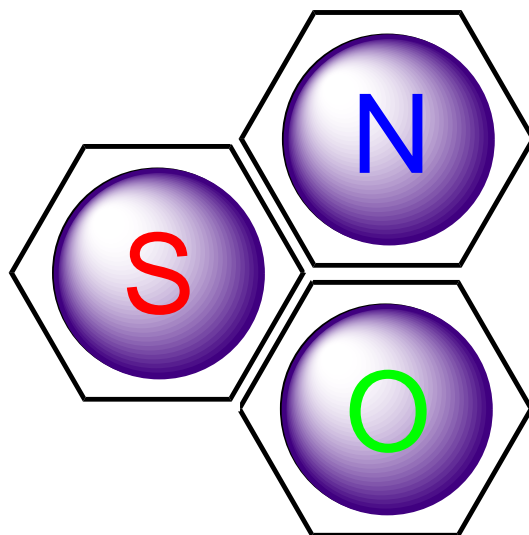




Heterocyclic Chemistry



**Five-membered
Heterocycles**
Pyrrole, Furan and Thiophene
Electrophilic Substitution Reactions

Heterocyclic Chemistry
Dr. Ayad

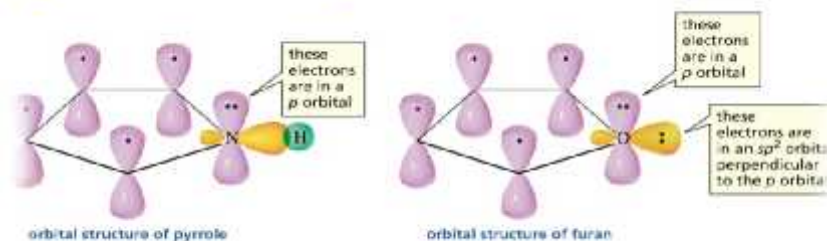




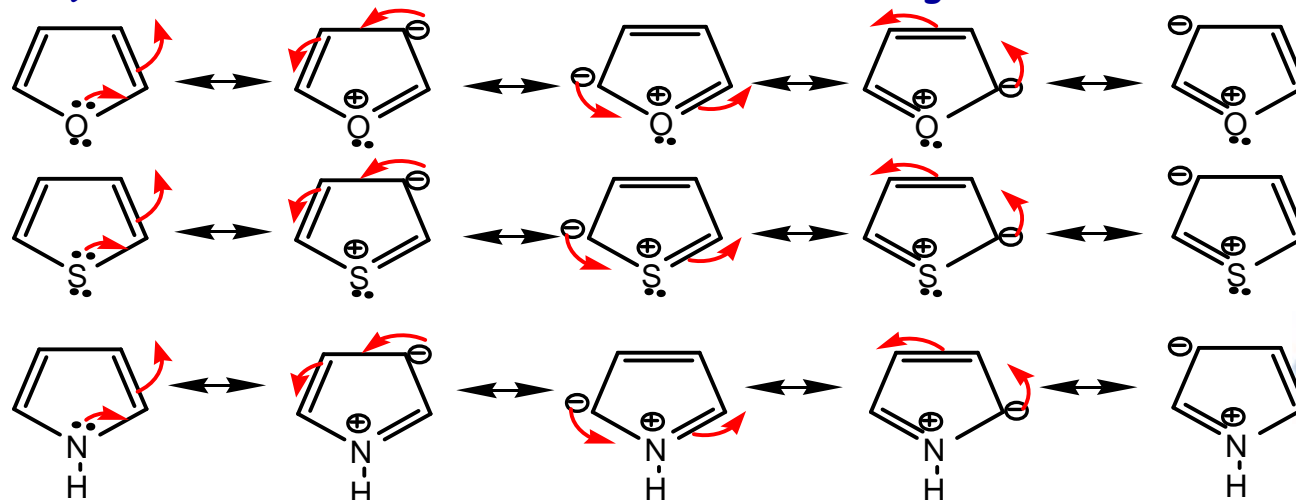
Structure and Aromaticity

❖ Pyrrole, furan and thiophene are aromatic because:

1) they fulfill the criteria for aromaticity, the extent of delocalization of the nonbonding electron pair is decisive for the aromaticity, thus the grading of aromaticity is in the order of: furan < pyrrole < thiophene < benzene this order is consistent with the order of electronegativity values for oxygen (3.44), nitrogen (3.04) and thiophene (2.56).



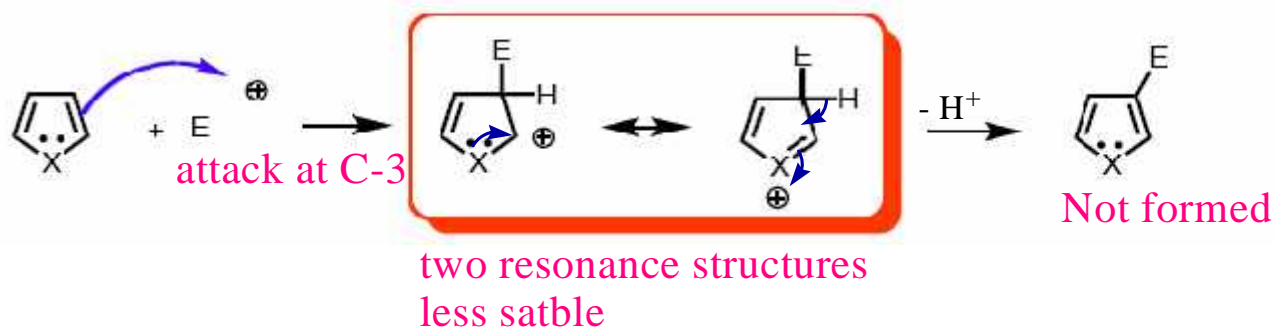
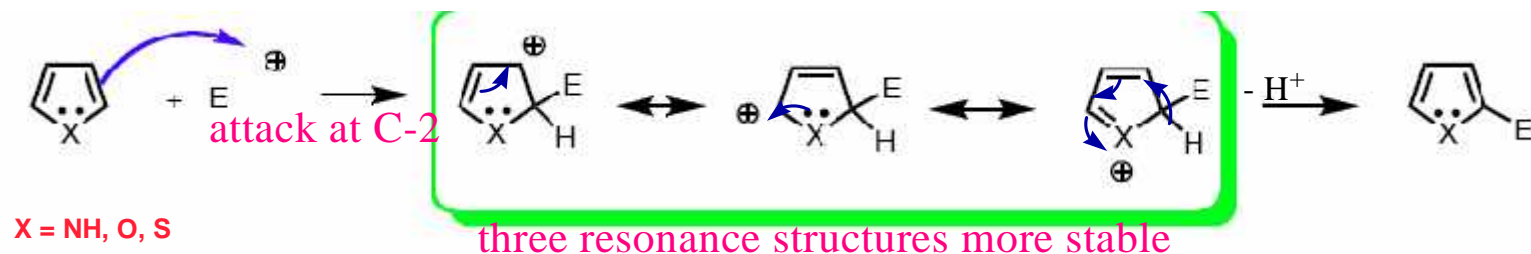
2) They tend to react by electrophilic substitution due appearance of -ve charge on carbon atoms (2 & 3) due to delocalization as shown in the following resonance structures





Orientation of Electrophilic Substitution in Pyrrole, Furan & Thiophene

- ❖ Electrophilic substitution normally occurs at a carbon atoms instead of at the nitrogen as explained before.
- ❖ Also it occurs preferentially at C-2 (the position next to the heteroatom) rather than at C-3 (if position 2- is occupied it occurs at position 3).
- ❖ This is due to attack at C-2 gives more stable intermediate (it is stabilized by three resonance structure) than the intermediate resulted from C-3 attack (it is stabilized by two resonance structure).

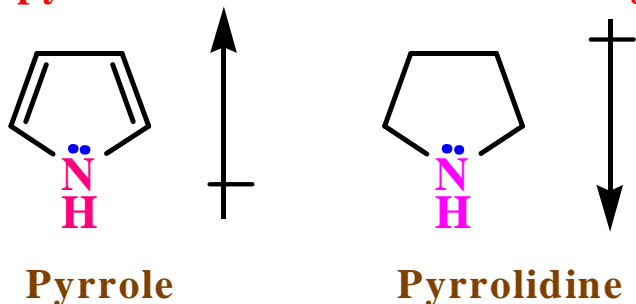




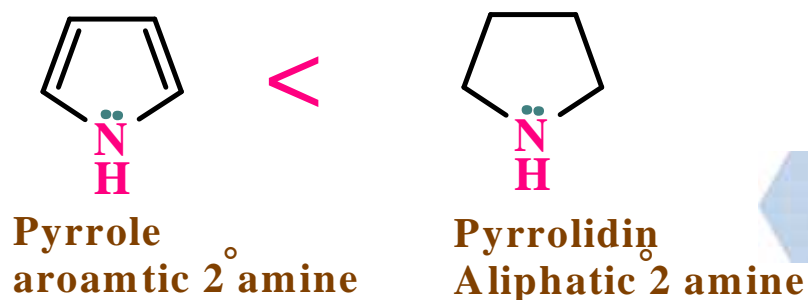
Pyrrole :Evidences of aromatic character in pyrrole

- 1) All ring bonds are intermediates between single and double bonds.
- 2) It tends to react by electrophilic substitution
- 3) Its exceptional **lack of basicity** and **strong acidity** as a secondary amine compared to the aliphatic analog (pyrrolidine). This can be explained on the basis of participation of N lone pair in aromatic sextet (see the previous resonance structures) thus the dipole moment of pyrrole compared with pyrrolidine

Dipole moment of pyrrole and its saturated analog



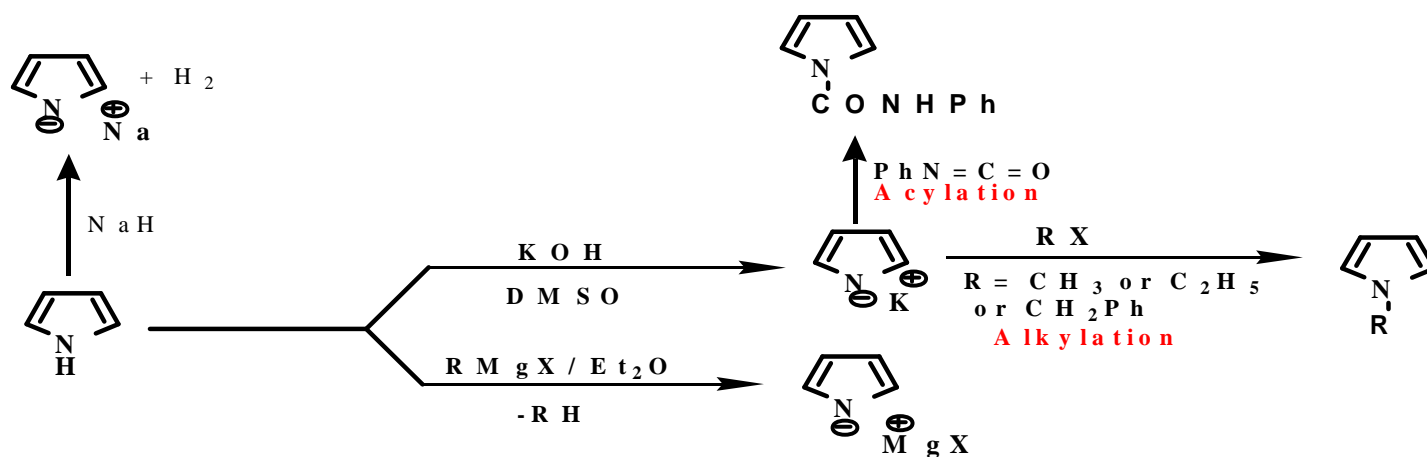
Basicity of pyrrole and its saturated analog



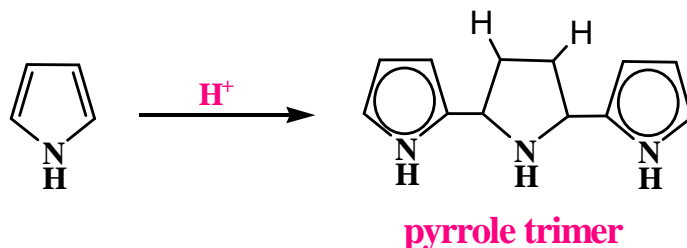


Acidic properties of pyrrole

❖ Due to participation of N lone pair in aromaticity), **pyrrole has exceptionally strong acidic properties** for a secondary amine for instance it can react with strong bases or Grignard reagent in inert solvents, and with sodium hydride, to give salt-like compounds which can be used to alkylate or acylate the nitrogen atom as shown below:



❖ Pyrrole is sensitive to strong acids, **protonation occurs at carbons not at N**
❖ This is due to protonation occurs at C-3 and the resulting protonated molecule will add to another unprotonated pyrrole molecule this continues to give pyrrole trimer. This reaction is considered as electrophilic addition to pyrrole

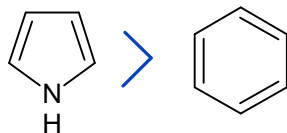




Electrophilic substitution in pyrrole

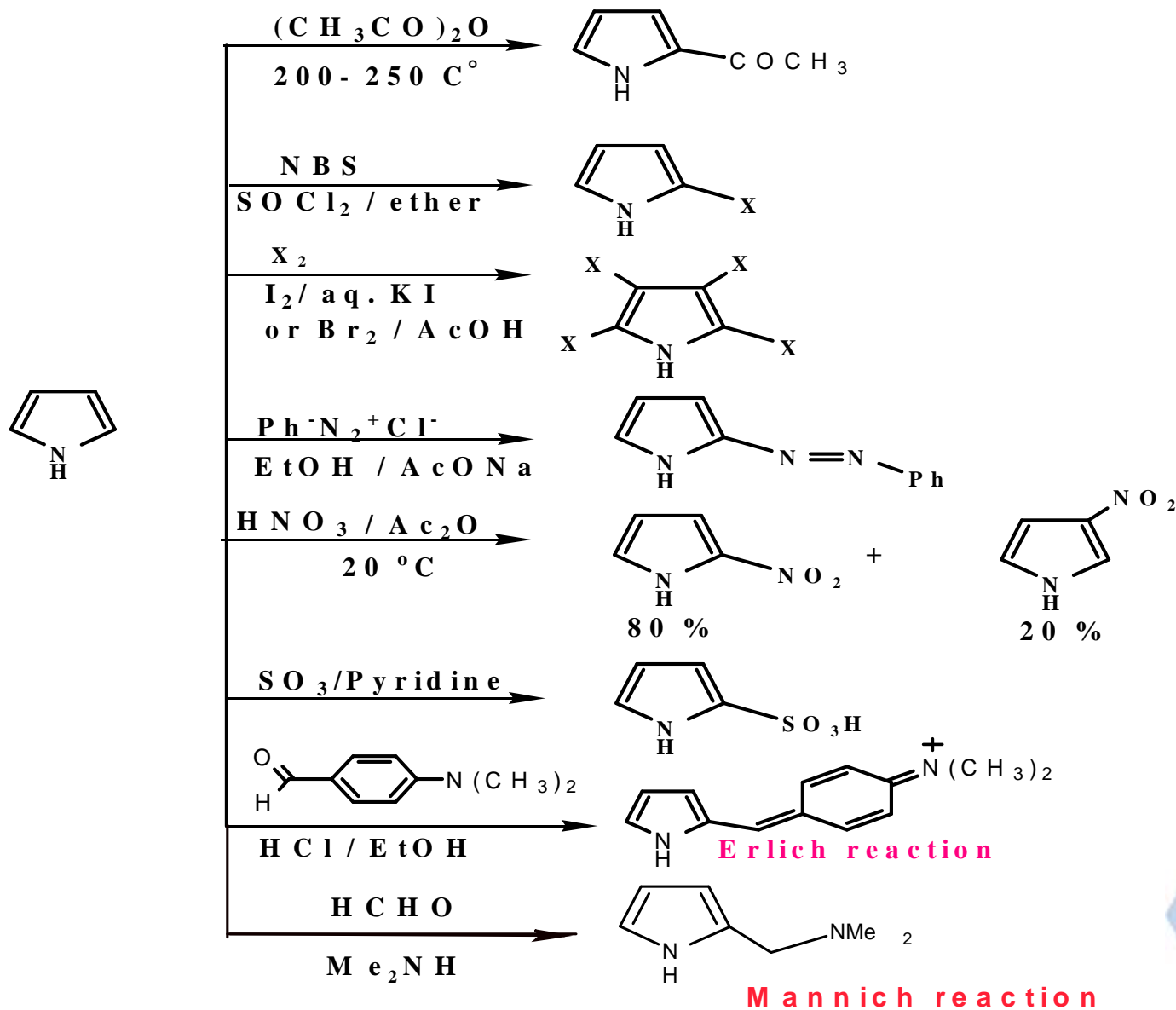
- ❖ As expected for aromatic compound, pyrrole can react by electrophilic substitution.
- ❖ In comparison to benzene pyrrole is more reactive thus the substitution is easier and milder reagents can be used.
- ❖ The increased reactivity is a result of resonance which pushes the electrons from the N-atom into the ring making the c-atoms of pyrrole ring more electron rich than in case of benzene. In fact pyrrole resembles most reactive benzene derivatives (phenols and amines) (see slide 5 for resonance structures of pyrrole).
- ❖ Consequently, there are some modifications in usual electrophilic reagents, for instance, sulphonating and nitrating reagents have been modified to avoid the use of strong acids (induce polymerization). Also reaction with halogens requires no Lewis acid.

Reactivity in electrophilic substitution





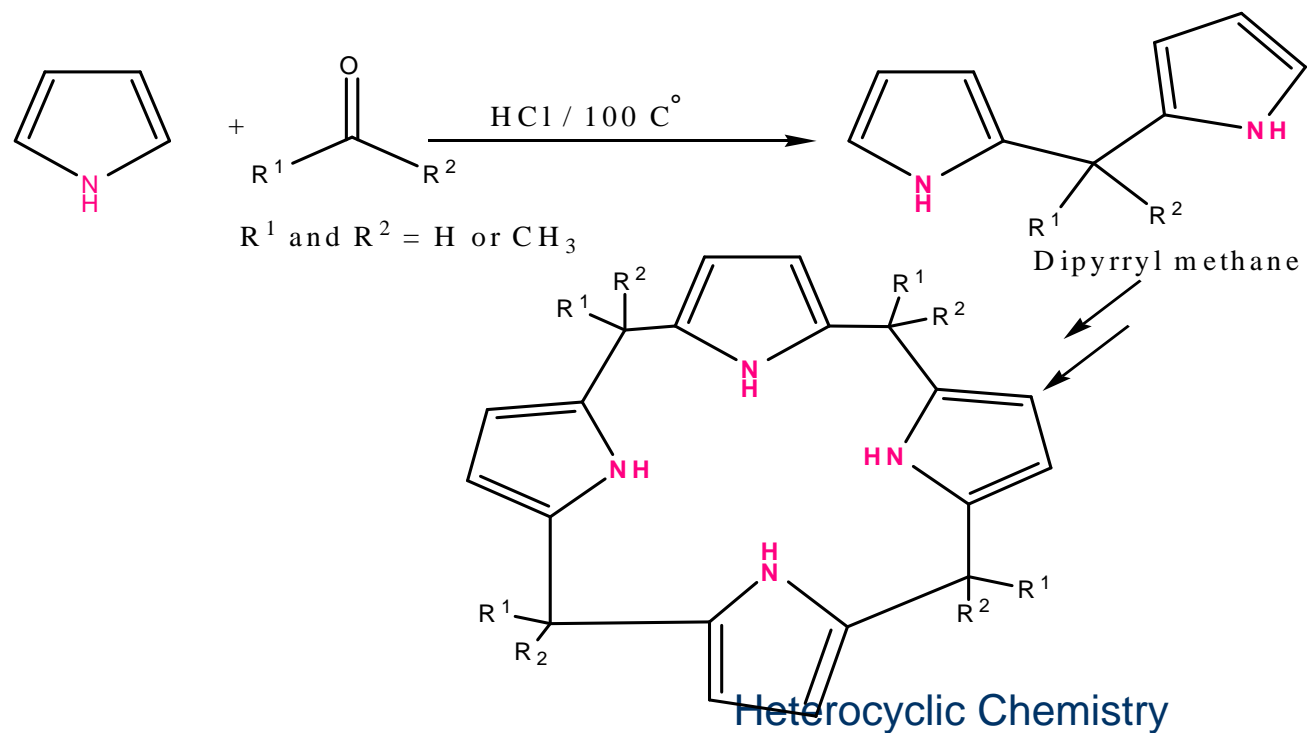
Electrophilic Substitution Reactions of Pyrrole





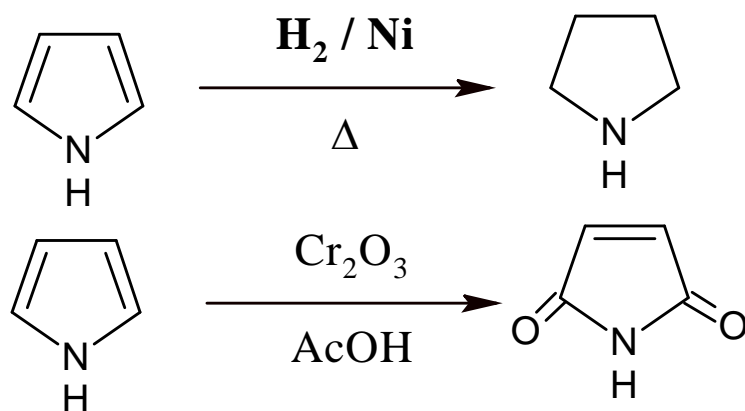
Reaction of pyrrole with aldehydes and ketones

- ❖ Aldehydes and ketones condense with unsubstituted pyrrole at α -position in acidic medium to give **dipyrlyl methane**. The condensation may continue to give **tetramer (4 pyrrole rings connected by methine bridge)**. The tetramers are known as **porphyrinogens**, they are stable, planar structures that can accommodate a wide range of metal ions.

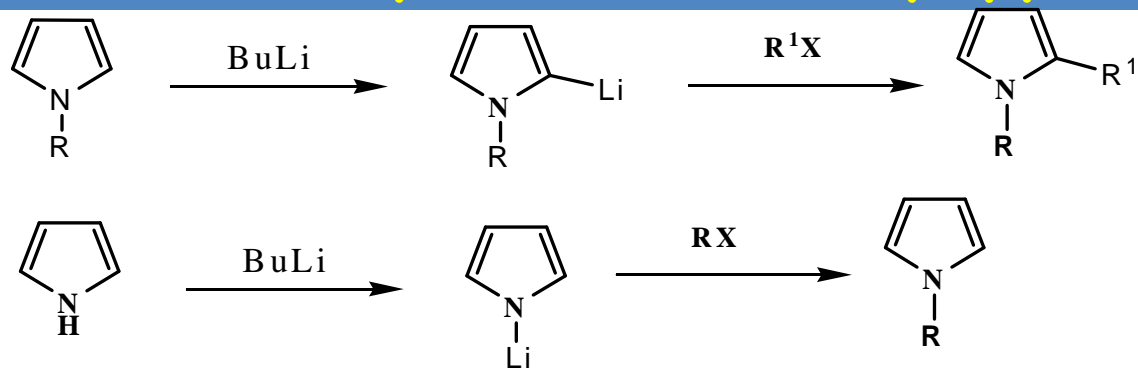




Oxidation-Reduction of Pyrrole



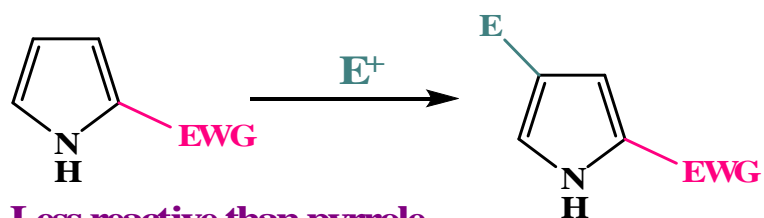
Lithiation of Pyrrole and N alkyl pyrrole





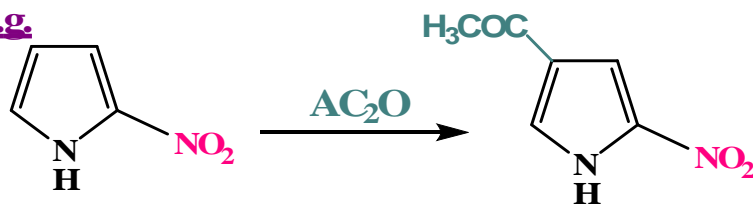
Second electrophilic substitution

a) Monosubstituted pyrrole with electron withdrawing group

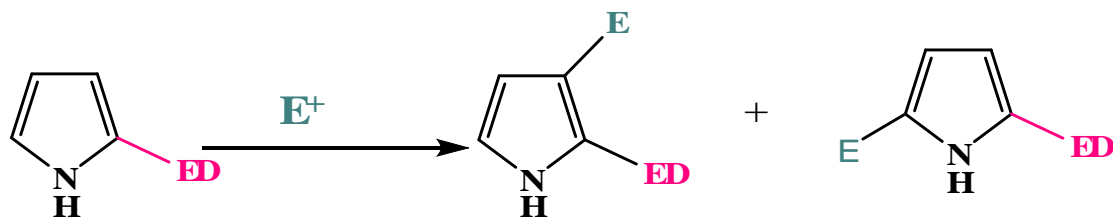


(incoming E^+ directed to *m*-position i.e. position 4)

e.g.



b) Monosubstituted pyrrole with electron donating group



More reactive than pyrrole

(incoming E^+ directed to *p* or *o*-positions i.e. position 3 or 5)

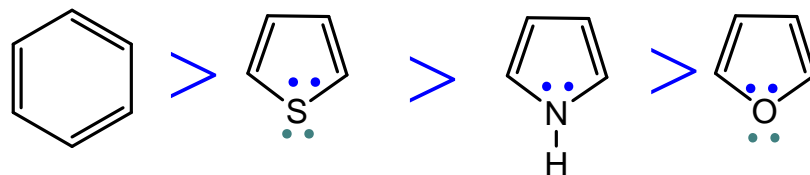


Furan and thiophene

Introduction

Furan is not very aromatic therefore if there is a possibility of forming stable bonds such as C-O bonds by addition, this may be preferred to substitution i.e. tendency to give addition products rather than substitution products increases as aromaticity decreases.

Order of aromaticity



In comparison to benzene the order of reactivity in electrophilic substitution is as follows: **Pyrrole > Furan > Thiophene > Benzene**

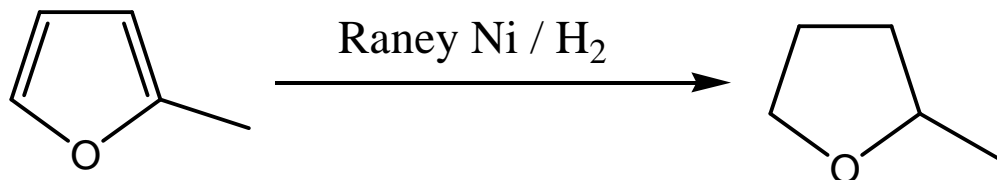
Electrophilic substitution on furan requires very mild **non acidic conditions** (acids may induce polymerization or ring opening), however, for thiophene the acidity is less critical since it is stable to aqueous mineral acids but not to 100 % strong acids or Lewis acids such as AlCl_3 .

Regioselectivity: The **2 & 5 (α)** positions are more reactive than **3 & 4 (β)** Positions. As in pyrrole the intermediate results from electrophilic attack at C2 can be stabilized by three resonance structures while the intermediate results from the attack C3 is only stabilized by two resonance structures. Thus the former is more preferred.



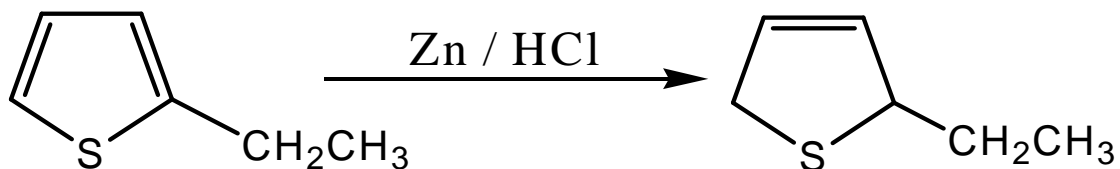
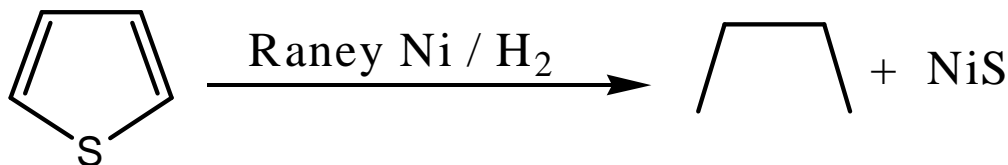
1 - Addition Reactions

Reduction



2-Methyltetrahydrofuran

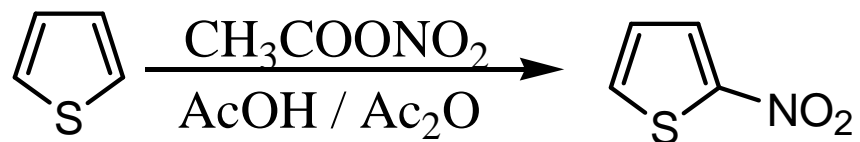
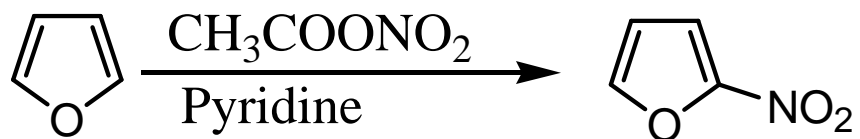
- ❖ On the other hand **thiophene can not be reduced** under the same conditions due to sulfur poison the catalyst and **desulphurization** occurs with ring opening.
- ❖ However, partial reduction can take place by metals in acidic medium.



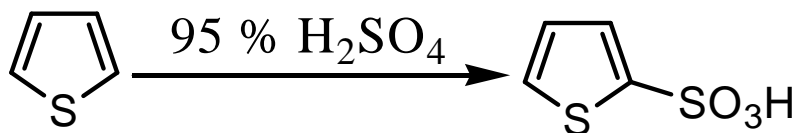
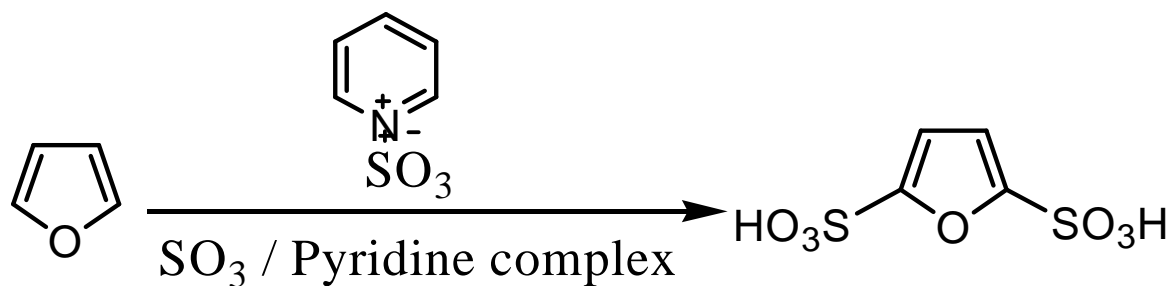


2- Electrophilic Aromatic substitution Reactions

1) Nitration



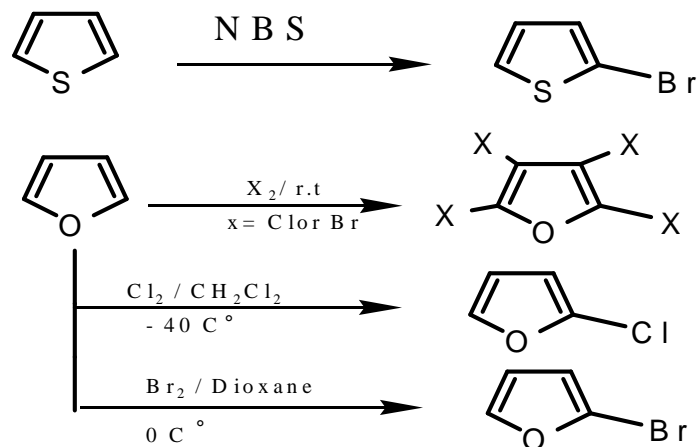
2) Sulphonation



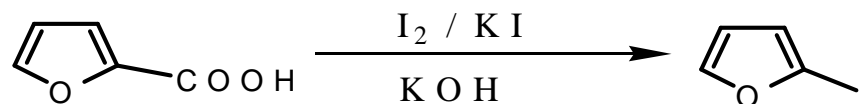


Electrophilic Aromatic substitution Reactions

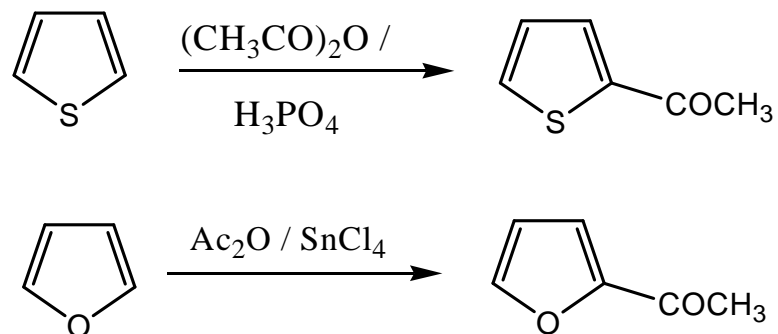
3) Halogenation



Indirect insertion of iodine in furan ring



4) Acylation

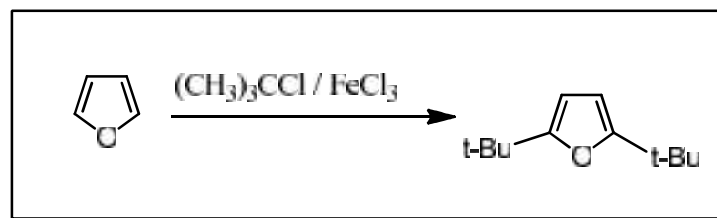




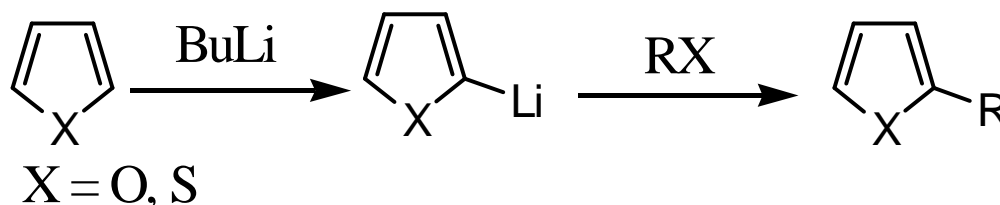
Electrophilic Aromatic substitution Reactions

5) Alkylation

It is very low yielding reaction due to formation of polyalkylated products or polymers.

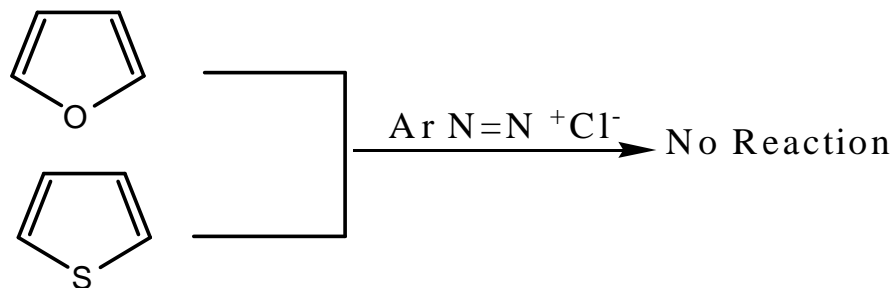


4) Lithiation



5) Diazocoupling:

Furan and thiophene can not couple with diazonium salts which shows that they are less reactive than pyrrole.





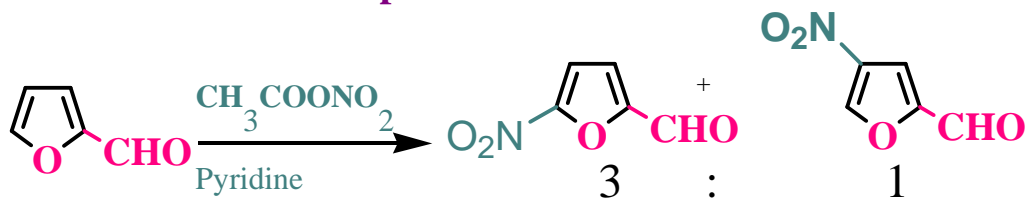
Second Electrophilic Substitution in Furan and Thiophene

a) Monosubstituted furan & thiophene with electron withdrawing groups such as COOH, CHO, CN, COR, SO₃H are less reactive than unsubstituted compounds

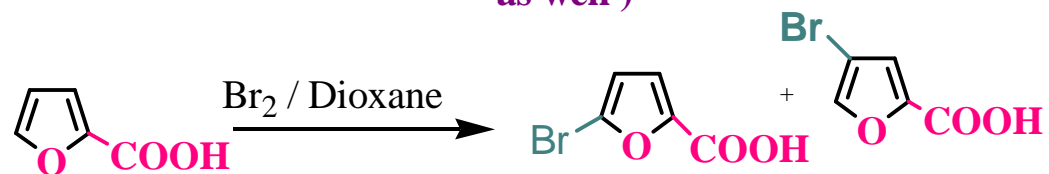
i) EWG at position 2



Less reactive than thiophene



Less reactive than furan (incoming E⁺ is directed to position 5 mainly and to position 4 as well)



ii) EWG at position 3

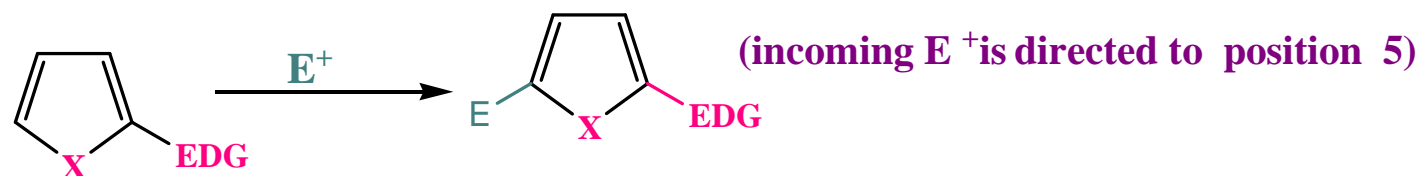




Second Electrophilic Substitution in Furan and Thiophene

b) Monosubstituted furan & thiophene with electron donating group such as CH₃, OH, NH₂, OCH₃

i) EDG at position 2



More reactive than unsubstituted compound

ii) EDG at position 3

