université PARIS-SACLAY | FACULTÉ DE PHARMACIE

TU 07 - The Medicinal Chemist's Toolbox 1 : Aromatic and Heteroaromatic chemistry

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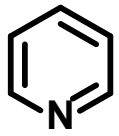
BioCIS
Biomolécules :
Conception, Isolement, Synthèse

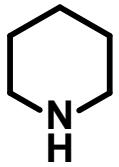
Chapter 2 :
Aromatic Heterocyclic Chemistry

a) Aromaticity and Heteroaromaticicty

- ✓ Any ring system containing at least **one heteroatom** (N, O ou S) can be described as **heterocyclic.**
- ✓ This definition encompasses both :
  - **Aromatic heterocycles**
  - **Non-aromatic heterocycles**



Pyridine



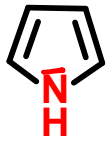
Piperidine

- ✓ Cyclic and planar
- ✓ Fully conjugated systems
- ✓ 4n+2 electrons delocalized

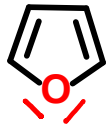
} Hückel's rule (1831)

b) Structures

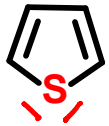
✓ Structures of five-membered heteroaromatic systems



pyrrole

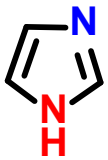


furan

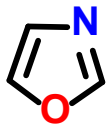


thiophene

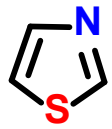
1,3-azoles



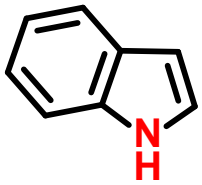
imidazole



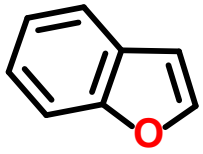
oxazole



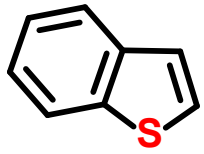
thiazole



indole



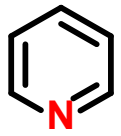
benzofurane



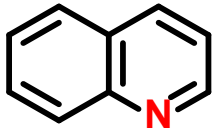
benzothiophène

b) Structures

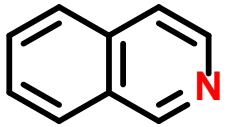
✓ Structures of six-membered heteroaromatic systems



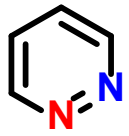
pyridine



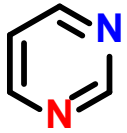
quinoline



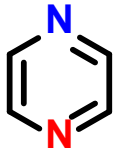
isoquinoline



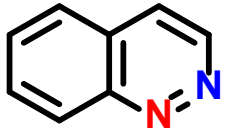
pyridazine



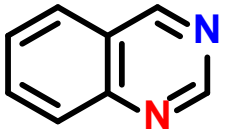
pyrimidine



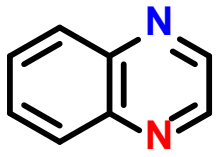
pyrazine



cinnoline



quinazoline

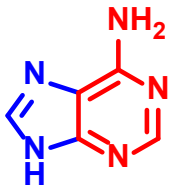


quinoxaline

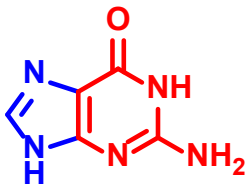
c) Examples

✓ Heterocycles in nature

- **Nucleic acids**

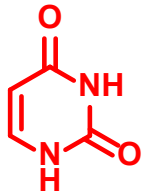


Adenine

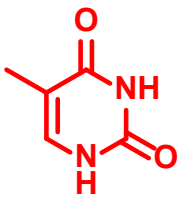


Guanine

Imidazole + ***pyrimidine***

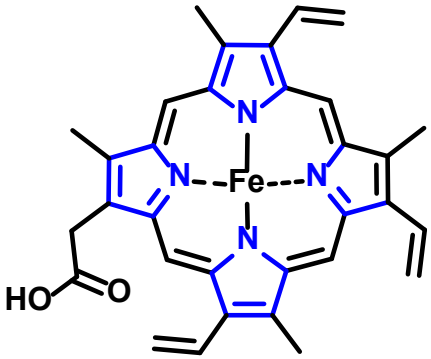


Cytosine

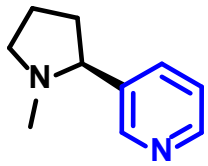


Thymine

Uracile

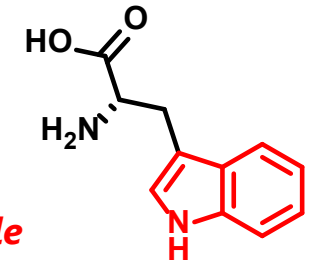


Heme



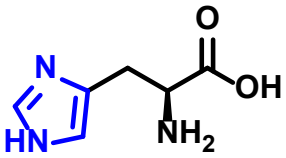
nicotine

- **Amino acids**

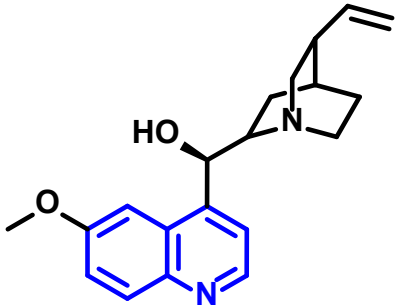


indole

Tryptophane
Trp



Histidine
His

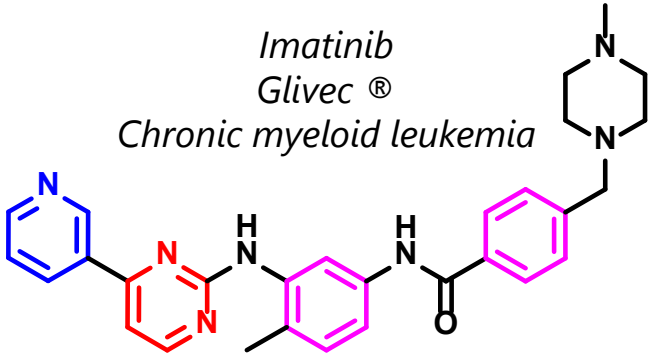


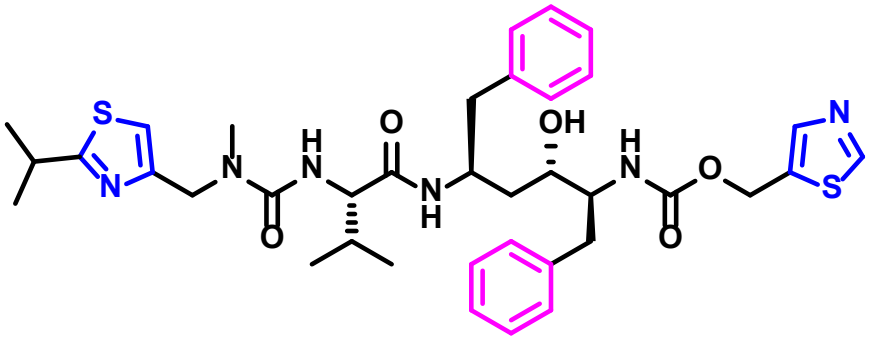
quinine

c) Examples

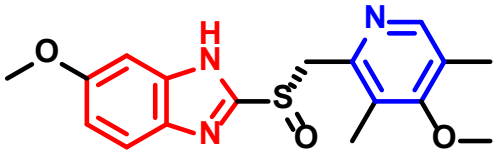
✓ Synthetic heterocycles in pharmaceuticals

Imatinib
Glivec ®
Chronic myeloid leukemia





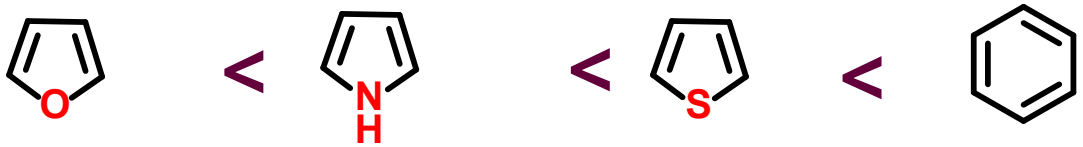
Ritonavir
Norvir®
Antiretroviral



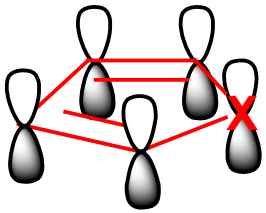
Esomeprazole
Nexium®
Gastrointestinal inflammations

a) Introduction

Order of aromaticity



	furan	*pyrrole*	*thiophène*	*benzène*
Resonance energy	68 kJ.mol^{-1}	90 kJ.mol^{-1}	122 kJ.mol^{-1}	152 kJ.mol^{-1}
Electronegativity	3,5	3,0	2,5	2,5

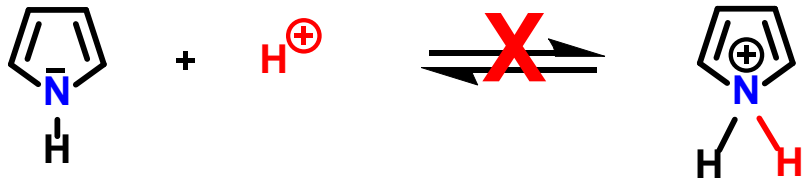


- ✓ 1 lone pair is localized in p orbital // 4 p orbitals of the carbon

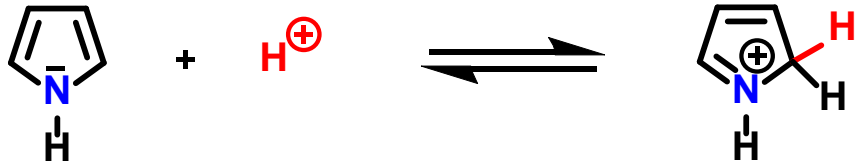
  → **lone pair is delocalized**
- ✓ Not basic
- ✓ π-excessive

a) Introduction

✓ **Protonation at the C-2 position only**



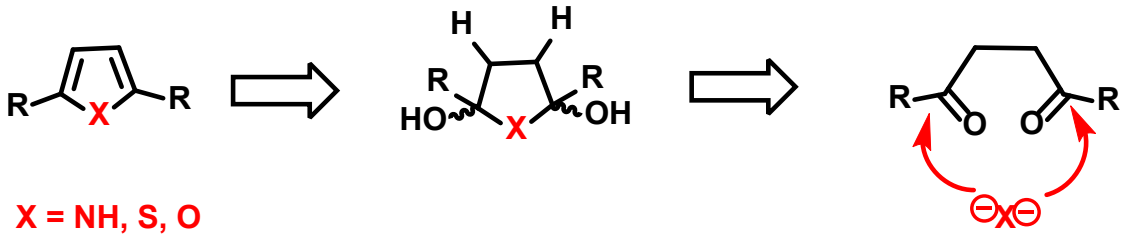
1*H*-pyrrolium

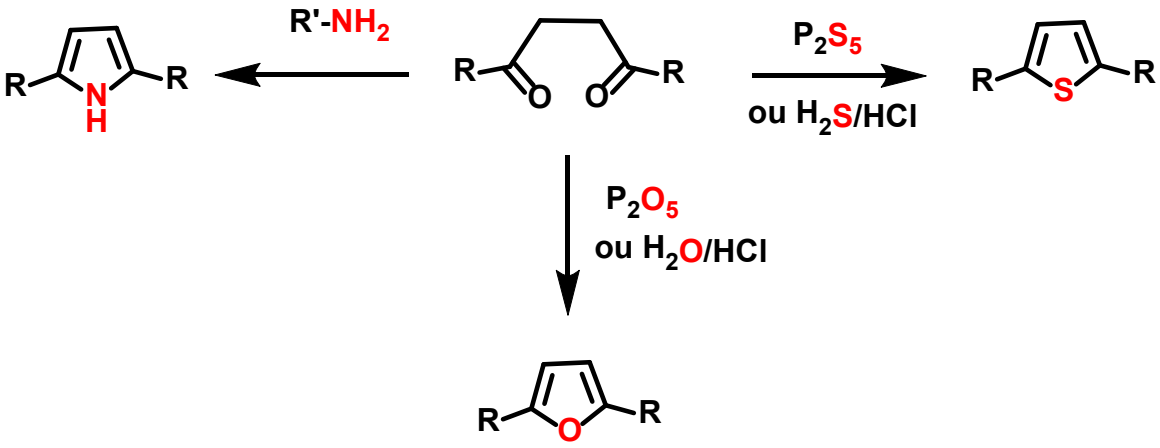


- Weak base
- pKa = -3.8

b) Synthesis of pyrroles, furans and thiophenes

✓ ***Paal-Knorr Synthesis*** from 1,4-dicarbonyl compounds

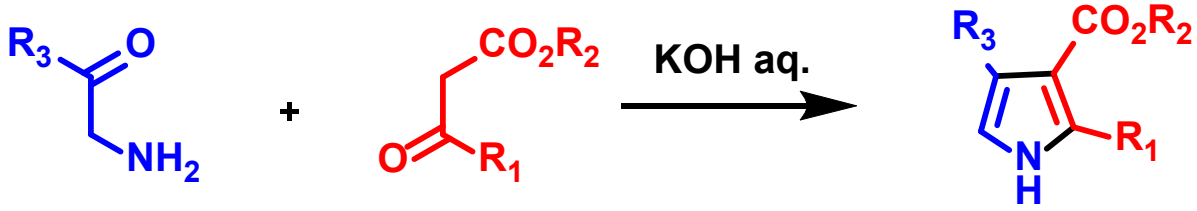




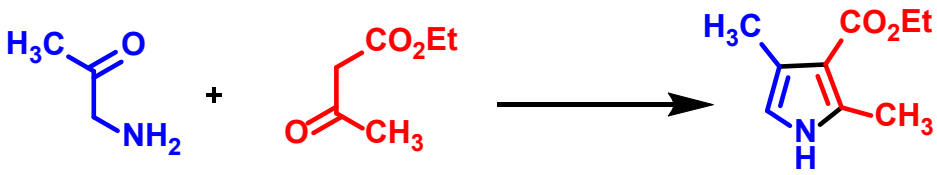
b) Synthesis of pyrroles, furans and thiophenes

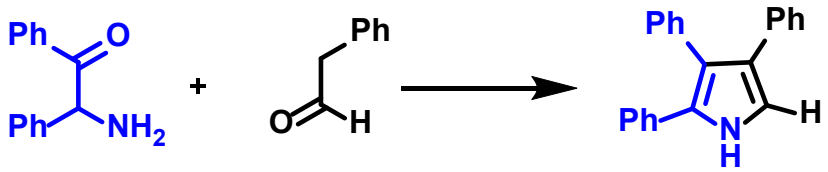
✓ ***Knorr synthesis → preparation of pyrroles***

Condensation reaction of an **α-aminoketone** with a **1,3-diketone** or **β-ketoester**



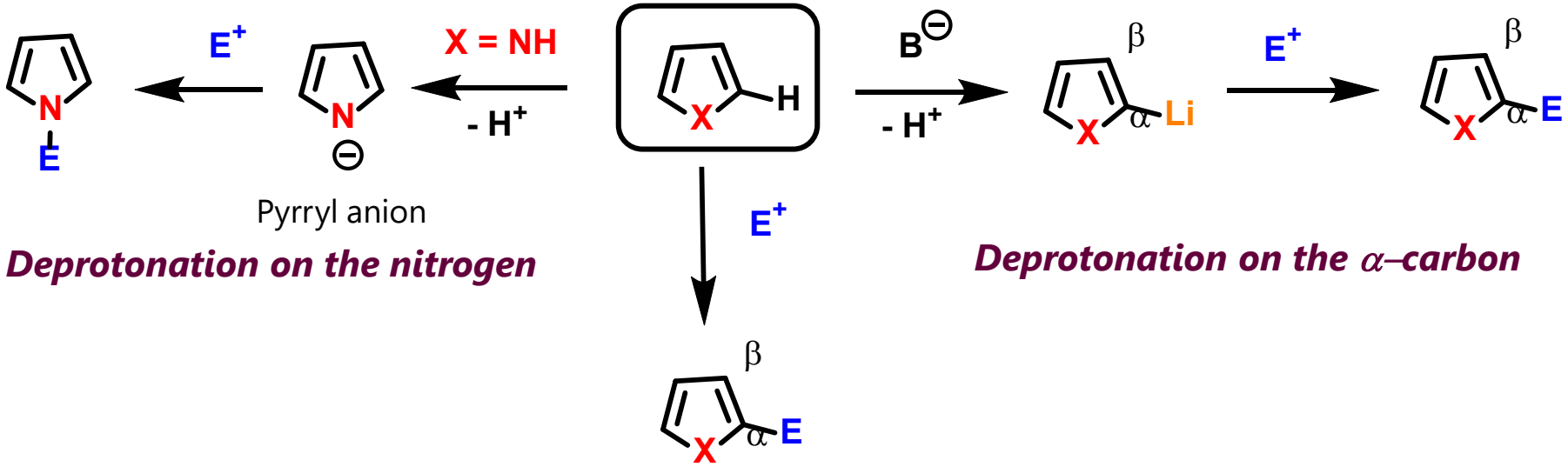
Examples :





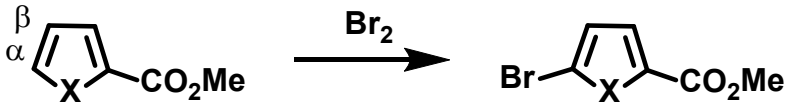
c) Reactivity of pyrroles, furans and thiophenes

Typical reactivity of pyrrole, furan, and thiophene :



c) Reactivity of pyrroles, furans and thiophenes

c.1) Electrophilic aromatic substitution



X	Relative rate
S	1
O	$1{,}2.10^2$
NH	$5{,}6.\ 10^8$

- ***C-2 (α-position) regioselective***
- *This regioselectivity depends on :*
  - *the heterocycle*
  - *The electrophile*
  - *The nature and position of the substituents already present on the heterocycle (Holleman' rule))*

- ***Order of reactivity : pyrrole > furan > thiophene***

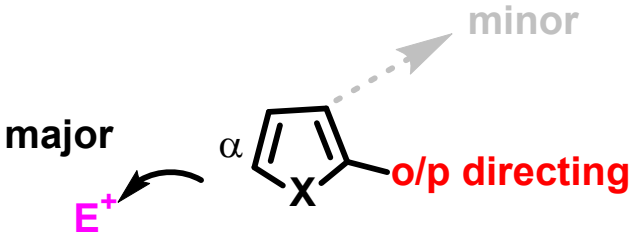
Attack at C-2 versus C-3 position :

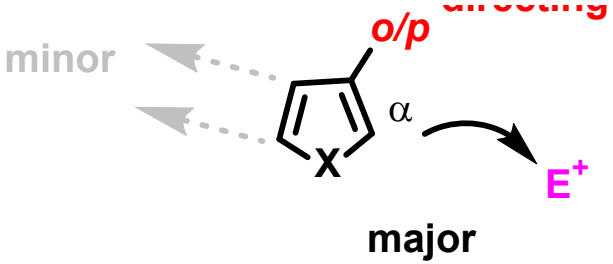
c) Reactivity of pyrroles, furans and thiophenes

c.1) Electrophilic aromatic substitution → Holleman's rules

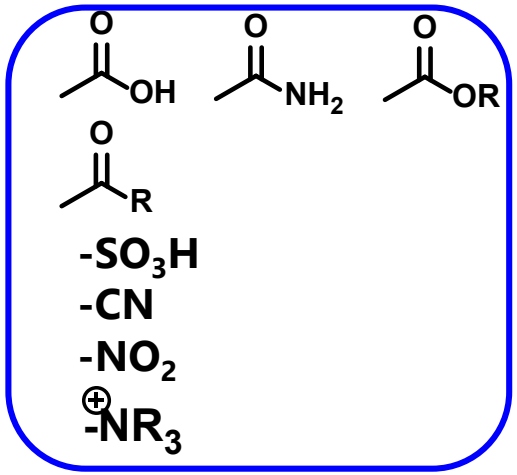
ortho- and *para*-directing

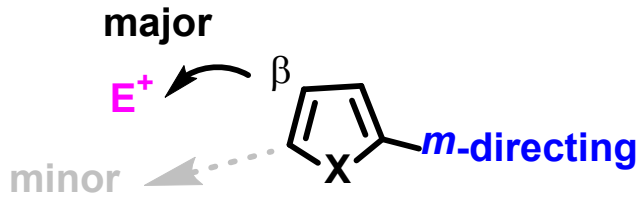
- $-NH_2$, $-NHR$, $-NR_2$
- $-OH$, $-OR$
- $-NHCOR$, $-OCOR$
- $-Ph$, $-CH{=}CH_2$
- $-CH_3$ (alkyl)
- $-F$,
- $-Cl$
- $-Br$
- $-I$

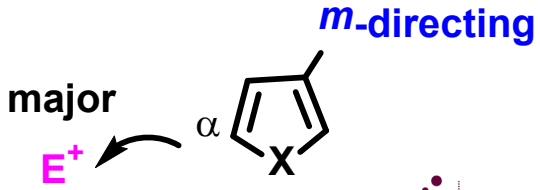




meta-directing







c) Reactivity of pyrroles, furans and thiophenes

c.1) Electrophilic aromatic substitution

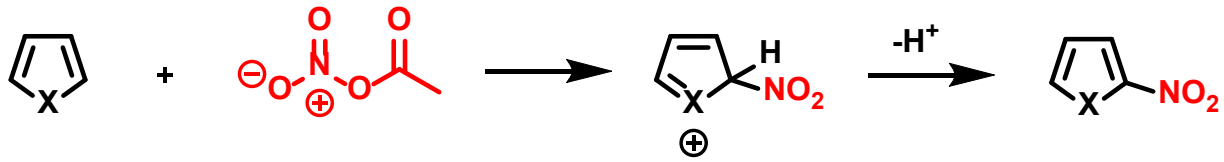
Furan and pyrrole are **not stable** to mineral acids (H_2SO_4, HNO_3, HCl...) → polymerization

→ **milder conditions required** as compared with benzene chemistry!

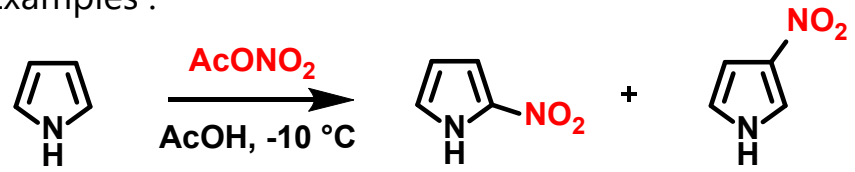
b.1.1) Nitration

$$HNO_3 + Ac_2O \longrightarrow \mathbf{AcONO_2} + AcOH$$

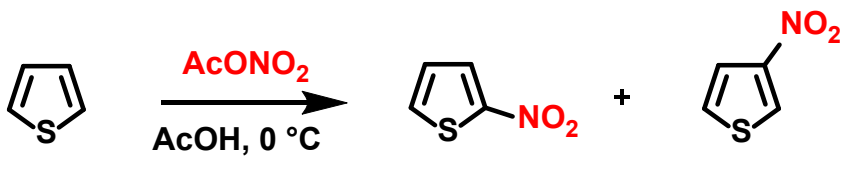
Acetyl nitrate



Examples :



2-nitropyrrole *3-nitropyrrole*

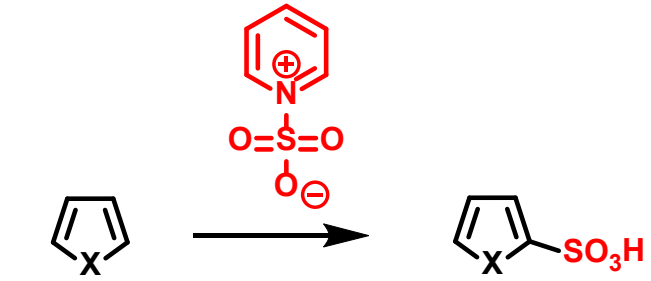


2-nitrothiophene *3-nitrothiophene*

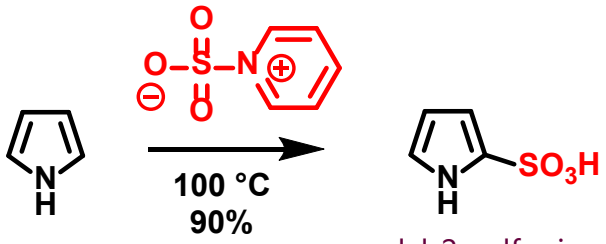
c) Reactivity of pyrroles, furans and thiophenes

c.1) Electrophilic aromatic substitution

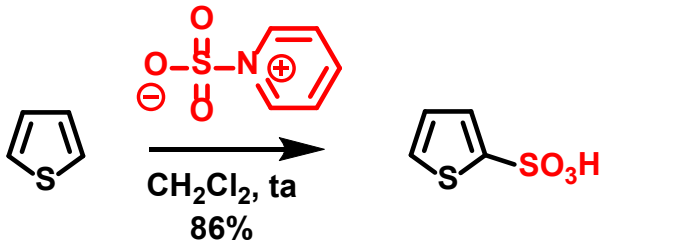
c.1.2) Sulfonation



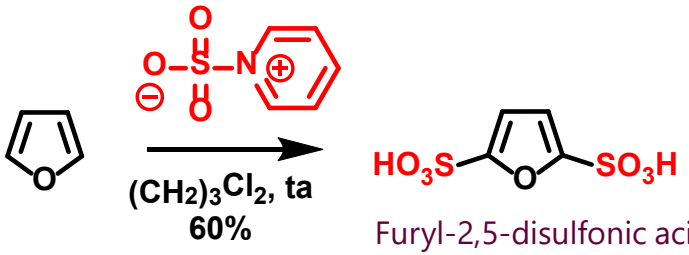
- Examples :



pyrrolyl-2-sulfonic acid



Thienyl-2-sulfonic Acid



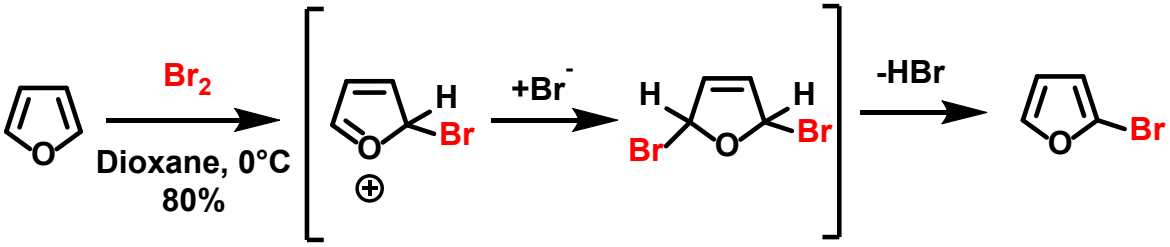
Furyl-2,5-disulfonic acid

c) Reactivity of pyrroles, furans and thiophenes

c.1) Electrophilic aromatic substitution

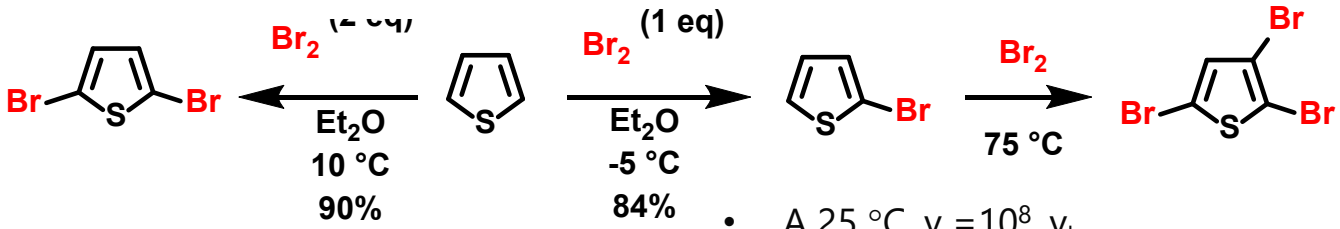
c.1.3) Halogenation

✓ Furans



- Furan reacts vigourously with Cl_2 et Br_2 → polyhalogenation
- No reaction with I_2

✓ Thiophenes



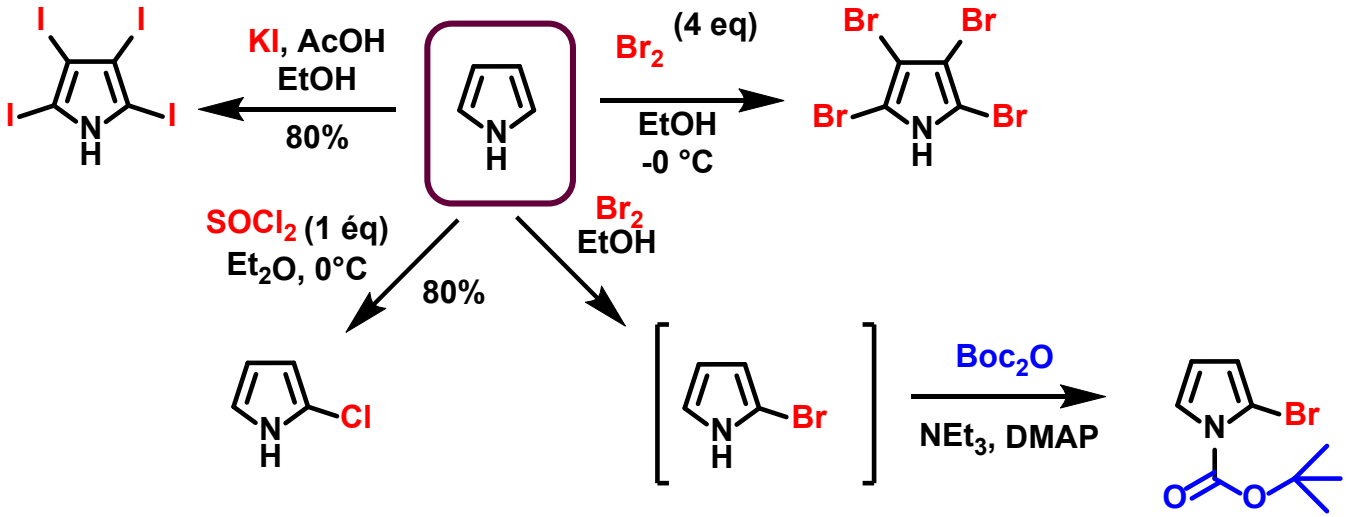
- A 25 °C, v = 10^8. $v_{benzene}$
- Regioselectivity can be controled

c) Reactivity of pyrroles, furans and thiophenes

c.1) Electrophilic aromatic substitution

c.1.3) Halogenation

✓ Pyrroles



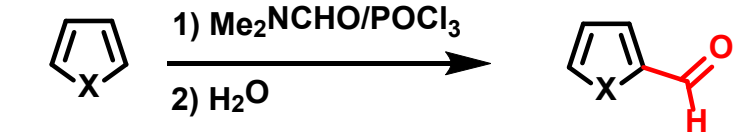
→ 2-chloro and 2-bromo pyrroles are unstable → need to use a protective group on the nitrogen

c) Reactivity of pyrroles, furans and thiophenes

c.1) Electrophilic aromatic substitution

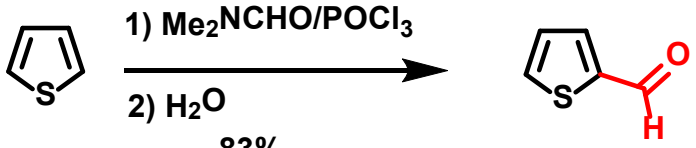
c.1.4) Friedel-Crafts acylation

- **Vilsmeier-Haack reaction: formylation**



X= NH, S, O

- Examples :



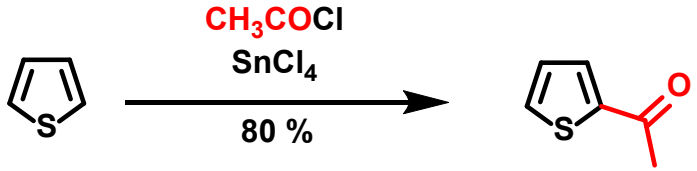
- **Vilsmeier-Haack mechanism :**

c) Reactivity of pyrroles, furans and thiophenes

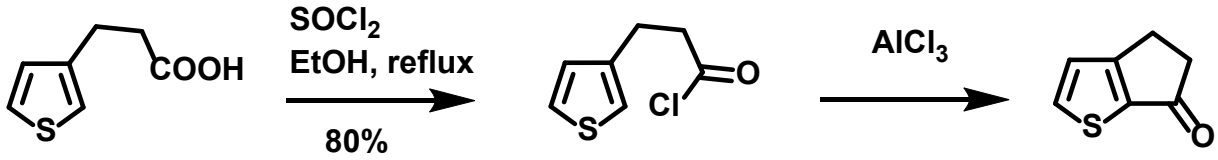
c.1) Electrophilic aromatic substitution

c.1.4) Friedel-Crafts acylation

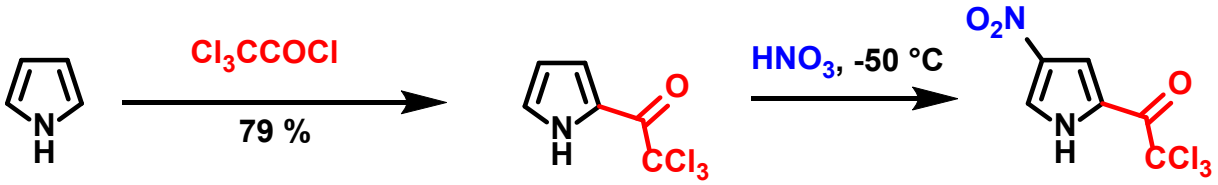
- **Thiophene**



→ intramolecular version



- **Pyrrole**

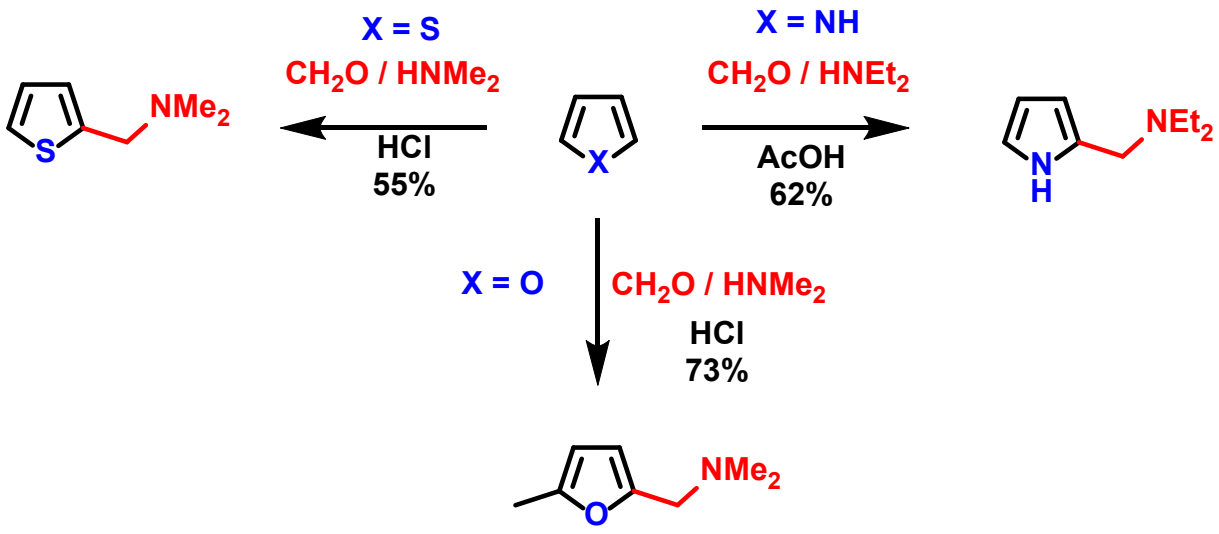


→ **Friedel-Crafts alkylation** is not applicable because of catalyst-caused polymerization

c) Reactivity of pyrroles, furans and thiophenes

c.1) Electrophilic aromatic substitution

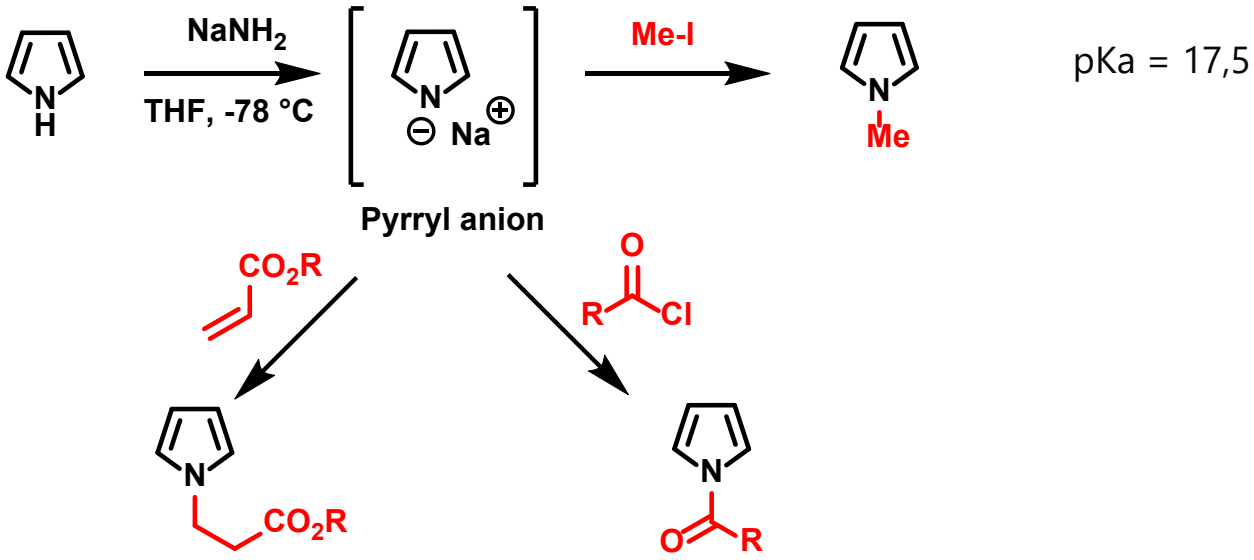
c.1.5) Mannich reaction



c) Reactivity of pyrroles, furans and thiophenes

c.2) Reactions with bases

- **Pyrrole**
  - Deprotonation of N-hydrogen



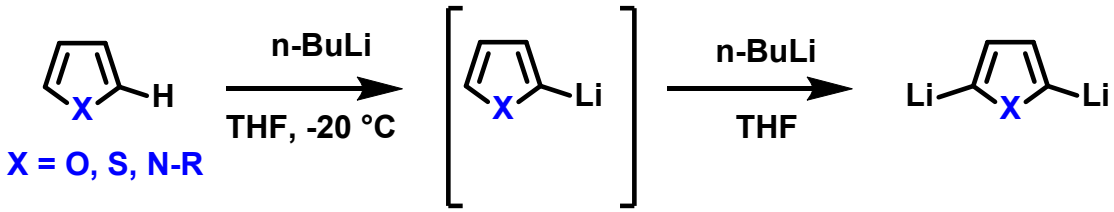
pKa = 17,5

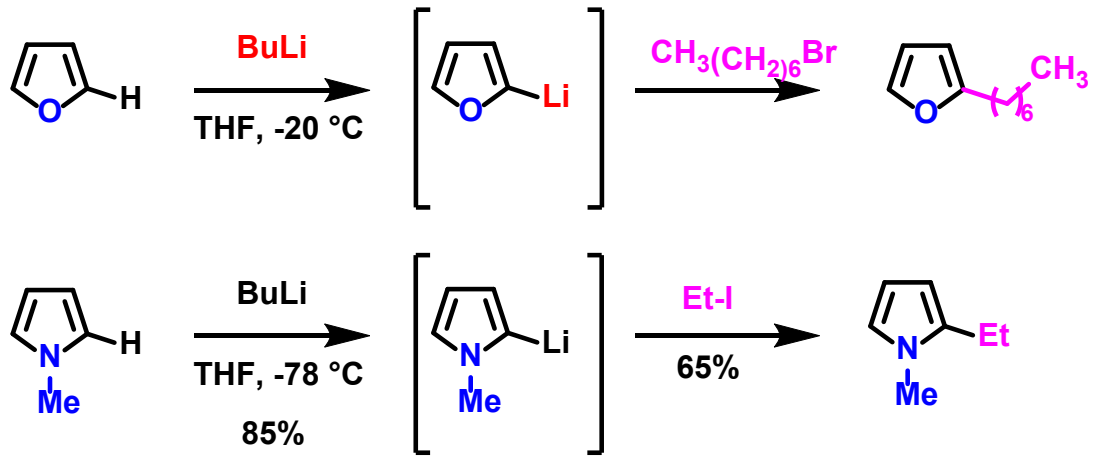
Other bases : NaH, KH

c) Reactivity of pyrroles, furans and thiophenes

c.2) Reactions with bases

- **N-substituted pyrroles, furans, and thiophene**
  - Regioselective deprotonation at the α-position: C-metallated heterocycles

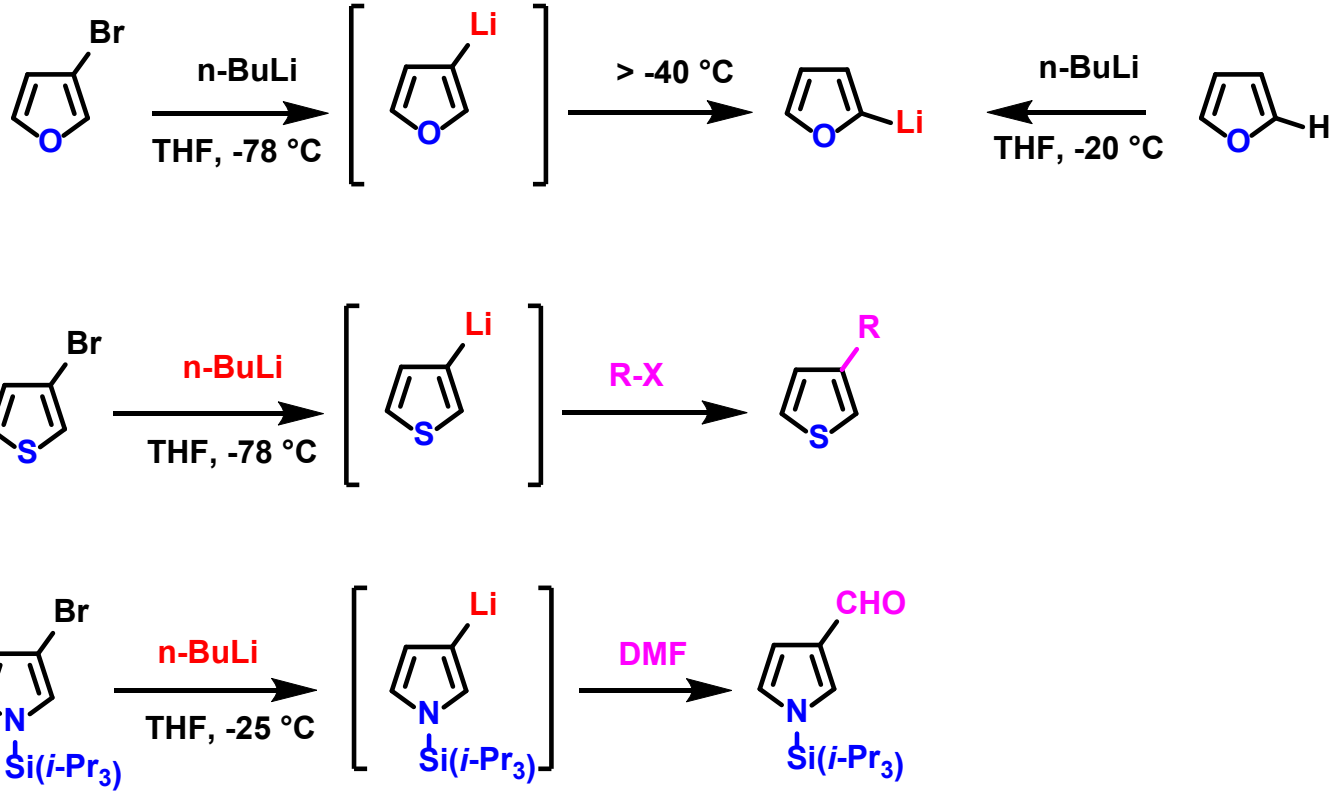




c) Reactivity of pyrroles, furans and thiophenes

c.2) Reactions with bases

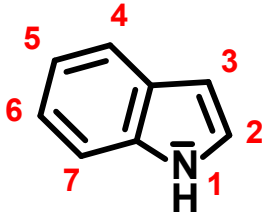
- **Metal-halogen exchange using a heteroaryl halogen :** C-metallated heterocycles



c) Indoles

c.1) Introduction

- indole = 1*H*-indole
  benzo[b]pyrrole
- Colorless solid



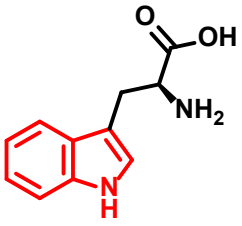
1*H*-indole

- ✓ cyclic and planar
- ✓ Fully conjugated polyenes
- ✓ 10 π electrons delocalized : $(4n+2)e^-$ with n=2

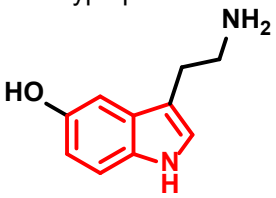
} Aromatic

- Weak base (pKa = -3,5)
- Electron-rich heterocycle

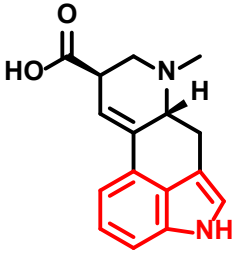
- The most widespread heterocycle in nature



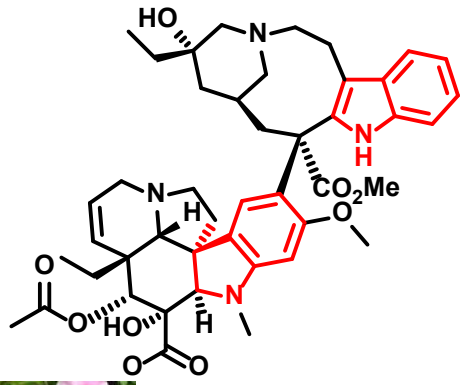
Tryptophan



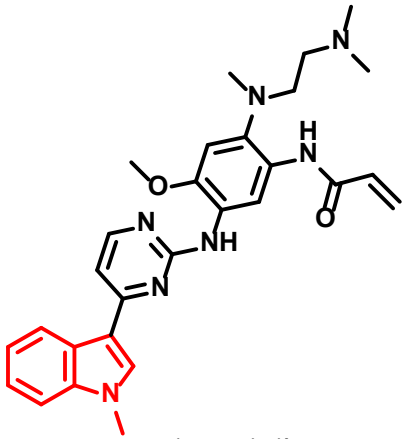
Serotonin



lysergic acid



Vinblastine
Anti-neoplasic

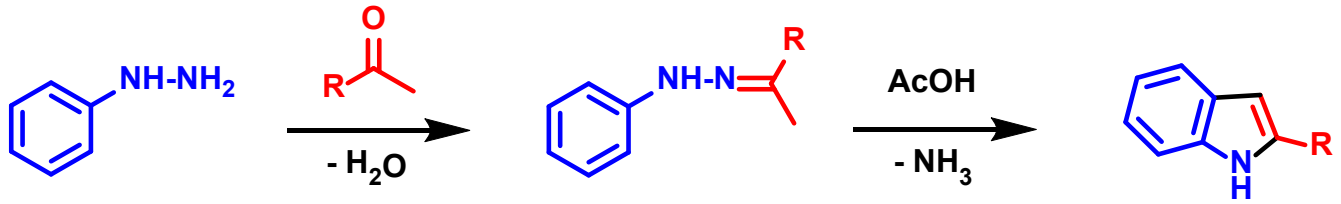


Osimertinib
EGFR protein kinase inhibitor
Oncology

c) Indoles

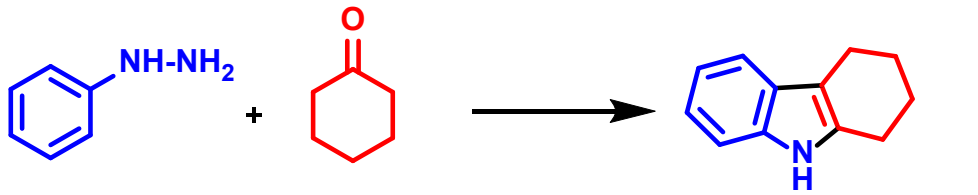
c.2) Preparation

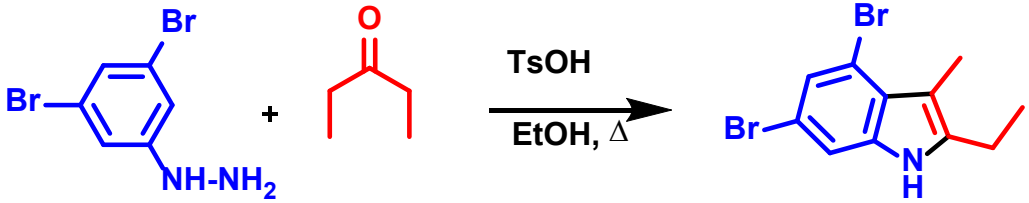
- Fischer indole synthesis (1883) from hydrazones



hydrazine hydrazone

Exemples :



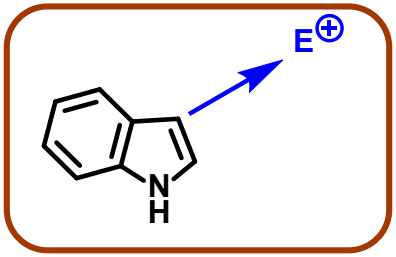


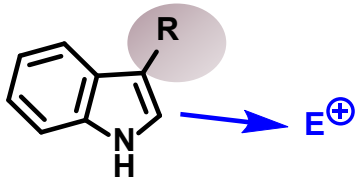
c) Indoles

c.3) Reactivity

c.3.1) Aromatic electrophilic substitution

- *Regioselective : indoles reacts preferentially at the C3 position*





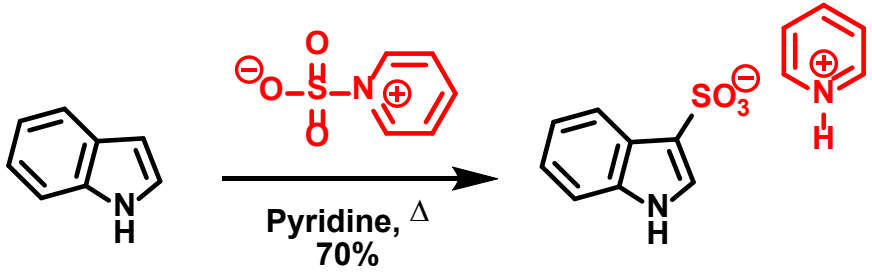
Position 2 is favored when C3 position is blocked

c) Indoles

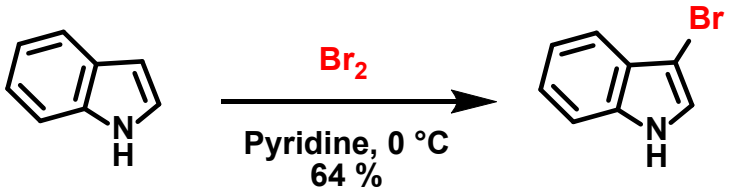
c.3) Reactivity

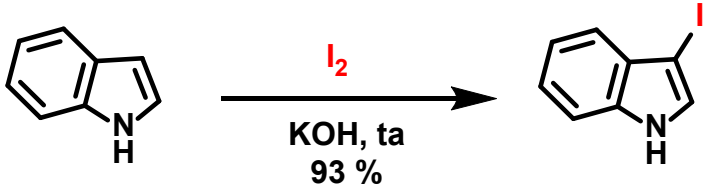
c.3.1) Aromatic electrophilic substitution

- *Sulfonation :*



- *Halogénation :*





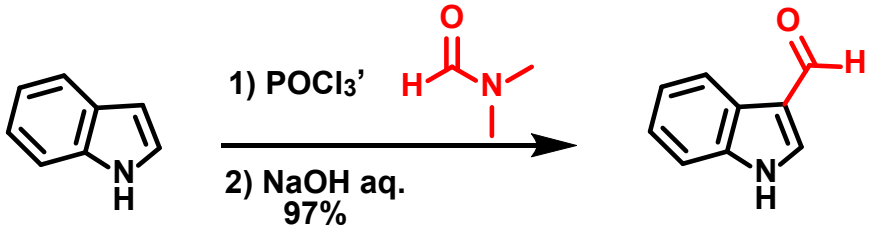
- *Nitration is complex → polymerization in usual conditions*

c) Indoles

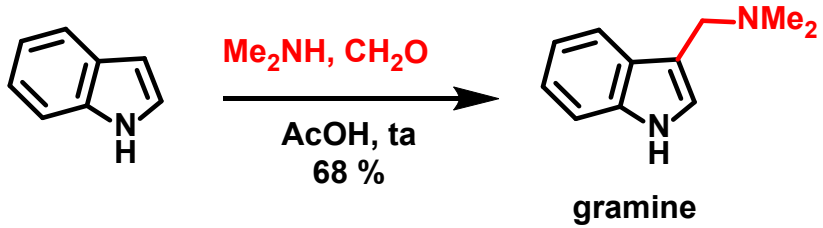
c.3) Reactivity

c.3.1) Aromatic electrophilic substitution

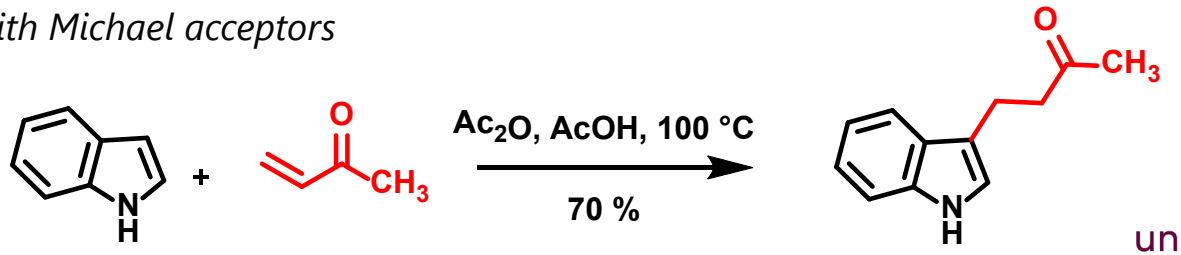
- *Acylation : Vilsmeier-Haack reaction (formylation)*



- *Alkylation : Mannich reaction*



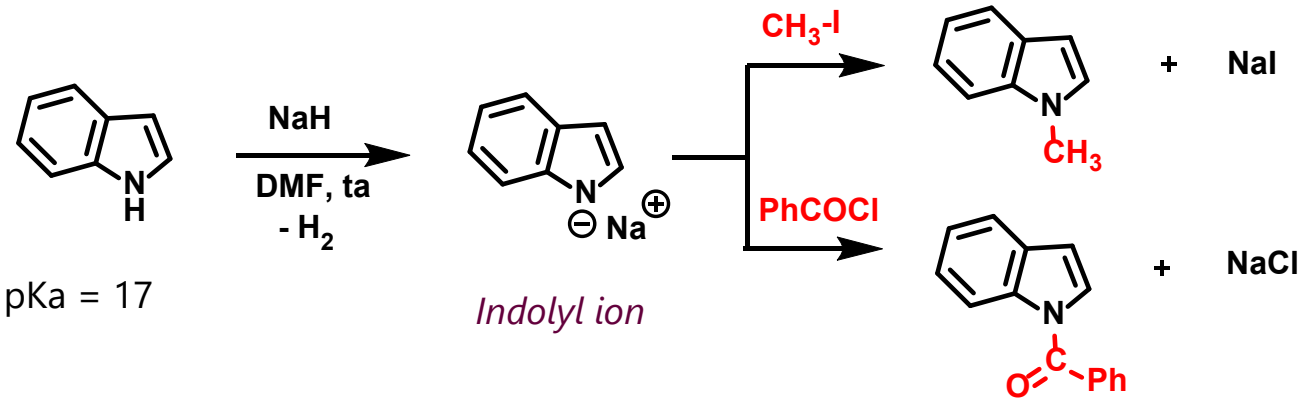
- *Alkylation with Michael acceptors*



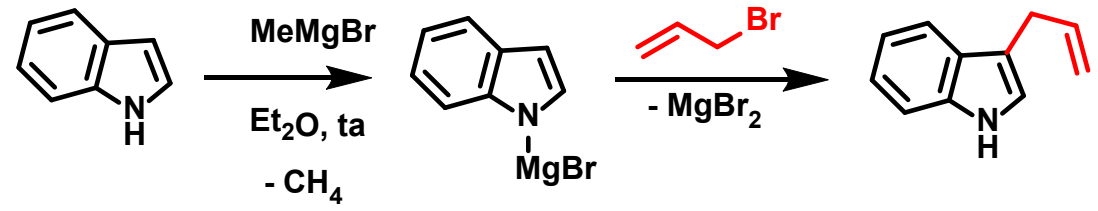
c) Indoles

c.3) Reactivity

c.3.2) N-Deprotonation/N-alkylation



c.3.3) N-Deprotonation/C-alkylation

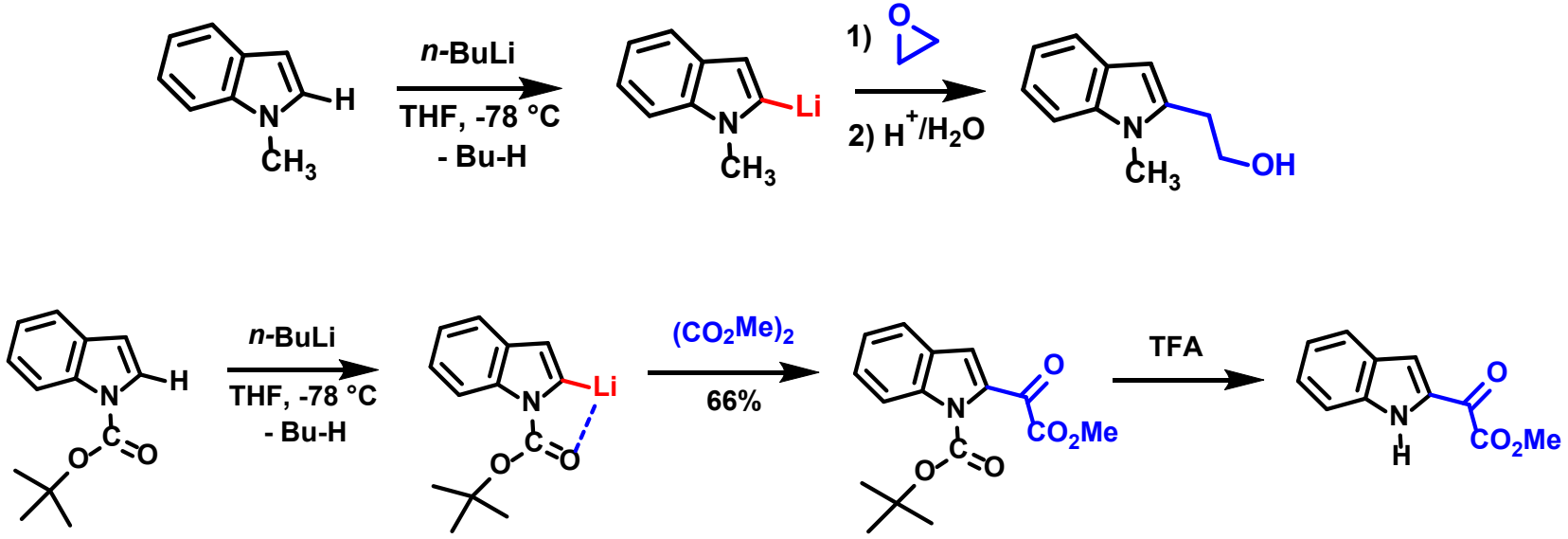


c) Indoles

c.3) Reactivity

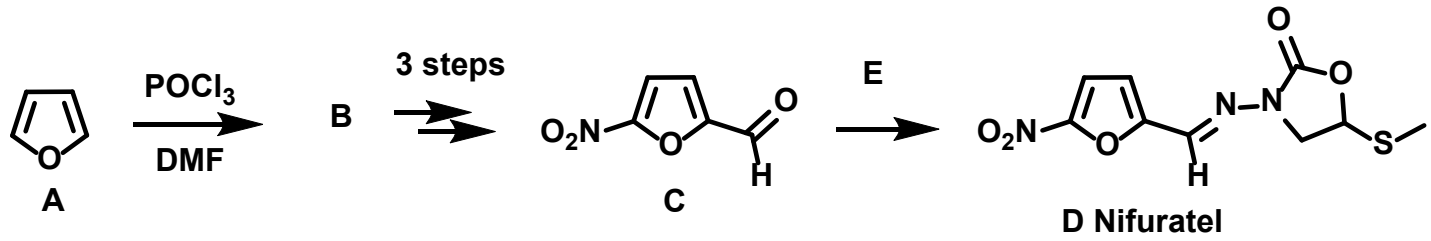
c.3.2) C-Deprotonation

- *When the nitrogen is blocked, deprotonation occurs at the C-2 position*



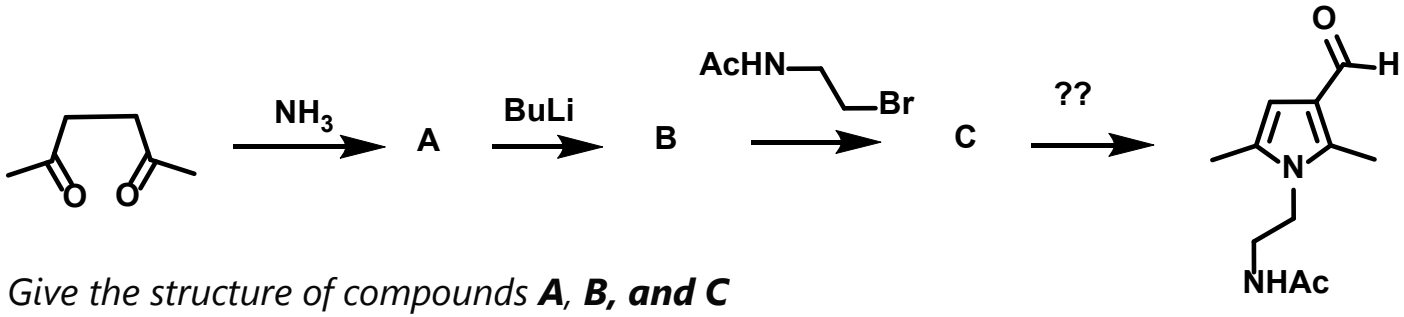
d) Exercices

Exercice 1 : *Synthesis of Nifuratel, a broad antibacterial spectrum agent*



1. *Give the structure of compound **B**.*
2. *Identify the 3 steps from **B** to **C** and justify the sequence.*
3. *Give the structure of reagent **E**.*

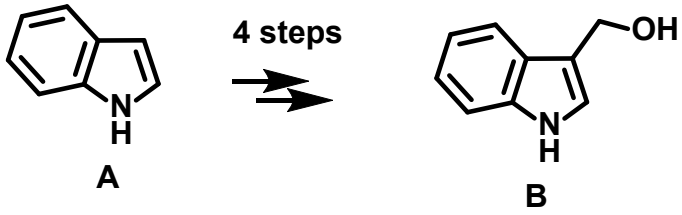
Exercice 2 : *Synthesis of Aloracetam, a nootropic agent studied for the treatment of Alzheimer's disease*



1. *Give the structure of compounds **A**, **B, and C***
2. *Give the structure of reagent **C** ->**D**. Explain the regioselectivity.*

d) Exercices

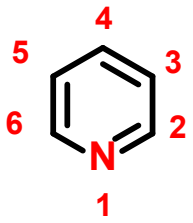
Exercice 3 : *Synthesis of indole 3-carbinol*



1. *Identify the 4 steps from **A** to **B** and justify the sequence.*

a) Pyridine

a.1) Introduction

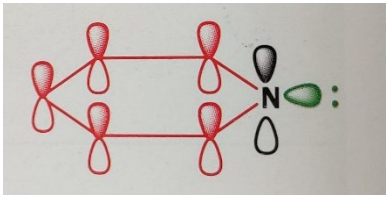


- ✓ cyclic and planar
- ✓ Fully conjugated polyenes
- ✓ 6 π electrons delocalized : $(4n+2)e^-$ with n=1

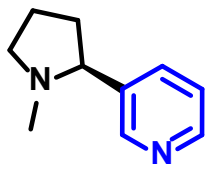
} Aromatic

- ✓ The lone pair **does not participate** in the aromaticity→ available for bonding
- ✓ Moderately basic (pKa = 5.2) and nucleophilic
- ✓ **π-deficient** → reactivity different from benzene

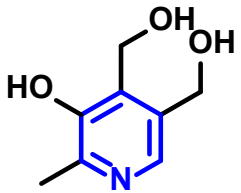
- Colorless and polar liquid
- b. p. = 115 °C
- Energy resonance = 117 kJ.mol^{-1}



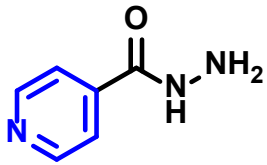
✓ Examples



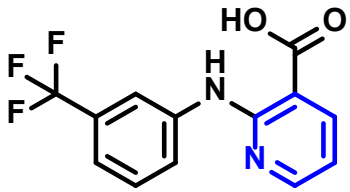
nicotine



Pyridoxine (vitamin B_6)



Isoniazide
Antibiotic
Rifater®

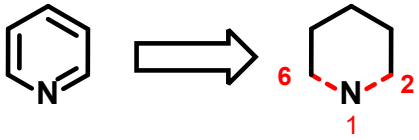


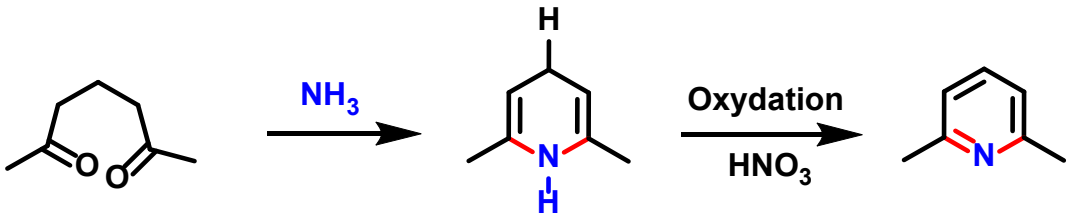
Niflumic acid
Analgesic

a) Pyridine

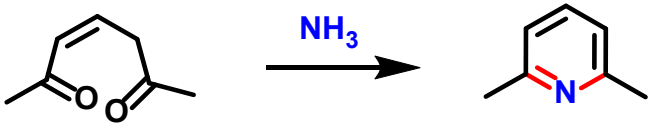
a.2) Preparation

- *Synthesis from 1,5-dicarbonyl compounds and a source of nitrogen: 1,2- and 1,6-bonds made*





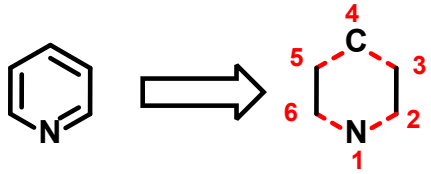
dihydropyridine



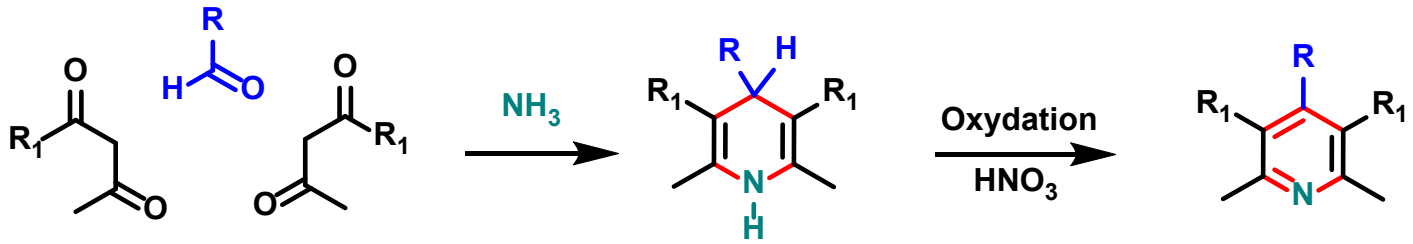
a) Pyridine

a.2) Preparation

- *Synthesis from an aldehyde, 2 equivalents of a 1,3-dicarbonyl compounds and ammonia:*
  1,2 ; 3,4 ; 4,5 and 1,6-bonds made



The Hantzsch synthesis:



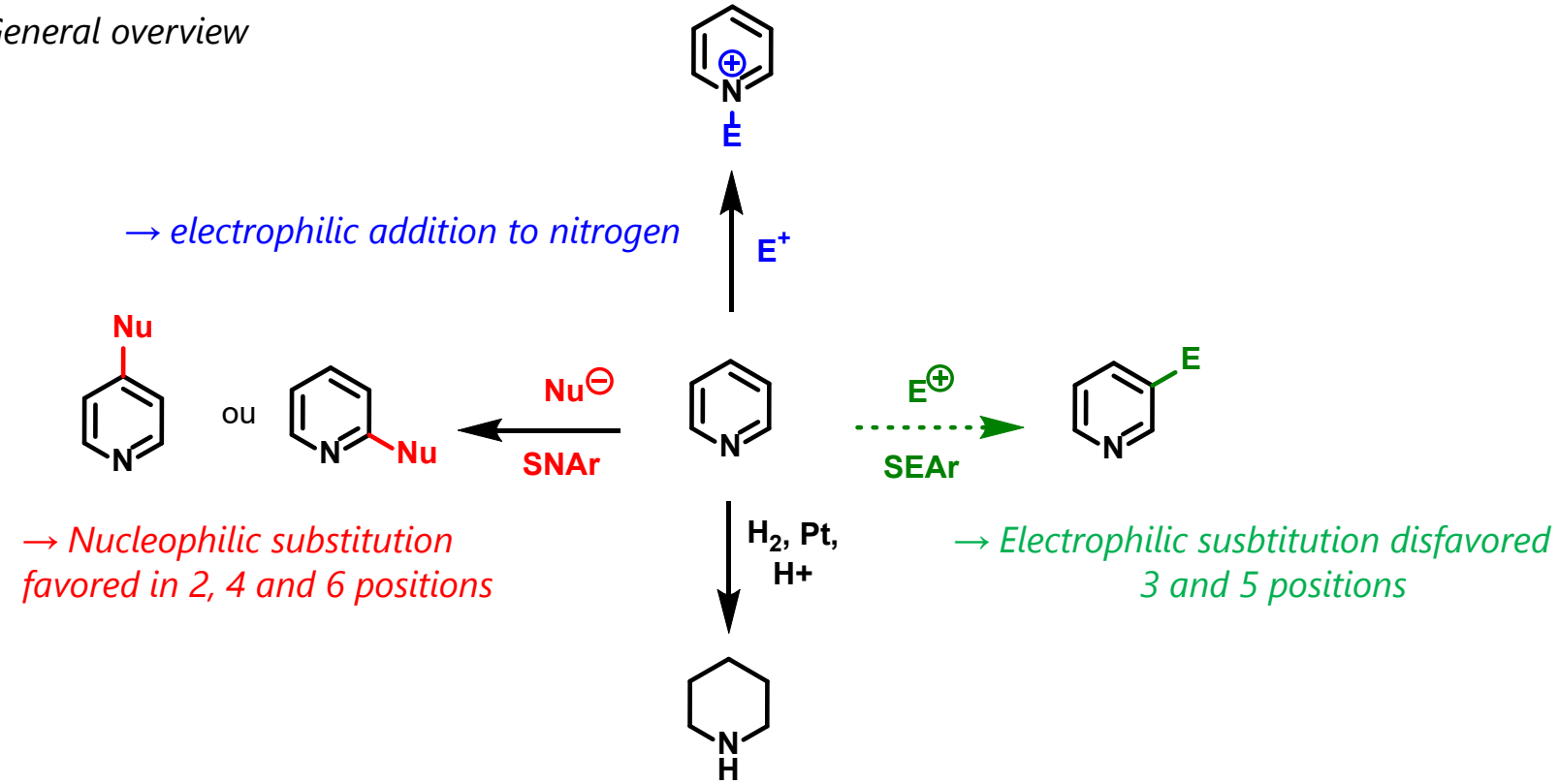
1,4-dihydropyridine

R_1 = CO_2Et, CN

a) Pyridine

a.3) Reactivity

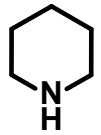
- *General overview*



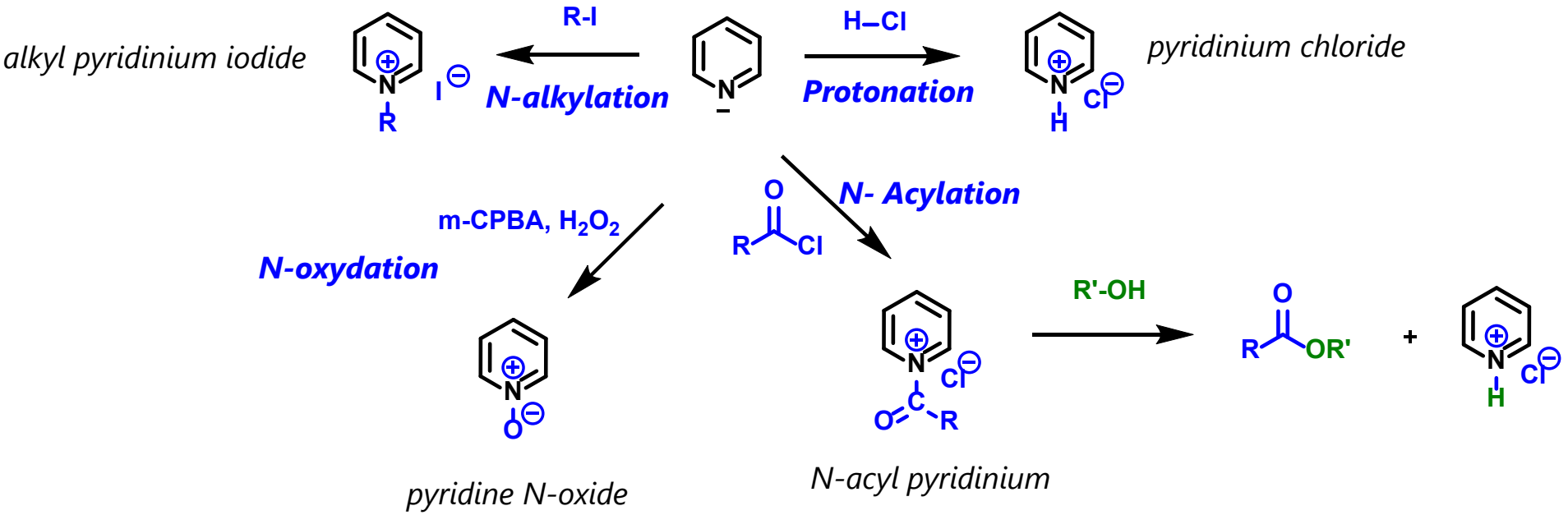
a) Pyridine

a.3) Reactivity

c.3.1) *Electrophilic addition to nitrogen*



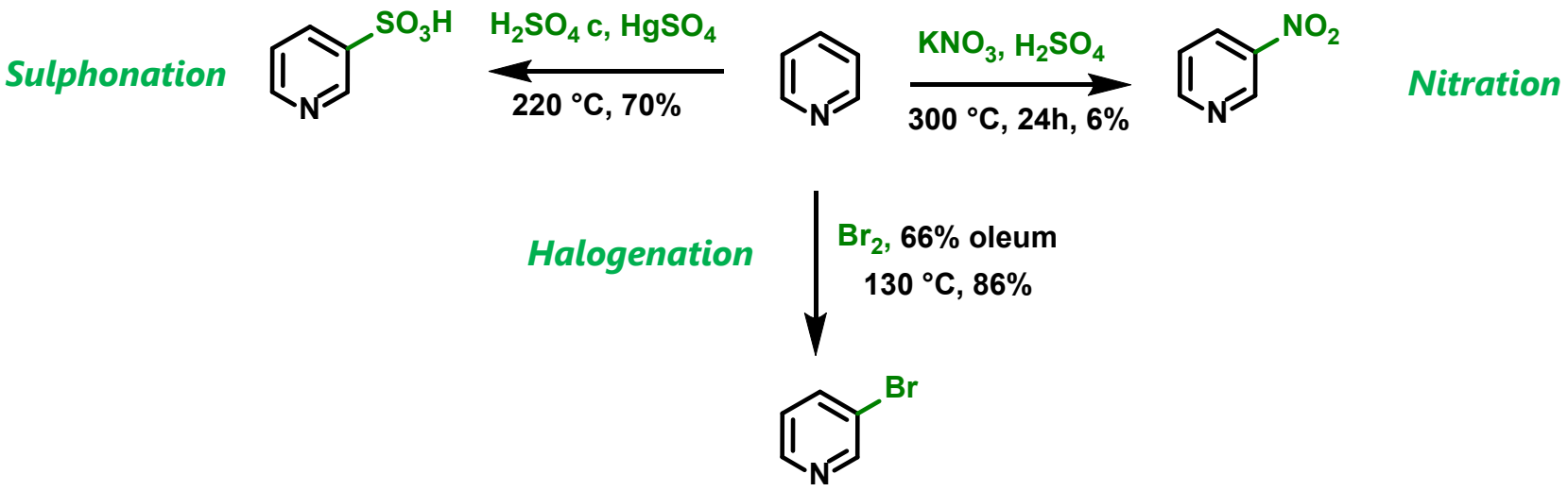
pKa = 11



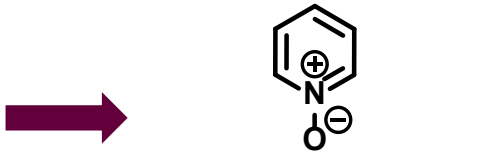
a) Pyridine

a.3) Reactivity

c.3.2) Electrophilic substitution



- Electron-deficient ring→ very difficult on an inactivated pyridine
- Electrophilic susbtitution is not preparatively useful
- **Regioselective : only at C-3**
- Harsh conditions
- No alkylation/acylation de Friedel-Crafts



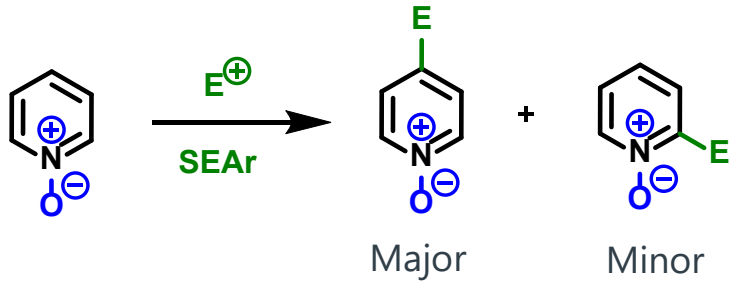
pyridine N-oxide

a) Pyridine

a.3) Reactivity

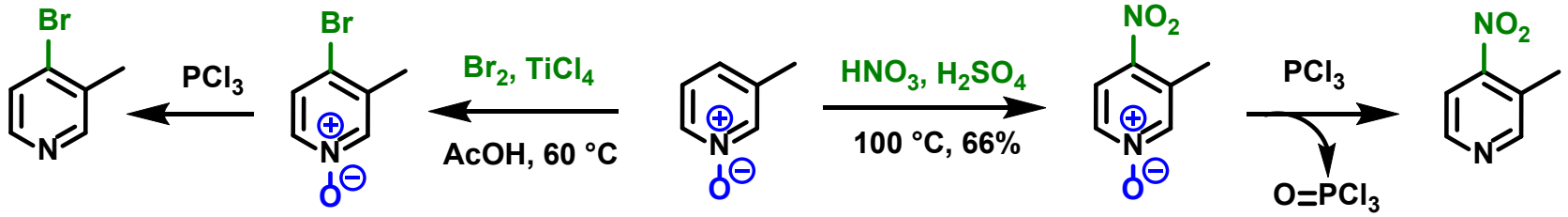
c.3.2) Electrophilic susbtitution

- *with pyridine N-oxide*



- Electron-rich ring→ electrophilic susbtitution is favored
- **Regioselective : C-2 and C-4 positions**

Examples:

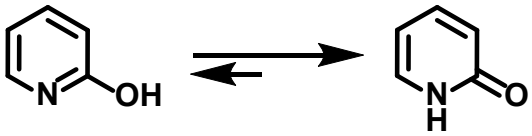


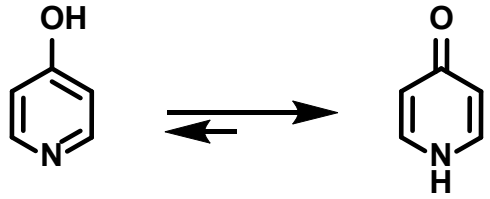
a) Pyridine

a.3) Reactivity

c.3.2) Electrophilic susbtitution

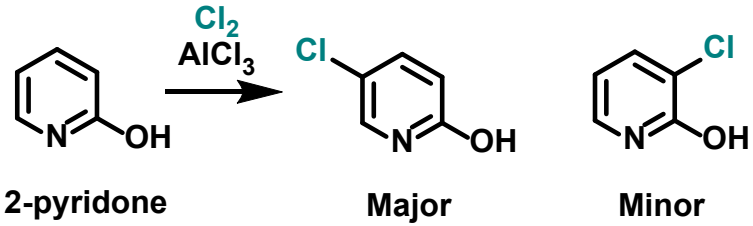
- *with 2- or 4-pyridone :*

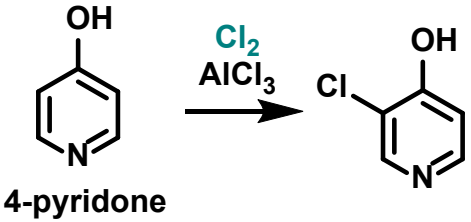




Examples:

- Electron-rich ring→ electrophilic susbtitution is favored
- **Regioselective : ortho and para positions to the oxygen**

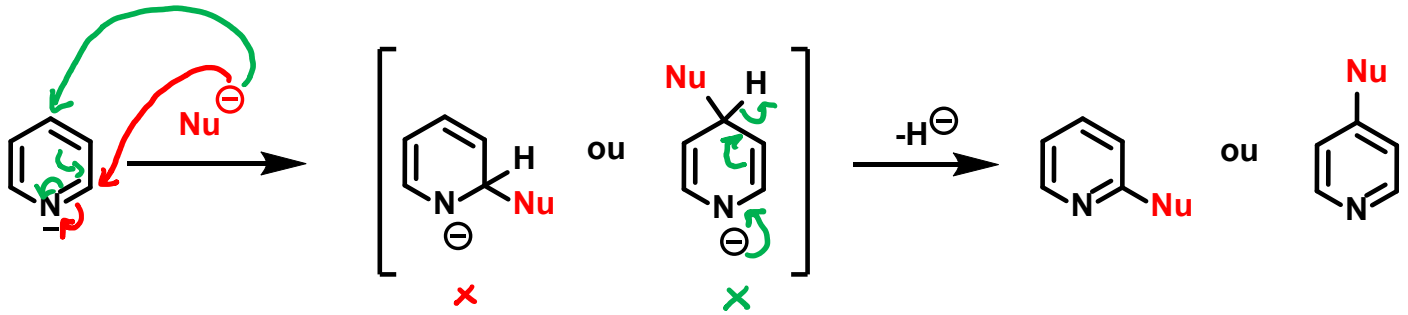




a) Pyridine

a.3) Reactivity

c.3.3) Nucleophilic substitution



- Very easy on the pyridine ring
- **Regioselective on C-2/6 or C-4 positions**

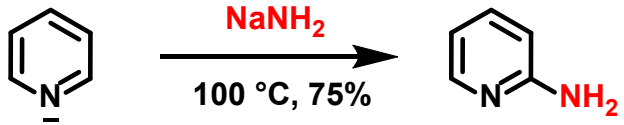
a) Pyridine

a.3) Reactivity

a.3.3) Nucleophilic substitution

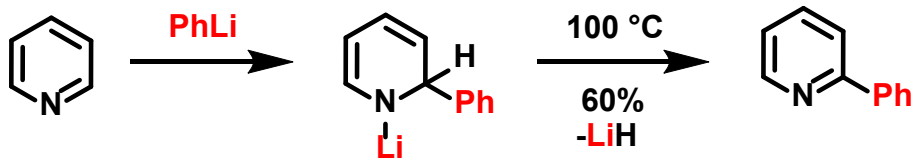
→ **Substitution of hydrogen**

- Reaction with sodium amide : Chichibabin reaction



2-aminopyridine

- Reaction with alkyl or aryllithiums

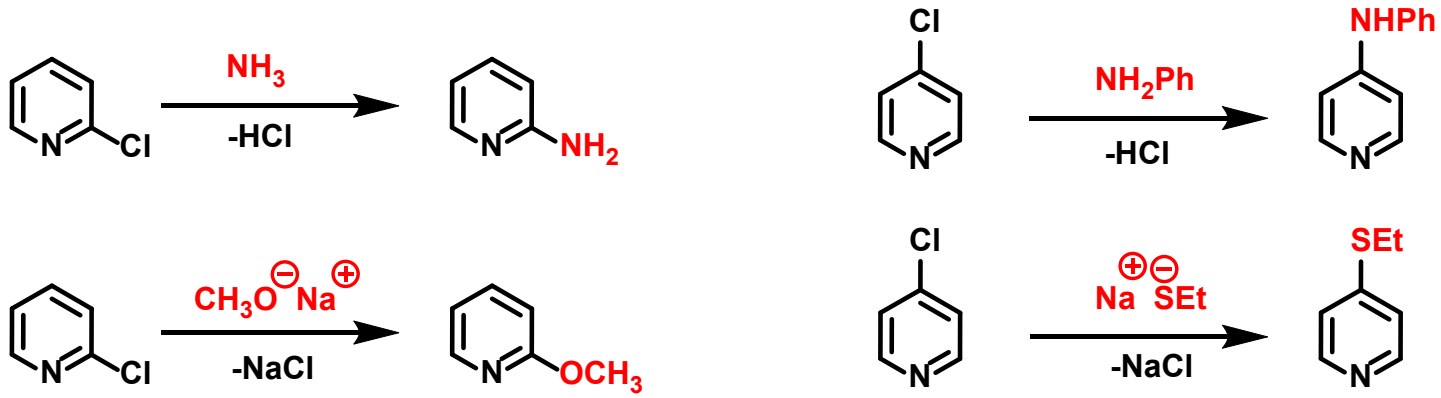


a) Pyridine

a.3) Reactivity

a.3.3) Nucleophilic substitution

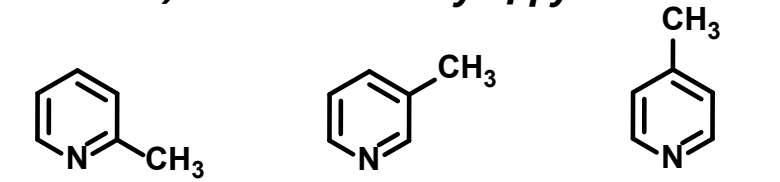
→ **Substitution of leaving groups**



a) Pyridine

a.3) Reactivity

a.3.4) Anion chemistry of pyridines

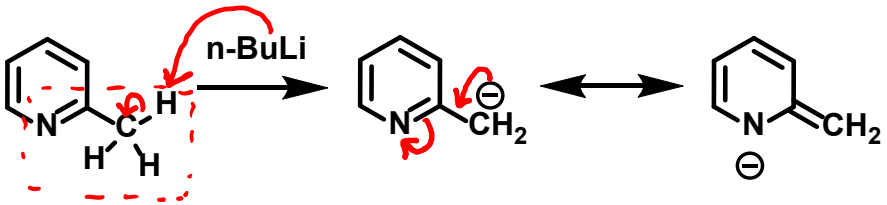


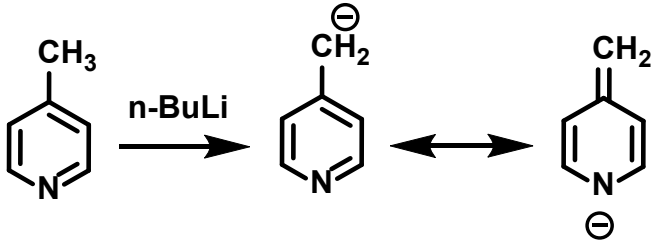
α-picoline β-picoline γ-picoline

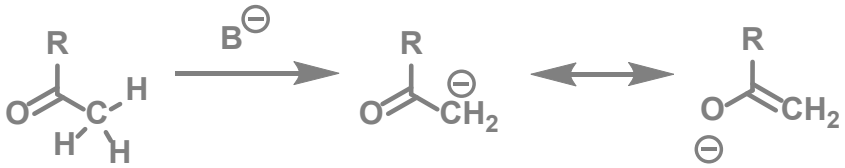
methylpyridines

- Hα et Hγ are more acidic than Hβ

- ***Deprotonation***



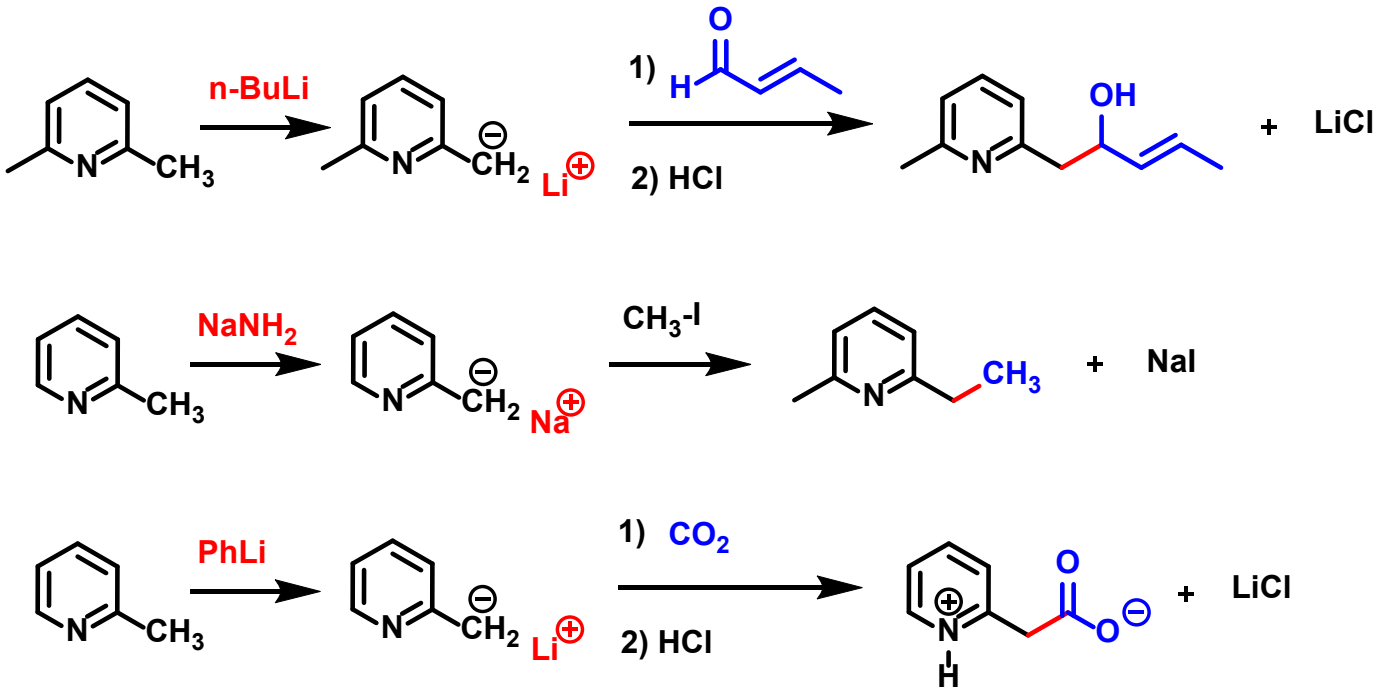




a) Pyridine

a.3) Reactivity

a.3.4) Anion chemistry of pyridines

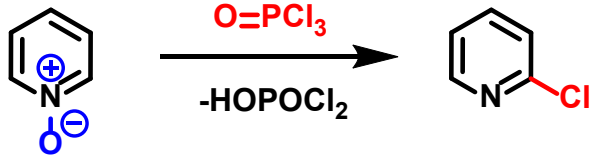


a) Pyridine

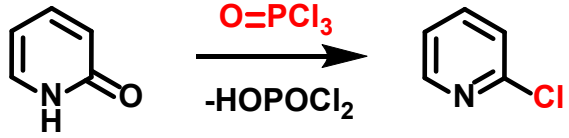
a.3) Reactivity

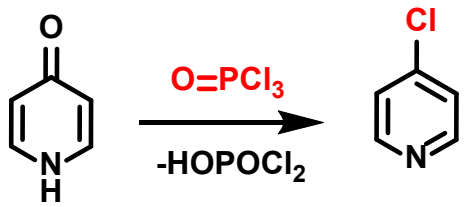
a.3.5) Miscellaneous reactions

- Reaction with pyridine *N*-oxide and phosphorous oxychloride→ 2-chloropyridine



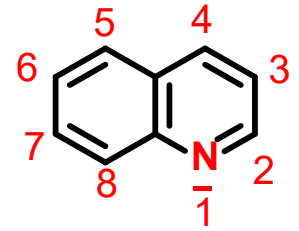
- Reaction with 2- or 4-pyridone and phosphorous oxychloride → 2- or 4-chloropyridine



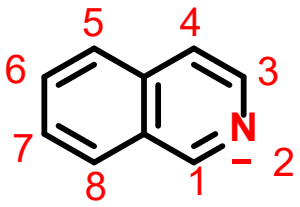


b) Quinoline and isoquinoline

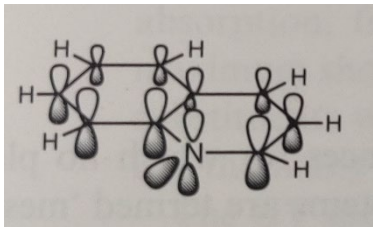
b.1) Introduction



Quinoline (pKa = 4.9)



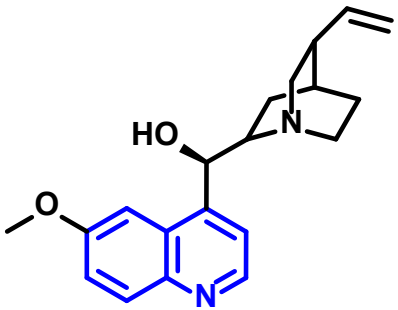
Isoquinoline (pKa = 5.1)



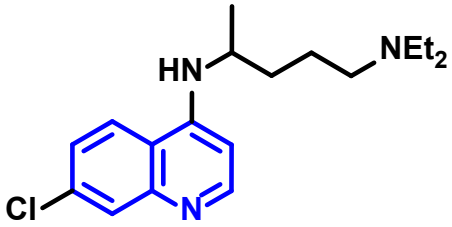
- Isolated from coal tar (1834 and 1885)
- Cyclic and planar
- Fully conjugated polyenes
- 10 $e^-\pi$ delocalized

} *aromatic*

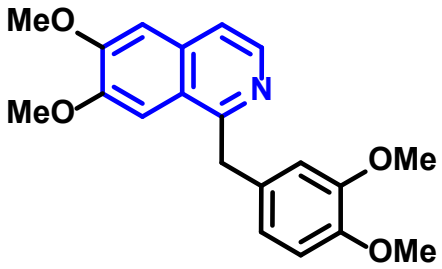
- Moderately basic
- π-deficient
- Lone pair is not delocalised



quinine



Chloroquinine

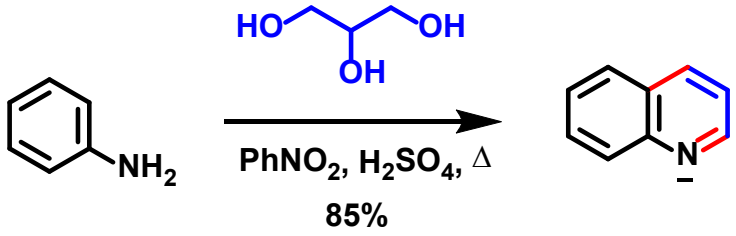


Papaverine

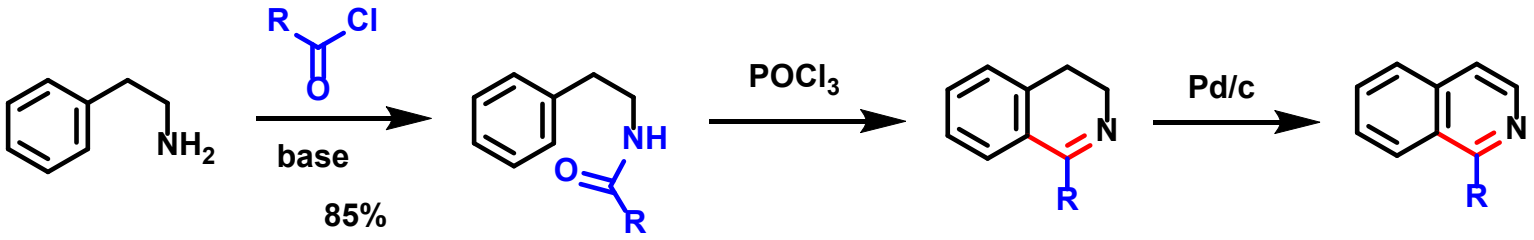
b) Quinoline and isoquinoline

b.2) Preparation

→ Skraup synthesis of quinolines



→ Bischler-Napieralski synthesis of isoquinolines



dihydroisoquinoline

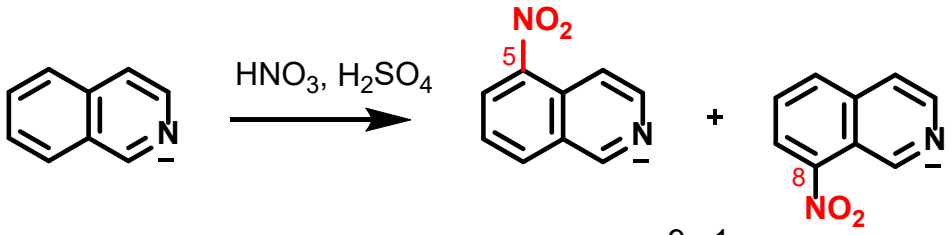
b) Quinoline and isoquinoline

b.3) Reactivity

b.3.1) Overview

- ✓ Mixture of the chemistry of benzene and pyridine
- ✓ Electrophilic susbtitution favours the benzene ring
- ✓ Nucleophilic substitution favours the pyridine ring

b.3.2) Electrophilic susbtitution



9 : 1

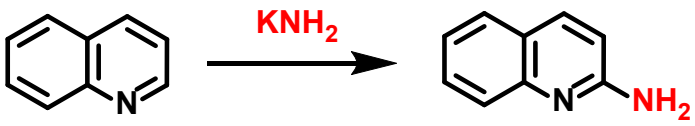
- ✓ Only on the benzene ring
- ✓ Regioslective : C5 or C-8 positions

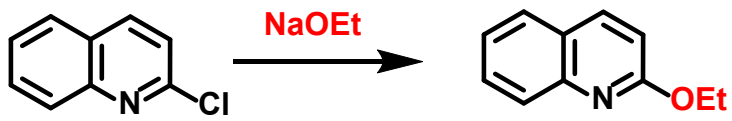
b) Quinoline and isoquinoline

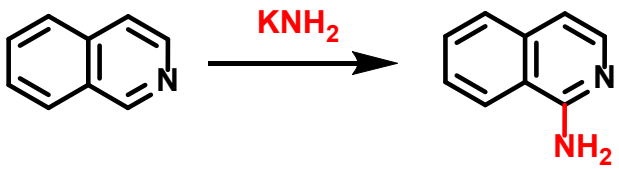
b.3) Reactivity

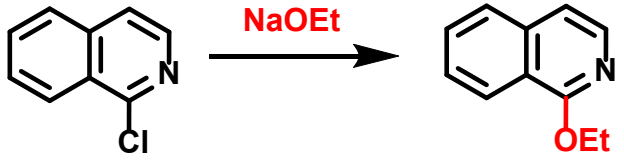
b.3.3) Nucleophilic substitution

✓ Chichibabin reaction



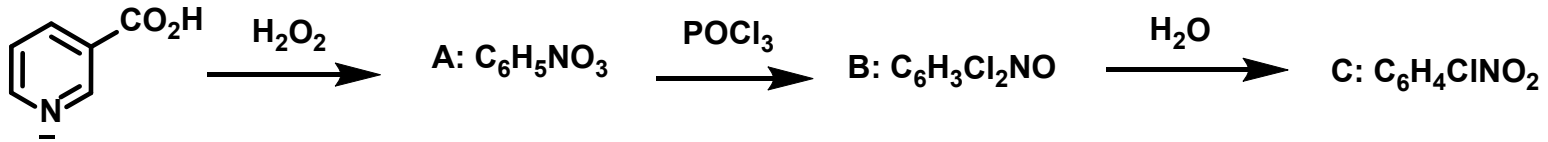


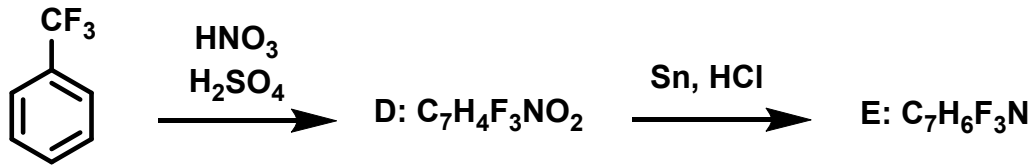


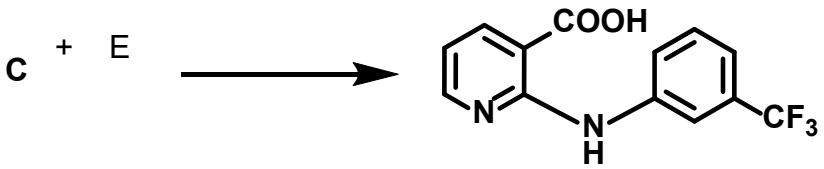


c) Exercices

Exercice 1 : Niflumic acid synthesis







Niflumic acid

c) Exercices

Exercice 2 :