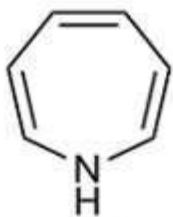


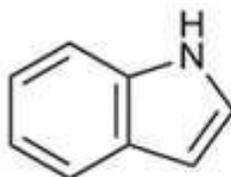
Heterocyclic Compounds

(PYRROLE, FURAN & THIOPHENE)

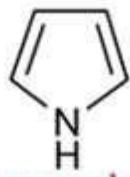
Structures of some heterocyclic compounds



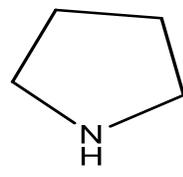
azepine



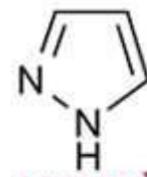
indole



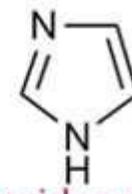
pyrrole



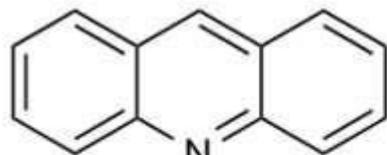
Pyrrolidine



pyrazole



imidazole



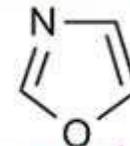
acridine



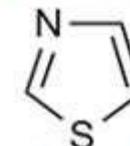
furan



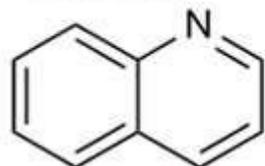
Tetrahydrofuran



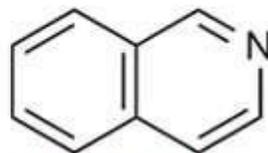
oxazole



thiazole



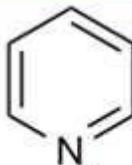
quinoline



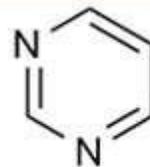
isoquinoline



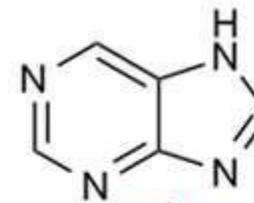
thiophene



pyridine



pyrimidine



purine

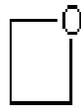
Cont...



ethylene oxide
oxirane



ethylenimine
aziridine



trimethylene oxide
oxetane



furan
oxole



tetrahydrofuran
oxolane



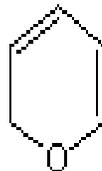
thiophene
thiole



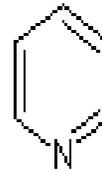
pyrrole
1*H*-azole



pyrrolidine
azolidine



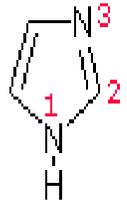
pyran
2*H*-pyran



pyridine
perhydropyridine



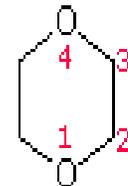
piperidine



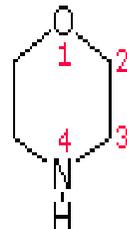
imidazole
1,3-diazole



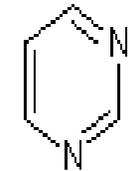
thiazole
1,3-thiazole



dioxane
1,4-dioxane

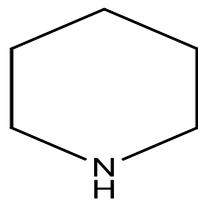


morpholine
tetrahydro-1,4-oxazine

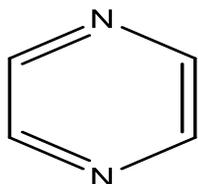


pyrimidine
1,3-diazine

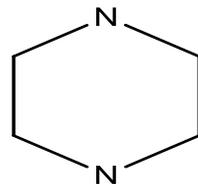
Cont...



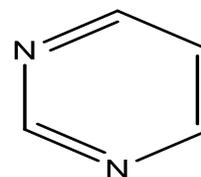
Piperidine



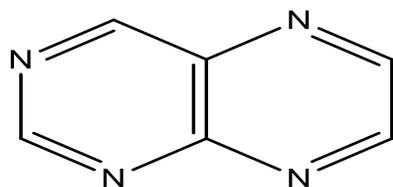
Pirazine



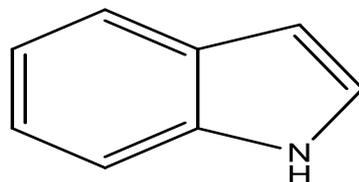
Piperazine



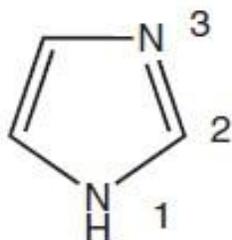
Pyrimidine



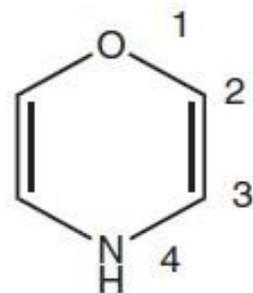
Pteridine



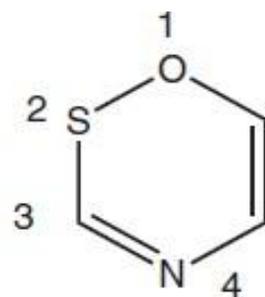
Indole



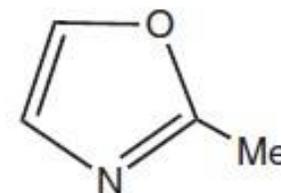
1H-1,3-diazole
(imidazole)



4H-1,4-oxazine



1,2,4-oxathiazine



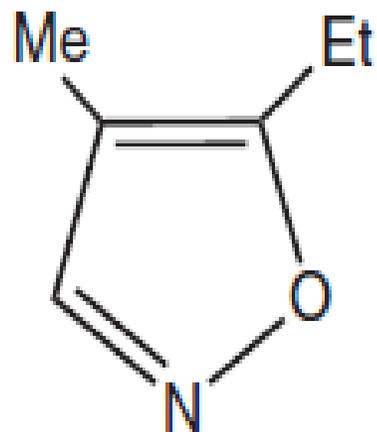
2-methyl-1,3-oxazole

Heterocyclic compounds

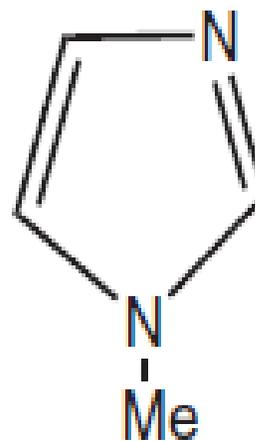
Rings with more than one heteroatom

- which gives $O > S > N > P$. Each heteroatom is then given a number as found in the ring, with that of highest priority given position 1.
- A saturated heteroatom with an extra-hydrogen attached is given priority over an unsaturated form of the same atom, as in 1H-1,3-diazole (see the following discussion).
- The numbers are grouped together in front of the heteroatom listings (thus, 1,3-oxazole, not 1-oxa-3-azole).
- The heteroatom prefixes follow the numbers in the priorities given previously

Rings with more than one heteroatom

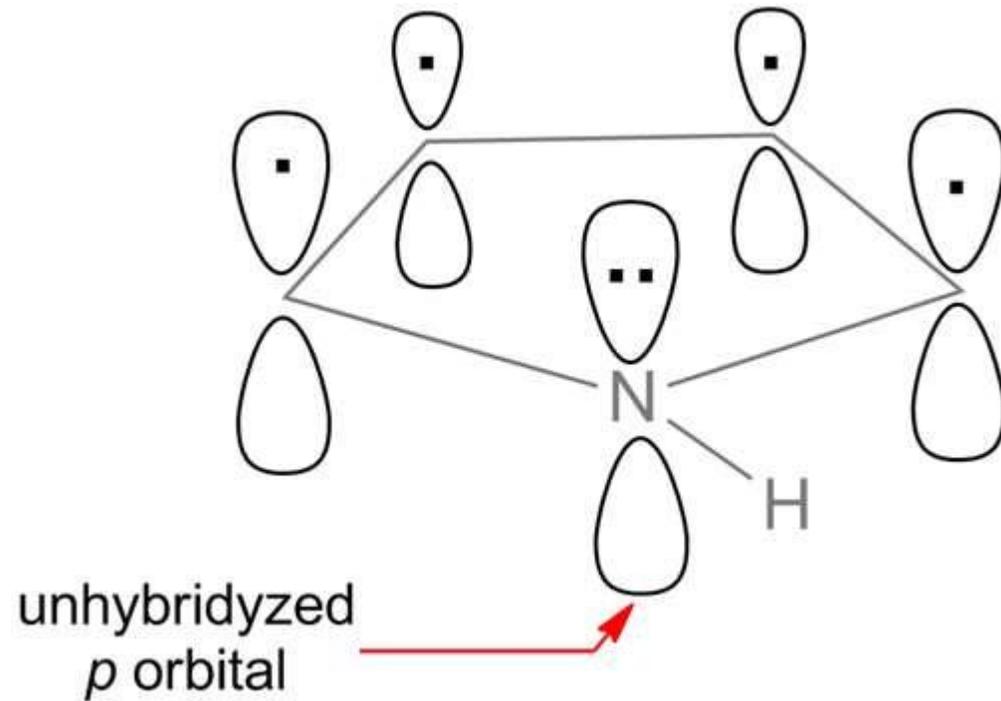


5-ethyl-4-methyl-1,2-oxazole



1-methyl-1H-1,3-diazole
(N-methylimidazole)

PYRROLE



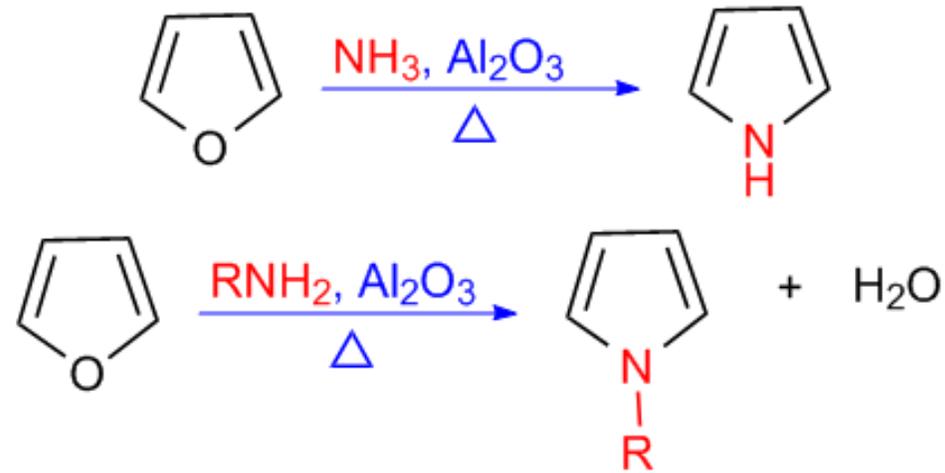
1. Aromaticity

- Pyrrole have 4 C and 1 N , all are sp^2 hybridized
- sp^2 hybridization is **planar**, it makes a planar pyrrole ring structure.
- Each ring atom also contains unhybridized p orbital that is perpendicular to the plane of σ bonds (plane of ring).
- Here p orbitals are parallel to each other, so overlapping btwn p orbitals is possible.
- the total nu of non bonding e- are 6 (4 of four C, 2 from one N)
- The resonance of 6 e- follows the Hückel's rule
- So the pyrrole is aromatic .

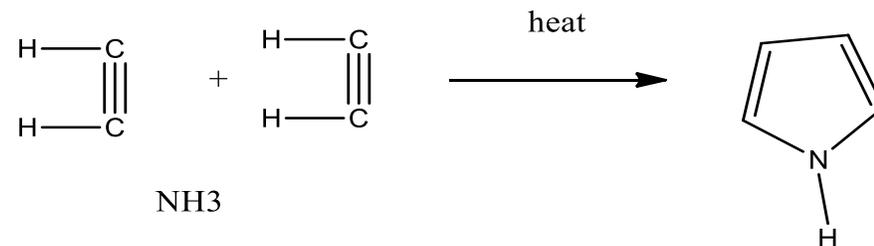
Method of preparation

1. From Furans

- Industrial process
- Passing furan over **ammonia** in presence of **alumina** as catalyst at high temp.

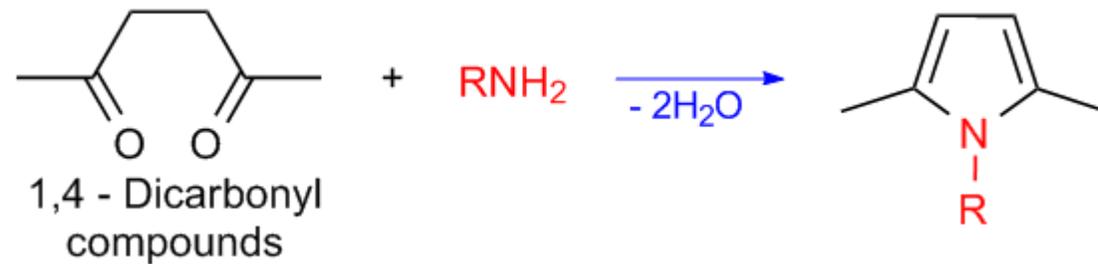


2. By passing a mixture of acetylene and ammonia through a red hot tube



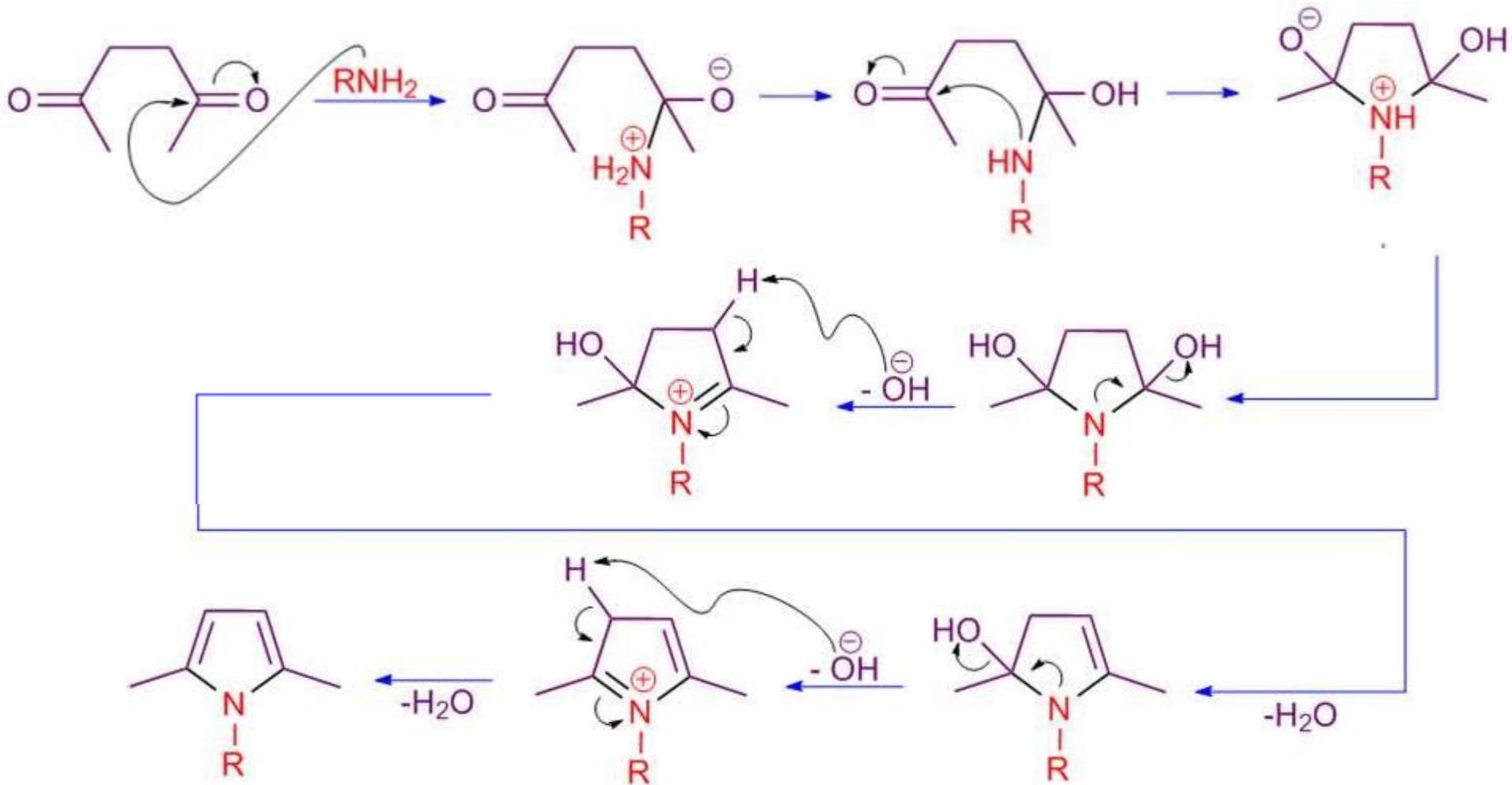
3. Paal-Knorr synthesis

- 1,4 - Dicarbonyl compounds react with **ammonia** *or* **primary amines** to give pyrroles.

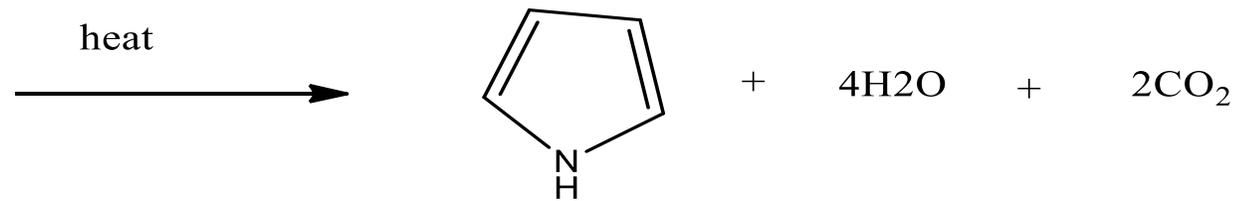
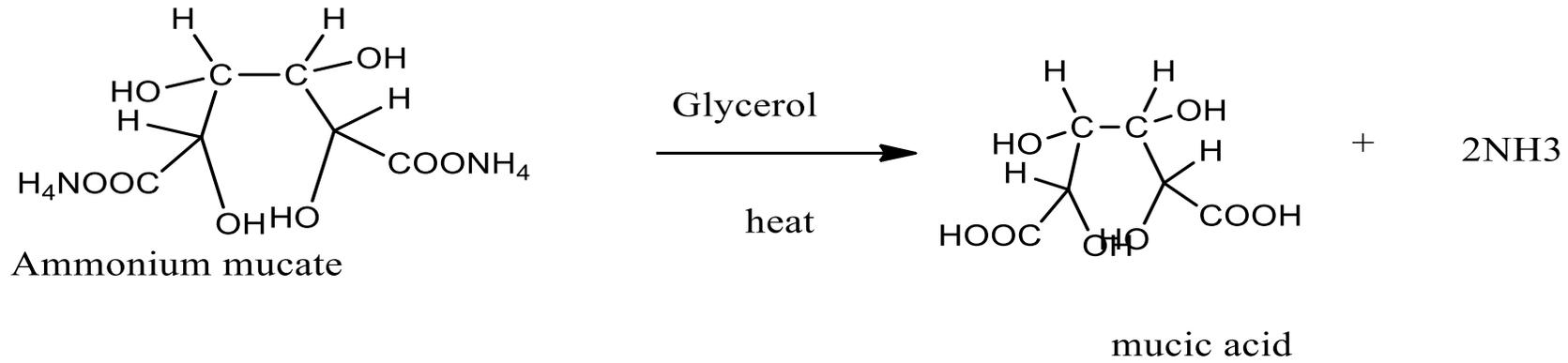


Mechanism

- Successive nucleophilic additions of the amine nitrogen to each of the two carbonyl carbon atoms, imine formation and the dehydration represent the net course of the synthesis.



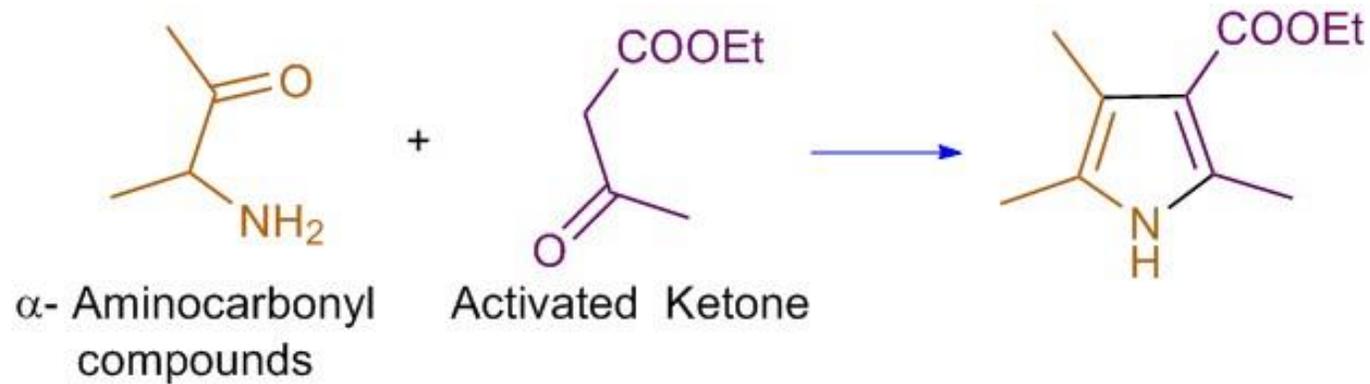
4. By heating ammonium mucate with glycerol at 200⁰ C



Synthesis

4. Knorr synthesis

- Condensation of α -aminocarbonyl component with 2nd component containing an electron-withdrawing group (e.g. an ester) α to a carbonyl group



Chemical properties

Basic character

Weak base P_{ka} 3.4

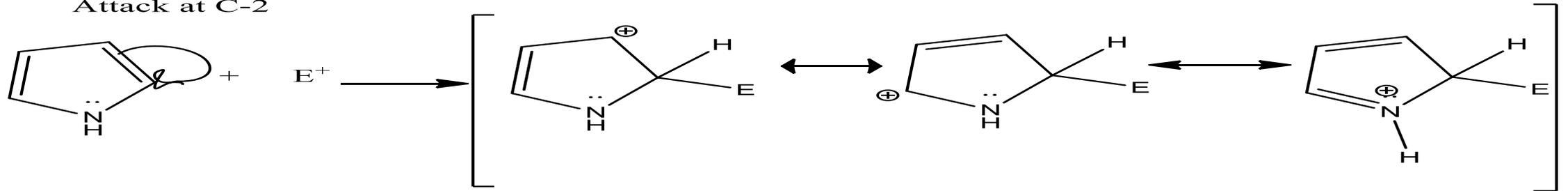
Acidic character

Weak acid P_{ka} 1.5

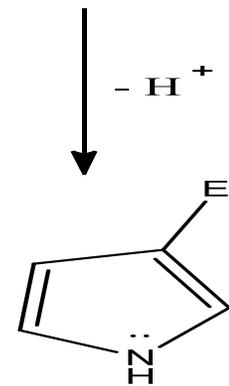
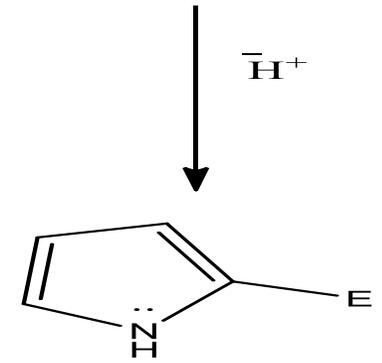
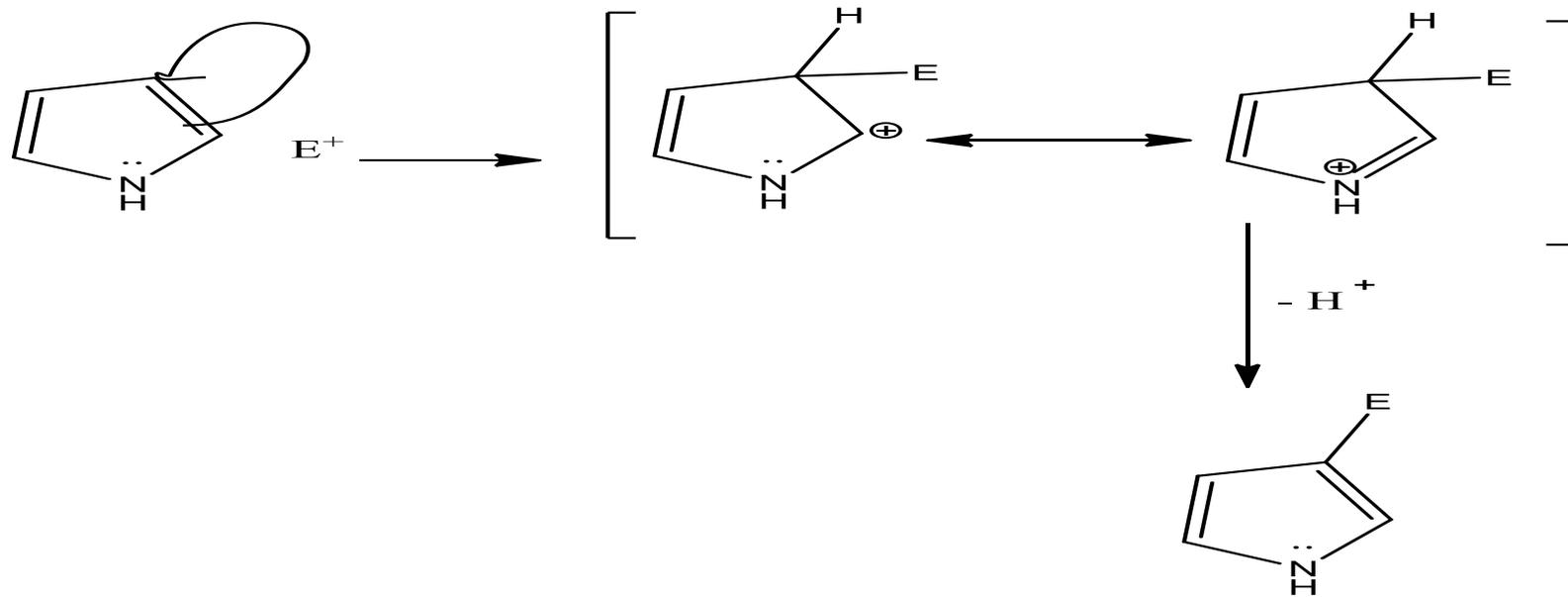
Electrophilic substitution reaction

Pyrrole undergoes electrophilic substitution reaction primarily at C-2

Attack at C-2



Attack at C-3



1. Electrophilic substitution

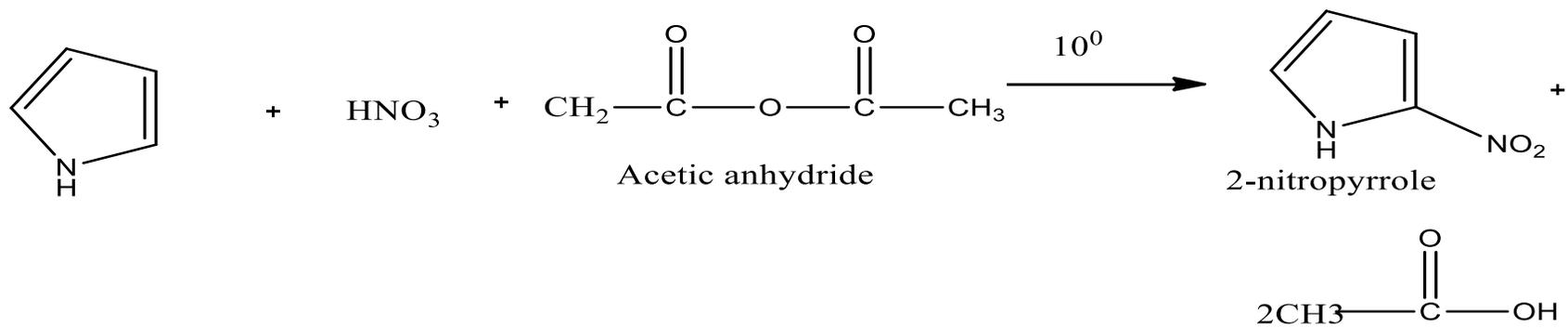
Pyrrole undergoes electrophilic substitution reaction at 2nd position

2 reasons...

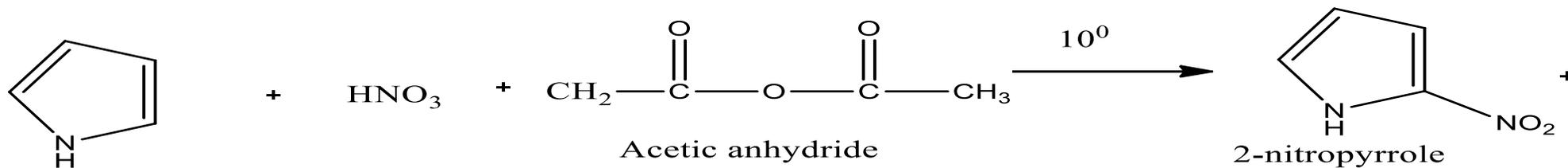
- C2 attack gives more resonance contributing structures than C3.
- Extra stable contributing structure generates upon C2 attack

Electrophilic substitution reactions of pyrrole are not carried in the presence of strong acids or reagents which give rise to strong acids, because under such conditions pyrrole undergoes polymerization and resinification

Nitration

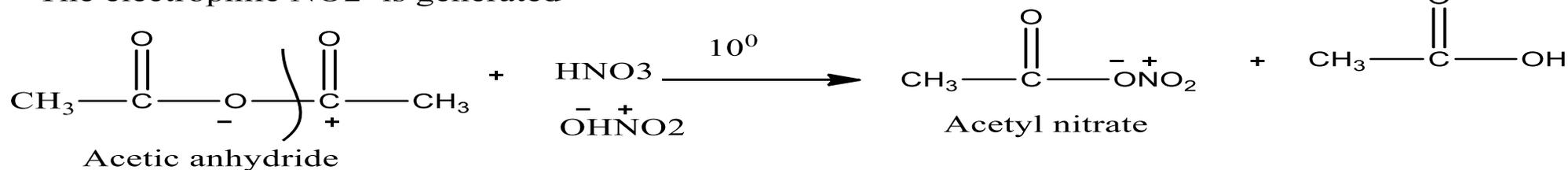


Mechanism



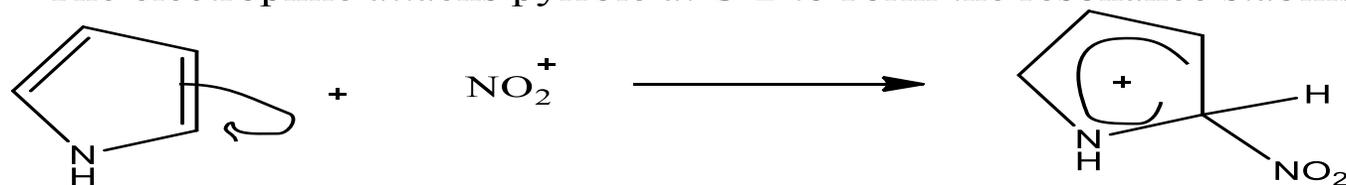
STEP-1

The electrophile NO_2^+ is generated



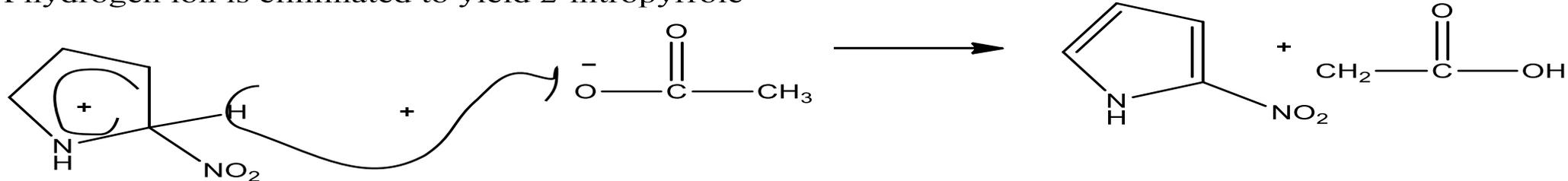
STEP-2

The electrophile attacks pyrrole at C-2 to form the resonance stabilised cation



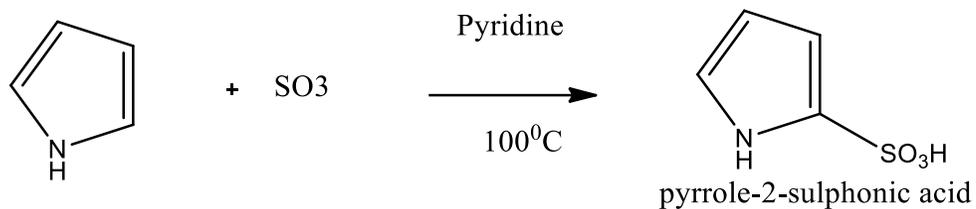
STEP-3

A hydrogen ion is eliminated to yield 2-nitropyrrole



Sulphonation

Pyrrole is sulphonated with sulphur trioxide in pyridine at about 100°C to yield pyrrole-2-sulphonic acid

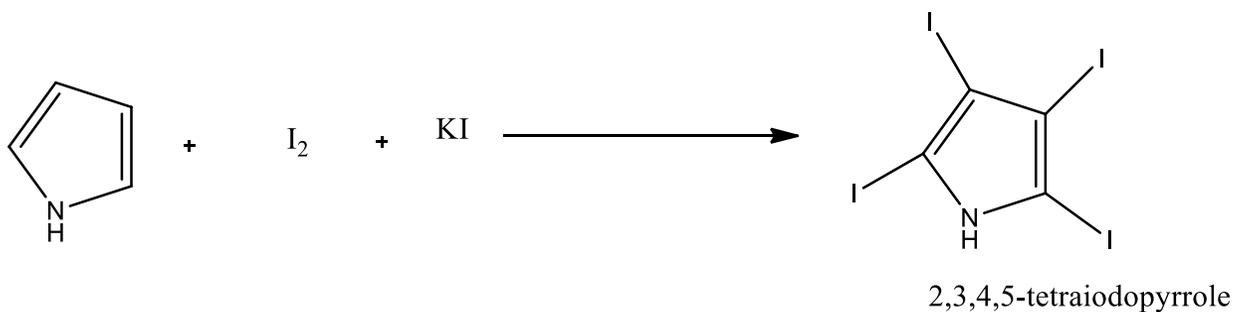
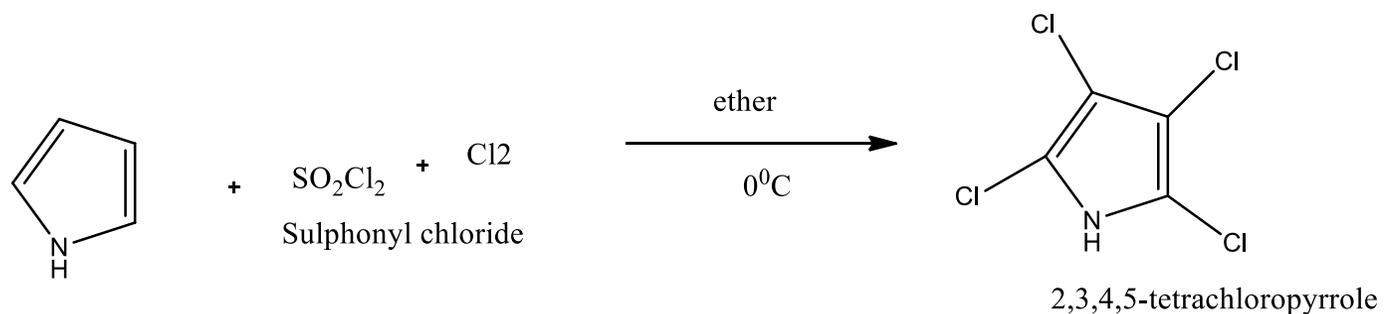


Halogenation

Chlorination--- with chlorine in sulphuryl chloride in ether 0°C

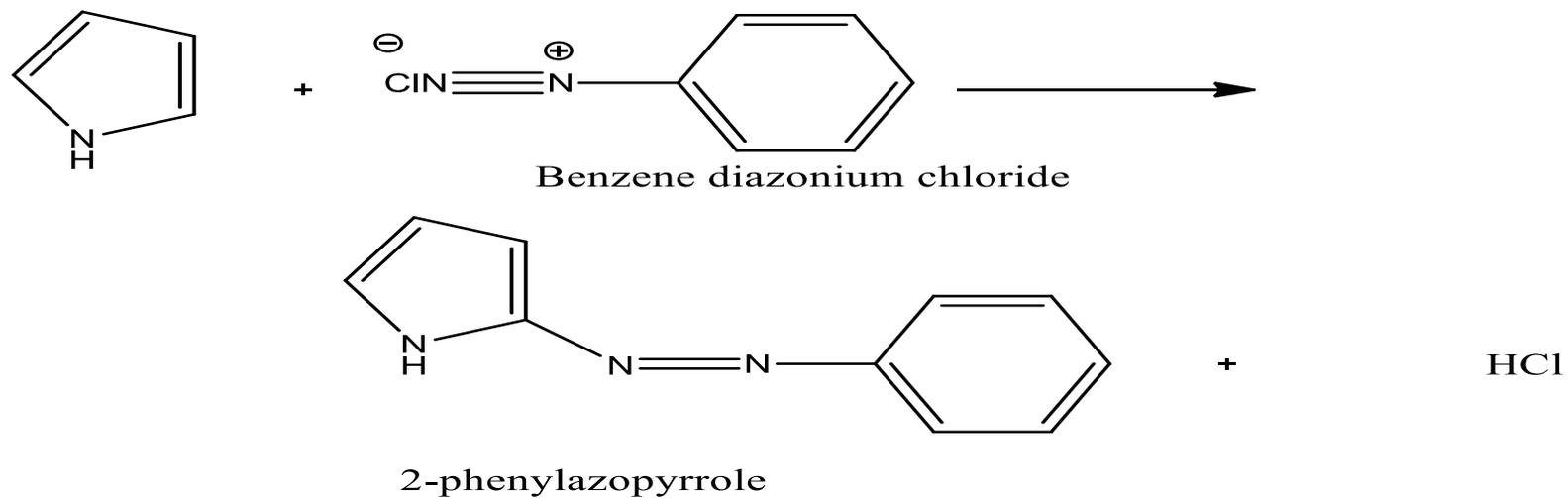
Bromination----with bromine in ethanol at 0°C

Iodination-----with iodine in an aq. Solution of KI



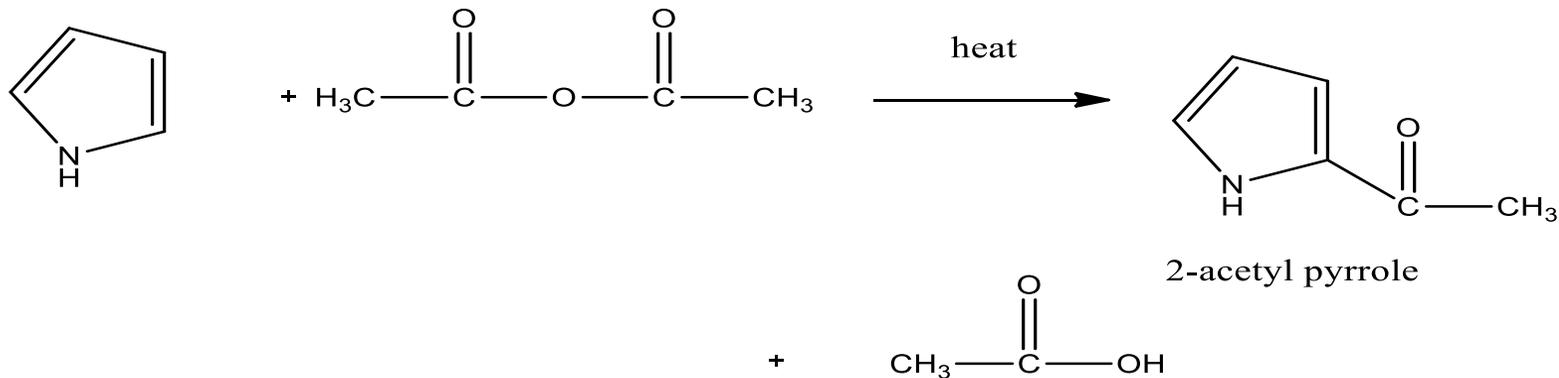
Diazocoupling

pyrrole couples with benzenediazonium chloride in a weakly acidic solution to give 2-phenylazopyrrole



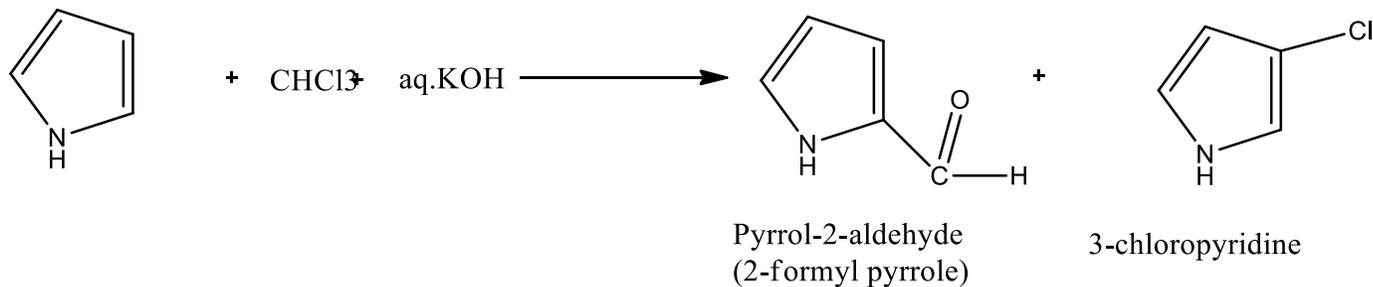
Friedel-craft's acylation

Pyrrole acetylated with acetic anhydride at 250°C to give 2-acetyl pyrrole

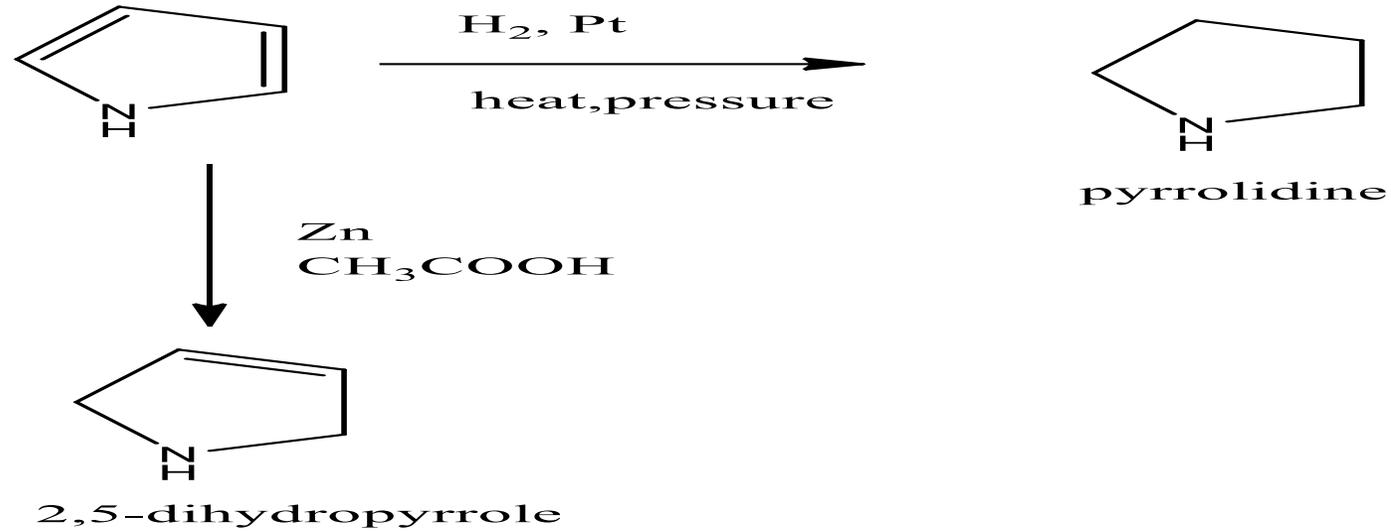


Reimer-Tiemann formylation

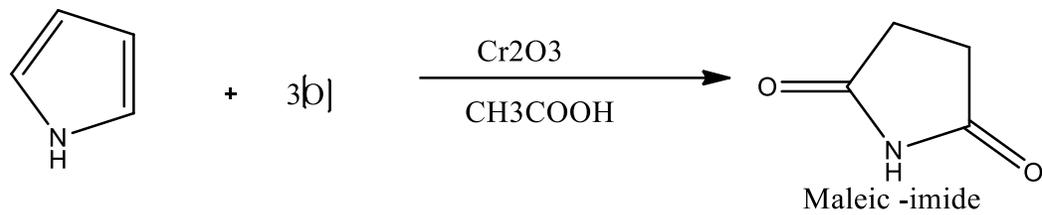
Pyrrole reacts with chloroform in the presence of alkali to yield pyrrole-2-aldehyde and 3-chloro pyridine



Reduction



Oxidation

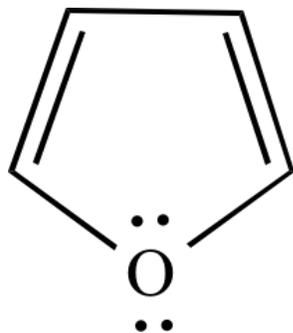


Application

- Pyrrole is a structural constituent of haem, chlorophyll, vit-B₁₂ and bile pigments
- Pyrrole ring is present in tolmetin, ketorolac(NSAID)sunitinib (anticancer)procyclidine(antimuscarinic) atorvastatin (lipid lowering drug)
- Antipsychotic, anxiolytic,antibacterial,antifungal, antimalarial and anticancer therapeutic activities

Furan

Furan is a Heterocyclic organic compound, consisting of a five-membered aromatic ring with four carbon atoms and one oxygen. The class of compounds containing such rings are also referred to as furans

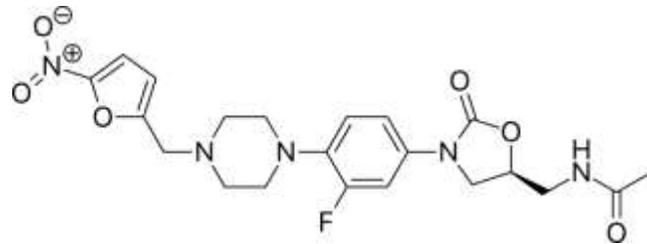


Physical Properties:

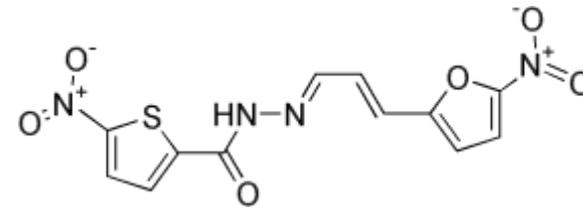
- It is colorless, flammable and highly volatile liquid.
- Melting point: -85.6°C
- Boiling Point: 31.3°C
- Soluble in alcohol, ether and acetone but slightly soluble in water
- Toxic and may be carcinogenic

FURAN

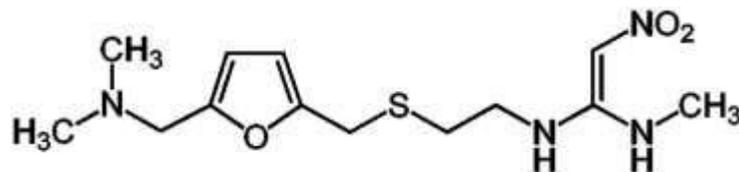
Interesting Furan Containing Drugs



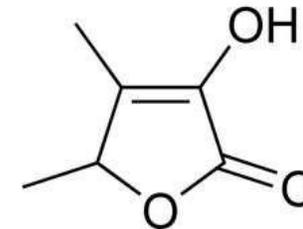
Ranbezolid
Anti-bacterial Drug



Nifurzide
Anti-Infective Drug



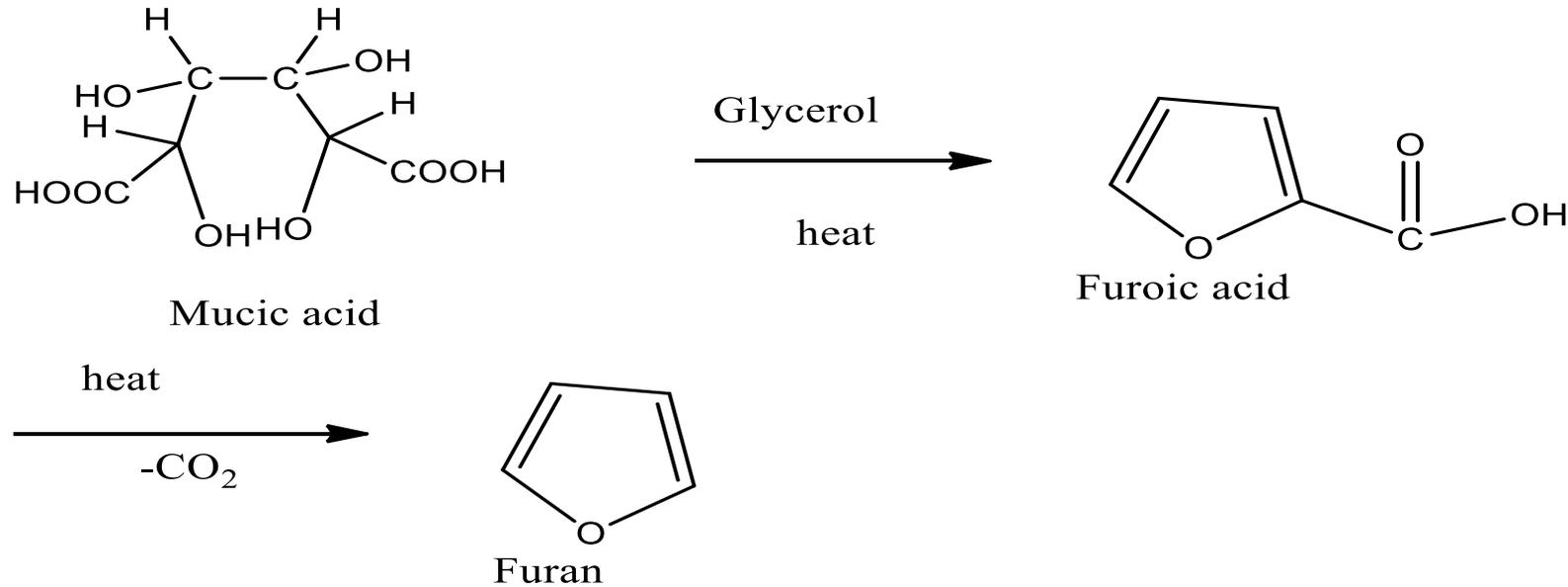
Ranitidine
H₂ receptor antagonist



Furaneol
Perfume distilled from
Strawberries

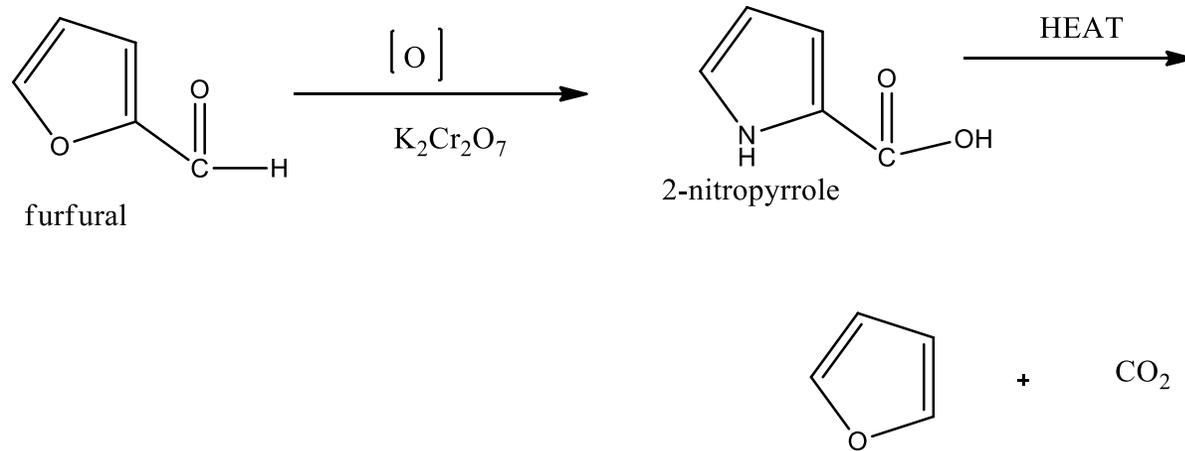
Method of preparation

1. By dry distillation of mucic acid

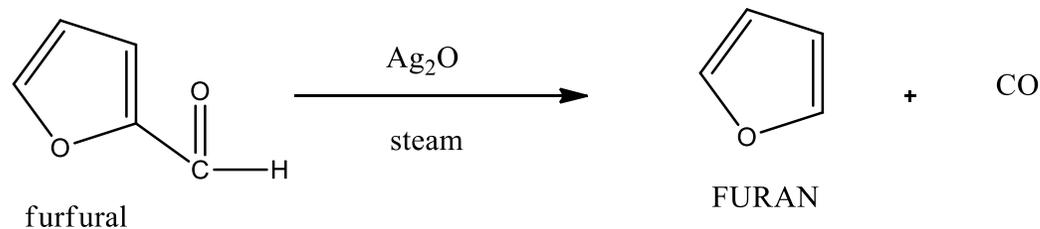


2. Oxidation of furfural

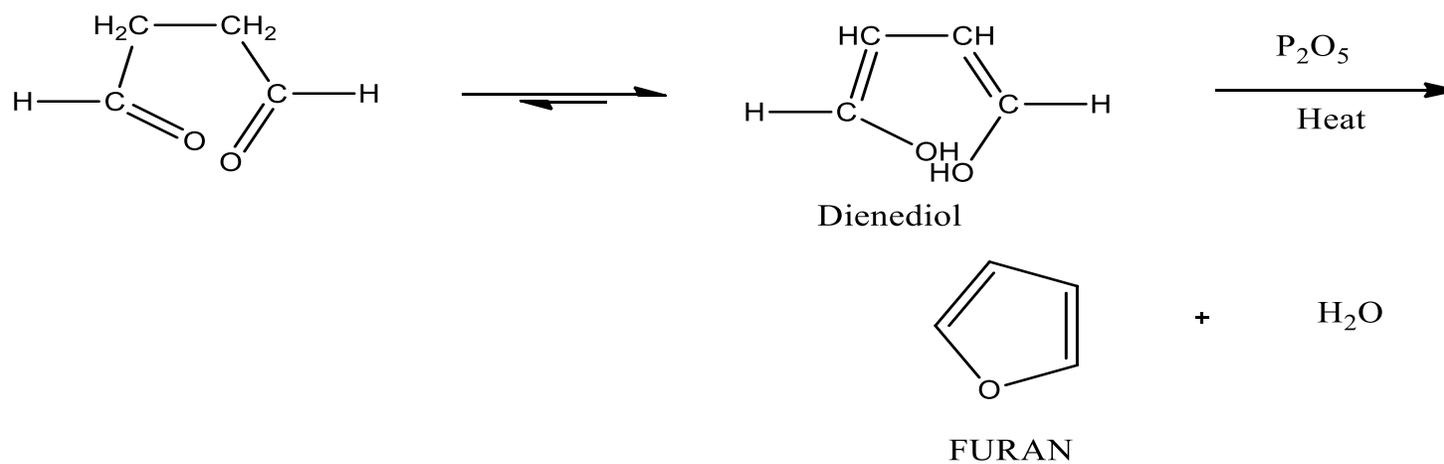
By oxidation of furfural with potassium dichromate to give furoic acid and subsequent decarboxylation at 200-300°C



3. By decarbonylation of furfural in steam in the presence of silver oxide catalyst



4. By dehydration of succinic dialdehyde by heating with P_2O_5 or $ZnCl_2$



Chemical Properties

Nitration

Sulphonation

Halogenation

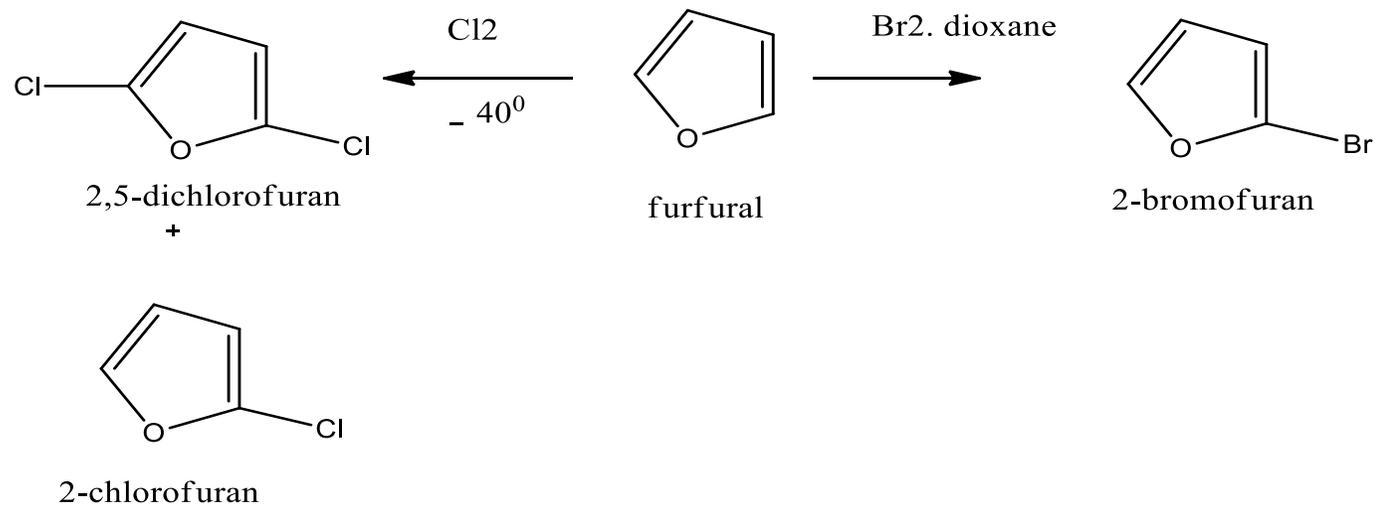
Above 3 reactions are same like pyrrole

Furan

☐ Reacts vigorously with Cl₂ and Br₂ at rt

☐ Does not react at all with iodine

☐ Milder conditions have to be used to obtain monochloro or monobromo derivatives

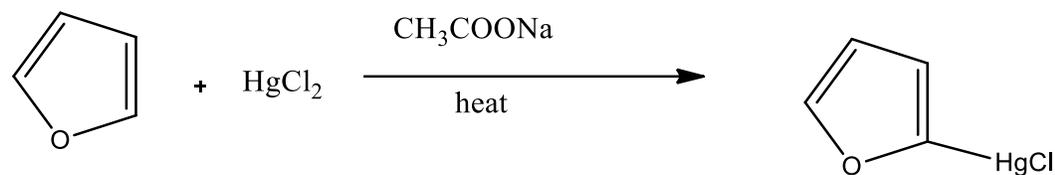


Friedel-Crafts Acylation

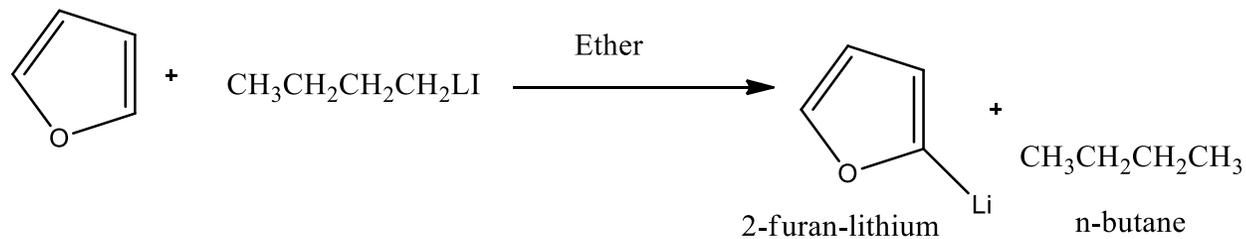
Furan undergoes acetylation with acetic anhydride in the presence of BF_3 or SnCl_4 at 0° to yield 2-acetyl furan

Mercuriation

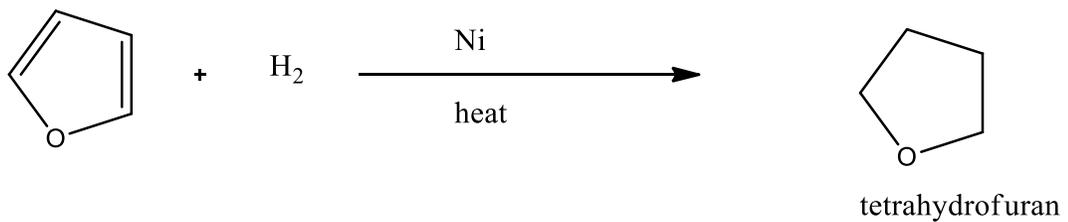
Furan undergoes mercuriation on heating with mercuric chloride in aq. sodium acetate to yield 2-chloromercurifuran



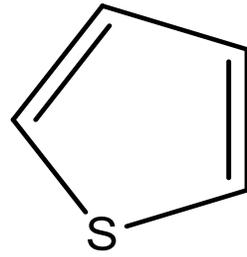
Reaction with n-butyl lithium



Diazocoupling : furan is not sufficiently reactive to undergo Reduction

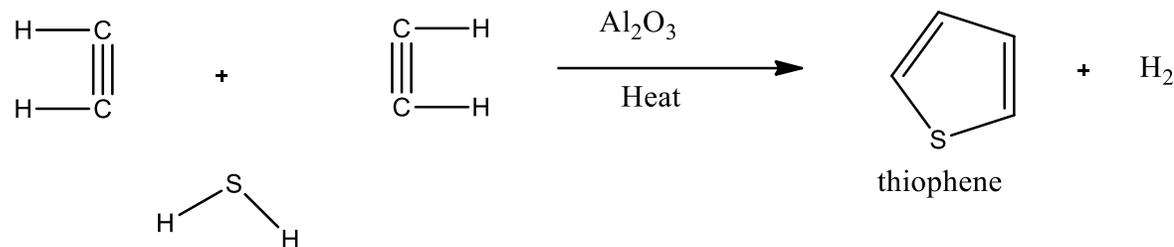


THIOPHENE

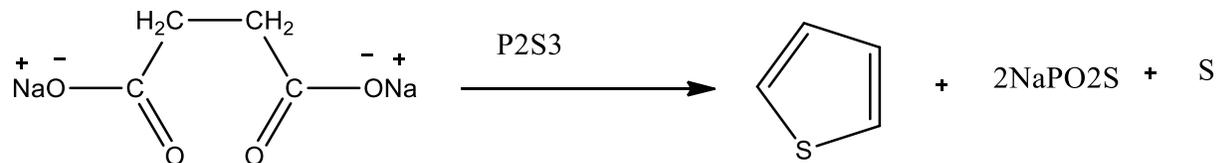


Method of Preparation

1. By passing a mixture of acetylene and hydrogen sulphide through a tube containing aluminium oxide at 400°C

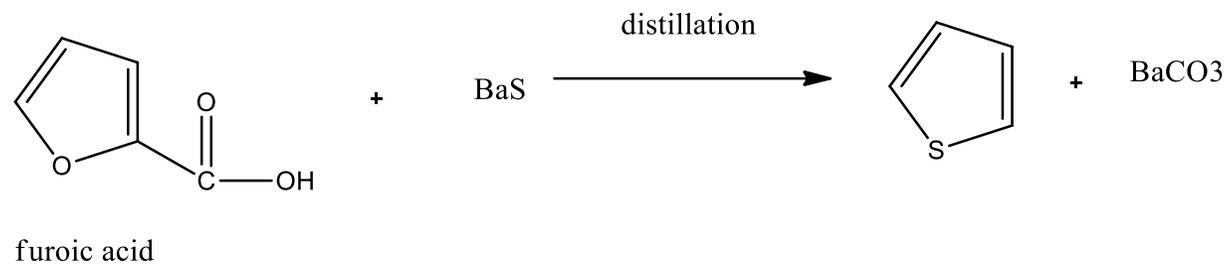


2. By heating sodium succinate with phosphorous trisulphide

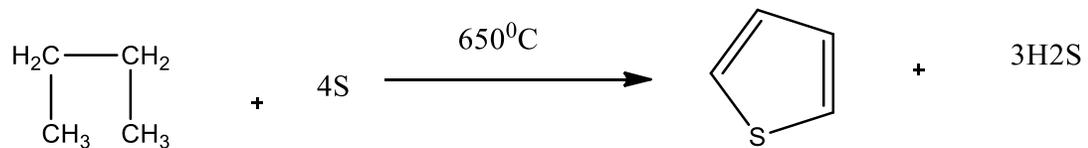


Cont..

3. By distillation of furoic acid with barium sulphide



4. By reaction of sulphur with n-butane in the gas phase at 650° C



Properties (physical)

- Colourless liquid
- Bp 84°C
- Benzene like odour
- Insoluble in water but miscible with most organic solvents

Chemical Properties

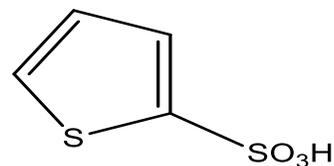
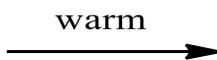
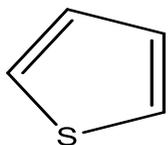
Thiophene does not show any basic properties

It is much more stable to acids than pyrrole and furan

Electrophilic substitution reaction

Nitration same

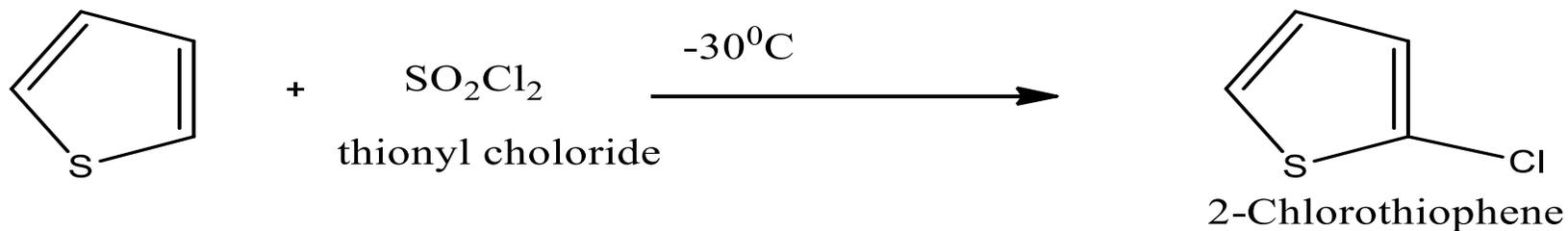
Sulphonation



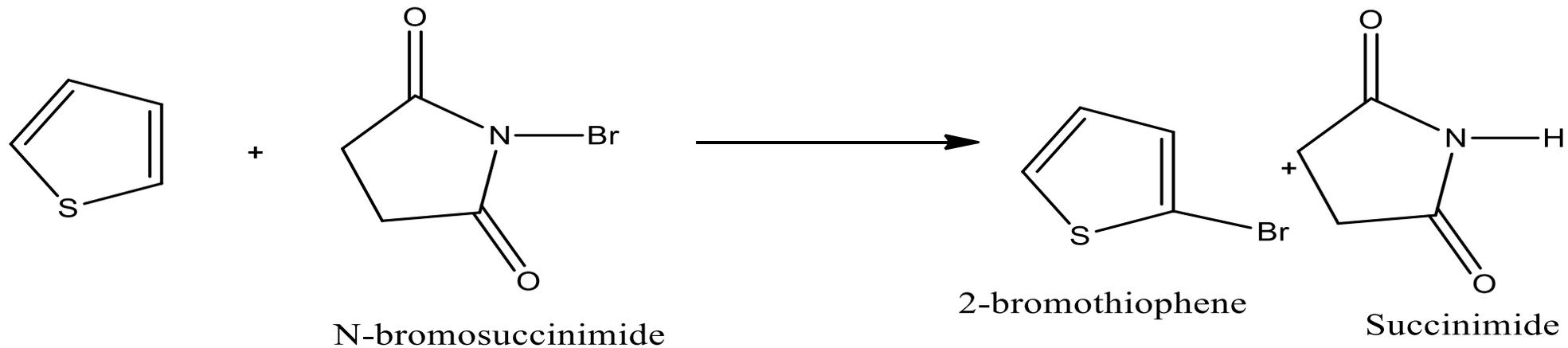
Thiophene-2-sulphonic acid

Halogenation

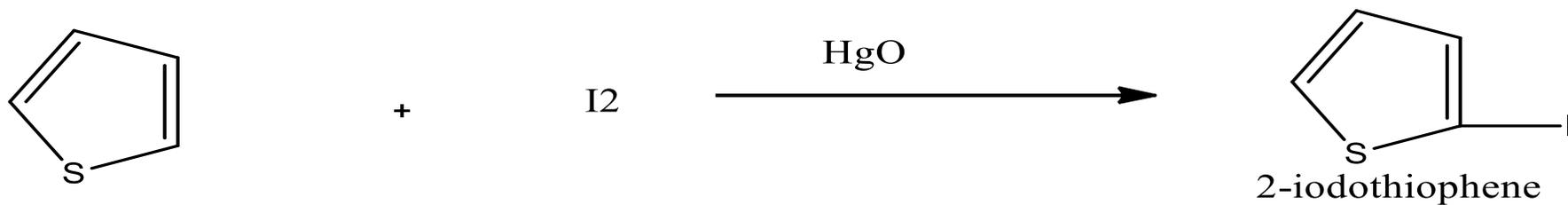
CHLORINATION



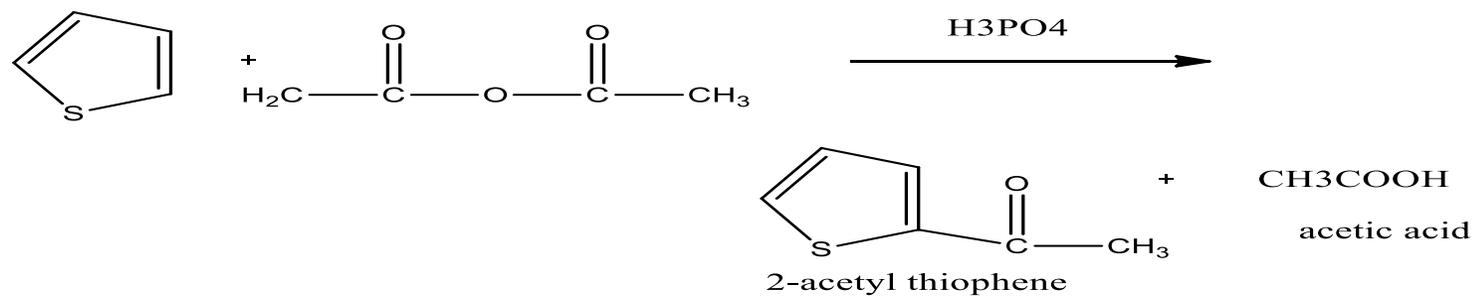
BROMINATION



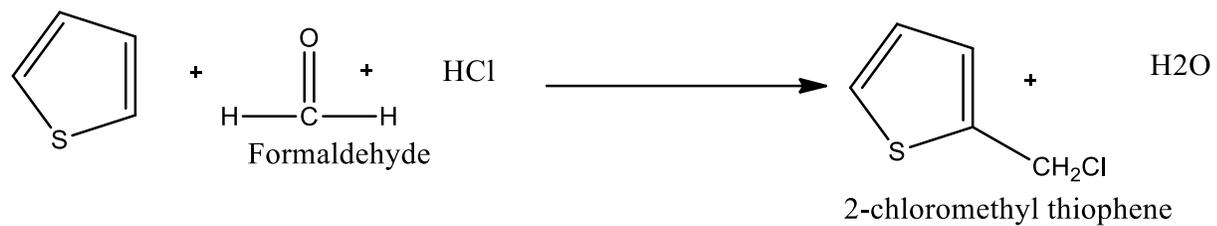
IODINATION



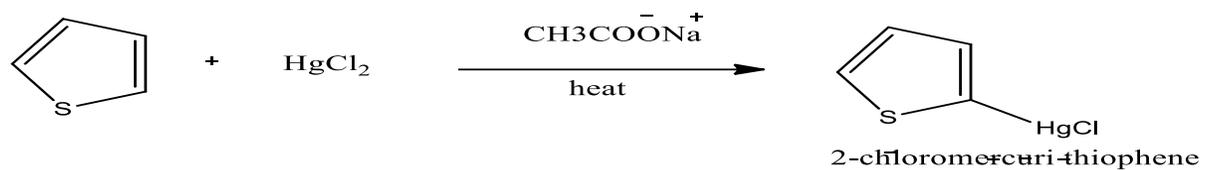
Friedel-Crafts Acylation



Chloromethylation



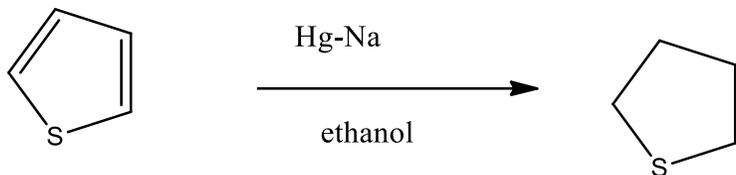
Mercuration



Reaction with n-Butyl-lithium same like furan

Diazocoupling: do not undergo

Reduction



USES

Thiophene derivatives have different activities like anti-bacterial, anti-inflammatory, anti-anxiety, antipsychotic, antiarrhythmic and anticancer activities

Ex lemoxicam

Pyrantel (antiparasitic)

Raltitriaxed (anticancer)

Cephalothin (antimicrobial)

Suprofen (anti-inflammatory)

Ticrynafen (antihypertensive) etc