Heterocyclic compounds

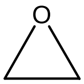
[A] Five Membered Heterocyclic Compounds

Introduction:

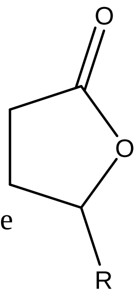
Hetero means other in the Greek language.The cyclic compounds contains at least one hetero atom other than carbons atom such compounds are known as heterocyclic compounds.

Generally in heterocyclic compounds nitrogen ,sulphur ,oxygen,atoms are present as hetero atom.

The heterocyclic compounds are relatively stable, aromatic compounds. They may be five or six membered, containing conjugated double bonds& obey Huckel rule (4n+2)π electrons. But ethylene oxide and lactones (ϒ-butyrolactone) are unstable therefore they doesn't consider to be heterocyclic compounds.



Ethylene oxide



ϒ -Lactone

Nomenclature:

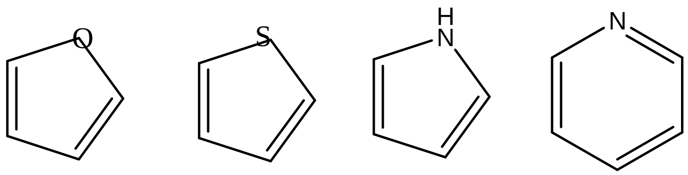
The international union of pure and applied chemistry (IUPAC) gives rules for the systematic naming to the heterocyclic compounds. Beside the IUPAC system many common (Trivial) names are also used which are widely accepted in world. The following rules are used for the IUPAC nomenclature of heterocyclic compounds.

1) The following prefixes are used according to the hetero atoms & suffixes are used according to the size of heterocyclic ring.(the

last word of prefixes are replaced by the respective name ending words that indicate the size of ring.)

Atoms	**Prefixes used**	**No. of atom in ring/ ring size**	**Ending names**
Oxygen	Oxa	3	-irine
Sulphur	Thia	4	-ete
Nitrogen	Aza	5	-ole
Phosphorus	Phospha	6	-ine
Silicon	Sila	7	-epine

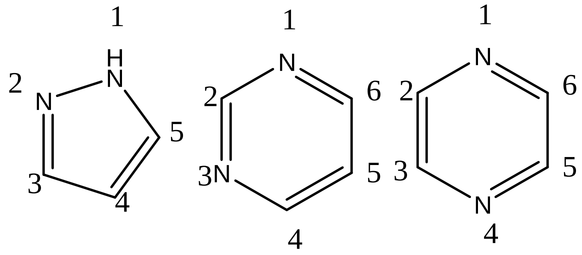
Examples:



Trivial Name: Furan ThiophenePyrrole Pyridine

IUPAC Name: OxoleThiole1H-Azole Azine

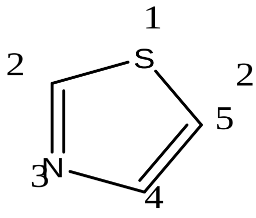
2) In monocyclic compounds the numbering start from the hetero atom gets the lowest number.
3) When two, three,fouror more of the same hetero atoms present in the ring, then use prefixes like di-, tri-, tetra-, etc.

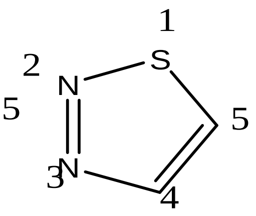


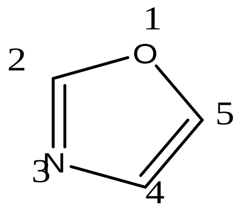
Trivial Name :1H-Pyrazole Pyrimidine Pyrazine

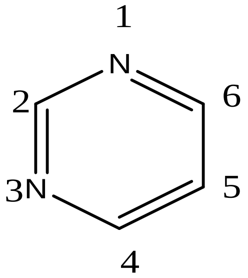
IUPAC Name :1H-1,2-Diazole 1,3-diazine 1,4-Diazine

4) When the ring containing more than one, different hetero atom, the numbering starts from that hetero atom which is in the highest group number in the periodic table.
5) If the two different hetero atoms belong to same group, then the numbering starts from those, which is having low atomic number, and numbering to the hetero atoms around the ring should be minimum.







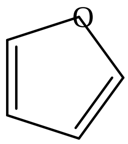


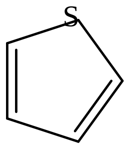
1,3-Thiazole 1,2,3-Thiadiazole 1,3-Oxazole 1,4,2-Oxathiazine

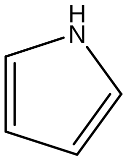
Classification:

They are classified according to size of heterocyclic ring containing one or more hetero atom& condensed system i.e. two or more ring gets fused .

1) Five member heterocyclic compounds containing one hetero atom.

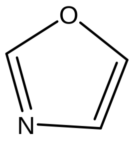


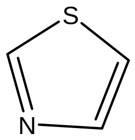


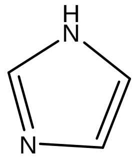


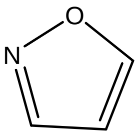
Trivial Name→ Furan Thiophene Pyrrole
IUPAC Name →Oxole Thiole Azole

2) Five membered heterocyclic compounds containing two hetero atoms.



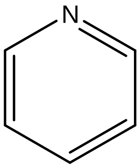


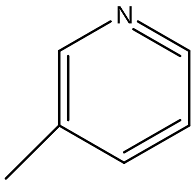




Trivial Name →Oxazole Thiazole Imidazole Pyrazole
IUPAC Name→ 1,3-Oxazole 1,3-Thiazole 1,3-Diazole 1,2-Diazole

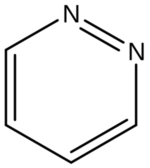
3) Six member heterocyclic compounds containg one hetero atom.

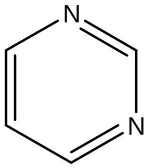


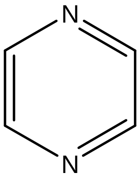


Trivial Name→ Pyridine β-methylpyridine
IUPAC Name→ Azine 3-Methylazine

4) Six member heterocyclic compounds containing two hetero atoms.

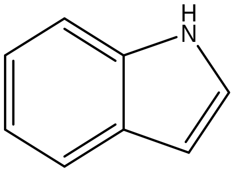


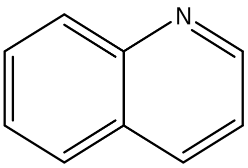


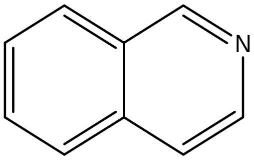


Trivial Name→ Pyridazine Pyrimidine Pyrazine
IUPAC Name→1,2-Diazine 1,3-Diazine 1,4-Diazine

5) Bicyclic compounds containing one hetero atom.

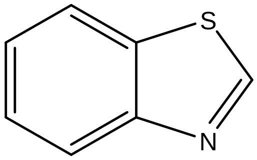


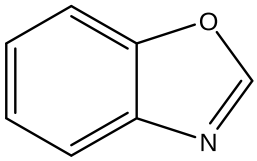




Trivial Name→Indole Quinoline Isoquinoline
IUPAC Name→1H-Benzopyrroleα,β-Benzopyridine 4,5-Benzopyridine

6) Bicyclic compounds containing two hetero atoms.





Trivial Name→Benzothiazole Benzoxazole
IUPAC Name→1,3-Benzothiazole 1,3-Benzoxazole

Molecular Orbital Structure and resonance structure of five membered heterocyclic compounds:

Molecular orbital structures of five member heterocyclic compounds like furan, thiphene, pyrrole are as follows.

1) Furan/Oxole:

Furan is five member aromatic heterocyclic compound containing an oxygen and four carbon atoms which are undergoes toSP^2.

Hybridization in Carbon atom	Hybridization in Oxygen atom
G.S. $C_6 = 1S^2\ 2S^2\ 2P_X^1\ 2P_y^1\ 2P_z^0$	G.S. $O_8 = 1S^2\ 2S^2\ 2P_X^2 2P_y^1\ 2P_z^1$
E.S. $C_6 = 1S^2\ \underbrace{2S^1 2P_X^1\ 2P_y^1}_{\text{Undergo } SP^2 \text{ hybridization}}\ 2P_z^1$	E.S. $O_8 = 1S^2\ \underbrace{2S^1 2P_X^2 2P_y^1}_{\text{Undergo } SP^2 \text{ hybridization}}\ 2P_z^2$

Unhybridization orbital: in C-atom :$2P_z^1$ & in O-atom :$2P_z^2$

Three SP^2 hybrid orbital's of each carbon atom form three sigma bonds , one sigma bond C-H Bondis formed by axial overlapping of SP^2– S hybrid orbital of carbon & hydrogen atom, and remaining two sigma bonds are formed by axial overlapping of hybridized orbitals in between four carbon and single oxygen atoms.

Each carbon atom has unhybridized $2P_z^1$ orbital with one electron, which is perpendicular to trigonal planner SP^2 hybridized carbon atom. The sidewise overlapping takes place in between $2P_x^1$ of each adjacent carbon atoms to formed two π bonds in furan.

An oxygen atom also formed two sigma bonds with adjacent two carbon atoms by axial overlapping of SP^2- SP^2 hybridized orbital of carbon and oxygen.

Oxygen atom containtwo electron in one SP^2 hybridized orbital, &unhybridized $2P_z^2$ of oxygen atom, which having lone pair of electron which is conjugated with two π bonds and completes the aromatic sextet by obeying he Huckel rule $(4n+2)\ \pi\ e^-$.

Molecular orbital picture of Furan:

Molecular orbital structure of Furan is represented in orbital picture diagram as follows.

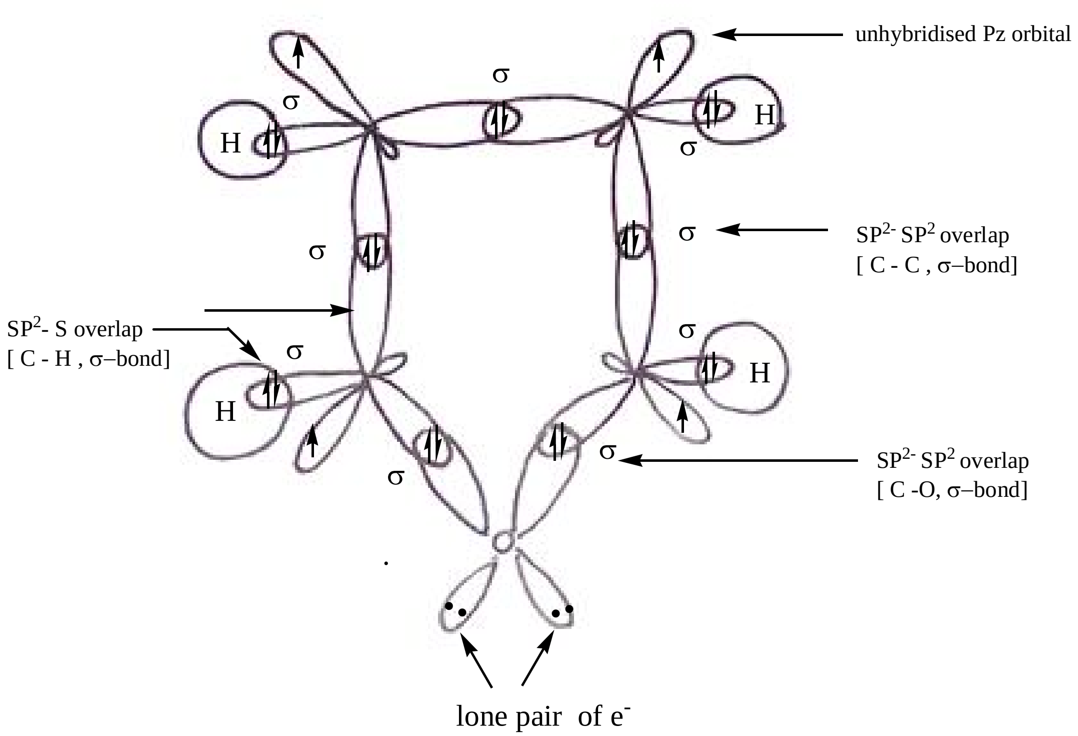
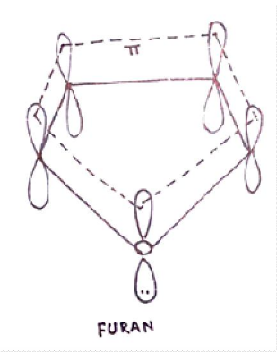
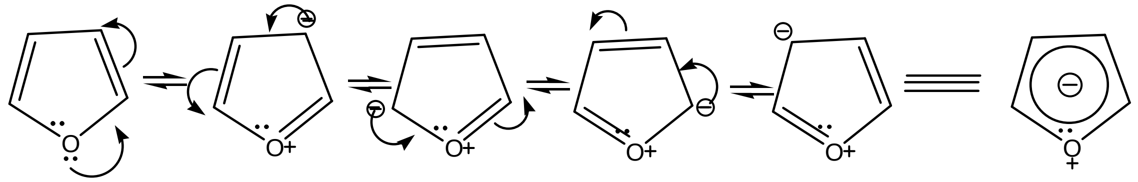


Fig. : Molecular Orbital Diagram of Furan



Resonance structure of Furan: Structure of Furan can be represented as resonance hybrid by following resonating structure.



2) Thiophene/ Thiole:

Thiophene is five member aromatic heterocyclic compound containing sulphurhetero atom& undergoes SP^2hybridization.

Hybridization in Carbon atom Hybridization in Sulphur atom

G.S. $C_6 = 1S^2\, 2S^2\, 2P_X^1\, 2P_y^1\, 2P_z^0$ G.S. $S_{16} = 1S^2 2S^2 2P^6 3S^2\, 3P_X^2 3P_y^1\, 3P_z^1$

E.S. $C_6 = 1S^2\, \underbrace{2S^1 2P_X^1\, 2P_y^1}_{\text{Undergo } SP^2 \text{ hybridization}}\, 2P_z^1$ E.S. $S_{16} = 1S^2 2S^2\, 2P^6\, \underbrace{3S^1 3P_X^2 3P_y^1}_{\text{Undergo } SP^2 \text{ hybridization}}\, 3P_z^2$

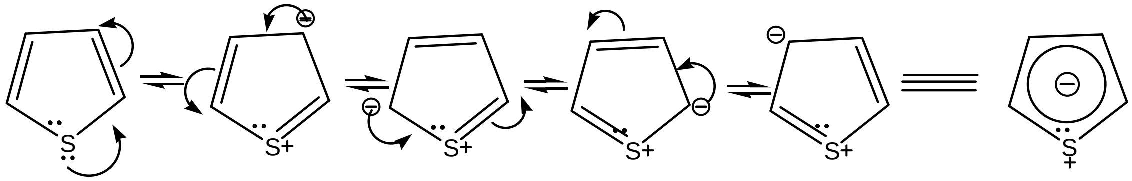
Unhybridization orbital: in C-atom :$2P_z^1$ & in S-atom : $3P_z^2$

The hybridization of four carbon atoms and sulphur atom in thiophene is SP^2. Three SP^2 hybrid orbitals form three σ bonds , two C-C/C-S bonds by of SP^2- SP^2axial overlap & one C-H bondsbonds by of SP^2- Soverlap. AP_z orbital of each carbon atom with one electron remains perpendicular to the trigonal planner SP^2 hybridized carbon atoms. The sidewise overlapping is takes place in between adjacent P_z orbitals of each carbon atom to form two π bonds in thiophene.

sulphuratom in thiopheneundergoes SP^2hybridization to form three bonds ,out of these two SP^2 hybridized orbitals contain single electron each, which form σ bonds with carbon. TheunhybridizedP_z orbital is remaining perpendicular to the trigonal planar sulphur atom with two electrons& are participated in the delocalization and satisfy the aromaticity of thiophene by obeying Huckel rule (4n+2) πe^-.

Resonance structure of Thiophene:

Structure of Thiophene can be represented as resonance hybrid by following resonating structure.



Molecular orbital picture of Thiophene:

Molecular orbital structure of Thiophene represented in orbital picture is as follows.

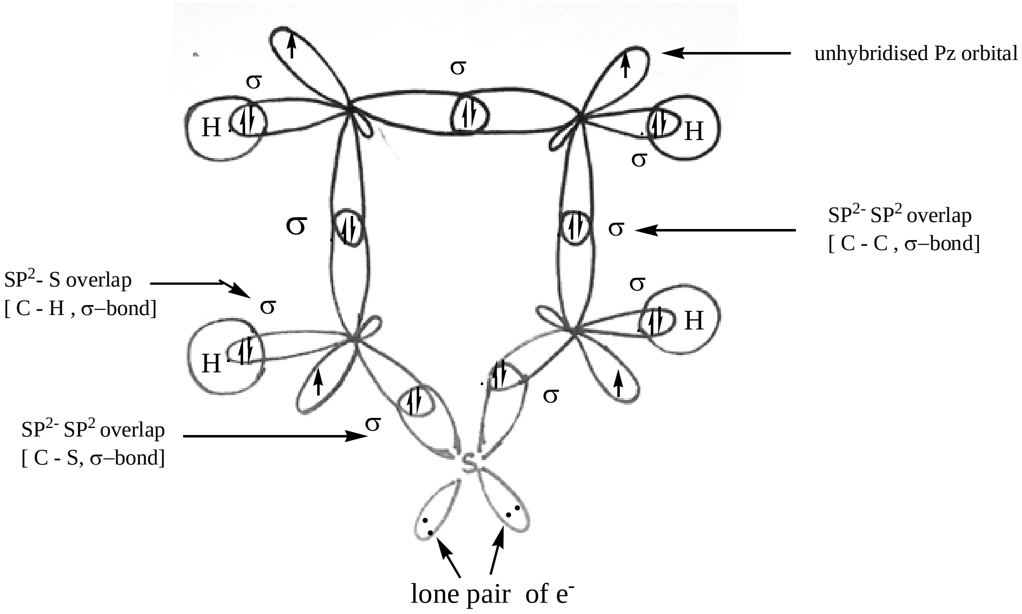
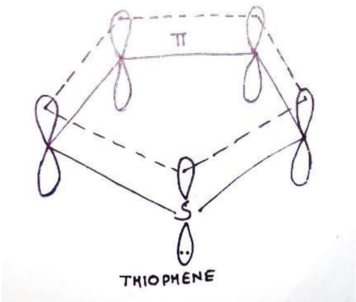


Fig. : Molecular Orbital Diagram of Thiophene



3) Pyrrole/Azole:

Pyrole is five member aromatic heterocyclic compound containing Nitrogen hetero atomand undergoes SP^2hybridization.

Hybridization in Carbon atom

G.S. $C_6 = 1S^2\,2S^2\,2P_X^1\,2P_y^1\,2P_z^0$

$$\text{E.S. } C_6 = 1S^2\,\underbrace{2S^1 2P_X^1\,2P_y^1}_{\text{Undergo } SP^2 \text{ hybridization}}\,2P_z^1$$

Hybridization in Nitrogen atom

G.S. $N_7 = 1S^2\,2S^2\,2P_X^1 2P_y^1\,2P_z^1$

$$\text{E.S. } N_7 = 1S^2\,\underbrace{2S^1 2P_X^1 2P_y^1}_{\text{Undergo } SP^2 \text{ hybridization}}\,2P_z^2$$

Unhybridization orbital: in C-atom :$2P_z^1$ & in N-atom :$2P_z^2$

Three SP^2 hybrid orbitals of each carbon atom form three sigma bonds (one C-H by SP^2 -S overlap and C-C/ C-N SP^{2} - SP^2overlap) by axially and P_z orbitals has one electronremain perpendicular to the trigonal planner SP^2 hybridized carbon atom. The sidewise overlapping between P_z orbitals of adjacent carbon atoms to form two π bonds in pyrrole.

Nitrogenundergoes SP^2hybridization. Three hybrid orbitals of nitrogen atom containing one electron are involved in the formation of three σ bonds with adjacent carbon and hydrogen atoms. The unhybridizedP_z orbital containing two electrons, acts as lone pair& delocalized over the ring to satisfyaromaticity of pyrrole by obeying Huckel rule $(4n+2)\ \pi e^-$.

Molecular orbital picture of Pyrrole: Molecular orbital structure of pyrrole can be represented as follows.

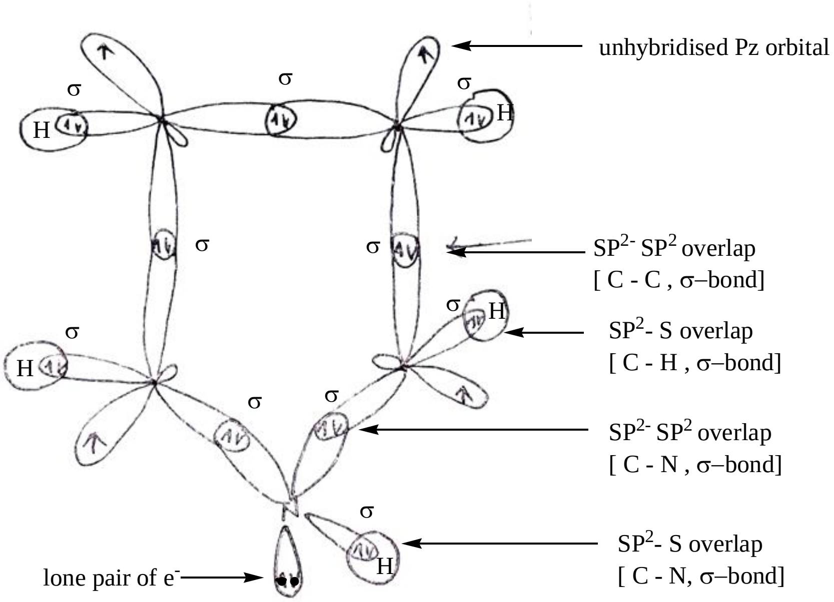
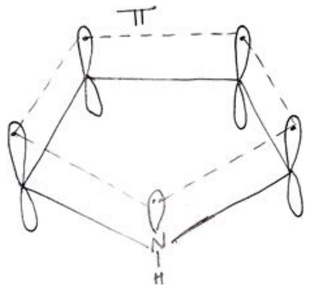
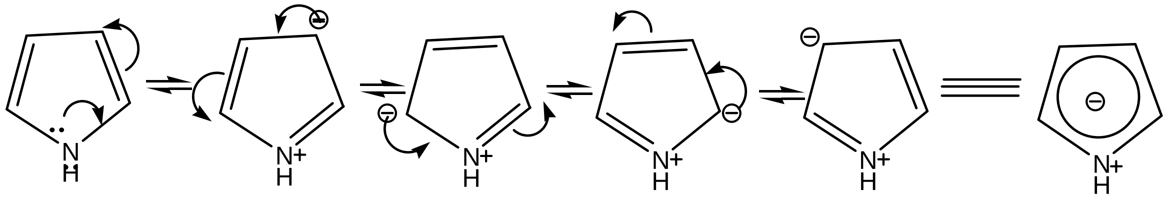


Fig. : Molecular Orbital Diagram of Pyrrol



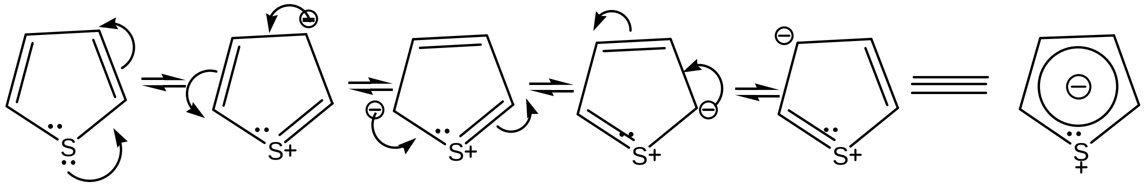
Resonance structure of Pyrrole:

Structure of pyrrole can be represented as resonance hybrid by following resonating structure.



Stability of furan, Thiophene and pyrrole

The resonance hybrid structure for thiophene can be represented as follows.



Moreover the sulphur atom with atomic number 16, can utilize 3d vacant orbitals (except oxygen and nitrogen) and become tetravalent. i.e. $1S^2,2S^2,2P^6,3S^2,3P_x^1,3P_y^1,3P_z^1$. Hence the more resonance hybrid structure can be obtained than Furan and Pyrrole. Therefore thiophene is more stable than furan and pyrrole.

Aromatic nature of Thiophene, Pyrrole, Furan.

Nitrogen and oxygen is greaterelectronegativity than sulphur atom. In Pyrrole and Furan the π electronsgets withdrawn towards N and O atoms, therefore electrophilic attack is slow in pyrrole& furan.

But in less electronegatesulphur atom, the π electrons in thiophene ring is not withdrawn toward sulphur atom within ring. Therefore the attack of electrophile to thiophene is take place more readily than Pyrrole and Furan.

Therefore, thiophene undergoes electrophilic substitution reaction readily than pyrrole& furan due to maximum aromaticity.

The aromaticityorder for ,Thiophene>Pyrrole>Furan.

General electrophilic substitution reaction in Furan/Thiophene/Pyrrole:

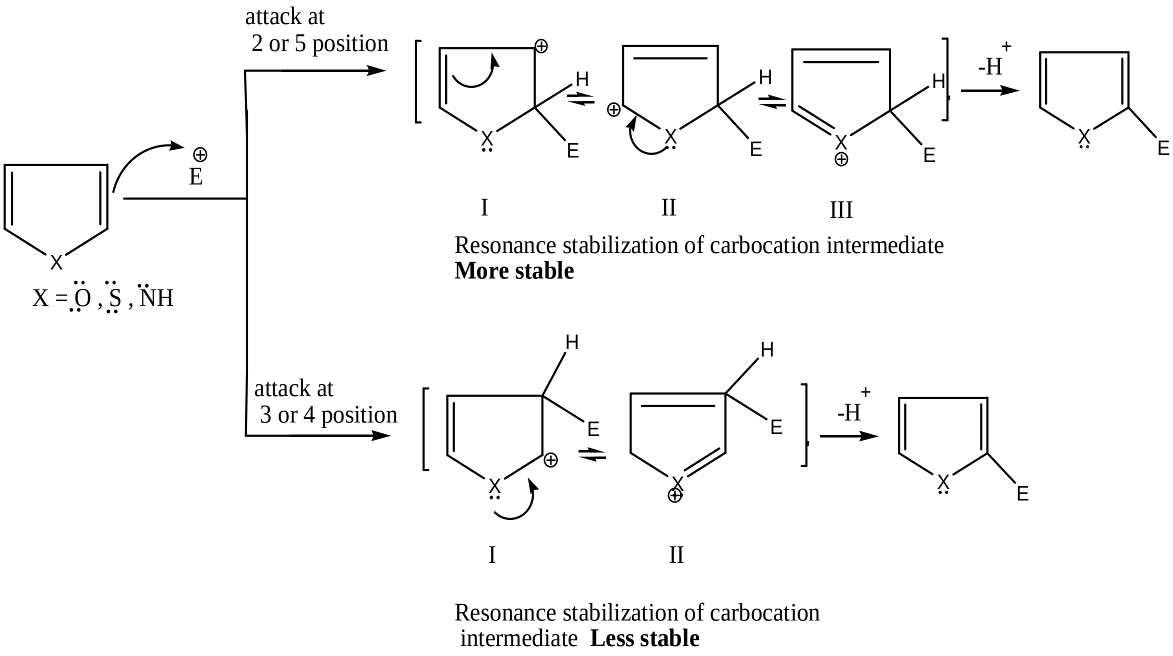
The electrophilic substitution reaction of furan/thiophene/ pyrroletakes place at 2 or 5 or (α) position. Electrophile attack at 2 or 5 position to formstable carbocation intermediate.

Electrophilic substitutionat 3 or 4 position, the resulting less stable carbocation intermediate as compared to at 2 or 5 position. If the 2 and 5 positions are blocked, substitution may be possible at 3 or

4 position because carbocation intermediate is stabilized by accommodation of the +ve charge on the hetero atom.

The general mechanism of electrophilic substitution reaction with furan, pyrrole and thiophene is as follow.

Electrophilic attack



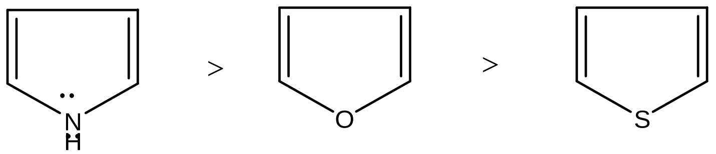
Rectivity of Furan, Pyrrole and Thiophene:

Nitrogen atom in pyrrol easily form positive charge than oxygen atom in furan. Therefore pyrrol is more reactive than furan

The +M effect of sulphur is smaller than oxygen, because the overlapping of different sized p-orbital of carbon-sulphur is less than the overlapping of carbon and oxygen. Hence thiophene is less reactive than furan.

The aromatic substitution reaction is carried out in mild conditiondue to the more reactivity.

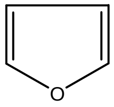
The reactivity order is as follows:



Five membered Heterocycles:

A. Furan / oxole:

Furan is five member heterocyclic compound containing oxygen and four carbon atoms in their cyclic structure.

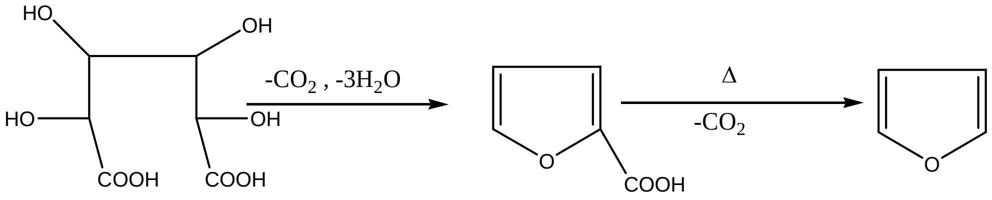


Furan

Synthesis of Furan:

1) From Mucic acid:

Distillation of mucic acid under dry condition gives furoic acid. Furoic acid on heating at its boiling point undergoes decarboxylation to obtain furan.



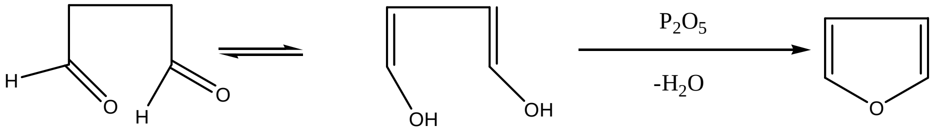
Mucic acid

Furoic acid

Furan

2) From Succinaldehyde:

Heating of succinaldehydefollowed by dehydrating agent like P_2O_5dehydration to form furan.



Keto form

Enol form

Furan

Succinaldehyde

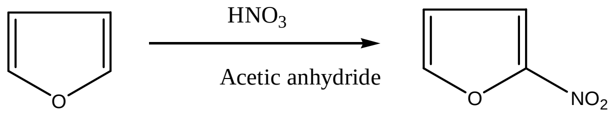
Physical properties of furan:

1) Furan is colourless liquid, with B.P.=32^0C ($305\ ^0$K)
2) It has smell of chloroform.
3) It is insoluble in water but soluble in alcohol and ether.
4) It produce green colour on pine splinters moistened with HCl.

Chemical properties of furan:

1) <u>Nitration:</u>

Furan treated with conc. HNO_3in presence of acetic anhydride toform 2-nitro furan.



Furan 2-Nitrofuran

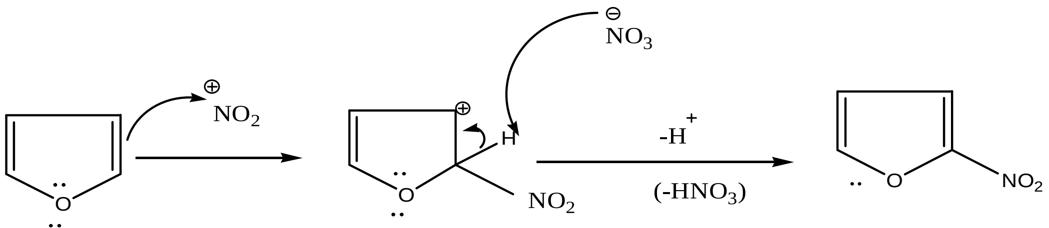
The mechanism for the formation of 2-nitro furan is given as follow.

Mechanism:

Step-I: Formation of Nitronium ion.

$$\underset{\text{Nitric acid}}{HO\text{-}NO_2} + \underset{\text{Acetic anhydride}}{CH_3\text{-}CO\text{-}O\text{-}CO\text{-}CH_3} \xrightarrow[-CH_3COOH]{} CH_3COO\text{-}NO_2 \xrightarrow[CH_3\text{-}CO\text{-}O\text{-}CO\text{-}CH_3]{} NO_2\text{-}O\text{-}NO_2 \longrightarrow \overset{\oplus}{NO_2} + \overset{\ominus}{NO_3}$$

Step-II: Attack of electrophile & formation of 2-Nitrofuran

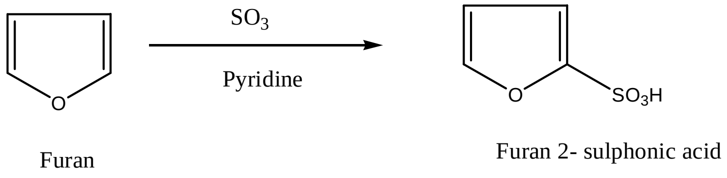


2-Nitrofuran

2) <u>Sulphonation:</u>

Sulphonation is carried out by passing SO_3 gas through solution of furan in presence of pyridine to obtain furan 2-

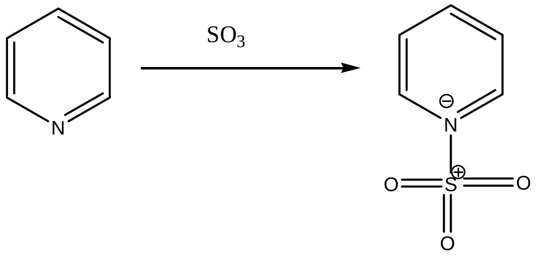
sulphonic acid. The direct use of conc. H_2SO_4 decomposes the furan. SO_3 group is electron deficient hence it acts as eletrophile.



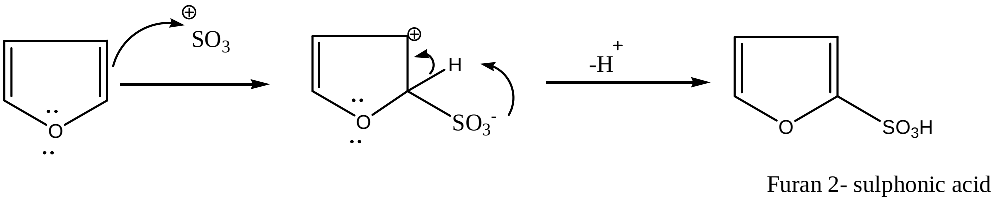
The mechanism for the formation of furan 2-sulphonic acid is as follow.

Mechanism:

Step-I: Generation of 1- Protopyridiumsulfonate

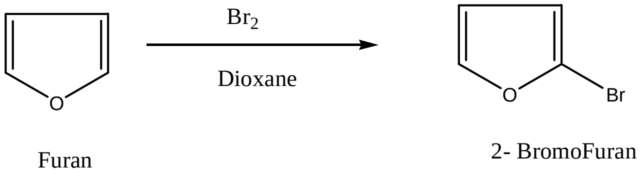


Step-II: Attack of electrophile to to form furan 2-sulphonic acid



3) Halogenation:

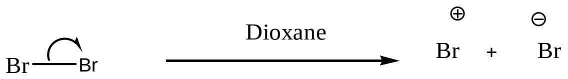
Halogenation (F, Cl, Br, I) of furan is example of electrophilic substitution reaction. The direct bromination of furan on presence of dioxane gives 2-bromo furan as major product.



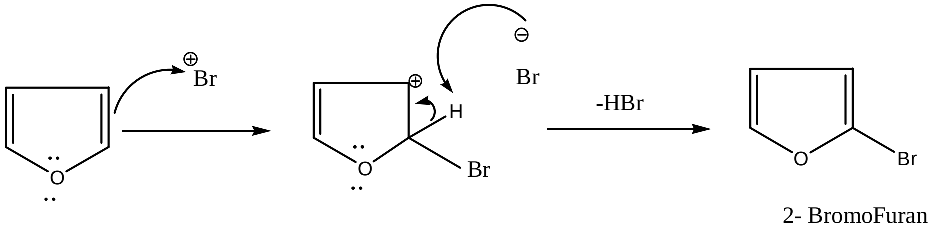
The mechanism for the formation of 2-bromo furan is as follow.

Mechanism:

Step-I: Formation of bromine electrophile

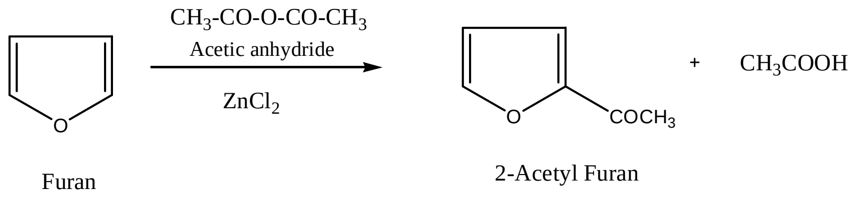


Step-II: Attack of electrophile to the Furan to obtain 2-bromo furan



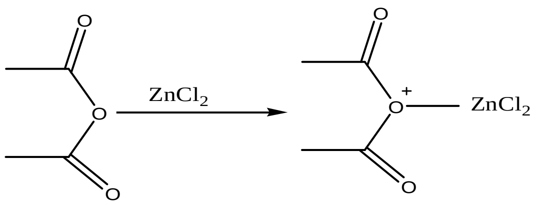
4) Friedel-Craft acylation:

When furan reacts with acetic anhydride or acetyl chloride in presence of Lewis acid $ZnCl_2$, $SnCl_2$, it forms 2-acetyl derivative of furan.

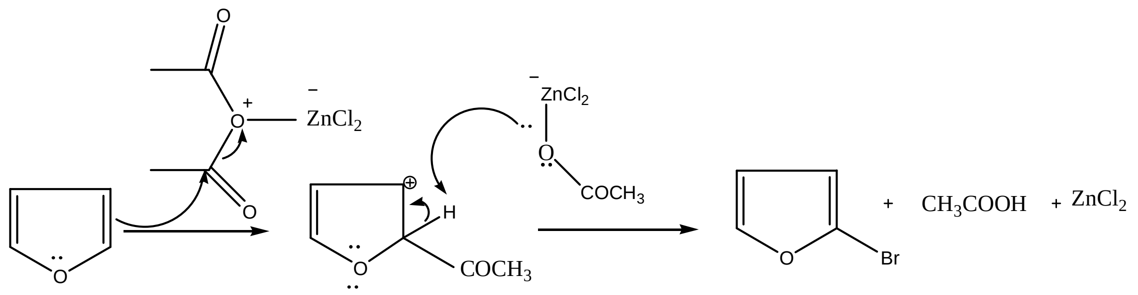


Mechanism:

Step-I: Formation of electrophile



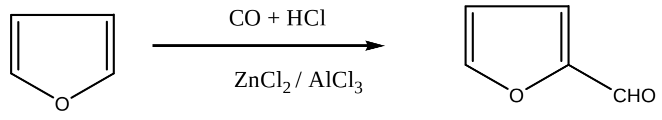
Step-II: Formation of 2-Acetyl furan.



2- BromoFuran

5) Gatterman Koch reaction:

It is the process of formylation, in which furan is reacts with CO and HCl in presence of $AlCl_3$ gives 2-formyl furan (Furfural).



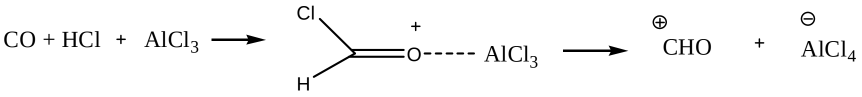
Furan

2-Formyl Furan

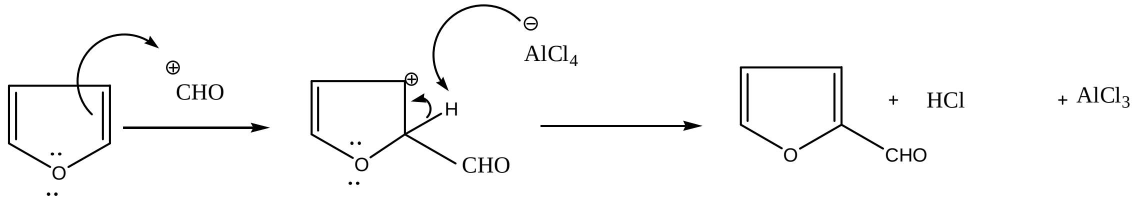
The mechanism for the formation of 2-formyl furan is as follows.

Mechanism:

Step-I: Formation of bromine electrophile



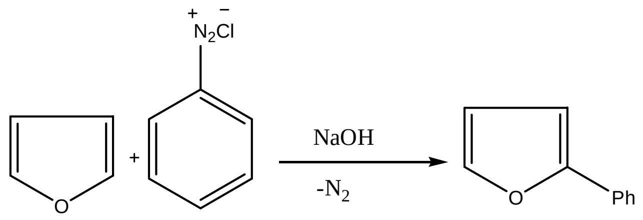
Step-II: Attack of formylcation to the Furan.to obtain 2-bromo furan.



2- Formyl Furan

6) Gomberg Reaction:

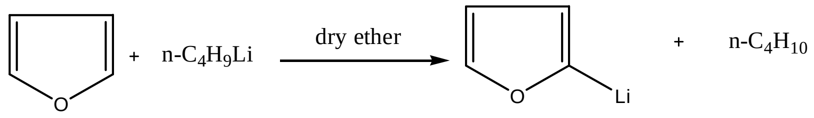
When furan is treated with phenyl dizonium chloride salt in presence of NaOH it gives 2-phenyl Furan with the evolution of nitrogen gas.



Furan 2-Phenyl Furan

7) Reaction with n-butyl lithium:

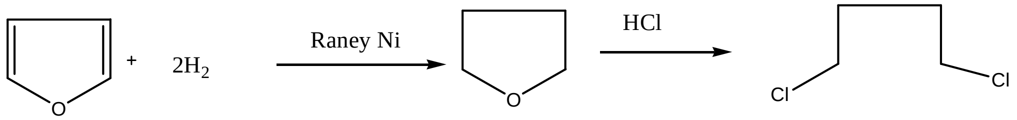
When furan reacts with n-butyl lithium gives 2-lithium furan.



Furan 2-Lithium Furan

8) Reduction of Furan:

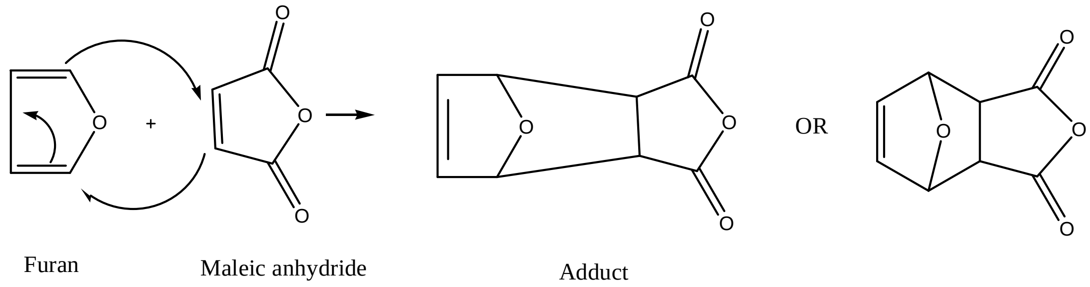
Reduction of furan can be carried out by using H_2 in presence of Raney Ni as catalyst to form tetrahydrofuran, which is industrially important solvent. When HCl is treated with tetrahydrofuran, ring opening takes place to obtain tetramethylenechlorohydrins.



Furan Tetrahydro Furan Tetramethylene chlorohydrin

9) Diel's-Alder reaction:

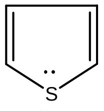
Furan is less aromatic compound than pyrrole and thiophene. It behave as diene, when it react with maleic anhydride (dienophile) forms adduct. This reaction is known as Diels-Alder reaction.



Uses of Furan :

1. Manufacturer of rubber as solvent
2. As preservative for leather and wood.

B. <u>Thiophene/Thiole:</u>



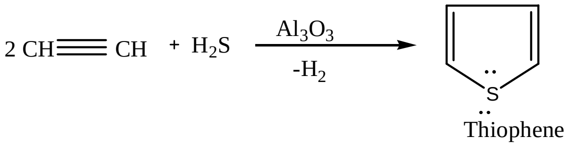
Thiophene

Thiophene is five member heterocylic compound containing a sulphur and four carbon atoms in its cyclic structure.

Synthesis of thiophene:

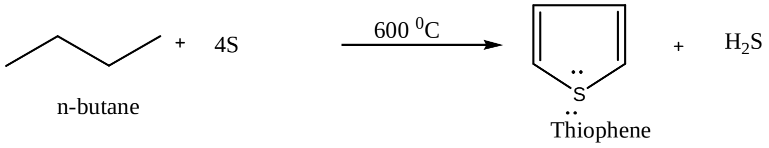
1) <u>From Acetylene</u>:

Thiopheneis prepared by passing a mixture of acetylene and H_2S over the heated alumina (Al_2O_3) at 673^0C.



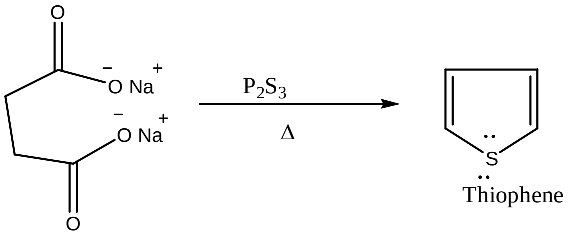
2) <u>From</u> n-butane<u>:</u>

Thiophene is Prepared by cyclization of n- butane reacting with vapoursulphur at 600 ^{0}C.



3) From Sodium succinate:

When sodium succinate is heated with phosphorous trisulphate to yield thiophene. It can be prepared in laboratory by this method.



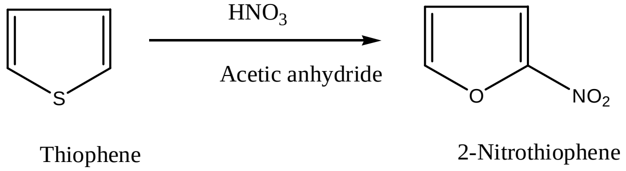
Physical properties of thiophene:

1) It is colourless liquid, and its B.P. = 84^{0}C.(357 ^{0}K)
2) It is insoluble in water, but soluble in organic solvent.
3) It gives lodophenin test (blue colour with isalin and conc. H_2SO_4), which is used for the detection of thiophene impurities in benzene.
4) It gives electrophilic substitution reaction.
5) It is not shows basic property and stable to aquous acids.

Chemical Properties of Thiophene:

1) Nitration:

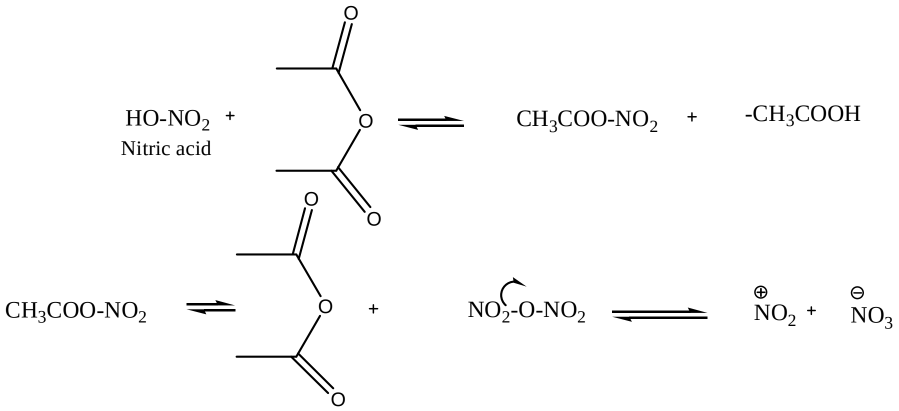
When thiophene is treated with fuming nitric acid in presence of acetic anhydride form 2-nitro thiophene.



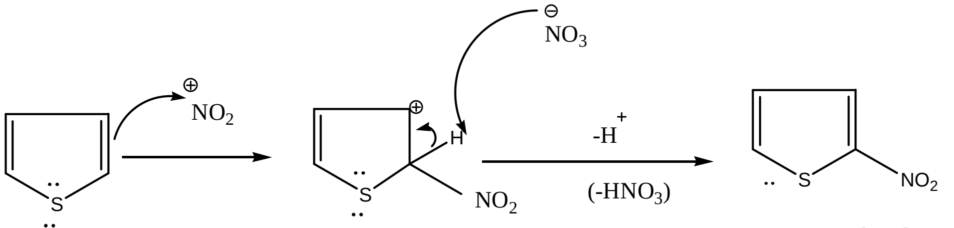
The mechanism for the nitration of thiophene is represented as follow

Mechanism:

Step-I: Formation of Nitronium ion.



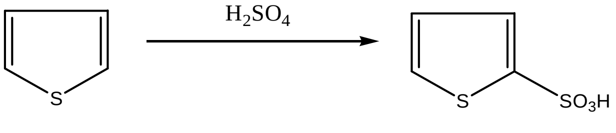
Step-II: Attack of electrophile to the thiophene to form 2-Nitro thiophene



2-Nitrothiophene

Sulphonation:

It is an electrophilic substitution reaction. When thiophene is treated with cold conc. H_2SO_4. It gives thiophene 2-sulphonic acid.



Thiophene thiophene 2- Sulphonic acid

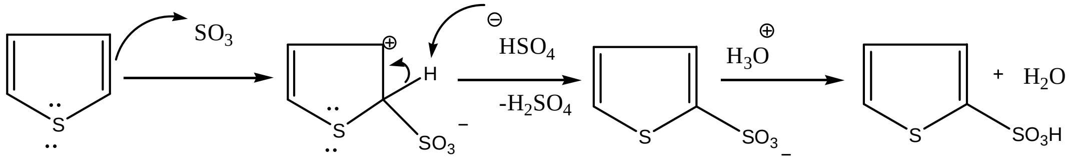
The mechanism for the formation of thiophene 2-sulphonic acid is represented as below.

Mechanism:

Step-I: Formation of electrophile

$$2\,H_2SO_4 \longrightarrow SO_3 + H_3O^+ + HSO_4^-$$

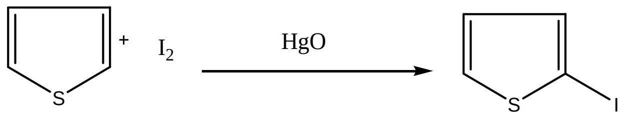
Step-II: Attack of electrophile to the Thiophene ,to form furan 2-sulphonic acid



thiophene 2- Sulphonic acid

2) **Halogenation:**

Halogenation reaction can be carried out by using halogens like F_2, Cl_2, Br_2, I_2 etc. it is an example of electrophilic substitution reaction. When thiophene is iodinated in presence of HgO (mercuric oxide) it form 2-iodothiophene (75%).

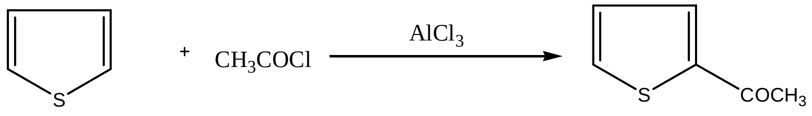


Thiophene

2-iodo thiophene

3) **Friedel-Craft acylation:**

This is an example of electrophilic substitution reaction. When is treated with acetyl chloride or acetic anhydride in presence of $SnCl_2$ as catalyst it gives 2-acetylthiophene.



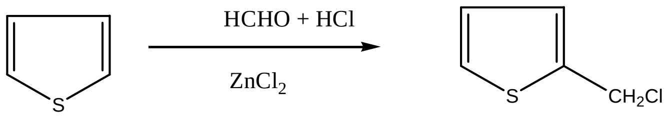
Thiophene

Acetyl Chloride

2- acetyl thiophene

4) **Chloromethylation:**

Chloromethylation is carried out by the reaction of thiophene with formaldehyde and dry HCl gas in presence of $ZnCl_2$ forms 2-chloromethyl thophene as product.

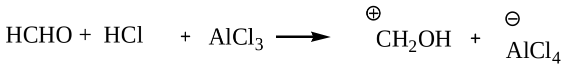


Thiophene 2-Chloromethyl thiophene

The mechanism for the chloromethylation is as follows.

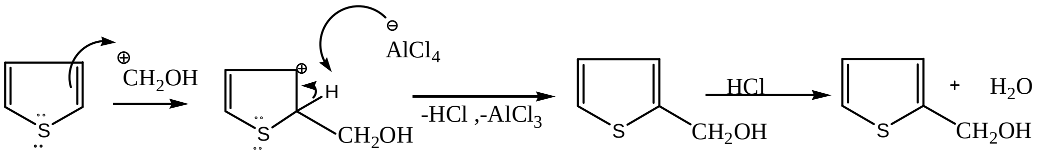
Mechanism:

Step-I: Formation of Electrophile



$$HCHO + HCl + AlCl_3 \longrightarrow \overset{\oplus}{C}H_2OH + \overset{\ominus}{AlCl_4}$$

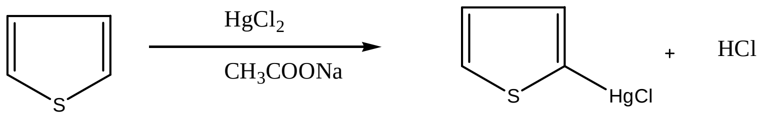
Step-II: Attack of electrophile to thiophene, to form 2-chloromethyl thiophene.



2-Chloromethyl thiophene

5) Mercuration:

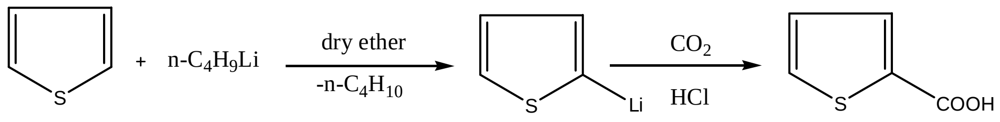
The reaction of thiophene with mercuric chloride in sodium acetate or mercuric acetate in water gives 2-mercuric chloride or 2-aceloxymercurate derivatives of thiophene respectively.



Thiophene 2-mercuric chloride thiophene

6) Reaction with n-butyllithium:

Reaction of thiophene with n-butyllithium in dry solvent like ether gives desired compound. i.e. 2-lithium thiophene. Further treatment of 2-lithio thiophene with CO_2 and HCl gives thiophene 2-carboxylic acid.

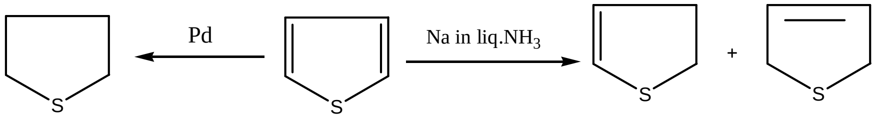


Thiophene

Thiophene 2-Carboxylic acid

B) Reduction:

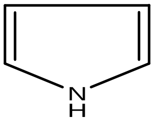
Thiophene on reduction with sodium in liquid ammonia (Birch reduction) gives a mixture of 2,3-dihydrothiophene (B) compounds. Whereas the hydrogenation in presence of large amount of catalyst, (palladium) produces tetrahydrothiophene (C) as product.



(C) Thiophene (A) (B)

C) Pyrrole/Azole:

Pyrrole is five member heterocyclic compound contain a nitrogen and fix carbon atoms in its cyclic structure.

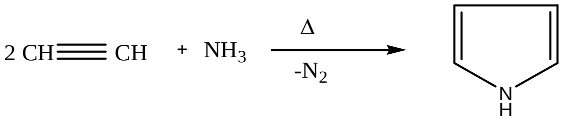


Pyrrol

Synthesis of Pyrrole:

1) From Acetylene:

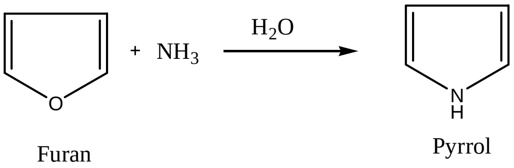
When a mixture of acetylene and ammonia is passed through a red hot tube it gives pyrrole.



Pyrrol

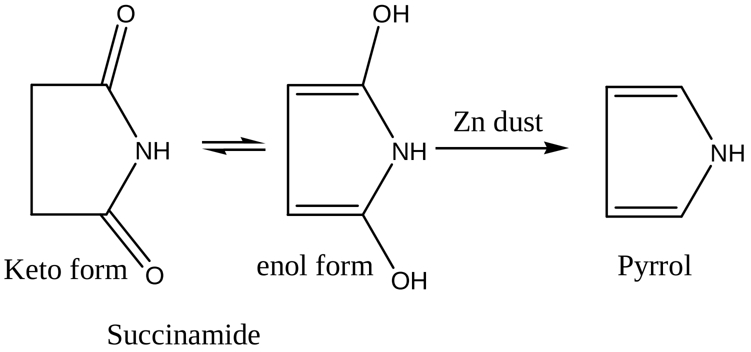
2) From Furan:

Pyrrole is prepared commercially by fraction distillation of bone oil. It is manufactured by passing a mixture of furan, ammonia and steam over a catalyst



3) <u>From succinamide:</u>

Succinamide on distillation with Zn dust produce pyrrole.



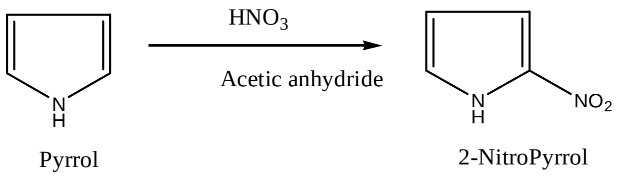
Physical properties of Pyrrole:

1) It is colorless liquid having B.P.=131^{0}C (404 ^{0}K)
2) It is soluble in organic solvent (alcohol , ether), but sparingly soluble in water.
3) It produces red colour on pine splinter moistened with HCl.
4) It is basic in nature.
5) It gives substitution reaction.

Chemical properties of Pyrrole:

1) <u>Nitration:</u>

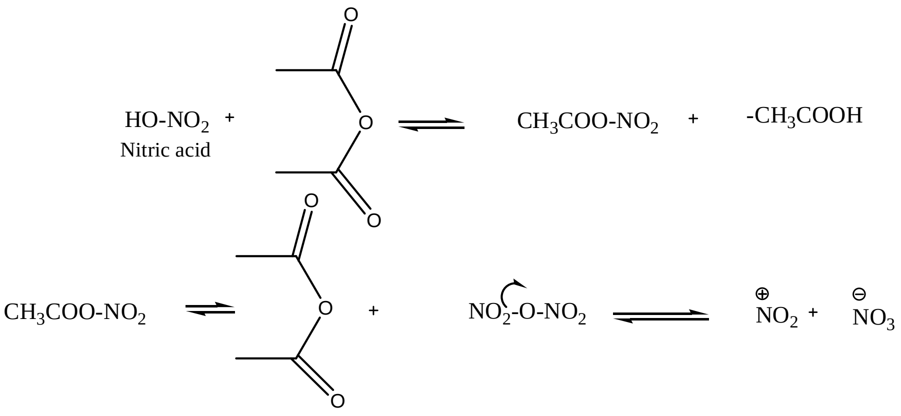
If the Pyrrole is treated with conc. Of HNO_3 or nitrating mixture, it undergoes polymerization. Hence, the nitration of pyrrole is carried out by the treatment of pyrrole with conc. HNO_3 in presence of acetic anhydride to yield 2-Nitropyrrole.



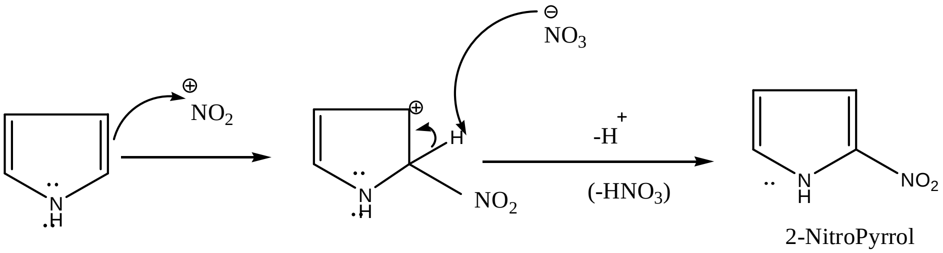
The mechanism of the formation of 2-Nitropyrrole is as follow.

Mechanism:

Step-I: Formation of Nitronium ion.

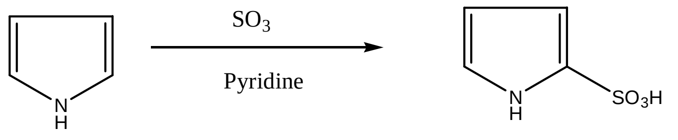


Step-II: Attack of electrophile form 2-Nitro pyrrole



2) <u>Sulphonation:</u>

SO_3 group acts as electrophile due to electron deficient sulphur atom. Sulphonation of Pyrrole is carried out by passing SO_3 gas in to the solution of pyrrole in presence of pyridine to obtain 2-sulphonic acid.



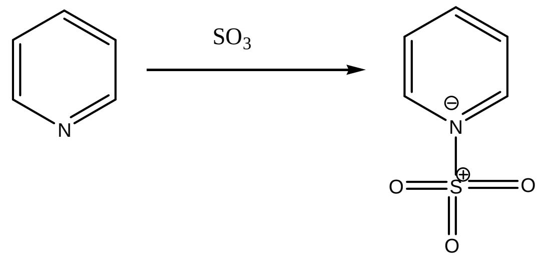
Pyrrol

Pyrrol 2- sulphonic acid

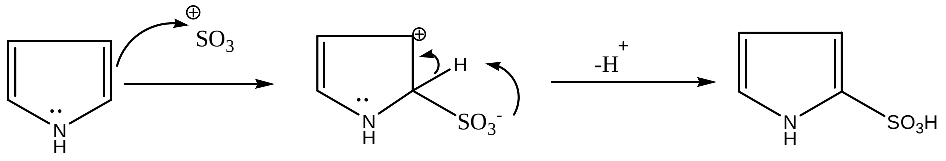
The mechanism for the formation of pyrrole 2-sulphonic acid is as follows.

Mechanism:

Step-I: Generation of 1-protopyridium sulfonateas source of electrophile.



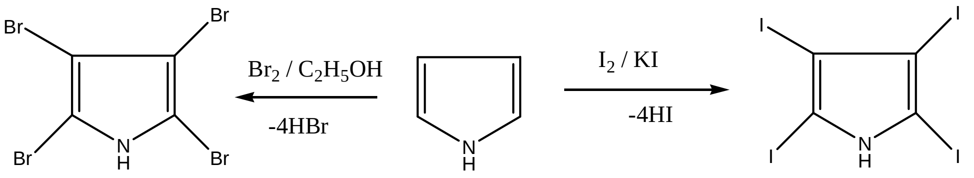
Step-II: Attack of electrophile to the pyrrole,formpyrrole 2-sulphonic acid



Pyrrol 2- sulphonic acid

3) <u>Halogenation:</u>

When the pyrrole is treated with bromine solution it forms tetrabromo and tetraiodopyrrole respectively.



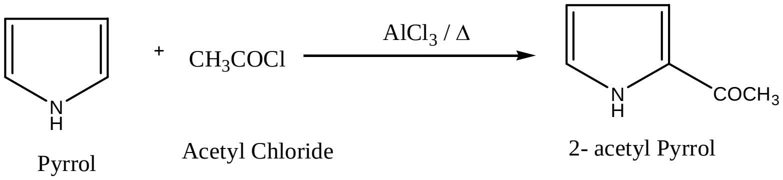
TetrabromoPyrrol

Pyrrol

Tetra iodoPyrrol

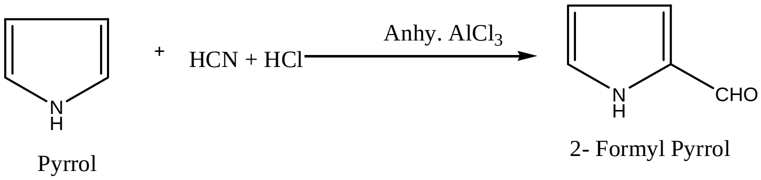
4) Friedel-Crafts acylation:

This is an example of electrophilic substitution reaction. The reaction of pyrrole with acetic anhydride at 250^0C to form 2-acetyl pyrrole.



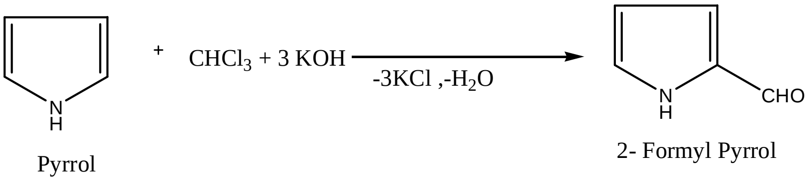
5) Gattermann Reaction:

It is the formylation of aromatic compounds. Pyrrole on treatment with HCN and HCl in presence of anhydrous $AlCl_3$ gives imine complex, further it undergoes decomposition with water to form 2-pyrroldehyde.



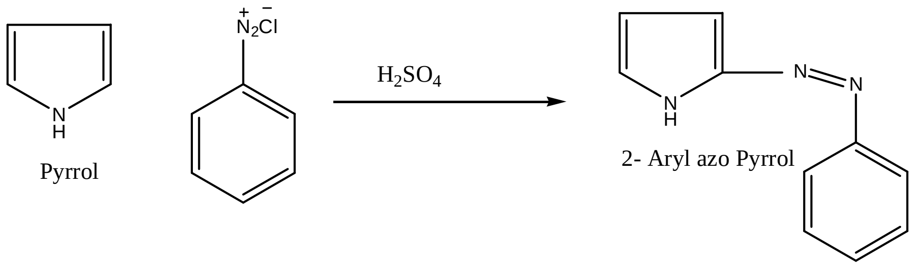
6) Reimer-Tiemann reaction:

Pyrrole reacts with chloroform in presence of alkali to gives pyrrole 2-carbaldehyde. This reaction is known as Reimer-Tiemann reaction.



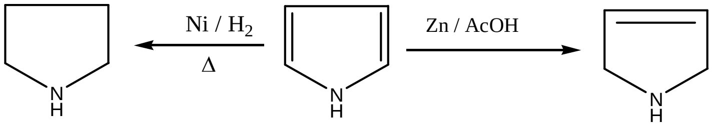
7) Coupling Reaction:

Coupling reaction takes place between pyrrole with the salt of benzene diazonium chloride in acid medium to form 2-Arylazopyrrole. It belongs to azo dye and used as dye.



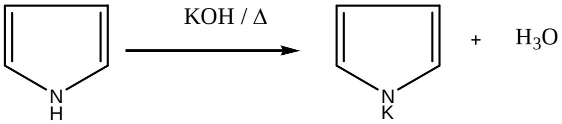
8) **Reduction of Pyrrole:**

Reduction reaction of pyrrole with Zinc and acetic acid produce pyrroline, further reduction is carried out by using hydrroiodic acid and red phosphorous yield pyrrolidine. Direct formation of pyrrolidine is also possible by the catalytic reduction of pyrrole.



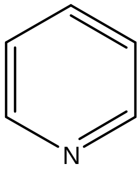
9) **Acidic character:**

When pyrrole is heated with solid KOH, the imino hydrogen of pyrrole is replaced potassium, it indicate the acidic character of pyrrole.



Section-B: Six Member Heterocyclic Compounds

Pyridine/Azine: Pyridine is six membered heterocyclic compound contains five carbons and single nitrogen atom in its cyclic structure.



Pyridine

Molecular Orbital Structure and resonance structure of six membered heterocyclic compounds:

Pyridine is six member aromatic heterocyclic compound containing Nitrogen hetero atom & undergoes SP^2hybridization.

Hybridization in Carbon atom	Hybridization in Nitrogen atom
G.S. $C_6 = 1S^2\, 2S^2\, 2P_X^1\, 2P_y^1\, 2P_z^0$	G.S. $N_7 = 1S^2\, 2S^2\, 2P_X^1 2P_y^1\, 2P_z^1$
E.S. $C_6 = 1S^2\, \underbrace{2S^1 2P_X^1\, 2P_y^1}_{\text{Undergo } SP^2 \text{ hybridization}}\, 2P_z^1$	E.S. $N_7 = 1S^2\, \underbrace{2S^1 2P_X^2 2P_y^1}_{\text{Undergo } SP^2 \text{ hybridization}}\, 2P_z^1$

Unhybridization orbital: in C-atom :$2P_z^1$ & in N-atom :$2P_z^2$

Three SP^2 hybrid orbitals of each carbon atom are involved in the formation of three sigma bonds one C-H bySP^2 – S overlap and C-C/C-N SP^2 – SP^2overlap by axially and P_z orbitals of each carbon atoms has one electon in each remain perpendicular to the trigonal planar SP^2 hybridized carbon atom.

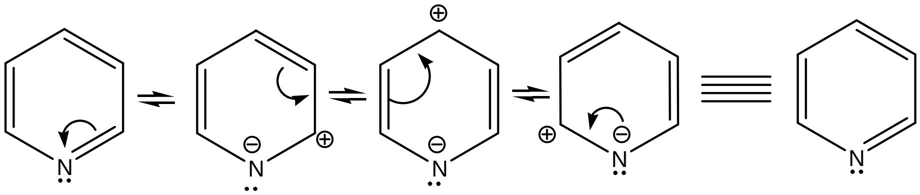
The hybridization of nitrogen atom in pyridine is SP^2. There are three hybrid orbitals of nitrogen among them each two hybrid orbitals containing single electron to form two sigma bonds with adjacent carbon atoms and one hybrid orbital with two electron unshared as lone pair of electron on nitrogen atom.

But each carbon & nitrogen atom contain unhybridizedP_z orbital with one e^- get sidewise overlapped to form new three π bonds get delocalized over all atoms in the ring and possess the aromaticity by obeying Huckel rule $(4n+2)\pi e^-$.

The lone pair of electron present on nitrogen is easily accept the acidic protons to form a salt, hence the pyridine is basic in nature and more basic than pyrrole& furan because of easily available of pair of e^- for protonation.

Resonance structure of Pyridine:

Structure of pyridine can be represented as resonance hybrid by following resonation structure.



Molecular orbital picture of Pyridine:

Molecular orbital structure of Pyridine can be represented as follows.

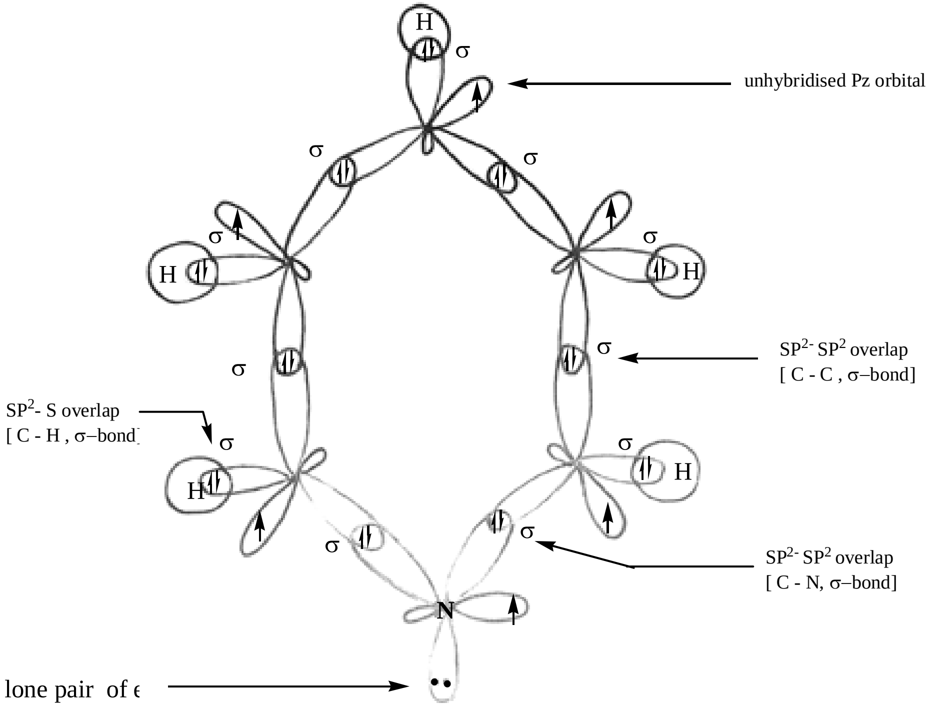
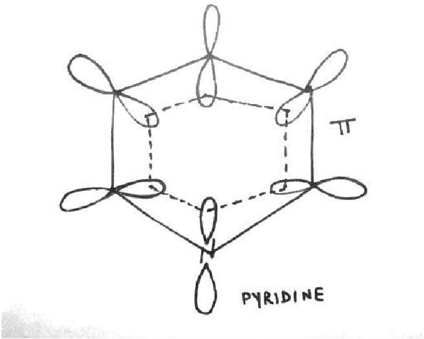


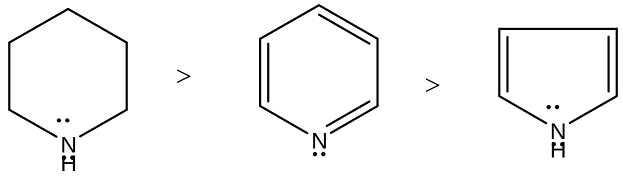
Fig. : Molecular Orbital Diagram of Pyridine



Pyridine is more basic than Pyrrole, and less basic than piperidine?

In pyrrole the lone pair of electron on nitrogen atom get delocalized over the ring, hence it is not easily available for protonation of acidic proton, and make it weak base.

In pyridine, the nitrogen atom has unshared pair of electrons & not involve in delocalization in the ring. Therefore they are easily available for acidic proton.



Piperidine
$K_b = 2 \text{ x } 10^{-3}$

Pyridine
$K_b = 2.3 \text{ x } 10^{-9}$

Pyrrol
$K_b = 2.5 \text{ x } 10^{-14}$

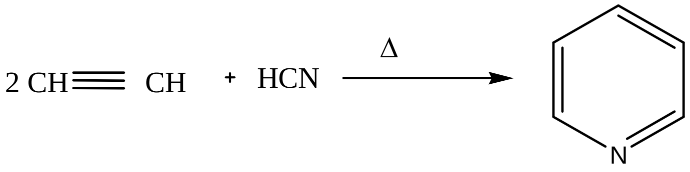
But as compareto pyridine, pipeidine is sec. amine, has more electron density on nitrogen atom than in pyridine ring. The pair of electron on nitrogen in piperidine is more easily available than pyridine.

Hence pyridine is more basic than pyrrole, and less basic than piperidine.

Synthesis of Pyridine:

1) **From Acetylene**:

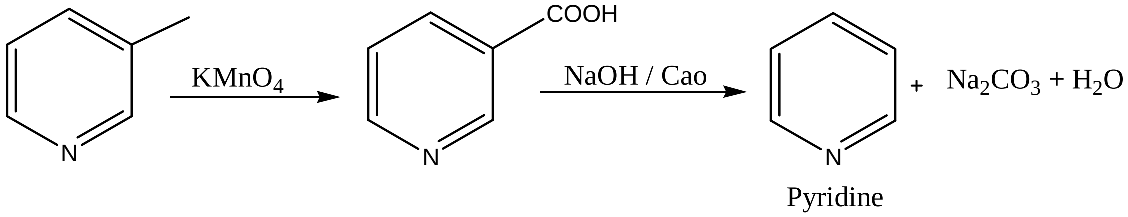
Pyridine can be prepared by passing a mixture of acetylene and hydrogen cyanide through a red hot tube.



Pyridine

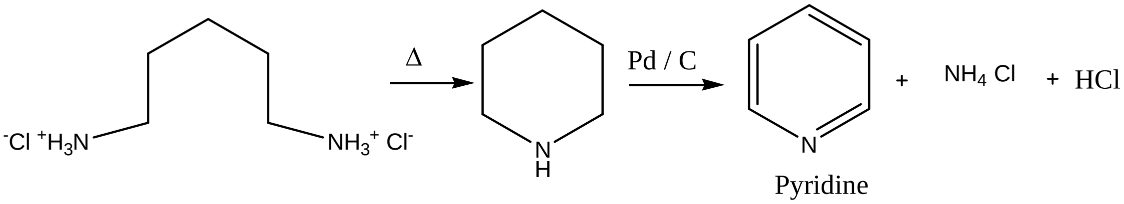
2) **From β-picoline:**

When β-picoline is oxidized to gives Nicotinic acid, further it is distilled with soda lime (NaOH+CaO) to yield Pyridine as product.



3) **<u>From pentamethylenediamine Hydrochloride</u>:**

Pyridine can be synthesized by heating of hydrochloride salt of pentamethylenediamine give piperidine, further oxidation of piperidine with conc. H_2SO_4 at 300^0C or by catalytic hydrogenation with Pd-C, yields pyridine.

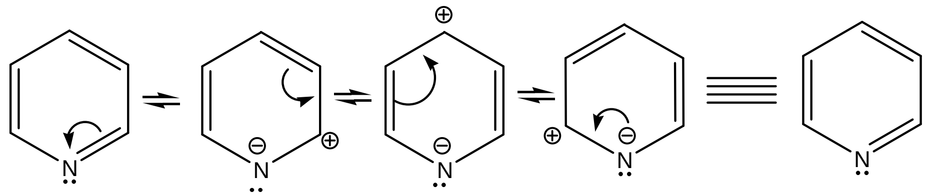


Physical properties of pyridine:

1) It is a colorless liquid with boiling point=115^0C.
2) It has characteristics unpleasant smell.
3) It is miscible with water and hygroscopic.
4) It is used good solvent for organic and inorganic compounds.
5) It is basic in nature.

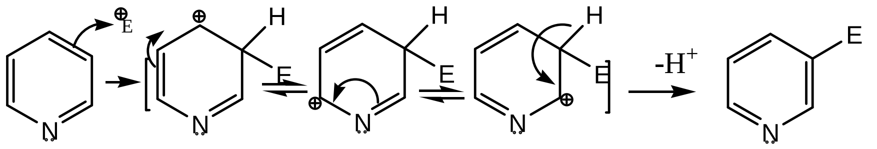
<u>General electrophilic substitution reaction of Pyridine:</u>

1) If we observe the resonance structure of pyridine it shown that, the positive charge appears at position 2,4,6 in pyridine structure. It indicates that due to electron deficiency, nucleophilic substitution reaction is possible at 2,4,6- position in peridine.
2) But the electron density is more at 3,5- position in resonating structure of pyridine. Hence the electrophilic substitution reaction is possible at 3,5- position.



3) If the elctrophilic substitution takes place at 3,5-position/ β-position, the resulting carbocation intermediate is stabilized by resonance without appearing +ve charge on nitrogen atom. Therefore it gives more stable product at 3,5-postion/ β-potion in pyridine structure.
4) If the electrophilic substitution reaction of pyridine takes place at 2,4,6-postions (α,γ-position), the resulting carbocation intermediate is not more stable. Because it is stabilized through resonance with the appearing of +ve charge on nitrogen atom which is unfavorable for electrophilic substitution reaction. Hence e^- substitution of pyridine takes place at 3,5- position.

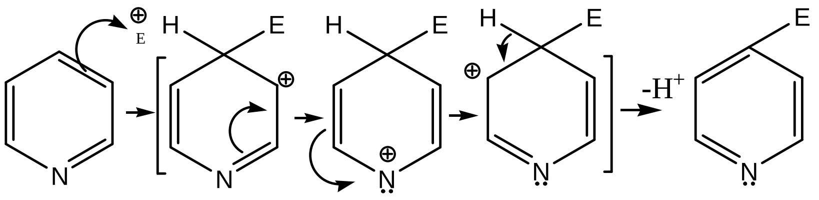
Substitution at 3 or β position



Stable intermediate resonance structure

Stable product

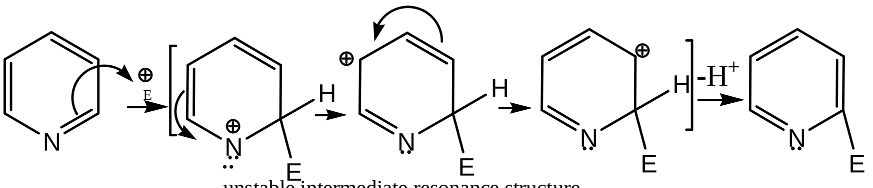
Substitution at 4 or γ position



unstable intermediate resonance structure

unstable product

Substitution at 2, 6 or α position



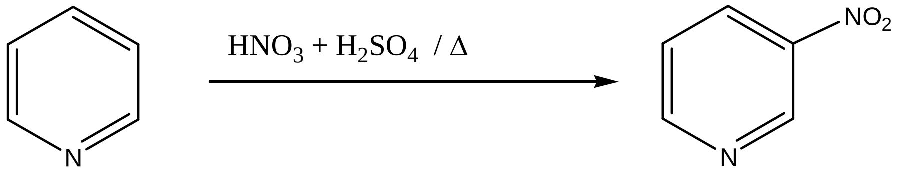
unstable intermediate resonance structure

unstable product

Chemical properties of pyridine:

1) Nitration:

Generally pyridine gives electrophilic substitution reaction at 3- and 5- (or) –β-position. Nitration of pyridine is an example of aromatic electrophilic substitution reaction. Pyridine on treatment with a mixture of fuming nitric acid and conc. H_2SO_4 at 573^0K gives 3-Nitropyridine.



Pyridine

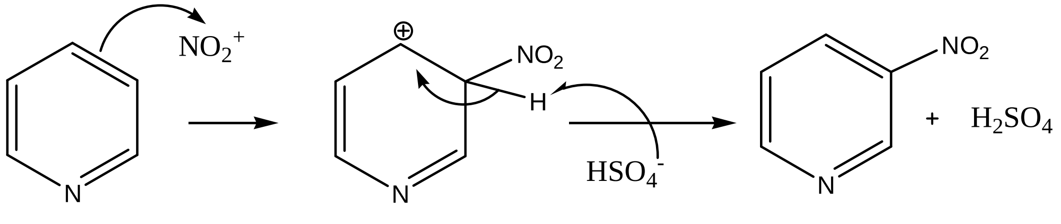
The mechanism for the formation 3-nitropyridine is as follows.

Mechanism:

Step-I: Generation of electrophile, Nitronium ion.

$$HNO_3 + 2\ H_2SO_4 \longrightarrow NO_2^+ + HSO_4^- + H_3O^+$$

Step-II: Attack of Nitronium ion to form cyclohexadienylcation to 3-Nitropyridine.

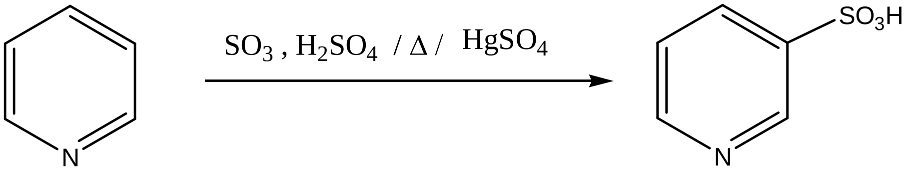


Pyridine

3-Nitro Pyridine

2) Sulphonation:

It is an electrophilic substitution reaction. SO_3 acts as electrophile due to electron deficient sulphur atom. Sulphonation of pyridine is carried by on treatment of pyridine with (SO_3) H_2SO_4 at 230^0C in presence of $HgSO_4$ as catalyst to give pyridine 3-sulphonic acid.

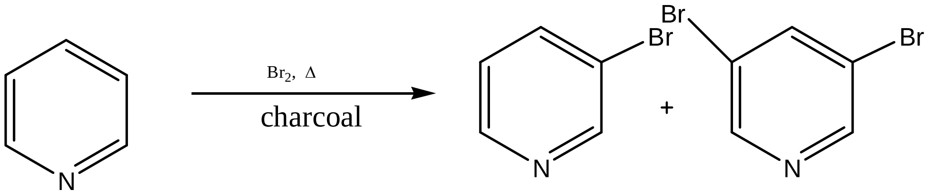


Pyridine

Pyridine3-Sulphonic acid

3) Bromination:

Bromination of pyridine is carried out by the reaction of pyridine with bromine (Br_2) at 300^0C in presence of charcoal as catalyst to give a mixture of 3-bromopyridine and 3,5-dibromopyridine.



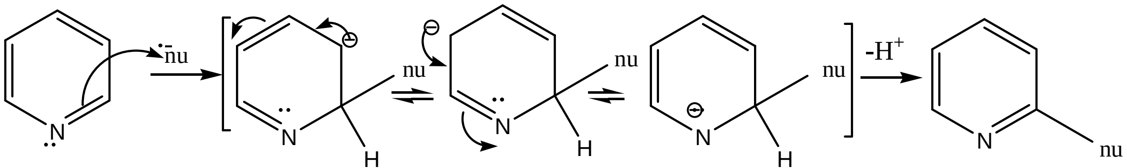
Pyridine

3-BromoPyridine

3,5-DibromoPyridine

General nucleophilic substitution reaction of Pyridine:

Nucleophilic substitutiof pyridine at 2 or 6 position (also same as 4 position)

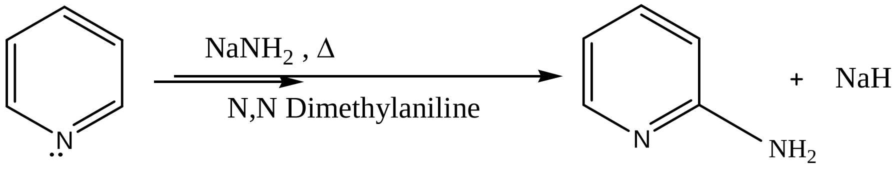


Pyridine

4) Amination of pyridine:

Amination of pyridine is an example of nucleophilic substitution reaction. Pyridine of nucleophile to the 2- or 4-position but not at 3-position permits the development of negative charge on the nitrogen rather than on carbon atom.

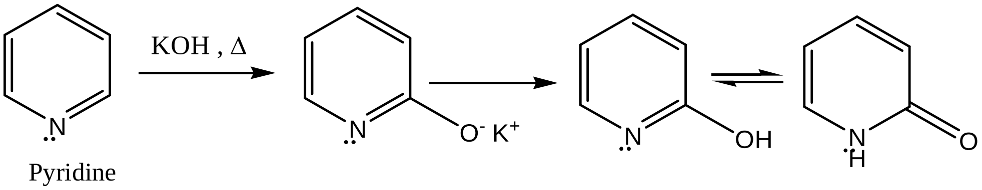
Pyridine on heating with sodamide in N,N-dimethylanlline as solvent forms 2-amino pyridine. This reaction is called tschitschibabin reaction.



Pyridine

5) Reaction with KOH:

It is an example of nucleophilic substitution reaction. When pyridine is heated with potassium hydroxide at 320^{0}C it forms 2-hydroxy pyridine (pyridol), it has more stability in another resonating form of amide i.e. pyridone.



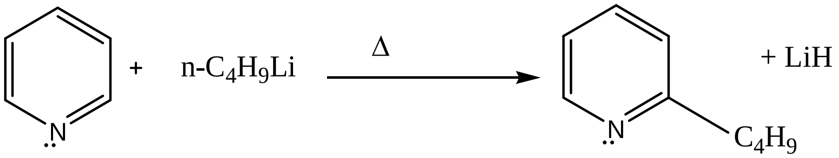
Pyridine

Pyridol

Pyridone

6) Reaction with n-Butylithium:

This is an example of nucleophilic substation reaction. Here the alkyl anion acts as nucleophile, because it is bonded to the electropositive metal. When pyridine is heated with n-butyl lithium it form 2-n-butylpyridine as product.

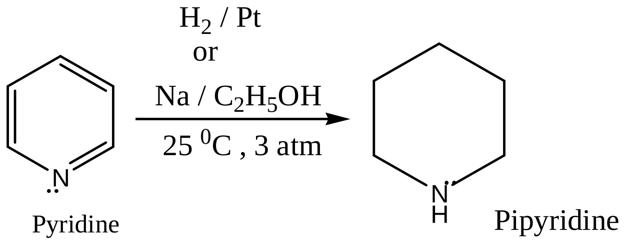


Pyridine

2-n-butyl pyridine

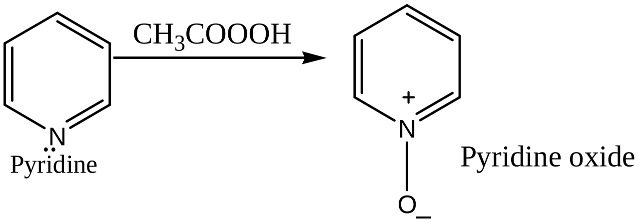
7) Reduction of pyridine:

Reduction of pyridine is carried with Na/C_2H_5OH or catalytic reduction in presenceof Ni or Pt as catalyst under 3-atm pressure to give piperidine as product.



8) **Oxidation of pyridine:**

Oxidation of pyridine by hydrogen peroxide or peracidlike per acetic acid to give pyridine N-oxide.



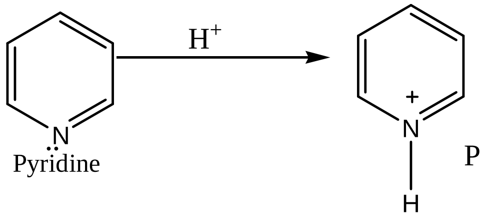
9) Basic character of Pyridine:

Pyridine is a base. Its strength is (K_D=1.4X10^{-9}) as in comparison with aniline (K_D=4.2X10^{-30}) and tertiary amine ($K_DH^+10^{-4}$):

Pyridine is basic in nature due to presence of lone pair of electron on nitrogen atom, which is available for the protonation to form pyridinium ion. In the pyrrole lone pair is conjugated with double bonds and is not easily available for protonation. Therefore pyrrole is weaker base than pyridine.

But pyridine is weaker base than aliphatic tertiary amine because, the hybridization of N atom in pyridine is SP^2 where as in aliphatic tertiary amne is SP^3, and electron in SP^2 is held more tightly than SP^3. Hence it is not easily available for protonation.

Therefore pyridine is stron base than pyrrole but weaker base than aliphatic tertiary amine.



Pyridine

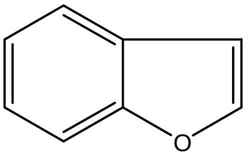
Pyridinium ion

Section-C: Condensed Heterocyclic Compounds:

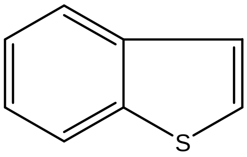
Other than five or six membered heterocyclic compounds, a number of heterocyclic compounds are formed by fusion of one ring into another ring having same or different ring sizeacross the bond are called as condensed heterocyclic compounds.

The benzene ring is fused with furan, pyrrole and thiophene at 2,3-position to formBenzofuran, Benzopyrrole (Indole) and Benzothiophene etc.

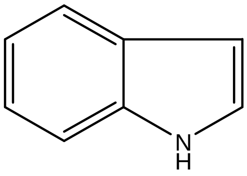
Similarly, benzene fused with pyridine at 2,3-position to formbenzopyridine (Quinoline).



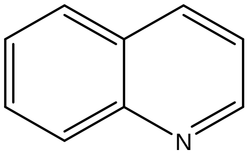
Benzofuran,



Benzothiophene



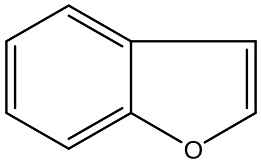
Benzopyrrole (Indole)



benzopyridine (Quinoline)

1) **Indole: (Benzopyrrole)**

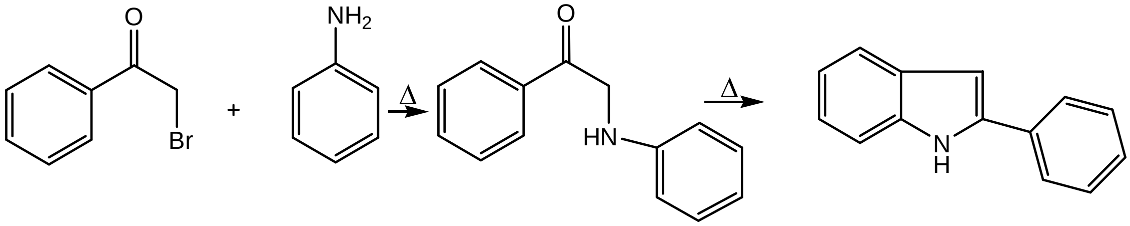
Indole is bicyclic heterocyclic compound containing Nitrogen as hetero atom in fused ring. Indole is a product of fusion of benzene pyrrol. It occurs in coal tar, jasmine flower and orange blossoms. It is parent compound of indigotin as Vat dye.



Benzofuran (IUPAC) & Indole (common)

Bischler'sindole synthesis:

In bischler'sindole synthesis, the substituted 2-phenyl indole is prepared by the heating phenacyl bromide with an excess of ammonia to yield 2-phenyl indole.



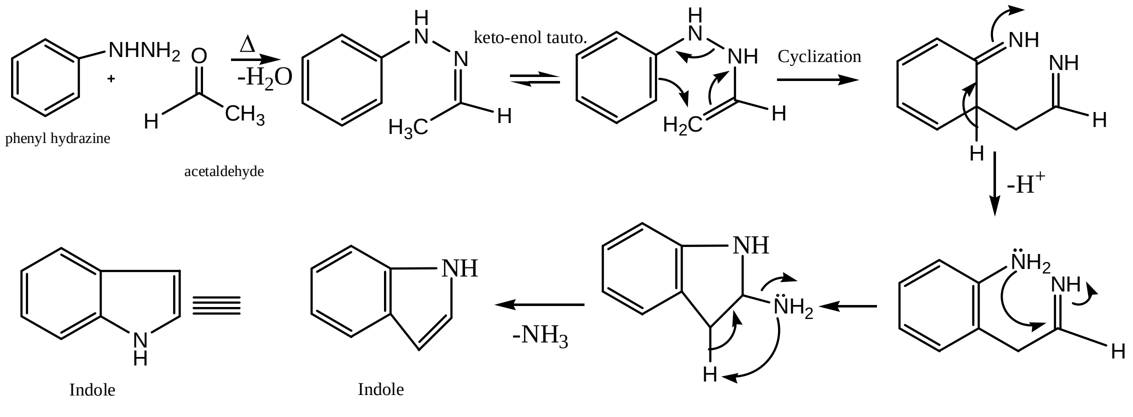
Phenacyl bromide aniline

2-phenyl indol

Fischer's indole synthesis:

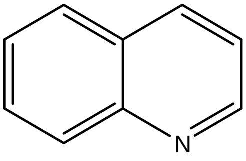
When phenyl hydrazine (or) substituted phenyl hydrazine react with aldehyde or ketone to form corresponding phenylhydrazone as intermediate which on heating with fused zinc chloride /sulphuric acid in ethanol get cyclised to gives indole/ substituted indol.

Mechanism :



2) Quinoline:

Quinoline is bicyclic heterocyclic compound containing nitrogen hetero atom, in which benzene fused to the pyridine at 2,3-position. It occurs in coal-tar and bone oil. Quinolinemolety is present in antimalarial agent (Quinine, cinchonine, chloroquine, pamaquine). Its derivatives are used as laboratory reagent.

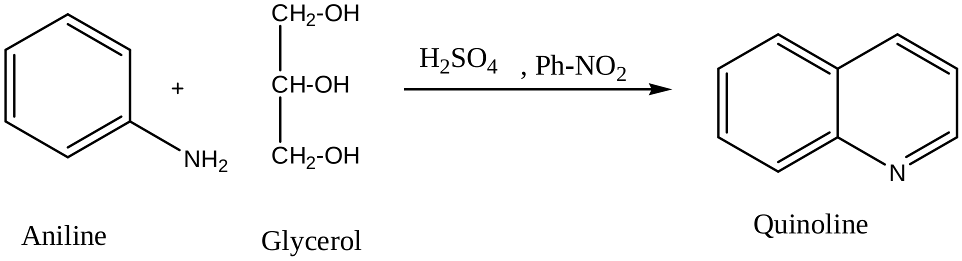


Benzopyridine
(Quinoline)

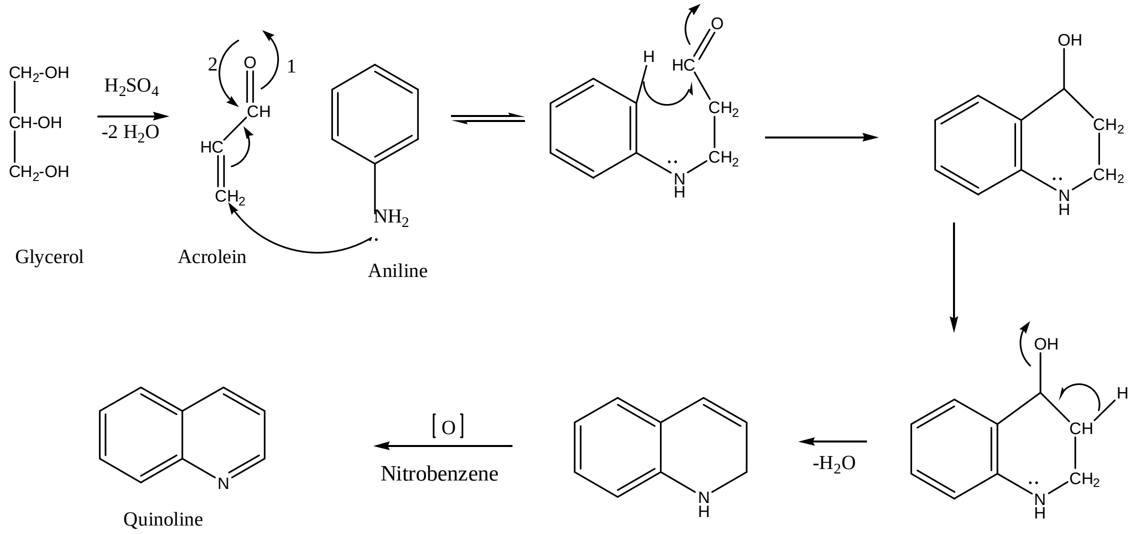
Skraup synthesis:

Heating a mixture of aniline, nitrobenzene, glycerol, conc. Sulphuric acid and ferrous sulphate for six hours to get quinolone. Where nitrobenzene acts as oxidizing agent and ferrous sulphatehelp the reaction making less violent.

Reaction involve formation of acrolineby dehydration of glycerol. Acrolien then reacts with aniline by 1,4-addition to form dihydroquinoline, followed by oxidation to get quinoline.

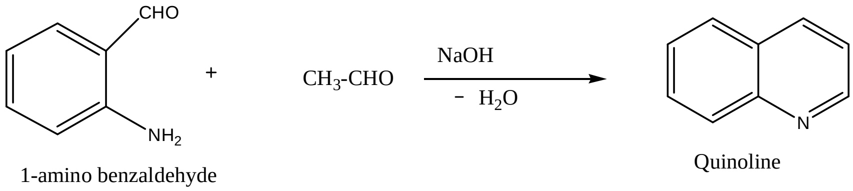


Mechanism :

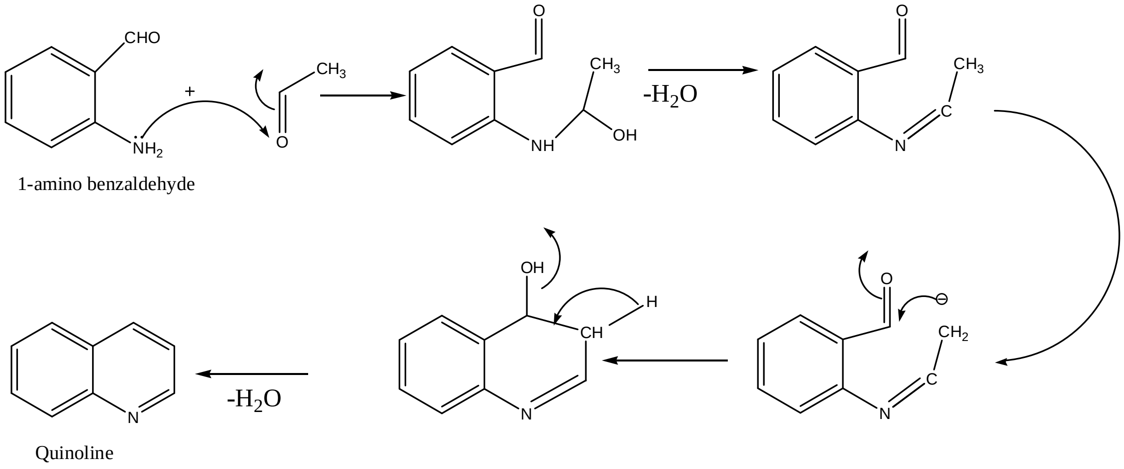


Friedlander' synthesis:

This method is used for the synthesis of quinoline and its derivatives. When the o-amino benzaldehyde is condensed with acetaldehyde in presence of aq. Sodium hydroxide forms quinoline



Mechanism :



Questions:

1) Define heterocyclic compounds? Give their classification .
2) Write the structures&IUPACnamesof following compounds Quinoline, pyrrole, oxole, pyrimidine, 1,3-thiazole.
3) Explain the molecular orbital picture of Furan .
4) Explain the molecular orbital picture of thiophene.
5) Describe the molecular orbital picture ofpyrrole.
6) Explain the molecular orbital picture ofpyridine.
7) Explain the reactivity of Furan, Thiophene and Pyrrole.
8) Explain the stability between Furan, pyrrole and thiophene.
9) Explain the aromaticity of furan, pyrrole and thiophene.
10) Explain, basic property of pyrrol ?
11) Give the synthesis of Furan .
12) Give the synthesis of pyrrole, thiophene and pyridine.
13) How will you convert-Furan in to pyrrole
14) Explain why pyridine undergoes nucleophilic substitution reaction?
15) Electrophilic substitution reaction in pyrrole is takes place at 2 position while in pyridine at 3position.Explain ?
16) Explain the reduction reaction of Furan, pyrrole, thiophene and pyridine?
17) Give the followingsynthesis with mechanism-
    a. Fischer's indole synthesis
    b. Bischler'sindole synthesis
    c. Skaup synthesis
    d. Friedlander synthesis
18) Discuss the acidity and basicity ofpyrrole and pyridine respectively.
19) Pyridine undergoes both electrophilic and nucleophilic substitution reaction, why?
20) How will you convert the following-
    a. Pyridine to 2-amino pyridine

  b. Pyrrole to 2-formyl pyrrole
  c. Thiophene to 2-chloromethyl thiophene
  d. Furan to 2-acetyl furan
  e. Thiophene to 2-acetyl thiophene
  f. Pyrrole to 2-phenylazopyrrole.

21) Gives the uses of of Furan, pyrrole, thiophene and pyridine