

Paper -1Heterocyclic Compounds

→ Classification, molecular orbital picture and aromatic character of furan, thiophene, pyrrole & pyridine,
Synthesis of following Compounds

① Furan and pyrrole from 1,4 diketones

② Pyridine by Hantzsch Synthesis.

→ Electrophilic substitution reactions of pyrrole, furan and pyridine (chlorination and nitration).

→ Comparison of basicities of pyridine, piperidine and pyrrole.

Alkaloids

→ Definition, Source, classification & general characteristics, Hofmann exhaustive methylation with pyridine as an example.

→ Isolation, Constitution & Confirmation by Synthesis - cocaine, hygrine and nicotine.

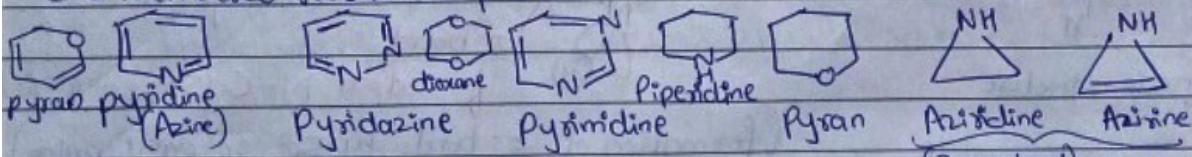
Green Chemistry

The need for green chemistry, and eco-efficiency, green methods, green products, recycling of wastes,

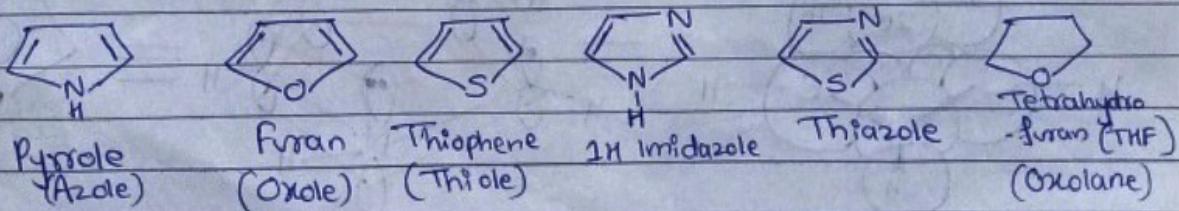
12 principles of green chemistry.

ClassificationHeterocyclic CompoundsNomenclature

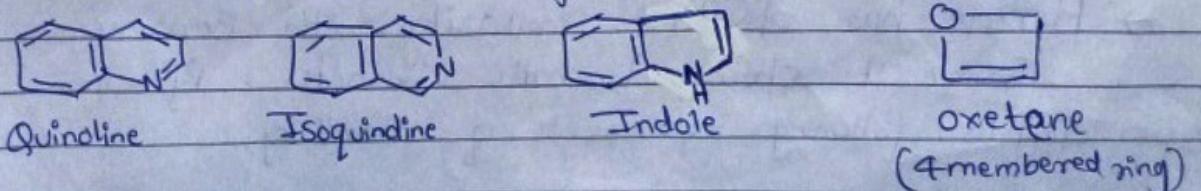
④ 6 membered HeteroCompounds



⑤ 5 membered HeteroCompounds



⑥ Fused aromatic heterocyclic Compounds

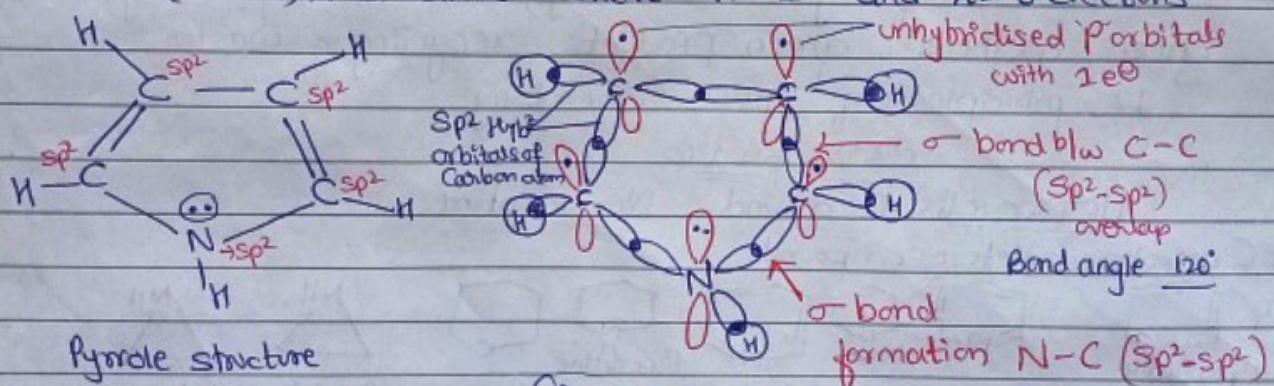


(*) Molecular orbital picture and Aromatic character of furan, Thiophene, pyrrole and pyridine.

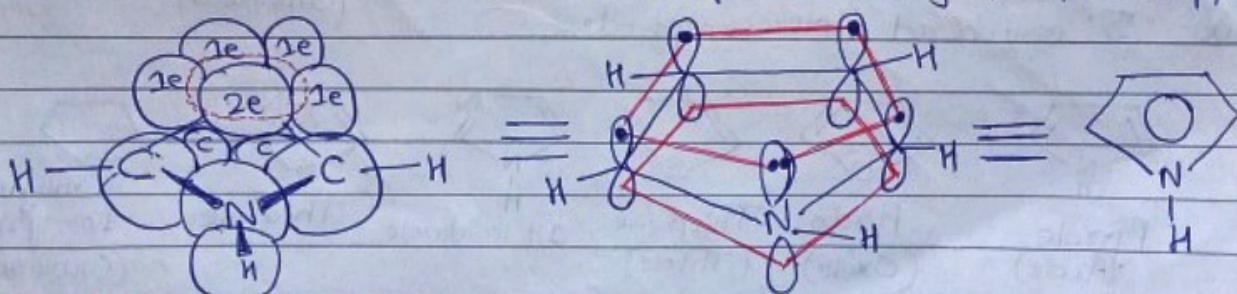
(I) Pyrrole

In Pyrrole Each atom of the ring, whether carbon or nitrogen, is held by a σ -bond to three other atoms. In forming these bonds, the atom uses three sp^2 orbitals, which lie in a plane and are 120° apart.

After contributing one electron to each σ -bond each carbon atom of the ring has left one electron and the nitrogen atom has left two electrons, these electrons occupy 'P' orbitals. Overlap of 'P' orbitals gives rise to π -electron clouds, one above and one below the plane of the ring, the π clouds contain a total of 6 electrons, the aromatic sextet and follow the Hückel rule for aromatic compound ie $[4n+2]\pi$ electrons ($4n+2)\pi$ electrons where $n=1$ and $\pi=6$ electrons



(Formation of σ -bonds by sp^2-sp^2 overlapping)



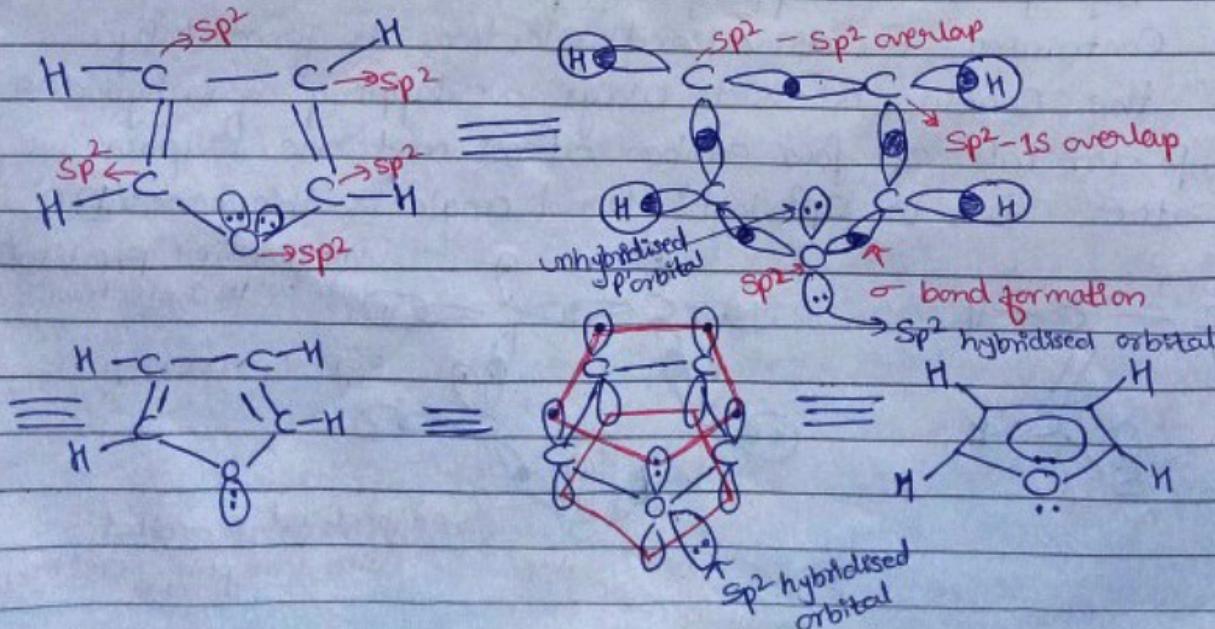
Aromaticity of pyrrole

→ Pyrrole has structural similarity with Benzene, hence it shows Aromatic character. Pyrrole fulfills following requirements of aromaticity.

- i) Pyrrole is planar Cyclic System
- ii) In pyrrole there are $(4n+2)\pi$ electrons according to Hückel's rule ($n=2$)
- iii) There is Conjugated System of π -bonds Containing Six electrons in π -molecular orbital.
- iv) Pyrrole undergoes electrophilic Substitution reactions similar to benzene.

Molecular Orbital Picture of FURAN

- Similar to pyrrole furan is also a five membered ring heterocyclic compound with hetero atom as oxygen.
- All the ring atoms are in state of sp^2 hybridisation.
In the ring C-C and C-O sigma bonds are formed by sp^2-sp^2 overlappings, C-H bonds are formed by sp^2-s overlappings, hence Sigma bond Skeleton.
- Further each Carbon atom contains one unhybridized p-orbital with unpaired electron, unhybridized p-orbital of oxygen contains a lone pair of electrons.
- Oxygen uses two sp^2 hybrid orbitals to form sigma bonds with adjacent Carbon atoms.
- Another sp^2 - hybrid orbital has a pair of electron (lone pair), unhybridized p-orbitals overlap laterally (side ways) to form π - molecular orbital having 6 delocalised electrons.



Aromaticity of furan

Furan behaves as an aromatic compound similar to pyrrole.

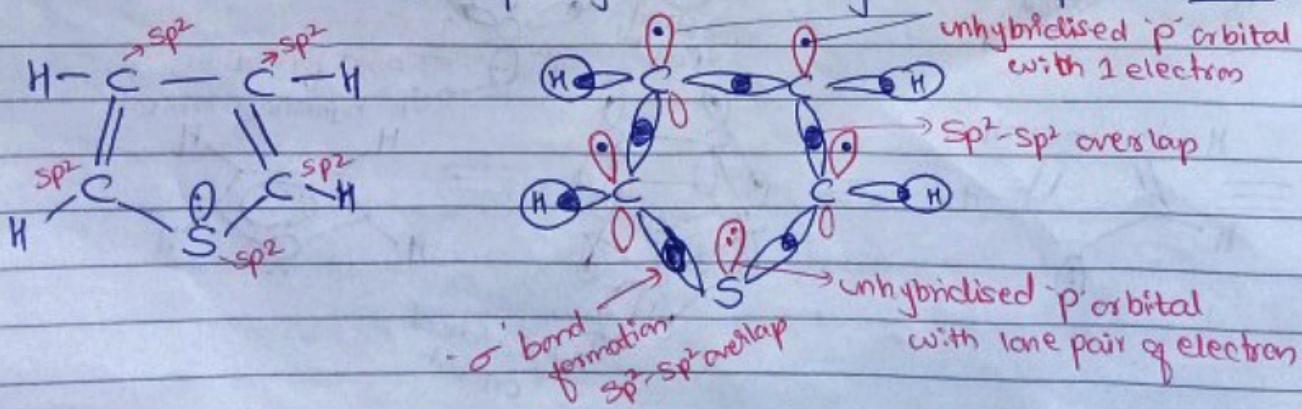
- (i) Furan has a planar cyclic system.
- (ii) There are six delocalized electrons in furan.
- (iii) Furan satisfies Hückel's rule as it contains $(4n+2)\pi$ electrons where $n=1$.
- (iv) Furan undergoes electrophilic substitution reactions like nitration, chlorination etc similar to benzene.

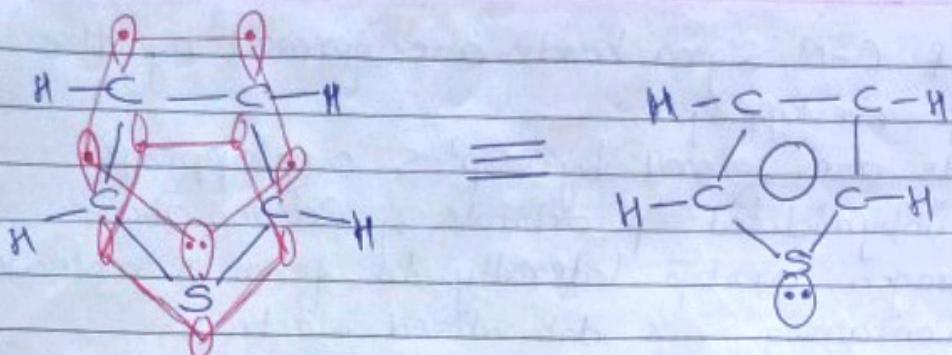
Molecular orbital Picture Thiophene

Thiophene is a five membered ring heterocyclic compound with Sulphur as heteroatom. In thiophene all the ring atoms are in a state of sp^2 hybridisation.

Four Carbon atoms contain three sp^2 hybridised orbitals and one unhybridised p-orbital each containing one unpaired electron. Sulphur atom has two sp^2 hybrid orbitals with unpaired electrons, one sp^2 hybrid orbital with a pair of electrons and unhybridised p-orbital containing a pair of electrons.

As usual unhybridised p-orbitals of carbon and sulphur atom are perpendicular to plane of hybrid orbitals. C-C & C-S sigma bonds are formed by sp^2 - sp^2 overlappings, C-H bonds are formed by sp^2 -S overlapping. A pi molecular orbital containing 6 delocalised electrons is formed by the continuous sideways overlapping of unhybridised p-orbitals of four carbon atoms and one sulphur atom. Due to sp^2 hybrid bond angle is thiophene is 120° .





Aromaticity of Thiophene

Thiophene behaves as Aromatic Compound similar to pyrrole and furan

- ① Thiophene has planar cyclic system
- ② There is π -molecular orbital containing 6-carbon delocalized electrons.
- ③ Hückel's rule is applicable in thiophene with $(4n+2)\pi$ electrons with $n=1$ & $(4n+2)\pi = 6\pi$ electrons
- ④ Thiophene also undergoes electrophilic Substitution reaction like other aromatic compounds.

Molecular orbital picture of Pyridine

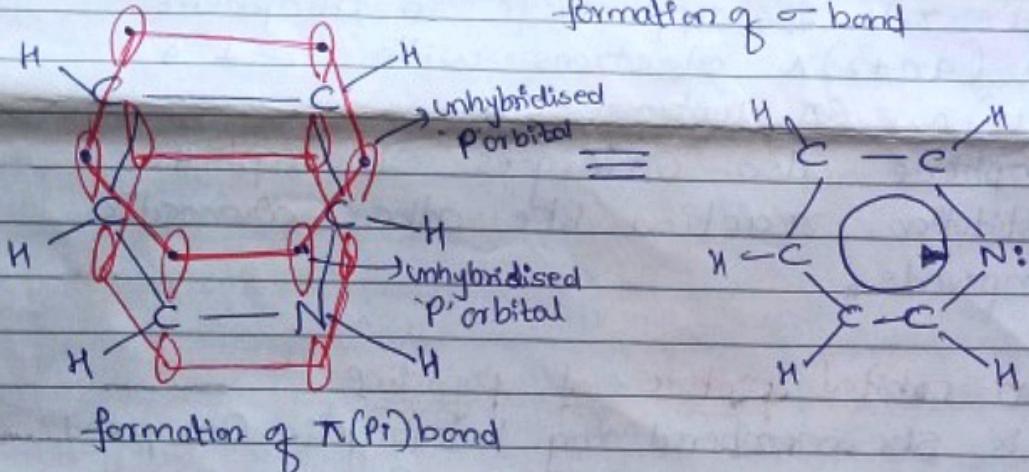
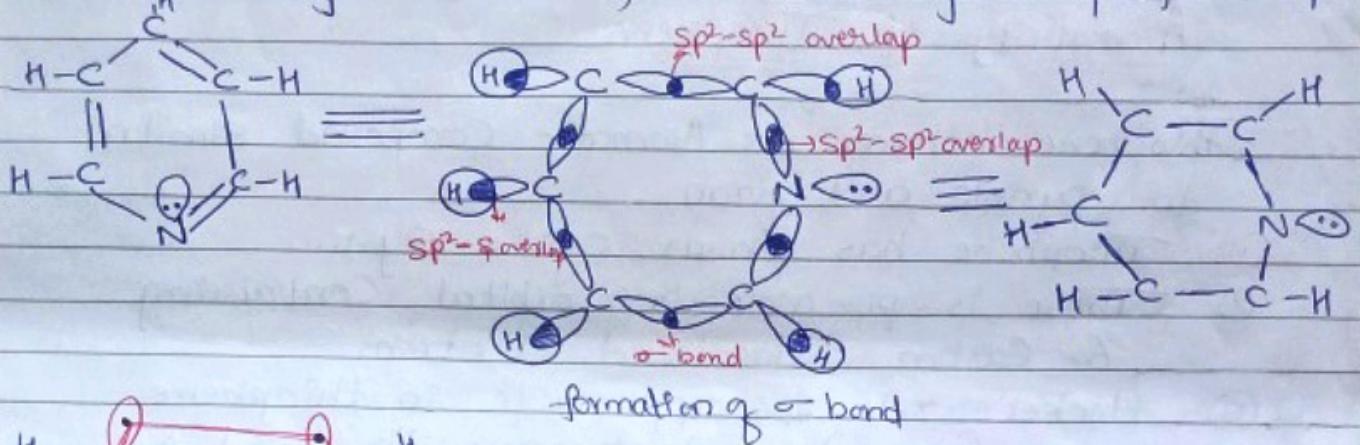
- # Pyridine is six membered ring heterocyclic Compound with hetero atom being nitrogen. Pyridine ring is planar hexagonal ring with all ring atoms in one plane. This is due to sp^2 hybridisation of all the five Carbon atoms and nitrogen atom.
- # As Every carbon atom contains three sp^2 hybrid orbitals, each of these orbitals contain one unpaired electron.
- # In nitrogen atom out of three sp^2 hybrid orbitals two sp^2 hybrid orbitals contain one unpaired electron and another sp^2 hybrid orbital has a lone pair of electrons.
- # Unhybridised P-orbital with an unpaired electron lies perpendicular to the plane of hybrid orbitals.

All C-C & C-N Sigma bonds are formed by the $sp^2 - sp^2$ overlappings.

C-H bonds are formed by $sp^2 - s$ overlappings.

Further unhybridised p-orbitals of Carbon atom and nitrogen overlap laterally to form π -molecular orbital containing six delocalised electrons.

Bond angle is 120° , C-C bond length 139 pm, C-N 137 pm



Aromaticity of Pyridine

Structure of pyridine resembles that of benzene but there is a nitrogen atom instead of a carbon atom in one of the positions.

- ① Pyridine has a planar cyclic system
- ② There is aromatic sextet is Six delocalised π electrons.
- ③ Pyridine satisfies Hückel's rule $(4n+2)\pi$ electron.
- ④ Pyridine does not readily undergo electrophilic substitution reactions unlike pyrrole, furan, or benzene because presence of electronegative atom nitrogen decreases electron density at ring atoms
- ⑤ Σ^{\oplus} get co-ordinated by nitrogen atom through its lone pair of Θ^-

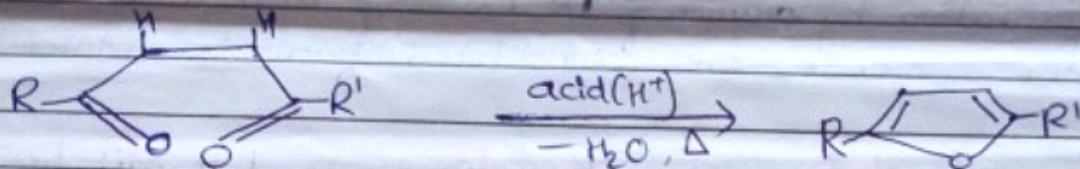
Synthesis of Furan & Pyrrole from 1,4-diketones (Paal Knorr Synthesis)

(I)

Synthesis of Furan

Many routes to synthesis furan are known, but the majority are variants on the first general method - the dehydrating ring closure of 1,4 dicarbonyl substrate.

1,4 Dicarbonyl Compounds can be dehydrated, with acids to form furan.

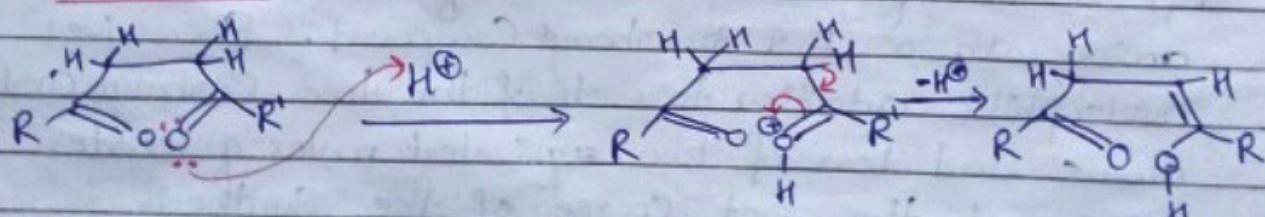


Paal Knorr Synthesis

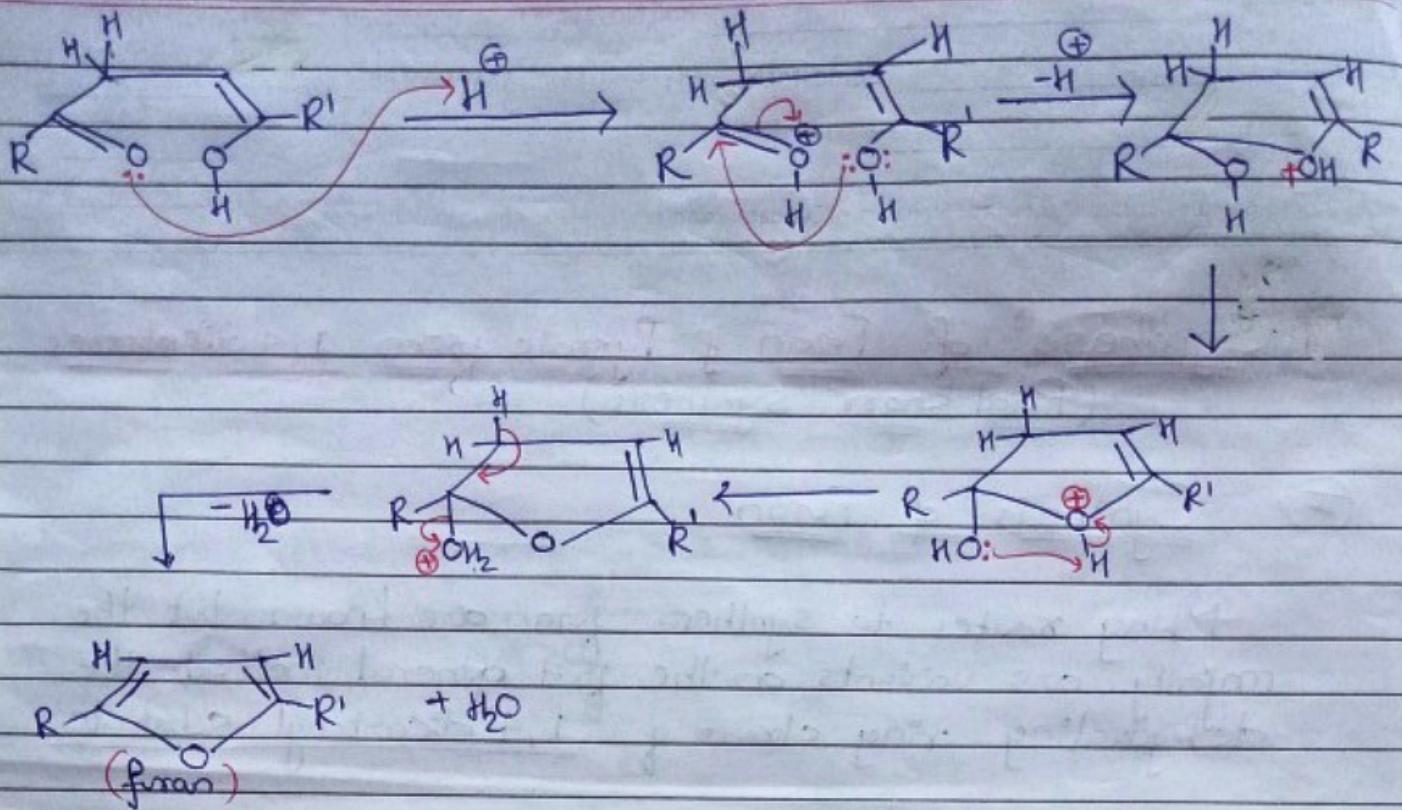
The most widely used approach to furan is the cyclising dehydration of 1,4 dicarbonyl Compounds. Usually non-aqueous acidic conditions are employed to encourage loss of water.

The process involves addition of enol oxygen of one carbonyl group to other carbonyl group, the elimination of water.

Mechanism



Oxygen of one of the Carbonyl group, abstracts proton from solvent and a positive charge is formed on oxygen, to neutralise this charge hydrogen of adjacent carbon

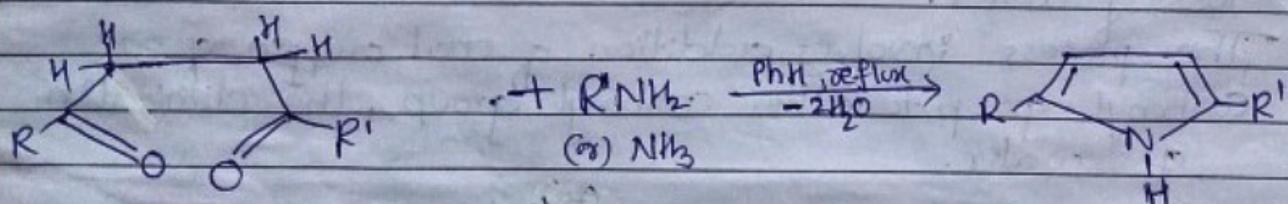


- rearranges and double bond is formed b/w 2 Carbon atoms, again the 2nd Carbonyl oxygen abstracts the proton and undergo rearrange with the ring formation by oxygen of 1st Carbonyl and with loss of 1 water molecule the Substituted furan is obtained

Synthesis of Pyrrole from 1,4 diketones

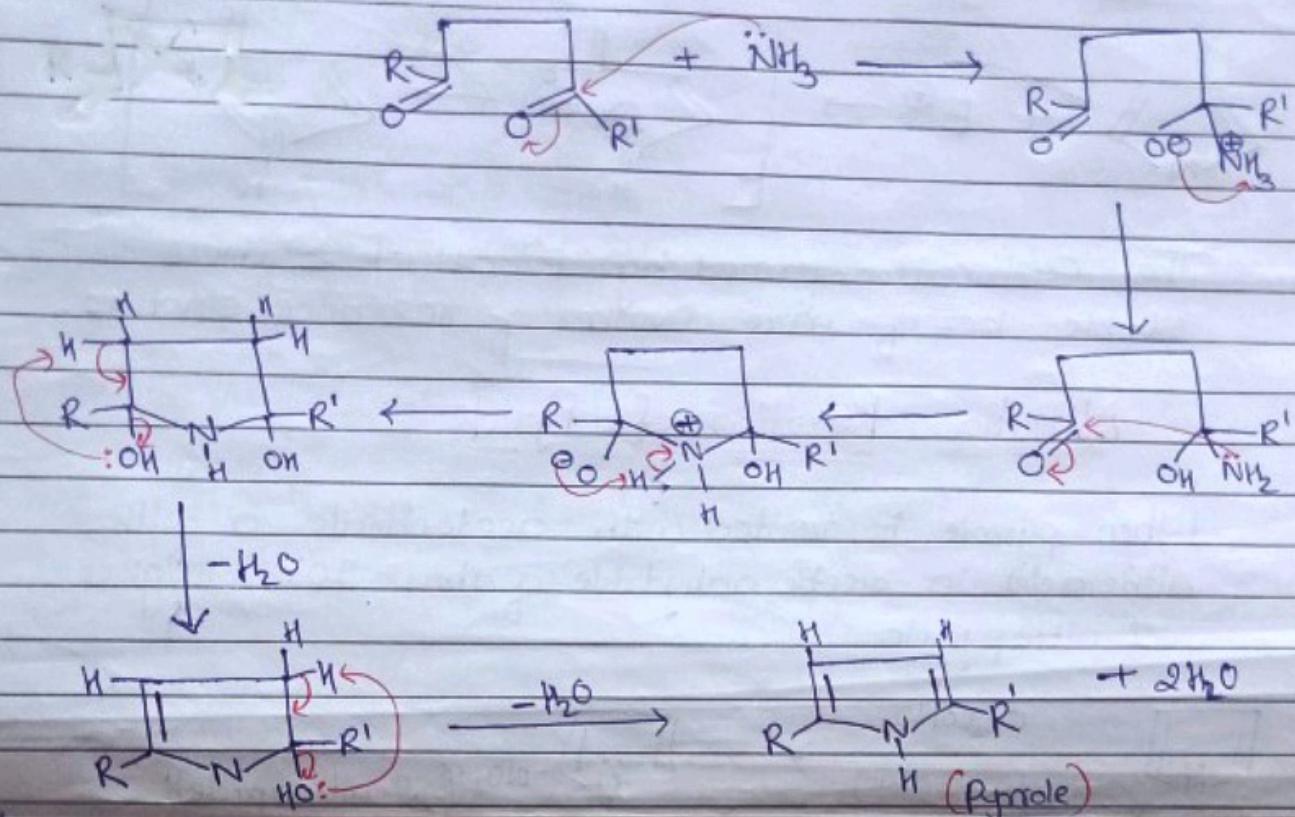
1,4 Dicarbonyl Compounds react with ammonia or primary amine to give Pyrroles

Paal-Knorr Synthesis



Pyrroles are formed by reaction of ammonia or a primary amine with a 1,4 dicarbonyl Compound. Successive nucleophilic addition to each of the two Carbonyl Carbon atoms and loss of two equivalent moles of water represent the net course of the Synthesis.

Mechanism

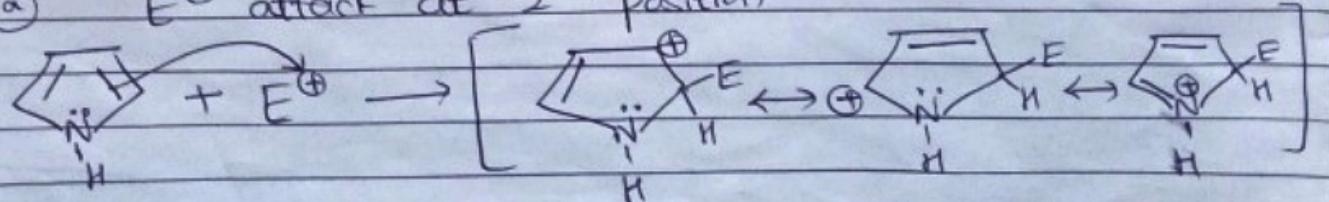


The ammonia or primary amine attacks the Carbonyl carbon and the oxygen of Carbonyl carbon convert into -OH group by abstract ring proton of ammonia and the amine of Nitrogen) attack the adjacent carbon of (2nd) Carbonyl group leading to ring formation with loss of two water molecule , pyrrole is obtained.

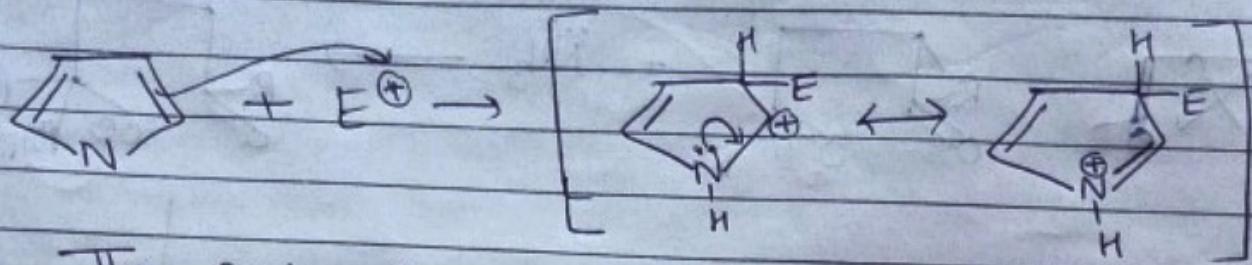
Electrophilic Substitution $\text{E}^{\oplus}\text{Sub}^{\ominus}$ of pyrrole

Pyrrole behaves as aromatic Compound & undergoes $\text{E}^{\oplus}\text{Sub}^{\ominus}$ These $\text{E}^{\oplus}\text{Sub}^{\ominus}$ takes place with greater ease when compared with benzene. In pyrrole ring position 2nd attack is mainly 2nd (5th) bcoz Intermediate carbocation formed after $\text{E}^{\oplus}\text{Sub}^{\ominus}$ attack at C-2 is more stable compared to carbocation formed after E^{\oplus} attack at 3rd (6th) carbon.

a) E^{\oplus} attack at 2nd position



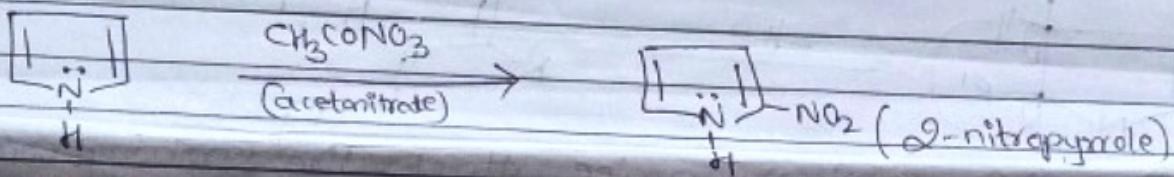
(b) E^+ attack at 3rd position



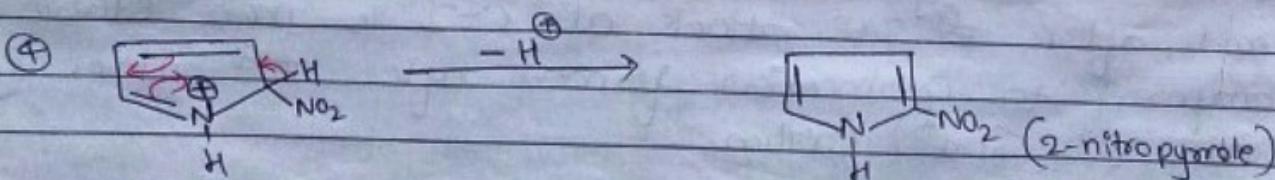
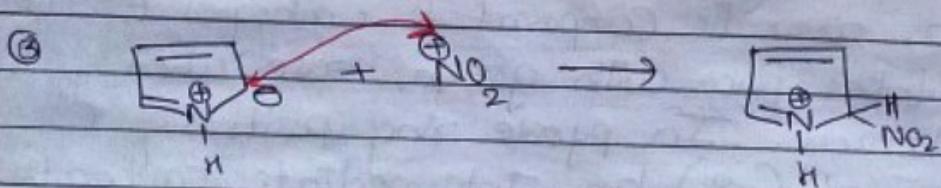
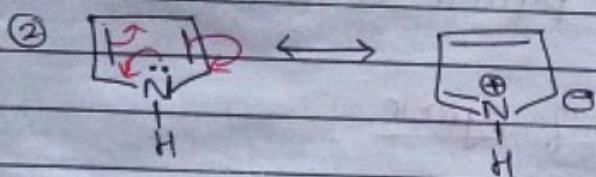
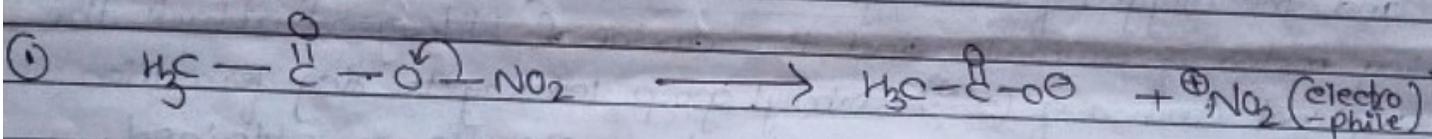
The Carbocation formed by E^+ attack is more stable bcz of more number of resonance structures.

Nitration Reaction of Pyrrole

When pyrrole is treated with acetonitrile or with nitric acid in acetic anhydride of about 10°C, it gives 2-nitropyrrole.

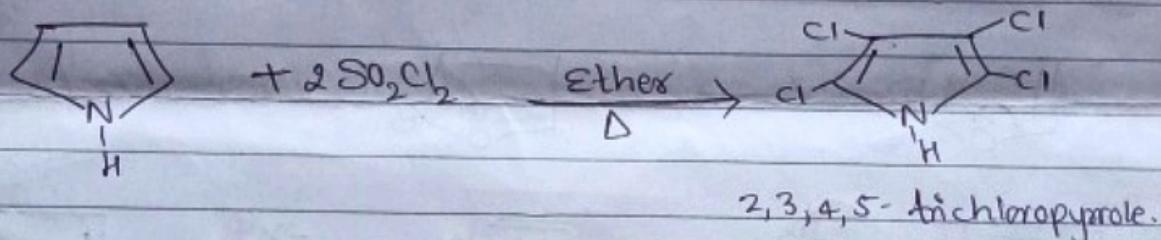


Mechanism



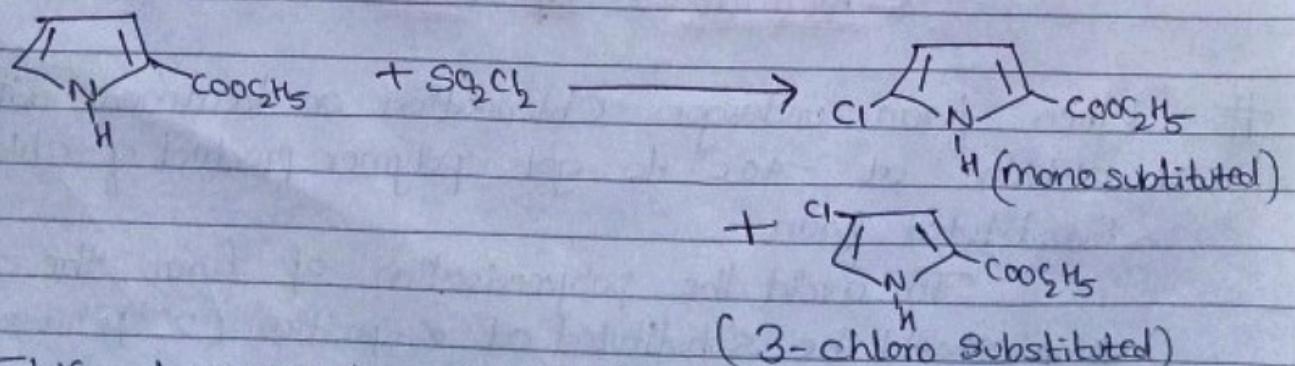
Chlorination of Pyrrole

- # When pyrrole is heated with Sulphuric chloride, ether as solvent and heated, the ~~tetra~~ tetrachloro pyrrole is obtained
- # The reaction is very vigorous and pyrrole is highly reactive with towards halogen and obtained product is tetra substituted halogen on pyrrole.
- # Halogenation (chlorination) of pyrrole is an example for Electrophilic Substitution reaction.



- # It is very difficult to obtain mono substituted chlorine (halogen) on pyrrole, because pyrrole is highly reactive towards halogens. (chlorine)

In order to obtain the mono substituted chlorine the pyrrole should be taken is Substituted pyrrole with Electron withdrawing group as an Substituted group for example $\text{EWG} \Rightarrow \text{COOC}_2\text{H}_5$ (ester)

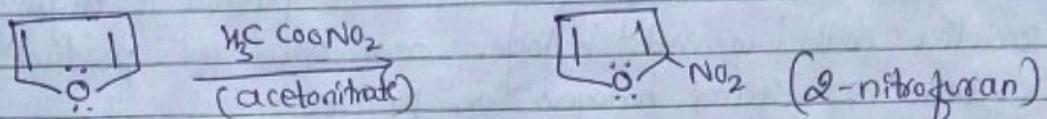


- # EWG decreases the electron density on the pyrrole and make pyrrole less reactive towards incoming electrophile ie chlorine, leading to formation of monosubstituted. Pyrrole

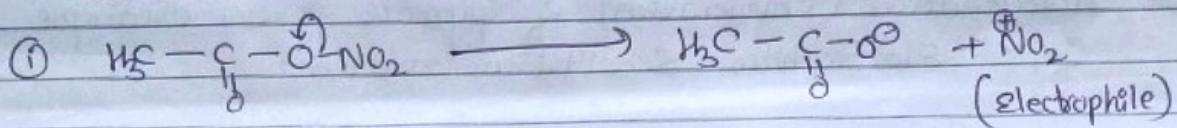
Electrophilic Substitution reaction of Furan

The resonance structure of Carbocation formed in furan, show that in electrophilic attack at 2nd position, there are three Canonical structures hence greater stability Compared to that of Carbocation in the electrophilic attack at 3rd position.

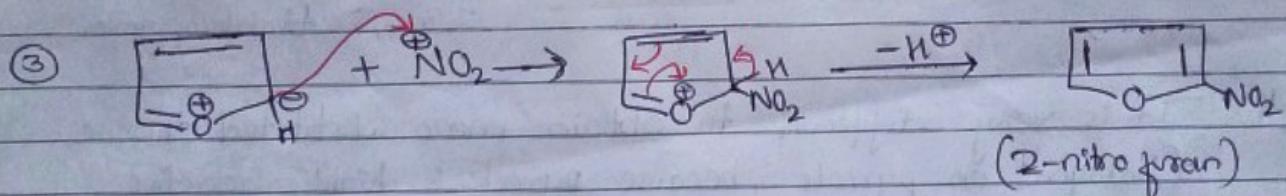
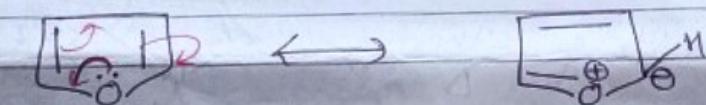
Nitration of Furan



Mechanism



②

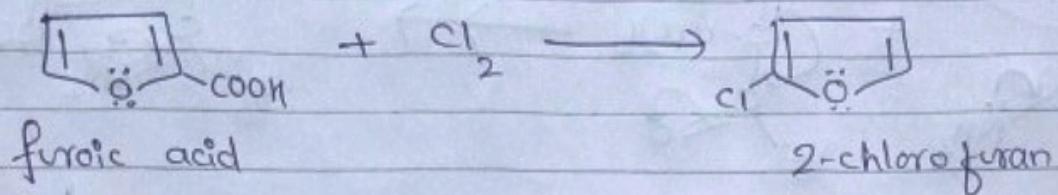


Chlorination of Furan

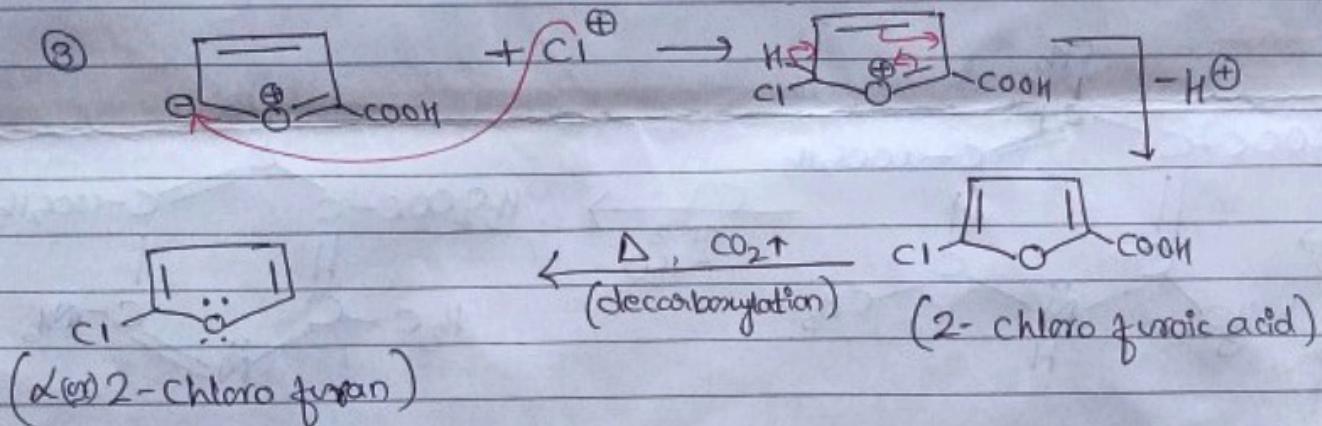
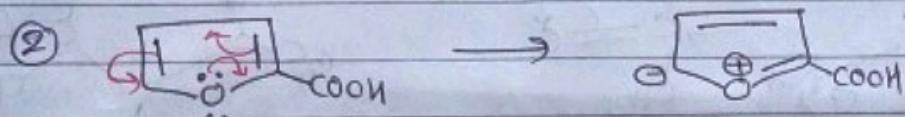
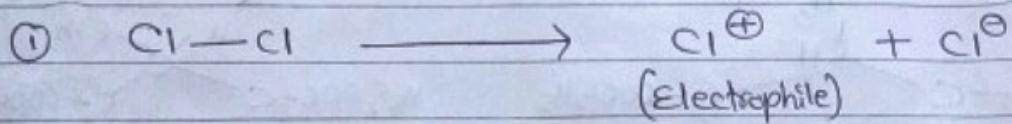
When furan undergoes chlorination on treatment with chlorine at -40°C to get polymer product of chloro Substituted furan.

To avoid the polymerisation of furan, the -COOH group should be substituted at α -position (2nd position) that is Furoic acid should be taken as reactant and after completion of reaction (chlorination) the furoic acid

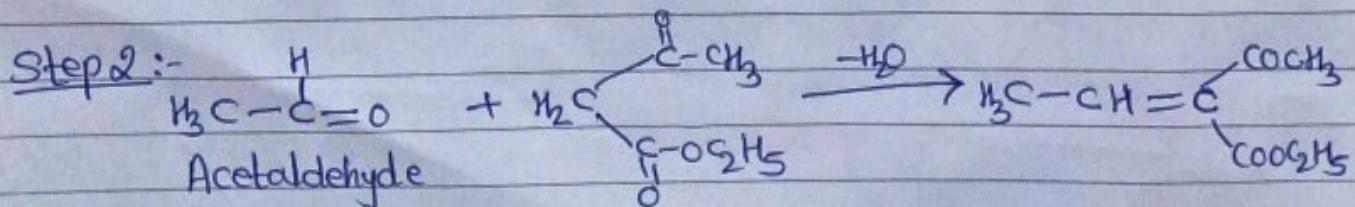
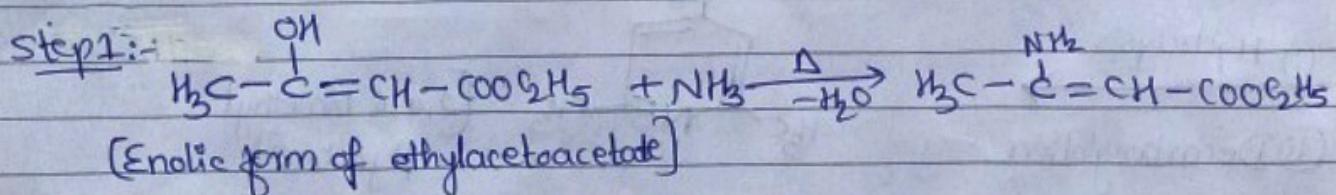
Can be undergo de carbonylation to form only chloro substituted furan.



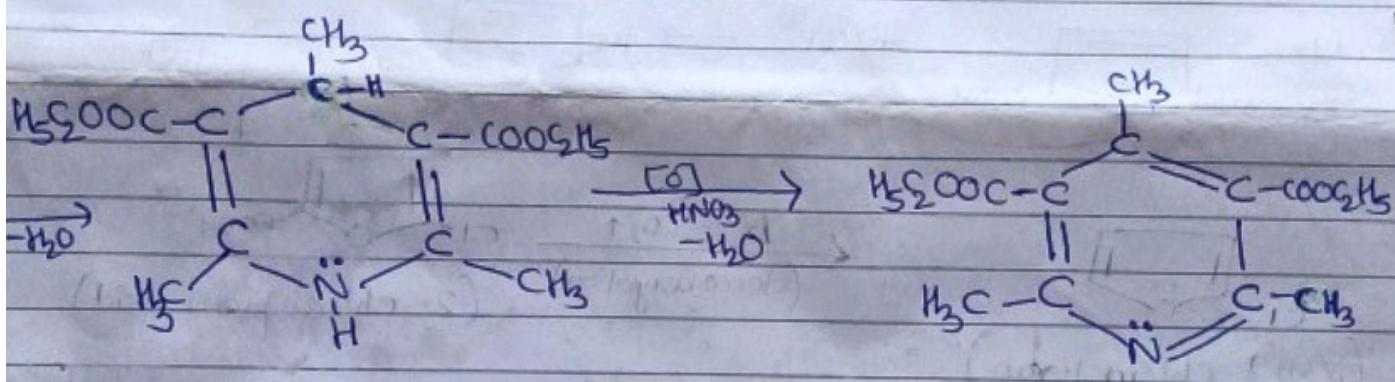
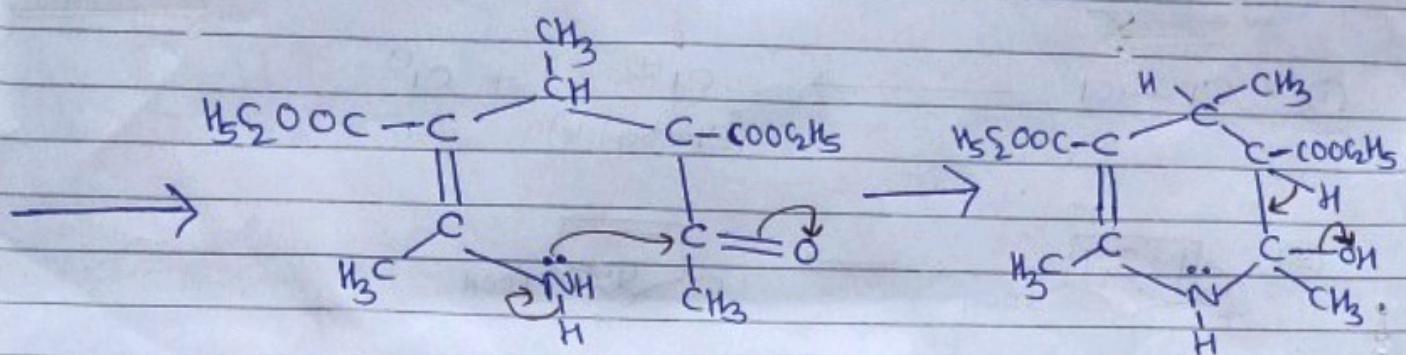
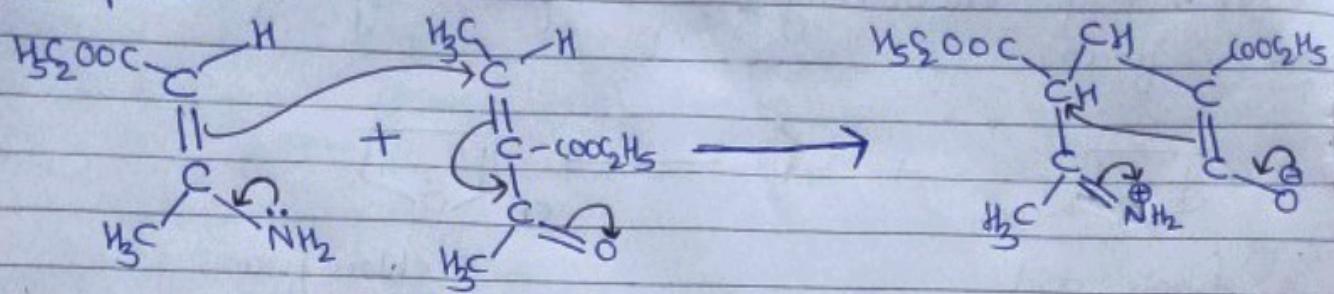
Mechanism



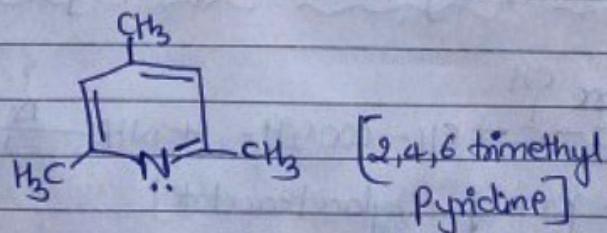
Hantzsch Synthesis of Pyridine Derivatives



Step 3



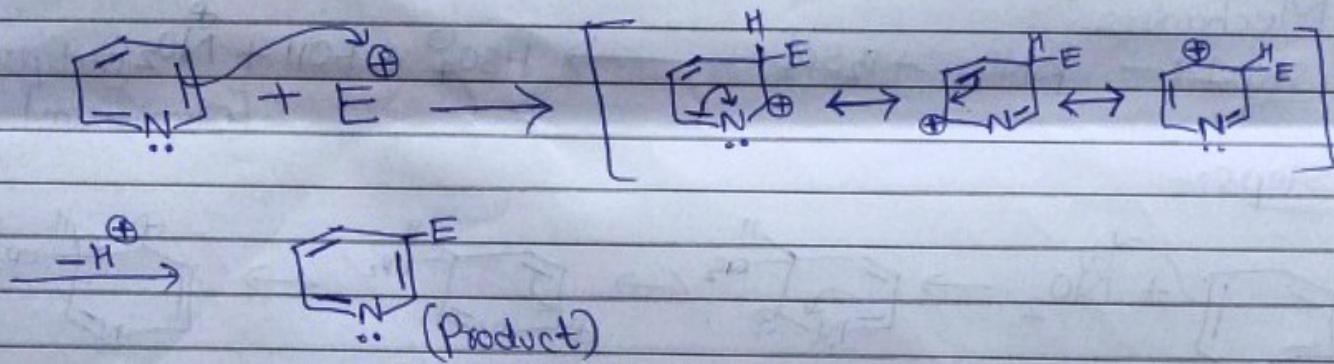
- ① Hydrolysis
- ② Decarbonylation



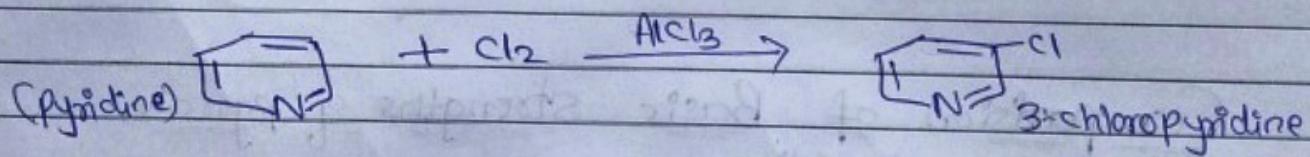
Electrophilic Substitution Reactions in Pyridine.

Compared to pyrrole and furan, pyridine is less reactive towards electrophilic substitution reaction.

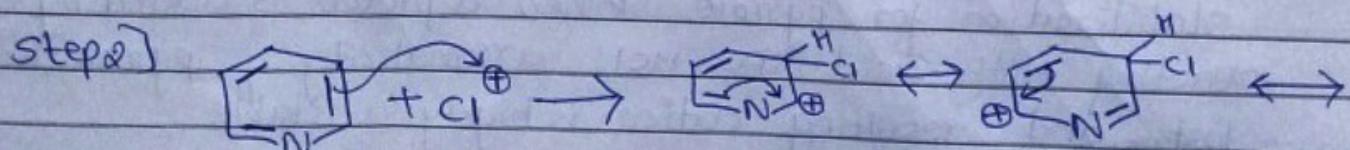
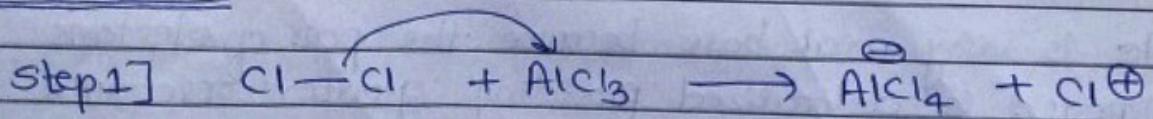
- ① Attack at 3rd position is greater stability of intermediate carbocation formed after electrophilic attack at 3rd position compared to electrophilic attack at 2nd and 4th positions.

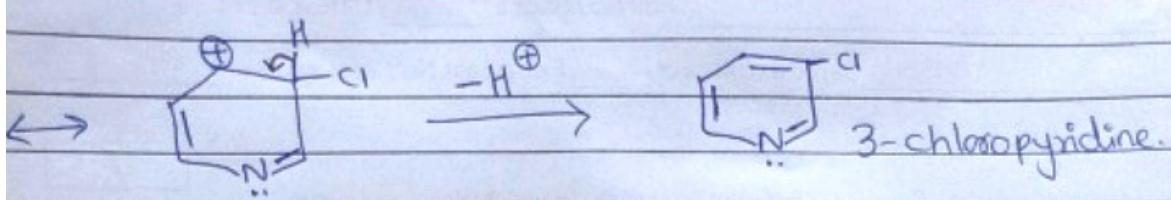


Halogenation of Pyridine



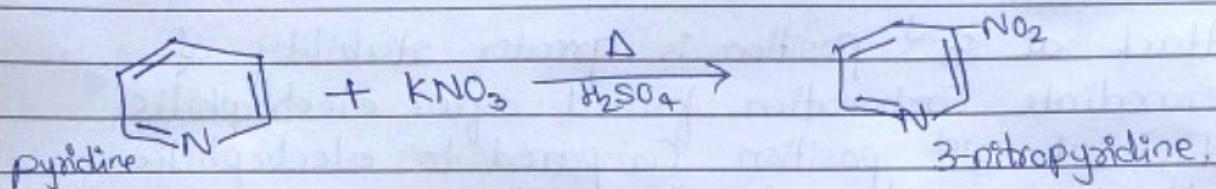
Mechanism



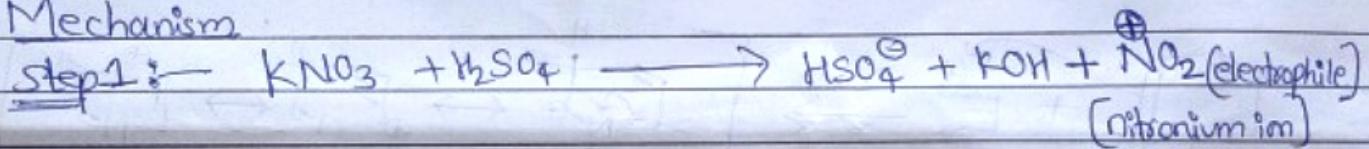


(II) Nitration of Pyridine

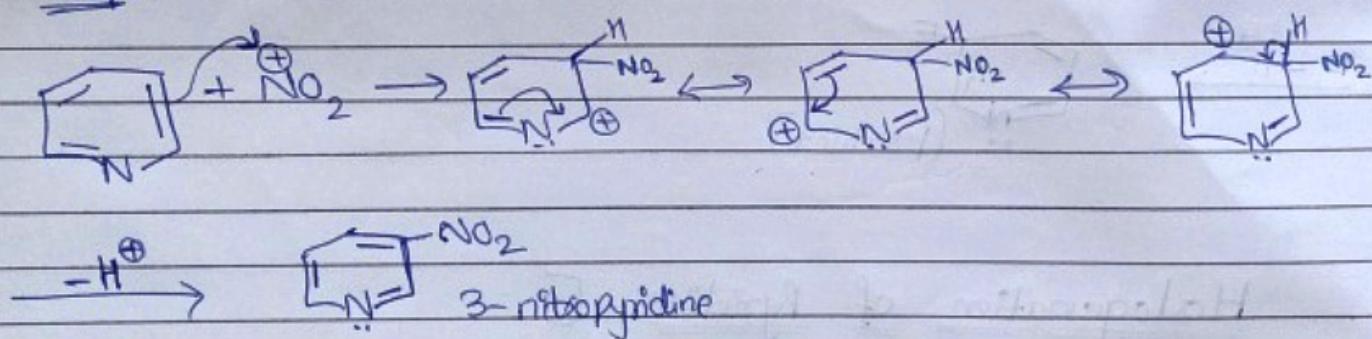
When heated with potassium nitrate in presence of conc. H_2SO_4 at about $300^\circ C$ gives 3-nitropyridine, but the yield is poor.



Mechanism



Step 2:-



Comparison of Basic strengths of pyrrole, pyridine & piperidine

Pyrrole is very weak base because the pair of electrons of nitrogen is delocalized providing greater resonance stabilization for pyrrole. When a proton is added by reacting with acid like HCl, aromaticity of pyrrole is lost and resulting cation is highly unstable.

In case of pyridine unlike pyrrole a pair of electrons of nitrogen in sp^2 hybrid orbital is free to accept proton without disturbing aromaticity and resonance stabilization hence pyridine behaves as stronger base compared to pyrrole.

Piperidine is like typical secondary amine similar to aliphatic secondary amines. This is stronger base even compared to ammonia. The decreasing order of basic strength among piperidine, pyridine and pyrrole is,

