1. General Information

1.1. Recommended textbooks

1. 'Heterocyclic Chemistry', *T.L. Gilchrist,* 2nd Edition, Longman, **1992**.

2. 'Heterocyclic Chemistry', *J.A. Joule , K. Mills and G.F. Smith*, Third Edition, Chapman and Hall, **1995**.

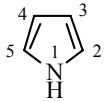
3. 'Aromatic Heterocyclic Chemistry', *D. T. Davies*, Oxford Chemistry Primers, **1992**.

1.2. Nomenclature

The heteroaromatics are typically described by trivial names and for the purposes of this lecture course these will suffice. For those interested in the authoritative method of naming such compounds they are referred to the recommendations published by the International Union of Pure and Applied Chemistry which have been summarised in a review article [McNaught, A.D. *Adv. Heterocycl. Chem.* **1976**, *20*, 175]. A method which is in more common use and which comprises a hybrid of trivial and systematic names made up of standard prefixes and suffixes has been described (the Hantzsch-Widman system). A good introduction to this system can be found in Gilchrist, Chapter 11, pp 369. Except for the isoquinolines, numbering always starts from the heteroatom (as shown below for pyrrole). The most frequently encountered heteroaromatic systems are:

5-Membered Rings

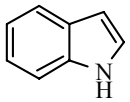
One Hetero-atom:



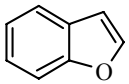
pyrrole
(azole)

furan
(oxole)

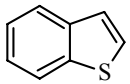
thiophene
(thiole)



indole
(benzo[*b*]azole)

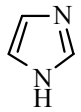


benzofuran
(benzo[*b*]oxole)



benzothiophene
(benzo[*b*]thiole)

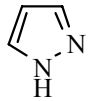
Two Hetero-atoms:



imidazole
(1,3-diazole)

oxazole
(1,3-oxazole)

thiazole
(1,3-thiazole)



pyrazole
(1,2-diazole)

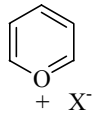
isoxazole
(1,2-oxazole)

isothiazole
(1,2-thiazole)

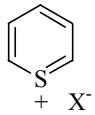
6-Membered Rings

One Hetero-atom:

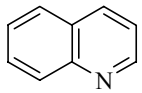
pyridine
(azine)



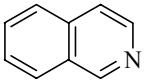
pyrilium
(oxinium)



thiapyrilium
(thiinium)



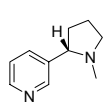
quinoline
(benzo[b]azine)



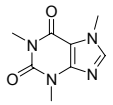
isoquinoline
(benzo[*c*]azine)

2. Introduction

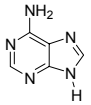
2.1. A few examples of important heteroaromatics



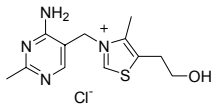
nicotine



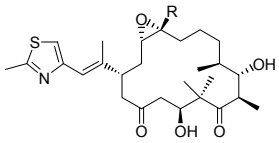
caffeine



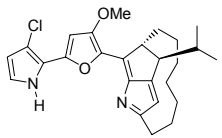
adenine
(RNA/DNA)



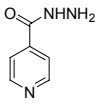
thiamin - vitamin B_1



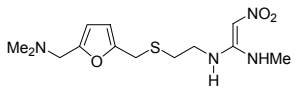
R = H; epothilone A
R = Me; epothilone B
more active than taxol
and much easier to make!



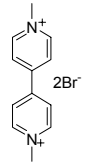
Roseophilin: exhibits submicromolar
cytotoxicity against several human
cancer cell lines



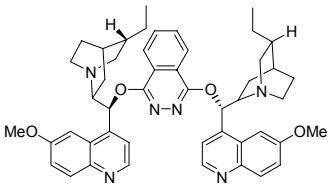
Isoniazid:
used for treatment
of tuberculosis



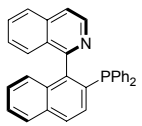
Ranitidine: extremely successful drug used
for treatment of stomach ulcers



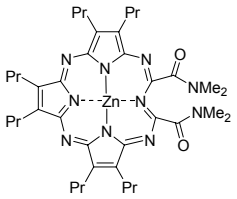
paraquat:
used as a
herbicide



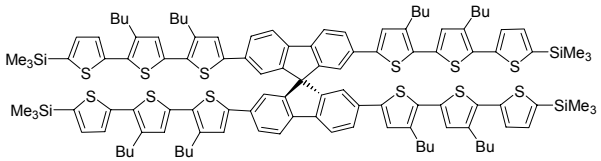
Ligand for the osmium catalysed
Sharpless Asymmetric dihydroxylation



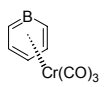
atropisomeric P-N
chelating ligand for
asymmetric catalysis



seco-Porphyrazine: Efficient
$^1O_2$ Photosensitizer



An example of an orthogonally fused conjugated oligomer comprised of
thiophene units as a potential molecular scale electronic device



"borabenzene"

2.2. Background and context

About one-half of all known compounds contain a heterocyclic ring, and many of these, an aromatic heterocyclic ring. Heteroaromatics are found in very many of the products of both primary and secondary metabolism as well as in many synthetic compounds of commercial interest such as drugs, pest control agents, colouring agents, flavourings. They comprise the basic building blocks for many new materials such as porphyrazines and semi-conducting polymers, and as ligands for homogeneous asymmetric catalysis. Thus they are of vital importance and (still) represent a very active area of current research.

2.3. Ring Synthesis

2.3.1. General Comments

There are a (seemingly overwhelming) number of methods (each of which generally has it own name) for the construction of heteroaromatic ring systems, but the heteroaromatics are typically synthesised by the pertinent use of a small family of well known reaction types:

1. **Aldol** Reactions
2. **Michael** Additions
3. **Enamine** Reactions
4. **Condensation** Reactions

2.3.2. Type I and Type II

As far as disconnection strategies go almost every angle has been explored, but the majority of the most efficient syntheses can be classified as either "Type I" or Type "II":

Type I	C_4 fragment + X (for a five membered ring)
	C_5 fragment + X (for a six membered ring)
Type II	C_2 fragment + C_2X (five)
	C_3 fragment + C_2X (six)

In these cases, X is a heteroatom and usually a nucleophile, hence the C-fragments must be electrophilic.

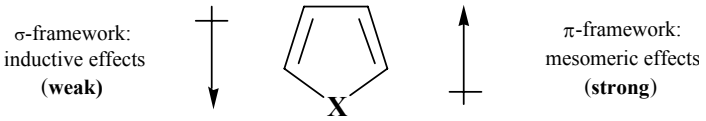
2.4. General properties of 5-membered rings

Furan, thiophene and pyrrole are **aromatic** by virtue of their planarity and the uninterrupted cycle of p-orbitals containing six electrons: four from the two double bonds and two from a lone pair of the heteroatom (*i.e.* obeys Hückel's 4n + 2 rule). However, the extent of aromaticity (as determined by resonance energies, see below) for these compounds is different from that of benzene (which undergoes electrophilic substitution reactions) and this is the determining factor in their chemistry (*vide infra*).

Resonance Energies (experimental and theoretical values):

Furan	88 KJmol^{-1}
Pyrrole	100 KJmol^{-1}
Thiophene	130 KJmol^{-1}
Benzene	151 KJmol^{-1}

Electron Distribution / Polarisation



Overall C-framework is **electron rich**, the heteroatom (X) is **electron deficient**

Reactivity

Consideration of the electron distribution within the π-framework shows that the 5-membered heteroaromatics should be susceptible to **electrophilic substitution** processes. Indeed, they undergo electrophilic substiution much more readily than benzene and attack is predominately in the 2-position (due to relative stabilities of Wheland intermediates).

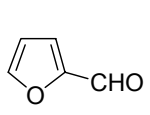
Other facets of their reactivity, including **metallation**, which are generally not available to benzene derivatives will be examined later in the course.

3. Furan

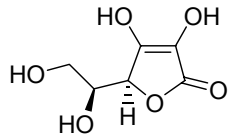
(read this before lecture 2)

3.1. General

The aromatic furan system is a familiar motif in many natural products, occurring widely in secondary plant metabolites. The extremely important Vitamin C (ascorbic acid) is formally a 1,2,3-trihydroxyfuran, but assumes a tautomeric lactone form. [This is a first clue towards the somewhat "lacklustre" aromaticity displayed by furans]. Furan is derived commercially from the decarbonylation of furfuraldehyde which in turn is readily available from the action of mineral acids on vegetable matter (*e.g.*, oats, maize *etc*) and hence the name furan (*furfur* is Latin for bran).



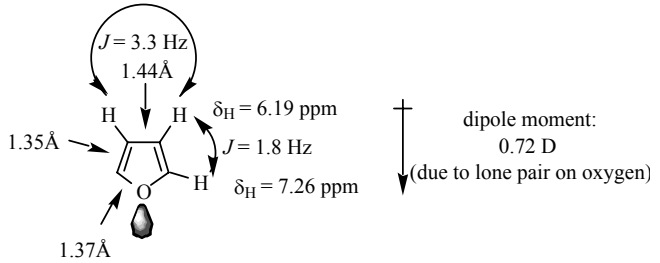
Furfuraldehyde



Vitamin C

3.2. Physical and spectroscopic properties

Low boiling (b.p. 31˚C), toxic liquid. Planar with 6π-electrons and hence aromatic. Bond lengths show intermediacy between single and double bonds characteristic of aromatics (*cf* typical bond lengths: C-C single bond, 1.53Å, isolated C=C bond, 1.34Å; aliphatic C-O bond, 1.43Å; benzene C-C bond 1.39Å).



Chemical shifts consistent with aromatic compound but resonances at somewhat higher field as expected from increased electron density on carbon atoms.

3.3. Syntheses and Reactivity

Syntheses:

Two classical methods:

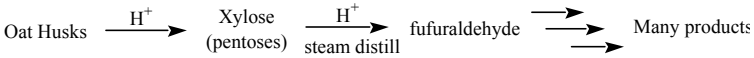
1. **Paal-Knorr** Synthesis (Type I). Very general

Involves the dehydration of *1,4-dicarbonyl* compounds (γ-hydoxy-α,β-unsaturated enones can also be employed) under *non-aqueous* acidic conditions.

2. **Feist-Benary** Synthesis (Type II). Very general

Involves an aldol addition of a (deprotonated) *1,3-dicarbonyl* compound to an α-halocarbonyl moiety followed by subsequent ring closure.

Commercial process:

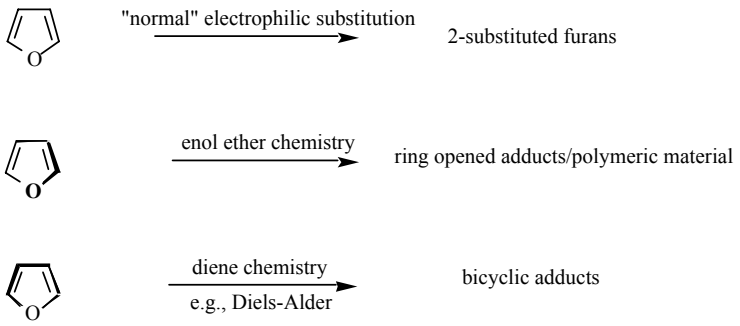


Miscellaneous methods:

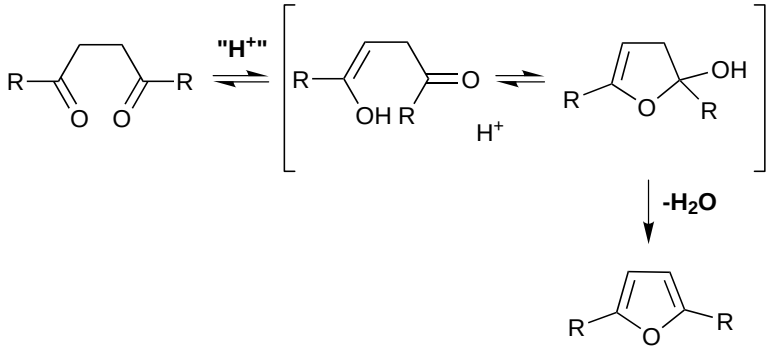
There are many, many, other elegant and efficient routes to access furans (browse through any recent copy of the journal *Heterocycles*) and these cannot be discussed at length here. Some representative examples will be given.

Reactivity of furans:

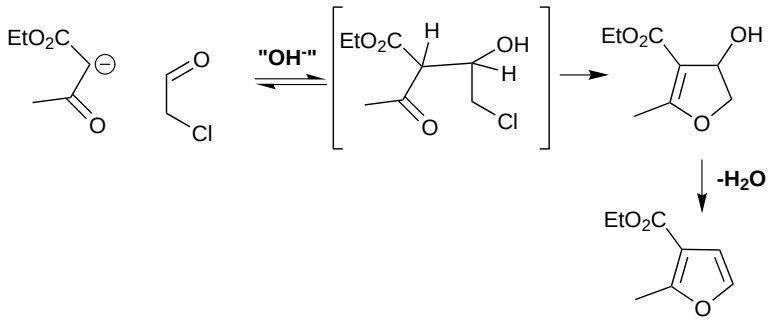
Due to the relatively small aromatic stabilisation in furan [resonance energy 88 $KJmol^{-1}$] the chemistry of furan is not only that of electrophilic substitution but also that of the other functionalities: enol ether and diene chemistry.



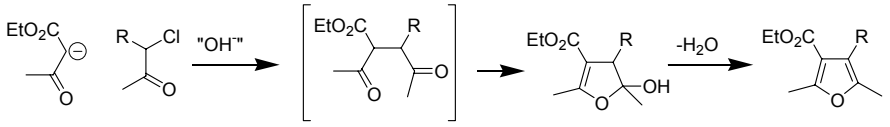
3.3.1. Paal-Knorr (Type I)



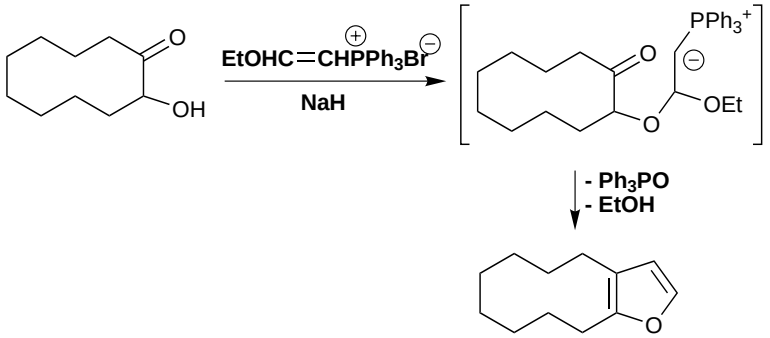
3.3.2. Feist-Benary (Type II)



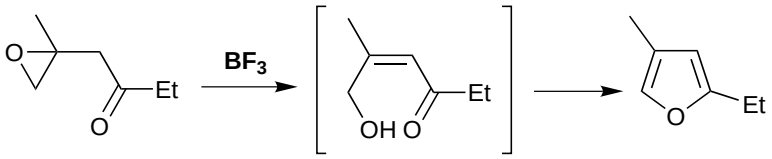
but



3.3.3. Representative example of a curious furan synthesis:



3.3.4. Miscellaneous



3.4. Reactivity

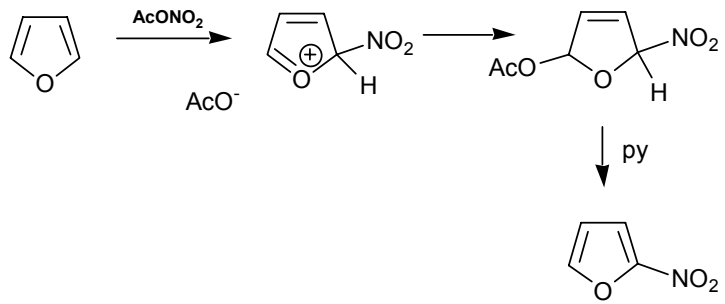
3.4.1. S_EAr Recap

In the absence of a nucleophile Wheland intermediates loose a proton to give the re-aromatised products.

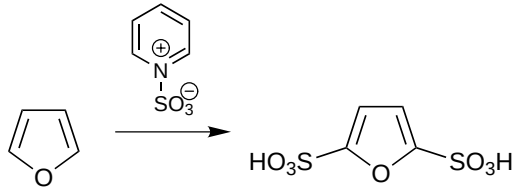
Electrophilic aromatic substitution on furan requires very mild non-acidic reagents.

1. Nitration using $^{+}NO_2BF_4^{-}$ or $AcONO_2$
2. Sulphonation with py/SO_3 complex
3. Halogenation
4. Alkylation not generally practicable
5. Acylation (Vilsmeier-Haack formylation) or using RCOCl in the presence of mild Lewis acids such as BF_3, $SnCl_4$
6. Electrophilic metallation using mercury salts $Hg(OAc)_2$ or $HgCl_2$

3.4.2. Nitration

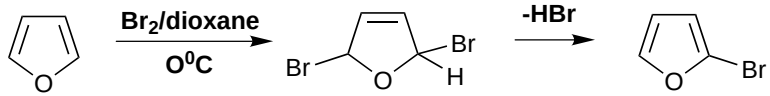


3.4.3. Sulphonation

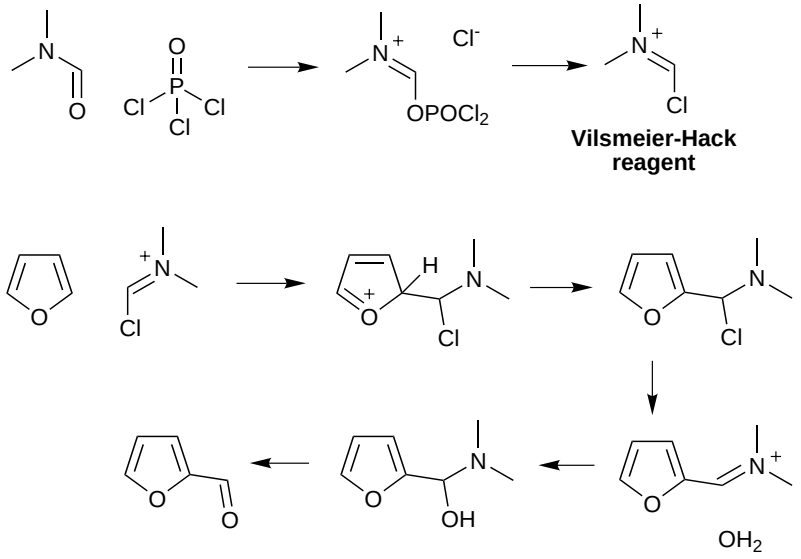


3.4.4. Halogenation

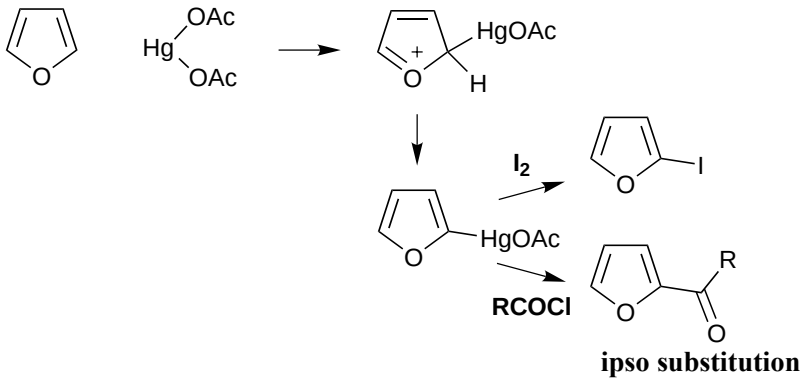
Reactions with Cl_2 or Br_2 result in polyhalogenation. Mild reaction conditions required



3.4.5. Formylation (Vilsmeier-Haack)

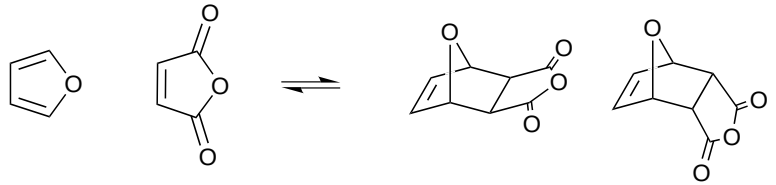


3.4.6. Metallation



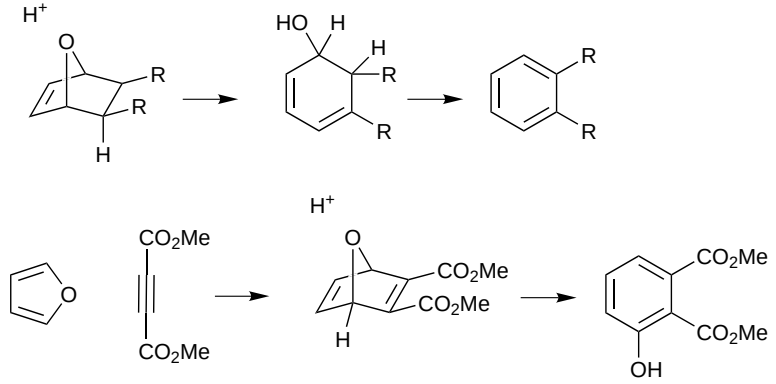
3.4.7. As a diene

Furan will react with reactive dienophiles in a Diels-Alder fashion (reversible)



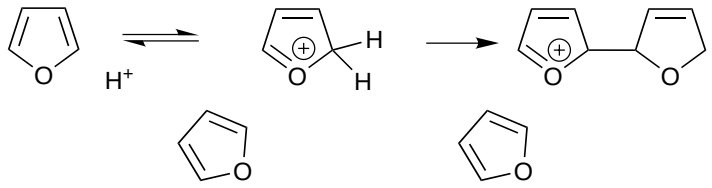
exo (thermodynamic) product formed preferentially

useful for syntheses of benzene derivatives



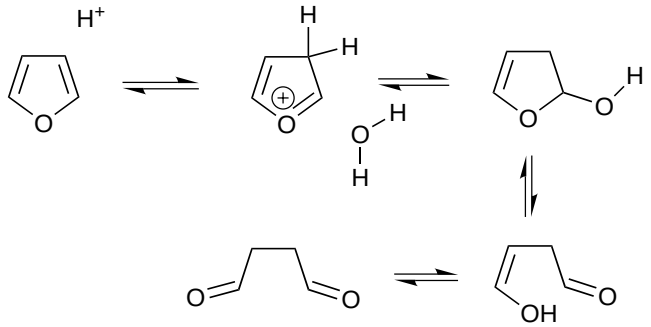
3.4.8. Miscellaneous

1. Enol ether chemistry: polymerises with conc. H_2SO_4 and $AlCl_3$

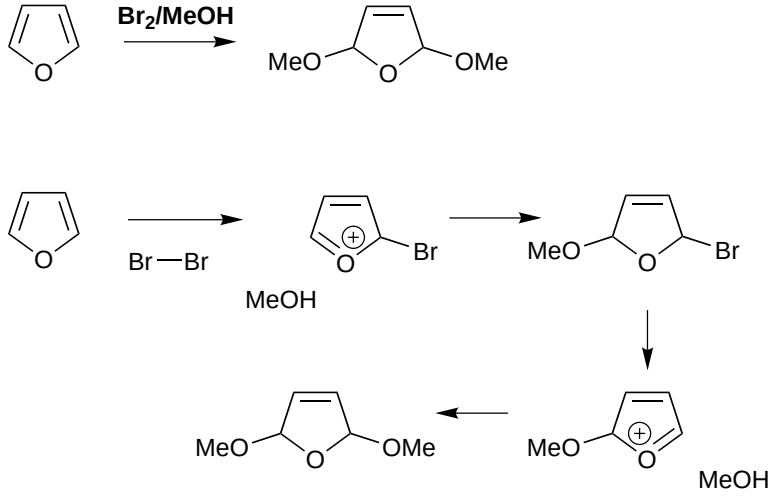


and again….

2. Ring opens in hot aqueous mineral acid.



3. Subjected to electrophilic attack in the presence of a nucleophile **then** an addition reaction is expected. Thus Br_2/MeOH yields:

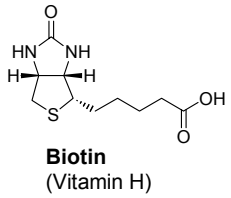


4. Pyrrole and Thiophene

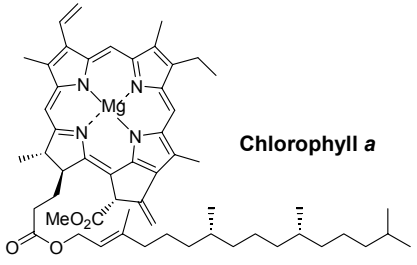
4.1. General

(read this before lecture 3)

Thiophenes and pyrroles are also extremely important compounds - vital for the chemistry of life. For instance, a tetrahydrothiophene unit is contained in Biotin (Vitamin H) and is one of the chief components in yeast and eggs. For the pyrroles, the classic examples are that of haem, chlorophyll *a* and vitamin B_{12}. Pyrrole was first isolated in 1857 and its name derives from the Greek for red - referring to the bright red colour which pyrrole imparts to pinewood shavings when moistened with concentrated hydrochloric acid(!). The name thiophene was coined by Victor Meyer in 1882 to highlight its apparent similarity to benzene (*theion* is greek for sulphur): it was discovered as a contaminant of coal-tar benzene.



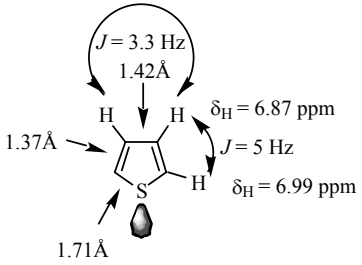
Biotin
(Vitamin H)

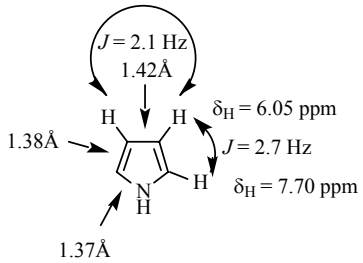


Chlorophyll *a*

4.2. Physical and spectroscopic properties

Both are liquids (thiophene, b.p. 84 ˚C; pyrrole, b.p. 139 ˚C). Both are expected to be **aromatic** since they comply with Hückel's rule. The bond lengths and ^{1}H NMR shifts are consistent with this expectation. Thiophene displays a dipole moment of 0.52 D towards the heteroatom by virtue of its lone pair whereas pyrrole (where the lone pair is directly involved in the π-cloud) shows a solvent dependent dipole moment of approx. 1.55 D away from the heteroatom.





4.3. Synthesis of pyrroles:

Three classical methods:

1. **Paal-Knorr** Synthesis (Type I).

As for furans, but involves the reaction of 1,4-dicarbonyl compounds with ammonia or primary amines. Gives 2,4-disubstituted or 1,2,4-trisubstituted pyrroles.

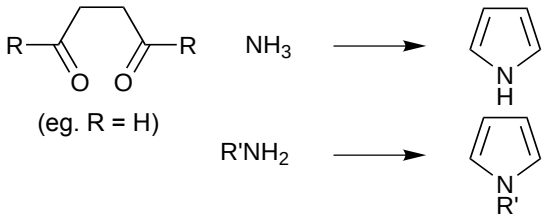
2. **Knorr** Synthesis (Type II).

Condensation between α-*aminoketones* and β-*ketoesters*. Gives 3-substituted pyrroles after hydrolysis and decarboxylation.

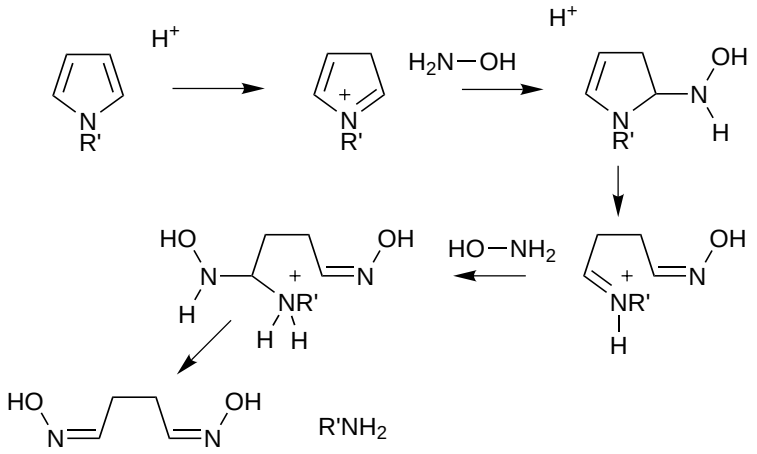
3. **Hantzsch** Synthesis (Type II).

Involves reaction between *enaminoester* and an α-*chloroketone*. Gives 2,5-disubstituted pyrroles after hydrolysis and decarboxylation.

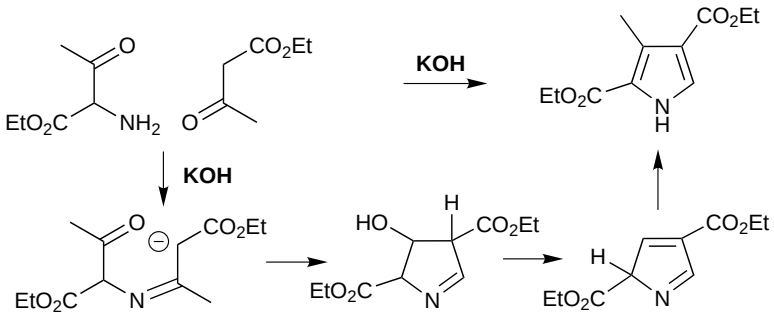
4.3.1. Paal-Knorr (Type I)



method for protecting primary amines:

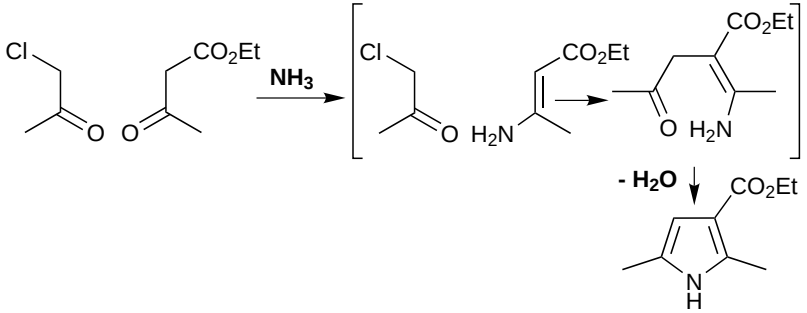


4.3.2. Knorr (Type II)

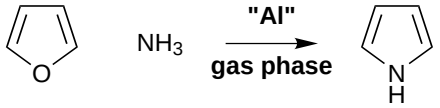


4.3.3. Hantzsch (Type II)

Modification of Feist-Benary

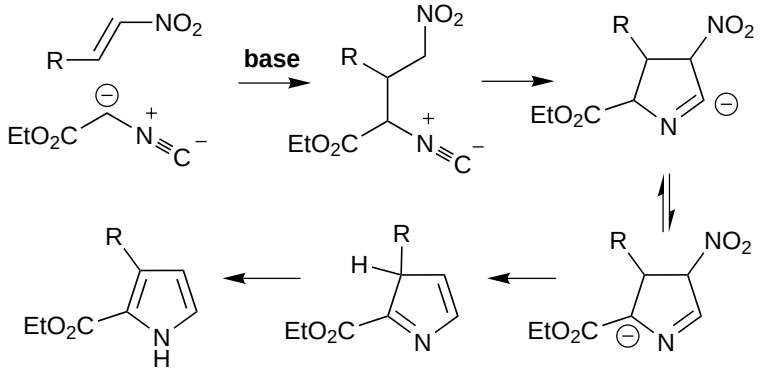


4.3.4. Commercial process



4.3.5. Miscellaneous

Barton-Zard pyrrole synthesis



4.4. Reactivity

(read also this for lecture 3)

More like furan than benzene (resonance energy for pyrrole 100 KJmol^{-1}). Very electron rich and so very reactive to electrophiles (approx. 10^6 more reactive than furan) but the presence of the N-H group provides additional scope for reactivity. Hence a more varied and complex chemistry than furan.

1. *Electrophilic reagents:*

As for furan. Sensitive to acid therefore mild reagents used (as per furan). 2-Substituted adducts.

2. *Carbene reactions* (**Reimer-Tiemann** reaction)

Reacts with *electrophilic* carbenes (*e.g.* :CCl_2). Product distribution dependent on reaction conditions.

3. *Metallation:*

Pyrrole itself is a weak acid (pKa 17.5) and the N-H is readily deprotonated. The resulting pyrryl anions are *ambident nucleophiles* and their reactivity is cation dependent. "*Ionic*" salts (K^+, Na^+) react with electrophiles at *nitrogen* whilst salts with more *covalent* character (Li^+, MgX^+) react with *soft* electrophiles (carbon, sulphur, halogen) at the 2-position (*i.e.* on **carbon**) but with *hard* electrophiles at nitrogen.

N-Protected pyrroles are readily deprotonated by strong lithium bases in the **2-position** and can be quenched with electrophiles giving 1,2-substituted pyrroles. The deprotonation can be deflected to the 3-position by judicious choice of a large protecting group (e.g. triisopropylsilyl) on the nitrogen.

4. *Reaction with dienophiles:*

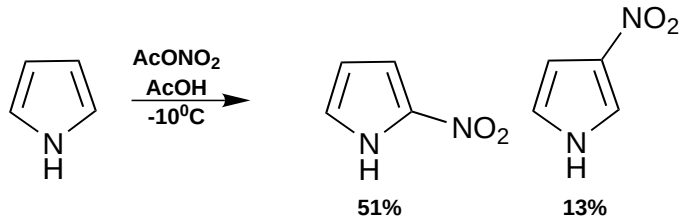
Pyrrole itself rarely undergoes direct Diels-Alder reactions; the usual result is 2-substitution (*via* an electrophilic substitution pathway) because the dienophile simply acts as an electrophile. *N-Acylated* pyrroles, however, are less electron rich and less "aromatic" and give **normal Diels-Alder adducts**.

5. *Condensations:*

The nucleophilic pyrrole ring reacts readily with ketones and aldehydes under *acidic catalysis* to form di-, tri- and **tetrapyrrolic** oligomers. The macrocyclic tetramers are especially stable and form planar species which accomodate a wide range of metal ions at their core (*vide supra*, introduction, lecture 1).

4.4.1. With electrophiles

4.4.1.1. Nitration

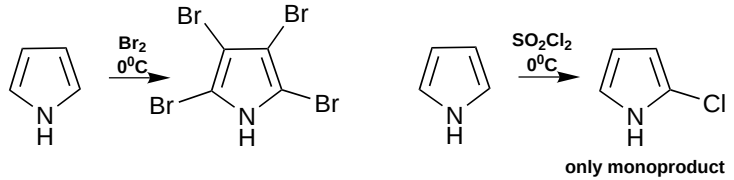


4.4.1.2. Sulphonation

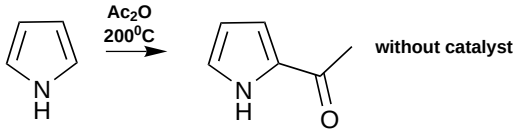
as with furan and thiophene

4.4.1.3. Halogenation

Monohalogenation is difficult and requires controlled conditions.

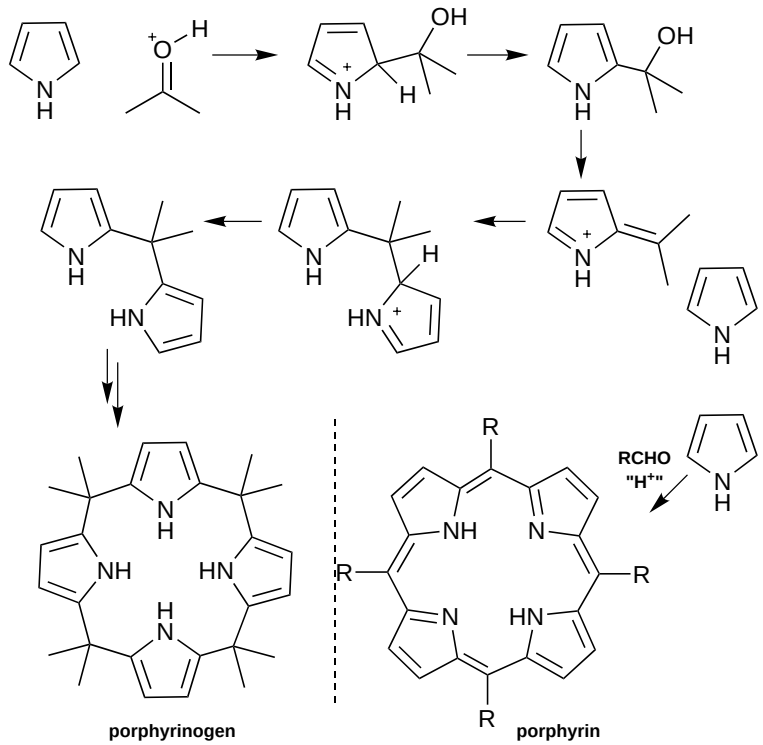


4.4.1.4. Acylation



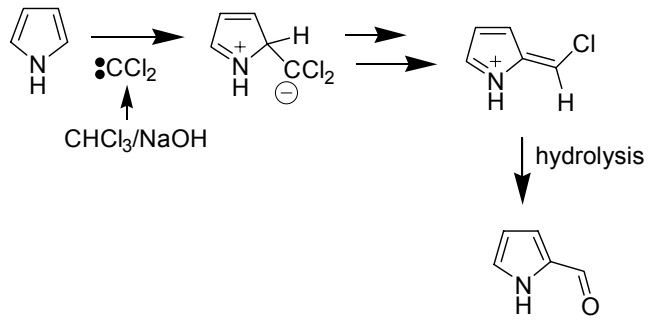
Reacts with Vilsmeier-Haack reagent (formylation) and in the Mannich reaction and with other acylating reagents.

4.4.1.5. Condensation with Aldehydes and Ketones

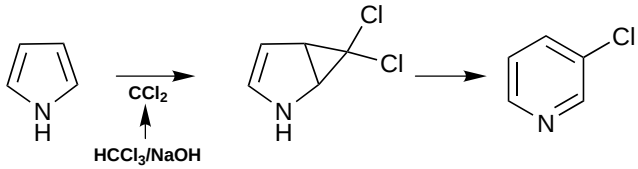


4.4.2. With Carbenes

Reimer-Tiemann Reaction

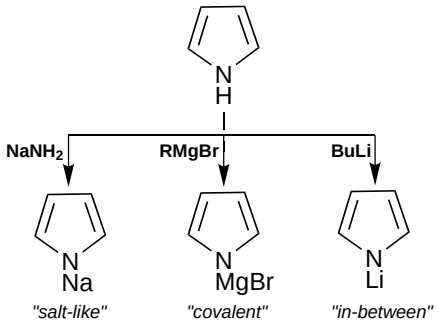


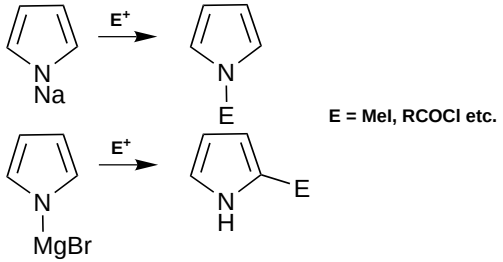
But under **non-aqueous** conditions:

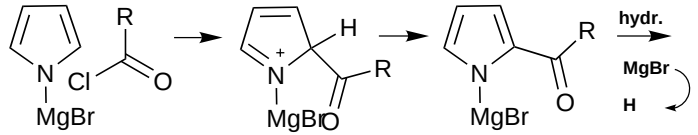


4.4.3. Reactions with Bases

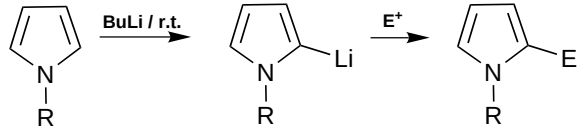
The NH proton is relatively acidic (pKa 17.5) and can be removed with bases:





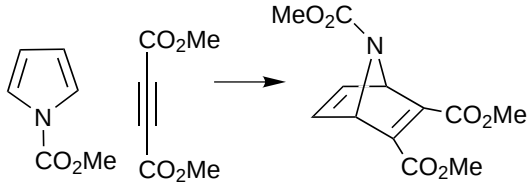


N-substituted pyrroles



4.4.4. With Dienophiles

Mainly Michael adducts, and only Diels-Alder reactions with electron withdrawing substituents on **N**.



4.5. Synthesis of thiophenes

(read this for lecture 4)

Two classical methods:

1. **Paal** Synthesis (Type I).

Similar to the Paal-Knorr for furan in that a *1,4-dicarbonyl* compound is involved. The sulphur atom derives from P_2S_5 or (more recently) Lawessons reagent. Gives 2,5-disubstituted adducts.

2. **Hinsberg** Synthesis (Type II). Very general

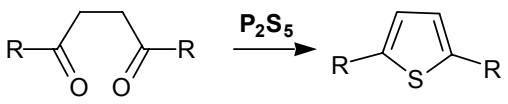
Involves two consecutive aldol type additions between *1,2-dicarbonyl* compounds and thiodiacetates.

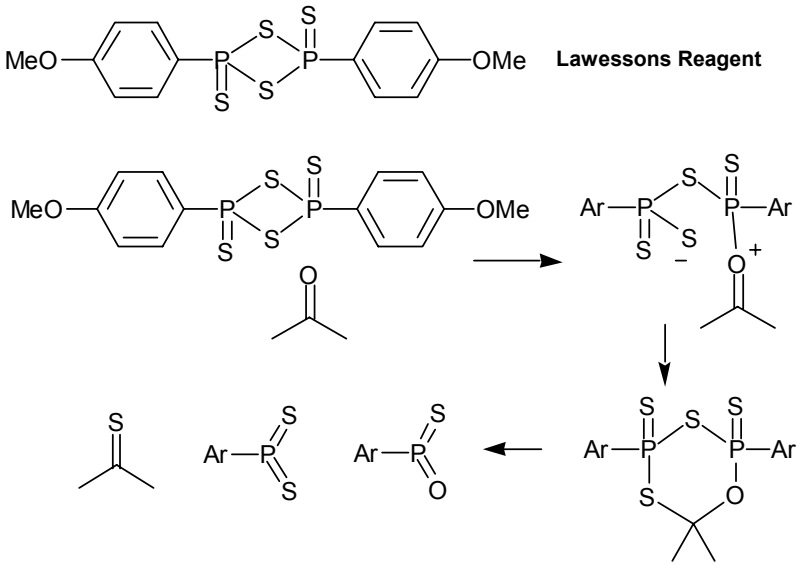
Commercial process:

Simply by pyrolysis of butane (C4)with sulphur (S8)

As with furan there are many other notable methods for the synthesis of thiophenes.

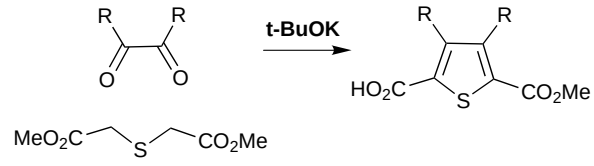
4.5.1. Paal-Knorr (Type I)

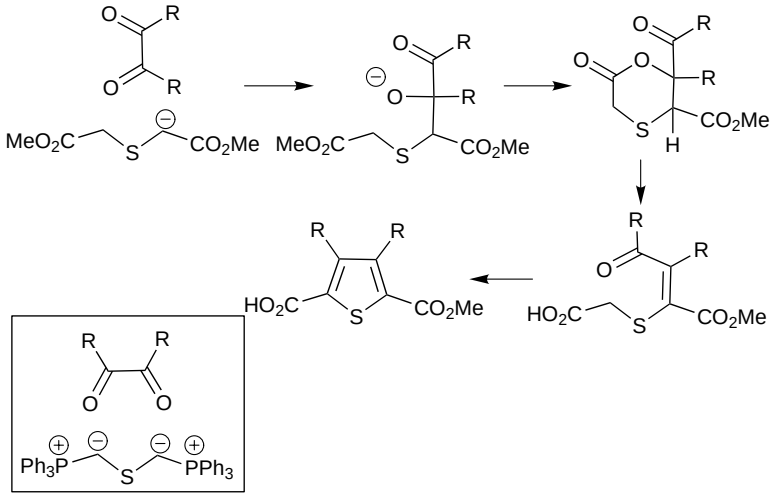




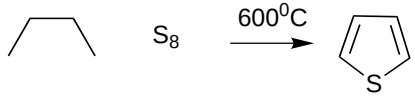
driving force is the formation of the particularly strong P=O double bond.

4.5.2. Hinsberg (Type II)

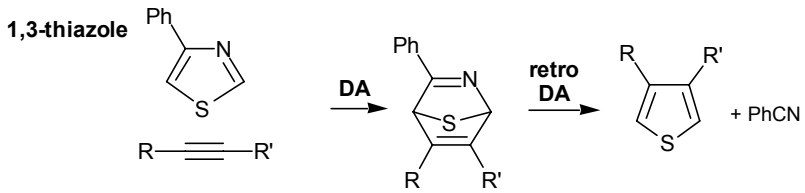




4.5.3. Commercial process



4.5.4. Miscellaneous



driving force is greater degree of resonance stabilisation (aromaticity)

4.6. Reactivity

(read this before lecture 4)

Thiophene is somewhat less reactive (10^2) than furan towards electrophiles (and much less reactive than pyrrole), but it is still much more reactive than benzene (approx. 10^4). By virtue of it high resonance energy (130 $KJmol^{-1}$) it is the most aromatic of the five-membered heteroaromatics and undergoes electrophilic substitution rather than addition/ring opening and there is **no** behaviour as an enolthioether or diene (contrast with furan). Thiophene is stable to aqueous mineral acids but not to 100% sulphuric acids or strong Lewis acids, exemplified by aluminium(III) chloride. Electrophilic substitution occurs in the 2-position (as for furan) with high positional selectivity.

1. *Electrophilic Reagents:*

Mild electrophilic reagents are used (as for furan) but the acidity is less critical.

2. *Nucleophilic reagents:*

Thiophenes do not react by nucleophilic substitution or addition [ring is already electron rich, and a relatively stable aromatic system] but are much more acidic than furans (pKas: thiophene 33.0; furan 35.6) and are subject to deprotonation in the 2-position with strong base (e.g., *n*-BuLi, *t*-BuLi and LDA). These α-metallated species react readily with electrophiles to give 2-substituted thiophenes. Metallation at the 3-position can be achieved by suitable substitution and/or directing groups.

3. *Reaction at sulphur:*

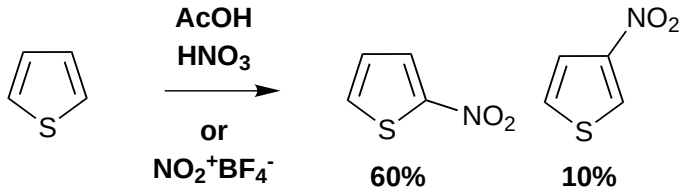
Due to its position in the periodic table, the sulphur atom in thiophene derivatives (unlike nitrogen and oxygen in pyrrole and furan respectively) can "expand its octet". Thus thiophene has chemistry associated with the heteroatom.

In summary:

Thiophenes are more stable to acid than furans and pyrroles. Enol ether chemistry is absent in thiophenes due to their highly aromatic character and thus mainly substitution chemistry is observed. Thiophenes are much more reactive than benzene.

4.6.1. With Electrophilic Reagents

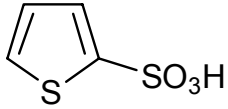
4.6.1.1. Nitration



less selective than pyrrole or furan

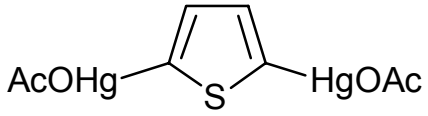
4.6.1.2. Sulphonation

as with furan and pyrrole

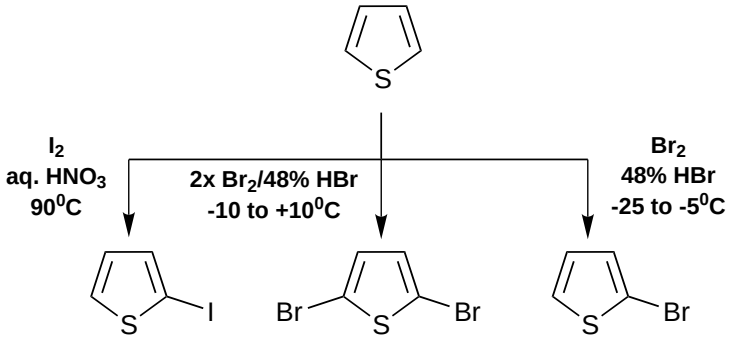


4.6.1.3. Electrophilic Metallation (Mercuration)

as with furan but more difficult to stop reaction at the monosubstituted stage.



4.6.1.4. Halogenation

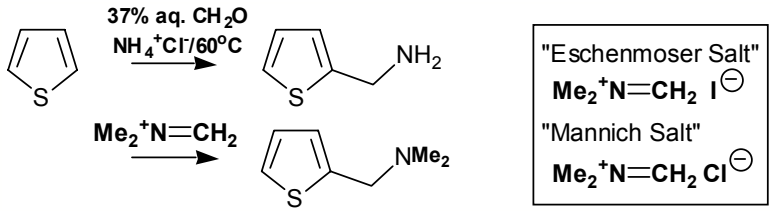


yields polyhalogenated species unless controlled

4.6.1.5. Acylation

Proceeds easily under the usual Friedel-Crafts conditions but only requires mild Lewis acids such as $SnCl_4$ to proceed. Also reacts with Vilsmeier-Haack reagent ($POCl_3$/DMF) similarly to Furan.

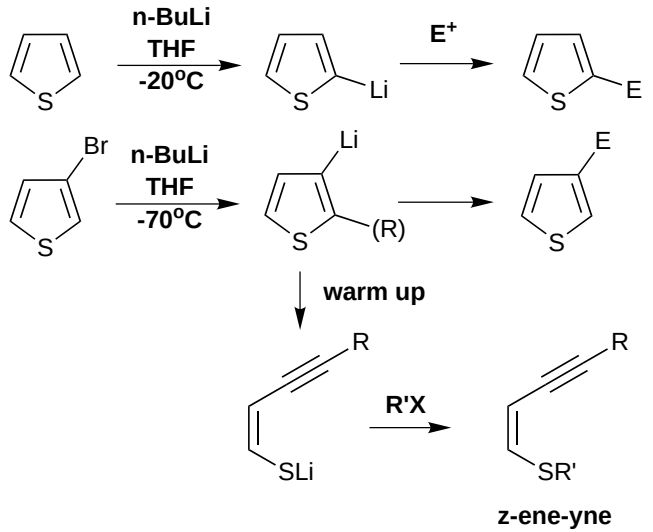
4.6.1.6. Aminomethylation (Mannich)



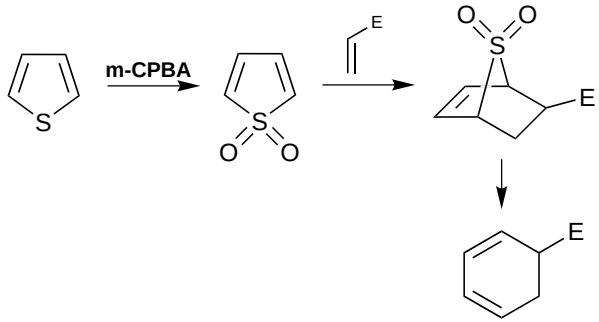
"Eschenmoser Salt"
$Me_2^+N{=}CH_2\ I^-$

"Mannich Salt"
$Me_2^+N{=}CH_2\ Cl^-$

4.6.2. Reaction with Bases

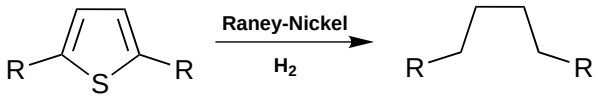


4.6.3. Reaction at Sulphur

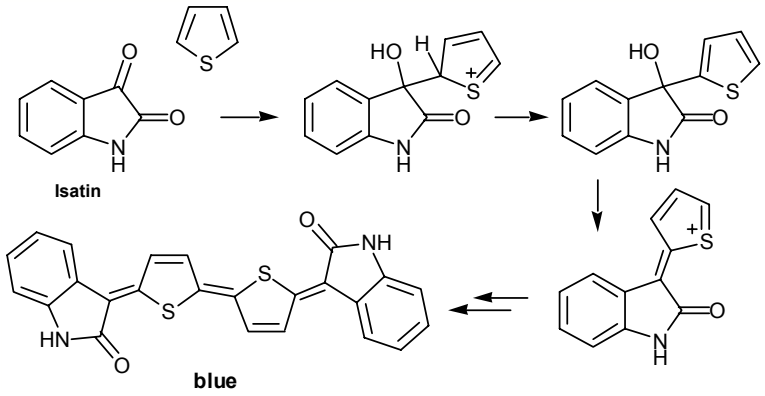


if E is a good leaving group aromatisation will follow

4.6.4. Reducing Reagents



4.6.5. Analytical Detection

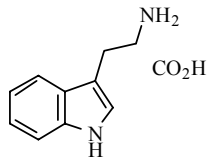


5. Indole

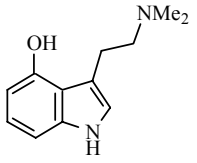
5.1. General

(read before lecture 5)

The Indole unit is found in over a thousand naturally occurring (indole) alkaloids and many of these have important physiological activity. The name indole derives from indigo (a blue-purple dye imported from India). Chemical degradation of indigo leads to oxygenated indoles which were named indoxyl and oxindole; indole itself was first prepared in 1866 by zinc dust distillation of oxindole. Most indole alkaloids are derived from the naturally occurring amino acid, (*S*)-tryptophan and an example is the hallucinogen compound psilocin, extracted from Mexican mushrooms by the Aztecs from as early as 1500 BC (although they certainly didn't know - nor care (!) - which chemical was responsible).



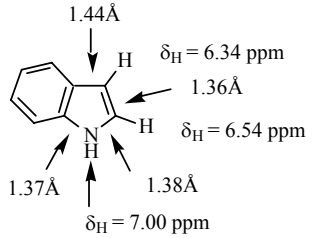
(*S*)-tryptophan



psilocin

5.2. Physical and spectroscopic properties

Colourless, crystalline solid; m.p. 52 °C; Oxidises in air, resonance energy 196 kJ mol^{-1} (most of which is accounted for by the benzene ring and *cf* naphthalene 241 kJ mol^{-1}). Has a persistent faecal odour - used, in high dilution in perfumery!



5.3. Syntheses

1. **Fischer Indole** Synthesis (Type II)

Condensation/rearrangement of an aryl hydrazine and a ketone (not applicable to aldehydes). Substituted benzenes generally work well, but m-substituted substrates give rise to mixtures of products. Very general and much used.

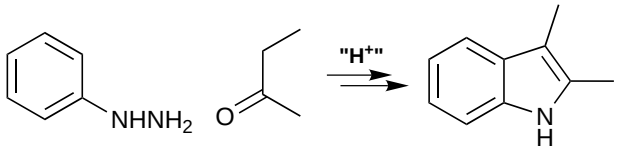
2. **Reissert** Synthesis

Deprotonation at the (most acidic) benzylic site in an *o*-methylnitrotoluene and ensuing condensation with ethyl oxalate. Dissolving metal reduction then completes the synthesis.

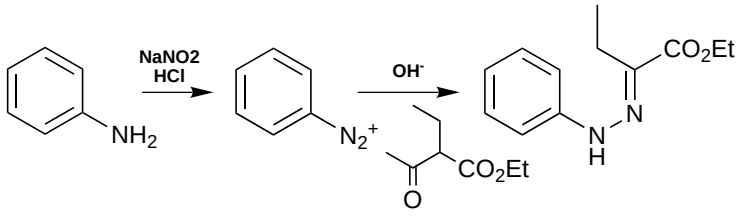
3. **Azidocinnamate** Synthesis

Unusual in that the aryl-nitrogen bond is not initially present. Involves condensation between an azidoester (acidic methylene protons) and an arylaldehyde. A nitrene is formed on heating which inserts into an aryl C-H bond thus giving 2-substituted indoles.

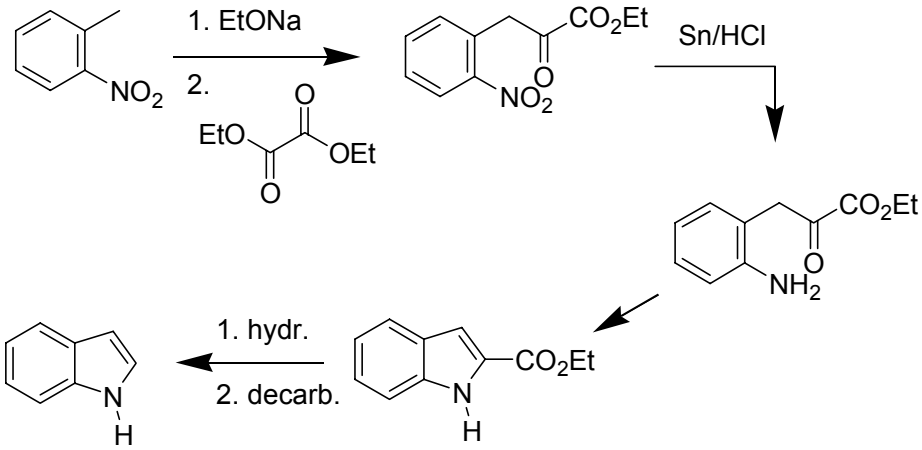
5.3.1. Fischer



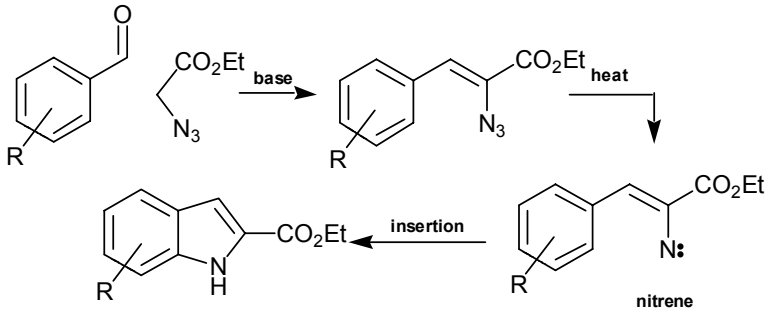
Japp-Klingeman hydrazone synthesis



5.3.2. Reissert



5.3.3. Azidocinnamate



5.4. Reactivity

(read before lecture 5)

Because of the presence of a carbocyclic aromatic ring which accounts for most of the "aromaticity" of the system, indole can be considered to behave as **a benzene** + **an enamine**. Consequently, indoles are unstable to acid and very susceptible to electrophilic attack.

1. Electrophilic substitution.

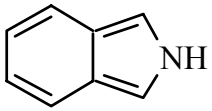
The pyrrolic ring in indole is electron rich and electrophilic substitution occurs preferentially in this ring (rather than the benzene ring). However, in direct contrast to pyrrole, substitution occurs at the **3-position**. This is a consequence of the stabilities of the Wheland intermediates where attack in the 2-position leads to loss of aromaticity in the benzenoid ring. When the indole is already substituted in the 3-position then apparent 2-substitution occurs but these products (normally) derive from a **migration** after initial attack at the 3-position.

2. Metallation.

Indole, like pyrrole, is a weak acid and can be readily *N*-deprotonated (pKa 16.2). As for pyrrole, the resulting anions are **ambident** and for similar reasons attack of **soft** electrophiles on **covalent** salts occurs at the **3-position.** *N*-Protected indoles lithiate regioselectively at the **2-position** and react readily with suitable electrophiles.

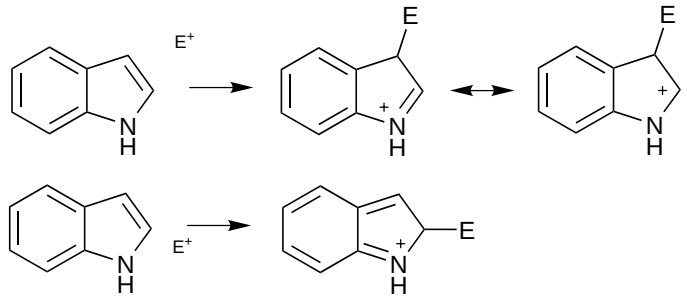
Isoindoles:

Chemistry is typically that of a diene in Diels-Alder reactions such that the aromaticity of the benzenoid ring is regained.



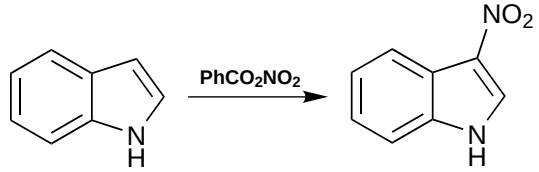
Isoindole

5.4.1. 2- vs 3-Position



5.4.2. With Electrophiles

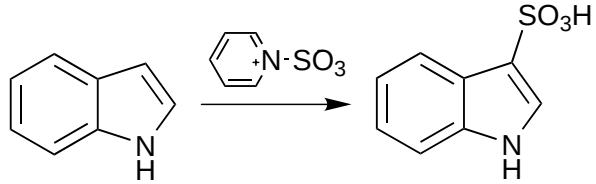
5.4.2.1. Nitration



Mild conditions required using benzoyl nitrate ($PhCOONO_2$)

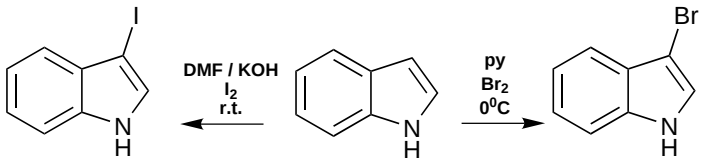
5.4.2.2. Sulphonation

as with furan and pyrrole using pyridine/SO_3 complex



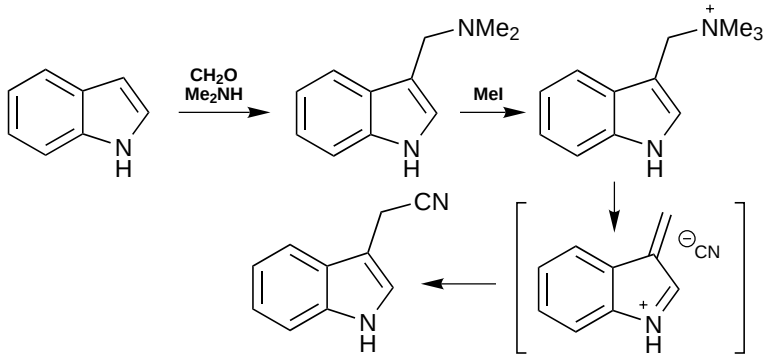
5.4.2.3. Halogenation

Mild conditions required. Haloderivatives are not very stable.

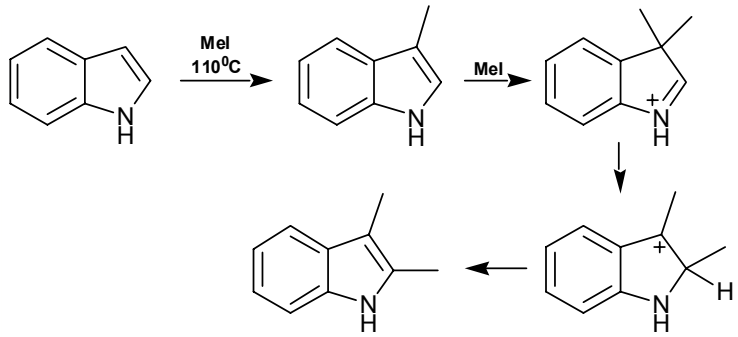


5.4.2.4. Acylation

Reacts with Vilsmeier and Mannich reagents, the former being the most efficient route to 3-formylindoles.

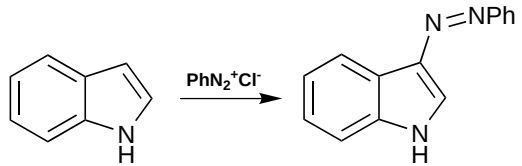


5.4.2.5. Alkylation

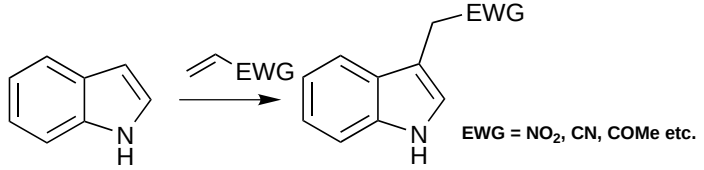


Rearrangement related to Wagner-Meerwein called Plancher rearrangement.

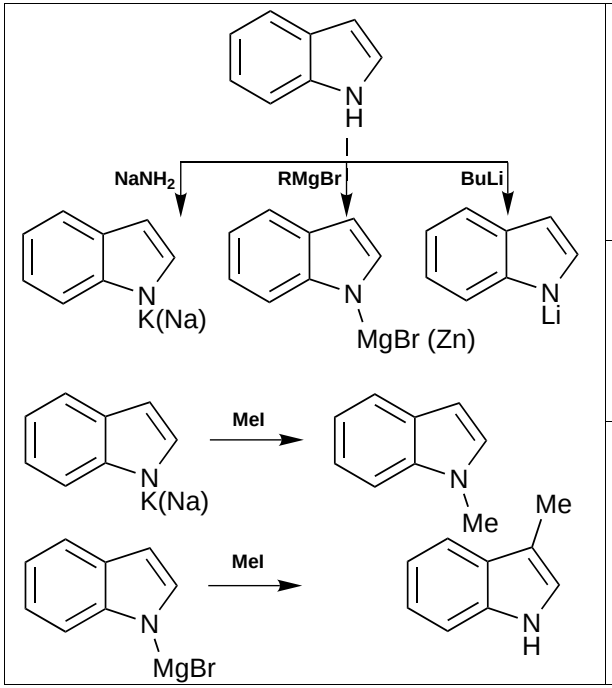
5.4.2.6. With Diazonium Salts



5.4.2.7. With Michael Acceptors



5.4.3. Reactions with Bases (Metallation)

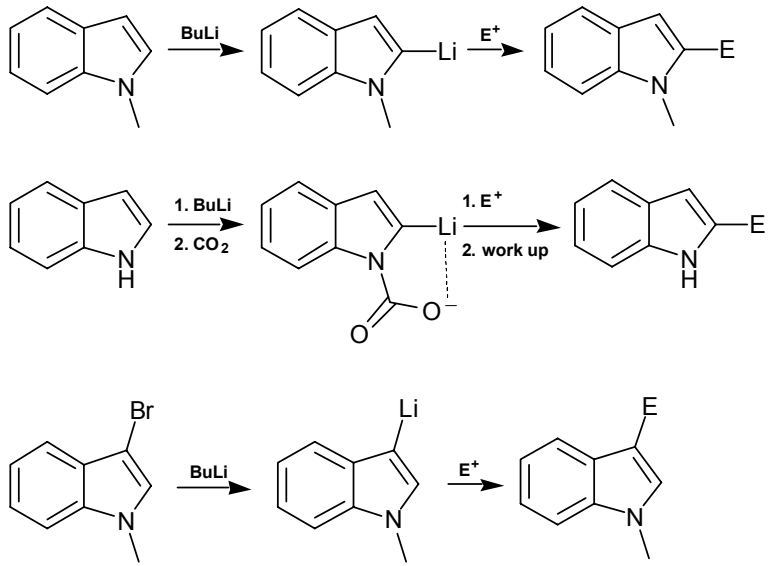


K
Reacts preferentially on nitrogen with (hard!) electrophiles

MgBr
Reacts preferentially at C-3

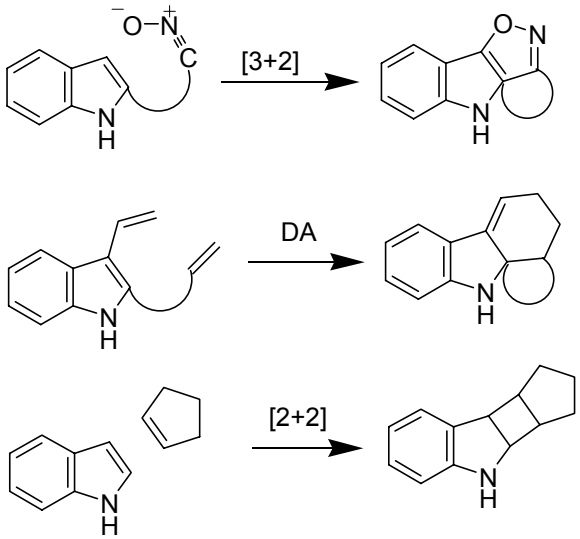
Li
Reacts on C-3 or nitrogen depending on conditions

If nitrogen substituted:



metallation at C-3 via metal-halide exchange

5.4.4. In Cycloadditions



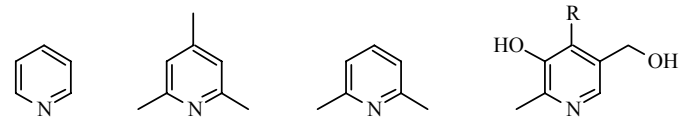
reacts with electron-deficient dienes (inverse electron demand)

6. Pyridine

6.1. General

(read this before lecture 6)

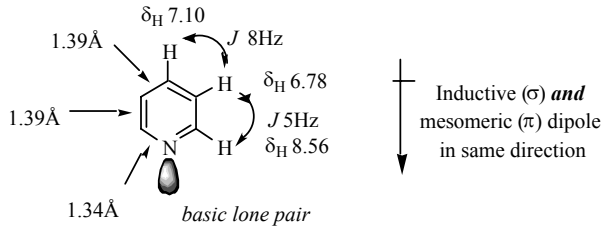
Pyridine and the methylpyridines (collidines, lutidines) are available on a large scale from the carbonisation of coal. Coal tar contains about 0.2% of a mixture of pyridine bases which are readily extracted with acid and then separated. As for the five-ring heterocycles they are familiar motifs in a large number of natural products. For instance, pyridoxol (Vitamin B_6) (R = CH_2OH, below) occurs in yeast and wheatgerm, and is an important food additive. Related compounds are pyridoxal (R = CHO) and pyridoxamine (R = CH_2NH_2). The 5-phosphate of pyridoxal is a co-enzyme in the decarboxylation and transamination reactions of α-amino amids. Pyridine, like pyrrole, was first isolated from bone pyrolysates. The name derives from the Greek for fire '*pyr*' and the suffix '*idine*' was given for all aromatic bases at the time it was named.



pyridine **2,4,6-collidine** **2,6-lutidine**

6.2. Physical and spectroscopic properties

Colourless liquid, characteristic odour, b.p. 115˚C, weakly basic (pK_a 5.2) with a resonance energy of 117 kJ mol^{-1}



6.3. Syntheses

1. **Kröhnke** Synthesis (Type I)

The reaction of a 1,5-dicarbonyl compound with ammonia to reveal a 1,4-dihydropyridine which is oxidised to a pyridine. The pyridine system can be formed directly either by introducing unsaturation into the dicarbonyl backbone or by judicious use of hyroxylamine (which eliminates water).

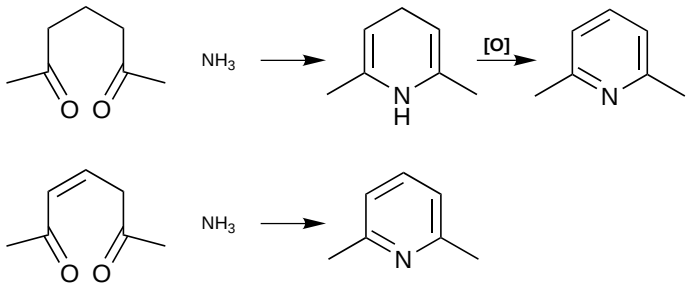
2. **Hantzsch** Synthesis

Condensation of 2 moles of a 1,3-dicarbonyl compound with one equivalent of an aldehyde and one equivalent of ammonia followed by oxidation. Very general and much used.

3. **Oxazole** Synthesis

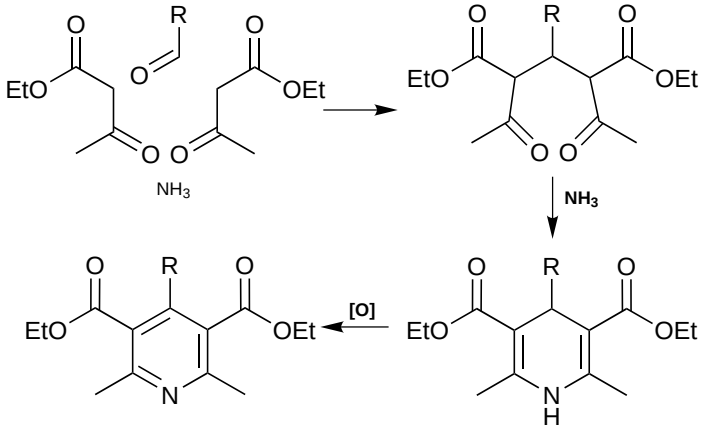
An example of the use of a pericyclic reaction in heterocyclic synthesis: these often start from another (less aromatic) heteroaromatic as here. This is a versatile synthesis the outcome of which depends on the exact functionality present.

6.3.1. Kröhnke

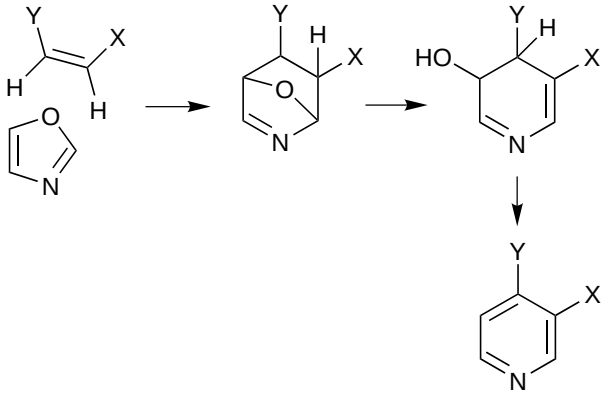


directly from unsaturated 1,5-dicarbonyl compounds

6.3.2. Hantzsch



6.3.3. Oxazole (via cycloaddition)



6.4. Reactivity

(read this before lecture 6)

Pyridine has a high resonance energy (117 kJ mol^{-1}) and its structure resembles that of benzene quite closely. The presence of the nitrogen atom in the ring does, of course, represent a major pertubation of the benzene structure. The lone pair orthogonal to the π-system provides a site for alkylation and protonation which has no analogy in benzene. Many of the properties of pyridine are thus those of a tertiary amine and the aromatic sextet is not involved in these reactions. The other major influence of the nitrogen atom is to distort the electron distribution both in the π-system and in the σ-bonds (by an inductive effect). This confers on the system some of the properties which are associated with conjugated imines or conjugated carbonyl compounds .

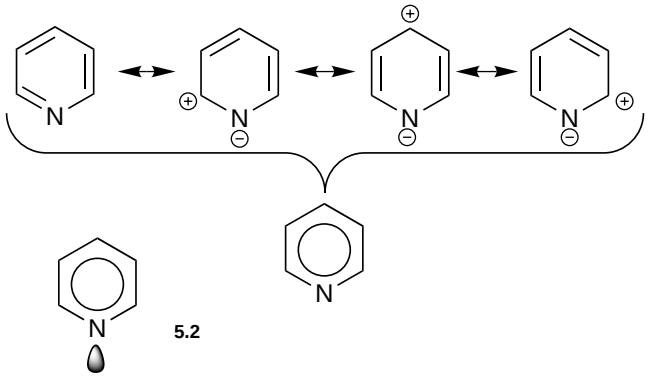
We can therefore expect to find reactions of pyridines which show analogies to three types of model systems:

A. Benzene: **substitution reactions** and resistance to addition and ring opening

B. Tertiary amine: **reactions at the nitrogen lone pair**, including protonation, alkylation, acylation, N-oxide formation and co-ordination to Lewis acids.

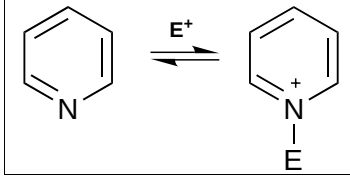
C. Conjugated imines or carbonyl compounds: **susceptibility to attack by nucleophiles** at the α and γ positions.

6.4.1. Basicity

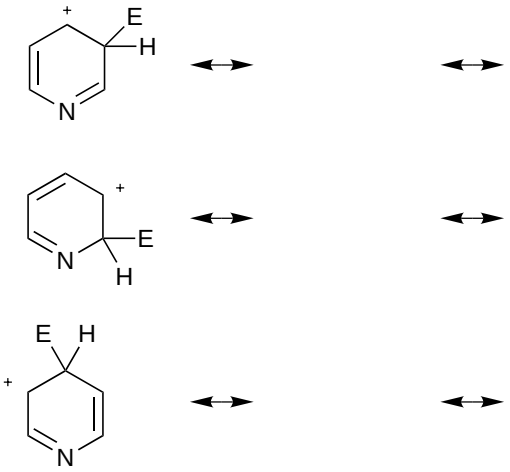


5.2

6.4.2. With Electrophiles

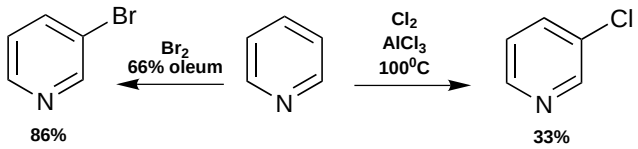


Much less reactive than pyridine itself for further electrophilic attack



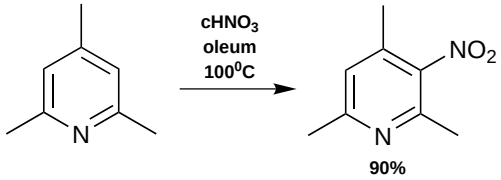
6.4.2.1. Sulphonation

6.4.2.2. Halogenation



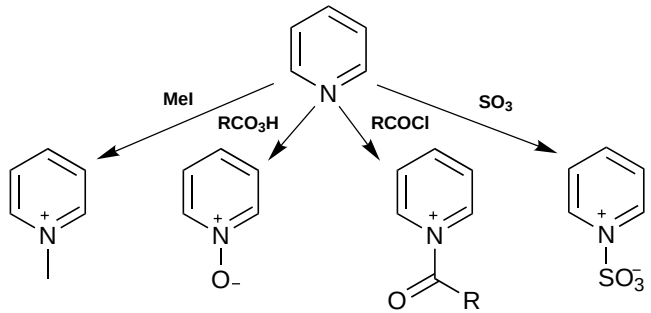
6.4.2.3. Nitration

…but with electron donating groups:



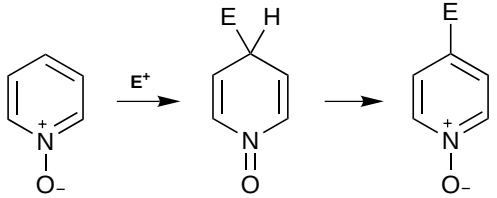
6.4.3. Reactions at Nitrogen

6.4.3.1. Alkylation



pyridine N-oxide

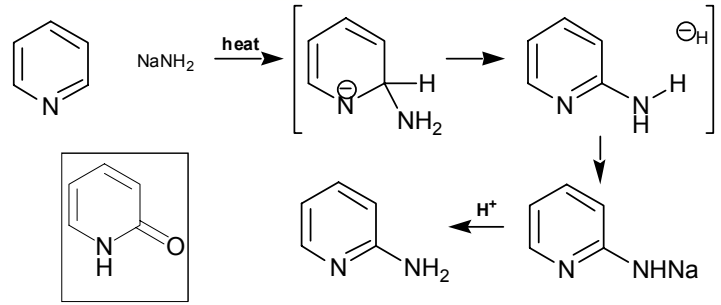
pyridine N-oxides are much more reactive towards electrophiles than pyridine itself:



6.4.4. With Nucleophiles

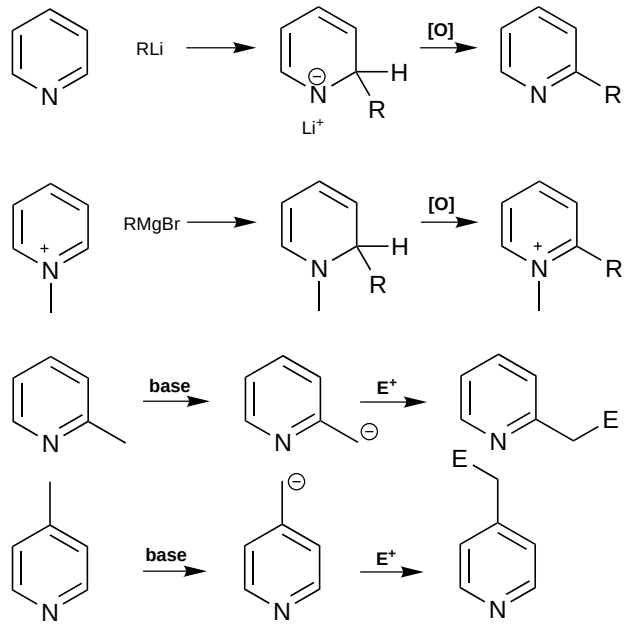
mainly 2-substituion (4-substitution minor product)

6.4.4.1. Amination (Chichibabin)



also with OH to give pyridones

6.4.4.2. Alkylation/Arylation



2- and 4-methyl pyridines can be deprotonated with strong bases and undergo enolate-type chemistry.