

Unit-3

Pharmaceutical Organic Chemistry-III

B.Pharma 4st Sem Notes

UNIT- III

Heterocyclic compounds:

- **Nomenclature and classification**
- **Synthesis, reactions and medicinal uses of following compounds/derivatives**
- **Pyrrole, Furan, and Thiophene**
- **Relative aromaticity and reactivity of Pyrrole, Furan and Thiophene**



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Heterocyclic Compounds:

- Heterocyclic compounds are organic compounds that contain a ring structure containing atoms in addition to carbon, such as sulfur, oxygen or nitrogen, as the heteroatom.
- The ring may be aromatic or non-aromatic.

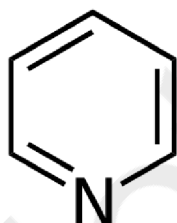
Nomenclature:

There are three systems for naming heterocyclic compounds:

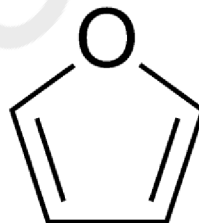
- **Common Name System (Trivial System)**
- **Replacement method**
- **Hantzsch-Widman nomenclature (IUPAC)**

1. Common Name System:

- It is also known as Trivial System.
- In this system, heterocyclic compounds are often named based on historical or common usage.
- For example, compounds like pyridine, furan, and thiophene are named using this system.



Pyridin



Furan

Replacement method:

- The heterocycle's name is composed of the corresponding carbocycle's name and an elemental prefix for the heteroatom introduced (if more than one heteroatom is present they should be listed according to the priority order)

Hantzsch-Widman nomenclature:

- Hantzsch-Widman nomenclature is named after the German chemists Arthur Hantzsch and Oskar Widman, who proposed similar methods for the systematic naming of heterocyclic compounds in 1887 and 1888 respectively.
- According to this system, It provides a standardized way to name heterocycles based on the number of atoms in the ring and the atoms present in the ring.

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- The Hantzsch-Widman system assigns prefixes and suffixes to indicate the type and position of heteroatoms in the ring.

IUPAC name = +Prefix + suffix

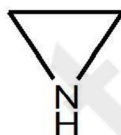
Some prefix of heteroatoms:

- Oxygen (O) – Oxa
- Nitrogen (N) – Aza
- Sulphur (S) – Thia

Suffix:

No. of membered	Saturated (-)		Unsaturated (=/ \equiv)	
	With 'N'	Without 'N'	With 'N'	Without 'N'
03-ir	iridine	irane	irine	Irene
04-et	etidine	etane	ete	et
05-ol	Olidine	olane	ole	ole

Eg: Aziridine



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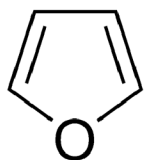
Classification of Heterocyclic compounds:

Heterocyclic compounds may be classified into three types:

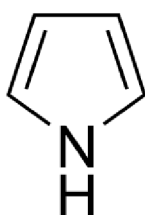
1. Five membered heterocyclic compounds
2. Six membered heterocyclic compounds
3. Fused or Condensed heterocyclic compounds.

1. Five membered heterocyclic compounds:

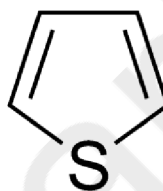
One Heteroatom



Furan

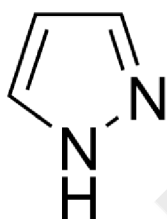


Pyrrole

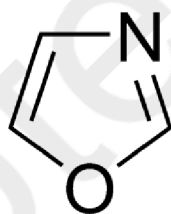


Thiophen

More than one heteroatom:



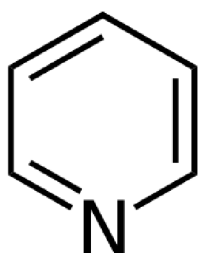
Pyrazole



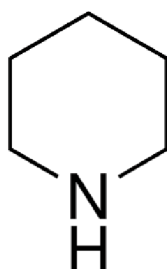
Oxazole

6- membered heterocyclic compound:

One heteroatom:



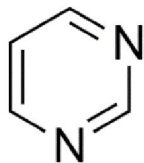
Pyridine



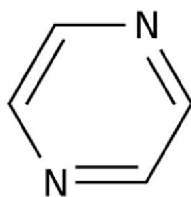
Piperidine

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More than one heteroatom:



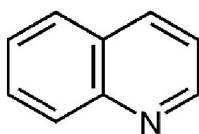
Pyrimidine



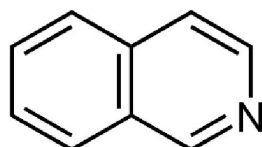
Pyrazine

Condensed heterocyclic Compounds: (Fused Polycyclic System)

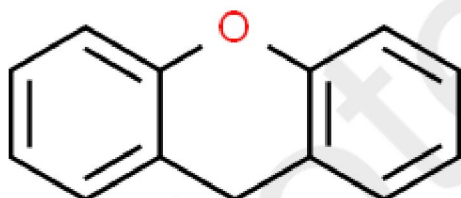
Quinoline



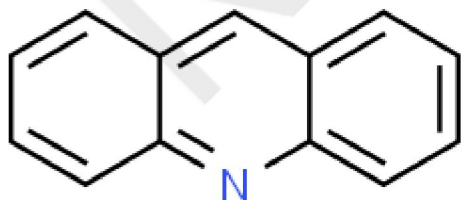
Isoquinoline



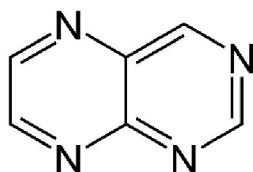
Xanthene



Acridine



Pteridine



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Synthesis, reactions and medicinal uses of following compounds/derivatives

Pyrrole, Furan, and Thiophene

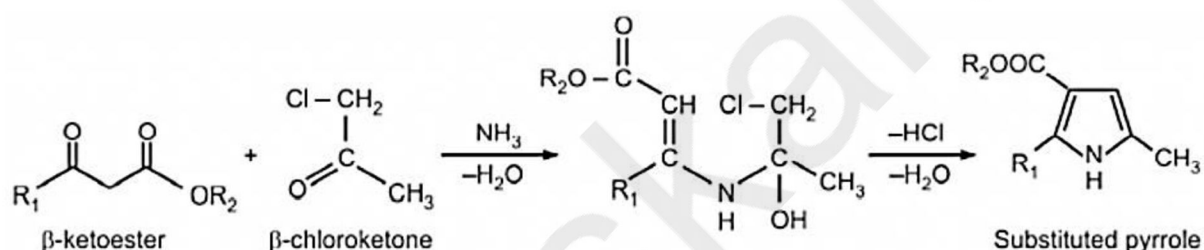
Pyrrole:

- Pyrrole is a heterocyclic aromatic organic compound, a five membered ring with the formula C_4H_4NH .

Synthesis of Pyrrole:

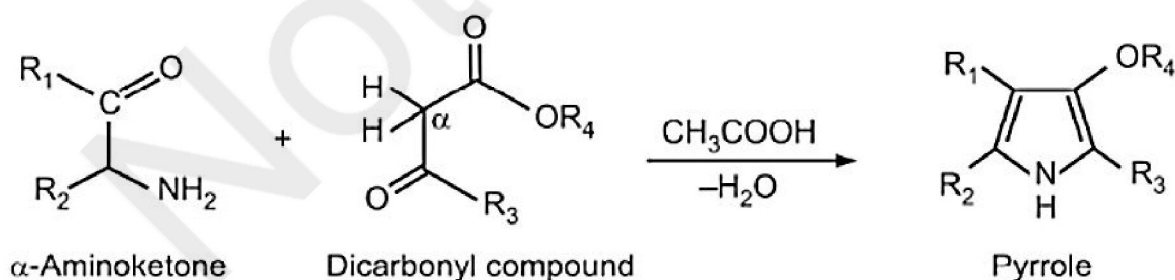
1. Hantzsch pyrrole synthesis –

- Pyrrole occurs when ammonia/primary amine is reacted with a β -haloketone or aldehyde and a β -ketoester or β -chloromethane. In addition to its role as a catalyst, the base is a reactant.



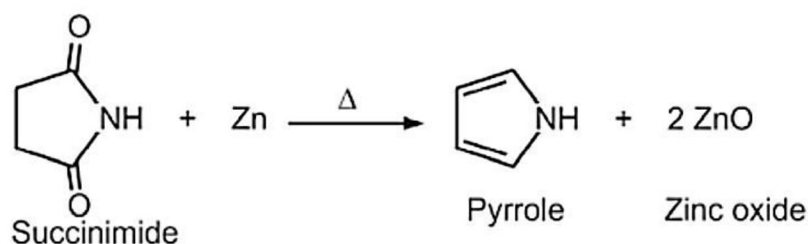
2. Knorr pyrrole synthesis –

- A widely used method is to condensate α -amino ketone with a dicarbonyl compound containing an electron-withdrawing group α , resulting in an activated methylene group (i.e., carbonyl).



3. From the distillation of succinimide –

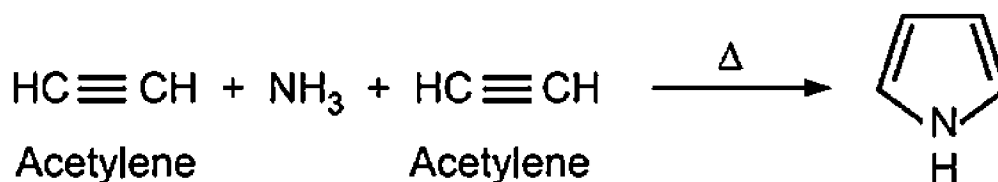
- Succinimide is distilled with zinc dust to produce pyrrole.



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4. From acetylene and ammonia –

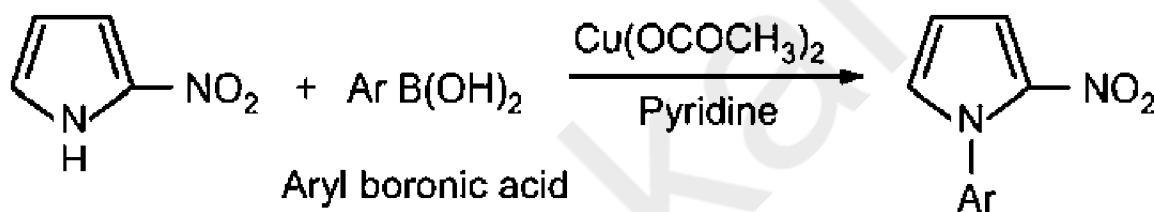
- Pyrrole is made by diluting acetylene and ammonia using a red hot tube.



Chemical Reactions:

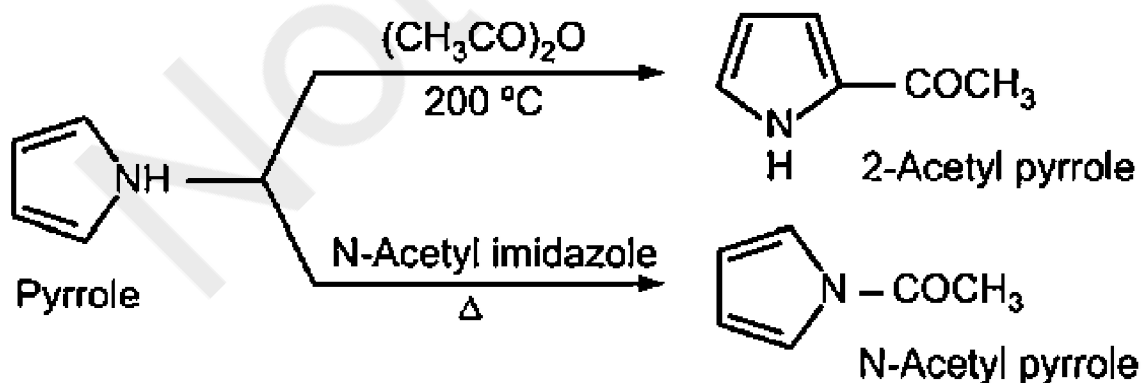
1. Alkylation and arylation –

- If an alkyl halide are dissolved in sodium or potassium salt, it forms an N-alkylpyrrole. A pyrrole ring with electron-withdrawing substituents is more likely to undergo N-alkylation and N-arylation.



2. Acylation –

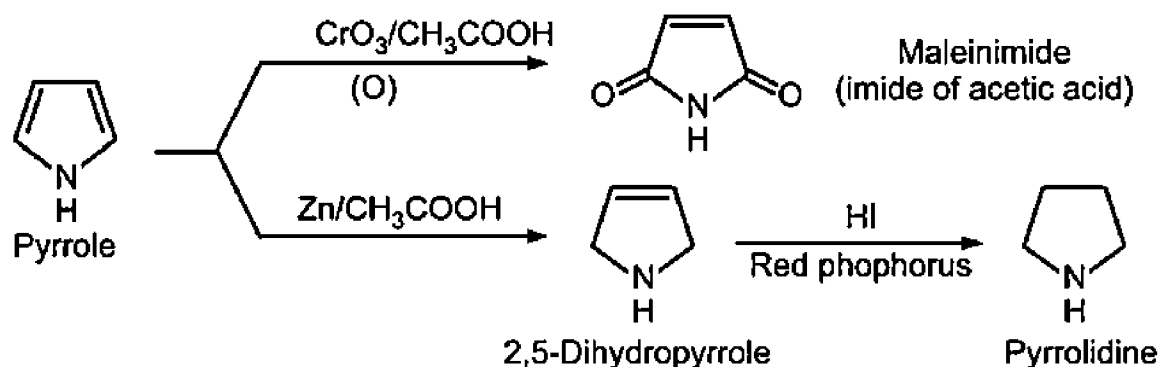
- The reaction between pyrrole and acetic anhydride produces 2-acetylpyrrole at 200°C, while the reaction between pyrrole and N-acetyl imidazole yields N-acetylpyrrole.



3. Oxidation and reduction –

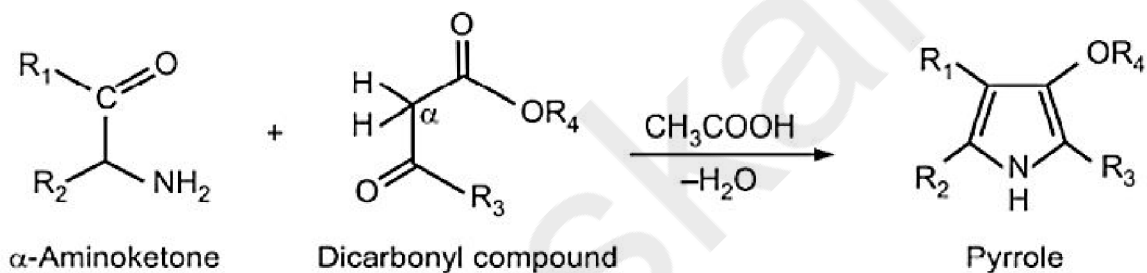
- Upon oxidation, Pyrrole is converted into maleimide, which on reduction is converted into Pyrolidine.

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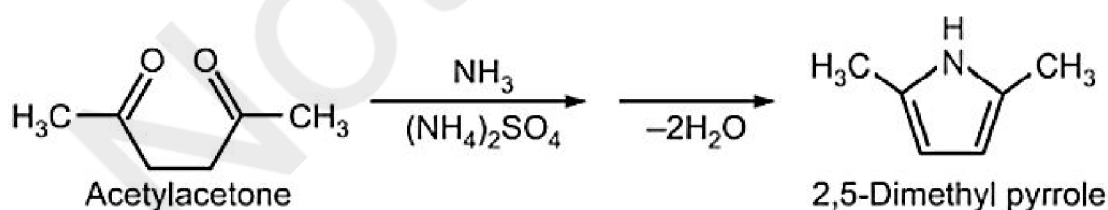
4. Knorr pyrrole synthesis –

- A widely used method is to condensate α - amino ketone with a dicarbonyl compound containing an electron-withdrawing group α , resulting in an activated methylene group (i.e., carbonyl).



5. Paal-Knorr pyrrole synthesis –

- A substituted pyrrole is formed by condensing 1,4-dicarbonyl compounds with ammonia or a primary amine. Succinaldehyde and ammonia are used to create pyrrole.

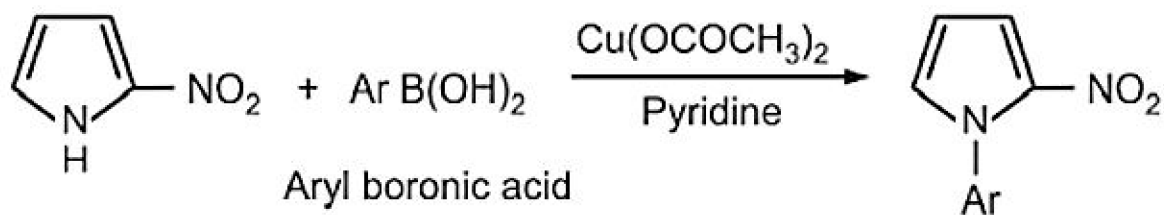


Chemical Structure:

1. Alkylation and arylation –

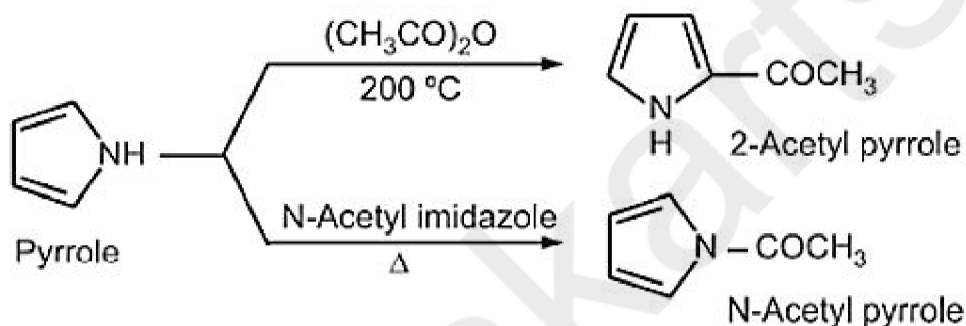
- If an alkyl halide are dissolved in sodium or potassium salt, it forms an N-alkylpyrrole. A pyrrole ring with electron-withdrawing substituents is more likely to undergo N-alkylation and N-arylation.
- A mono-C-alkylation of pyrrole cannot be achieved by direct reaction with alkyl halides

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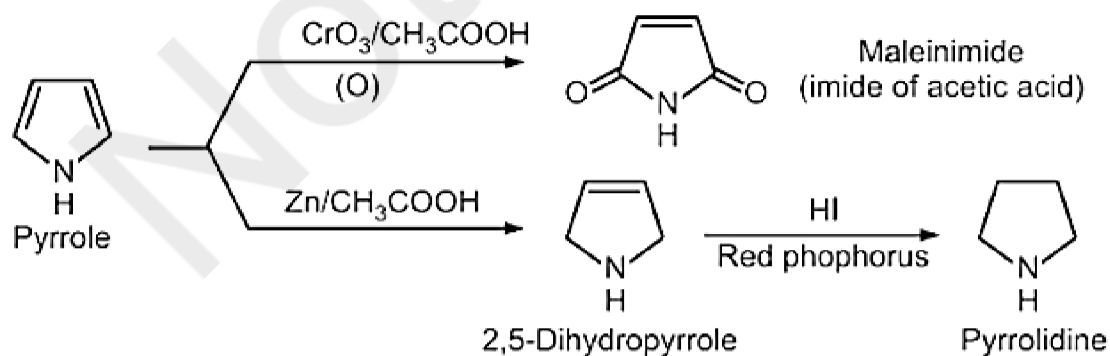
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- The reaction between pyrrole and acetic anhydride produces 2-acetylpyrrole at 200°C, while the reaction between pyrrole and N-acetyl imidazole yields N-acetylpyrrole.



3. Oxidation and reduction –

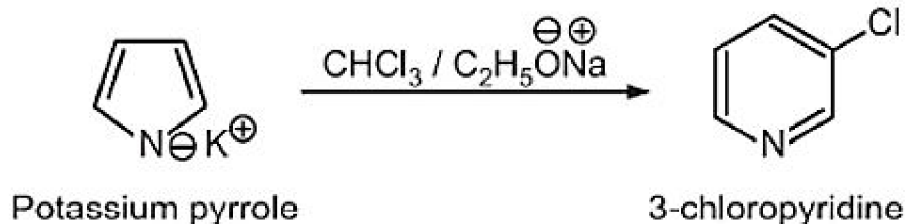
- Upon oxidation, Pyrrole is converted into maleimide, which on reduction is converted into Pyrrolidine.



4. Ring expansion –

- Heat and sodium ethoxide expand pyrrole into pyridine (six-membered ring).

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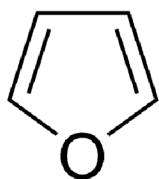
Medicinal Uses:

- Pyrrole moiety has been found in various active compounds with anti-inflammatory, antiseptic, antibacterial, lipid-lowering and anticancer properties.

Furan:

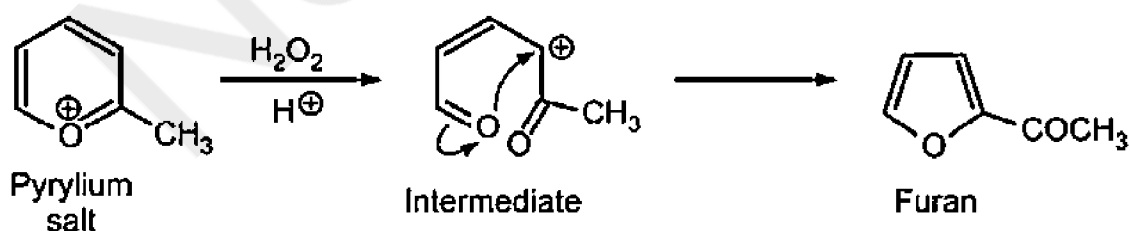
- Furan is a heterocyclic organic compound, consisting of a five membered aromatic ring with four carbon atoms and one oxygen atom.
- It is a colourless, inflammable, volatile, liquid with boiling point of 32°C.

Structure:

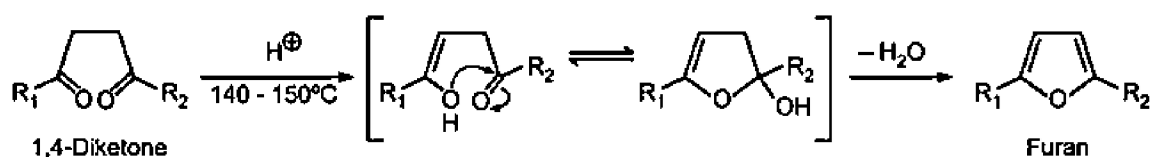


Synthesis of Furan:

1. From ring contraction - Aqueous hydrogen peroxide and perchloric acid oxidize pyrylium salts to form 2-acylfurans through ring contraction.

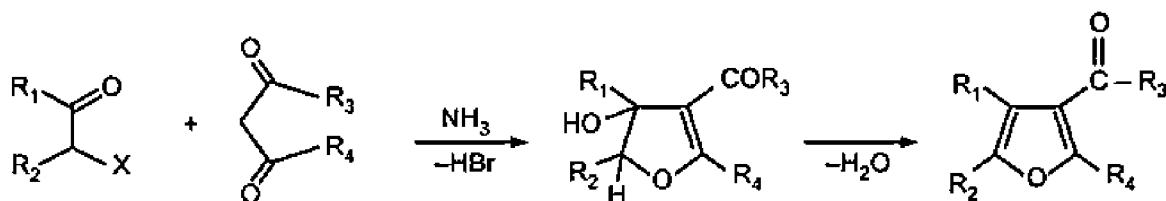


2. Paal-Knorr synthesis - A cyclization of 1,4-diketones followed by dehydration produces furans under non-aqueous acidic conditions.

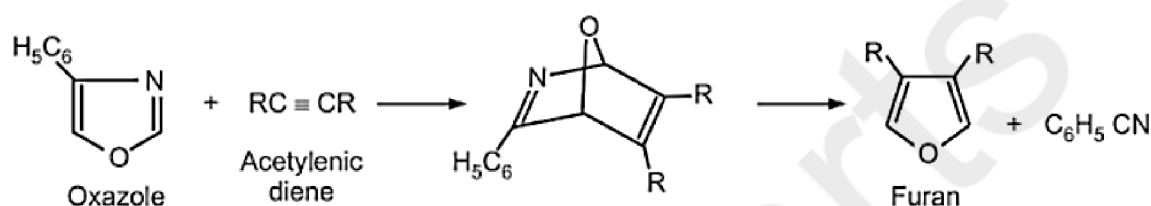


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3. Fiest-Binary synthesis - An ammonia or pyridine base converts a α - halo ketone (or diketone) to a β - ketone (or diketone).

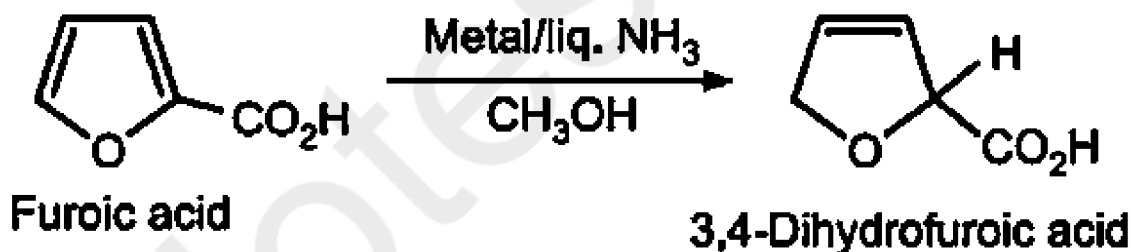


4. From other heterocycles - The cycloaddition of oxazoles with acetylenic dienophiles is a Diels-Alder reaction. Nitrile is lost in the reaction and furan is formed.



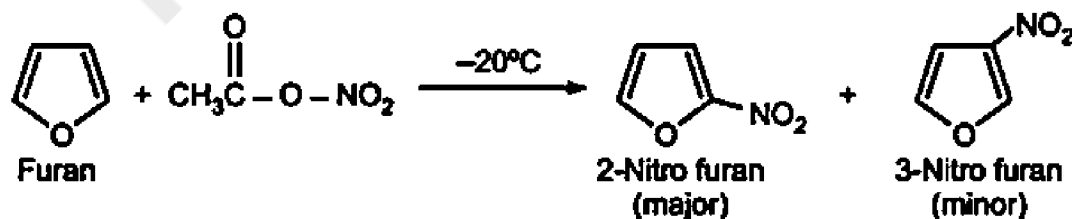
Chemical Reaction:

1. Reduction - A simple furan cannot be reduced to a tetrahydrofuran without opening its ring. It is possible to decompose furoic acid into dihydrofurans.



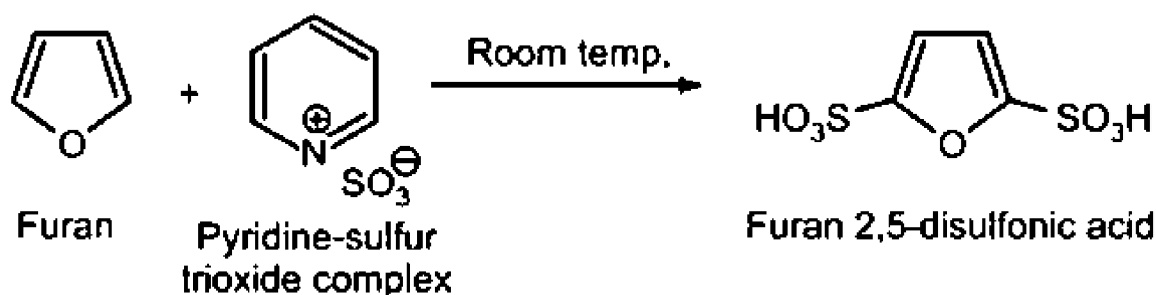
Electrophilic Substitution

1. Nitration - Furan is nitrated at a low temperature with acetyl nitrate, a mild nitrating agent.

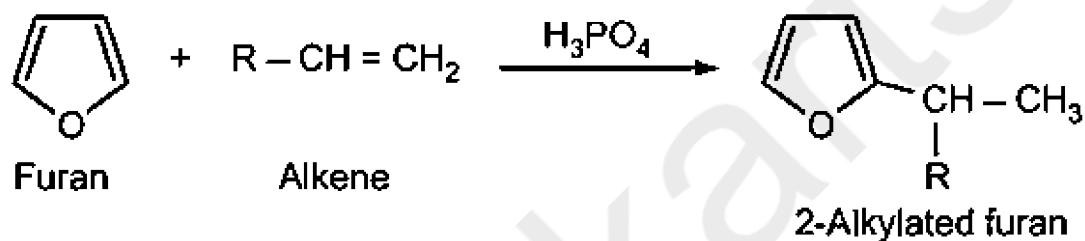


2. Sulphonation - Furan can be sulfonated with sulfur trioxide, pyridine, or dioxane at room temperature to form 2,5-disubstituted furan.

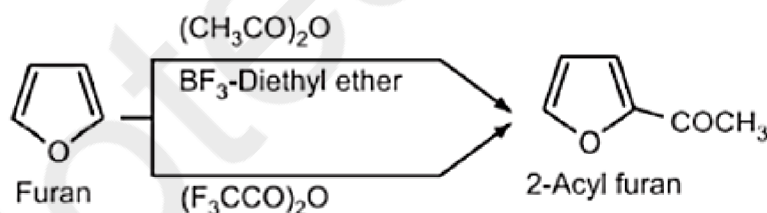
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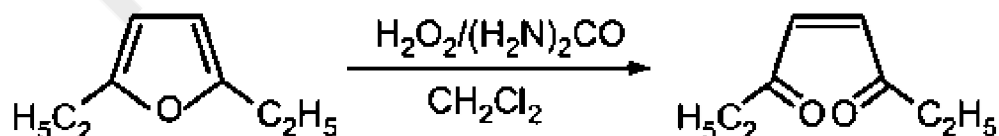
3. Alkylation - Friedel-Crafts alkylation does not occur with furan because of its acid sensitivity. A mild catalyst, such as phosphoric or boron trifluoride, can be used to alkylate furan at position-2 with alkene.



4. Acylation - The acylation of furans with acids anhydrides or acids halides normally requires a mild catalyst, such as phosphoric acid or boron trifluoride. It is not necessary to use a catalyst to acylate trifluoroacetic anhydride.



5. Oxidation - If sodium hypochlorite, hydrogen peroxide, or meta chloroperbenzoic acid is used to treat furan, ring opening occurs.



Medicinal Uses:

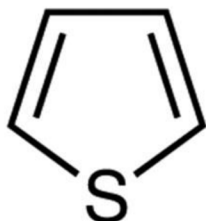
- These compounds are widely employed as antibacterial, antiviral, anti-inflammatory, anti-fungal, anti-tumor, anti-hyperglycemic, analgesic, anti-convulsant, etc.
- It is used as solvent for resins
- Uses in the production of agriculture chemicals stabilizers and insecticides.

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Thiophene:

- Thiophene is a monocyclic heteroarene that is furan in which the oxygen atom is replaced by a sulfur.
- It has a role as a non-polar solvent.
- It is a mancude organic heteromonocyclic parent, a member of thiophenes, a monocyclic heteroarene and a volatile organic compound.

Structure:

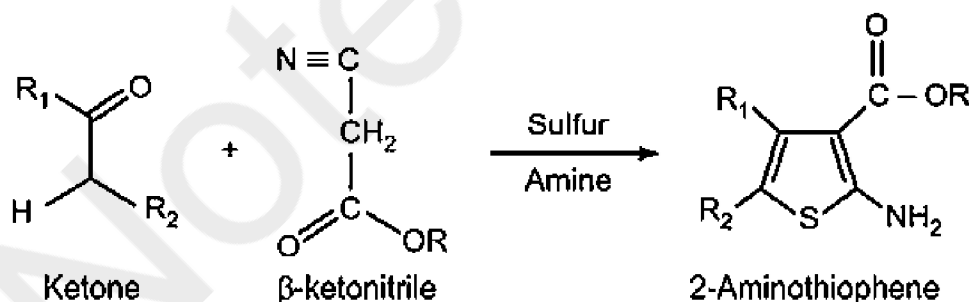


Chemical Formula: C₄H₄S

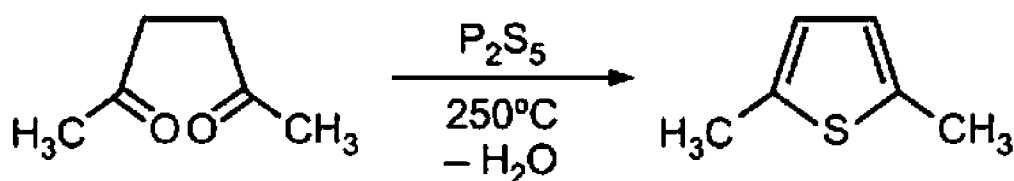
Molecular Weight: 84

Synthesis of Thiophene:

1. Gewald Aminothiophene synthesis - Base-catalyzed condensation of a ketone with a β -ketonitrile yields an olefin, which is the precursor for 2-aminothiophenes upon cyclization with sulfur.



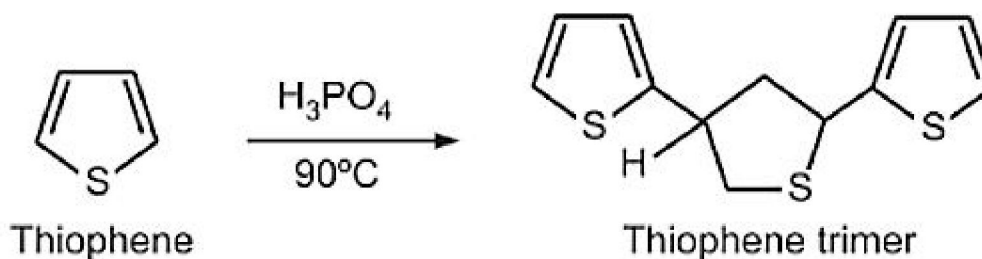
2. Paal-Knorr synthesis – In this reaction Acetylacetone reacted with phosphorus pentasulphide and formed derivatives of pyrrole (2,5-dimethyl thiophene).



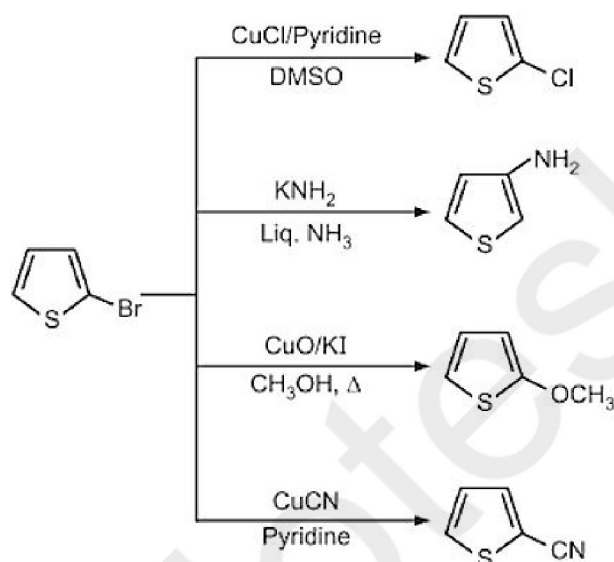
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Chemical Reactions:

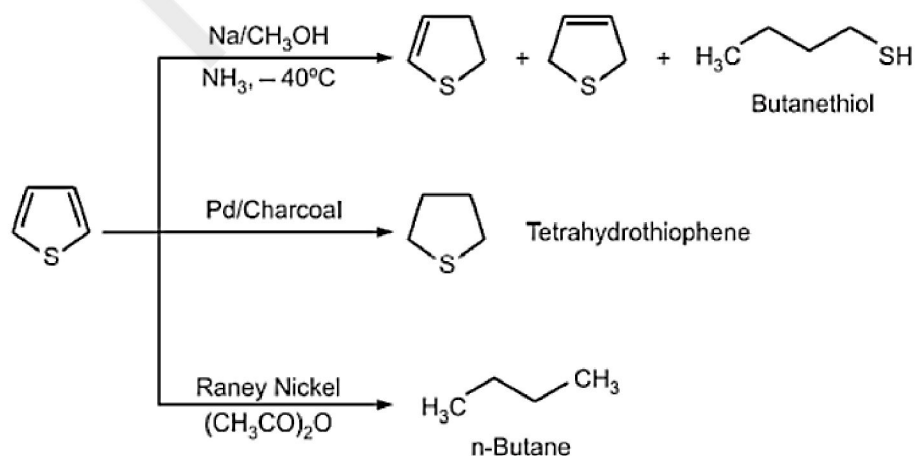
1. Protonation: Acids have little effect on thiophene. Hot phosphoric acid, for example, produces thiophene trimer when exposed to very strong acids.



2. Nucleophilic reaction - Substituted thiophenes containing electron-withdrawing substituents have a much higher nucleophilicity.



3. Reduction:



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Medicinal Uses:

- They are widely used as building blocks in many agrochemical & pharmaceutical.
- The benzene ring of a biologically active compound may after be relieved by a thiophene without loss of activity.
- Thiophene derivatives possess remarkable activities like antibacterial, anti-inflammatory, anti-anxiety, anti-psychotic and anticancer.

Relative aromaticity and reactivity of Pyrrole, Furan and Thiophene

- Furan, Pyrrole and thiophene each consists of a flat ring of four carbon atoms and a hetero atom with a cyclic electron cloud of six delocalized π -electrons. So according to Huckel rule, all these compound shows aromatic character.
- All the three compounds have five contributing structure in which there is only one structure in each case which does not involve charge separation.
- The relative aromaticity of Pyrrole, Thiophene and Furan depends upon the electronegativities of the hetero atoms present in pyrrole, furan and thiophene and it is in the order as follows:



- It means oxygen has very less tendency to release or donate its pair of electrons to the aromatic sextet. So number of ionic resonating structure should be least in case of Furan followed by Pyrrole and should be maximum in case of Thiophene. So the order of aromaticity will be



- All these heterocycles are less aromatic than benzene as all the resonating structures of benzene are uncharged and equally stable and involves no separation of +ve and -ve charges.
- The resonance energies of these heterocycles is less than that of benzene. So the aromatic character of these heterocycles relatives to benzene decreases in order as

