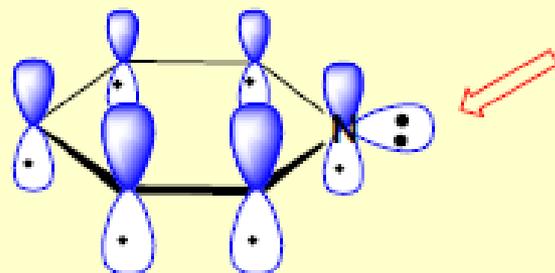
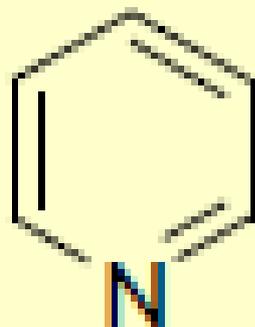


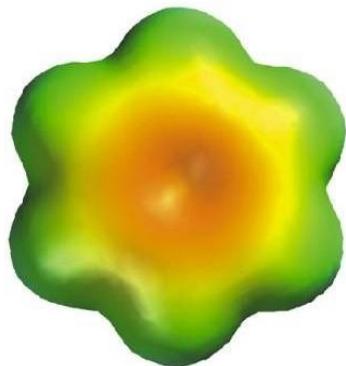
# Heterocycles: Pyridine

# Pyridine



$sp^2$  lone pair in the plane of the ring  
NOT involved in aromatic sextet

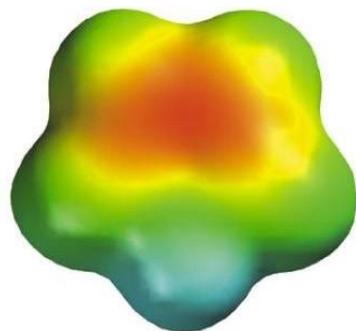
# Electron density



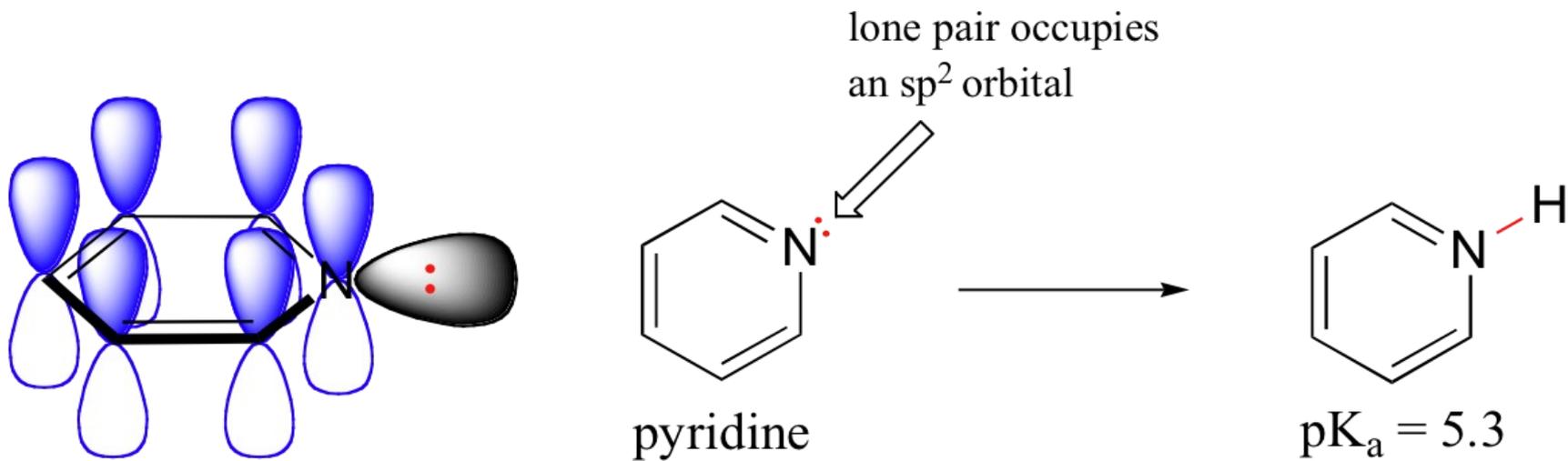
benzene



pyridine

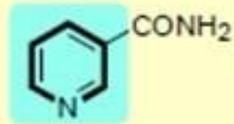


pyrrole

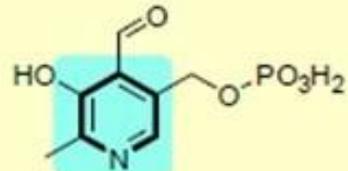


**Used in synthetic chemistry as Weak base and solvent**

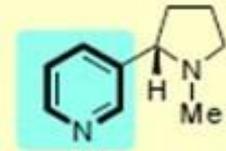
## Natural products:



niacin - vitamin B3  
(skin growth promotor)

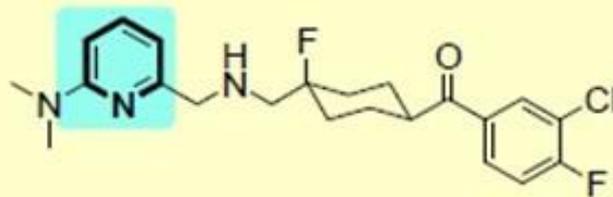


pyridoxal phosphate  
(cofactor for transaminases)



nicotine  
(tobacco alkaloid stimulant)

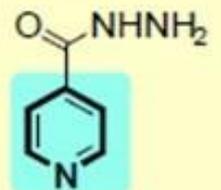
## Pharmaceuticals:



5-HT<sub>1A</sub> receptor antagonist  
(antidepressant)

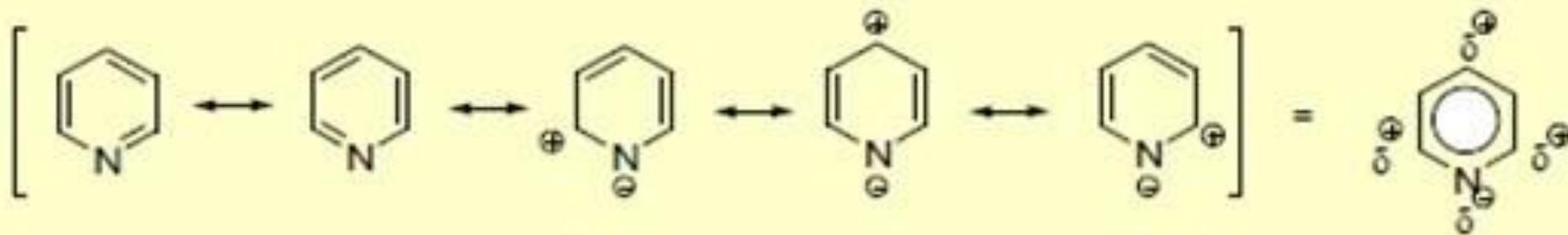


sulphapyridine  
(antibacterial)



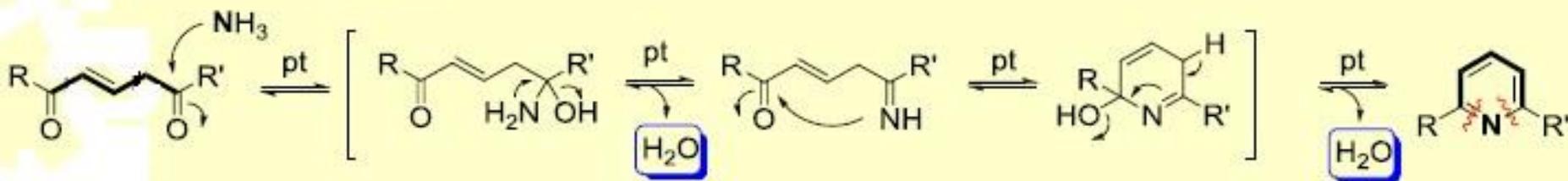
isoniazide  
(antituberculosis)

Like benzene, pyridine has 6  $\pi$ -electrons distributed over 6 atoms; However, both *induction* and *resonance* effects draw electron density towards the **N** atom so that the carbon framework is **ELECTRON DEFICIENT**



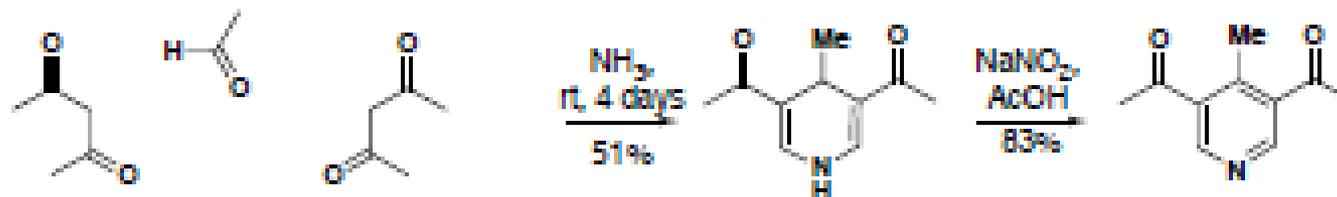
# Synthesis of Pyridine:

**Paal-Knorr** 1,5-dicarbonyl with  $\text{NH}_3$

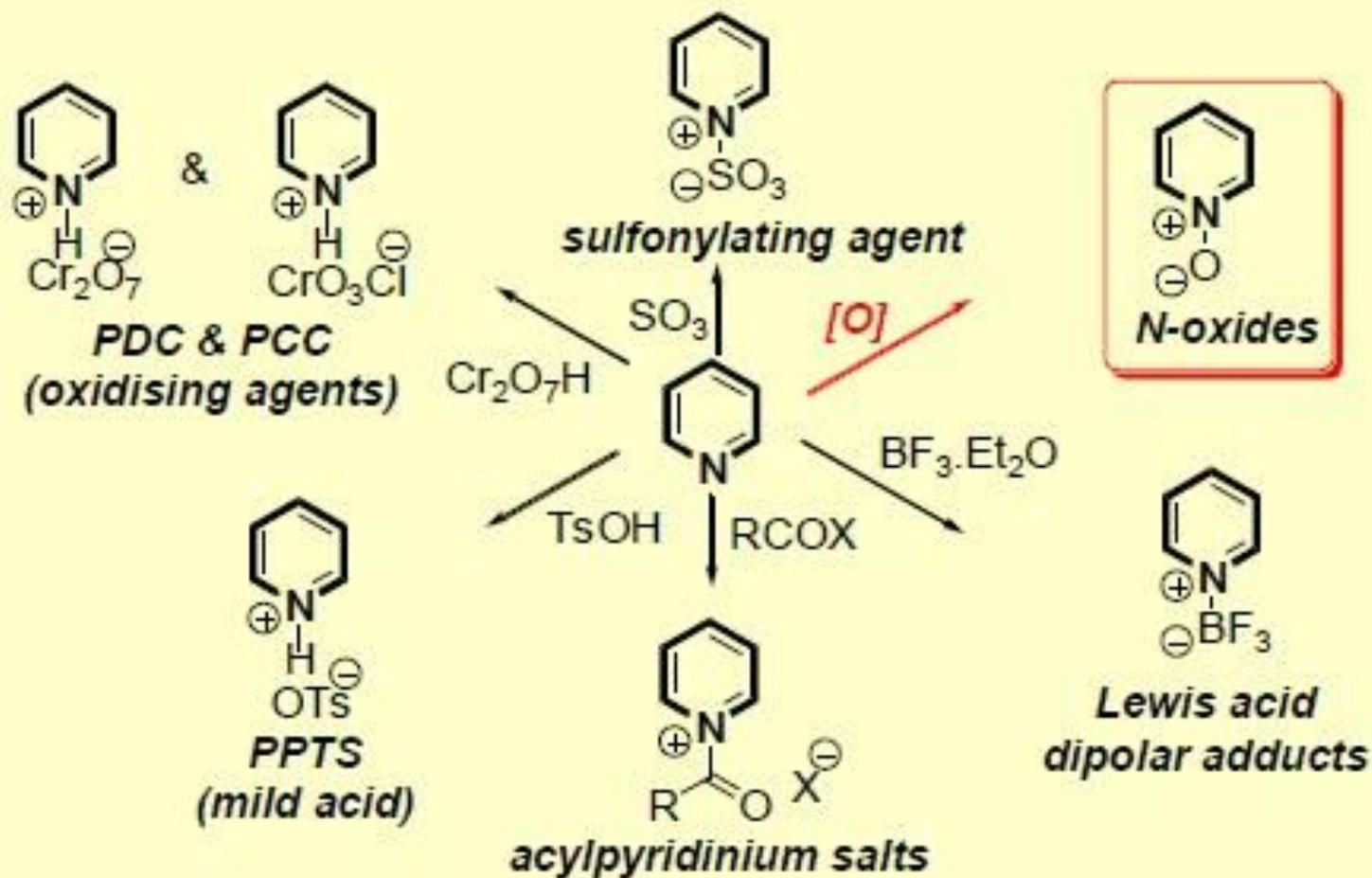


## Hantzsch pyridine synthesis:

Condensation of aldehyde, dicarbonyl compound X 2 and  $\text{NH}_3$



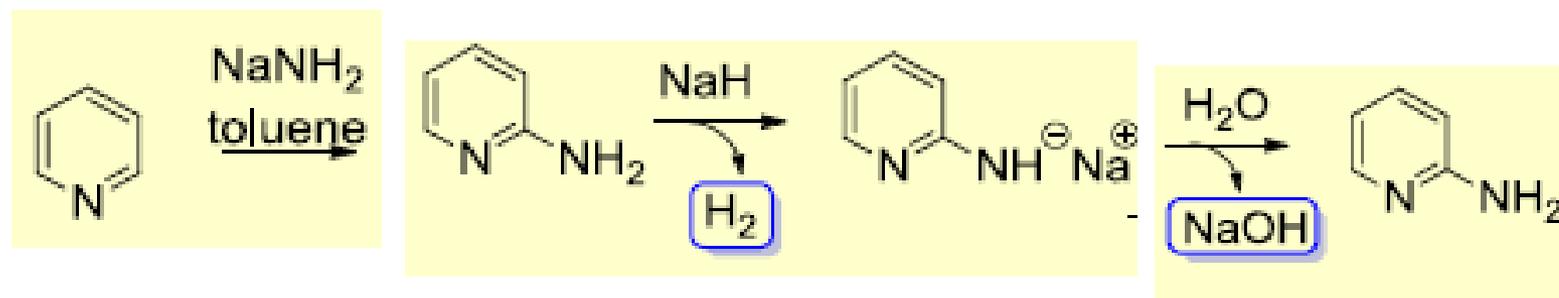
## Electrophilic addition to the pyridyl N:



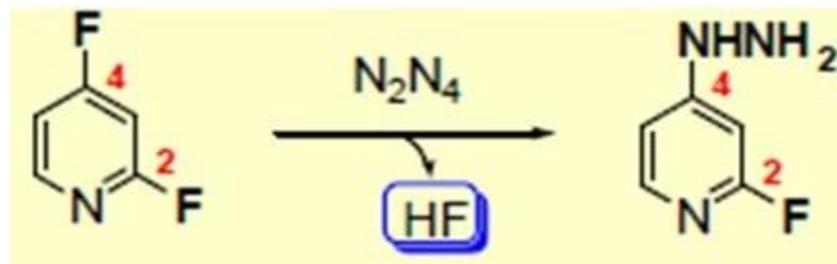
**reactivity:** reactive towards strong nucleophiles (Nu<sup>-</sup>)

**regioselectivity:** substitution at 4 & 2 positions (C4 > C2)

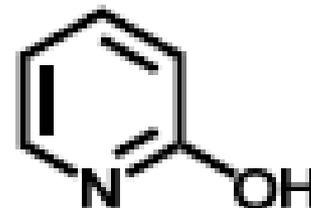
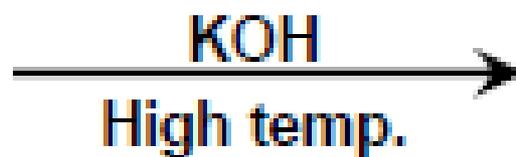
**Chichibabin reaction:**



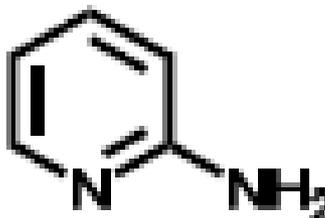
**Reaction with Hydrazine:**



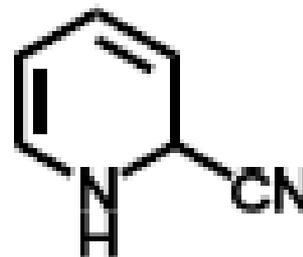
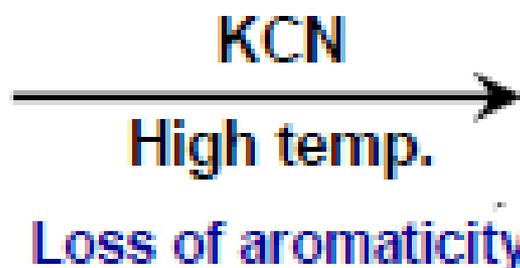
Hydroxylation:



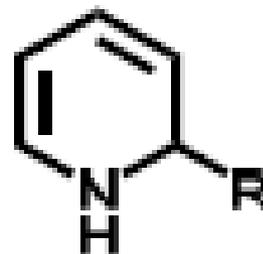
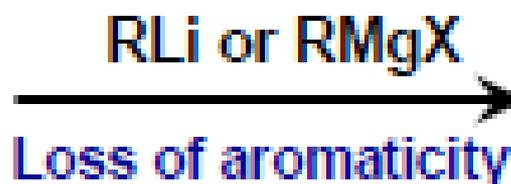
Amination:



Cyanation:



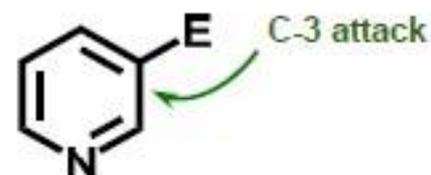
Alkylation:



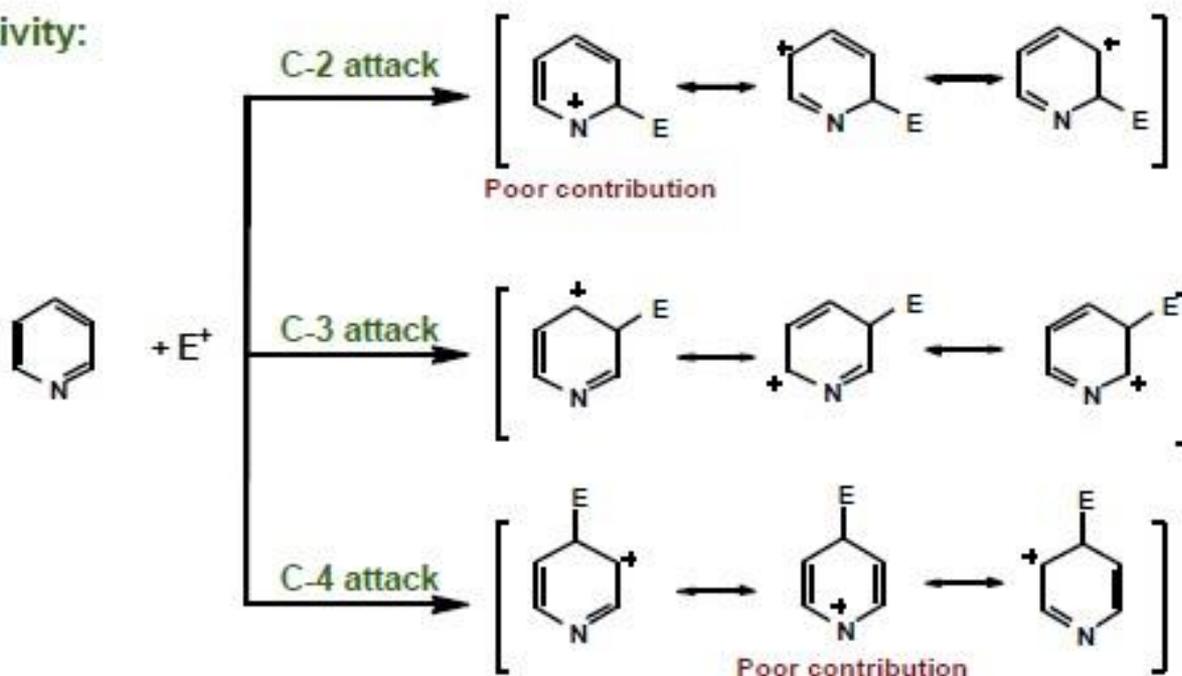
$E^+$ 

# REACTIONS AT CARBON ATOMS

$S_EAr$ : Pyridine as nitrogen nucleophile: Behaves essentially as benzene, although due to its p-deficient character reactions are slower and require harsher conditions

 $+ E^+$ 

Regioselectivity:



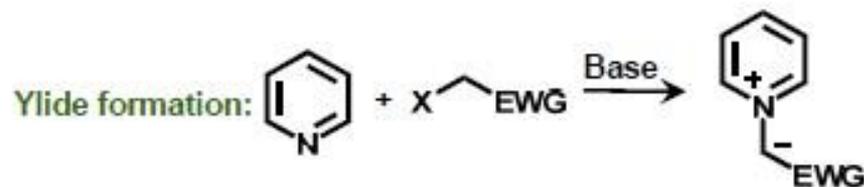
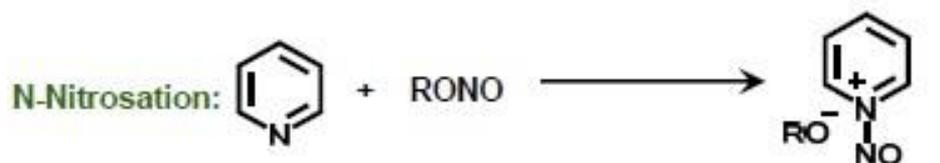
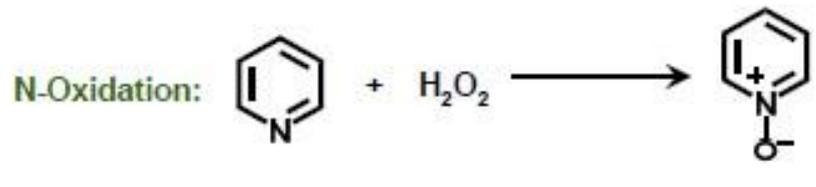
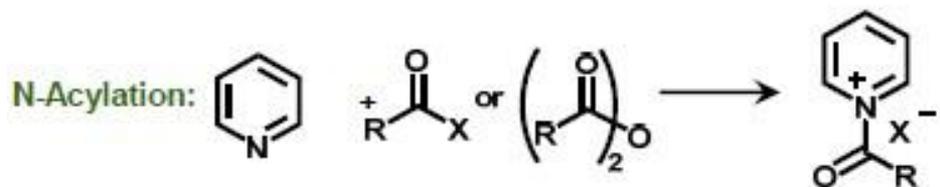
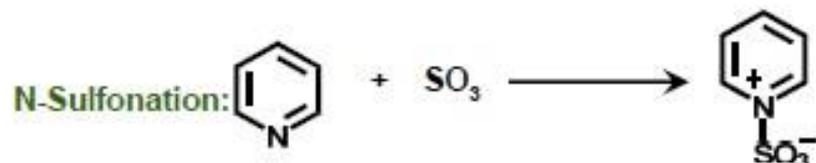
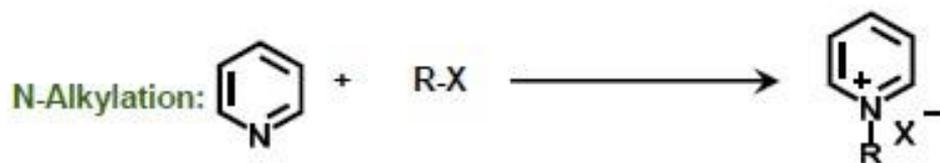
# REACTIONS AT NITROGEN

Pyridine itself act as Nu

➤ Acid-Base: Pyridine as a Bronsted base



➤ A<sub>N</sub>: Pyridine as nitrogen nucleophile: The nitrogen lone pair (it does not participate in conjugation) reacts with electrophiles



## Reaction at P position of substituents

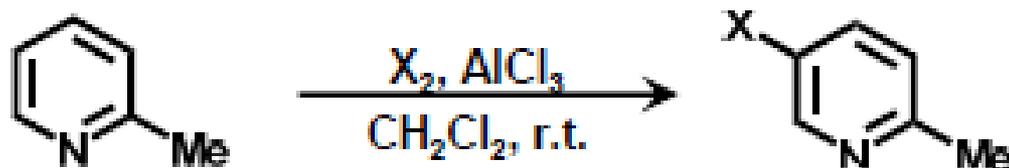
Pyridine as carbon nucleophile:



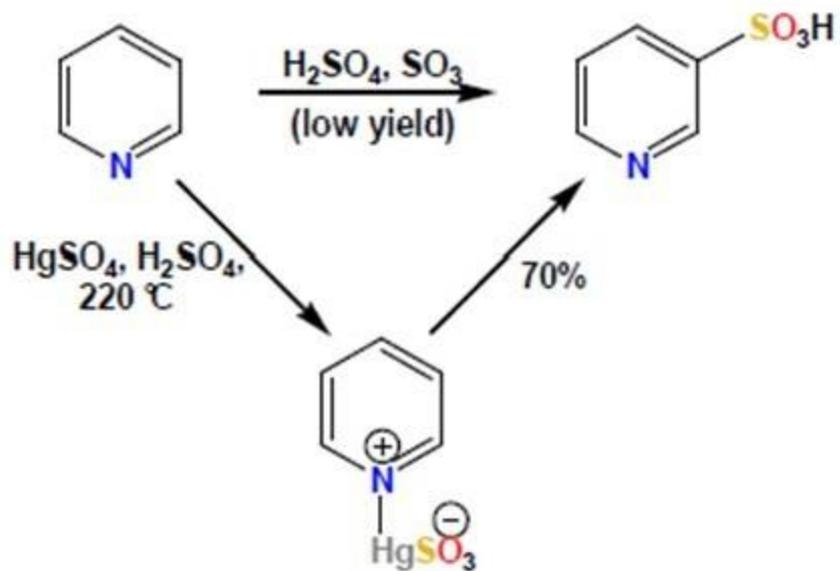
*Activating substituent*

Reactivity: Higher than the corresponding unsubstituted pyridine  
Regioselectivity: *ortho* and/or *para* with respect to the activating substituent

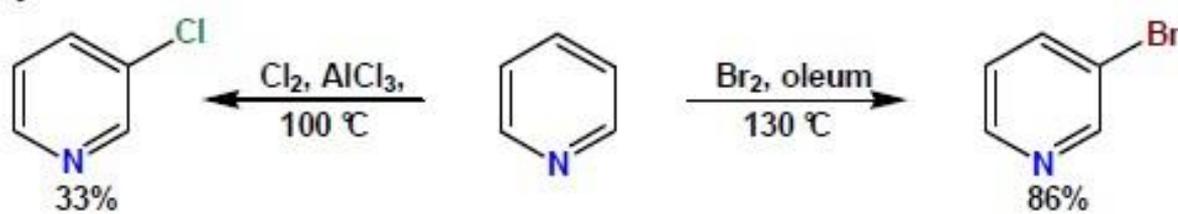
Halogenation of methylpyridines:



## Sulfonation of Pyridine

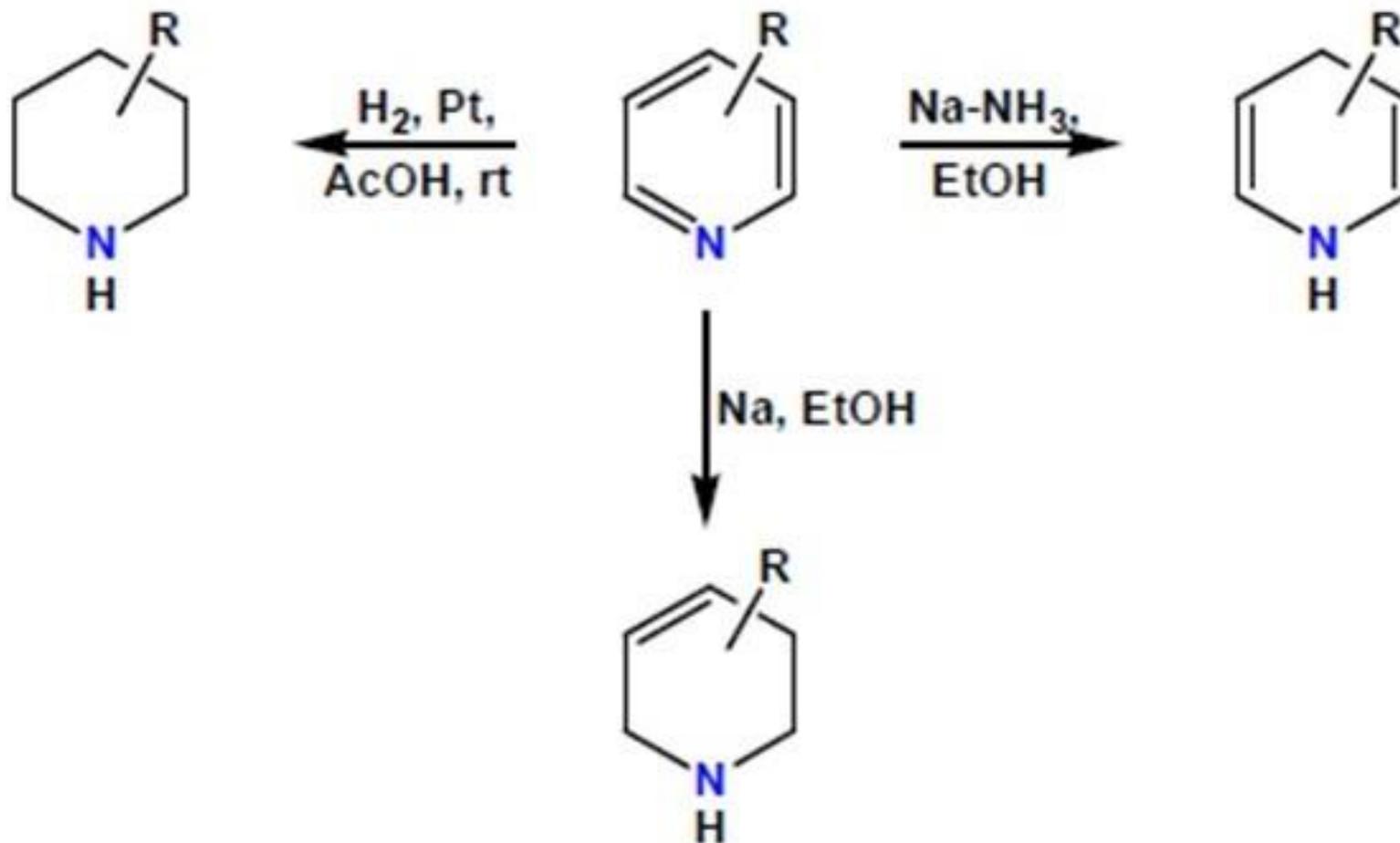


## Halogenation of Pyridine



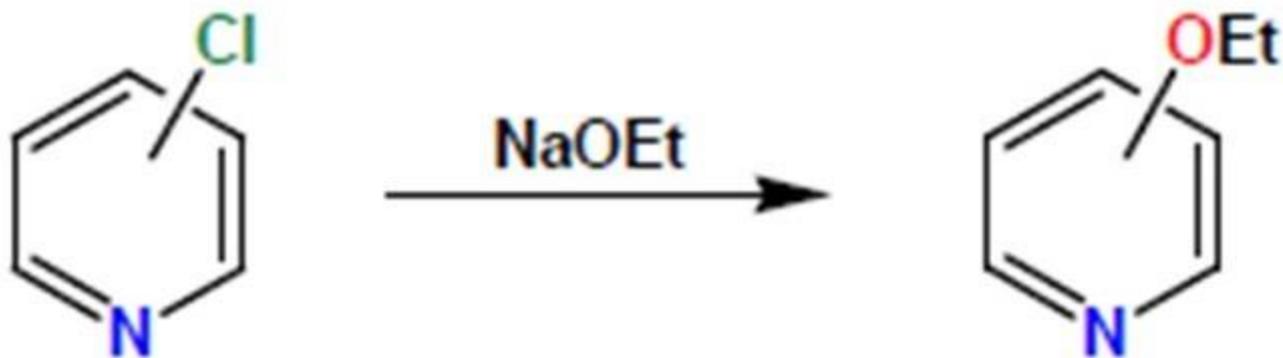
- Forcing reaction conditions are required for direct halogenation

## Reduction of pyridine:



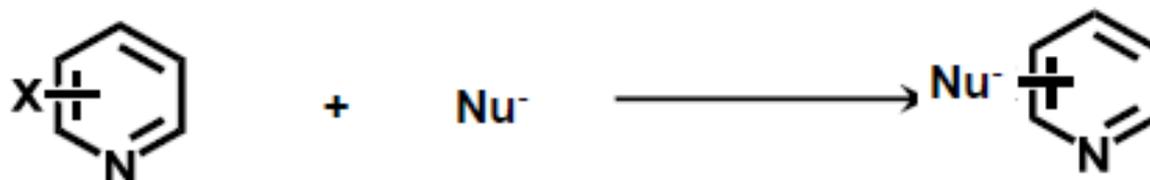
**Oxidation:** Leads to formation of pyridine N-Oxide

## Nucleophilic Reactions:

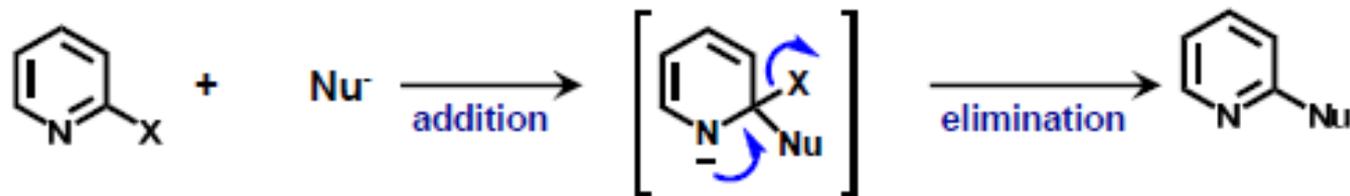


## Other reaction at C atom:

### $S_NAr$ : Pyridine as electrophile:



#### Mechanism:



### Alkylation of 2-methoxypyridine

