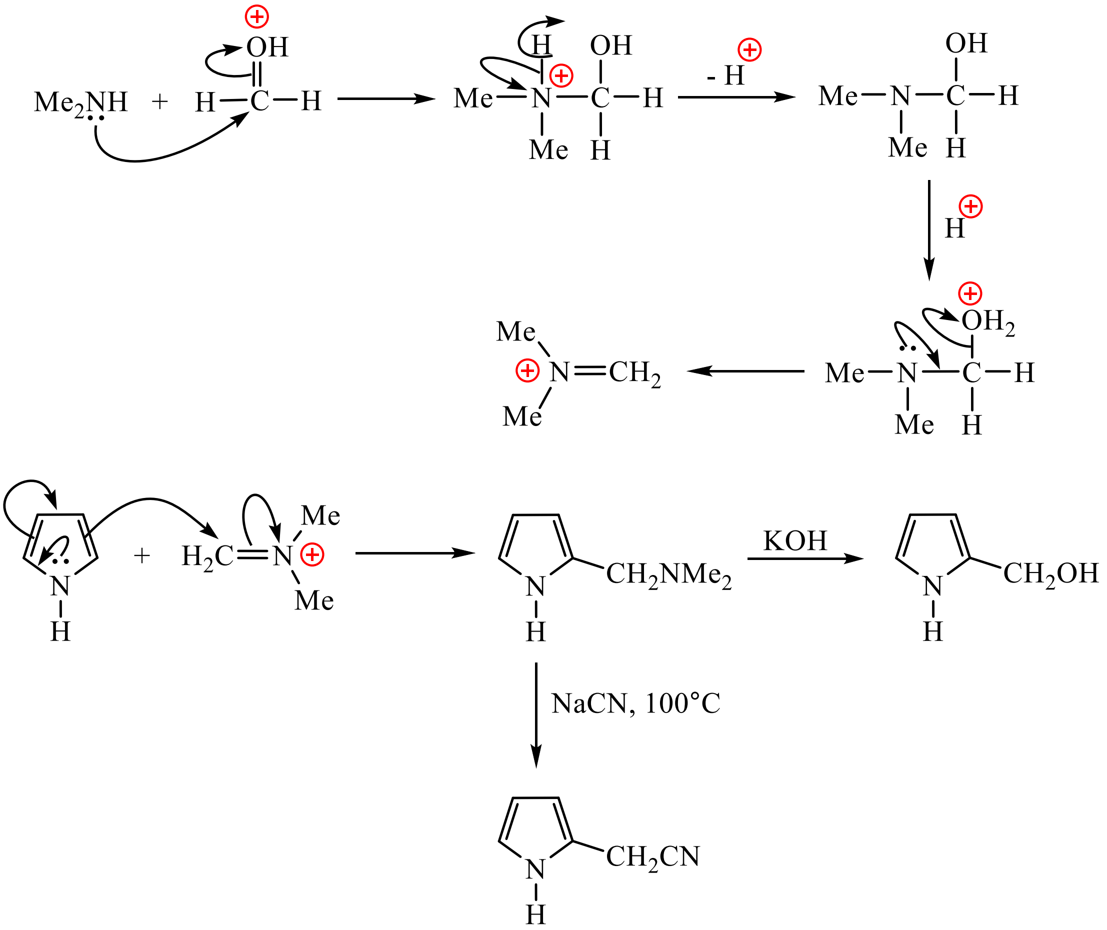
2) Mannich reaction:

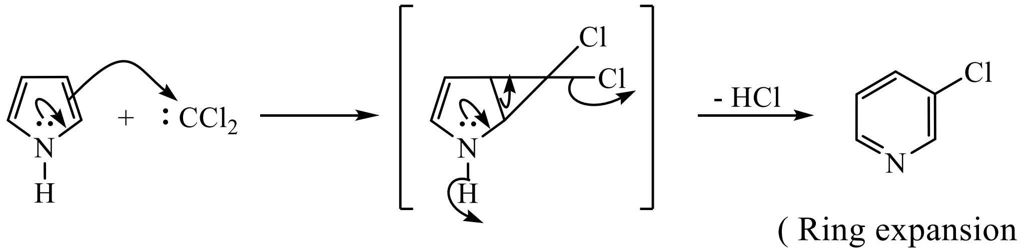
Treatement of pyrrole with formaldehyde and dimethylamine will produce pyrrole-2-methanol in the case of use of KOH, while if we use KCN, pyrrole-2-acetonitrile will formed.



3) Reimer – Tiemann reaction:

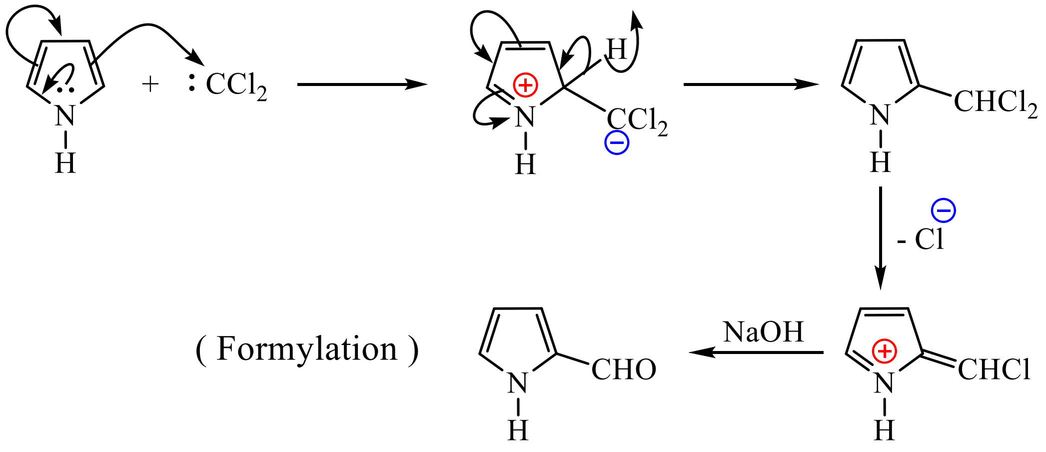
The reaction of pyrrole with chloroform in the presence of KOH (at chloroform b.p.) give a mixture of 3-chloropyridine (reaction 1) and 2-formyl pyrrole (reaction 2) as the following:

1)

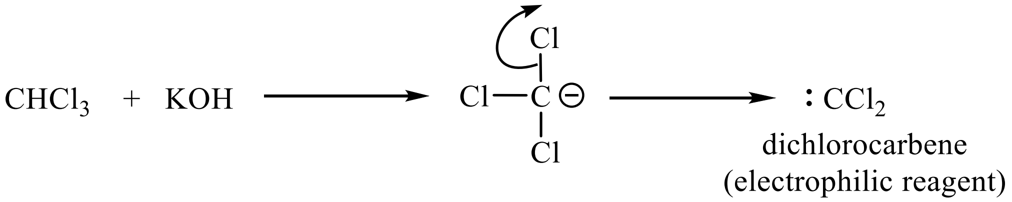


(Ring expansion)

2)



<u>Note</u>: Dichlorocarbene ($:CCl_2$) was generated from the reaction of chloroform with potassium hydroxide as the following:

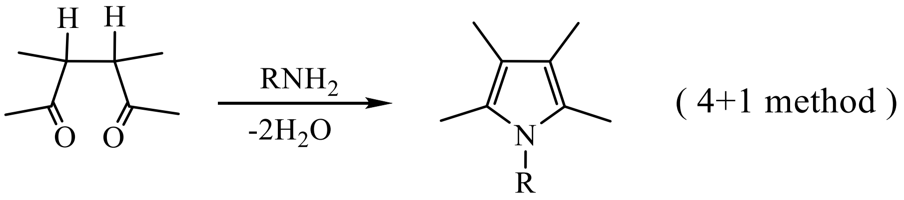


5.1.4) Synthesis of pyrrole:

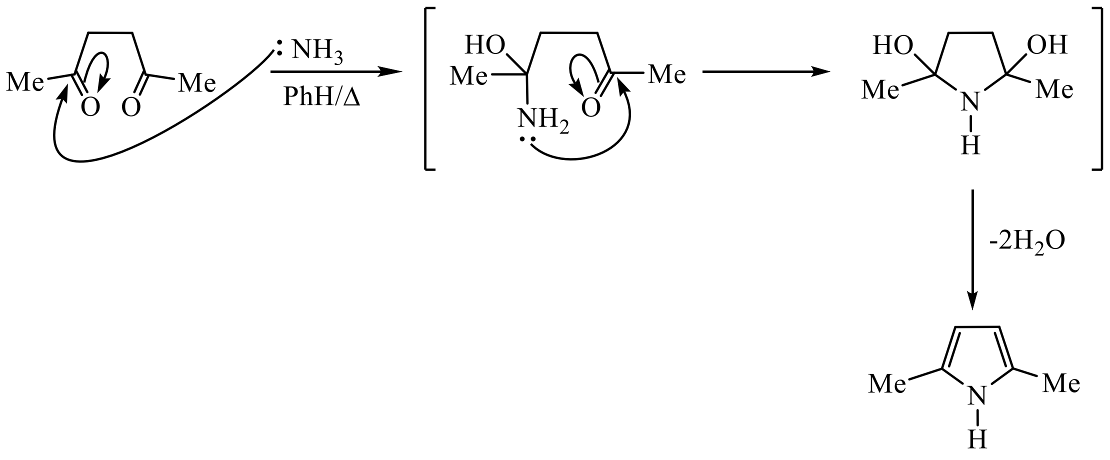
Different methods have been used to synthesize pyrrole or its derivatives from acyclic materials.

1) From 1,4-dicarbonyl compounds (Pall – Knorr synthesis):

This method involve the reaction of 1,4-dicarbonyl with ammonia or primary amines (4+1 method).



The reaction proceed through nucleophilic addition of amine at both carbonyl groups followed by loss of two water molecules. This reaction proceed in one step, without isolation of intermediates.

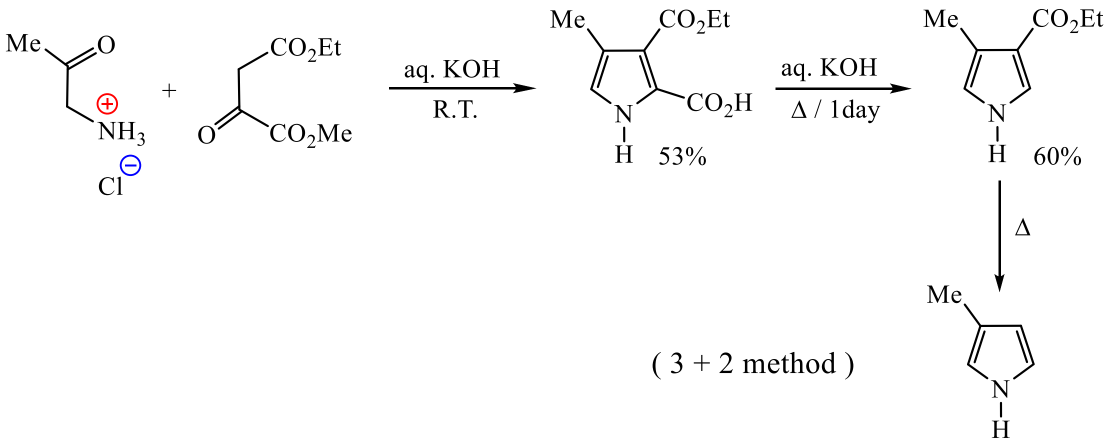


Note: The 1,4-dicarbonyl compound provide four carbon atoms while the primary amine provide the nitrogen atom.

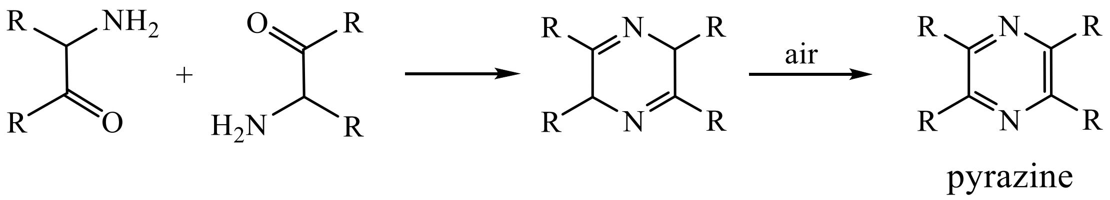
2) From α-aminocarbonyl (Knorr method):

This method is widely used to synthesize substituted pyrrole since it involve the use of two different compounds that give pyrrole with different substituents depending on starting materials.

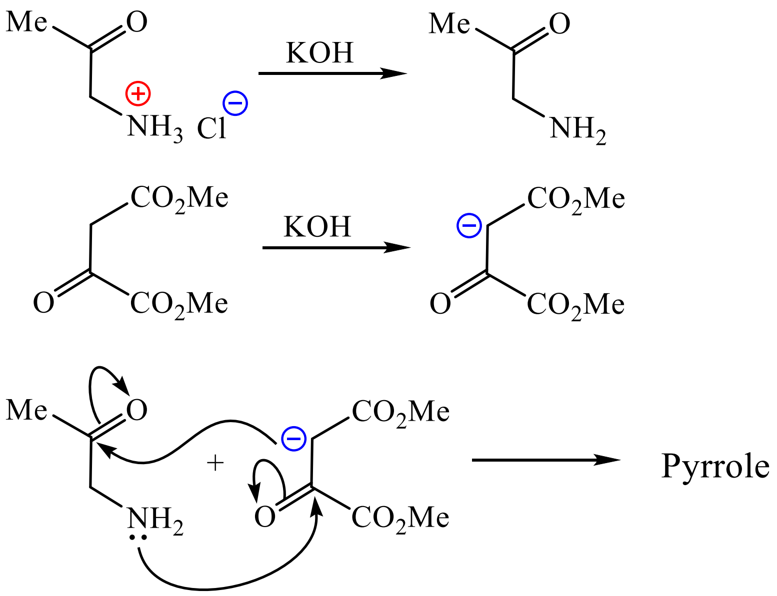
The first molecule is an α-aminocarbonyl that provide nitrogen atom and both of C2 & C3 atoms, while the second molecule is a carbonyl compound possessing α-methylene group and this provide both of C4 & C5 atoms.



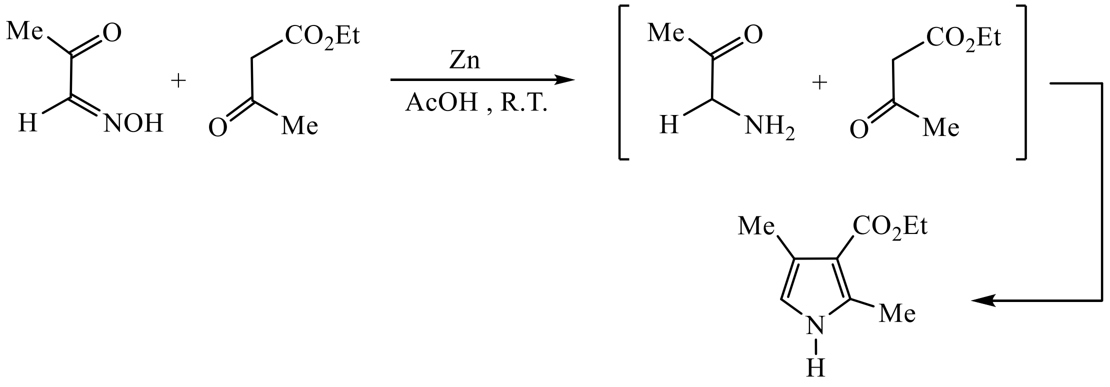
Note: α-aminocarbonyl compounds react with itself readily to form the dimer, thus they will be used as their hydrochloride salts. These salts when react with a base (KOH) will give the amine that react directly with the second molecule (α-methylene carbonyl compound) to form substituted pyrrole.



Note: The reaction proceed faster when the α-methylene carbonyl compound contain an EWG like CO_2R group.



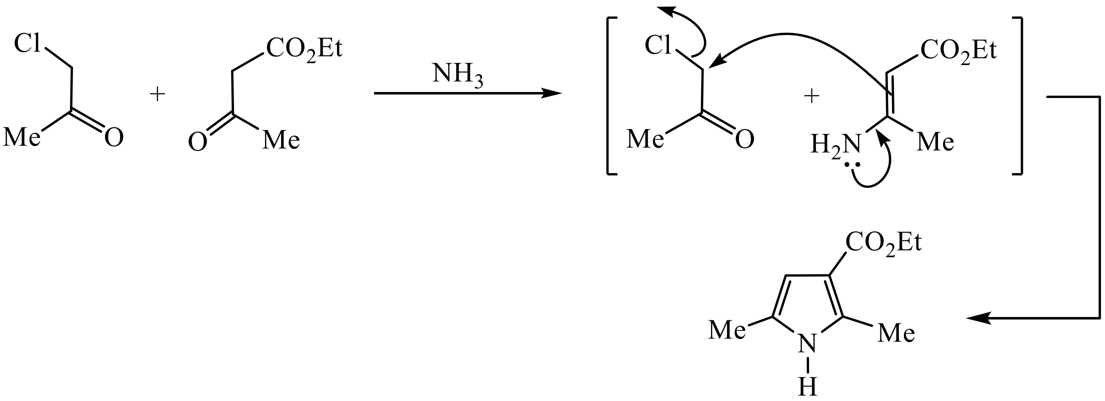
A modification for this method have been done in which the oxime was used instead of amine in the presence of zinc and acetic acid in which the oxime reduced to the proper amine then react in the same manner with the second molecule.



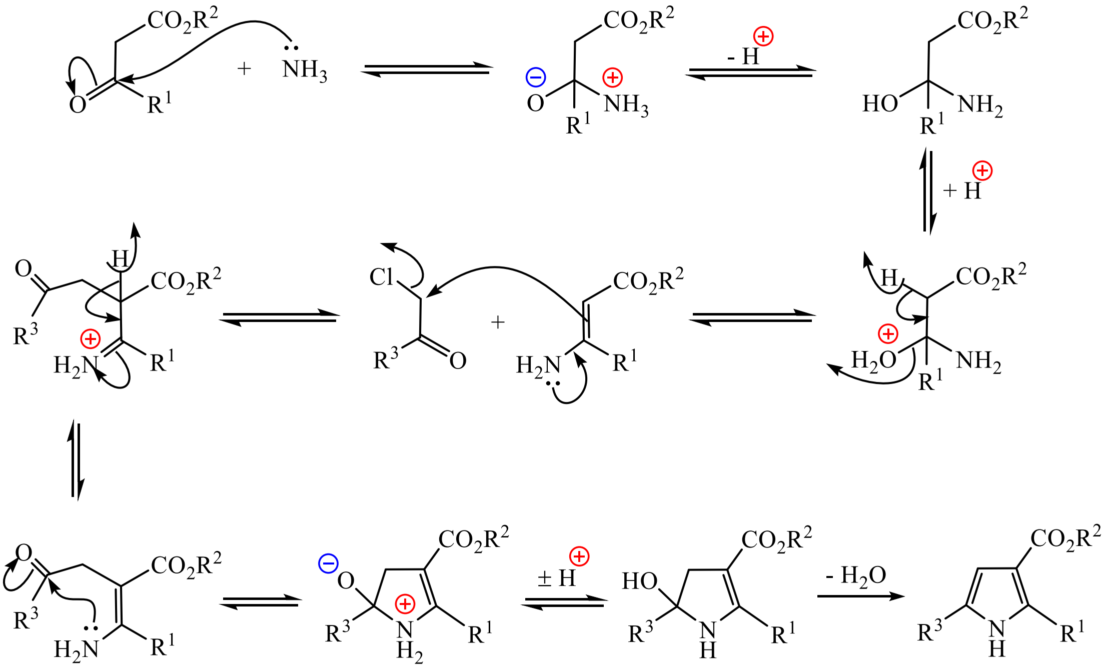
3) From α-halocarbonyl (Hantzsch method)

This method is a modified version of the Feist – Benary synthesis (that used in furan synthesis as we will see later) using the same starting materials: an α-halocarbonyl compound and a β-ketoester in the presence of ammonia.

This mean that the reaction proceed with two carbonyl compounds, one of them contain halogen atom at α-position while the other contain active methylene in the same position in the presence of ammonia.



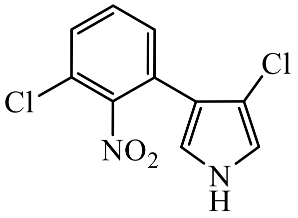
The reaction proceeds via the following mechanism:



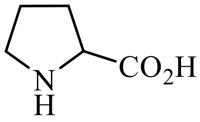
5.2) Naturally occurring pyrrole compounds:

Pyrrole itself is not naturally occurring, but many of its derivatives are found in a variety of cofactors and natural products.

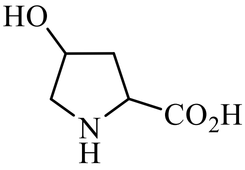
Pyrrole derivatives found in amino acids like proline and 4-hydroxyproline, furthermore pyrrole derivatives like pyrrolnitrin was used as antibiotic.



Pyrrolnitrin

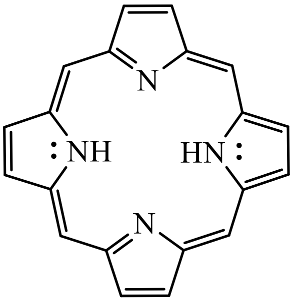


Proline



4-Hydroxy proline

Finally pyrrole found in a complicated natural products like porphyrins that consist of four pyrrole rings connected by methine group, porphyrin is the main component of heme and chlorophyll.



Porphyrin