HETEROCYCLIC AROMATIC COMPOUNDS

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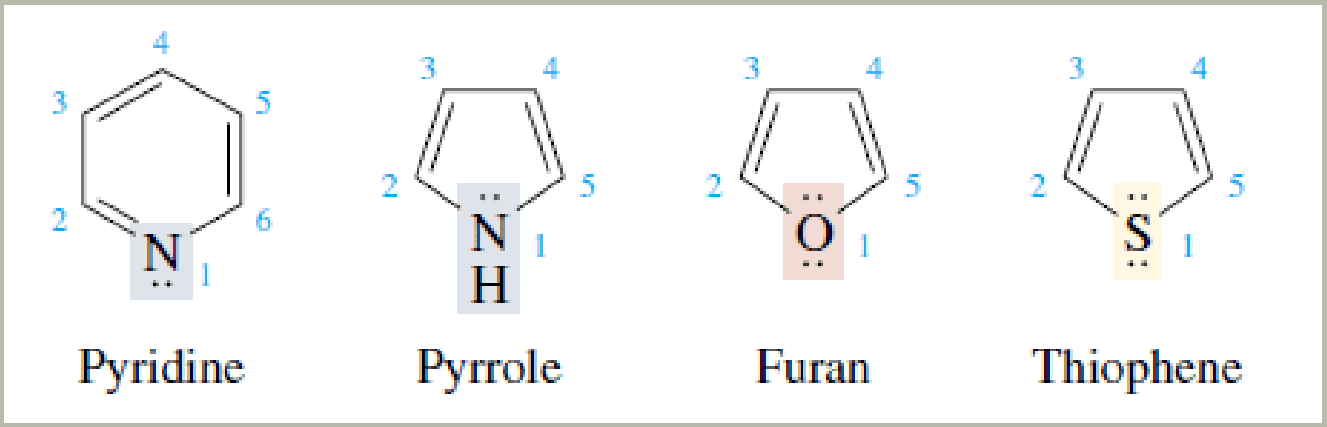
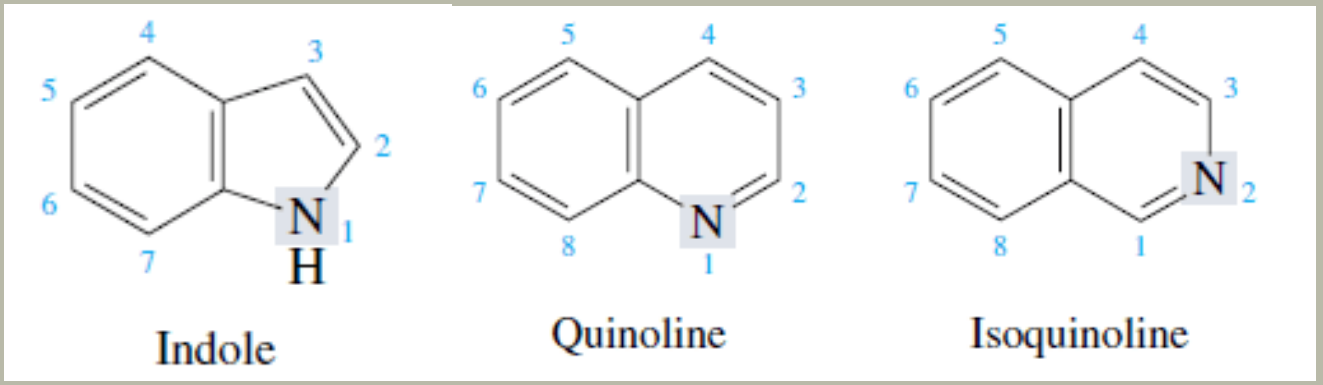
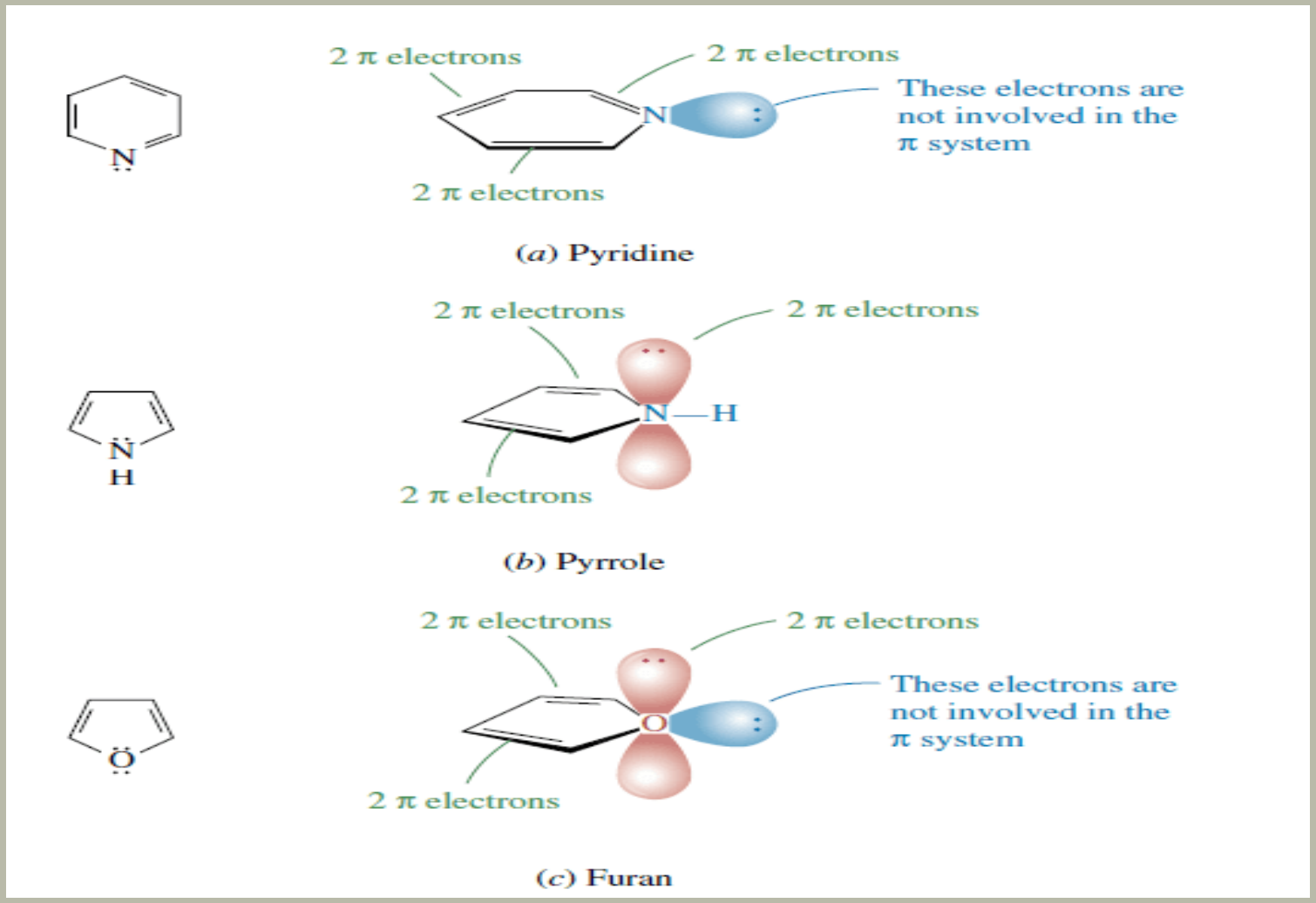
Cyclic compounds that contain at least one atom other than carbon within their ring are called **heterocyclic compounds,** and those that possess aromatic stability are called **heterocyclic aromatic compounds.** Some representative heterocyclic aromatic compounds are *pyridine*, *pyrrole*, *furan*, and *thiophene.*





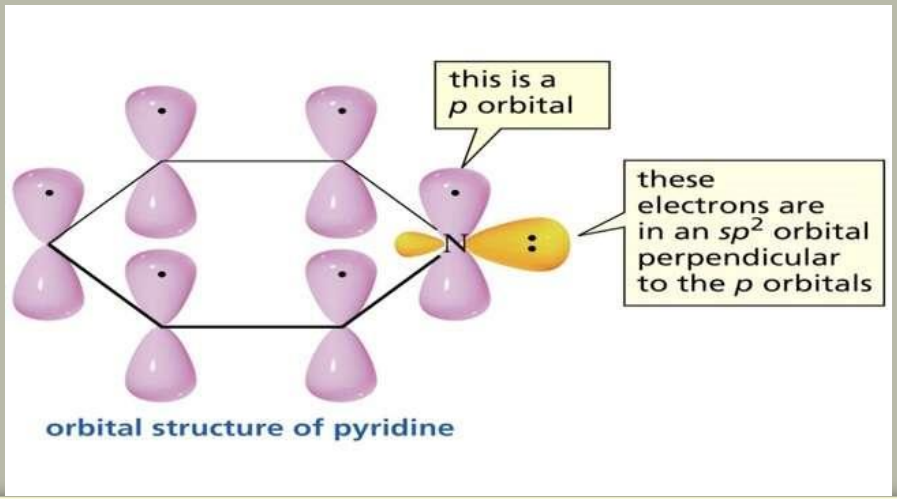
HETEROCYCLIC AROMATIC COMPOUNDS AND HÜCKEL'S RULE

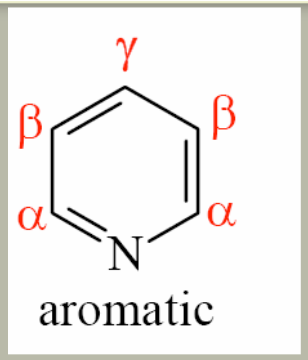


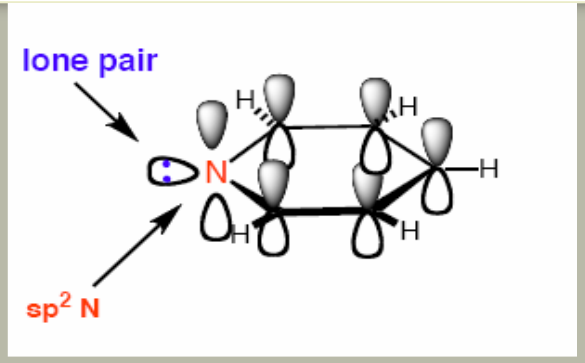
The order of aromaticity of these compounds is benzene > thiophene > pyrrole > furan,

PYRIDINE (Azine)- Structure and Aromaticity

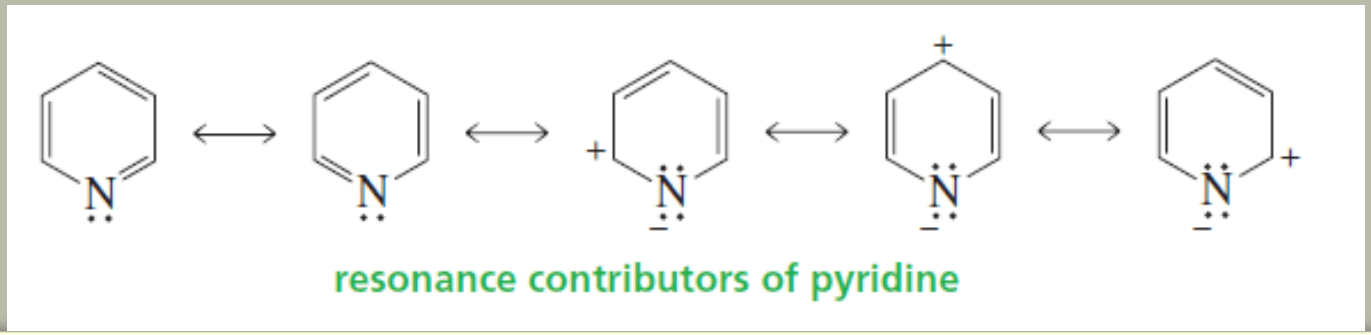
- Pyridine is a six membered heterocyclic compound with molecular formula of C_6H_5N and it is obtained from coal tar.
- It may be formally derived from the structure of benzene through the exchange of one ring carbon for a *sp2* hybridized nitrogen a nitrogen.
- Pyridine is an aromatic compound, however, the nitrogen's lone pair of electrons is in an *sp2* orbital orthogonal to the *p* orbitals of the ring, therefore it is not involved in maintaining aromaticity but it is available to react with protons thus pyridine is basic







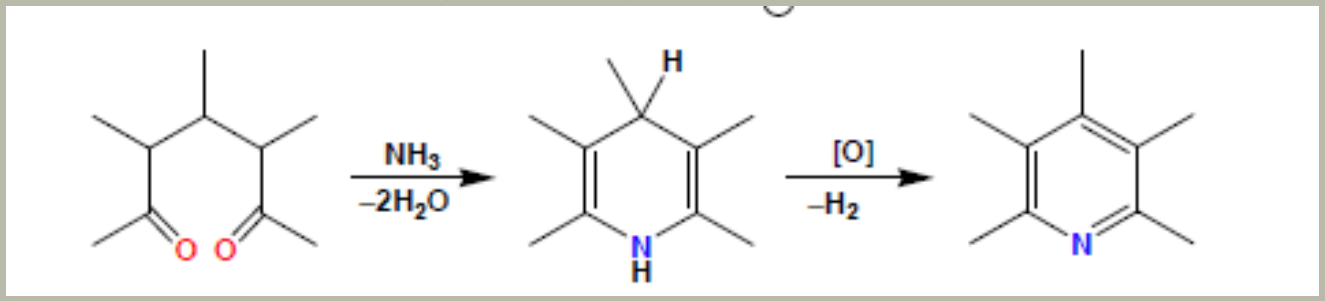
- Due to the greater electronegativity of nitrogen (relative to carbons) it tends to withdraw the electron density from carbon atoms at positions 2, 4 and 6 which therefore acquire partial positive charges while the N atom acquires partial negative charge while the carbons at positions 3 and 5 remain neutral.
- It has two uncharged resonance contributors. Because of the electron-withdrawing nitrogen, it also has three charged resonance contributors that benzene does not have.

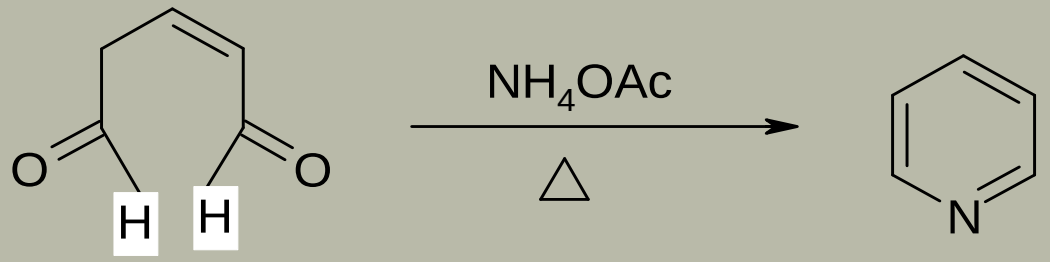


resonance contributors of pyridine

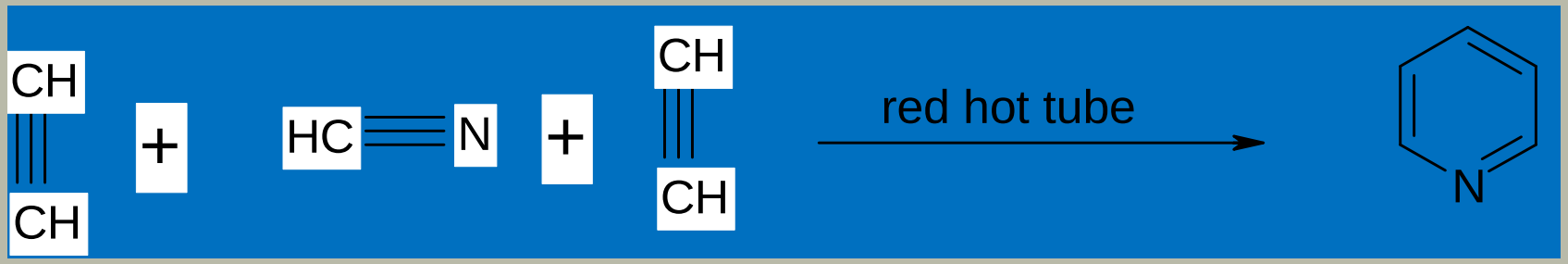
Synthesis of Pyridine

1. From 1,5-dicarbonyl compounds:

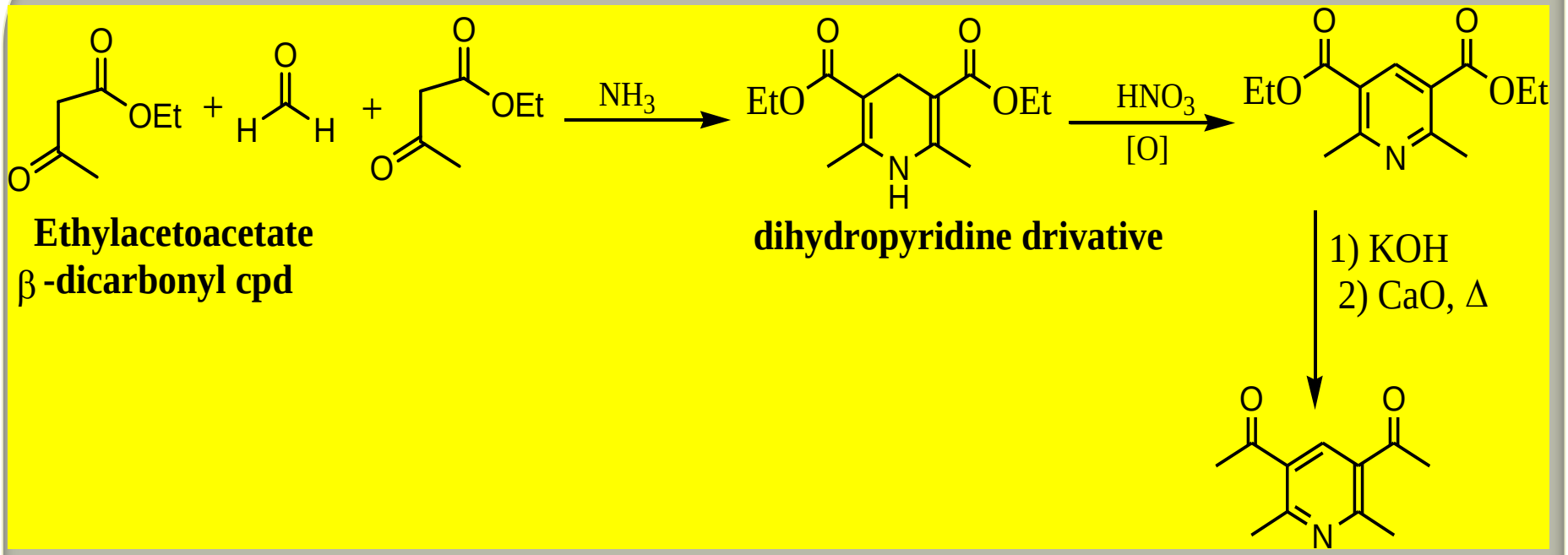




2. Bönnemann cyclization:



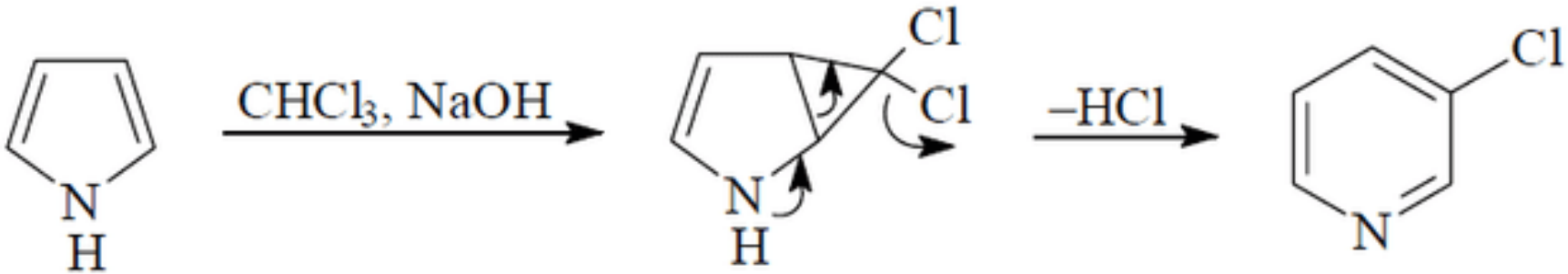
3. Hantzsch Synthesis:



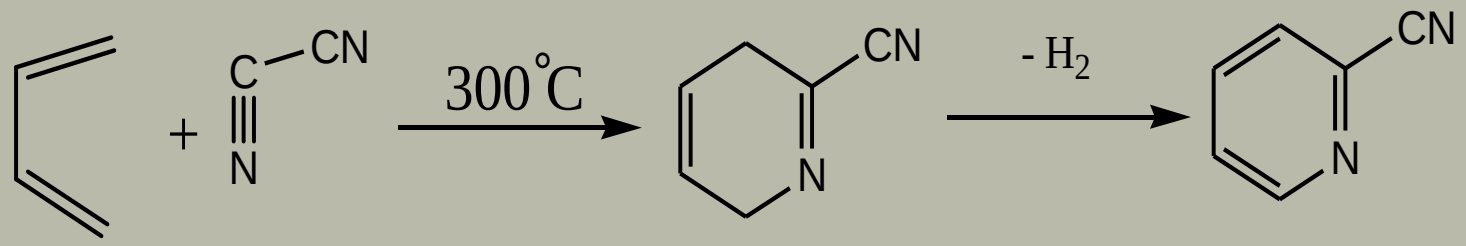
Ethylacetoacetate
β -dicarbonyl cpd

dihydropyridine drivative

4- From pyrrole:



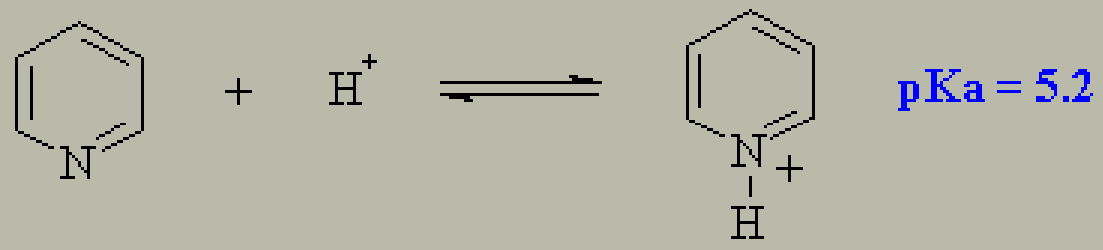
5. By Diels Alder reaction



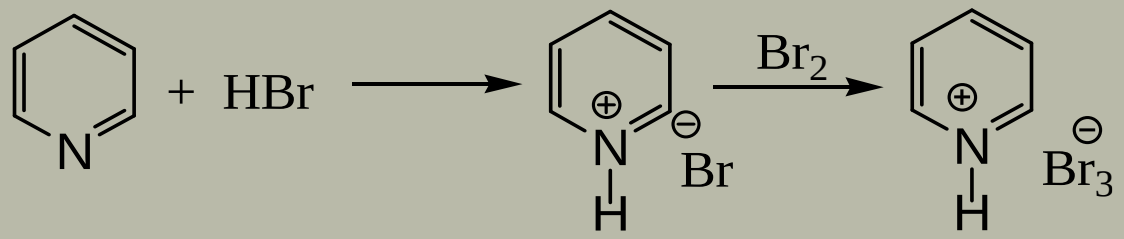
1,3-butadiene

Basicity of pyridine

- Pyridine is a weak base; since lone pair is in an sp^2 hybrid orbital. Is the conjugate acid aromatic?



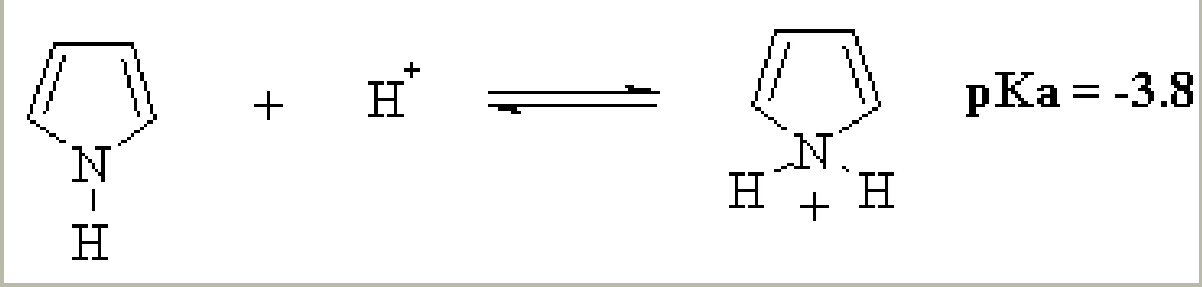
- It undergoes many reactions typical of amines such as reaction with Bronsted acids such as chromic acid and hydrobromic acid.



Pyridinium salt

Basicity of pyridine

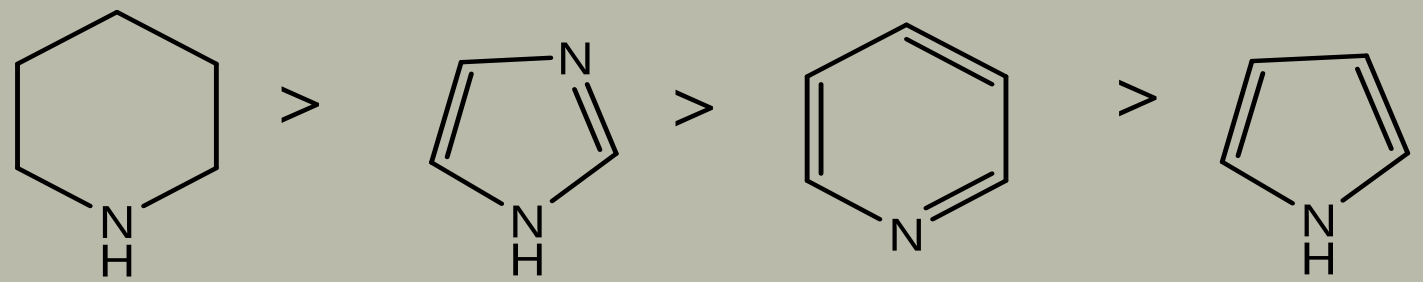
Compared to pyrrole, pyridine is much stronger base this is due to the nitrogen lone pair is not involved in maintaining the aromaticity thus it free for protonation, however, in pyrrole the lone pair on the N atom is already involved in the aromatic array of p electrons. Protonation of pyrrole on N atom results in loss of aromaticity and is therefore unfavorable.



Compared to imidazole, pyridine is less basic this is due to the on protonation the + ve charge can be delocalized over two nitrogen atoms while in case of pyridine it is delocalized over the ring which interrupt aromatcity.

Basicity of pyridine

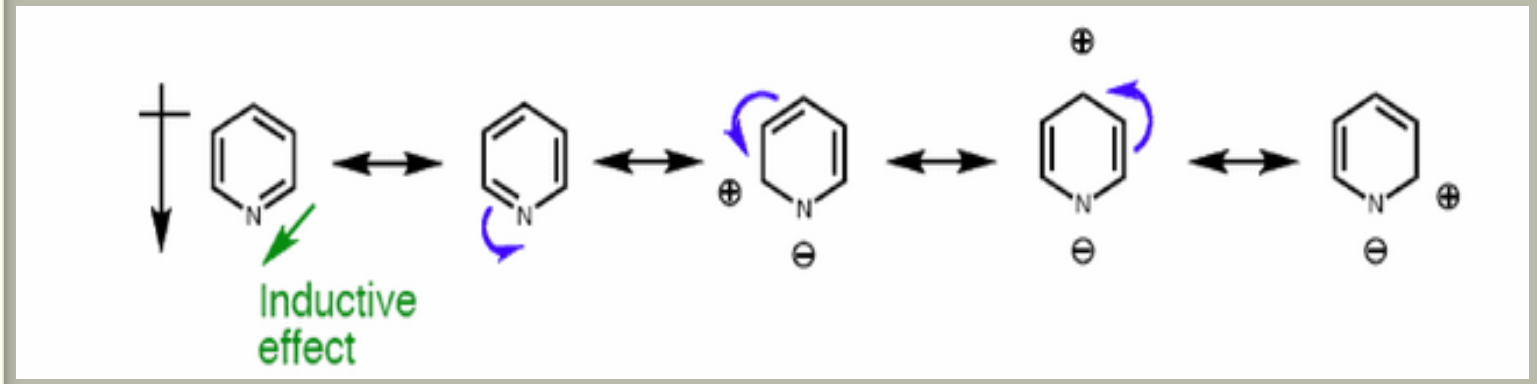
Compared to analogous aliphatic amines, pyridine is less basic this is due to the nitrogen atom in pyridine is *sp2* hybridized (more electronegative) and the lone pair of electrons occupies an *sp2* orbital thus it is held more tightly by the nucleus than the lone pair of electron in aliphatic amines with *sp3* hybrdized N atom and the lone pair of electrons occupies an *sp3* orbital (less electronegative).

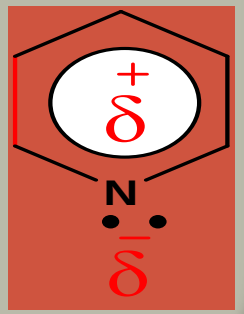


Chemical properties: 1-Electrophilic substitution

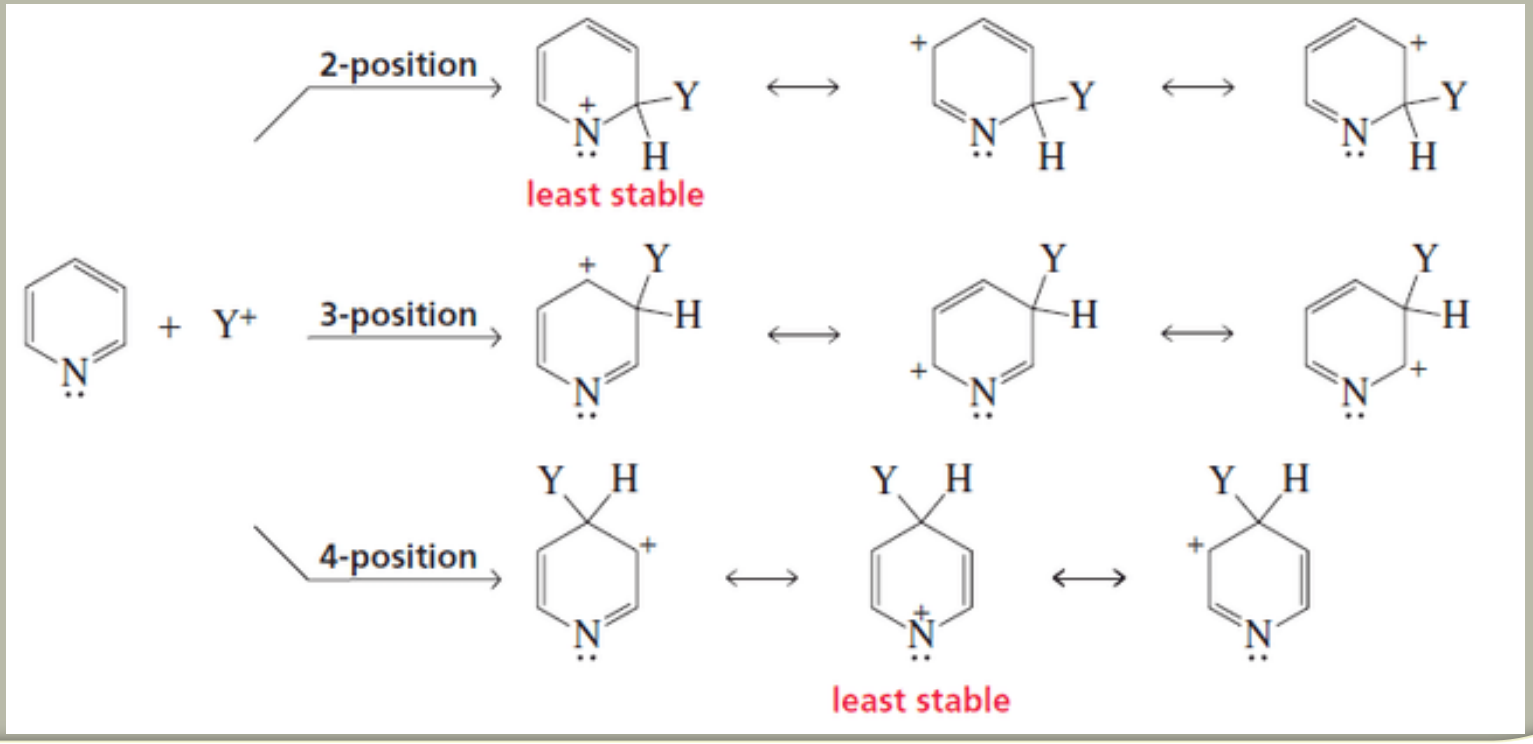
- the negative pole in pyridine ring is at N while the positive pole is at carbon skeleton which is opposite to what happens in pyrrole.

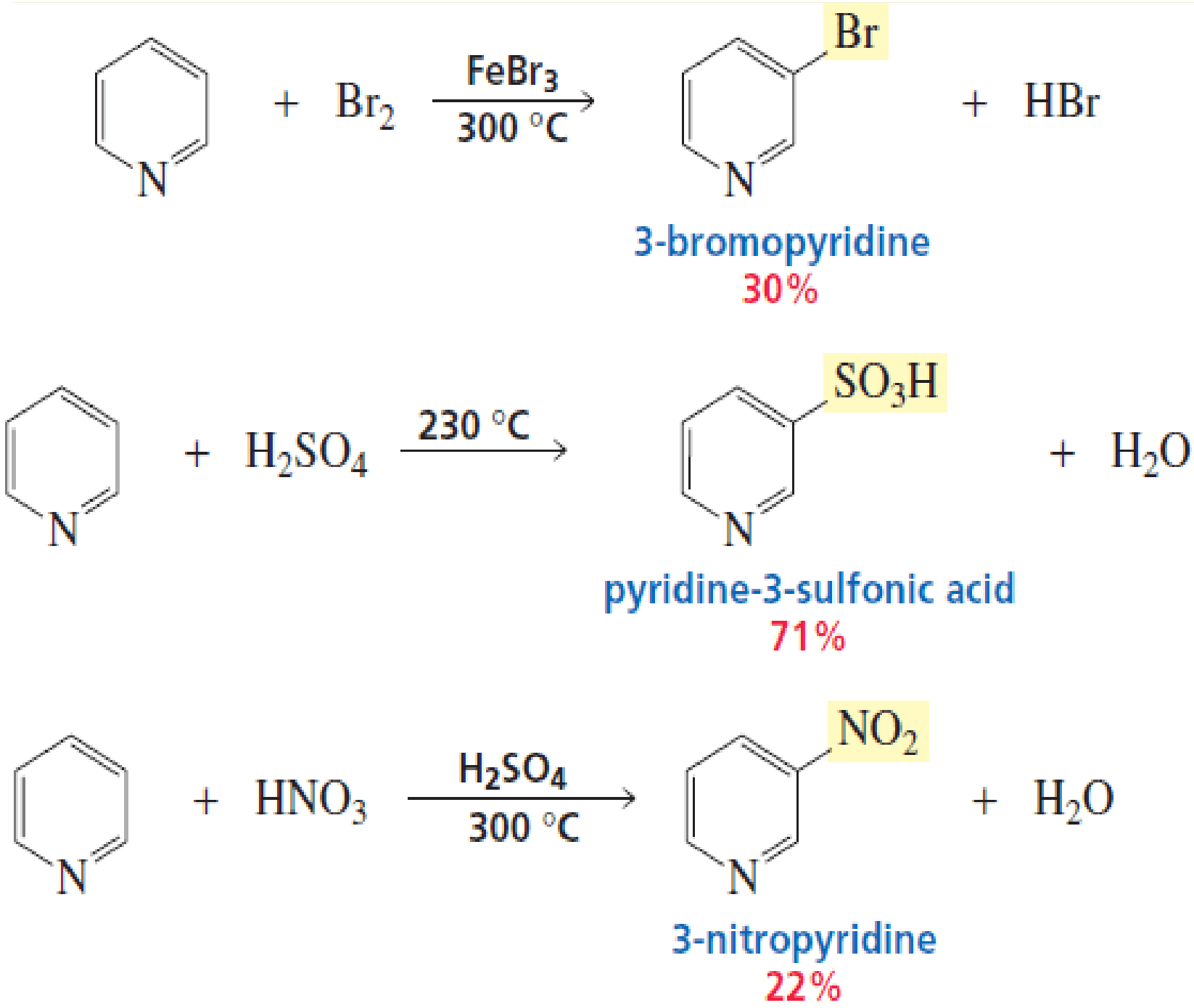
- This is due to the greater electronegativity of nitrogen (relative to carbons) it tends to withdraw the electron density from carbon atoms at positions 2, 4 and 6 which therefore acquire partial positive charges while the N atom acquires partial negative charge and the carbons at positions 3 and 5 (β-position) remain neutral therefore these positions are the most preferred for elctrophilic attack.





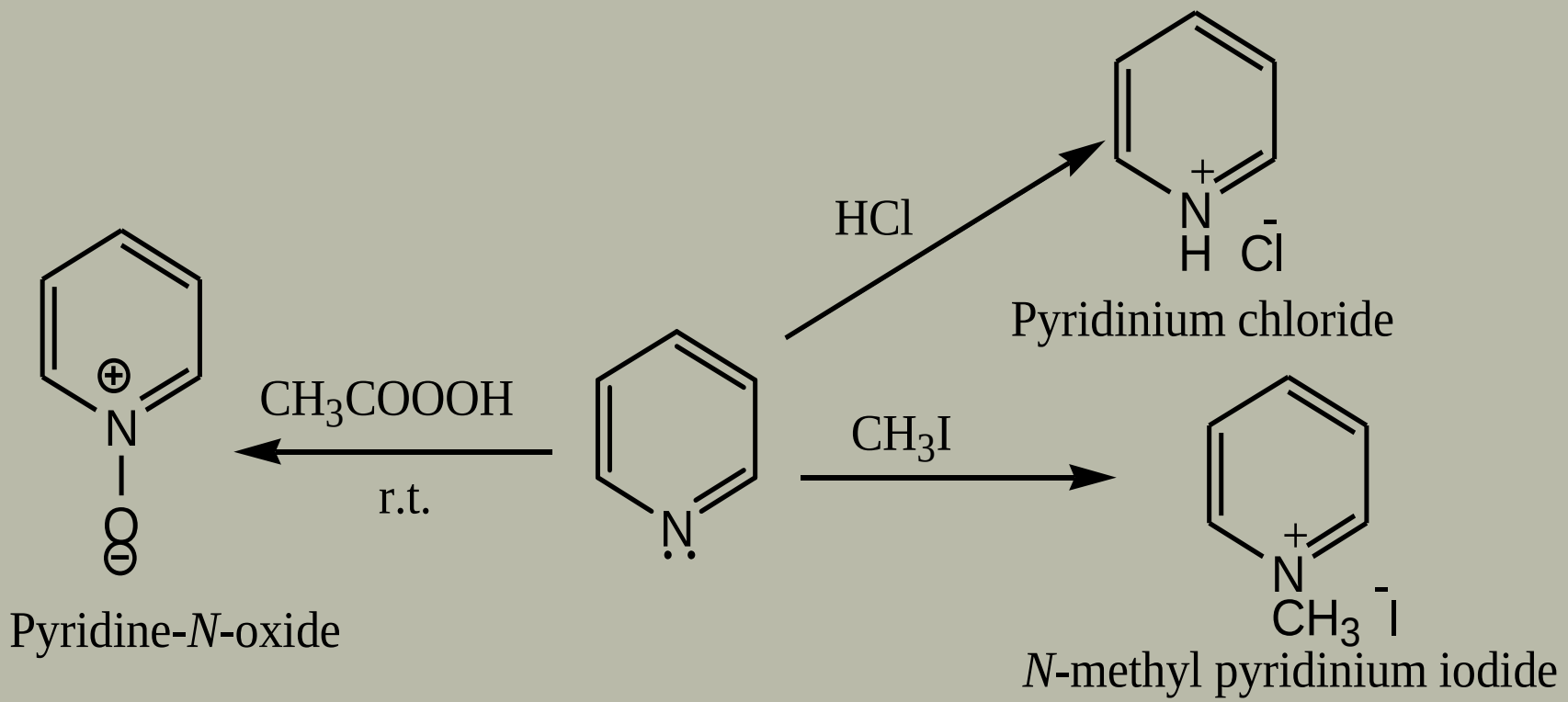
- Also as a consequence of electron deficiency on pyridine ring , pyridine is less reactive towards electrophiles than pyrrole and benzene (it resembles highly deactivated benzene derivatives), where it does not undergo Friedel-Craft's alkylation or acylation or coupling with diazonium salts.
- Moreover, electrophilic substitution reactions of pyridine require very harsh conditions (e.g. v. high temp.) to take place and are low yielding .




+ Br2
FeBr3
300 °C
Br
N
+ HBr
3-bromopyridine
30%
+ H2SO4
230 °C
SO3H
+ H2O
pyridine-3-sulfonic acid
71%
+ HNO3
H2SO4
300 °C
NO2
+ H2O
3-nitropyridine
22%

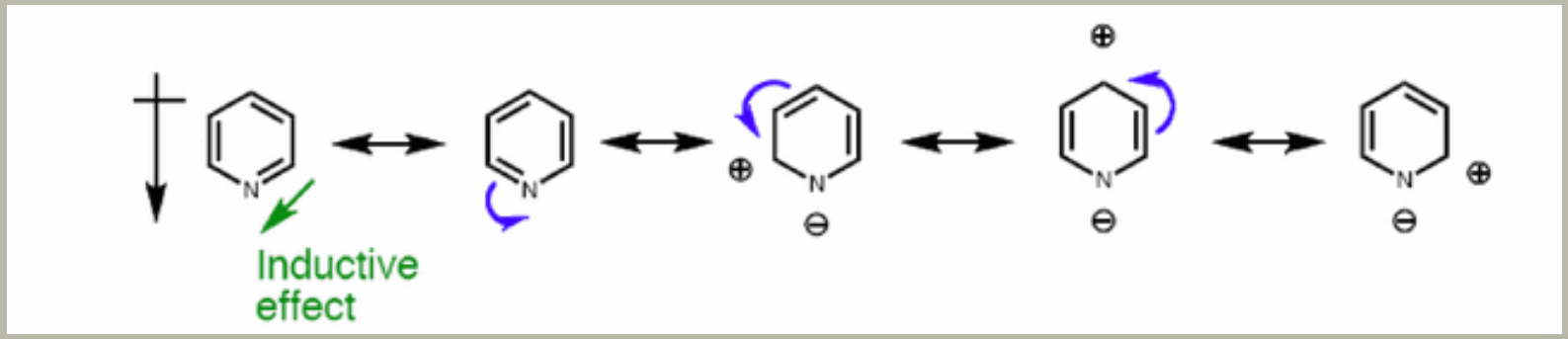
Pyridine as a nucleophile (reactions on N atom)

- As a tertiary amine pyridine has nucleophilic properties thus it reacts with electrophiles:

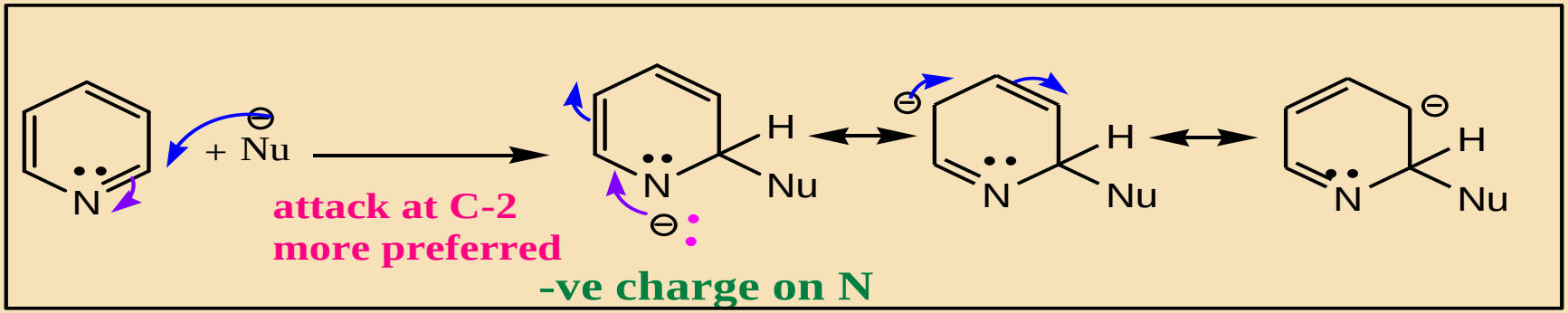


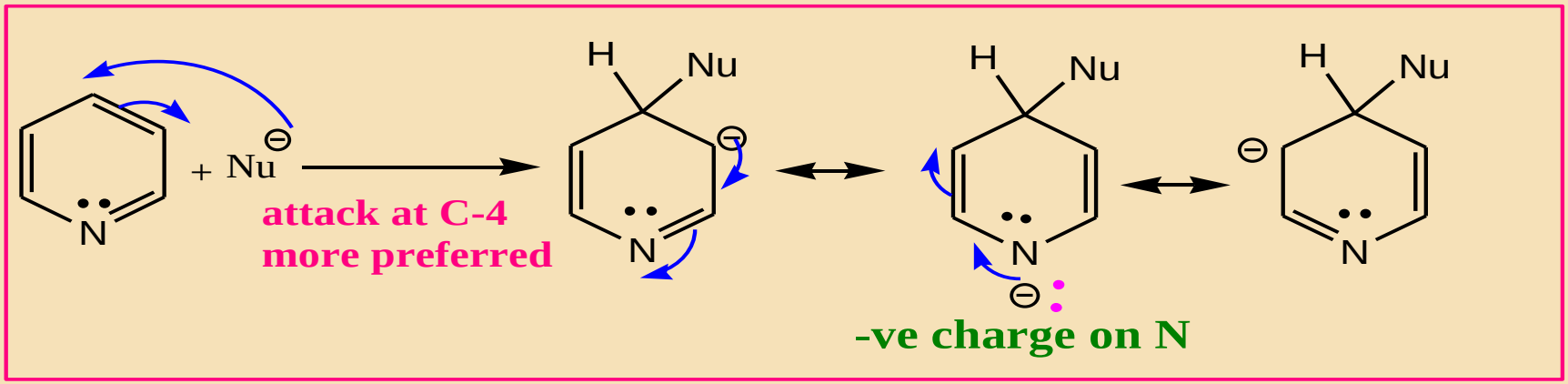
Nucleophilic substitution on carbon

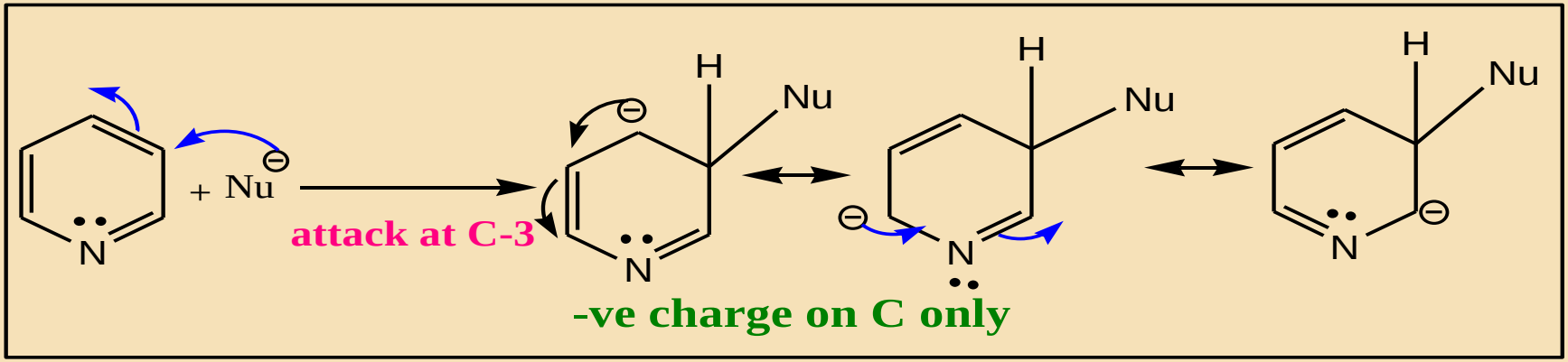
- **Pyridine is very reactive towards nucleophiles than benzene it resembles benzene having strong E.W.G due to the withdrawing effect of the electronegative N atom .**
- **AS appeared from the canonical structures of pyridine positions 2, 4 and 6 carry partial positive charges thus ncleophilic substitution proceeds readily at the 2-position followed by 4-position but not at the 3-position.**
- **Additionally, attack at positions 2, 4 or 6 results in resonance structure in which the negative charge is delocalized at N thus it is more preferred while attack at position 3 or 5 results in resonance structures in which the negative charge is delocalized over carbons only.**



Orientation of nucleophilic substitution in pyridine

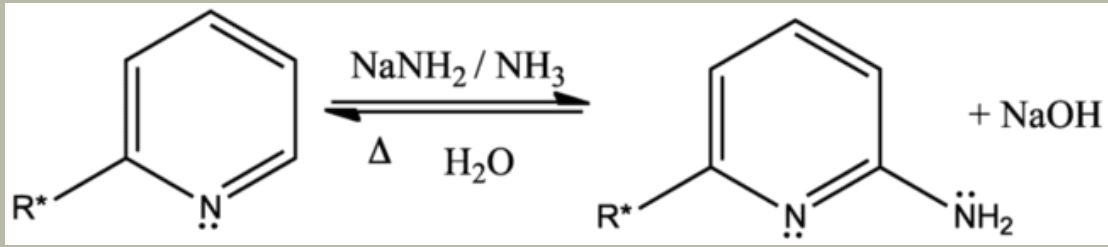






Nucleophilic Substitution reactions

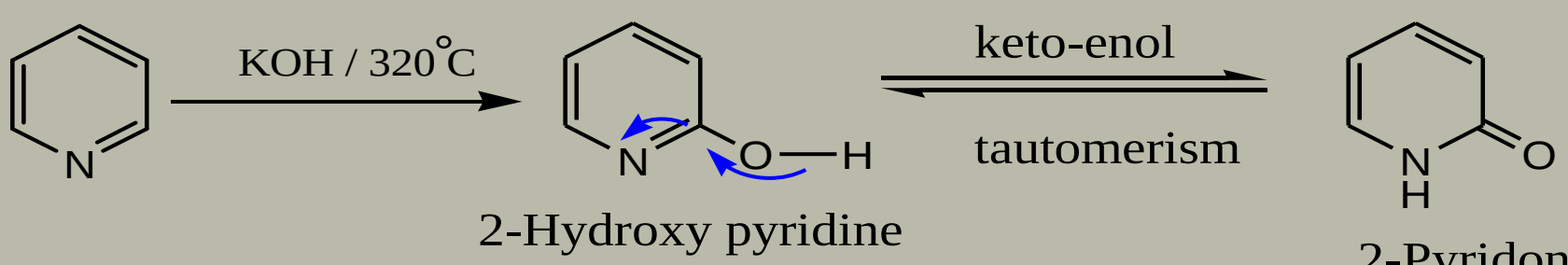
i) The Chichibabin reaction



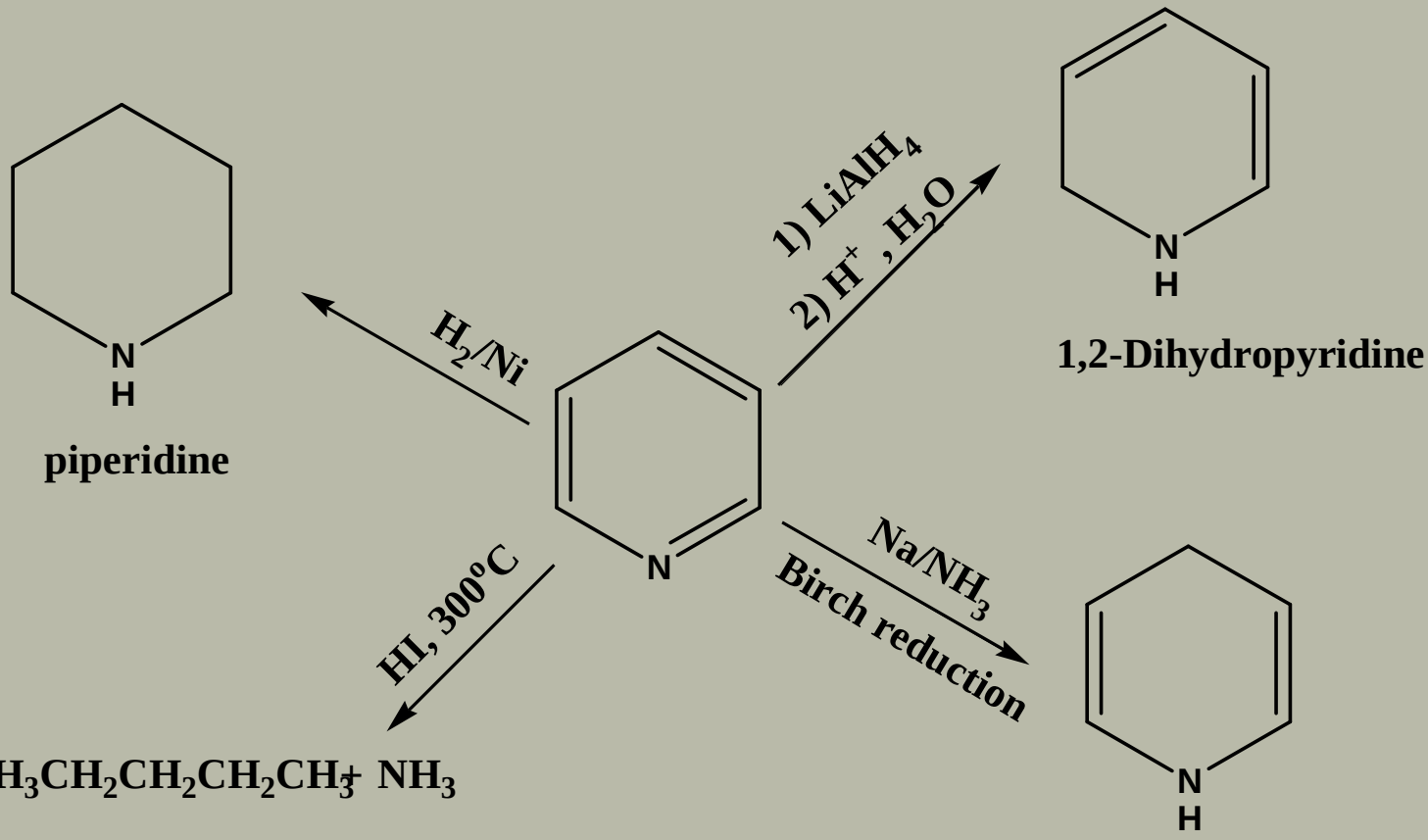
R can be *o-*, *m-*, *or p-* substituent

ii) Reaction with organometallic compounds lithium reagents

iii) Reaction with potassium hydroxide

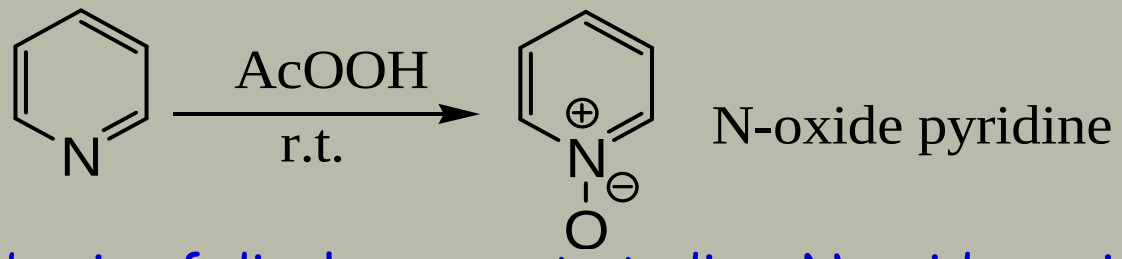


REDUCTION REACTIONS

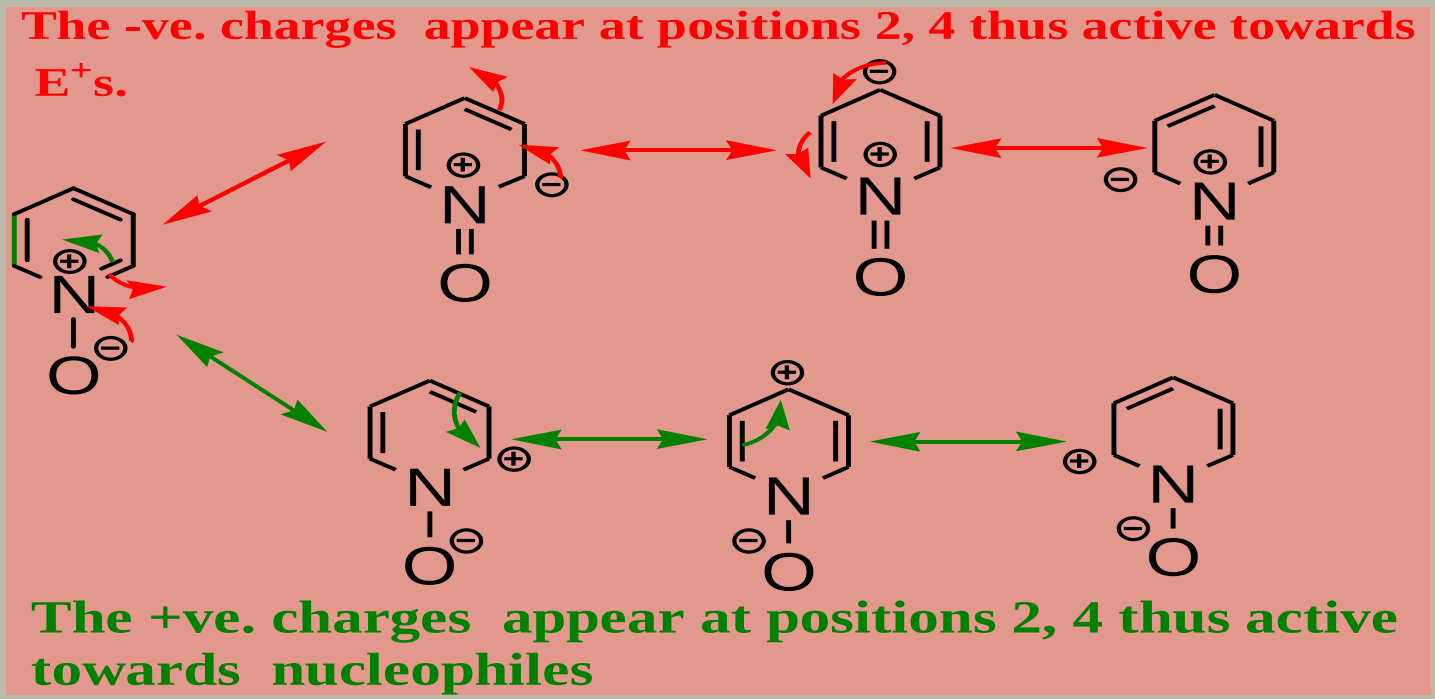


Derivative of pyridine: N-oxide pyridine

- Pyridine can be oxidized easily to N-oxide pyridine by peracids.



- On the basis of dipole moment studies, N-oxide pyridine is considered as a resonance hybrid of the following structures



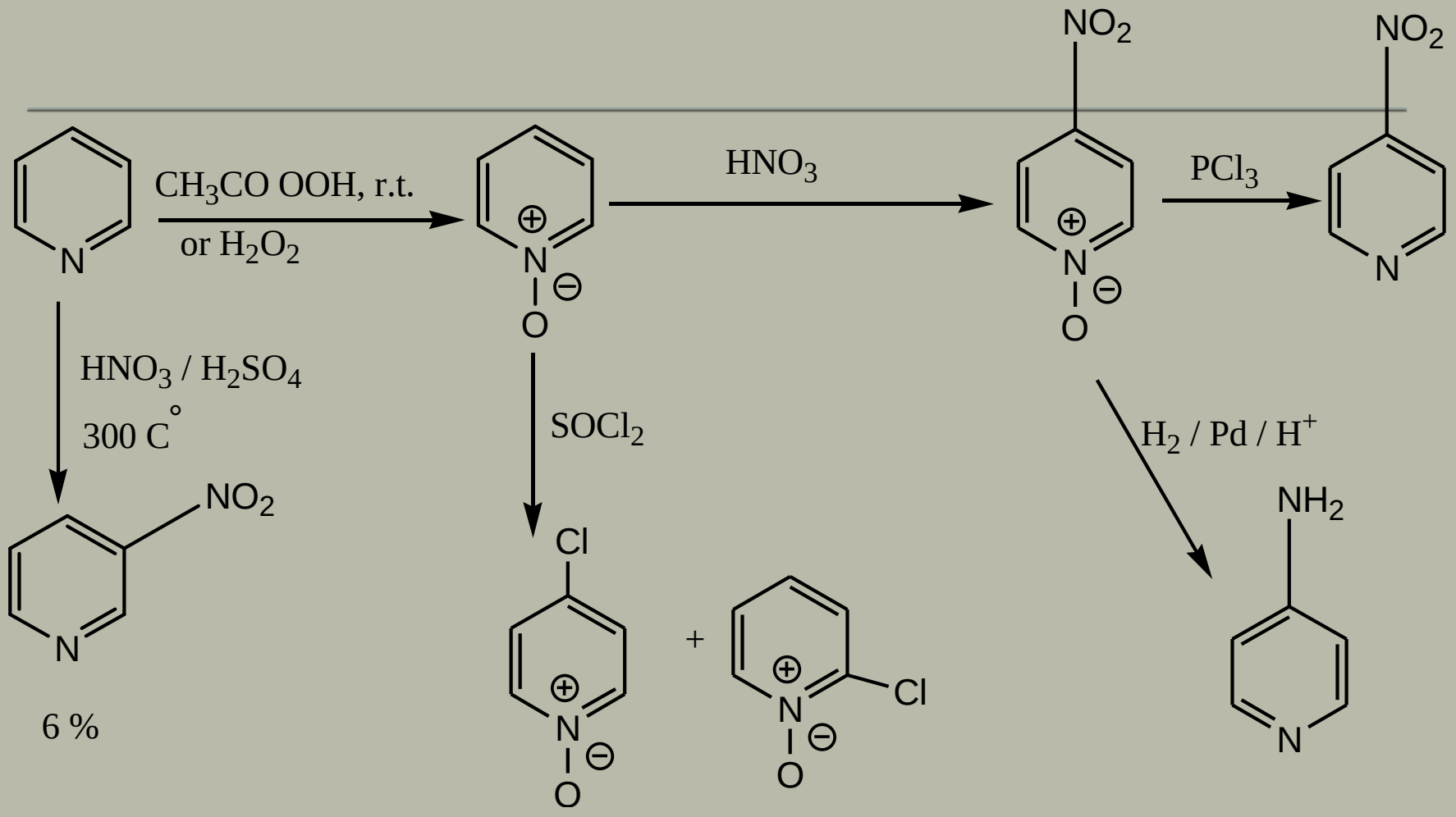
N-oxide pyridine

- As appears from the previous canonical forms , there are positive and negative charges at positions 2 and 4 thus N-oxide pyridine is more activated for electrophilic and nucleophilic attack at these positions than pyridine itself.

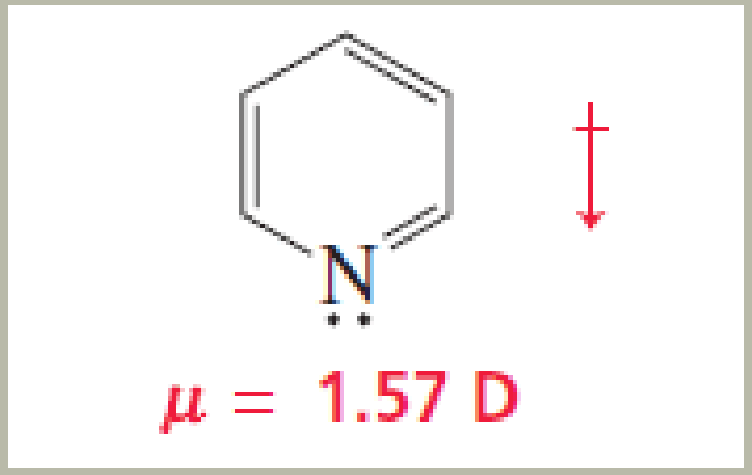
- N-oxide pyridines are very important intermediates for preparing pyridine derivatives that are difficult to prepare due to the easiness of removal of oxygen atom by reduction.

- For instance, nitration of pyridine is very difficult and low yielding reaction and it occurs at position 3, however using N-oxide pyridine will direct the nitration to position 4 and then the oxygen can be easily removed by reduction as shown in the following scheme.

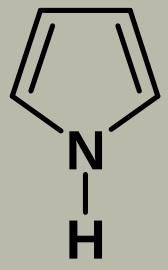
Reactions of N-oxide pyridine



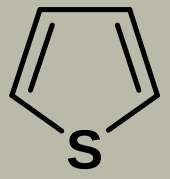
The dipole moment of pyridine is 1.57 D. As the resonance contributors and the electrostatic potential map indicate, the electron-withdrawing nitrogen is the negative end of the dipole.



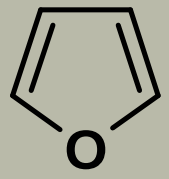
Five Membered Heterocycles



Pyrrole



Thiophene



Furan

Least reactive

More aromatic than Furan

Electrophilic Substitution, not addition

Thiophene has similar reactivity to benzene

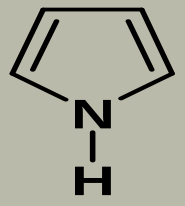
The least aromatic:
The O atom is too electronegative

Less reactive than pyrrole, but substitution always at 2-position

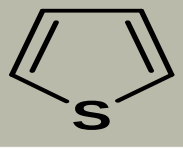
Can give addition, as well as substitution products when reacted with E^+

Five Membered Heterocycles-Introduction

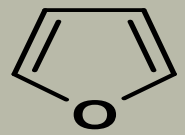
- The main reason for the study of pyrrole came from the work on the structure of haem; the blood respiratory pigment, and the chlorophyll; the green photosynthetic pigment of plants.
- Thiophen does occur in plants in association with polyacetylenes with which they are biogenetically closely linked.
- Furan occurs widely in secondary plant metabolites, especially in terpenoids.
- Unsubstituted pyrrole, furan, and thiophene are usually obtained from petroleum



Pyrrole



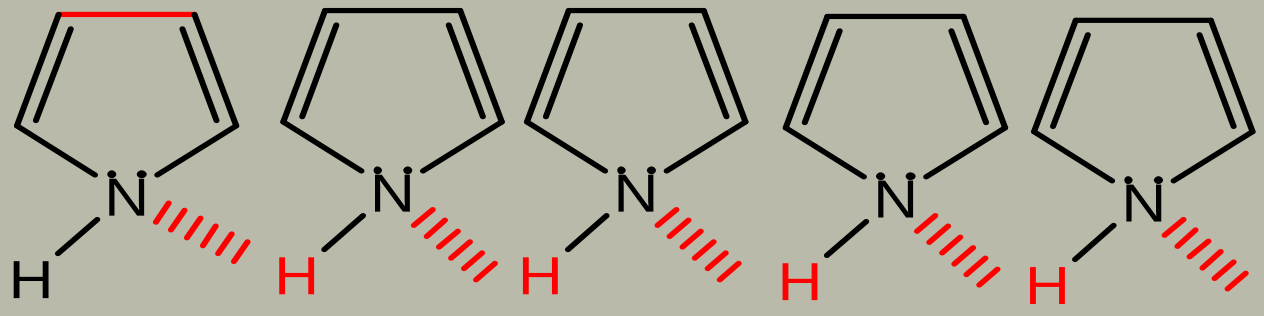
Thiophene



Furan

General Characteristics

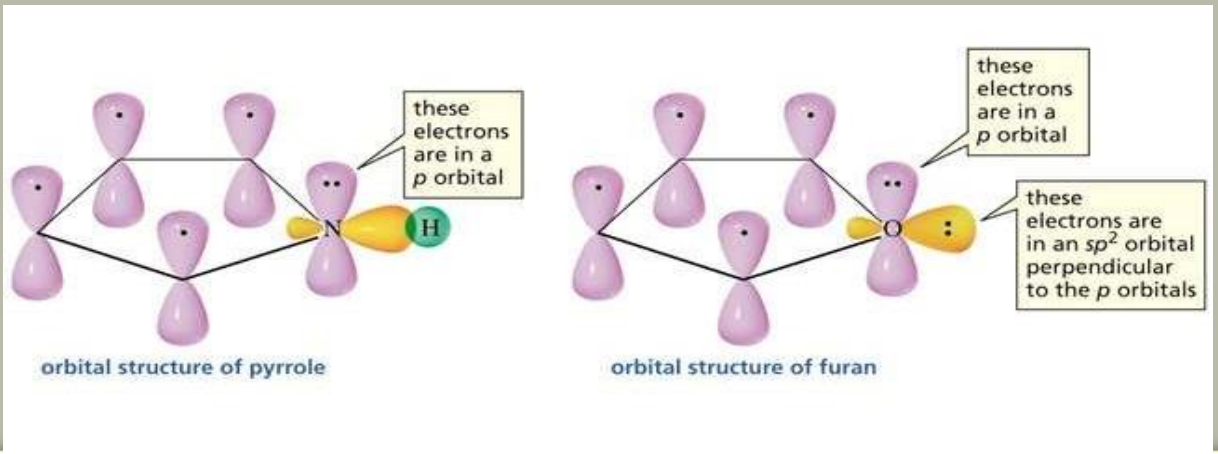
- Pyrrole, furan and thiophene are colorless liquids of boiling points 126°, 32°, and 84° respectively.
- Pyrrole has a relatively high boiling point as compared to furan and thiophene, this is due to the presence of intermolecular hydrogen bonding in pyrrole.



Structure and Aromaticity

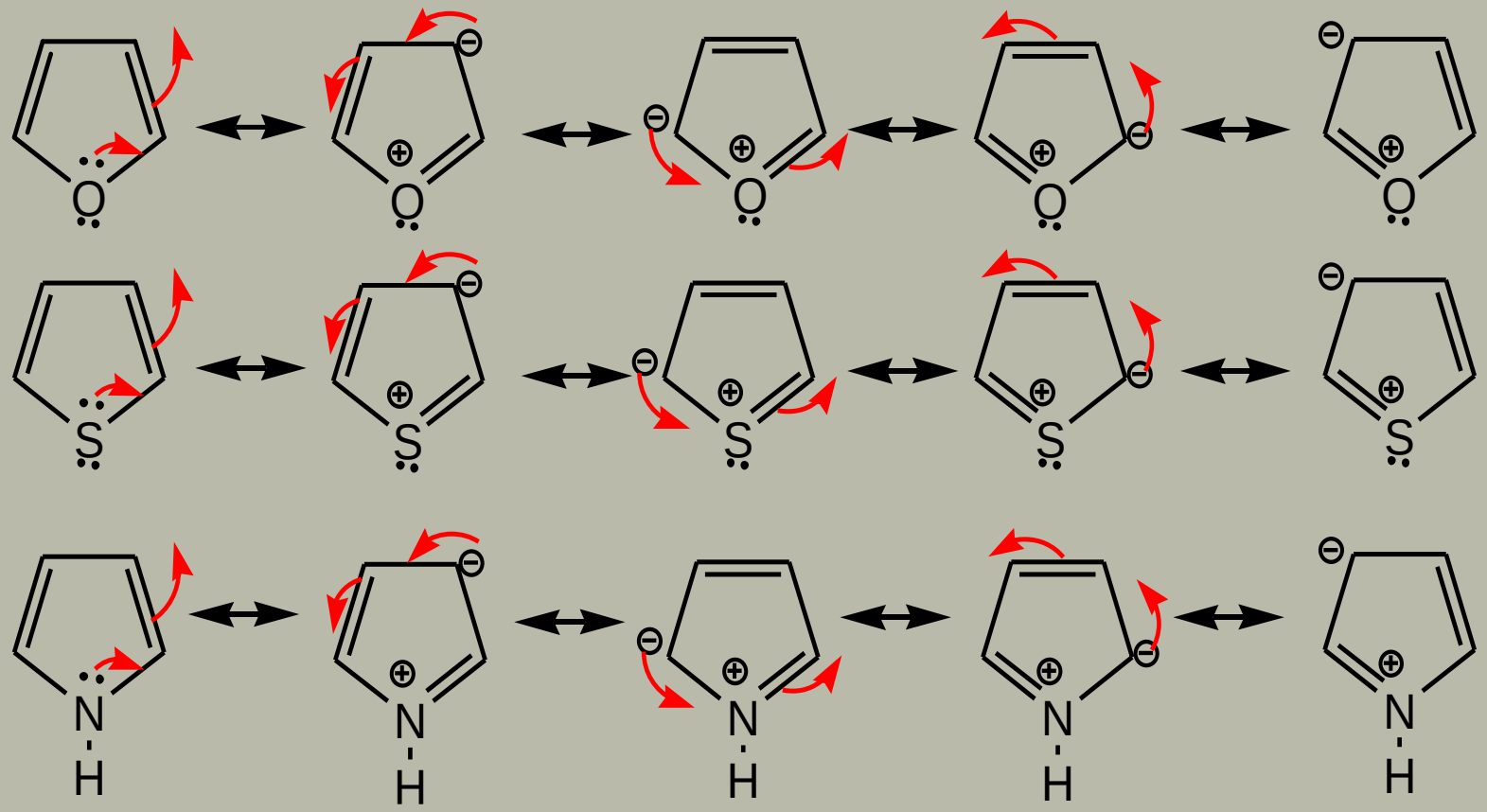
❖ Pyrrole furan and thiophene are aromatic because:

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).

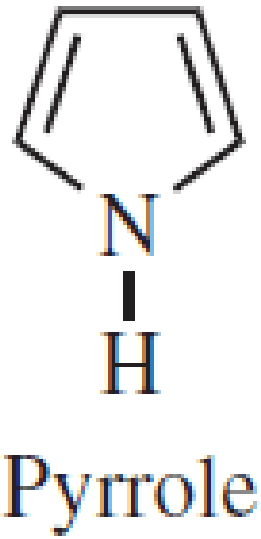


Structure and Aromaticity

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



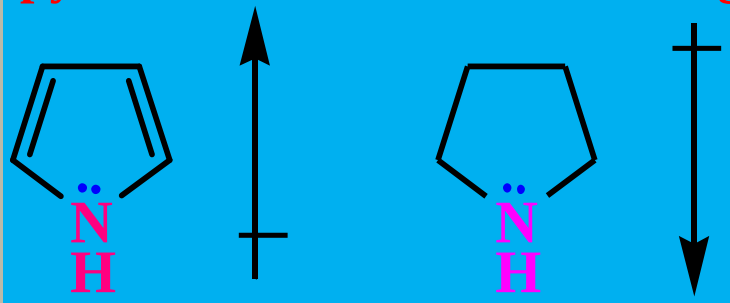
PYRROLE



Pyrrole

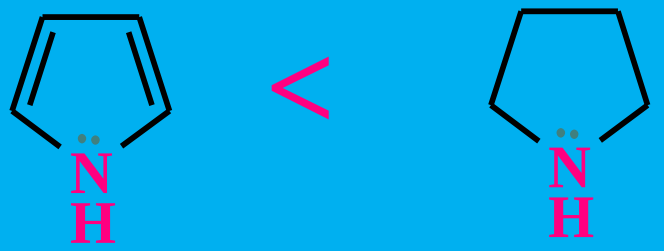
The dipole moment of pyrrole compared with pyrolidine is reverted and thus protonation occurs at carbons not at N

Dipole monent of pyrrole and its saturated analog



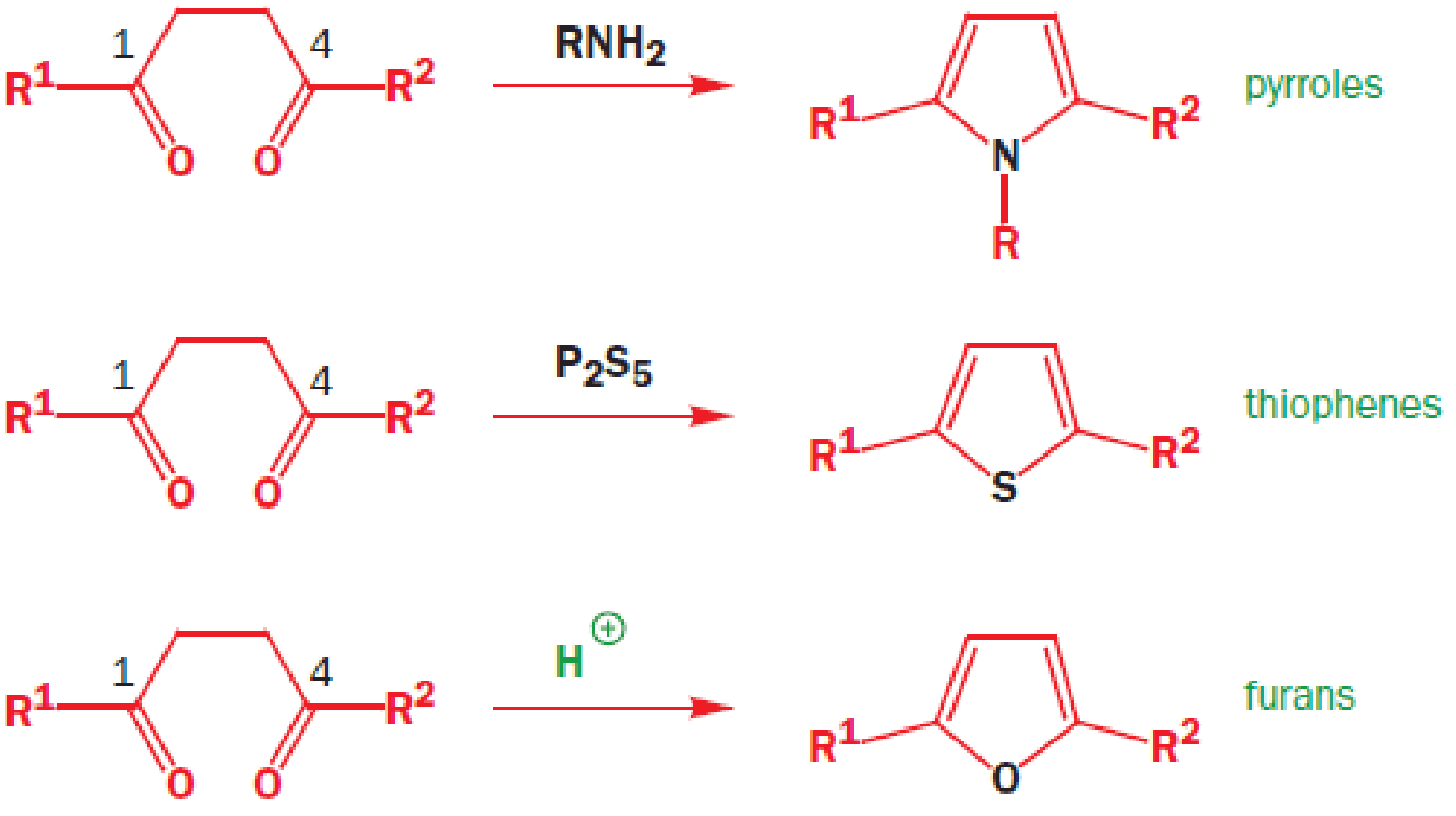
Pyrrole **Pyrrolidine**

Basicity of pyrrole and its saturated analog



Pyrrole aroamtic 2° amine **Pyrrolidin Aliphatic 2° amine**

Five membered heterocyclic compound preparation

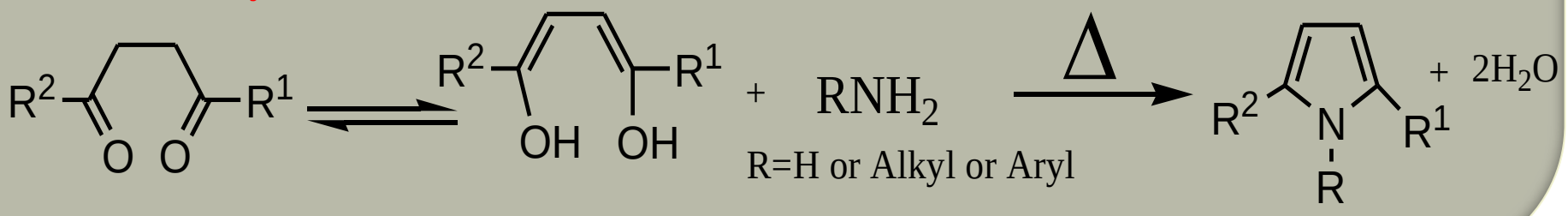


SYNTHESIS OF PYRROLE

1) From 1,4-dicarbonyl compounds (Paal-Knorr Synthesis)

Generally Substituted pyrrole may be synthesized through the cyclization of 1,4-diketones in combination with ammonia (NH_3) or amines, The ring-closure is proceeded by dehydration (condensation), which then yields the two double bonds and thus the aromatic π system. The formation of the energetically favored aromatic system is one of the driving forces of the reaction.

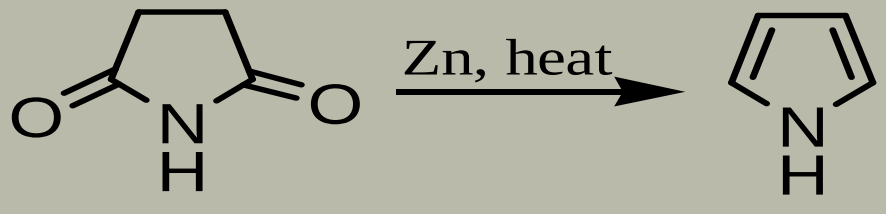
Paal-Knorr Synthesis



1,4-Dicarbony compound

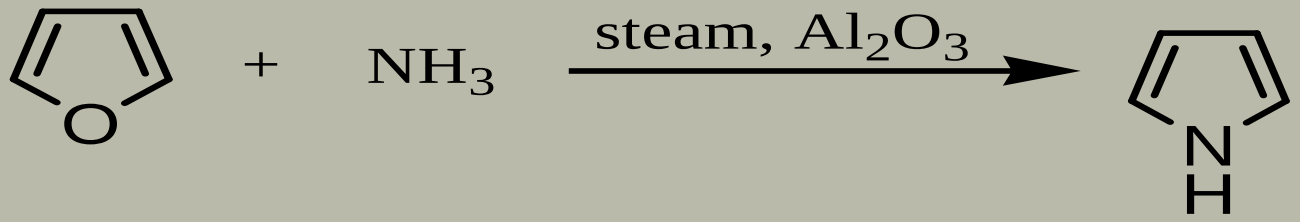
SYNTHESIS OF PYRROLE

2) Pyrrole is obtained by distillation of succinimide over zinc dust.



Succinimide

3) By heating a mixture of furan, ammonia and steam over alumina catalyst

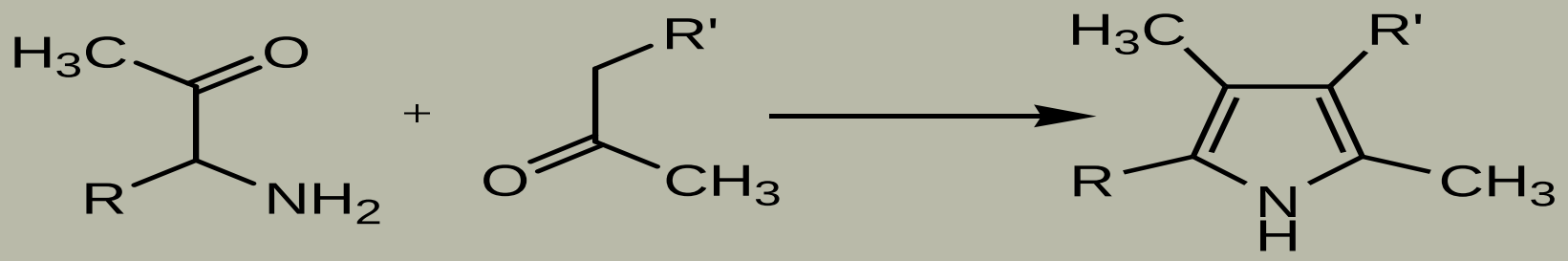


4) By passing a mixture of acetylene and ammonia over red hot tube.

SYNTHESIS OF PYRROLE

5) Knorr-pyrrole synthesis:

This involves the condensation of α-amino ketones with a β-diketone or a β-ketoester to give a substituted pyrrole.

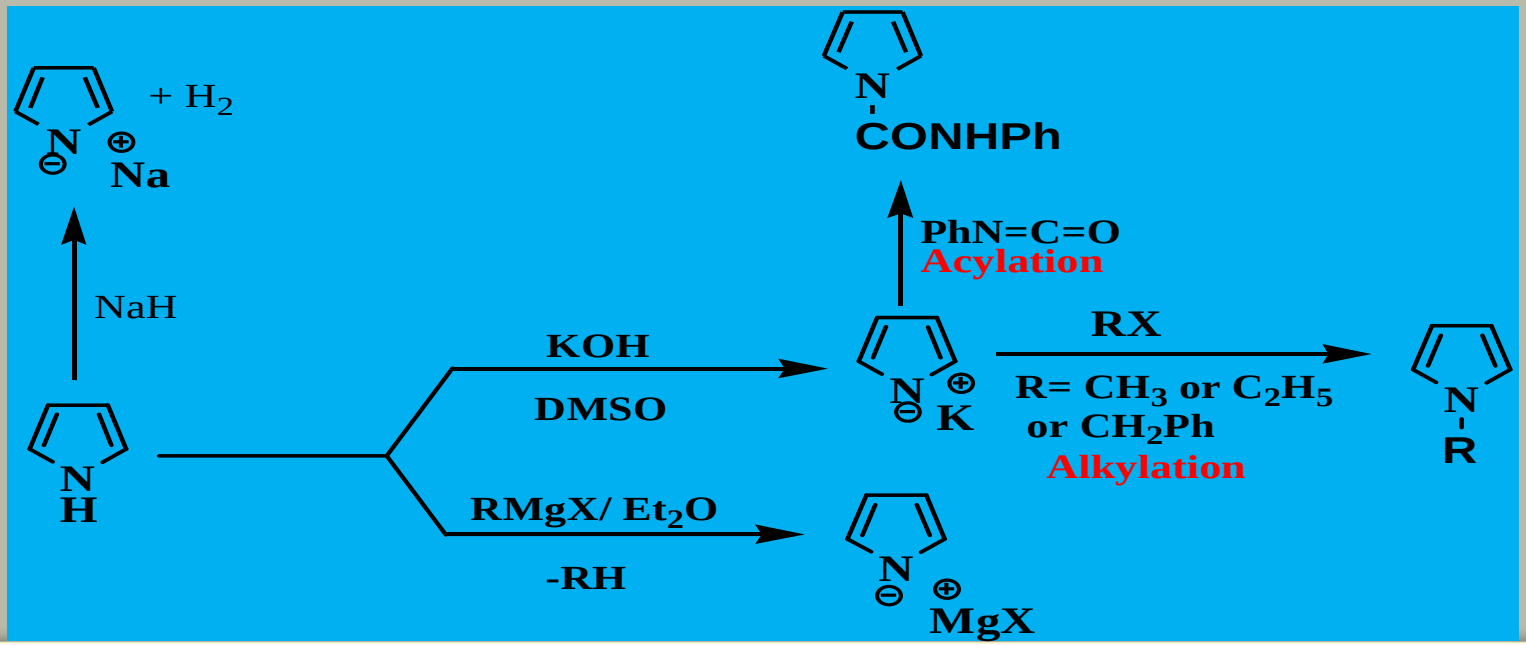


R' = -COR; β— diketone

= $-COOC_2H_5$; β— diester

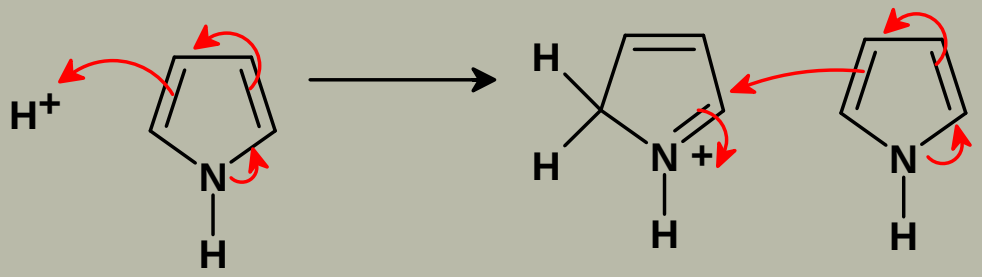
Acidic properties of pyrrole

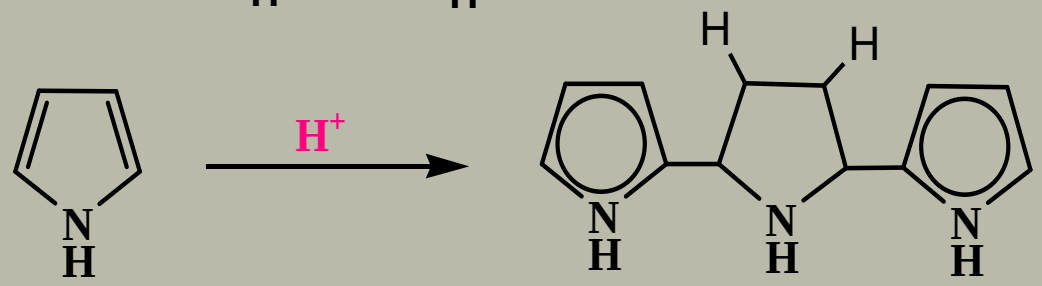
❖Due to participation of N lone pair in aromaticity), pyrrole has exceptionally strong acidic properties for a secondary amine for instance it can react with strong bases or Grignard reagent or potassium metal in inert solvents, and with sodium amide in liquid ammonia, to give salt-like compounds which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



Sensitivity of pyrrole to acids

- Pyrrole is sensitive to strong acids.
- This is due to protonation occurs at one of 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



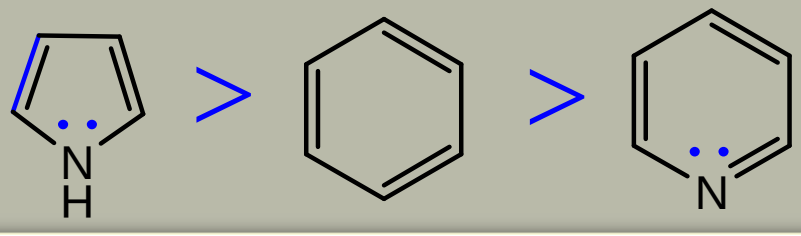


pyrrole trimer

Electrophilic substitution in pyrrole

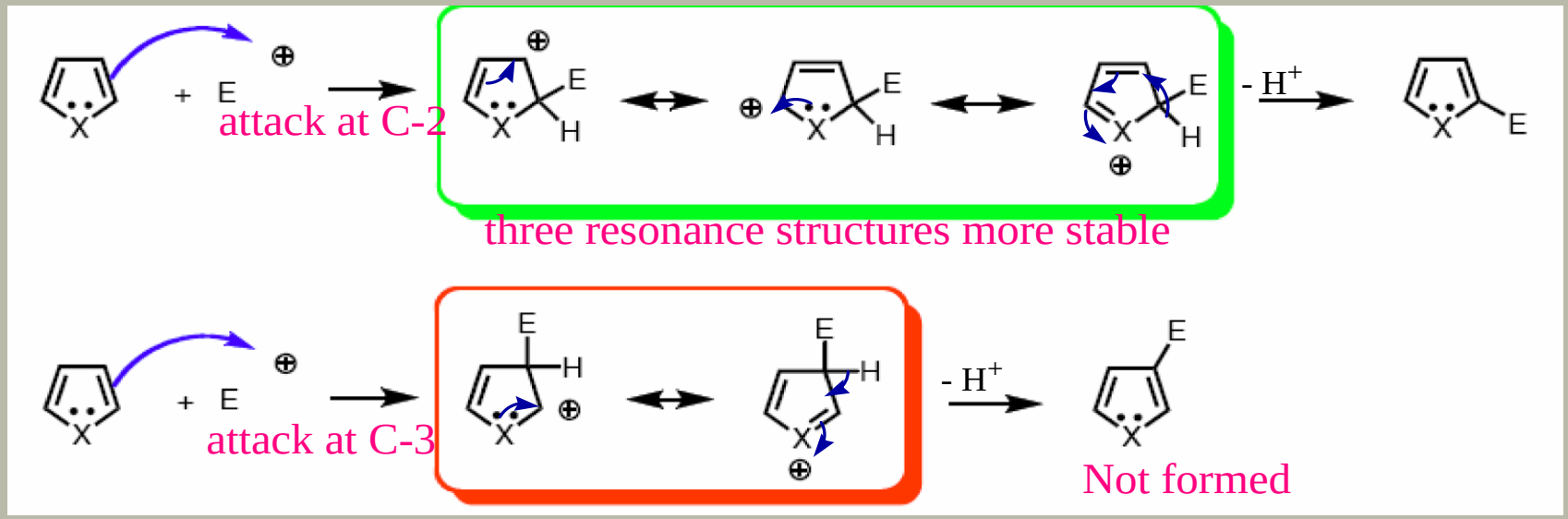
- As expected for aromatic compound, pyrrole can react by electrophilic substitution.
- In comparison to benzene pyrrole is more reactive thus the substitution is easier and milder reagents can be used.
- The increased reactivity is a result of resonance which pushes the electrons from the N-atom into 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)
- 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

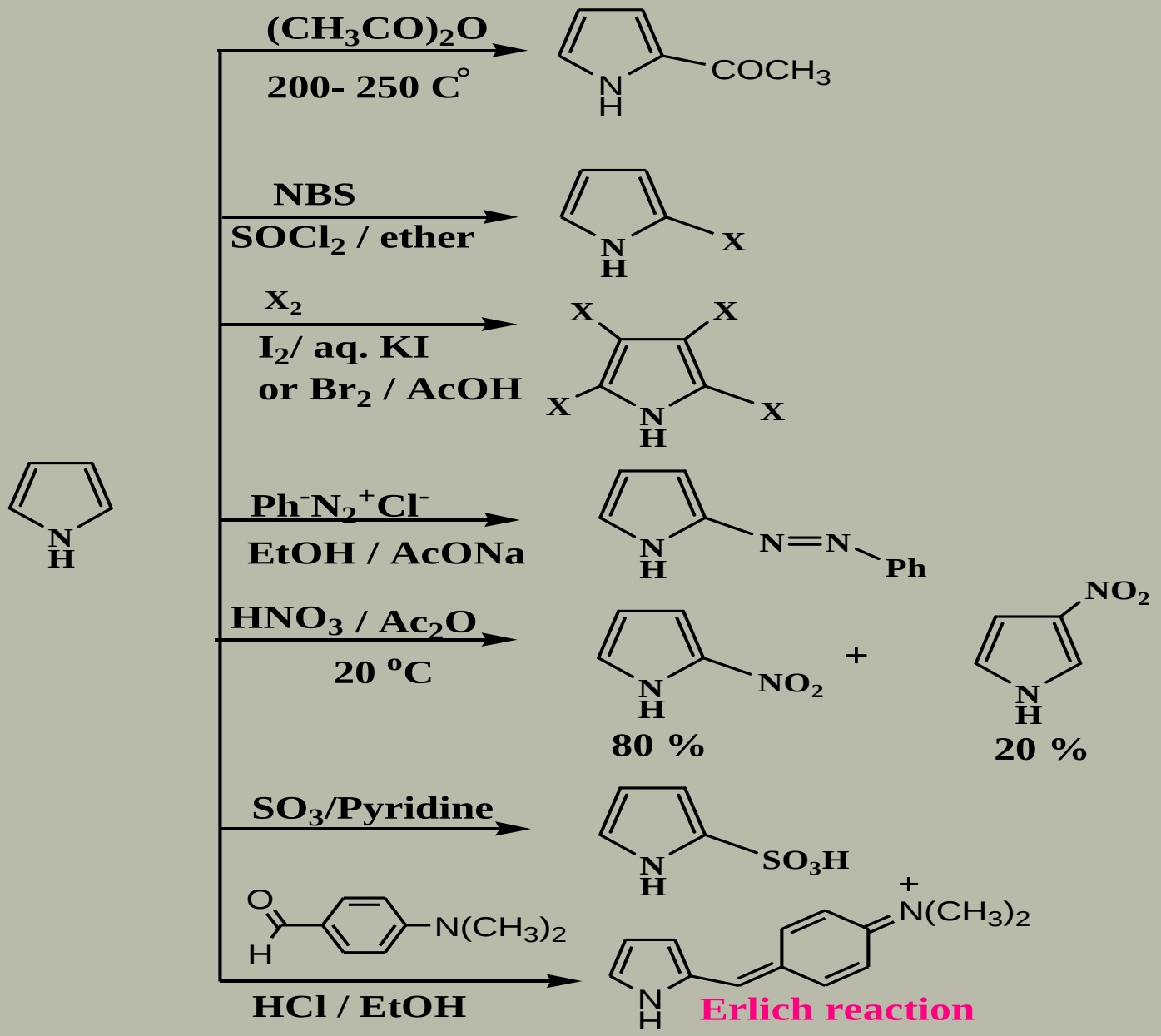


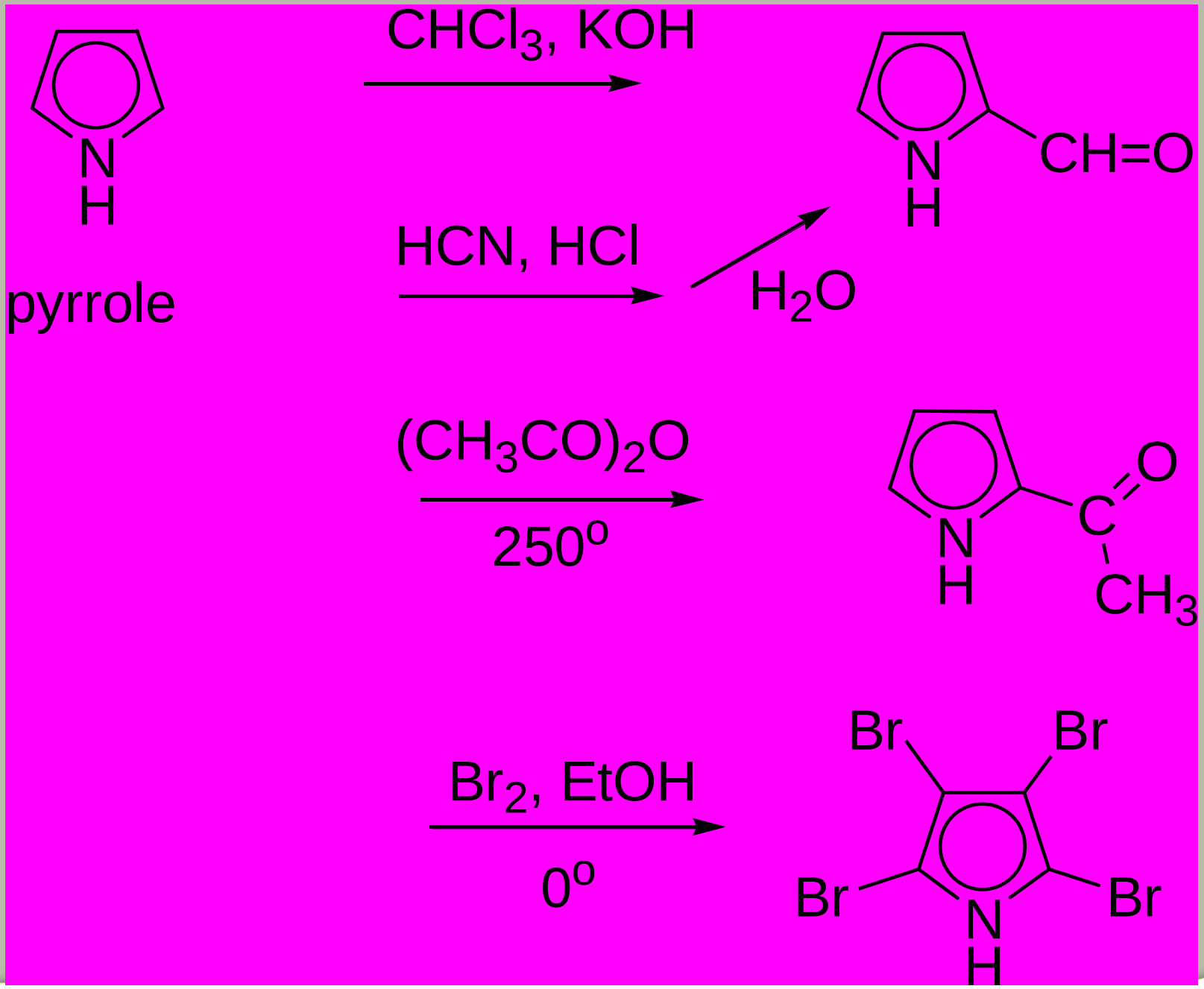
Orientation of Electrophilic Substitution in Pyrrole

- 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) .



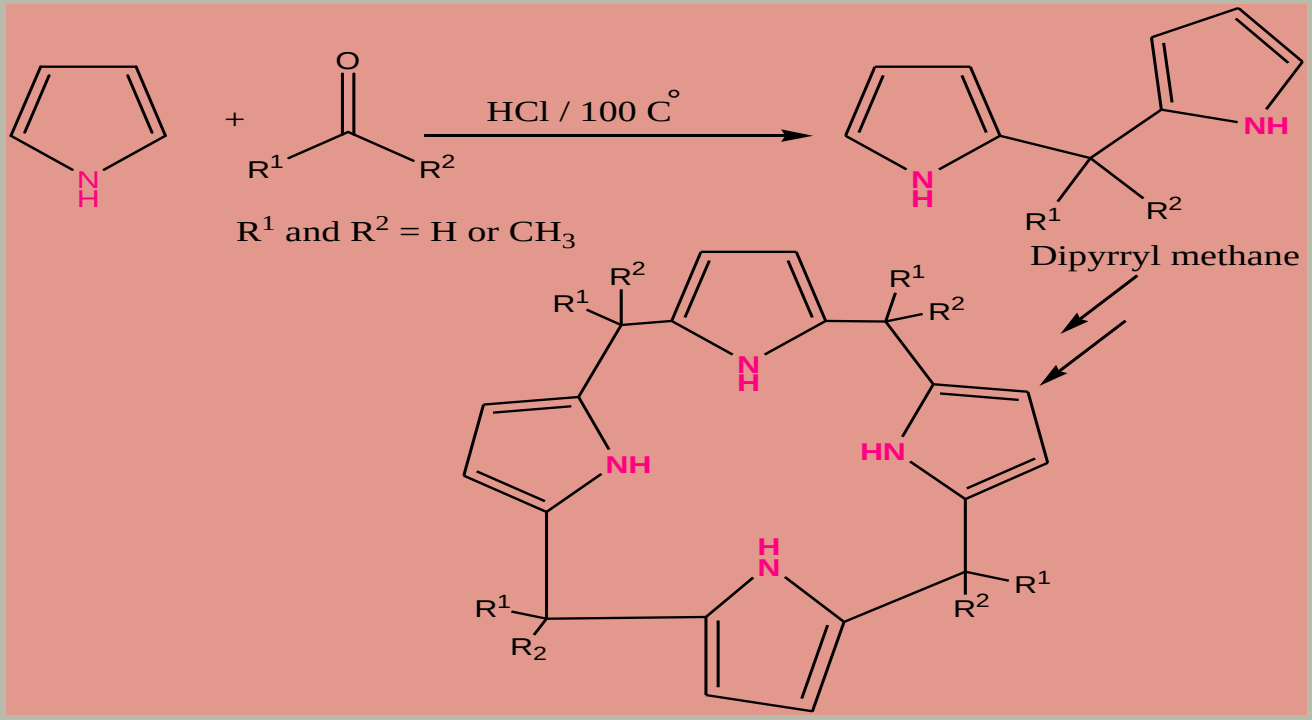
Electrophilic Substitution Reactions of Pyrrole




CHCl3, KOH
N
H
CH=O
pyrrole
HCN, HCl
H2O
(CH3CO)2O
250o
O
C
CH3
Br2, EtOH
0o
Br

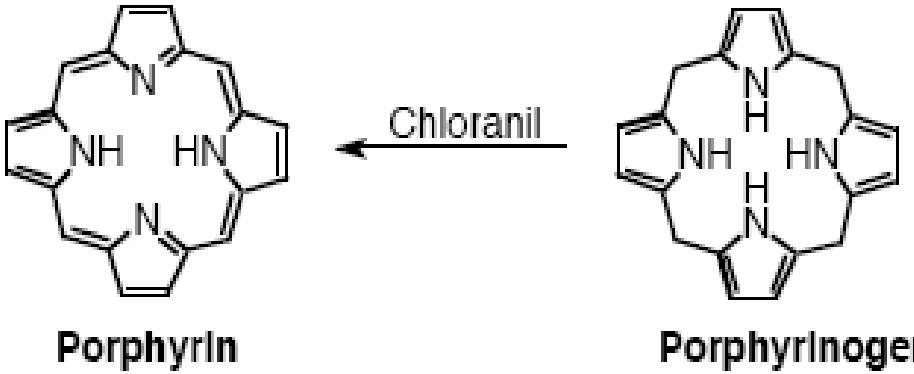
Reaction of pyrrole with aldehyes and ketones

- Aldehydes and ketones condense with unsubstituted pyrrole at α-position in acidic medium to give dipyrryl 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.

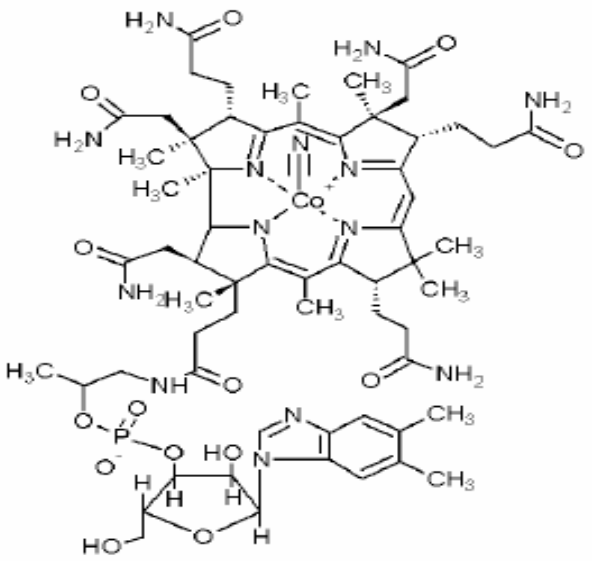


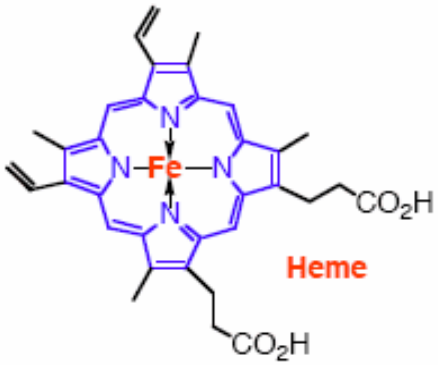
Application in Porphyrine Synthesis

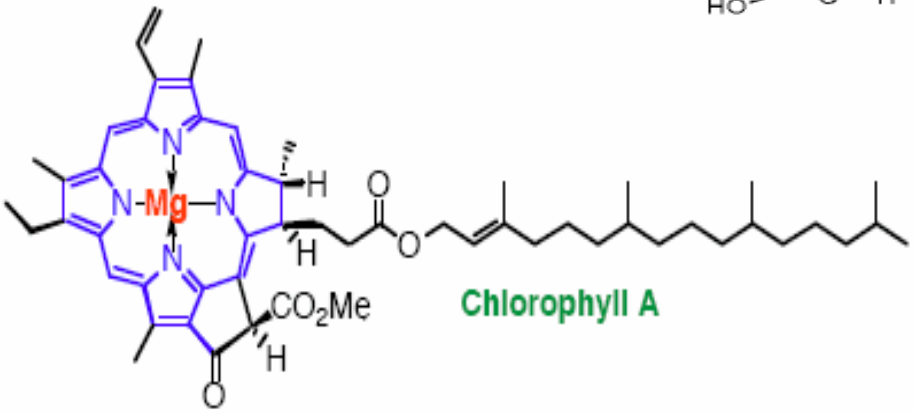
❖ Oxidation of porphyrinogen results in structures known as porphyrins that found in many natural compounds such as haem in animal kingdom and in chlorophyll in plant.



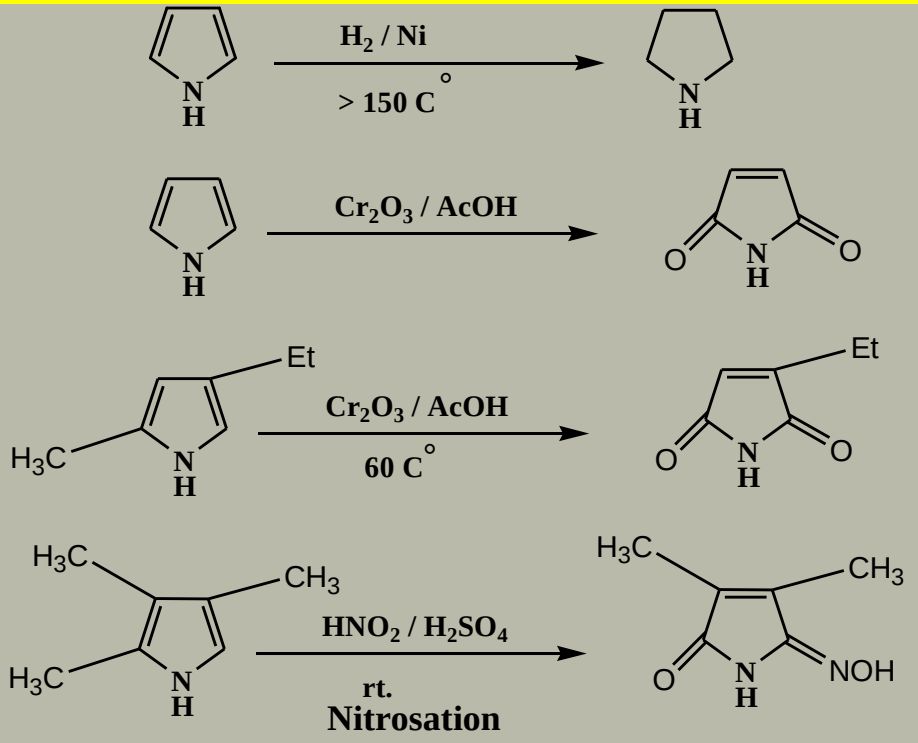
Vit. B12



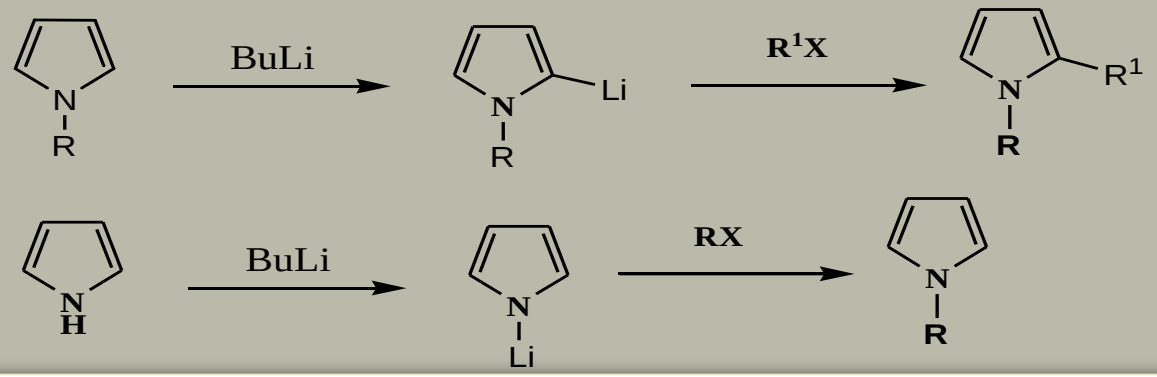




Oxidation-Reduction of Pyrrole

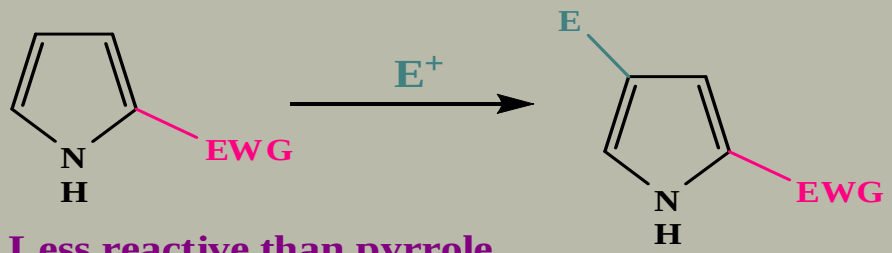


Lithiation of Pyrrole and N alkyl pyrrole



Second electrophilic substitution

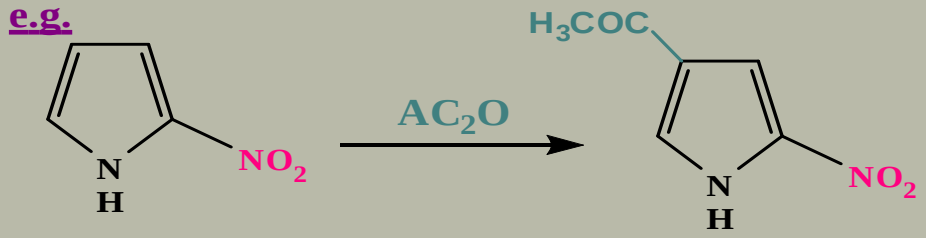
a) Monosubstituted pyrrole with electron withdrawing group



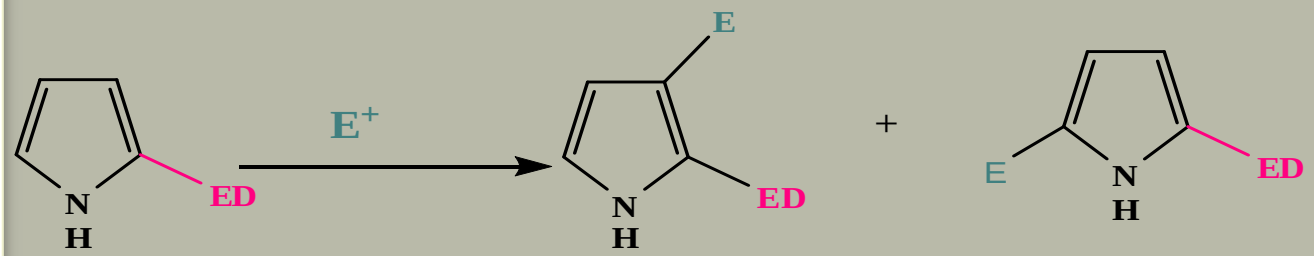
(incoming E^+ directed to *m*-position i.e. position 4)

Less reactive than pyrrole

e.g.



b) Monosubstituted pyrrole with electron donating group

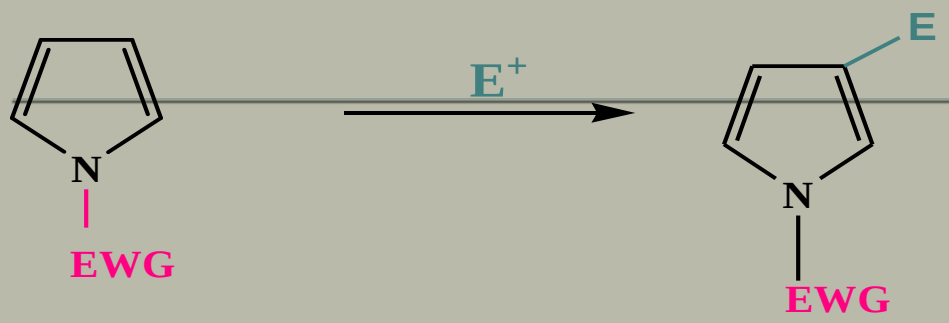


More reactive than pyrrole

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

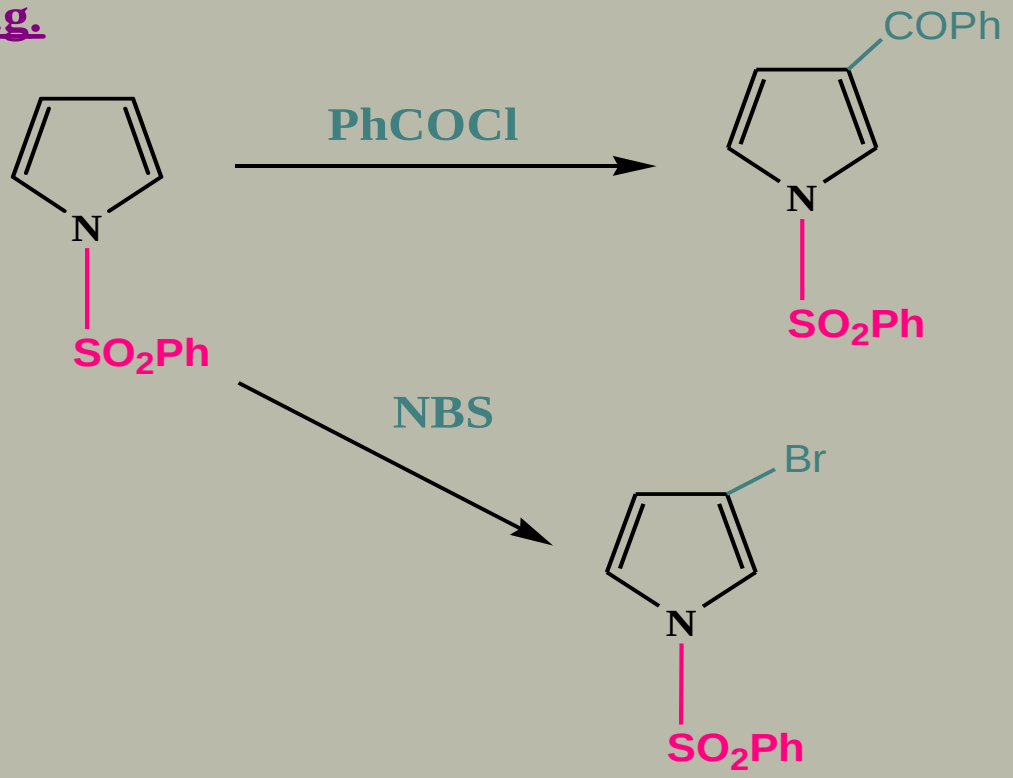
SECOND ELECTROPHILIC SUBSTITUTION

c) N-substituted pyrrole with electron withdrawing group



(incoming E^+ directed to position 3) due to steric effects

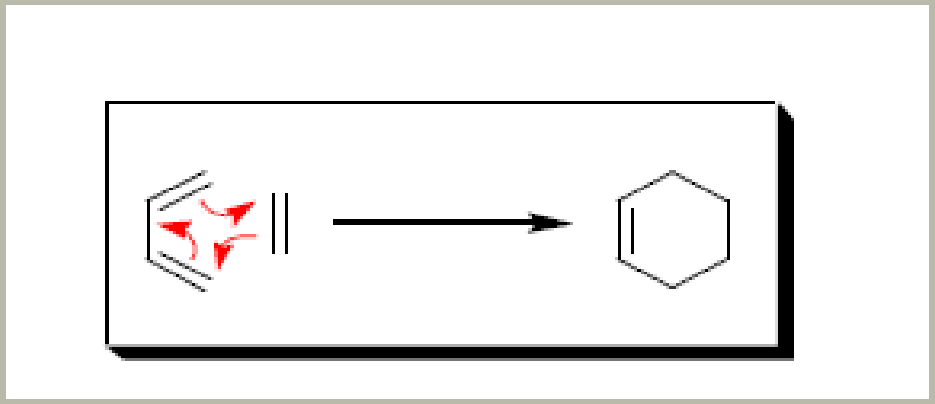
e.g.



CYCLOADDITION REACTIONS (DIELS ALDER REACTION)

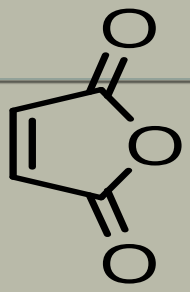
❖Cycloaddition reaction is one in which two reactants add together with formation of 2 new C-C bonds at the same time to give a cyclic product e.g. Diels-Alder reaction.

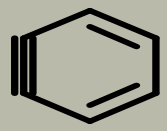
❖Diels – Alder reaction involves addition of a compound containing a double or a triple bond (2 π e it is Called dienophile) across the 1,4- position of a conjugated system (4π e, 1,3-diene), with the formation of a six membered ring.



❖The heterocyclic compounds can react as a 1,3-diene in D. A. reaction with reactive dienophiles (e.g. maleic anhydride, or benzyne) or with less reactive dienophiles (e.g. acrylonitrile) in presence of catalyst.

Cycloaddition reactions of pyrrole (Diels Alder Reaction)





Maleic anhydride Benzyne Acrylonitrile

❖The diene can be activated by E.D.G while the dienophile by EWG.

❖Thus N-alkyl pyrrole and N-amino pyrrole are more reactive than pyrrole itself in D.A reaction but less reactive than furan (the least aromatic 5- membered heterocycle thus the most reactive in addition) .

❖The order of reactivity in D.A reaction is as follows which is the reverse of aromaticity order:

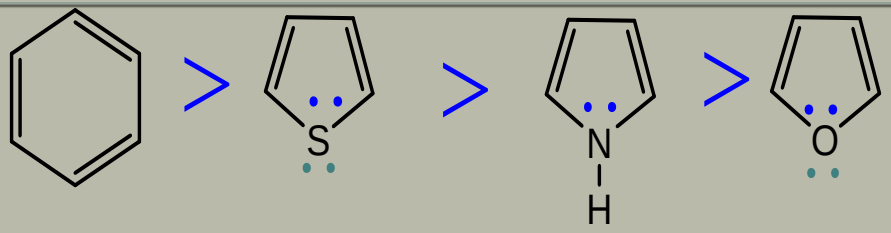
Furan > N-alkyl pyrrole > Pyrrole > Thiophene.

FURAN

AND

THIOPHENE

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 increses as aromaticity decreases.

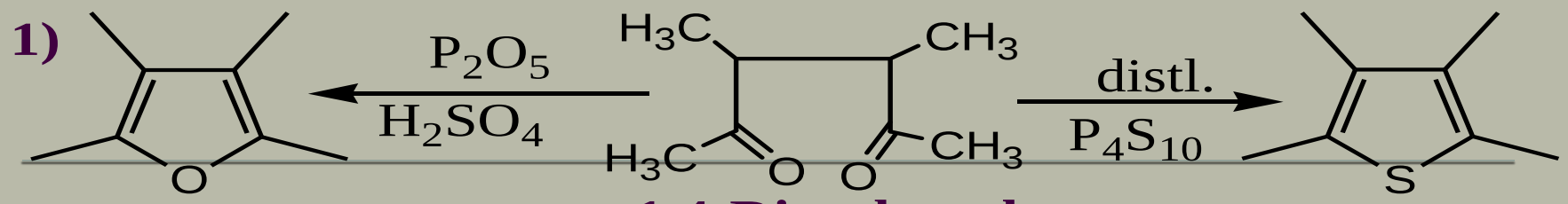
Order of aromaticity 

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

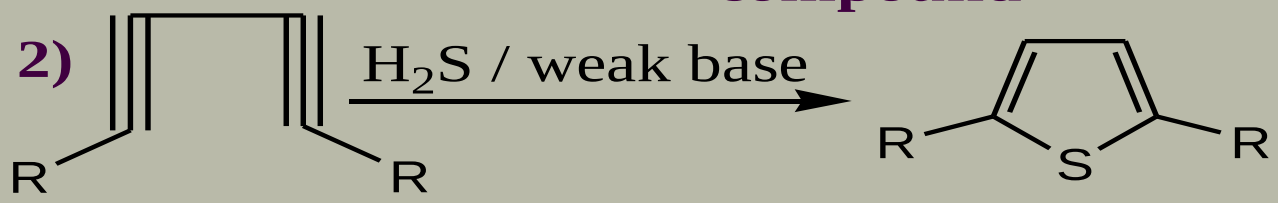
Eelectrophilic substitution on furan requires very mild non acidic conditions (acids may induce polymerization or ring opening), however, for thiophene the acidity is less critical since it is stable to aqueous minral acids but not to 100 % strong acids or Lewis acids such as $AlCl_3$.

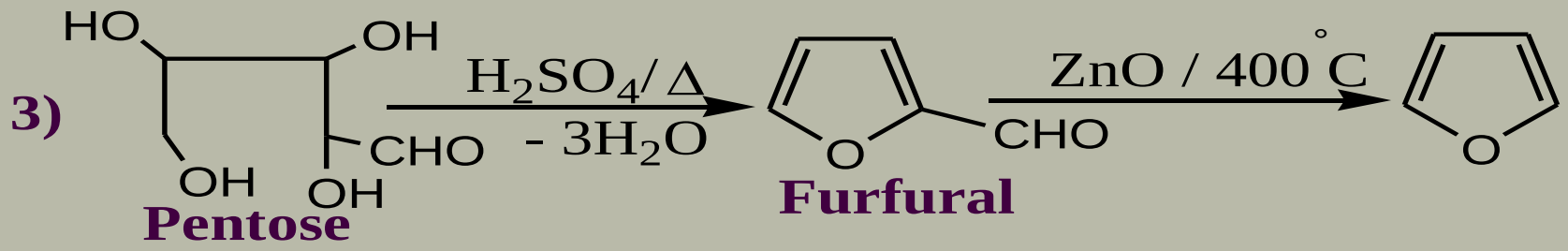
Regioselectivity: The 2 & 5 (α) positions are more reactive than 3 & 4 (β) Positions As in pyrrole the intermediate results from electrophilic attack at C2 can be stabillized by three resonance structure while the intermaediate results from the attack C3 is only satbilized by two resonance structures.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

Synthesis of Furan and Thiophene



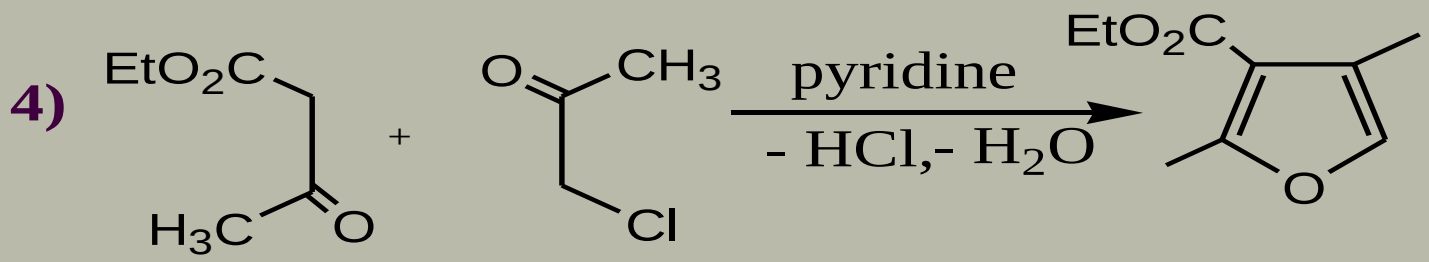
1,4-Dicarbonyl compound





Pentose

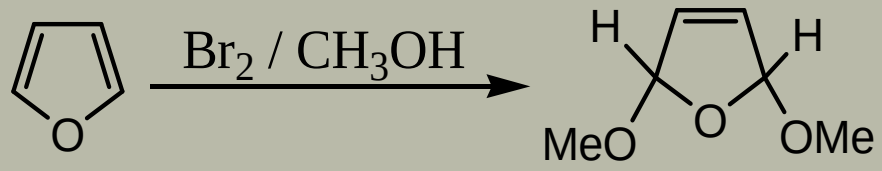
Furfural



Feist-Benary Furan Synthesis

Addition Reactions

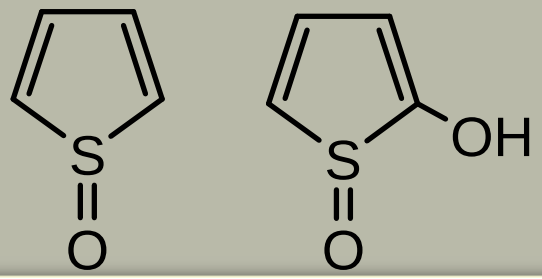
a) Oxidation



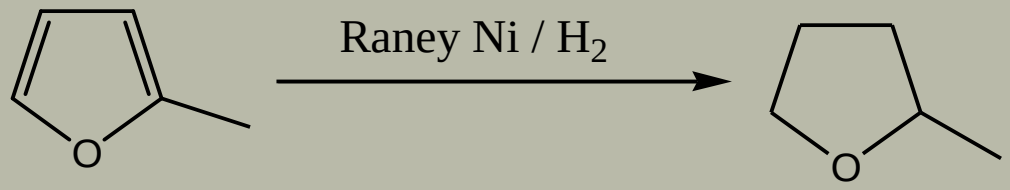
cis / trans

2,5-Dihydro-2,5-dimethoxyfuran

- This reaction involves electrophilic addition of bromine in presence of methanol at 2 & 5 positions which is characteristic of 1,3-dienes followed by substitution by methanol.
- Thiophene is oxidized by peracids to Thiophene-1-oxide and 2-hydroxythiophene oxide.



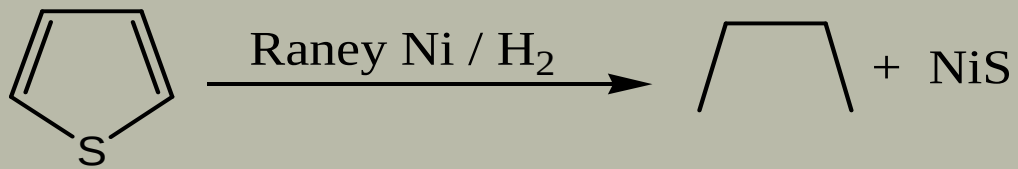
b) Reduction

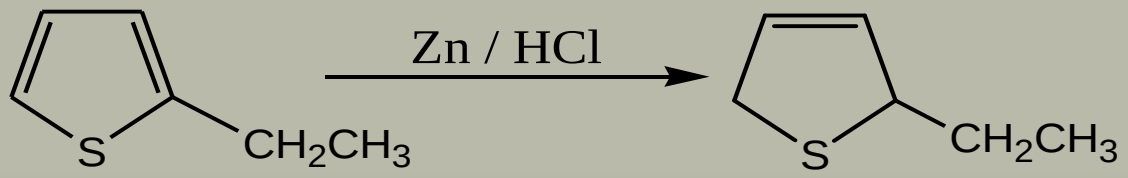


2-Methyltetrahydrofuran

❖ **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.**

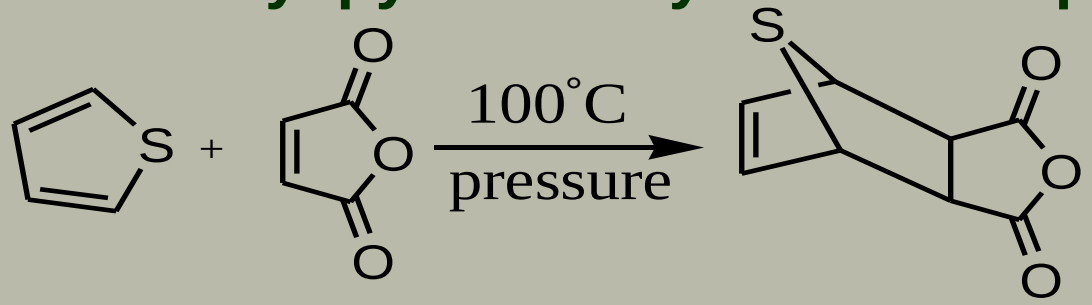


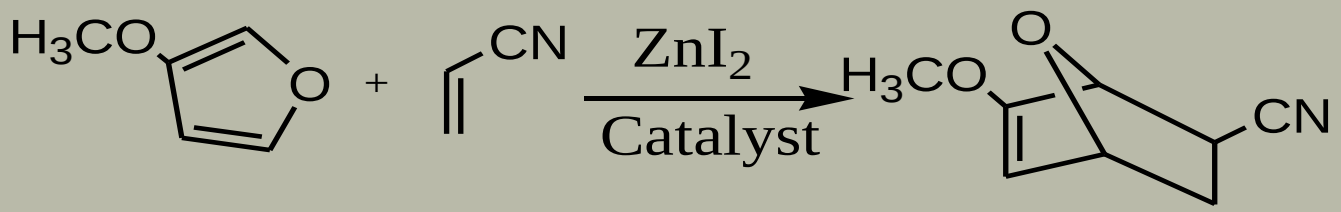


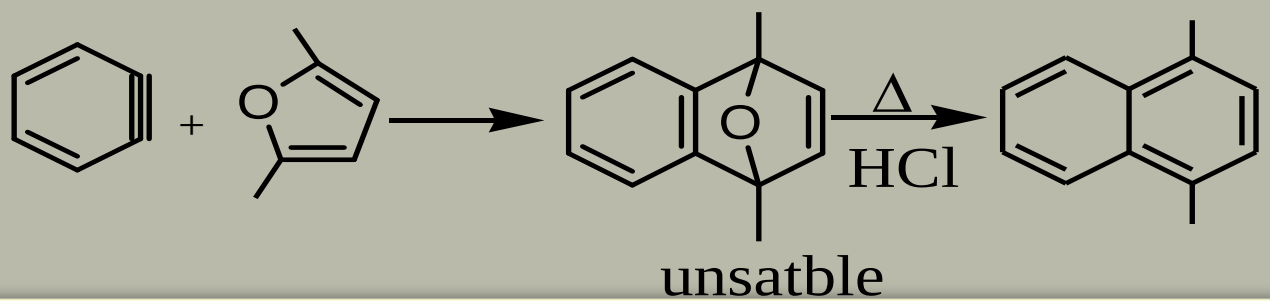
c) Diels- Alder Reaction:

- **Reaction of thiophene with maleic anhydride requires more drastic conditions than in case of furan and pyrrole (high pressure and temperature), this is because it is the most aromatic thus it is the least reactive as a diene.**
- **The order of reactivity in D.A reaction is as follows:**

Furan > N-alkyl pyrrole > Pyrrole > Thiophene.



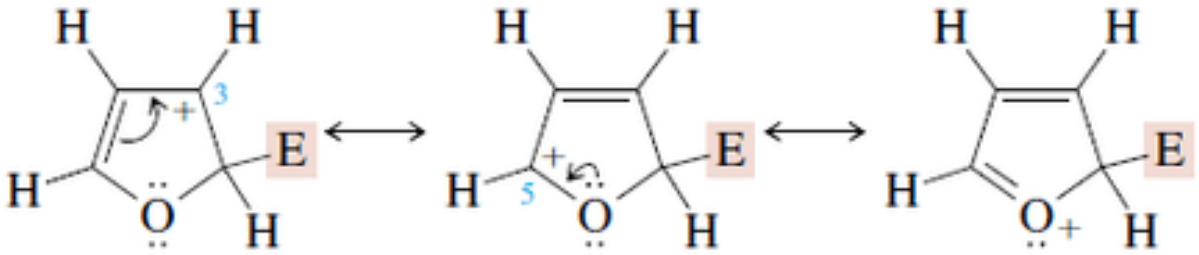




Orientation of Electrophilic Substitution in Furan

Attack at C-2

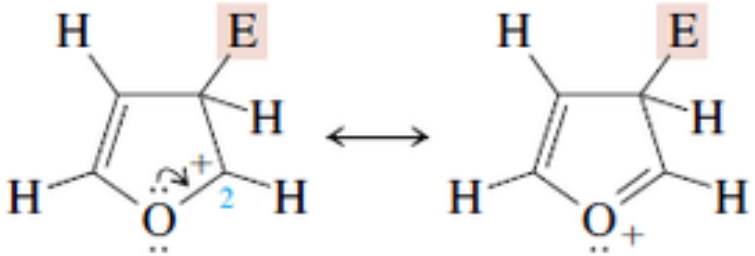
Carbocation *more stable;* positive charge shared by C-3, C-5, and O.

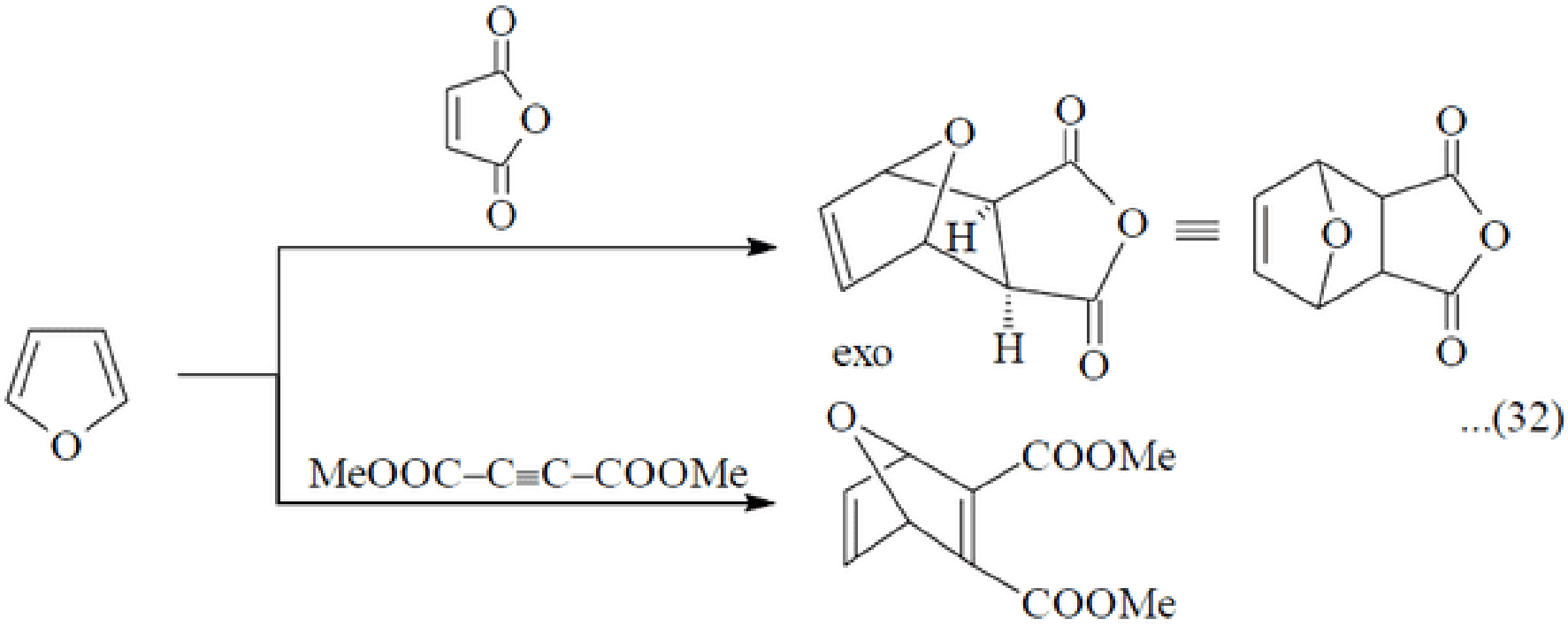


When the electrophile attacks at C-3, the positive charge is shared by only two atoms, C-2 and O, and the carbocation intermediate is less stable and formed more slowly.

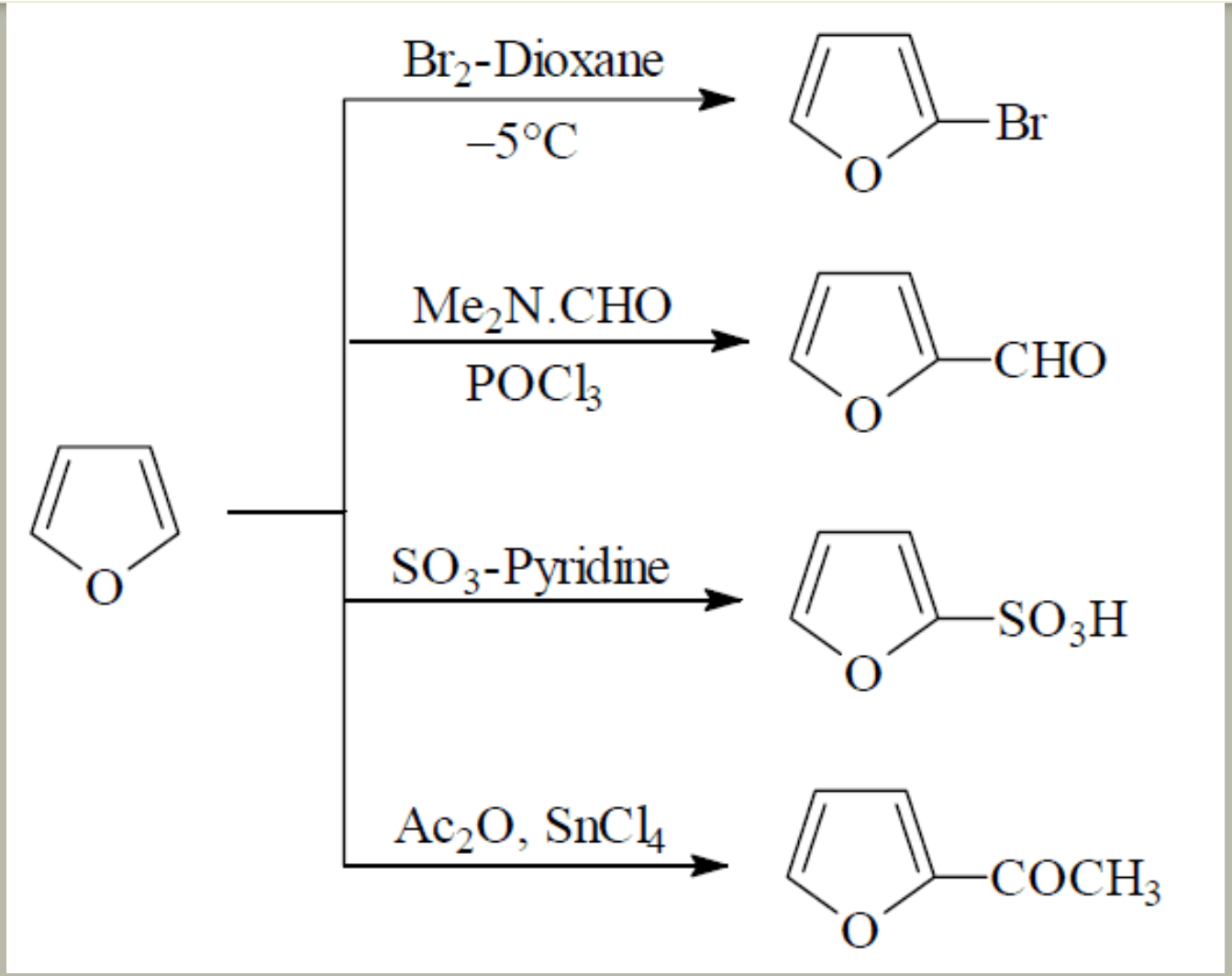
Attack at C-3

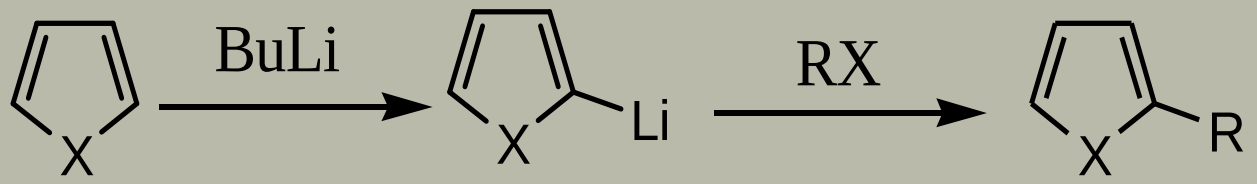
Carbocation *less stable;* positive charge shared by C-2 and O.



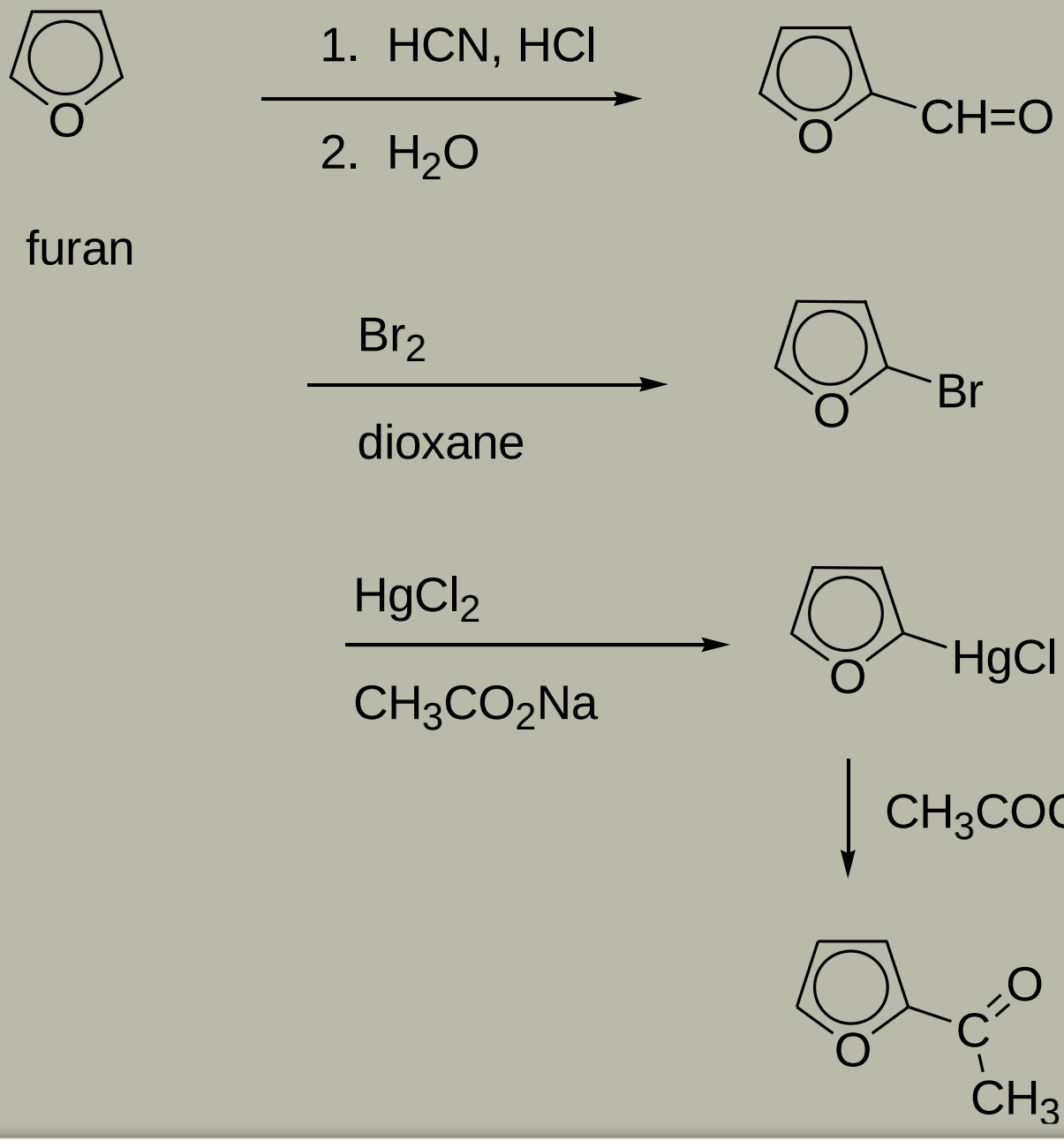


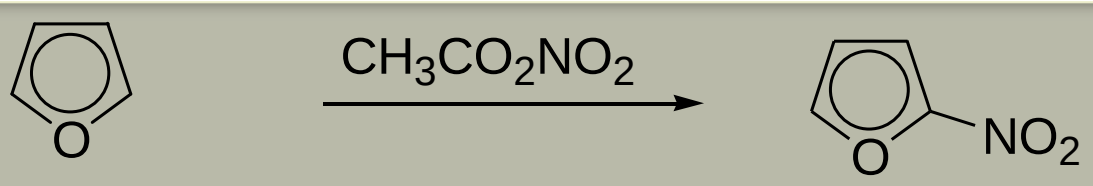
...(32)


Br2-Dioxane
–5°C
Br
Me2N.CHO
POCl3
CHO
SO3-Pyridine
SO3H
Ac2O, SnCl4
COCH3
O

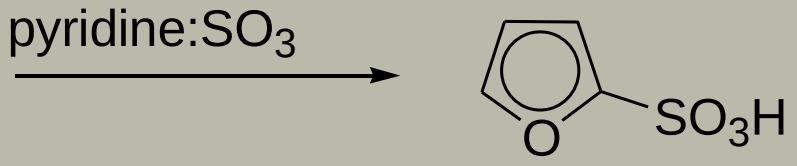

BuLi
RX
X
Li
R

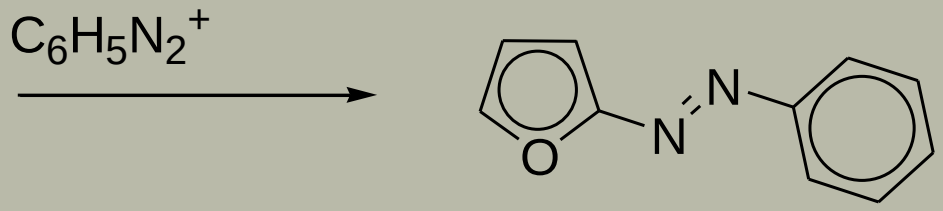
X = O, S

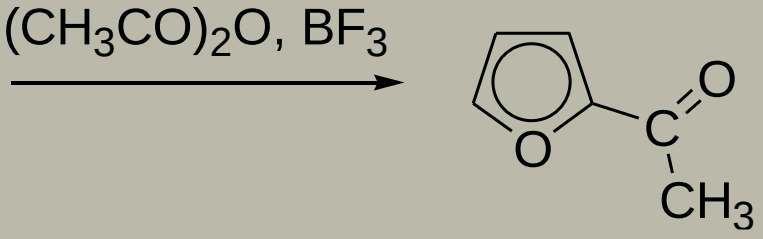

1. HCN, HCl
2. H2O
O
CH=O
furan
Br2
dioxane
Br
HgCl2
CH3CO2Na
HgCl
I2
I
CH3COCl
C
CH3

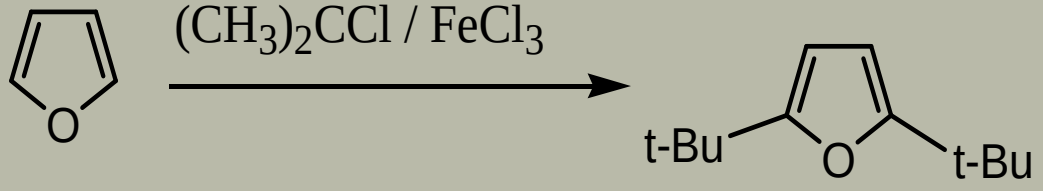

$CH_3CO_2NO_2$
O
O
NO_2

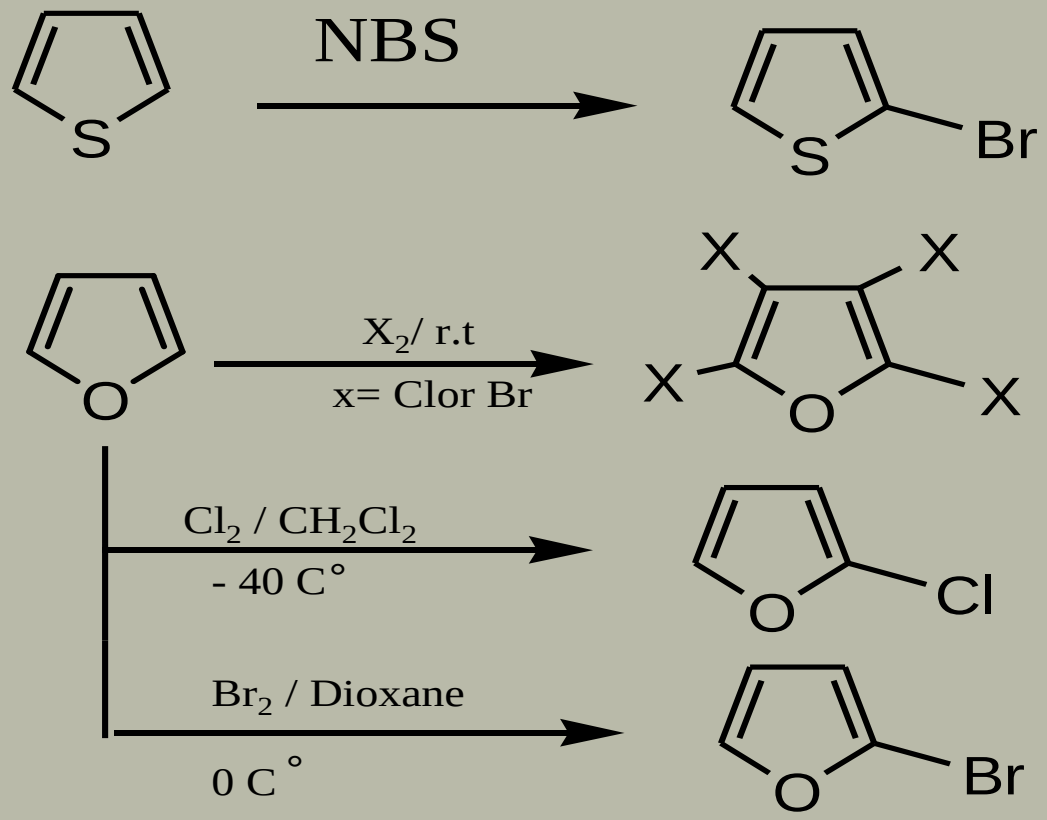
furan


pyridine:SO_3
O
SO_3H

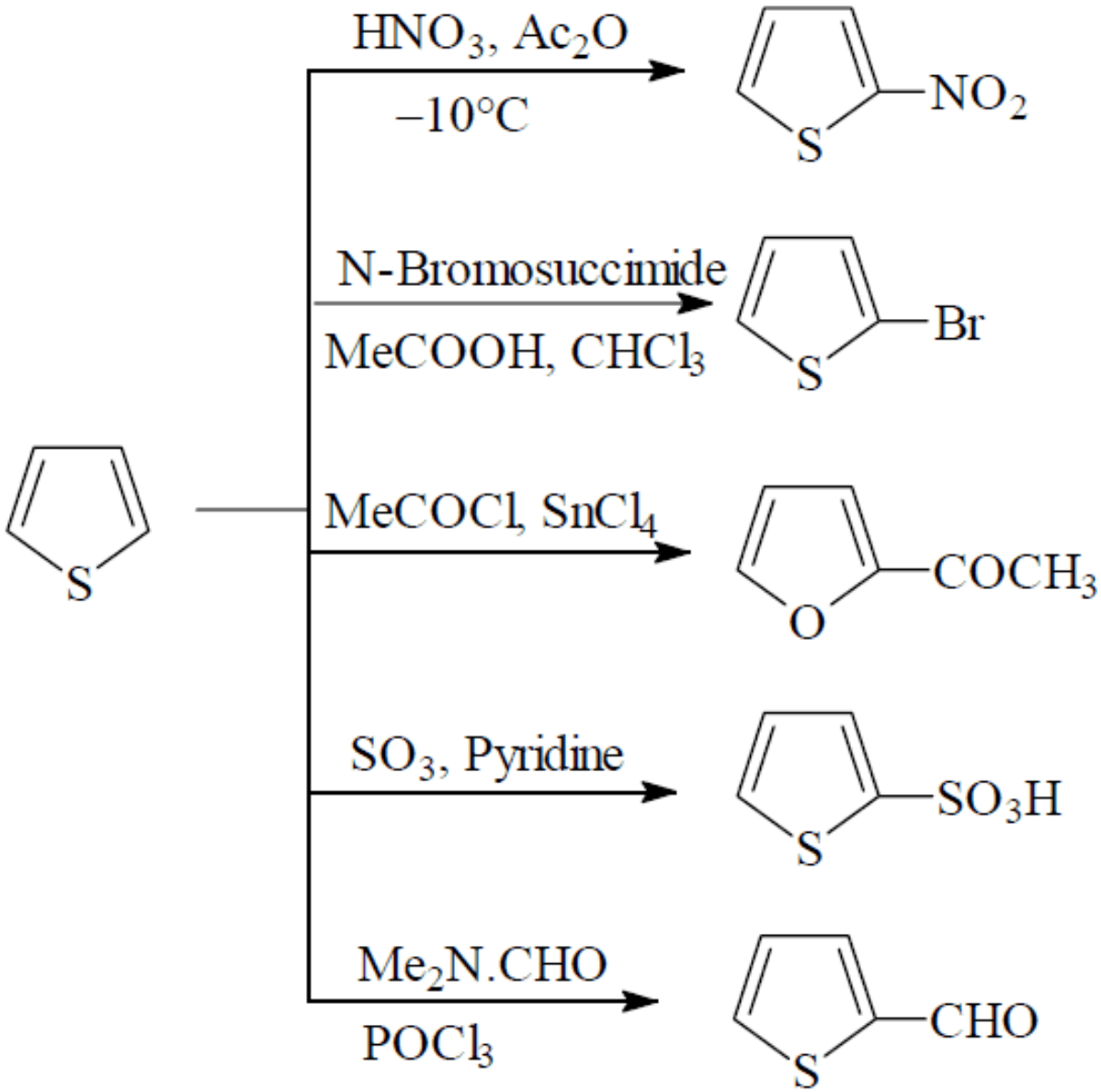

$C_6H_5N_2^+$
O
N
N


$(CH_3CO)_2O$, BF_3
O
O
C
CH_3

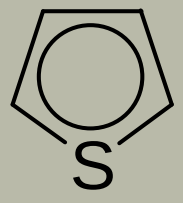

$(CH_3)_2CCl$ / $FeCl_3$
O
t-Bu
O
t-Bu



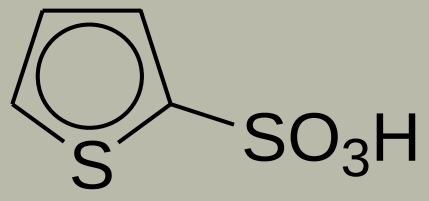
Indirect insertion of iodine in furan ring


HNO3, Ac2O
–10°C
NO2
N-Bromosuccinimide
MeCOOH, CHCl3
Br
MeCOCl, SnCl4
COCH3
SO3, Pyridine
SO3H
Me2N.CHO
POCl3
CHO
S
O

less reactive, can use acids

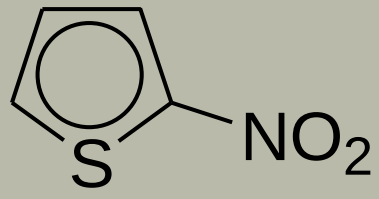


H_2SO_4

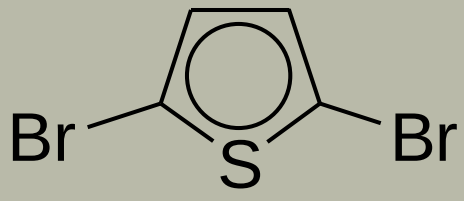


$CH_3CO_2NO_2$

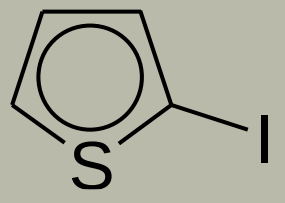
$(CH_3CO)_2O$



Br_2, benzene



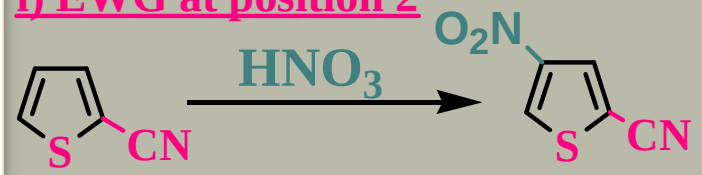
I_2, HgO



Second Electrophilic Substitution in Furan and Thiophene

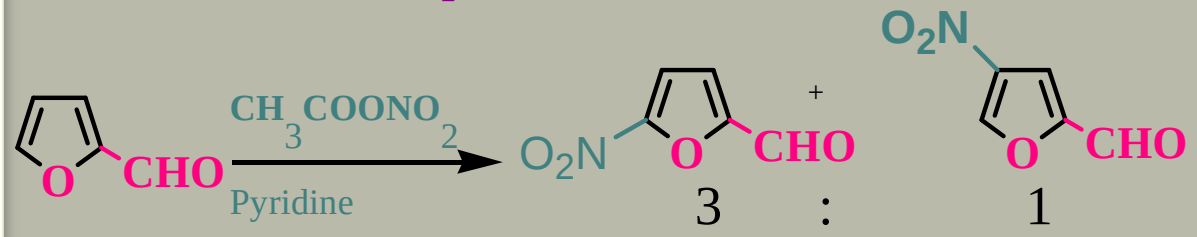
a) Monosubstituted furan & thiophene with electron withdrawing groups such as COOH, CHO, CN, COR, SO_3H are less reactive than unsubstitutted compounds

i) EWG at position 2



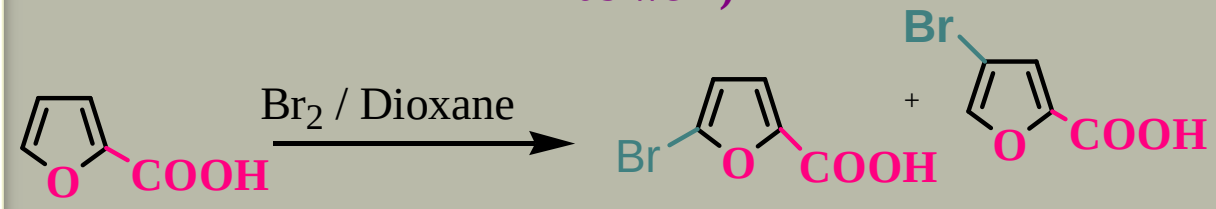
(incoming E^+ is directed to *m*-position i.e. position 4)

Less reactive than thiopene

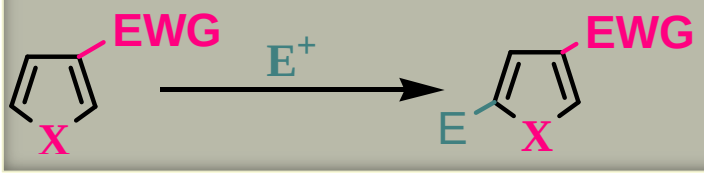


Less reactive than furan

(incoming E^+ is directed to position 5 mainly and to position 4 as well)



ii) EWG at position 3

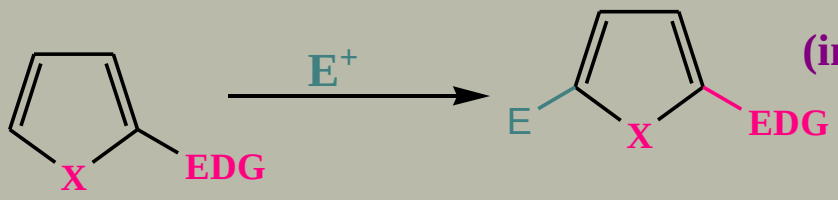


(incoming E^+ is directed to position 5)

Second Electrophilic Substitution in Furan and Thiophene

b) Monosubstituted furan & thiophene with electron donating group such as CH_3, OH, NH_2, OCH_3

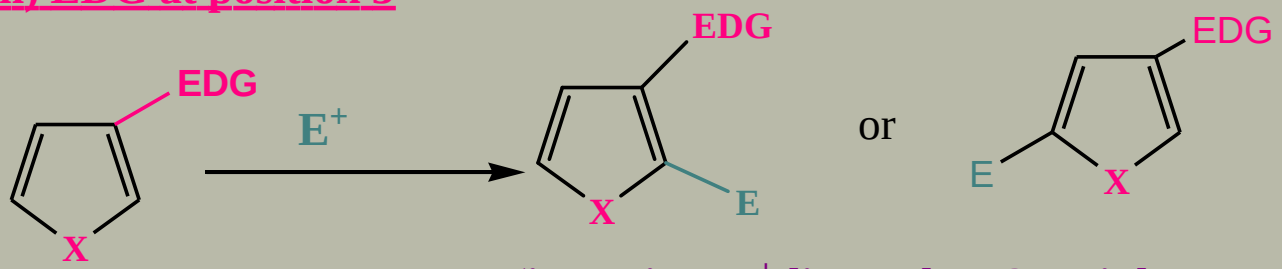
i) EDG at position 2



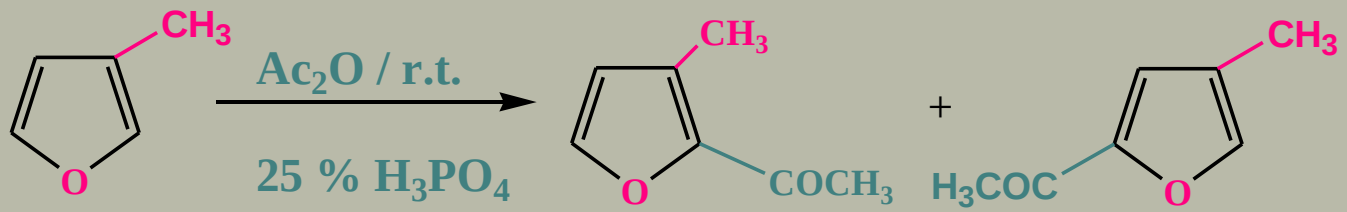
(incoming E^+ is directed to position 5)

More reactive than unsubstituted compound

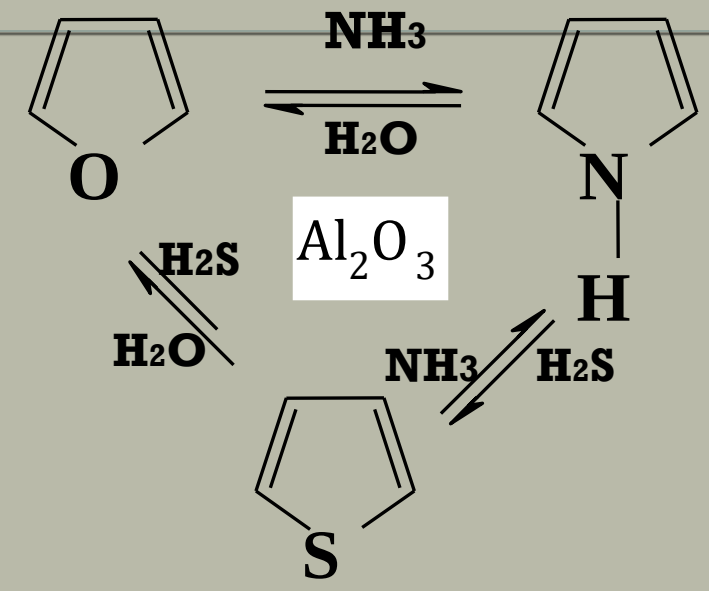
ii) EDG at position 3



(incoming E^+ directed to 2 mainly or 5 due to steric effects)

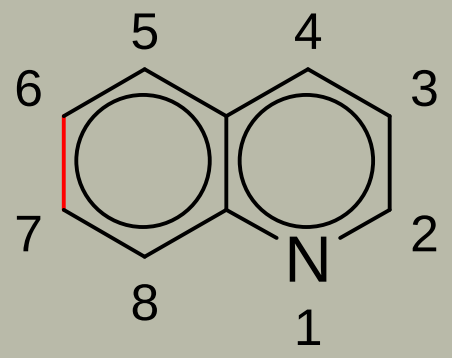


Reciprocal transformation of furan, pyrrole, thiophene (Yurie`s cycle reactions)



POLYNUCLEAR HETEROAROMATICS

EAS

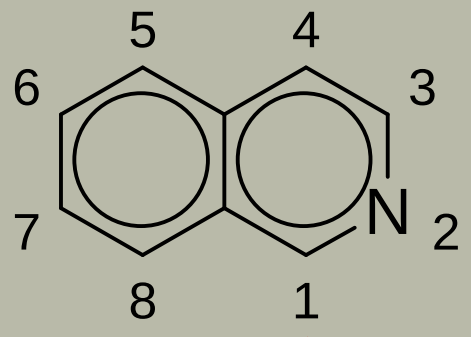


NAS

quinoline

Benzo[b]pyridine

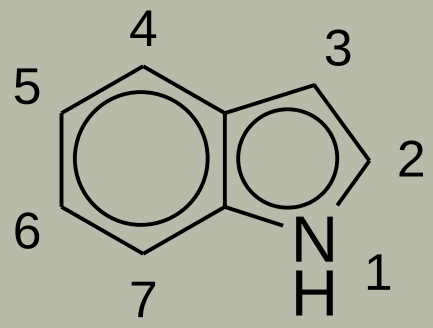
EAS



NAS

isoquinoline

Benzo[c]pyridine



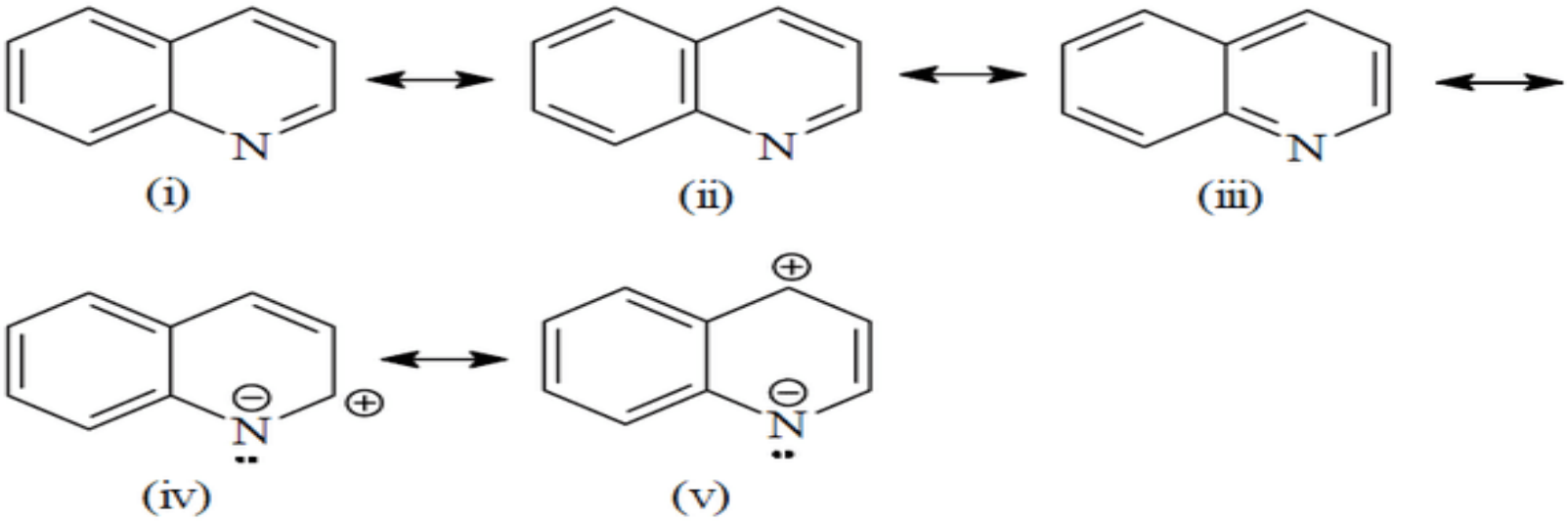
EAS

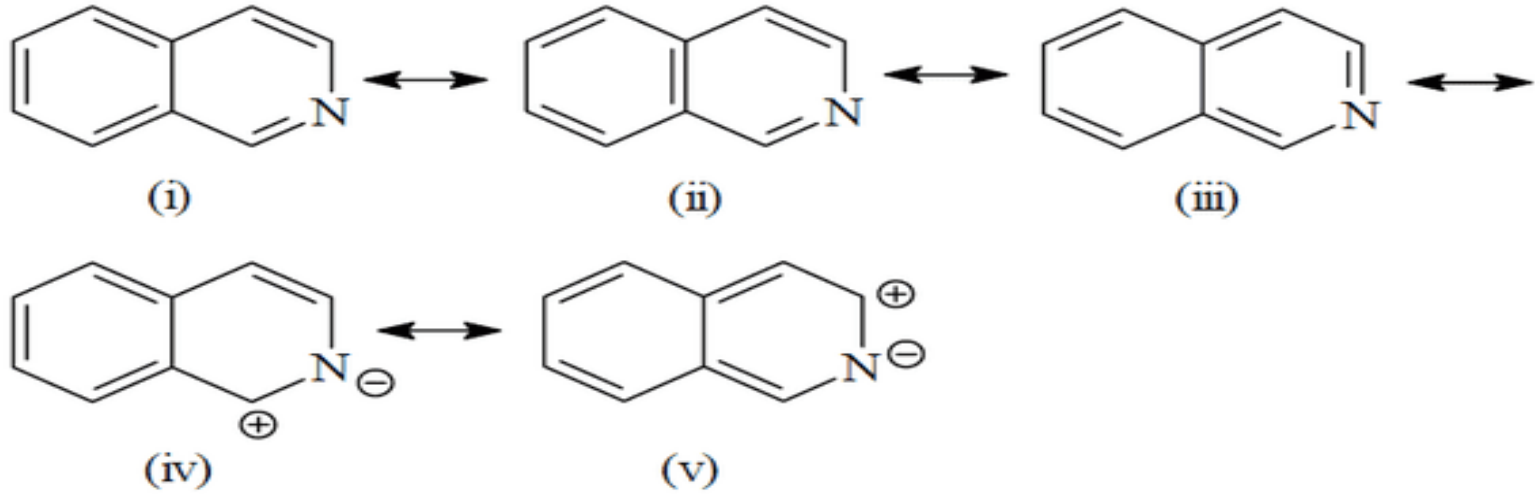
indole

Introduction :

- Quninoline and isoquinoline are two fused heterocycles derived by fusion of pyridine ring with a benzene ring.
- Quinoline is high boiling liquid (b.p. 237°C) and smells like pyridine while isoquinoline is a low melting solid (m.p. 26.5°C, b.p. 243°C).
- Both quinoline and isoquinoline are planar 10π-electron aromatic systems in which all atoms are sp^2 hybridized and contribute one electron each in orthogonal p-orbitals for delocalization over the rings with resonance energies of 198 and 143 KJ/mol respectively

Resonance structures of Quinoline and isoquinoline

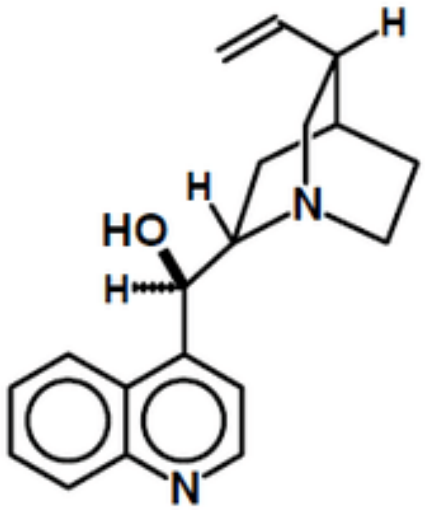




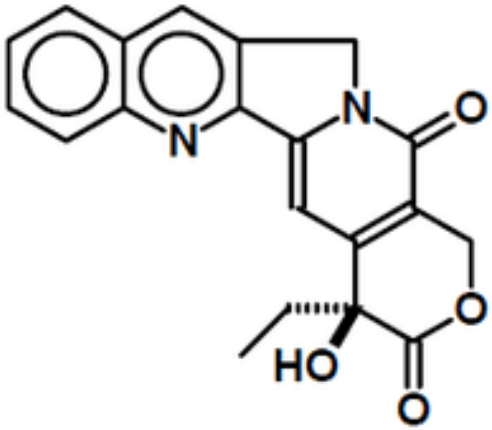
Occurrence of quinoline

- Both ring systems occur naturally and were originally isolated from coal tar.

Quinoline Alkaloids:



Quinine - Primary alkaloid of *Cinchona* bark; shows antimalarial activity



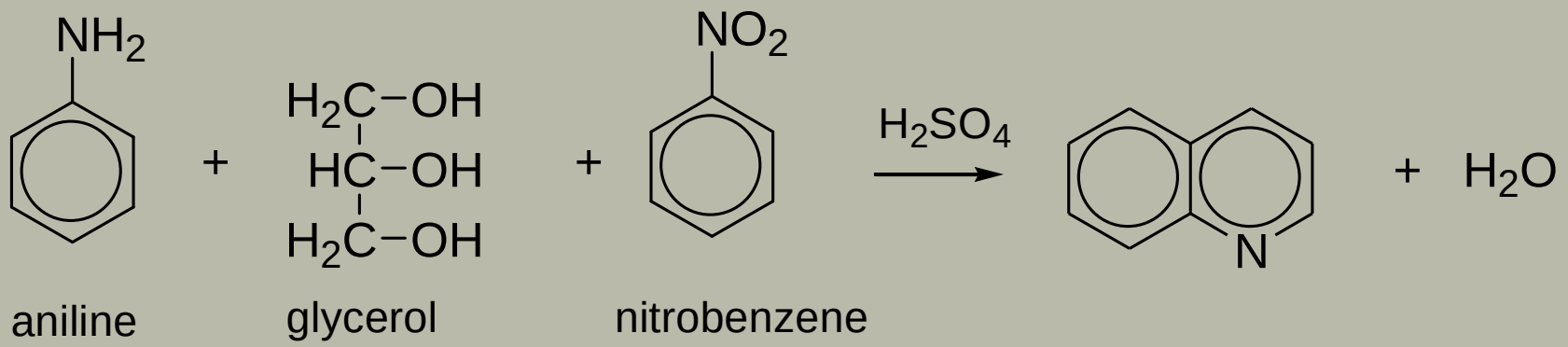
Camptothecine - from the wood of *Camptocheca acuminata*; shows antitumor activity

Basicity

- Quinoline and isoquinoline are weak bases but slightly more basic than pyridine (why?) but less basic than anilines since the nitrogen in quinoline and isoquinoline is more electronegative being sp^2 hybridized compared to sp^3 hybridized nitrogen of anilines.

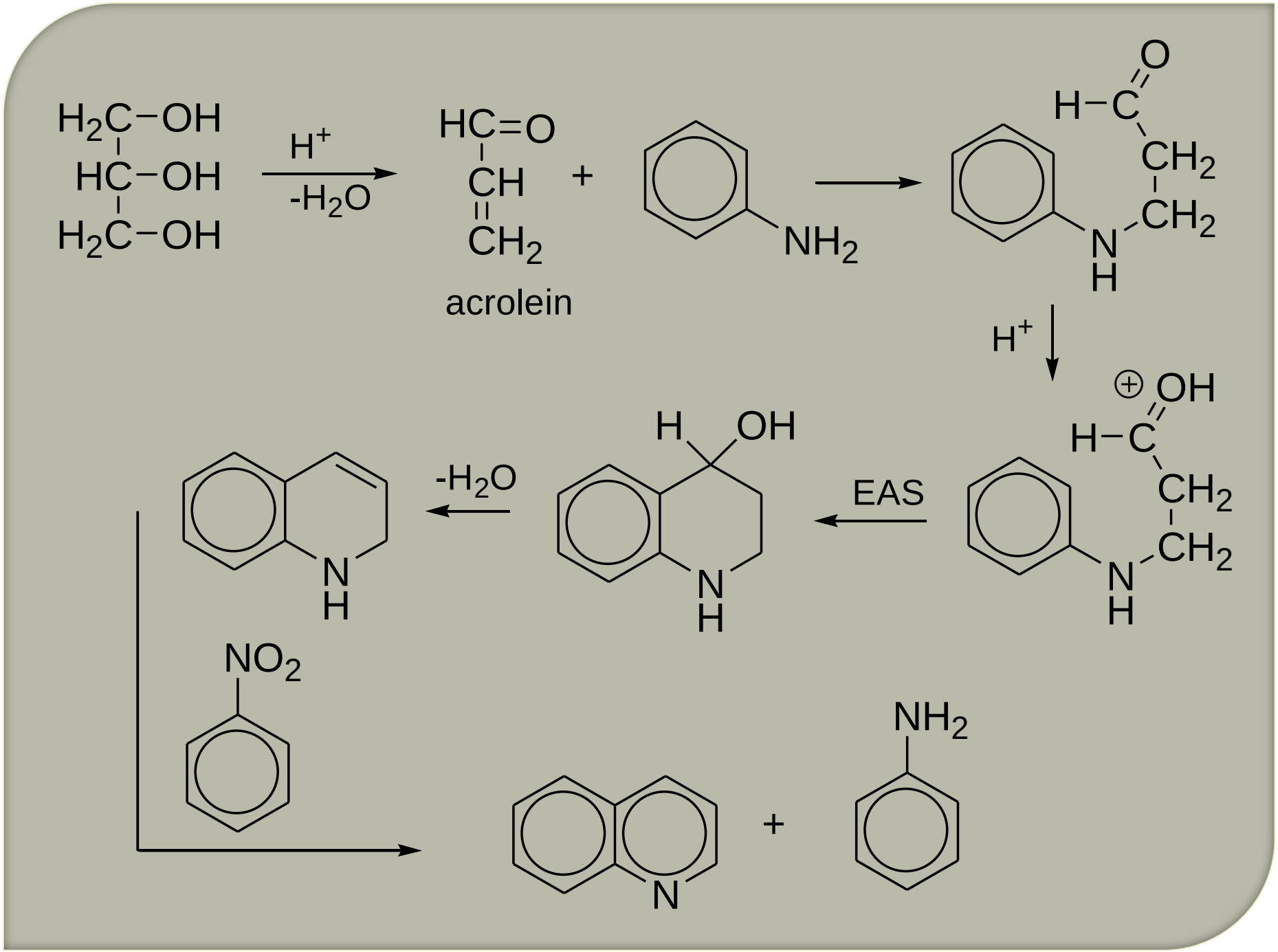
SKRAUP SYNTHESIS OF QUINOLINE

The Skraup synthesis consists of heating an aniline derivative having free ortho position with glycerol and sulphuric acid and an oxidising agent like nitrobenzene corresponding to aniline . The acid acts as a dehydrating agent and an acid catalyst.



aniline glycerol nitrobenzene

The nitrobenzene is not only the solvent, but is also one of the reactants.


H2C−OH
HC−OH
H2C−OH
H+
-H2O
HC=O
CH
CH2
acrolein
+
NH2
O
H−C
CH2
CH2
N
H
H+
⊕OH
H−C
CH2
CH2
N
H
EAS
H
OH
N
H
-H2O
N
H
NO2
NH2
+
N