REACTIONS AND PROPERTIES OF AROMATIC HETEROCYLCES

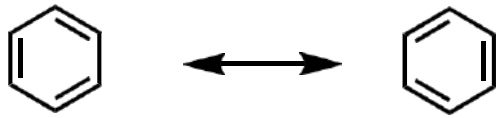
Dr. Solomon Derese

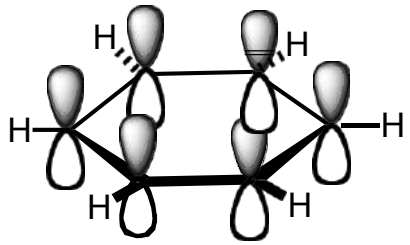
Aromaticity

Hückel

4n + 2

Benzene





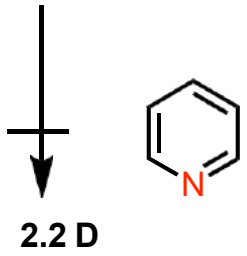
All C sp^2

↳ مايدخلها conjugation

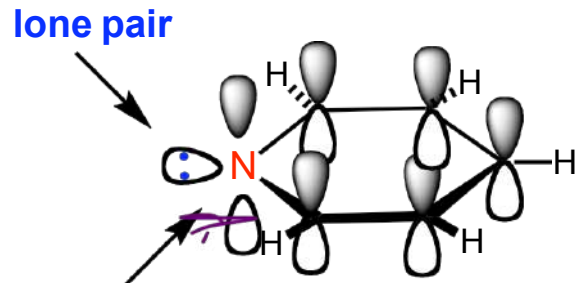
6-Membered heterocyclic rings

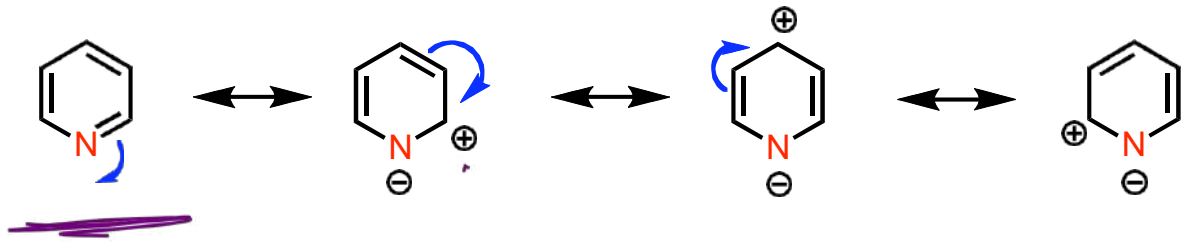
Heteroatom: N (or O)

Pyridine



N more electroneg. than C



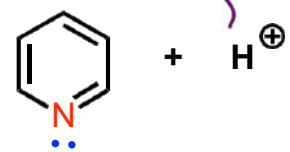


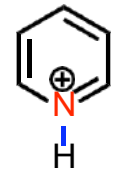
C-2, C-4 and C-6
Electron defficient

6-Membered heterocyclic rings

Heteroatom: N (or O)

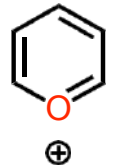
Pyridine as a base

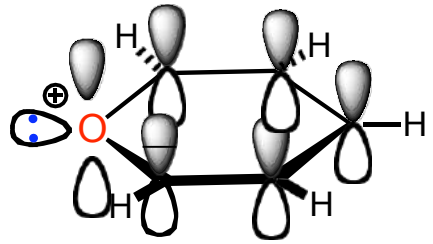


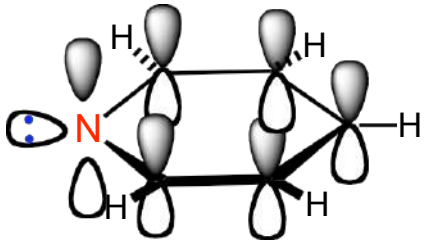


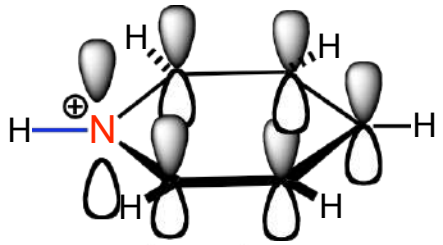
*p*Ka 5.2

Pyrylium cation









Still aromatic!

bi exissiv
ديوين

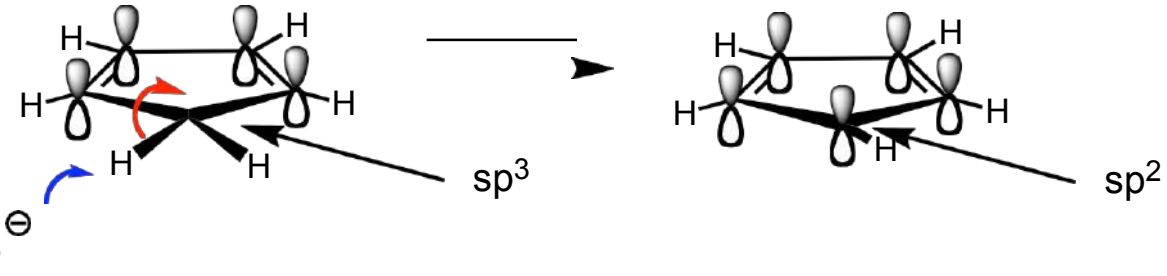
5-Membered heterocyclic rings

they share the pair of electron

Heteroatom: N, O, S

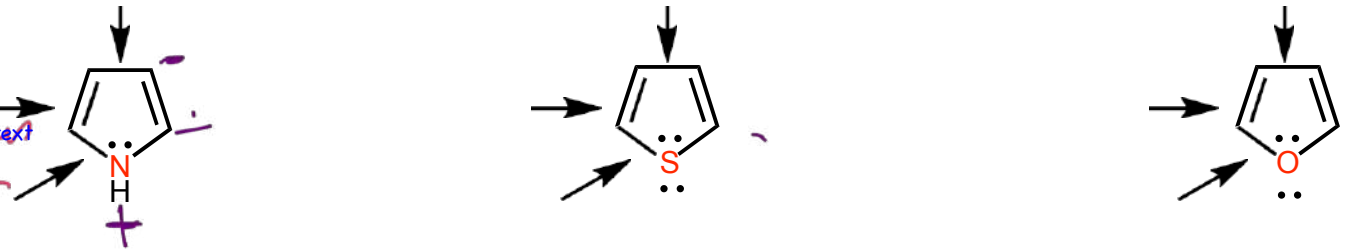
Cyclopentadiene

Cyclopentadienyl
6 π–electrons

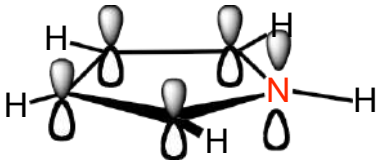


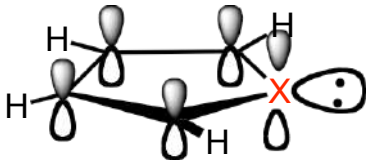
degree of aromaticity

Pyrrole **Thiophene** **Furan**



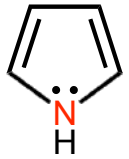
benzen > thiophe > pyrol > furan



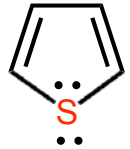


pyrol >> furan > thiopher > Benz. electrophilic substitute, ie ← order of reactivity

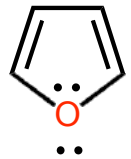
Pyrrole

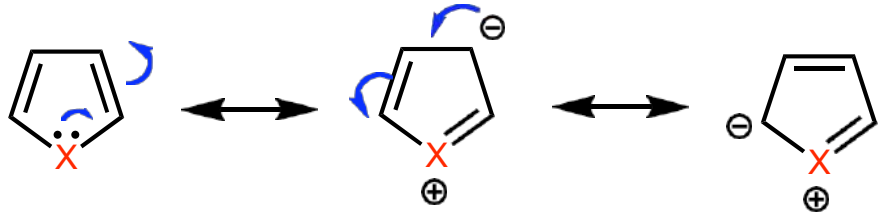


Thiophene



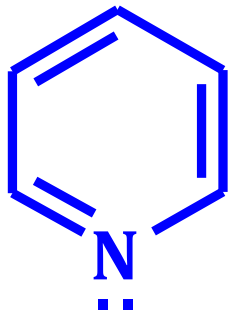
Furan



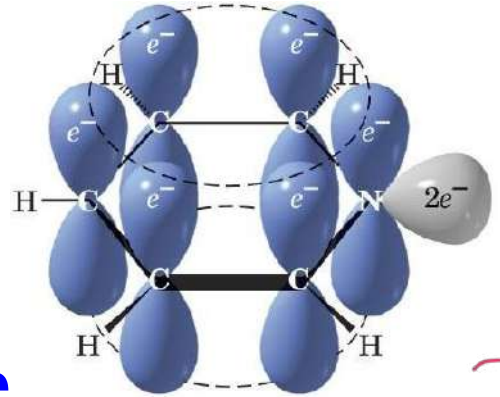


All C electron rich

SIX MEMBERED AROMATIC HETEROCYCLES



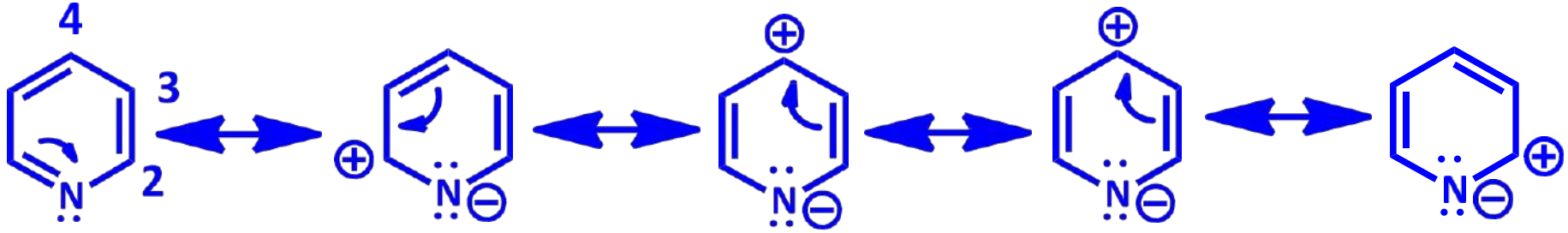
Pyridine



Pyridine is aromatic as there are six delocalized electrons in the ring.

Six-membered heterocycles are more closely related to benzene as they are aromatic on the basis of their π-electron systems without the need for delocalization of heteroatom lone pairs. The empirical resonance energy for pyridine is about 28 Kcal/mol, only slightly lower than that for benzene.

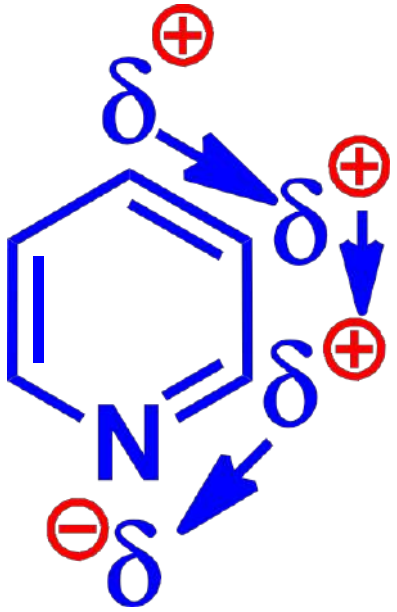
Structure of Pyridine

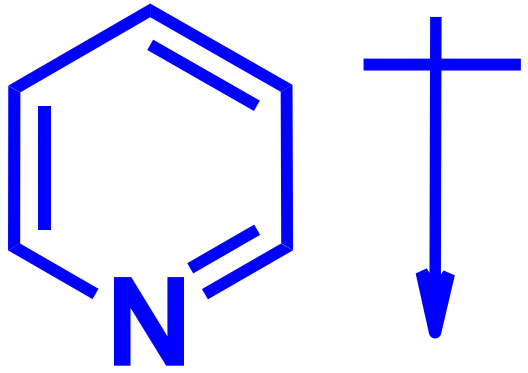


Pyridine has divalent negatively charged N, which is a stable condition for N. The positive charge is dispersed to carbons around the ring, specifically to C-2 and C-4.

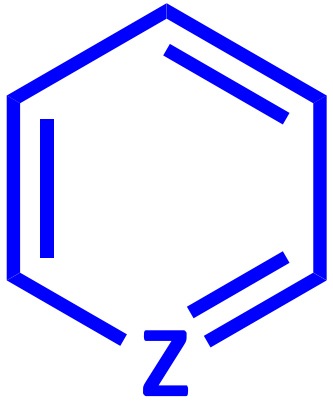
The net effect is to reduce the π-electron density in the ring relative to benzene, and as result pyridine is electron deficient compared to benzene.

As a result, unlike benzene pyridine is polar molecule due to the electronegative nitrogen.





$\mu = 2.2$ D

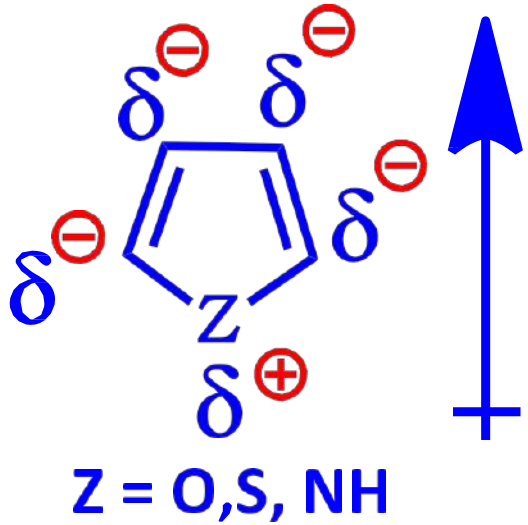


Z = O^+, S^+, N

Six membered heterocycles with an electronegative heteroatom are generally electron deficient compared to benzene. Such compounds are classified as π-deficient.

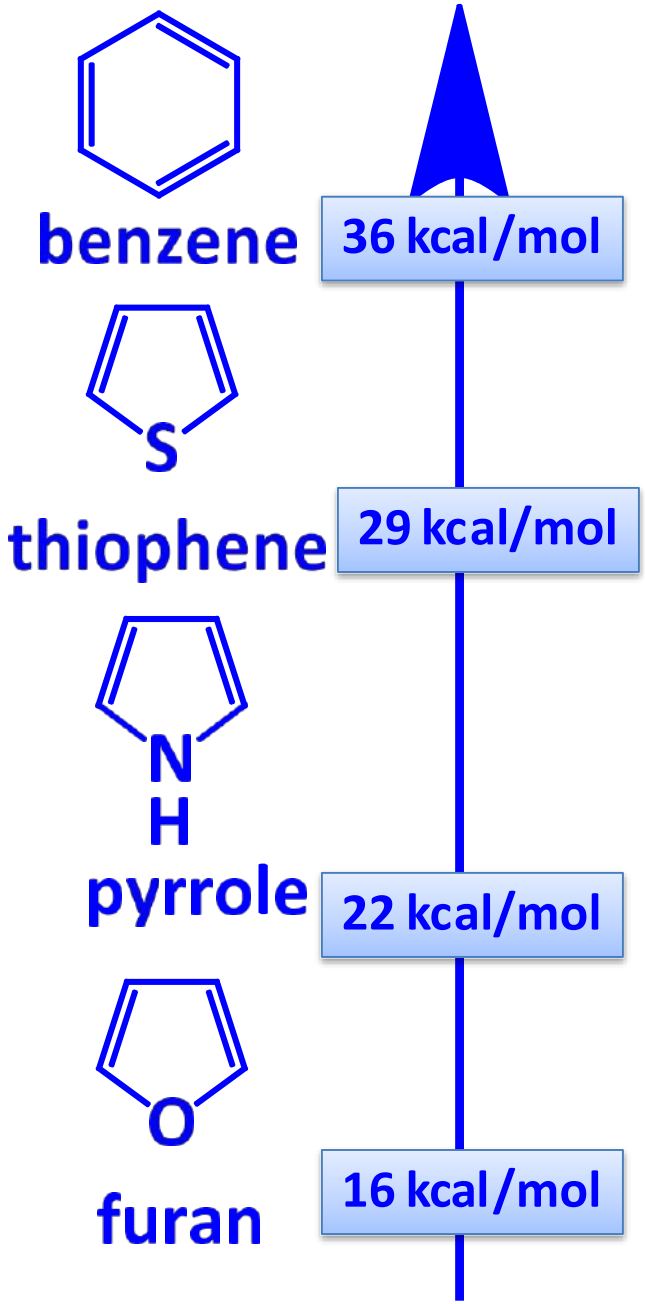
Electron-withdrawing heteroatoms decrease the π-electron density at the carbon atoms and are thus π-deficient relative to benzene.

Structure of five membered heterocycles



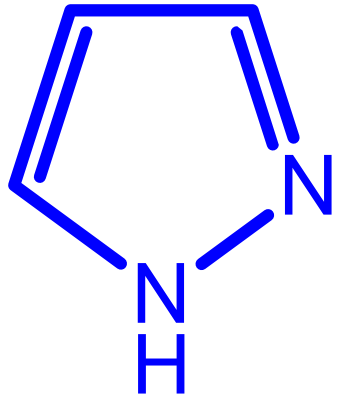
The five-membered aromatic heterocycle ring has a π-electron excess (six on five atoms), while in benzene, the π-electron density is one on each ring atom.

Five membered heterocycles with an electronegative heteroatom are generally electron rich compared to benzene (six electrons for five carbons). Such compounds are classified as π-excessive.

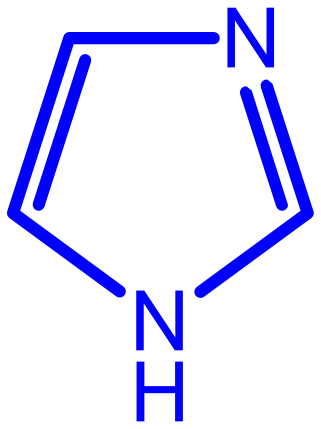


The degree of aromatic character in a five membered ring is determined by the ease with which the lone pair may be released into the delocalized system.

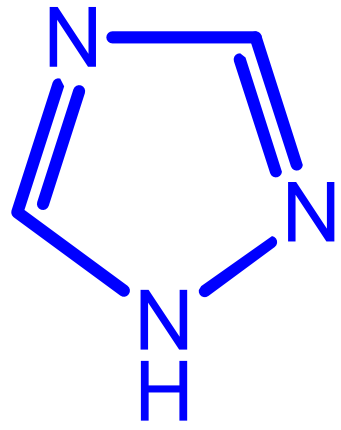
The ease with which the lone pair electron is released is directly related to the electronegativity of the heteroatom. Thus the lower the electronegativity of the heteroatom, the higher the aromaticity.



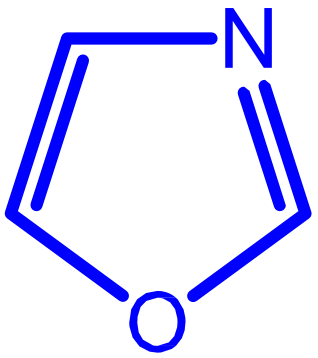
pyrazole



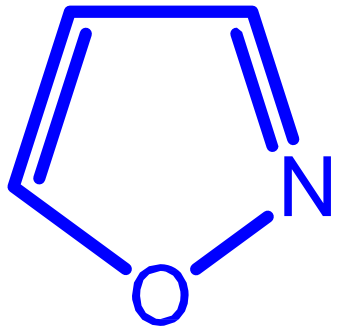
imidazole



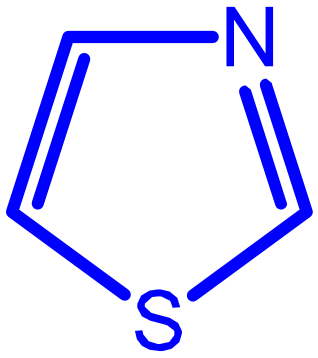
1,2,4-triazole



oxazole



isooxazole



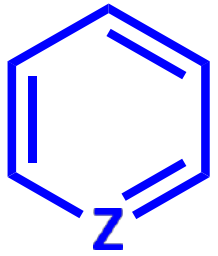
thiazole

Aromatic Heterocycles

π- Excessive

Z = O, S, NH

π- Deficient



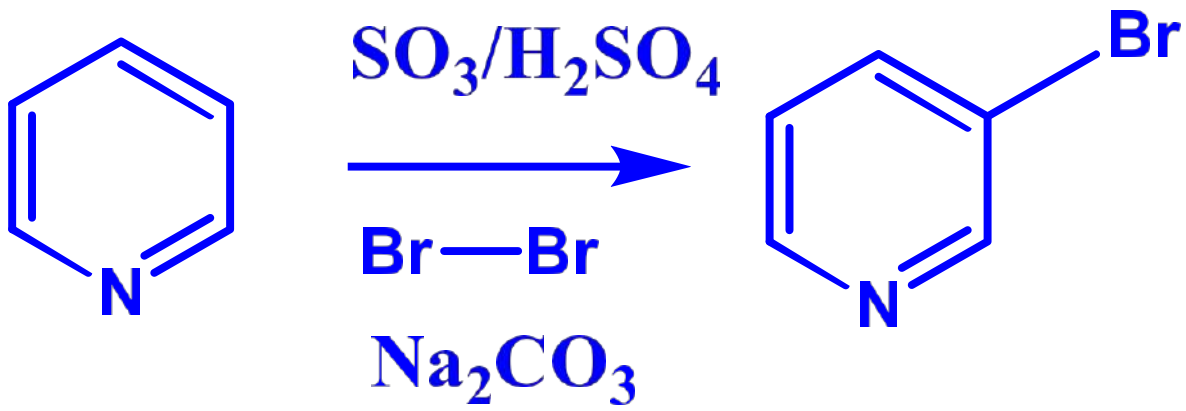
Z = O^+, S^+, N

This classification is not trivial; there is a vast difference between the properties of the two types of aromatic compounds.

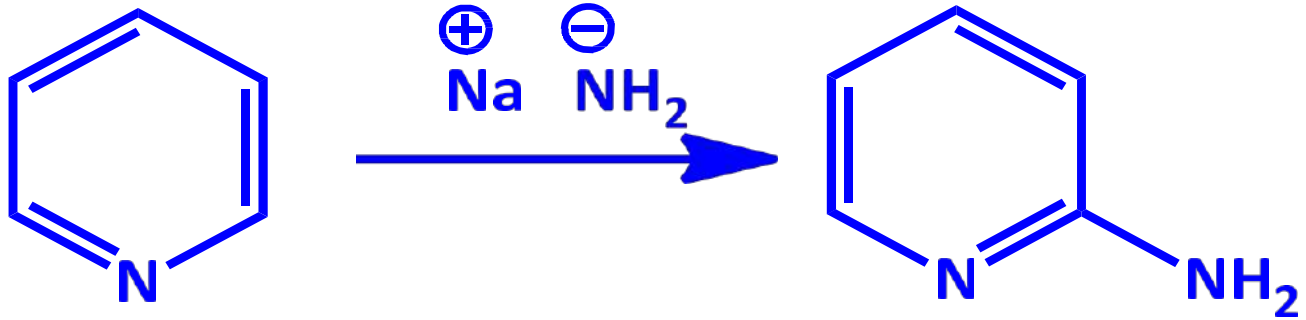
Reactions of π-deficient heterocyclic aromatic compounds

A hallmark of π-deficient heterocyclic systems is their low reactivity with electrophilic agents, slower than benzene. For example, pyridine is less reactive than benzene by a factor of 10^6 when subjected to conditions of nitration. The reactivity is on the order of that of nitrobenzene, which is well known to require much more drastic conditions than those for benzene itself.

For example, 3-bromopyridine is formed when pyridine is reacted with bromine in the presence of oleum (sulfur trioxide in conc. sulfuric acid) at 130˚C.



Conversely pyridines are susceptible to nucleophilic attack.



Reactions of π-excessive heterocyclic aromatic compounds

A significant feature of the π-excessive ring systems is that they undergo electrophilic aromatic reactions faster than benzene.

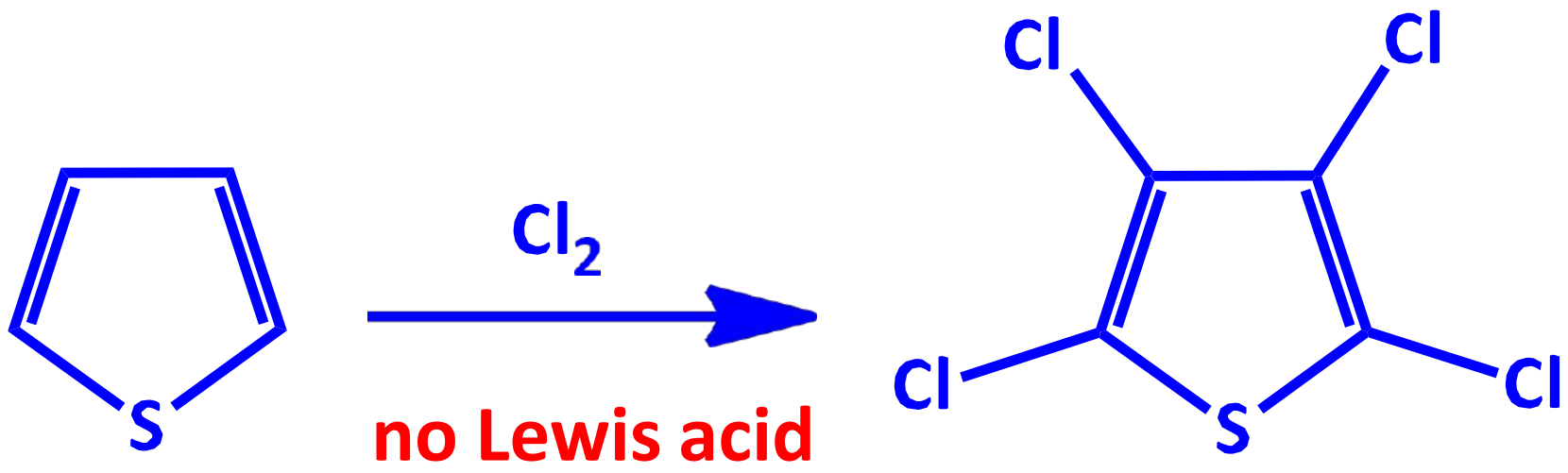
The reactivity is greater than that of benzene and is in roughly the same range as found for benzenes bearing electron releasing groups such as in aniline. The greater electron density in these rings accounts for this higher reactivity.

These heterocycles undergo electrophilic aromatic substitution reactions much faster than benzene under similar conditions. The reasons for this are:

I. **The resonance energy of the heterocycles is less than that of benzene, i.e. less aromatic than benzene.**

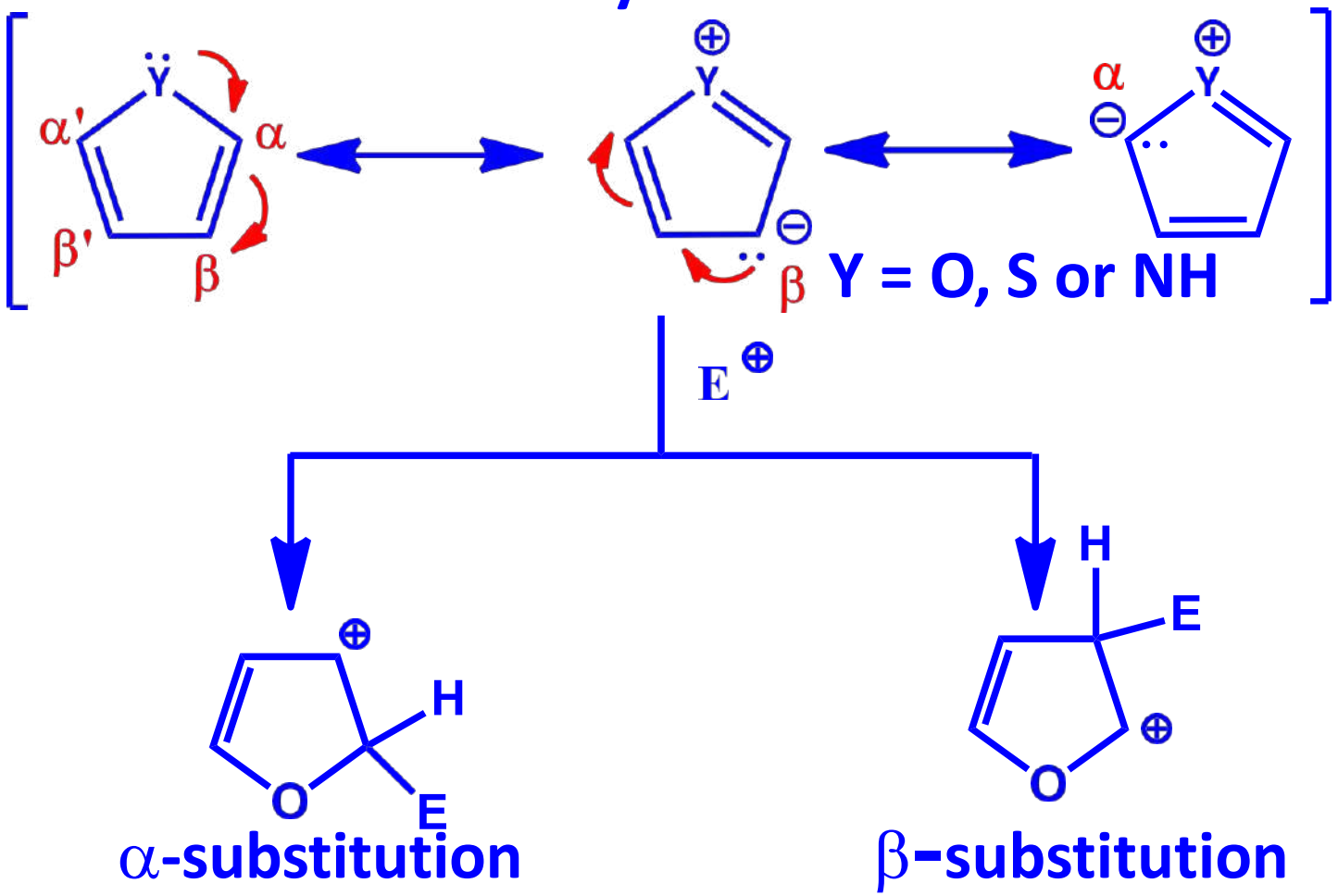
II. **The five-membered aromatic heterocycle ring has a π-electron excess (six on five atoms), while in benzene, the p-electron density is one on each ring atom.**

Reaction with bromine requires no Lewis acid and leads to substitution at all four free positions.



FIVE MEMBERED AROMATIC HETEROCYCLES

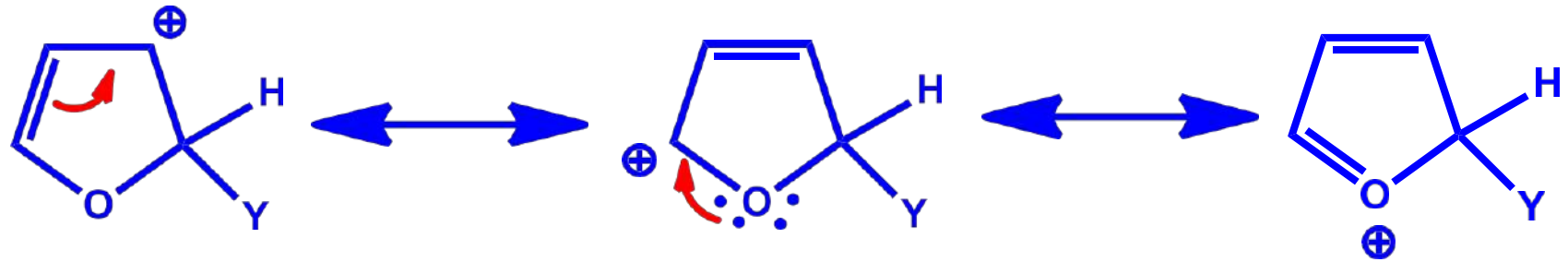
Electrophilic aromatic substitution reaction of five membered aromatic heterocycles



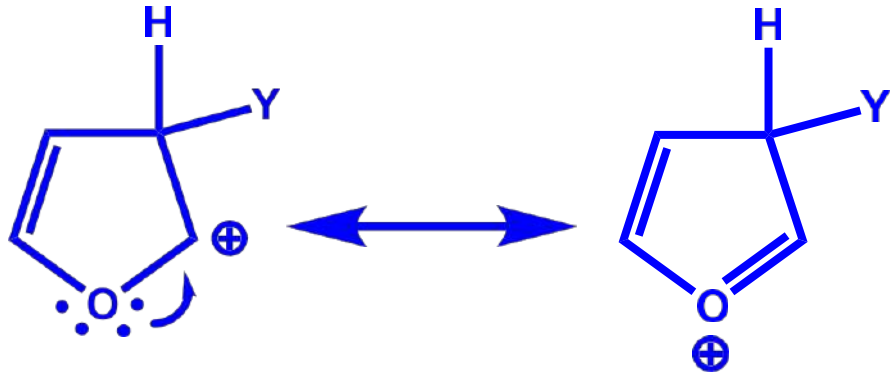
The Substitution is regioselective to the α position; when these positions are occupied, the β-position is substituted.

WHY?

The +ve charge is better resonance stabilized when the substitution is at the α-position than at β-position.



A more stable intermediate carbocation having 3 resonance forms.

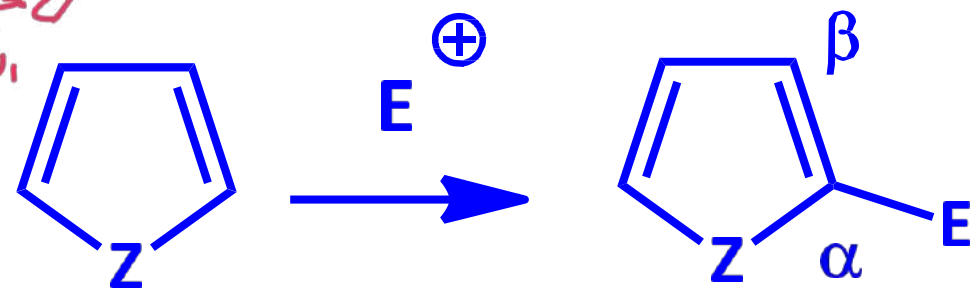


only 2 resonance forms

Common reactions of pyrrole, furan, and thiophene

The following reaction are common to the three five membered aromatic heterocycles.

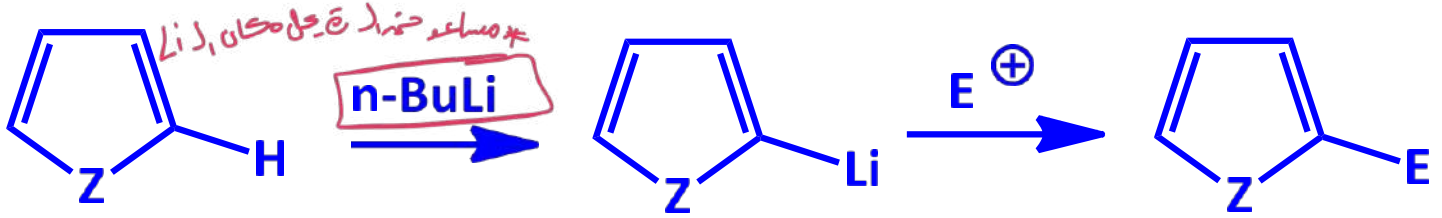
A. Electrophilic Aromatic Substitution



Z = O, S, NH

Electrophilic aromatic substitution reaction is easy and is preferred at α-position; also easy at β-position.

B. Substitution at α-position via α-lithiated Intermediates

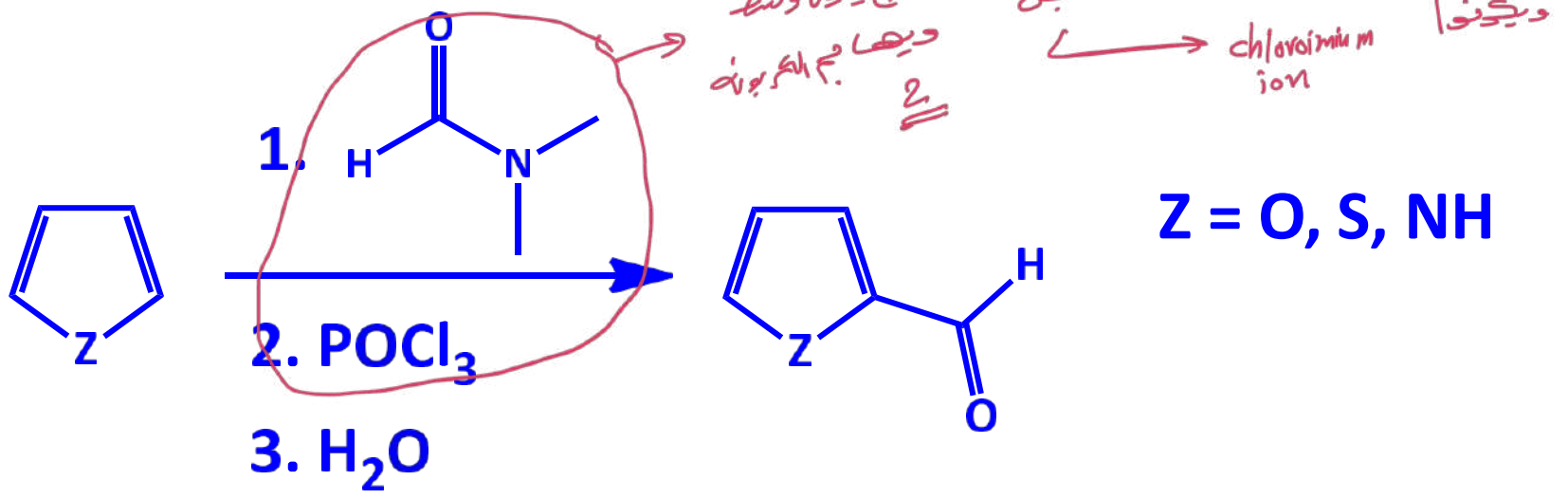


Z = O, S, NR

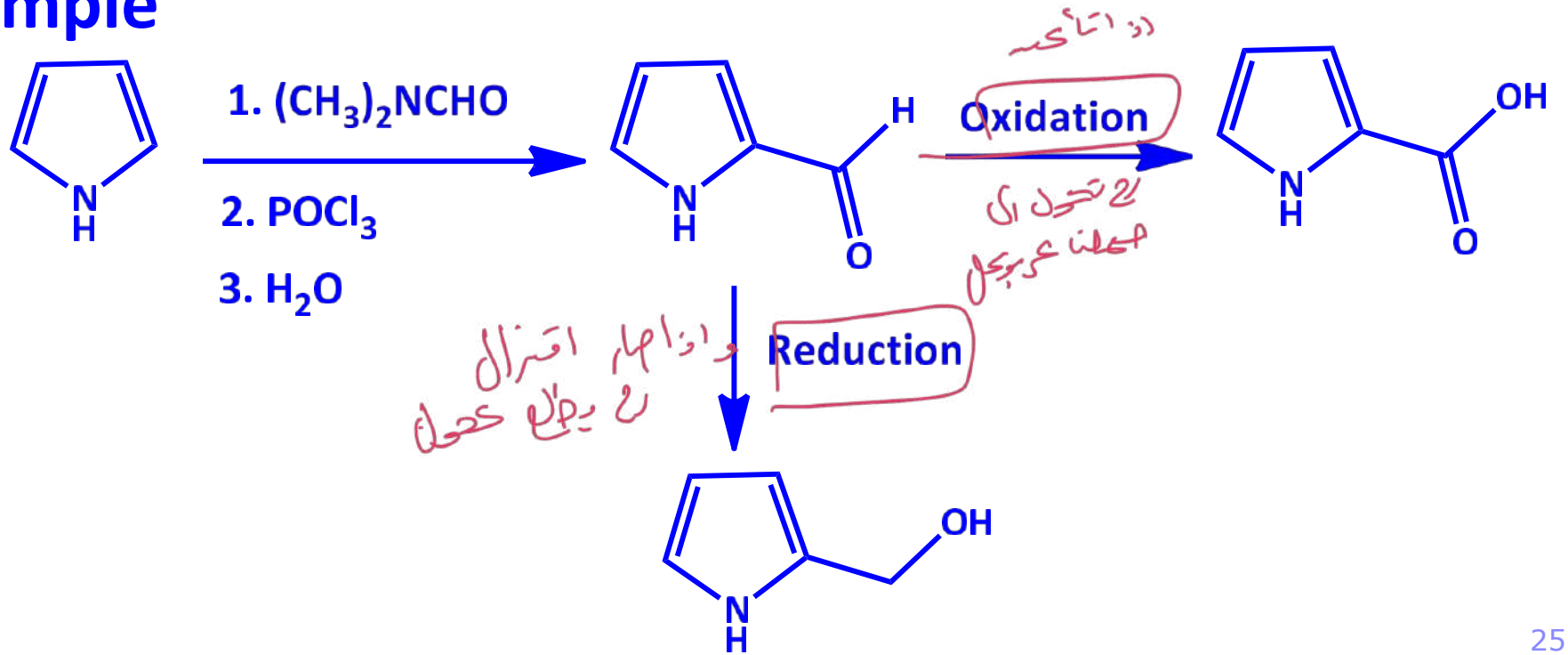
C. Vilsmeier-Haack reaction

Vilsmeier reaction (Vilsmeier-Haack reaction) allows the formylation (addition of -CHO) of heterocyclic molecules. The formylating agent, chloroiminium ion, is formed in situ from N,N-dimethylamide and $POCl_3$.

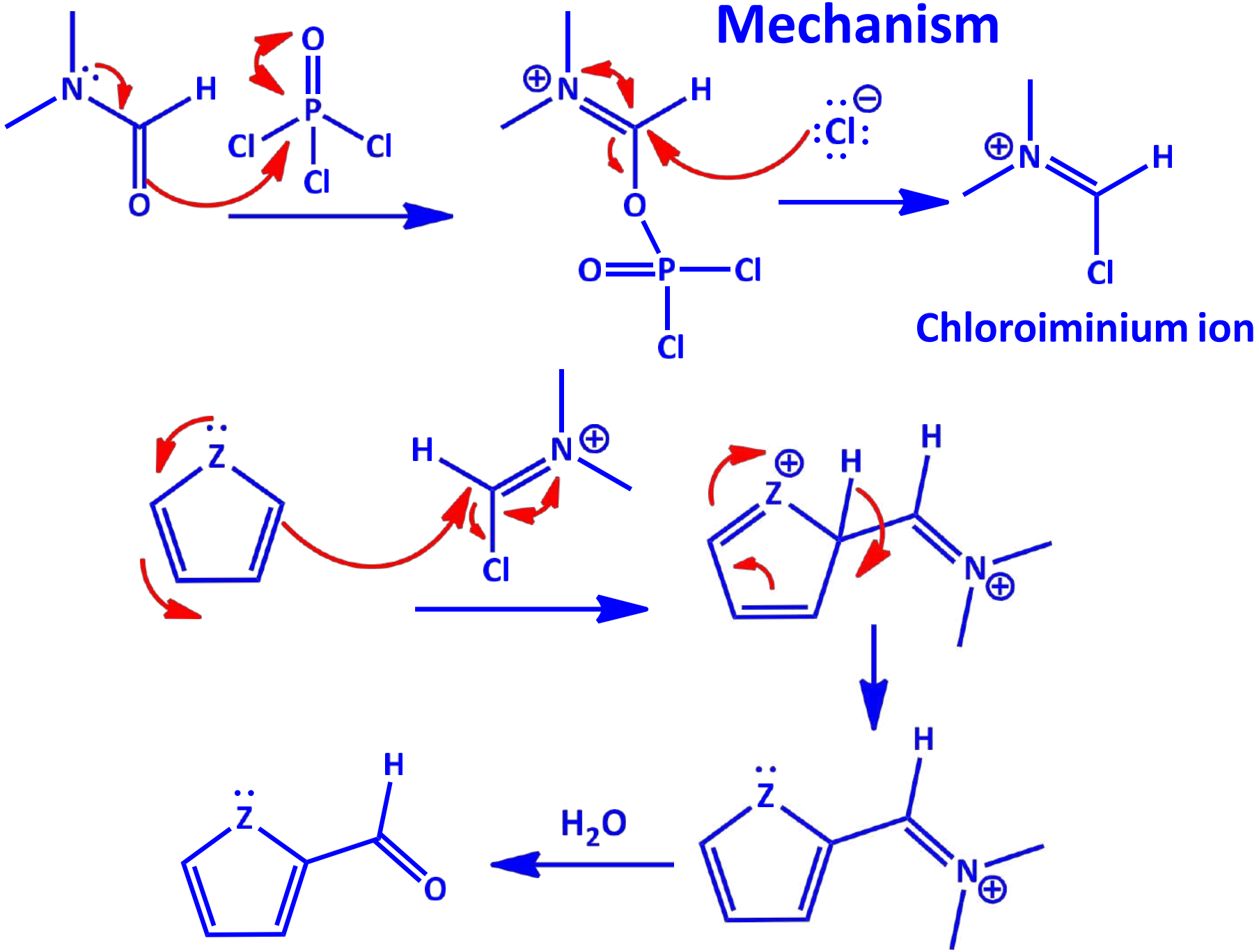
Vilsmeier-Haack reaction



Example

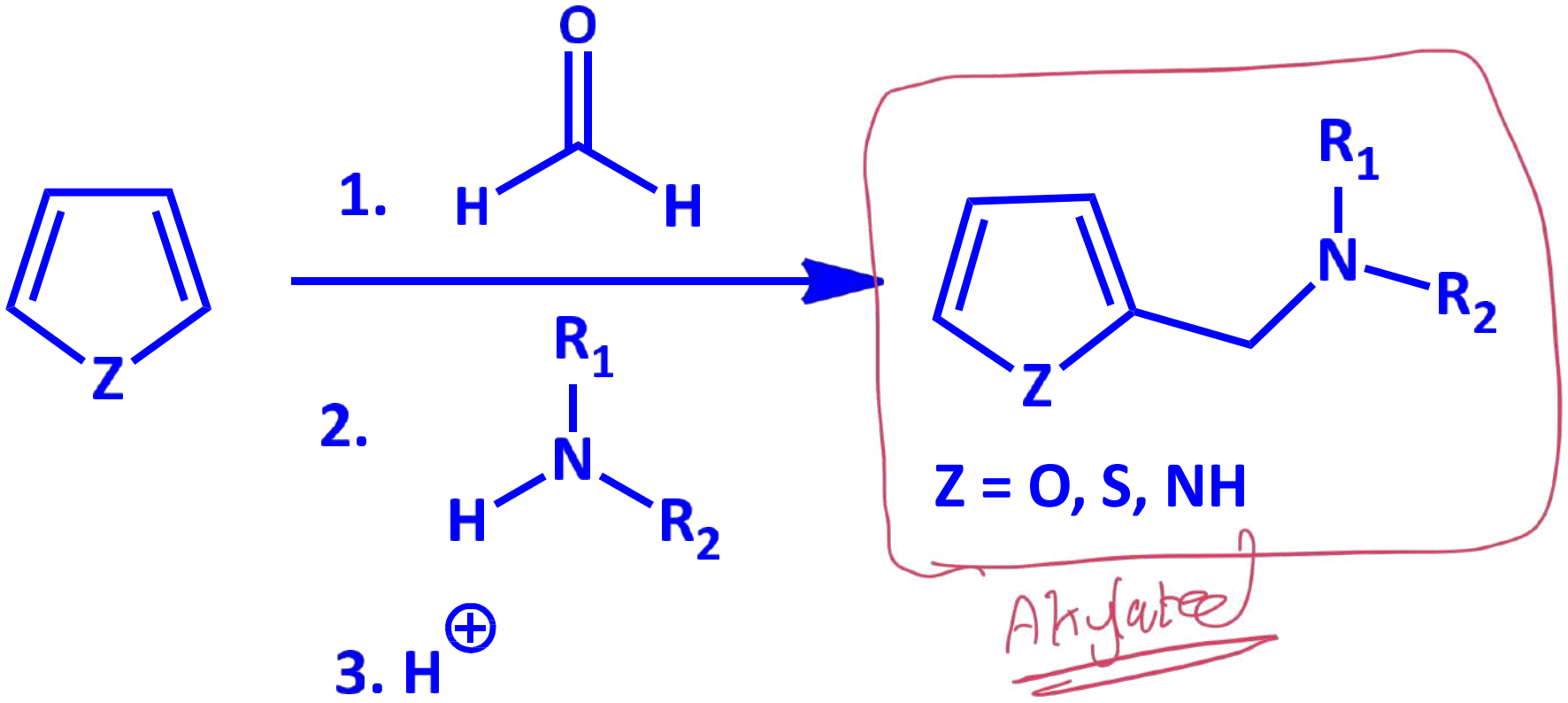


Mechanism

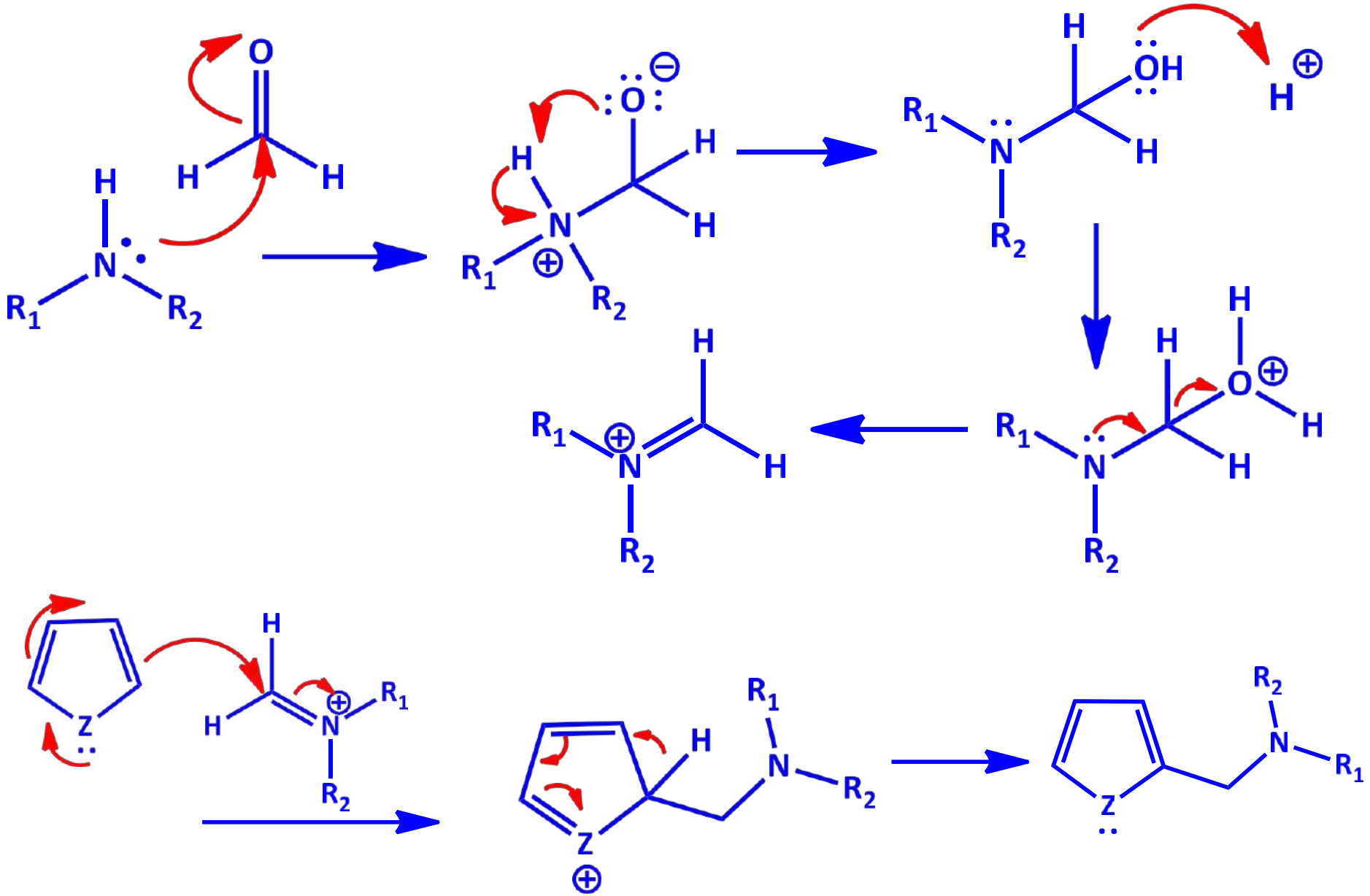


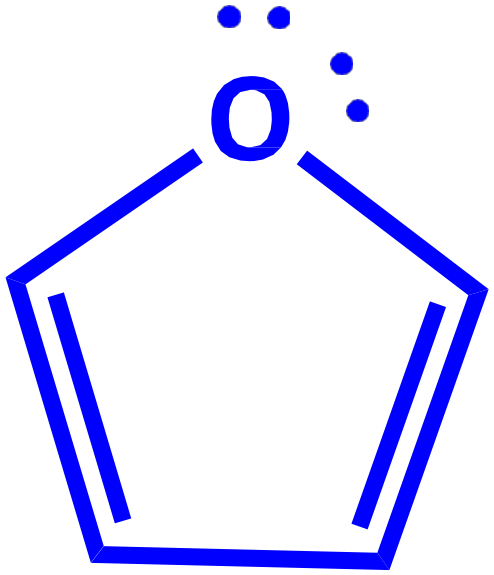
D. Mannich reaction

The reaction of electron rich heterocycles with formaldehyde and primary/secondary amine forming an amino alkylated heterocylcic compound is called the Mannich reaction.



Mechanism





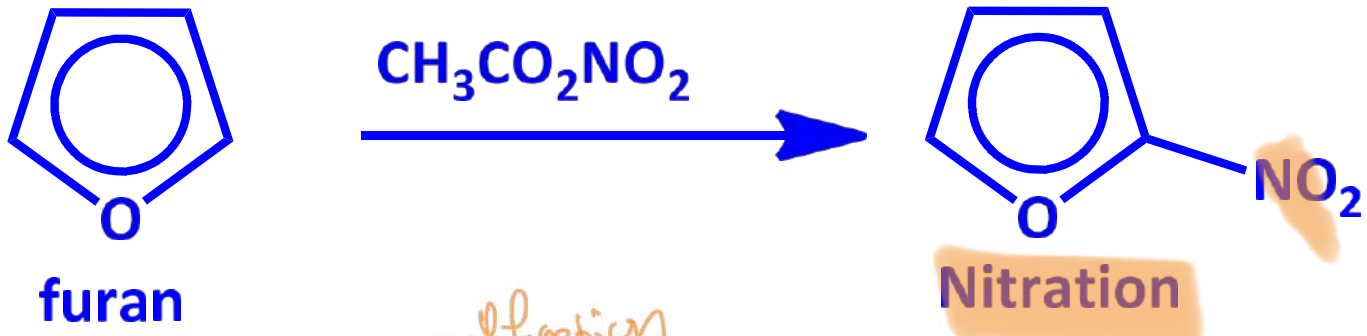
Furan

Furans are volatile, fairly stable compounds with pleasant odours. Furan itself is slightly soluble in water. It is readily available, and its commercial importance is mainly due to its role as the precursor of the very widely used solvent tetrahydrofuran (THF).

Reactions of Furans

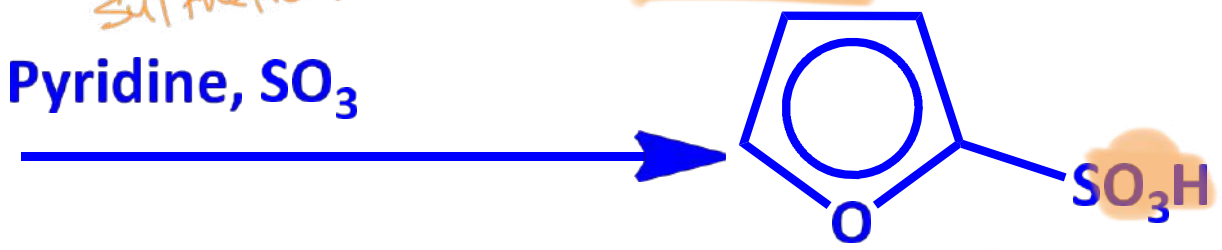
By analogy with benzene, furan undergoes reactions with electrophilic reagents, often with substitution. However, it can also react by addition and/or ring-opening depending on reagent and reaction conditions.

Electrophilic Aromatic Substitution Reaction

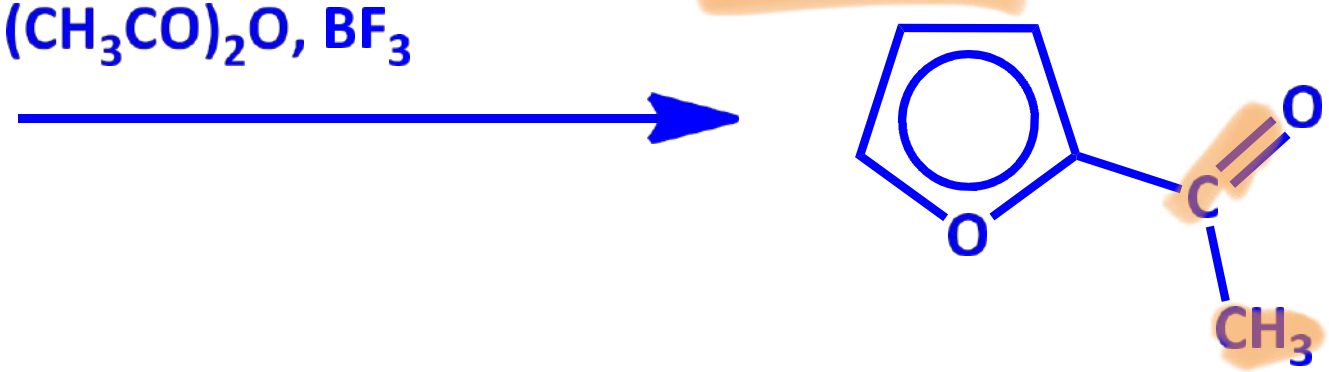


furan

Nitration



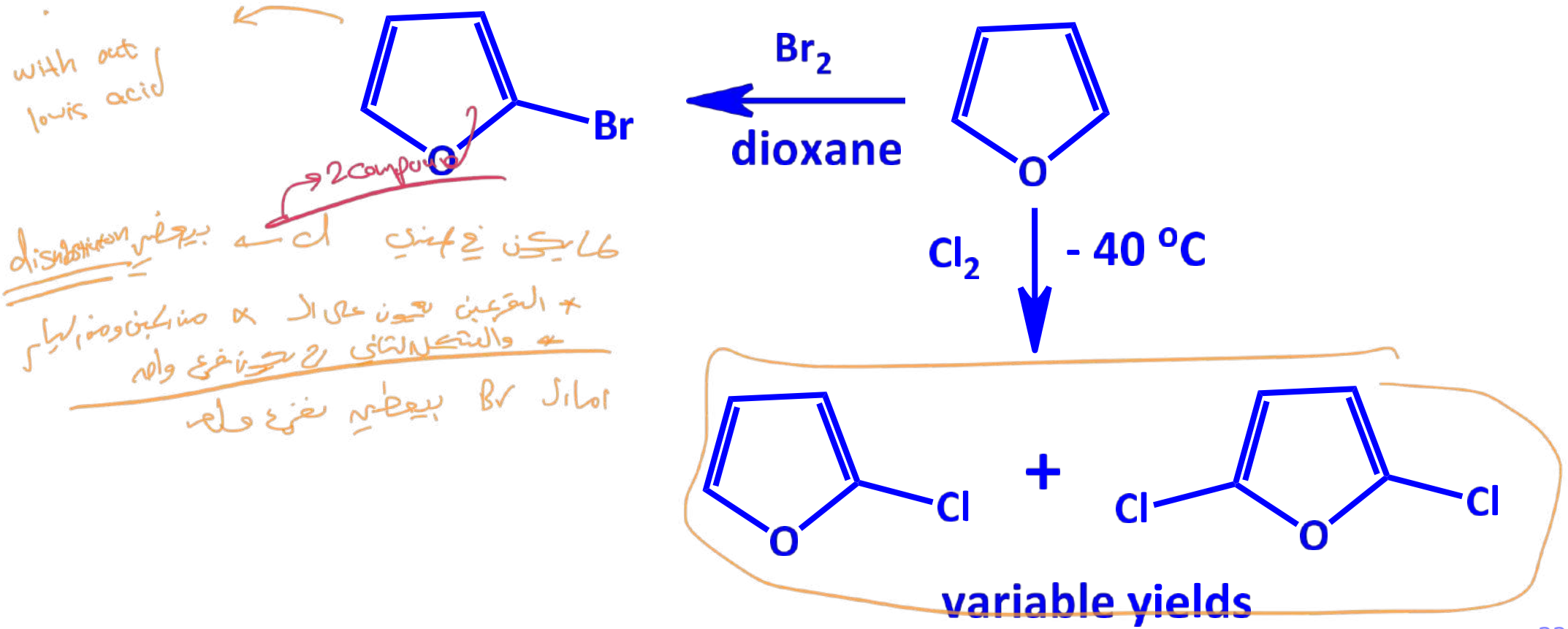
Sulfonation



Friedel Crafts acylation

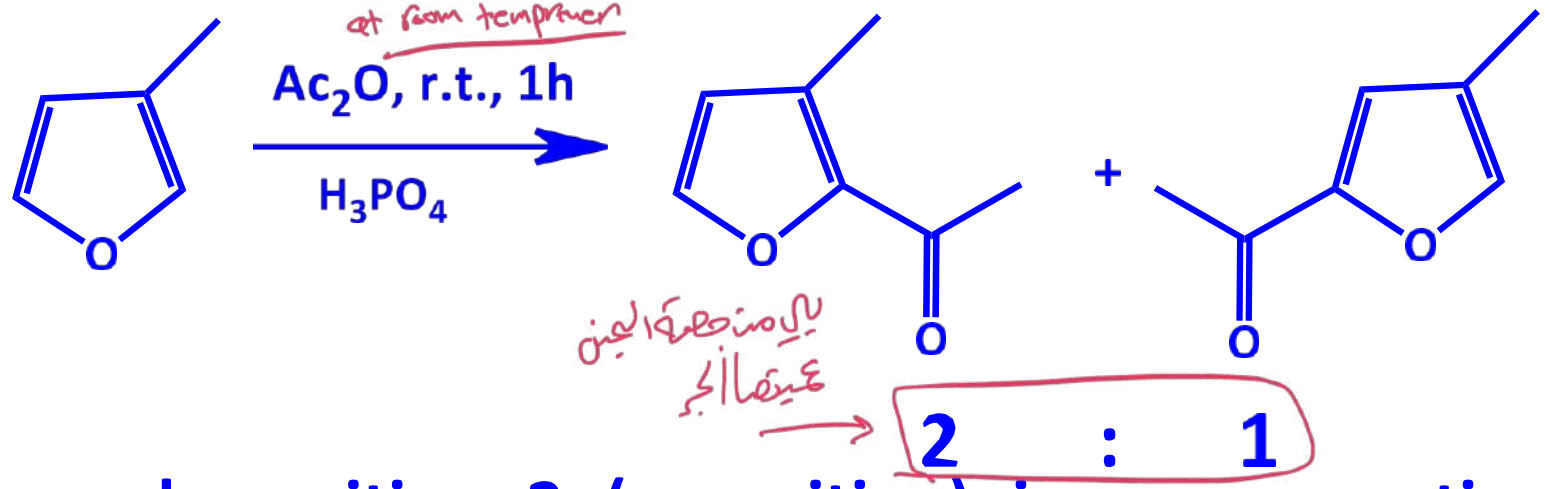
Halogenation

Furan can be halogenated at α-position. Bromination and iodination are easy to control as only one halogen atoms adds to furan. In the case of chlorination, di-substitution has been known to occur.

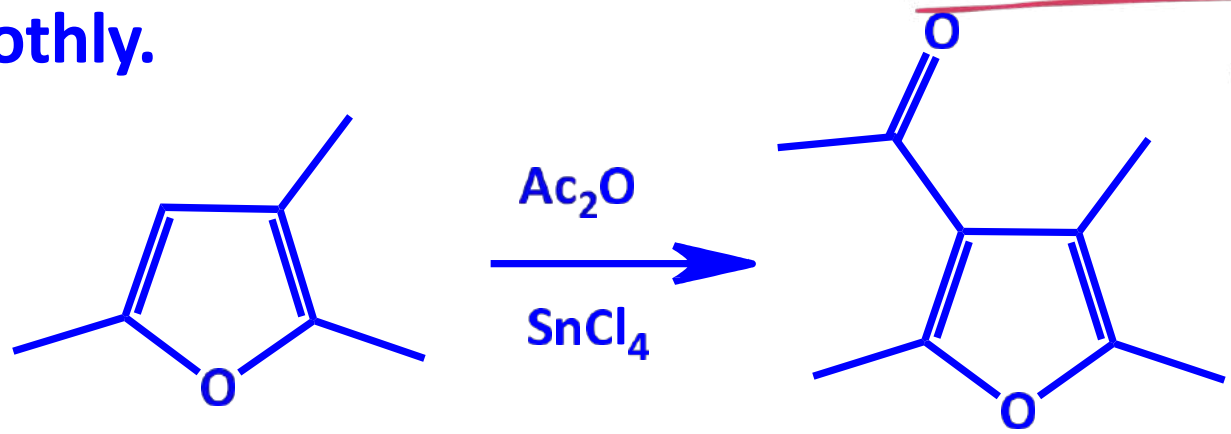


Acylation

Acetyl groups in the presence of phosphoric acid (or a Lewis acid) add at α-position of furans.

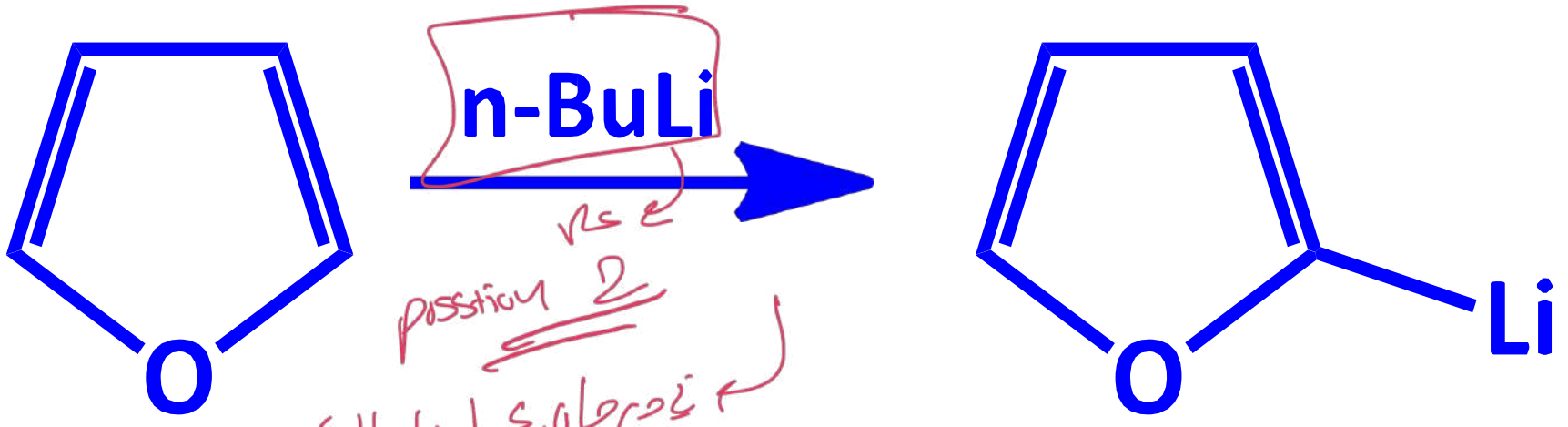


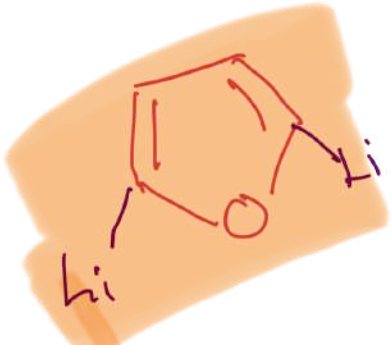
In general, position 2 (α-position) is more reactive than position 3. When position 2 is blocked, β-acylation can proceed smoothly.



Metalation

n-Butyllithium in hexane metalates furan in the 2-position, while excess of reagent at higher temperature produces 2,5-dilithiofuran.

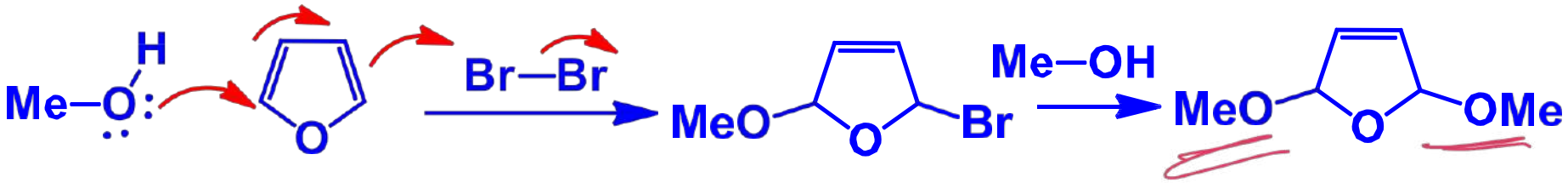




Addition reactions

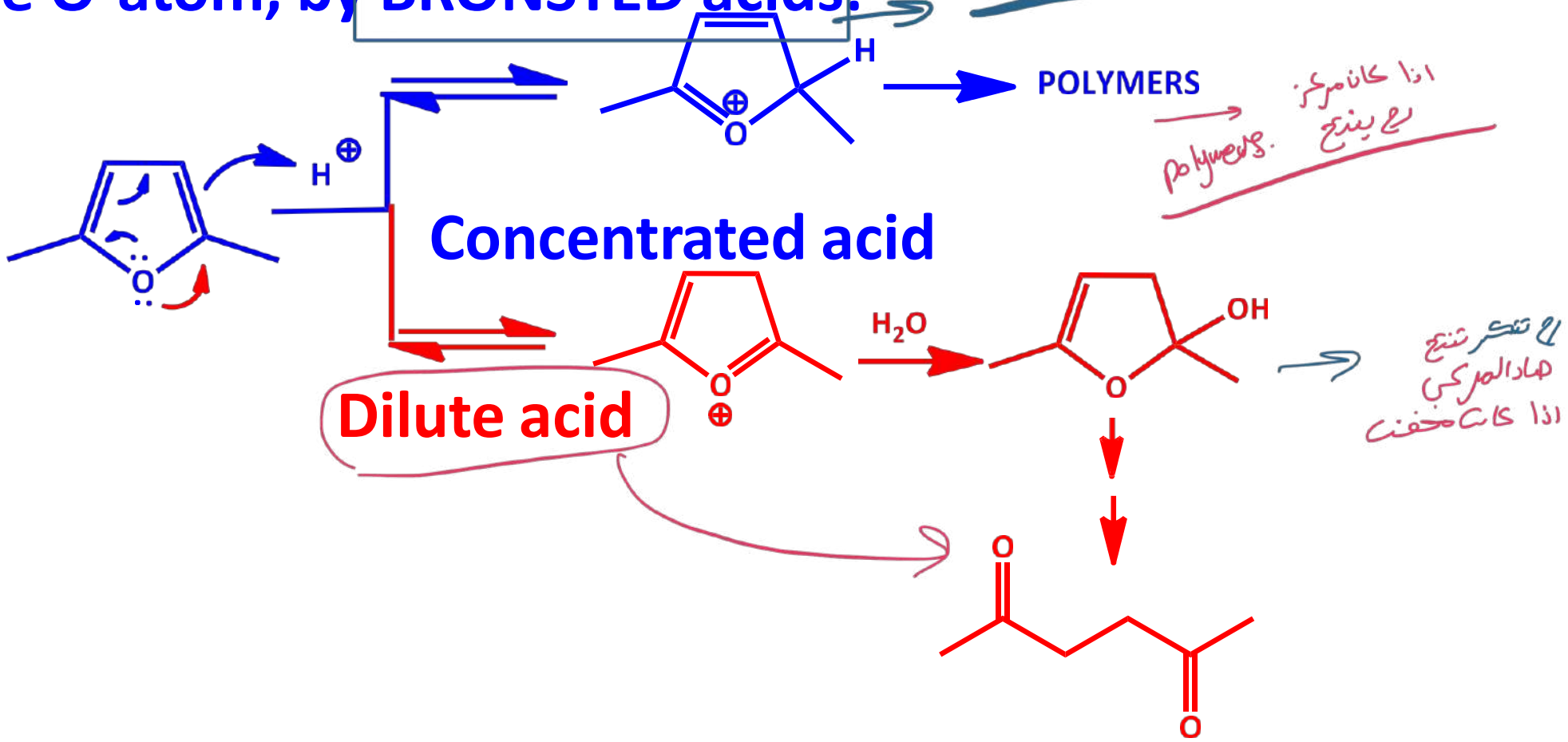
Furans yield the corresponding tetrahydrofurans by catalytic hydrogenation.

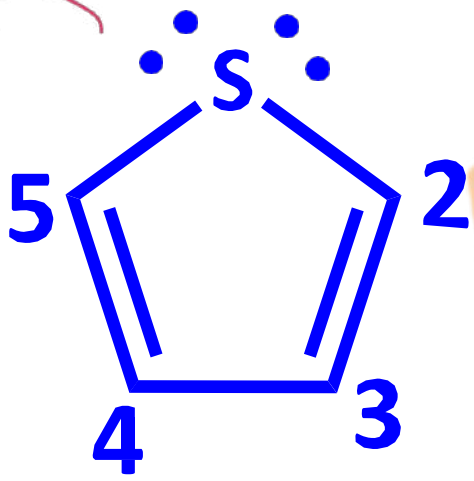
In some addition reactions, furans behave as 1,3-dienes. For example, furan reacts with bromine in methanol in the presence of potassium acetate to give 2,5-dimethoxy-2,5-dihydrofuran by a 1,4-addition:



Ring-opening reactions

Furans are protonated in the 2-position, and not on the O-atom, by BRÖNSTED acids:





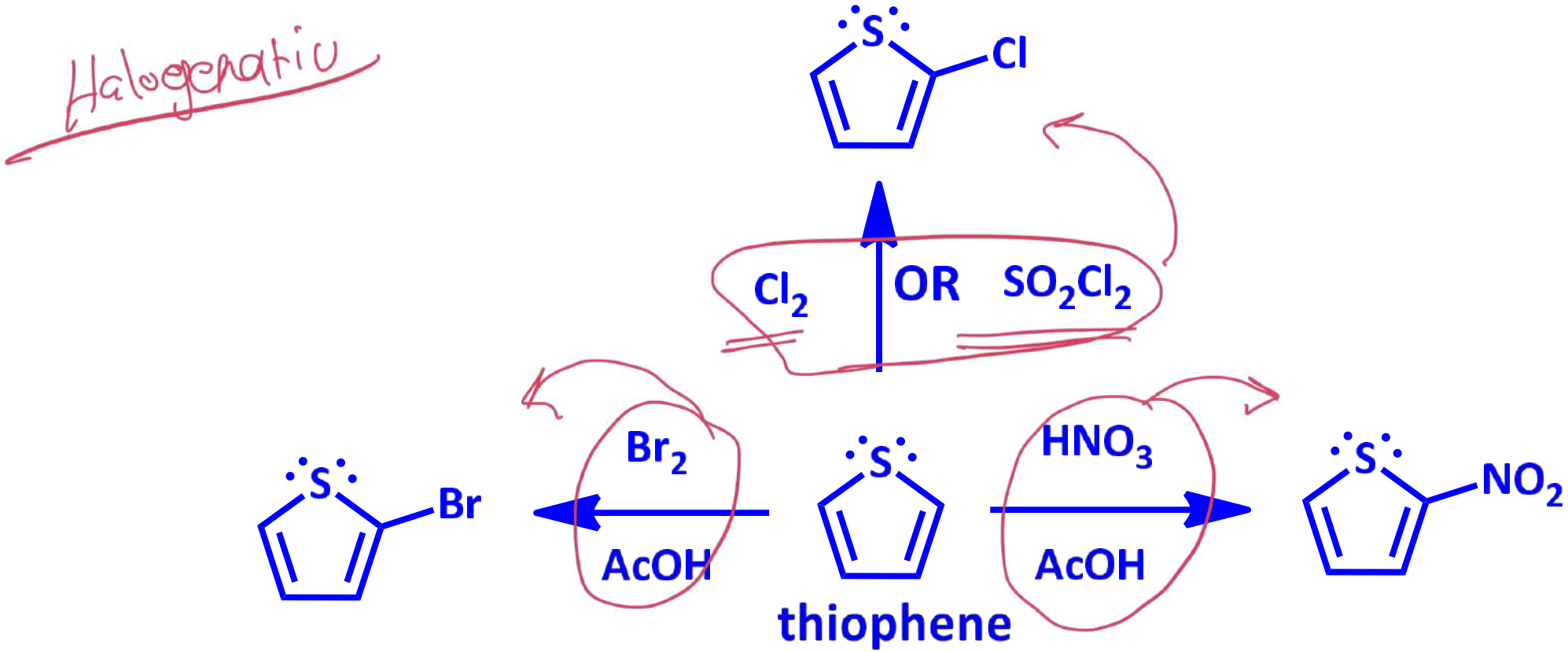
thiophene

Thiophene prefers reactions with electrophilic reagents. Additions and ring-opening reactions are less important than with furan, and substitution reactions are dominant.

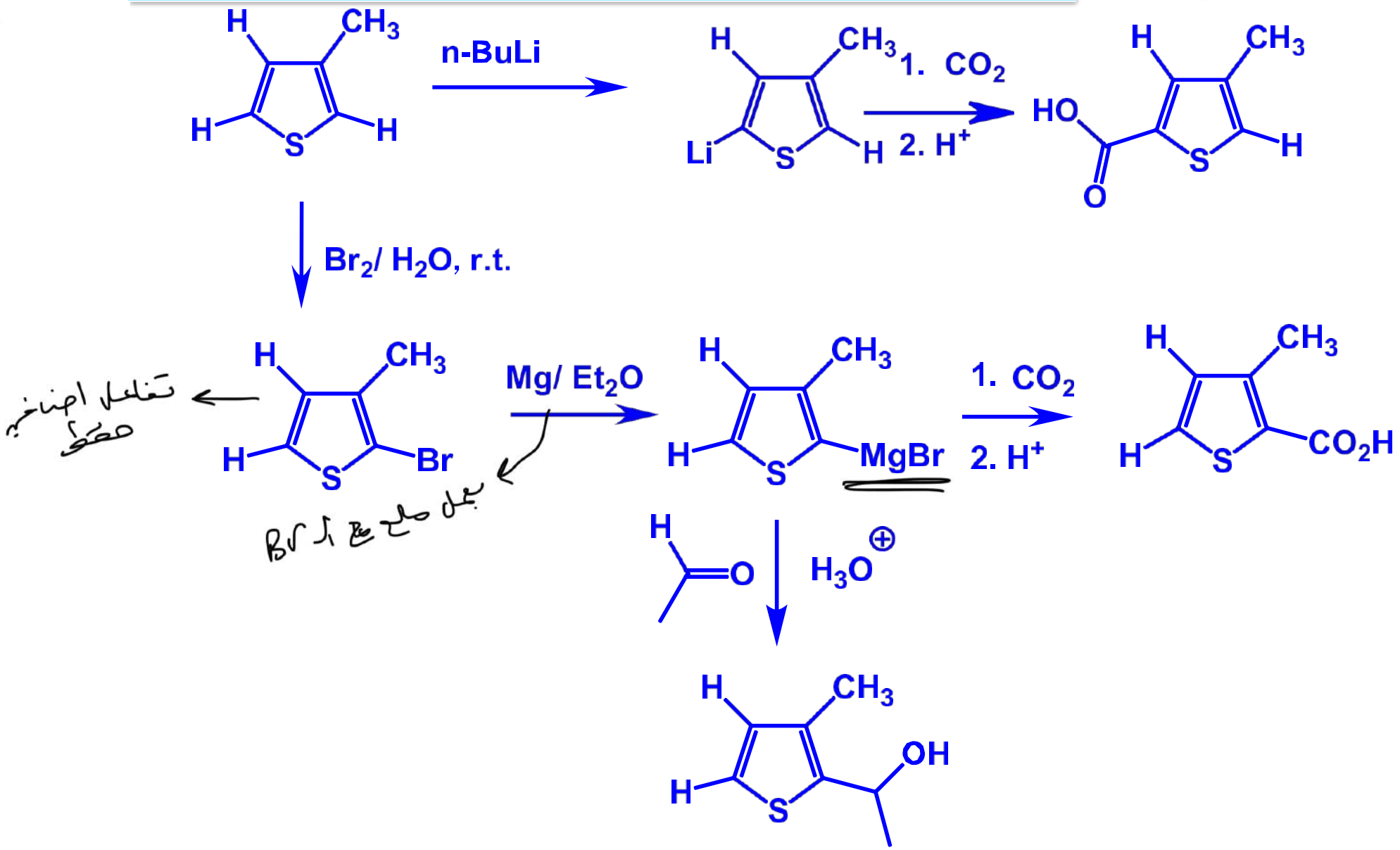
Some additional reactions, such as oxidation and desulfurization, are due to the presence of sulfur and are thus confined to thiophenes.

Electrophilic substitutions

Thiophene reacts more slowly than furan but faster than benzene. Substitution is regioselective in the 2- or in the 2,5-position.

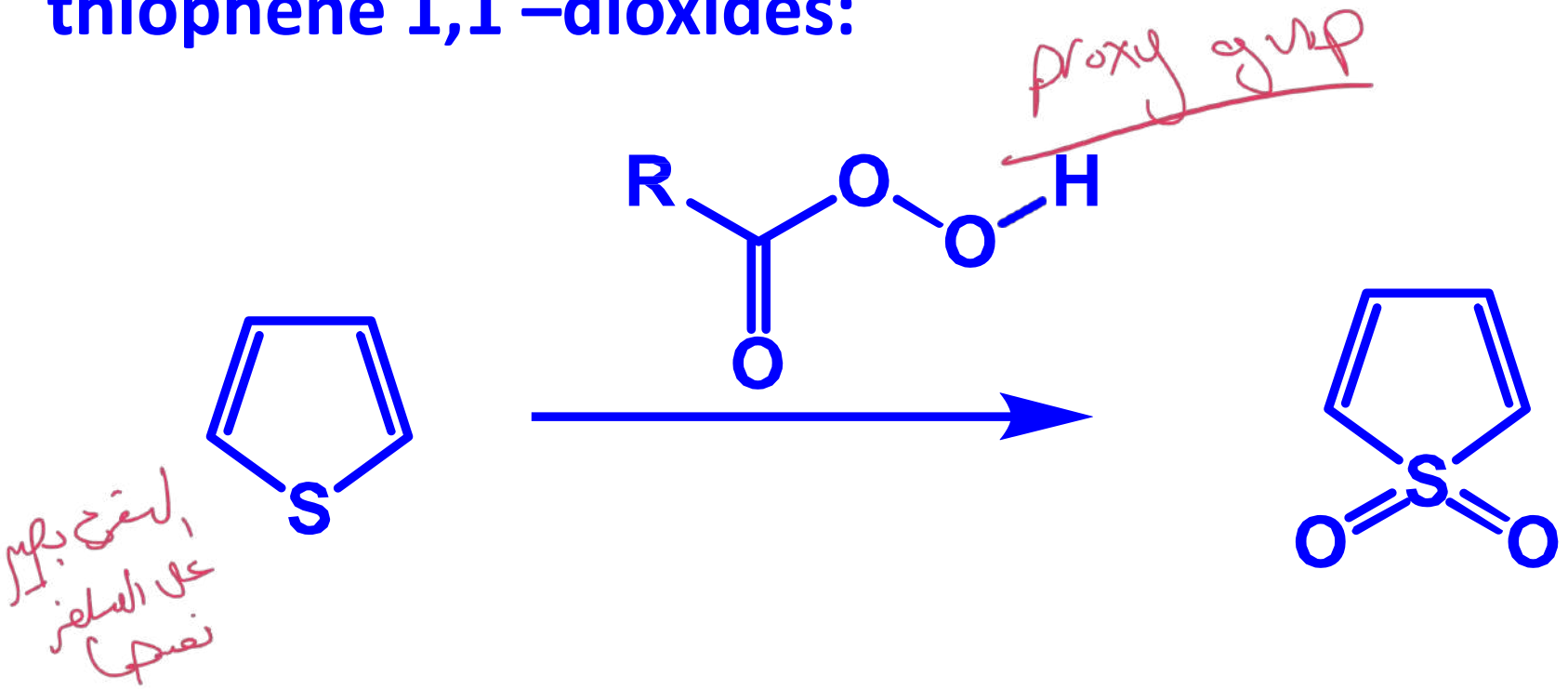


Reactions with nucleophilic reagents

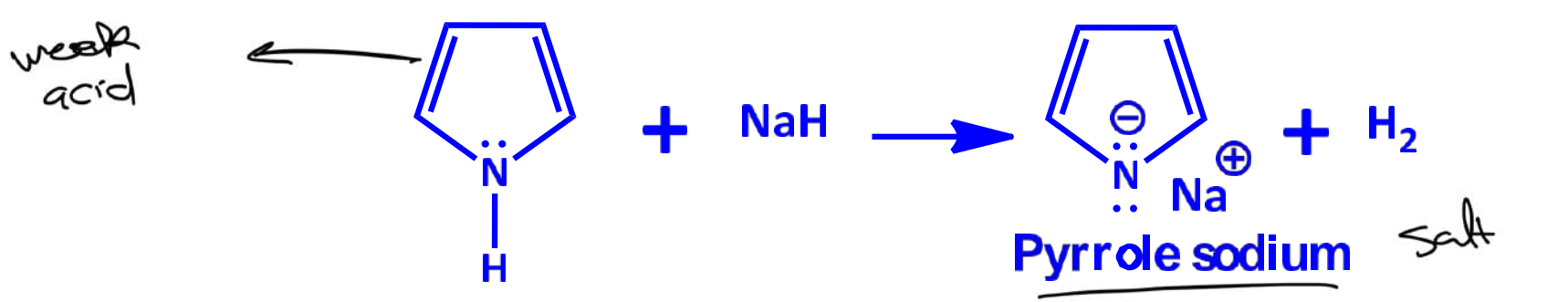


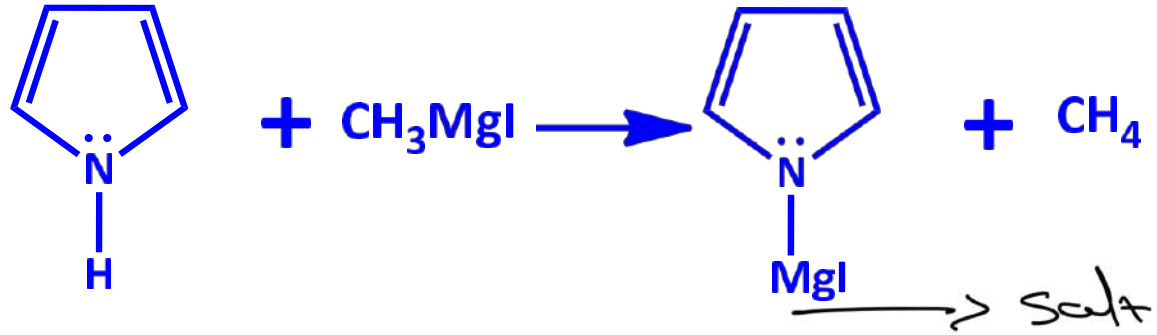
Oxidation

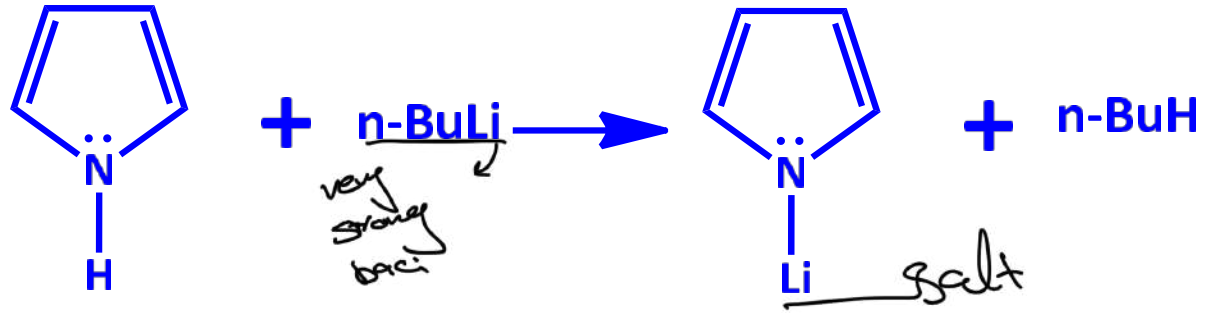
Thiophenes are oxidized by peroxy acids to give thiophene 1,1 –dioxides:



Pyrrole reacts with sodium, sodium hydride or potassium in inert solv with sodium amide in liquid ammonia, to give salt-like compounds:



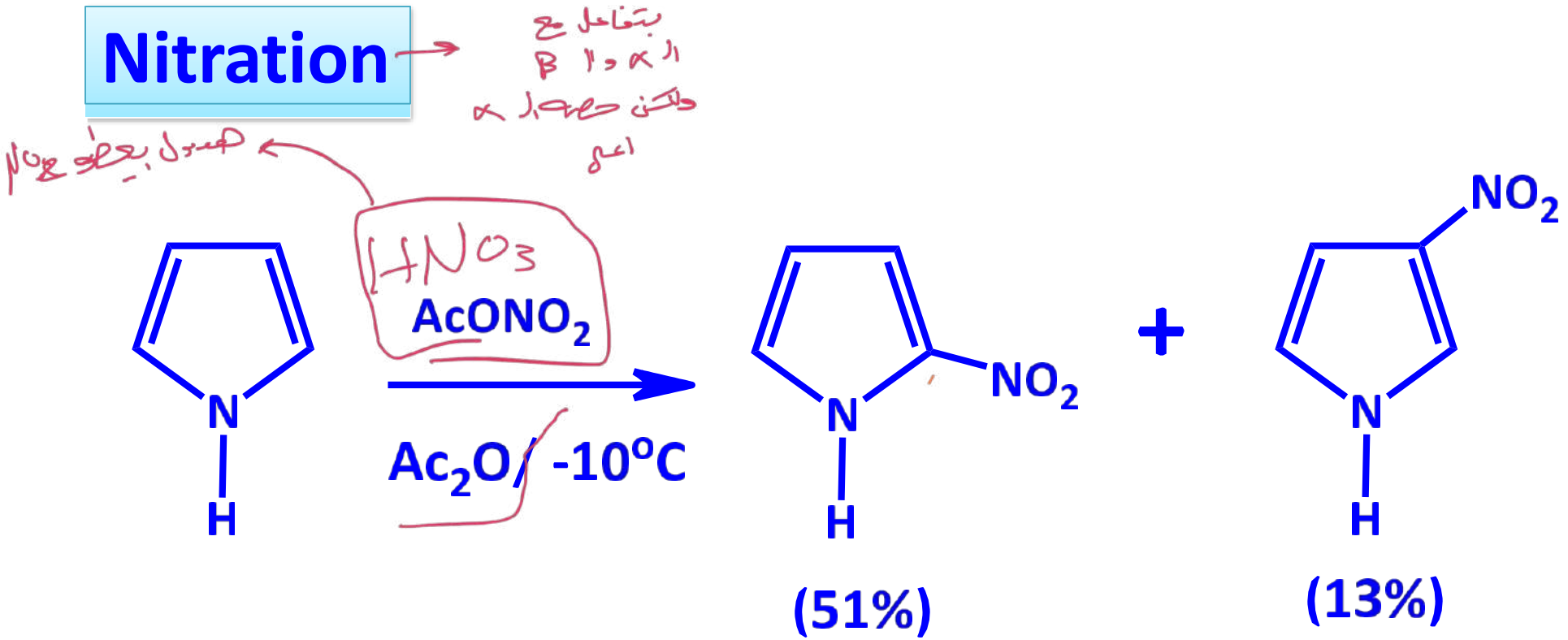




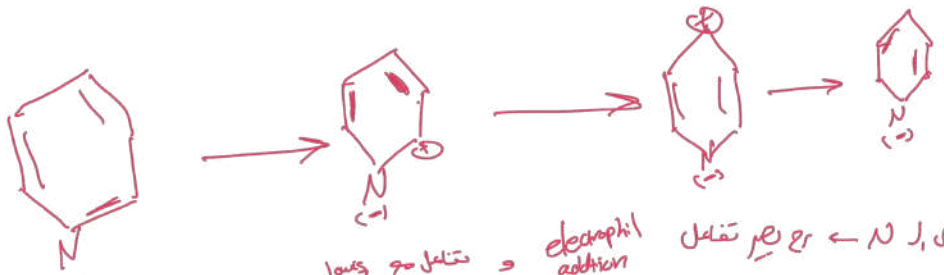
Electrophilic substitution reactions on carbon

for pyrrol

Nitration



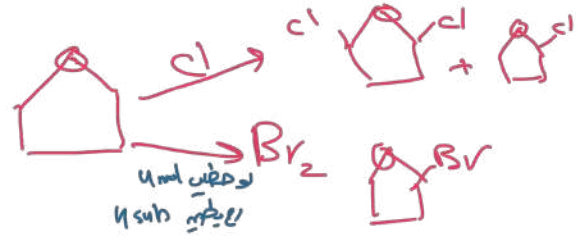
Reseron of pyridin

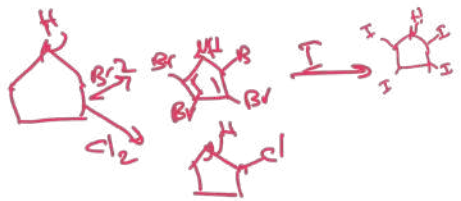


lewis acid → electrophil addition

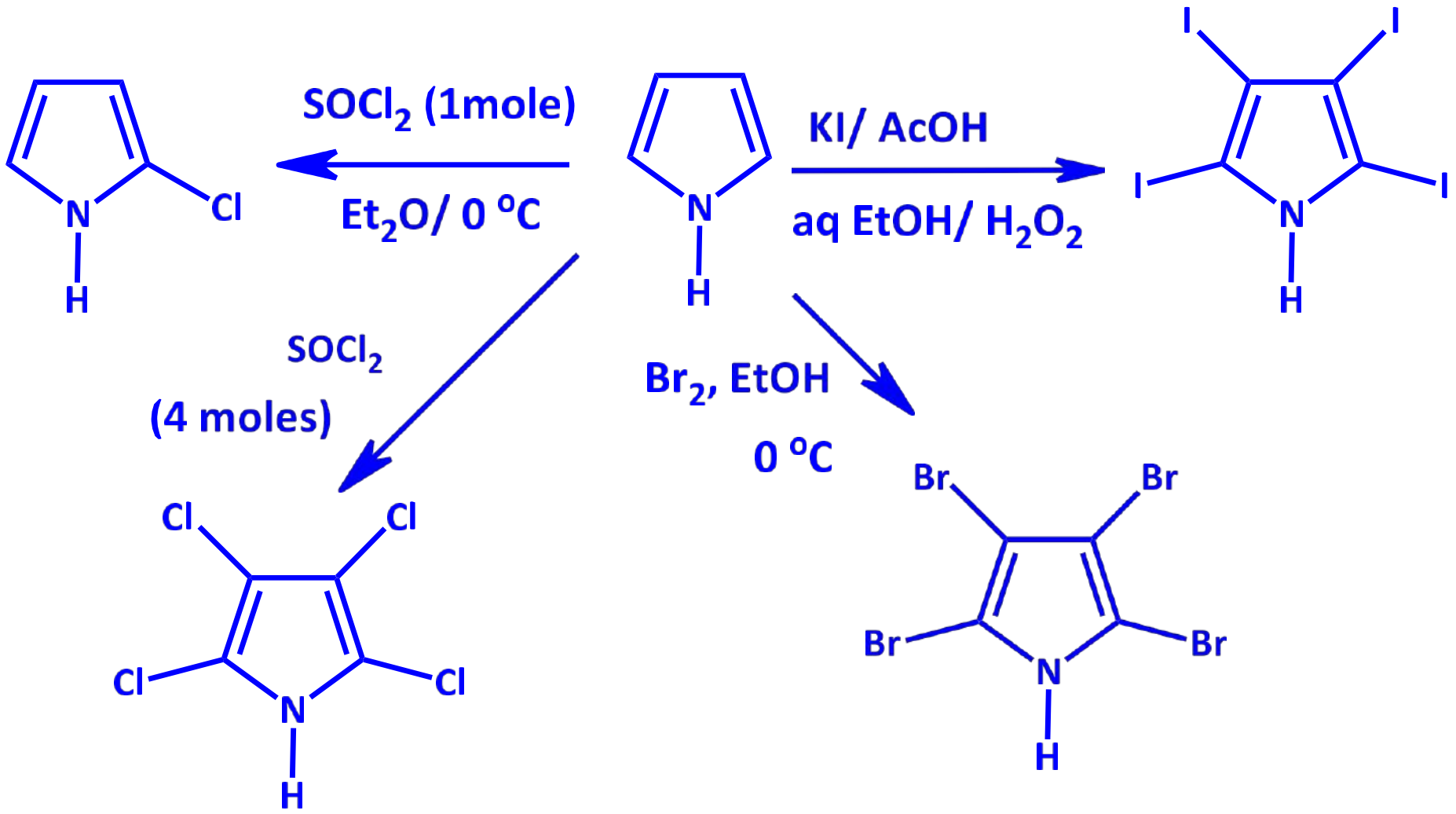
3. 5 → electrophilic substaturion → under hargh condition → very high T / strong acid

2.4.6 → (+) → nucluphile substamon



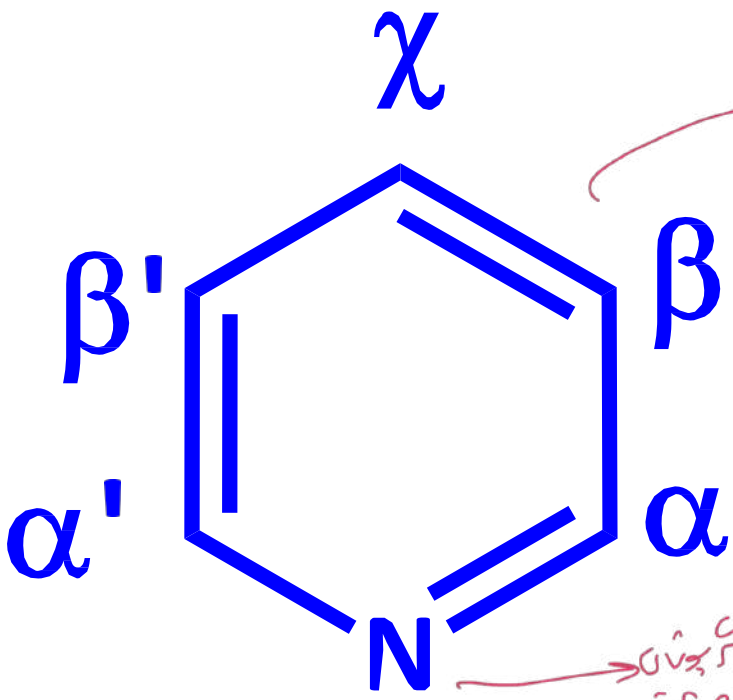


Halogenation



6-Membered Aromatic Heterocycles Containing one Heteroatom

Pyridines



Pyridine is the simplest heterocycle of the azine type. It is derived from benzene by replacement of a CH group by a N-atom.

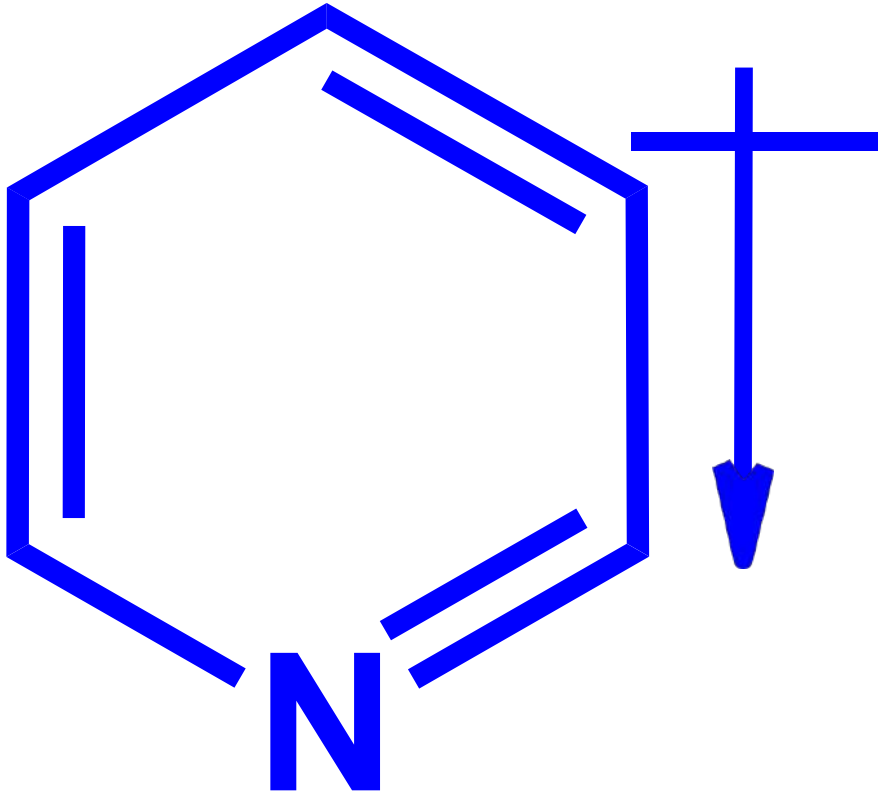
The structure of pyridine is completely analogous to that of benzene, being related by replacement of CH by N.

The key differences are:

I. The departure from perfectly regular hexagonal geometry caused by the presence of the hetero atom, in particular the shorter carbon-nitrogen bonds,

II. The replacement of a hydrogen in the plane of the ring with an unshaired electron pair, likewise in the plane of the ring, located in an sp^2 hybrid orbital, and not at all involved in the aromatic π-electron sextet; it is this nitrogen lone pair which is responsible for the basic properties of pyridines, and

III. A strong permanent dipole, traceable to the greater electronegativity of the nitrogen compared with carbon.



$\mu = 2.2$ D

The following reactions can be predicted for pyridines on the basis of their electronic structure:

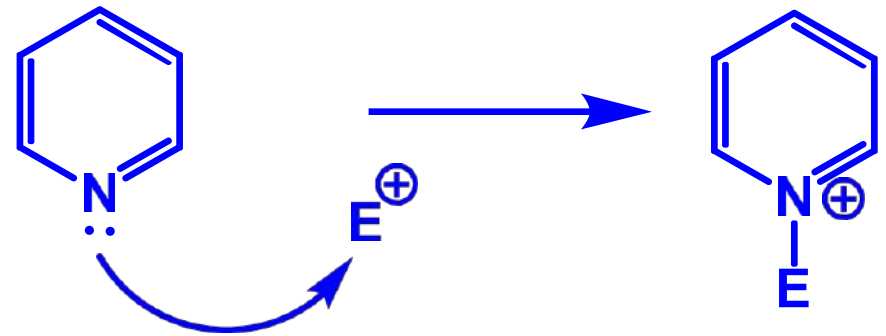
I. The heteroatom make pyridines very unreactive to normal electrophilic aromatic substitution reactions. Conversely pyridines are susceptible to nucleophilic attack. Pyridines undergo electrophilic substitution reactions (S_EAr) more reluctantly but nucleophilic substitution (S_NAr) more readily than benzene.

II. Electrophilic reagents attack preferably at the N-atom and at the β-C-atoms, while nucleophilic reagents prefer the α- and χ-C-atoms.

Reactions of Pyridine

Electrophilic Addition at Nitrogen

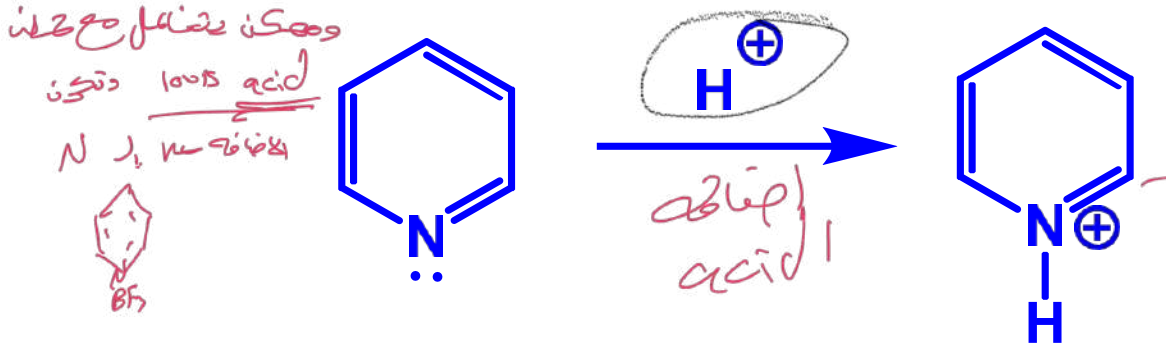
In reactions which involve bond formation using the lone pair of electrons on the ring nitrogen, such as protonation and quaternisation, pyridines behave just like tertiary aliphatic or aromatic amines.



BOTH ARE AROMATIC

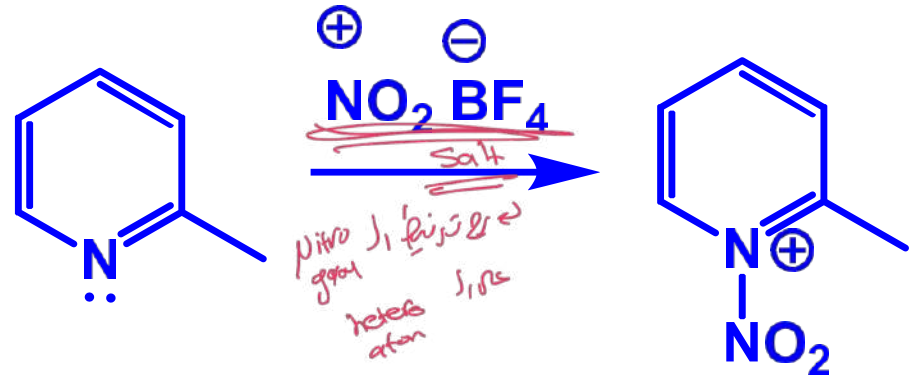
When a pyridine reacts as a base or a nucleophile it forms a pyridinium cation in which the aromatic sextet is retained and the nitrogen acquires a formal positive charge.

Protonation at Nitrogen



Pyridines form crystalline, frequently hygroscopic, salts with most protic acids.

Nitration at Nitrogen

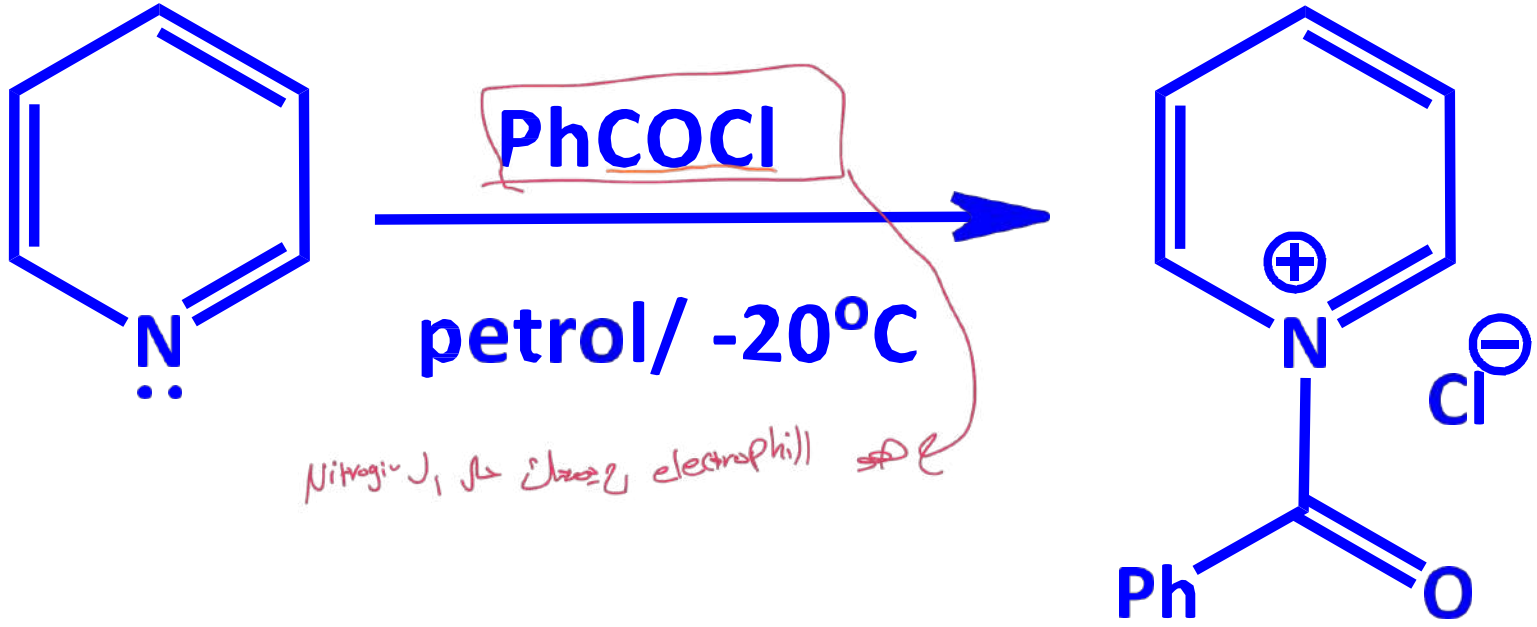


This occurs readily by reaction of pyridines with nitronium salts, such as nitronium tetrafluoroborate.

Protic nitrating agents such as nitric acid of course lead exclusively to N-protonation.

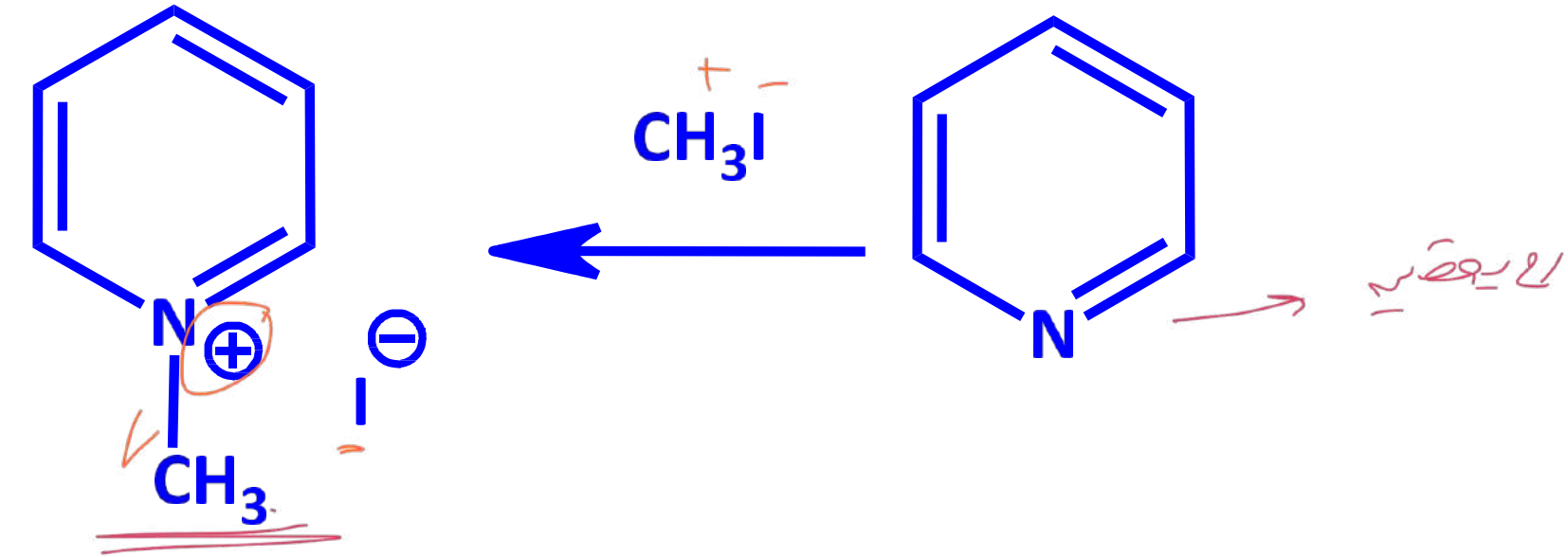
Acylation at nitrogen

Acid chlorides and arylsulfonic acids react rapidly with pyridines generating 1-acyl- and 1-arylsulfonylpyridinium salts in solution.



Alkylation at nitrogen

Alkyl halides and sulfates react readily with pyridines giving quaternary pyridinium salts.

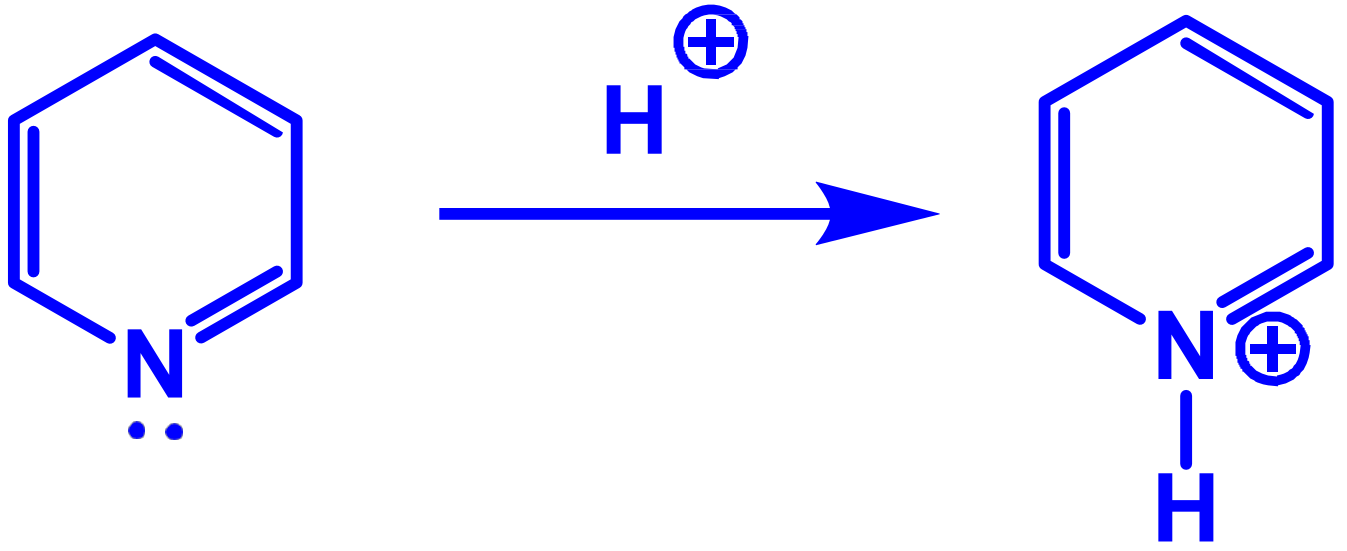


Electrophilic substitution at Carbon atoms of the pyridine ring

Electrophilic substitution of pyridines at a carbon is very difficult. Two factors seem to be responsible for this unreactivity:

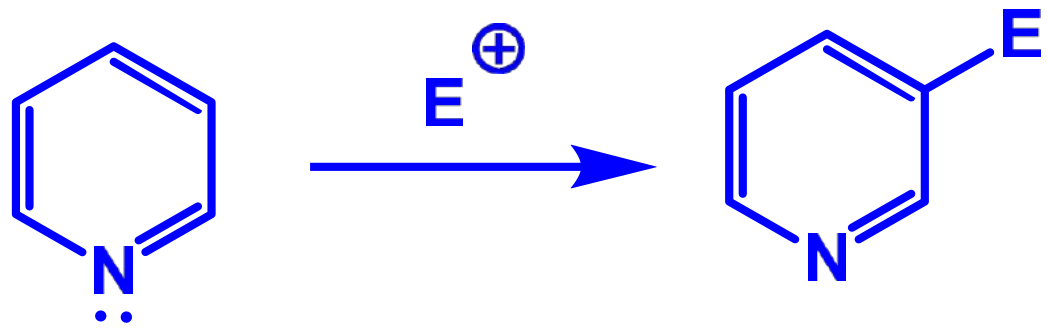
I. Pyridine ring is less nucleophilic than the benzene ring; nitrogen ring atom is more electronegative than carbon atoms and therefore it pulls electrons away from the carbon atoms inductively leaving a partial plus on the carbon atoms.

II. When pyridine compound is exposed to an acidic medium, it forms pyridinium salt. This increases resistance to electrophilic attack since the reaction will lead to doubly positive charged species.



Less reactive than pyridine

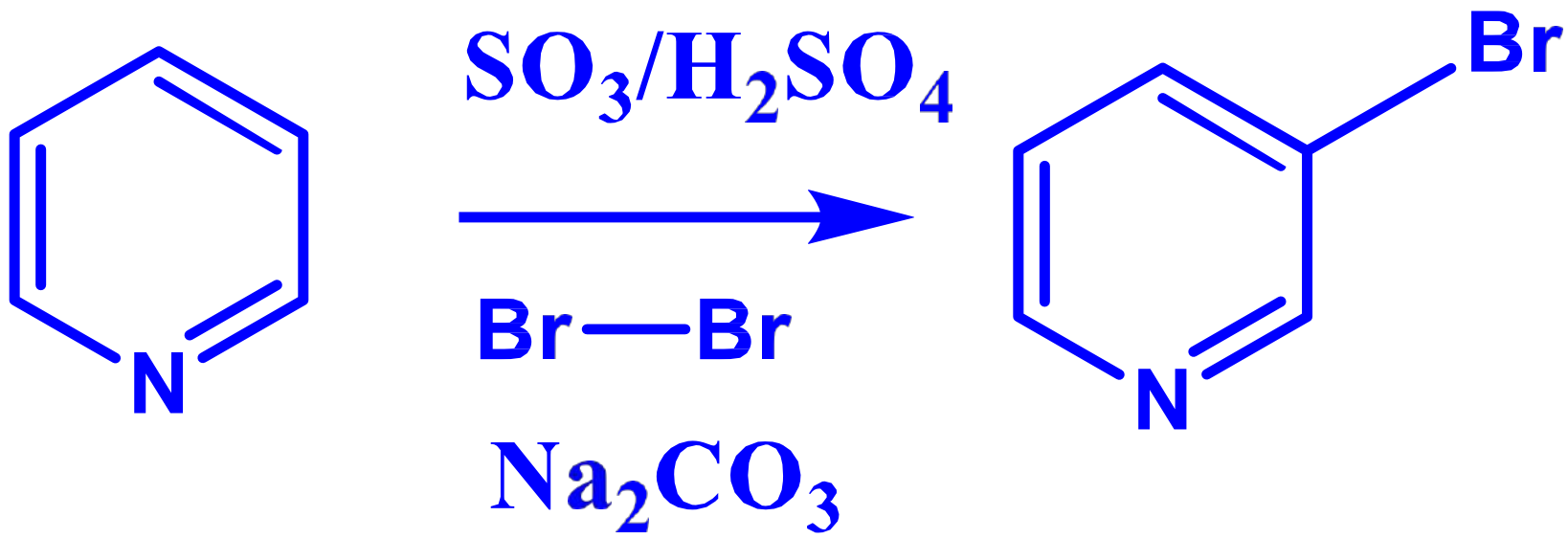
When an electrophile attacks the pyridine ring, only position 3 attacked.

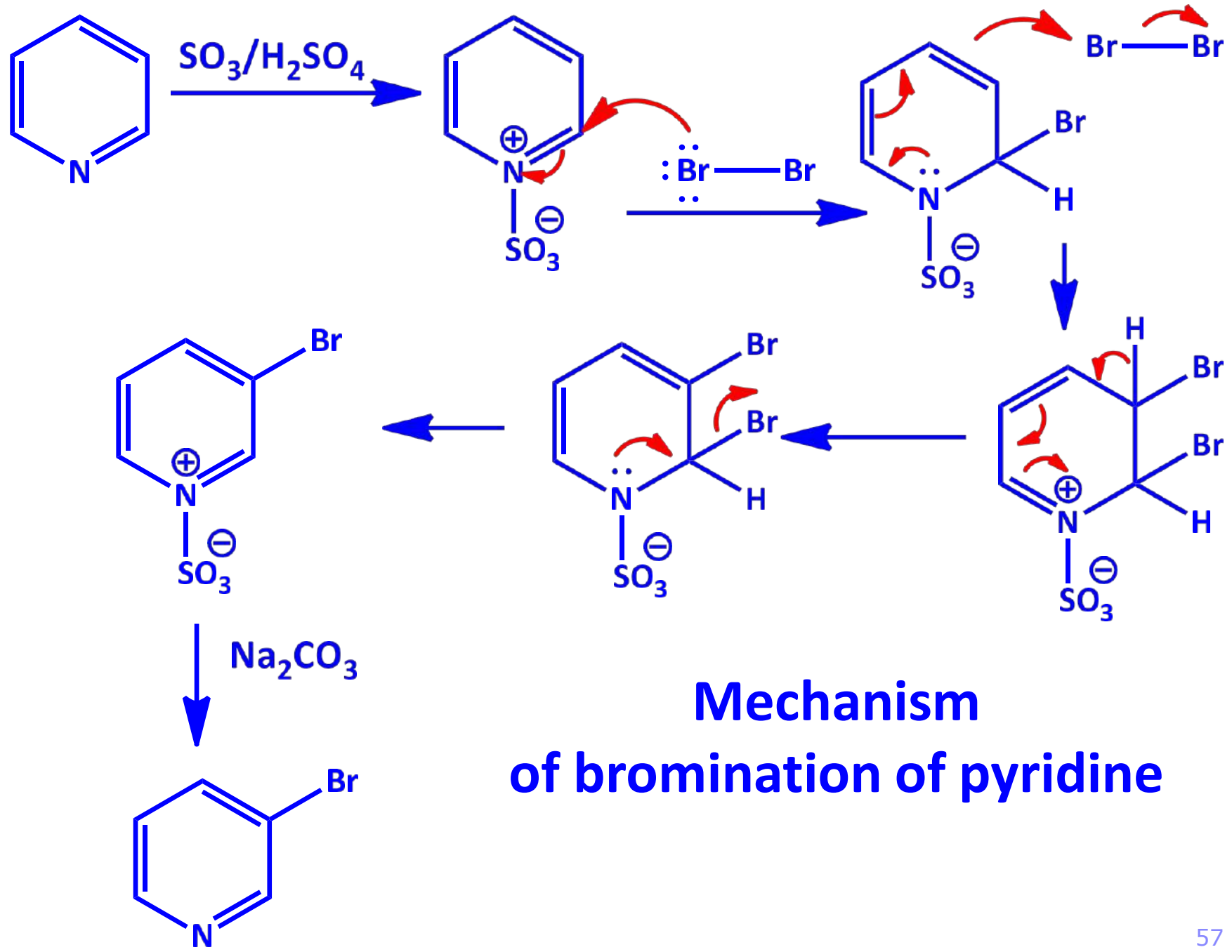


Why?

Hint: draw resonance structures that result from electrophilic attack at various positions. The positive charge residing on an electronegative element with sextet configuration is unfavoured.

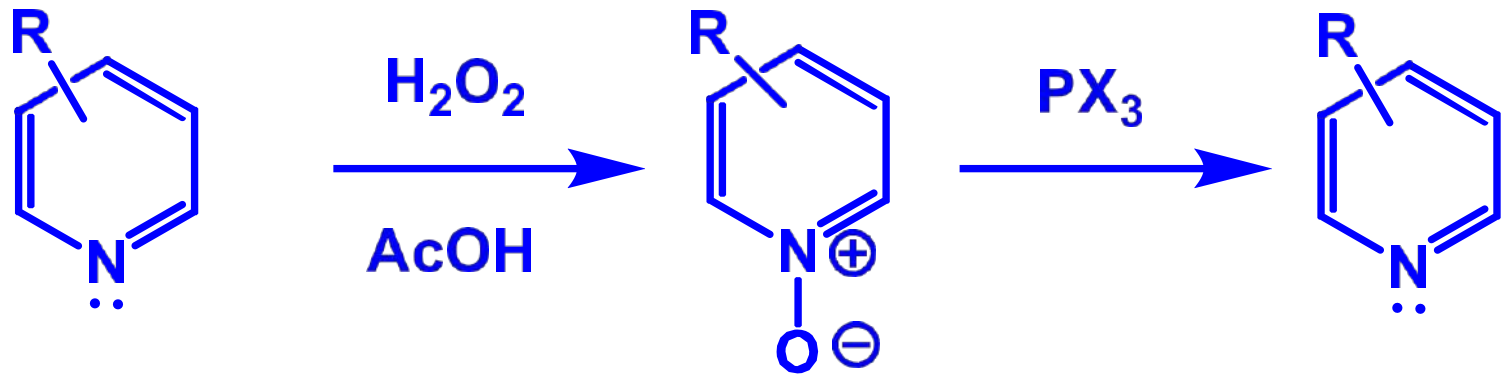
For example, 3-bromopyridine is formed when pyridine is reacted with bromine in the presence of oleum (sulfur trioxide in conc. sulfuric acid) at 130˚C.





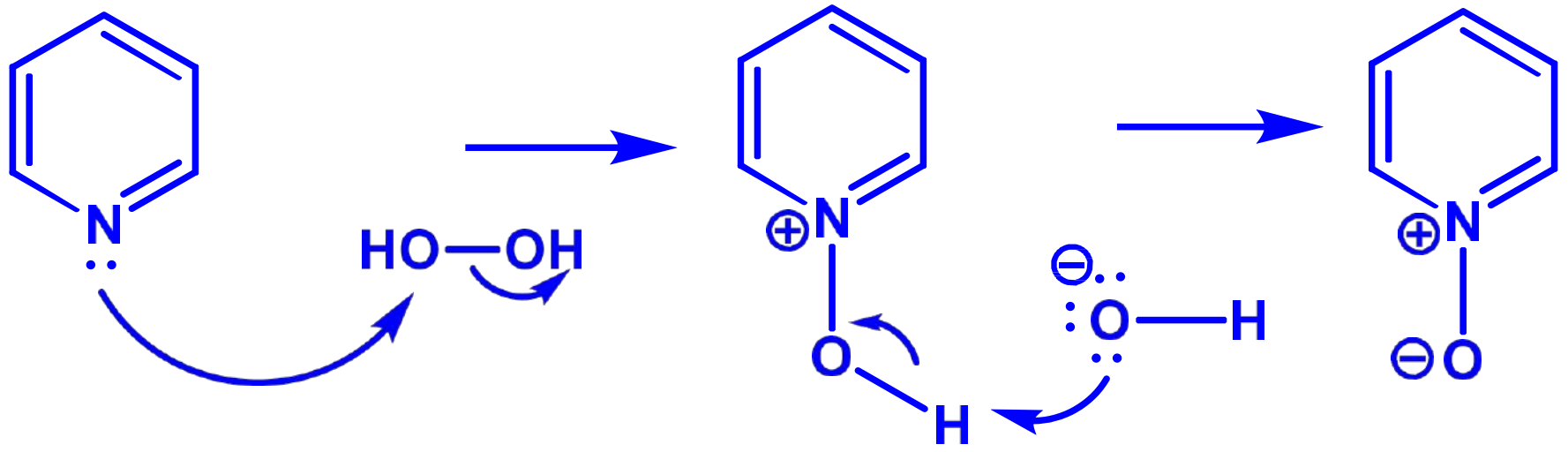
Mechanism of bromination of pyridine

Pyridine can be activated to electrophilic substitution by conversion to pyridine-N-oxides.

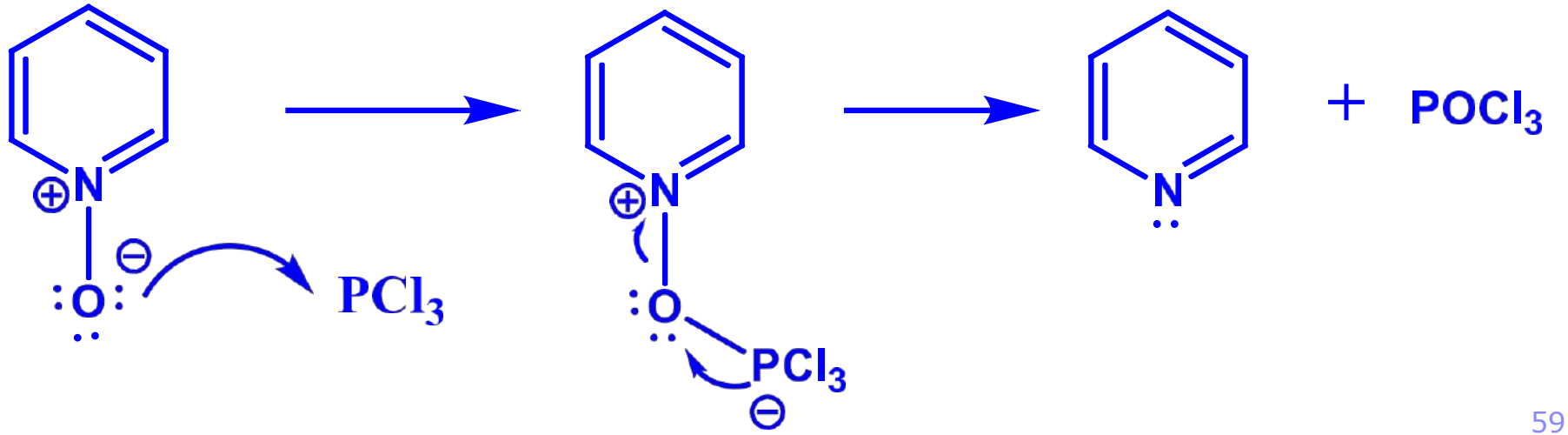


pyridine N-oxide

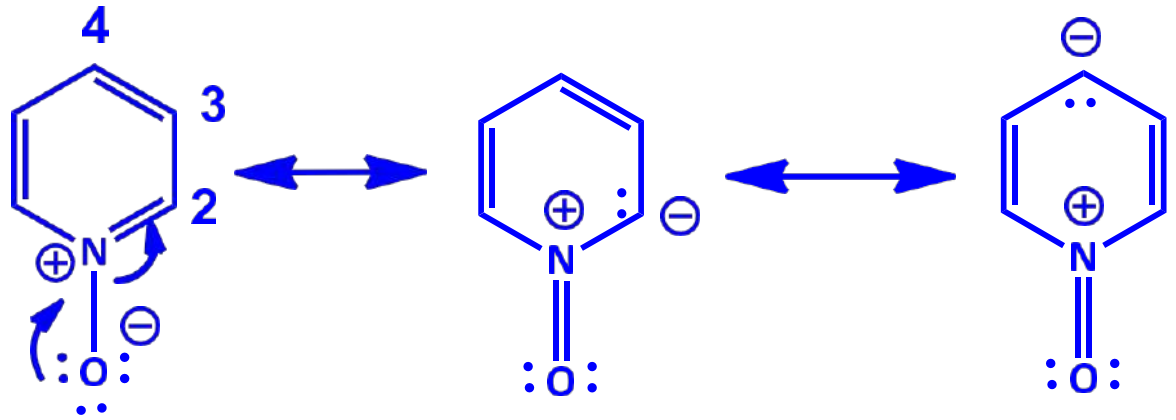
A series of preparatively interesting reactions on pyridine can be carried out by means of pyridine *N-oxides* such as the introduction of certain functions into the ring and side-chain which cannot be achieved in the parent system by direct methods.



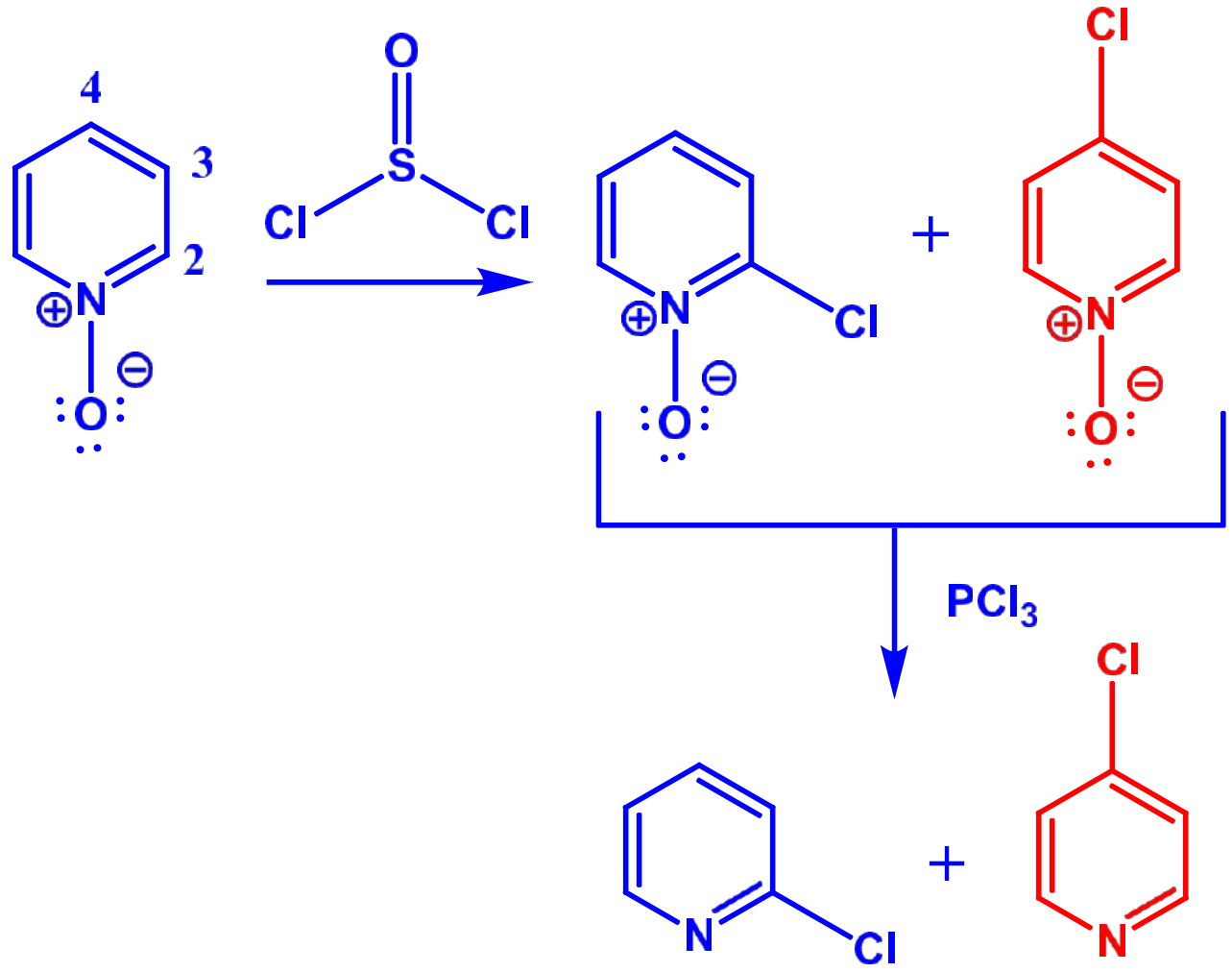
The activating oxygen atom can be removed by reacting the pyridine N-oxide with phosphorous trichloride.



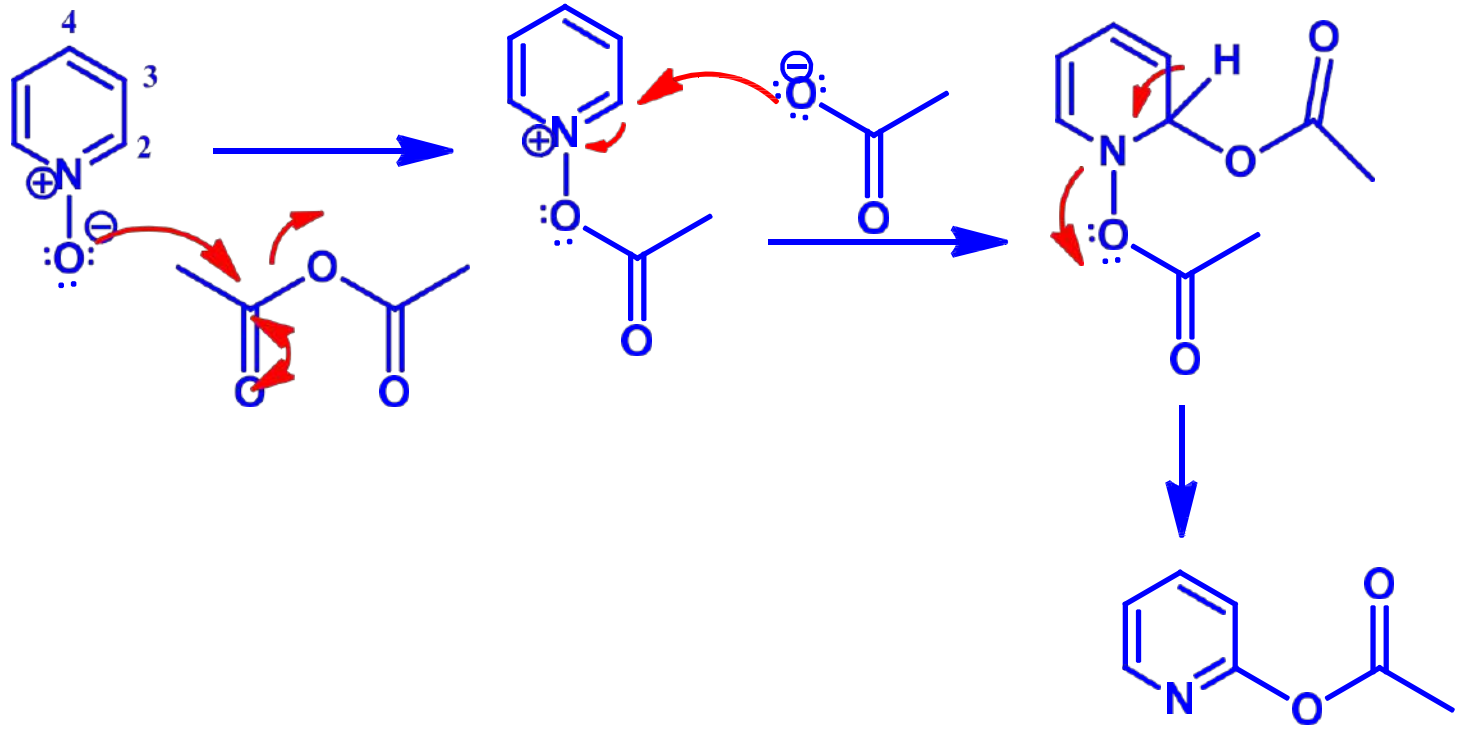
In such reactions there is a balance between electron withdrawal, caused by the inductive effect of the oxygen atom, and electron release through resonance from the same atom in the opposite direction. Here, the resonance effect is more important, and electrophiles react at C-2(6) and C-4.



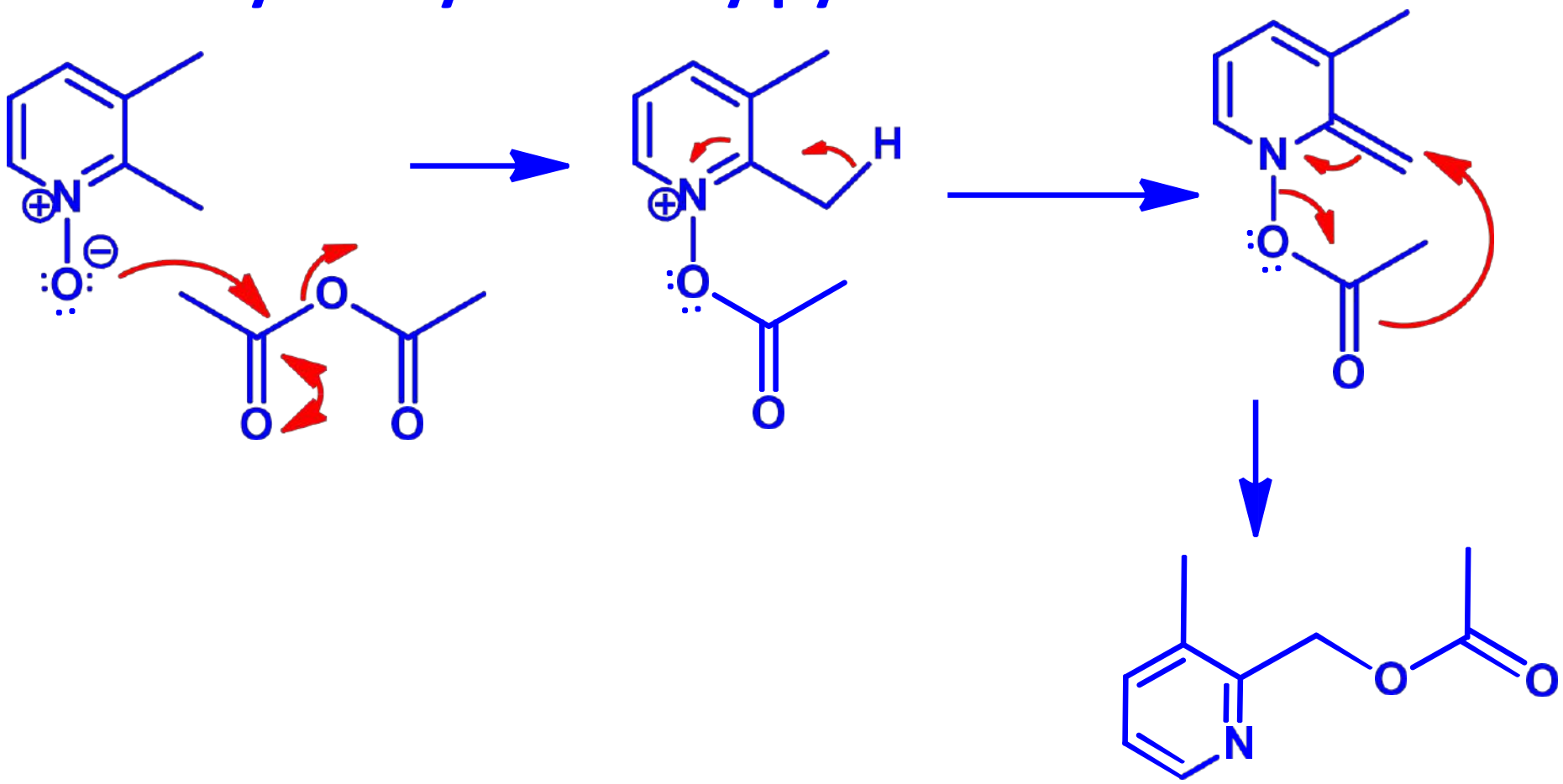
Thionyl chloride, for example, gives a mixture of 2- and 4-chloropyridine N-oxides in which the 4-isomer is predominant.

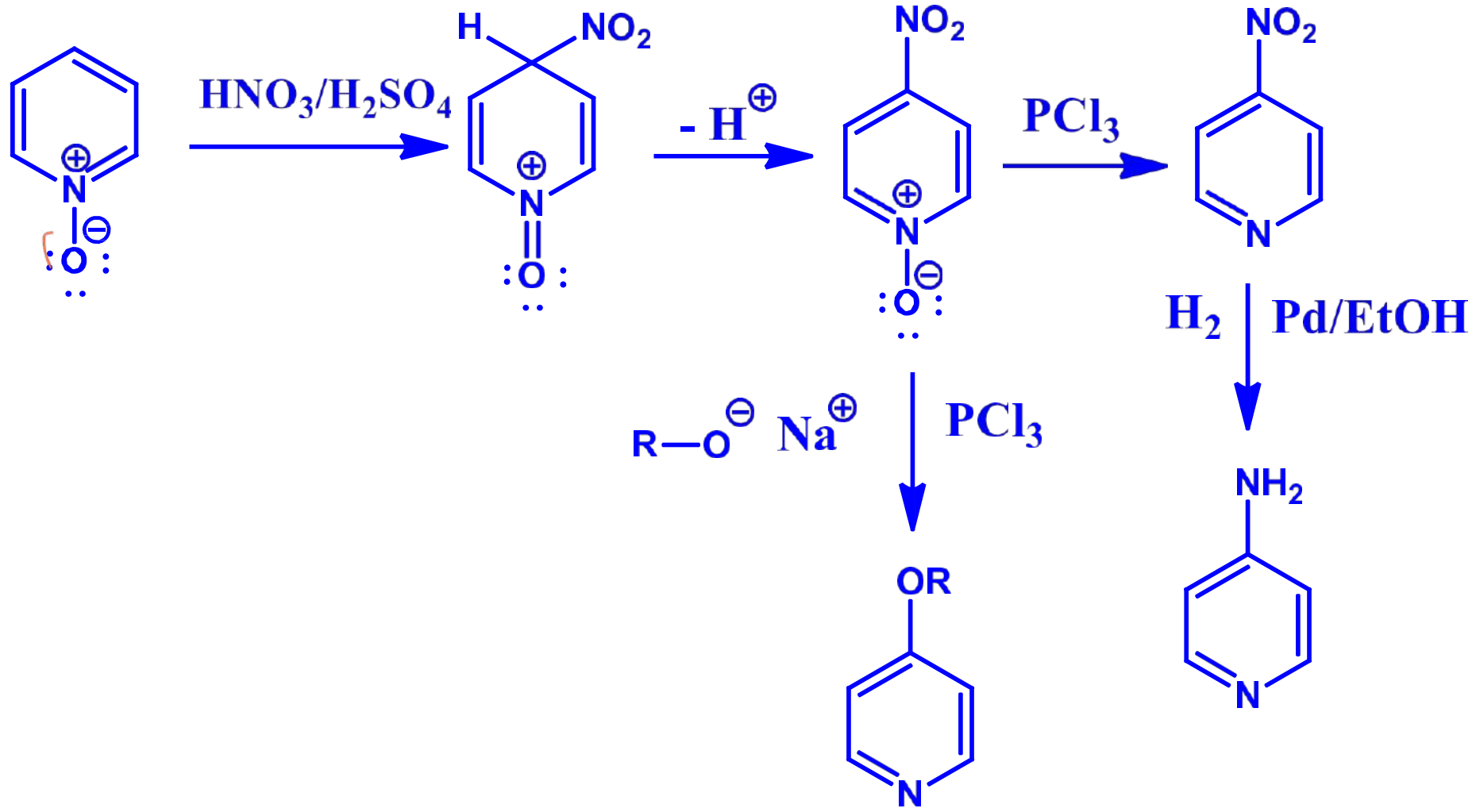


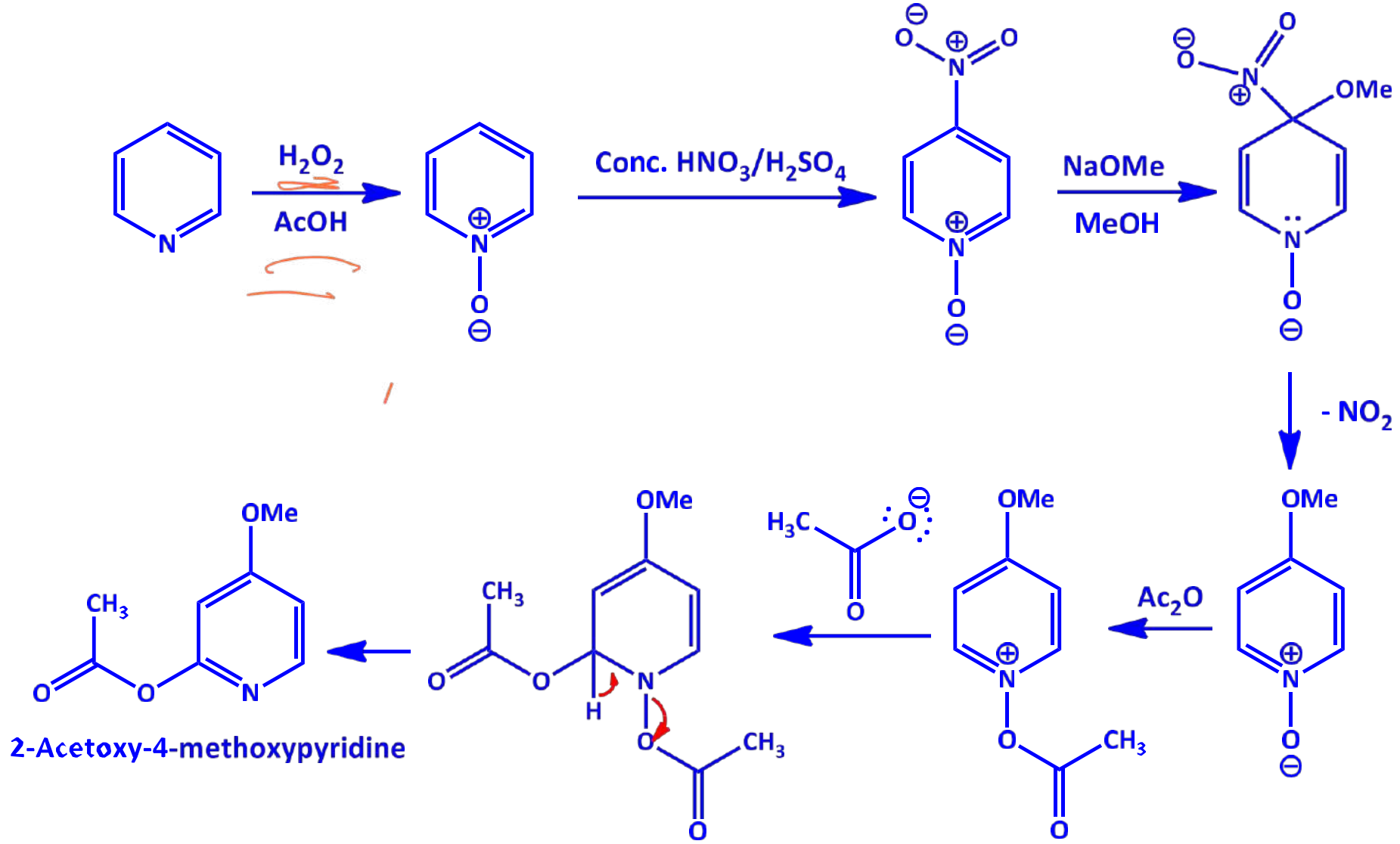
However, pyridine N-oxide reacts with acetic anhydride first to give 1-acetoxypyridinium acetate and then, on heating, to yield 2-acetoxypyridine through an addition-elimination process.



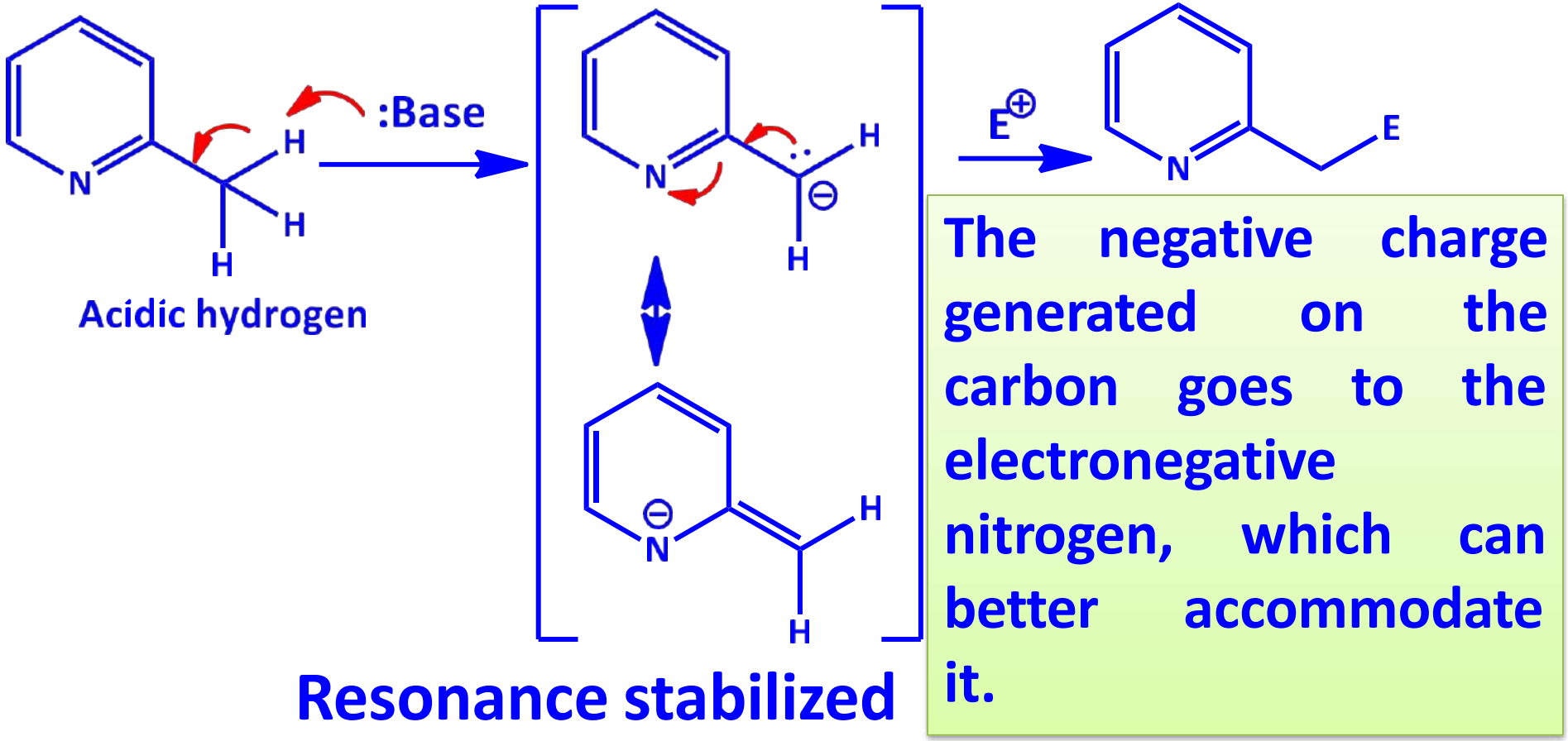
When a similar reaction is carried out upon the 2,3-dimethyl analogue, the acetoxy group rearranges from N-1 to the C-2 methyl group, at 180^{0}C, to form 2-acetoxymethyl-3-methylpyridine.




HNO3/H2SO4
- H⊕
PCl3
H2
Pd/EtOH
R—O⊖ Na⊕
PCl3
NO2
H
NO2
NO2
NH2
OR
N
O


H2O2
AcOH
Conc. HNO3/H2SO4
NaOMe
MeOH
OMe
- NO2
Ac2O
H3C
CH3
2-Acetoxy-4-methoxypyridine

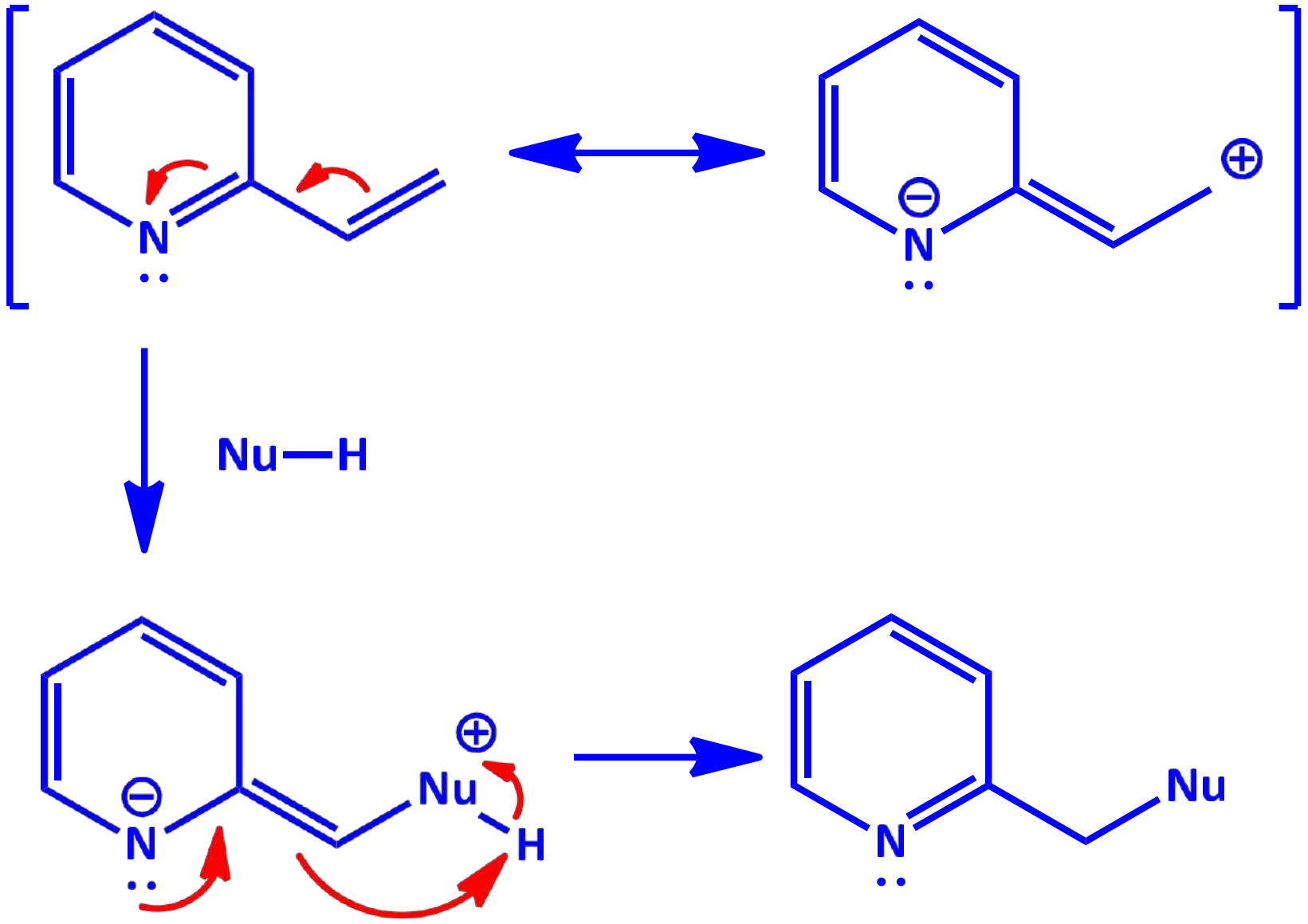
Anion Chemistry of Pyridine

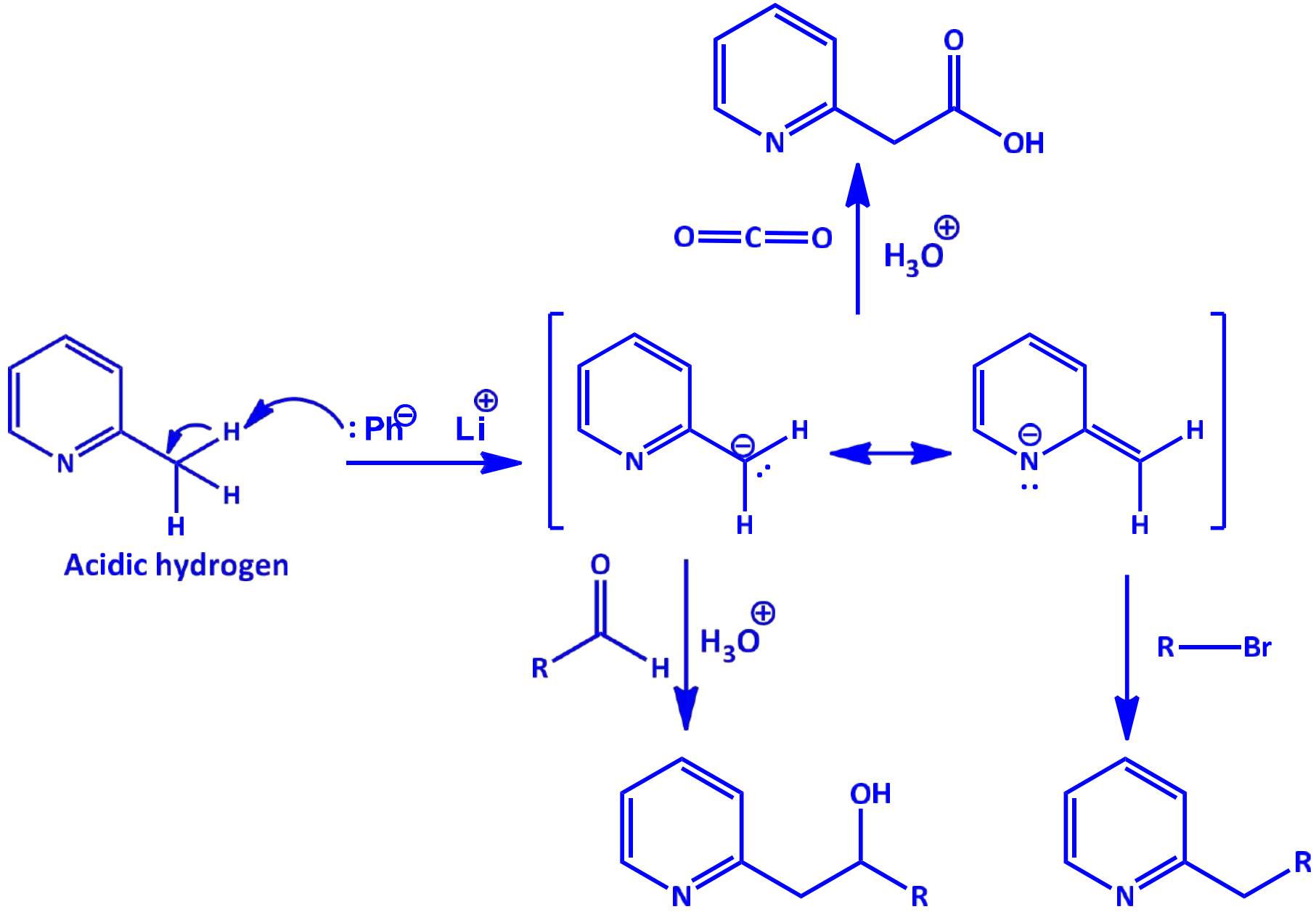


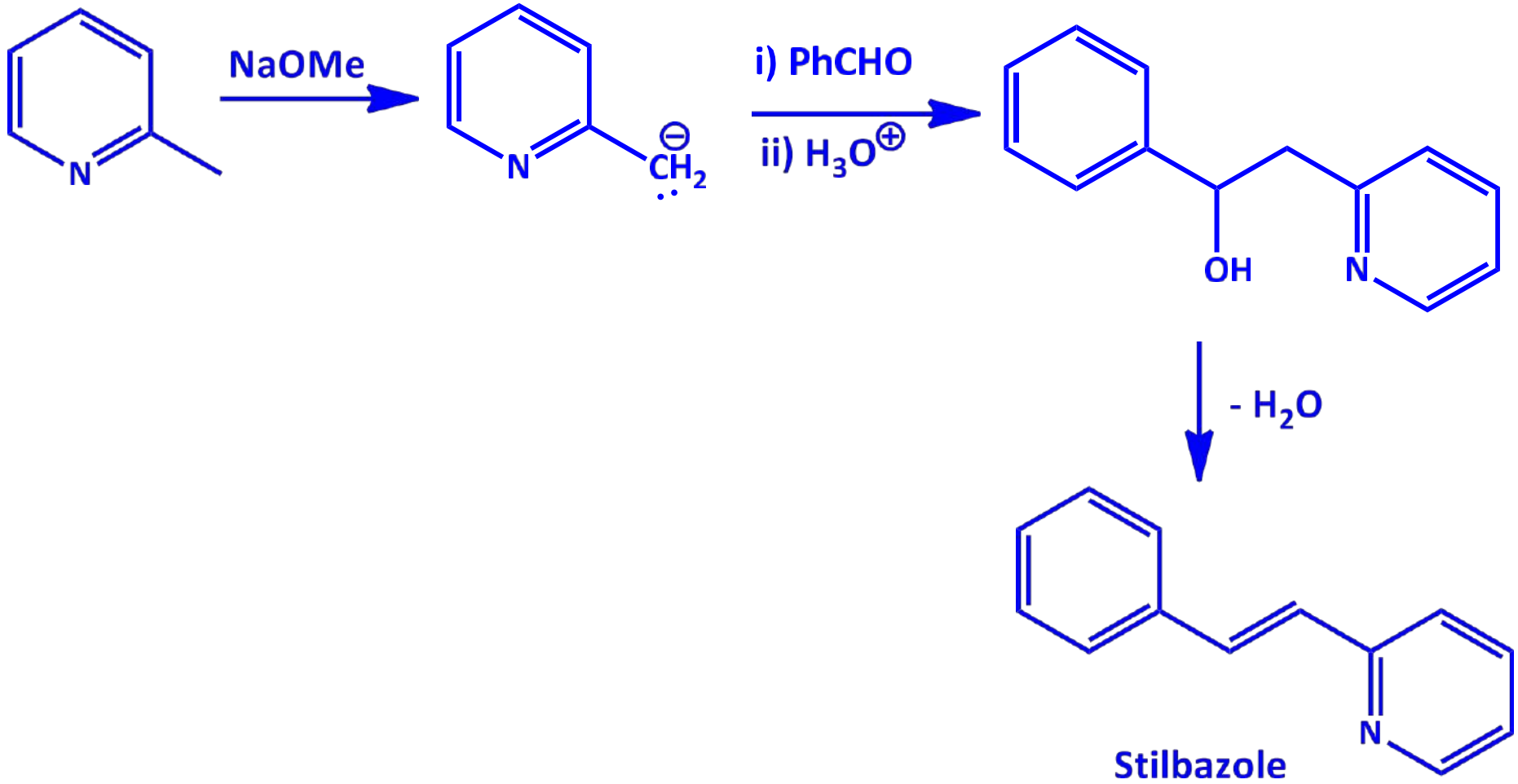
Resonance stabilized

The negative charge generated on the carbon goes to the electronegative nitrogen, which can better accommodate it.

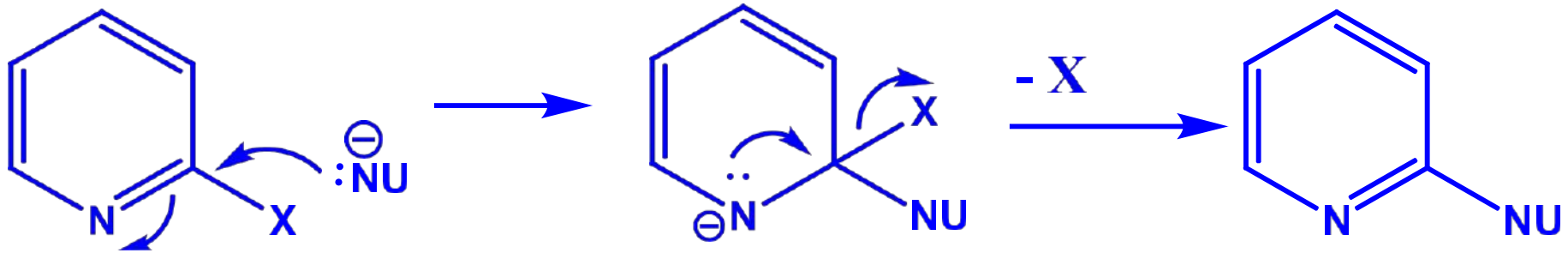
Works for 2(6)- and 4-alkylpyridines not for 3(5)-alkyl pyridines, why?


N
N
Nu—H
N
Nu
H
N
Nu


O
N
OH
O=C=O
$H_3O^{\oplus}$
H
N
H
H
: Ph
Li
Acidic hydrogen
O
R
H
$H_3O^{\oplus}$
R—Br
OH
N
R
N
R


NaOMe
i) PhCHO
ii) $H_3O^{\oplus}$
OH
N
$CH_2^{\ominus}$
- H_2O
Stilbazole

Nucleophilic substituition of pyridine



a) X=H

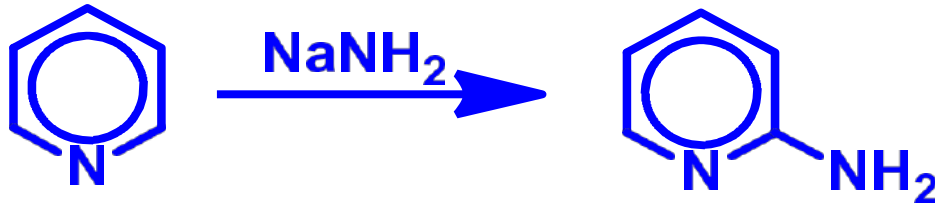
b) X=Good leaving group

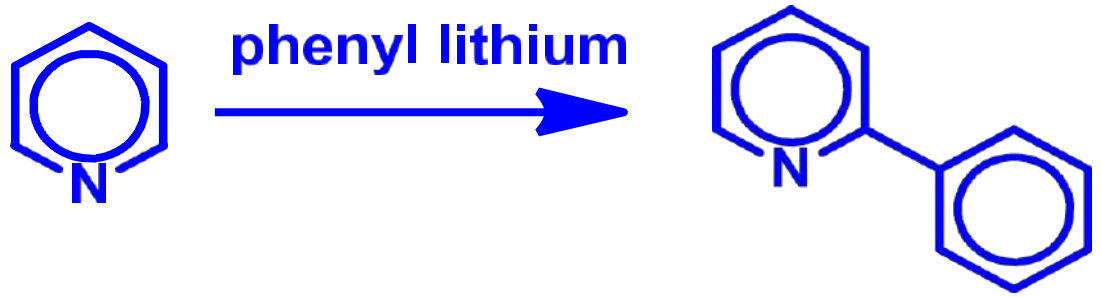
X=H, Substitution with “hydride” transfer

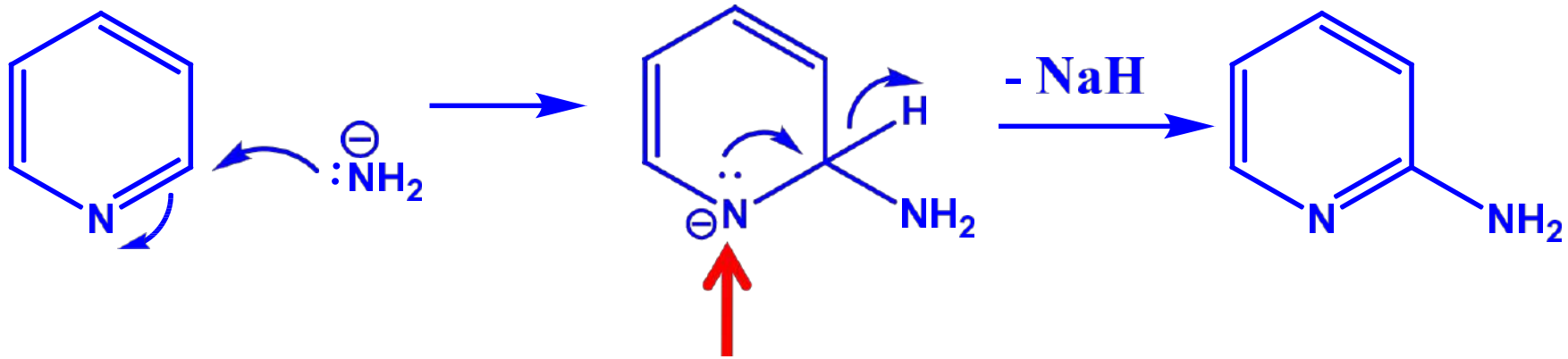
Nu: $NaNH_2$ - amination

Nu: BuLi, PhLi etc - alkylation / arylation

Nu: NaOH - “hydroxylation”

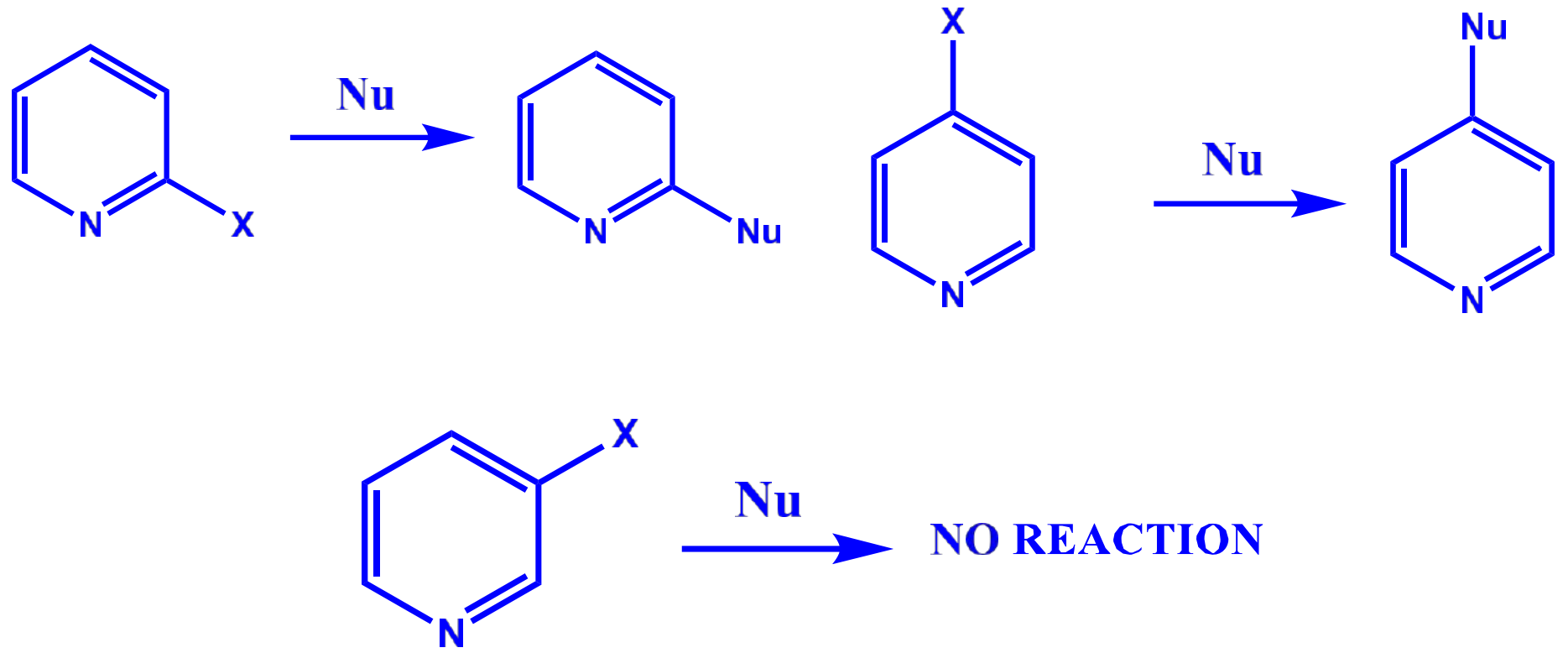


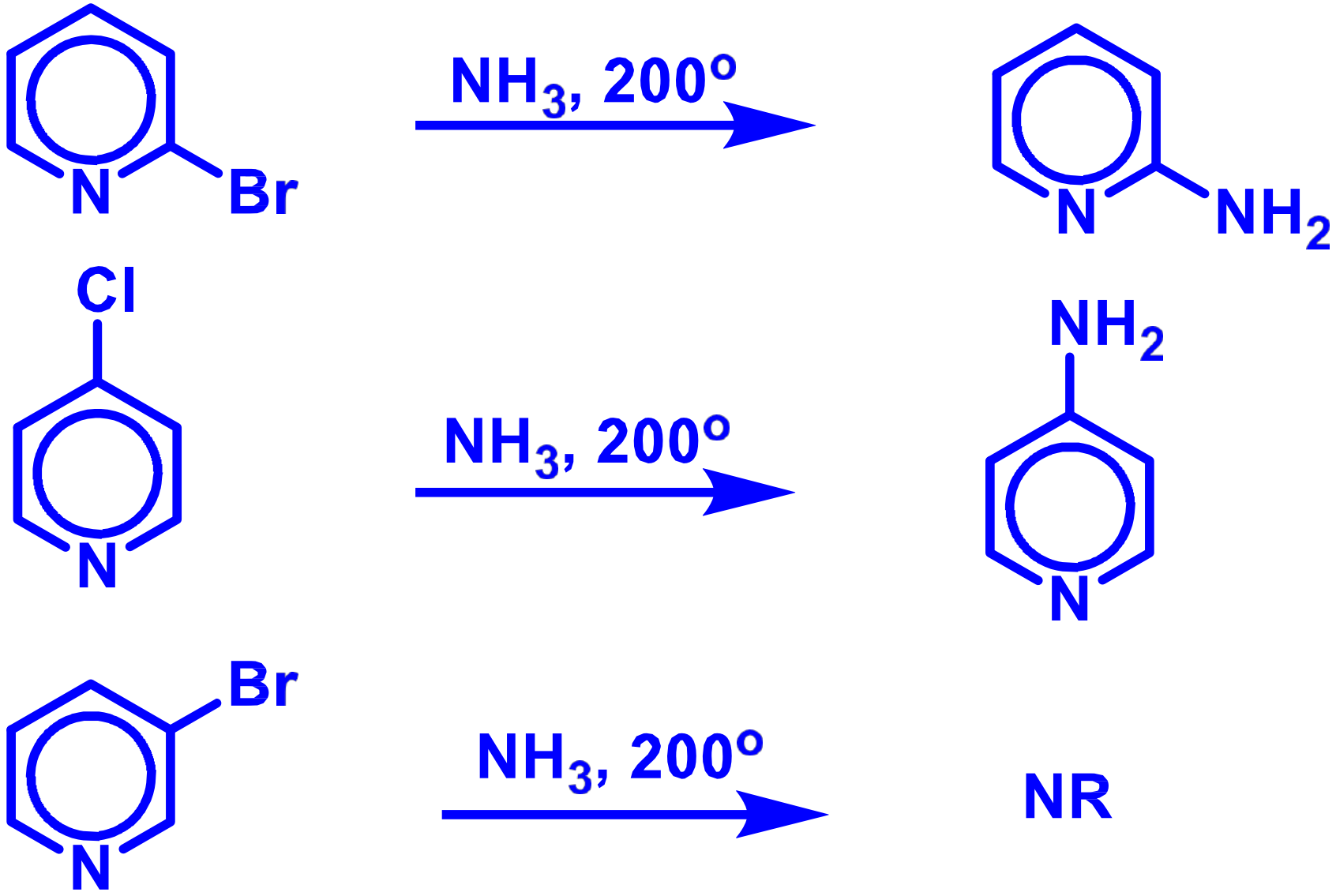


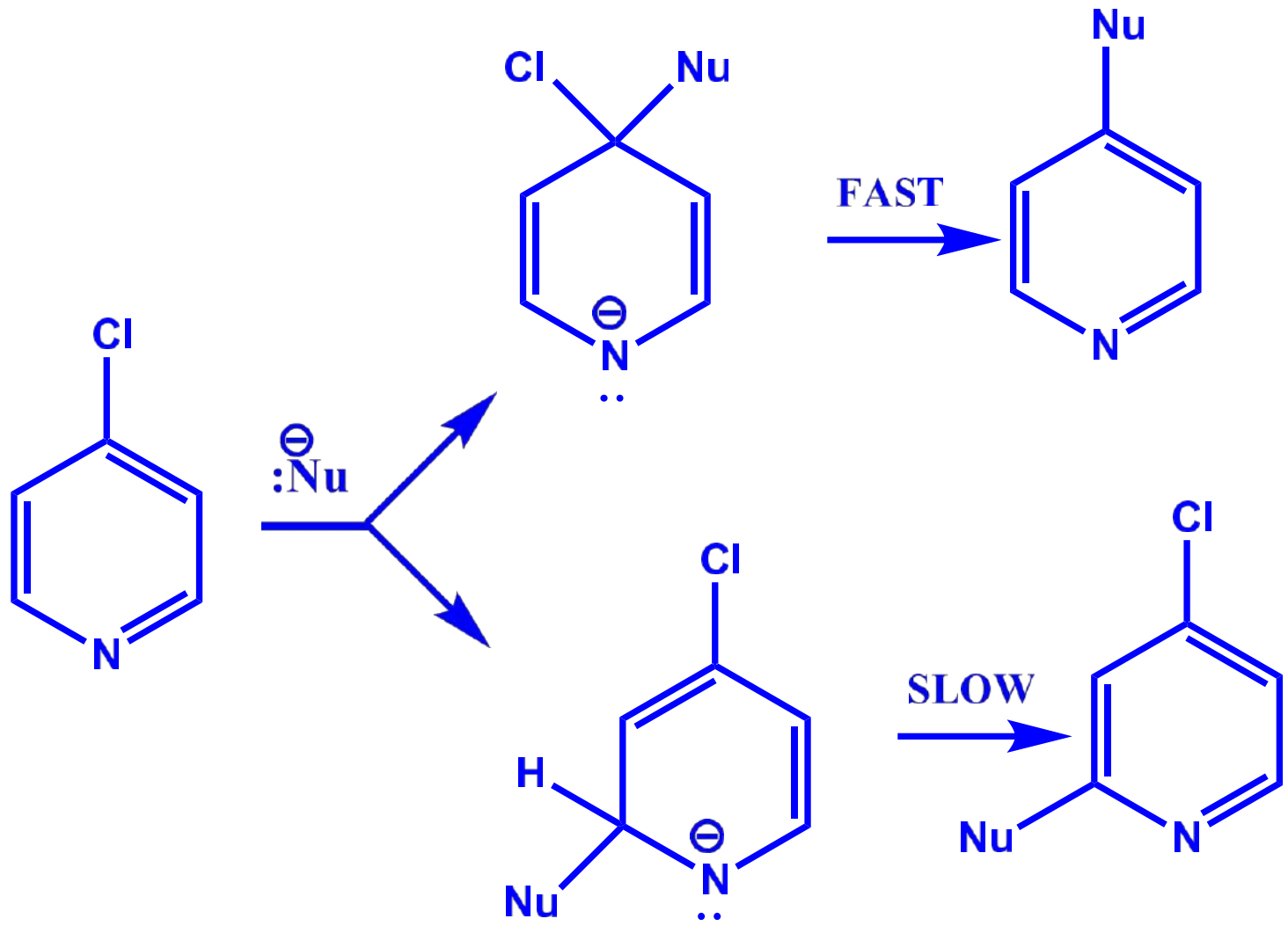


At high temperature the intermediate anion can aromatize by loss of a hydride ion, eventhough, it is a poor leaving group.

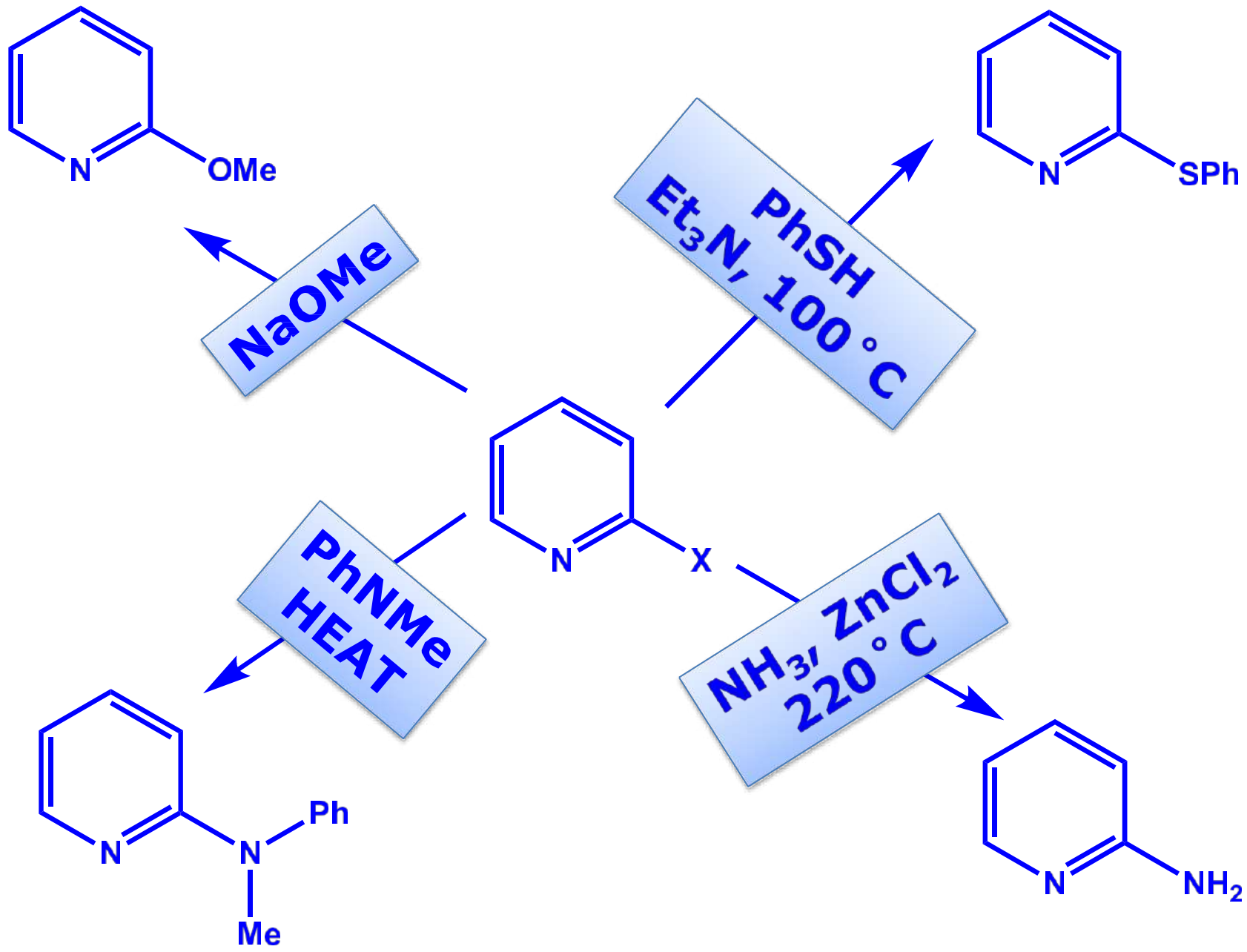
b) X=LG, The nucleophilic substitution is much more facile when good leaving group such as X: Halogen (F>>Cl,>Br,>I), $-OSO_2R$, $-NO_2$, -OR, are employed.




N
Br
NH3, 200°
N
NH2
Cl
N
NH3, 200°
NH2
N
Br
N
NH3, 200°
NR



$^{-}$H: is a bad leaving group


N
OMe
NaOMe
PhSH
Et3N, 100 °C
N
SPh
N
X
PhNMe
HEAT
NH3, ZnCl2
220 °C
N
Ph
N
Me
N
NH2

Halogenopyridines can undergo metal-halogen exchange when treated with butyllithium. The lithium derivatives then behave in a similar manner to arylithiums and Grignard reagents and react with electrophiles such as aldehydes, ketones and nitriles.