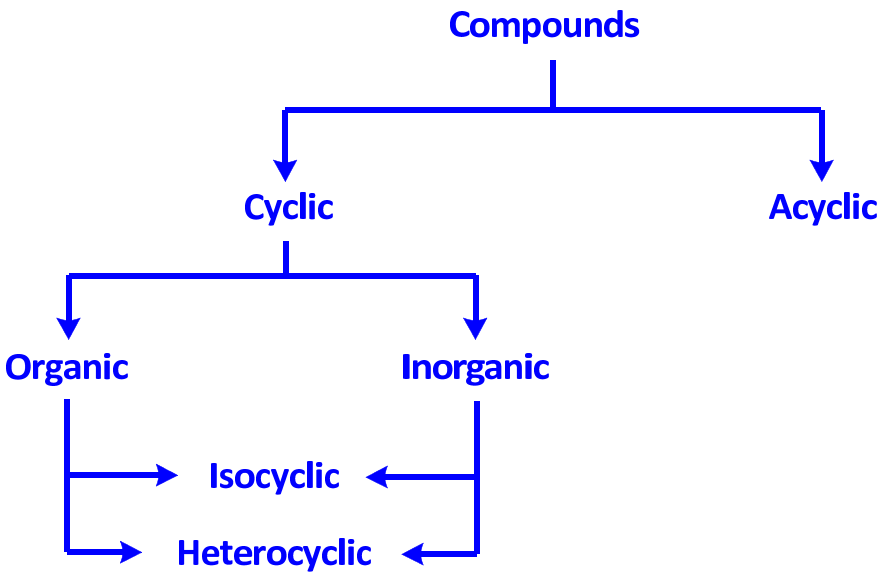
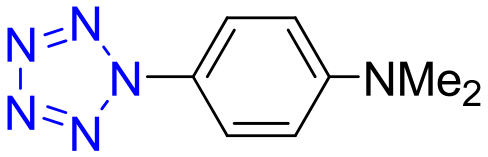
Heterocyclic Chemistry

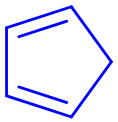
- It is the chemistry branch dealing exclusively with synthesis, properties, and applications of heterocycles (heterocyclic compounds).



Isocyclic Compounds



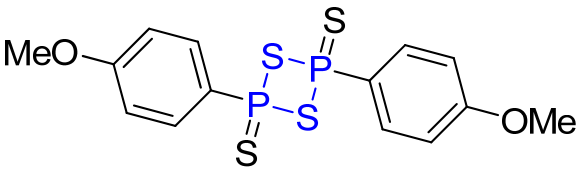
isocyclic



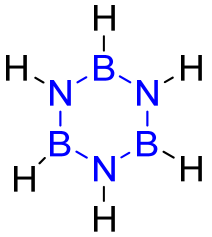
isocyclic
(cabocyclic)

- The ring is made up of atoms of one element only.

Inorganic Heterocyclic Compounds



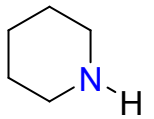
Lawesson - Reagent



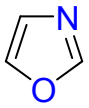
borazine

- The heterocycle contains no C-atom.

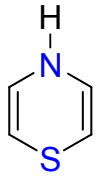
Organic Heterocycles



piperidine
heteroatom N



oxazole
heteroatoms O and N



4-*H*-1,4-thiazine
heteroatoms N and S

- Are organic compounds (at least one carbon atom).
- Containing at least one heteroatom (e.g. sulfur, oxygen or nitrogen).
- Ring structure (aromatic or non-aromatic).

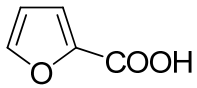
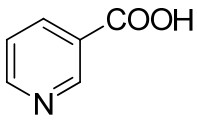
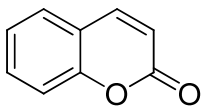
Nomencalture of Heterocycles

- Trivial Names:

  Originates from the compound's occurrence, its first preparation or its special properties.

- Systematic names:

  Hantzsch-Widman nomenclature.

Structure	Trivial name	Systematic name
	ethylene oxide	oxirane
	pyromucic acid	furan-2-carboxylic acid
	nicotinic acid	pyridine-3-carboxylic acid
	coumarin	2*H*-chromen-2-one

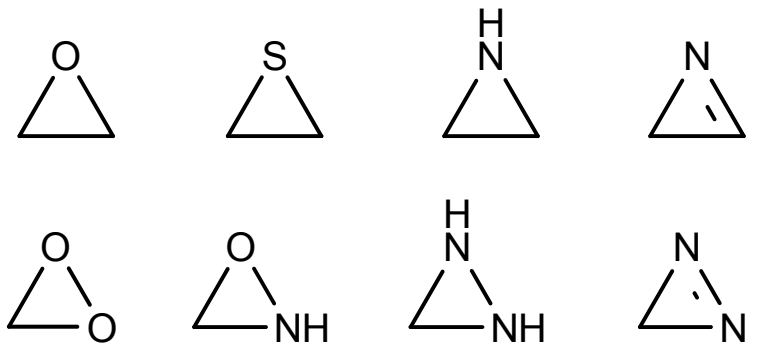
Hantzsch-Widman Nomenclature

- Recommended by IUPAC (three- to ten-membered heterocyclic compounds).
- Prefix indicates the type of heteroatom, for example:

  Aza for N-atom, oxa for O-atom, thia for S-atom.

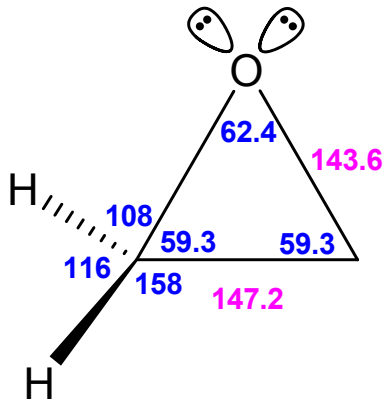
- Suffix indicate both the total number of atoms and the presence or absence of double bonds.

Three-Membered Heterocycles



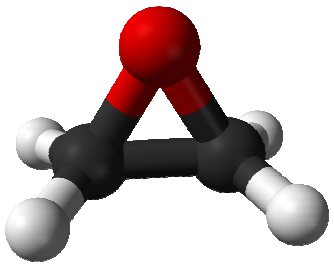
- High reactivity (Baeyer strain)
- Ring opening leading to acyclic products is typical.

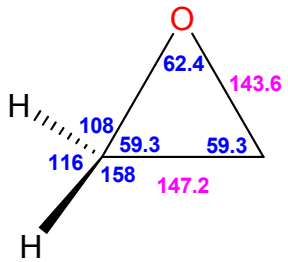
Oxirane

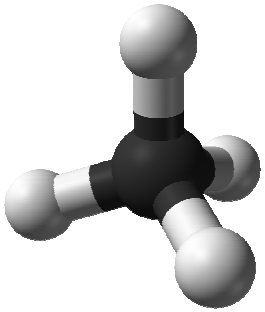


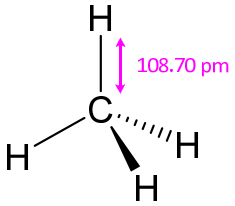
Bond lengths in pm.
Bond angles in degrees.

- Baeyer strain (ring opening).
- Bronsted and Lewis base (react with acids).



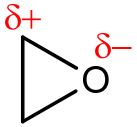




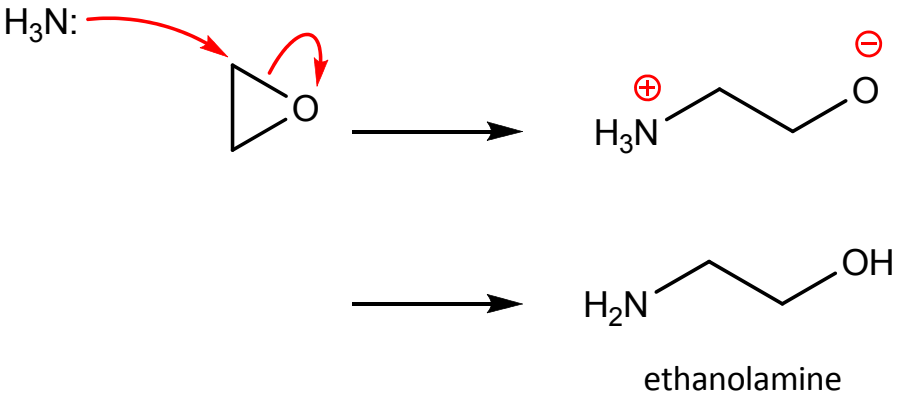


Ring-Opening by Nucleophiles

H_3N:

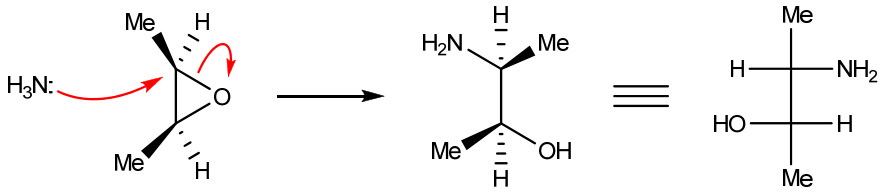


Ring-Opening by Nucleophiles



ethanolamine

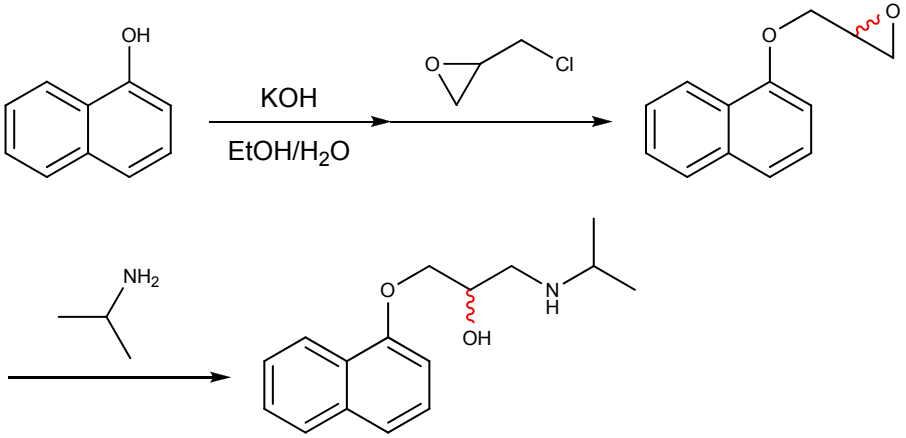
Stereospecific Ring-Opening



cis-2,3-dimethyloxirane (±)-*threo*-3-aminobutan-2-ol

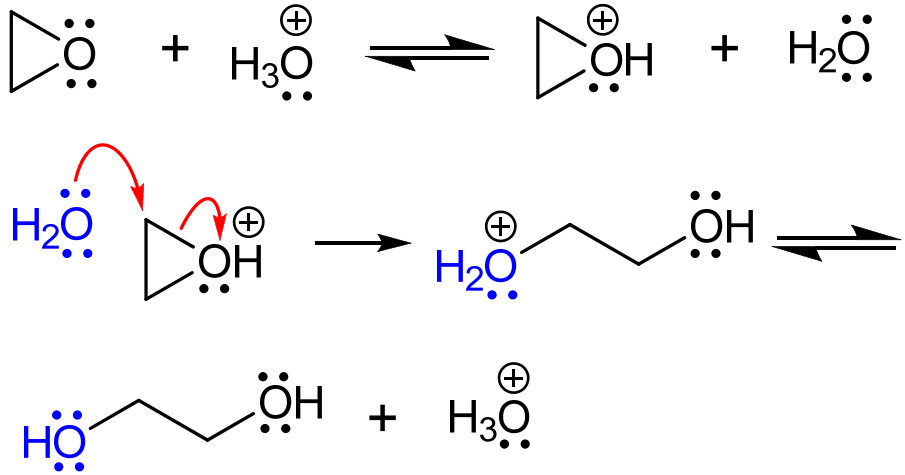
- *trans*-2,3-Dimethyloxirane will give (±)-*erythro*-3-aminobutan-2-ol.

Racemic Synthesis of (*RS*)-Propranolol

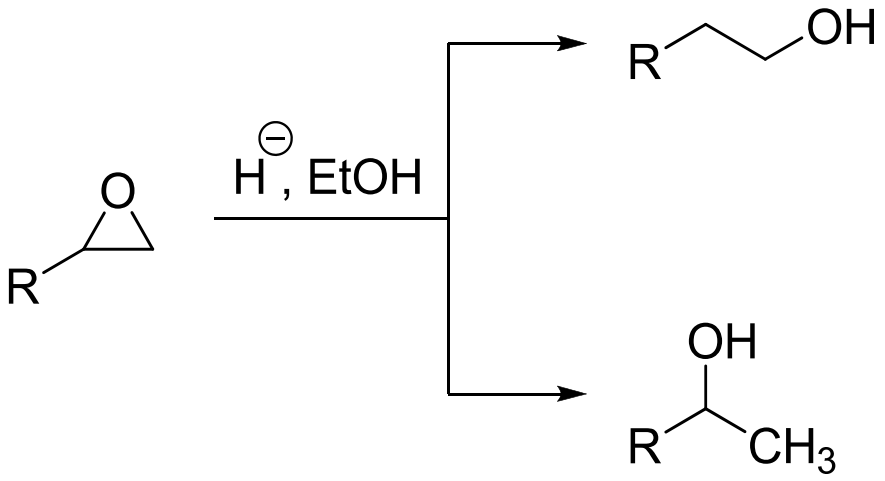


(*RS*)-propranolol

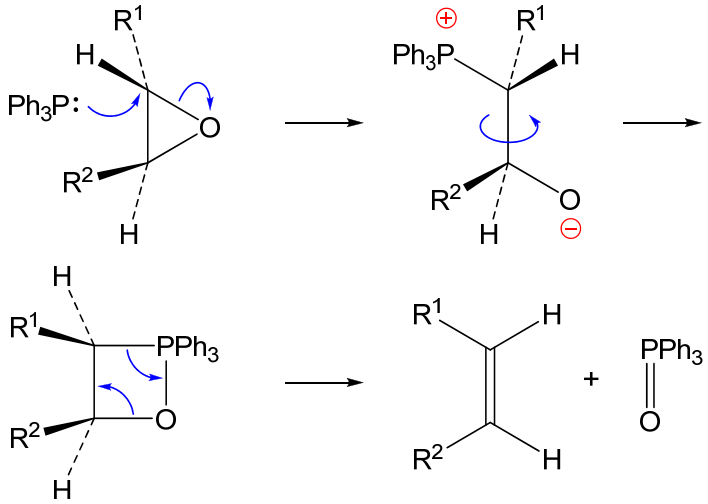
Acid-Catalyzed Hydrolysis to 1,2-Diol (glycol)



Reduction to Alcohols

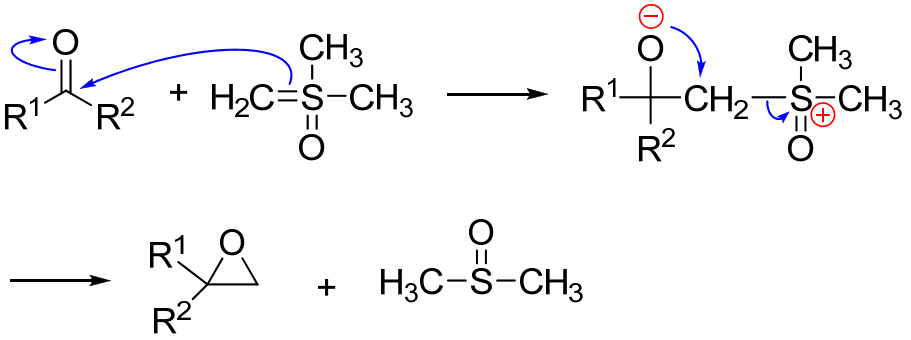


Deoxygenation to Olefins



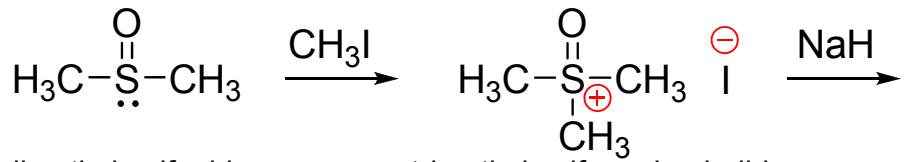
(*E*)-olefin ⟶ (*Z*)-olefin ???

Corey Synthesis of Oxiranes

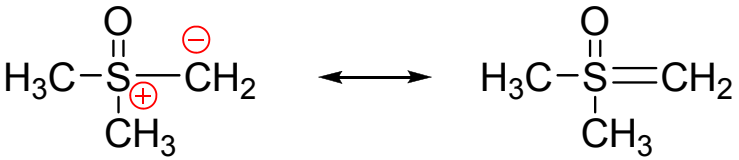


- Reaction of carbonyl compounds and S-ylide nucleophiles.

Synthesis of S-ylides

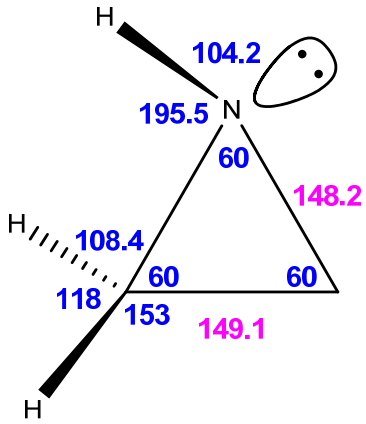


dimethyl sulfoxide — trimethyl sulfoxoniumiodide



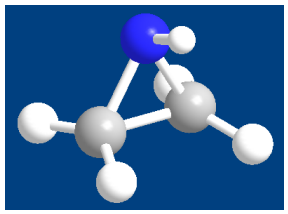
S-ylide dimethyl sulfoxoniummethylide

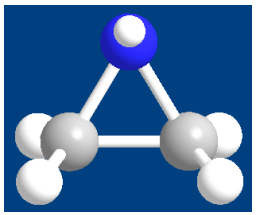
Aziridine

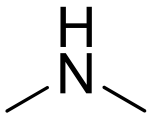


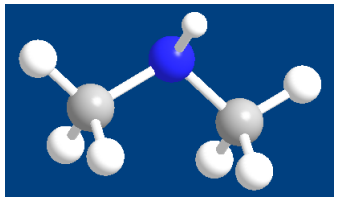
Bond lengths in pm.
Bond angles in degrees.

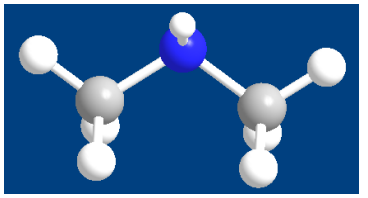
- Bond lengths and bond angles are essentially the same as those of oxirane.



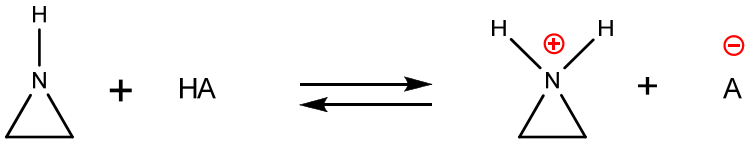




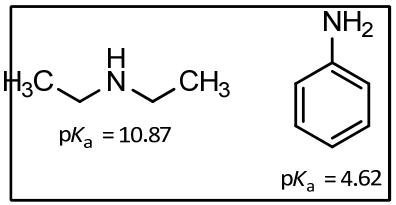




Acid-Base Reaction



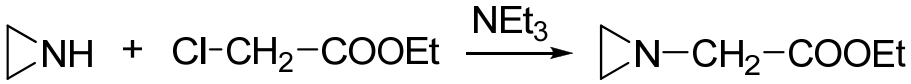
pK_a = 7.98



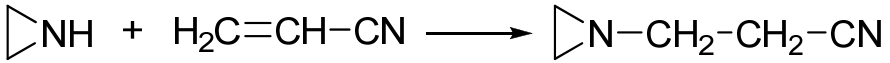
- Behaves like secondary amines; React with acids to give aziridinium salts (pK_a = 7.98).

Reaction with Electrophilic Reagents

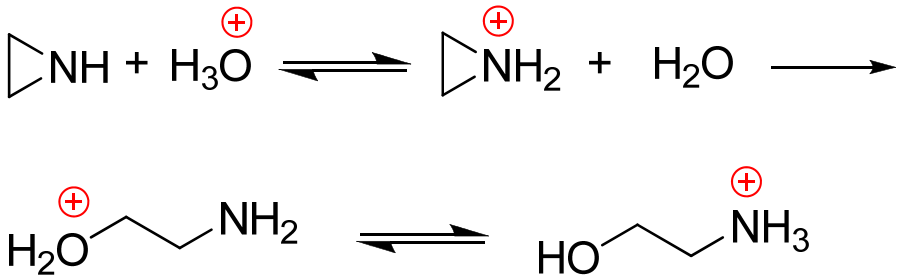
- Nucleophilic substitution:



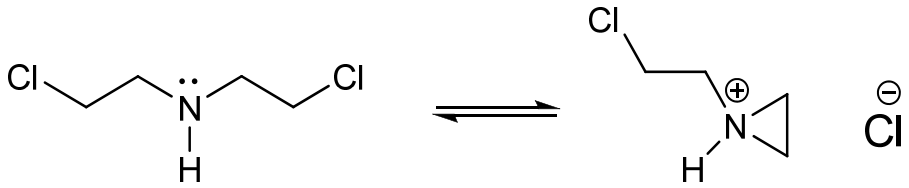
- Nucleophilic addition:

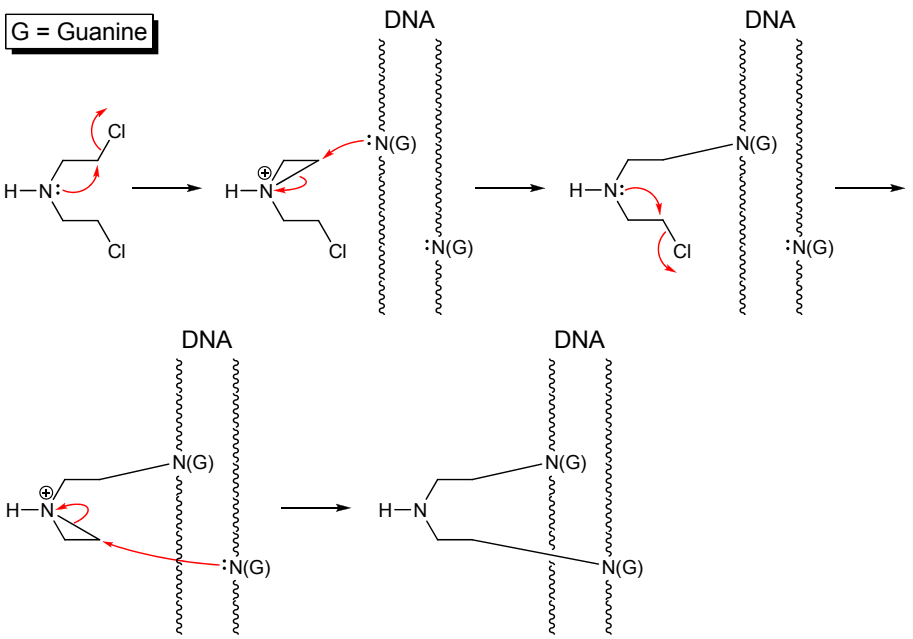


Acid-Catalyzed Hydrolysis

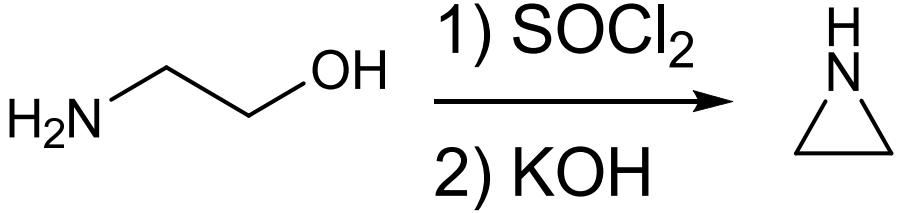


Antitumor Action of Aziridines

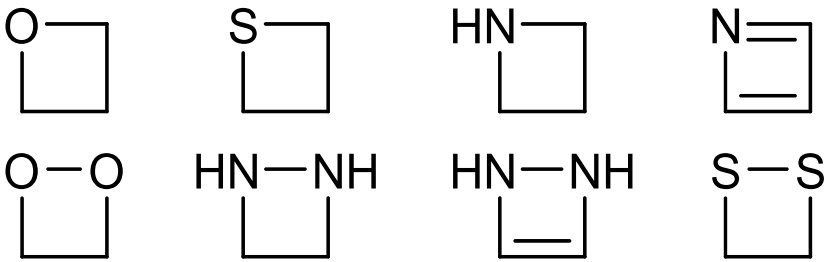


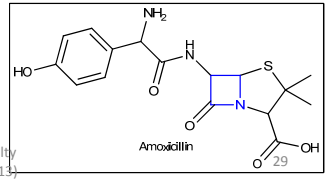


Gabriel Synthesis of Aziridines

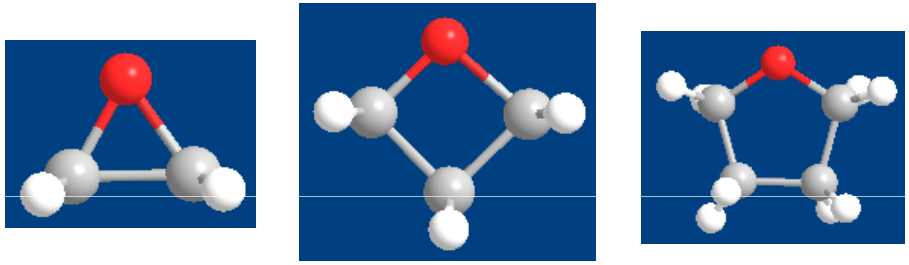


Four-Membered Heterocycles





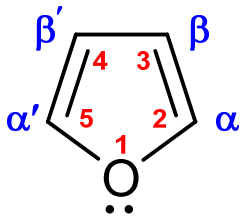
Five-Membered Heterocycles



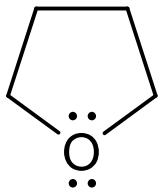
3-Membered 4-Membered 5-Membered

- Ring strain ⟶ Ring-opening reactions.

Furan



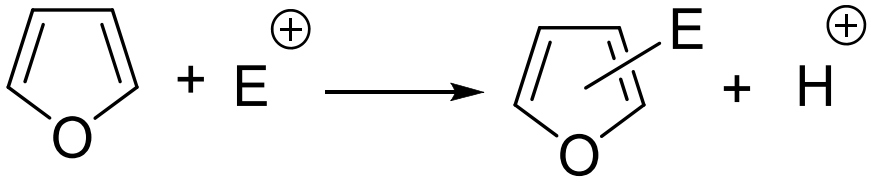
Furan



THF

- Smaller dipole moment (0.71 D;1.75 D).
- Delocalization.
- Aromatic heterocycle.
- E.A.S, Addition and/or ring-opening reactions.

Electrophilic Aromatic Substitution Reactions



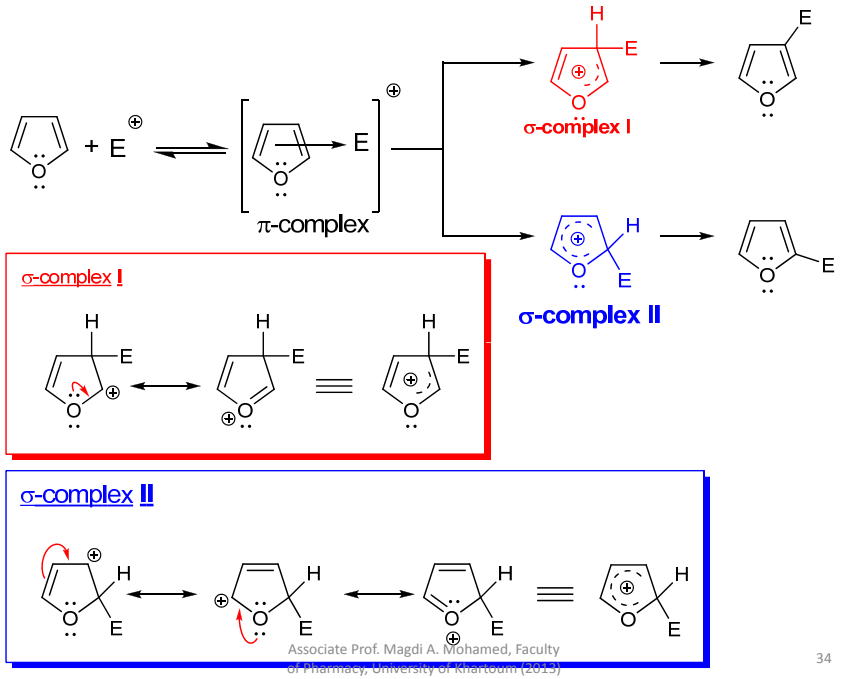
- 10^{11} More reactive than benzene:
  - ✓ The resonance energy is less than that of benzene.
  - ✓ The furan ring has a π-electron excess, while in benzene, the π-electron density is one on each ring atom.

Regioselectivity for E.A.S.

- The substitution is regioselective to the α-position; when these positions are occupied, the β-position is substituted. There are two reasons for this:

✓ The delocalization of the positive charge in the σ-complex II is more efficient, as it is not impaired by the heteroatom.

- The HOMO coefficient is greater on the *α*-C-atoms than on the *β*-C-atoms.



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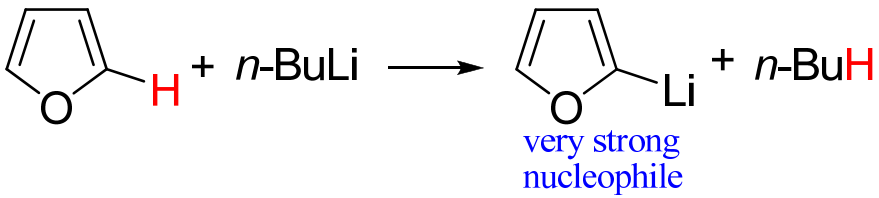
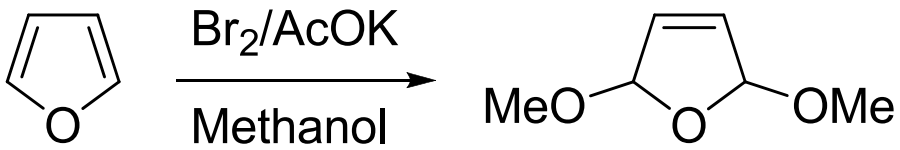
Metalation

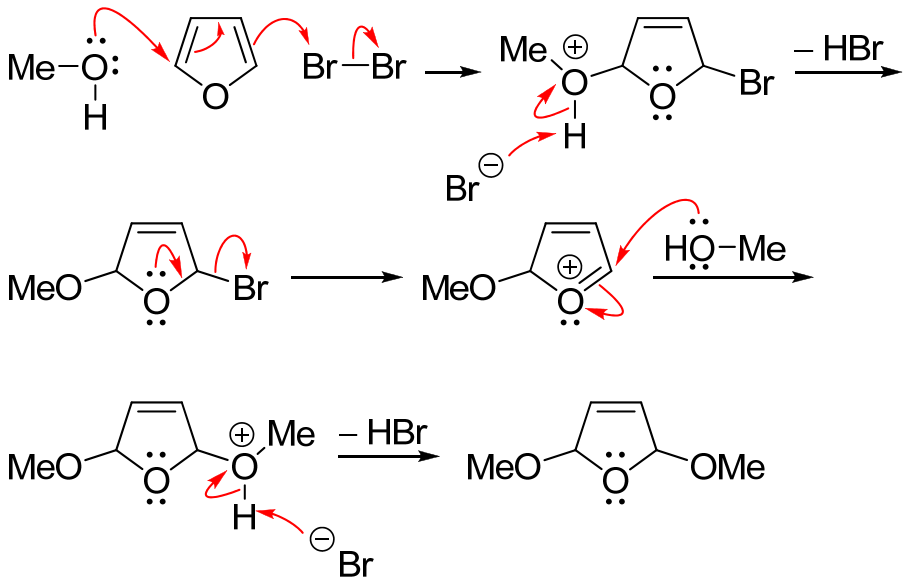


- *n*-BuLi metalates furan in the 2-position.
- The strong base butylate deprotonates furan (acid-base reaction).
- The resulting 2-lithiofuran is a very strong nucleophile.

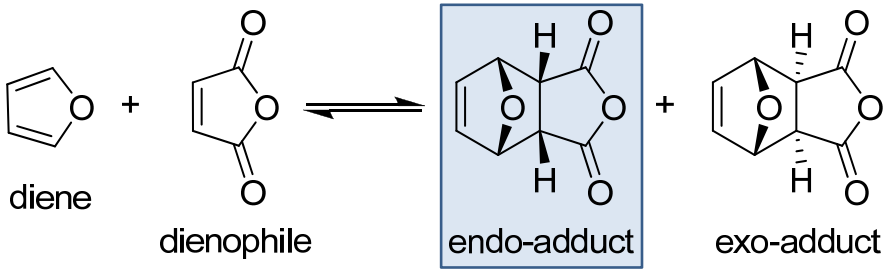
Addition Reactions

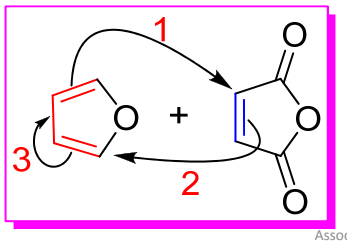


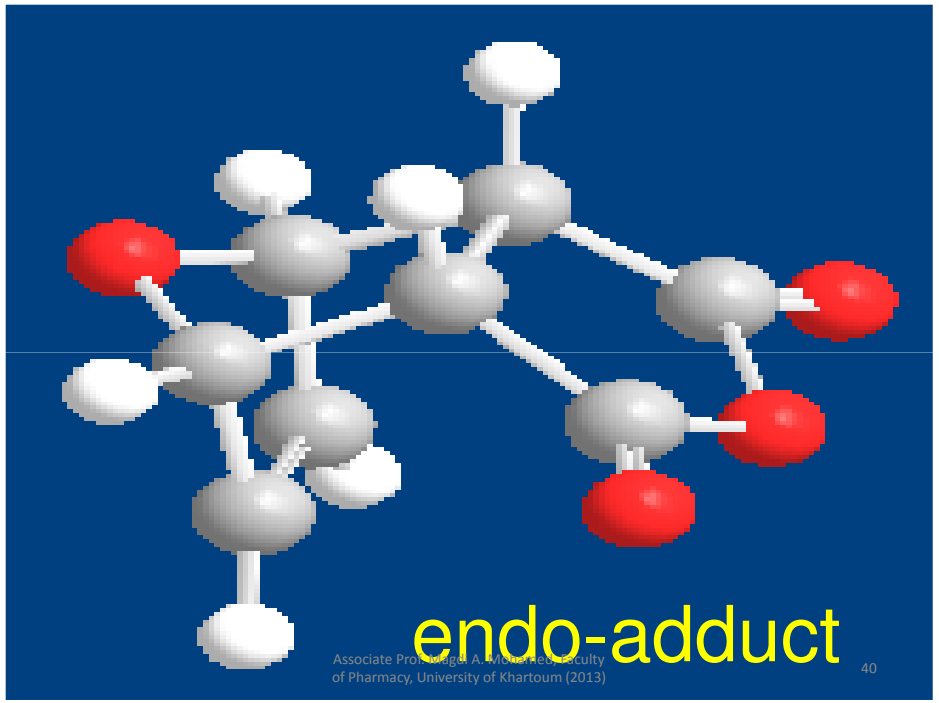
- In some addition reactions, furan behave as 1,3-dienes.



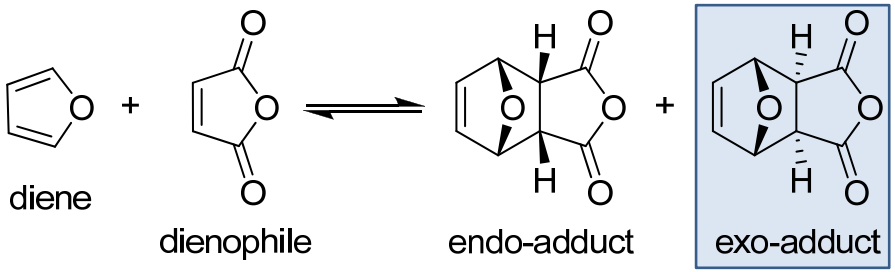
Diels-Alder Reaction

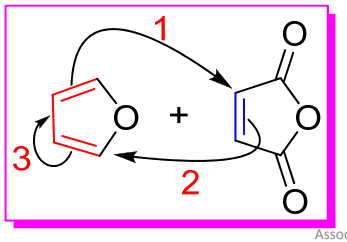


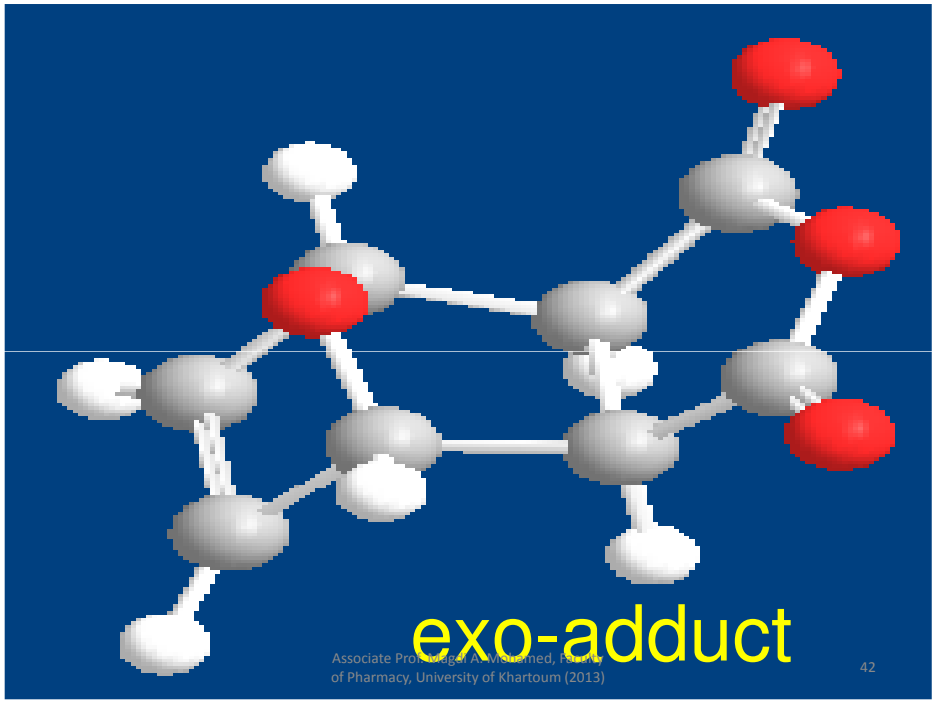




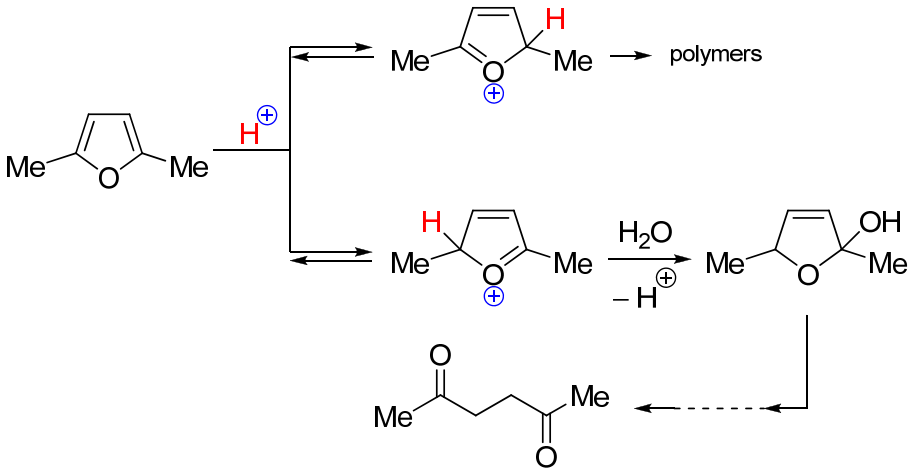
Diels-Alder Reaction



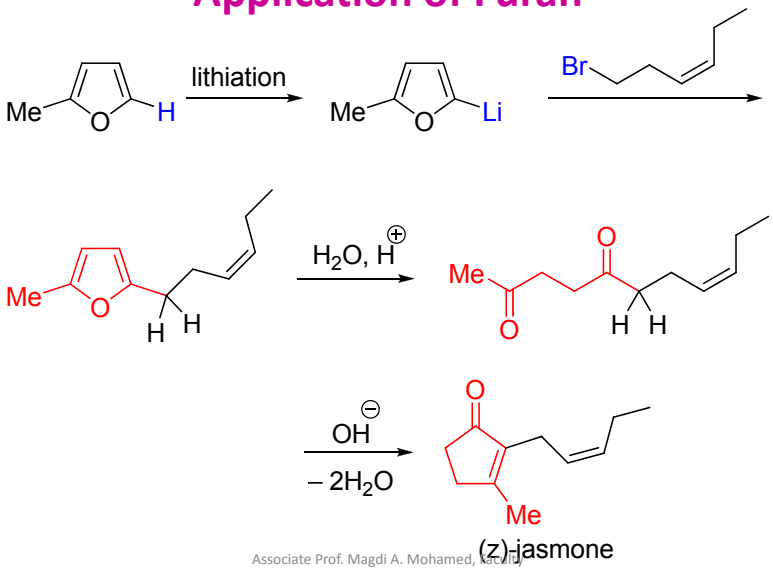




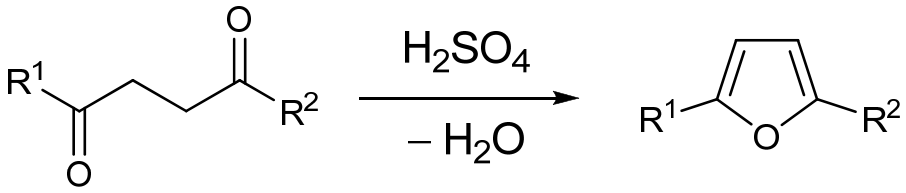
Ring-Opening Reactions



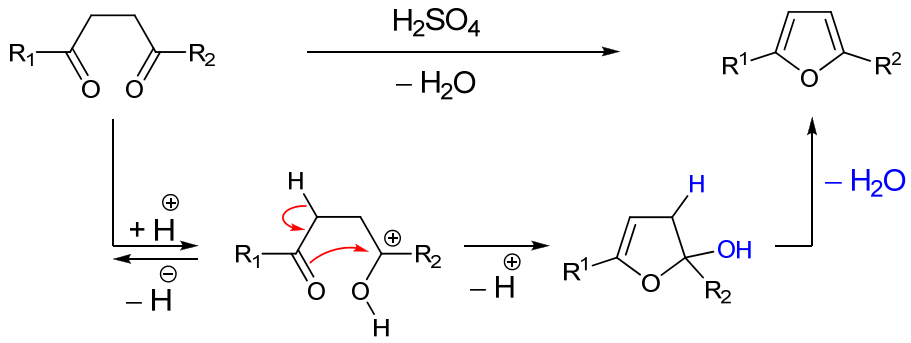
Synthesis of (Z)-Jasmone: a Synthetic Application of Furan



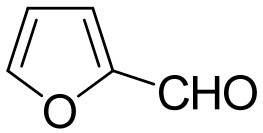
Paal-Knorr Synthesis of Furans



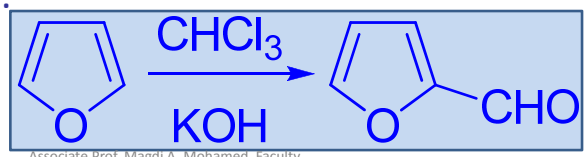
- 1,4-Dicarbonyl compounds, especially 1,4-diketones, undergo cyclodehydration when treated with either Bronsted or Lewis Acid, providing 2,5-disubstituted furans.



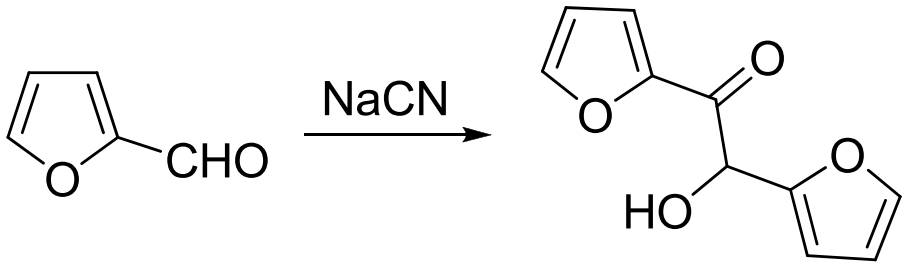
2-Furaldehyde (Furfural)

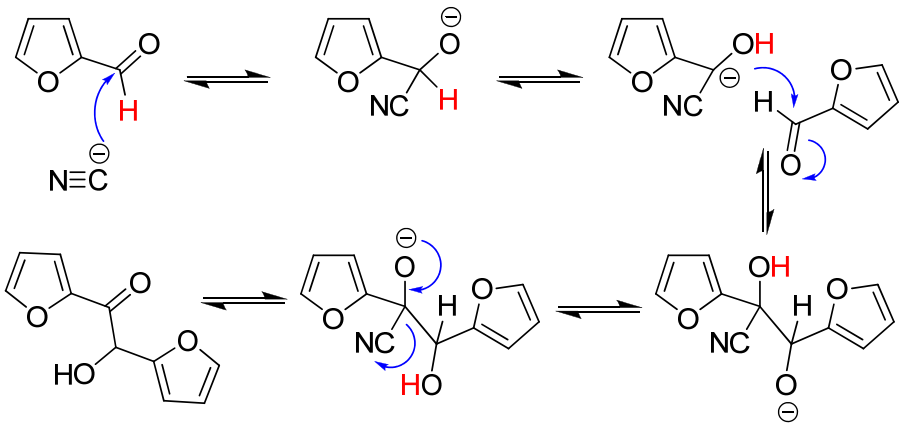


- Treatment of plant residues (pentoses), by dil. H_2SO_4 followed by steam distillation (industrial preparation).
- Using Reimer-Tiemman reaction (Laboratory preparation).

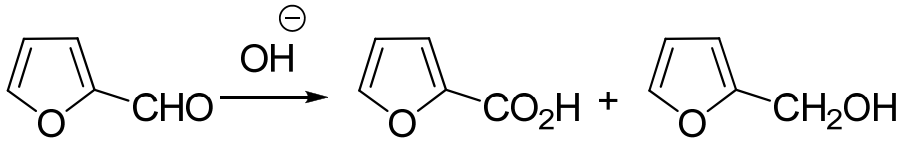


Benzoin Condensation of Furfural



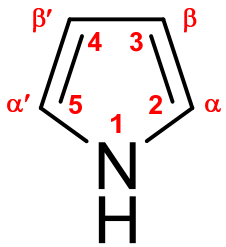


Cannizzaro Reaction of Furfural



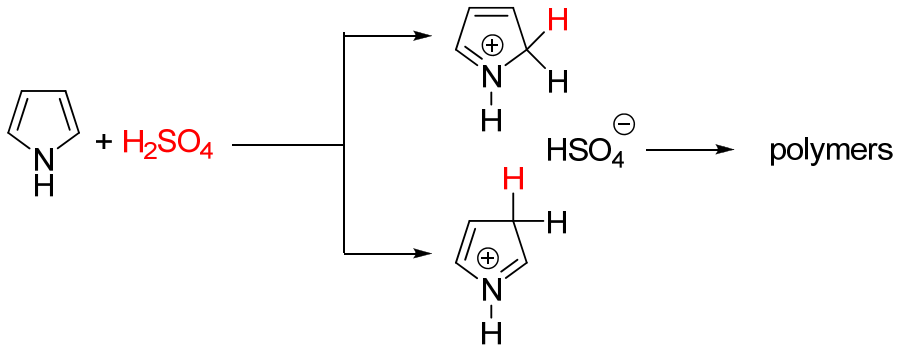
- Quench with acid.

Pyrrole



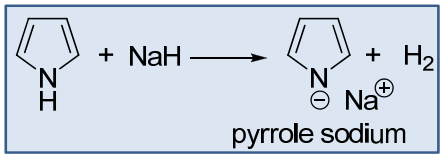
- π-electron excessive heterocycle.
- The resonance energy of pyrrole is greater than that of furan.
- The aomaticity of pyrrole is thus greater than that of the furan.

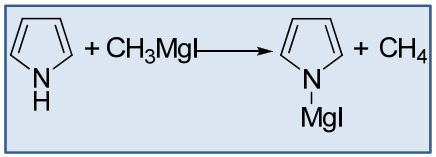
Basicity of Pyrrole

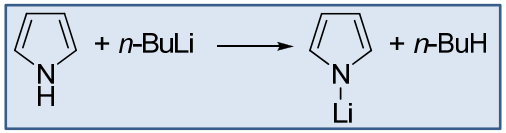


- Protonation doesn't occur on the N-atom (delocaliztion).
- Protonation occurs on C-2 (80%) & C-3 (20%) leading to rapid polymerization.

Acidity of Pyrrole



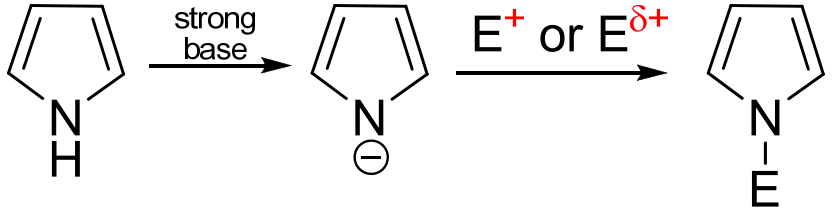




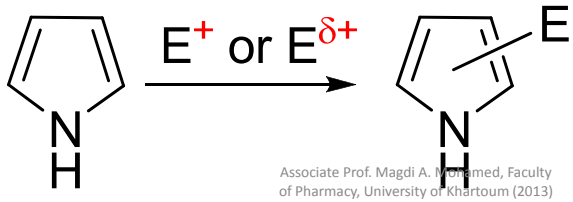
- It is an NH acidic.
- It reacts with strong bases.
- It reacts with Grignard reagents.
- It reacts with n-BuLi.

Electrophilic Substitution Reactions

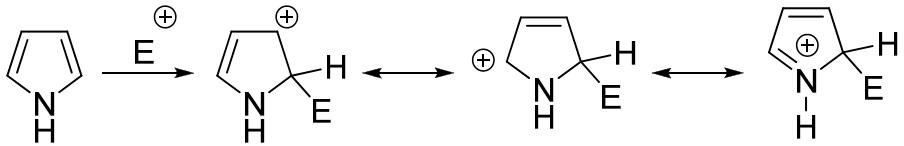
Electrophilic substitution on N:



Electrophilic substitution on C (E.A.S.):

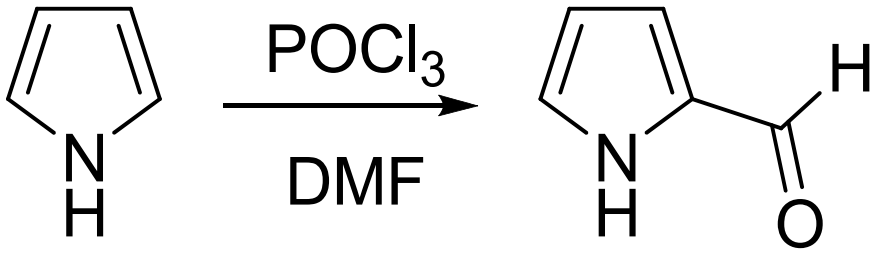


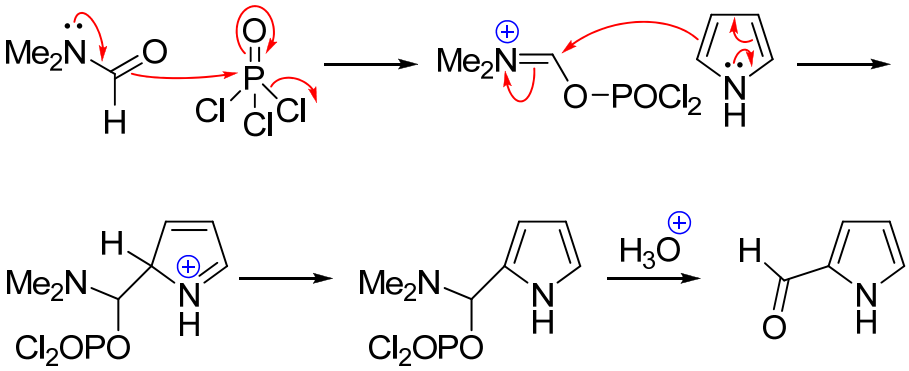
Electrophilic Aromatic Substitutions (E.A.S.)



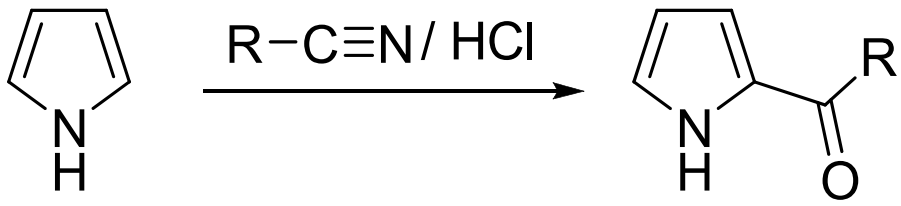
- More reactive (10^5) than furan (N versus O).
- Substitution occurs at 2-position more favorably than 3-position.
- Lewis acid-catalyzed alkylation reactions are problematic (because of polymerization).

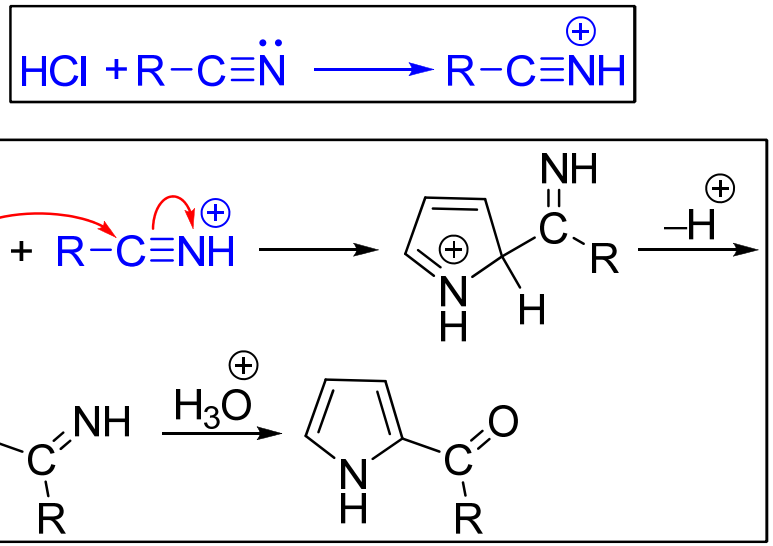
Vilsmeier-Haak Formylation of Pyrrole



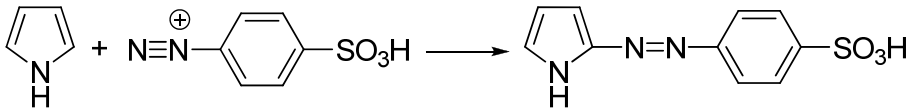


Houben-Hoesch Acylation of Pyrrole



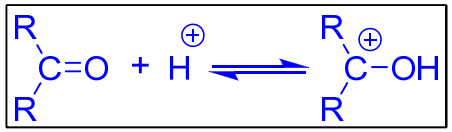


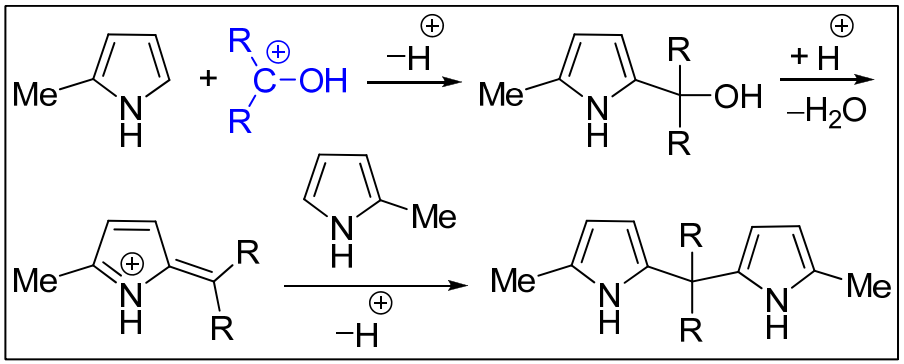
Coupling with Diazonium Salts



- Not observed in furan.

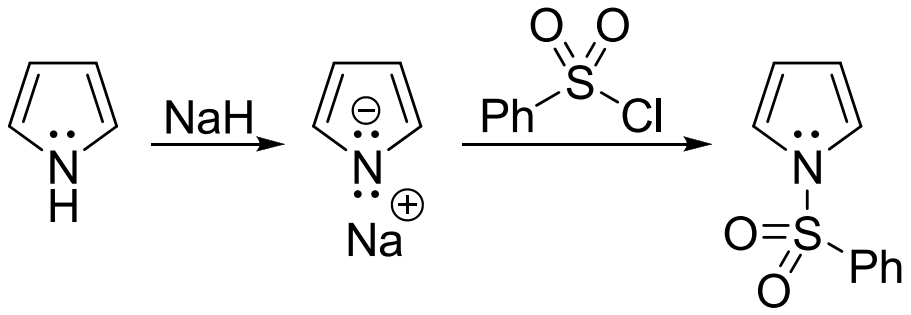
Hydroxymethylation of Pyrroles





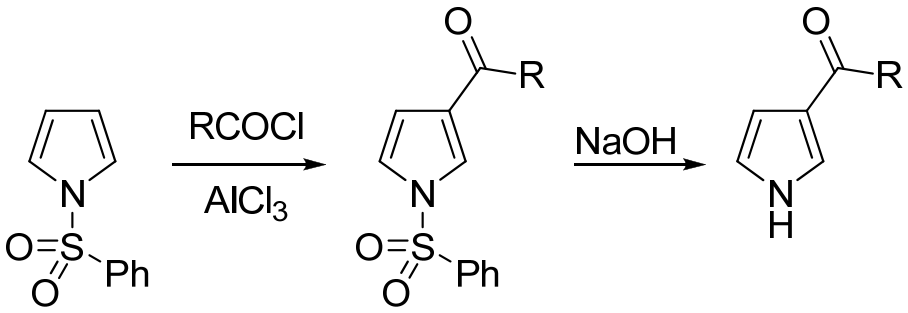
- Not observed in furan.

Electrophilic Substitution Reactions on Nitrogen

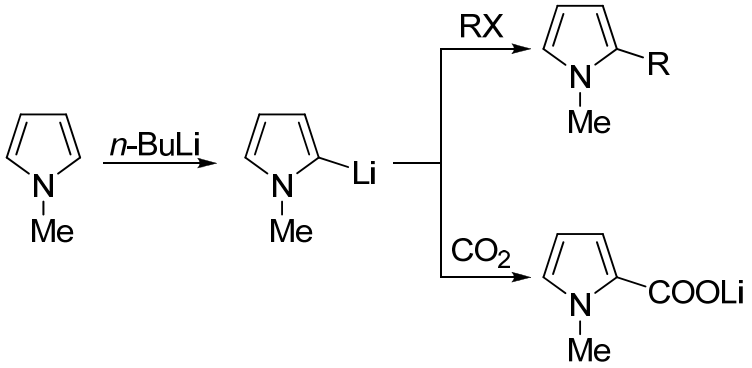


- Pyrrole sodium yields 1-substituted pyrrole with haloalkanes, acylhalides, sulfonyl halides as well as with chlorotrimethylsilane.

Introduction of an Acyl Group at β-Position

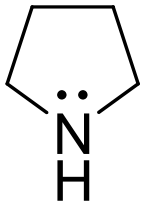


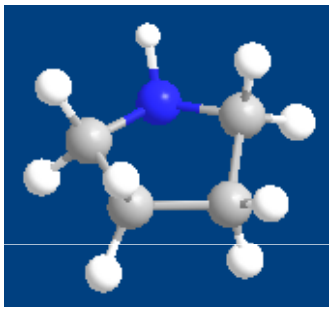
Lithiation of N-Alkylpyrroles



- If 1-position is blocked by a substituent, then 2-lithiopyrroles are formed regioselectively.
- They can be used for the synthesis of the substituted pyrroles.

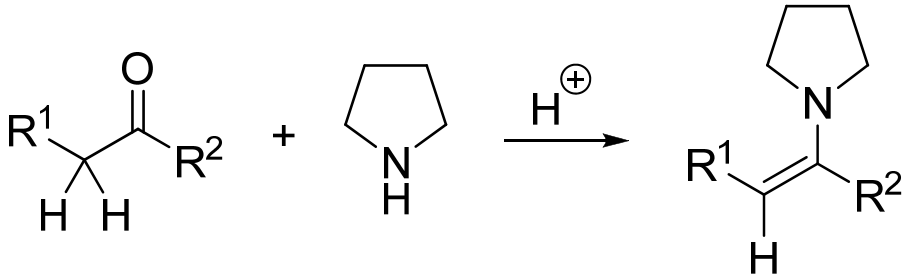
Pyrrolidine





- Pyrrolidines and N-substituted pyrrolidines react as secondary and tertiary alkylamines.
- Greater basicity and nucleophilicity than those of diethylamine.

Enamine Formation

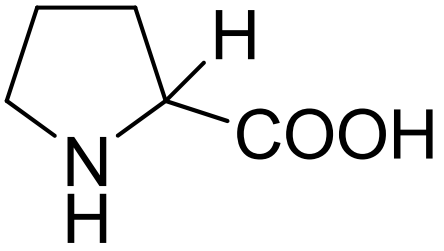


- Can form stable enamines because of its greater basicity and nucleophilicity.

Asymmetric Synthesis

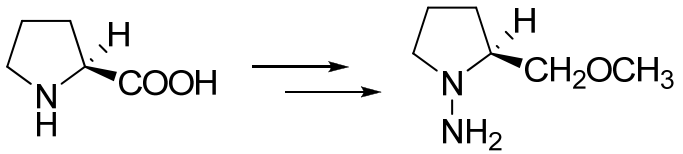
- Synthesis of an stereoisomer in a pure (or nearly pure) stereoisomeric form.
- Most important strategies are:
  - ✓ Chiral pool.
  - ✓ Chiral ligand controlled.
  - ✓ Chiral auxilliary.
  - ✓ Substrate controlled.

Proline

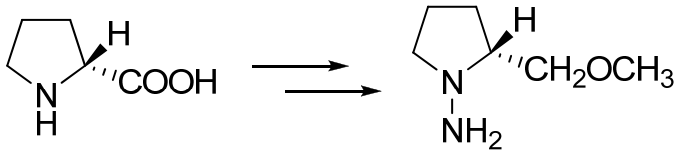


(*RS*)-proline

- Pyrrolidine-2-carboxylic acid is one of the 20 essential amino acids.



(*S*)-proline SAMP

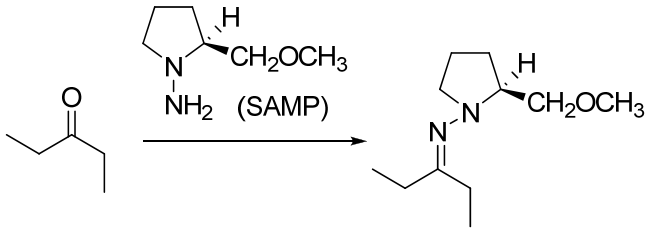


(*R*)-proline RAMP

- Enders synthesized the chiral auxiliaries (S)- and (R)-1-amino-2-methoxymethyl pyrrolidine by a chiral pool strategy from (S)- and (R)-proline, respectively, in several steps.

Asymmetric Synthesis: Chiral Auxiliary Strategy

- The chiral auxiliary (one enantiomer) is attached to the starting material.
- A diastereoselective reaction is carried out (Asymmetric synthesis).
- The chiral auxiliary is removed by, for example, hydrolysis, leaving the product of the reaction as a single enantiomer.



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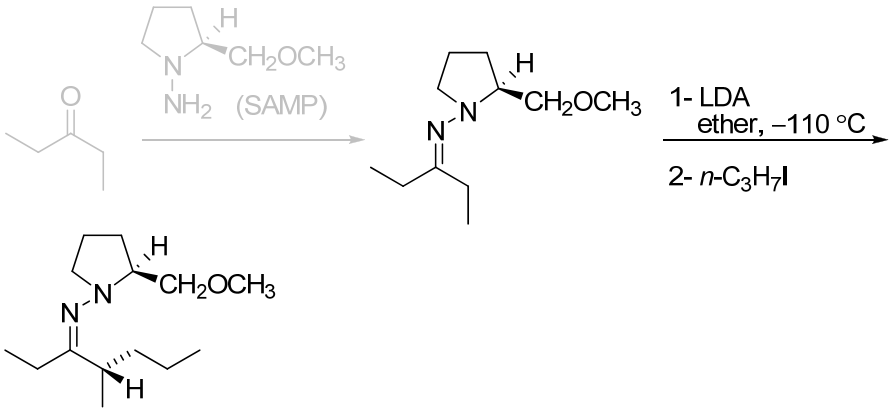

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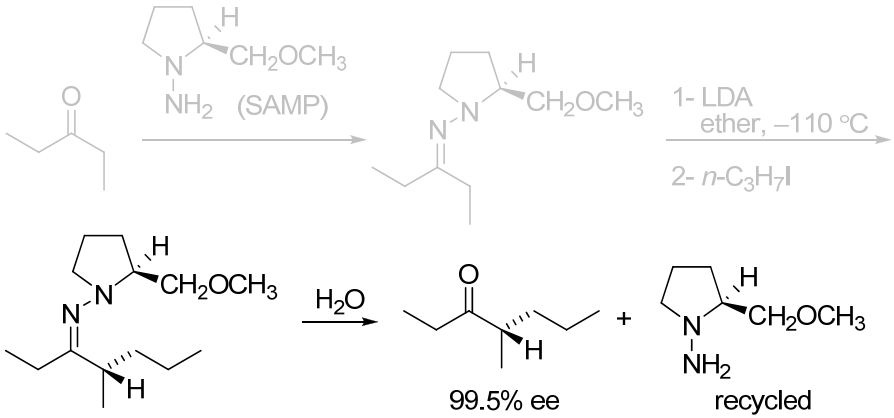
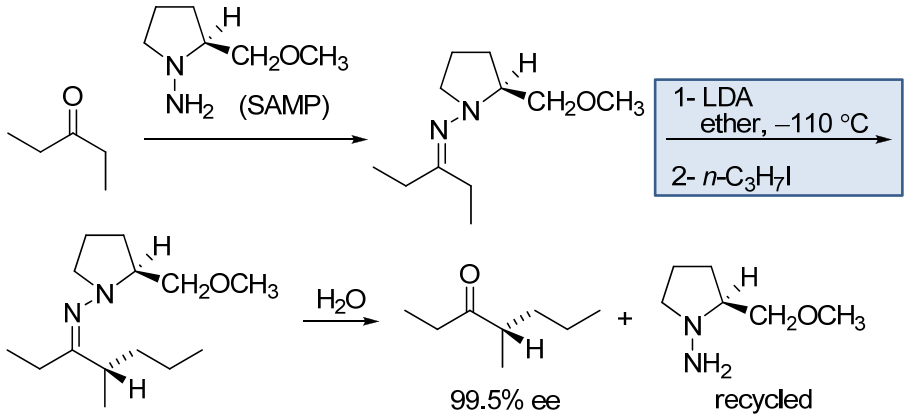
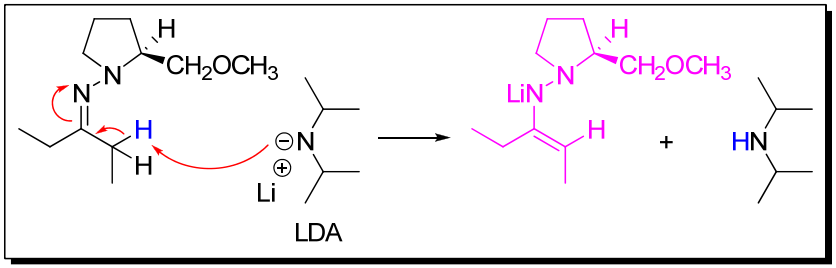
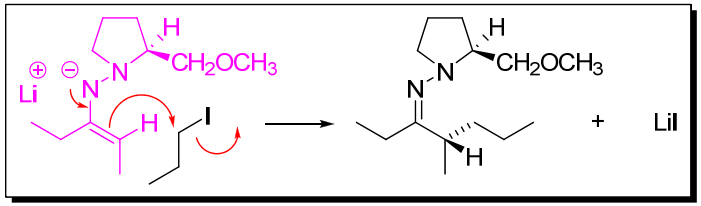
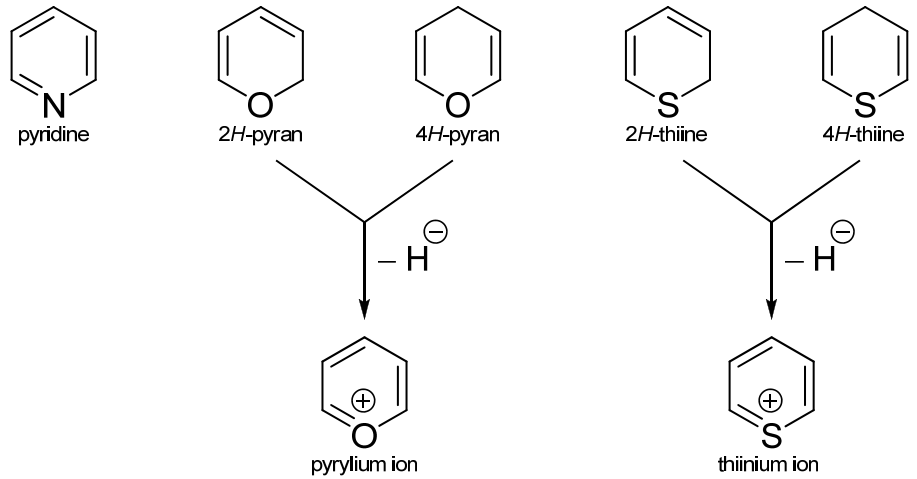


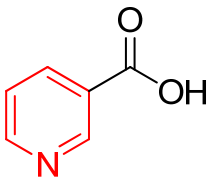




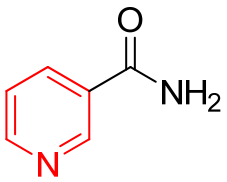


Six-Membered Heterocycles

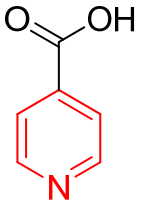




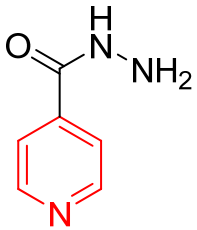
nicotinic acid



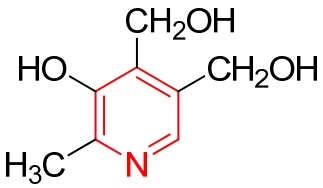
nicotinamide



isonicotinic acid

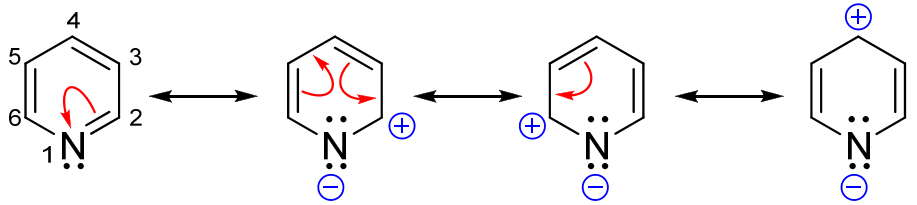


isoniazide



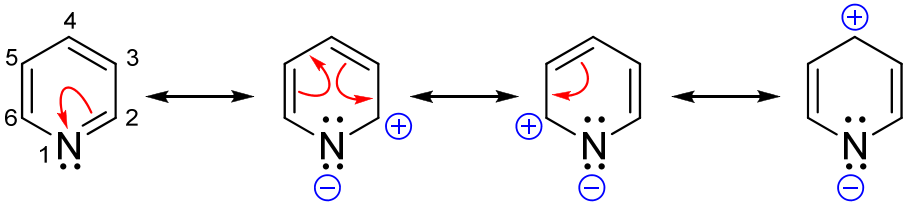
pyridoxine

Pyridine

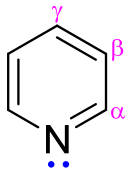


- Three canonical structures.
- The π-electron density is lowest on the 2, 4 and 6 C-atoms, and highest on the N-atom.

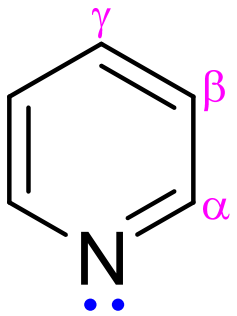
Reactions of Pyridine



- Reaction with electrophiles (E).
- Reaction with nucleophiles (Nu).

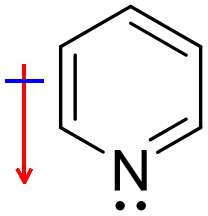


Reactions of Pyridine



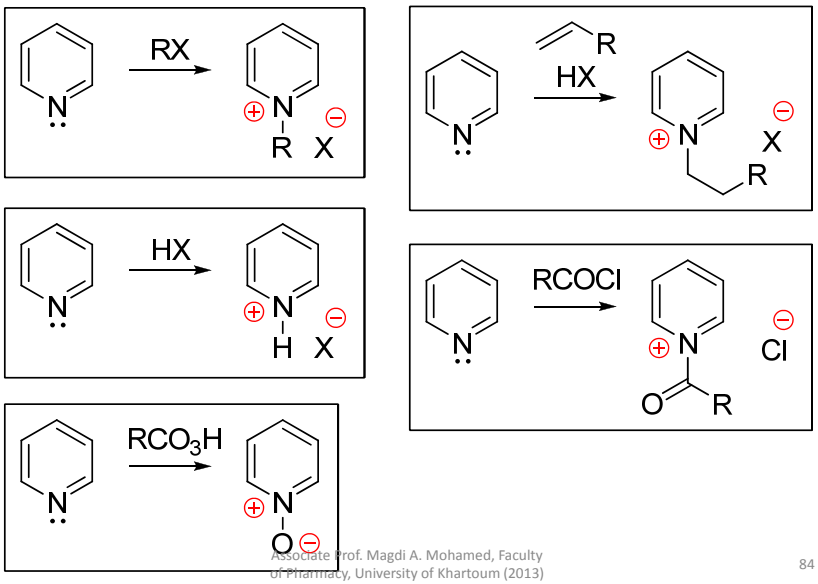
- Electrophilic reagents (E) attack preferably at the N-atom and at the β-C-atoms.
- Nucleophilic reagents (Nu) prefer α-and γ-C-atoms.

Effect of N-atom on the Reactivity of Pyridine

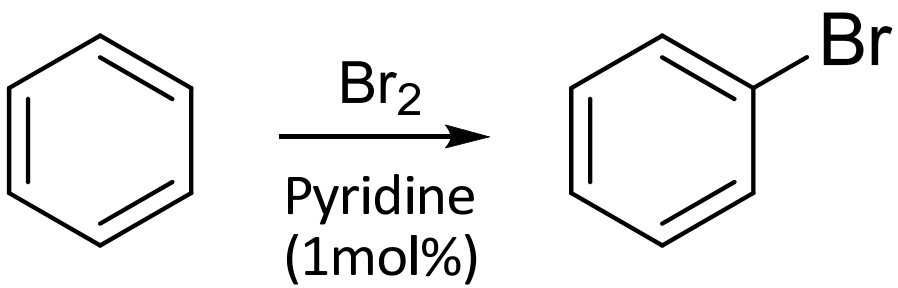


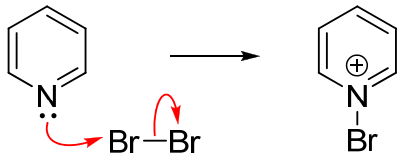
- Electron withdrawing atom.
- The ring is electron-deficient.
- Pyridine undergoes electrophilic substitution reactions more reluctantly But nucleophilic substitution more readily than benzene.

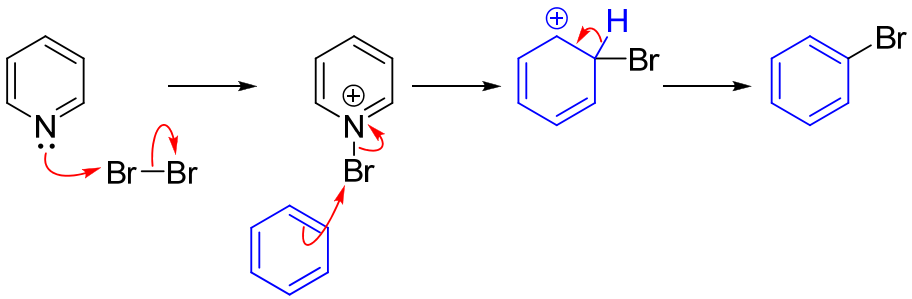
Electrophilic Reactions on Nitrogen

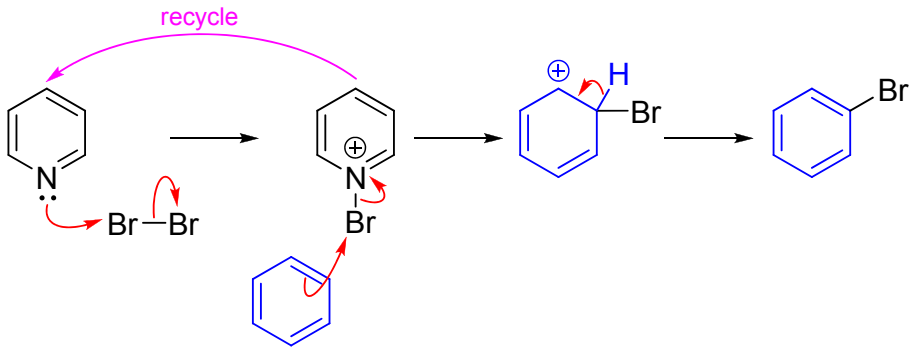


Example (1):



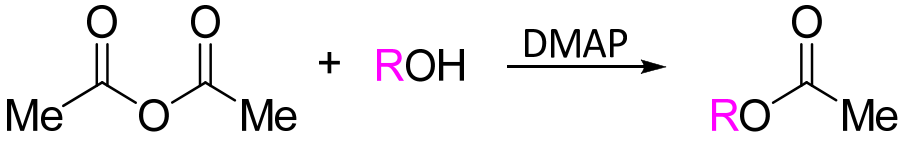




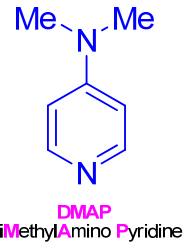


- 1 mol% of pyridine as a nucleophilic catalyst.

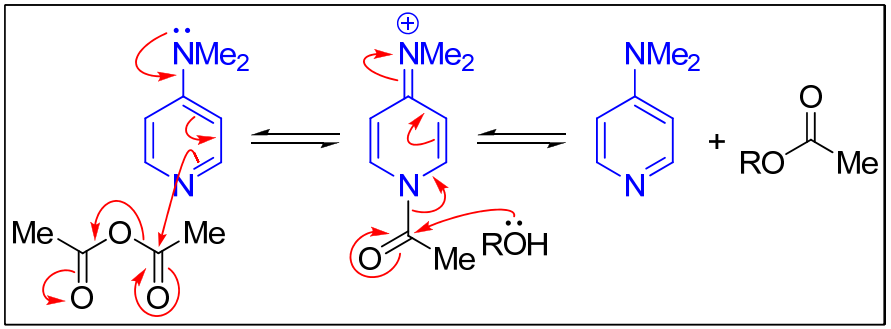
Example (2):



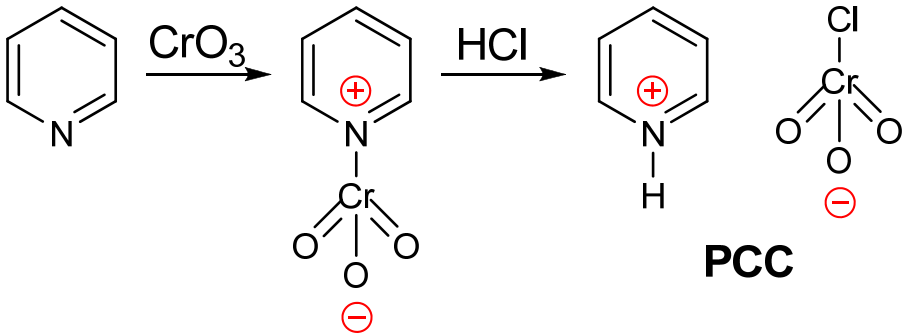
- If (R) is acid-sensitive, an acid-catalyzed esterification will not work.
- A base-catalyzed esterification will result on hydrolysis of the anhydride.
- Activation!!!!!!!!



DMAP
DiMethylAmino Pyridine



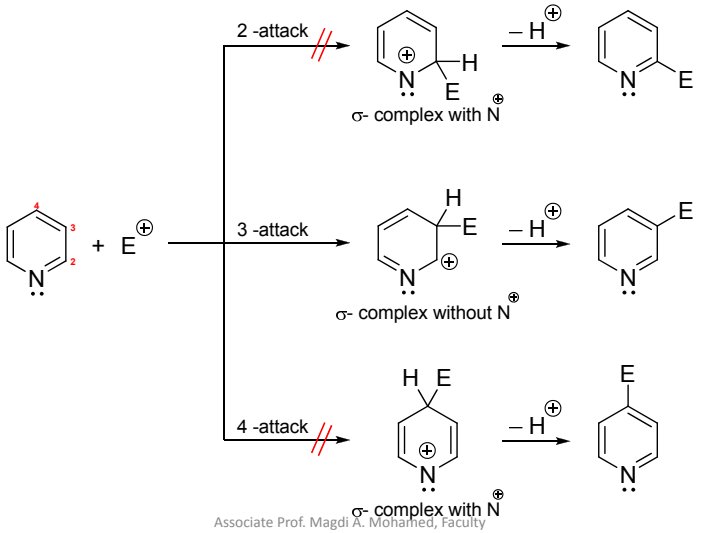
Example (3):



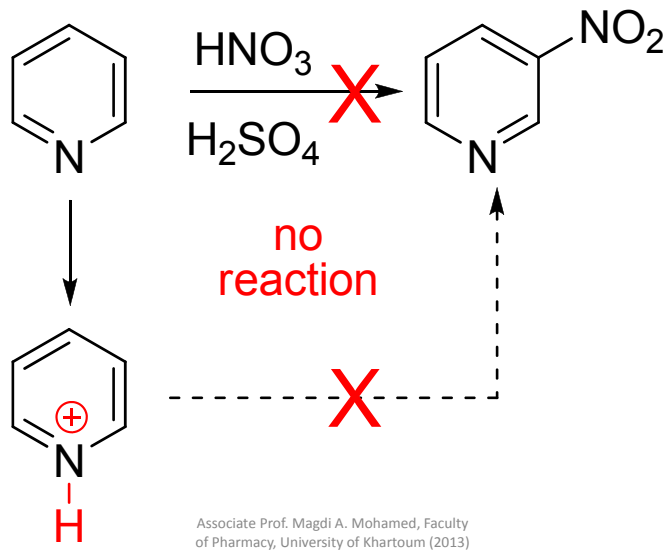
PCC

- Oxidation of primary alcohols to aldehydes.
- Prevent overoxidation.

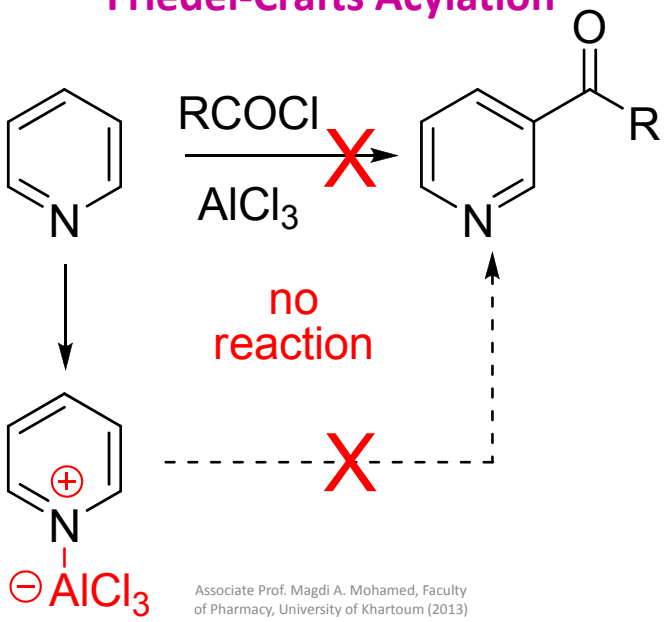
Electrophilic Aromatic Substitution Reactions



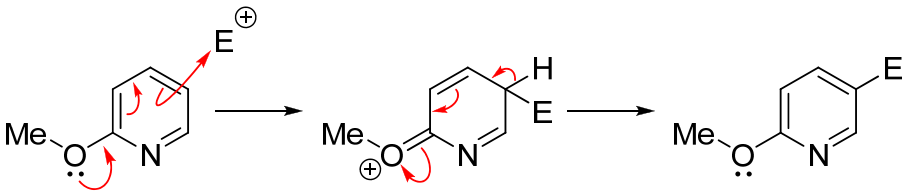
Nitration of Pyridine



Friedel-Crafts Acylation

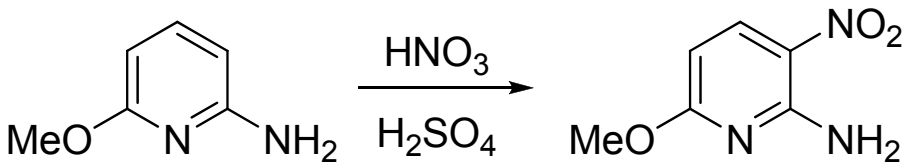


Electrophilic Aromatic Substitutions of Activated Pyridines



- HOMO is the unshared pair of electrons.

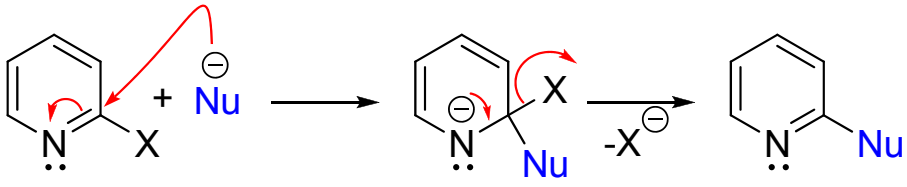
Example:



Nucleophilic Substitution Reactions

- High reactivity (N-atom Lowers LUMO energy).
- Preferably in the 2- and 4-positions and less readily in the 3-position.

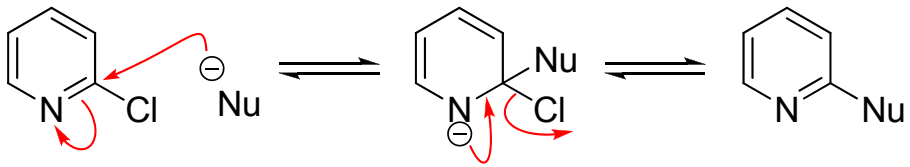
Nucleophilic Substitution Reactions

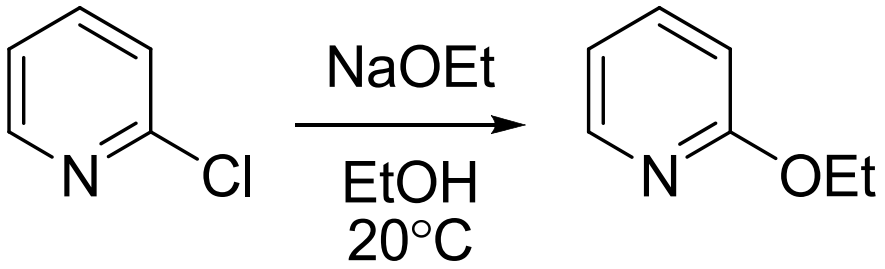


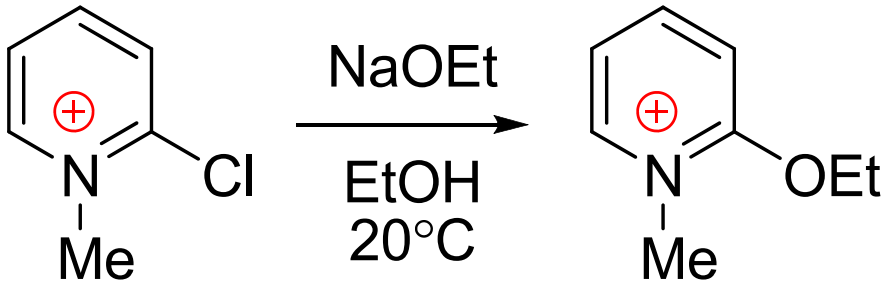
X = halogen, also H.

Nu = NH_2^- , OH^- , RO^- , RS^- , RLi,

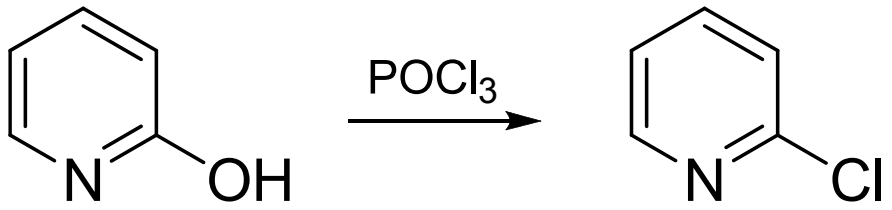
AlH_4^- , NH_3, amines.

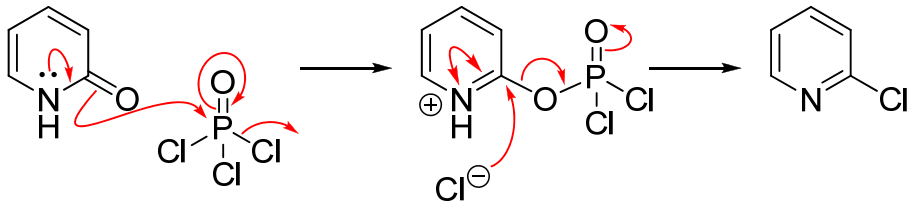


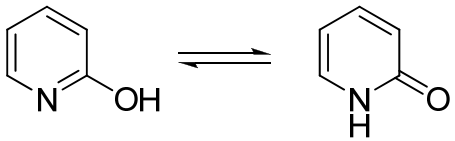


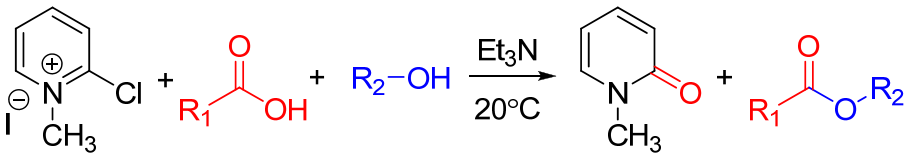


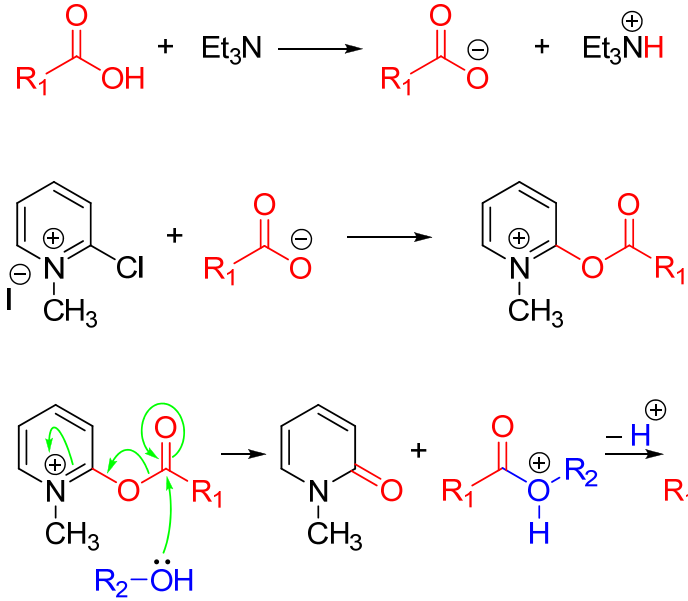
more reactive


POCl3
N
OH
N
Cl

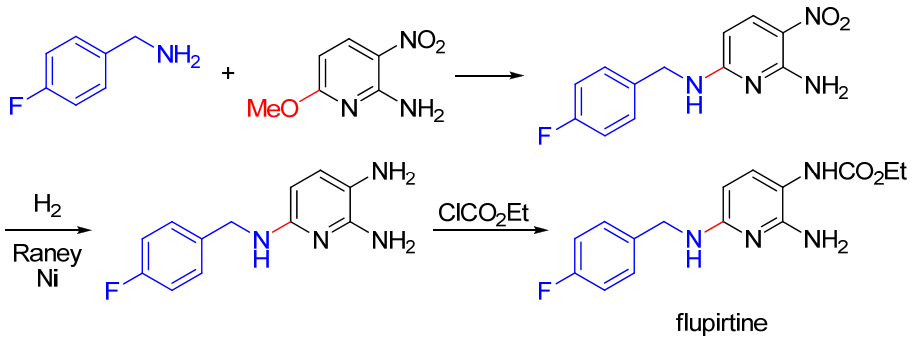

N
H
O
O
P
Cl
Cl
Cl
N
H
O
O
P
Cl
Cl
Cl
N
Cl


N
OH
N
H
O

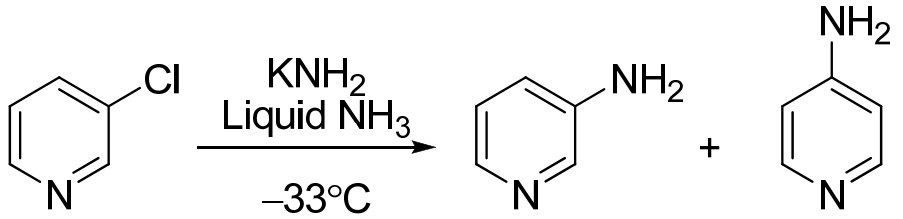

N
CH3
I
Cl
+
R1
O
OH
+
R2–OH
Et3N
20°C
N
CH3
O
+
R1
O
O
R2


R1
O
OH
+
Et3N
R1
O
O
+
Et3NH
N
CH3
I
Cl
+
R1
O
O
N
CH3
O
O
R1
N
CH3
O
R2–OH
+
N
CH3
O
R1
O
R1
O
R2
H
– H
R1
O
O
R2

Synthesis of Analgesic Flupirtine

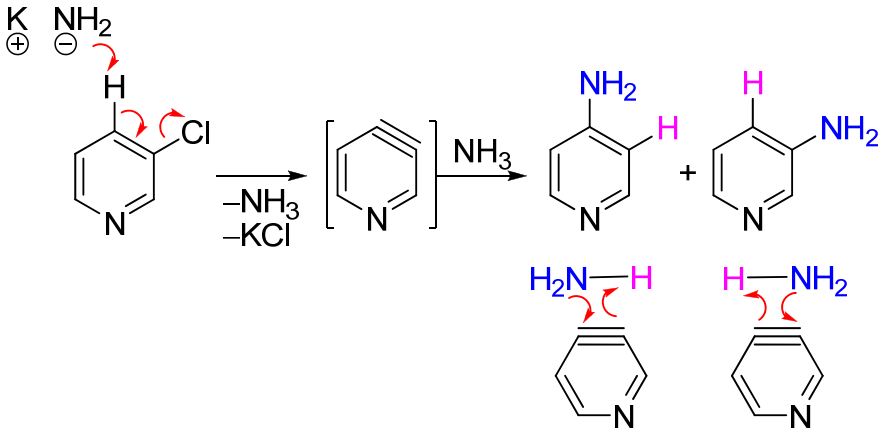


Nucleophilic Substitution Reactions of 3-Halopyridine!!!????

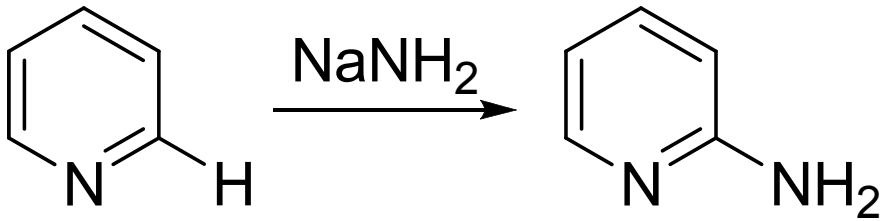


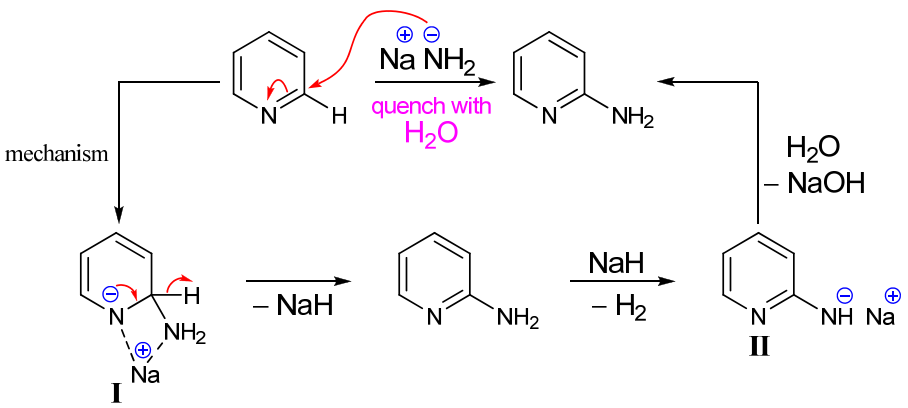
- It can not be a substitution.

Aryne Mechanism

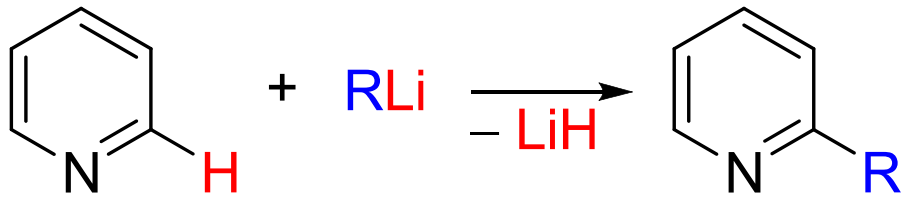


Chichibabin Reaction

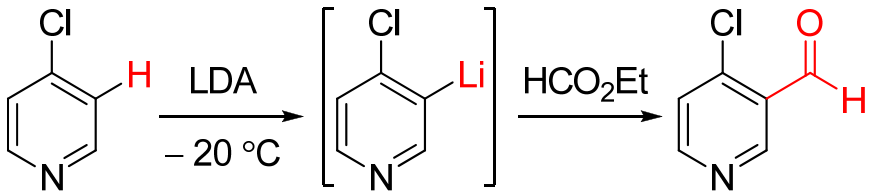


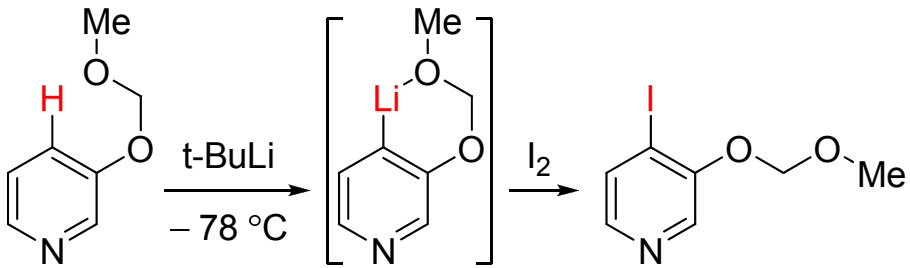


Reaction with Organolithium Compounds

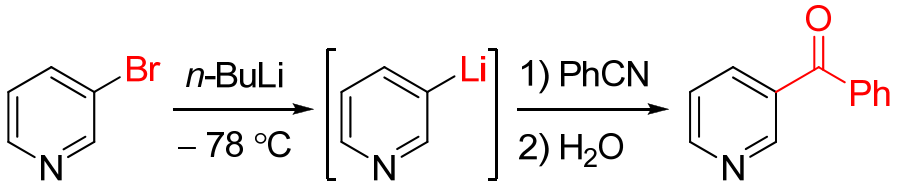


Metalation (H-Metal Exchange)

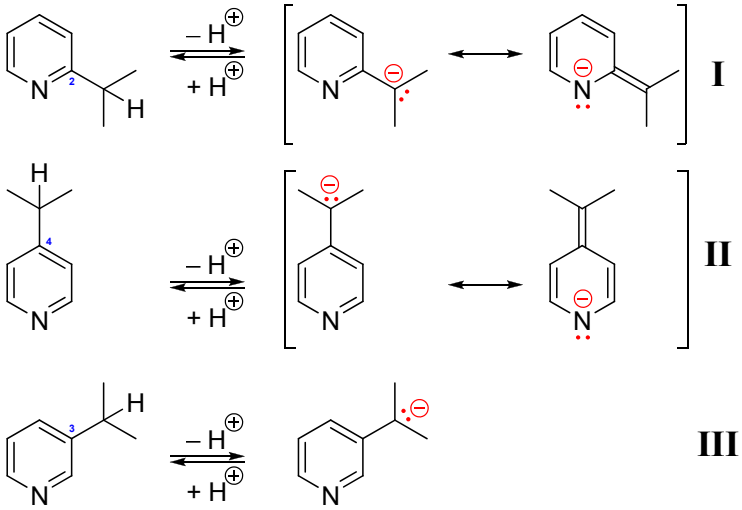




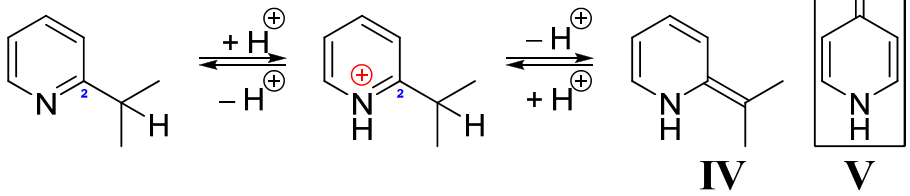
Metalation (Halogen-Metal Exchange)



Side-Chain Reactivity of Pyridine

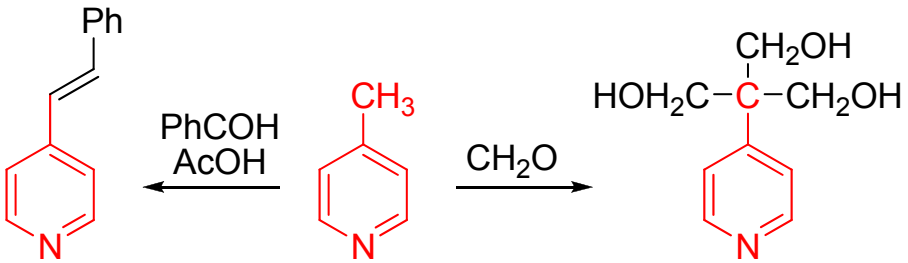


- By strong bases in an aprotic medium.

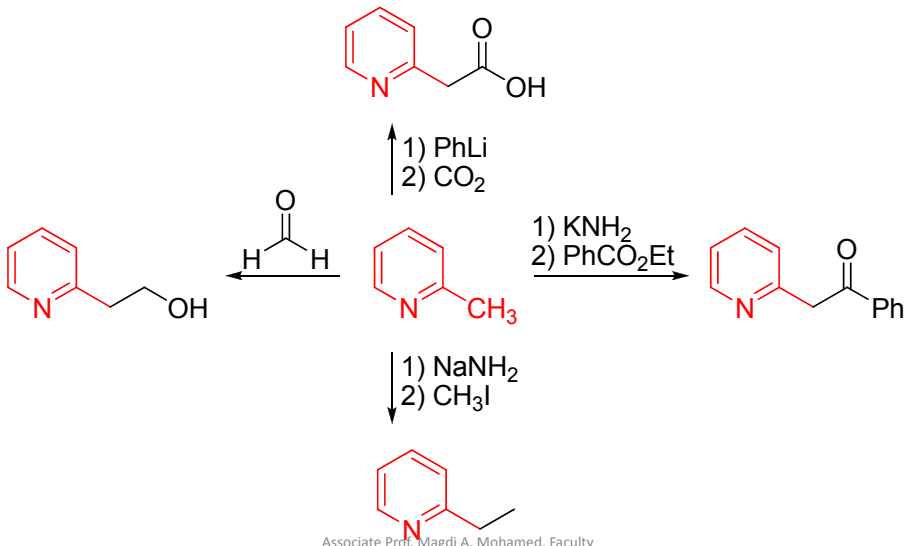


- By weaker bases in a protic medium.

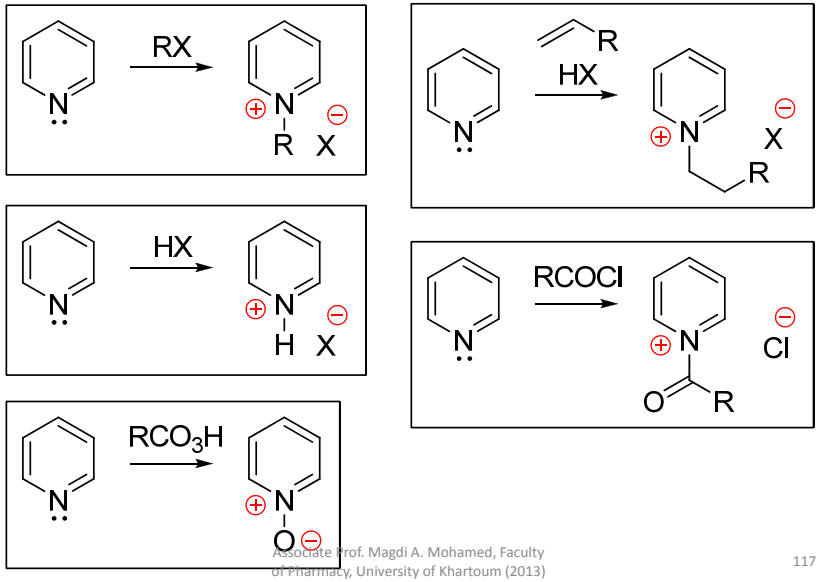
4-Methylpyridine (4-Picoline)



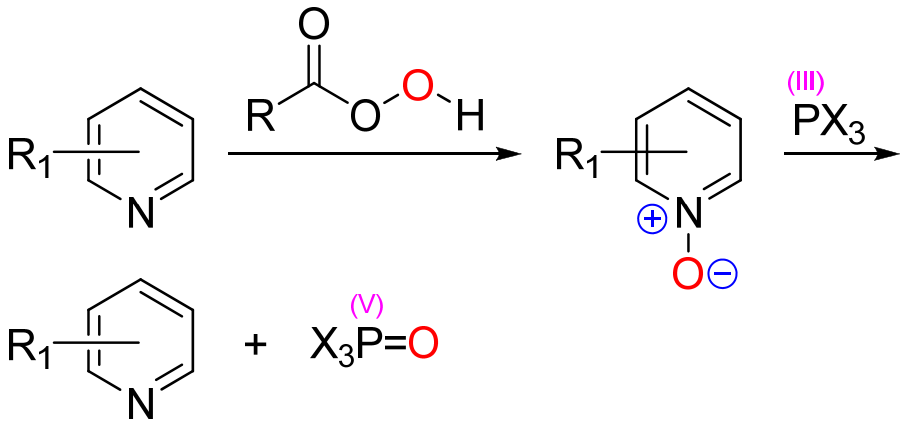
2-Methylpyridine (2-Picoline)

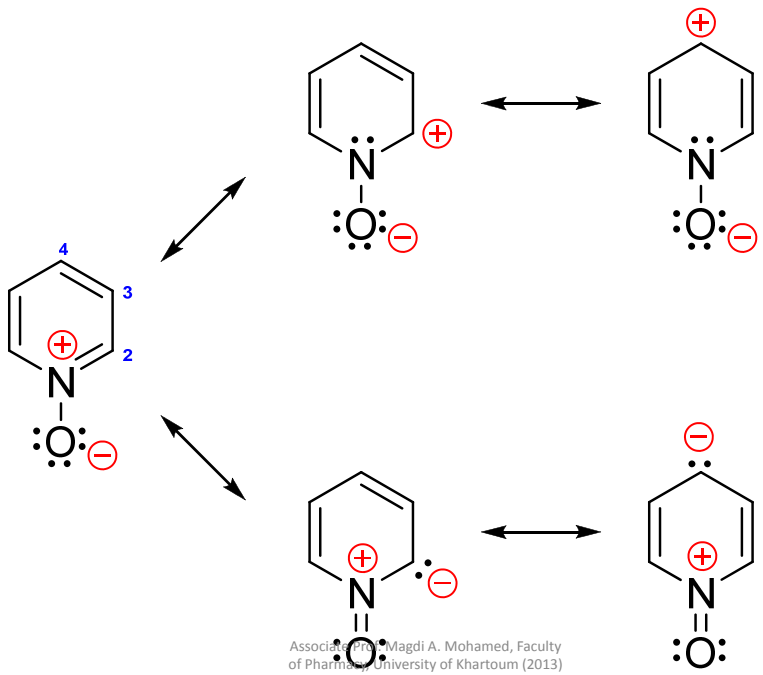


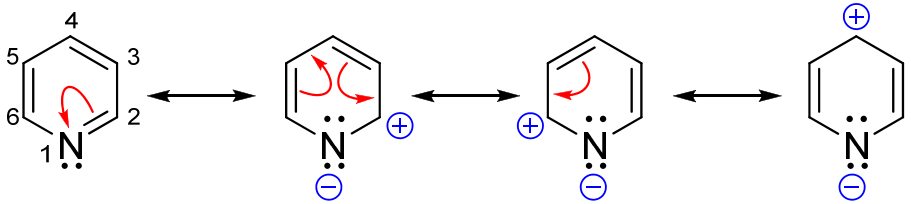
Electrophilic Reactions on Nitrogen



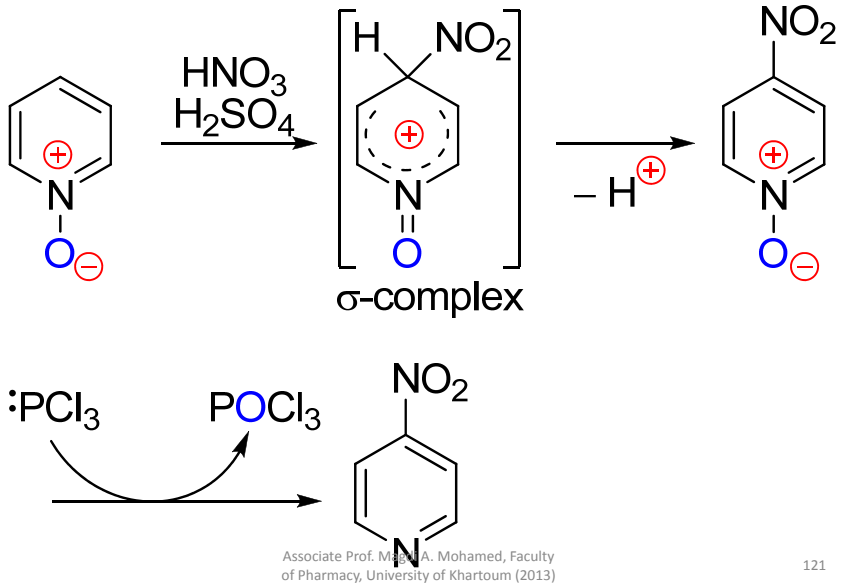
Pyridine-N-Oxide



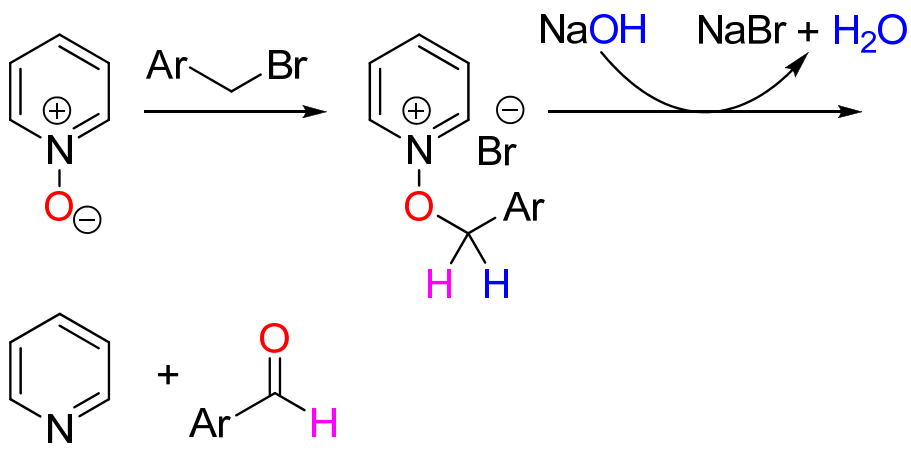




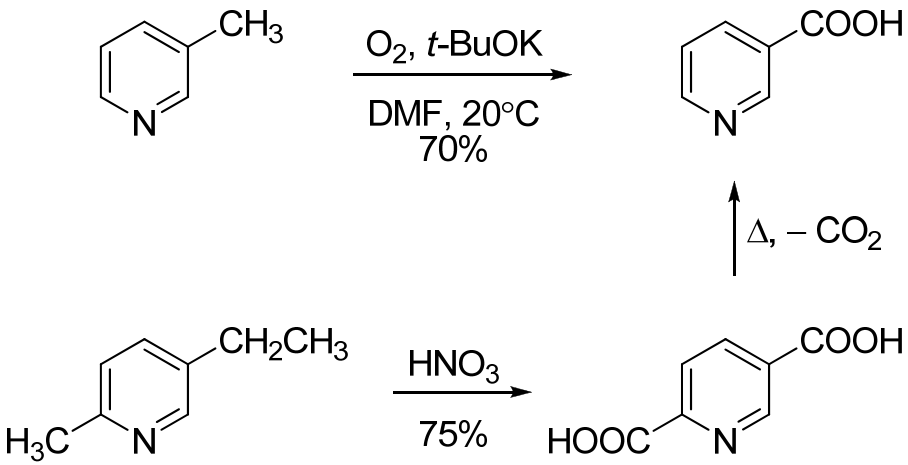
Nitration of Pyridine-N-Oxide



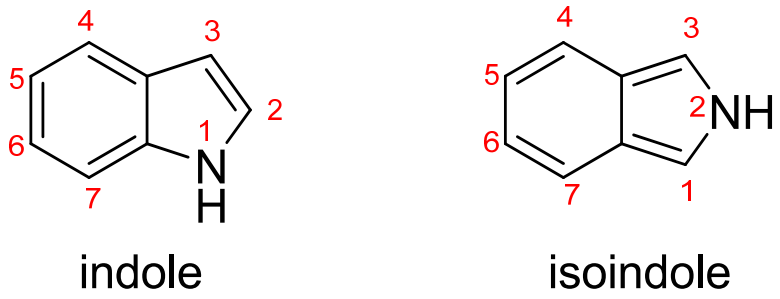
O-Alkylation of Pyridine-N-Oxide



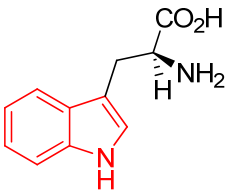
Oxidation of Alkylpyridines



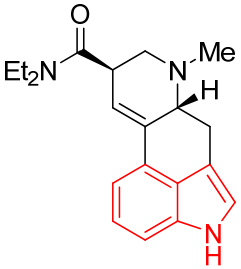
Indoles & Isoindoles



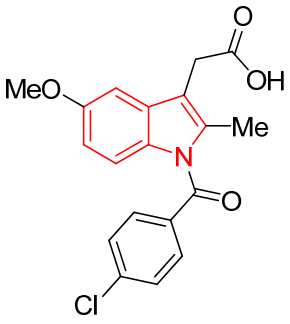
- Benzo-fused pyrroles.
- Indole is benzo(*b*) pyrrole.
- Isoindole is benzo(*c*) pyrrole.



tryptophan



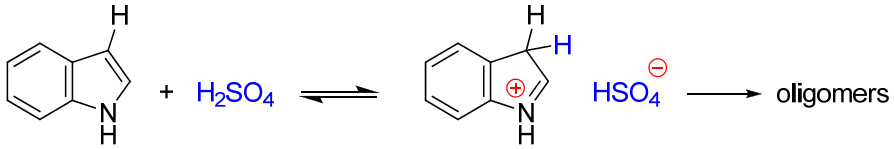
LSD
(Lysergic Acid Diethylamide)



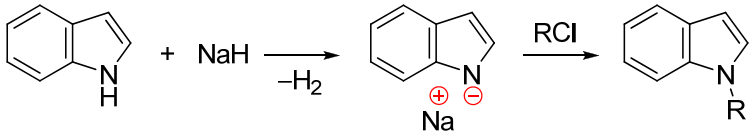
indomethacin

- Protein structure.
- Biologically active Indole alkaloids.
- Important drugs such as indomethacin.

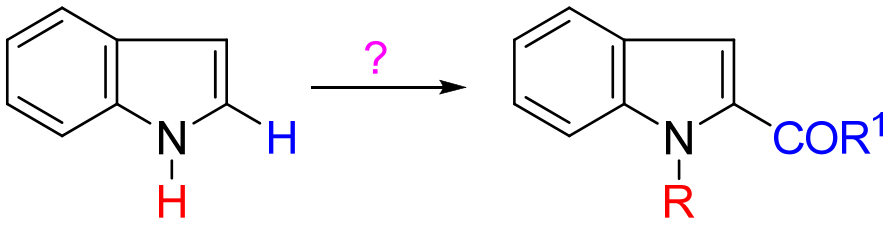
Acidity and Basicity of Indole



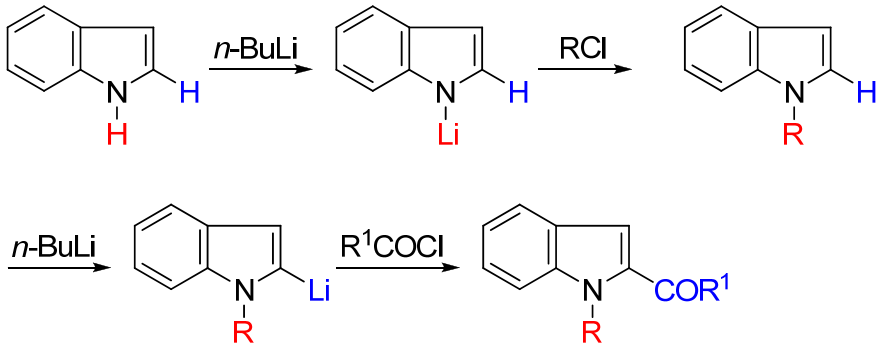
- Not basic.
- Protonation occurs on C-3.



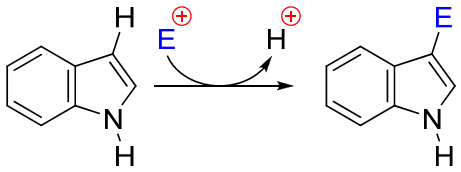
- NH-acidity.
- Deprotonation gives strong nucleophile.

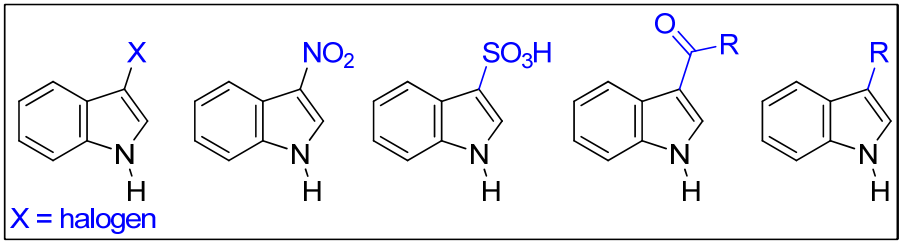


- How can you accomplish the above synthesis?

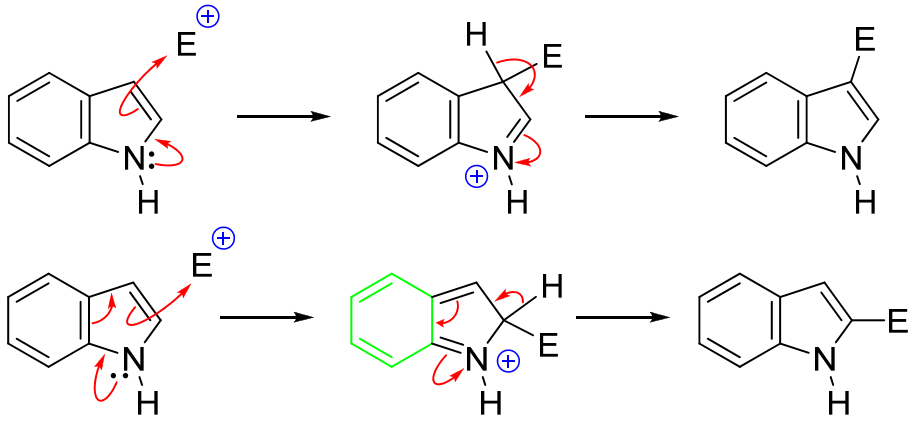


Electrophilic Aromatic Substitution Reactions (E.A.S.)

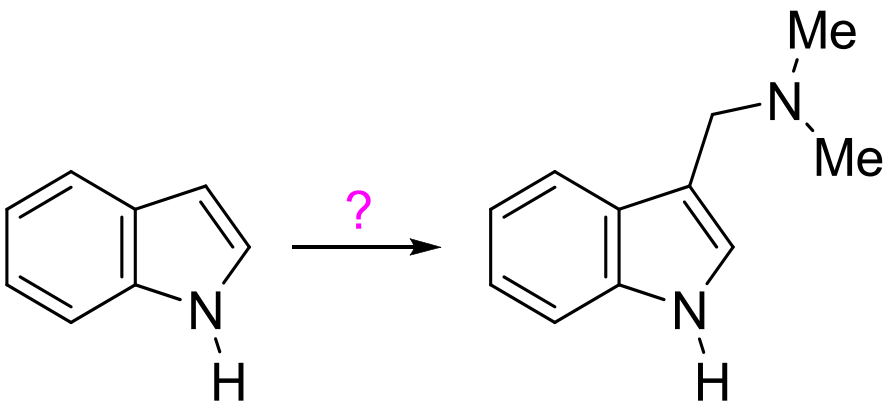




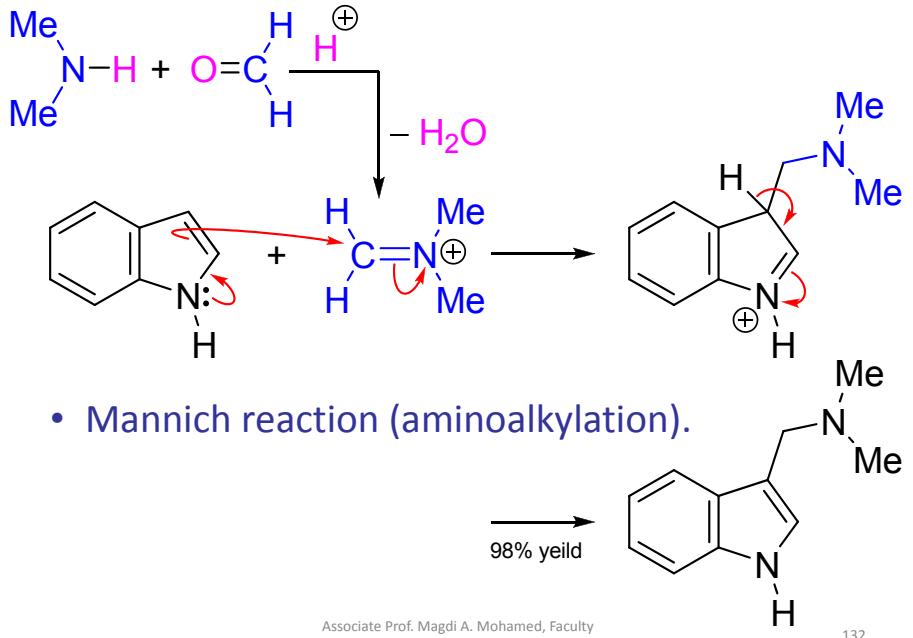
Regioselectivity?



- Pyrrole is more reactive than benzene!
- 3-position is favored over 2-position (why)

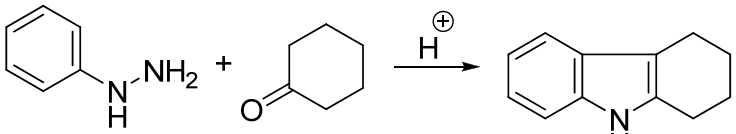


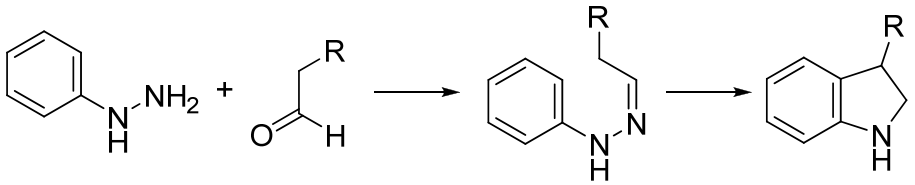
- How can you convert indole into the product shown above.



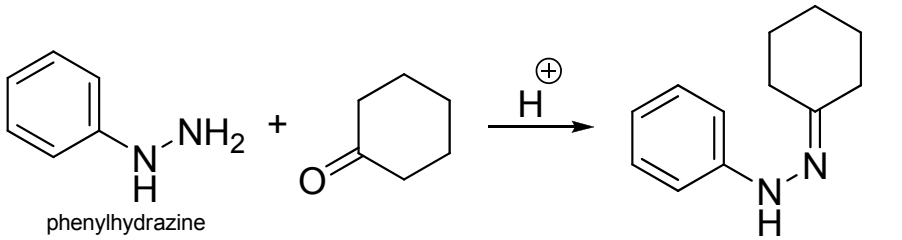
- Mannich reaction (aminoalkylation).

Fischer Indole Synthesis



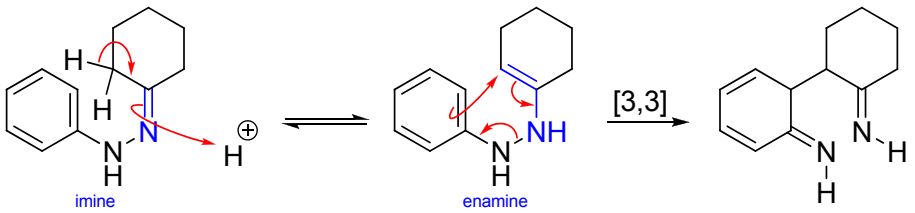


Mechanism



phenylhydrazine

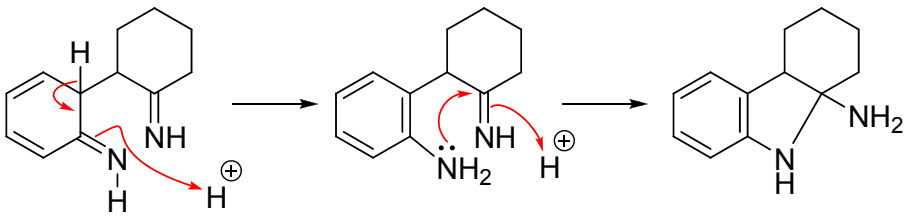
cyclohexanone phenylhydrazone

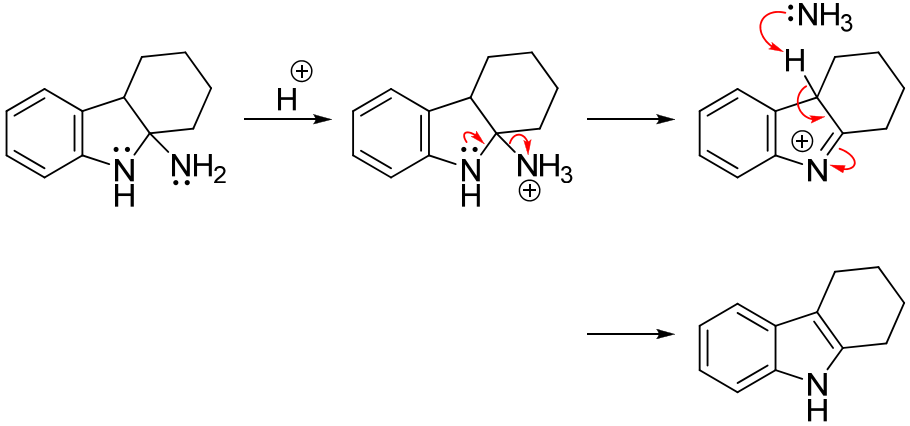


imine

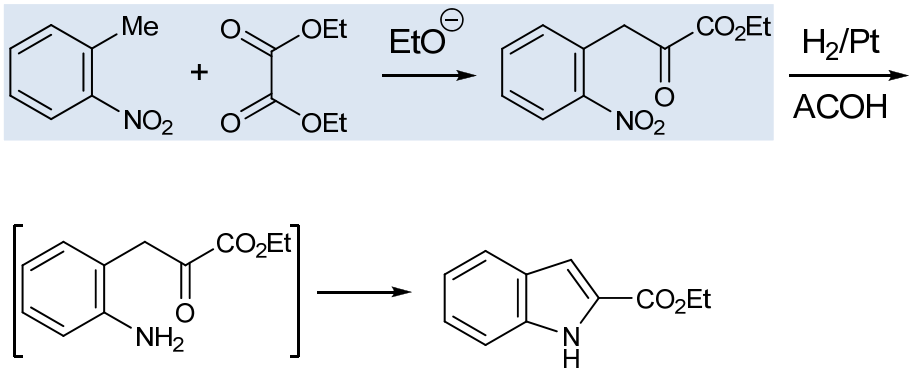
enamine

[3,3]

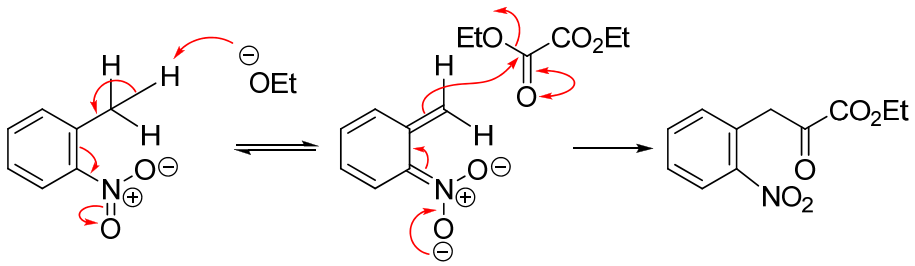




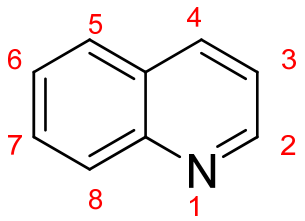
Reissert Indole Synthesis



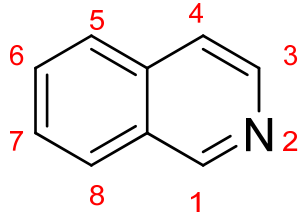
Mechanism



Quinolines & Isoquinolines

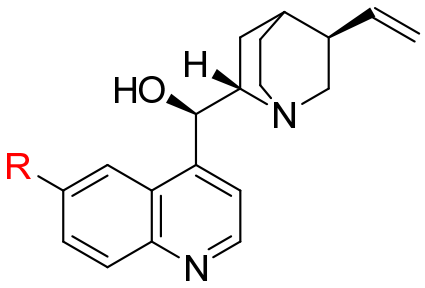


quinoline

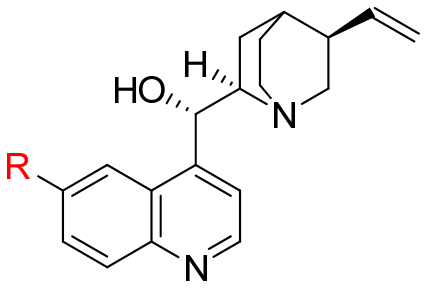


isoquinoline

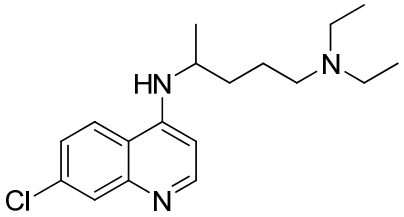
- Benzo-fused pyridines.
- Nitrogen next to the benzene ring: Quinoline.
- Nitrogen in the other possible position: Isoquinoline.



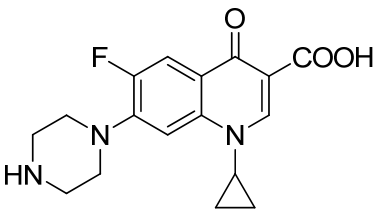
R = H: cinchonidine
R = OCH_3: quinine



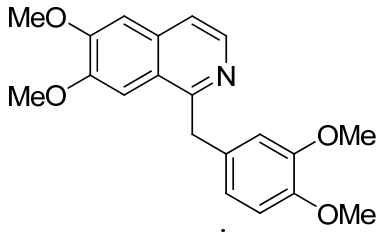
R = H: cinchonine
R = OCH_3: quinidine



chloroquine



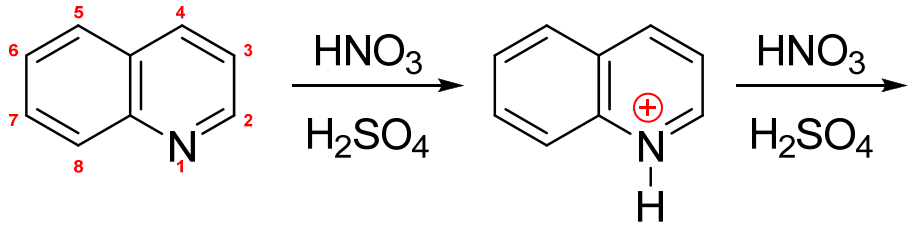
ciprofloxacin

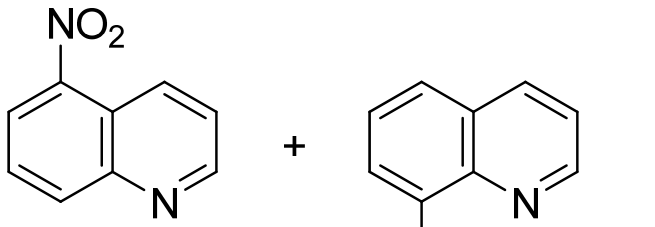


papaverine

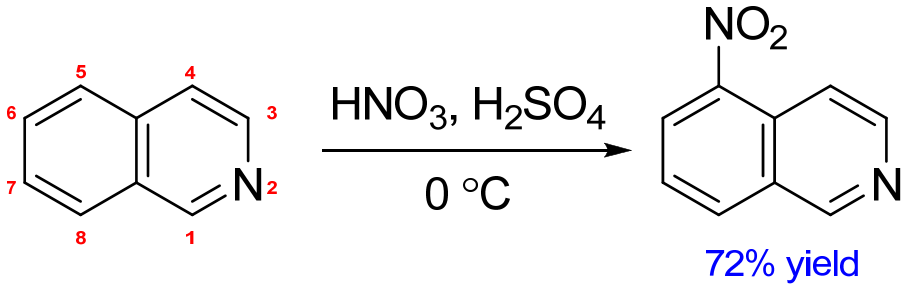
Electrophilic Substitution Reactions

- As in pyridine, it is the nitrogen in quinoline which undergoes protonation, alkylation, acylation and, with peroxyacids, oxidation to the N-oxide.
- The electrophilic aromatic substitution reactions occur on the ring C-atoms, preferentially on those of more activated benzene moiety.



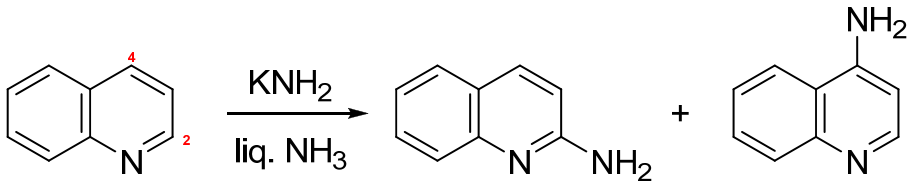


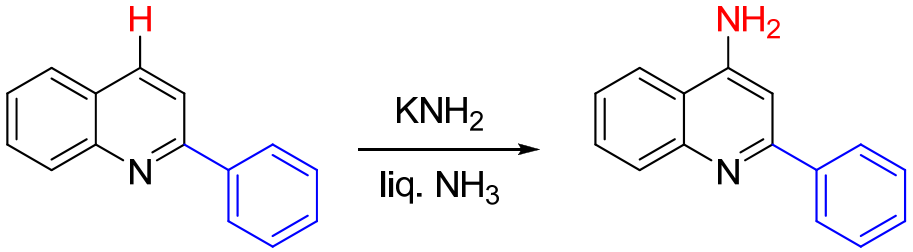
50% yield 42% yield

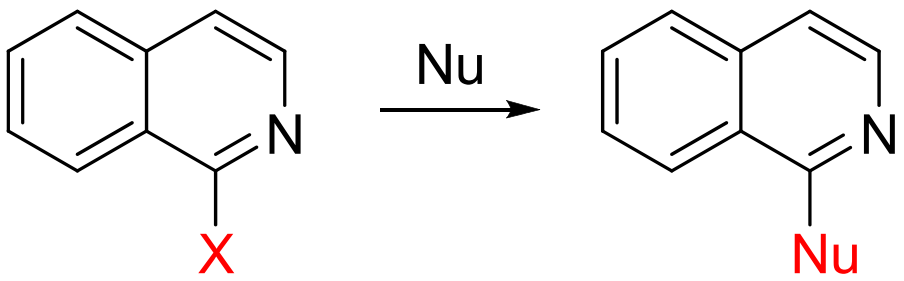


Nucleophilic Substitution Reactions

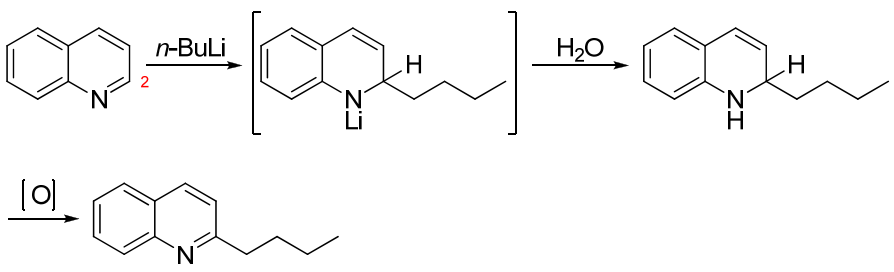
- Nucleophilic substitution reaction of quinoline occurs in the hetero ring, as a rule in the 2- or 4- position.
- Nucleophilic substitution reactions proceed faster in quinoline than in pyridine, because the fused benzene ring stabilizes the addition products by conjugation.



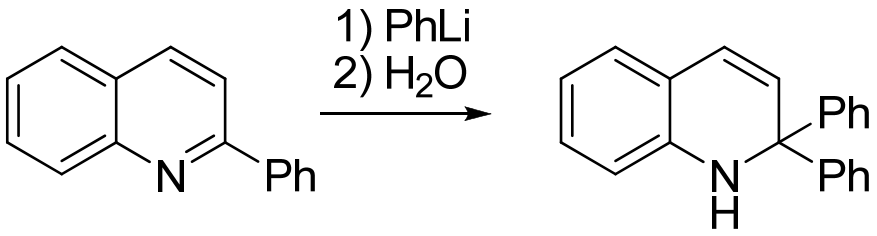




Reaction with Organolithium Compounds

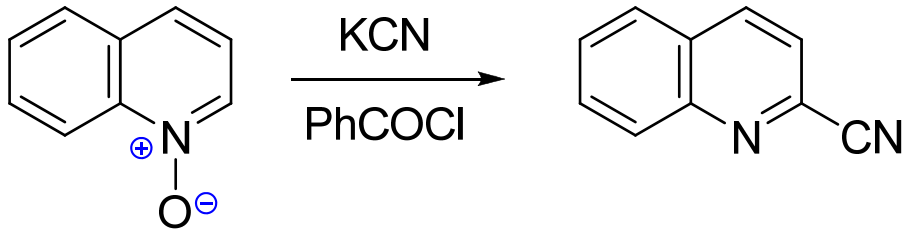


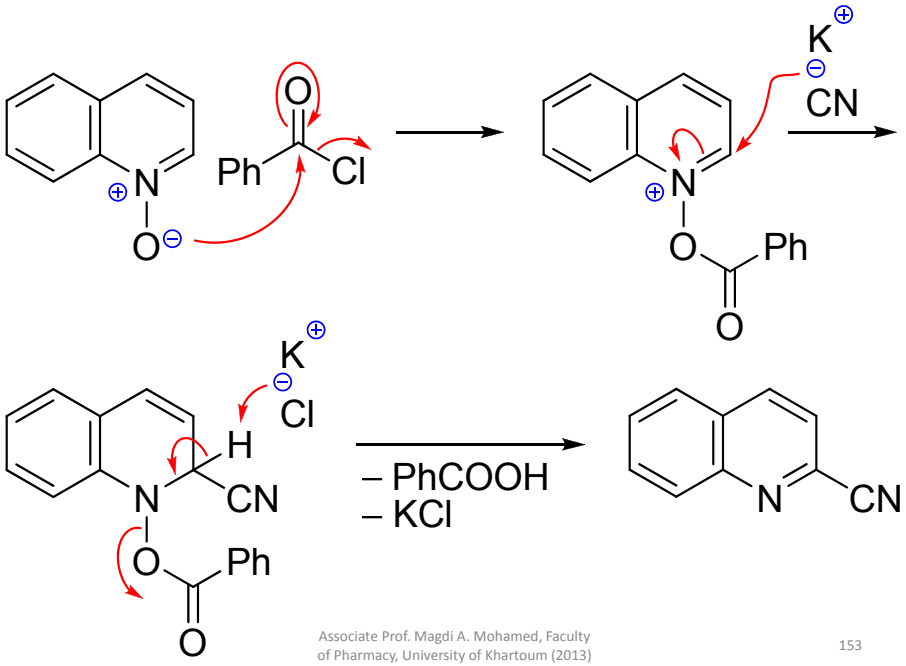
- The reaction of quinoline with organolithium compounds leads exclusively to 2-alkyl or 2-arylquinolines (addition product).



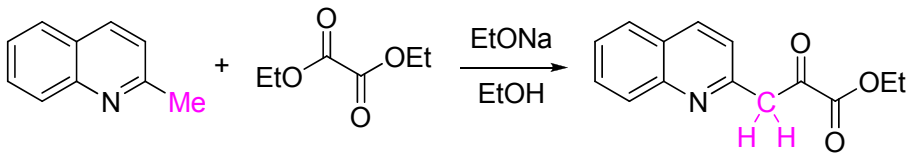
- The control of the organolithium addition occurs through coordination, because even 2-substituted quinolines yield mainly 2-addition products.

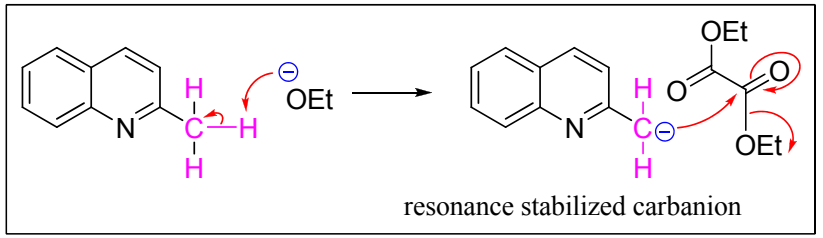
Nucleophilic Substitution of Quinoline-N-Oxide



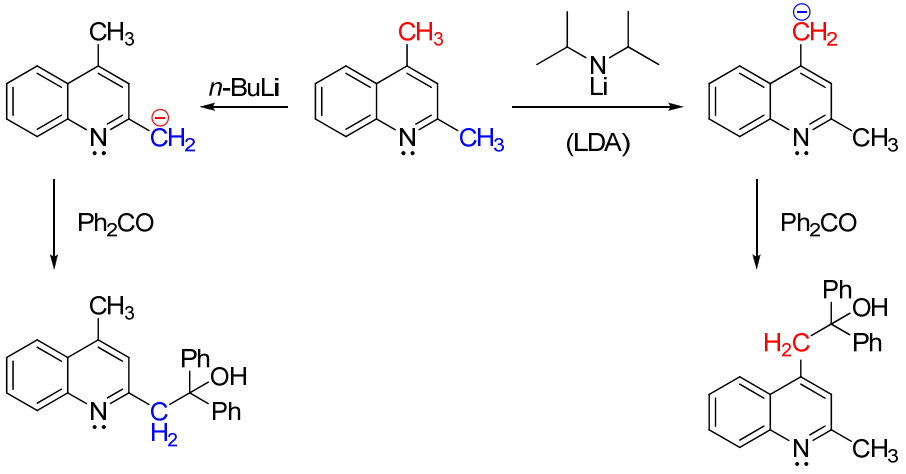


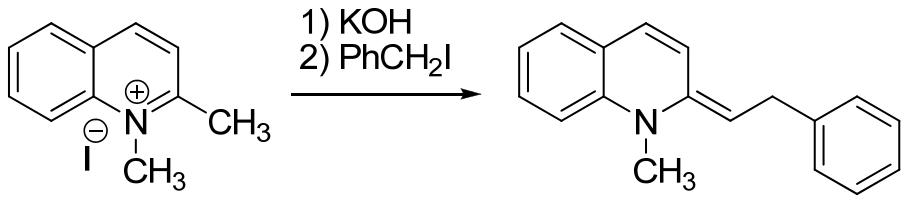
Side Chain Reactivity

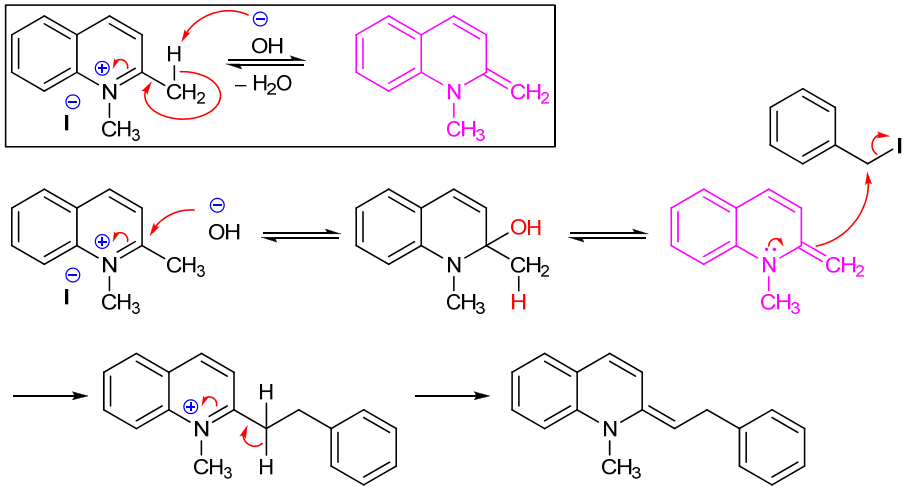




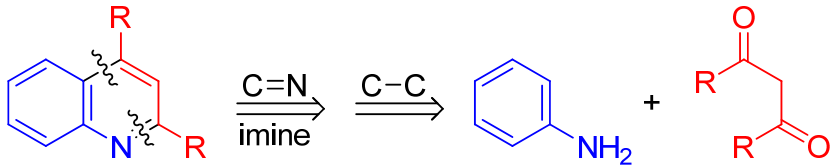
- CH-acidity.
- 4-CH_3> 2-CH_3 >> 3-CH_3.

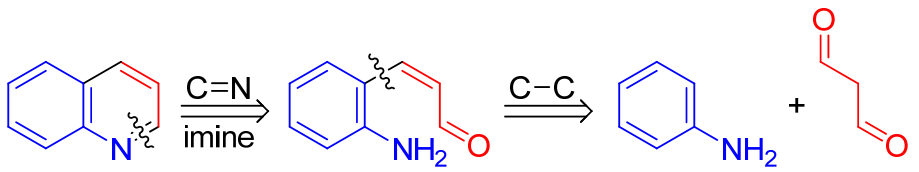


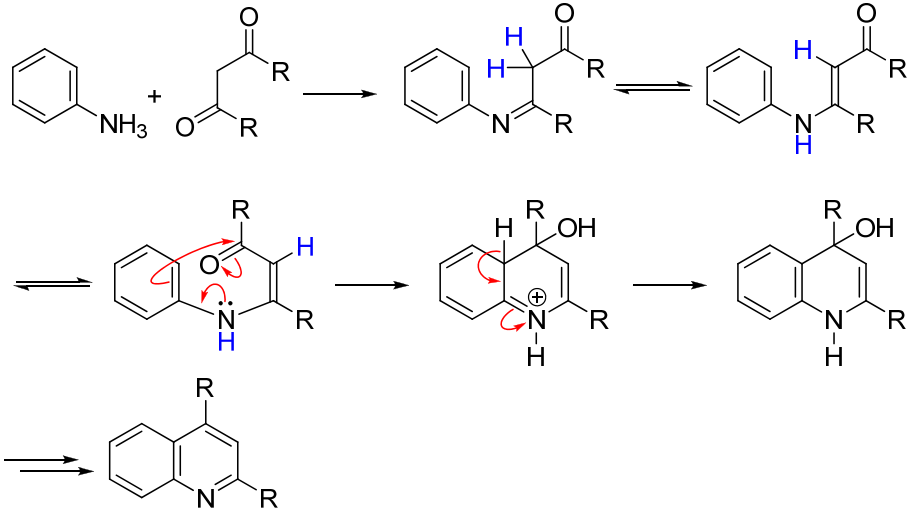


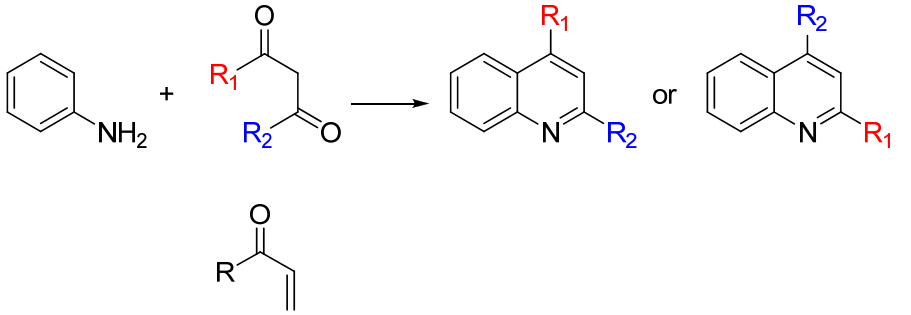


Retrosynthetic Analysis of Quinoline: Disconnection

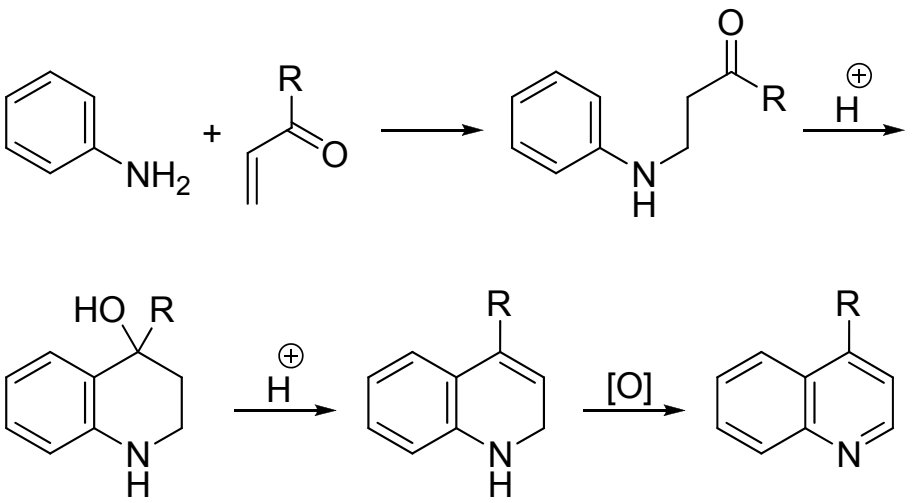




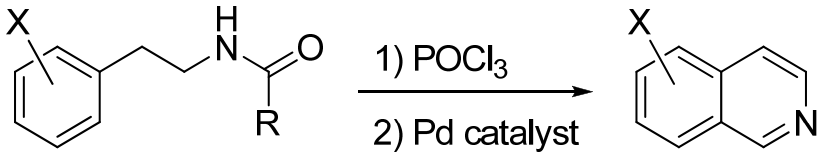




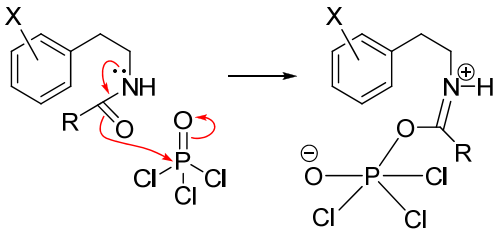
Skraup Synthesis of Quinoline

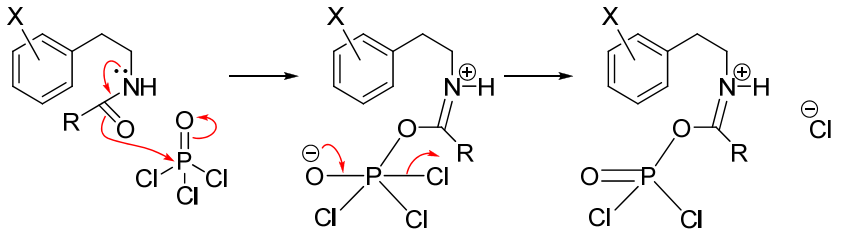


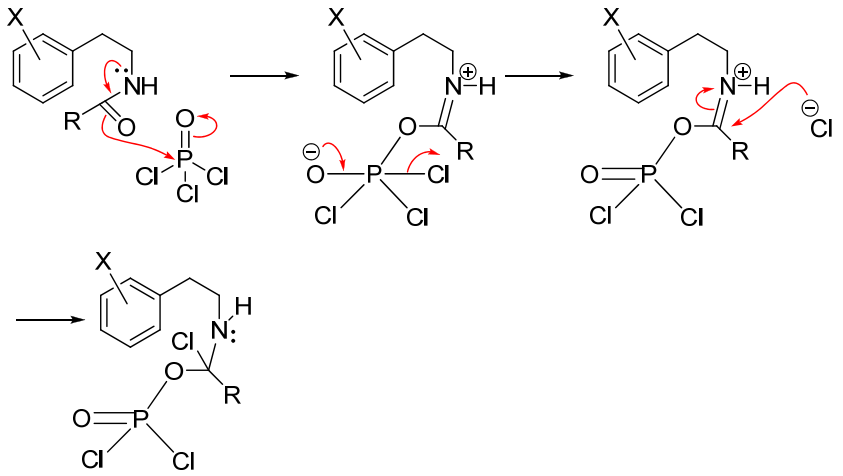
Bischler – Napieralski Synthesis of Isoquinoline

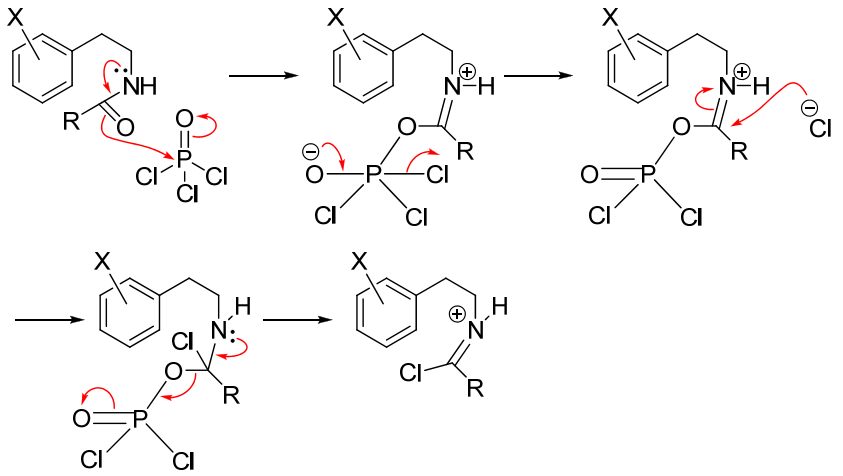


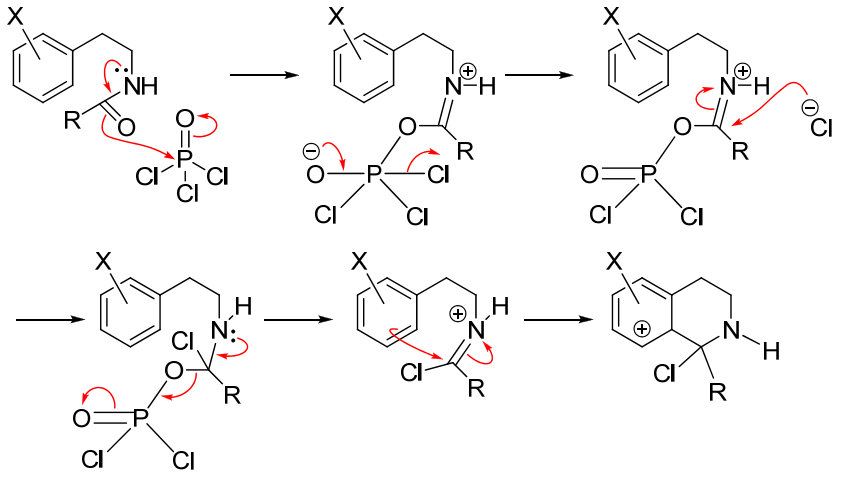
X = electron donating substituent

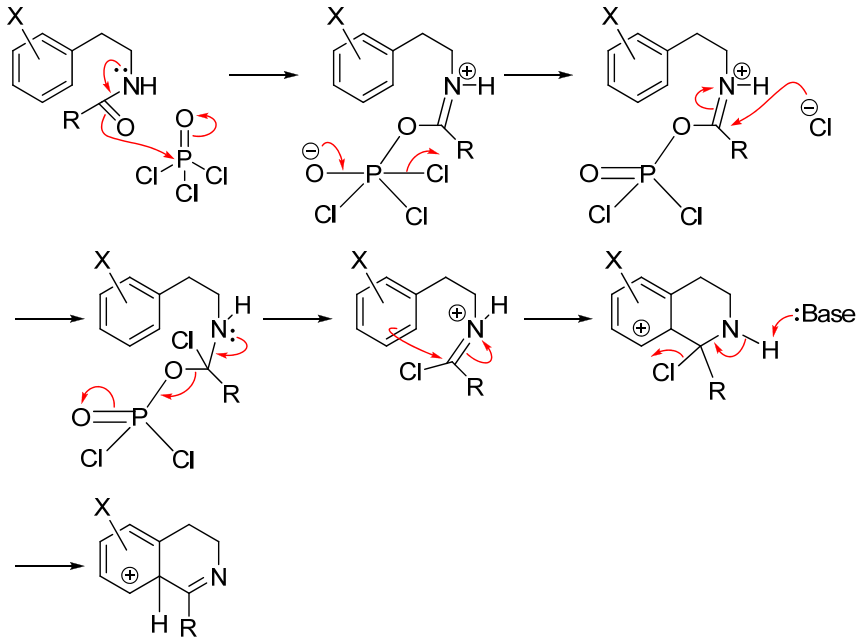


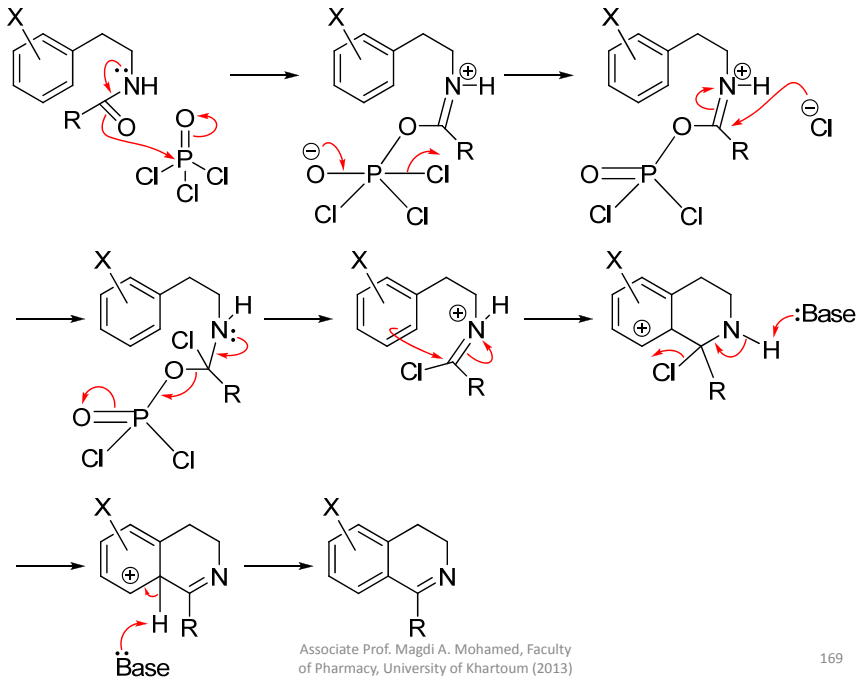


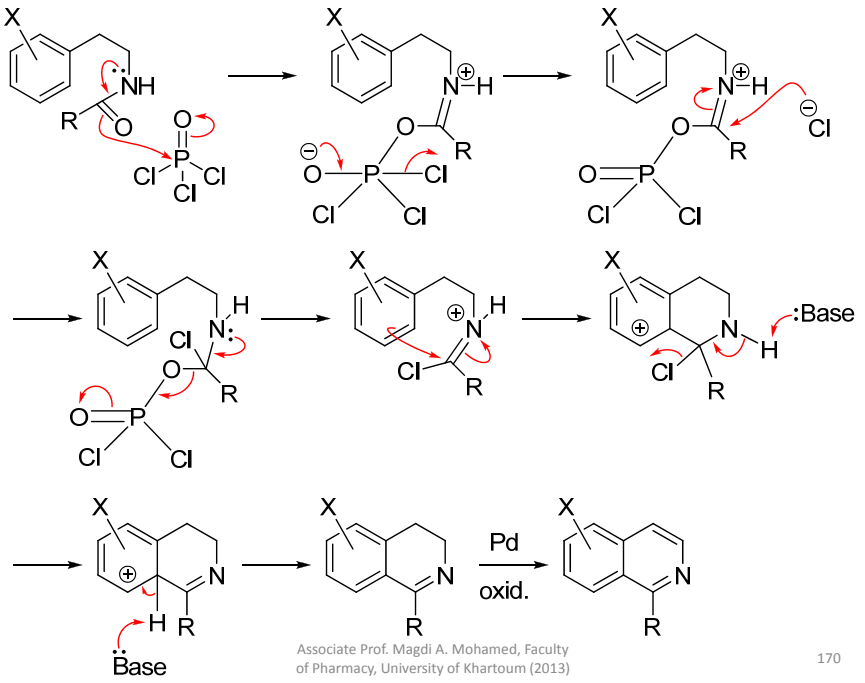







:Base


X
NH
R
O
O
P
Cl
Cl
Cl
N
H
Cl
:Base
Base


X
NH
R
O
O
P
Cl
Cl
Cl
N
H
Cl
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Base
Pd
oxid.