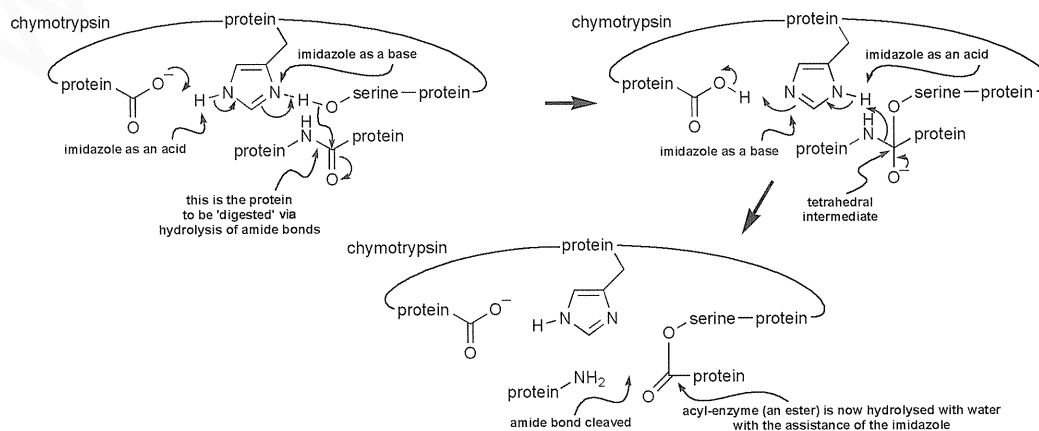
The role of histidine in chymotrypsin hydrolysis of peptides.

17.2 Porphobilinogen and the 'Pigments of Life'

Two 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 is the red pigment in blood which transports oxygen, attached to the iron at its centre, around the body.
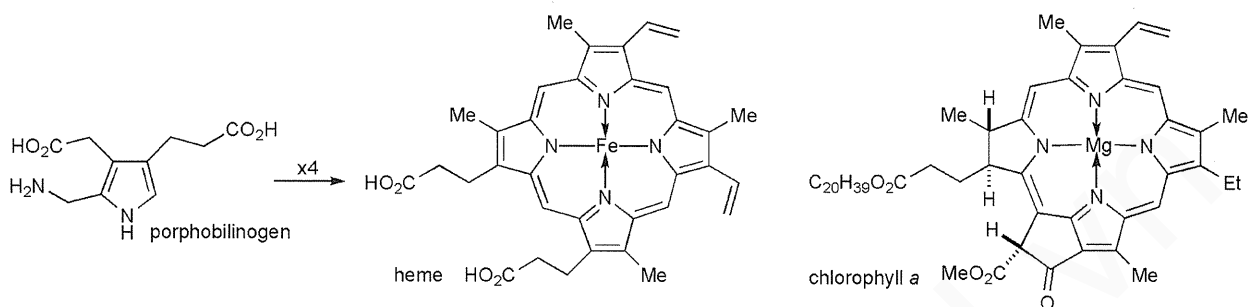
The pyrrole-containing 'pigments of life'.

All the tetrapyrrole pigments are biosynthesised by the combination of four molecules of porphobilinogen (PBG); this is made from δ-aminolevulinic acid ($H_2NCH_2CO(CH_2)_2CO_2H$) and which in turn is made from glycine and succinic acid. There are complexities late in the tetramerisation sequence which we cannot go into here, but the essence of the process can be easily understood on the basis of simple pyrrole chemistry: consider the first step as typical. Protonation of the amino group of PBG converts it into a leaving group, generating an electrophilic azafulvene 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.

$A = HO_2CCH_2$
$B = HO_2C(CH_2)_2$
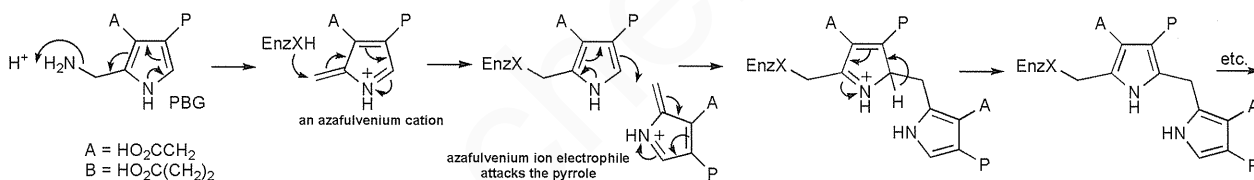
The first steps in the biosynthesis of porphyrins from porphobilinogen.

It is amazing how easy it is to construct such complex macrocycles in the laboratory. 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.
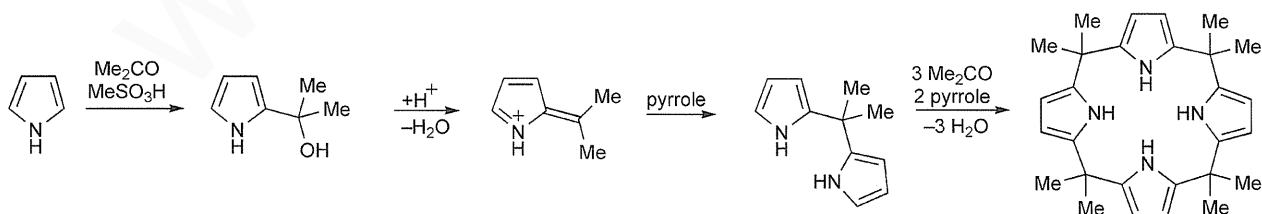
Formation of a tetrapyrrole-macrocycle from pyrrole and acetone.

17.3 Heterocyclic Vitamins – Coenzymes

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 *vital amine*. 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 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 (see also below) 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.
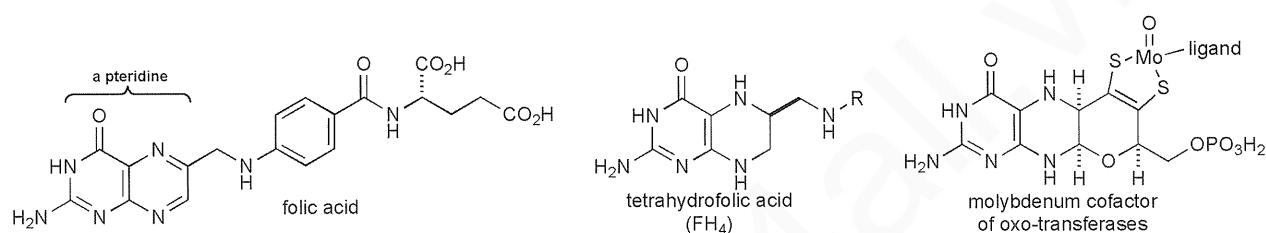
Significant pteridines.

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.
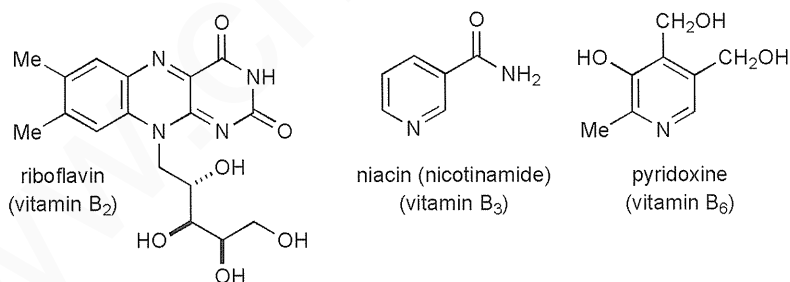
Heterocyclic B vitamins.

17.3.1   Niacin (vitamin B₃) and nicotinamide adenine dinucleotide phosphate (NADP⁺)

Nicotinamide adenine dinucleotide phosphate ($NADP^+$) is a large complicated coenzyme, 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 coenzyme to accept two electrons and a hydrogen, i.e. 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 feasible because it is a stabilised 1,4-dihydropyridine in which the ring nitrogen is conjugated to the carbonyl of the 3-substitutent (compare with the products of a Hantzsch

synthesis; page 26). 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 aromaticity in the coenzyme product – a pyridinium ion.
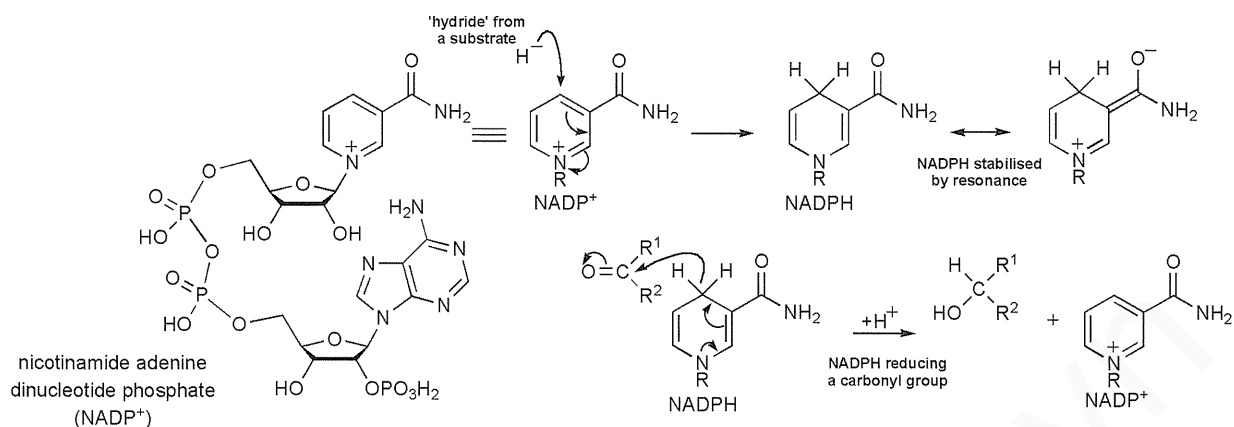
The role of the pyridinium ion in enzyme-catalysed oxidation/reduction processes.

Riboflavin is incorporated into another complex coenzyme, flavin adenine dinucleotide (FAD). This is involved in enzyme-catalysed reductions of carbon–carbon double bonds, and the reverse. After accepting two hydrogens, the coenzyme 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.
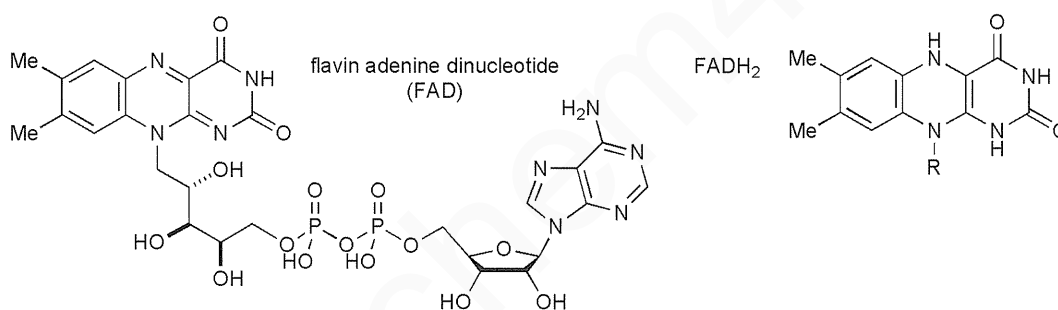
Riboflavin-containing coenzyme and its active form.

17.3.2 Pyridoxine (vitamin B₆) and pyridoxal phosphate (PLP)

The vitamin 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 amino acids. Amongst other activities, PLP-containing enzymes can effect transfer of an amino group from an amino acid to an α-keto acid, bring about decarboxylation of an amino acid, or bring about deamination of an amino acid. In each case, the chemistry of the process depends critically on the pyridine. Consider decarboxylation: condensation of the pyridine-4-aldehyde with the amino group of an amino acid generates an imine, 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 amino acid, together with the regenerated coenzyme.
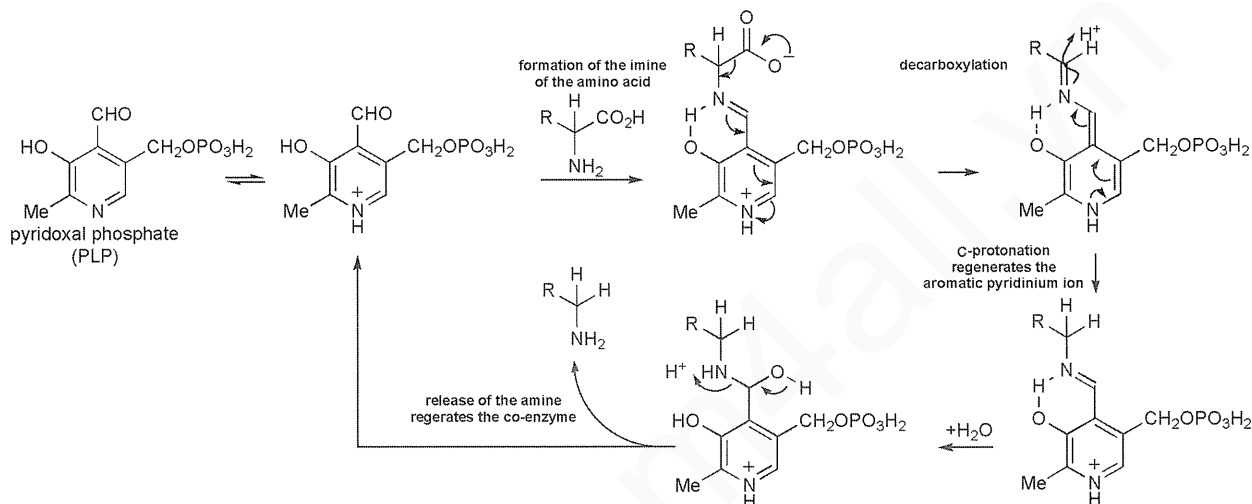
The role of a pyridinium-4-aldehyde in enzyme-catalysed amino acid decarboxylation.

17.3.3 Thiamin (vitamin B₁) and thiamine pyrophosphate

Thiamin pyrophosphate acts as a coenzyme in several biochemical processes and in each case its mode of action depends on the intermediacy of a 2-deprotonated species – an ylide (see page 74 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.
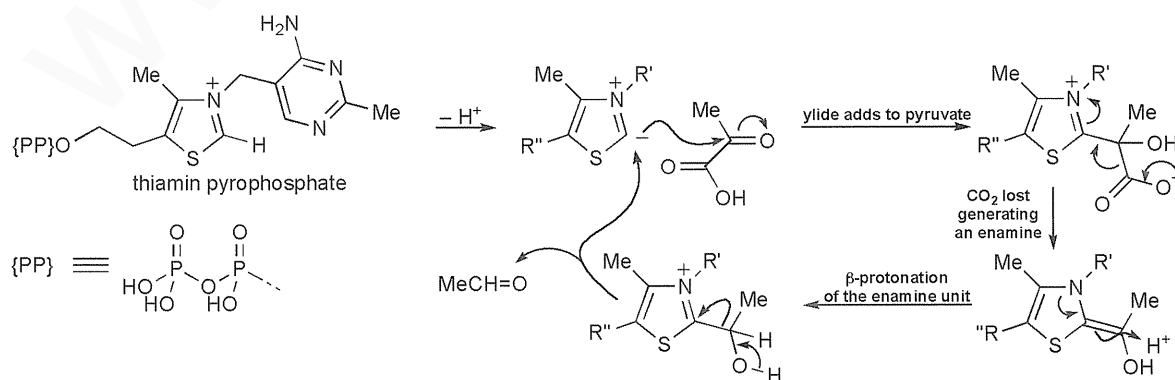
The role of a thiazolium ylide in the enzyme-catalysed decarboxylation of pyruvate.

17.3.4   Other vitamins

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 to be a human dietary requirement in 2003.

vitamin B_{12}

methoxatin
a pyrroloquinoline quinone
(PPQ)
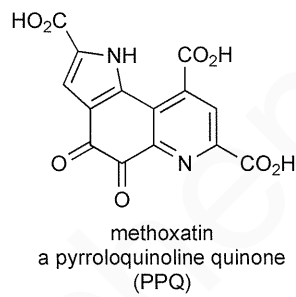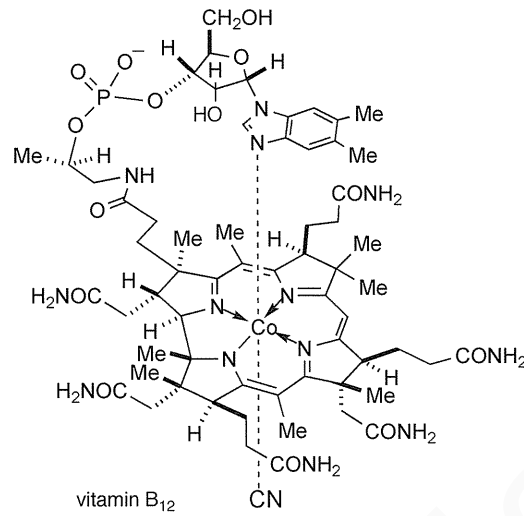
Vitamin B_{12} and the most recently identified vitamin.

17.4 Deoxyribonucleic Acid (DNA) – Genetic Information

Nucleic acids occur in every living cell. Deoxyribonucleic acid (DNA), the carrier of all genetic information, consists of two intertwining helices. Each intertwining strand is a polymer with a backbone, on the outside, consisting of alternating sugar (ribose) and dialkyl phosphate units. From each sugar, protruding 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 and N-9 of the purine bases. 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 two strands separate, each strand acts as a template to form a new strand through the specific AT and CG base pairings, of DNA *or* of RNA (ribonucleic acid). The information in messenger RNA (mRNA) thus produced is translated into protein.

the (- - - -phosphate–sugar–phosphate–sugar- - -) backbone of DNA
B^1, B^2, etc., are the heterocyclic bases

adenine (A)   guanine (G)

cytosine (C)   thymine (T)

the four heterocyclic bases found in DNA
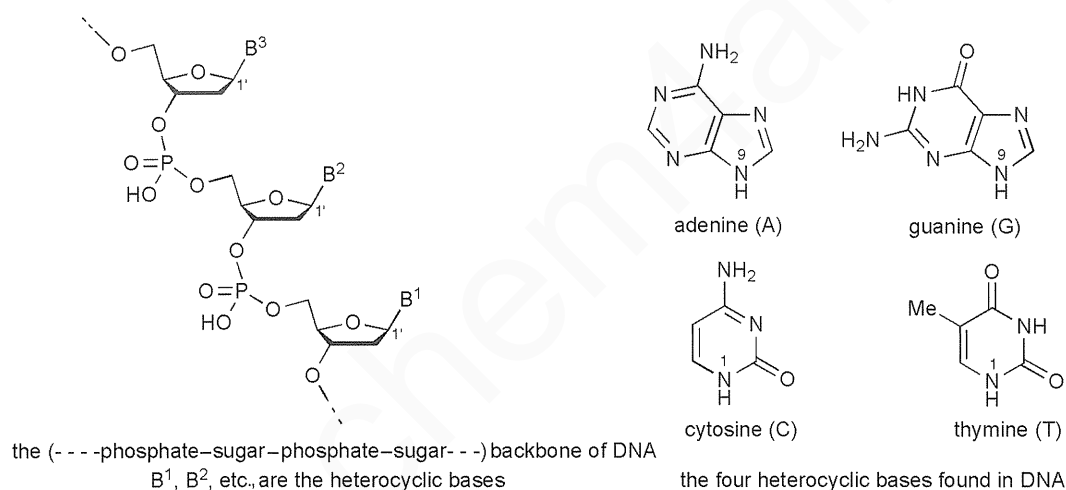
The general structure of a nucleic acid and the four bases of DNA.

In order to understand the specific hydrogen bonding which is the genetic basis of all life, we need to recall the tautomeric forms that six-membered nitrogen heterocycles with amino and hydroxy substituents adopt: the amino heterocycles *exist as amino tautomers*; the heterocycles with a potential hydroxyl α or γ to the nitrogen *exist in the carbonyl tautomeric form*. These two preferences are illustrated in the structures for the four DNA bases shown above. Only when this propensity is recalled can the hydrogen bonding interactions be understood. Ring imine nitrogens and carbonyl oxygens are hydrogen bond acceptors and *N*-hydrogens are donors.

There is another purine derivative of crucial biochemical importance – adenosine triphosphate (ATP). This substance is a carrier of energy, for when a phosphate link is broken a large amount of energy is released. Note some trivial nomenclature: the moieties produced by linking one of the heterocyclic bases to a ribose or 2′-deoxyribose sugar are

known as 'nucleosides' (e.g. adenosine, guanosine, cytidine, thymidine). A 'nucleotide' is a 5′-phosphate (or di- or triphosphate) of a nucleoside – ATP is a nucleotide.
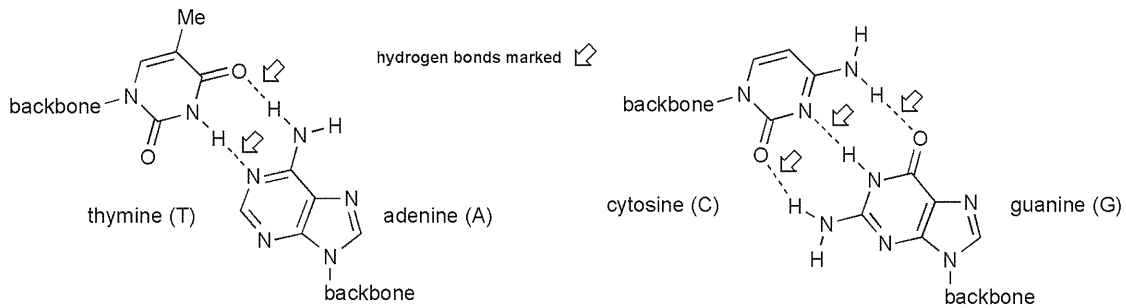
The only effective hydrogen bonding pairings in DNA: adenine/thymine (AT) and guanine/cytosine (GC).
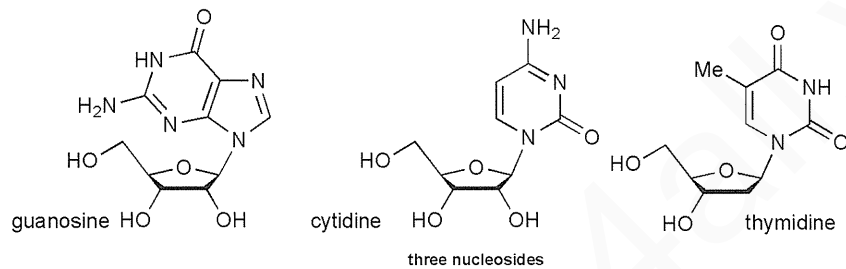
three nucleosides

Typical nucleosides.
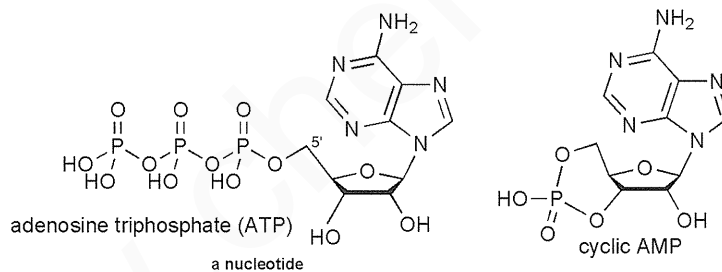
Typical nucleotides.

Finally, but perhaps no less significant for those using this book for study, caffeine is a purine and so is uric acid – the end product of nucleic acid metabolism in birds and reptiles; uric acid was one of the first (heterocyclic) compounds to be isolated as a pure substance, by the Swedish chemist Carl Scheele in 1776.
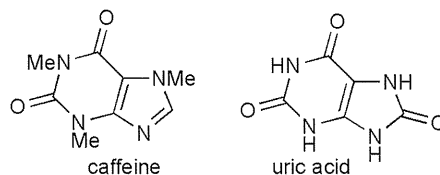
Polyoxy-purines.

Heterocycles in Medicine

18.1 Medicinal Chemistry – How Drugs Function

Heterocycles dominate medicinal chemistry – the majority of drugs are heterocyclic or have heterocyclic structural components. 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.

Drugs exert their effects by a number of mechanisms, the most important being the following:

(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, and 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.

18.2 Drug Discovery and Development

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

competititve antagonist of $H_2NCH_2CO_2H$

glycine
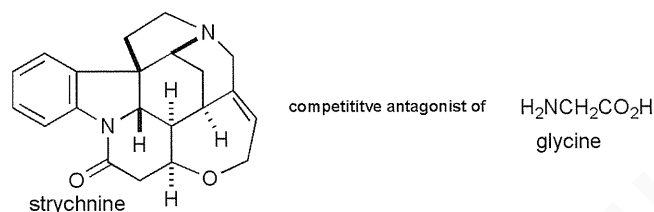
Other routes to drug discovery include isolation and screening of compounds ('natural products') from natural sources that may have been reported in folklore to have medicinal properties, the fortuitous discovery of unexpected activity in a compound being investigated in another disease area, and the crude but reasonably effective method of screening large numbers of random compounds synthesised by combinatorial chemistry. When a *lead compound* has been obtained by one of these methods, more rational optimisation can be carried out.

18.2.1 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; i.e. it relates to the amount of the chemical substance used in the final formulation (tablets, etc.). This is the most demanding area for the heterocyclic 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% are not uncommon.

18.3 The Neurotransmitters

The major neurotransmitters shown below act in both the *peripheral system* (the muscles, blood vessels and organs) and the *central nervous system* (CNS), which comprises the brain and spinal cord. These neurotransmitters include hetero-cyclic (histamine, 5-hydroxytryptamine) and non-heterocyclic substances (catecholamines: adrenaline–noradrenaline, and dopamine; acetylcholine). 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 from 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.
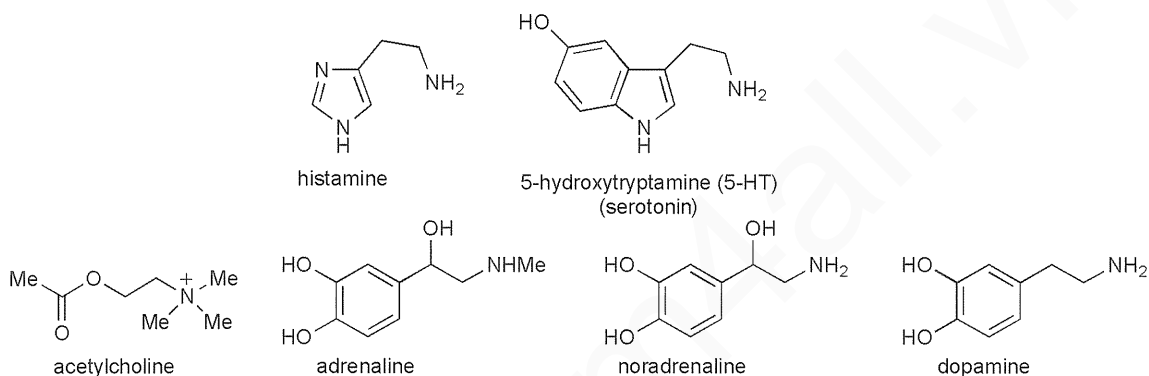
Major neurotransmitters acting in both the central and peripheral systems.

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. Later major sections (infection and cancer) are, of necessity, related to disease areas.

Commercial drugs are given non-systematic 'generic' names – here we give first the generic name with, where appropriate, the proprietary name in parentheses.

18.3.1 Histamine

More than one histamine receptor has been identified. Histamine, acting 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 of this receptor, which suppress these actions of histamine, are well-known to the layman, under the loose description 'antihistamines', as hay fever remedies.

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
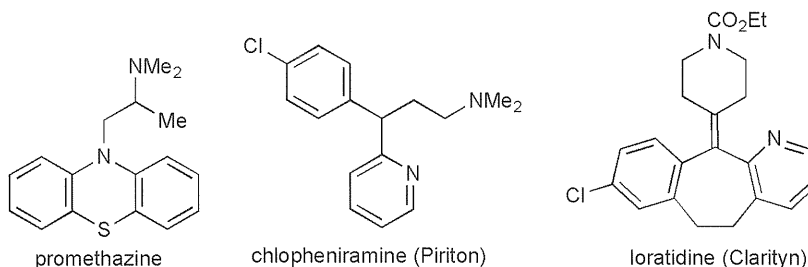
H_1 antagonists – for treatment of allergic reactions – e.g. 'hay fever'.

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 prepared that do not enter the CNS and are therefore free from sedative effects.

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 but can also cause or aggravate the more serious medical problem of peptic ulcers. The development of selective H_2 antagonists, which inhibit the release of gastric acid, in the 1970s, 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 (Tagamet), which is obviously closely structurally related to histamine and as such is a more 'logically' designed compound than the H_1 antagonists. Other H_2 antagonists, particularly ranitidine (Zantac), followed, which had an even more favourable side-effect profile. The dimethylamino-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)   famotidine (Pepcid)
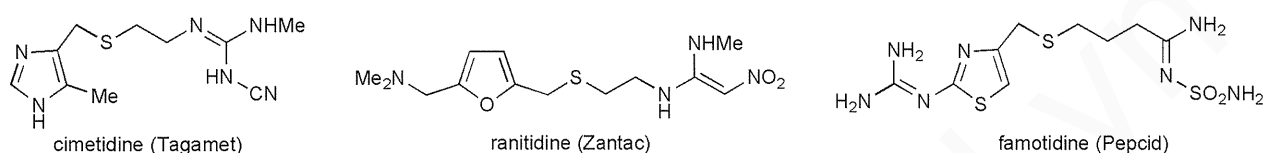
H_2 antagonists – for treatment of peptic ulcers.

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 outside. Omeprazole (Losec) was designed to inactivate 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 the competitive H_2 antagonism. The drug is 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 (the mechanism of formation of the active sulfenylating agent from omeprazole is too complex to discuss here).

omeprazole (Losec)
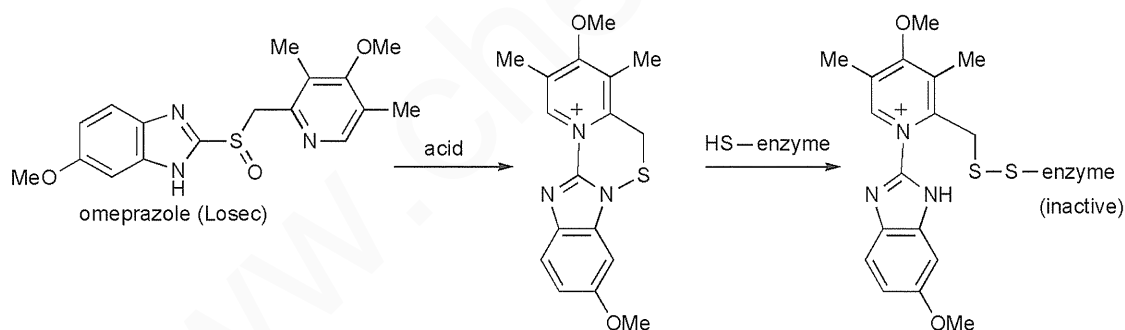
Proton pump inhibitor (omeprazole) and its mechanism of action – for treatment of peptic ulcers.

18.3.2 Acetylcholine

Acetylcholine mediates two different types of activity, and 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.

Clinically useful muscarinic agents tend to be 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. Other muscarinic antagonists include saturated heterocyclic alkaloids such as atropine. The best known nicotinic agonist is nicotine! Nicotinic antagonists include the natural bis-quaternary isoquinoline curare alkaloid tubocurarine, the paralytic agent from curare which is used in surgery as a muscle relaxant.
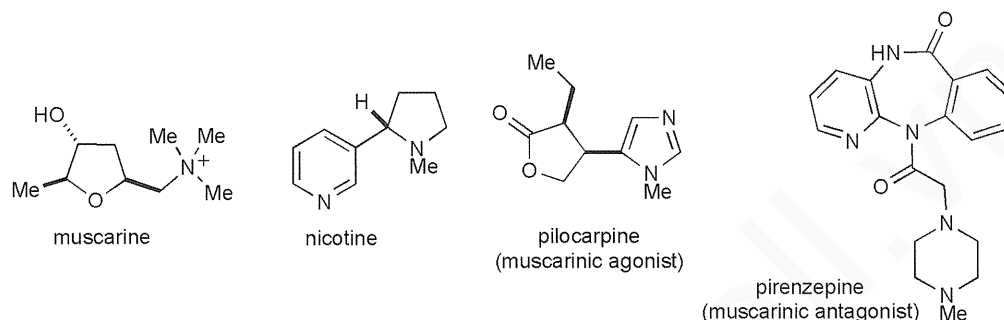
Drugs acting at acetylcholine receptors.

18.3.2.1. Anticholinesterase agents

The physiological activity of acetylcholine relies on local release, stimulation of the receptor, and 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 acetylcholine, is useful in conditions such as myasthenia gravis, a muscle weakness which is caused by insufficient production of acetylcholine.
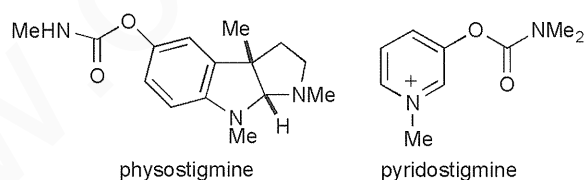
Reversible inhibitors of acetylcholinesterase – for treatment of myasthenia gravis.

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 OH 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

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N-methylpyridinium binds via electrostatic forces to the same site as the choline trimethylammonium, bringing the very nucleophilic oxime oxygen close enough to attack the phosphoryl group, releasing the serine OH.
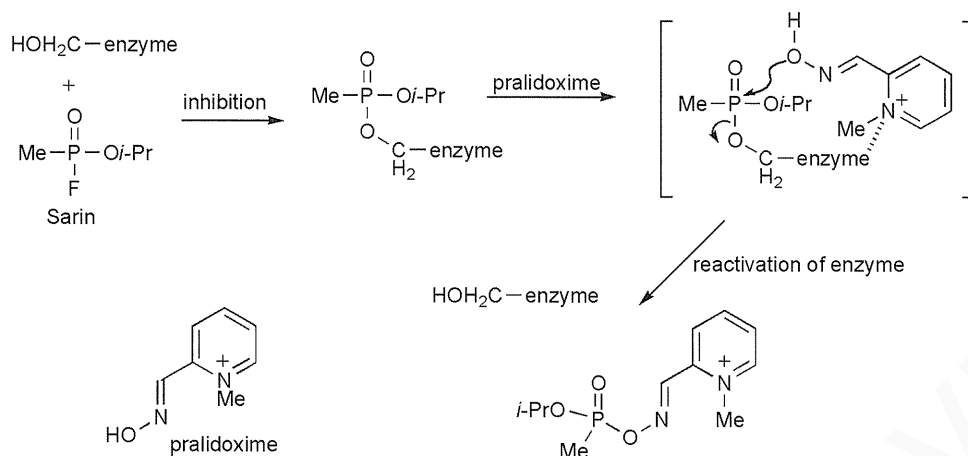
Inhibition of acetylcholinesterase by the nerve gas Sarin and reactivation by the antidote pralidoxime.

18.3.3   5-Hydroxytryptamine (5-HT) (serotonin)

5-Hydroxytryptamine has at least 14 receptors and subtypes. Compounds acting on these receptors are drugs for the treatment of cardiovascular, gastrointestinal and central nervous systems. Sumatriptan, a 5-HT$_{1D}$ agonist, in part, causes vasoconstriction selectively in intracranial blood vessels, opposing the vasodilation which is 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 which are side effects of radiotherapy and treatment with cytotoxic drugs. They probably function by a combination of central and peripheral actions.
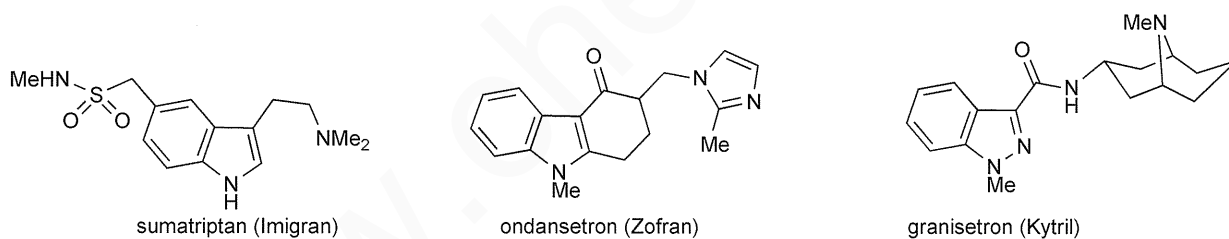
A 5-HT $_{1D}$ agonist: sumatriptan – for treatment of migraine. 5-HT$_3$ antagonists: ondansetron and granisetron – for relief from nausea and vomiting due to cancer therapy.

18.3.4   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 interaction 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.
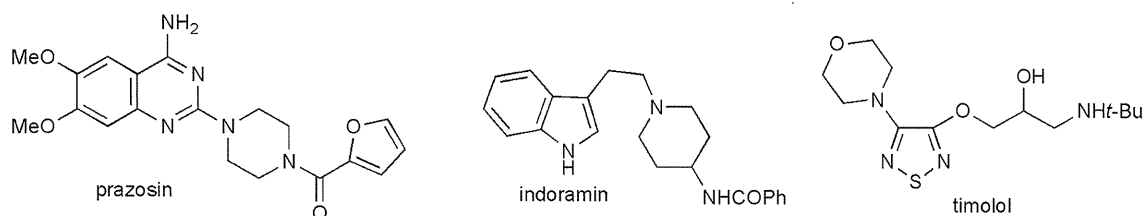
Adrenergic α-antagonists: prazosin and indoramin – for treatment of hypertension and benign prostatic hypertrophy. An adrenergic β-antagonist: timolol – for treatment of hypertension, angina, and arrhythmia.

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18.3.5 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 for treatment of insomnia are hypnotics/sedatives. 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.
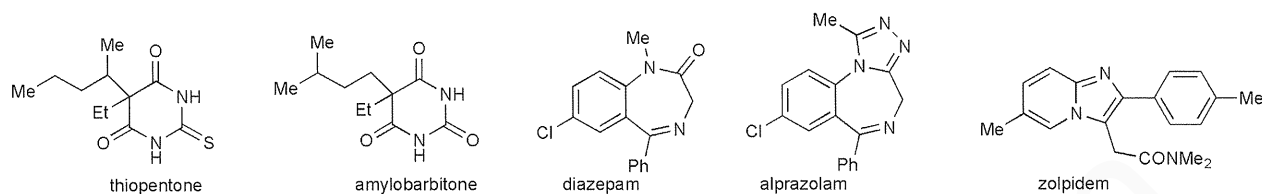
Barbiturates: thiopentone (anaesthetic) and amylobarbitone (hypnotic and sedative). Benzodiazepines: diazepam (anxiolytic and muscleneloxant) and alprazolam (anxiolytic); zolpidem (hypnotic).

Phenobarbitone (another barbiturate) and a newer drug lamotrigine are used to treat epilepsy. Trazodone is a useful anti-depressant with fewer side effects than some of the older drugs.
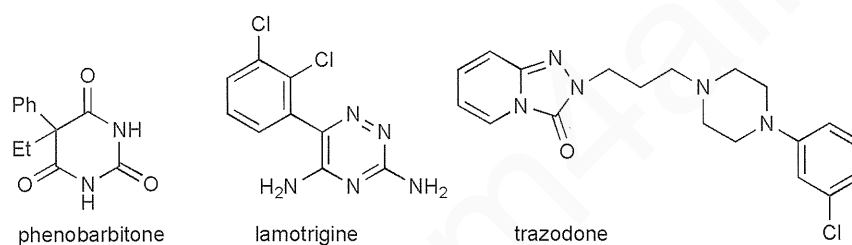
Anti-epileptic agents: phenobarbitone and lamotrigine; anti-depressant: trazadone.

Anti-psychotic agents, acting primarily as dopamine and 5-HT antagonists, are used mainly to treat schizophrenia. Newer agents such as olanzapine and risperidone have fewer side effects than the traditional phenothiazines such as chlorpromazine.
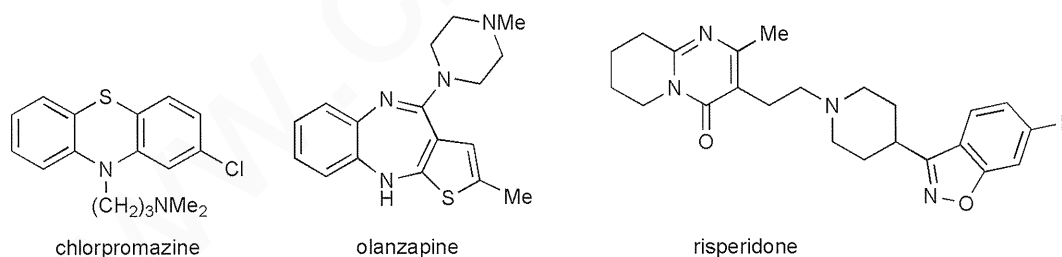
Anti-psychotic agents.

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.
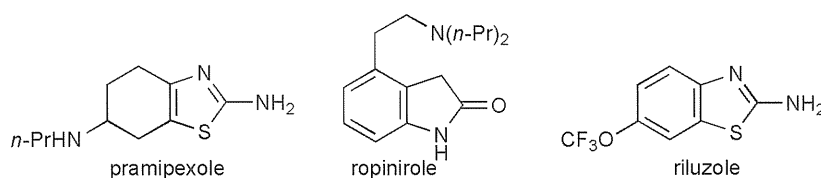
Dopamine agonists: pramipexole and ropinirole – for treatment of Parkinson's disease. Riluzole – for treatment of motor neurone disease.

18.4 Other Enzyme Inhibitors

COX (cyclooxygenase) enzymes are involved in the first stage of prostaglandin synthesis and their inhibition is the basis of action of the *n*on-*s*teroidal *a*nti-*i*nflammatory *d*rugs (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), although 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.
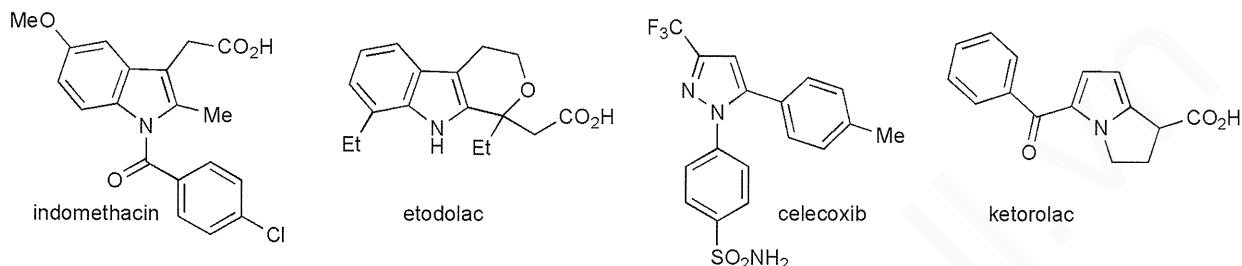
Anti-inflammatory/analgesic COX inhibitors.

Statins reduce the amount of cholesterol in the blood by inhibition of one of the enzymes (HMG-CoA reductase) involved in its synthesis 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 cerivastatin.

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 ATP.
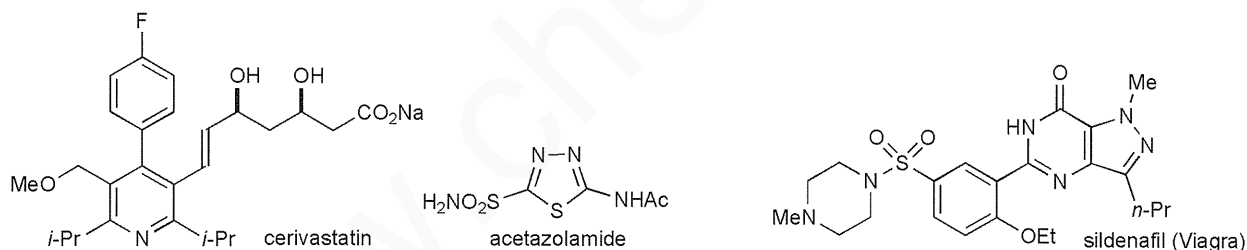
A statin, cerivastatin – for reducing blood cholesterol; acetazolamide – for treatment of glaucoma and motion sickness. Sildenafil – for treatment of impotence.

18.5 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 one of the few drugs of proven value for the treatment of baldness (alopecia).
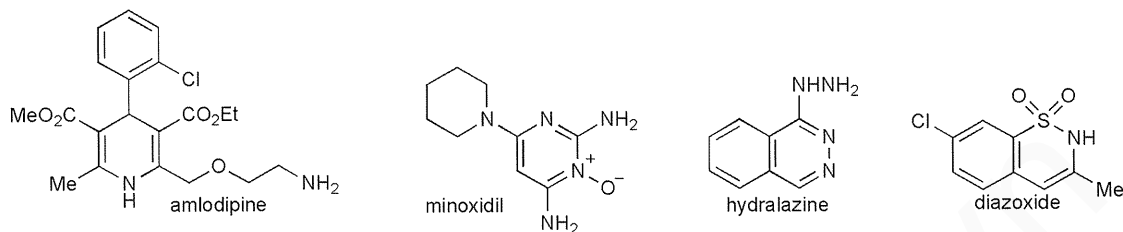
Amlodipine – for treatment of hypertension and angina; minoxidil – for treatment of hypertension and baldness. Hydralazine and diazoxide – for treatment of hypertension.

18.6 Anti-infective Agents

This subsection covers 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.

18.6.1 Anti-parasitic 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 anti-malarial 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).
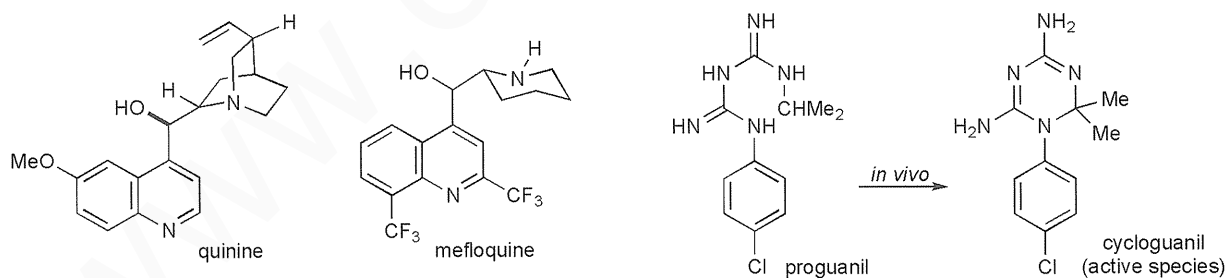
Some anti-malarial drugs.

Metronidazole is used for both anti-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 anti-fungal agents are triazoles such as fluconazole (Diflucan).
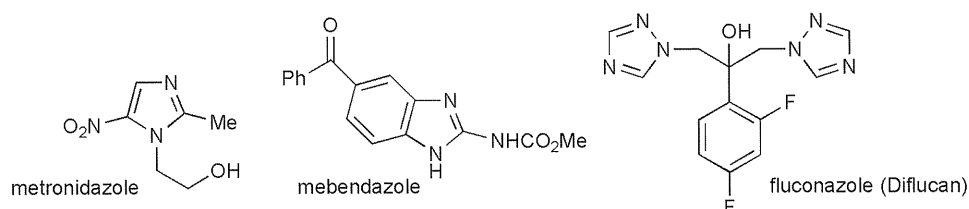
An anti-protozoal/anti-bacterial (metronidazole), an anthelmintic (mebendazole) and an anti-fungal (fluconazole).

18.6.2 Anti-bacterial drugs

Among anti-bacterial agents, the simplest must be the pyridine-hydrazide, isoniazide, an important anti-tuberculosis drug. Heterocyclic contributions to mainstream antibiotics include a group of quinolones, e.g. the broad spectrum anti-bacterial ciprofloxacin (perhaps best known in connection with recent terrorist use of anthrax), and the diaminopyrimidine trimethoprim. Many of the sulfonamides, the first synthetic antibiotics, contain heterocyclic residues. Of course, penicillins and cephalosporins (see page 110) 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*; i.e. there is a greater activity than the sum of the two components.

These two are frequently used in combination as Co-trimoxazole
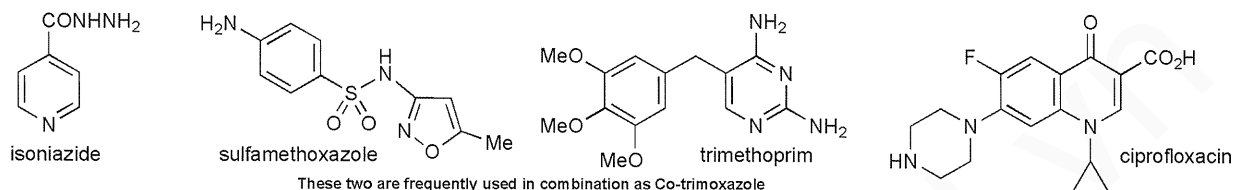
Anti-bacterial agents.

18.6.3 Anti-viral drugs

Many anti-viral 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.
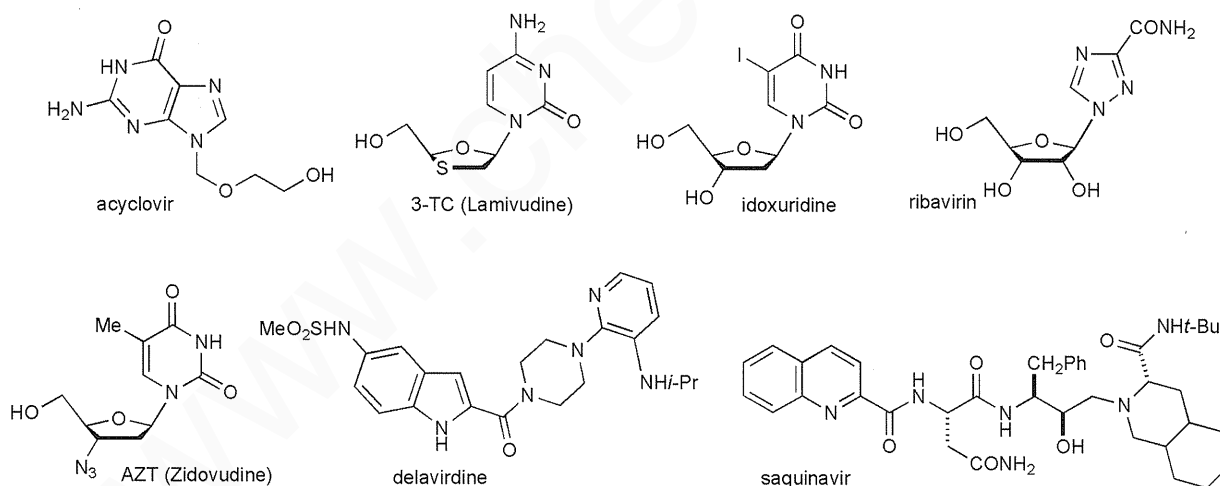
Anti-viral drugs: acyclovir (anti-herpes), 3-TC (anti-hepatitis B and anti-HIV), idoxuridine (anti-herpes), ribavirin (general anti-viral), AZT and delavirdine (anti-HIV reverse transcriptase inhibitors) and saquinavir (anti-HIV protease inhibitor).

18.7 Anti-cancer Drugs

Anti-cancer drugs generally act by disrupting the growth of cells and therefore oppose the excessive and abnormal growth, which is the basis of cancer pathology. They are often referred to as cytotoxic or anti-metabolites. 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 temozolamide, which breaks down *in vivo* to give the powerful alkylating agent diazomethane. Possibly the resemblance of temozolamide to a nucleic acid base allows it to come into close contact with its target.

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 anti-cancer and immunosuppressive agent which acts in this manner.
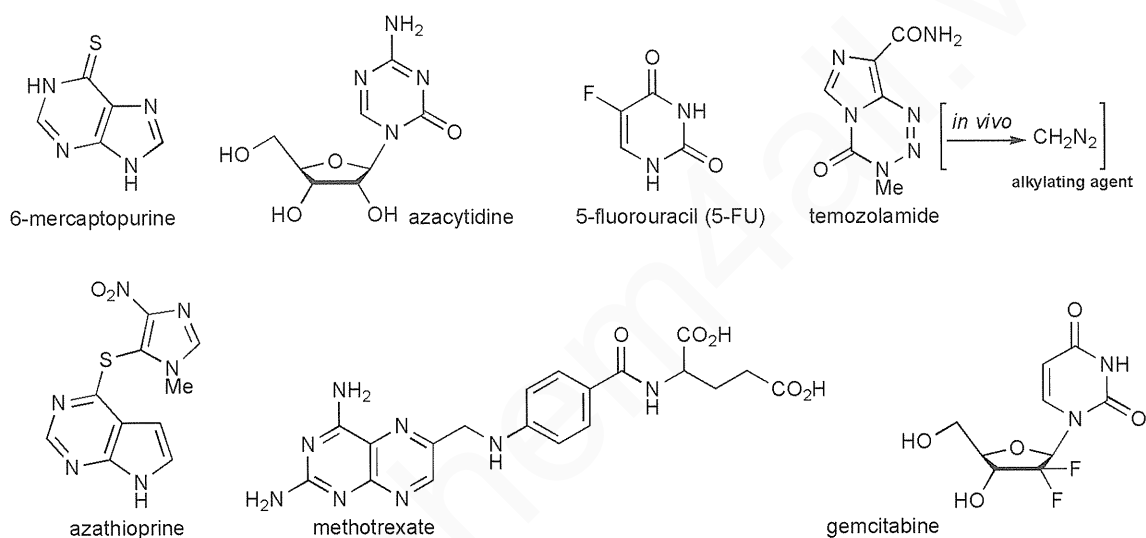
Anti-cancer drugs: 6-mercaptopurine and azacytidine – for treatment of leukaemia; 5-fluorouracil – for treatment of solid tumours; temozolamide – for treatment of glioma and melanoma; azathioprine – an immunosuppressive; methotrexate – anti-cancer agent and an immunosuppressive; gemcitabine – for treatment of pancreas and lung cancers.

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.
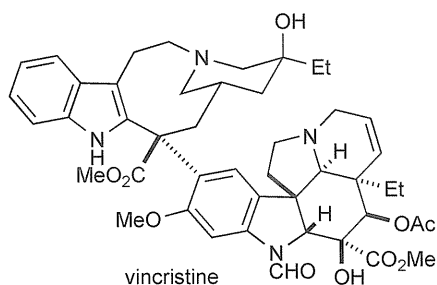
Vincristine, binds to tubulin – for treatment of leukaemia.

Irinotecan, a more selective synthetic analogue of camptothecin (a natural but toxic anti-cancer alkaloid), acts by inhibiting topoisomerase I, an enzyme involved in ordering the strands of DNA.
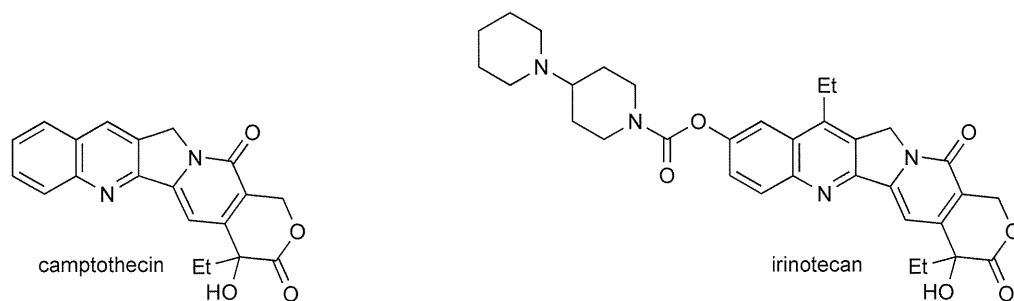
Topoisomerase inhibitors: camptothecin, a natural product, and its synthetic analogue irinotecan.

Imatinib (Glivec) is highly effective in the treatment of chronic myeloid leukaemia and is also used to treat some rare gastrointestinal tumours. Its mechanism of action involves inhibition of the enzyme tyrosine kinase.

imatinib (Glivec)
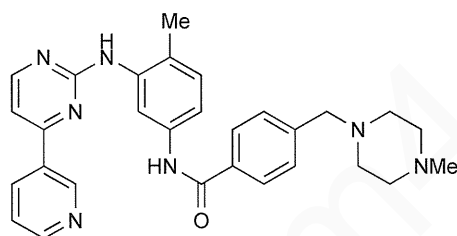
Imatinib – for treatment of chronic myeloid leukemia.

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