Heterocyclic Chemistry

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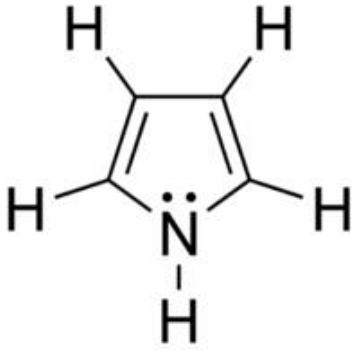
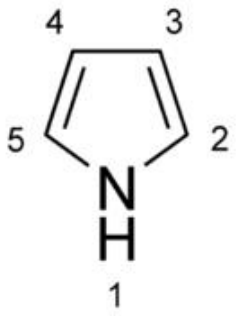
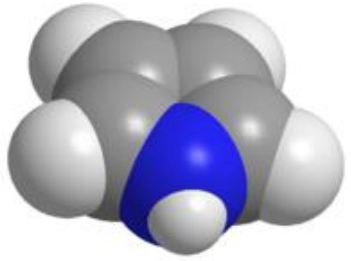
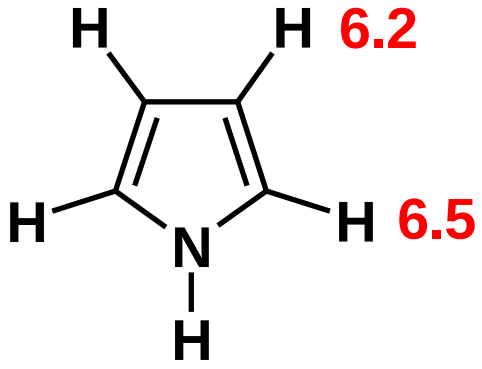
Five Membered Heterocycles: Pyrrole







^{1}H NMR: δ



Pyrrole

Aromatic: Thus, 6π electrons

Sp^2 hybridised and planar

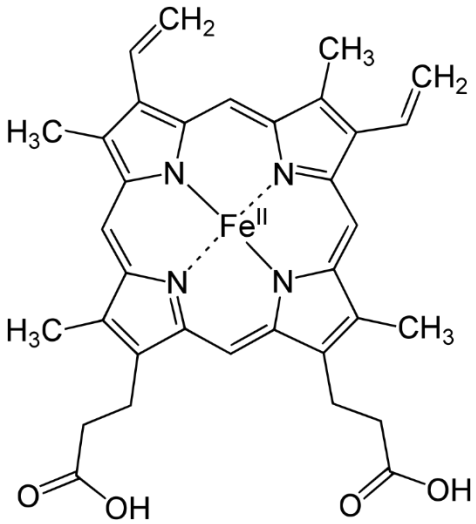
Lone pair tied up in aromatic ring

Pyrrole is π-electron excessive

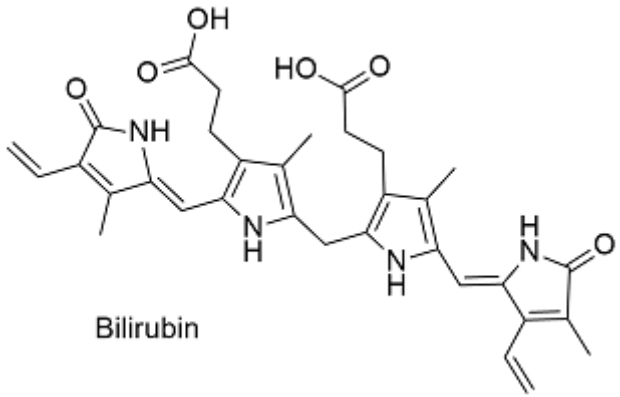
Thus, Electrophilic Aromatic Substitution is Easy

Nucleophilic Substitution is Difficult

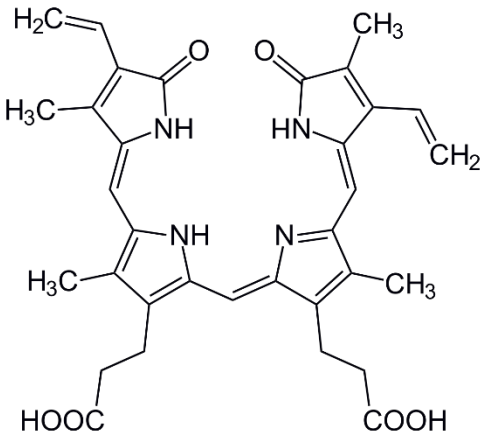
- Pyrrole itself is not naturally occurring, but many of its derivatives are found in a variety of cofactors and natural products.
- Common naturally produced molecules containing pyrroles include vitamin B_{12}, bile pigments like bilirubin and biliverdin, and the porphyrins of heme, chlorophyll, chlorins, bacteriochlorins, and porphyrinogens.
- The syntheses of pyrrole-containing haemin, synthesized by Hans Fischer was recognized by the Nobel Prize.
- Pyrrole is a constituent of tobacco smoke and may contribute to its toxic effects.



vitamin B_{12}

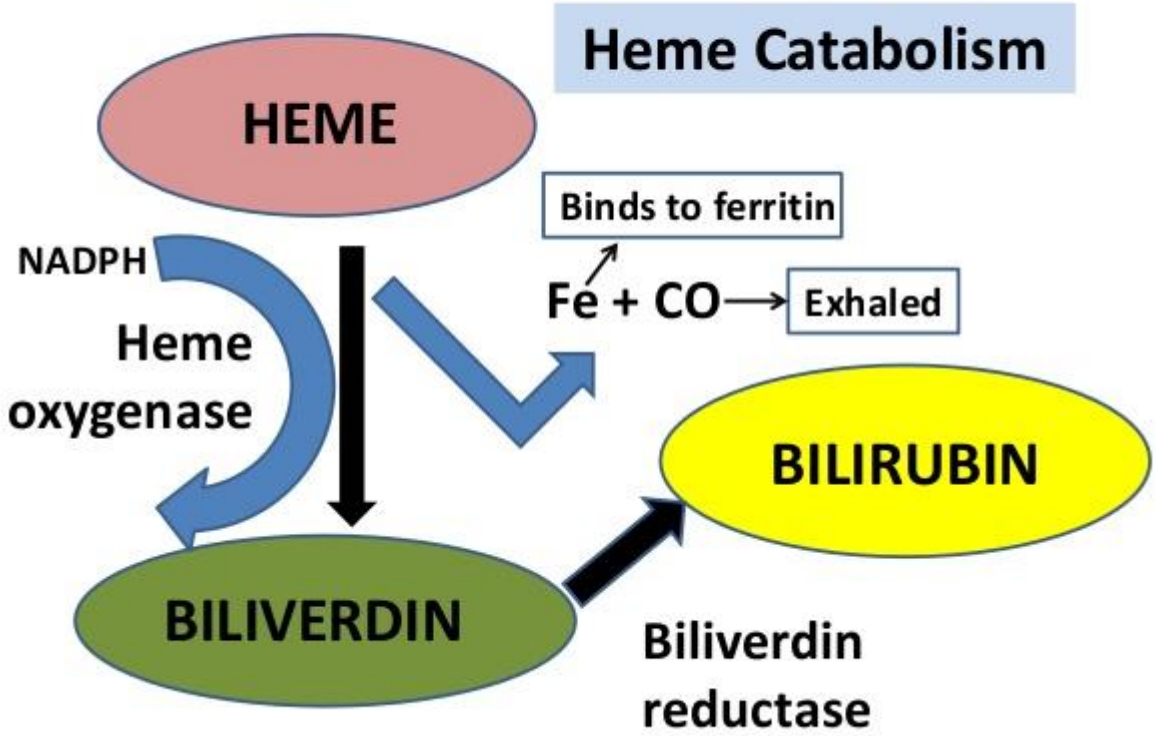


Bilirubin



biliverdin

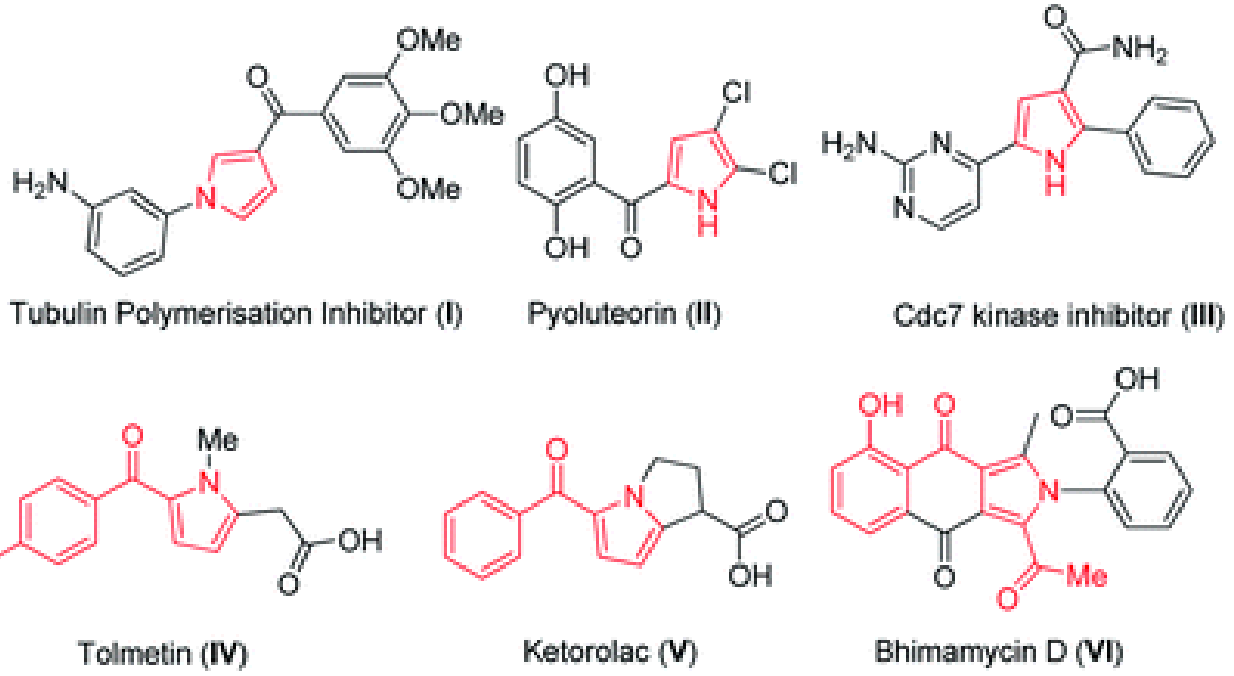
Bilirubin Production

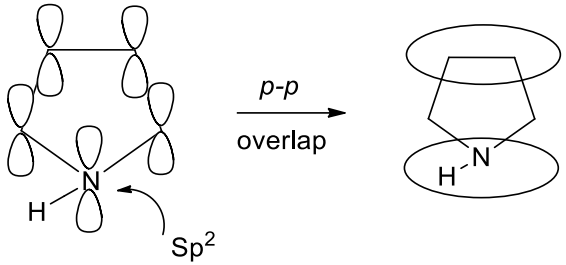


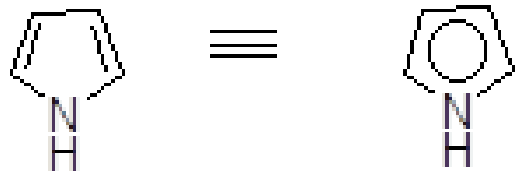
Bilirubin is a pigment produced by breakdown of **haemoglobin** or other haeme containing proteins. Bilirubin carried in blood is taken up by liver cells and processed to a form that can be excreted into the intestine through bile. Bilirubin is partly converted to **biliverdin** by bacteria in the intestine . Both bilirubin and biliverdin are excretory products and serve no particular function.

In Nature

Pyrroles are ubiquitous and important privileged scaffolds amongst the family of five membered N-heterocyclic pharmacophores which are widely distributed in natural products, medicinal agents and agrochemical research. Pyrroles are also having broad applications in electronics, molecular optics and widely used as versatile building blocks in organic synthesis.





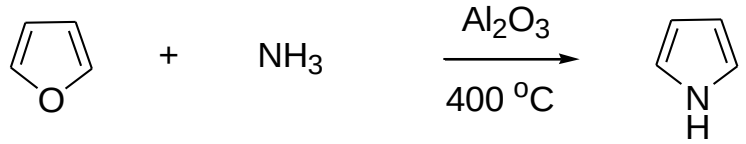


R.E. = 125.6 kJ/mole(~ 24 kcal/mole); b.p. 131 ^{o}C

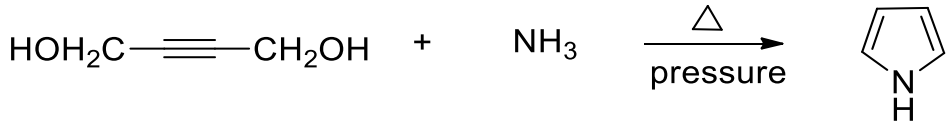
Source: Coal tar and bone oil.

Preparation: Pyrrole is obtained

i) Industrially it is obtained from furan and NH_3

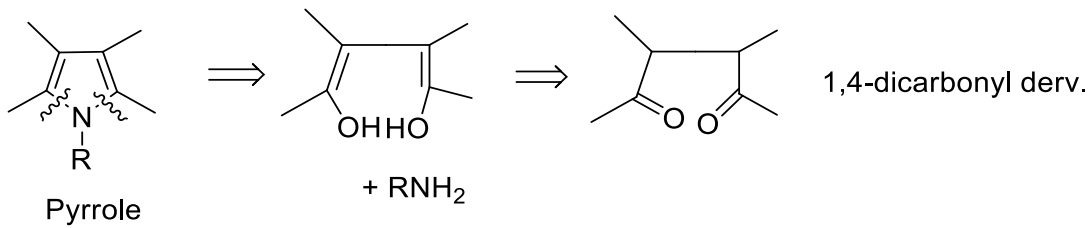


ii) From 2-butyne-1,4-diol

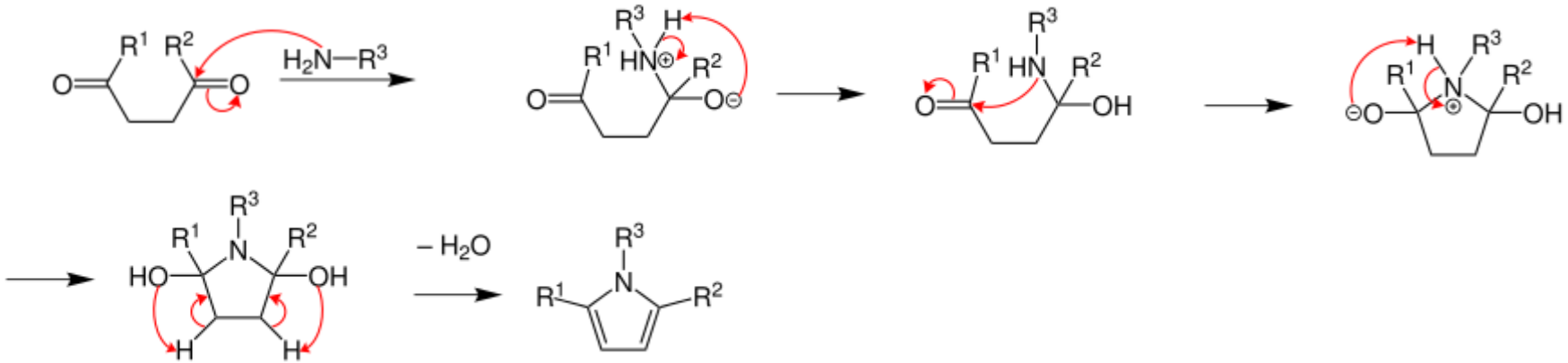


Chemical synthesis:

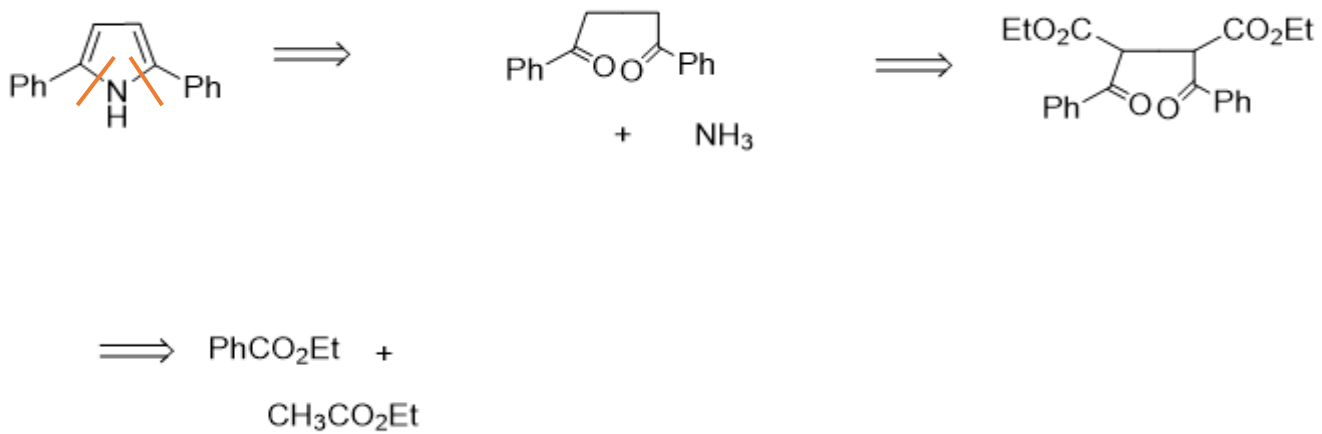
1. Paal-Knorr synthesis:



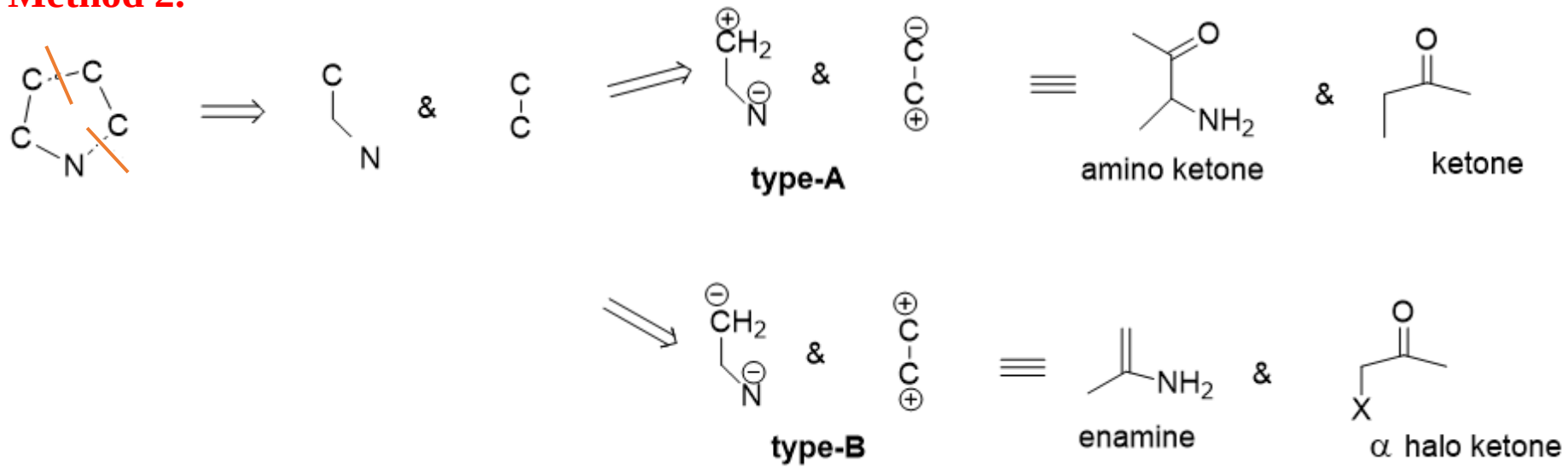
Mechanism of Paal-Knorr synthesis:



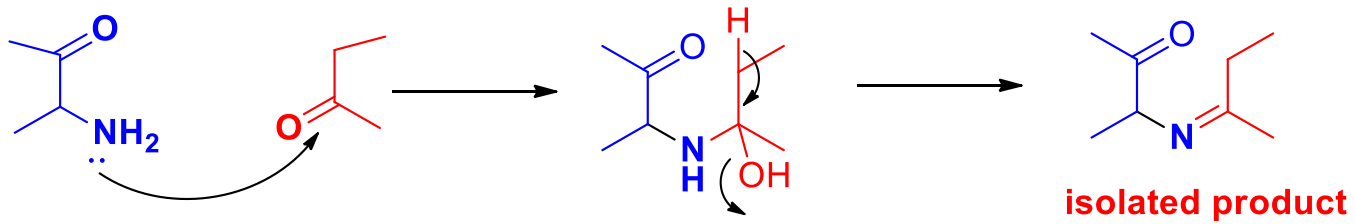
Example 1.



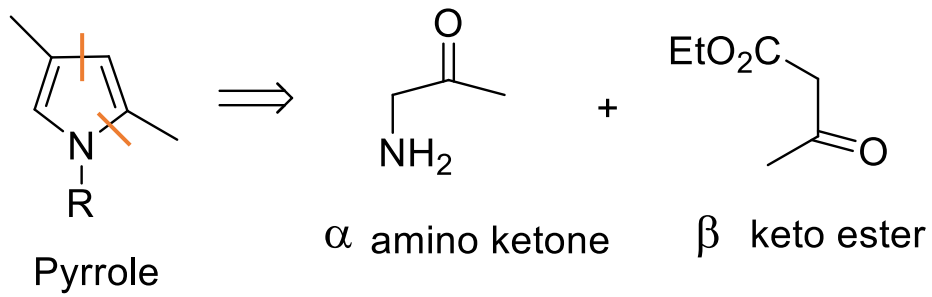
Method 2.



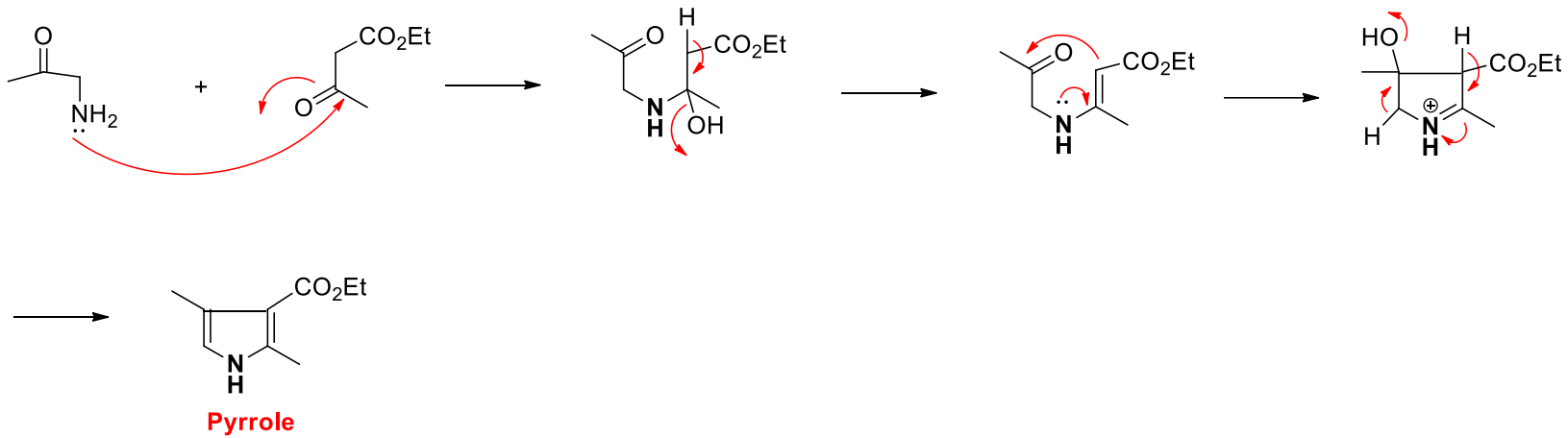
Type A: The pyrrole derv. can be synthesized by using α-amino ketone and a ketone having protons. But, here N-H is more acidic than C-H so the following compound is formed.



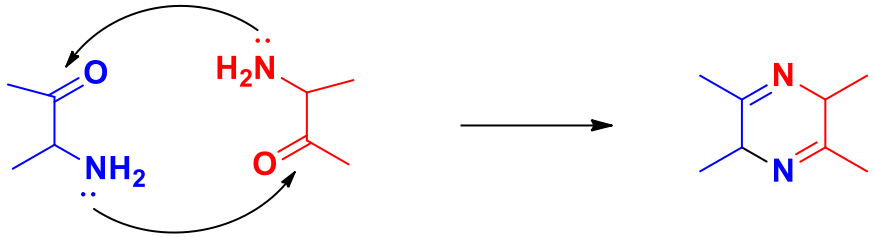
2. Hence, the reaction path is failed to give pyrrole ring. To solve this problem, β-keto ester is used in place of a ketone which is known **Knorr pyrrole synthesis**.



Mechanism:

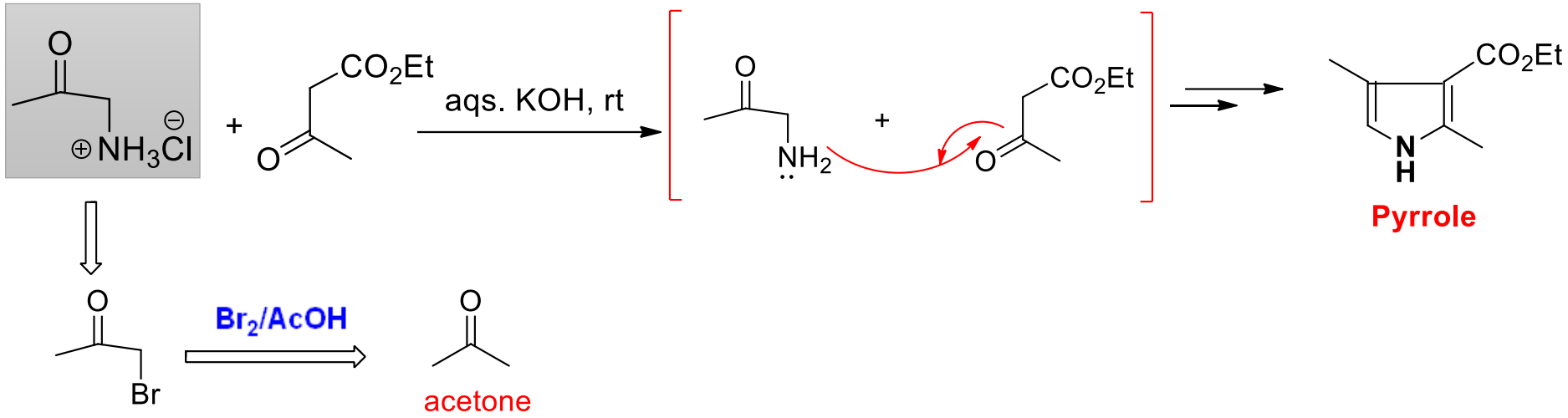


Note: There is a problem of dimerization of amino ketone

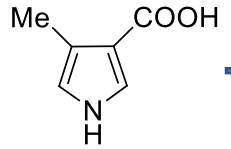


That can be avoided by the following modifications:

α-amino ketone is replaced by hydrochloride salt of amine instead of free amine



Problem:



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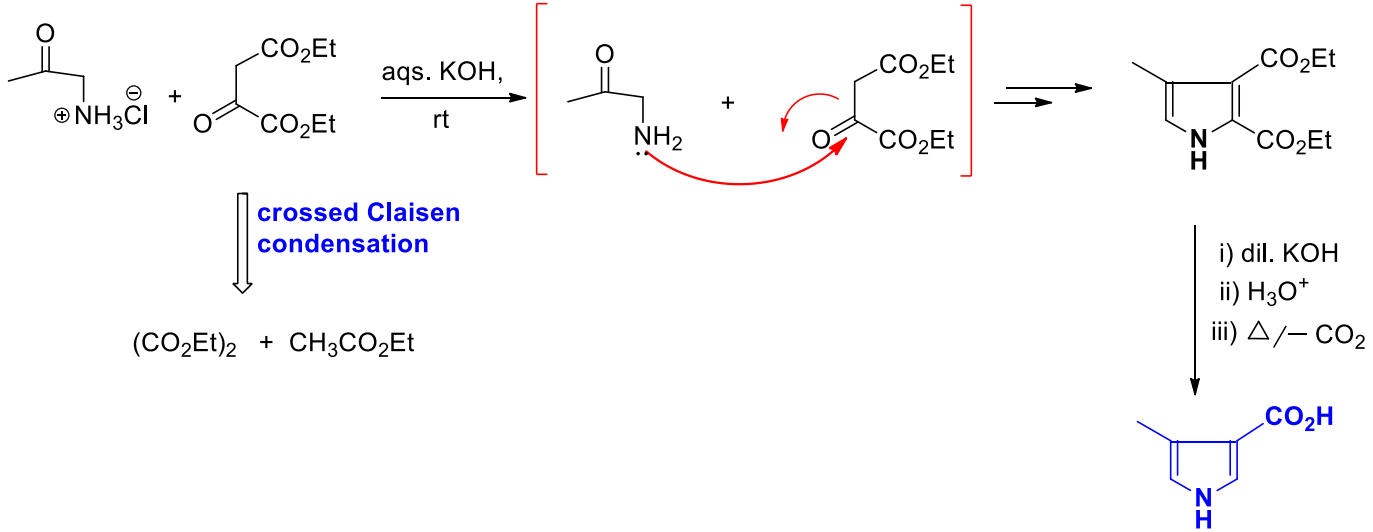
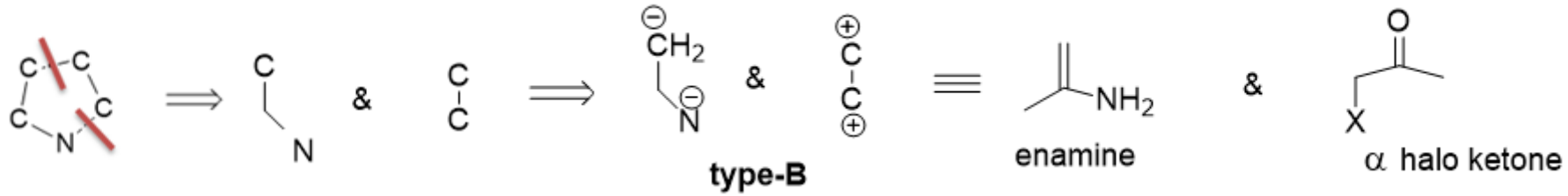
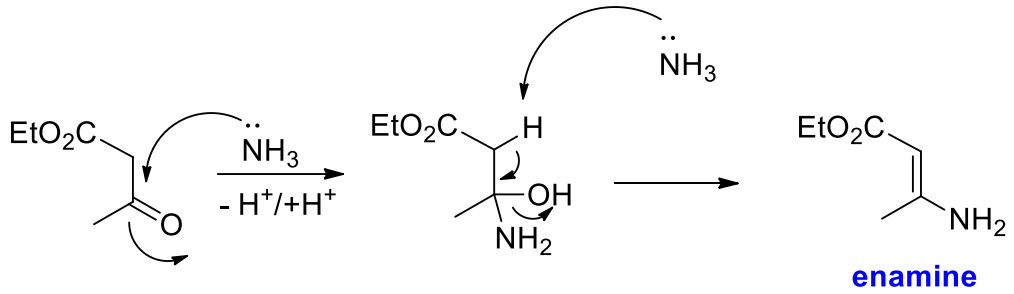


Type B: Let us consider the synthesis of pyrrole derv. using B-type synthons i.e. an enamine and α-halo ketone derv.

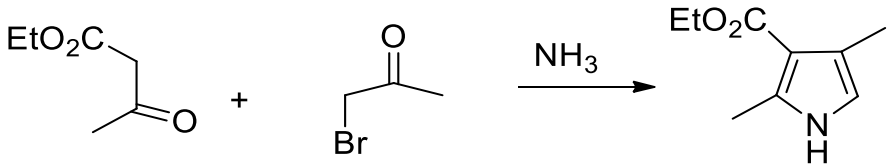


Again, an enamine can be obtained from β-keto ester and NH_3 as base.

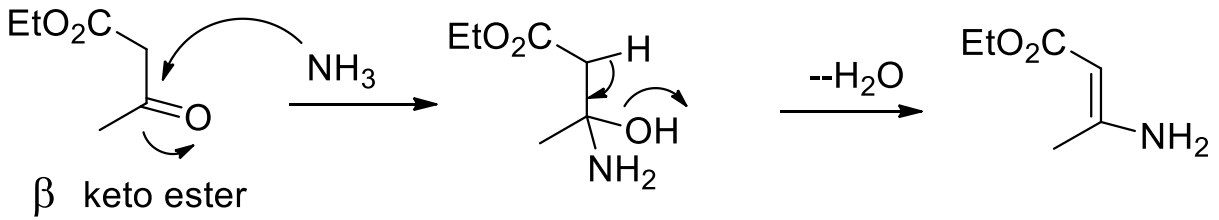


enamine

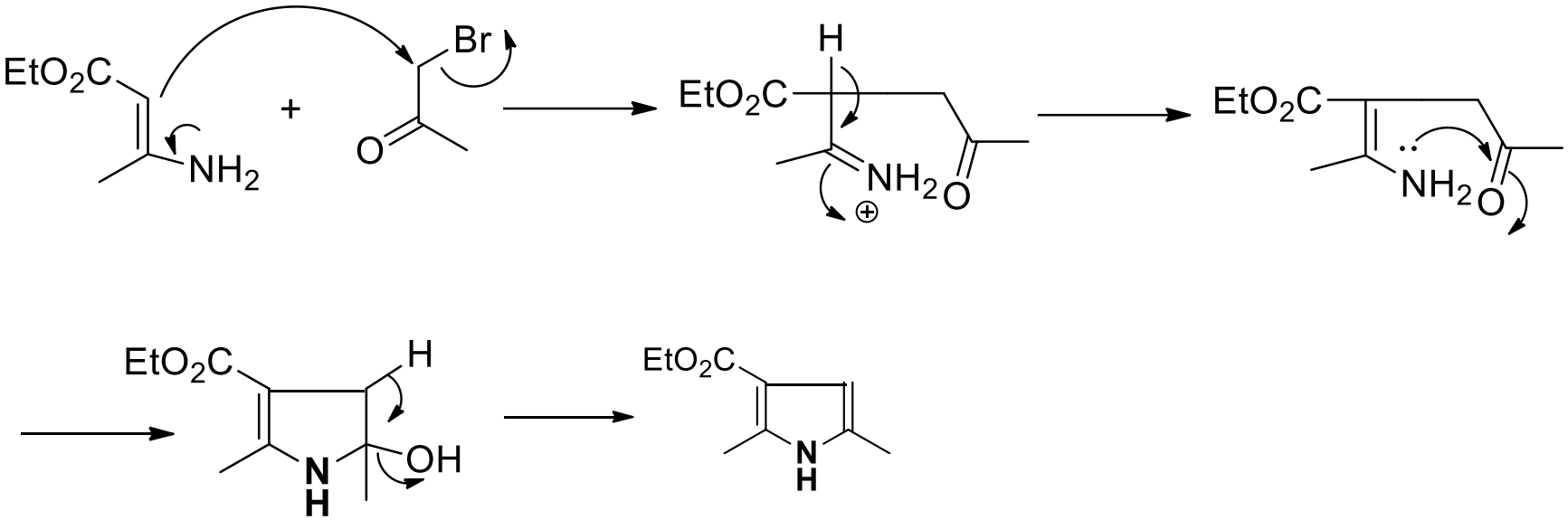
3. Thus **HANTZSCH pyrrole synthesis** can be achieved by treating a mixture of β-keto ester and α-halo ketone with NH_3.

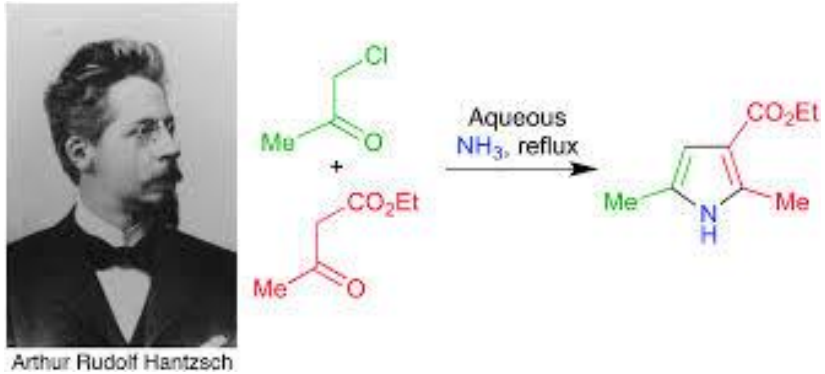


Pathway: *Step 1.* Formation of enamine from β-keto ester



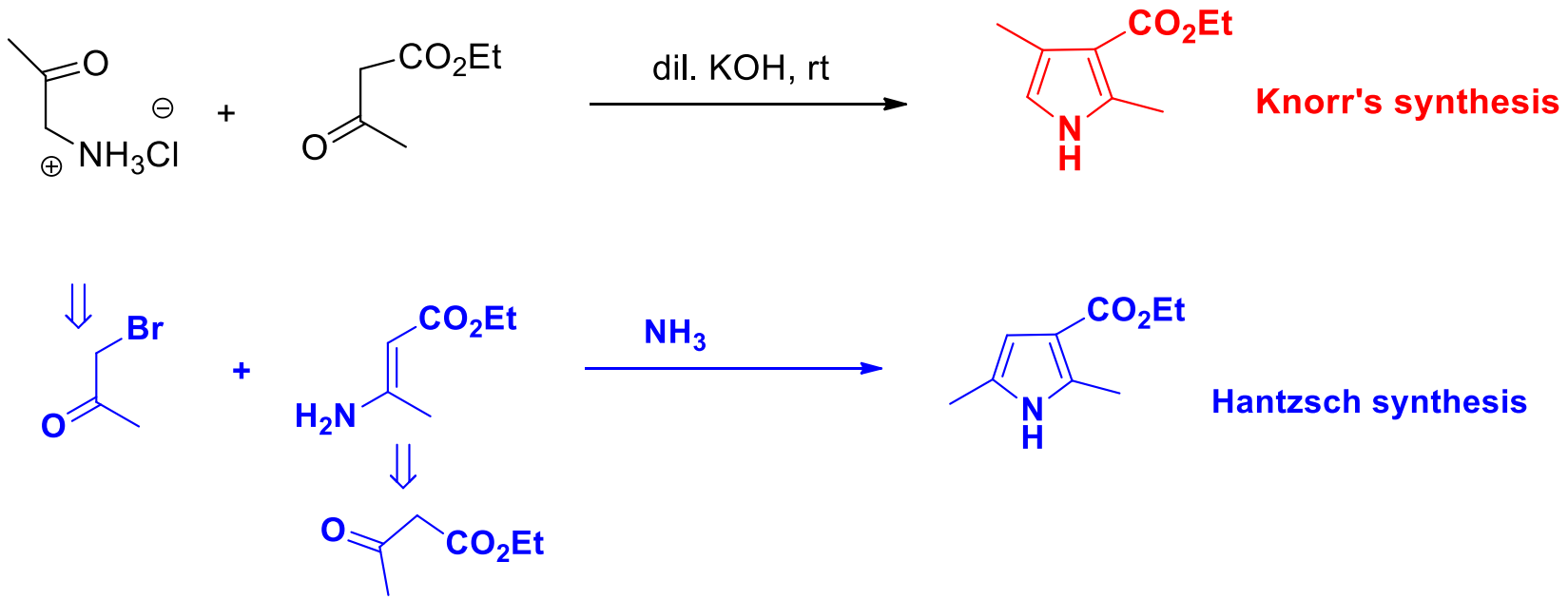
Step 2. Condensation of enamine with α-halo ketone





Arthur Rudolf Hantzsch

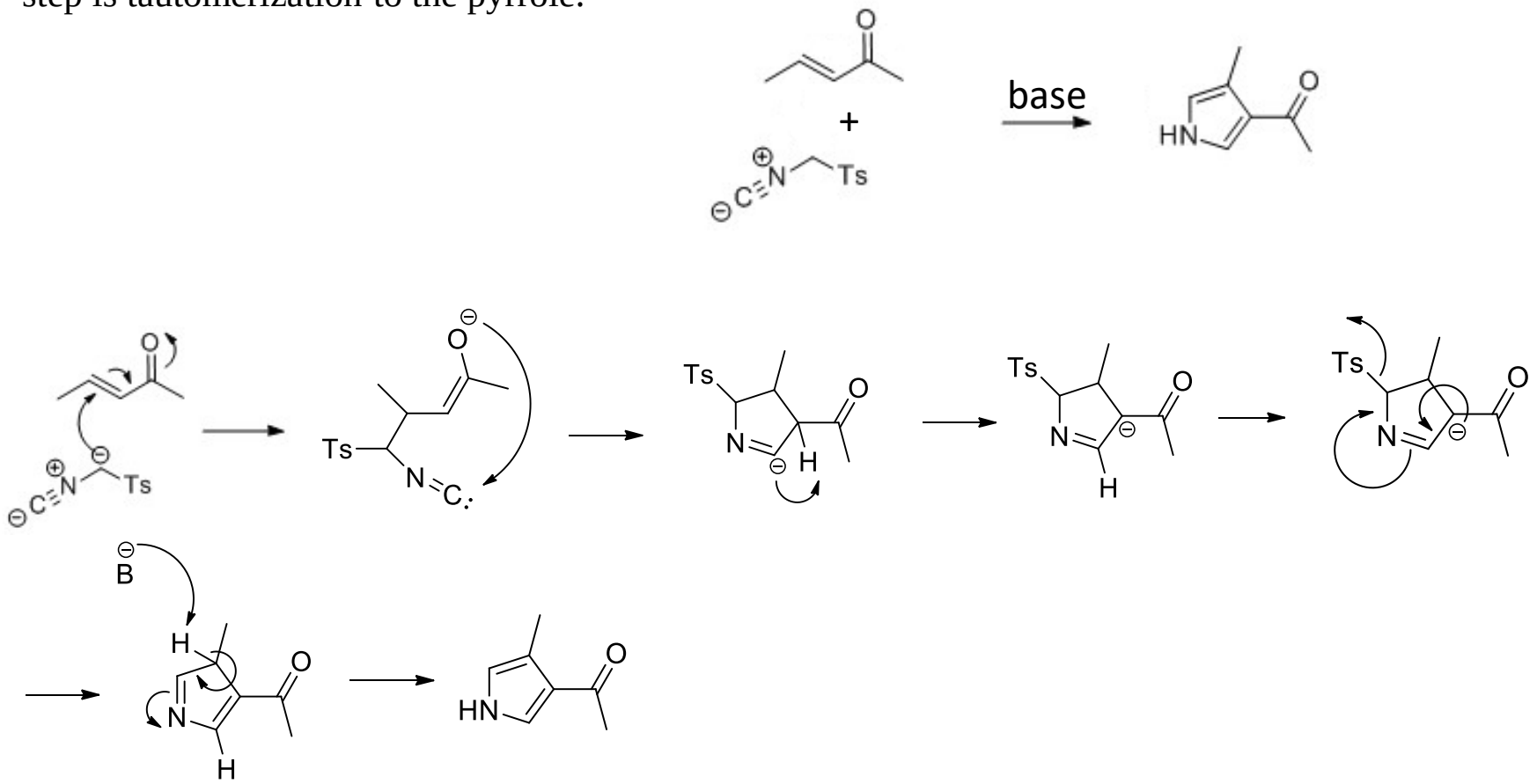
If we give a close looks on **Knorr's** and **Hantzsch synthesis** of pyrrole derv. it may be concluded that the two methods are complementary of each other to give properly substituted pyrrole derv.



More about pyrrole synthesis……

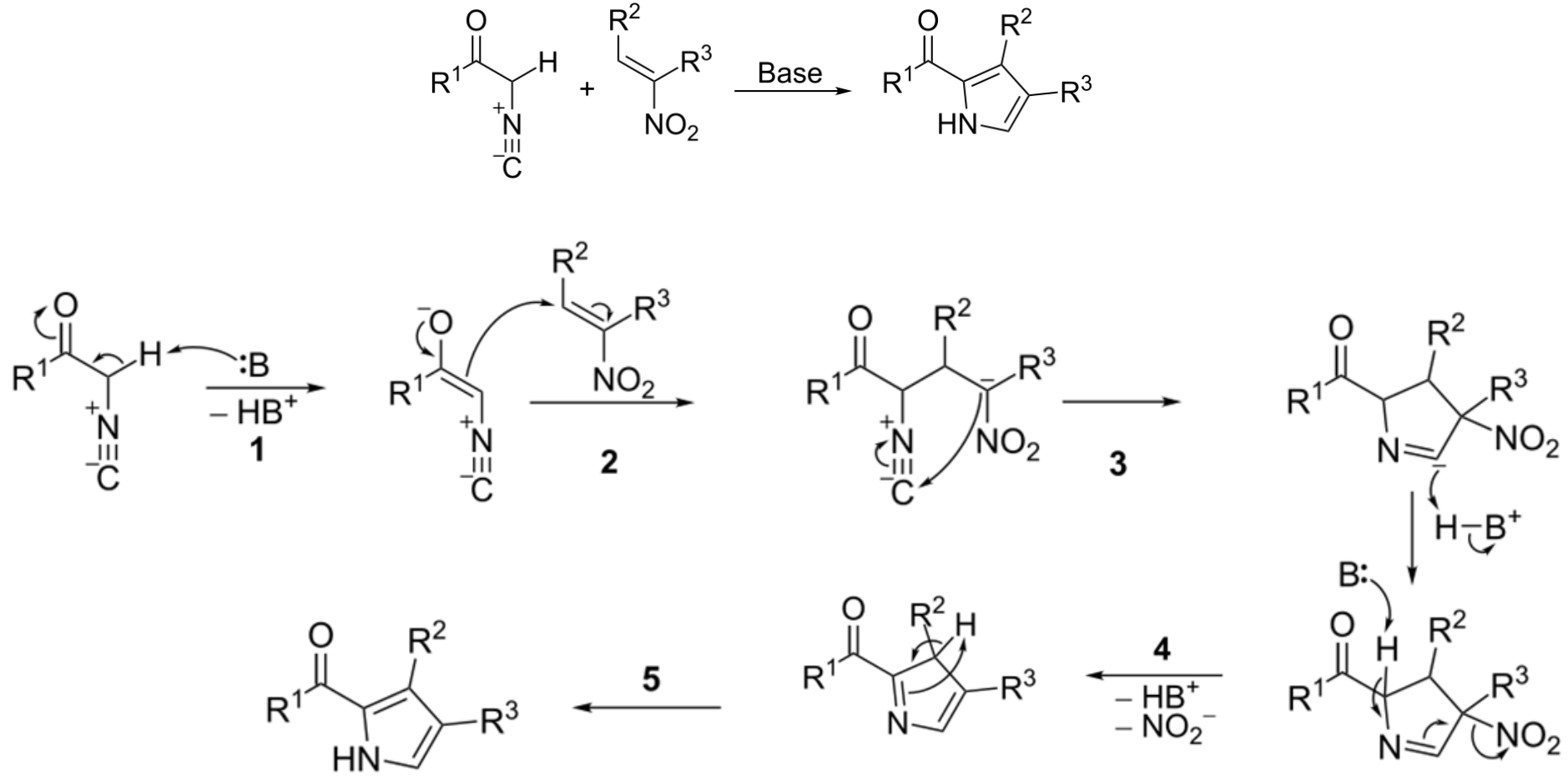
4. Van Leusen reaction

The Van Leusen reaction can be used to form pyrroles, by reaction of tosylmethyl isocyanide (TosMIC) with an enone in the presence of base, in a Michael addition. A 5-*endo* cyclization then forms the 5-membered ring, which reacts to eliminate the tosyl group. The last step is tautomerization to the pyrrole.

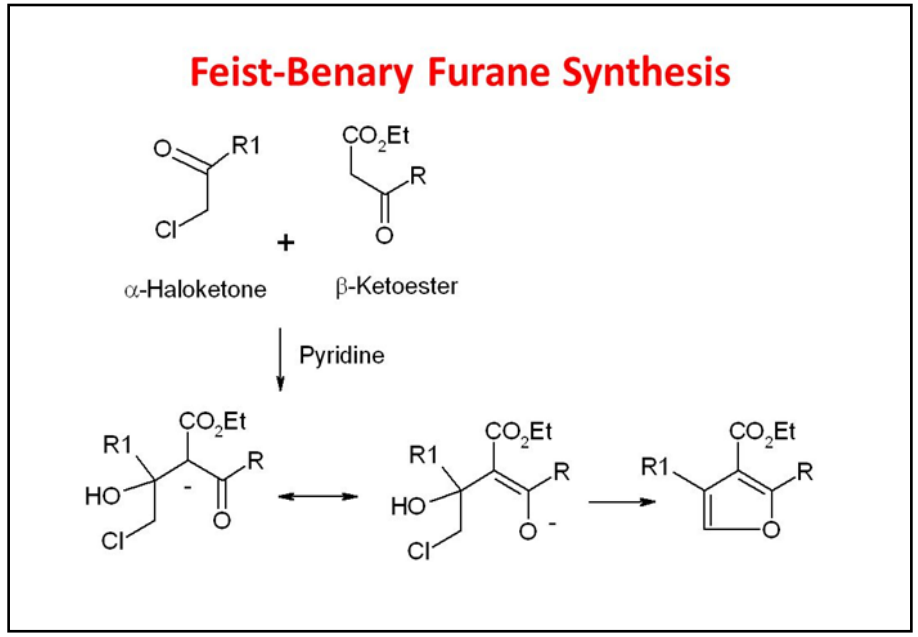


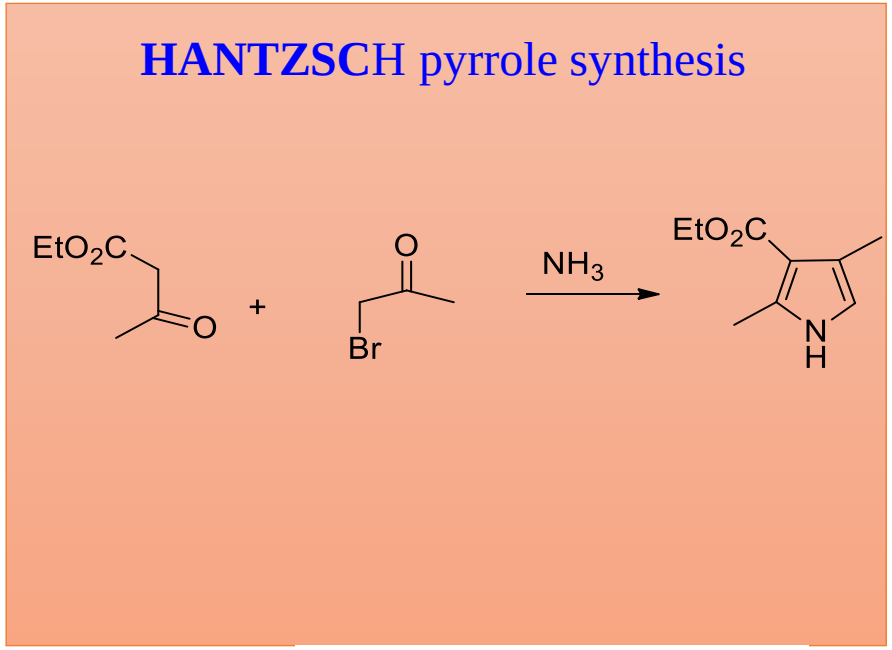
5. Barton–Zard synthesis

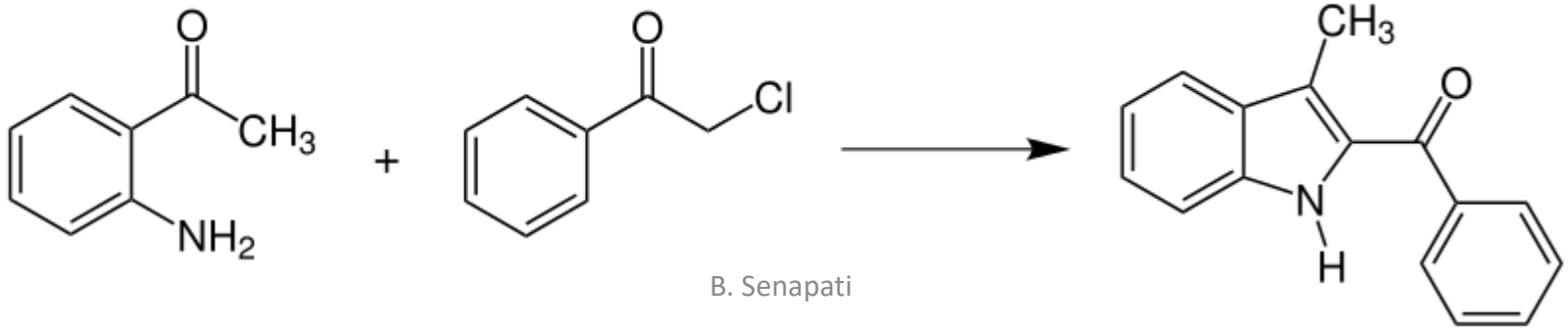
The Barton–Zard synthesis proceeds in a manner similar to the Van Leusen synthesis. An isocyanoacetate reacts with a nitroalkene in a 1,4-addition, followed by 5-*endo-dig* cyclization, elimination of the nitro group, and tautomerization



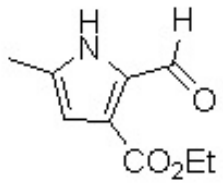
1. During Hantzsch synthesis of pyrrole, some amount of furan derivative is also obtained----- Why ?

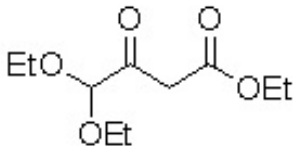


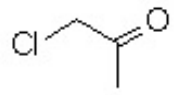


2. 

Mechanism ??

3. 

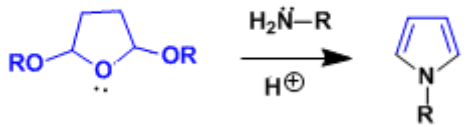

? 

+ 

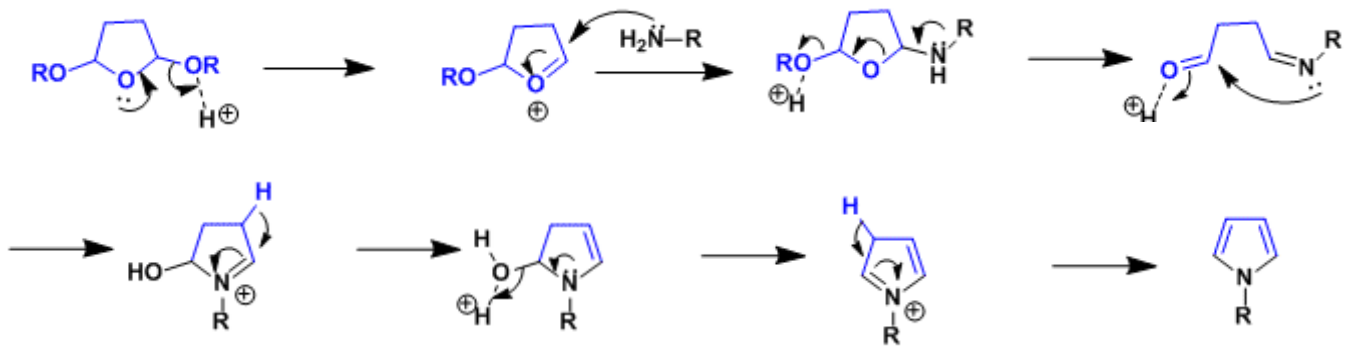
Mechanism ??

Reagents: NH_4OAc, yield 56%

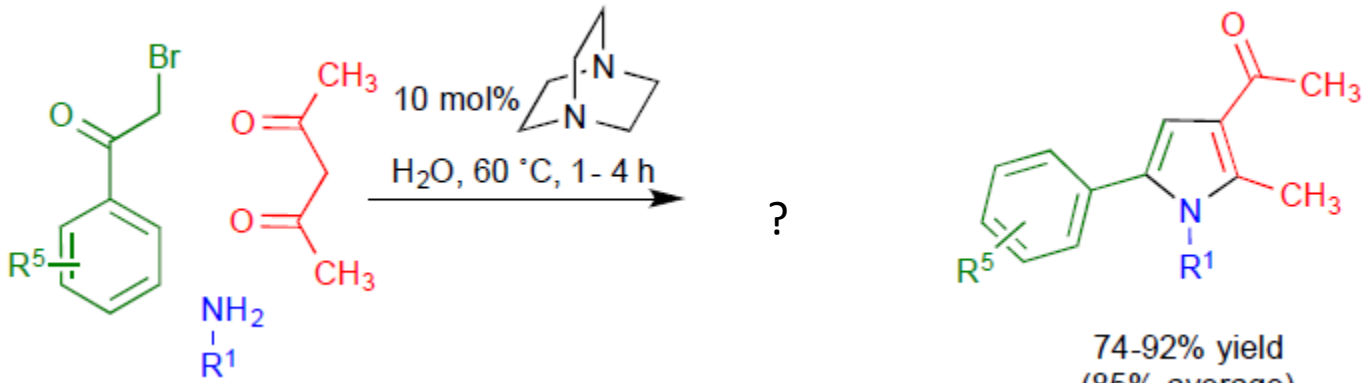
Clauson –Kaas pyrrole synthesis



Mechanism:

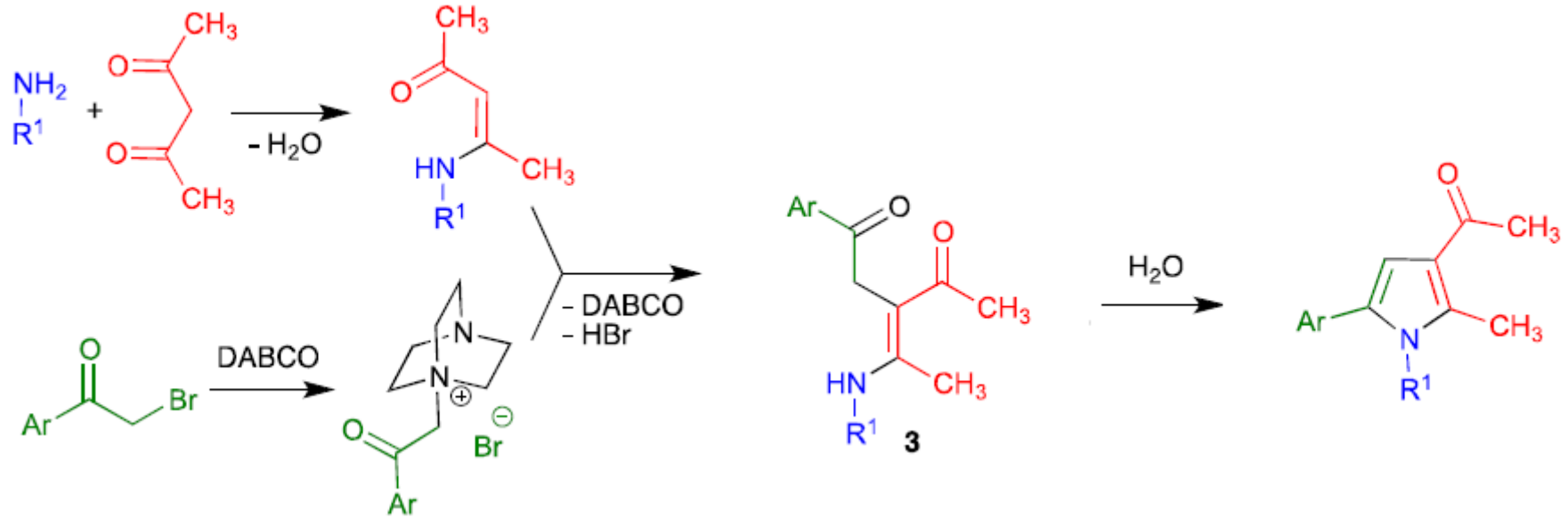


Base (DABCO) promoted Hantzsch pyrrole synthesis in water:



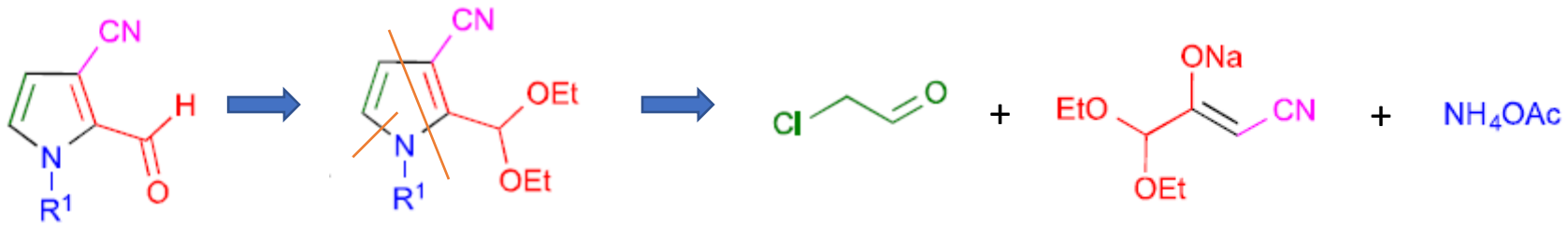
74-92% yield
(85% average)

Mechanism:

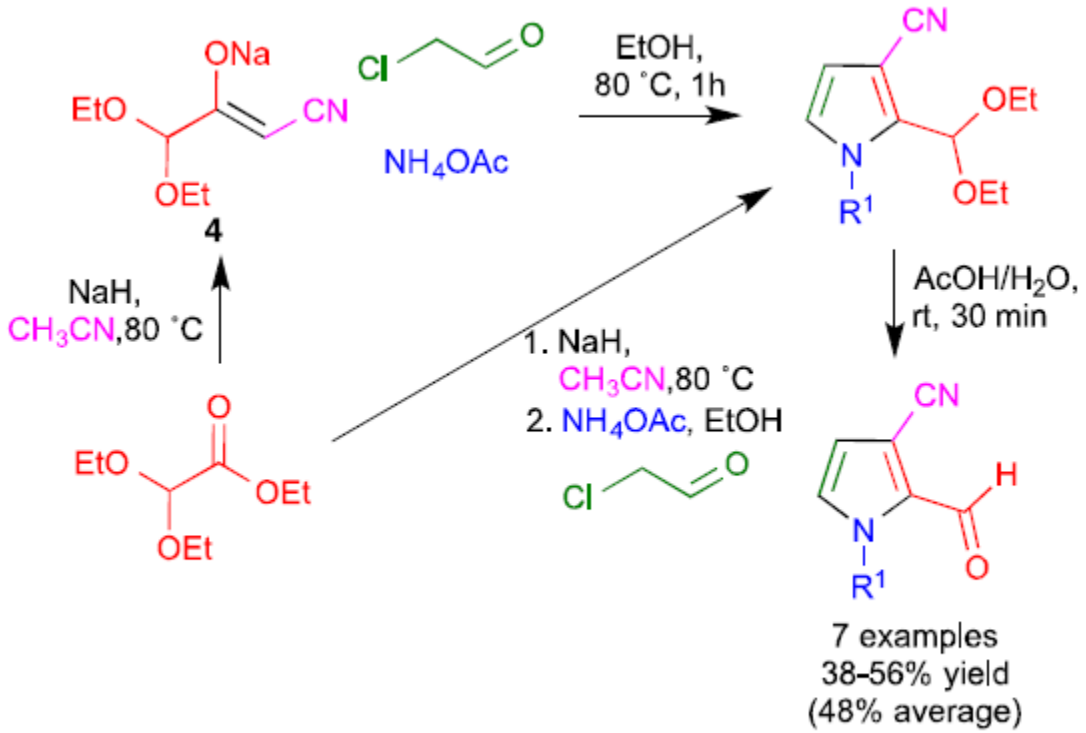


H. M. Meshram, V. M. Bangade, B. C. Reddy, G. S. Kumar and P. B. Thakur, Int. J. Org. Chem., **2012**, 2, 159

The Hantzsch synthesis has been adapted to the preparation of specific classes of pyrroles difficult to reach by alternative methods.

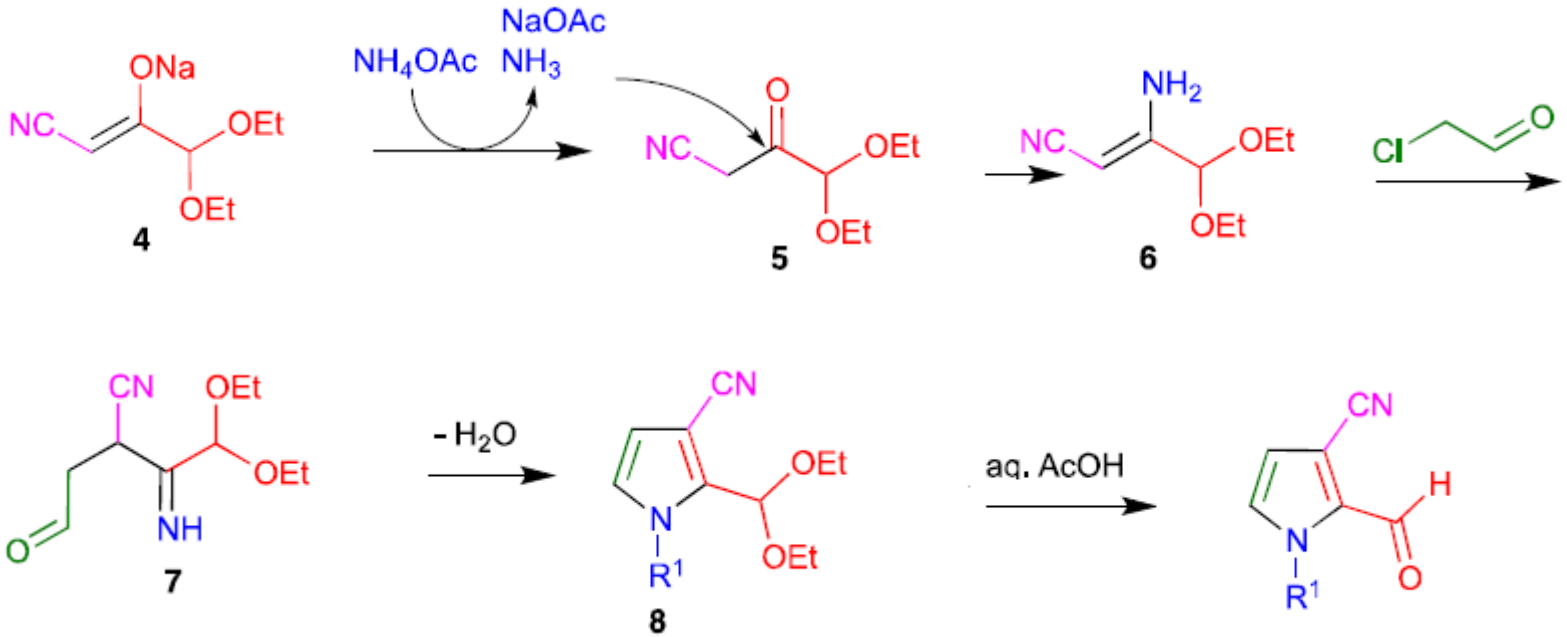


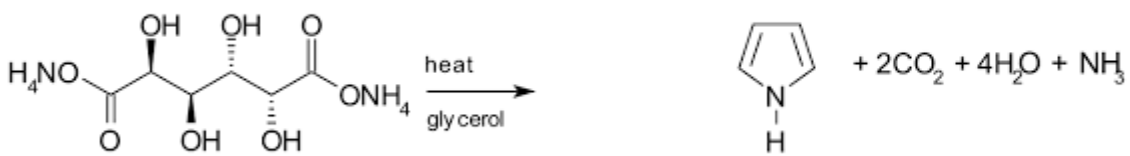
2-formyl pyrrole



T. A. Moss and T. Nowak, Tetrahedron Lett., **2012**, 53, 3056

Mechanism:





Mechanism ??