CHEM2201: Section 2 - Aromatic & Heteroaromatic Compounds

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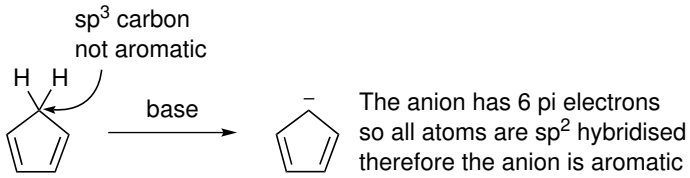
Contents

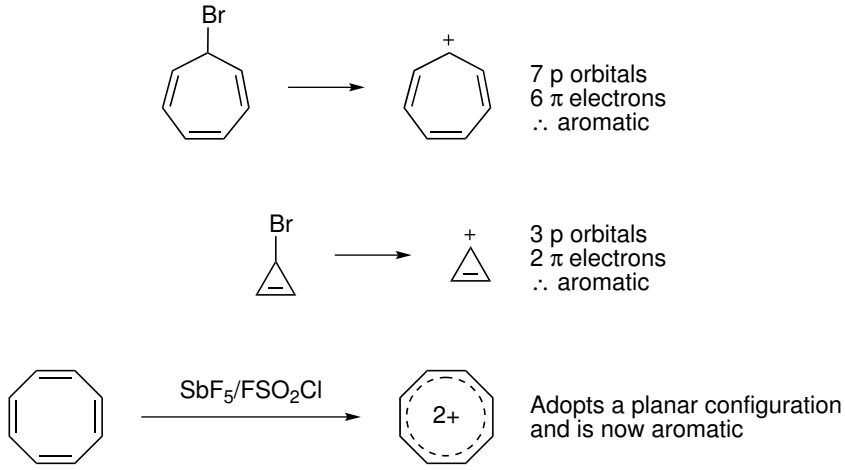
1 Aromaticity

Benzene is very stable and therefore it does not behave like alkenes. Rather than undergoing addition reactions, it undergoes substitution reactions.

Hückels rule: A planar, fully conjugated cyclic compound with 4n+2 electrons is aromatic. However we can also have 3, 5, 7 and 8 carbon aromatic compounds.

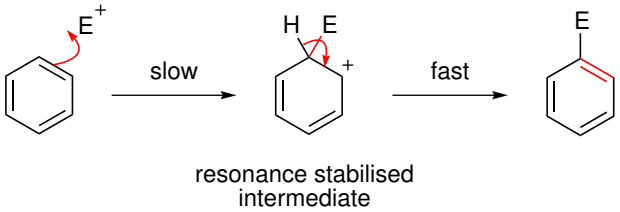


Similarly:



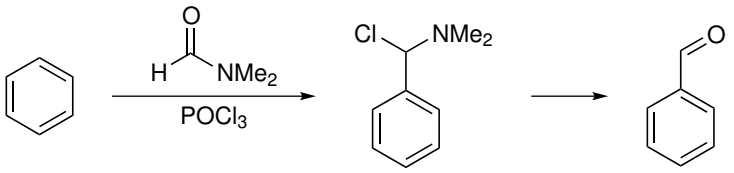
1.1 Reactions of Benzene

The typical reaction of bezene is electrophilic substitution, one of the H's is replaced by an electrophile:



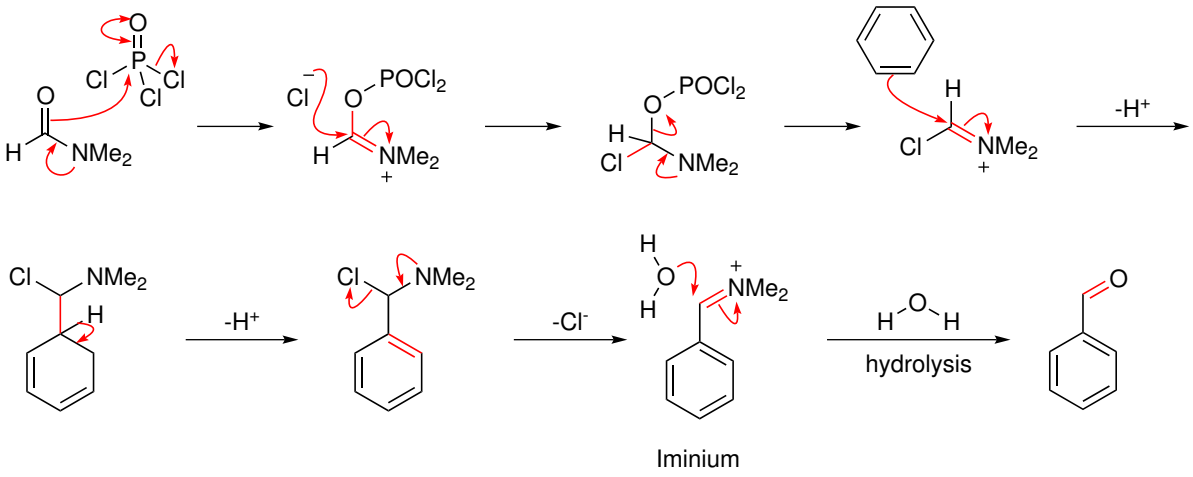
Because of the stabilised intermediate, the 1°C is no good for friedel crafts acylation or alkylation therefore the reaction is different, using DMF and phosphorus oxychloride.

a) Vilsmeier–Haack Formylation



Aldehyde

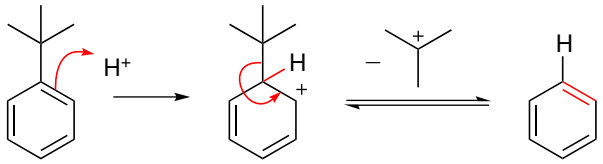
Mechanism:



Iminium

b) Dealkylation

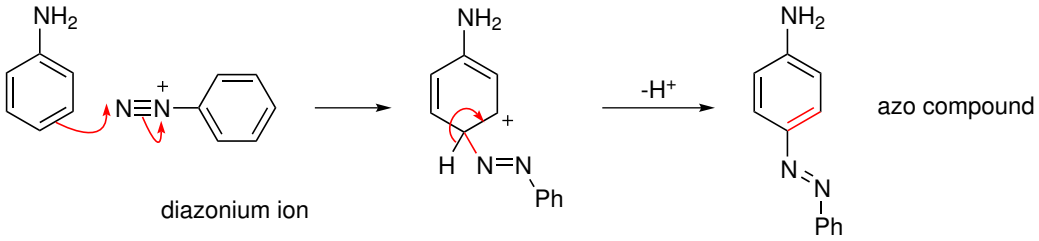
E.g. Removal of tertiary alkyl group with protic acid. Reverse of Friedel crafts alkylation.



Position of equilibrium depends on reaction conditions

c) Diazo coupling

React aromatic diazonium ion with phenol or aniline (e.g. Electron rich aromitc) to get azo compounds.



Azo compounds have 2 aromatic groups either side of $-(N=N)-$

1.2 Directing Effects in Electrophilic Aromatic Substition

Substituents will influence rate and position:

a) Activating - Ortho/Para directing

- Alkyl Groups
- Oxygen substituents
- Nitrogen substituents (NH_2, NR_2, NHCOR) I.e. Electron donating hence activating, either inductively or resonance.

b) Deactivating - Meta directing

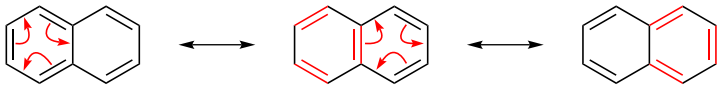
- Nitro groups and nitriles
- Carbonyl groups (COR, CO_2R)
- Positively charged substituents (NR_3^+) I.e. Electron withdrawing and therefore deactivating.

c) Deactivating - Ortho/Para directing

- Halogen atoms - inductively electron withdrawing but donating through resonance.

2 Polycyclic Aromatic Hydrocarbons

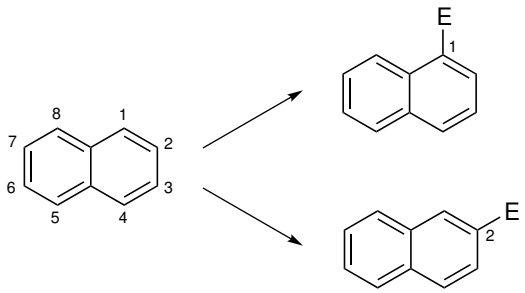
2.1 Napthalene



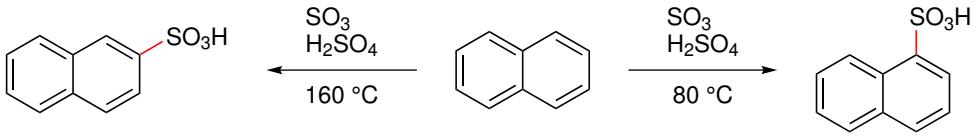
napthalene

Hückels rule applies here with n=2

The aromatic stability of napthalene is higher than benzene but less than twice as large. For this reason it is easier to disrupt aromatically and so napthalene is more reactive than benzene in electrophilic substitutions. E.g. It will react with Cl_2 without a catalyst.
There are 2 points of electrophilic attack, C-1 or C-2:



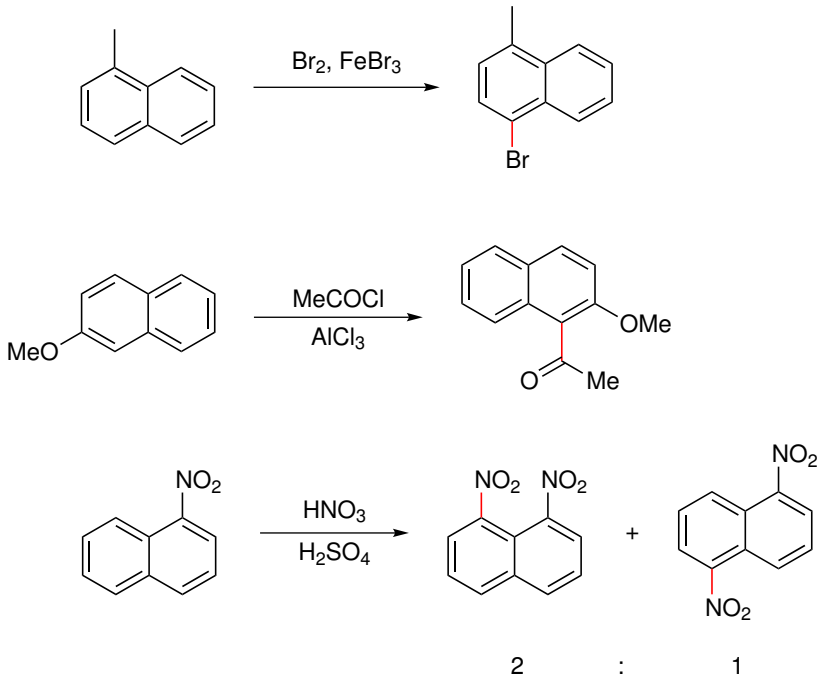
The lowest resonance forms retain aromaticity in the left hand ring. C-1 attack has two such forms, C-2 has only one. Therefore, the energy of the intermediate from attack at C-1 is lower than C2 so substitution is more rapid at C-1. In general, in polycyclic aromatic hydrocarbons, electrophilic substitution occurs most readily to a ring junction. However, the major product in the sulfonation of napthalene depends on the conditions under which the reaction is carried out.



This is because at 80 °C the reaction is irreversible and therefore the product obtained is fasted formed (kinetic product). At 160 °C the reaction is reversible therefore the product formed is the most stable (thermodynamic production).
If we carry out electrophilic substitutions on substituted napthalene:

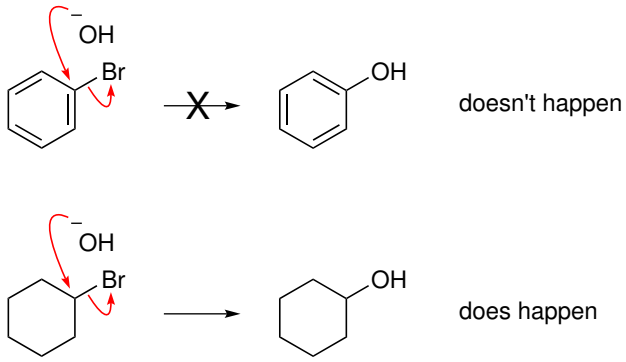
- Substitution will occur in the more electron rich ring
- Substitution will occur adjacent to the ring junction
- Normal directing effects apply

E.g.



2.2 Nucleophilic Substitution in Aromatic Compounds

Nucleophilic substitution in aromatic compounds is rare as the S_N2 mechanism is impossible at the sp^2 hybridised carbons of benzene.

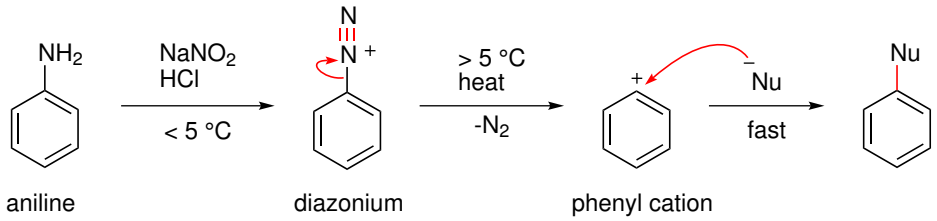


It only occurs under 3 sets of circumstances:

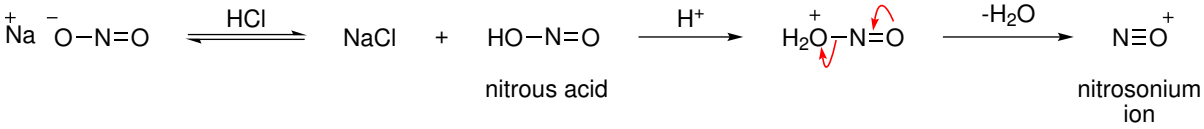
1. There is a very good leaving group e.g. N_2 (g)
2. The nucleophile is also a strong base e.g. $^{-}NH_2$
3. There are strongly electron withdrawing substituents ortho and/or para to the leaving group.

Each of these has a different mechanism.

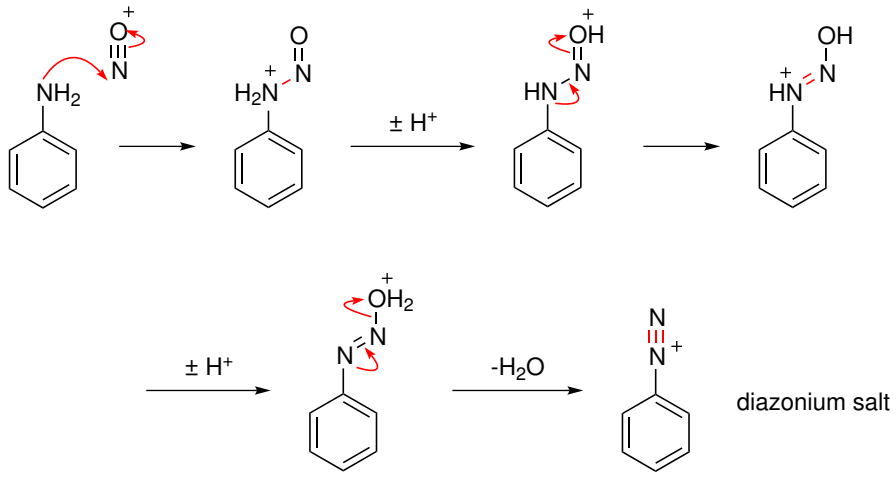
a) S_N1 Mechanism



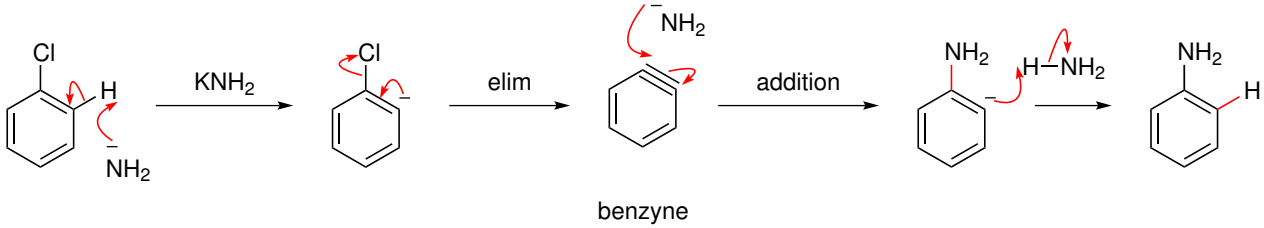
Diazonium formation



Mechanism

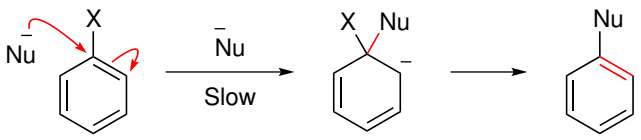


b) Benzyne Mechanism



The nucleophile must be a strong base, HO^- or $^-NH_2$ are most commonly used.

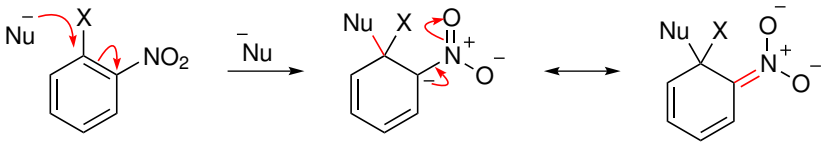
c) S_NAr Mechanism



Addition of Nu is the rate determining step therefore leaving group ability of X is not important but electronegativity of X is important (F > Cl > Br)

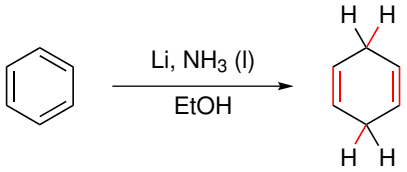
This mechanism requires strongly electron withdrawing groups ortho and/or para to the leaving group.

NO_2 is best for this purpose followed by carbonyl groups.

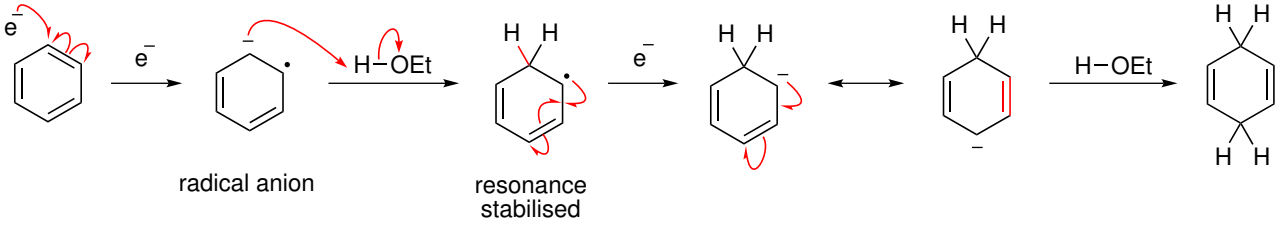


2.3 Birch Reduction

This is the partial reduction of aromatic rings.

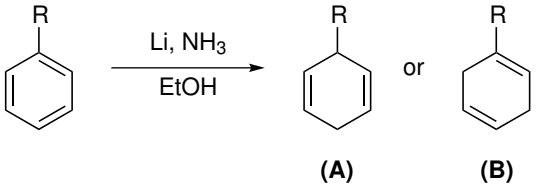


Mechanism:



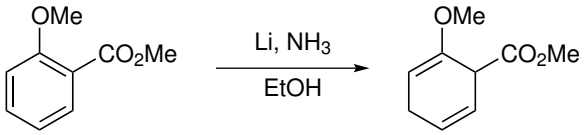
The product formed depends on which resonance ion is protonated first

If the Birch reduction is carried out with monosubstituted benzene then there are 2 possible products.

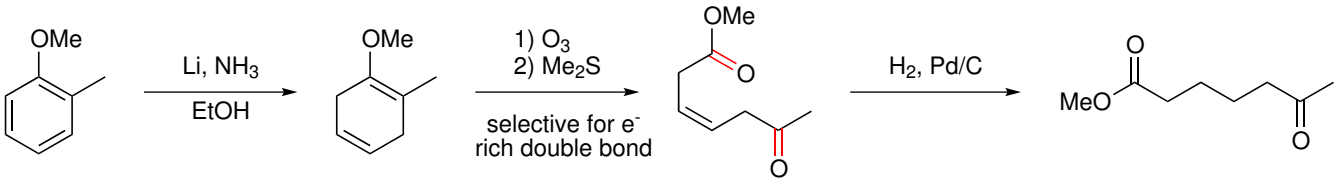


The isomer obtained depends on the nature of the substituent:

- If R is e^- withdrawing (e.g. carbonyl group) isomer A is obtained.
- If R is e^- donating (e.g. alkyl or OR), isomer B is obtained.
- If there is more than one substituent, it occurs as much as possible to put e^- donating substituents on the double bond and e^- withdrawing ones off them.



Birch reduction followed by ozonolysis is useful for generating 1,6 dicarbonyl compounds.



3 Aromatic Heterocycles

Heterocycles are aromatic compounds with at least one atom that is other than carbon. We will look at two classes:

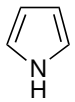
1. 6 Membered Heterocycles

   E.g. Pyridine

   - 5 sp^2 hybridised carbon atoms with each contributing 1 electon to the π system.
   - 1 sp^2 hybridised nitrogen atom which also contributes to the π system.

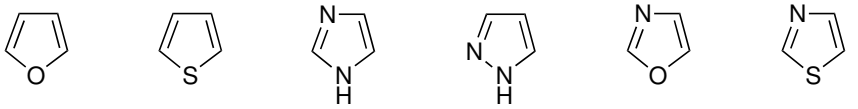
2. 5 Membered Heterocycles

   E.g. Pyrrole



   - 4 sp^2 carbon atoms, each contributing 1 electron to the π system.
   - 1 nitrogen atom contributing 2 electons to the π system.
   - Because the nitrogen lone pair is part of the aromatic ring, it is not available for bonding (e.g. to a proton) therefore pyrrole is not a base.

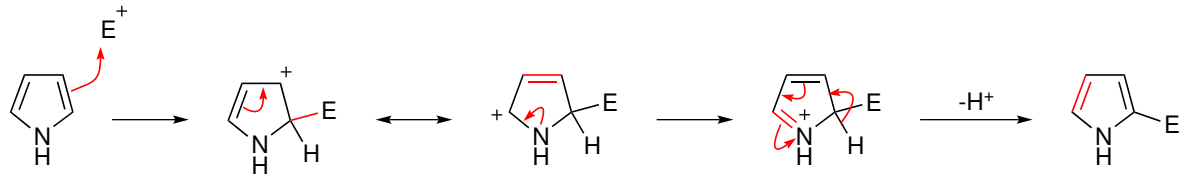
   Other 5 membered rings:



furan thiophene imidazole pyrazole oxazole thiazole

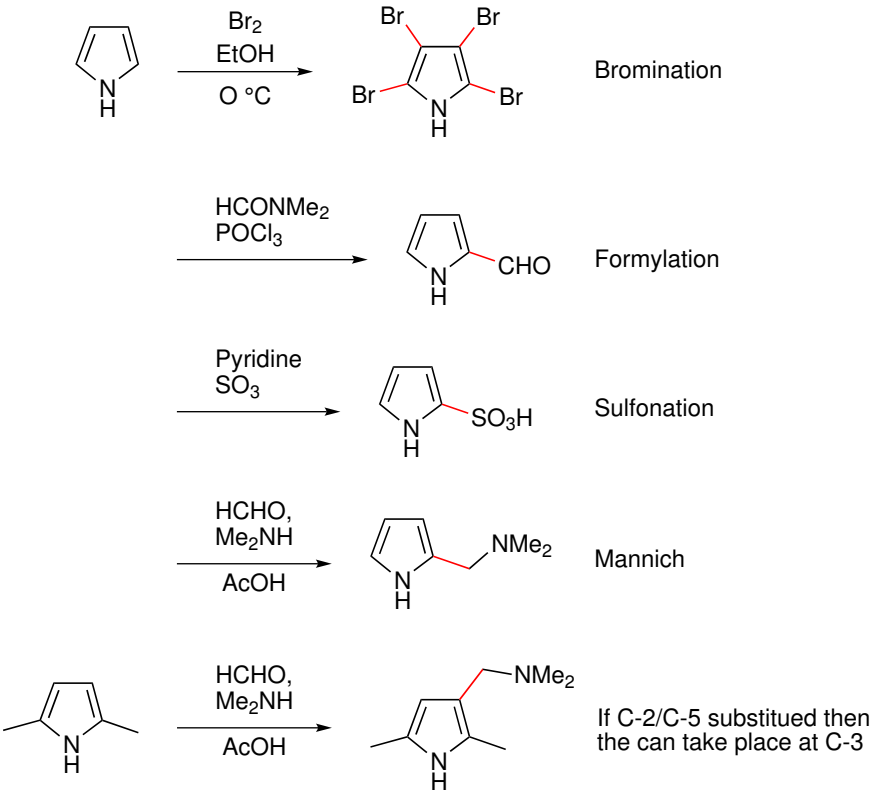
3.1 Pyrrole

Pyrrole is aromatic due to the delocalisation of the nitrogen lone pair into the πsystem. Counteracting this resonance effect is an inductive effect. Nitrogen is less electronegative than carbon. The resonance effect is dominant however the nitrogen atom has a partial positive charge. Pyrrole is very reactive towards electrophilic substitution.
C-2 is the favourite position for substitution due to the large number of resonance forms.



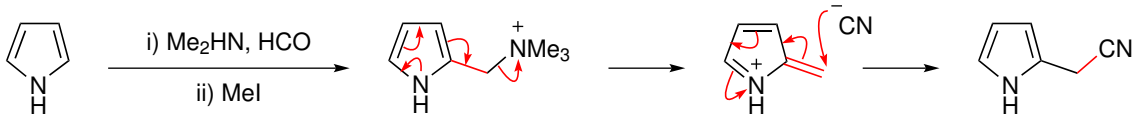
3.1.1 Electrophilic Substitutions of Pyrrole

Some typical electrophilic substitutions of pyrrole include:



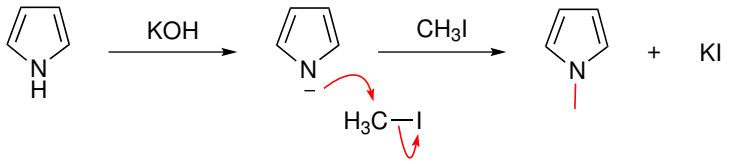
3.1.2 Nucleophilic Substitutions of Pyrrole

This process involves taking the Mannich product and treating with methyl iodide to get an ammonium salt. This salt then undergoes the nucleophilic substitution.

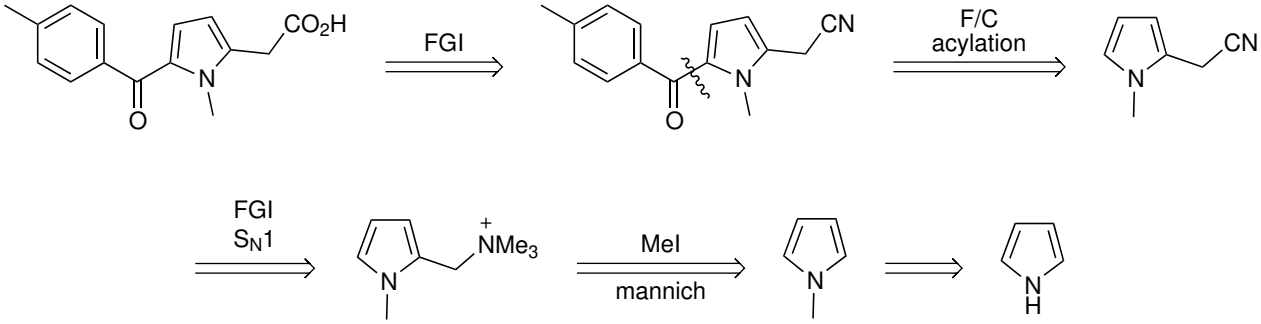


ammonium salt

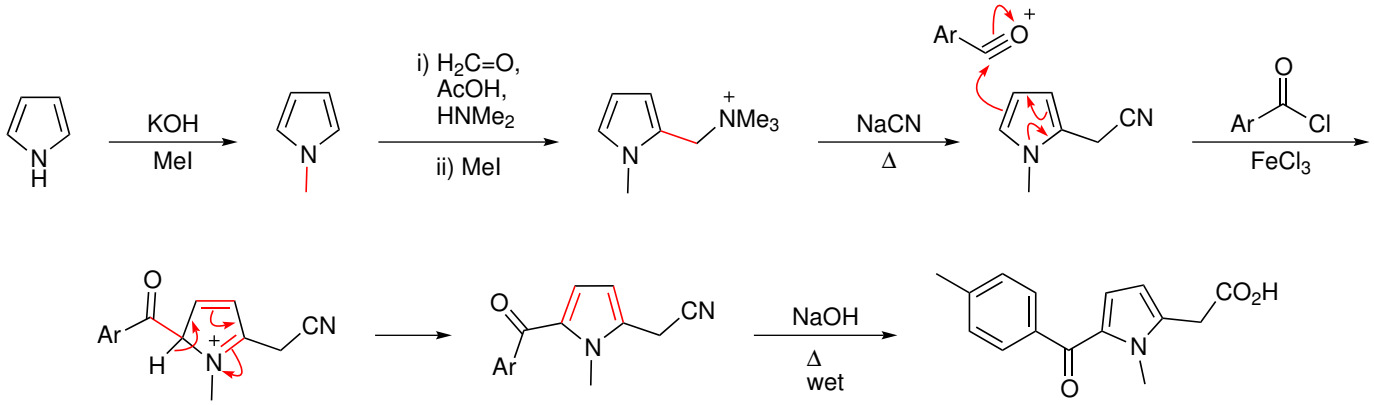
To react the nitrogen with an electrophile, it is deprotonated with a strong base resulting in the pyrryl anion.



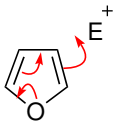
E.g. Retrosynthesis of Tolmetin



Synthesis:

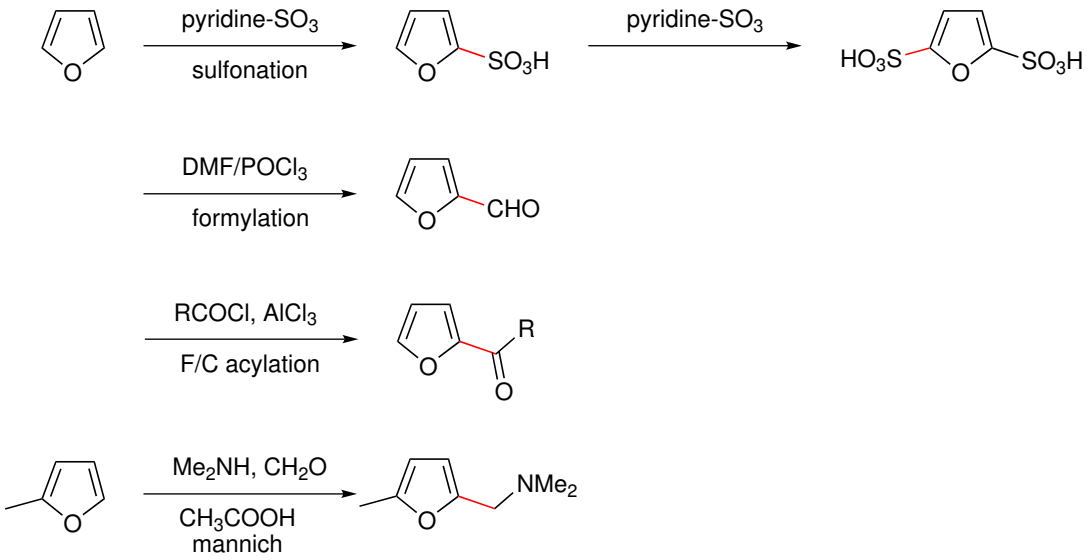


3.2 Furan



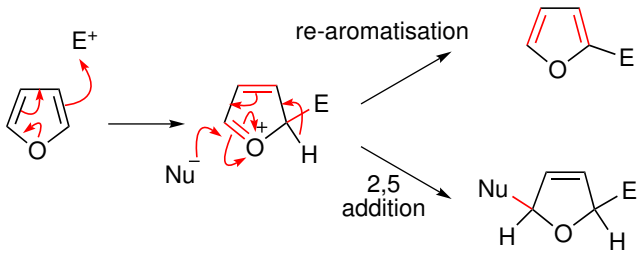
Oxygen is more electronegative than nitrogen therefore furan is less reactive than pyrrole towards electrophiles (but still more than benzene). Like pyrrole, reaction with E^+ is preferentially at the 2- and 5-positions and it is unstable in strongly acidic conditions. Furan is less aromatic than pyrrole.

3.2.1 Electrophilic Substitutions of Furan

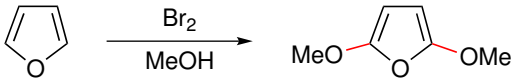


3.2.2 Other Reactions of Furan

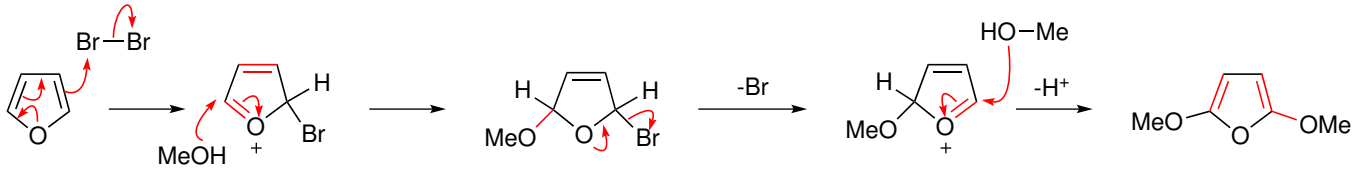
a) 2,5-addition to Furan



In some cases a nucleophile adds to the 5 position on the furan instead of re-aromatisation.

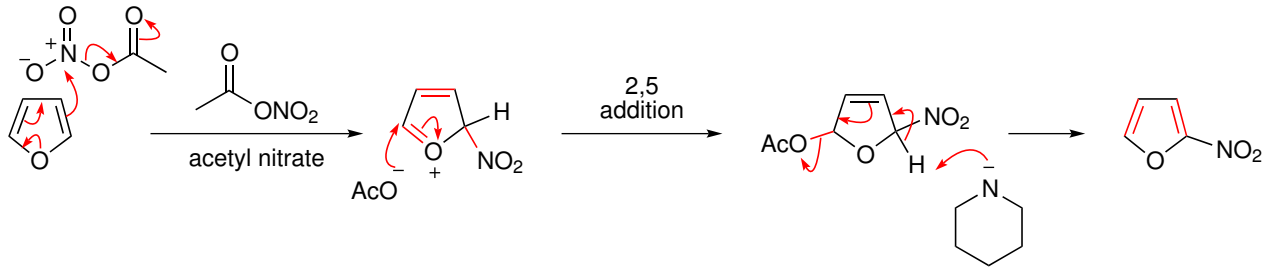


Mechanism



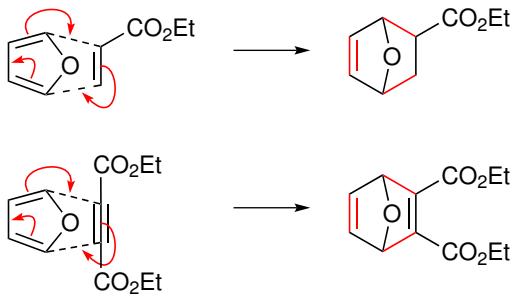
b) Nitration

Occurs by a similar process, addition followed by elimination via pyridine.



c) Diels-Alder reaction of Furans

Furans behave as dienes in diels-alder reactions with electron deficit alkenes and alkynes.

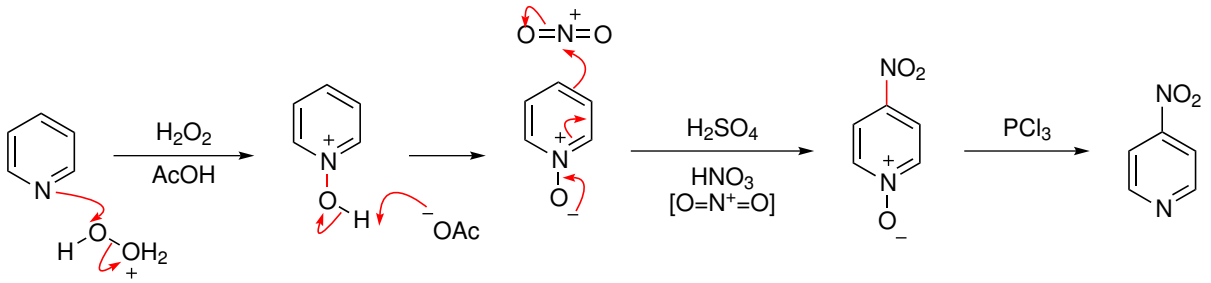


3.3 Pyridine

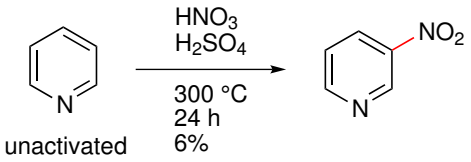
The inductive effect of nitrogen means that the nitrogen has a slight negative charge and the carbons are left slight positive. Therefore pyridine is referred to as an electron deficient heterocycle and pyridine is unreactive in electrophilic substitution reactions.

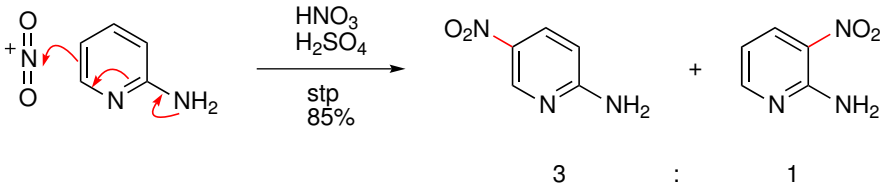
Electrophilic substitution normally occurs at C-3 as attack at C2/C4 gives rise to an intermediate where the electronegative nitrogen is deficient (high in energy). Substitution in pyridine is 10^7 times slower than in benzene.

Conversion of pyridine to the pyridine N-oxide using H_2O_2 enables electrophilic substitution. However substitution commonly takes place in the C-4 position.



If relatively activating substituents are present in the pyridine ring then electrophilic substitution can occur more readily, usually ortho/para to the activating group. E.g. Amino pyridines.

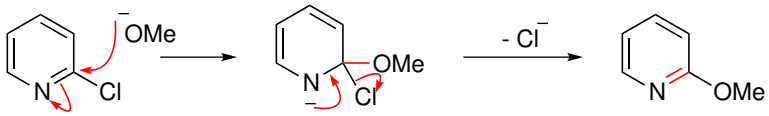




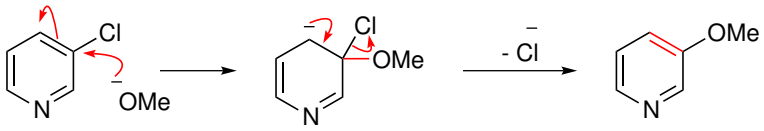
3.3.1 Nucleophilic Substitution of Pyridine

The electron deficient nature of pyridines makes them good in nucleophilic substitution reactions, particularly when the negative charge can be stabilised by the nitrogen.

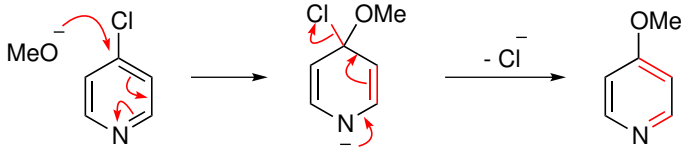
Substitution of a leaving group in the 2 position:



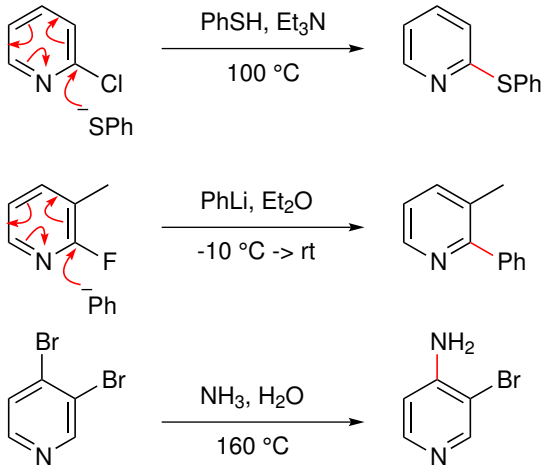
In the 3 position:



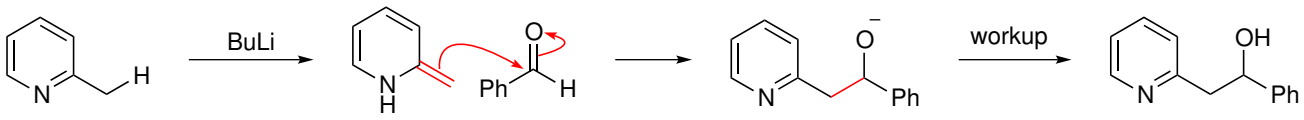
In the 4 position:



With attack at C2/C4, the anion is stabilised by the nitrogen:

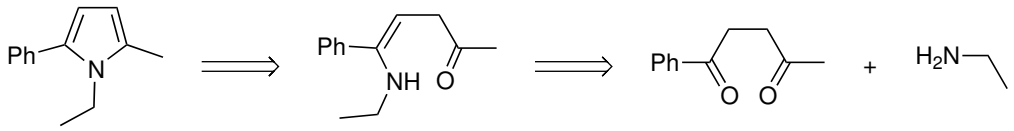


2-alkyl and 4-alkyl pyridines are acidic:

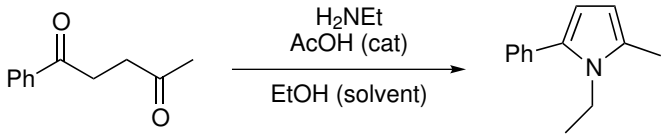


4 Heterocycle Synthesis

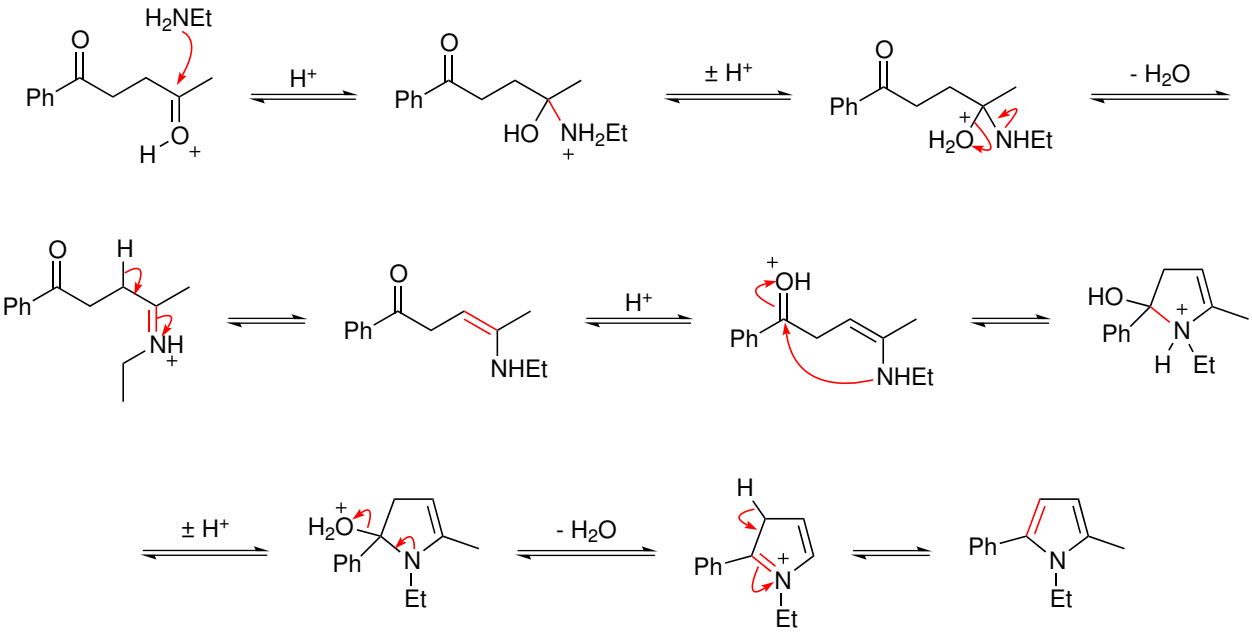
4.1 Paal-Knorr Pyrrole Synthesis



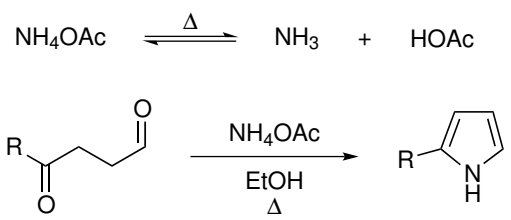
So if we react a 1,4 diketone and an amine (with acid) we get a pyrrole.



Mechanism

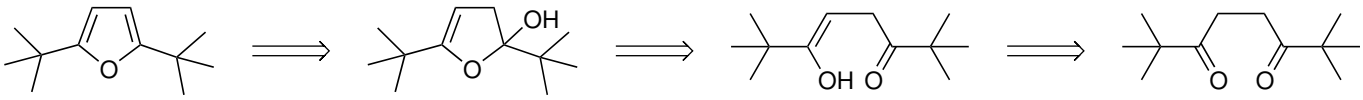


If we don't want a substituent on the nitrogen we can use ammonium acetate as a source of NH_3.

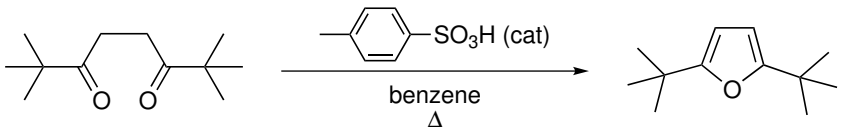


4.2 Paal-Knoor Furan Synthesis

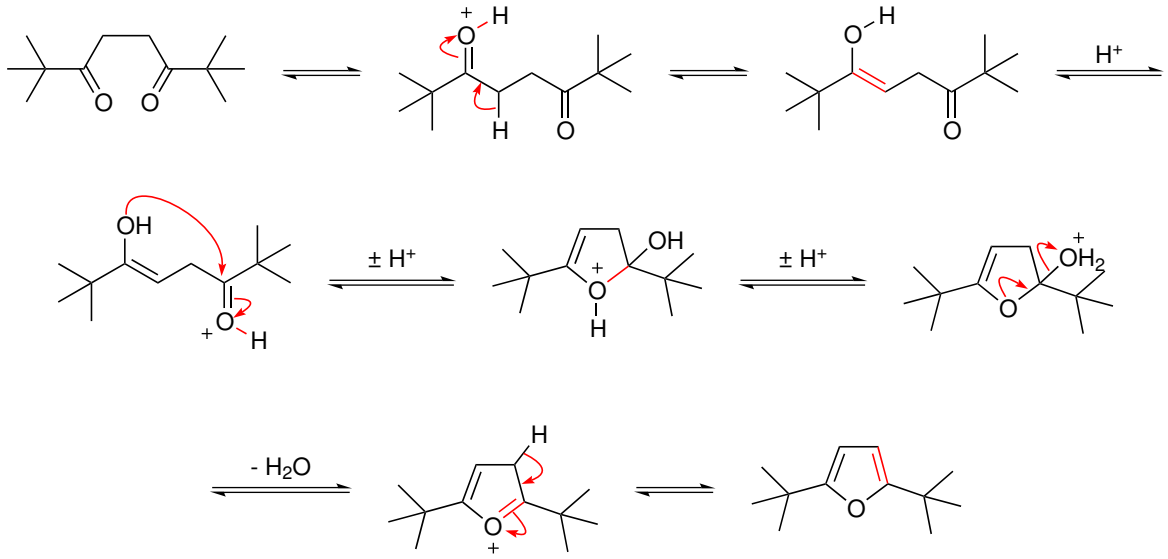
Via a slight modification to the retrosynthesis we can apply the same method to furans:



This is dehyration of a 1,4 dikenone (anhydrous conditions).

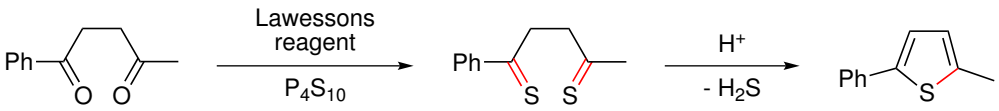


Mechanism

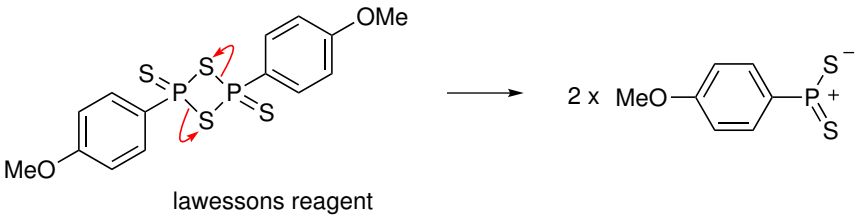


4.3 Synthesis of Thiophenes

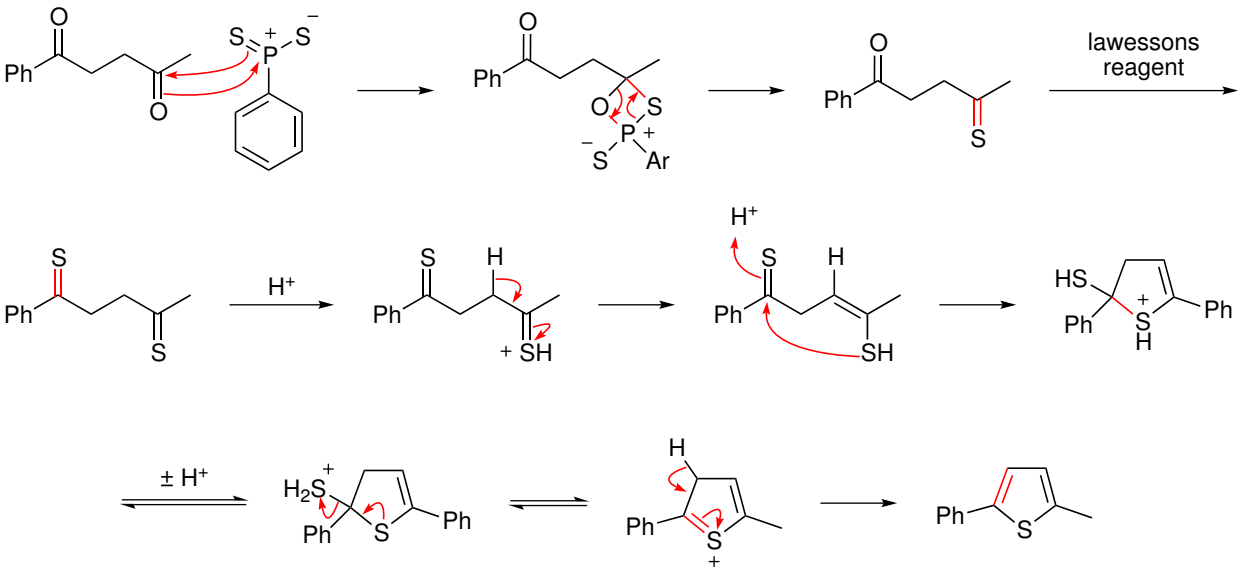
Prepared from 1,4 diketone and a source of sulfur such as H_2S, P_4S_{10} or Lawessons reagent.



Using:

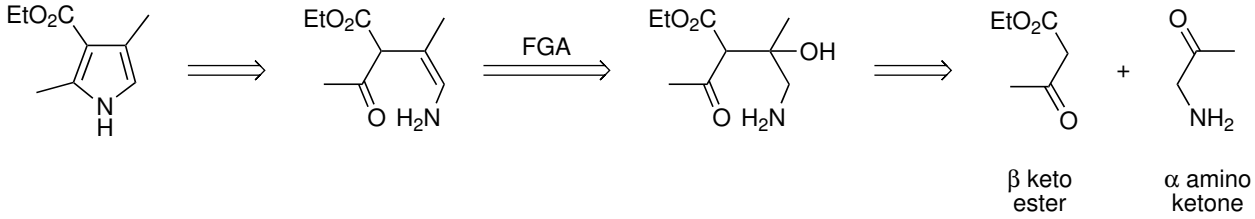


With the mechanism:

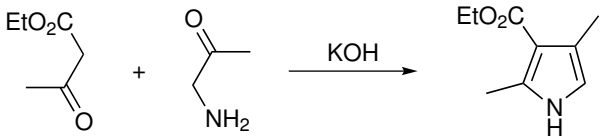


4.4 Knorr Pyrrole Synthesis

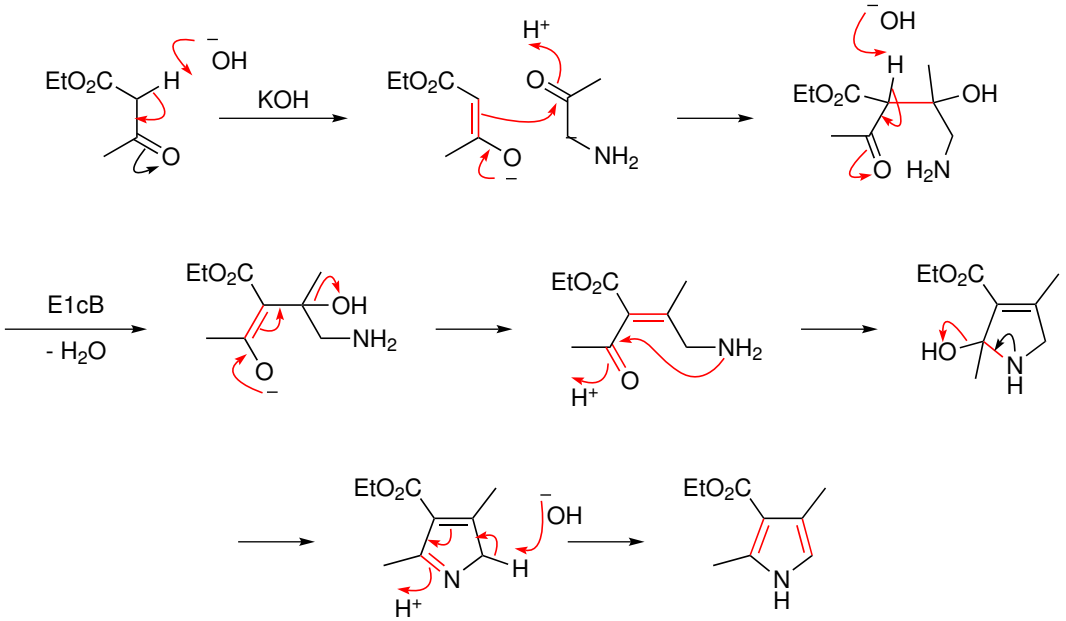
If there is an electron withdrawing group in the 3 position of a pyrrole, another disconnection is possible.



Therefore β keto ester + α amino ketone + base results in a ketone.

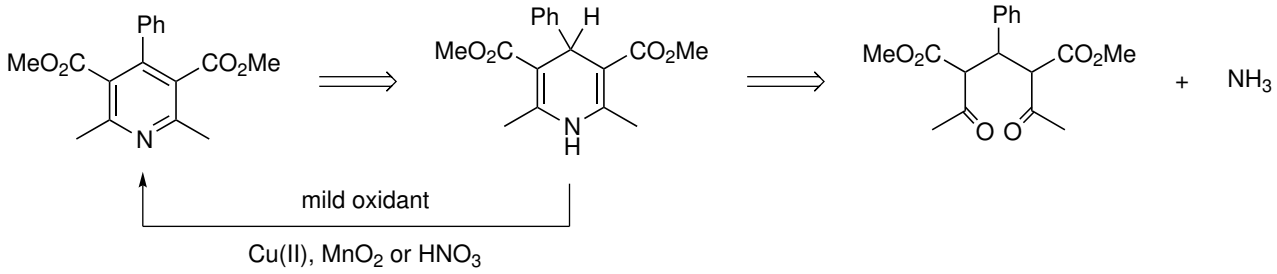


Mechanism - slightly different to disconnection:

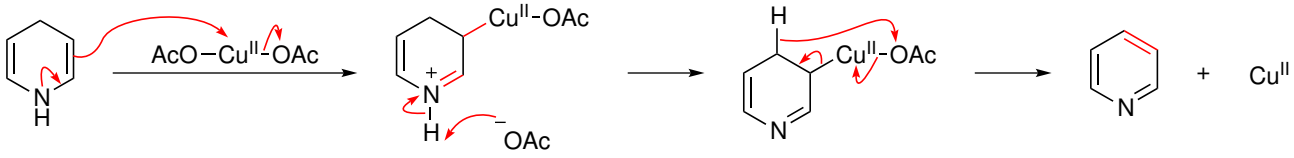


4.5 Synthesis of Pyridines

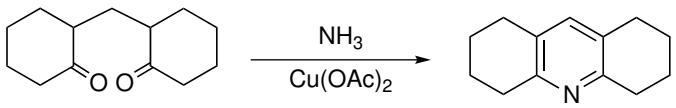
The disconnections similar to those above work but the starting materials are not easy to make and therefore the last step is changed to an oxidation.



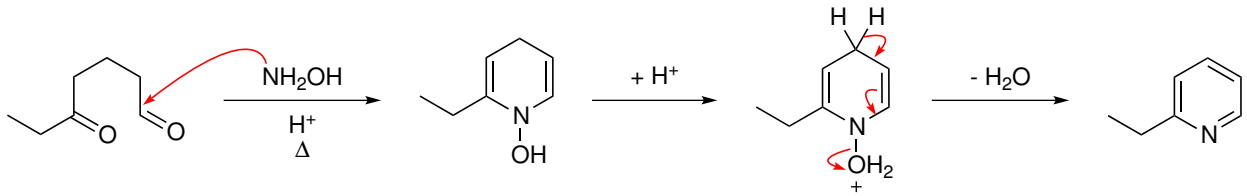
Oxidation to pyridines:



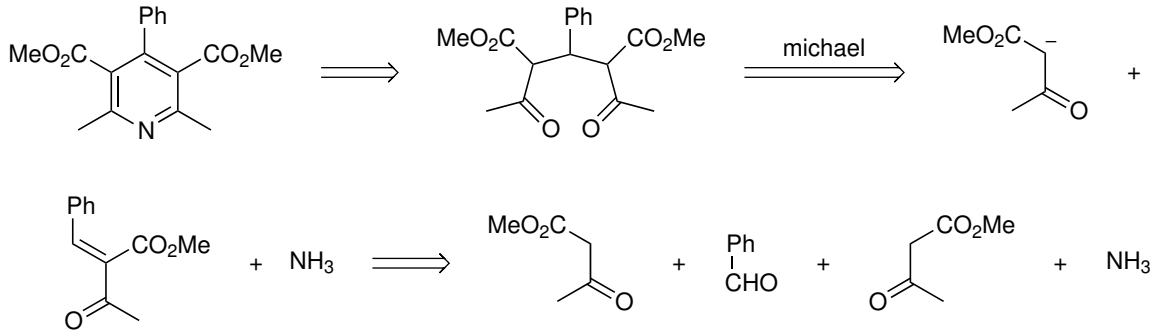
Therefore 1,5 dicarbonyl + NH_3 + oxidation results in a pyridine.
e.g.



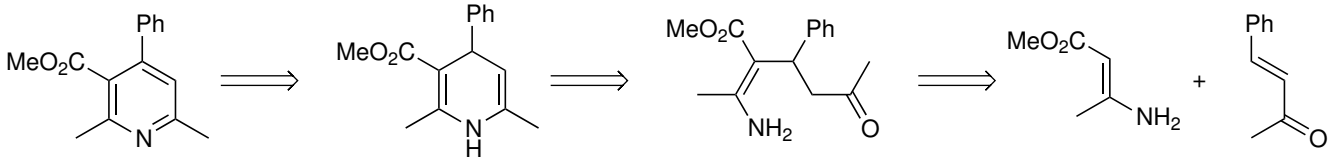
Alternatively we can make the last step a dehydration rather than oxidation by using hydroxylamine (H_2N-OH) rather than ammonia.



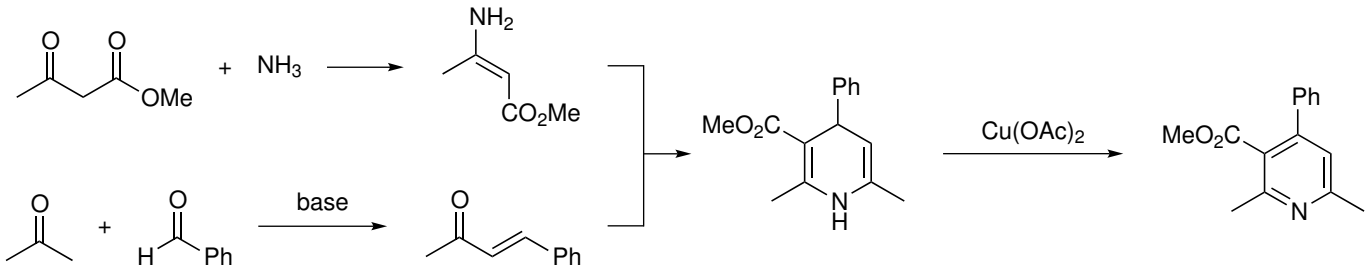
4.6 Hantzsch Pyridine Synthesis



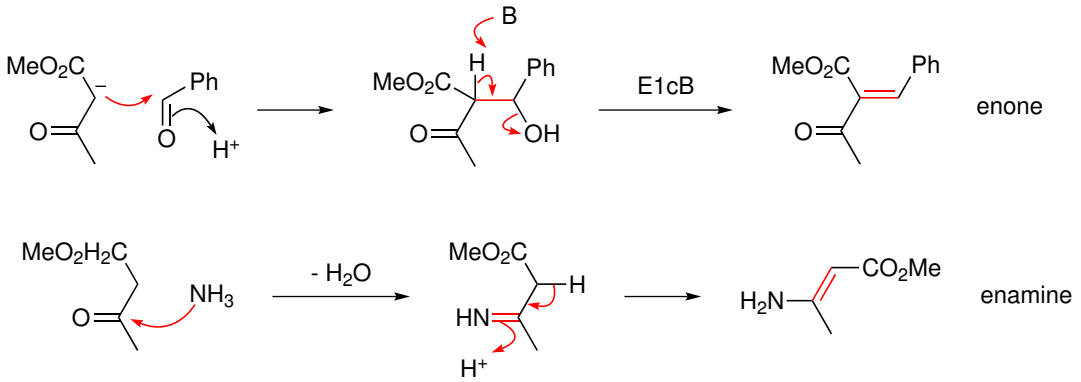
The C3/C5 substituents must be electron withdrawing groups (usually esters). If the target is unsymmetrical pyridine or dihydropyridine we can seperate the 2 halfs (i.e. keep the enamine seperate from the enone formation).



Forward synthesis:



Formation of enone and enamine:



Combination mechanism: