Five-membered Heterocycles

Pyrrole, Furan and Thiophene

Heterocyclic Chemistry

- **Heterocyclic compound** is the class of cyclic organic compounds those having at least one hetero atom (i.e. atom other than carbon) in the cyclic ring system.
- The most common heteroatoms are nitrogen (**N**), oxygen (**O**) and sulphur (**S**).
- Heterocyclic compounds are frequently abundant in plants and animal products; and they are one of the important constituent of almost one half of the natural organic compounds known. Alkaloids, natural dyes, drugs, proteins, enzymes etc. are the some important class of natural heterocyclic compounds
- Based on the structural and electronic arrangement the heterocyclic compounds may be classified into two categories.
- **i.Aliphatic heterocyclic compounds**
- **ii.Aromatic heterocyclic compounds**

Heterocyclic Chemistry

- The aliphatic heterocyclic compounds are the cyclic amines, cyclic amides, cyclic ethers and cyclic thioethers.
- Aliphatic heterocycles those do not contain double bonds are called saturated heterocycles. Examples of aliphatic heterocyclic compounds are shown in figure 1.

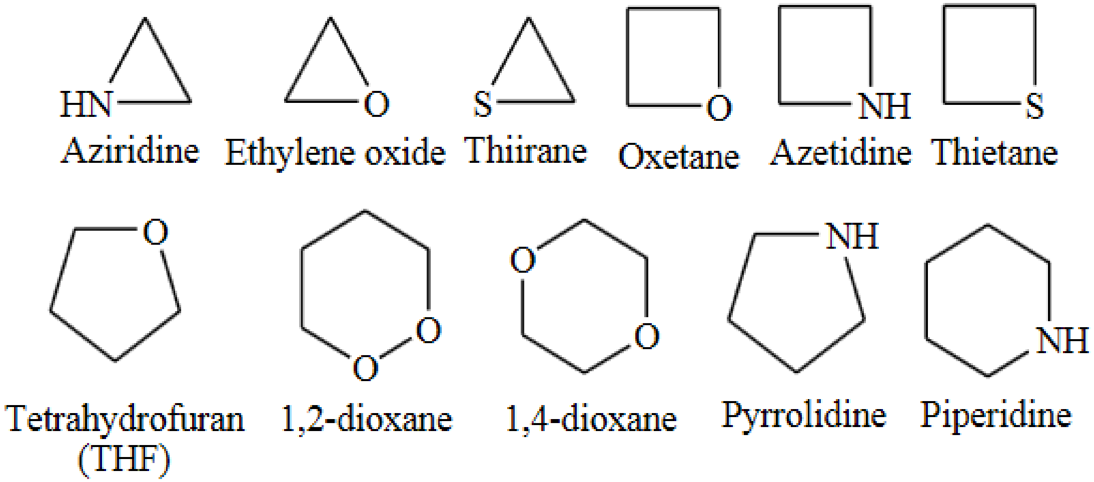


Figure 1. Examples of aliphatic heterocyclic compounds

Heterocyclic Chemistry

- However, aromatic heterocyclic compounds are similars of benzene. The aromatic heterocyclic compounds also follow the Huckel’s rule. According to Huckel’s rule an aromatic compounds must be cyclic in nature with planar geometry due to conjugate double bonds and must have $(4n+2)\pi$ electrons. Examples of aromatic heterocyclic compounds are shown in figure 2.

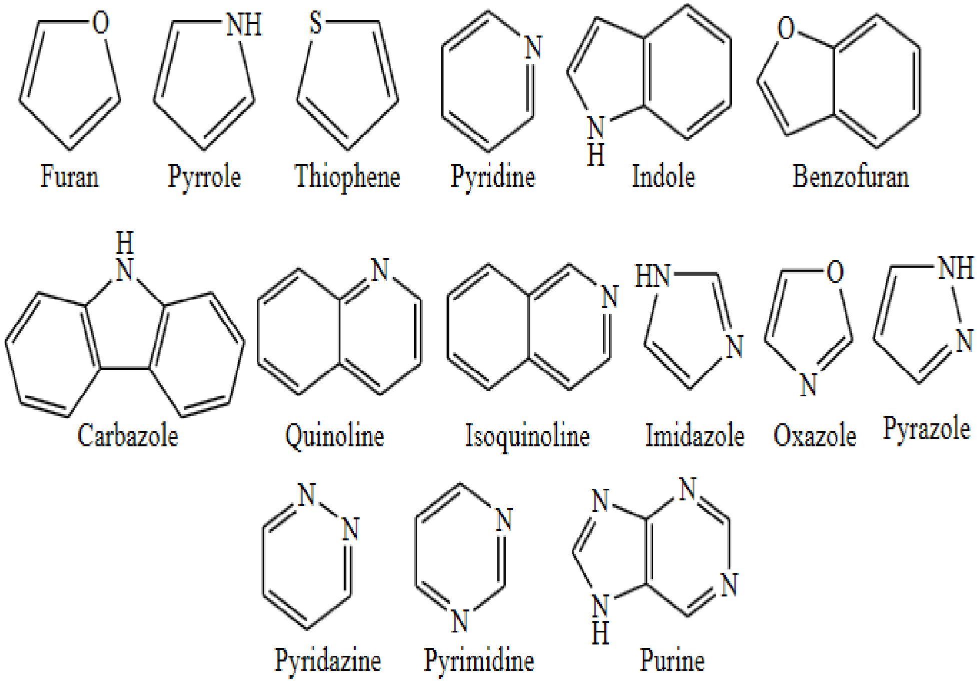
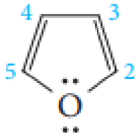


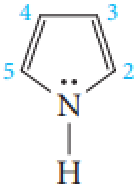
Figure 2. Examples of aromatic heterocyclic compounds

Five Membered Heterocycles-Introduction

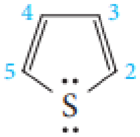
- The main reason for the study of pyrrole came from the work on the structure of hemoglobin, the blood respiratory pigment, and the chlorophyll; the green photosynthetic pigment of plants.
- Thiophen does occur in plants in association with polyacetylenes with which they are biogenetically closely linked.
- Furan occurs widely in secondary plant metabolites, especially in terpenoids.
- Unsubstituted pyrrole, furan, and thiophene are usually obtained from petroleum.



furan
(bp 32°C)



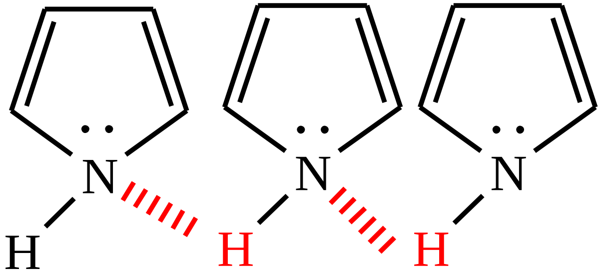
pyrrole
(bp 131°C)



thiophene
(bp 84°C)

General Characteristics

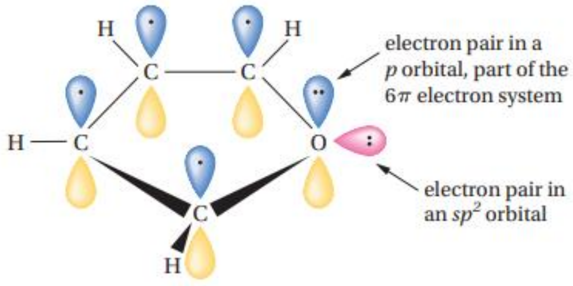
- Pyrrole, thiophene and furan are colorless liquids of boiling points 131º, 84º and 32º respectively.
- Pyrrole has a relatively high boiling point as compared to furan and thiophene, this is due to the presence of intermolecular hydrogen bonding in pyrrole.



Structure and Aromaticity

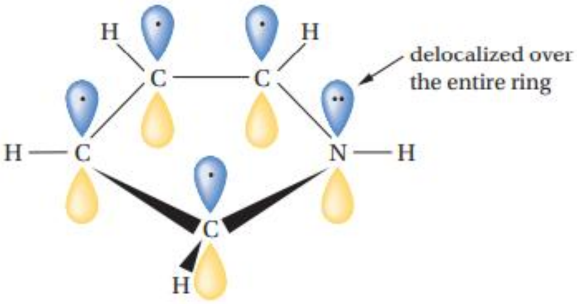
- Pyrrole, furan and thiophene are aromatic because:

1) They fulfill the criteria for aromaticity, the extent of delocalization of the nonbonding electron pair is decisive for the aromaticity, thus the grading of aromaticity is in the order of: furan < pyrrole < thiophene < benzene this order is consistent with the order of electronegativity values for oxygen (3.44), nitrogen (3.04) and thiophene (2.56).



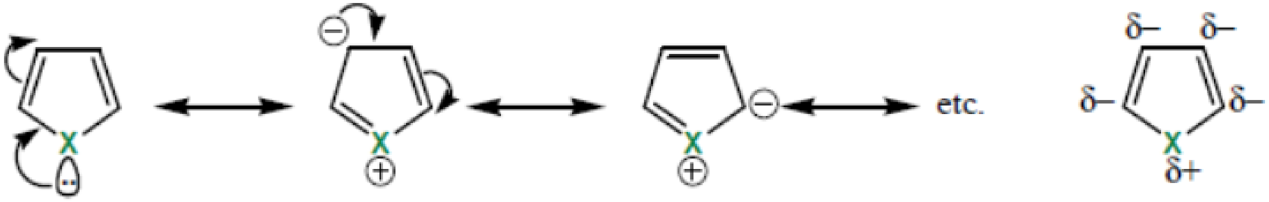
electron pair in a *p* orbital, part of the 6π electron system

electron pair in an sp^2 orbital



delocalized over the entire ring

2) They tend to react by electrophilic substitution due appearance of –ve charge on carbon atoms due to delocalization as shown in the following resonance structures.



Structure and Aromaticity

- The **order of aromatic character** of these three heterocycles compared to benzene is as follows:

Benzene > Thiophene > pyrrole > Furan

This order is consistent with the *resonance Energies and* order of the electronegativity values.

- In comparison to benzene the order of reactivity in **electrophilic substitution** is as follows:

Pyrrole > Furan > Thiophene > Benzene

- Eelectrophilic substitution on furan requires very mild non acidic conditions (acids may induce polymerization or ring opening), however, for thiophene the acidity is less critical since it is stable to aqueous minral acids but not to 100 % strong acids or Lewis acids such as $AlCl_3$.

- Regioselectivity: The 2 & 5 (α) positions are more reactive than 3 & 4 (β) Positions, as in pyrrole the intermediate results from electrophilic attack at C2 can be stabillized by three resonance structure while the intermaediate results from the attack C3 is only satbilized by two resonance structures.

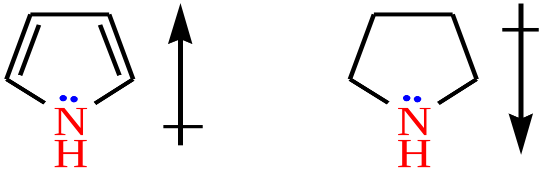
Evidences of aromatic character in pyrrole

1) All ring bonds are intermediates between single and double bonds.

2) It tends to react by electrophilic substitution.

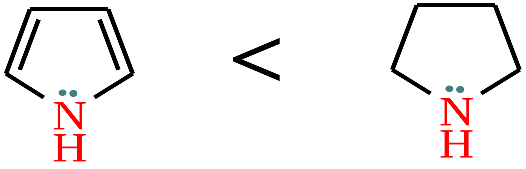
3) Its exceptional lack of basicity and strong acidity as a secondary amine compared to the aliphatic analog (pyrrolidine). This can be explained on the basis of participation of N lone pair in aromatic sextet (see the previous resonance structures) thus the dipole moment of pyrrole compared with pyrolidine is reverted and thus protonation occurs at carbons not at N.

Dipole monent of pyrrole and its saturated analog



Pyrrole **Pyrrolidine**

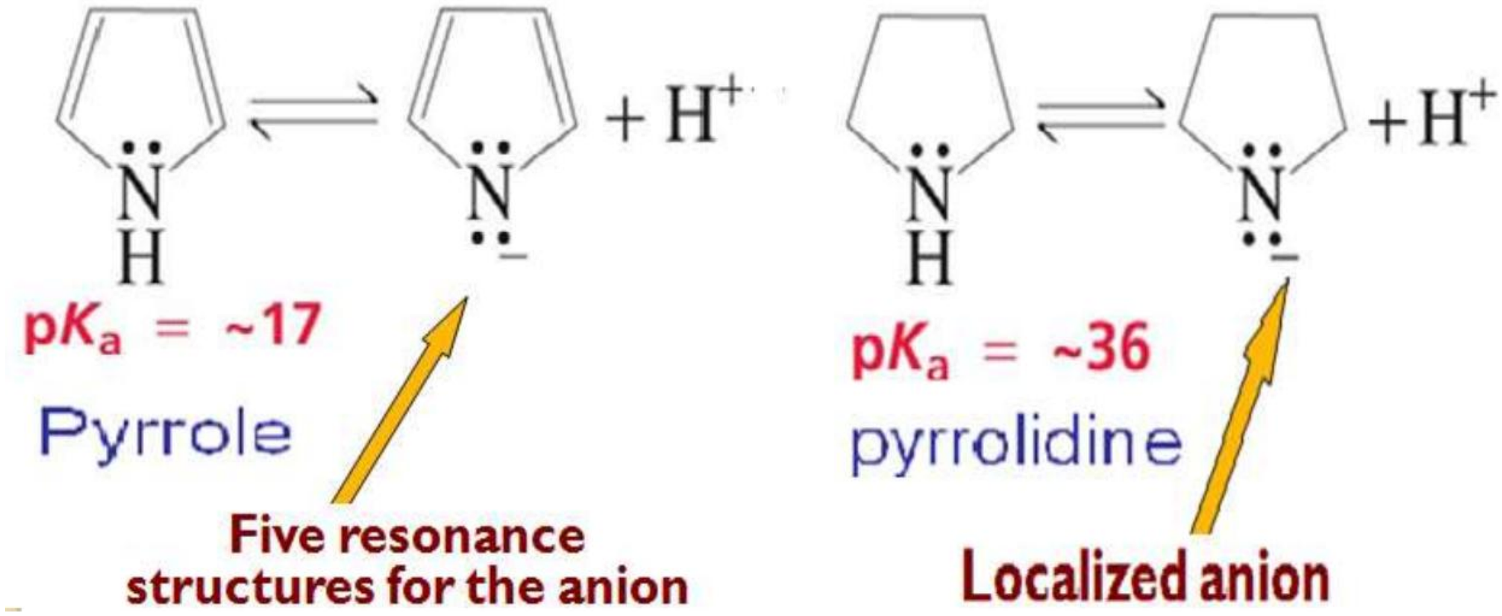
Basicity of pyrrole and its saturated analog



Pyrrole
aroamtic 2° amine

Pyrrolidin
Aliphatic 2° amine

- **Pyrrole is more acidic than pyrrolidine because of stabilization of its conjugated base by resonance**



pK_a = ~17

Pyrrole

Five resonance structures for the anion

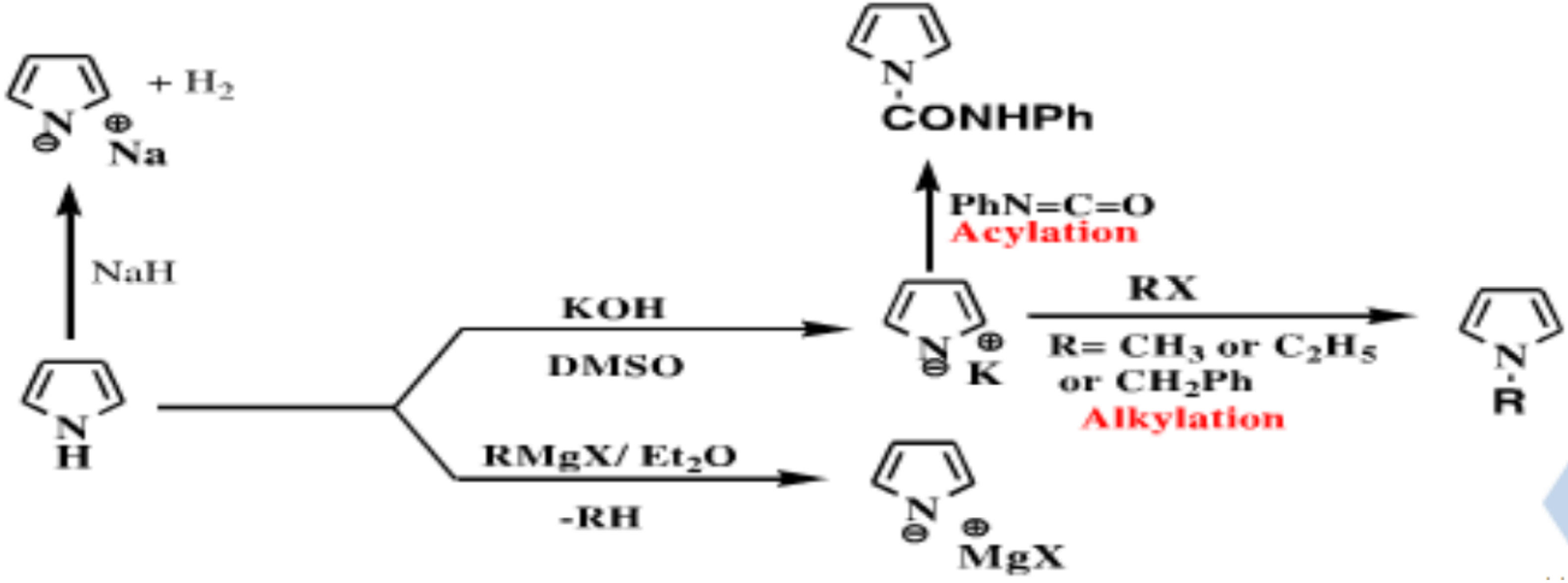
pK_a = ~36

pyrrolidine

Localized anion

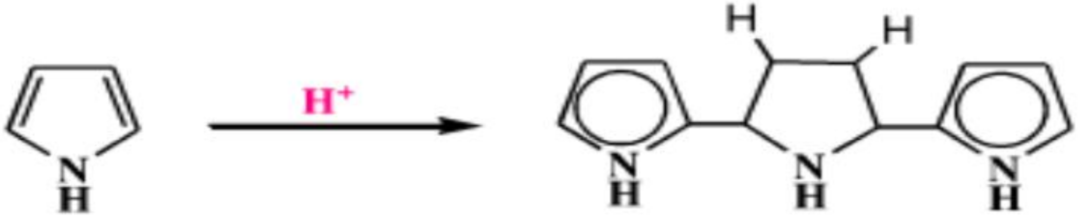
Acidic property of pyrrole:

- Due to participation of N lone pair in aromaticity),(it can loss the hydrogen attached with NITROGEN when reacting with any base) pyrrole has exceptionally strong acidic properties for a secondary amine for instance it can react with strong bases or Grignard reagent or potassium metal in inert solvents, and with sodium amide in liquid ammonia, to give salt-like compounds which can be used to alkylate or acylate the nitrogen atom as shown below:

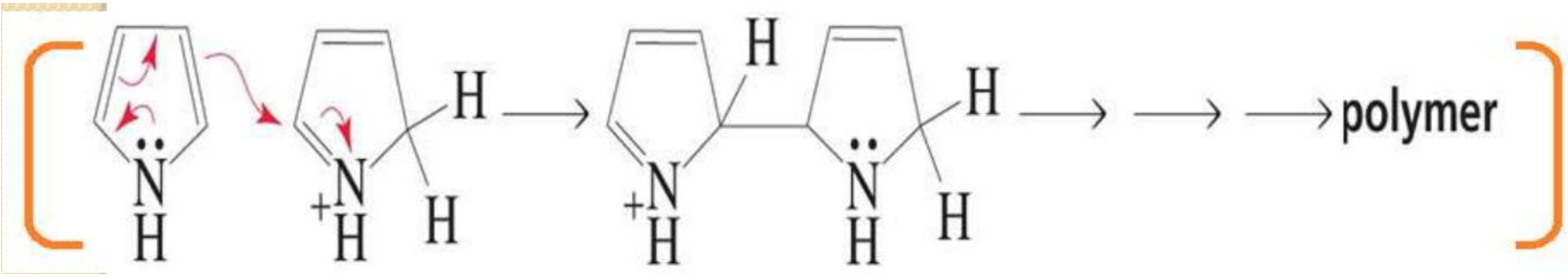


Sensitivity toward strong acids:

- Pyrrole is sensitive (unstable) towards strong acids. This is due to protonation occur at one of the carbon & the resulting protonated molecule will add to another unprotonated pyrrole molecule this continues until a pyrrole trimer is formed. (pyrrole polymerizes)
- The reaction is considered as electrophilic addition of pyrrole.



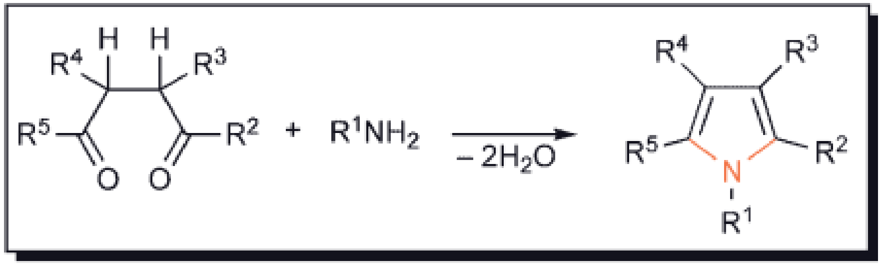
pyrrole trimer

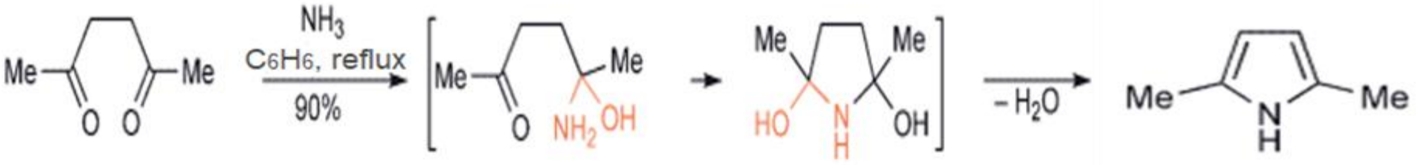


Synthesis of Pyrrole, Furan and Thiophene

1) From 1,4-dicarbonyl compounds (Paal-Knorr Synthesis)

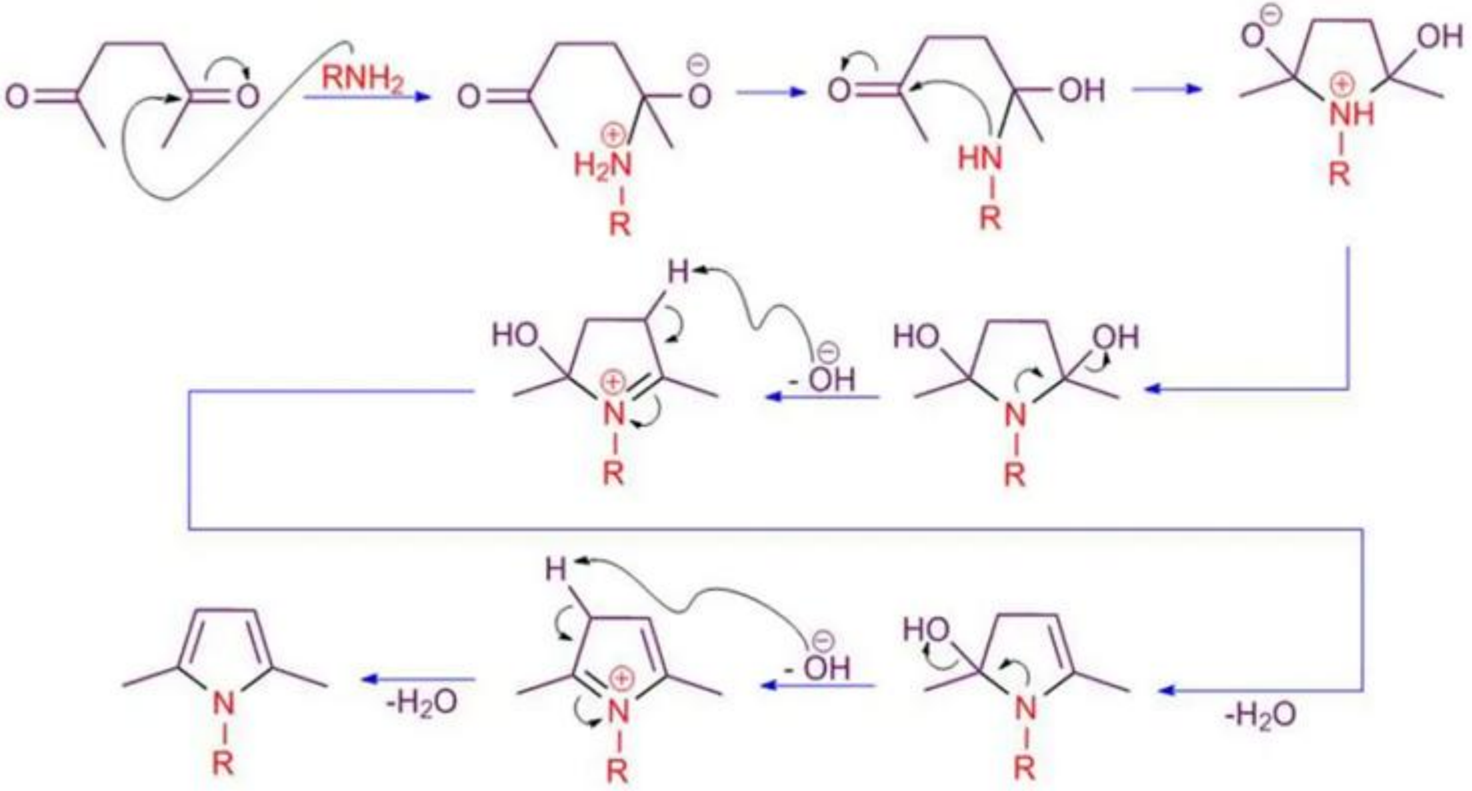
Pyrrol: 1,4-Dicarbonyl compounds can be dehydrated, with ammonia (NH_3) or amines, to form pyrrole.





Mechanism of paal - knorr synthesis:

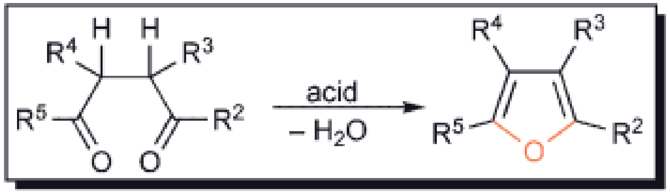
Nucleophilic addition of the amine nitrogen to each of the two carbon atoms, imine formation and the dehydration represent the course of the synthesis.

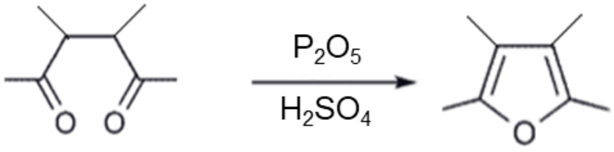


RNH$_2$
O
H_2N
R
OH
HN
NH
- OH
HO
H
N
-H$_2$O

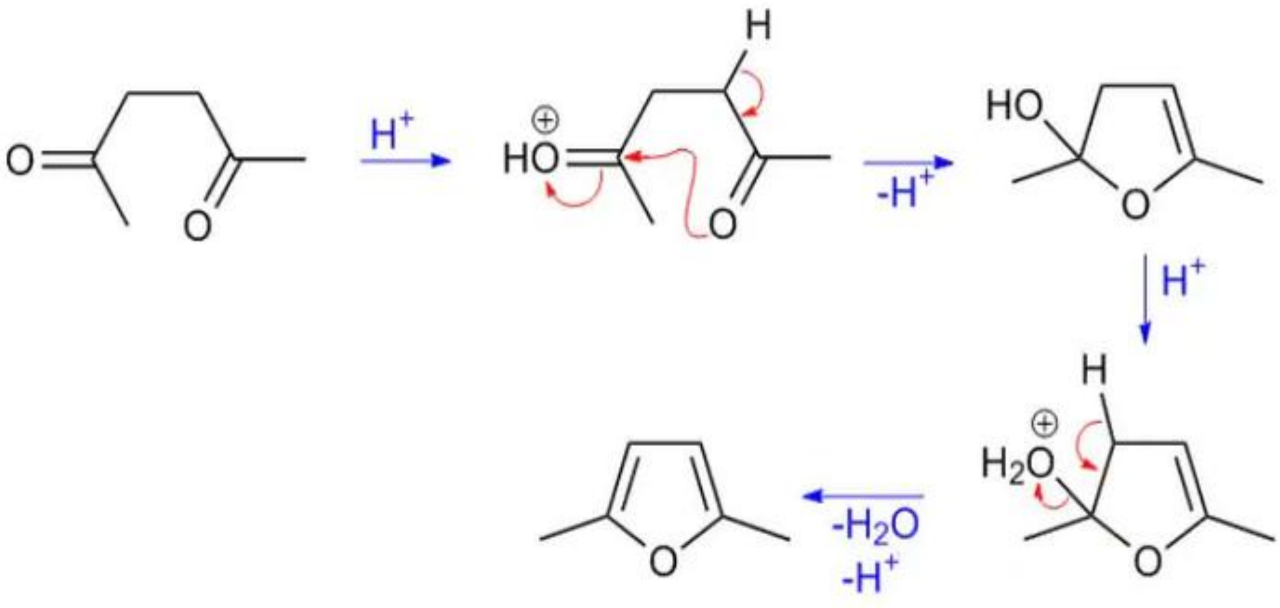
Synthesis of Pyrrole, Furan and Thiophene

Furan: 1,4-Dicarbonyl compounds can be dehydrated, with acids, to form furans.



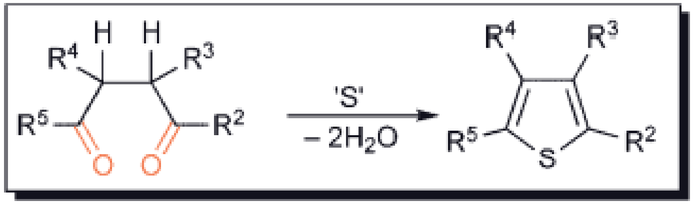


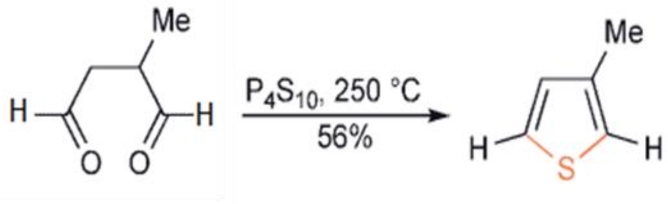
Mechanism



Synthesis of Pyrrole, Furan and Thiophene

Thiophene: 1,4 - Dicarbonyl compound with a source of sulfide, traditionally phosphorus sulfides, to form thiophenes.





Mechanism