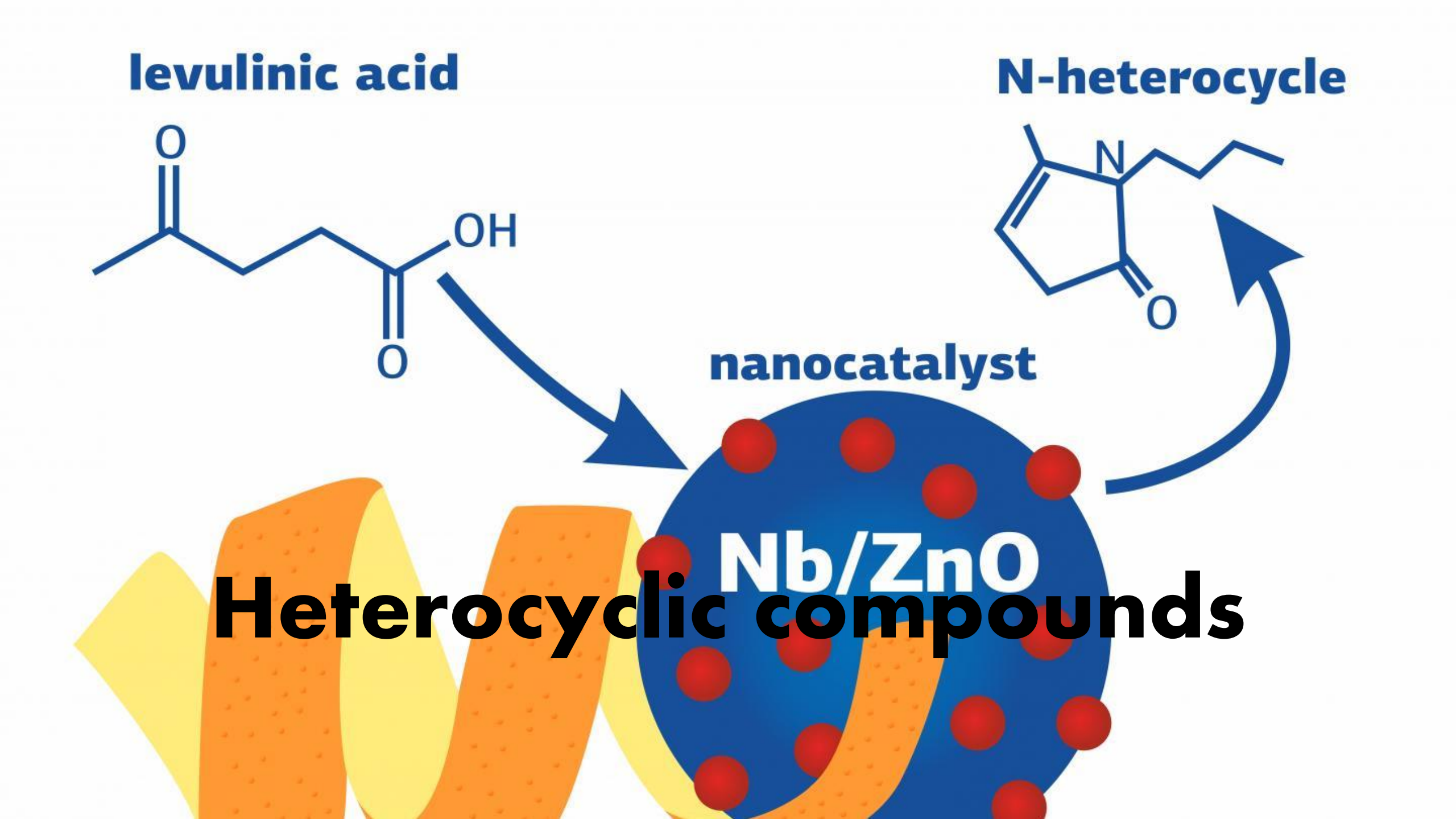


Heterocyclic compounds

Heterocyclic Compounds

- are characterized by rings containing at least one atom other than carbon
- rich diversity of physical and biological properties
- a wide range of application:

pharmaceuticals, as agrochemicals and as veterinary products,

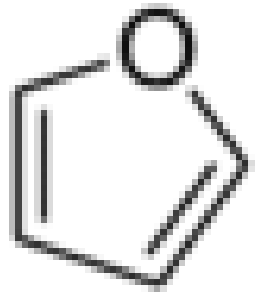
sanitizers, developers, antioxidants, as corrosion inhibitors, as copolymers, dye stuff.

as vehicles in the synthesis of other organic compounds,

they play a vital role in the metabolism of all living cells

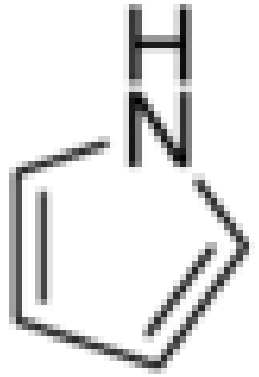
Classification

- according to the nature of a heteroatom:



Furan

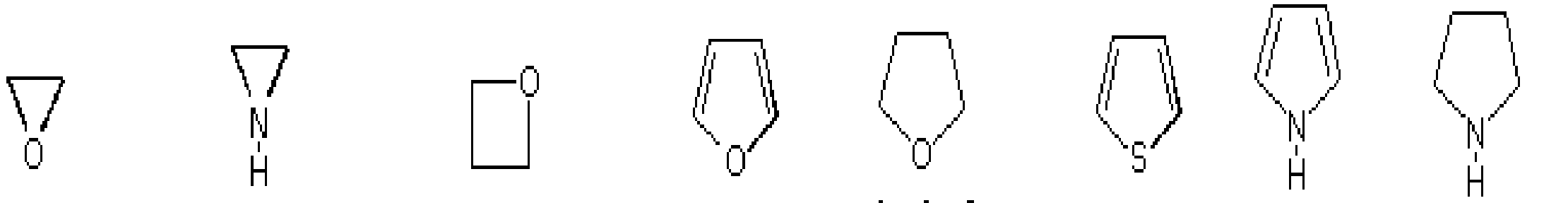
Thiophene



Pyrrole

Classification

- according to the number of atoms in the cycle:



ethylene oxide
oxirane

ethylenimine
aziridine

trimethylene oxide
oxetane

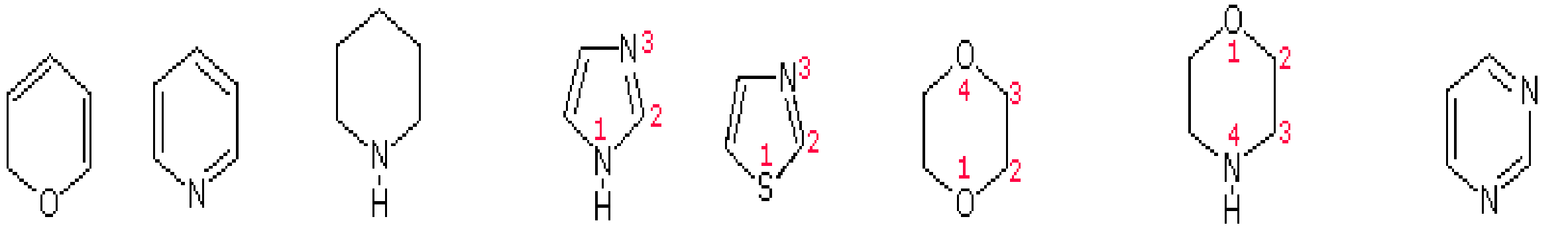
furan
oxole

tetrahydrofuran
oxolane

thiophene
thiole

pyrrole
1*H*-azole

pyrrolidine
azolidine



pyran
2*H*-pyran

pyridine

piperidine
perhydropyridine

imidazole
1,3-diazole

thiazole
1,3-thiazole

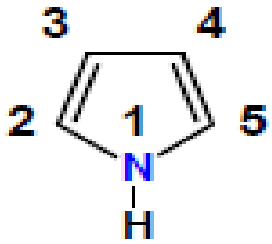
dioxane
1,4-dioxane

morpholine
tetrahydro-1,4-oxazine

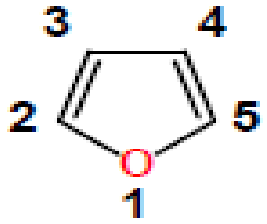
pyrimidine
1,3-diazine

Classification

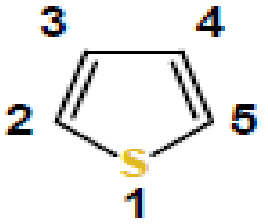
- according to the number of heteroatoms contained in a cycle:



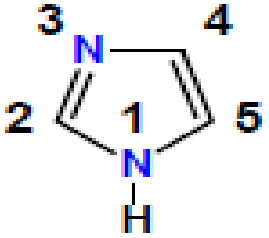
pyrrole



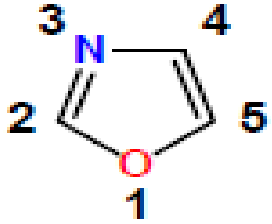
furan



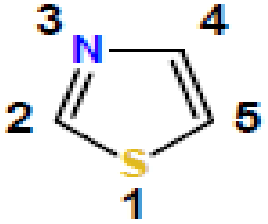
thiophene



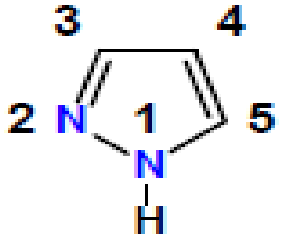
imidazole



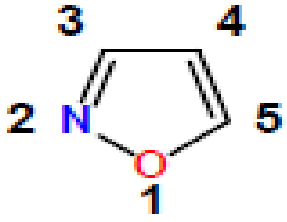
oxazole



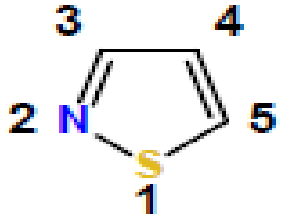
thiazole



pyrazole



isoxazole

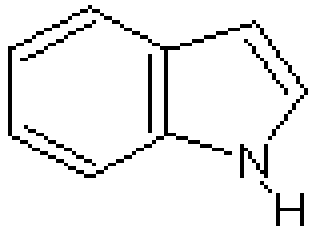


isothiazole

Classification

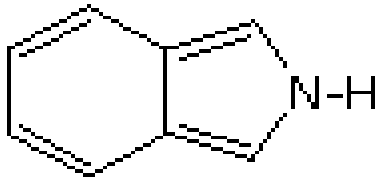
- According to the number of cycles

Fused rings:

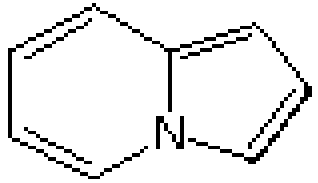


indole

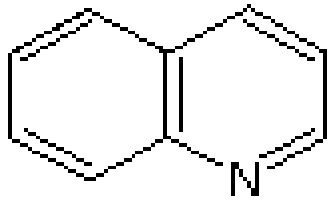
2,3-benzopyrrole



isoindole



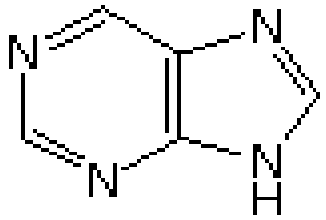
indolizine



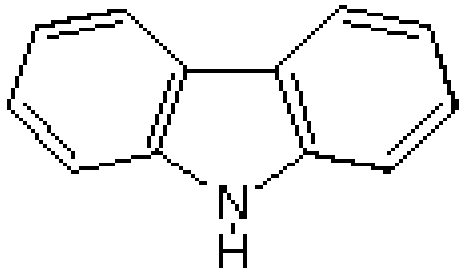
quinoline

1-azanaphthalene

benzo[b]pyridine

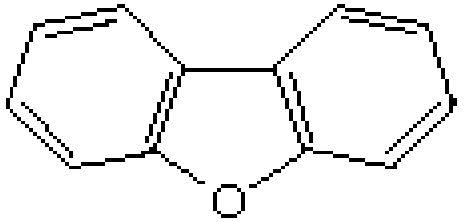


purine

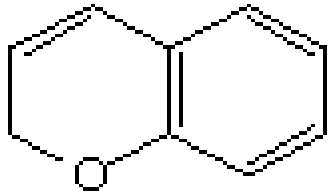


carbazole

dibenzopyrrole



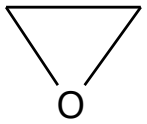
dibenzofuran



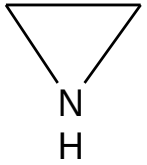
2*H*-chromene

Classification

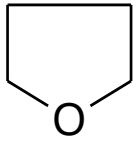
- According to the saturation of structure:
- saturated,.



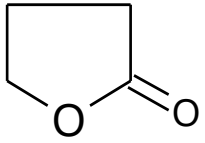
ethylene oxide



ethylene imine

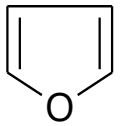


tetrahydrofuran

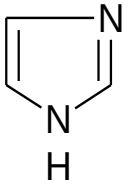


butyrolactone

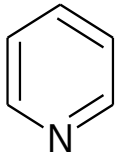
- Unsaturated
- Aromatic



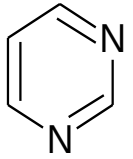
furan (five-membered with one heteroatom



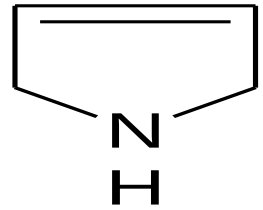
imidazole (five-membered with two heteroatoms)



pyridine (six-membered with one heteroatom)

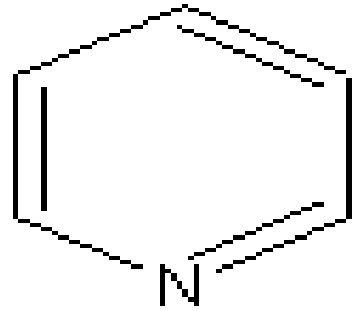


pyrimidine (six-membered with two heteroatoms)



pyrroline

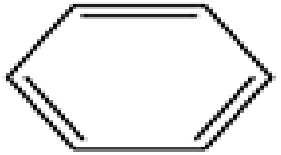
Criteria for Aromaticity



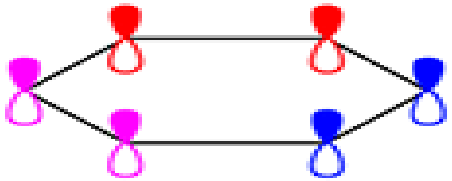
- The molecule is cyclic (a ring of atoms).
- The molecule is planar (all atoms in the molecule lie in the same plane).
- The molecule is fully conjugated (p orbitals at every atom in the ring).
- The molecule has 4n+2 pi electrons (n=0 or any positive integer).

If a molecule does not satisfy any of the rules 1-3, it is considered nonaromatic. Huckel's rule does not apply to nonaromatic molecules.

Criteria for Aromaticity

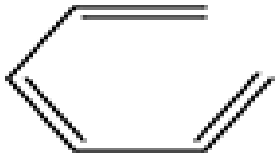


benzene

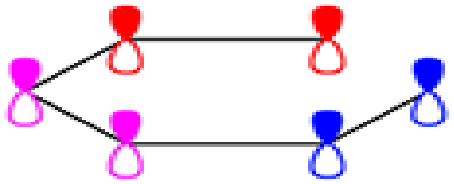


1. Cyclic
2. *p*-orbital for each member of the ring
3. Planar ring (sp^2 hybridized)
4. **4n+2 π–bond electron count.**

Aromatic



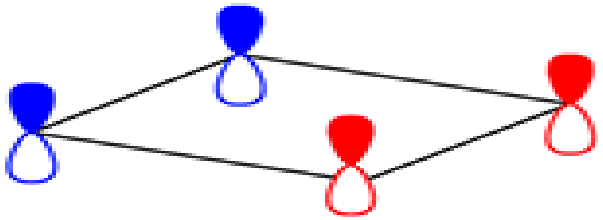
hexatriene



1. NOT Cyclic
2. *p*-orbital for each member of the ring
3. Planar ring (sp^2 hybridized)
4. **4n+2 π–bond electron count.**

Non-Aromatic

cyclobutadiene

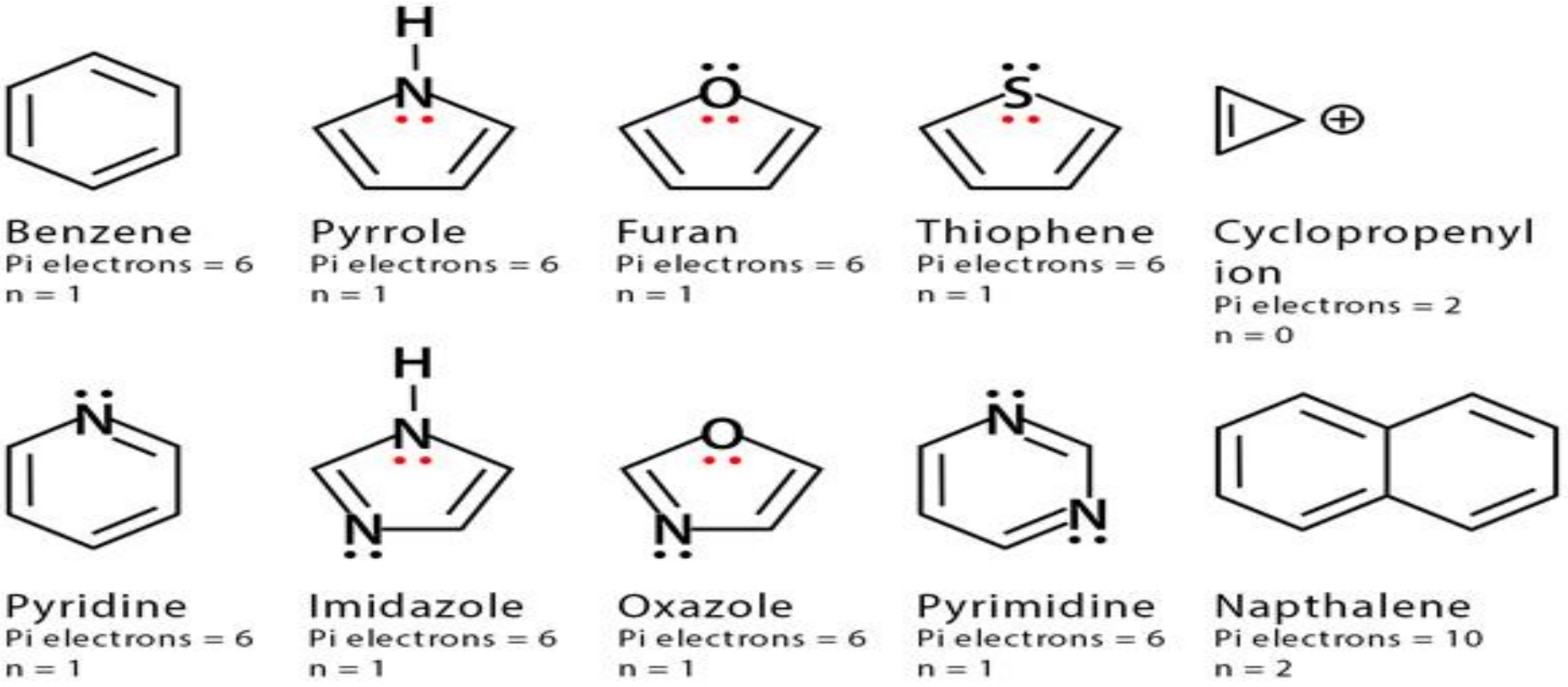


1. Cyclic
2. *p*-orbital for each member of the ring
3. Planar ring (sp^2 hybridized)
4. **Closed 4n π–bond electron count.**

Anti-Aromatic

Criteria for Aromaticity

Huckel's Rule for Aromatic Compounds
(Number of Pi Electrons = 4n + 2)



Note: Red dots indicate pi electrons

ChemistryLearner.com

Nomenclature of heterocycles

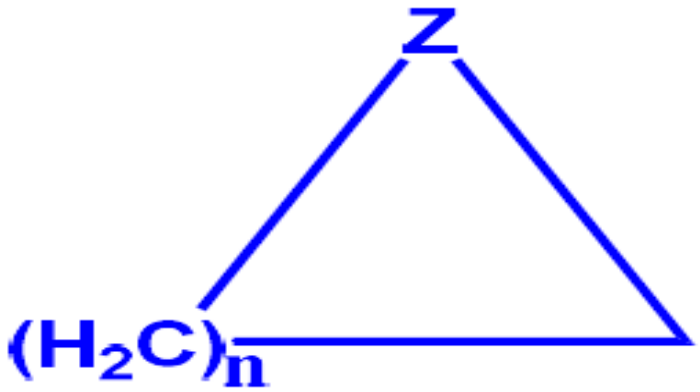
I. The Hantzsch-Widman Nomenclature.

II. Common Names

III. The Replacement Nomenclature

Nomenclature of heterocycles

I. Hantzsch-Widman Nomenclature



n = 1,2,3, ...

The Hantzsch-Widman nomenclature is based on the type (Z) of the heteroatom; the ring size (n) and nature of the ring, whether it is saturated or unsaturated .

This system of nomenclature applies to monocyclic three-to-ten-membered ring heterocycles.

Nomenclature of heterocycles

I. Type of the heteroatom

The type of heteroatom is indicated by a prefix as shown below for common hetreroatoms:

Hetreroatom	Prefix
O	Oxa
N	Aza
S	Thia
P	Phospha

Nomenclature of heterocycles

II. Ring size (n)

The ring size is indicated by a suffix according to Table I below. Some of the syllables are derived from Latin numerals, namely ir from tri, et from tetra, ep from hepta, oc from octa, on from nona, ec from deca.

Table I: Stems to indicate the ring size of heterocycles

Ring size	Suffix	Ring size	Suffix
3	ir	7	ep
4	et	8	oc
5	ol	9	on
6	in	10	ec

Nomenclature of heterocycles

The endings indicate the size and degree of unsaturation of the ring.

Table II: Stems to indicate the ring size and degree of unsaturation of heterocycles

Ring size	Saturated	Unsaturated	Saturated (With Nitrogen)
3	-irane	-irine	-iridine
4	-etane	-ete	-etidine
5	-olane	-ole	-olidine
6	-inane	-ine	
7	-epane	-epine	
8	-ocane	-ocine	
9	-onane	-onine	
10	-ecane	-ecine	

Nomenclature of heterocycles

According to this system heterocyles are named by combining appropriate prefix/prefixes with a stem from Table II. The letter “a” in the prefix is omitted where necessary.

Each suffix consists of a ring size root and an ending intended to designate the degree of unsaturation in the ring.

It is important to recognize that the saturated suffix applies only to completely saturated ring systems, and the unsaturated suffix applies to rings incorporating the maximum number of non-cumulated double bonds.

Nomenclature of heterocycles

Systems having a lesser degree of unsaturation require an appropriate prefix, such as "dihydro"or "tetrahydro".

Saturated 3, 4 & 5-membered nitrogen heterocycles should use respectively the traditional "iridine", "etidine" & "olidine" suffix.

Nomenclature of heterocycles

Examples

Oxa+irane= Oxirane

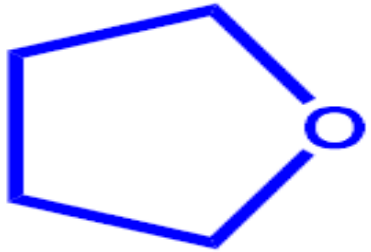
Thia+irane= Thiirane

Aza+iridine= Aziridine

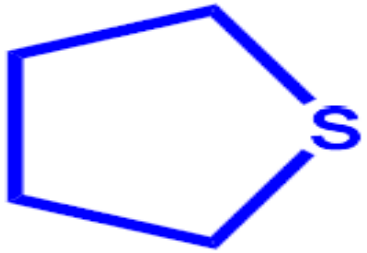
Oxa+etane=Oxetane

Thia+etane=Thietane

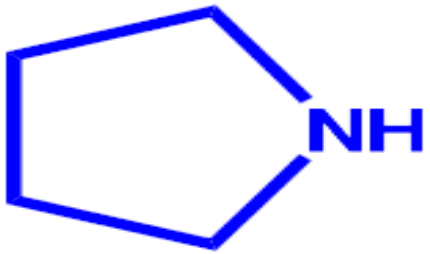
Aza+etidine=Azetidine



Oxa+olane= Oxolane



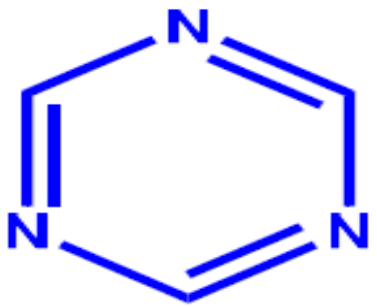
Thia+olane= Thiolane



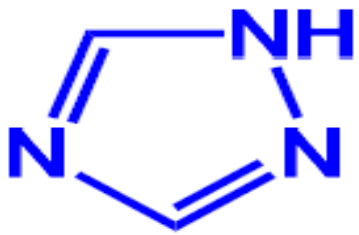
Aza+olidine= Azolidine

Nomenclature of heterocycles

Two or more similar atoms contained in a ring are indicated by the prefixes *'di-', 'tri', etc.*



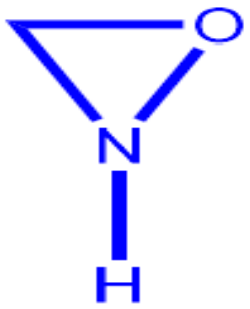
1,3,5-Triazine



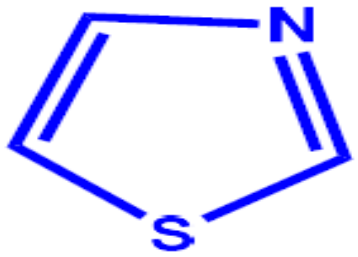
1,2,4 - Triazole

If more than one hetero atom occur in the ring, then the heterocycle is named by combining the appropriate prefixes with the ending in Table I in order of their preference, O > S > N.

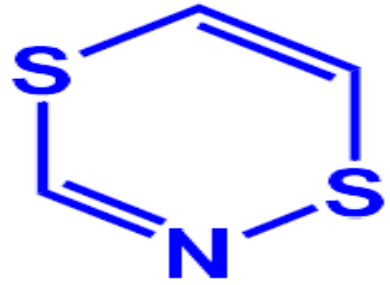
Nomenclature of heterocycles



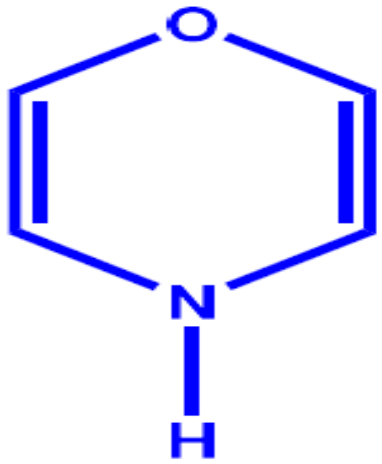
Oxaziridine



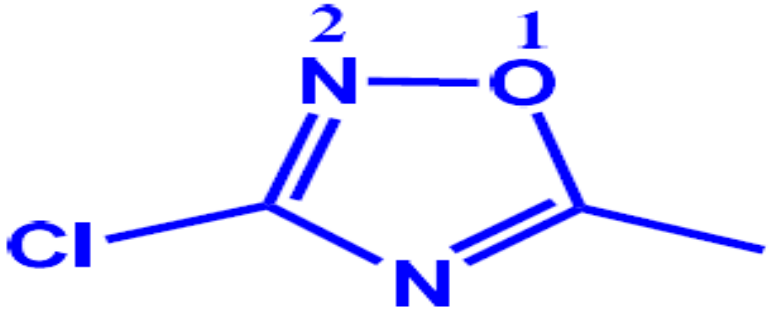
1,3-Thiazole
(Thiazole)



1,4,2 - Dithiazine



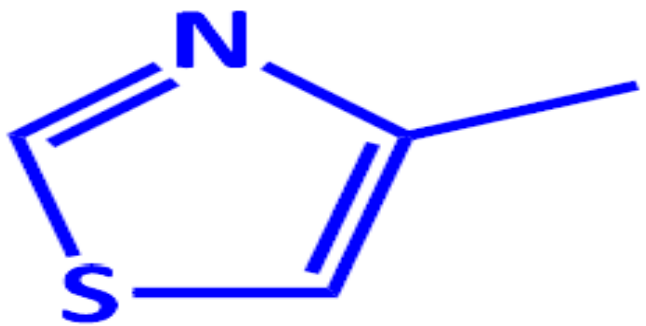
1,4-Oxazine



3-chloro-5-methyl-1,2,4-oxadiazole

Nomenclature of heterocycles

The ring is numbered from the atom of preference in such a way so as to give the smallest possible number to the other hetero atoms in the ring. As a result the position of the substituent plays no part in determining how the ring is numbered in such compounds.

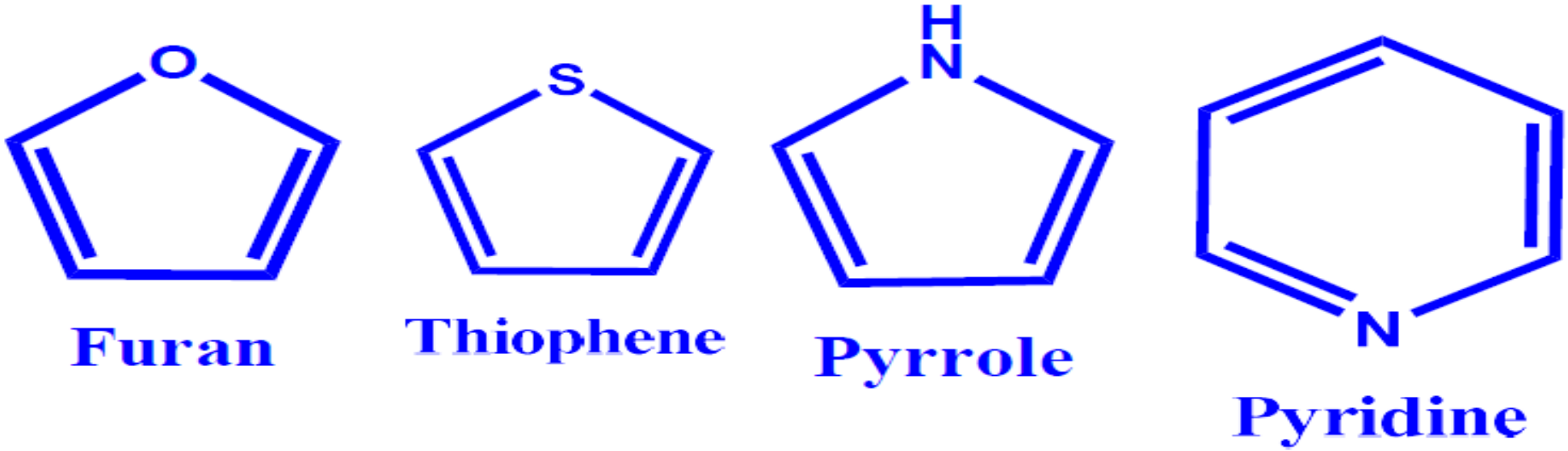


4-Methyl-1,3-thiazole

Nomenclature of heterocycles

II. Common Names

There are a large number of important ring systems which are named widely known with their non-systematic or common names.

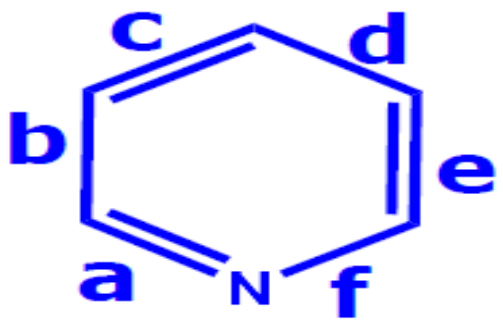


Furan Thiophene Pyrrole Pyridine

Nomenclature of heterocycles

Naming Hetrocycles with fused rings

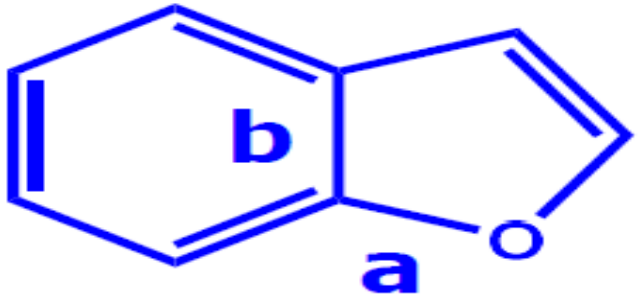
When naming such compounds the side of the heterocyclic ring is labeled by the letters a, b, c, etc., starting from the atom numbered 1. Therefore side *'a' being between atoms 1 and 2, side 'b' between atoms 2 and* 3, and so on as shown below for pyridine.



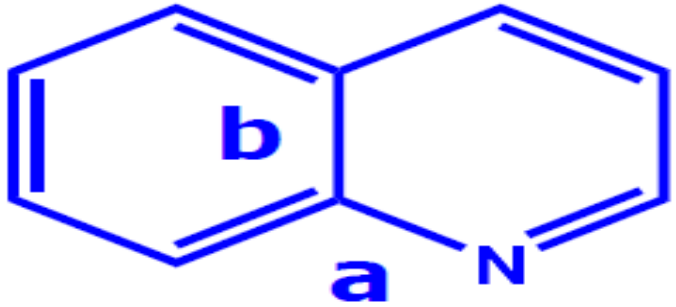
Pyridine

Nomenclature of heterocycles

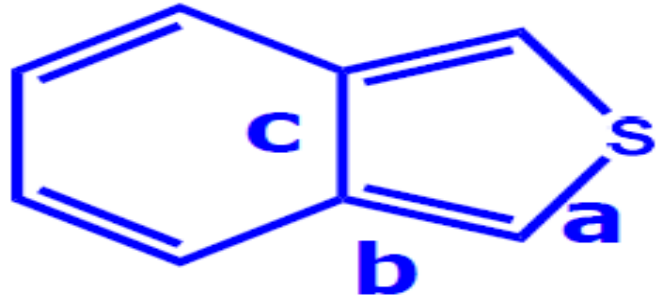
The name of the heterocyclic ring is chosen as the parent compound and the name of the fused ring is attached as a prefix. The prefix in such names has the ending *'o', i.e., benzo, naphtho and so on.*



Benzo [b] furan



Benzo [b] pyridine



Benzo [c] thiophene

Nomenclature of heterocycles

III. The Replacement Nomenclature

In replacement nomenclature, the heterocycle's name is composed of the carbocycle's name and a prefix that denotes the heteroatom.

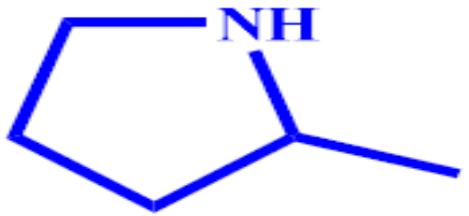
Thus, "aza", "oxa", and "thia" are prefixes for a nitrogen ring atom, an oxygen ring atom, and a sulfur ring atom, respectively.

Notice that heterocyclic rings are numbered so that the heteroatom has the lowest possible number.

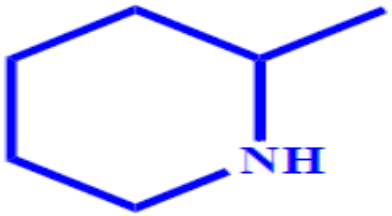
Nomenclature of heterocycles

Azacyclopropane
or
Aziridine

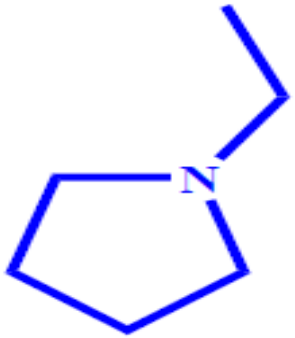
Azacyclobutane
or
Azetidine



2-Methylazolidine
or
2-Methylazacyclopentane



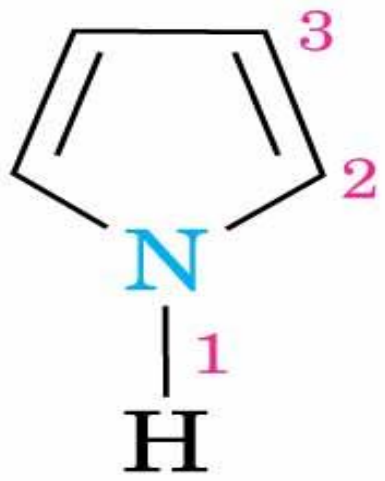
2-Methylazacyclohexane
or
2-Methylpiperidine



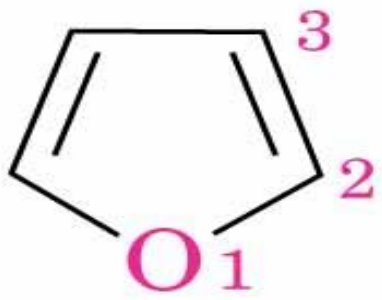
N-Ethylazacyclopentane
or
N-Ethylpyrrolidine

Five – membered heterocycles with one heteroatom

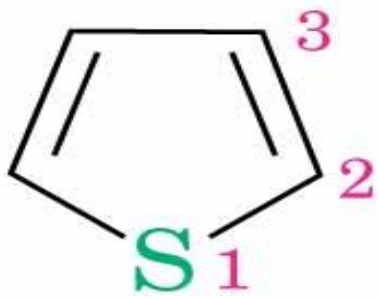
- Pyrrole, furan, and thiophene are common five-membered aromatic heterocycles
- Each has two double bonds and N, O, or S



Pyrrole



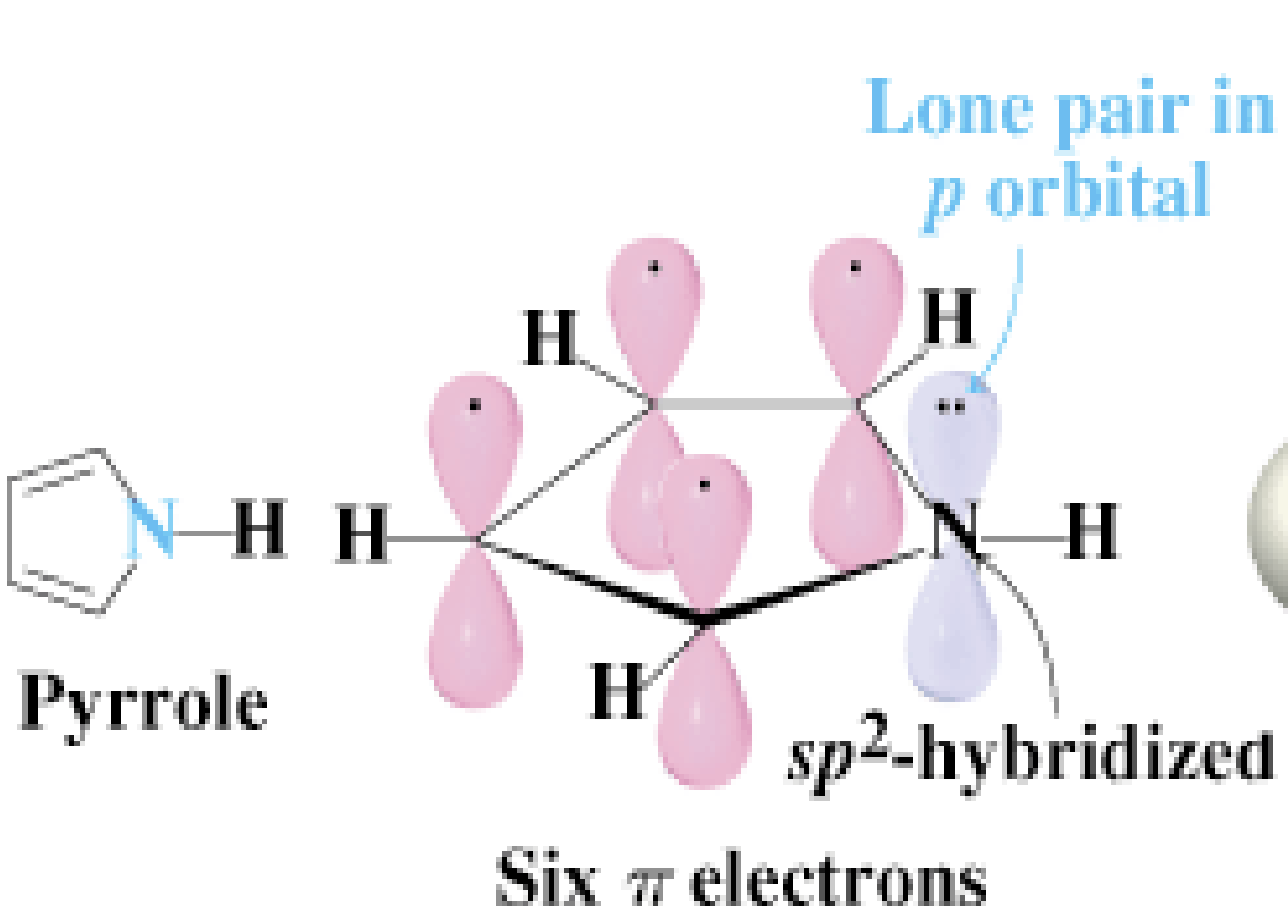
Furan

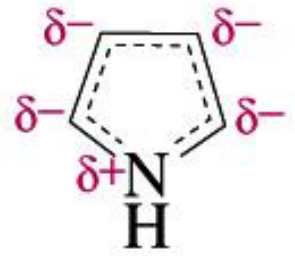


Thiophene

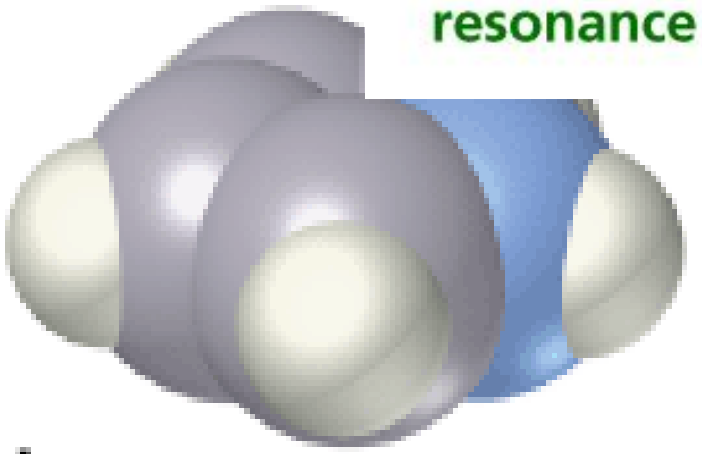
Aromaticity

- Pyrrole, furan, and thiophene are aromatic (Six π electrons in a cyclic conjugated system of overlapping p orbitals)
- In pyrrole π electrons come from C atoms and lone pair on sp^2-N





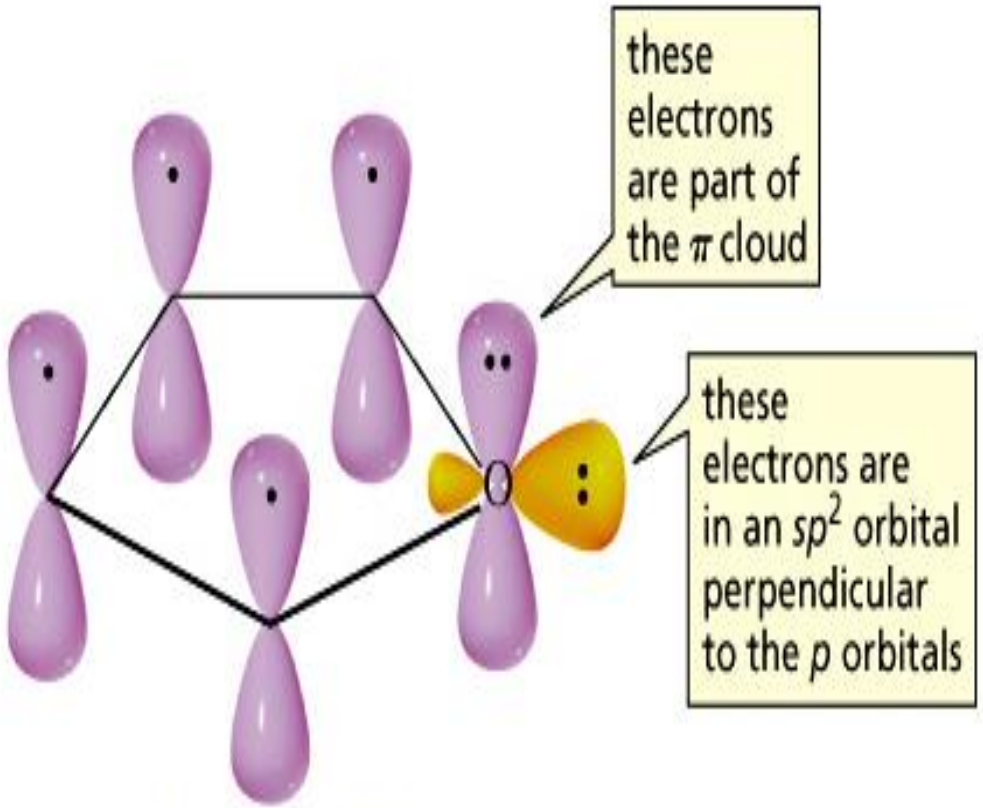
resonance hybrid



Aromaticity

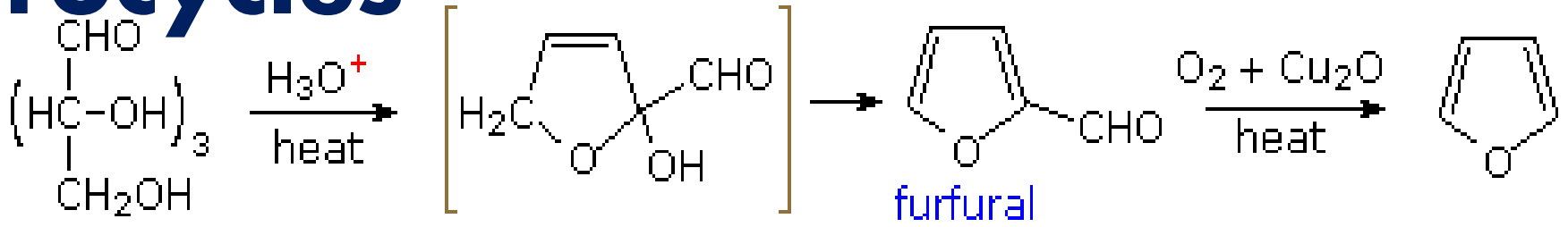
- Furan, and thiophene are aromatic

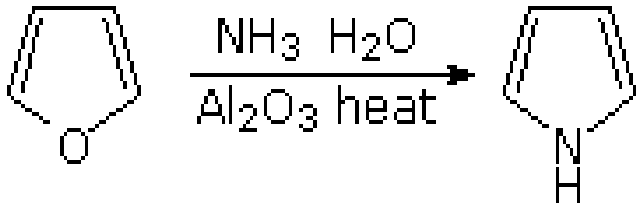
(Six π electrons in a cyclic conjugated system of overlapping p orbitals)



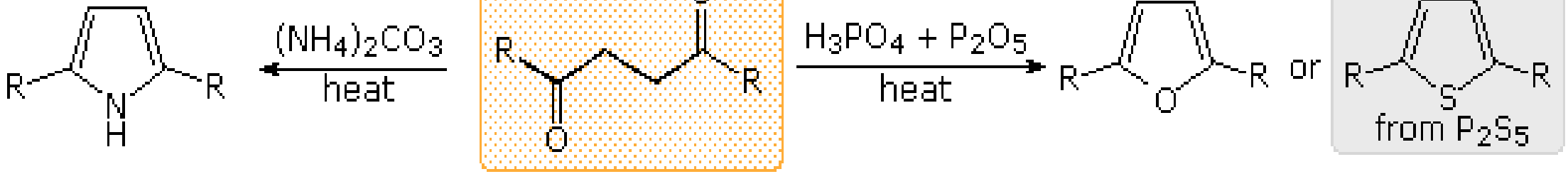
orbital structure of furan

Preparation of five – membered heterocycles

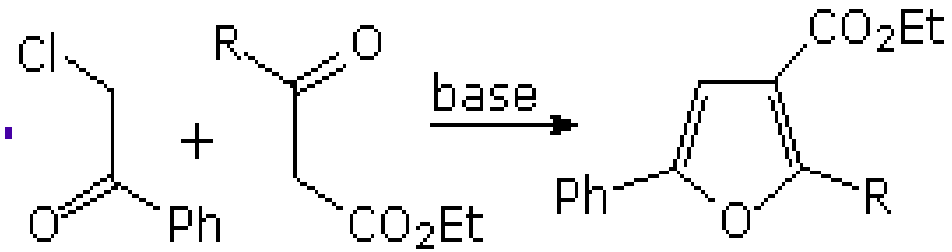




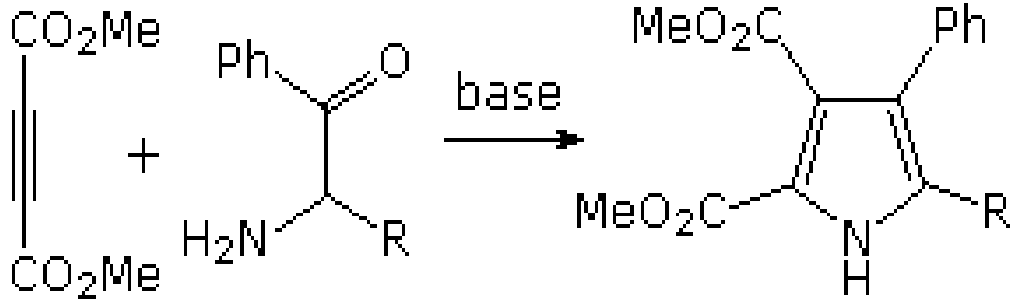
1.



2.



3.

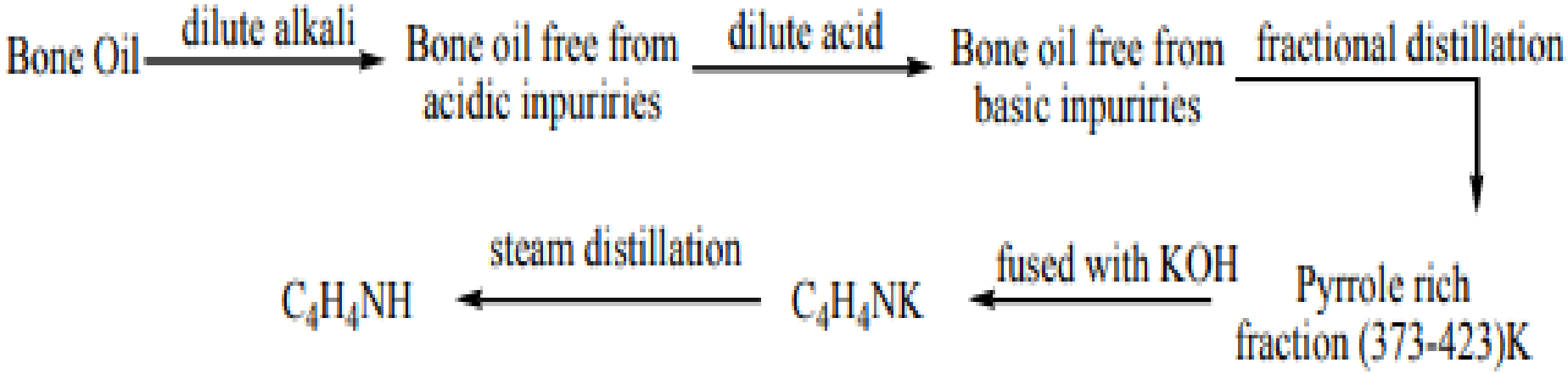


Chemical reactions of five-membered heterocycles

- Acid-base properties
- Electrophilic substitution reaction – Se
- Nucleophilic substitution reaction – Sn
- Reactions of heteroatom exchange
- Oxidation and reduction reactions
- Specific reactions

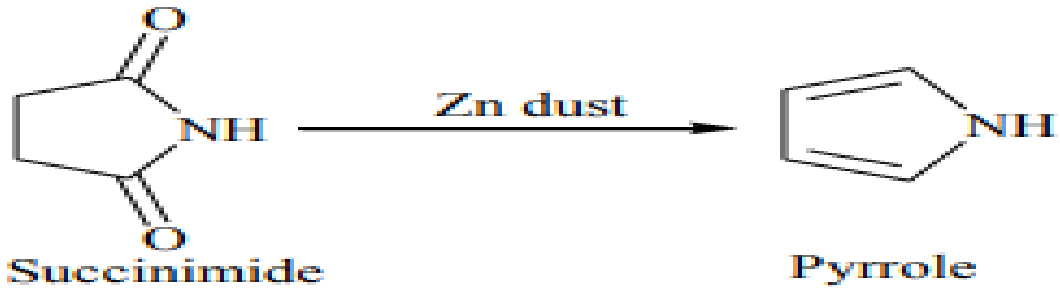
Pyrrole – methods of preparation

From bone oil: Bone oil is rich of pyrrole. The basic and acidic impurities of Bone oil are removed by sequential treatment of it with dilute acidic and dilute basic solutions. The treated Bone oil is then subjected for fractional distillation, the fraction obtained between 373K and 423K is collected. The collected fraction is then purified with KOH to obtained potassiopyrrole. Steam distillation of potassiopyrrole gives pure pyrrole.

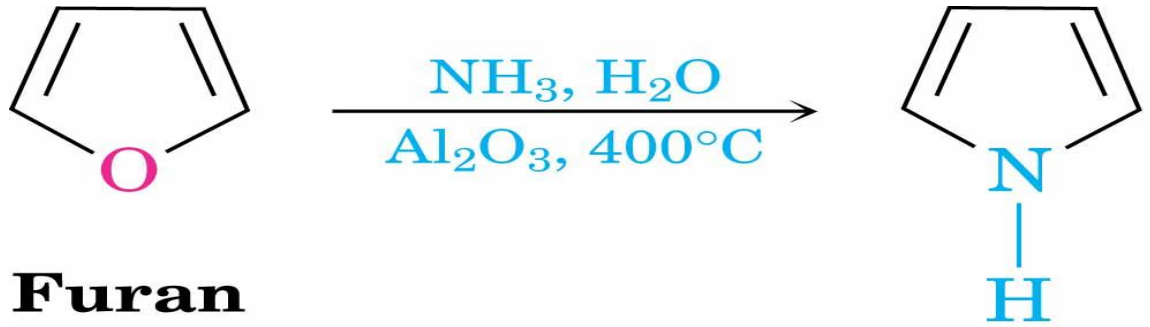


Pyrrole – methods of preparation

From succinimide: Succinimide when is distilled with Zn dust it reduces the succinimide to pyrrole.

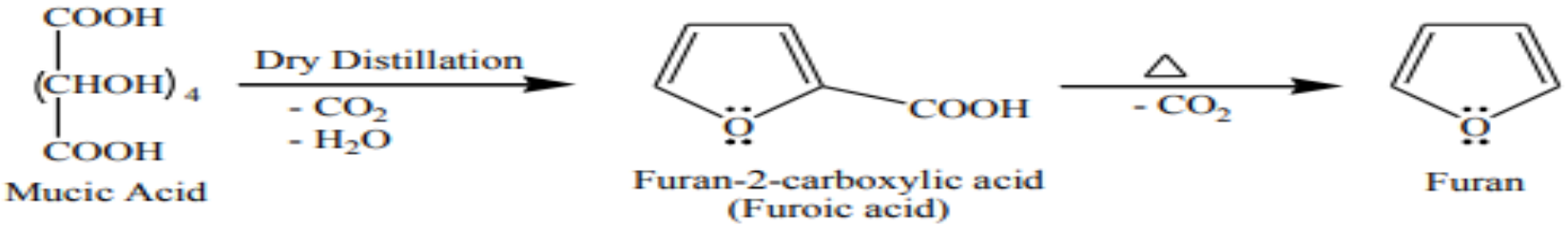


From Furan: Industrially pyrrole is prepared by passing a mixture of furan and ammonia over alumina over 400° C.

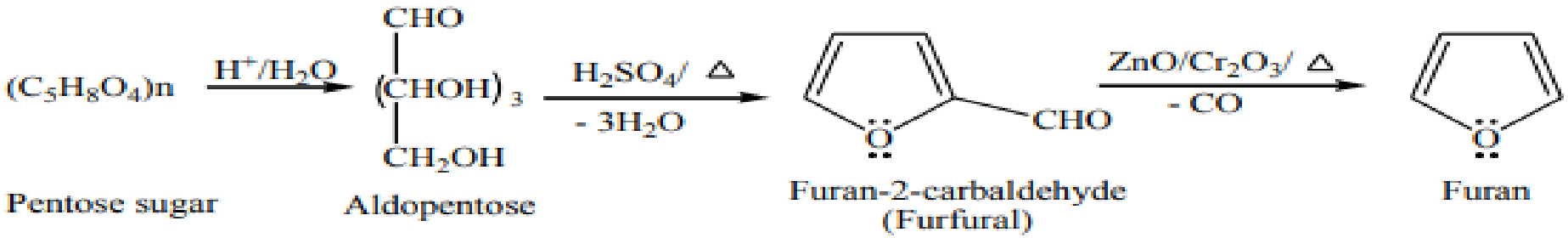


Furan – methods of preparation

- From Mucic acid: Dry distillation of mucic acid first gives Furoic acid which on decarboxylation by heating gives Furan.

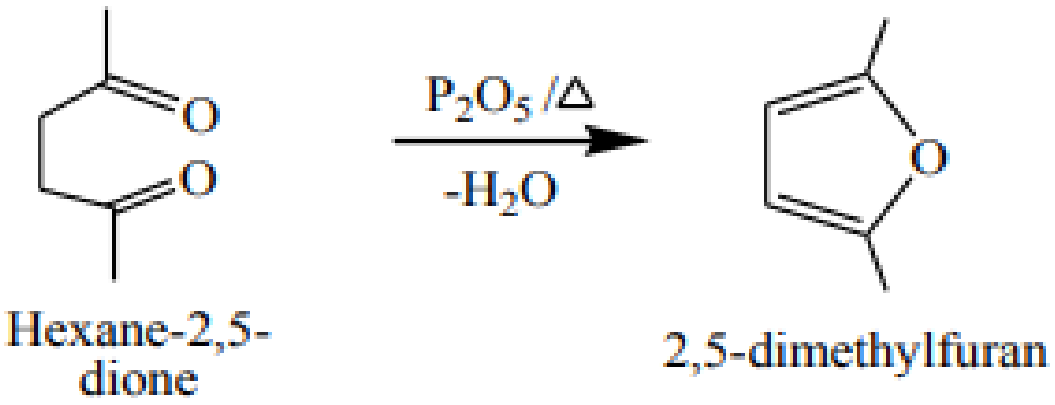


- From Furfural: Furan is synthesized from furfural which is obtained by acid-hydrolysis of pentose sugars.



Furan – methods of preparation

- Paal-Knorr Synthesis: Dehydration of 1,4-diketone with P2O5 (phosphorous Pentaoxide) gives derivatives of Furan.

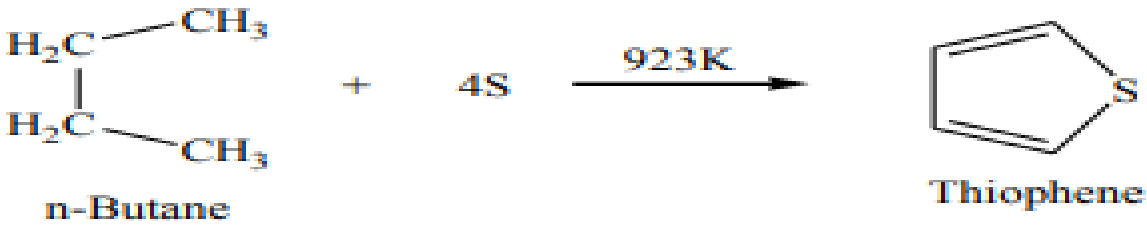


Hexane-2,5-dione

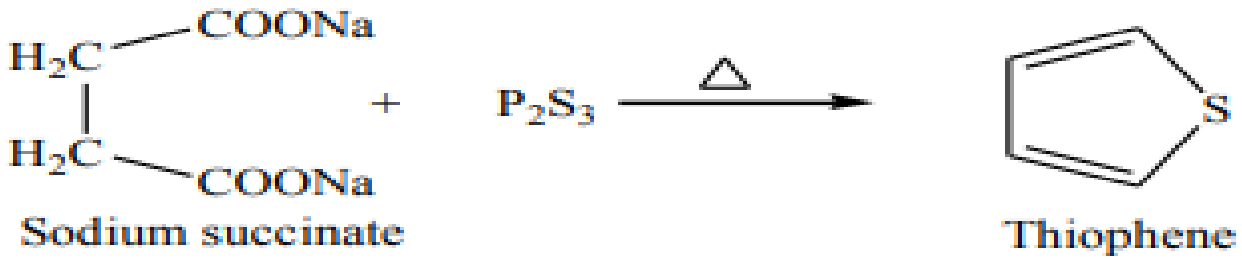
2,5-dimethylfuran

Thiophene – methods of preparation

- From n-Butane: Thiophene is obtained when n-butane is heated with elemental sulphur at very high temperature (923K).

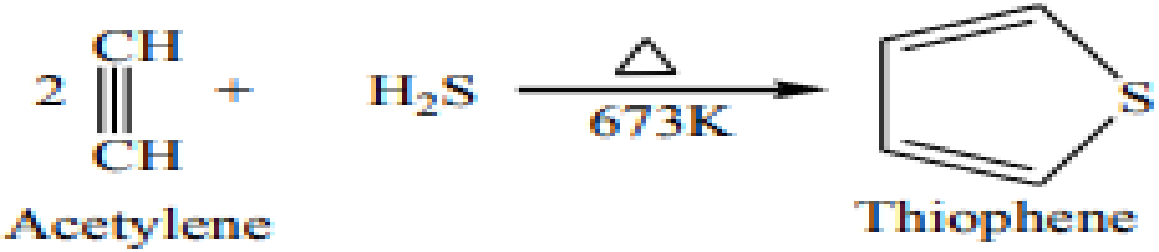


- Laboratory Method: When sodium succinate is heated with phosphorous sulphide, thiophene is obtained.



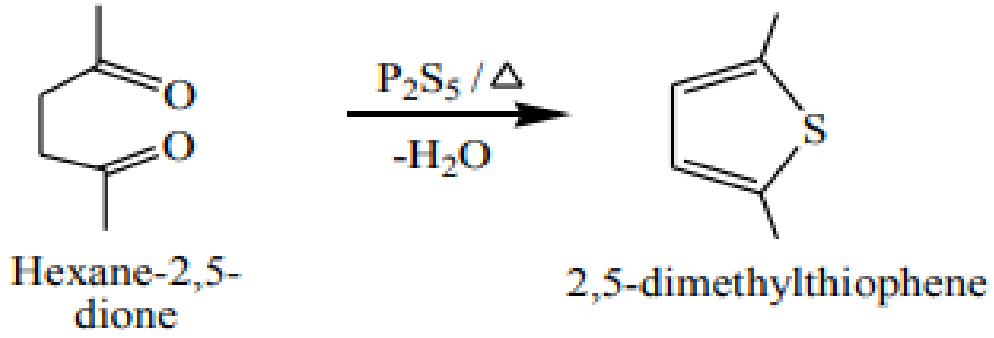
Thiophene – methods of preparation

- Industrial Method: Industrially, thiophene is prepared by passing a mixture of acetylene and hydrogen sulphide through a tube containing alumina (Al2O3) at 673K.



- Pall-Knorr synthesis of thiophene derivatives: In this method, dehydration of 1,4- diketone

with (phosphorous Pentasulphide) gives derivatives of thiophene.



Physical Properties

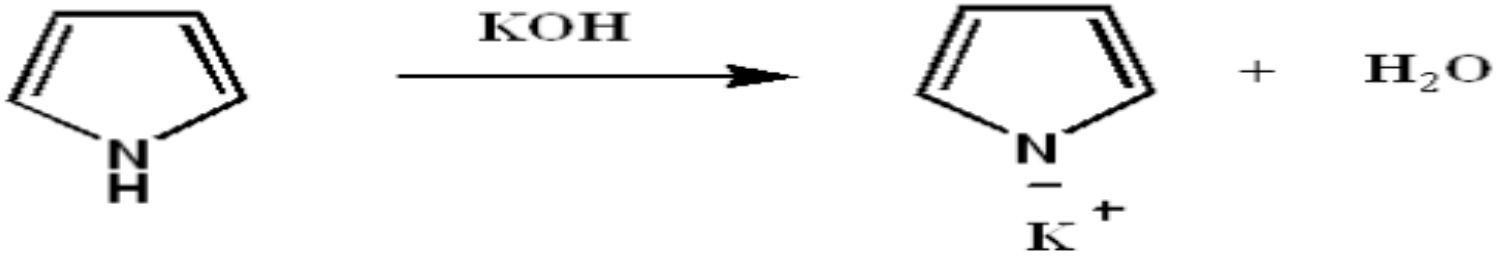
- Physical Properties of **Pyrrole:** Pyrrole is a colorless liquid with boiling point 131° C. It is highly sensitive to air, when pyrrole is exposed to air it turns brown and gradually resinifies. Pyrrole is slightly soluble in water but completely miscible in ether and ethanol.
- Physical Properties of **Furan**: Furan is colorless liquid. Its boiling point is 31.4° C. It has an odor similar to Chloroform. It is insoluble in ether but soluble in most of the organic solvents.
- Physical Properties of **Thiophene:** Thiophene is colorless liquid. Boiling point of thiophene is 357 K. It smells like benzene. It is soluble in alcohol and ether but insoluble in water.

Chemical reactions of five-membered heterocycles

- **Acid-base properties**

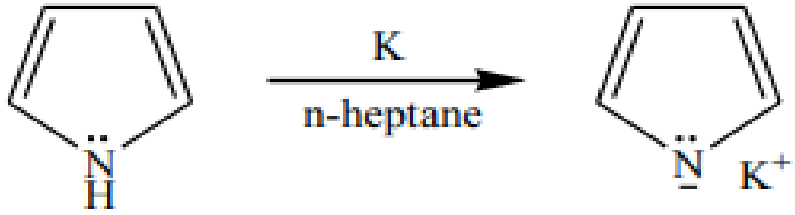
Acidic character of pyrrole

Unlike furan and thiophene, pyrrole is weakly acidic in nature. Thus, on reaction with metallic potassium or potassium hydroxide it forms a potassium salt, which is hydrolyzed back to pyrrole on treatment with water.



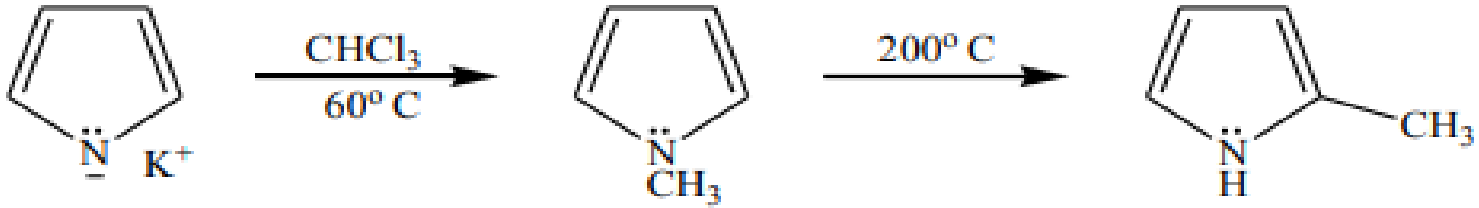
Chemical reactions of five-membered heterocycles

- **Acid-base properties**
- Acidic Character of Pyrrole



Pyrrole Potassium pyrrolide

Potassium pyrrolide when reacts with alkyl halide at 60° C to give *N*-alkyl pyrrole. The *N*-alkyl pyrrole can easily rearrange to C-alkyl pyrrole.

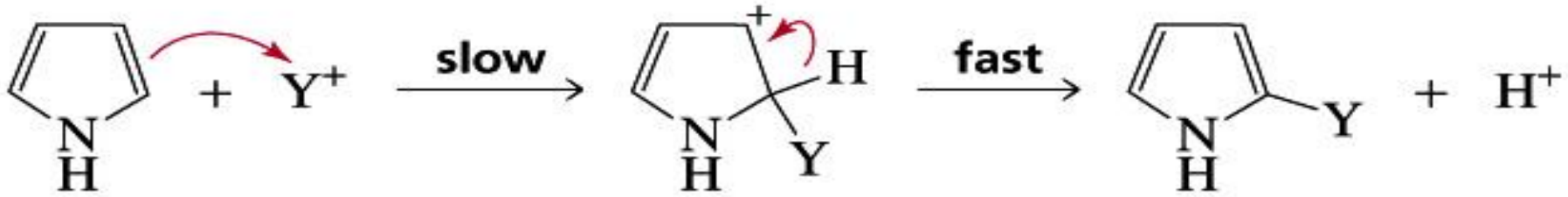


Potassium pyrrolide 1-Methylpyrrole 2-Methylpyrrole

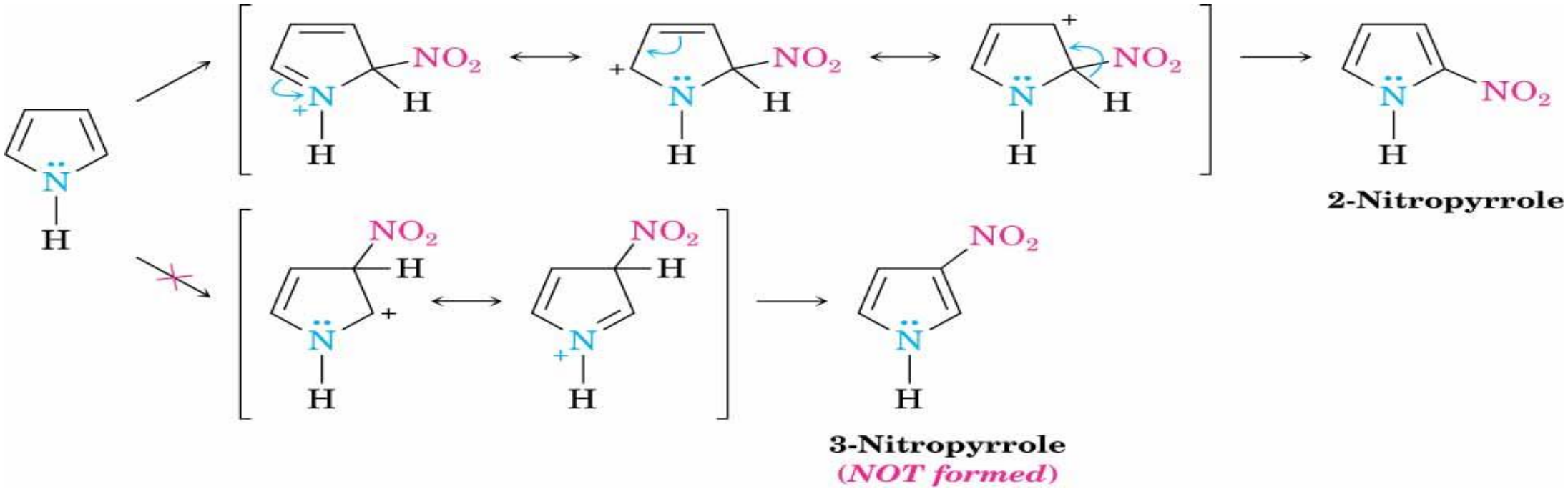
Chemical reactions of five-membered heterocycles

- Electrophilic substitution reactions
- Pyrrole, furan, and thiophene undergo electrophilic
- substitution preferentially at C-2

mechanism for electrophilic aromatic substitution



Chemical reactions of five-membered heterocycles

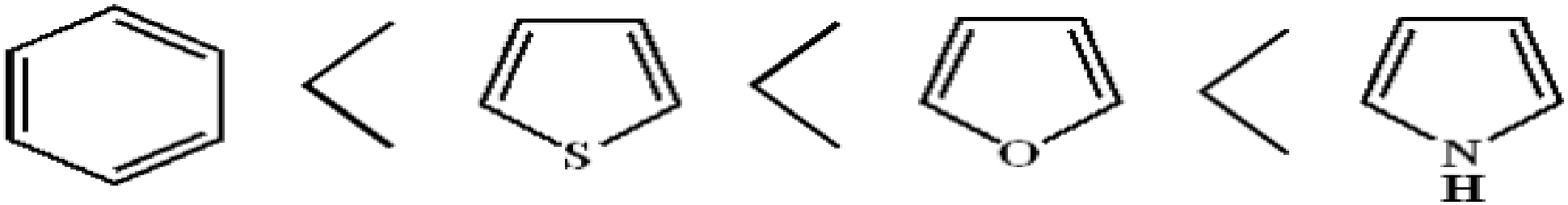


- There are two position for electrophilic attack, C-2 and C-3.
- Attack at C-2 is preferred because it yields a more stable carbocation (3 resonance structures, while attack at C-3 gives only 2 resonance structures(
- E^+ substitution occurs predominately at the 2-position (and if that position is already substituted, substitution occurs at the C-5).
- If 2- and 5-position are already occupied, electrophilic substitution takes place at 3-position.

Reactivity of Five membered pi-Excessive Heterocyclic ring

Reactivity towards electrophilic substitution

Pyrrole, furan and thiophene are all much more reactive than benzene toward electrophilic substitution .

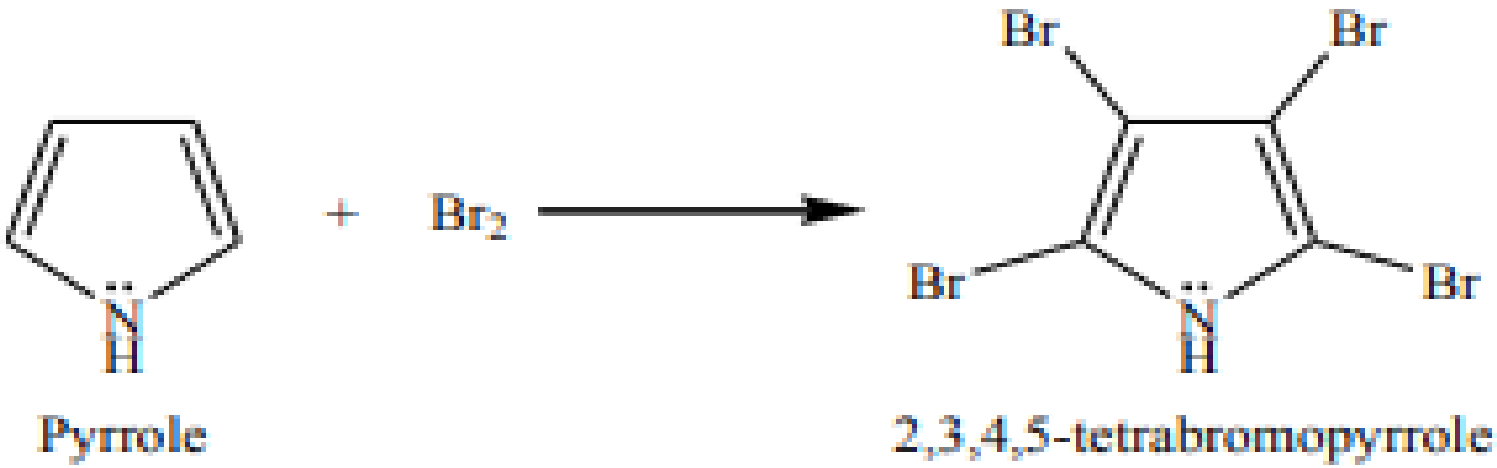


benzene < thiophene < furan < pyrrole

Thiophene is 100 times more reactive than benzene and pyrrole is the most reactive. Furan is less reactive than pyrrole because oxygen is more electronegative than nitrogen .

Chemical reactions of five-membered heterocycles

- Electrophilic substitution reactions for Pyrrole
- 1. Halogenation: Pyrrole reacts with halogens (X_2 = Cl_2, Br_2 and I_2)] to give tetrahalopyrrole. For example, Reaction of bromine with pyrrole gives tetrabromopyrrole.

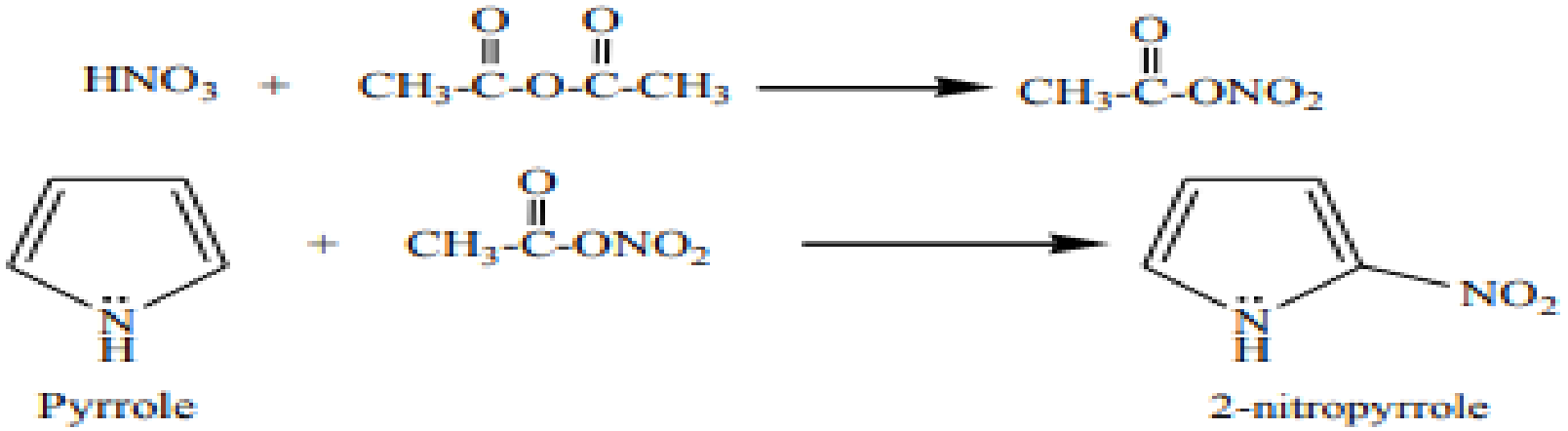


Pyrrole

2,3,4,5-tetrabromopyrrole

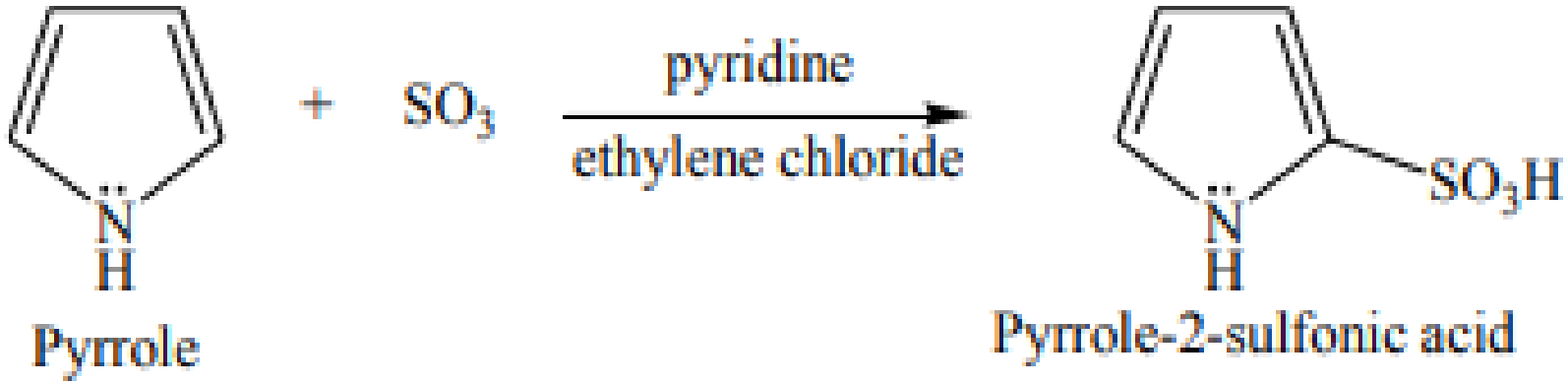
Chemical reactions of five-membered heterocycles

- Electrophilic substitution reactions for Pyrrole
- 2. Nitration: Nitration of pyrrole is achieved by reacting it with HNO_3 in acetic anhydride. The reaction of HNO_3 and acetic anhydride resulted acetyl nitrate in which $–NO_2$ acts as an electrophile



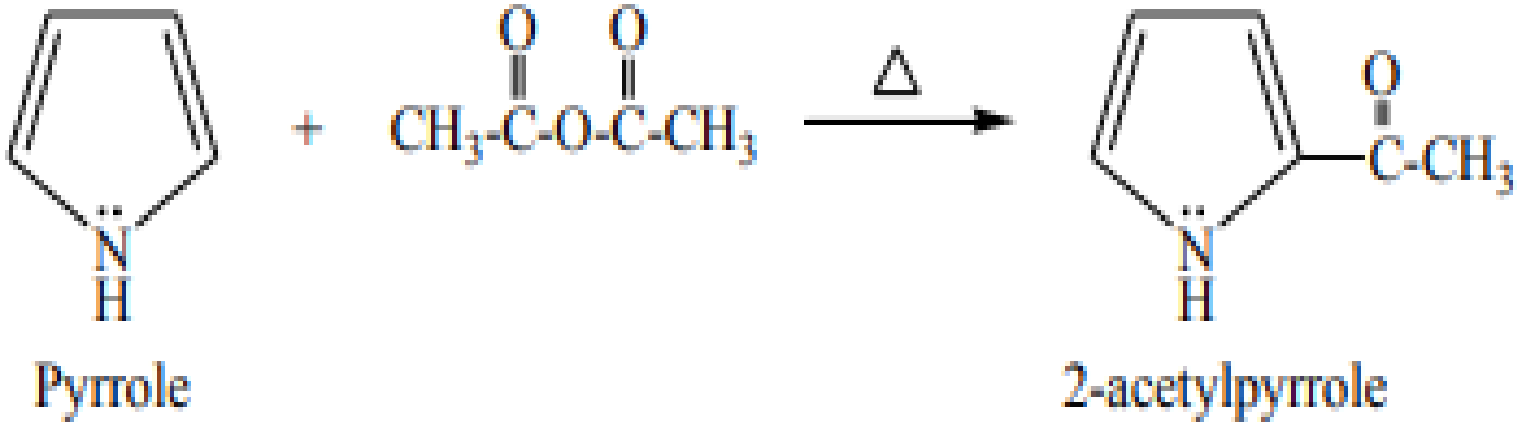
Chemical reactions of five-membered heterocycles

- Electrophilic substitution reactions for Pyrrole
- 3. Sulphonation: Sulphonation of pyrrole is achieved by reacting it with sulfur trioxide (SO_3) – pyridine mixture in ethylene chloride.



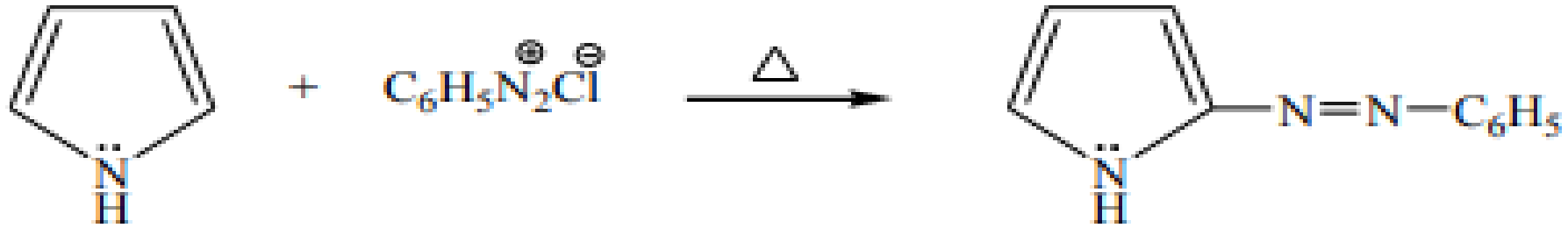
Chemical reactions of five-membered heterocycles

- Electrophilic substitution reactions for Pyrrole
- 4. Friedel-Crafts Acylation: Reaction of pyrrole with acetic anhydride under heating condition gives 2-acetylpyrrole



Chemical reactions of five-membered heterocycles

- Electrophilic substitution reactions for Pyrrole
- 5. Diazotization: Pyrrole reacts with benzenediazonium chloride in acidic medium to give 2-phenylazopyrrole.

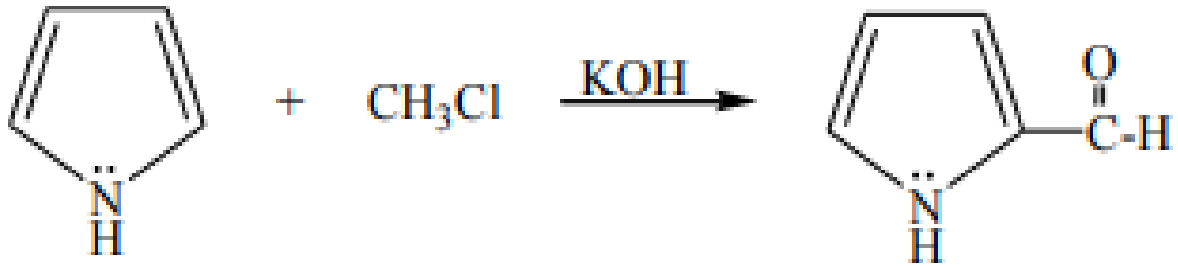


Pyrrole

2-Phenylazopyrrole

Chemical reactions of five-membered heterocycles

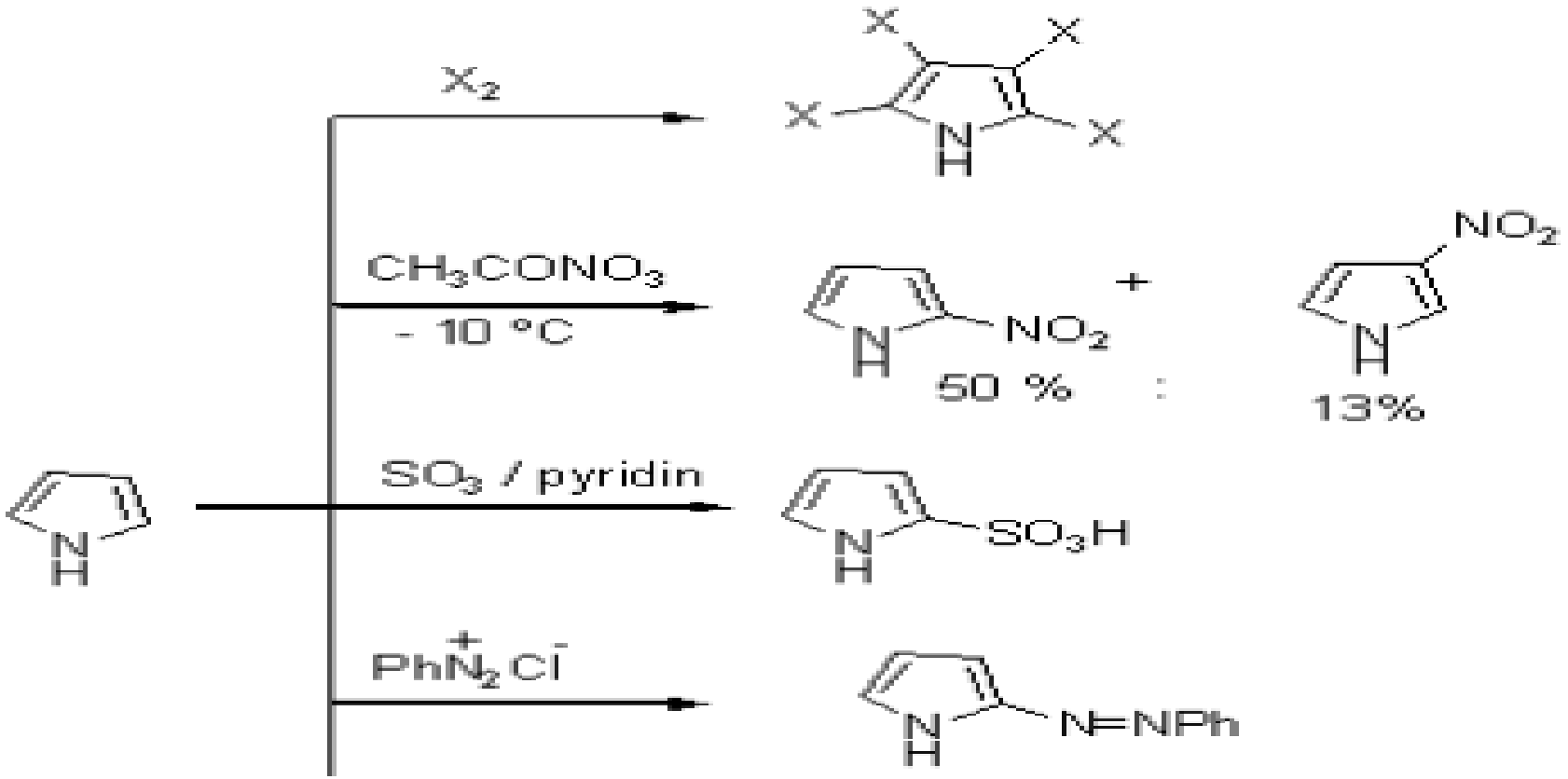
- Electrophilic substitution reactions for Pyrrole
- 6. Reimer-Tiemann Reaction: Pyrrole reacts with Chloroform in presence of KOH to give 2-Formylpyrrole. This reaction is known as Reimer-Tiemann reaction. It also takes place through electrophilic substitution reaction mechanism



Pyrrole 2-Formylpyrrole

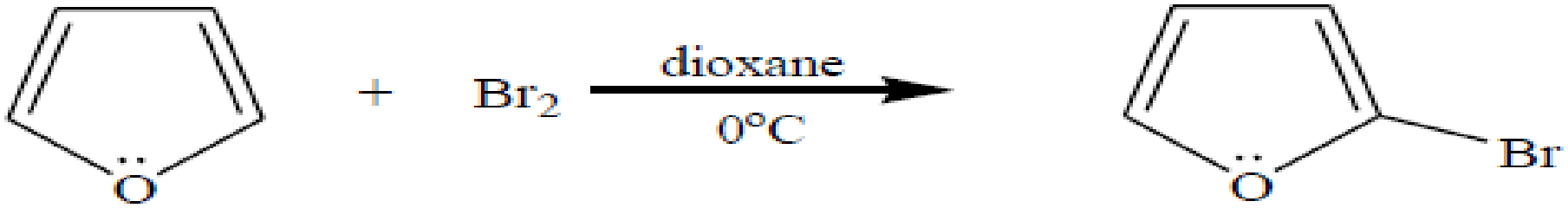
Chemical reactions of five-membered heterocycles

- Electrophilic substitution reactions for Pyrrole



Chemical reactions of five-membered heterocycles

- Electrophilic substitution reactions for Furan
- 1.**Halogenation:** Furan reacts with halogens [X2 (X2 = Cl2, Br2 and I2)] to give 2- halofuran. For example, reaction of bromine with Furan gives 2-bromofuran.

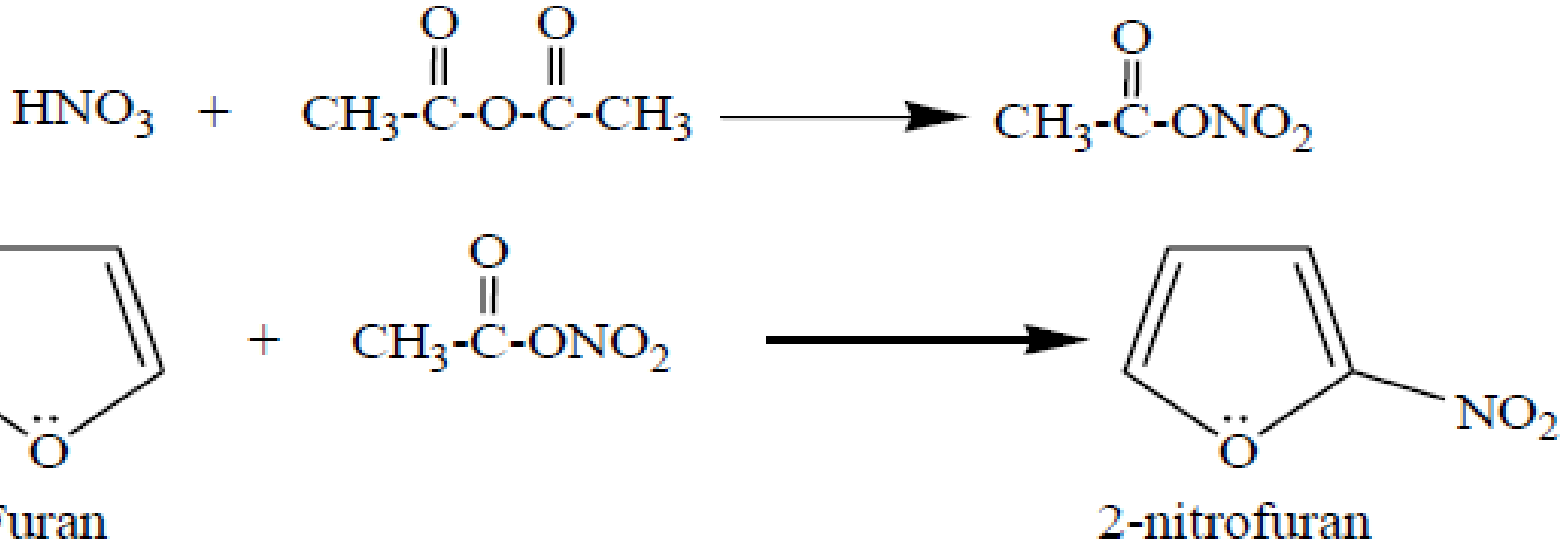


Furan

2-bromofuran

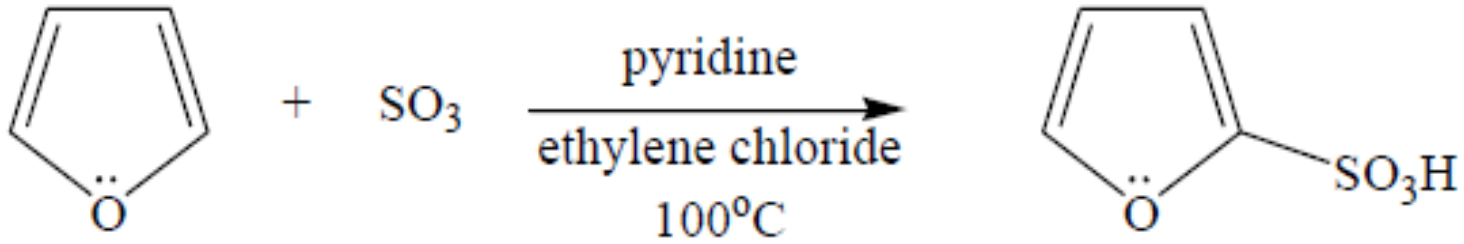
Chemical reactions of five-membered heterocycles

- Electrophilic substitution reactions for Furan
- 2.**Nitration:** Nitration of furan is achieved by reacting it with HNO_3 in acetic anhydride. The reaction of HNO_3 and acetic anhydride resulted acetyl nitrate in which $–NO_2$ acts as an electrophile.



Chemical reactions of five-membered heterocycles

- Electrophilic substitution reactions for Furan
- 3.**Sulphonation:** Sulphonation of Furan is achieved by reacting it with sulfur trioxide (SO3) – pyridine mixture in ethylene chloride at 100° C.

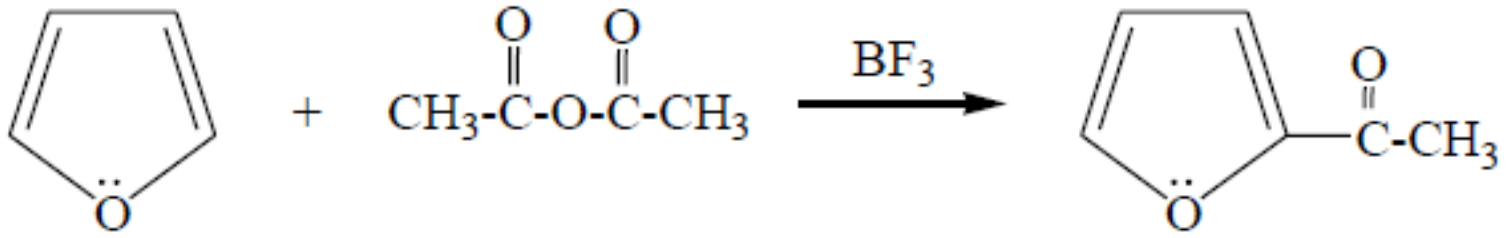


Furan

Furan-2-sulfonic acid

Chemical reactions of five-membered heterocycles

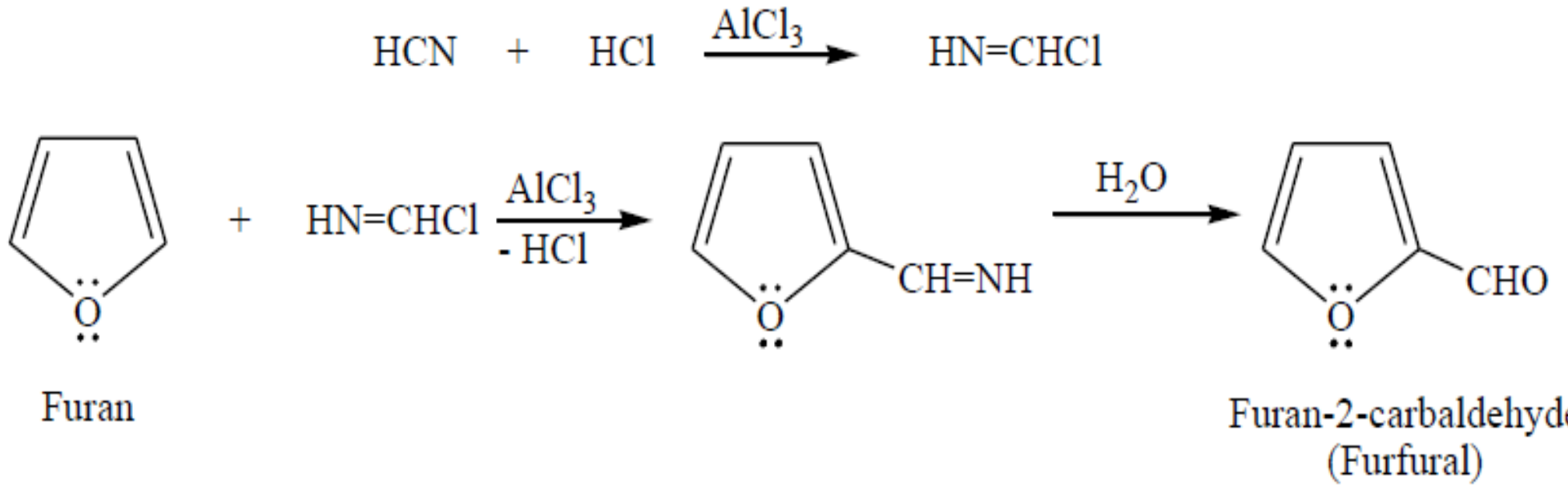
- Electrophilic substitution reactions for Furan
- 4.**Friedel-Crafts Acylation:** Reaction of furan with acetic anhydride in presence of BF_3 gives 2-acetylfuran.



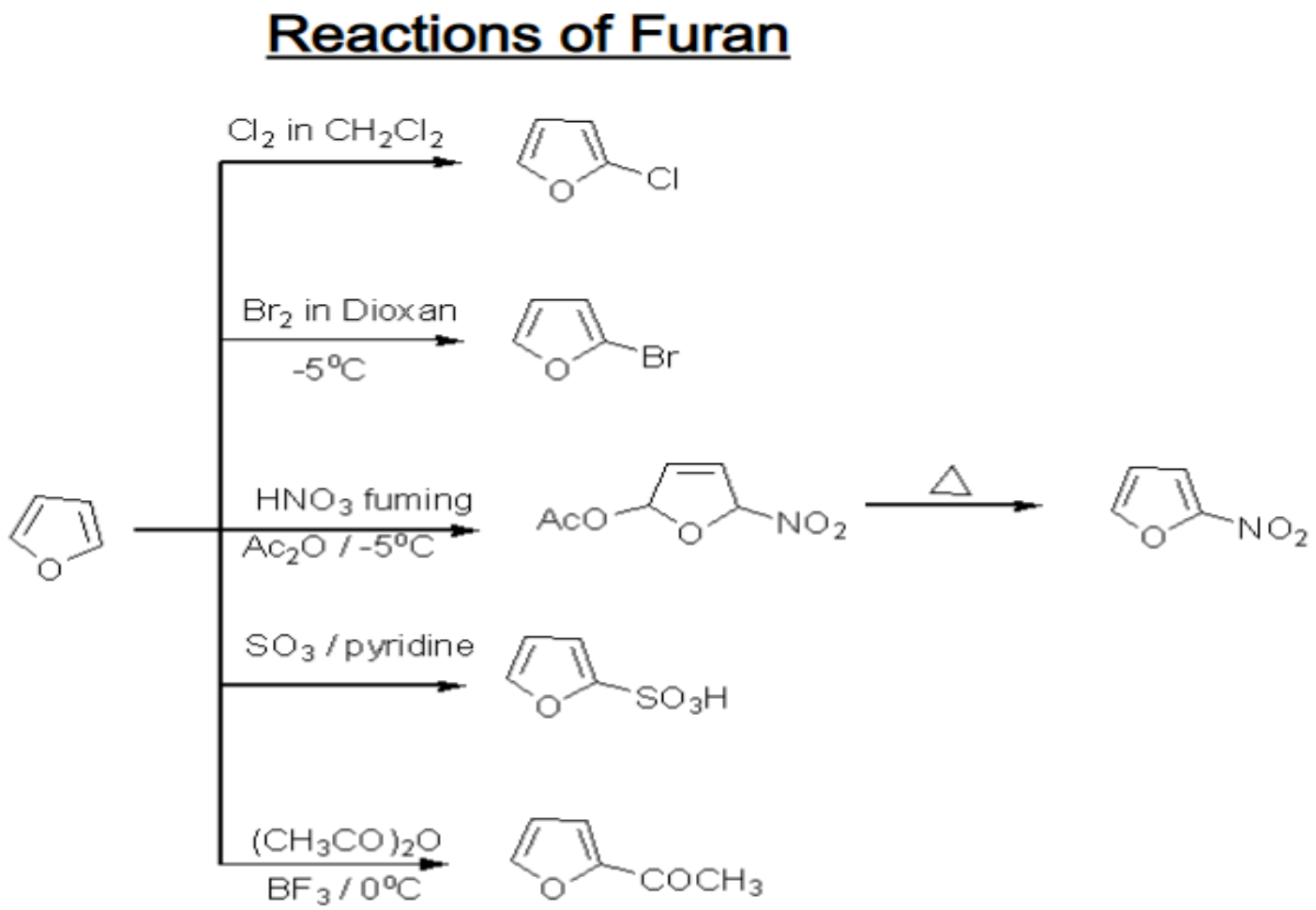
Furan + CH_3-C(=O)-O-C(=O)-CH_3 $\xrightarrow{BF_3}$ 2-acetylfuran

Chemical reactions of five-membered heterocycles

- Electrophilic substitution reactions for Furan
- 5.**Gattermann Koch Synthesis:** When furan is treated with a mixture of HCN and HCl in the presence of Lewis acid catalyst AlCl3, furfural is obtained as final product.

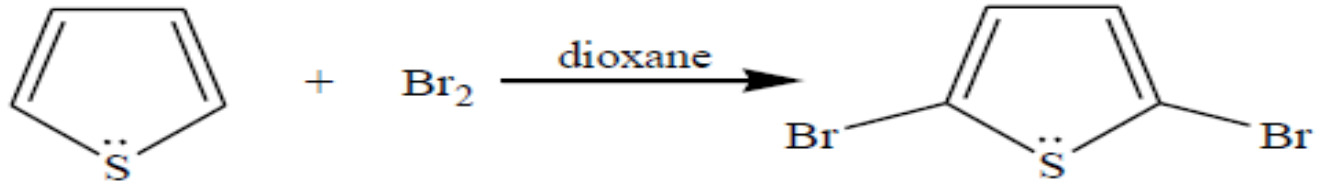


Chemical reactions of five-membered heterocycles



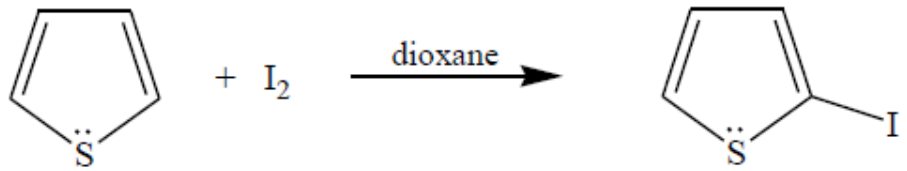
Chemical reactions of five-membered heterocycles

- Electrophilic substitution reactions for Thiophene
- 1. Halogenation: Thiophene reacts with halogens (X_2 = Cl_2, Br_2 and I_2)] to give 2-halothiophene. For example, Reaction of bromine



Thiophene 2,5-dibromothiophene

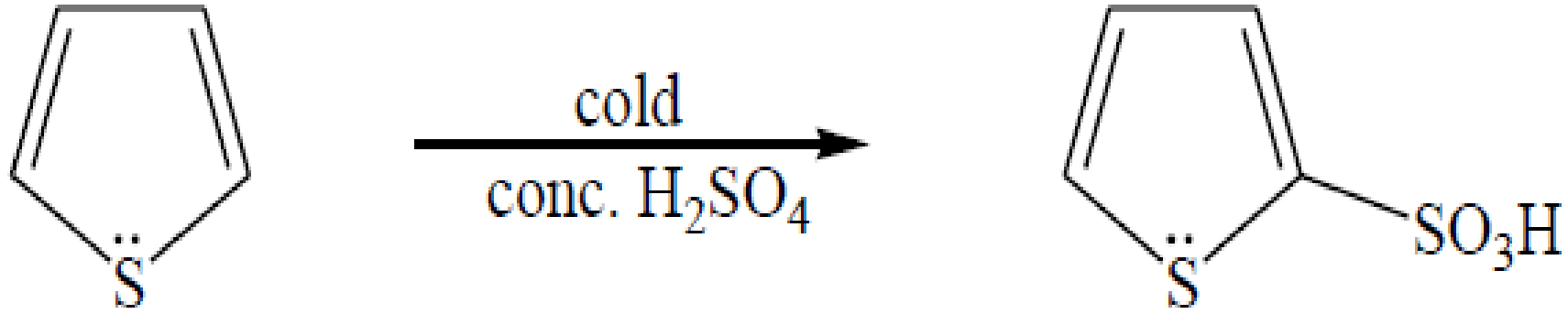
- However, Iodination of thiophene in presence of yellow mercuric oxide gives 2-iodothiophene.



Thiophene 2-Iodothiophene

Chemical reactions of five-membered heterocycles

- Electrophilic substitution reactions for Thiophene
- 3. **Sulphonation:** Sulphonation of thiophene is achieved by reacting it with cold concentrated H2SO4. Thiophene-2-sulphonic acid is obtained as product.

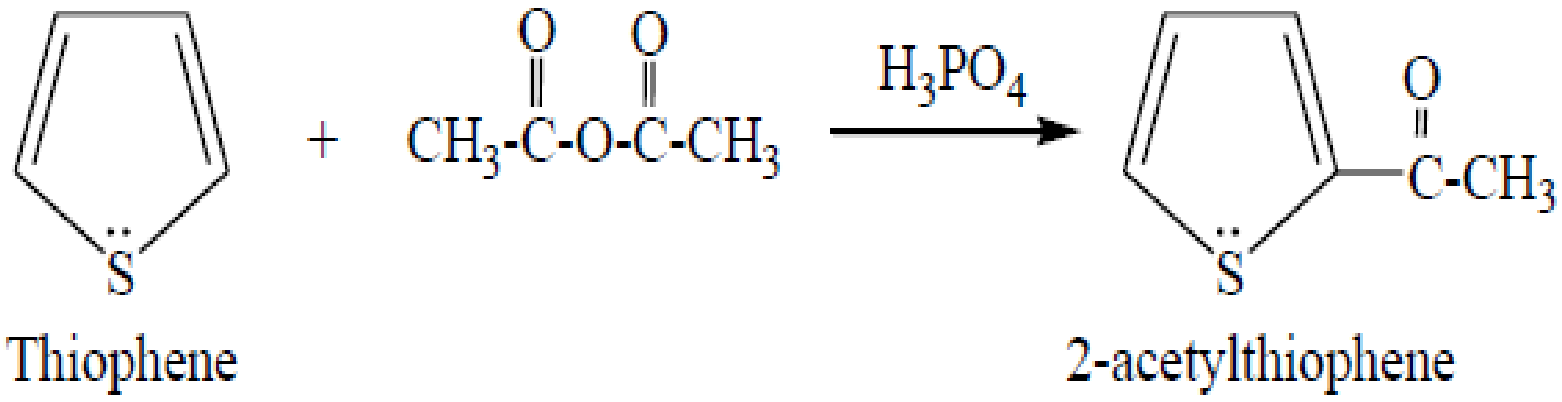


Thiophene

Thiophene-2-sulfonic acid

Chemical reactions of five-membered heterocycles

- Electrophilic substitution reactions for Thiophene
- 4. **Friedel-Crafts Acylation:** Reaction of thiophene with acetic anhydride in presence of H3PO4 gives 2-acetylthiophene.

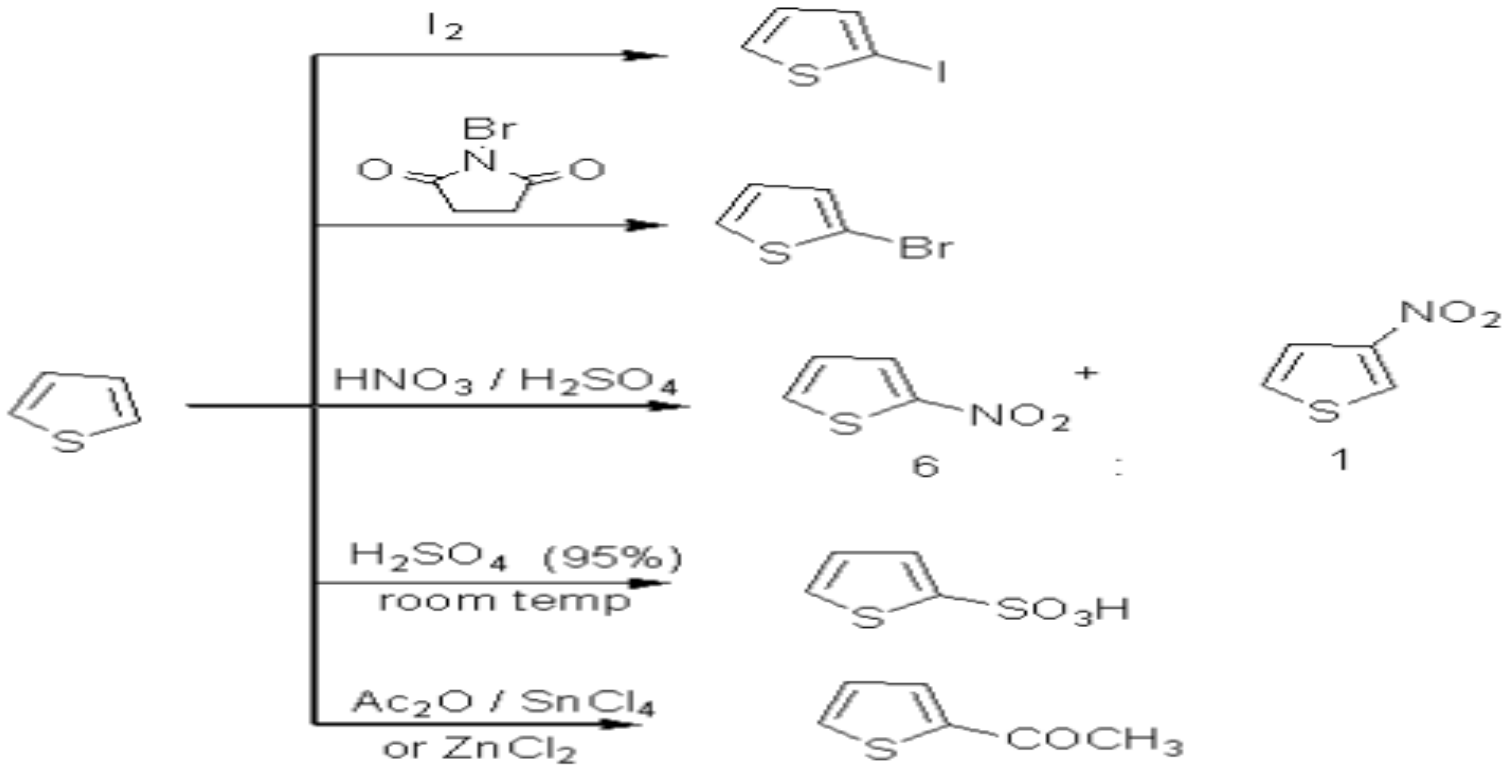


Thiophene

2-acetylthiophene

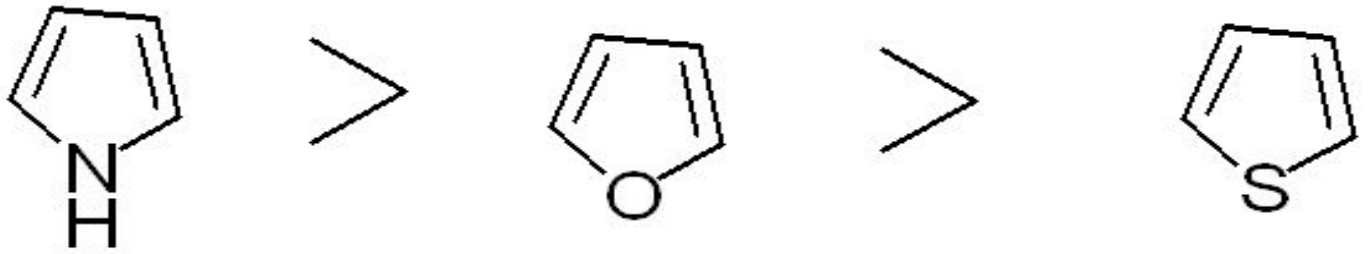
Chemical reactions of five-membered heterocycles

- Electrophilic substitution reactions for Thiophene

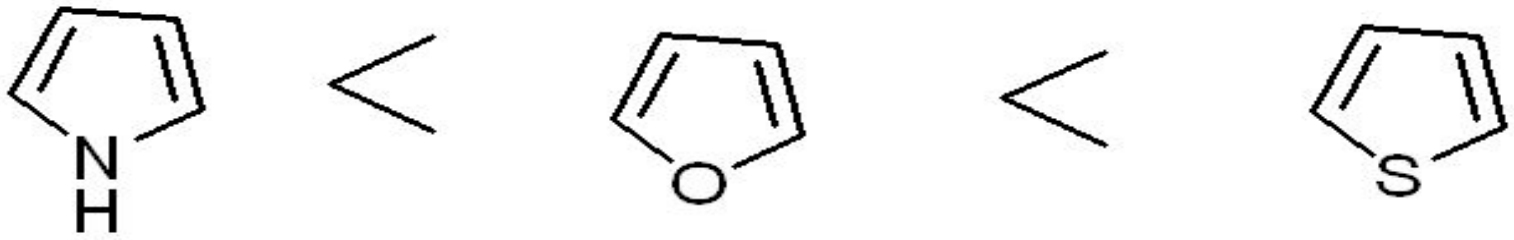


Reactivity

We have seen that the reactivity of pyrrole, furan and thiophene towards electrophilic substitution is in the following order



The reactivity of these rings towards nucleophilic substitution is in the opposite order

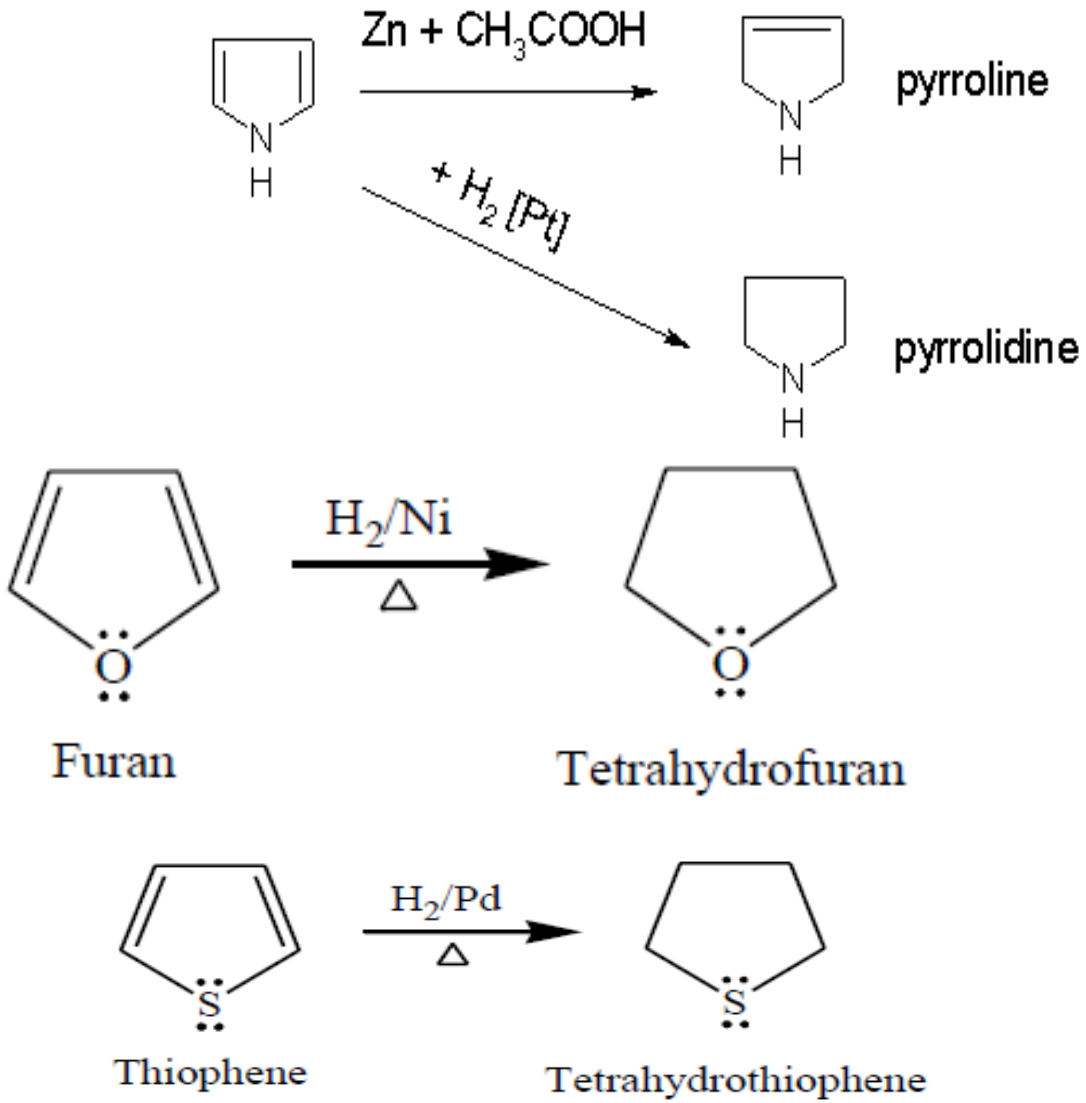


Chemical reactions of five-membered heterocycles

- Reduction reactions

- Pyrrole can be reduced to pyrrolidine (tetrahydropyrrole) by H2 gas in Raney Ni at very high temperature (473K).

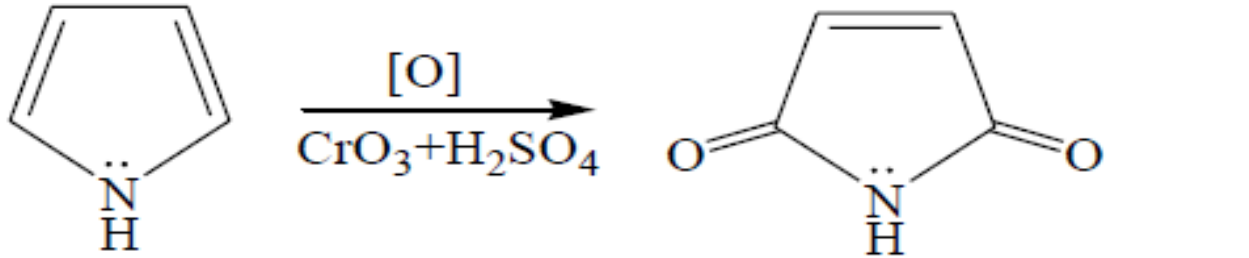
- On catalytic hydrogenation of furan, the tetrahydrofuran (THF) is obtained. THF is used as a solvent in place of ether in the Grignard reactions.
- On catalytic hydrogenation of thiophene, the tetrahydrothiophene (Thiophane) is obtained.



Chemical reactions of five-membered heterocycles

- Oxidation reaction

- **Oxidation:** Pyrrole when oxidized with Chromium trioxide in H2SO4, it gives Malecimide.

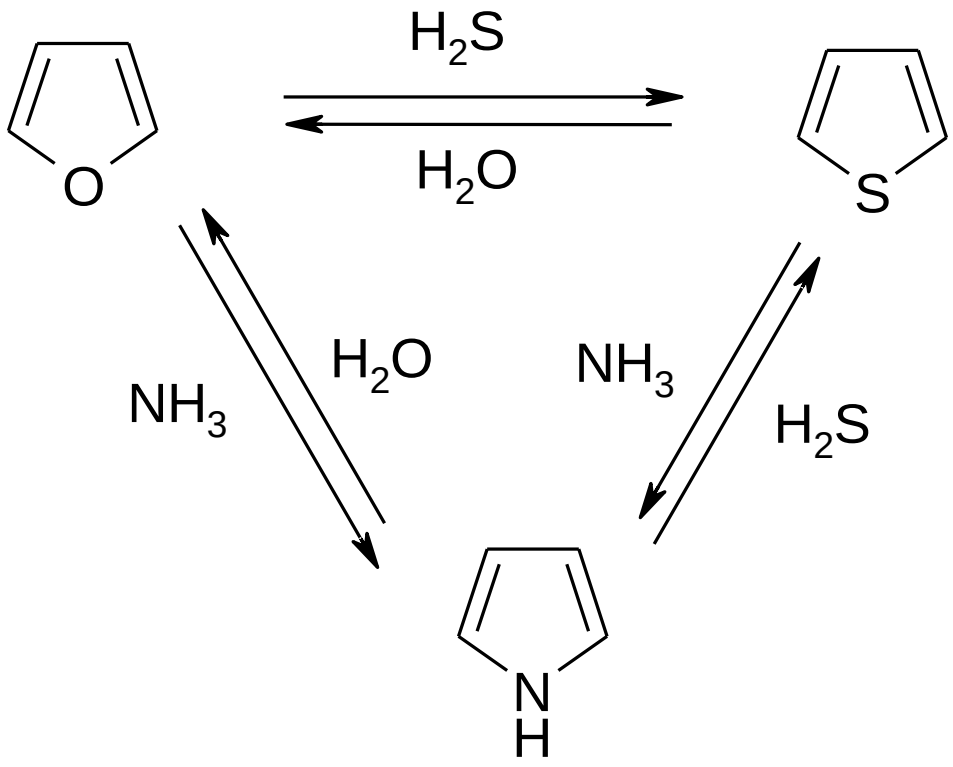


Pyrrole

Pyrrole-2,5-dione (Malecimide)

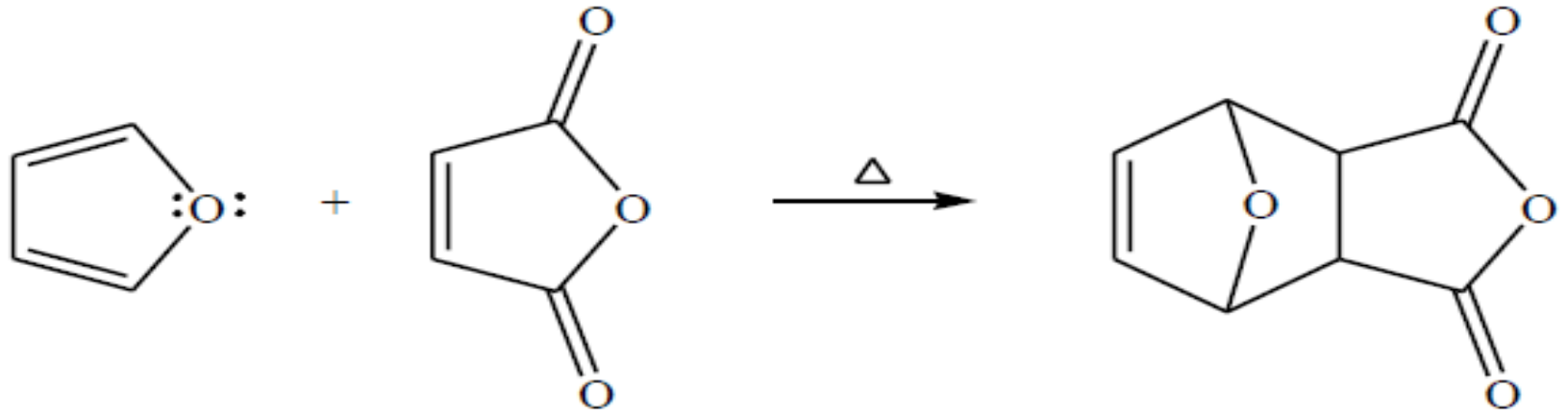
Chemical reactions of five-membered heterocycles

•Reactions of heteroatom exchange (Yuriev's reaction): catalyst Al_2O_3, t = 400-450^{0}C



Chemical reactions of five-membered heterocycles

Diels-Elder Reaction: Furan is the only heterocyclic compound which undergoes Diels-Elder reaction. Diels-Elder reaction is a cycloaddtion reaction of 4π-system to 2π- system.



Furan Maleic Anhydride Adduct

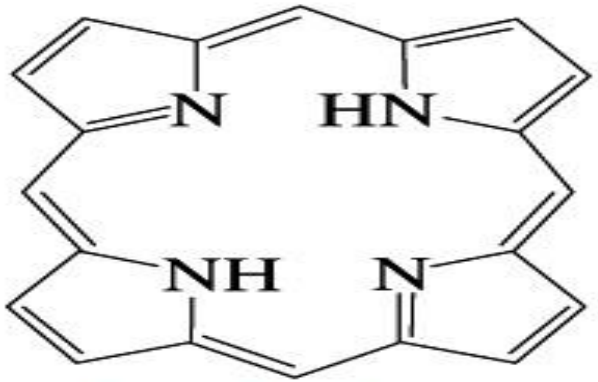
Derivatives of five-membered cycles of pyrrole

Porhyrin ring system:

Chlorophyll

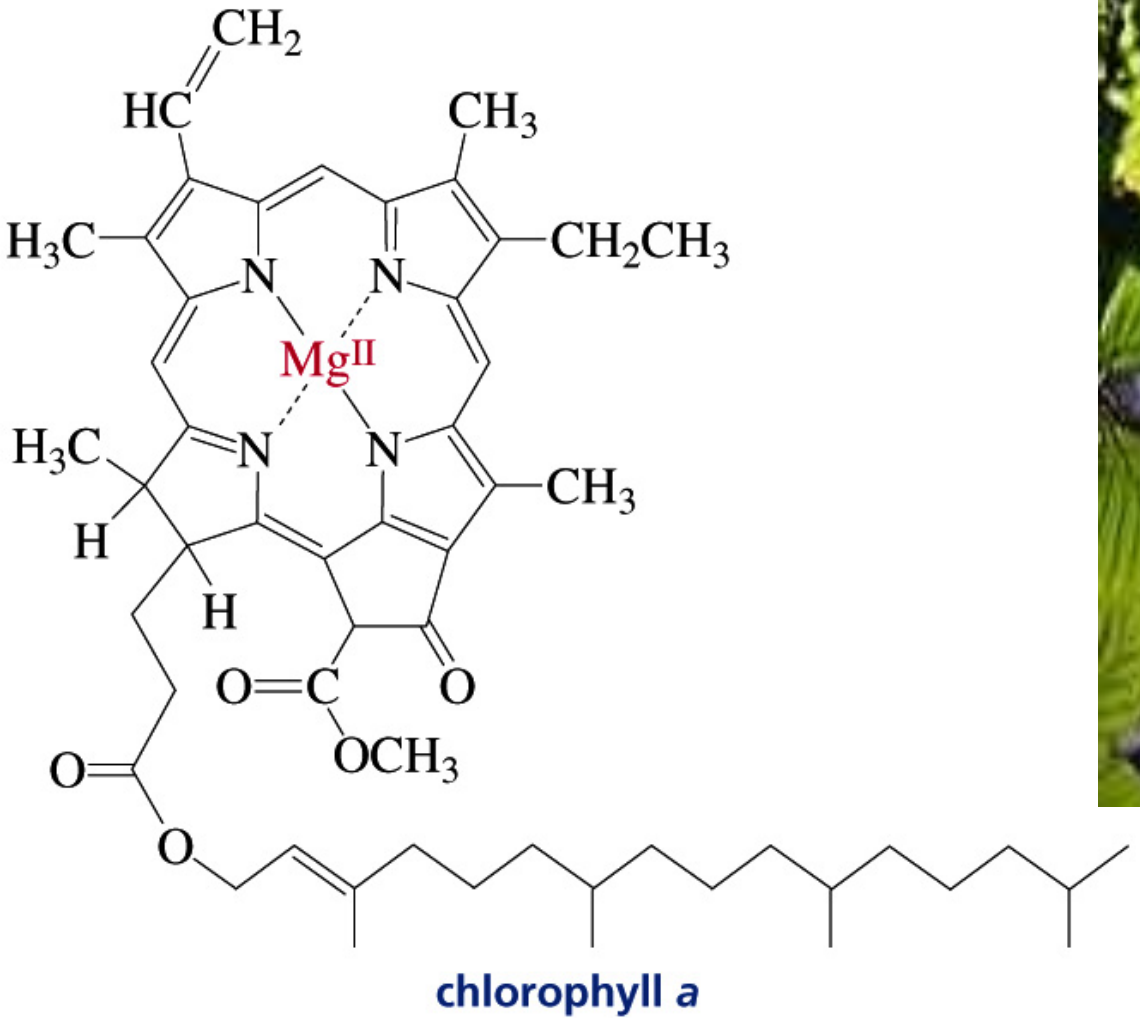
Haemoglobin

Vitamin B12



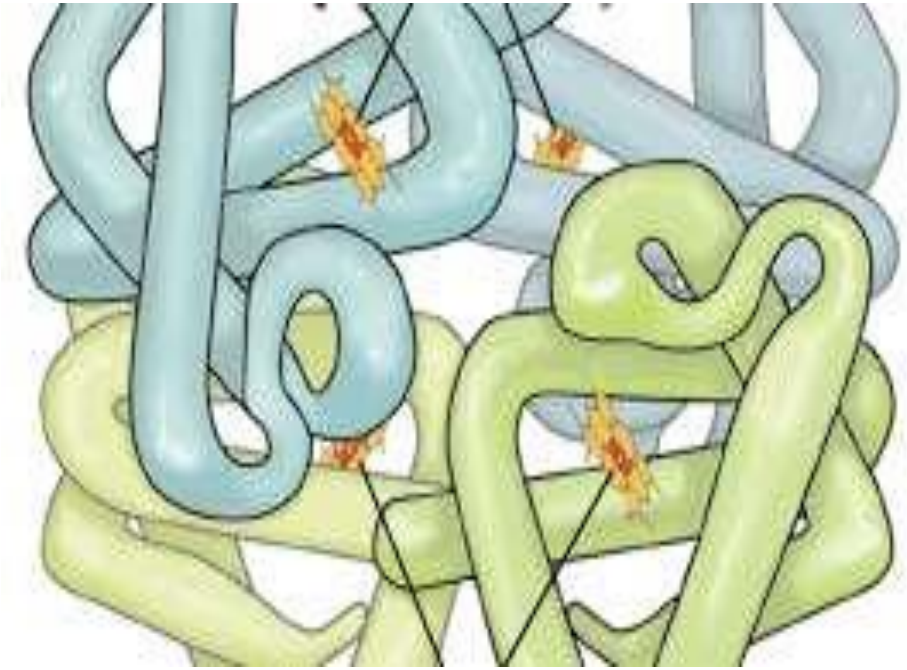
a porphyrin ring system

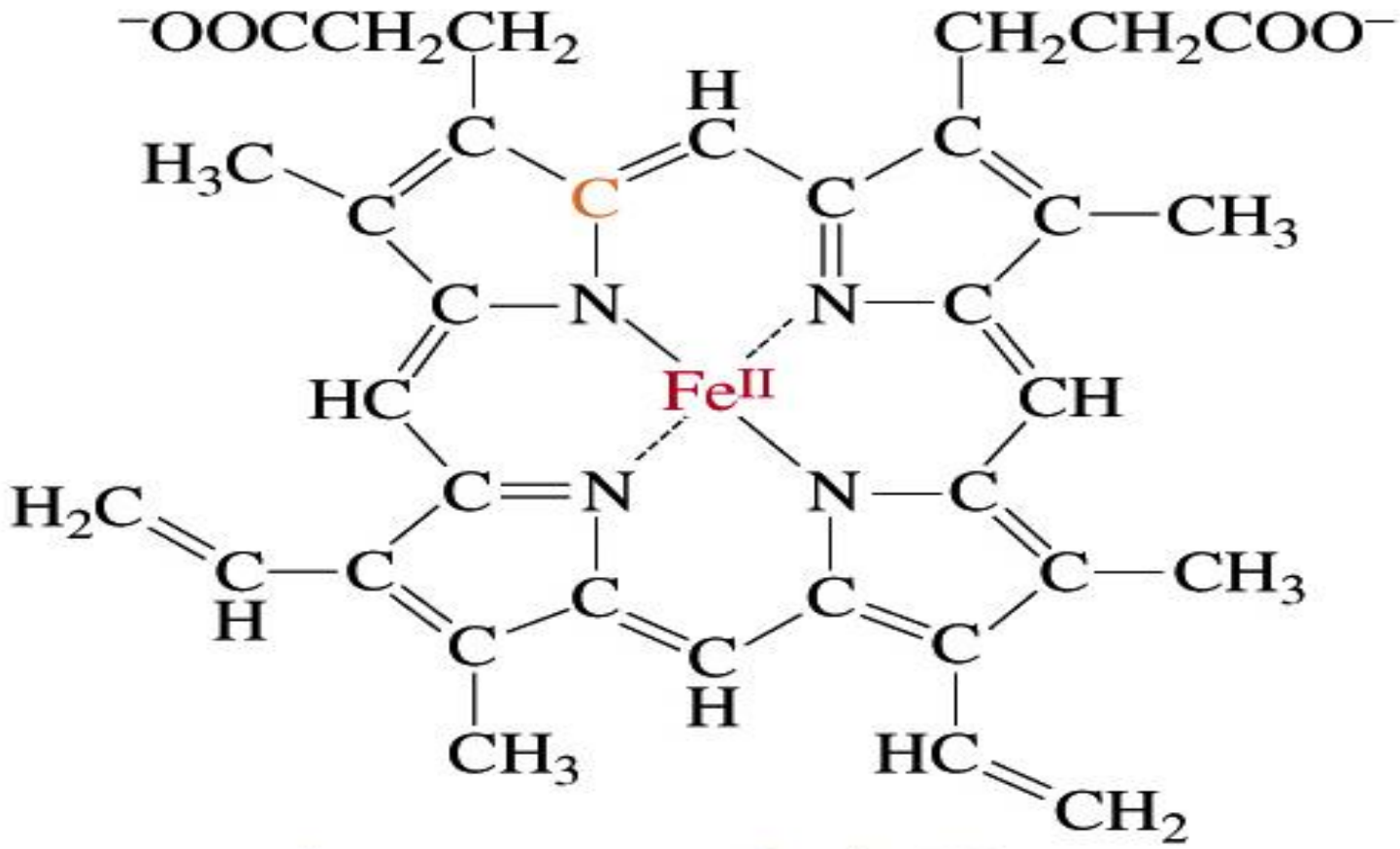
Derivatives of five-membered cycles of pyrrole



chlorophyll *a*

Derivatives of five-membered cycles of pyrrole

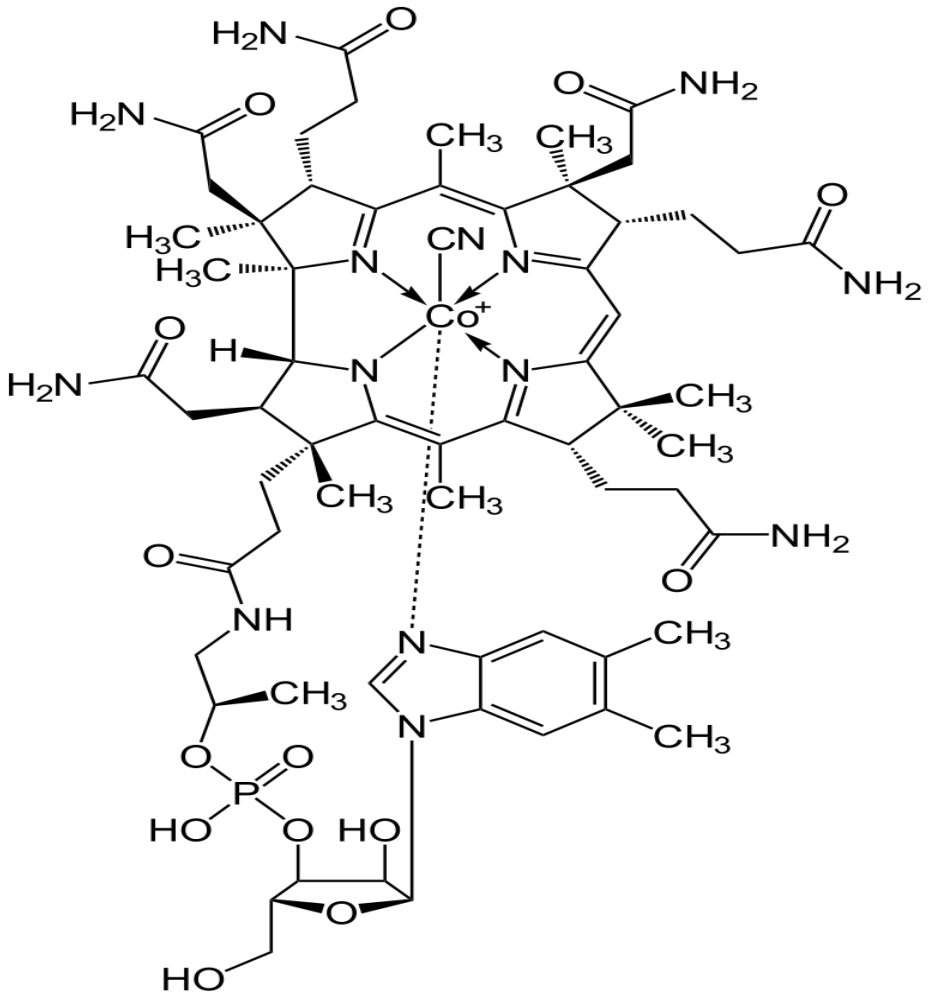




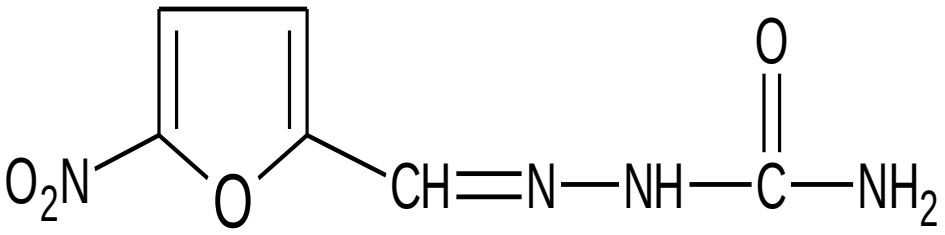
iron protoporphyrin IX
heme

Derivatives of five-membered cycles of pyrrole

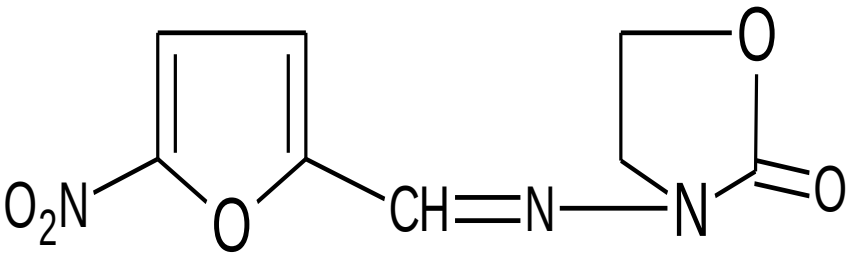
- Vitamin B 12



Derivatives of five-membered cycles of furan

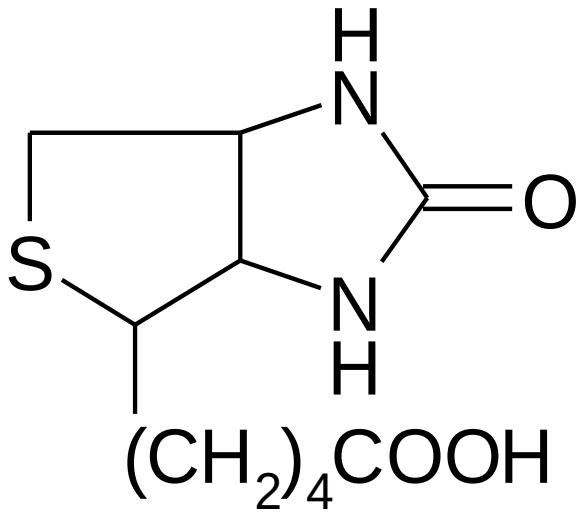


furacin (nitrofural)



furazolidone

Derivatives of five-membered cycles of thiofene



Vitamin H