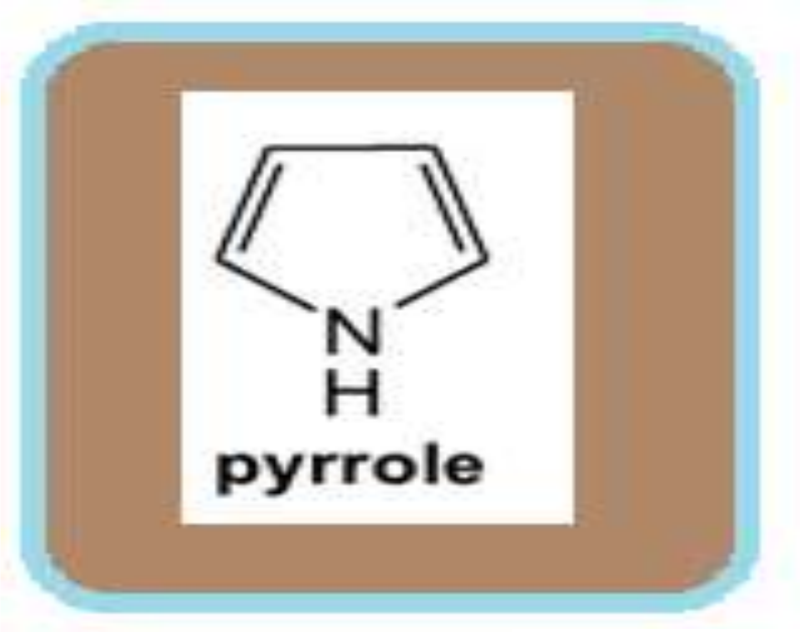
HETEROCYCLIC AROMATIC COMPOUNDS;

PYRROLE

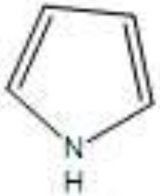


Assist.Prof.Tagreed N-A Omar

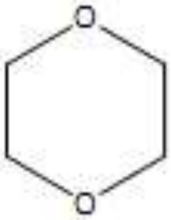
Cyclic compounds

Heterocyclic

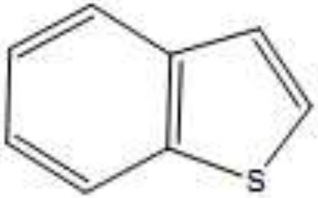
Compounds containing ring made up of carbon atoms and another kind of atoms. (most commonly N, O, S)



pyrrole



1,4-dioxane

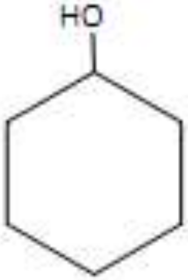


benzothiophene

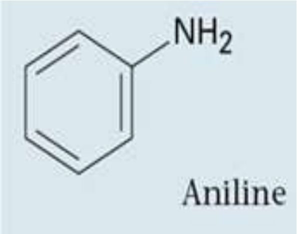
Homocyclic

Compounds containing ring made up **only** of carbon atoms

benzene



cyclohexanol

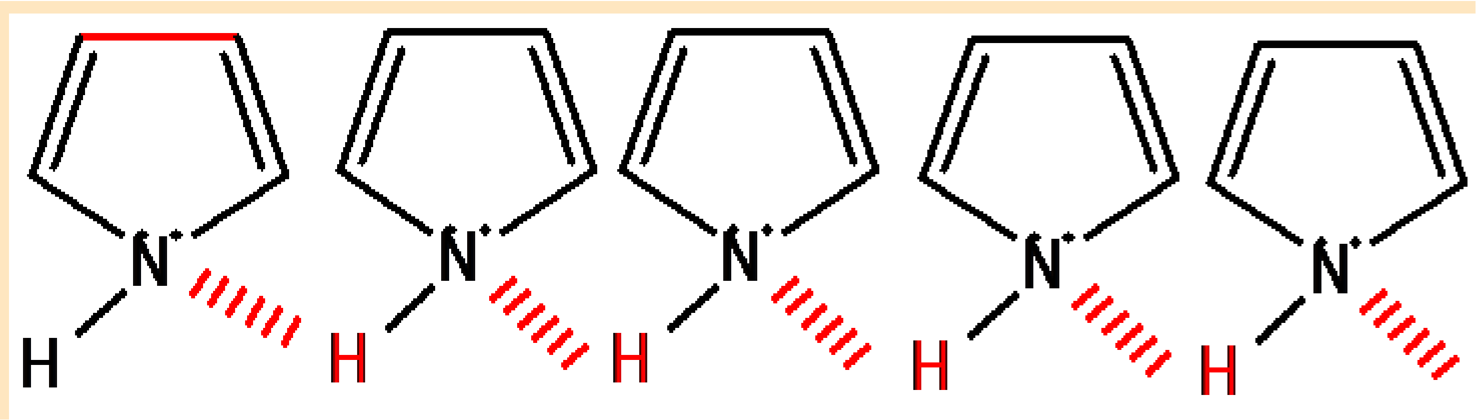


Aniline

cyclopentadiene

PYRROLE is :

- a heterocyclic aromatic organic compound,
- a five-membered ring with the formula (C4H4NH).
- It is a colourless volatile liquid that darkens readily upon exposure to air.
- Substituted derivatives are also called pyrroles.
- 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

- For a molecule to be aromatic it must:
  1. Be cyclic
  2. Have a *p*-orbital on every atom in ring
  3. Posses 4n+2 p electrons (n = any integer i.e 0,1,2....)

     Hückel's rule
  4. Be planar

Pyrrole :Aromatic; Thus, 6π electrons

Sp^2 hybridised and planar

Lone pair tied up in aromatic ring

Pyrrole is π-electron excessive

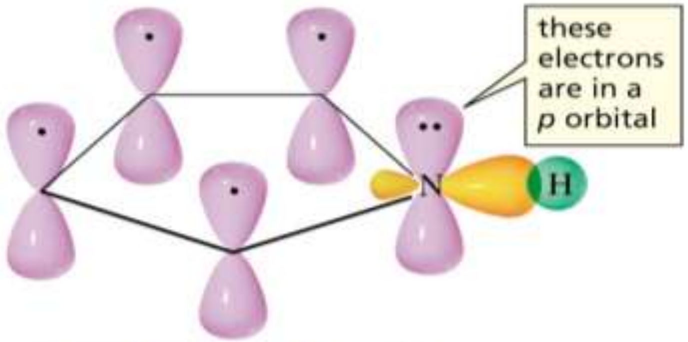
Thus, Electrophilic Aromatic Substitution is Easy

Nucleophilic Substitution is Difficult

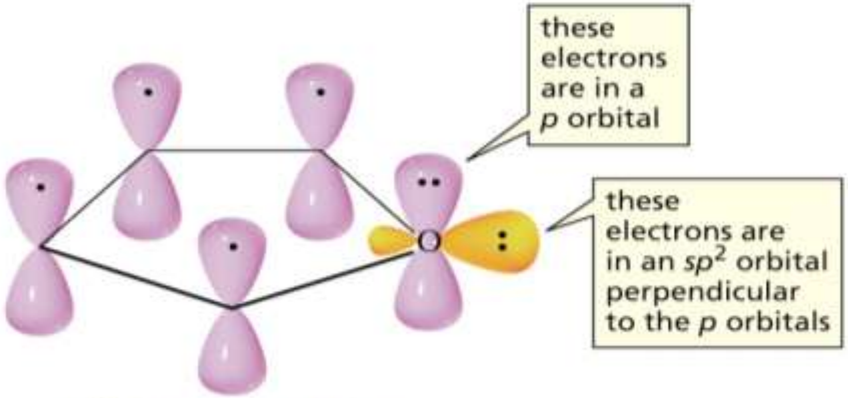
Pyrrole is an aromatic because:

it is 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).

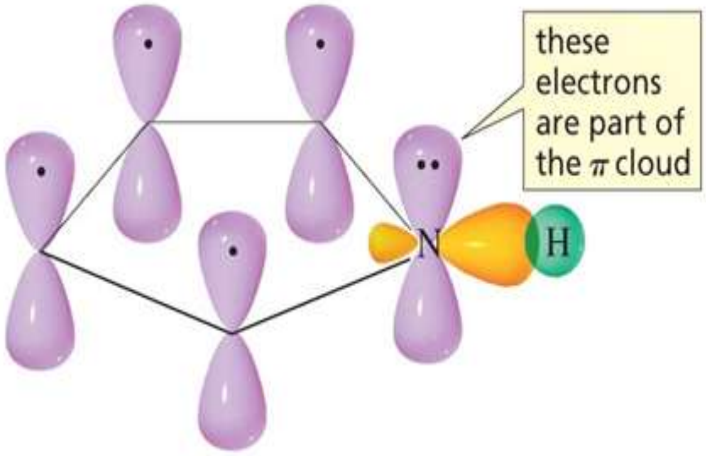


orbital structure of pyrrole



orbital structure of furan

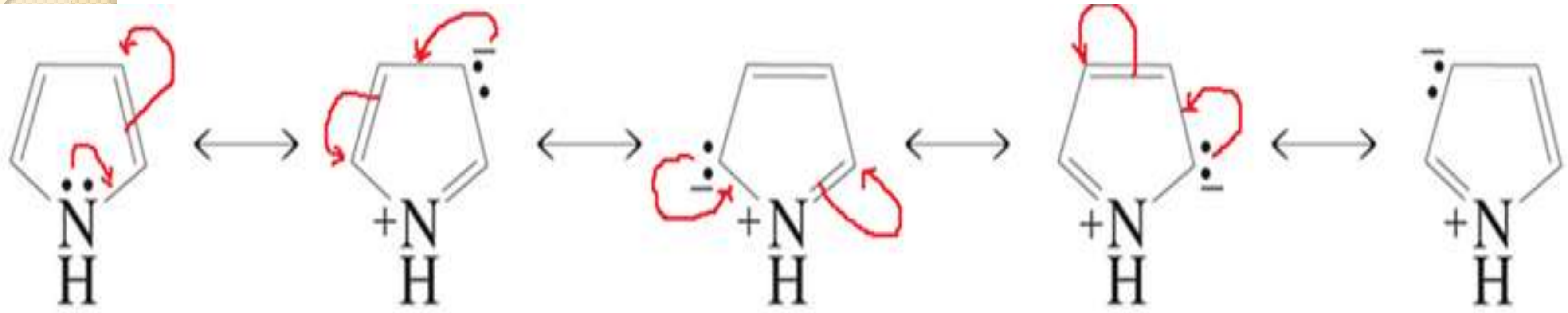
Resonance structure :



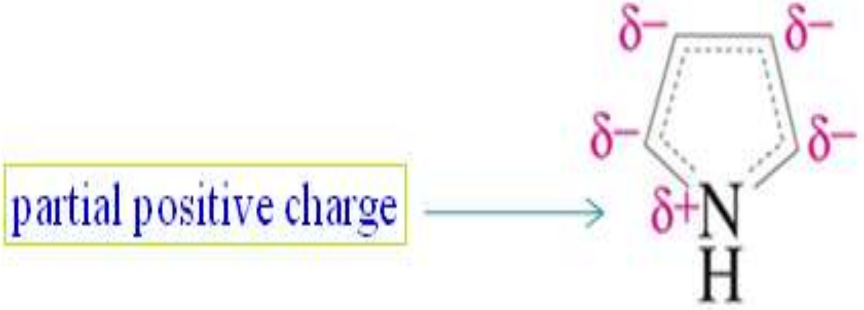
orbital structure of pyrrole

- The lone pair on nitrogen is in the p orbital so it is involved in the 6 pi-electron aromatic system.

- Hence pyrrole is not very nucleophilic and is only weakly basic at nitrogen.
- Because of the lobes are much bigger at the 2- and 5- positions, this indicates that the reactions of pyrrole are most likely to take place at these positions .



resonance contributors of pyrrole



resonance hybrid

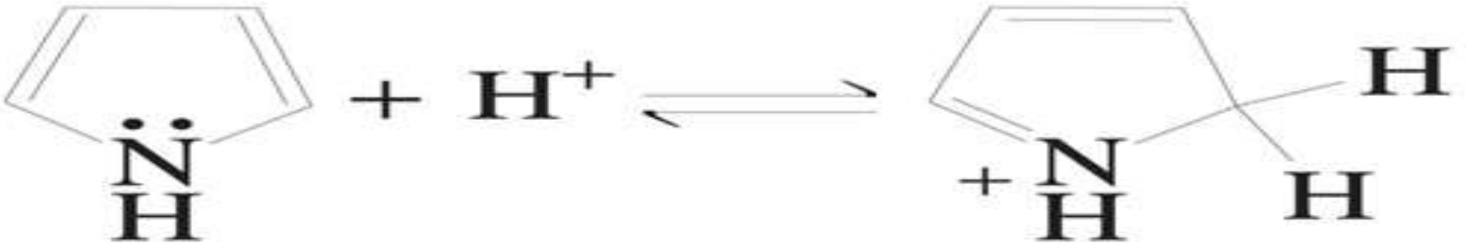
- The resonance contributors of pyrrole provide insight to the reactivity of the compound. Like furan and thiophene,
- pyrrole is more reactive than benzene towards electrophilic aromatic substitution because it is able to stabilize the positive charge of the intermediate carbocation.

The resonance hybrid of pyrrole indicates that there is a partial positive charge on the nitrogen.

Pyrrole is unstable in strongly acid solution because the protonated pyrrole polymerizes.

Pyrrole’s acidity is increased due to its conjugated base being stabilized by resonance.

The resonance hybrid of pyrrole indicates that there is a partial positive charge on the nitrogen:



$pK_a = -3.8$

Evidences of aromatic character in pyrrole

1) All ring bonds are intermediates between single &double bonds.

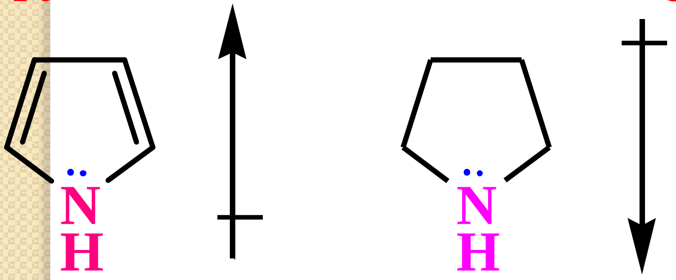
2) It tends to react by electrophilic substitution

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 thus the dipole moment of

pyrrole compared with pyrolidine is reverted and

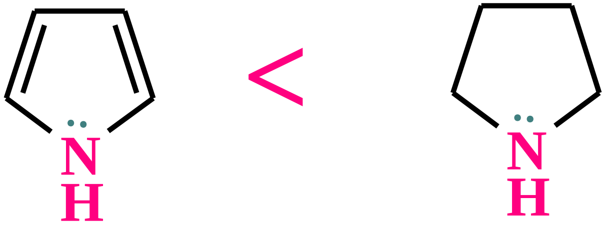
thus protonation occurs at carbons not at N

Dipole monent of pyrrole and its saturated analog



Pyrrole **Pyrrolidine**

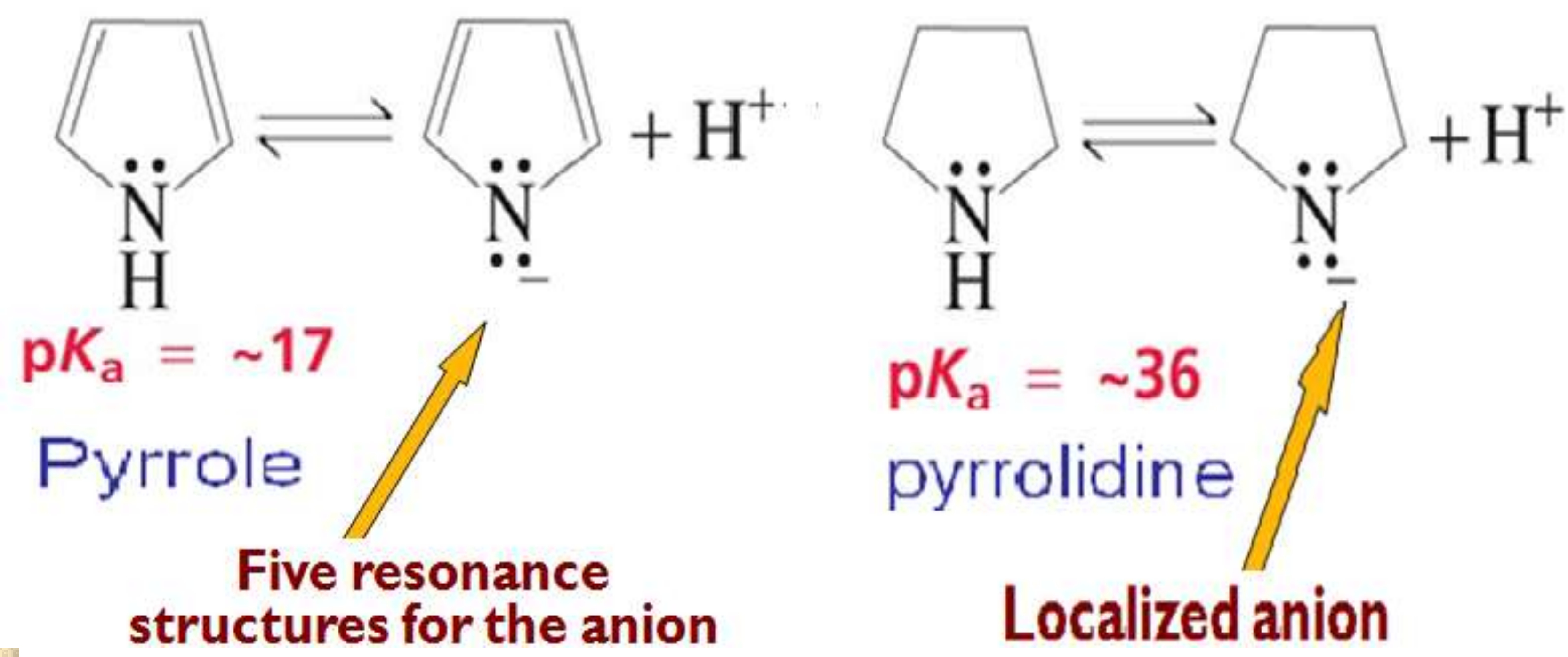
Basicity of pyrrole and its saturated analog



Pyrrole aroamtic 2° amine

Pyrrolidin Aliphatic 2° amine

Pyrrole is more acidic than pyrrolidine because of stabilization of its conjugated base by resonance

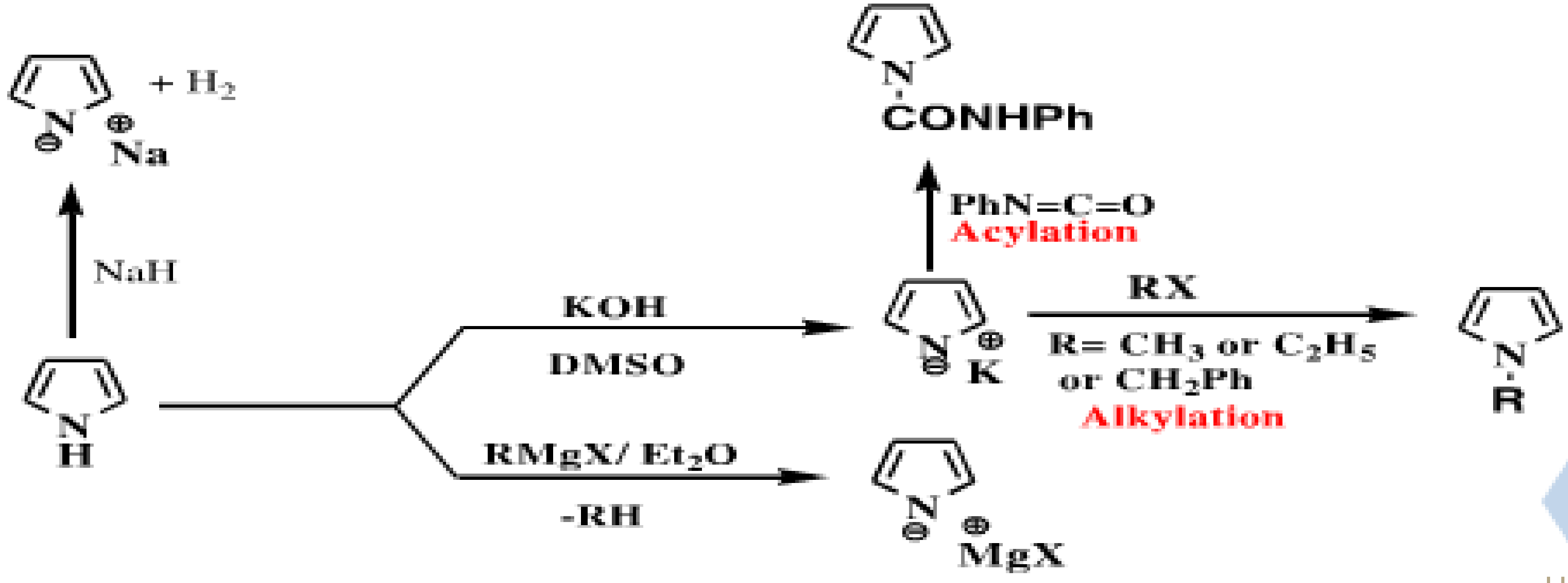


Five resonance structures for the anion

Localized anion

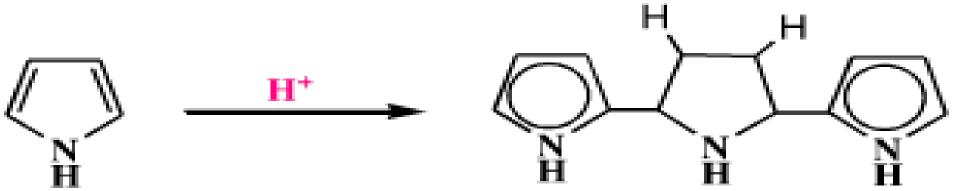
Acidic property of pyrrole:

- Due to participation of N lone pair in aromaticity),(it can loss the hydrogen attached with NITROGEN when reacting with any base) 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 can be used to alkylate or acylate the nitrogen atom as shown below:

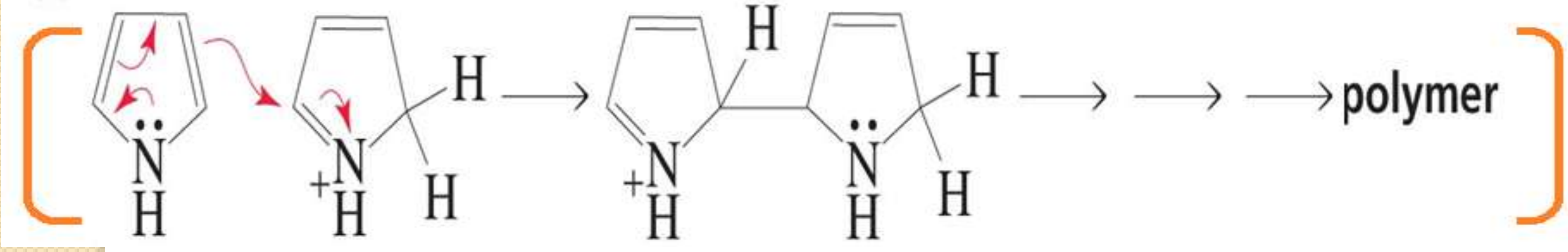


Sensitivity towards strong acids:

- Pyrrole is sensitive (unstable) towards strong acids. This is due to protonation occur at one of the carbon & the resulting protonated molecule will add to another unprotonated pyrrole molecule this continues until a pyrrole trimer is formed. (pyrrole polymerizes)
- The reaction is considered as electrophilic addition of pyrrole.



pyrrole trimer

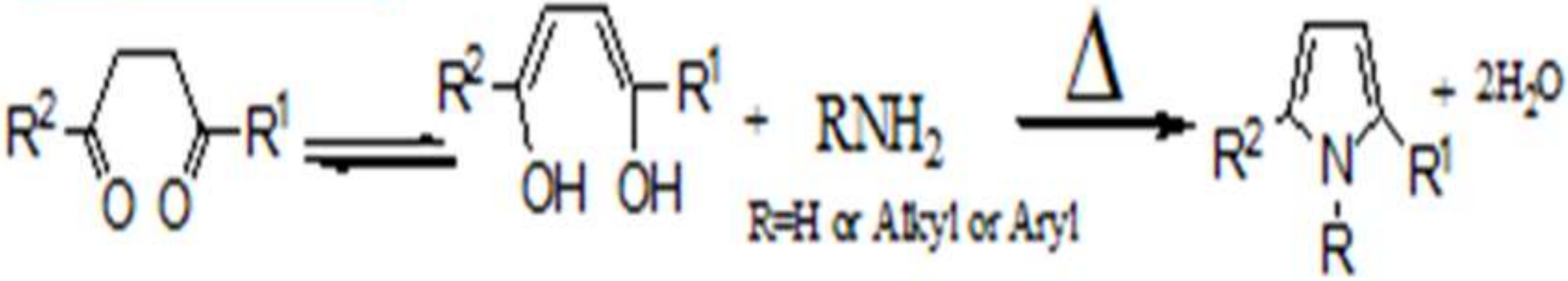


SYNTHESIS OF PYRROLE:

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

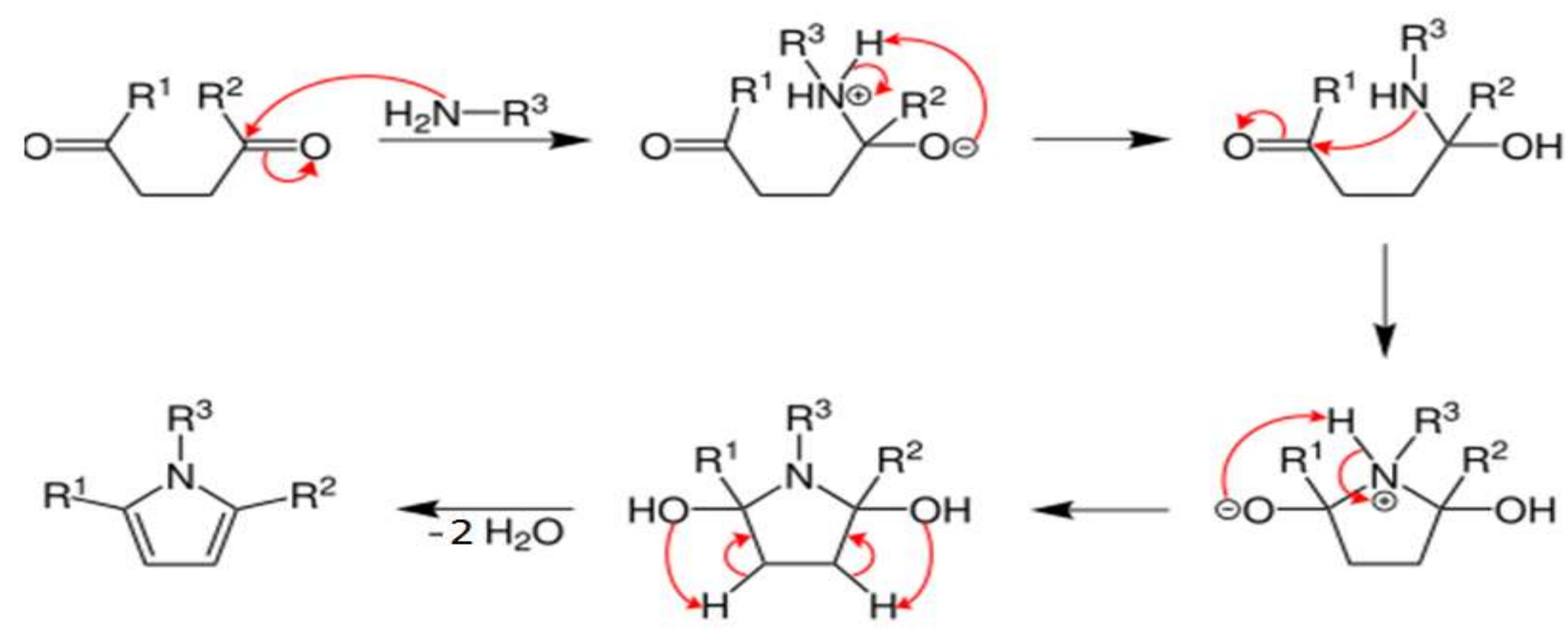
- Generally Substituted pyrrole may be synthesized through the cyclization of 1,4-diketones in combination with ammonia (NH_3) or amines, The ring-closure is proceeded by dehydration (condensation), which then yields the two double bonds and thus the aromatic π system. The formation of the energetically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

Paal-Knorr Synthesis



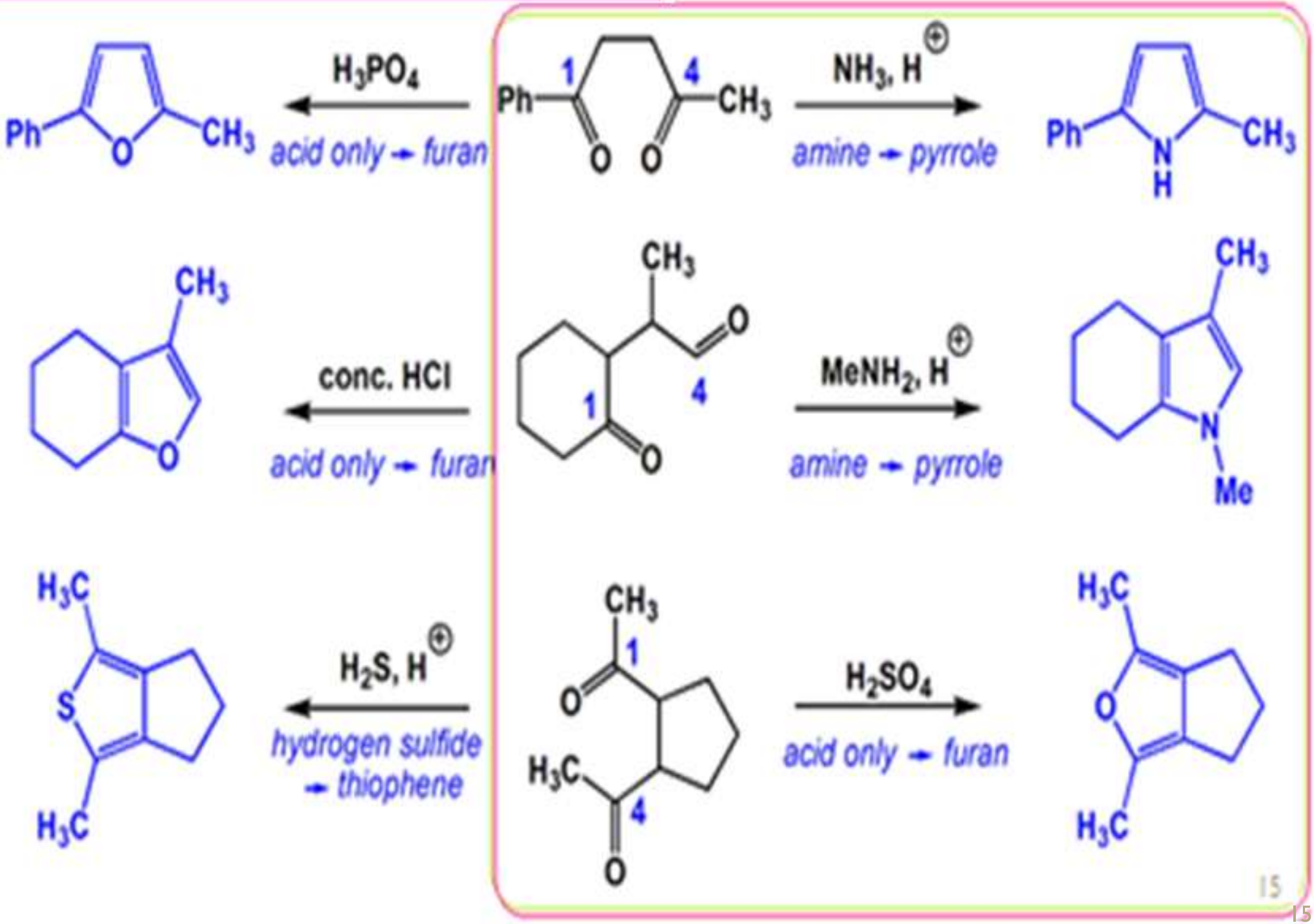
1,4-Dicarbony compound

The mechanism for the synthesis of the pyrrole suggests that: The protonated carbonyl is attacked by the amine to form the hemiaminal. The amine attacks the other carbonyl to form a 2,5-dihydroxy-tetrahydropyrrole derivative which undergoes dehydration to give the corresponding substituted pyrrole.

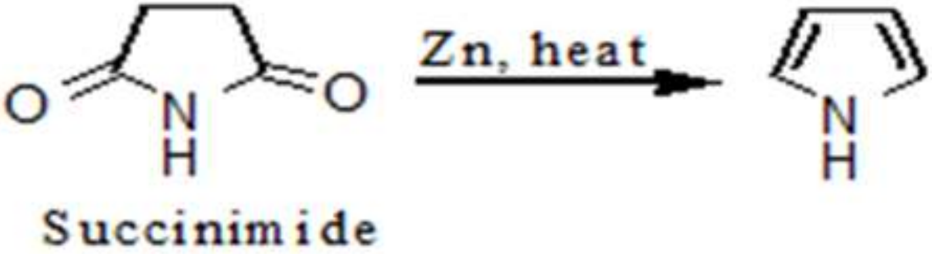


Note: by this method we can prepare different pyrrole derivatives as:1,2,5 substituted pyrrole or 2,5 substituted pyrrole or 1,2,3,4,5 substituted pyrrole

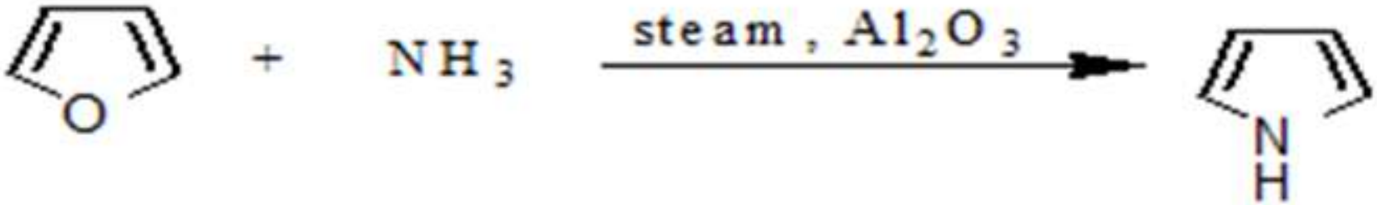
Paal-Knorr synthesis: examples



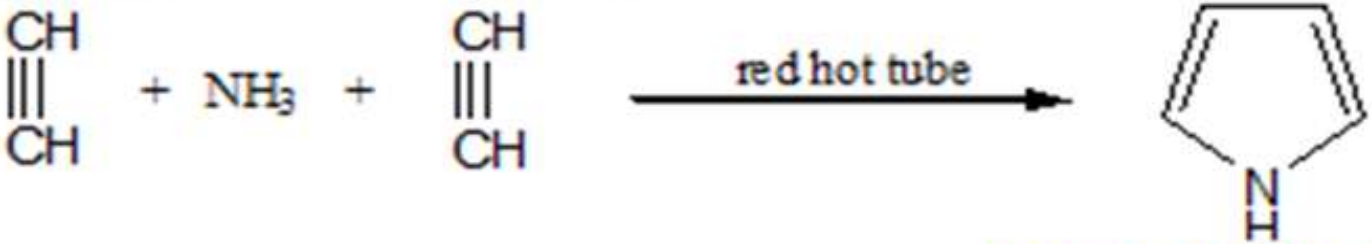
2) Pyrrole is obtained by distillation of succinimide over zinc dust.



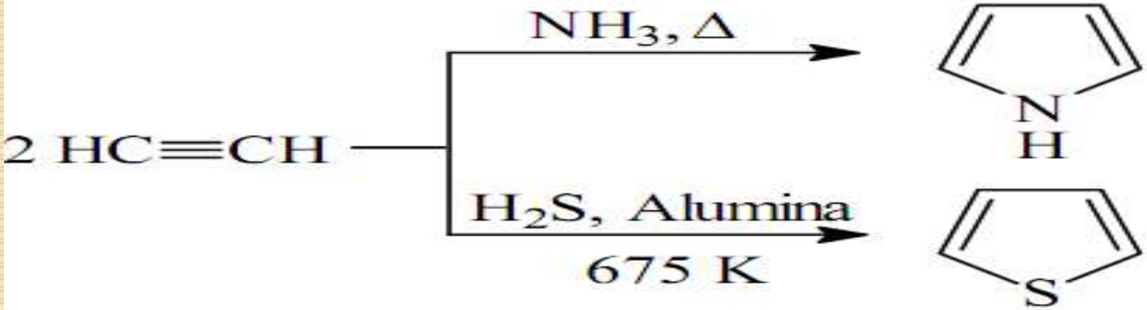
3) By heating a mixture of furan, ammonia and steam over alumina catalyst



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

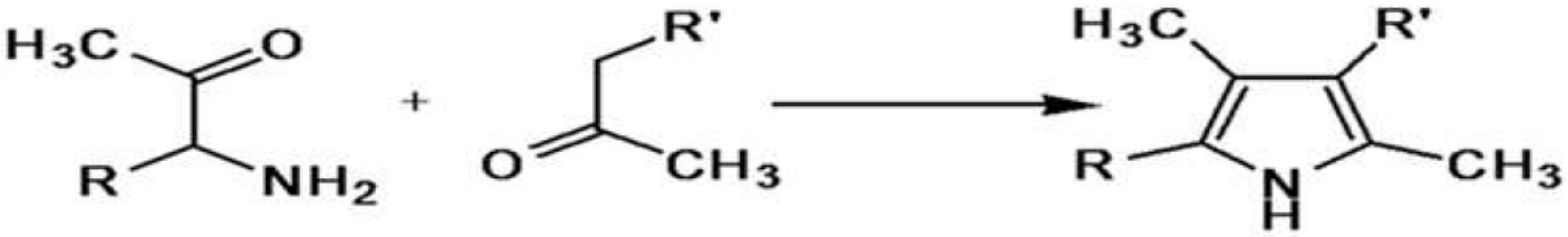


HeterocyclicChemistry



5) Knorr-pyrrole synthesis:

This involves the condensation of α-amino ketones with a β-diketone or a β-ketoester **(a compound containing a methylene group α- to a carbonyl group)** to give a substituted pyrrole.

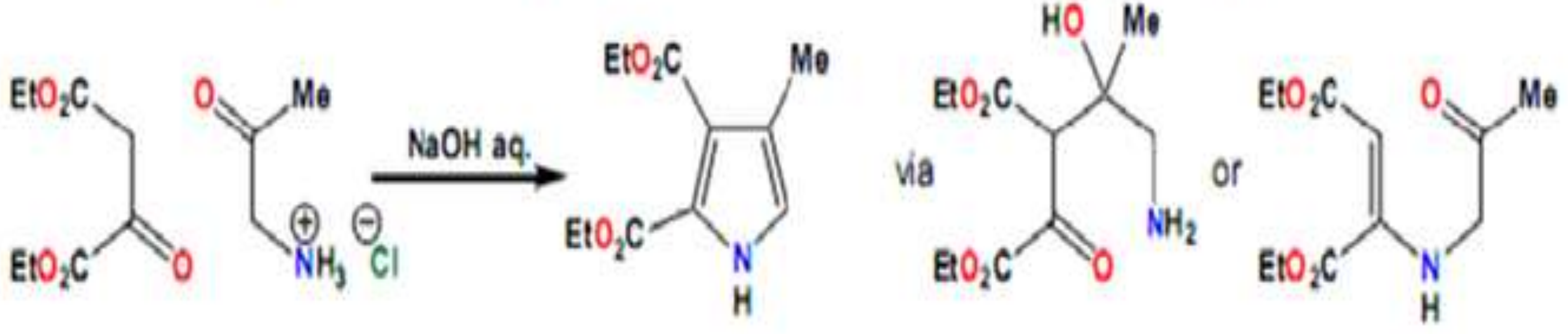


R' = -COR; β– diketone

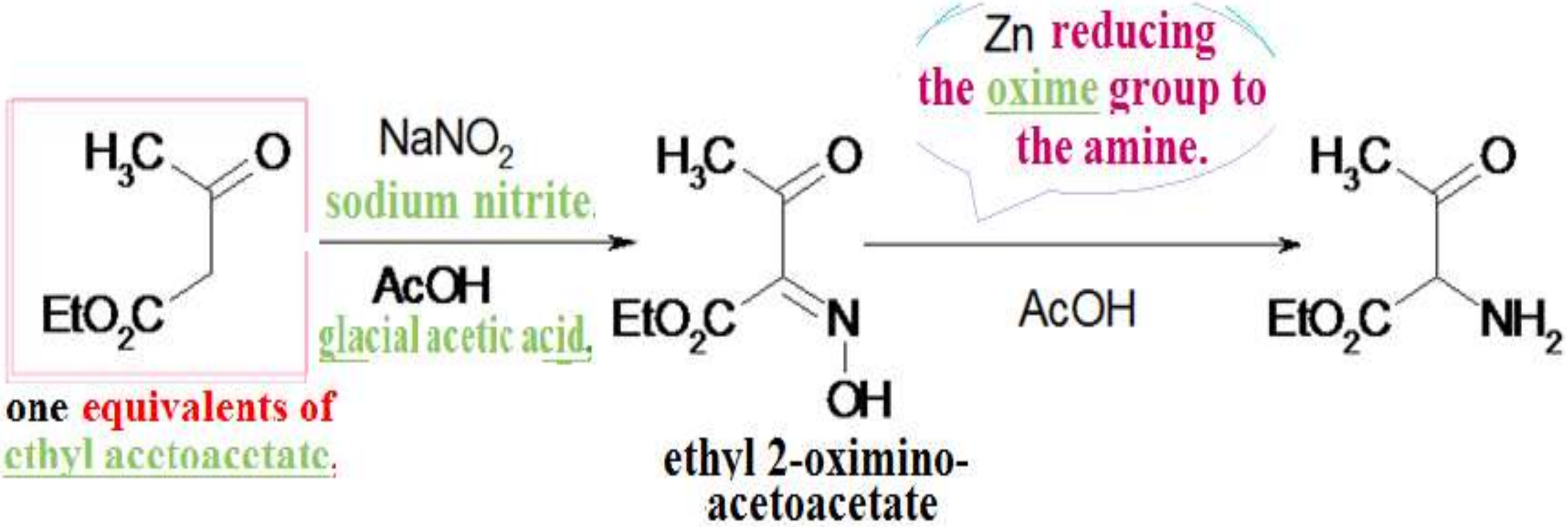
= -COOC$_2$H$_5$; β– diester

The Knorr pyrrole synthesis is a widely used chemical reaction that synthesizes substituted pyrroles

- Use of a free amino ketone is problematic ⟹ dimer formation



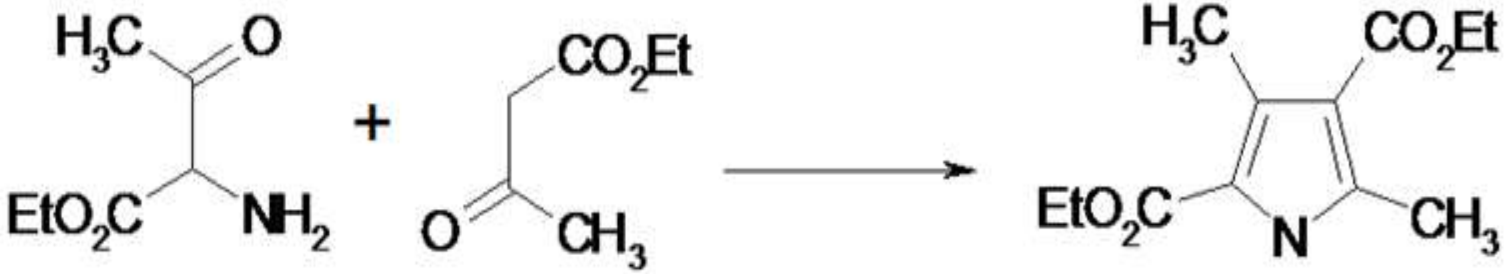
Problem can be overcome by storing amino carbonyl compound in a protected form

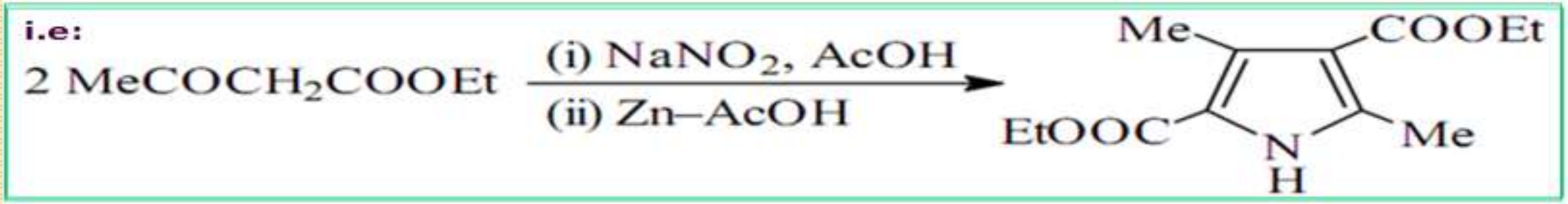


Zn reducing the oxime group to the amine.

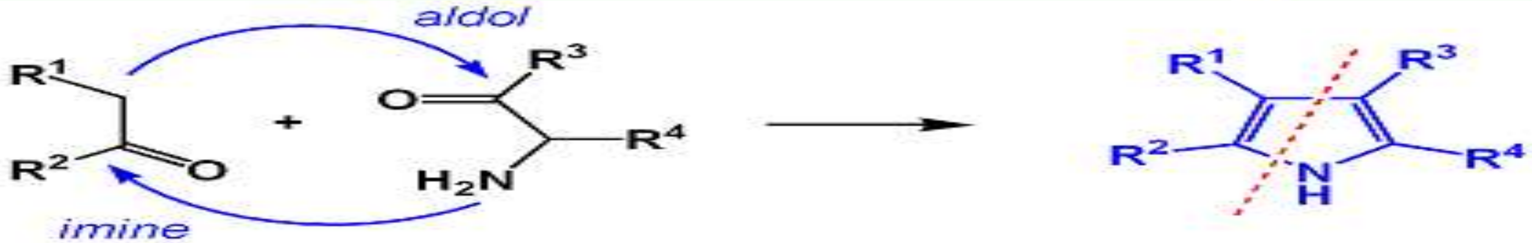
one equivalents of ethyl acetoacetate.

ethyl 2-oximino-acetoacetate



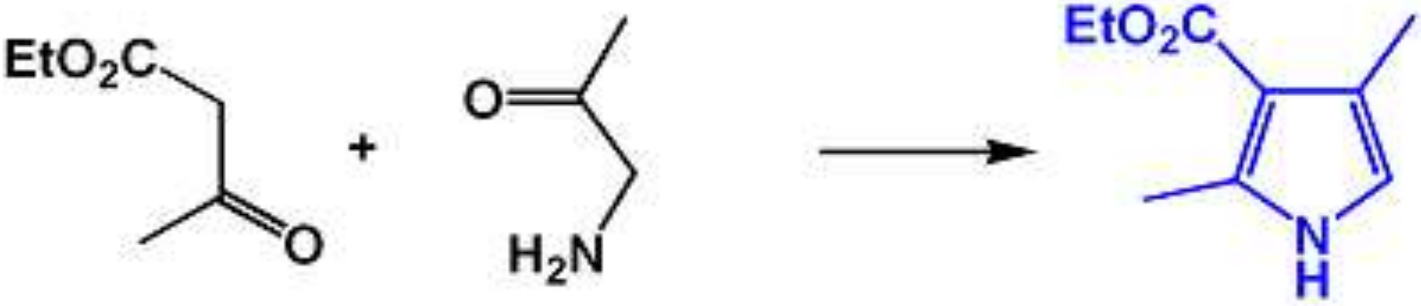

i.e:

$$2\ \mathrm{MeCOCH_2COOEt} \xrightarrow[\text{(ii) Zn–AcOH}]{\text{(i) NaNO}_2\text{, AcOH}}$$

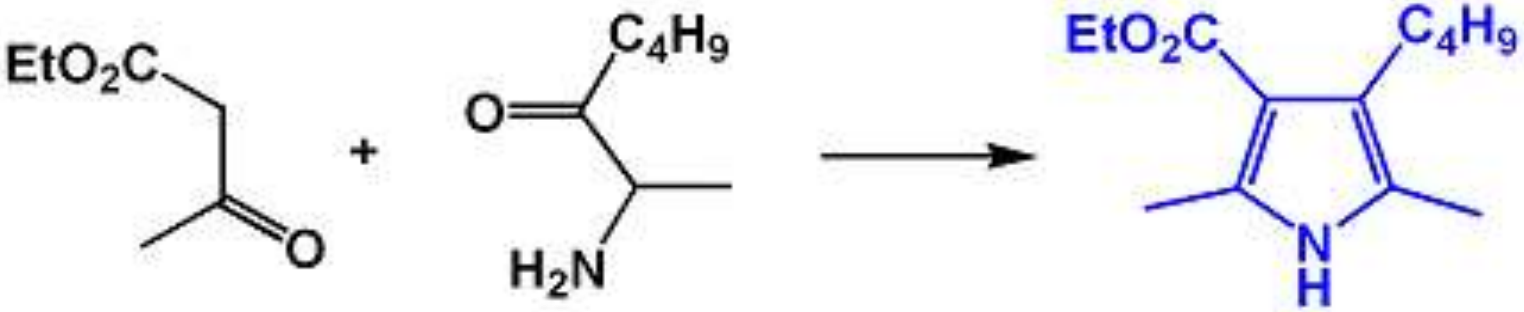


The Knorr pyrrole synthesis: examples

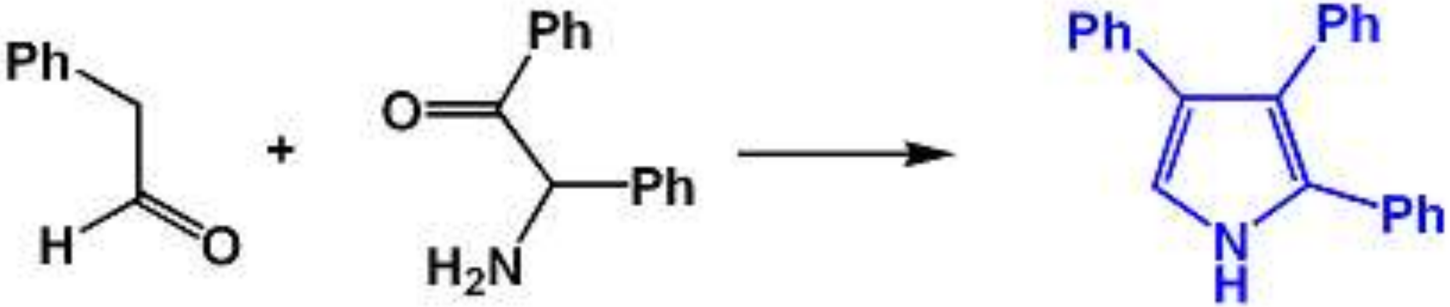
1)



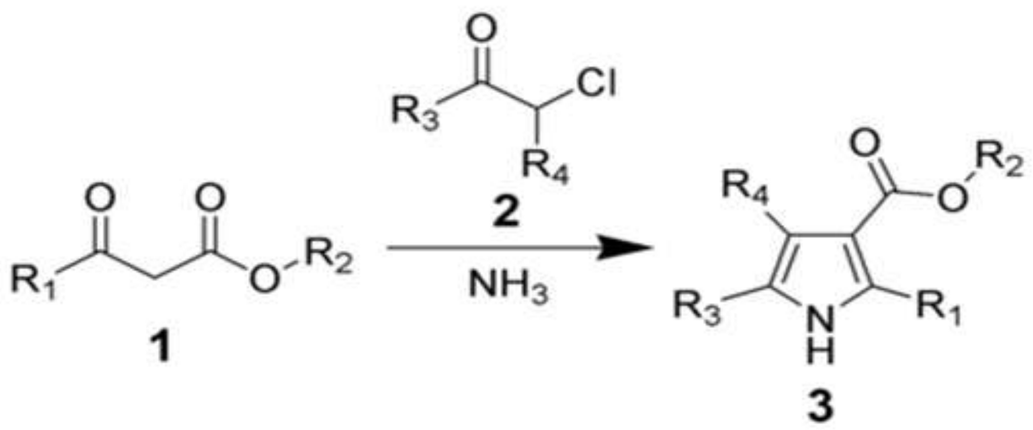
2)



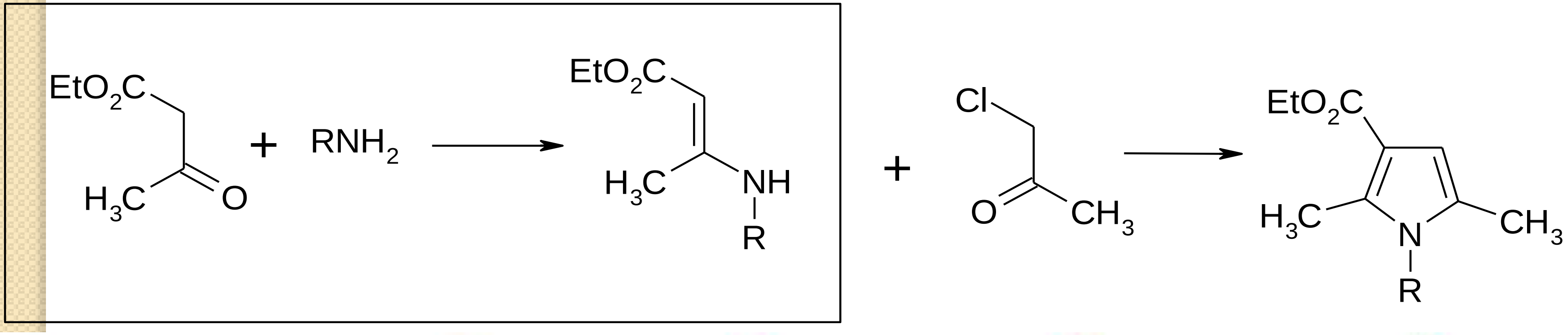
3)

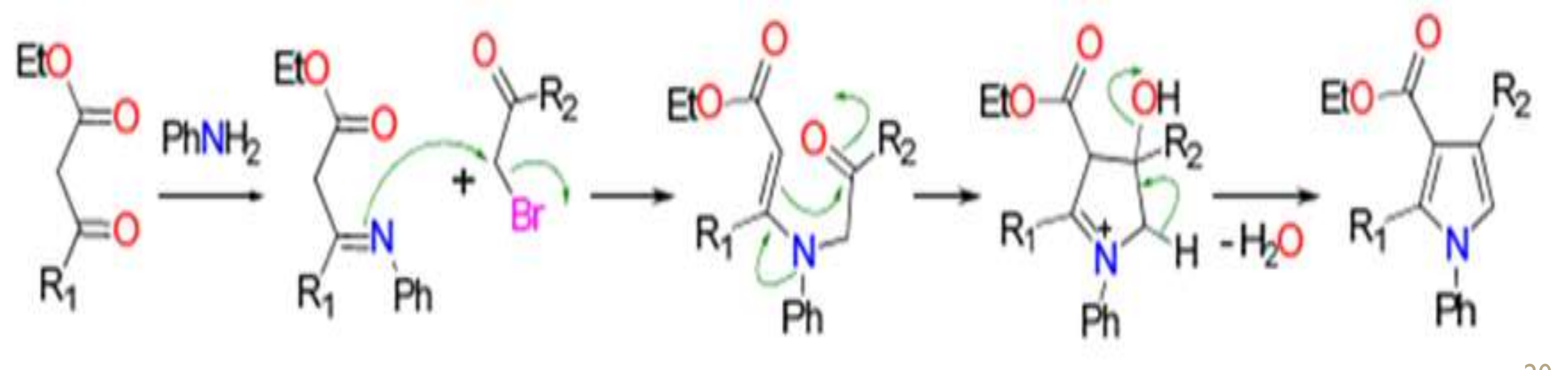


- Hantzsch pyrrole synthesis: from α-halomethyl ketones, β-keto esters and ammonia or amines

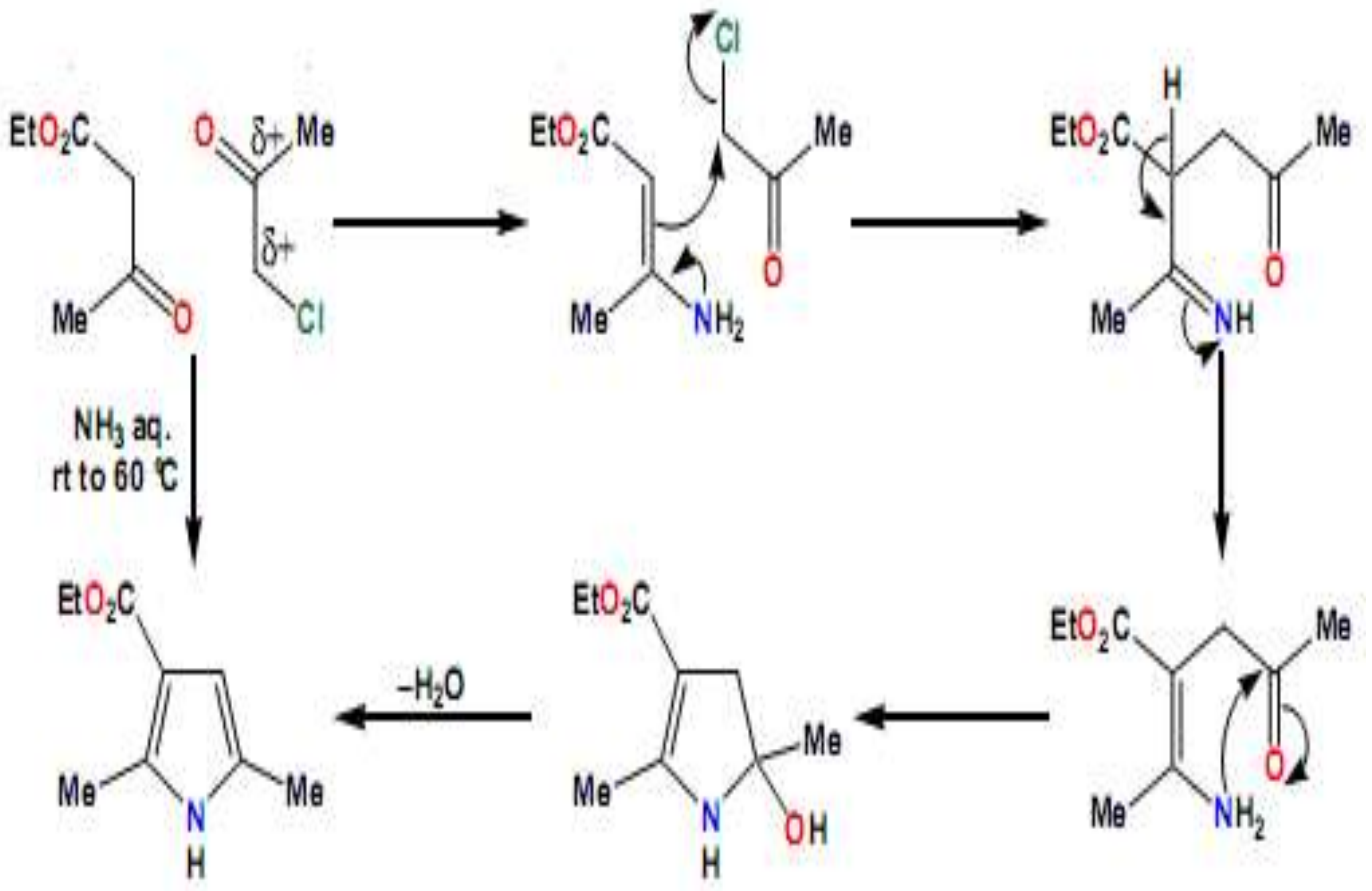


: by this method we can prepare different pyrrole derivatives as: 1,2,5 substituted pyrrole or 2,5 substituted pyrrole or 1,2,3,5 substituted pyrrole or 2,3,5 substituted pyrrole or 1,2,3,5 substituted pyrrole or 1,2,3,4,5 substituted pyrrole

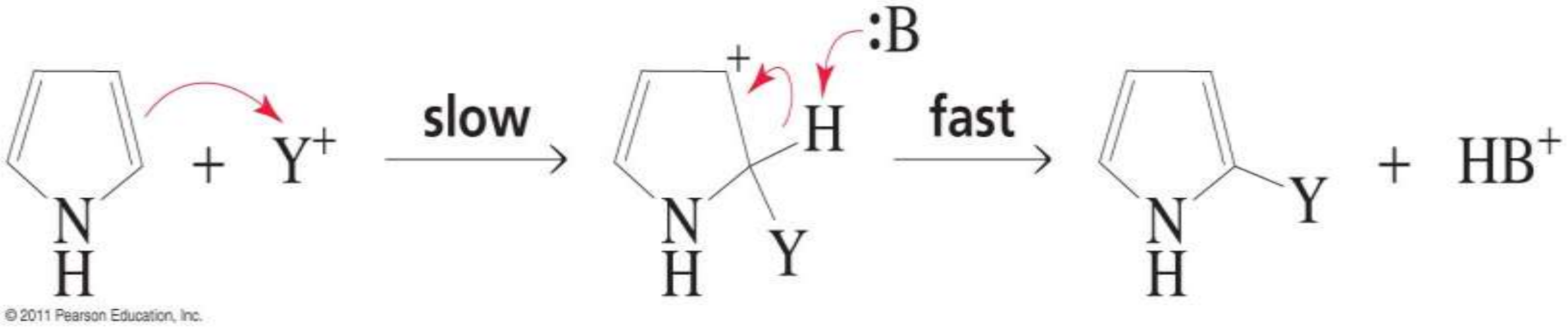




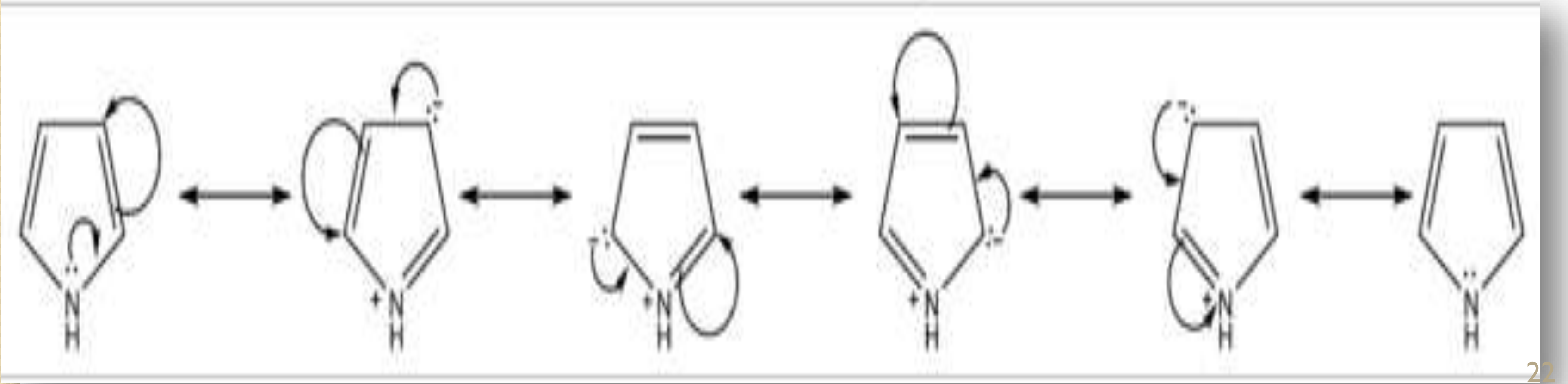
Another one :



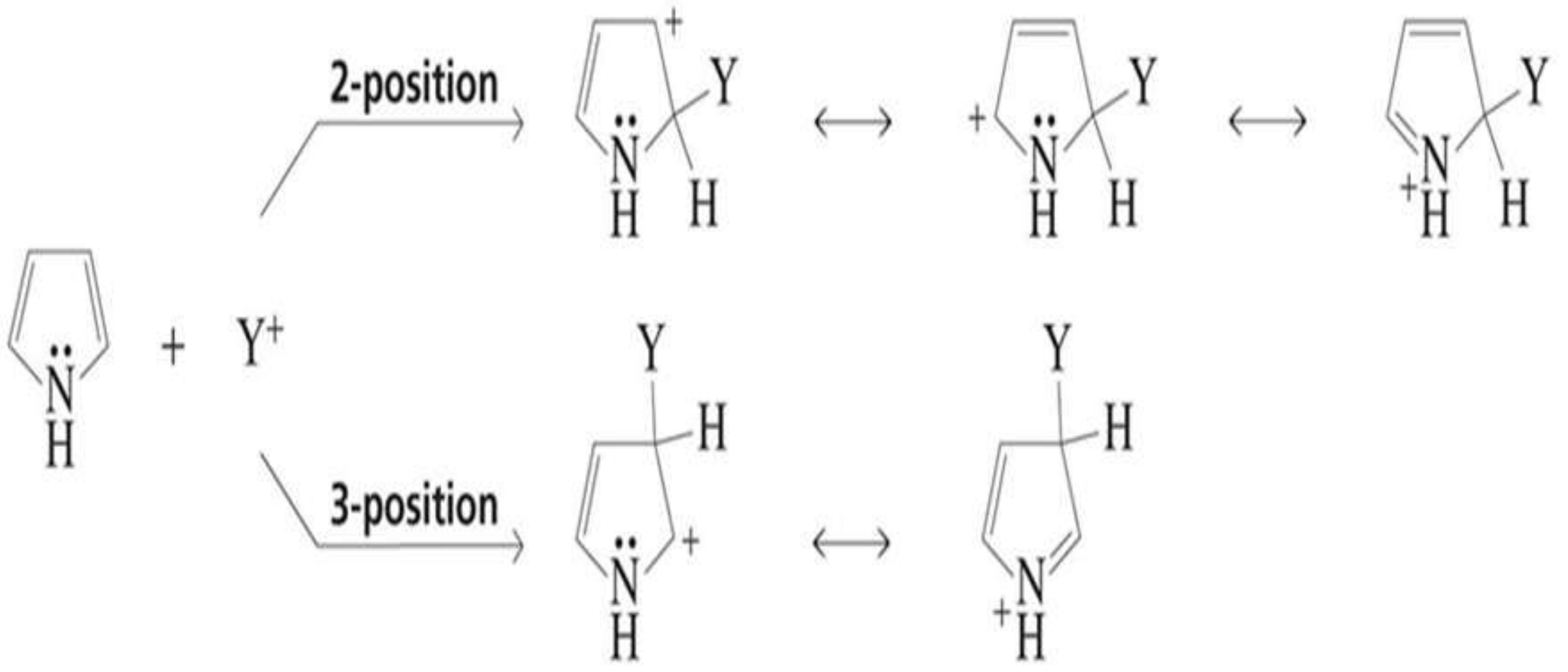
ELECTROPHILIC SUBSITUTION IN PYRROLE:



- Pyrrole is reactive towards electrophilic substitution reaction.
- It is more reactive than benzene because of the resonances that pushes away the electron density from nitrogen towards carbons ,thus making the ring electron rich.
- The substitution is easier and mild reagents can be used.

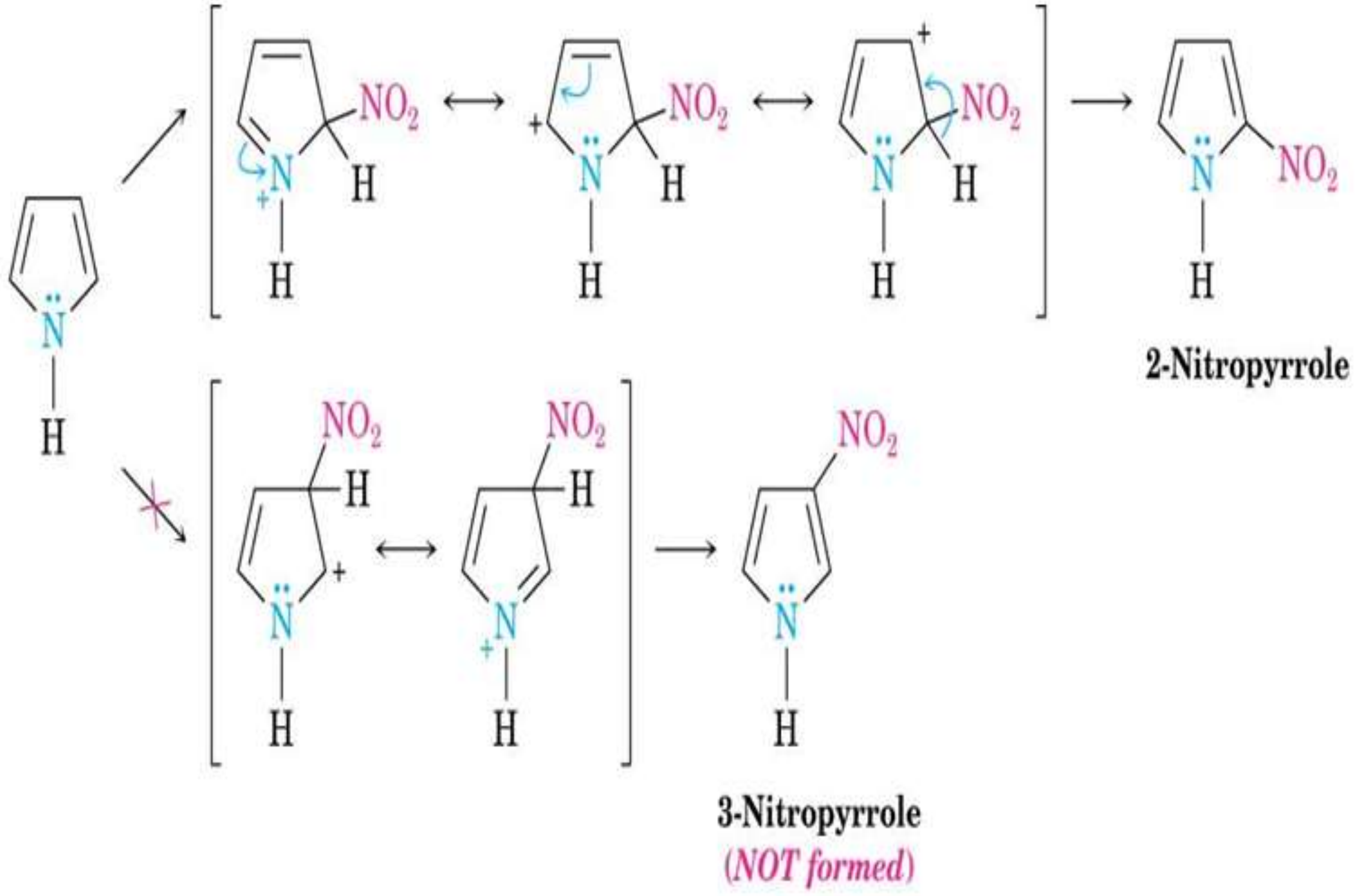


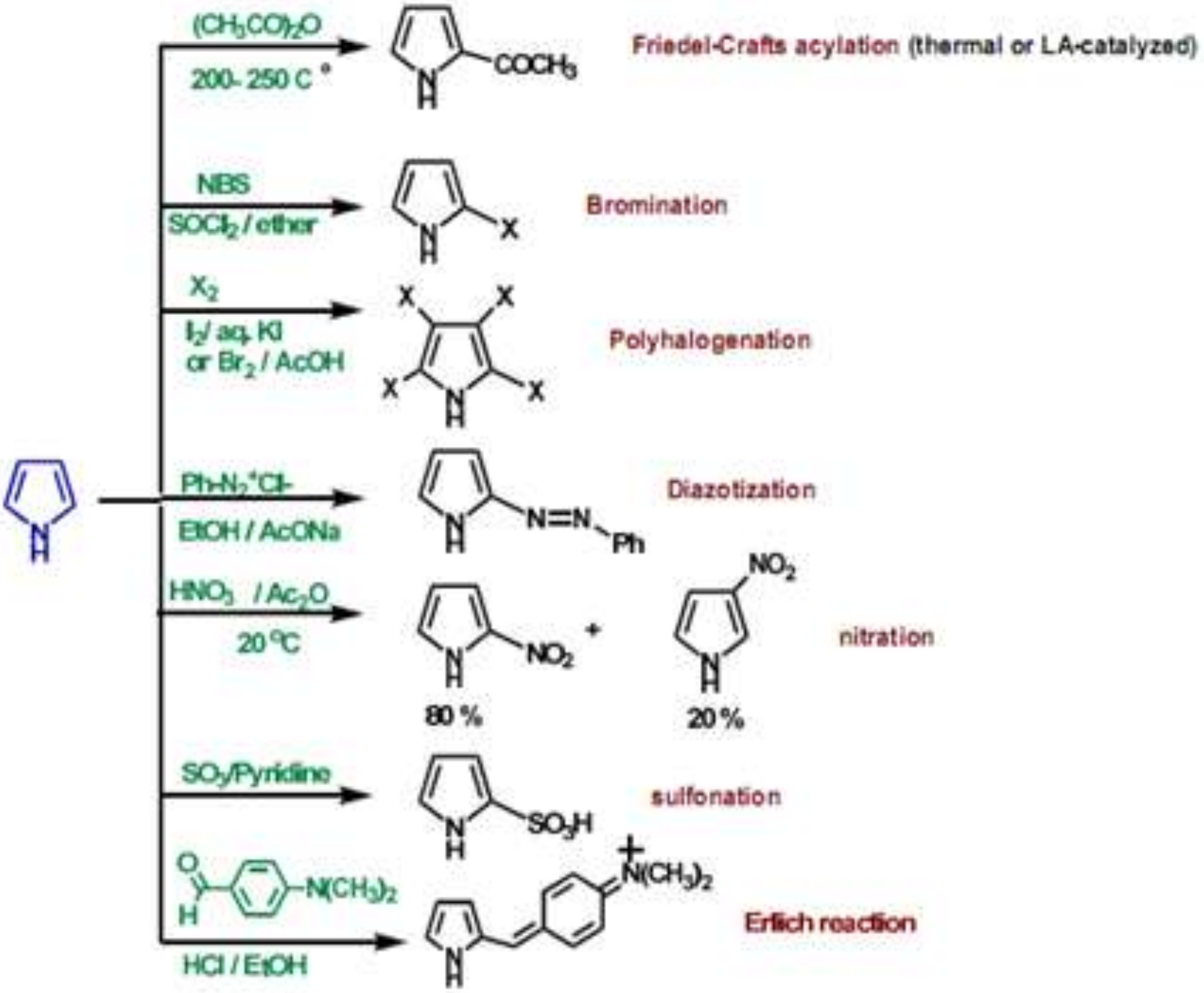
- Electrophilic aromatic substitution normally occurs at carbon atoms instead of at the nitrogen.
- Also it occurs preferentially at C-2 (the position next to the heteroatom) rather than at C-3 (if position 2- is occupied it occurs at position 3).
- This is because attack at C-2 gives a more stable intermediate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



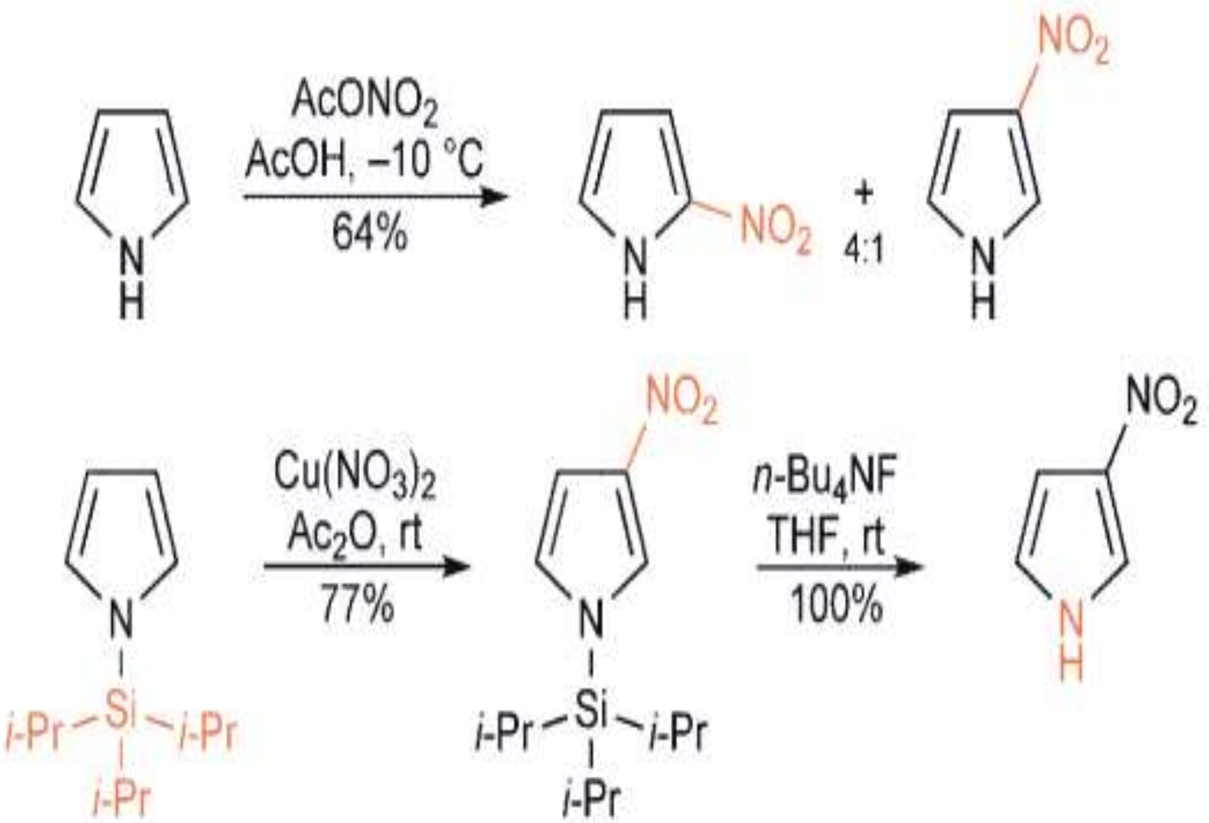
Resonance Stabilization of 2-Substitution Intermediate is greater than that of the 3-Substitution Intermediate

- Electrophilic substitution normally occurs at C2, the position next to the heteroatom, giving more stable intermediate




(CH3CO)2O
200-250 C°
COCH3
Friedel-Crafts acylation (thermal or LA-catalyzed)
NBS
SOCl2 / ether
X
Bromination
X2
I2/ aq. KI
or Br2 / AcOH
X
X
X
X
Polyhalogenation
Ph-N2+Cl-
EtOH / AcONa
N=N
Ph
Diazotization
HNO3 / Ac2O
20 °C
NO2
+
NO2
nitration
80 %
20 %
SO3/Pyridine
SO3H
sulfonation
O
H
N(CH3)2
HCl / EtOH
+
N(CH3)2
Erlich reaction
N
H

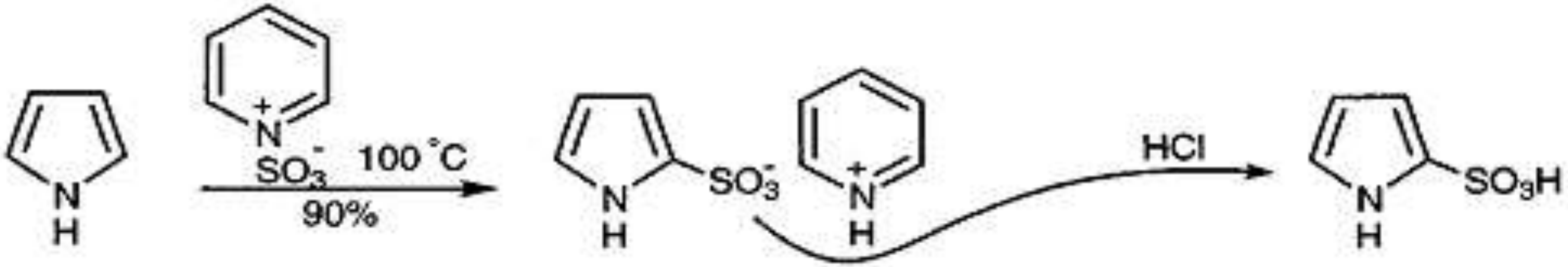
About nitration reaction:



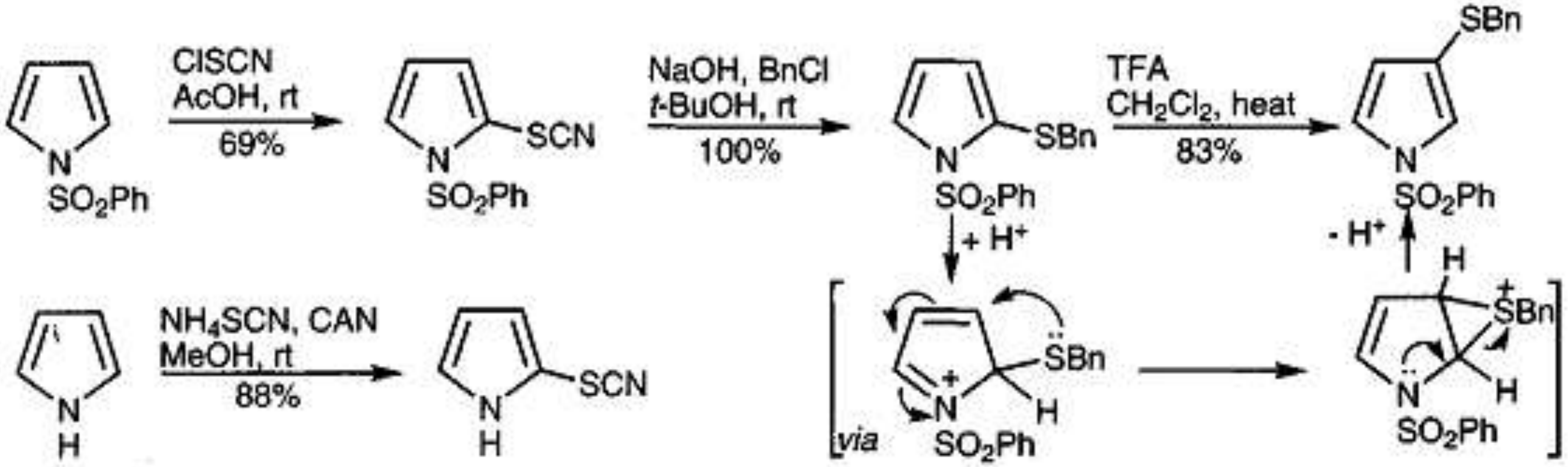
N-Substitution of pyrroles gives rise to increased proportions of β-nitration, even an *N*-methyl producing a β:α ratio of 1:3, and the much larger *t*-butyl actually reverses the relative positional reactivities, with a β:α ratio of 4:1.The intrinsic α-reactivity can be effectively completely blocked with a very large substituent such as a triisopropylsilyl(TIPS) group, especially useful since it can be subsequently easily removed.

Sulfonation and reactions with other sulfur electrophiles

For sulfonation, a mild reagent of low acidity must be used: the pyridine-sulfur trioxide compound smoothly converts pyrrole into the 2-sulfonate.



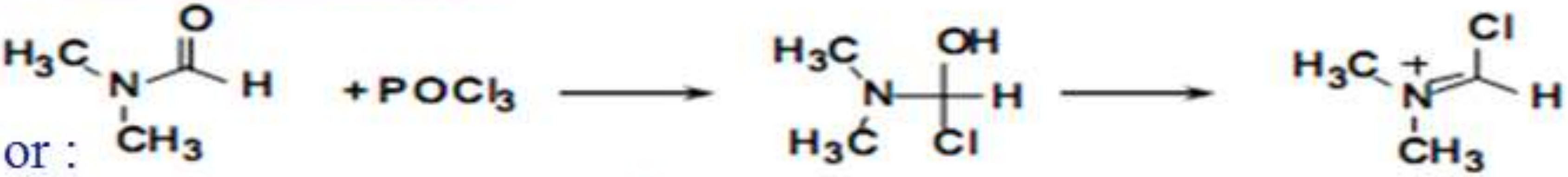
Sulfinylation of pyrrole and thiocyanation of pyrrole or of 1-phenylsulfonylpyrrole also provide means for the electrophilic introduction of sulfur, but at lower oxidation levels.



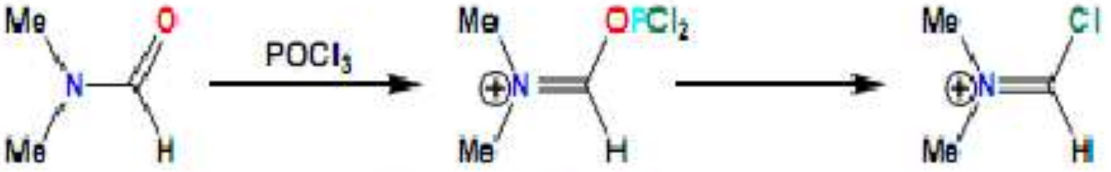
Acid catalyses rearrangement of sulfur substituents from the α-position (kinetically-controlled substitution) to give β-substituted pyrroles

Formylation: Vilsmeier-Haack:

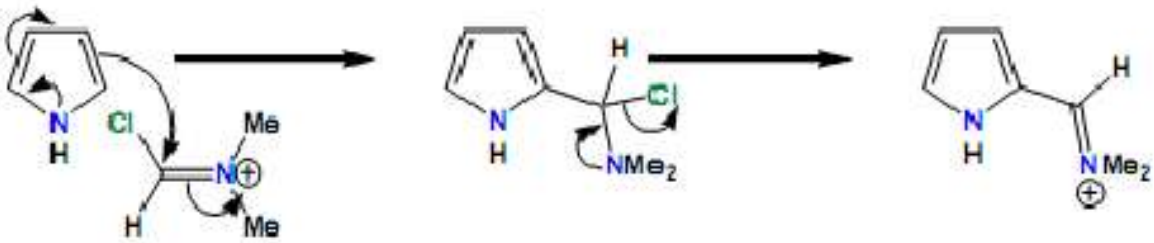
1.- Formation of electrophile



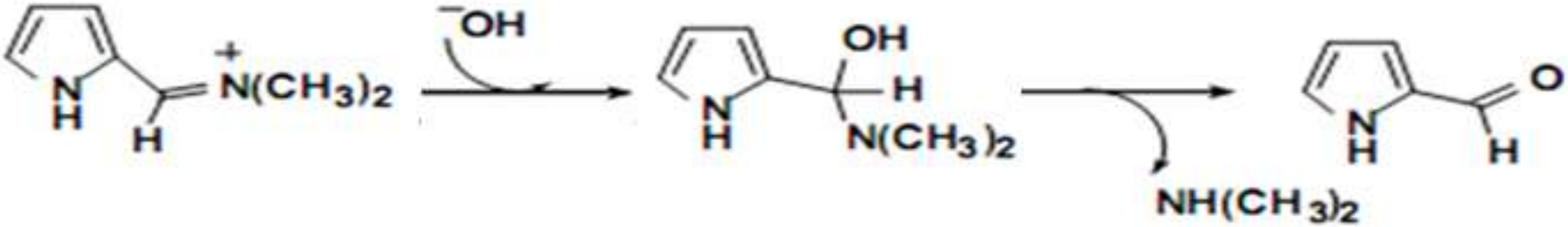
or :



2.- Electrophilic aromatic substitution

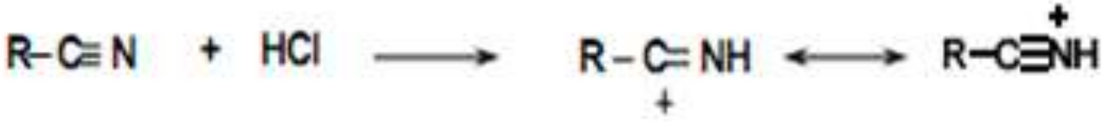


3.- Hydrolysis of iminium salt

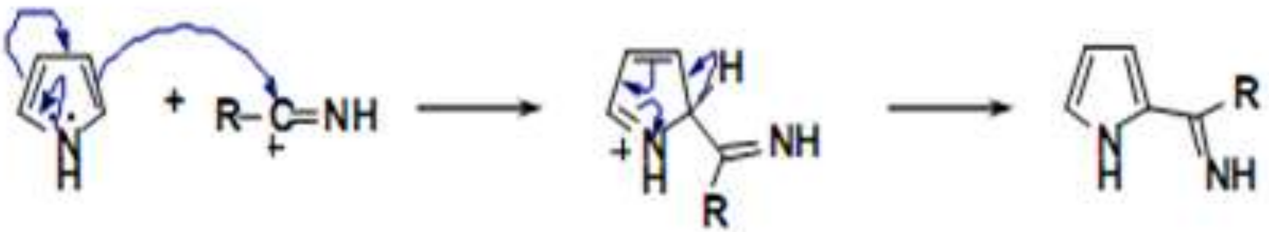


Acylation: Houben-Hoesch:

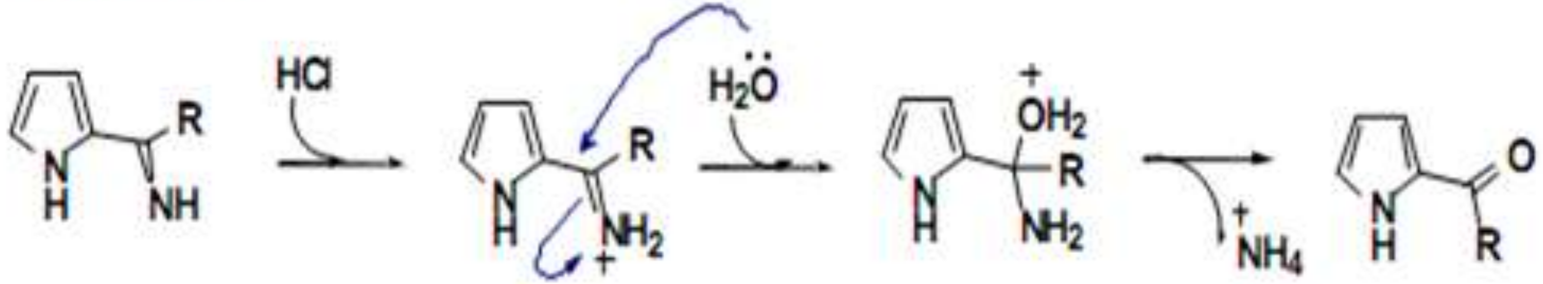
1.- Formation of electrophile


$$R-C\equiv N + HCl \longrightarrow R-\underset{+}{C}=NH \longleftrightarrow R-C\equiv\overset{+}{N}H$$

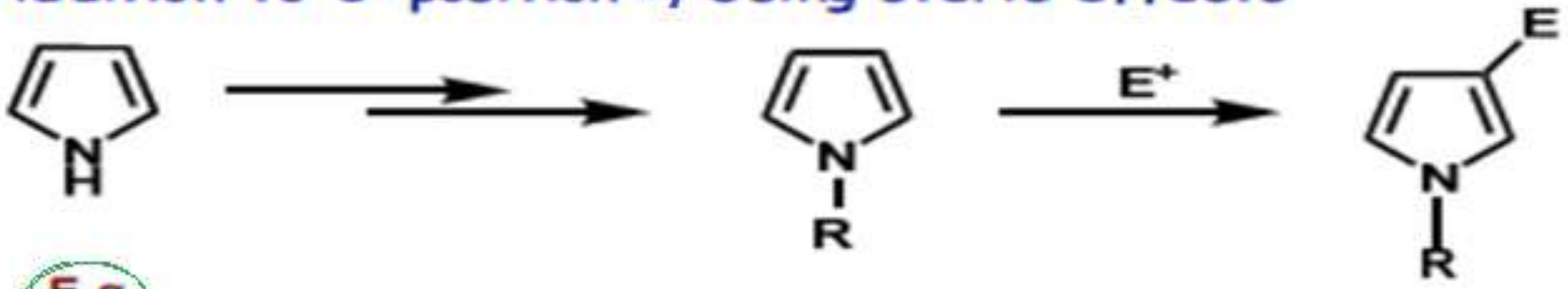
2.- Electrophilic aromatic substitution



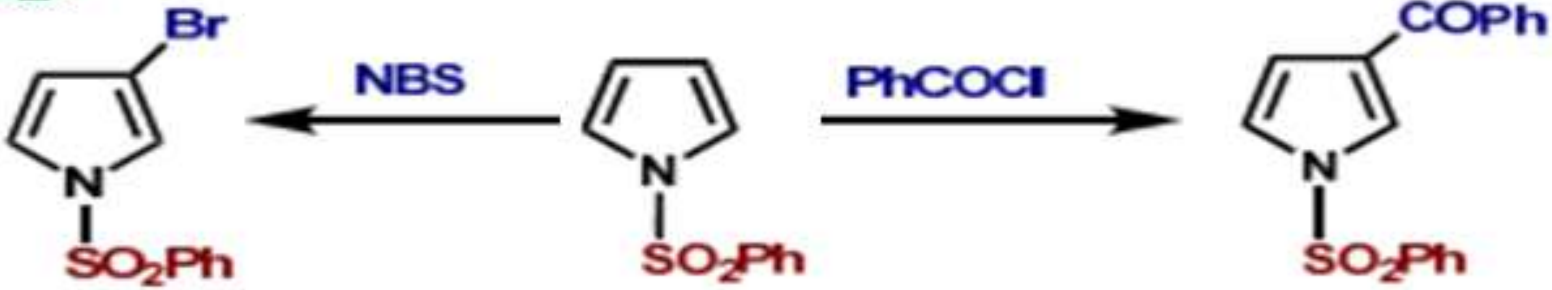
3.- Hydrolysis of imine



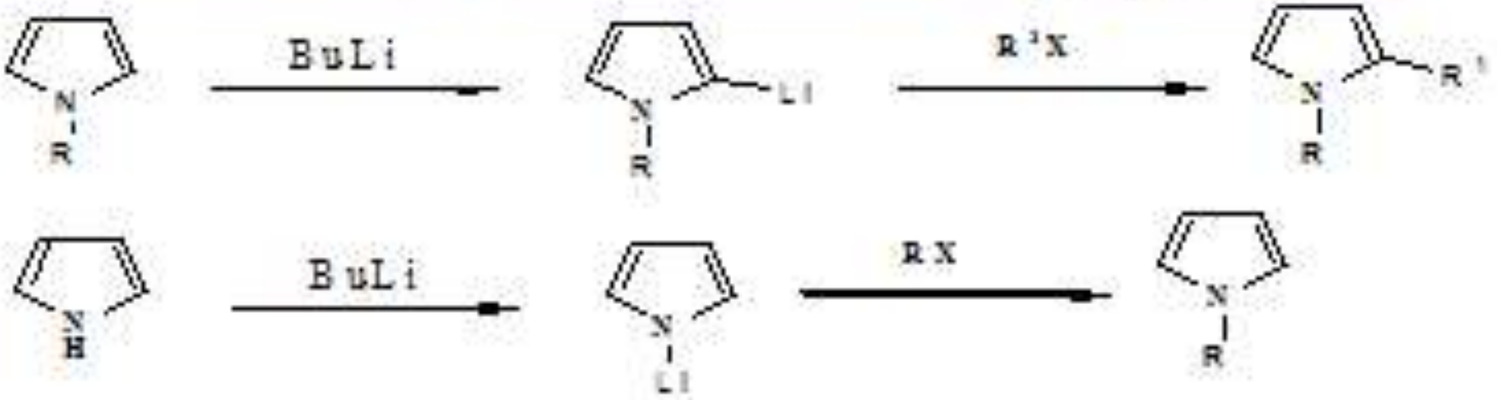
Addition to 3-position by Using steric effects



E.g.



Lithiation of Pyrrole and N alkyl pyrrole

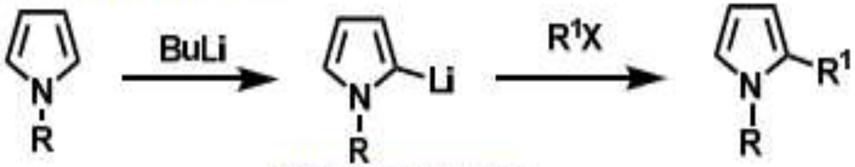


METALLATION

Metallation of pyrrol:

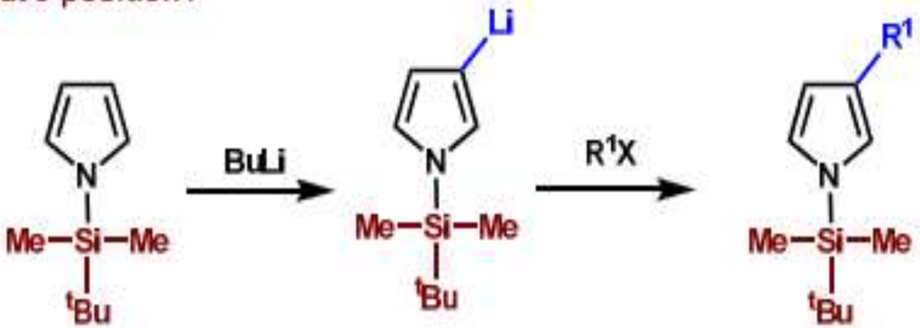
Most acidic proton

Metallation of N-substituted pyrrol:

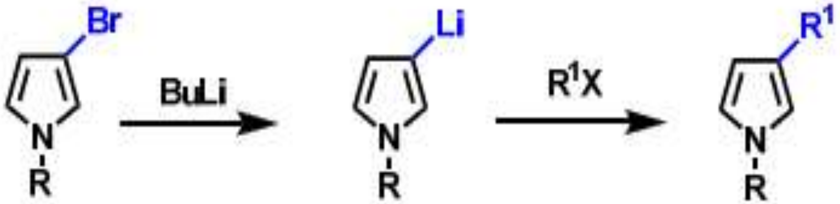


Ortho-metallation

Metallation at 3-position?



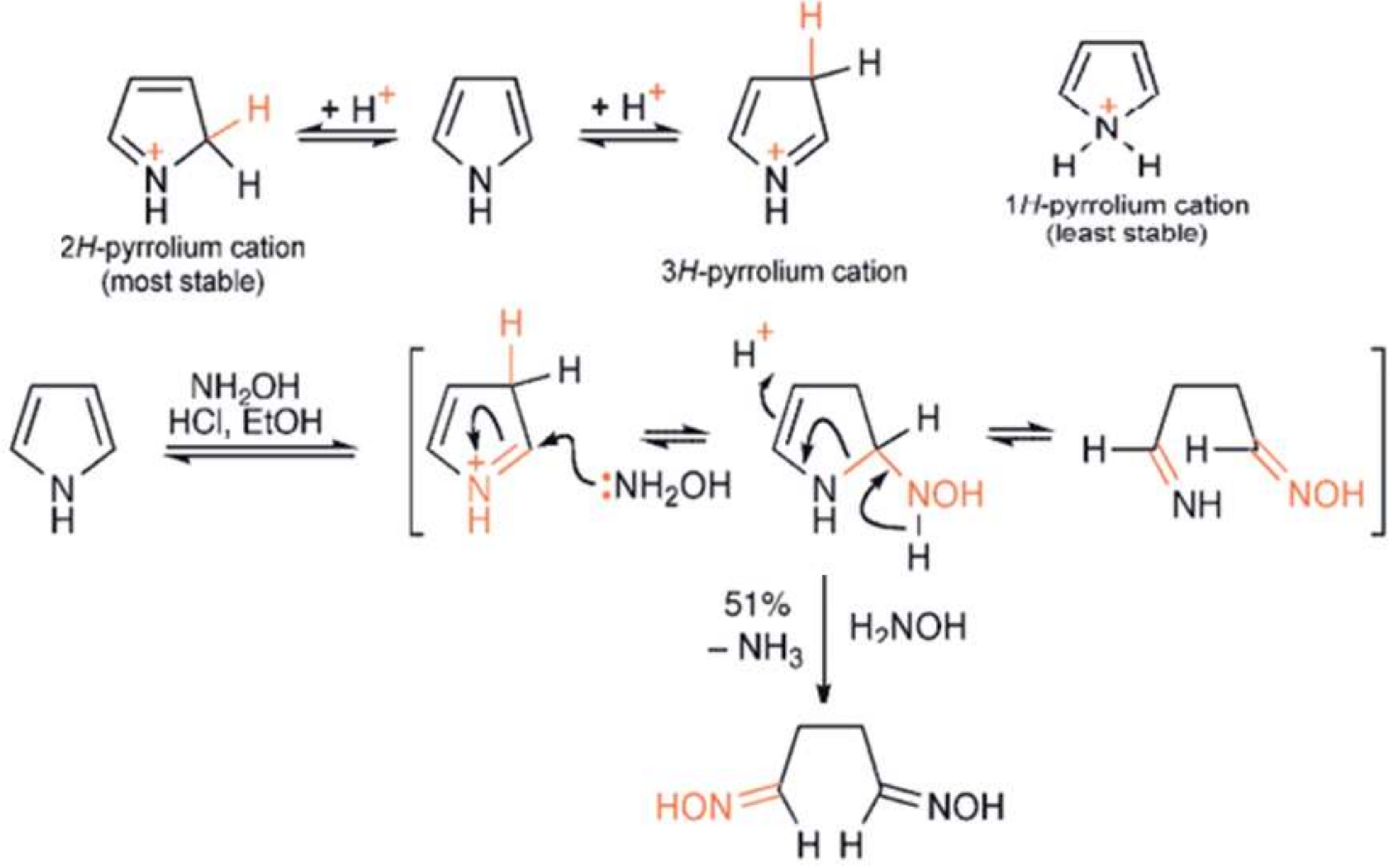
Steric effect
(be careful with basic o-directing groups capable of chelation)



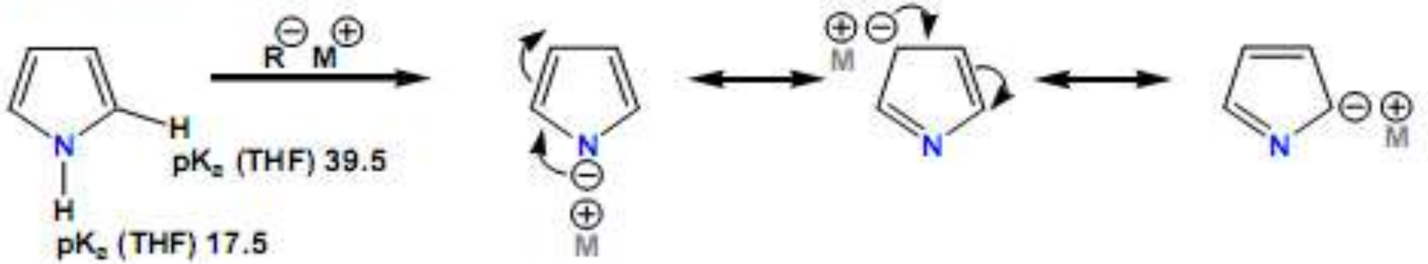
Metal-Halogen exchange
(Requires introduction of the halogen at 3-position)

Reactions of Protonated Pyrroles

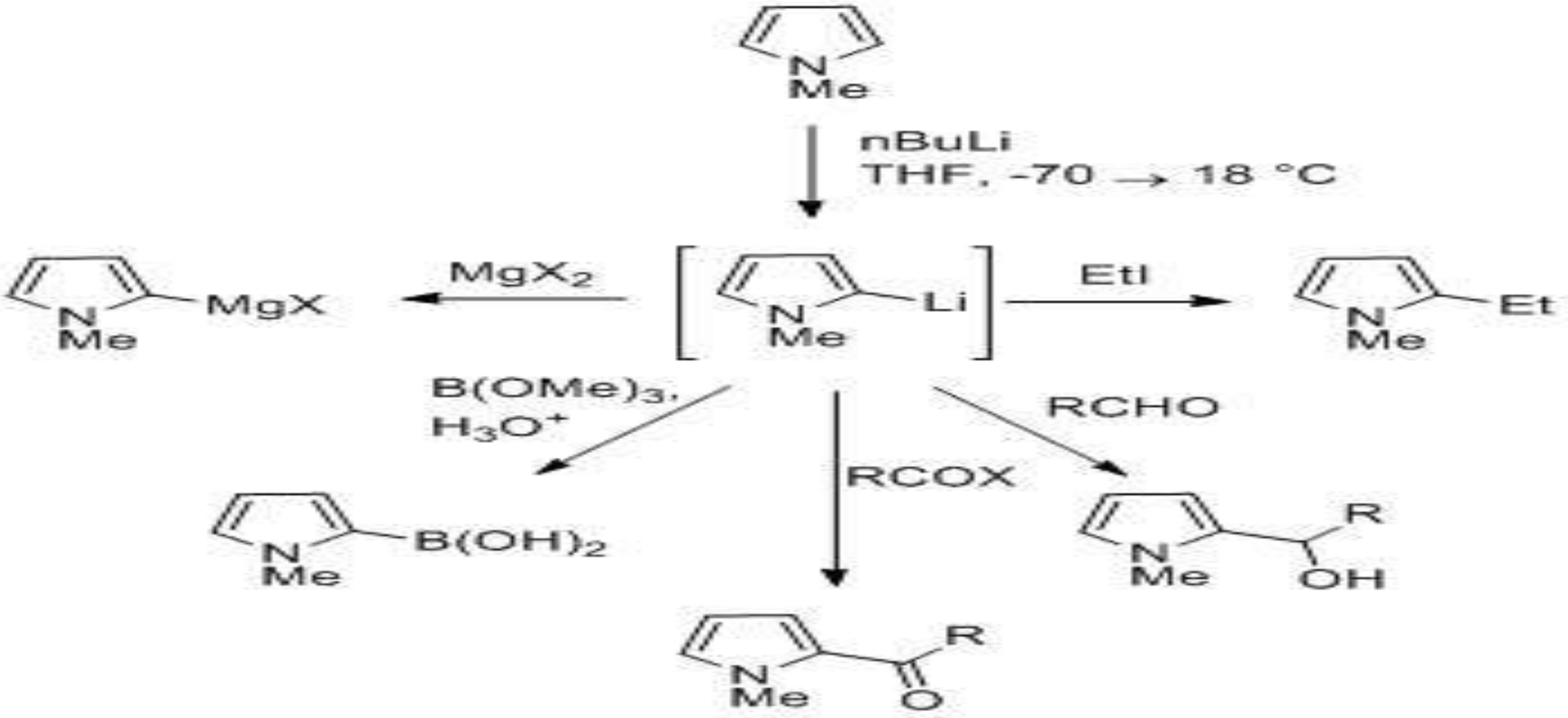
The 2*H*- and 3*H*-pyrrolium cations are essentially iminium ions and as such are electrophilic: they play the key role in polymerisation and reduction of pyrroles in acid.In the reaction of pyrroles with hydroxylamine hydrochloride, which produces ring-opened 1,4-dioximes, recovery of the amine being by way of this reaction with hydroxylamine

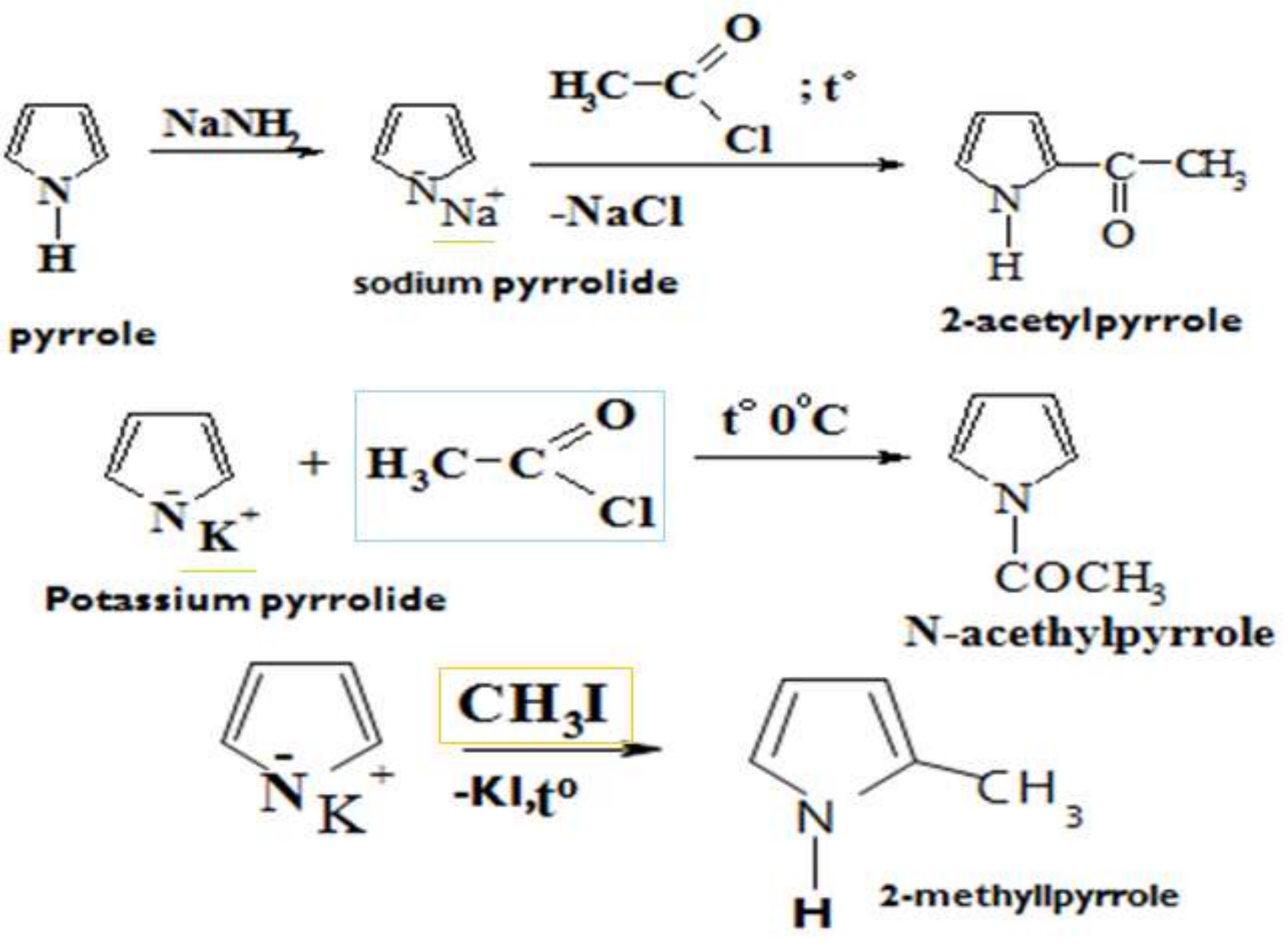


Deprotonation of Pyrroles



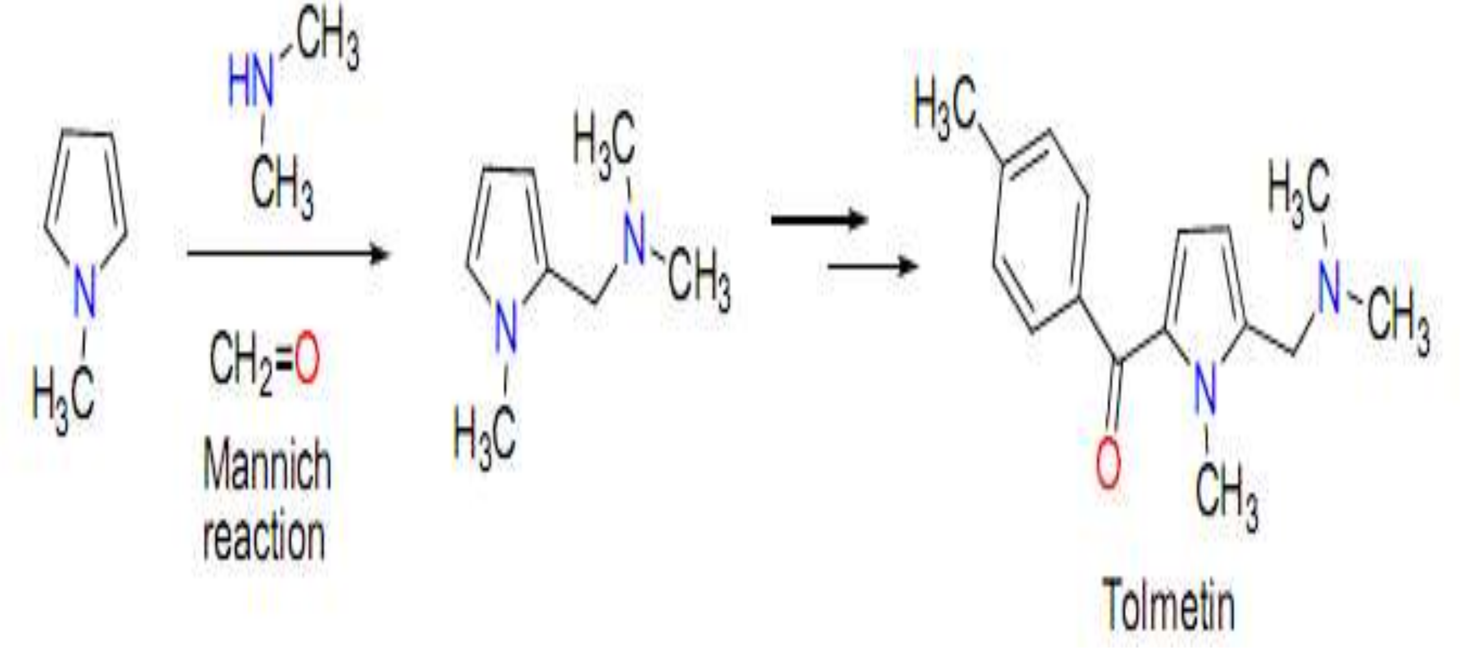
- Free pyrroles can undergo N or C deprotonation
- Large cations and polar solvents favour N substitution
- A temporary blocking group on N can be used to obtain the C-substituted compound





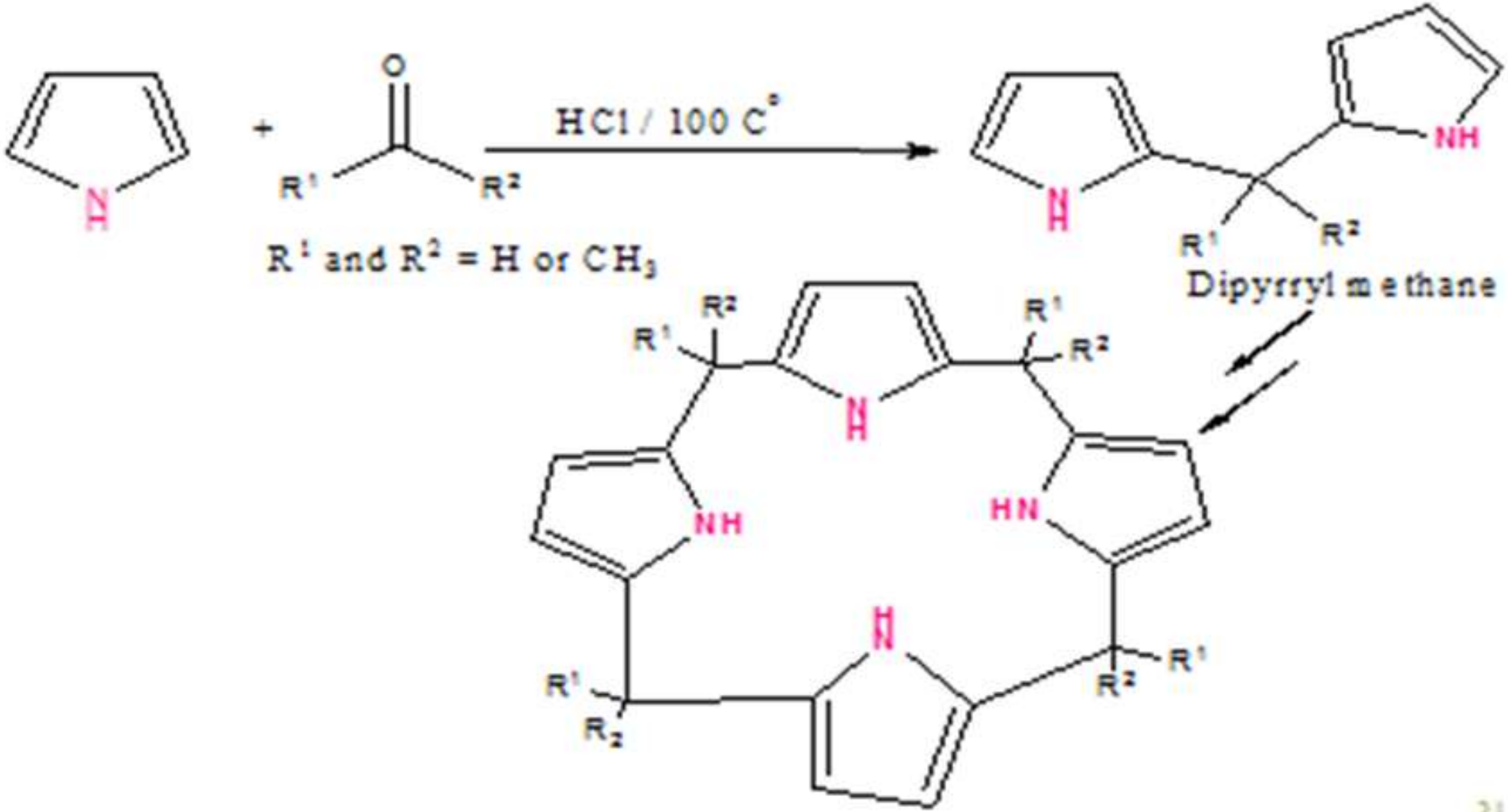
NaNH2
pyrrole
sodium pyrrolide
H3C−C(=O)Cl ; t°
-NaCl
2-acetylpyrrole
Potassium pyrrolide
t° 0°C
COCH3
N-acethylpyrrole
CH3I
-KI,t0
CH3
2-methyllpyrrole

- Aromatic heterocycles undergoes aminoalkylation (Mannich reaction)
- For example N-methylpyrrole reacts at the 2-position . Reaction is used in the manufacture of the nonsteroidal anti-inflammatory compound, tolmetin.

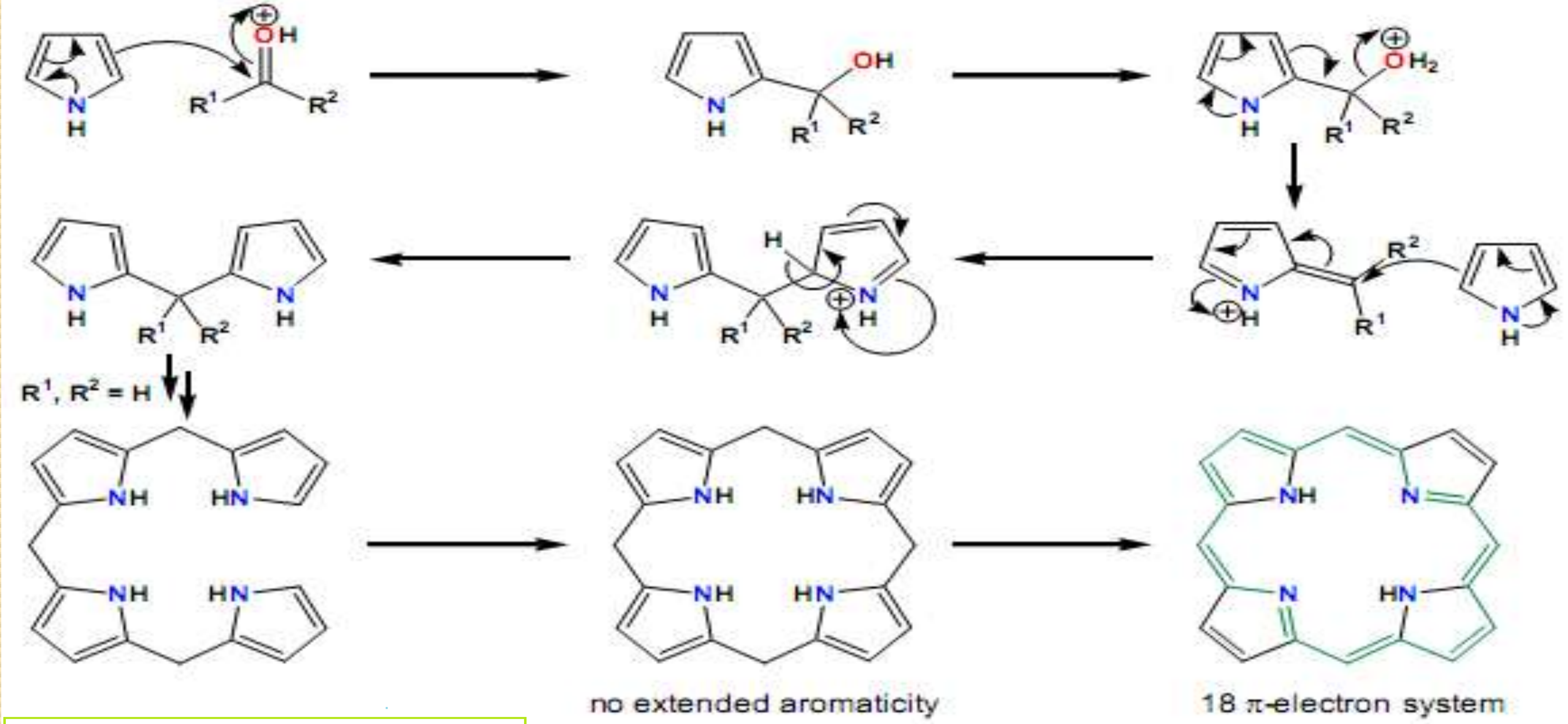


Reaction of pyrrole with aldehyes and ketones

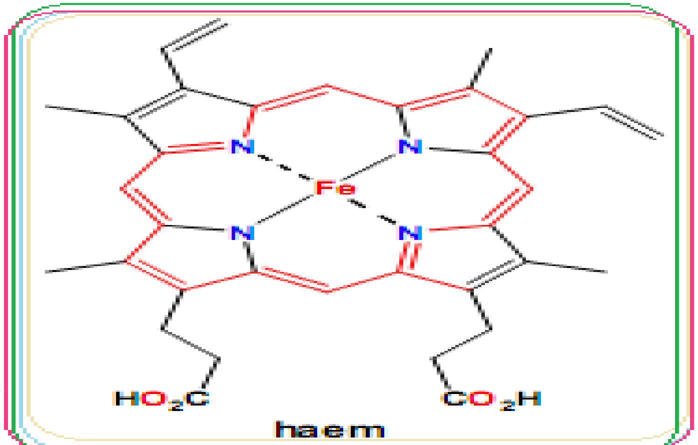
- *Aldehydes and ketones condense with unsubstituted pyrrole at a-position in acidic medium to give dipyrryl methane. The condensation may continue to give tetramer (4 pyrrole rings connected by methine bridge). The tetramers are known as porphyrinogens, they are stable, planar structures that can accommodate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



Pyrroles – Porphyrin Formation



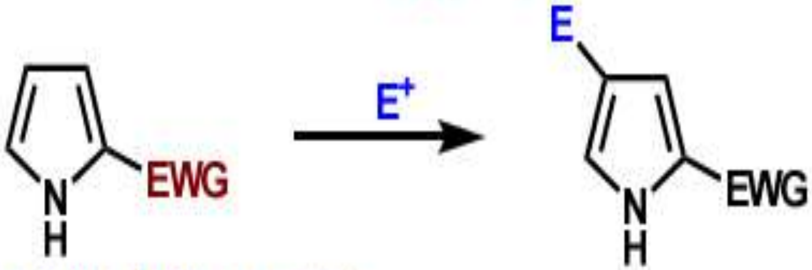
- The pigment haem is found in the oxygen carrier haemoglobin
- Chlorophyll-a is responsible for photosynthesis in plants



The extended aromatic 18 π-electron system is more stable than that having four isolated aromatic pyrroles

Second electrophilic substitution

a) Monosubstituted pyrrole with electron withdrawing group

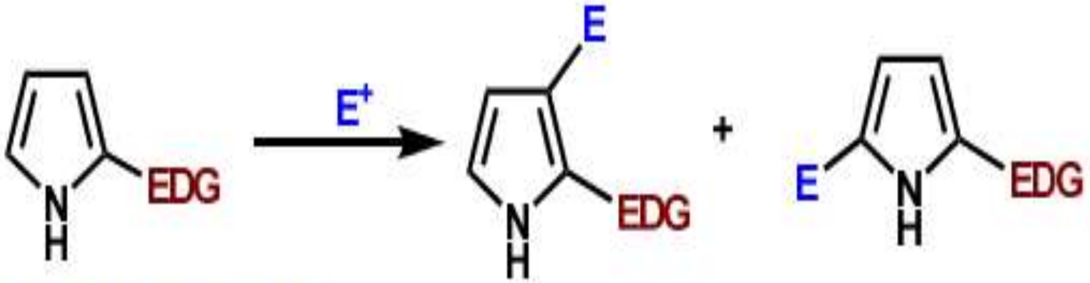


Less reactive than pyrrole

(incoming Electrophile directed to m-position i.e. position 4)

due to steric effects

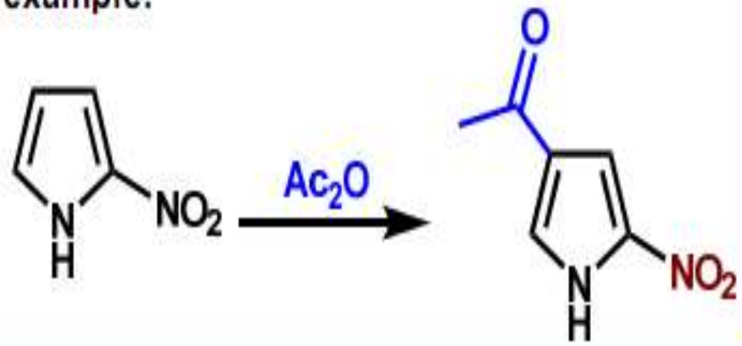
b) Monosubstituted pyrrole with electron donating group

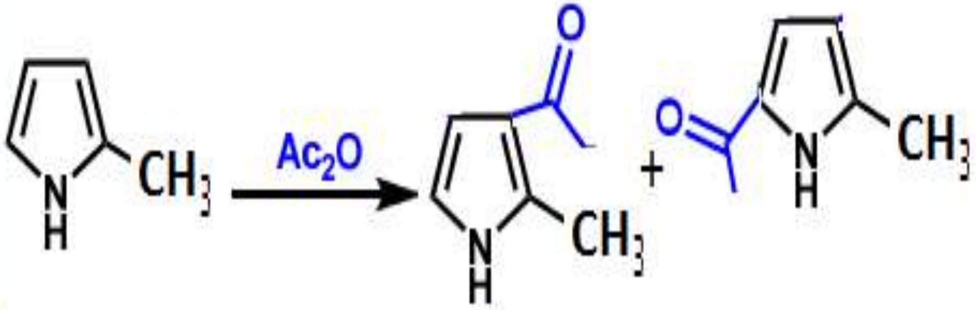


(incoming Electrophile directed to p or o-positions i.e. position 3 or 5)

More reactive than pyrrole

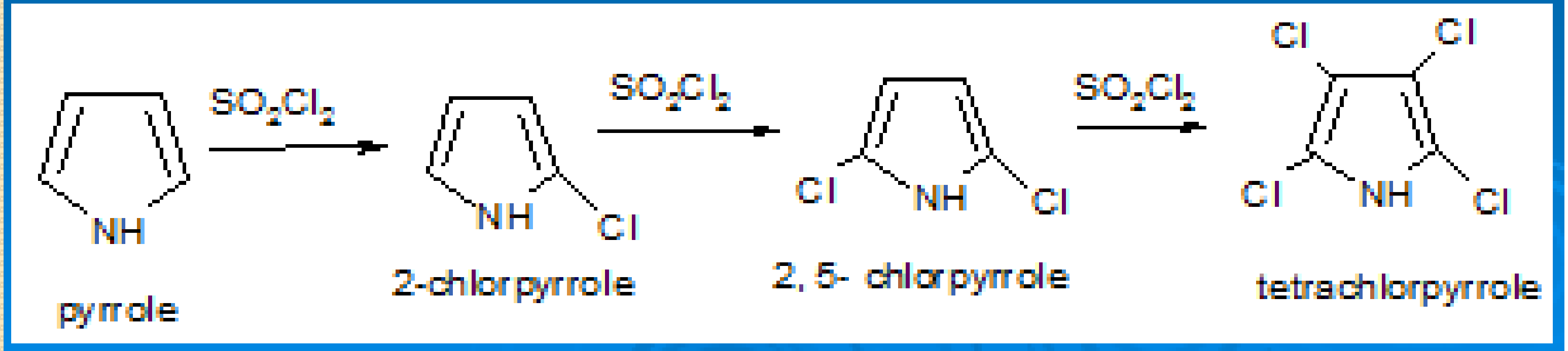
example:





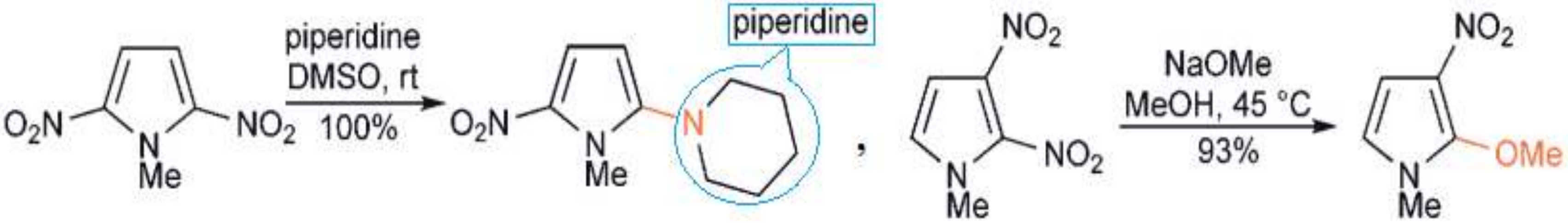
About halogenation reaction:

The position of second substitution in a monosubstituted furan, pyrrole, or lhiophene is governed by a combination of the directing effect of the group present and the inherent α-directing effect of the heteroatom. Substitution on 3-substituted compounds occurs exclusively at an α-position. When the substituent present is electron attracting (meta directing), reaction occurs at the nonadjacent α-position (that is, meta to the group present).



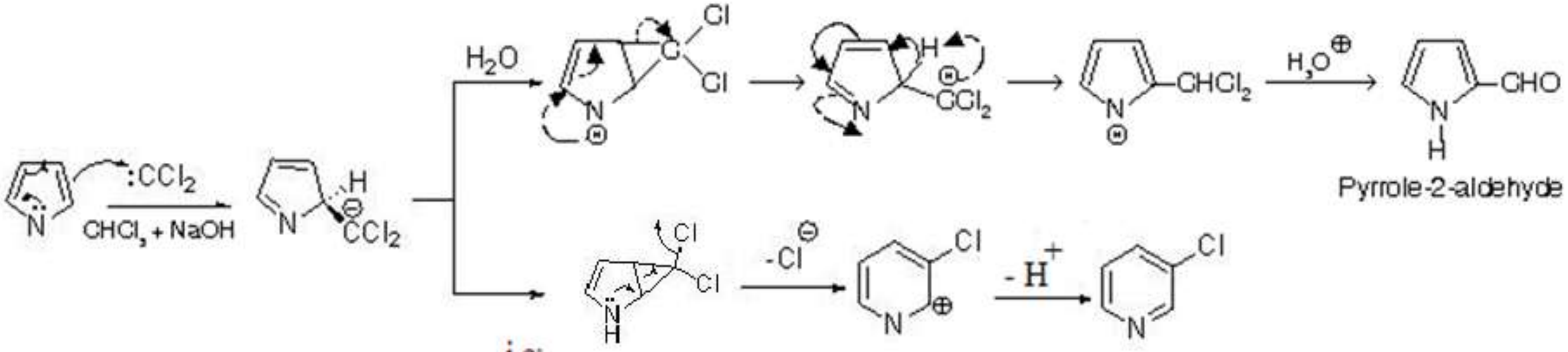
Reactions with Nucleophilic Reagents

Pyrrole and its derivatives do not react with nucleophilic reagents by addition or by substitution, except in the same type of situation that allows nucleophilic substitution in benzene chemistry, i.e. where the leaving group is *ortho* or *para* to an electron-withdrawing group:

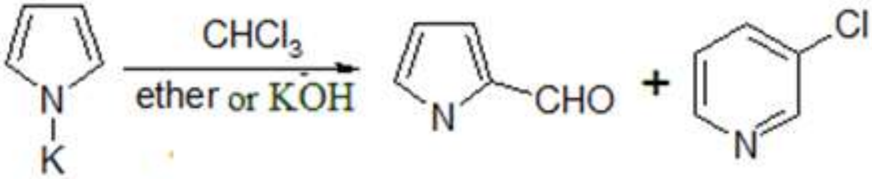


Ring Expansion of Pyrrole or Cycloaddition Reactions with dichlorocarbene {Reimer-Tieman Reaction}

Pyrrole adds on dichlorocarbene generated from chloroform and base to give a bicyclic compound which undergoes ring expansion to give 3-chloropyridine



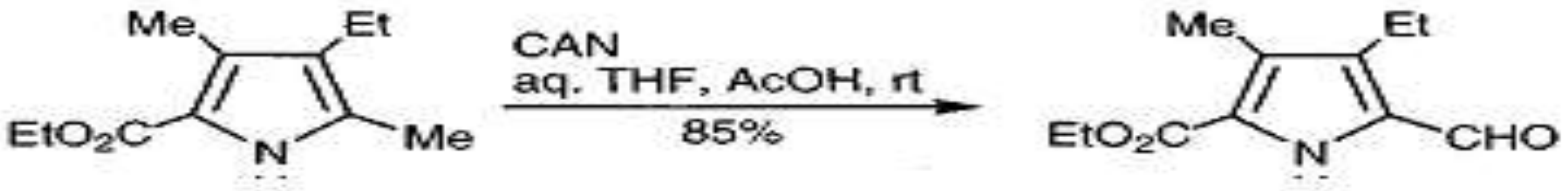
i.e:

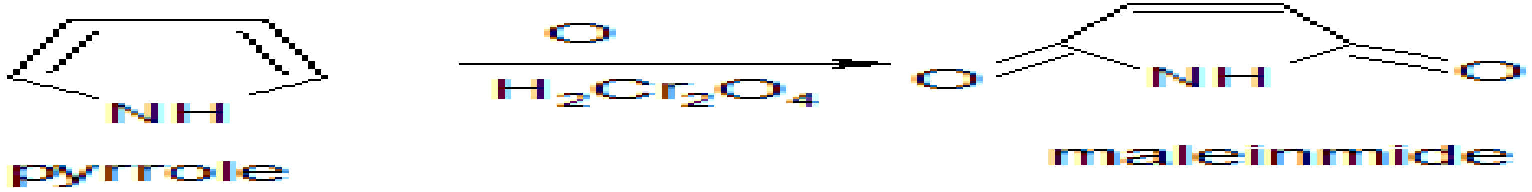


Reactions with oxidizing agents

Simple pyrroles are generally easily attacked by strong chemical oxidizing agents, frequently with complete breakdown. When the ring does survive, maleimide derivatives are the commonest products, even when there was originally a 2- or 5-alkyl substituent.

This kind of oxidative degradation played an important part in early porphyrin structure determination, in which chromium trioxide in aqueous sulfuric acid or fuming nitric acid were usually used as oxidising agents.





Pyrroles which have a ketone or ester substituent are more resistant to ring degradation and high yielding side-chain oxidation can be achieved using cerium(IV) ammonium nitrate with selectivity for an α-alkyl.

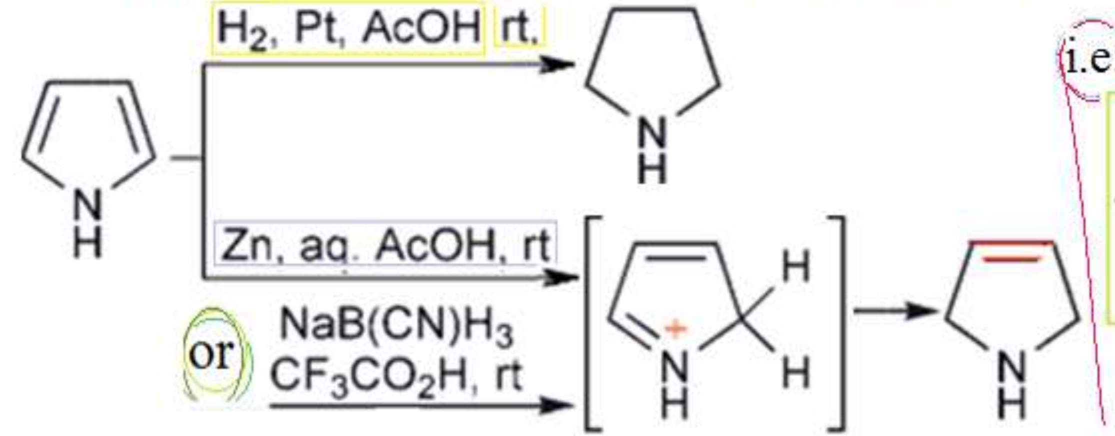
Reactions with Reducing Agents {Reduction}

Simple pyrroles are not reduced by hydride reducing agents or diborane, but are reduced in acidic media, in which the species under attack is the protonated pyrrole. The products are 2,5-dihydropyrroles

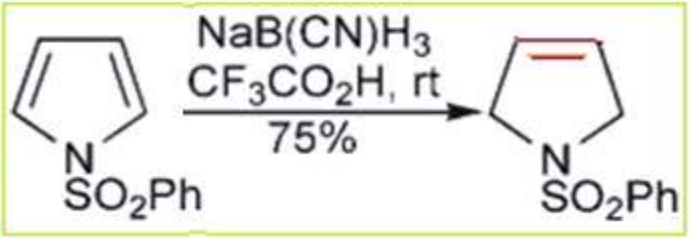
Reduction of pyrroles to pyrrolidines can be effected catalytically over a range of catalysts, is especially easy if the nitrogen carries an electron-withdrawing group & is not complicated by:

carbon–heteroatom hydrogenolysis and ring opening

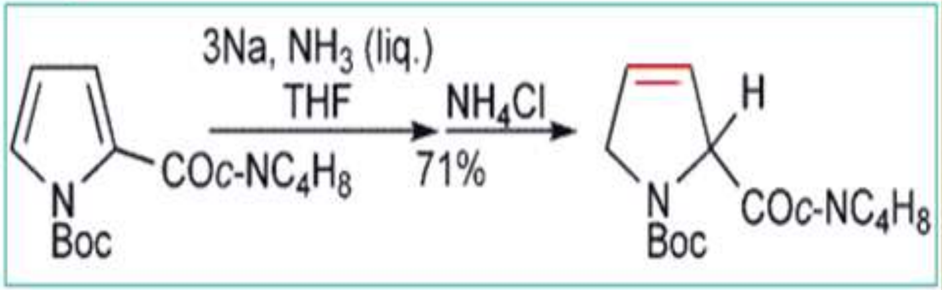
Pyrrole, can be reduced to pyrrolidine by catalytic hydrogenation.

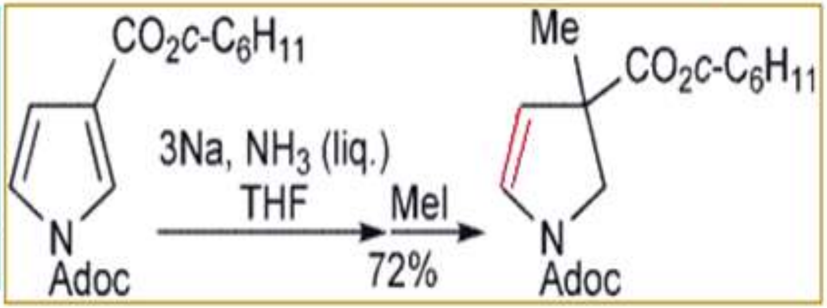


i.e:



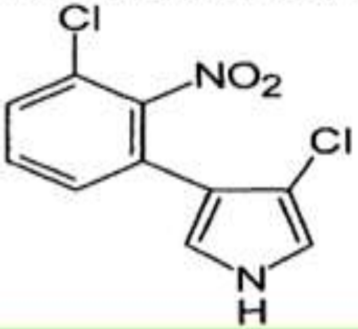
Birch reduction of pyrrole carboxylic esters & tertiary amides gives dihydro-derivatives; the presence of an electron-withdrawing group on the nitrogen serves both to remove the acidic *N*-hydrogen and also to reduce the electron density on the ring.



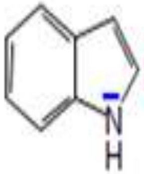


Pharmaceutical Importance A number of pharmaceuticals are derived from pyrrole,

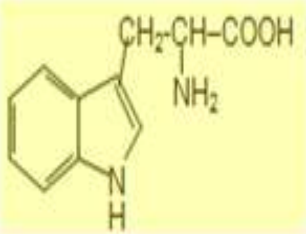
The pyrrole ring, although not very common in nature, occurs in some very important natural products. A few antibiotics contain a pyrrole ring, one of the simplest is pyrrolnitrin :



Indole (2,3-benzopyrrole) or (benzo [*b*] pyrrole)

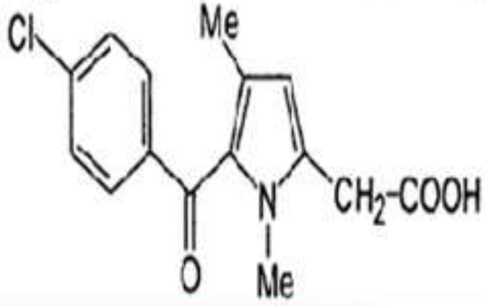


i.e: **Tryptophan**

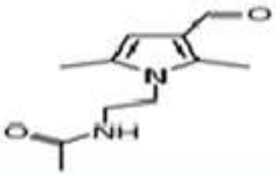


للأطلاع فقط

the analgesic and anti-inflammatory zomepirac



Aloracetam:used for treatment of Alzheimer's disease



Atorvastatin :used for the prevention of cardiovascular disease