Organic chemistry

Heterocyclic Chemistry (3)

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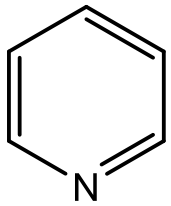
I- Give IUPAC and common name for each of the following:



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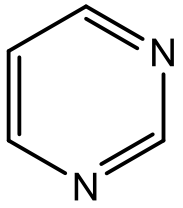

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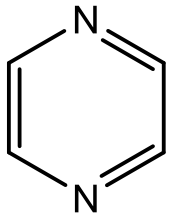

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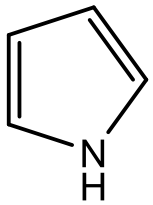

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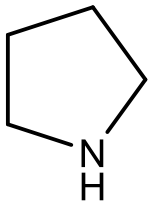

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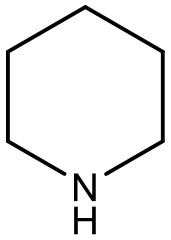

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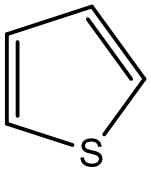

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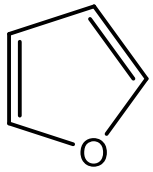

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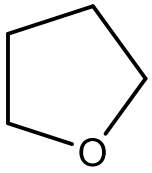

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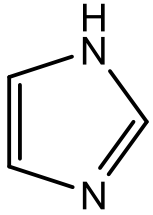

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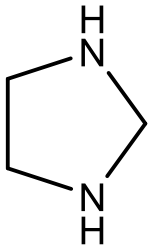

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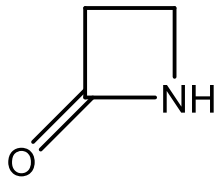

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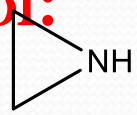
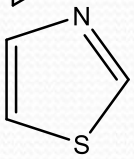
IUPAC	Common name
1- Azine	1- Pyridine
2- 1,3-Diazine	2- Pyrimidine
3- 1,4-Diazine	3- Pyrazine
4- 1-H-Azole	4- Pyrrole
5- Azolidine	5- Pyrrolidine
6- Perhydroazine	6- Piperidine
7- Thiole	7- Thiophene
8- Oxole	8- Furan
9- Oxolane	9- Tetrahydrofuran (THF)
10- 1-H-1,3-Diazole	10- Imidazole
11- 1,3-Diazolidine	11- Imidazolidine
12- Azetidin-2-one	12-β- Lactam

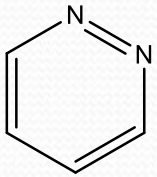
II- Draw the structure of:

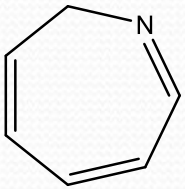
- Aziridine
- Oxirane
- 1,3- thiazole
- 1,2- diazine
- 2-H-Azepine
- Oxathiete
- Oxazetidine
- Pyrane
- morpholine



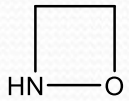


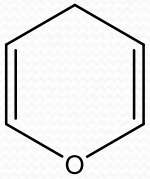


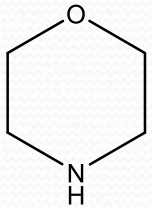






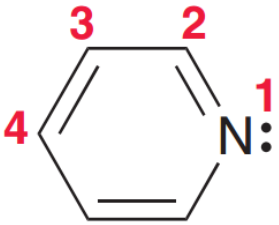






Six membered Heterocycles: Pyridine

- Pyridine is a six-membered aromatic ring containing one nitrogen atom. Why aromatic ?



Pyridine

- A compound will be aromatic if it satisfies the following four criteria:

1. Cyclic

2. Planar

3. Continuous overlapping *p* orbitals (*Sp*^{2} hybridized atoms)

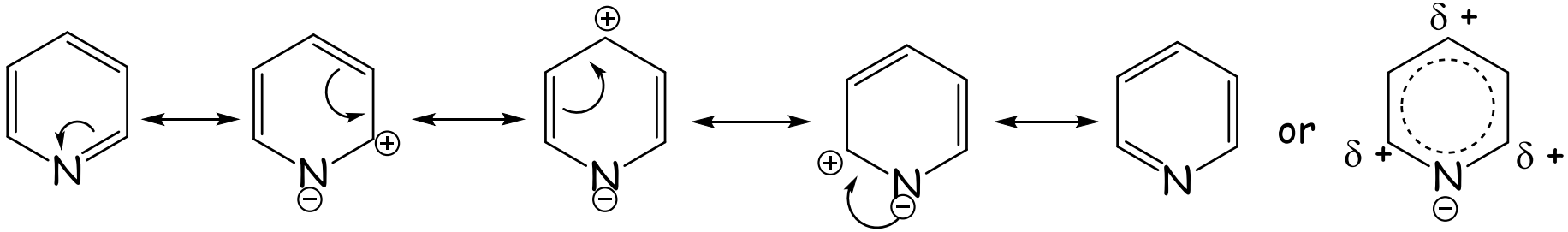
4. Obeys Huckel's rule ($4n+2 = \pi$ electrons, where n is a whole number.)

$4n+2 = 6$ $\quad 4n = 4$ $\quad n = 1$ so, pyridine is aromatic

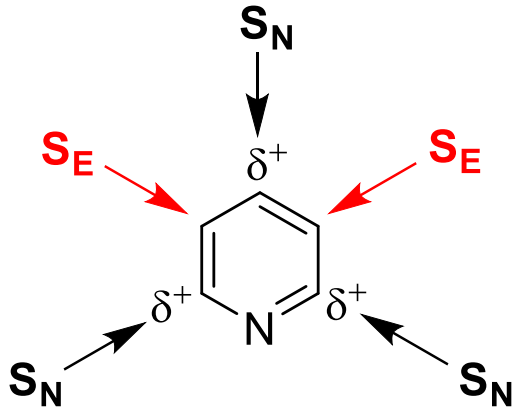
Six membered Heterocycles: Pyridine

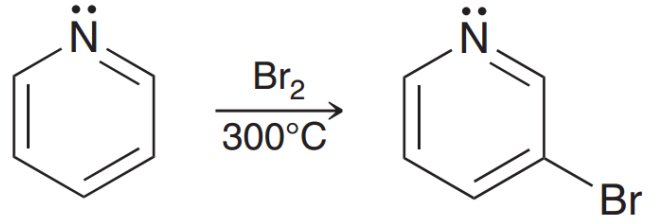
Chemical and Physical Properties:

- Resonance structure:



- The electron withdrawing effect of the nitrogen atom (-I and -M) renders the ring electron poor. High temperatures are required for electrophilic substitution reaction.





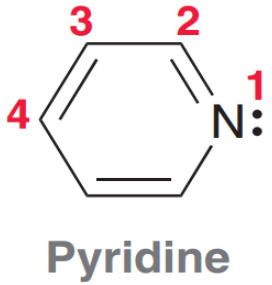
Six membered Heterocycles: Pyridine

Chemical and Physical Properties:

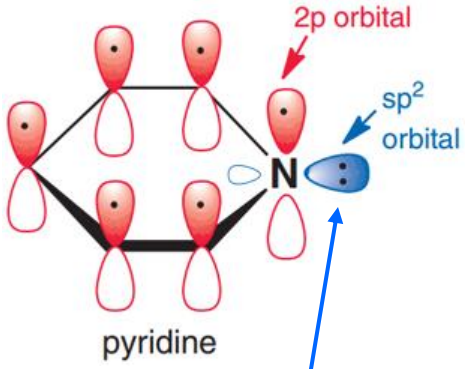
I. It is basic and its basicity is greater than that of pyrrole.
II. It is highly deactivated toward electrophilic substitution (S_E) and oxidation reactions.
III. It is highly activated toward nucleophilic substitution (S_N) and reduction reactions.

I. Basic character, formation of salts:

- pyridine is a stronger base than pyrrole. The lone pair of the nitrogen atom is localized and does not participate in the aromaticity.
- While in pyrrole, the lone pair of the nitrogen atom participates in aromaticity and is therefore significantly less basic and less nucleophilic than pyridine.

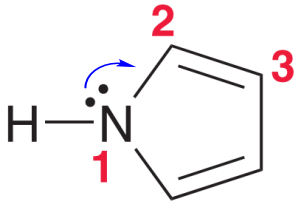


Pyridine

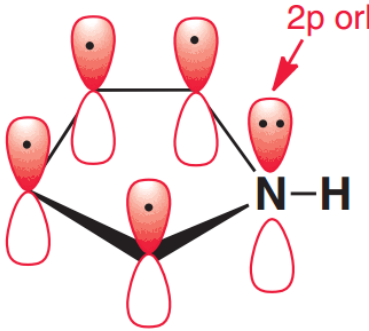


pyridine

ready for protonation

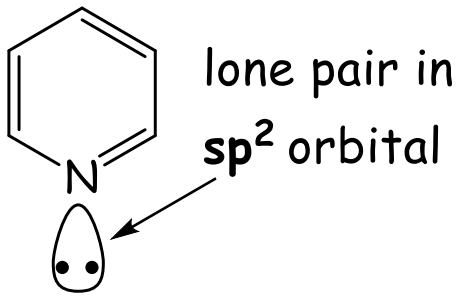


Pyrrole

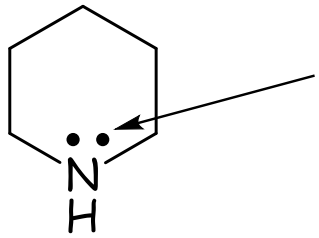


pyrrole

- Nevertheless, pyridine is still a weaker base than alkyl amines, because the lone pair is housed in sp^2-hybridized orbital, rather than sp^3-hybridized orbital.



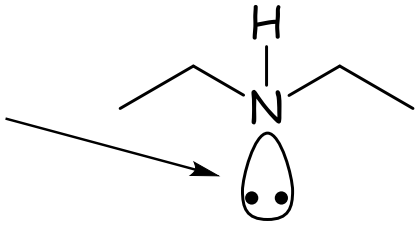
pyridine



piperidine

lone pairin
sp3 orbital

Aliphatic amine
(more basic)



diethylamine

- By occupying sp^2-hybridized orbital, the electrons of the lone pair have more *s* character and are therefore closer to the positively charged nucleus, rendering them less basic and not available for protonation.

Thus we have the following sequences of acidity of hydrocarbons and basicity of their anions:

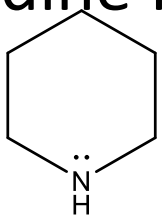
Acidity	$HC{\equiv}C{:}H > C_6H_5{:}H > R{:}H$
Basicity	$HC{\equiv}C{:}^- < C_6H_5{:}^- < R{:}^-$

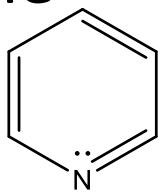
A possible explanation for these sequences can be found in the electronic configuration of the carbanions. In the alkyl, phenyl, and acetylide anions, the unshared pair of electrons occupies respectively an sp3 , an sp2 , and an sp orbital. The availability of this pair for sharing with acids determines the basicity of the particular anion. As we proceed along the series sp3 , sp2 , sp, the p character of the orbital decreases and the s character increases. Now, an electron in a p orbital is at some distance from the nucleus and is held relatively loosely; an electron in an s orbital, on the other hand, is close to the nucleus and is held more tightly. Of the three anions, the alkyl ion is the strongest base since its pair of electrons is held most loosely, in an sp3 orbital. The acetylide ion is the weakest base since its pair of electrons is held most tightly, in an sp orbital.

Pyridine bears the same relationship to an aliphatic amine as the phenyl anion bears to an alkyl anion. The pair of electrons that gives pyridine its basicity occupies an sp2 orbital; it is held more tightly and is less available for sharing with acids than the pair of electrons of an aliphatic amine, which occupies an sp3 orbital.

As S character increased (pyridine) the basicity decreased because the electrons in S orbital is close to the nucleus (the electron Is tight and not available for protonation

Piperidine is more basic than pyridine





SP3

Low S character

Lone pair is far from the nucleus

Lone pair of N is loose

Ease of protonation

More Basic

SP2

High S character

Lone pair is far from the nucleus

Lone pair of N is tight

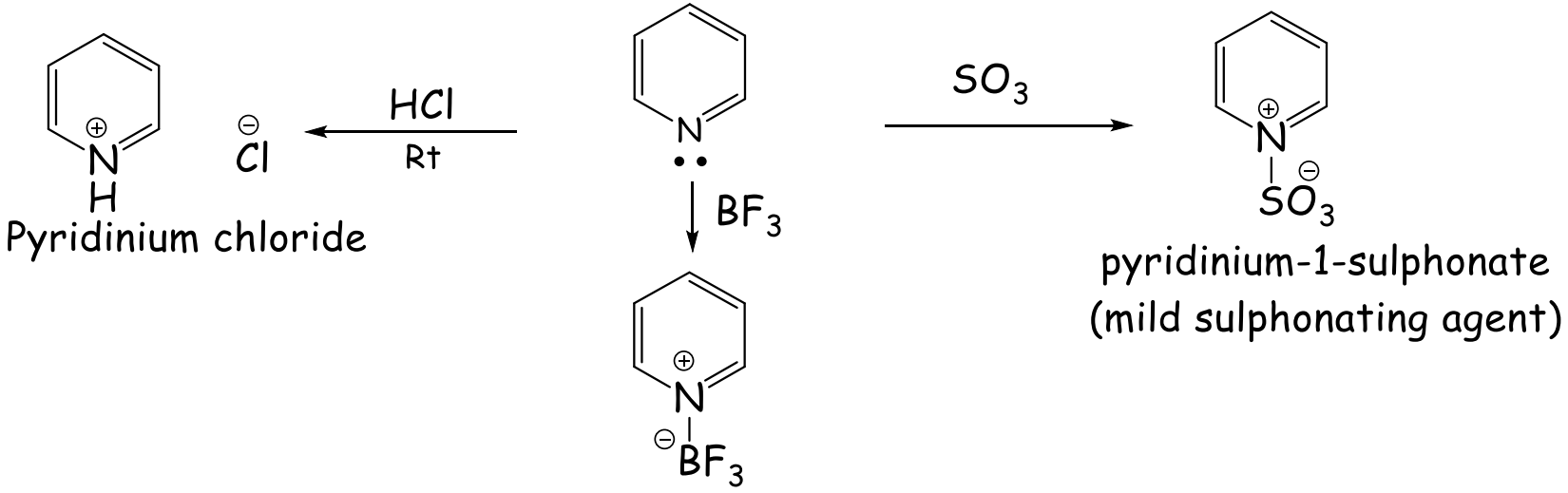
Not ease of protonation

Less Basic

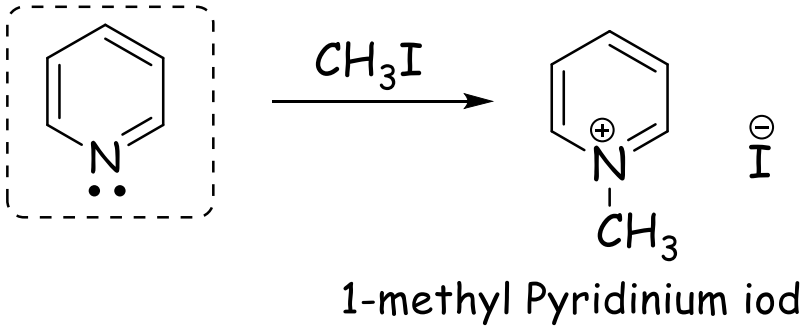
Problem 16.14 Predict the relative basicities of amines (RCH_2NH_2), imines (RCH=NH), and nitriles (RC≡N).

- <u>Examples of reactions involving lone pair of nitrogen:</u>

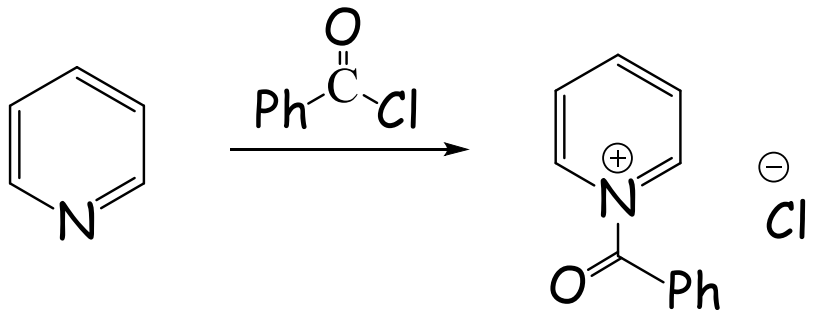
1. Reaction with mineral acids and Lewis acids



2. Alkylation of N:

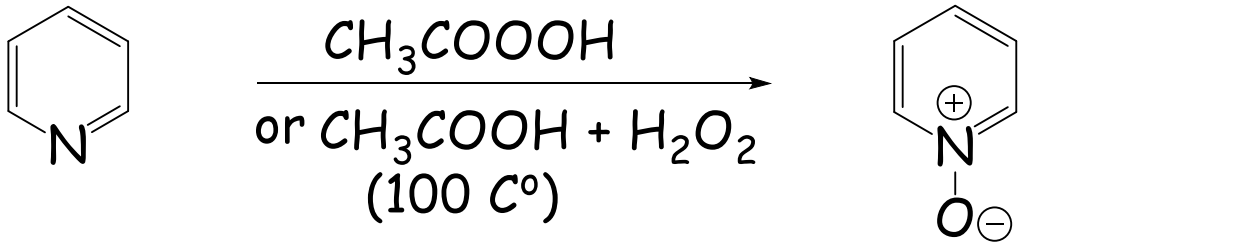


3. Acylation of N:



strong acylating agent.

4. Reaction with percarboxylic acids: to produce pyridine-*N*-oxide:



Pyridine *N*-oxide

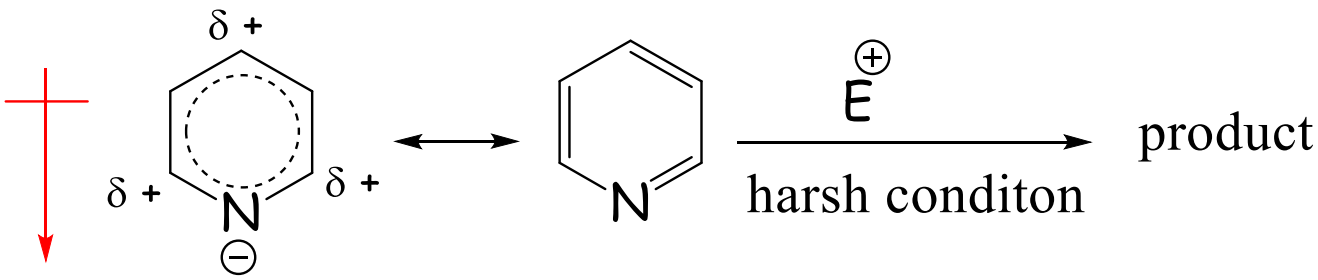
II. Electrophilic substitution (S_E) of pyridine:

- In most cases, **S_E** of pyridines occurs very much less readily than for the correspondingly substituted benzene. The main reasons are:

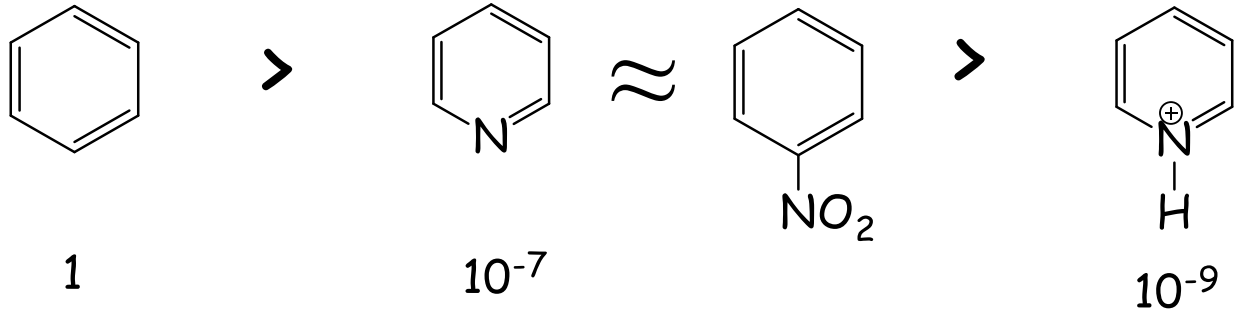
➢ The rapid formation of pyridinium cation which is very resistant to further S_E reactions.

➢ Electron withdrawing (-*M* and –*I*) effects of the ring N.

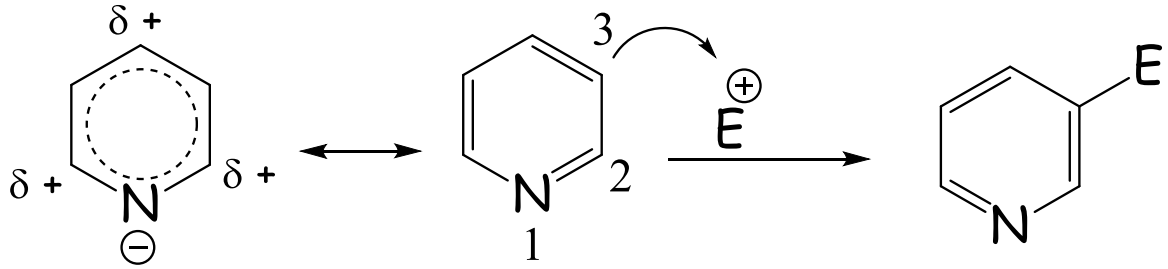
➢ The intermediate σ complex is destabilized by the –*I* effect of the N atom.



- The order of reactivity toward S_E is as follows:

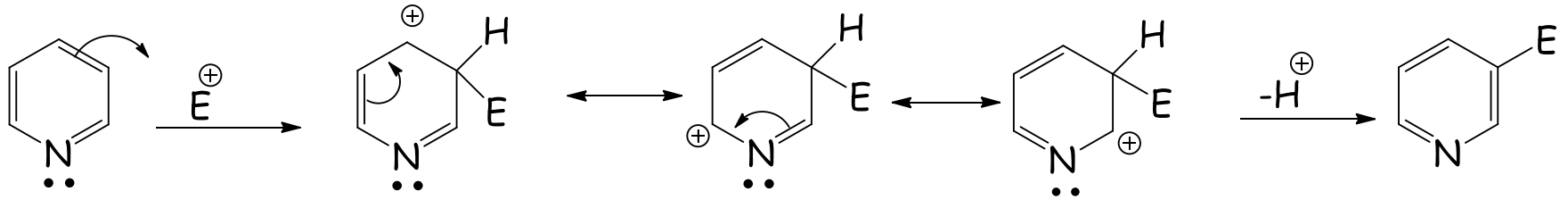


- Electrophilic substitution in pyridine takes place at position 3 or 5 (*β*-position).

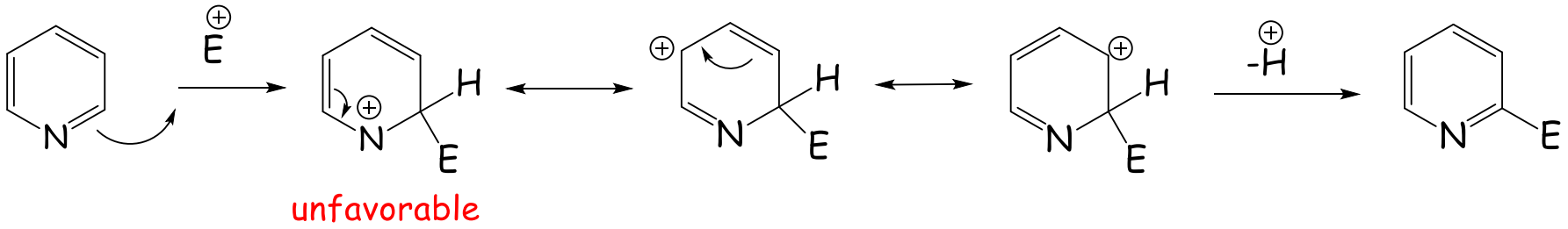


Six membered Heterocycles: Pyridine

- **Attack at position-3 or 5:**

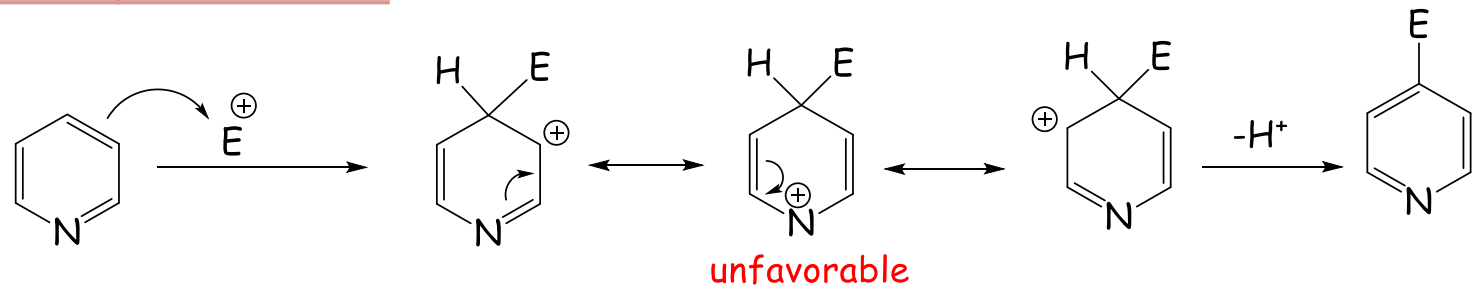


- Attack at position-2 or 6:



unfavorable

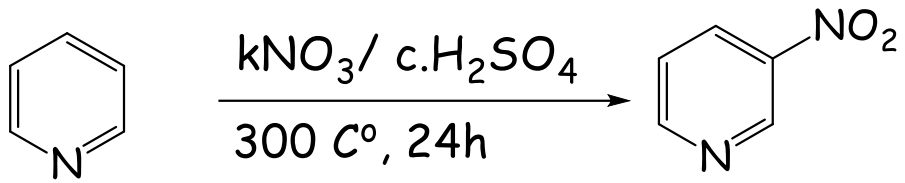
- Attack at position-4:



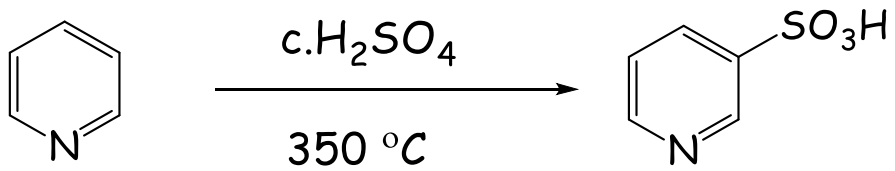
unfavorable

Six membered Heterocycles: Pyridine

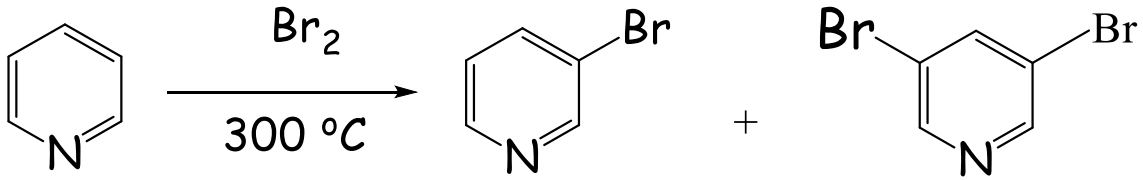
- Examples of electrophilic substitution reactions in pyridine:



3-Nitro pyridine



pyridine-3-sulfonic acid



3-bromopyridine

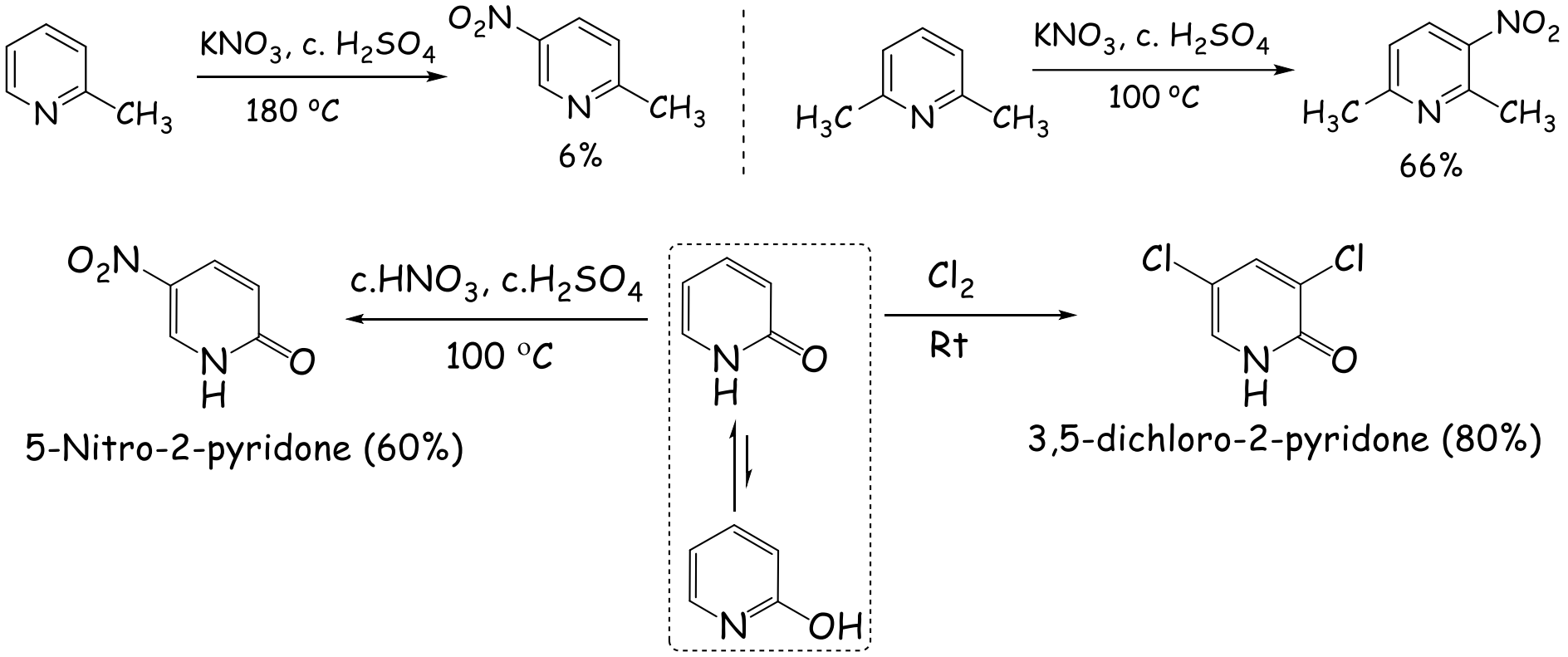
- No Freidel-Crafts reaction occurs at all with pyridine.

Six membered Heterocycles: Pyridine

How can we activate pyridine towards S_E?

1- By conversion of pyridine to pyridine *N*-oxide.

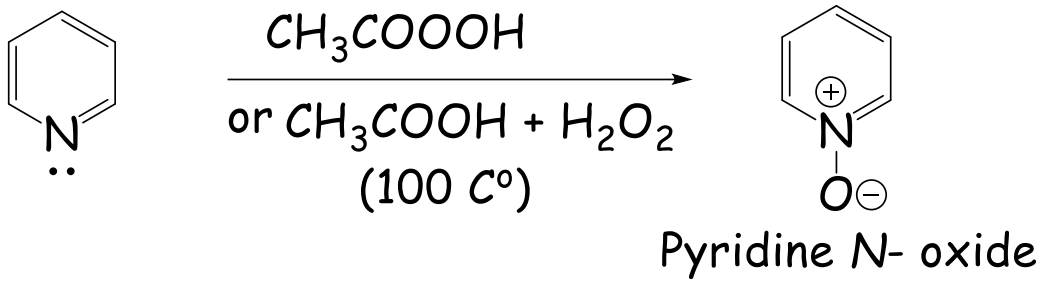
2- Presence of electron donating group (OH, NH_2, CH_3)



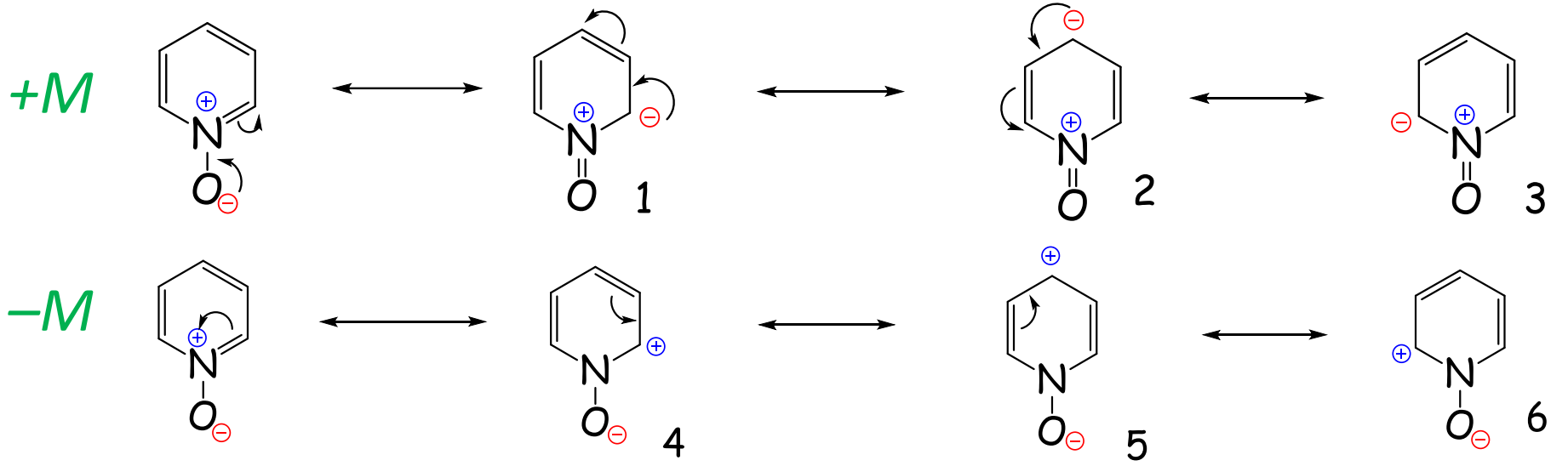
3. Six membered Heterocycles: Pyridine

Pyridine Derivatives: Pyridine-1-Oxide

- It is prepared by reacting pyridine with peracetic acid:

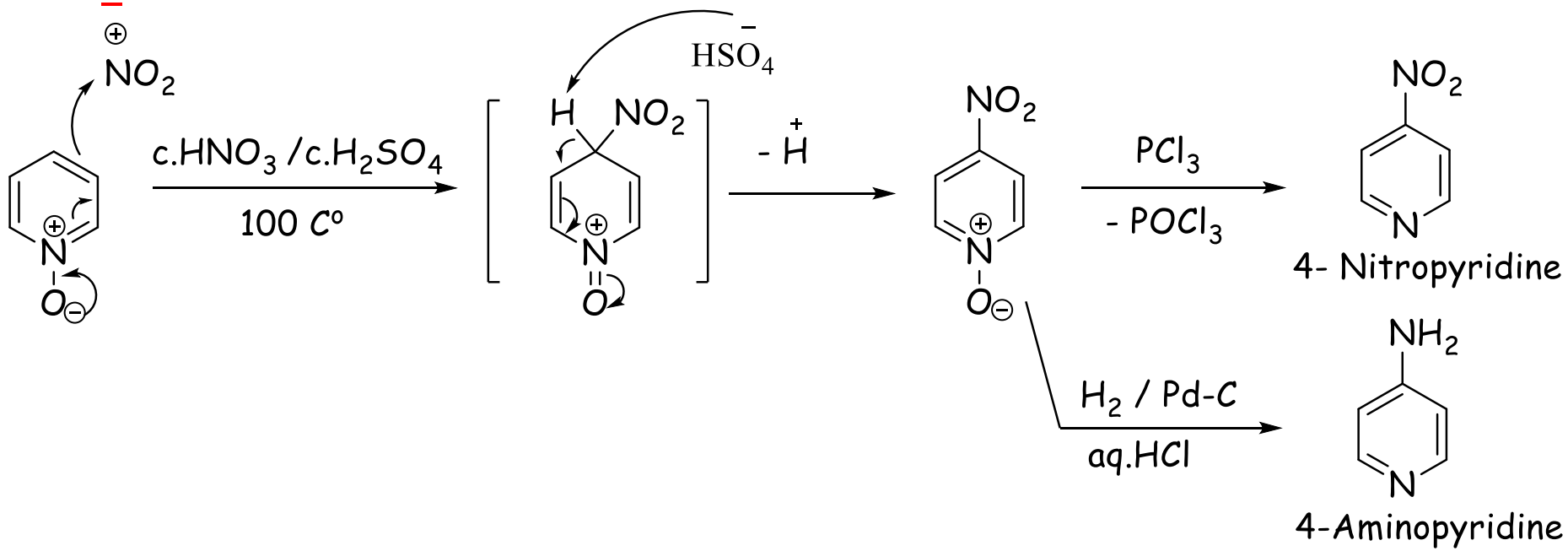


- The *N*-oxide group have +M and –M effect, and thus serve to facilitate on demand both S_E and S_N reactions.



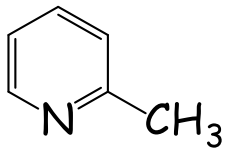
3. Six membered Heterocycles: Pyridine

- **S_E** Reactions of *pyridine-N-oxide*:

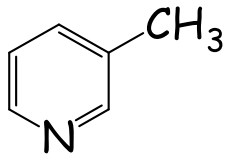


3. Six membered Heterocycles: Pyridine

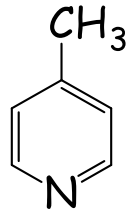
Pyridine Derivatives: Alkyl pyridines



2- or α- picoline



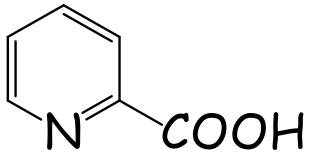
3-or B- picoline



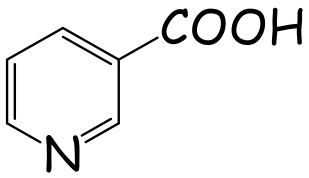
4-or γ- picoline

3. Six membered Heterocycles: Pyridine

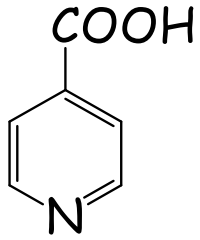
Pyridine Derivatives: Pyridine Carboxylic acids



α- Picolinic acid
(Picolinic acid)

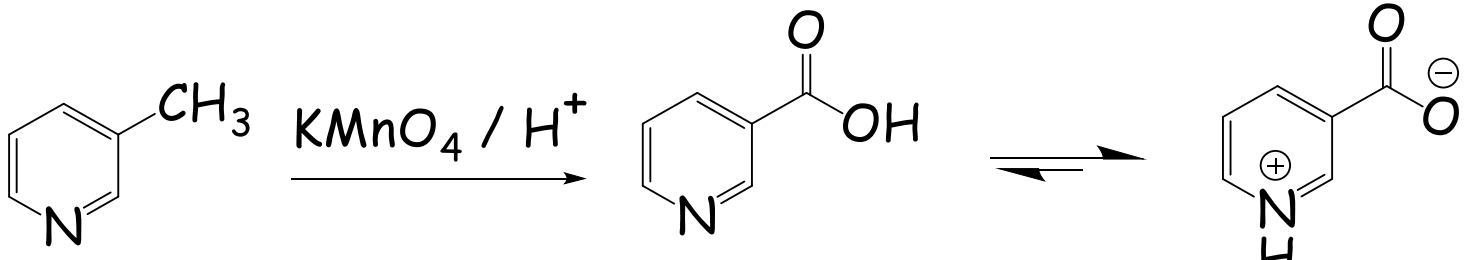


β- Picolinic acid
(Nicotinic acid)



γ- Picolinic acid
(Isonicotinic acid)

- Prepared from the corresponding alkyl pyridines by oxidation with alkaline $KMnO_4$:



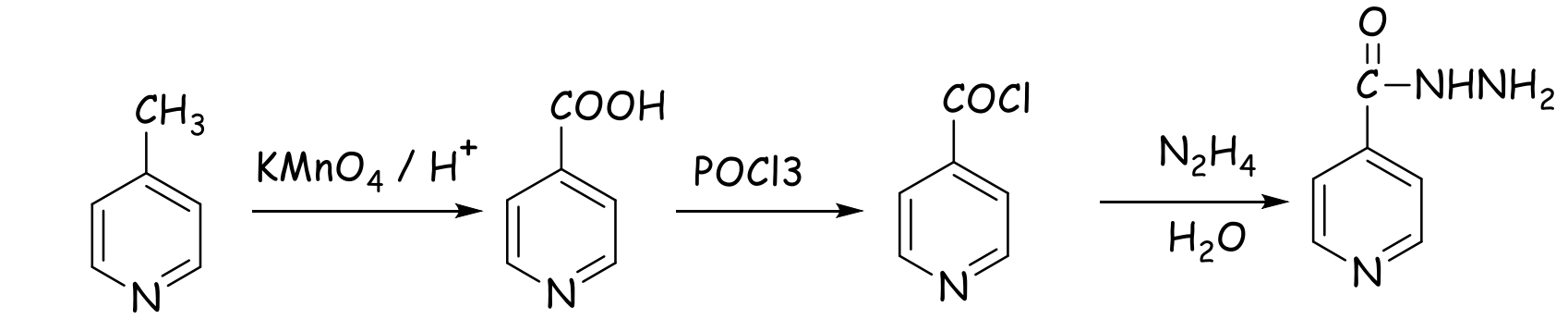
nicotinic acid
(niacin)

zwitter ion
(in aq. solution)



3. Six membered Heterocycles: Pyridine

- Isonicotinic acid is useful in preparation of isonicotinic acid hydrazide (isoniazide) which used as anti-tuberculous drug.





From β picoline, how can you prepare 3-aminopyridine

1-vitamin B3 (niacin)

2- 3-aminopyridine

From γ picoline, how can you prepare INH

Q1. Which position on pyridine is most susceptible to electrophilic aromatic substitution under standard conditions?

- 2-position (alpha)
- 3-position (beta)
- 4-position (gamma)
- The nitrogen atom

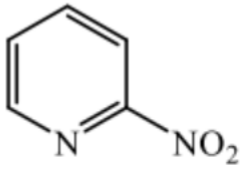
Correct Answer: **3-position (beta)**

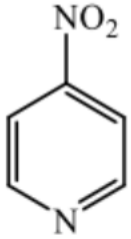
Q5. Which reagent is typically used to reduce pyridine to piperidine?

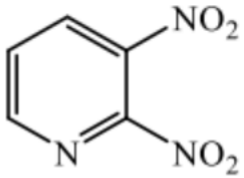
- NaBH4
- H2 with Pd/C under pressure
- KMnO4
- mCPBA

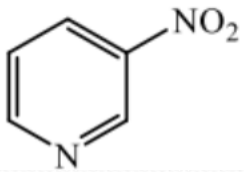
Correct Answer: **H2 with Pd/C under pressure**

Pyridine undergoes electrophilic nitration at elevated temperatures to give the following as a major product

(1) 

(2) 

(3) 

(4) 

Q6. What is the effect of the pyridine nitrogen on the ring's electron density?

- Strong electron-donating by resonance increases reactivity
- Electron-withdrawing by inductive effect deactivates ring toward electrophiles
- No effect; ring behaves like benzene
- Makes ring highly nucleophilic

Correct Answer: **Electron-withdrawing by inductive effect deactivates ring toward electrophiles**

Q12. Which of the following best explains why pyridine is less reactive than benzene toward electrophilic aromatic substitution?

- Pyridine has less aromatic stabilization
- The sp2 nitrogen withdraws electron density by inductive and resonance effects
- Pyridine is more basic than benzene
- Presence of an extra hydrogen reduces reactivity

Correct Answer: **The sp2 nitrogen withdraws electron density by inductive and resonance effects**

Q18. Which statement about the basicity of pyridine is true?

- Pyridine is more basic than tertiary amines
- Pyridine has a pKa of conjugate acid around 5.2, making it a weak base
- Pyridine is nonbasic due to aromaticity
- Pyridine is a strong base with pKa > 10

Q22. In Friedel–Crafts type reactions, why is pyridine generally unreactive under normal AlCl3-catalyzed conditions?

- AlCl3 oxidizes pyridine
- Pyridine nitrogen coordinates to Lewis acid, deactivating the ring
- Pyridine undergoes rapid polymerization
- Pyridine is too basic for AlCl3

Correct Answer: **Pyridine nitrogen coordinates to Lewis acid, deactivating the ring**

Q24. Which of the following best describes the mechanism of normal electrophilic substitution on pyridine N-oxide compared to pyridine?

- N-oxide is more deactivated than pyridine toward electrophiles
- N-oxide activates the ring allowing electrophilic substitution at 2- and 4-positions
- N-oxide directs substitution exclusively to the nitrogen
- Mechanisms are identical with no change in reactivity

Correct Answer: **N-oxide activates the ring allowing electrophilic substitution at**

Q25. Which product is expected from catalytic hydrogenation of pyridine under harsh conditions?

- Benzene
- Piperidine
- 2,3-Dihydropyridine only
- Pyridine N-oxide

Correct Answer: **Piperidine**

Q26. Which reagent is used to prepare N-alkylpyridinium salts?

- Alkyl halide (e.g., methyl iodide) reacting with pyridine
- Sodium borohydride and an alkene
- Acid-catalyzed hydration
- Direct reaction with alcohol in absence of catalyst

Q29. In medicinal chemistry, why are pyridine rings commonly found in drug molecules?

- Pyridine is highly lipophilic and always improves bioavailability
- The ring provides metabolic instability desirable for drugs
- Pyridine can act as hydrogen bond acceptor, tune basicity and improve solubility and binding
- Pyridine rings are non-aromatic and flexible

Correct Answer: **Pyridine can act as hydrogen bond acceptor, tune basicity and improve solubility and binding**

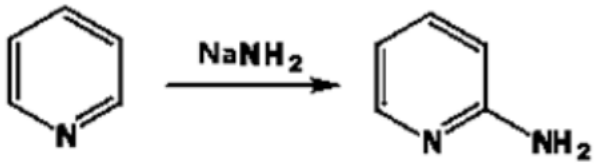
1 At which position of pyridine nucleophilic substitution reaction is most preferred?

A First and third
B Second
C Third
D Second and Forth

2 Pyridine undergoes nucleophilic substitution with NaNH2 at 100°C to give which of the following?

A 3-aminopyridine
B 2-aminopyridine
C 3,5-diaminopyridine
D 2,5-diaminopyridine

7 What is the name of the following reaction?



A Chichibabin reaction
B Dealkylation of pyridine
C Hantzsch pyridine synthesis
D Bonnemann cyclisation

3 The electron of Nitrogen participating in the resonance in pyridine is present in which orbital?

A p-orbital
B sp2-orbital
C sp3-orbital
D sp -orbital

6 Pyridine come under which category of heterocycle classification on the basis of chemical behavior?

A -excessive heterocycle
B -deficient heterocycle
C -equivalent heterocycle
D can’t say about the five membered rings

Q11. Chichibabin amination requires which reagent as the nucleophilic nitrogen source?

- Ammonia gas only
- Sodium amide (NaNH2)
- Hydroxylamine
- Hydrazine

Correct Answer: **Sodium amide (NaNH2)**

Q20. Which reaction pathway is favored when 2-chloropyridine reacts with sodium methoxide?

- Elimination to give pyridine
- Nucleophilic aromatic substitution to give 2-methoxypyridine
- Electrophilic aromatic substitution
- Reduction of the ring to dihydropyridine

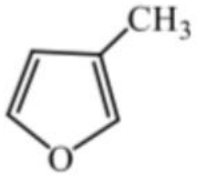
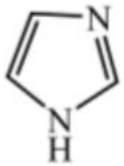
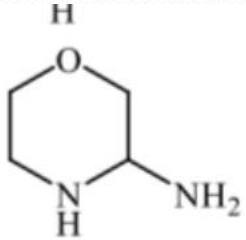
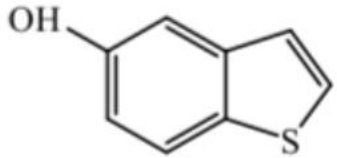
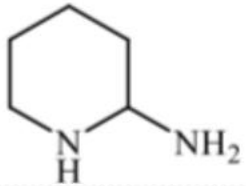
Correct Answer: **Nucleophilic aromatic substitution to give 2-methoxypyridine**

Q43. Which reagent is useful to activate pyridine for subsequent nucleophilic attack by converting it to a better leaving group at C2?

- Tosylation of the ring carbons directly
- Formation of 2-halopyridine by directed halogenation
- Direct protonation at C2
- Hydrogenation of the ring

Correct Answer: **Formation of 2-halopyridine by directed halogenation**

Match the structures in List I with their correct names in List II.

List I		List II	
(a)		(i)	3-methyl furan
(b)		(ii)	Imidazole
(c)		(iii)	5-hydroxy benzothiazole
(d)		(vi)	2-amino piperidine
(e)		(v)	2-amino morpholine