Chapter 2

REACTIVITY OF HETEROCYCLIC COMPOUNDS

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SUMMARY

- Relevance of heterocycles as chemical reagents
- Acid-base behavior of nitrogen heterocycles
- Reactivity of heterocycles.
  - Reactivity of five-membered heterocycles: pyrrol, furane and thiophene
  - Reactivity of six-membered heterocycles: pyridine
Heterocycles participate in most of the chemical processes associated with life.

- Energetic processes (ATP, ...)
- Nerve impulse transmission (neurotransmitters, ...)
- Processes associated with vision
- Metabolic processes
- Transmission of genetic information
- Effect on virus and bacteria
- And many more...
RELEVANCE OF HETEROCYCLES AS CHEMICAL REAGENTS

HETEROCYCLES AS REAGENTS IN INDUSTRIAL CHEMISTRY

The reactivity of heterocycles is crucial in many chemical processes used in industry

Pharmaceutical industry (drugs)

Catalysts in petroleum processing

Catalysts and reagents in Fine Chemical Synthesis

Dyes (OLEDs, etc.)

Agrochemicals

Health-care consumables

Additives in polymer manufacturing

And many more...
ACID-BASE BEHAVIOR OF NITROGEN HETEROCYCLES

ACIDITY AND BASICITY

Measuring of the acidity of a substance: The pKa

\[ \text{H}^- \text{A} \rightleftharpoons \text{A}^- + \text{H}^+ \]

\[ K_a = [\text{A}^-][\text{H}^+] / [\text{HA}] \]

\[ pK_a = -\log K_a = \log [\text{HA}] / [\text{A}^-] + \text{pH} \]

**Strong acids** have low pKa values. The conjugate base is a weak base. The equilibrium is shifted to the right

**Weak acids** have high pKa values. The conjugate base is a strong base. The equilibrium is shifted to the left
**Pyrrole-type heterocycles**

**Bronsted acidity**

\[
\text{Pyrrole} \rightleftharpoons \text{Pyrrolyl anion} + \text{H}^+ \]

\[ \text{pKa} = 17.5 \]

- Pyrrole is a weak acid
- Pyrrolyl anion is a strong base

**Bronsted basicity**

- Pyrrole is a weak base: Protonation breaks aromaticity (lone pair participates in conjugation and thus it is not readily available)

\[
\text{Pyrrole} + \text{H}^+ \rightleftharpoons \text{Non-aromatic cation} \]

Aromatic compound

Non-aromatic cation
PYRIDINE-TYPE HETEROCYCLES

Bronsted acidity
- Pyridine does not have any acidic hydrogen (no N-H group)
- Can not behave as Bronsted acid

Bronsted basicity
- The lone pair at nitrogen does not participate in conjugation
- Pyridine is a Bronsted base

\[
\begin{align*}
\text{Pyridinium cation} & \quad \text{Pyridine} + H^+ \\
pK_a &= 5.23
\end{align*}
\]
- Pyridinium cation is a strong base
- Pyridine is a weak base
HETEROCYCLES CONTAINING PYRIDINE- AND PYRROL-TYPE MOIETIES

E. g. Imidazole

- Imidazole is an amphoteric compound
  - Acidic compound
    - Pyrrol-type heteroatom linked to hydrogen atom
  - Basic character
    - Pyridine-type heteroatom with an Electron lone pair on sp$^2$ orbital of Nitrogen atom

- Comparing acidity: imidazole vs pyrazole
  - Imidazole can donate NH hydrogen
  - Imidazole is a $10^{3.3}$ ($\approx 2000$) times stronger acid than pyrrole ($pK_a = 17.5$)

- Comparing basicity: imidazole vs pyridine
  - Imidazole can donate the lone pair on pyridine-like nitrogen
  - Imidazole is a $10^{1.72}$ ($\approx 2000$) times stronger base than pyridine (pyridinium cation $pK_a = 5.23$)

- All these effects can be rationalized in terms of resonance-stabilized forms
RELEVANCE OF ACID-BASE BEHAVIOR OF HETEROCYCLES IN BIOCHEMICAL PROCESSES

- Enzymes are proteins which participate in the chemical reactions associated with life processes by catalyzing them
- Enzymes can also be used in chemical synthesis (both in academic laboratories or in industrial processes)
- Enzymes are fully substrate-selective catalysts and only work on aqueous buffered media
- The catalytic action takes place at the enzyme active site. The rest of the protein domains are only required as an architectural feature associated with stability and shape of the complete molecule.

**Acid-Base catalytic enzymes**

- Very often enzymes which catalyze reactions through acid-base mechanisms operate with an histidine residue at the active site

- Imidazole is a weak base which at physiological pH is in equilibrium with its protonated form
- Imidazole ring participates as a “proton bank”, accepting protons on its free base form and donating them when it is protonated
Example: Epoxide hydrolase

- Epoxide hydrolase functions in detoxification during drug metabolism. It converts epoxides to trans-diols, which can be conjugated and excreted from the body. Epoxides result from the degradation of aromatic compounds. Deficiency in this enzyme in patients receiving aromatic-type anti-epileptic drugs such as phenytoin is reported to lead to DRESS syndrome (a syndrome, caused by exposure to certain medications, that may cause fever or inflammation of internal organs. The syndrome carries about a 10% mortality.

![Enzyme active site](image1)
![Enzyme crystal structure](image2)

Phenytoin (antiepileptic)
HETEROCYCLES AS METAL LIGANDS

Heterocycles can act bound to metals through their lone pairs (Bronsted basicity) forming coordination compounds

**Coordination compound (metal complex):** A chemical entity formed by a central metal atom (typically a transition metal) surrounded by groups of neutral or ionic molecules called ligands

- Heterocycles can play the role of metal ligands by donating a pair (monodentate ligand) or more than one pair of electrons (polydentate ligand or chelating ligand) to the metal therefore forming a coordinated complex.
- The coordinating ability (cationic capacity) is related to its basicity (proton affinity).
- The coordination index of the complex refers to the number of ligands directly attached to the central ion.
- The number of ligands (heterocycles) that are coordinated with a metal depends on the type and number of orbitals available in the outer layer of metal.
- The complex may be neutral (no net charge) or ionic (with positive or negative net charge).
- The metals that form complexes are generally transition metals. They provide the empty d orbitals of the penultimate level to accommodate the ligand which donates the electron pair.
HETEROCYCLES AS METAL LIGANDS

Metal complexes with pyridine: Pyridine complexes with all metals through its nitrogen lone pair (highly basic). Therefore pyridine is a monodentate ligand. Geometry depends on metal atom.

- Ag (I): Linear
- Al (III): Tetrahedral
- Cu (II): Square planar
- Co (IV): Octahedral

Other examples: Protoporphyrin is widely found in nature.
REACTIVITY OF FIVE-MEMBERED HETEROCYCLES

GENERAL REACTIVITY TREND

Most important five-membered heterocycles: Furane, thiophene and pyrrol

Typical reactions:

- **Electrophilic aromatic substitution** \((S_{EAr})\): They are \(\pi\)-excedent systems

  Order of reactivity: Model system

  ![Chemical equation]

<table>
<thead>
<tr>
<th>(X)</th>
<th>Reaction rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>NH</td>
<td>(5,3 \times 10^7)</td>
</tr>
<tr>
<td>O</td>
<td>(1,4 \times 10^2)</td>
</tr>
<tr>
<td>S</td>
<td>1</td>
</tr>
</tbody>
</table>

  **Pyrrol > Furane > Thiophene > Benzene**

- **Electrophilic addition**: Leads to loss of aromaticity

  Resonance-stabilization energies: Benzene > thiophene > pyrrol > furane

  This means that furane has the highest tendency to undergo electrophilic addition

- **Diels-Alder-type reactivity**: They are electron-rich dienes
Electrophilic aromatic substitution normally occurs at carbon atoms instead of at the nitrogen. Also it occurs preferentially at C-2 (the position next to the heteroatom) rather than at C-3 (if position 2- is occupied it occurs at position 3). This is because attack at C-2 gives a more stable intermediate (it is stabilized by three resonance structures) than the one resulted from C-3 attack (it is stabilized by two resonance structures).
Formylation: Vilsmeier-Haack:

1.- Formation of electrophile

\[
\begin{align*}
\text{H}_3\text{C} \quad \text{N} & \quad \text{CH}_3 \\
\text{O} & \quad + \quad \text{POCl}_3 \\
\text{H}_3\text{C} & \quad \text{N} \quad \text{OH} \\
\text{H}_3\text{C} & \quad \text{Cl} \\
\text{NH}_3 & \quad \text{H} \\
\text{N(CH}_3\text{)_2} & \quad \text{OH} \\
\text{N(CH}_3\text{)_2} & \quad \text{H} \\
\text{N(CH}_3\text{)_2} & \quad \text{NH}(\text{CH}_3\text{)_2}
\end{align*}
\]

2.- Electrophilic aromatic substitution

3.- Hydrolysis of iminium salt

\[
\begin{align*}
\text{H}_3\text{C} \quad \text{N} & \quad \text{CH}_3 \\
\text{H}_3\text{C} \quad \text{Cl} & \quad \text{H} \\
\text{N(CH}_3\text{)_2} & \quad \text{H} \\
\text{N(CH}_3\text{)_2} & \quad \text{NH}(\text{CH}_3\text{)_2}
\end{align*}
\]
**REACTIVITY OF PYRROL: \( S_{EAr} \)**

**Acylation: Houben-Hoesch:**

\[
\text{Acrylonitrile} + \text{HCl (aq.)} \rightarrow \text{Acylated Pyrrole} \]

1. **Formation of electrophile**

\[
R-\overset{\equiv}{\text{C}} \overset{\text{N}}{\text{H}} + \text{HCl} \rightarrow R-\overset{\equiv}{\text{C}} \overset{\text{N}}{\text{H}} + \overset{+}{R-\overset{\equiv}{\text{C}} \overset{\text{N}}{\text{H}}} \]

2. **Electrophilic aromatic substitution**

3. **Hydrolysis of imine**
Other reactions:

- Friedel-Crafts acylation (thermal or LA-catalyzed)
- Bromination
- Polyhalogenation
- Diazotization
- Nitration
- Sulfonation
- Erlich reaction
REACTIVITY OF PYRROL: $S_{E}Ar$

Addition to 3-position?: Using steric effects

\[
\text{pyrrole} \rightarrow \text{pyrrole with } R \rightarrow \text{pyrrole with } E
\]

E.g.

\[
\begin{align*}
\text{pyrrole with } \text{SO}_2\text{Ph} & \xrightarrow{\text{NBS}} \text{pyrrole with } \text{Br} \\
\text{pyrrole with } \text{SO}_2\text{Ph} & \xrightarrow{\text{PhCOCl}} \text{pyrrole with } \text{COPh}
\end{align*}
\]
And the second substitution?:

a) Monosubstituted pyrrole with electron withdrawing group

Less reactive than pyrrol

One example:

a) Monosubstituted pyrrole with electron donating group

More reactive than pyrrol
Metallation of pyrrol:

\[
\text{BuLi} \implies \text{Li} \implies \text{R}
\]

Most acidic proton

Metallation of N-substituted pyrrol:

\[
\text{BuLi} \implies \text{Li} \implies \text{R}^1
\]

Ortho-metallation

Metallation at 3-position?

\[
\text{BuLi} \implies \text{Li} \implies \text{R}^1
\]

Steric effect
(\text{be careful with basic o-directing groups capable of chelation})

Metal-Halogen exchange
(Requires introduction of the halogen at 3-position)
**REACTIVITY OF PYRROL**

**CYCLOADDITION CHEMISTRY**

*Pyrrole is an electron-rich 1,3-diene: Diels–Alder reactivity*

- **Diels – Alder reaction** involves addition of a compound containing a double or a triple bond (2 π e it is Called dienophile) across the 1,4- position of a conjugated system (4π e, 1,3-diene), with the formation of a six membered ring.

- The heterocyclic compounds can react as a 1,3-diene in D. A. reaction with reactive dienophiles (e.g. maleic anhydride, or benzyne) or with less reactive dienophiles (e.g. acrylonitrile) in presence of catalyst.

- The diene can be activated by E.D.G while the dienophile by EWG.

- Thus N-alkyl pyrrole and N-amino pyrrole are more reactive than pyrrole itself in D.A reaction but less reactive than furan (The order of reactivity in D.A reaction is the reverse of aromaticity order:).

![Diagram of Diels–Alder reaction](image-url)
SYNTHESIS OF PYRROLES

1.- From 1,4-dicarbonyl compounds (Paal-Knorr synthesis): Generally Substituted pyrrole may be synthesized through the cyclization of 1,4-diketones in combination with ammonia (NH3) or amines. The ring-closure is proceeded by dehydration (condensation), which then yields the two double bonds and thus the aromatic π system. The formation of the energetically favored aromatic system is one of the driving forces of the reaction.

\[
\begin{align*}
\text{R}^2\text{C} = \text{O} & \quad \text{R}^2\text{C} = \text{O} \\
\text{R}^1 & \quad \text{R}^1
\end{align*}
\]

1,4-Dicarbonyl compound

\[
\text{R}^2\text{OH} \quad \text{R}^2\text{OH} + \text{RNH}_2 \xrightarrow{\Delta} \text{R}^2\text{N} \quad \text{R}^1 + 2\text{H}_2\text{O}
\]

R=H or Alkyl or Aryl

2.- Pyrrole is obtained by distillation of succinimide over zinc dust.

\[
\text{O} \quad \text{N}
\]

Succinimide

\[
\xrightarrow{\text{Zn, heat}} \quad \text{N}
\]

3.- Pyrrole is obtained by heating a mixture of furan, ammonia and steam over alumina catalyst.

\[
\text{Furan} + \text{NH}_3 \xrightarrow{\text{steam, Al}_2\text{O}_3} \text{Pyrrole}
\]
4. - By passing a mixture of acetylene and ammonia over red hot tube

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{C} & \quad \text{C} \\
\text{H} & \quad \text{H}
\end{align*}
\quad + \quad \text{NH}_3
\quad + \quad \begin{align*}
\text{H} & \quad \text{H} \\
\text{C} & \quad \text{C} \\
\text{C} & \quad \text{CH}
\end{align*}
\quad \xrightarrow{\text{red hot tube}}
\begin{align*}
\text{H} & \\
\text{C} & \\
\text{N} & \\
\text{H}
\end{align*}
\]

5. - Knorr-pyrrole synthesis: This involves the condensation of α-amino ketones with a β-diketone or a β-ketoester to give a substituted pyrrole.

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
\text{R} & \quad \text{NH}_2
\end{align*}
\quad + \quad \begin{align*}
\text{O} & \quad \text{CH}_3 \\
\text{R}'
\end{align*}
\quad \xrightarrow{} \quad \begin{align*}
\text{H}_3\text{C} & \\
\text{R} & \\
\text{N} & \\
\text{CH}_3
\end{align*}
\]

\[R' = -\text{COR}; \beta\text{-diketone}\]
\[= -\text{COOR}; \beta\text{-ketoester}\]
FURANE AND THIOPHENE COMPOUNDS. OCCURRENCE

• Furanes as flavor agents.

- 2-Furylmethanethiol: Constituent of coffee flavor
- Rose furan: Constituent of rose scent
- Mentofuran: Constituent of mint oil

• Furocumarines
  - Furocumarines are coumarins with a fused furan ring.
  - These show high UV-absorption which can be used for the generation of singlet oxygen.
  - Therefore these compounds are used as antioxidants (for the preservation of food and cosmetics) and also as UV filters.
  - The capacity to absorb UV light makes them useful for binding to bioactive compounds which are released after irradiation (serve as an “antenna”).

Psolarene: Drug for psoriasis
Isosoraleno: Preservation of cosmetics
Angelicin
REACTIVITY OF FURANE AND THIOPHENE

REATIONS

- Electrophilic aromatic substitution
- Electrophilic addition (loss of aromaticity)
- Cycloaddition

Order of reactivity: Remember, The order of reactivity is the reverse of aromaticity order

Pyrrol > Furane > Thiophene > Benzene
**REACTIVITY OF FURANE AND THIOPHENE**

**ELECTROPHILIC AROMATIC SUBSTITUTION**

- Similar reactivity pattern as pyrrole
  
  Order of reactivity: Remember: Pyrrol > Furane > Thiophene > Benzene

- Electrophilic aromatic substitution only occurs at carbon atoms instead of at the oxygen.
- Also, it occurs preferentially at C-2 (the position next to the heteroatom) rather than at C-3 (if position 2 is occupied it occurs at position 3).
- This is because attack at C-2 gives a more stable intermediate (it is stabilized by three resonance structures) than the one resulted from C-3 attack (it is stabilized by two resonance structures).

![Diagram showing electrophilic substitution on furane and thiophene]

- **Attack at C-2**
  - Three resonance structures

- **Attack at C-3**
  - Two resonance structures
  - Not formed
### ELECTROPHILIC AROMATIC SUBSTITUTION

$$\text{O} + \text{E}^+ \rightarrow \text{O-E}$$

<table>
<thead>
<tr>
<th>Reaction type</th>
<th>Reagents and conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halogenation</td>
<td>$\text{Br}_2$ / dioxane, 0°C</td>
<td><img src="image" alt="Brominated Furane" /></td>
</tr>
<tr>
<td>Nitration</td>
<td>$\text{NO}_2^+$ $\text{AcO}^-$, 5°C</td>
<td><img src="image" alt="Nitrofurane" /></td>
</tr>
<tr>
<td>Sulfonation</td>
<td>Pyridine-$\text{SO}_3$ complex, 100°C</td>
<td><img src="image" alt="Sulfonated Furane" /></td>
</tr>
</tbody>
</table>
| Formylation     | 1) $\text{POCl}_3$, $\text{Me}_2\text{NCHO}$  
2) $\text{CH}_3\text{COO}^-$ $\text{Na}^+$ | ![Furfural](image) |
| Acetylation     | $\text{COO}^-$ / $\text{SnCl}_4$   | ![Acetylated Furane](image) |
**REACTIVITY OF FURANE AND THIOPHENE**

**ELECTROPHILIC AROMATIC SUBSTITUTION through lithiation**

\[
\text{furane} + \text{RLi} \rightarrow \text{furane-Li} \rightarrow \text{furane-}E
\]

Highly reactive nucleophile

1) t-BuLi, THF, -78°C
2) DMF, 0°C

1) t-BuLi, THF, -78°C
2) R-X, 0°C

Cross-coupling (Low yield, needs Pd or Cu-catalysis)
REACTIVITY OF FURANE AND THIOPHEN

ELECTROPHILIC ADDITIONS (oxidation)

Furane as 1,4-dicarbonyl equivalent

Mechanism:
**REACTIVITY OF FURANE AND THIOPHENE**

**CYCLOADDITIONS** (Diels-Alder reactivity)

![Chemical reaction diagram](image)

**Example: Application to the synthesis of a natural product**

- Poison secreted by many species of blister beetle and by the Spanish fly
- It is secreted by the male and given to the female during mating. Afterwards the female will cover its eggs as a defense against predators.
- Diluted solutions of cantharidin can be used to remove warts (papiloma) and tattoos and to treat the small papules of *Molluscum contagiosum*
- When ingested by humans, a dose of 10mg is potentially fatal. (causes severe damage to the lining of the gastrointestinal and urinary tract, and may also cause permanent renal damage)

---

*Cantharidin*
REACTIVITY OF FURANE AND THIOPHENE

CYCLOADDITIONS (Diels-Alder reactivity)

Initial approach:

\[
\text{Initial approach:} \quad \begin{array}{c}
\text{starting materia}\l
\text{starting materia}\r
\end{array}
\]

\[
\text{but:} \quad \begin{array}{c}
\text{but:} \l
\text{but:} \r
\end{array}
\]

\[
\text{so:} \quad \begin{array}{c}
\text{so:} \l
\text{so:} \r
\end{array}
\]

1) H, Pd/C
2) Raney-Ni
High aromatic character, $\pi$-excedent aromatic ring with high tendency to undergo electrophilic aromatic substitution

- SEAr reactions preferably to C-2.
- Less reactive towards addition reactions (loss of aromaticity).
- Only undergoes cycloaddition reactions with good dienophiles

Example: Application to the synthesis of a natural product

- Active ingredient of musk (natural perfume and highly appreciated)
- Musk is extracted from a glandular secretion of the musk deer which is native from central Asia (Asia Central)
- Physiological function: pheromone
- For obtaining 1 kg of muscone 3000 animals have to be killed (chemical synthesis required)
- Natural muscone is enantiomerically pure (-)-muscone
- Synthetic muscone is prepared in racemic form but is much less active

$$\text{ThF}_4 \quad \text{H}_3\text{PO}_4$$

$$\text{Raney-Ni}$$

$$\text{BuLi} \quad \text{Br} \quad \text{HCl (aq.)}$$

Example reaction:

1) $\text{BuLi}$
2) $\text{Br(CH}_2\text{)}_{10}\text{Br}$

$\text{C}_{10}\text{H}_{20}\text{Br}$

1) $\text{KCN}$
2) $\text{HCl (aq.)}$

COOH

$\text{Raney-Ni}$
REACTIVITY OF PYRIDINE

GENERAL REACTIVITY

UNSUBSTITUTED PYRIDINES

REATIONS AT NITROGEN
- $A_N$: Pyridine as nitrogen nucleophile
- Acid-Base: Pyridine as a Bronsted base

REATIONS AT CARBON ATOMS
- $S_NAr$: Pyridine as carbon electrophile
- $S_EAr$: Pyridine as carbon nucleophile

C-SUBSTITUTED PYRIDINES

REATIONS AT CARBON ATOMS
- $S_NAr$: Pyridine as carbon electrophile
- $S_EAr$: Pyridine as carbon nucleophile

N-SUBSTITUTED PYRIDINES

REATIONS AT CARBON ATOMS
- $S_NAr$: Pyridine as carbon electrophile
REACTIVITY OF UNSUBSTITUTED PYRIDINE

REACTIONS AT NITROGEN

➢ Acid-Base: Pyridine as a Bronsted base

\[
\text{Pyridine} + \text{HCl} \rightarrow \text{Pyridinium chloride} \quad \text{Pka} = 5.2
\]

➢ \( \text{A}_N \): Pyridine as nitrogen nucleophile: The nitrogen lone pair (it does not participate in conjugation) reacts with electrophiles

- **N-Alkylation:**
  \[
  \text{Pyridine} + R-X \rightarrow \text{Pyridinium X-}
  \]

- **N-Acylation:**
  \[
  \text{Pyridine} + \text{Acyl chloride} \rightarrow \text{Pyridinium acyl chloride}
  \]

- **N-Sulfonation:**
  \[
  \text{Pyridine} + \text{SO}_3 \rightarrow \text{Pyridinium sulfonate}
  \]

- **N-Oxidation:**
  \[
  \text{Pyridine} + \text{H}_2\text{O}_2 \rightarrow \text{Pyridinium nitrate}
  \]

- **N-Nitrosation:**
  \[
  \text{Pyridine} + \text{RONO} \rightarrow \text{Pyridinium nitroso}
  \]

- **Ylide formation:**
  \[
  \text{Pyridine} + X^\text{EWG} \quad \text{Base} \rightarrow \text{Ylide}
  \]
**REACTIVITY OF UNSUBSTITUTED PYRIDINE**

**REACTIONS AT CARBON ATOMS**

- **$S_{E}Ar$: Pyridine as nitrogen nucleophile:** Behaves essentially as benzene, although due to its $p$-deficient character reactions are slower and require harsher conditions.

\[
\text{C-3 attack}
\]

Regioselectivity:

- **C-2 attack**

\[
\text{Poor contribution}
\]

- **C-3 attack**

\[
\text{Poor contribution}
\]

- **C-4 attack**

\[
\text{Poor contribution}
\]
**REACTIVITY OF UNSUBSTITUTED PYRIDINE**

**REACTIONS AT CARBON ATOMS**

- **S<sub>N</sub>Ar: Pyridine as nitrogen electrophile:** DOES NOT behave as benzene. Reaction does not proceed via benzyne intermediates. Pyridine should be regarded essentially as a cyclic imine.

\[
\text{Pyridine} + \text{Nu}^- \rightarrow \text{Pyridine product}
\]

**Mechanism:**
- Hydride anion is a bad leaving group
- Second step is very slow
- Sometimes the elimination does not take place:

**EXAMPLES**

- **Hydroxylation:**
  \[
  \text{Pyridine} \xrightarrow{\text{KOH, High temp.}} \text{PyridineOH}
  \]

- **Cyanation:**
  \[
  \text{Pyridine} \xrightarrow{\text{KCN, High temp.}} \text{PyridineCN}
  \]
  Loss of aromaticity, slow reaction

- **Amination:**
  \[
  \text{Pyridine} \xrightarrow{\text{NaNH}_2} \text{PyridineNH}_2
  \]
  Chichibabin reaction

- **Alkylation:**
  \[
  \text{Pyridine} \xrightarrow{\text{RLi or RMgX}} \text{PyridineR}
  \]
  Loss of aromaticity, slow reaction
  Highly reactive organometallic reagents
  Previous N-acylation can be carried out for accelerating the reaction

**REACTIONS AT CARBON ATOM**

- **S_EAr**: Pyridine as carbon nucleophile:

  ![Reaction diagram](image)

  **Deactivating substituent**: No reaction

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

**EXAMPLE**

**Halogenation of methylpyridines:**

\[
\begin{align*}
\text{Pyridine} + \text{Halogen} & \rightarrow \text{Substituted Pyridine} \\
\text{CH}_2\text{Cl}_2, \text{r.t.} & \rightarrow \text{Substituted Pyridine}
\end{align*}
\]
**REACTIVITY OF C-SUBSTITUTED PYRIDINE**

**REACTIONS AT CARBON ATOM**

- **S_NAr**: Pyridine as electrophile:

  ![Reaction Mechanism Diagram](image)

  **Mechanism:**

  ![Addition and Elimination Steps](image)

- **X** should be a good leaving group (Halogen, sulfonate, etc.)
- **High reactivity** (**X** is a better leaving group than hydride)
- **Regioselectivity** controlled by the stability of intermediate anion

**EXAMPLE**

**Alkylation of 2-methoxypyridine**

![Alkylation Reaction](image)
REACTIVITY OF N-SUBSTITUTED PYRIDINE

REACTIONS AT CARBON ATOM

- **S_NAr:** Pyridinium ions as electrophiles:
  
  ![Reaction Scheme](image)

  - Highly reactive (positive nitrogen results in enhanced electrophilicity)
  - Final product arises from the evolution of the addition intermediate
  - Evolution of addition intermediate depends on different factors

Stabilization through elimination

- **R=good leaving group**
  
  ![Stabilization Mechanism](image)

Stabilization through ring opening

- **R=bad leaving group**
  
  ![Ring Opening Mechanism](image)