

**B.Sc. Semester-VI
Organic Chemistry
Paper-XIV**



3. Heterocyclic Compounds

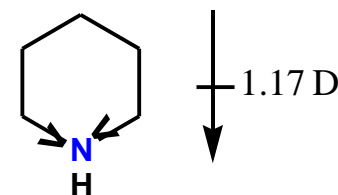
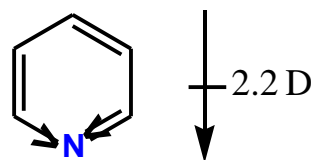
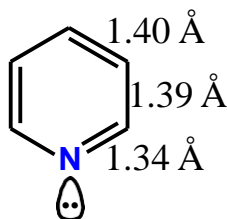
Coverage:

6. Pyridines : Structure, Synthesis, Electrophilic Substitution Reactions and Partial Reduction

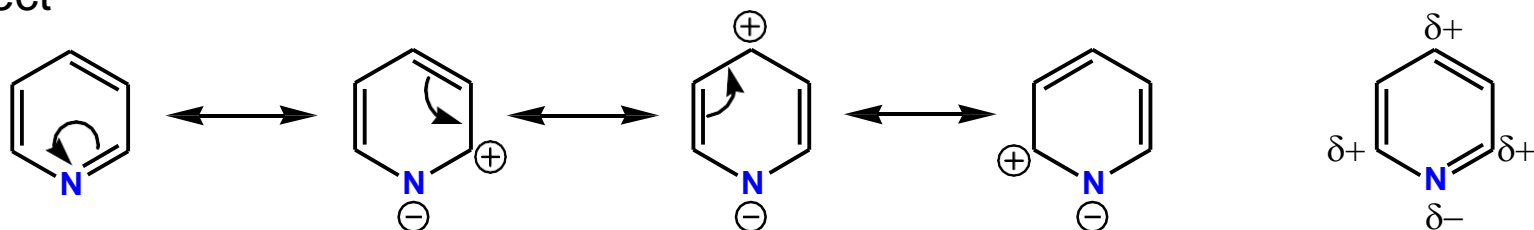


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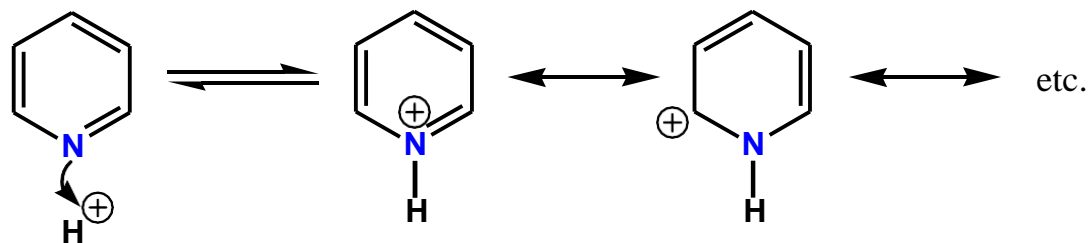
Pyridines – Structure



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

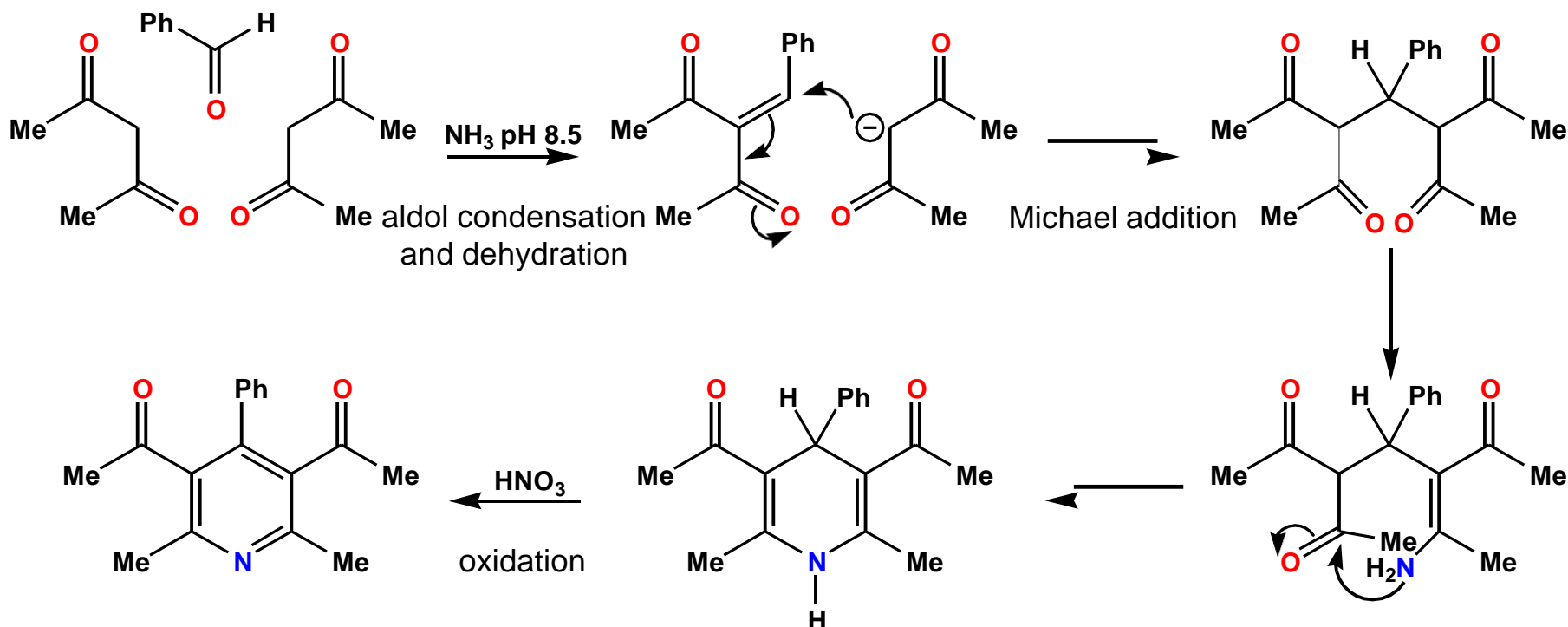


- Weakly basic – $pK_a \sim 5.2$ in H_2O (lone pair is **not** in aromatic sextet)
- Pyridinium salts are also aromatic – ring carbons are more $\delta+$ than in parent pyridine



Pyridines – Synthesis

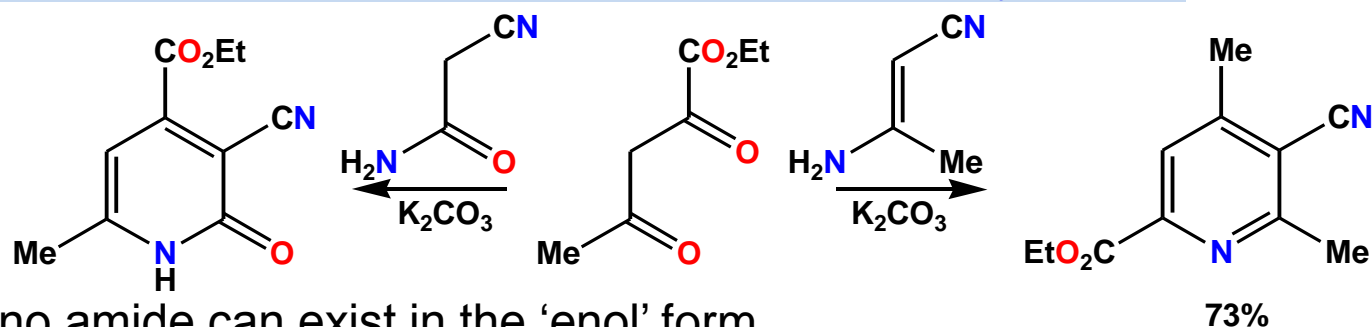
The Hantzsch synthesis



- 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 aromatise the dihydropyridine

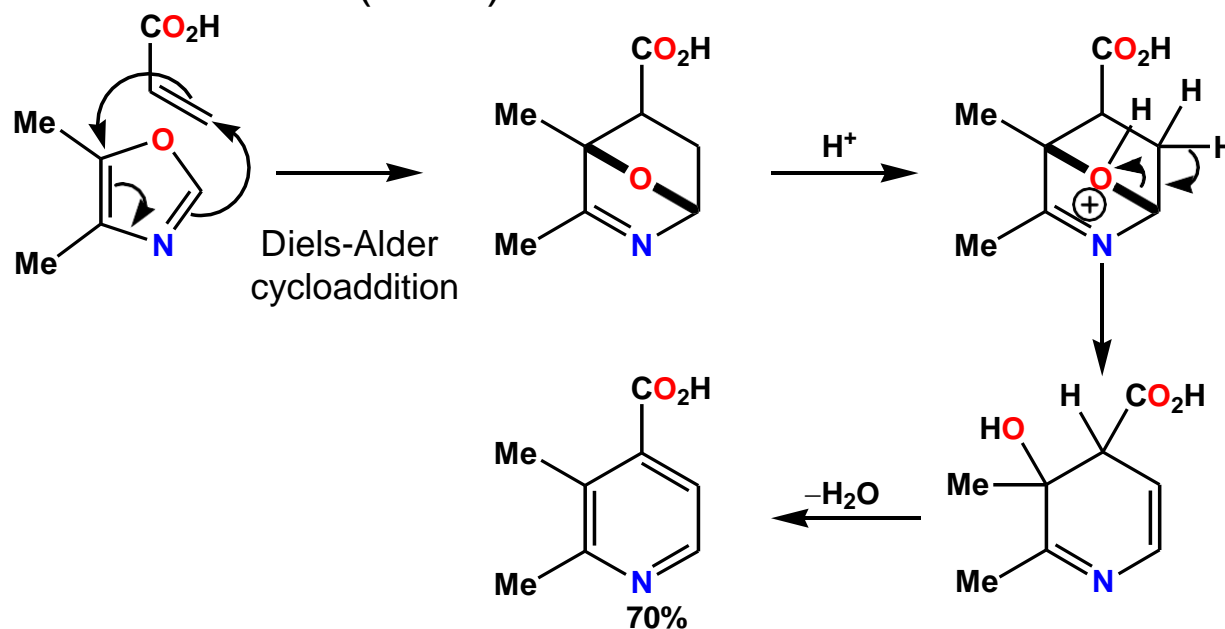
Pyridines – Synthesis

From Enamines or Enamine Equivalents – the **Guareschi synthesis**



- The β -cyano amide can exist in the 'enol' form

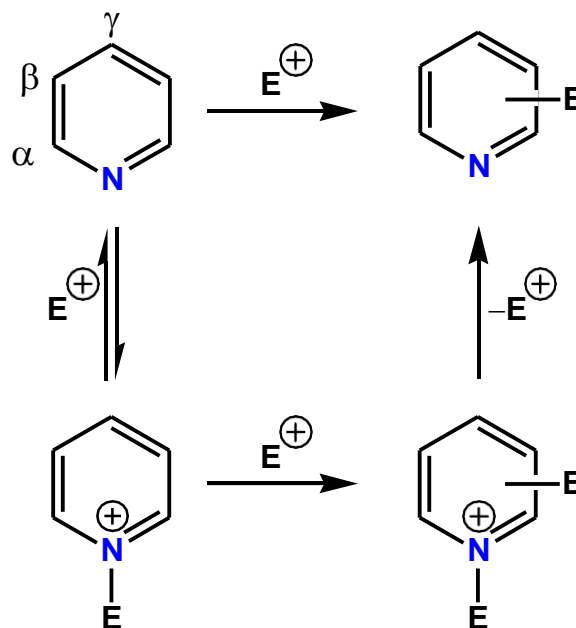
Using Cycloaddition Reactions (“4+2”)



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

Pyridines – Electrophilic Substitution Reactions

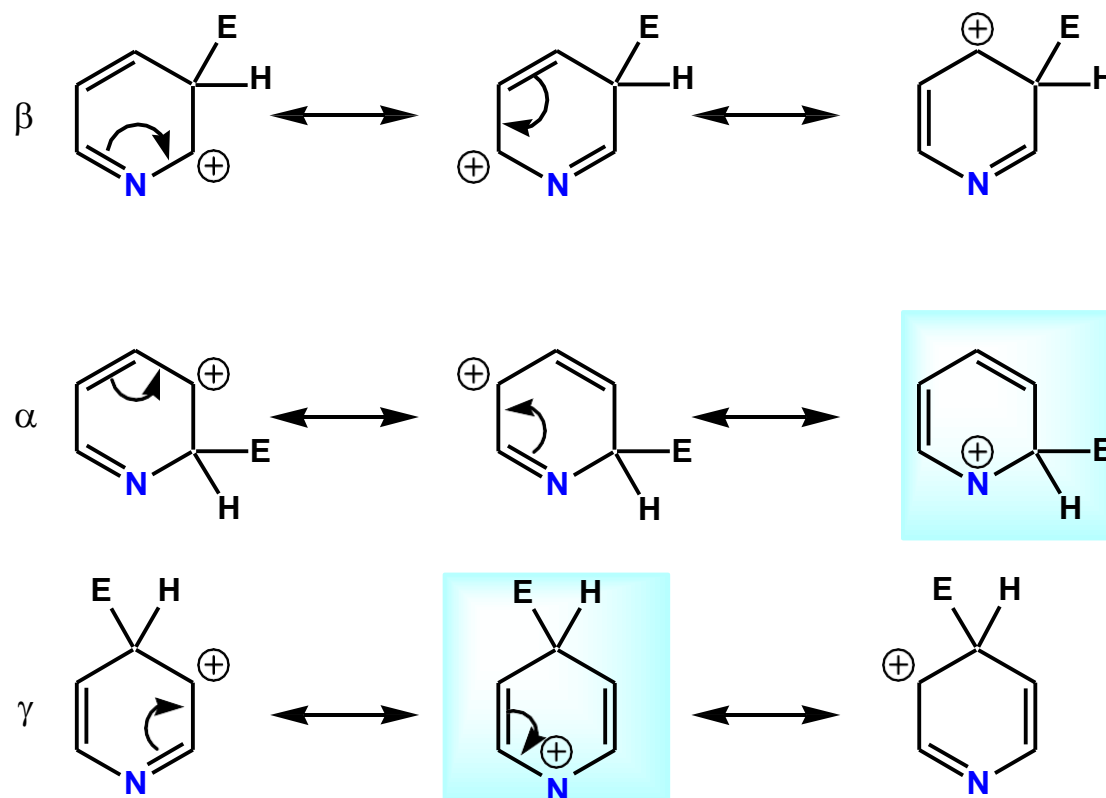
Pathways for the Electrophilic Aromatic Substitution of Pyridines



- 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 Substitution Reactions

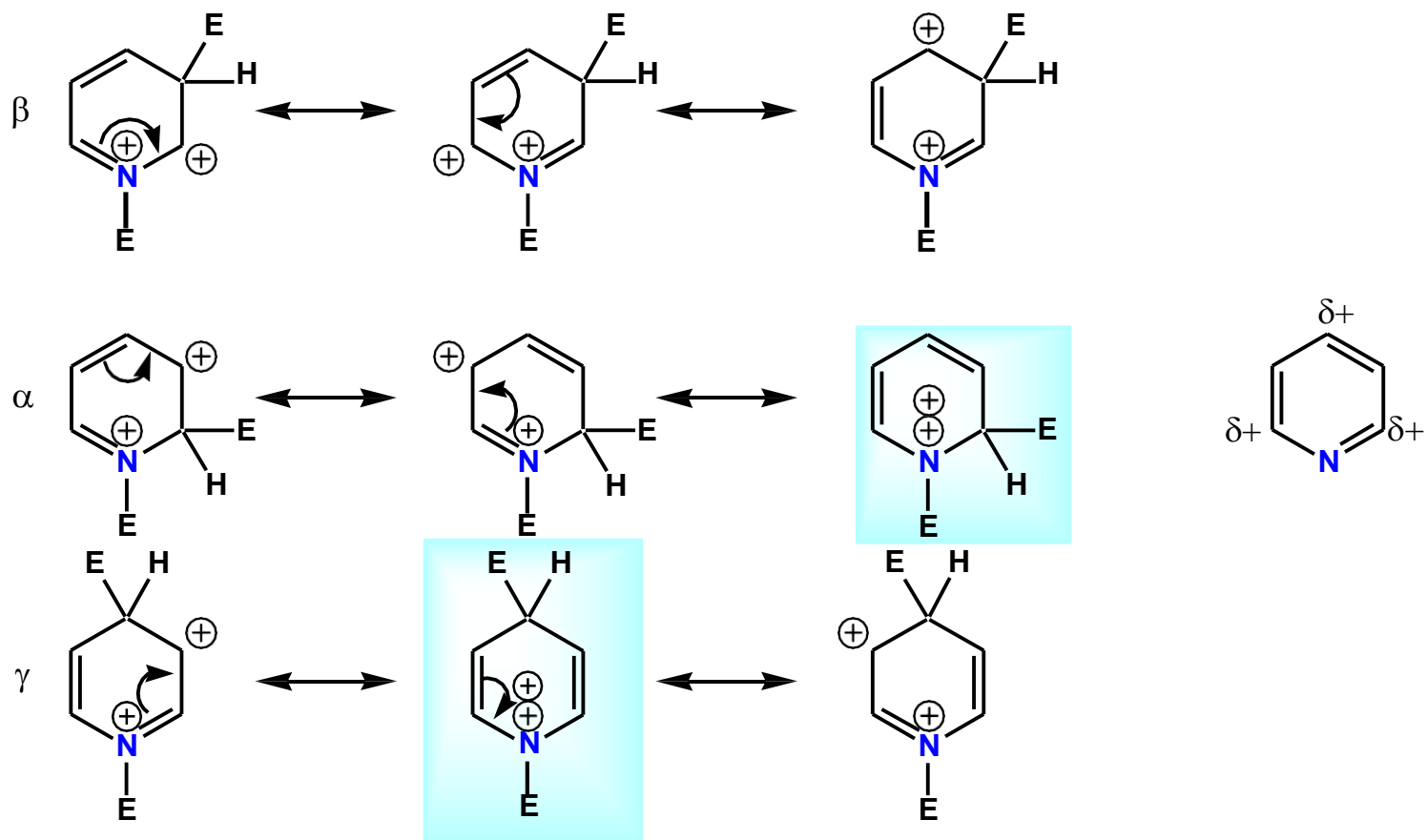
Regiochemical Outcome of Electrophilic Substitution of Pyridines



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

Pyridines – Electrophilic Substitution Reactions

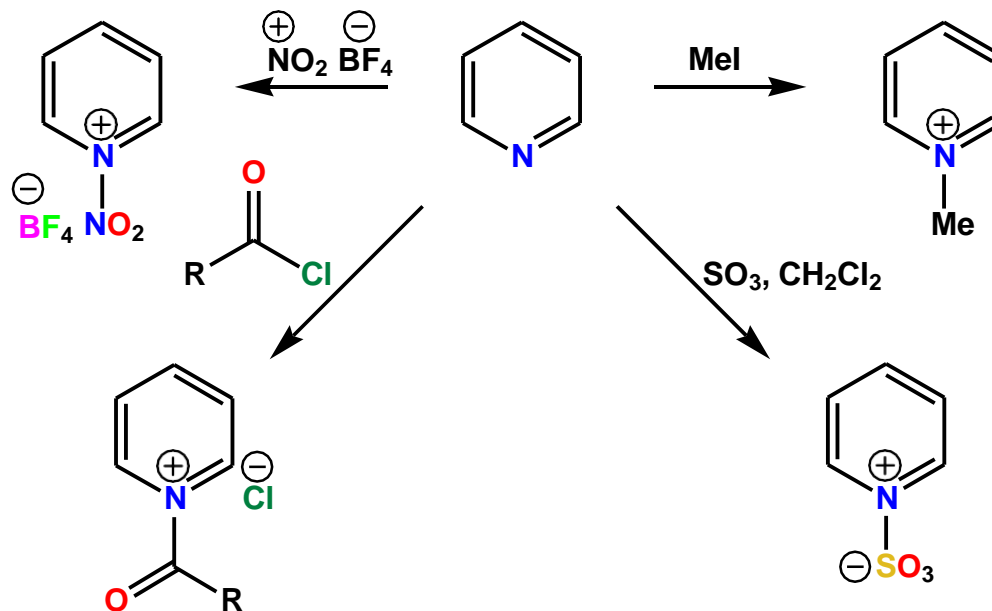
Regiochemical Outcome of Electrophilic Substitution of Pyridinium Ions



- 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 Substitution Reactions

N Substitution

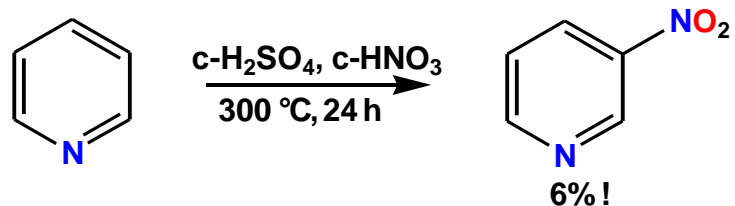


C Substitution

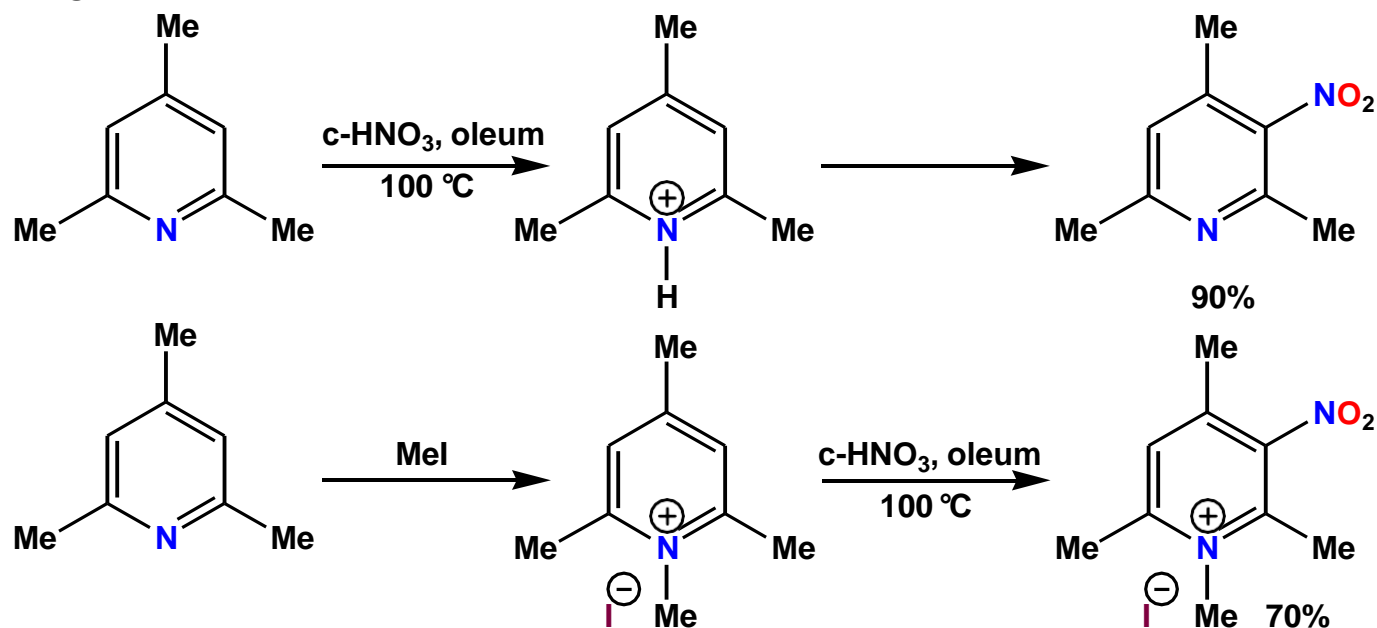
- Reaction at C is usually difficult and slow, requiring forcing conditions
- **Friedel-Crafts reactions** are not usually possible on free pyridines

Pyridines – Electrophilic Substitution Reactions

Nitration of Pyridine



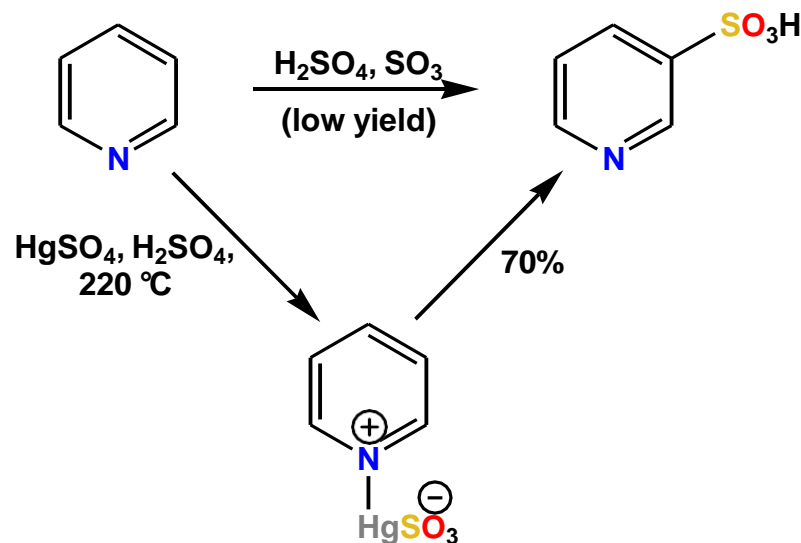
Use of Activating Groups



- 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

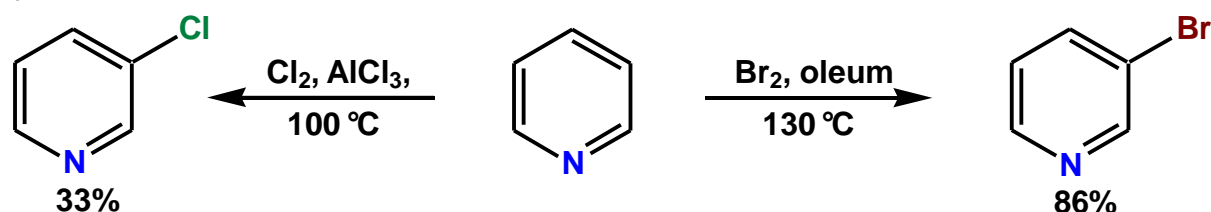
Pyridines – Electrophilic Substitution Reactions

Sulfonation of Pyridine



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

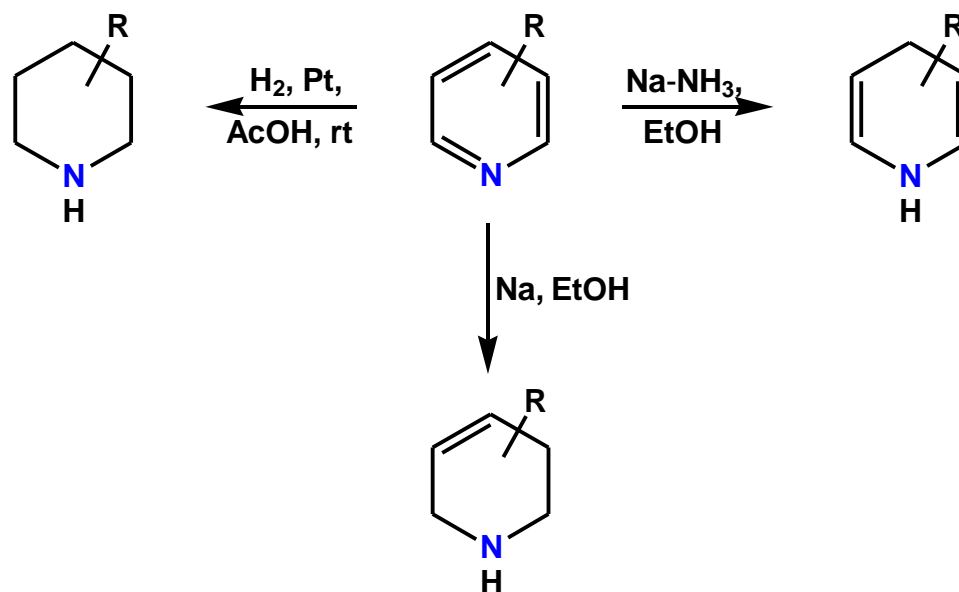
Halogenation of Pyridine



- 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