

**B.Sc. Semester-IV  
Core Course-IX (CC-IX)  
Organic Chemistry-III**



### **III. Heterocyclic Compounds**

#### **23. Pyridines : Structure, Synthesis, Electrophilic Reactions and Partial Reduction**



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## **Heterocyclic Compounds**

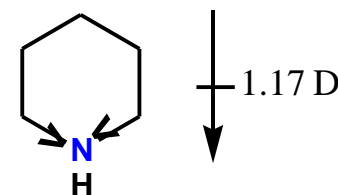
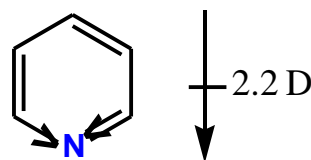
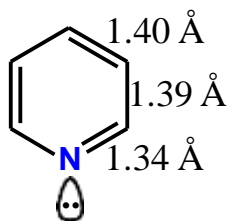
**22 Lectures**

Classification and nomenclature, Structure, aromaticity in 5-numbered and 6-membered rings containing one heteroatom; Synthesis, reactions and mechanism of substitution reactions of: Furan, Pyrrole (Paal-Knorr synthesis, Knorr pyrrole synthesis, Hantzsch synthesis), Thiophene, Pyridine (Hantzsch synthesis), Pyrimidine, Structure elucidation of indole, Fischer indole synthesis and Madelung synthesis), Structure elucidation of quinoline and isoquinoline, Skraup synthesis, Friedlander's synthesis, Knorr quinoline synthesis, Doebner- Miller synthesis, Bischler-Napieralski reaction, Pictet-Spengler reaction, Pomeranz-Fritsch reaction  
Derivatives of furan: Furfural and furoic acid.

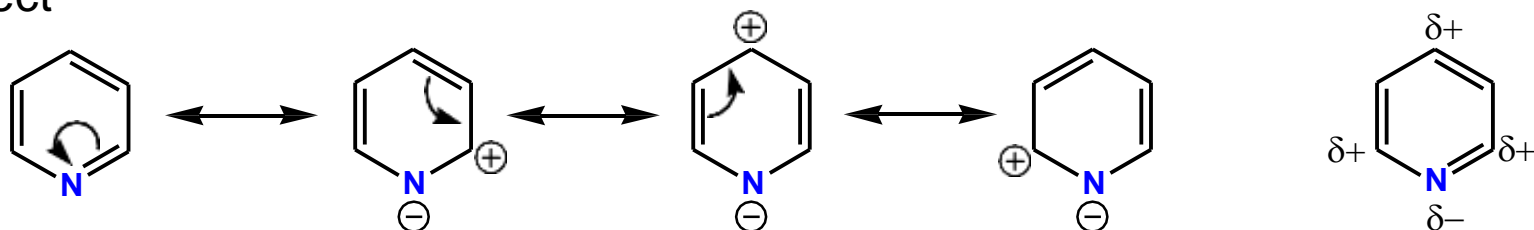
## **Coverage:**

1. Pyridines : Structure, Synthesis, Electrophilic Reactions and Partial Reduction

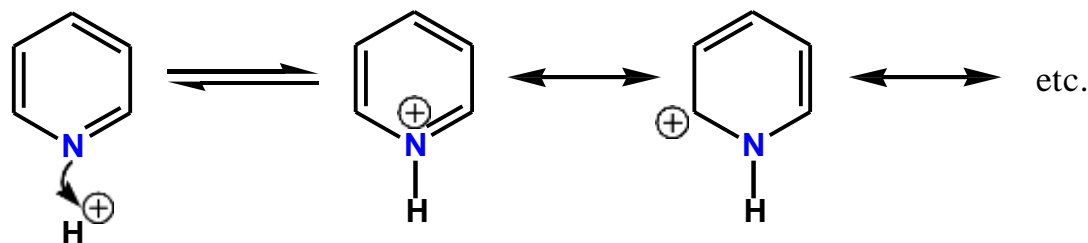
## Pyridines – Structure



- Isoelectronic with and analogous to benzene
- Stable, not easily oxidised at C, undergoes substitution rather than addition
- -I Effect (inductive electron withdrawal)
- -M Effect

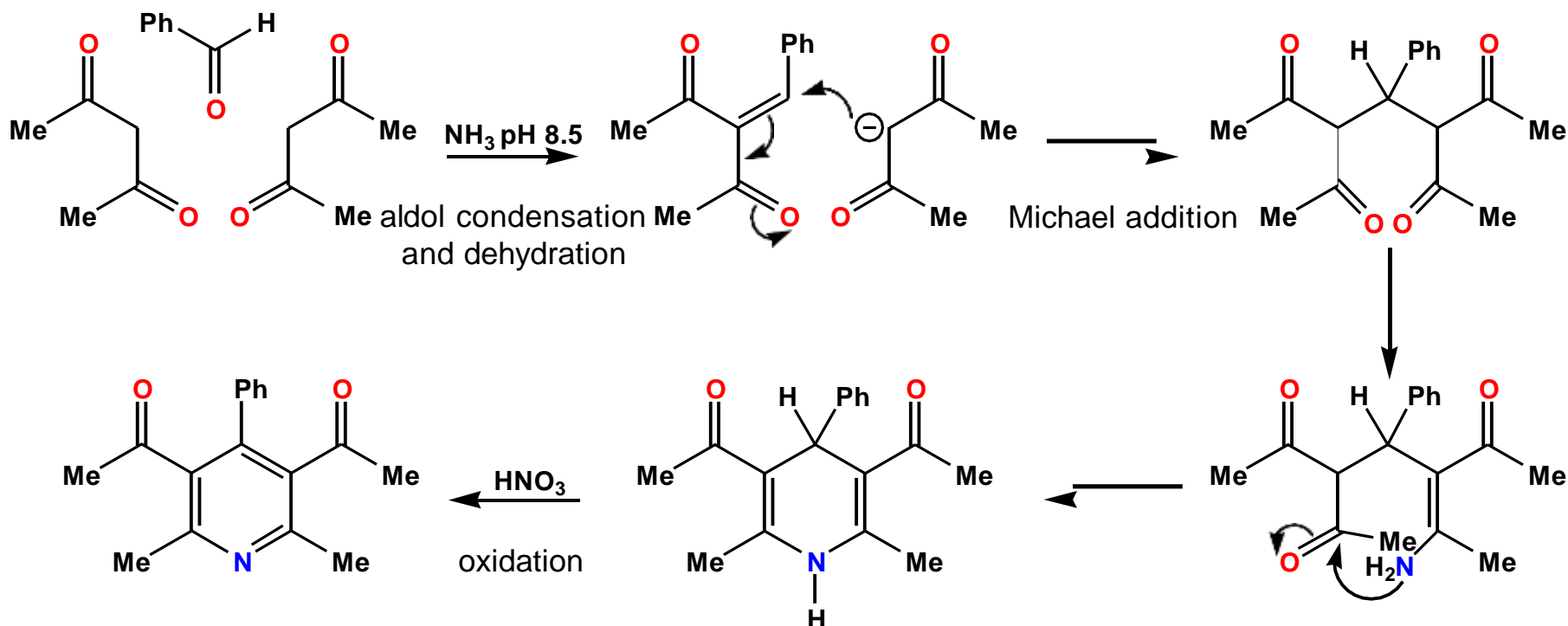


- Weakly basic –  $pK_a \sim 5.2$  in  $H_2O$  (lone pair is **not** in aromatic sextet)
- Pyridinium salts are also aromatic – ring carbons are more  $\delta+$  than in parent pyridine



# Pyridines – Synthesis

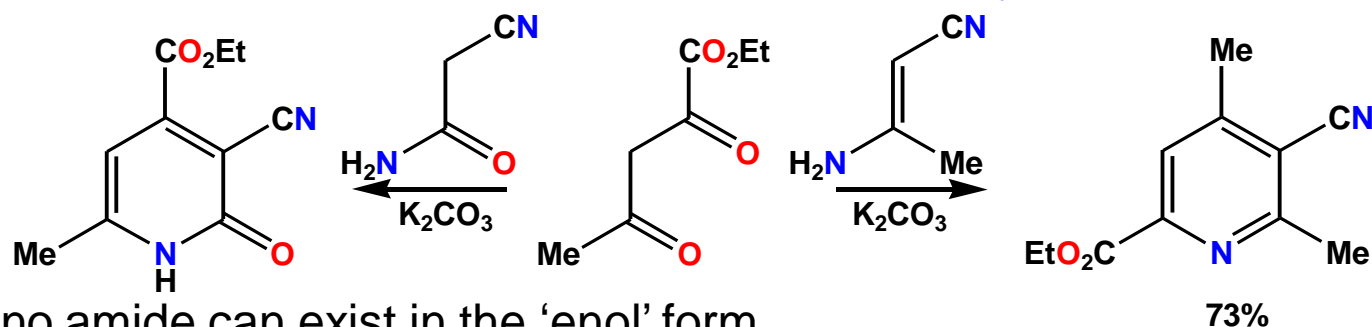
The Hantzsch synthesis (“5+1”)



- The reaction is useful for the synthesis of symmetrical pyridines
- The 1,5-diketone intermediate can be isolated in certain circumstances
- A separate oxidation reaction is required to aromatised the dihydropyridine

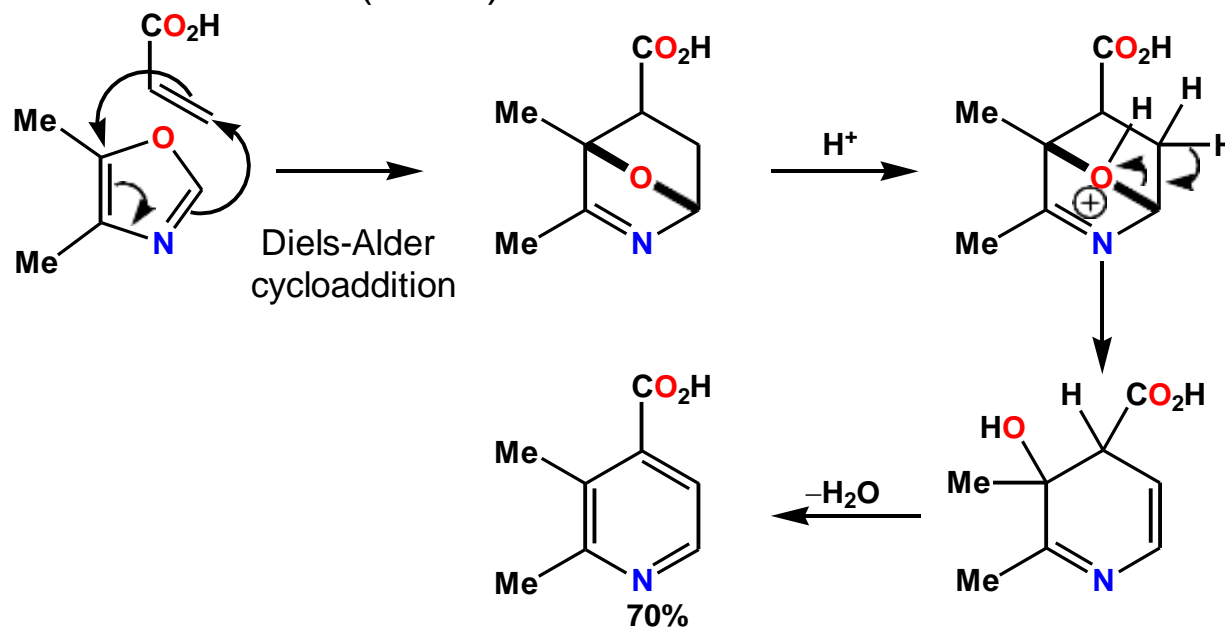
# Pyridines – Synthesis

From Enamines or Enamine Equivalents – the **Guareschi synthesis** (“3+3”)



- The β-cyano amide can exist in the ‘enol’ form

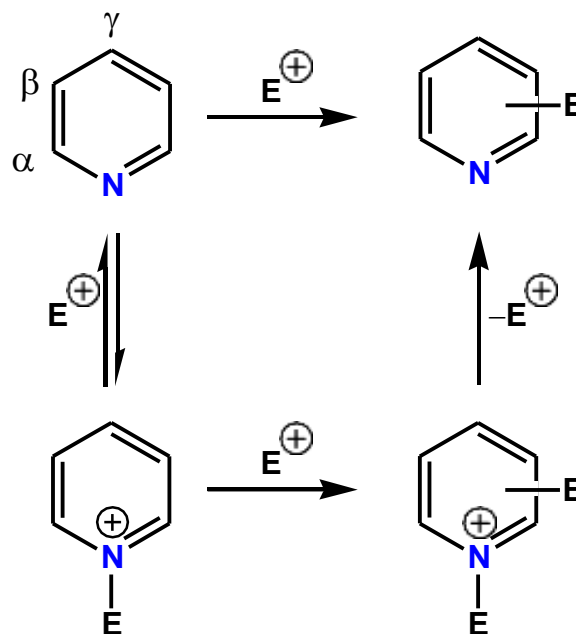
Using Cycloaddition Reactions (“4+2”)



- Oxazoles are sufficiently low in aromatic character to react in the **Diels-Alder reaction**

# Pyridines – Electrophilic Reactions

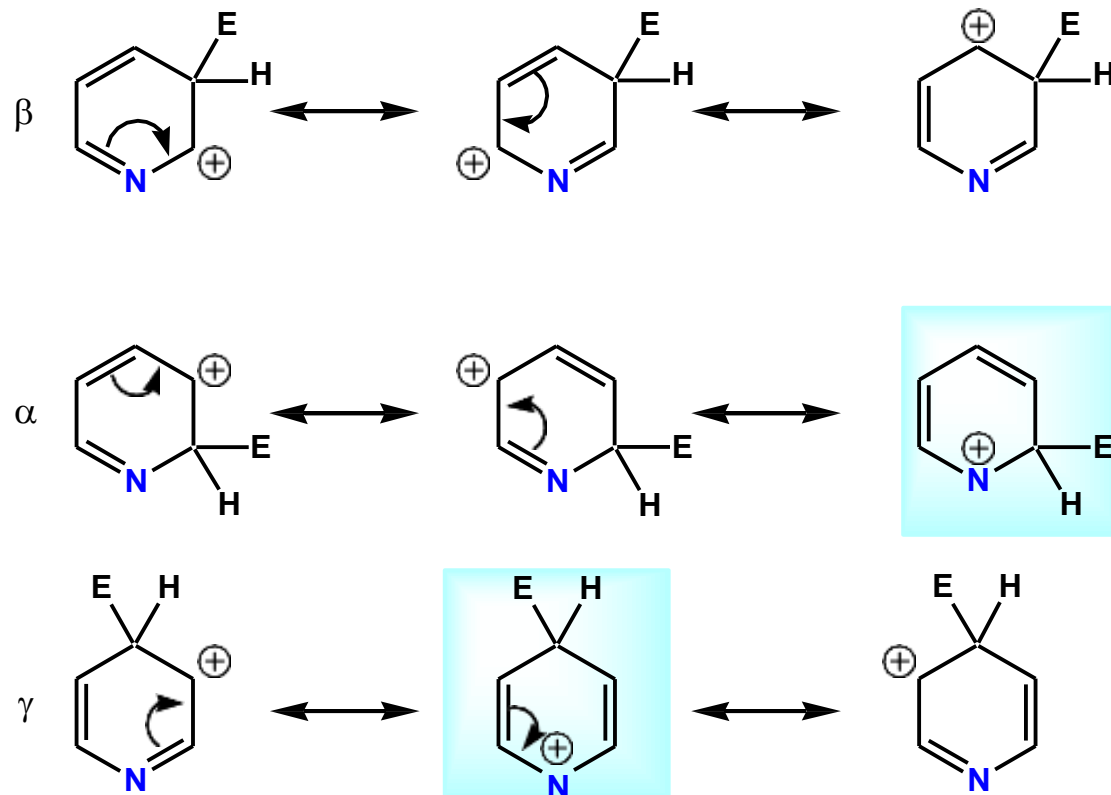
Pathways for the Electrophilic Aromatic Substitution of Pyridines



- The position of the equilibrium between the pyridine and pyridinium salt depends on the substitution pattern and nature of the substituents, but usually favours the salt

# Pyridines – Electrophilic Reactions

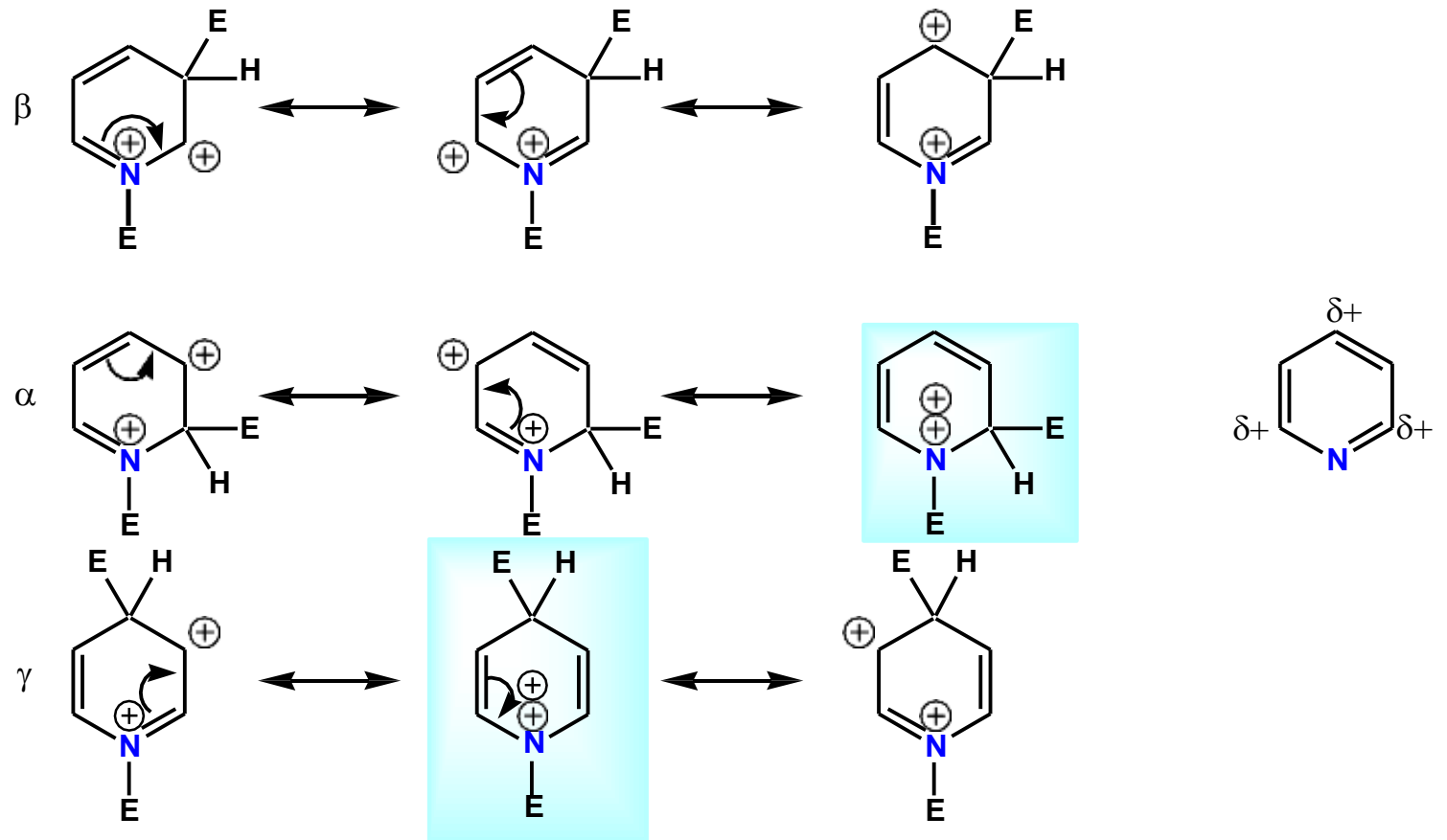
## Regiochemical Outcome of Electrophilic Substitution of Pyridines



- Resonance forms with a positive charge on *N* (i.e. 6 electrons) are very unfavourable
- The  $\beta$ -substituted intermediate, and the transition state leading to this product, have more stable resonance forms than the intermediates/transition states leading to the  $\alpha/\gamma$  products

# Pyridines – Electrophilic Reactions

Regiochemical Outcome of Electrophilic Substitution of Pyridinium Ions

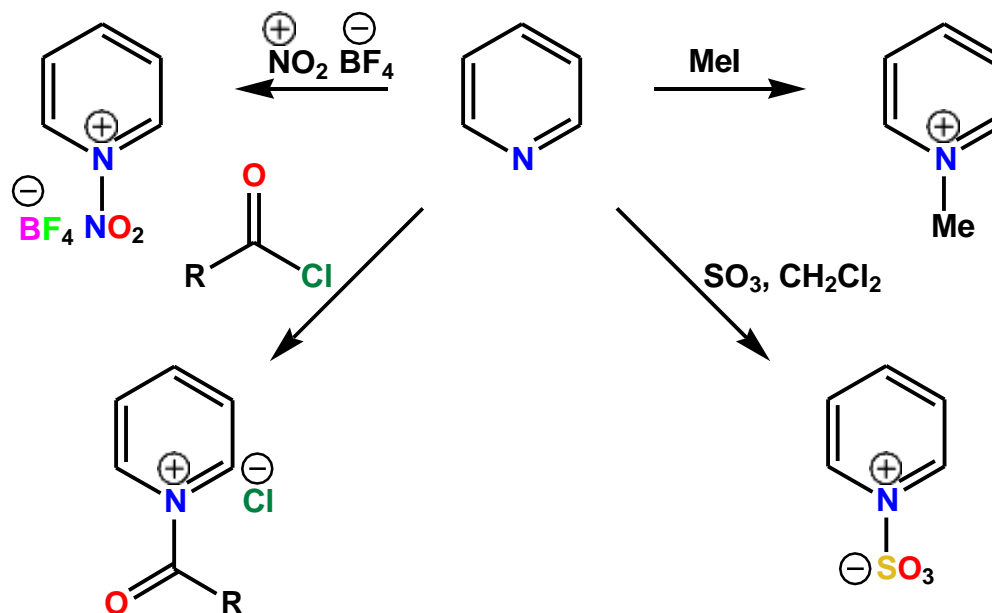


- Regiochemical control is even more pronounced in the case of pyridinium ions
- In both pyridine and pyridinium systems, β substitution is favoured but the reaction is slower than that of benzene
- Reaction will usually proceed through the small amount of the free pyridine available



# Pyridines – Electrophilic Reactions

## N Substitution

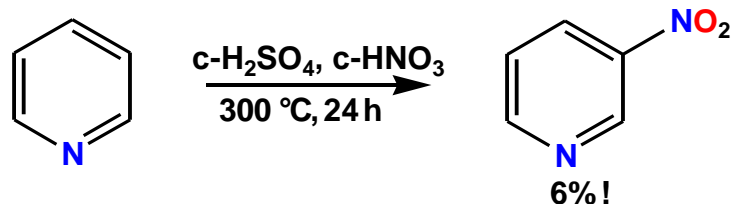


## C Substitution

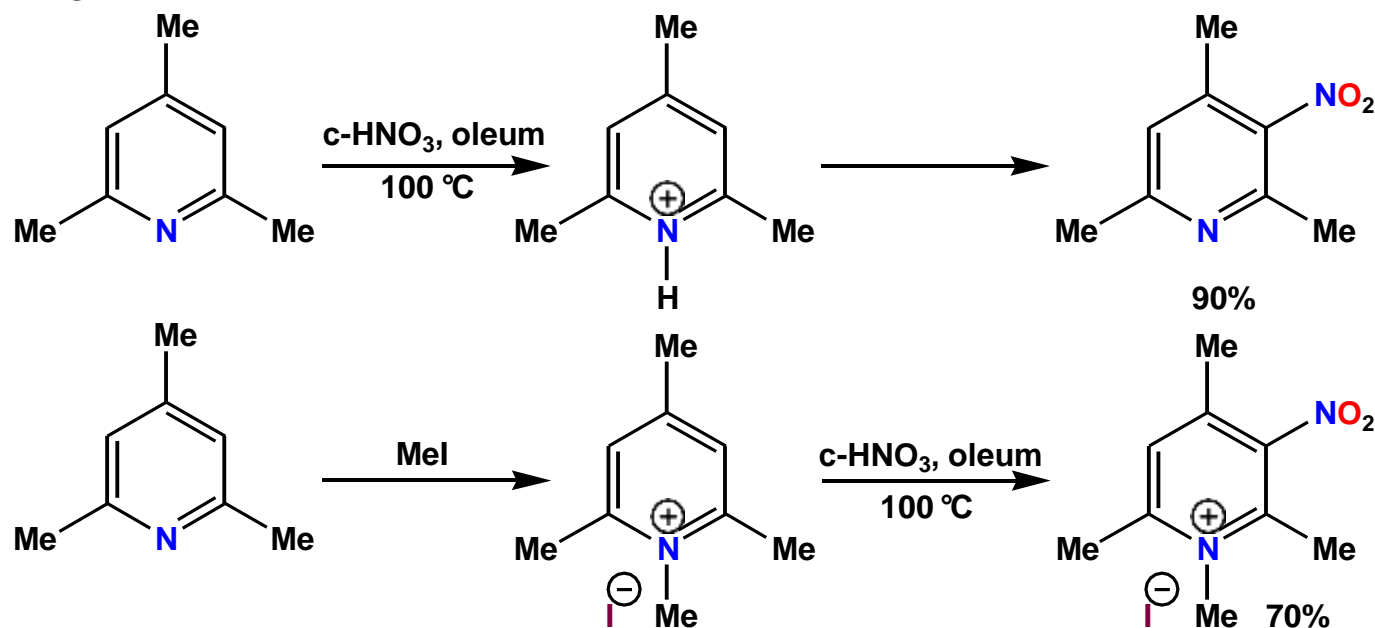
- Reaction at C is usually difficult and slow, requiring forcing conditions
- **Friedel-Crafts reactions** are not usually possible on free pyridines

# Pyridines – Electrophilic Reactions

## Nitration of Pyridine



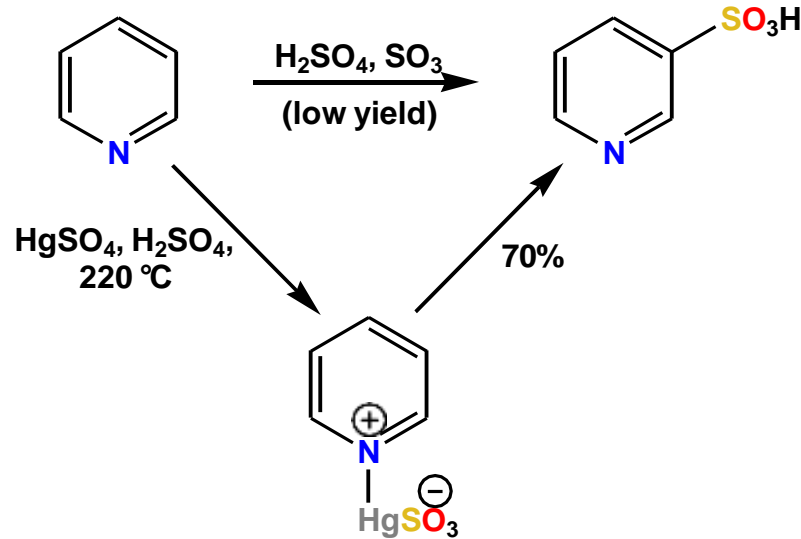
## Use of Activating Groups



- Multiple electron-donating groups accelerate the reaction
- Both reactions proceed at similar rates which indicates that the protonation at *N* occurs prior to nitration in the first case

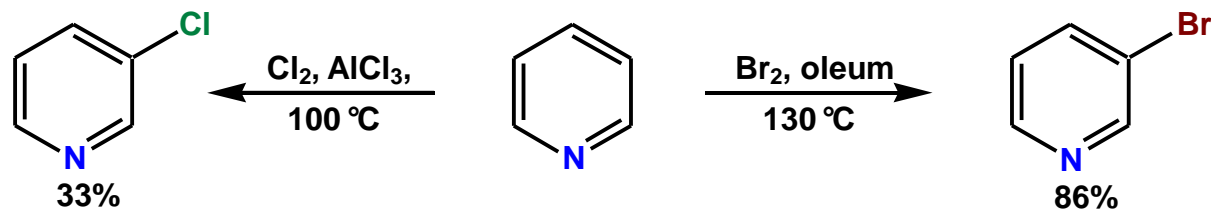
# Pyridines – Electrophilic Reactions

## Sulfonation of Pyridine



- Low yield from direct nitration but good yield via a mercury intermediate

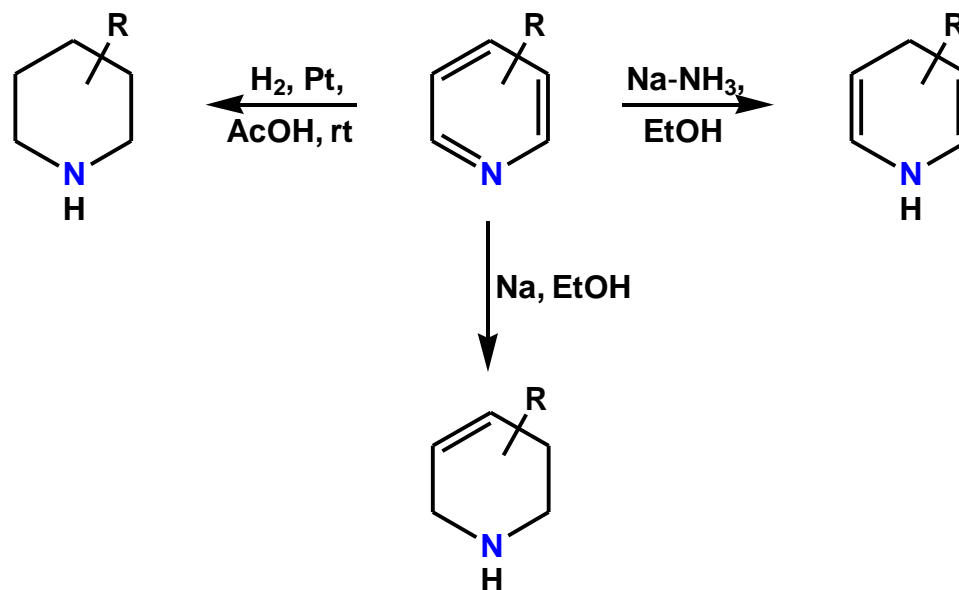
## Halogenation of Pyridine



- Forcing reaction conditions are required for direct halogenation

# Pyridines – Partial Reduction

Full or Partial Reduction of Pyridines



- Pyridines generally resist oxidation at ring carbon atoms and will often undergo side-chain oxidation in preference to oxidation of the ring
- Full or partial reduction of the ring is usually easier than in the case of benzene