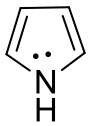
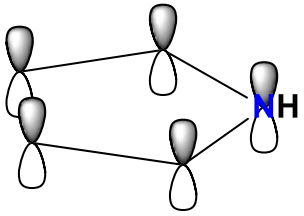
2.2.1. Comparison between pyrrole and pyridine

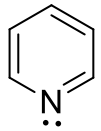


5 membered ring
electron rich

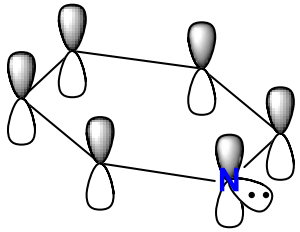


N is not basic (cannot be protonated)
lone pair is integral part of the aromatic system

why electron rich?
for benzene: 6 π electrons on 6 atoms
here: 6 π electrons on 5 atoms
-> higher electron density



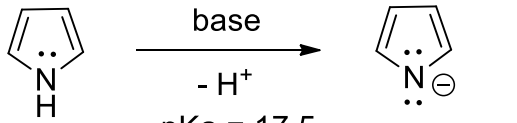
6 membered ring
electron poor



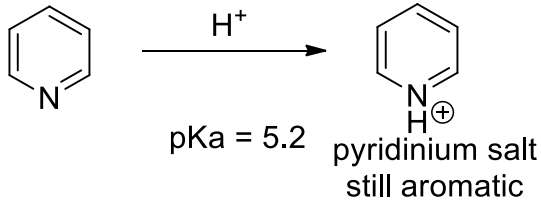
N is basic (can be protonated)
lone pair available; orthogonal to the aromatic system

why electron poor?
6 π electrons on 6 atoms
N has a higher electronegativity than carbon
and pulls elctrons

- Examples:



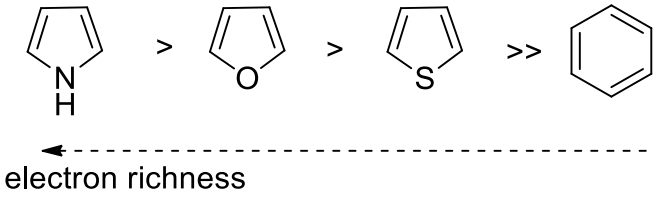
Pyrrole can be deprotonated



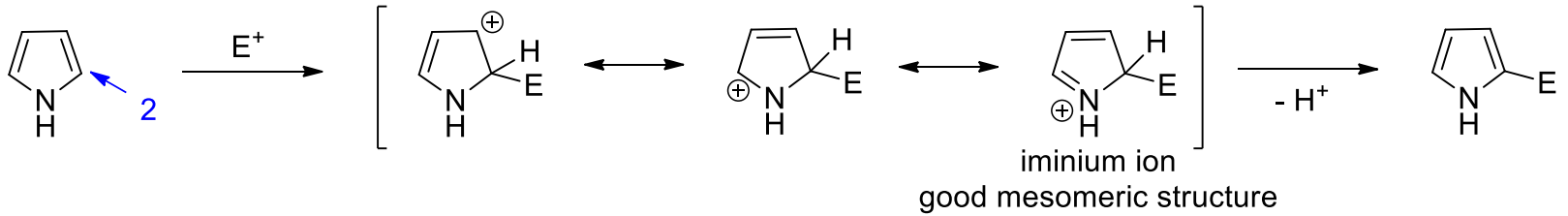
Pyridine can be protonated

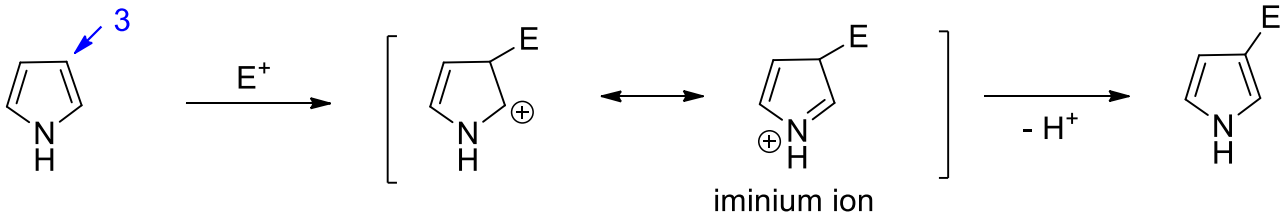
2.2.2. Reactivity of electron rich heteroaromatics

- S_EAr for electron rich heteroaromatics:



- The 2-position is the most activated:





One additionnal mesomeric structure possible by an addition to the 2-position

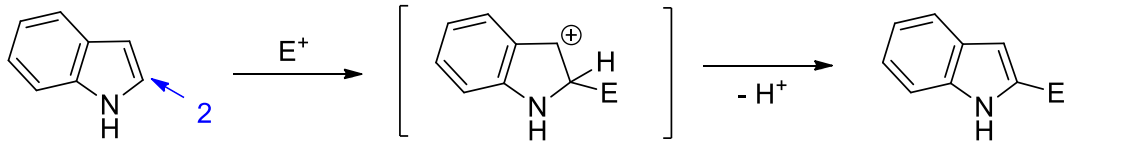
→ better stabilization

Similar reactivity for furane and thiophene

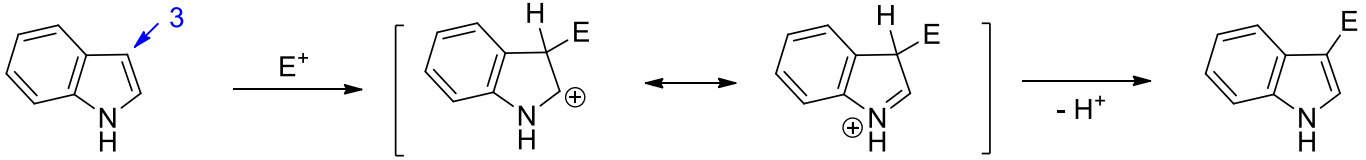
2.2.2. Reactivity of electron rich heteroaromatics

- S_EAr for indole:

- The 3-position is the most activated:

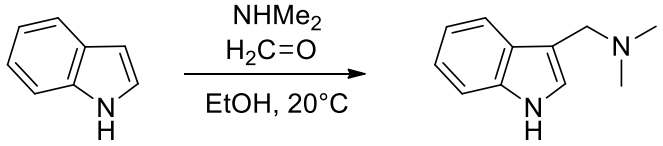


only one mesomeric structure possible without destroying the aromaticity of the annulated benzene ring

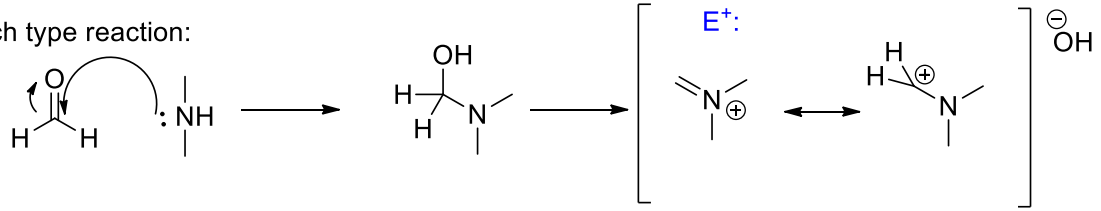


imminium salt
better stabilization

- Example: gramine synthesis

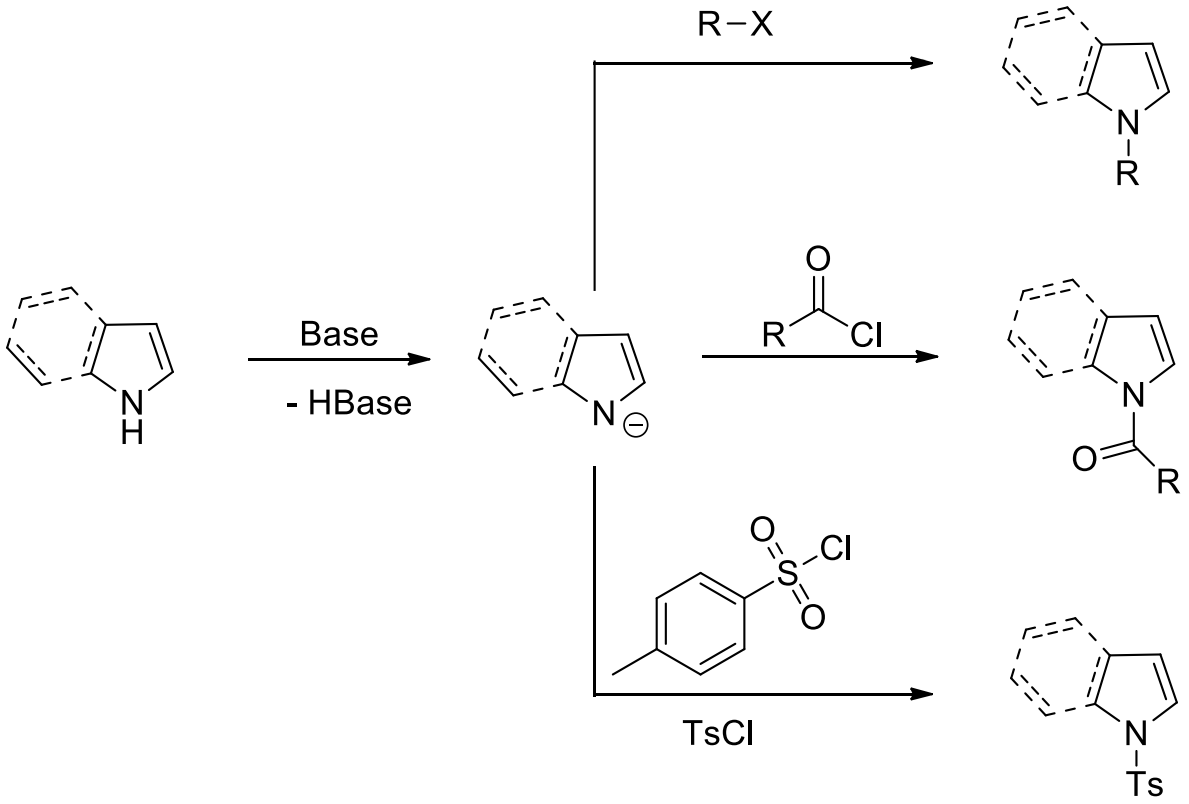


Mannich type reaction:



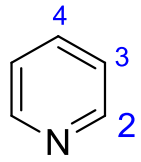
2.2.2. Reactivity of electron rich heteroaromatics

- N-Alkylation / N-Acylation of indoles or pyrroles:



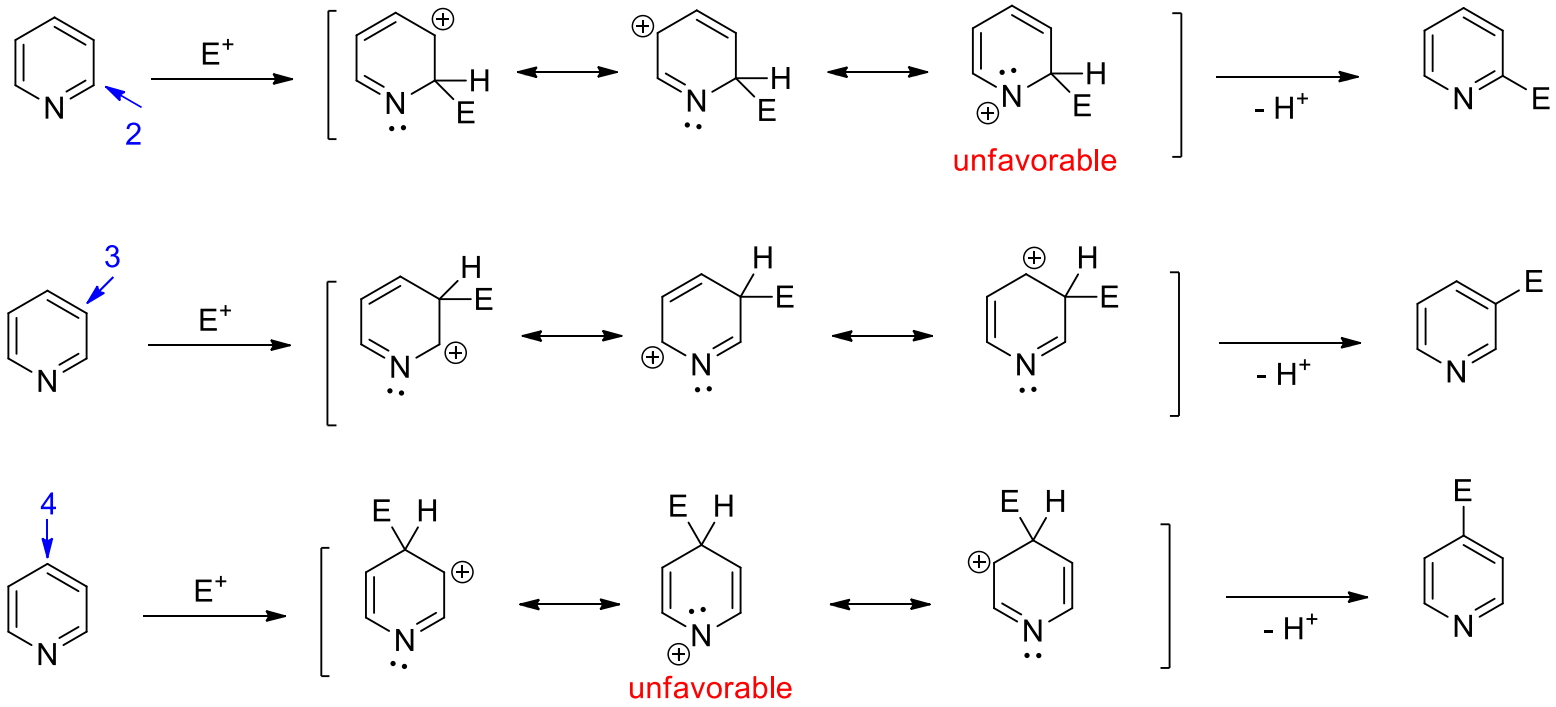
2.2.3. Reactivity of electron poor heteroaromatics

- S_EAr for electron poor heteroaromatics:



Pyridine is electron poor and therefore a very deactivated substrate for S_EAr
All positions are deactivated

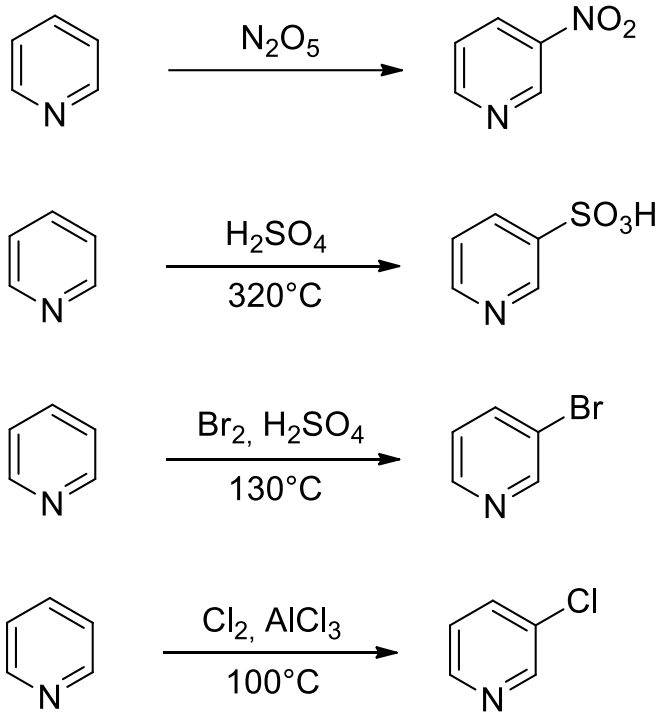
- The 3 position is the least deactivated one and reacts preferentially:



2.2.3. Reactivity of electron poor heteroaromatics

S_EAr on pyridines require forcing conditions:

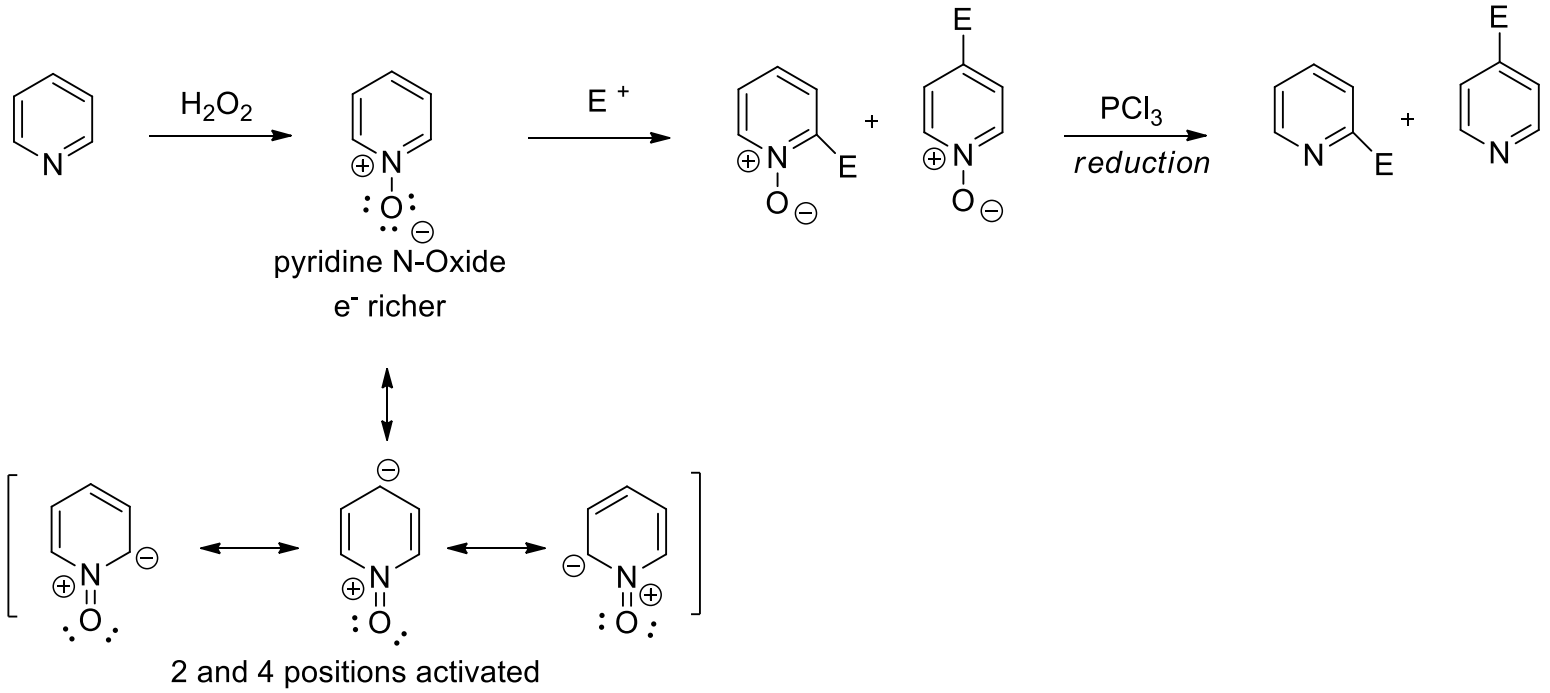
Examples:



2.2.3. Reactivity of electron poor heteroaromatics

- Method to address the 2- and 4-position of pyridine with S_EAr

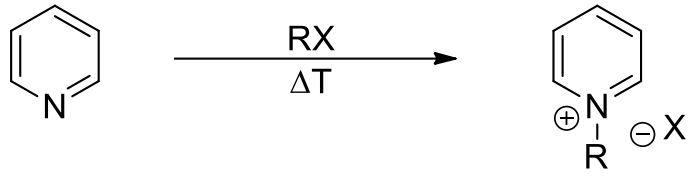
→ oxidation into the more electron rich pyridine N-oxide



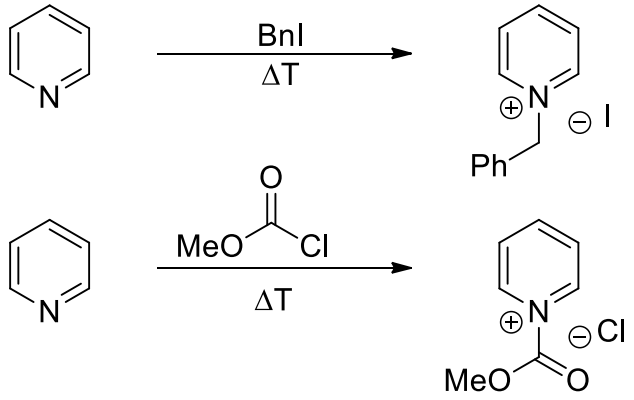
PCl_3 selectively reduces the N-Oxyde and regenerate the original pyridine

2.2.3. Reactivity of electron poor heteroaromatics

- Under forcing conditions the nitrogen atom of the pyridine can be alkylated or acylated to give pyridinium salts:

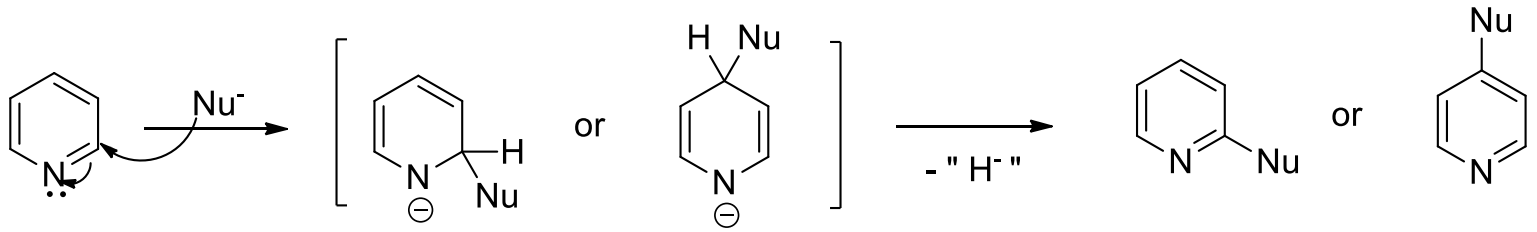


- Examples:

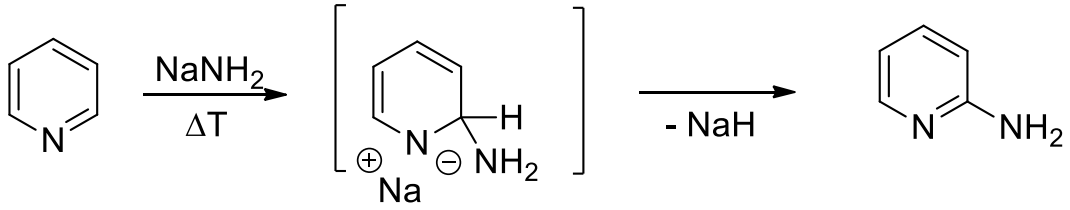


2.2.4. The Tschitschibabin reaction

- The Tschitschibabin reaction is equivalent to S_NAr reaction on a pyridine:



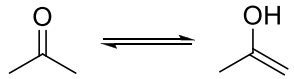
- Example for the synthesis of 2-aminopyridine:



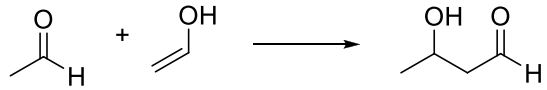
2.3.1. Synthesis of five-membered ring heteroaromatics

- Recapitulation of some relevant carbonyl chemistry

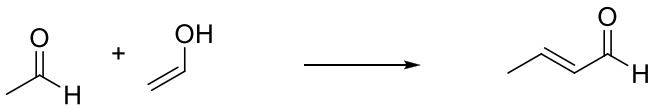
Keto-Enol tautomerization:



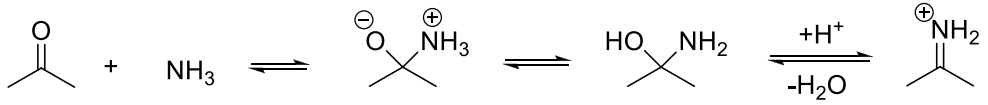
Aldol-addition:



Aldol condensation:

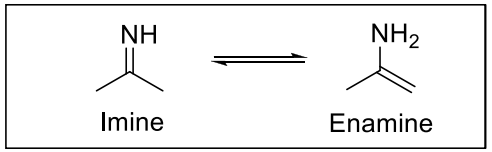


Formation of Iminium ion:



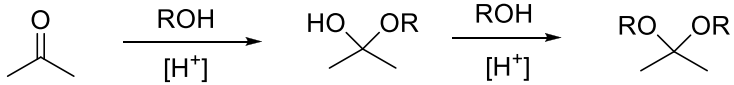
Iminium Ion

$-H^+$



Imine-Enamine tautomerization

Acetalization:



Conjugate Additions: