CHAPTER 25: HETEROCYCLES

Heteroatoms in Cyclic Organic Compounds

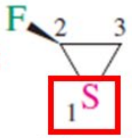
Cyclic molecules that contain at least 1 heteroatom

- Oxacyloalkane: Oxygen-containing heterocycle
- Azacycloalkane: Nitrogen-containing heterocycle
- Thiacyloalkane: Sulfur-containing heterocycle

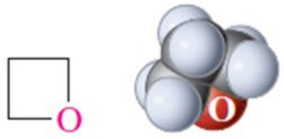
Oxacyclopropane
(Oxirane, ethylene oxide)

N-Methylazacyclopropane
(*N*-Methylaziridine)

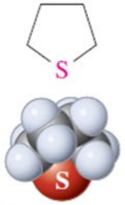
Numbering starts at heteroatom



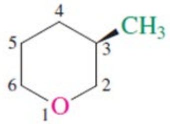
(*R*)-2-Fluorothiacyclopropane
[(*R*)-2-Fluorothiirane]



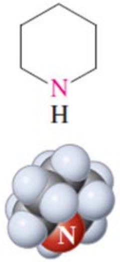
Oxacyclobutane
(Oxetane)



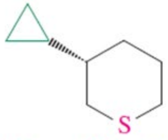
Thiacyclopentane
(Tetrahydrothiophene)



(*R*)-3-Methyloxacyclohexane
[(*R*)-3-Methyltetrahydropyran]



Azacyclohexane
(Piperidine)



(*S*)-3-Cyclopropylthiacyclohexane
[(*S*)-3-Cyclopropyltetrahydrothiopyran]

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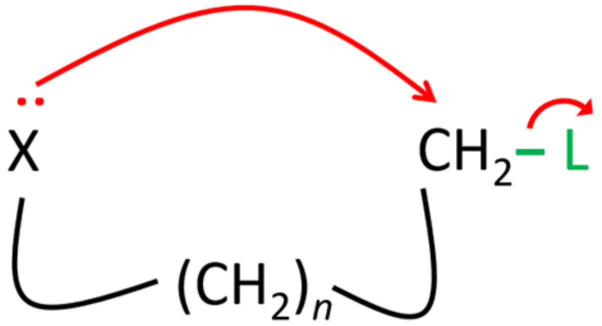
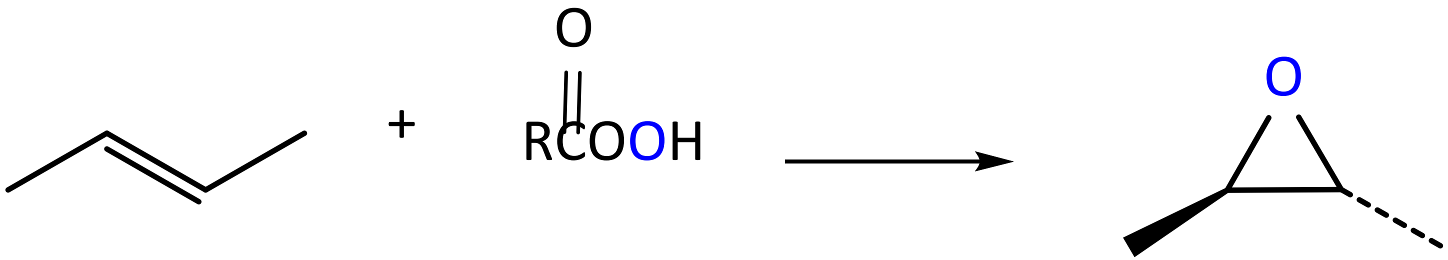
Preparation of Heterocloalkanes

1. Intramolecular S_N2 reaction



2. Special reaction for oxacyclopropanes



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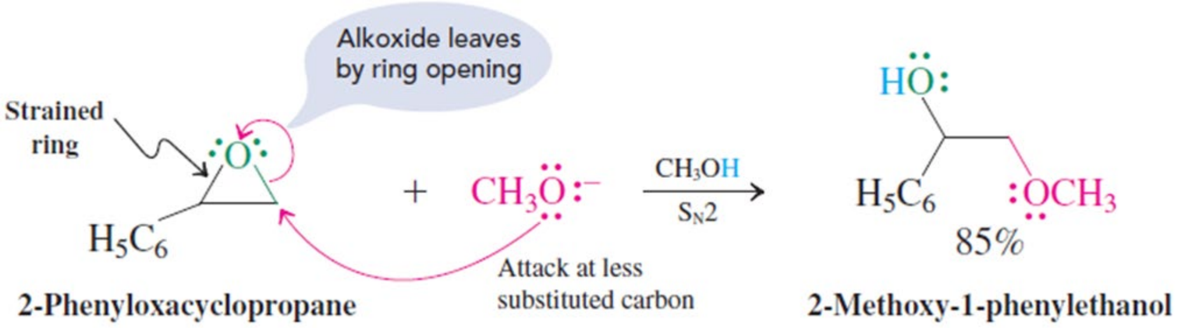
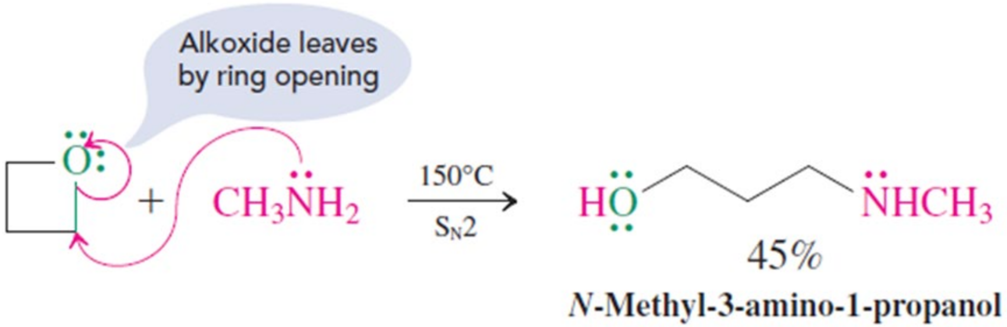
Reactions (1 of 4)

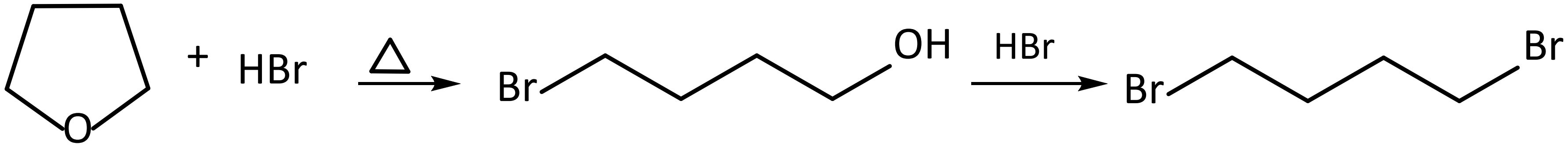
Three- and four-membered rings open: ring strain





Usual conditions are basic.

For rings larger than four, no ring strain: Need strong acid



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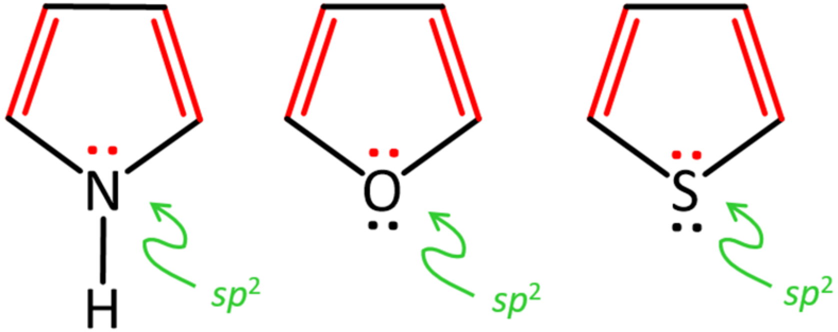
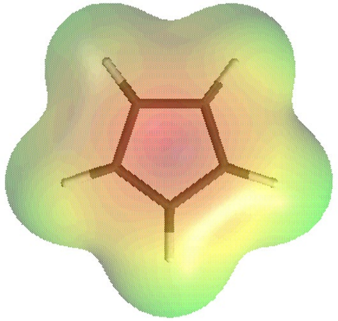
Heterocyclopentadienes: Pyrrole, Furan, and Thiophene

The lone pairs participate in the aromatic cyclic six e system: Like the cyclopentadienyl anion

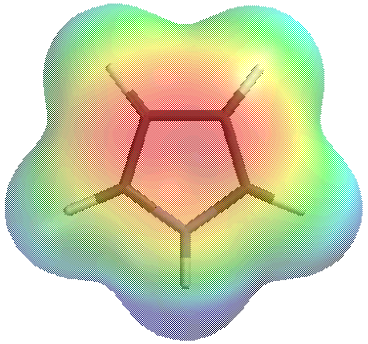


Furan

Thiophene



Cyclopentadienyl anion



Pyrrole

The distribution of 6 π electrons over five atoms makes these systems relatively e-rich, compared to benzene.

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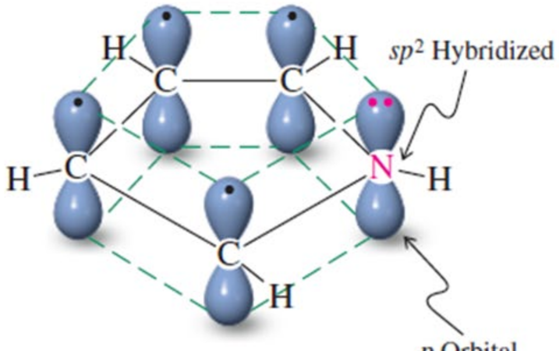
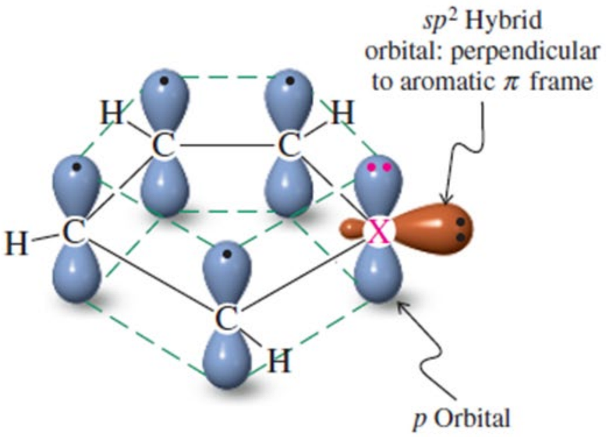
Orbitals

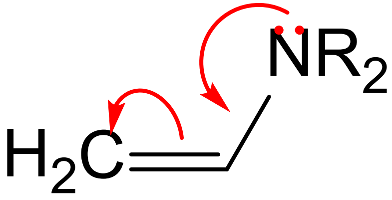


Pyrrole

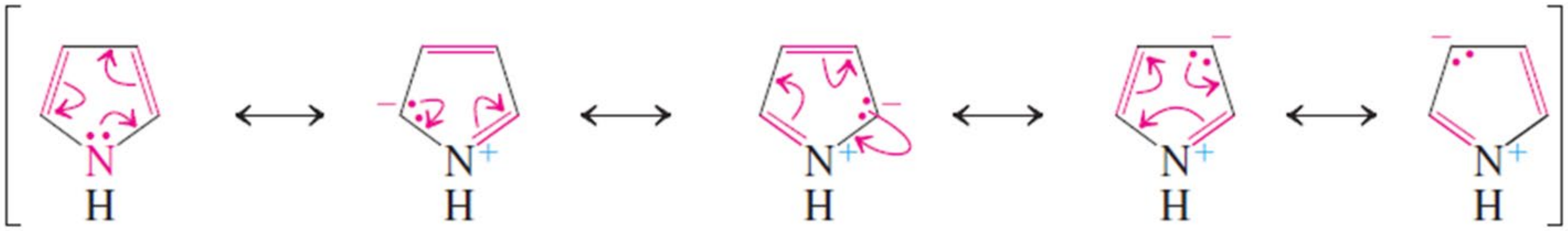


Furan (X = O)
Thiophene (X = S)

Resonance: recall enamines



Resonance Forms of Pyrrole



Relative to benzene: electron rich – e^- pair can deposit on each C

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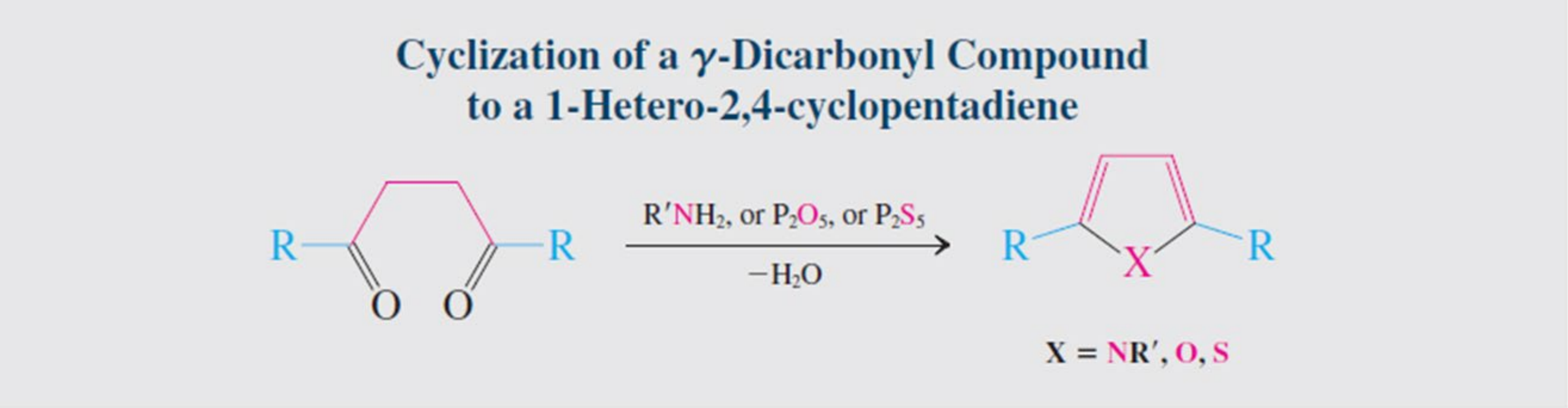
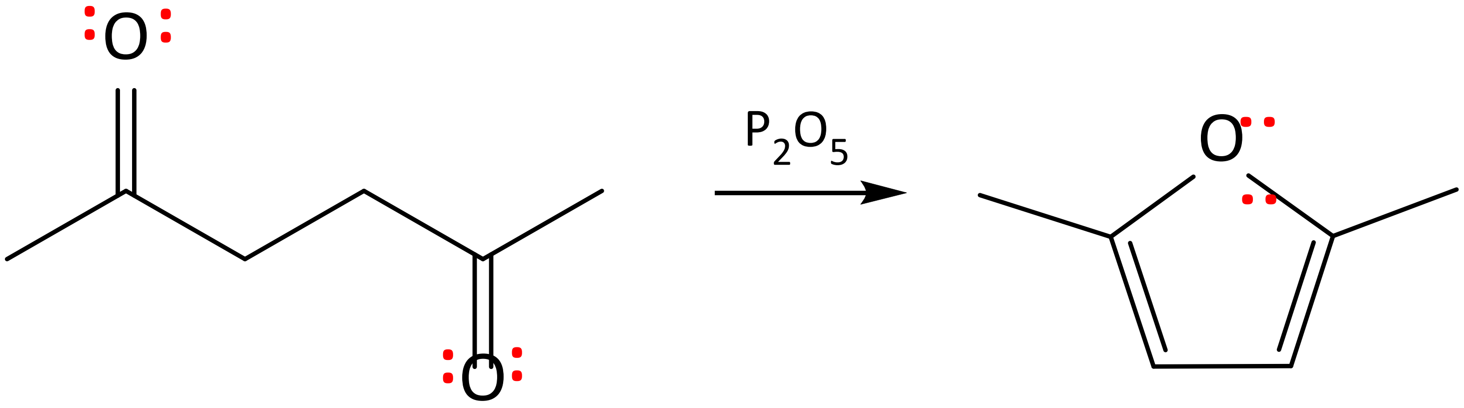
Synthesis of Heterocyclopentadienes

Paal-Knorr synthesis of pyrroles and its variations



Cyclization of a γ-Dicarbonyl Compound to a 1-Hetero-2,4-cyclopentadiene

X = NR′, O, S



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Furan synthesis

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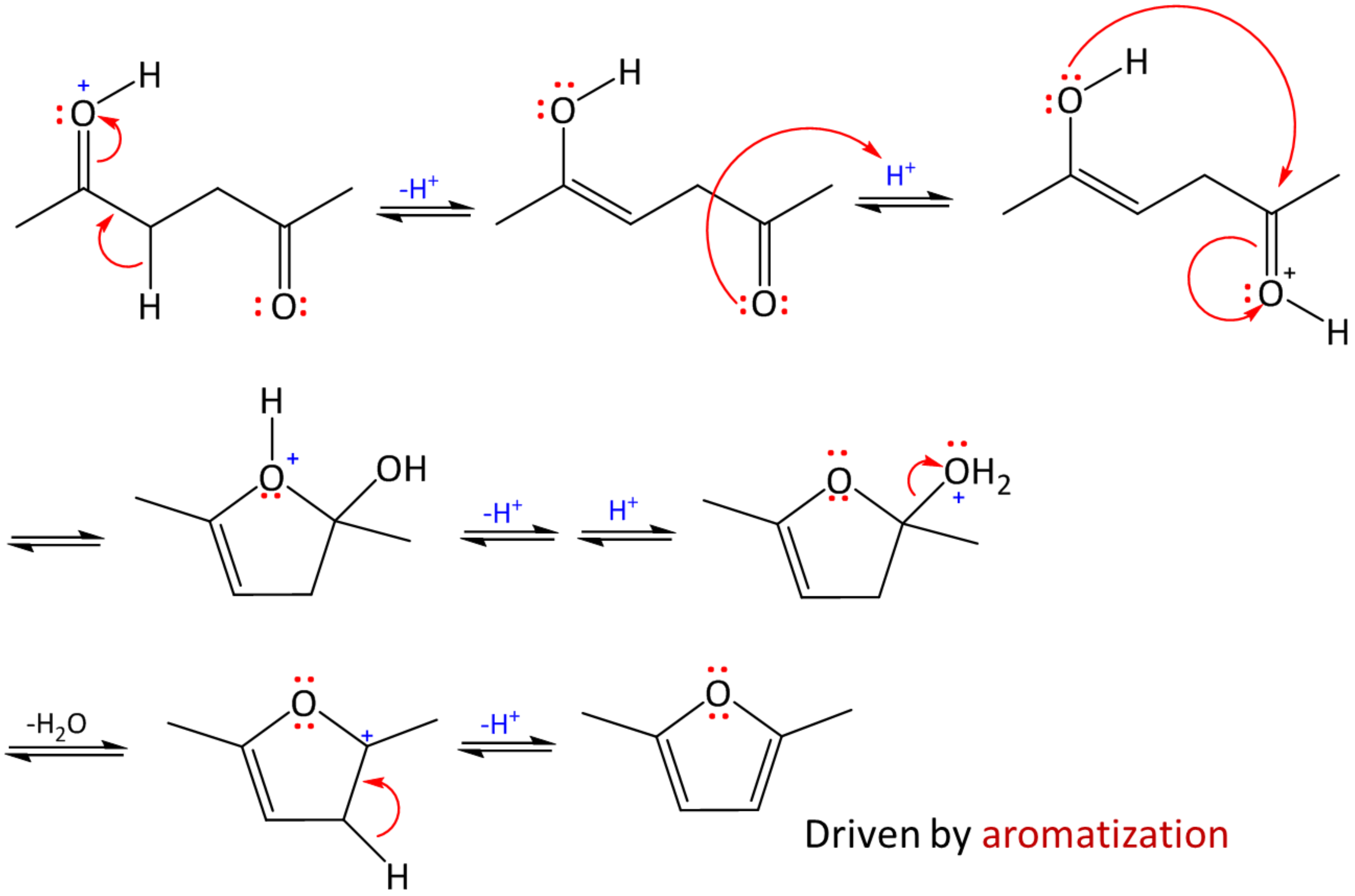
Mechanism



Driven by aromatization

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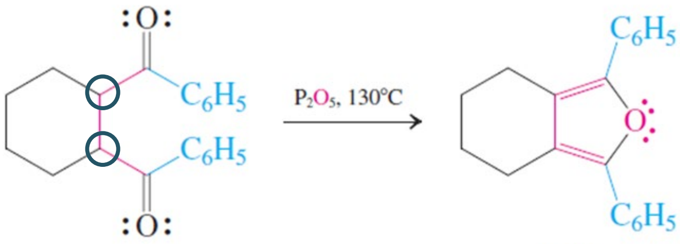
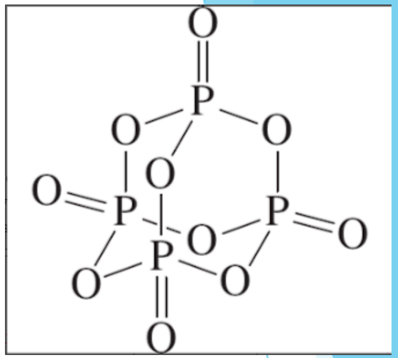
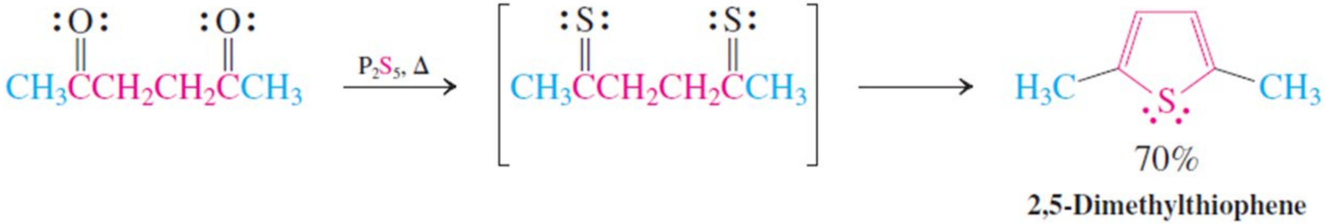
Mechanism: Thiophene/Pyrrole

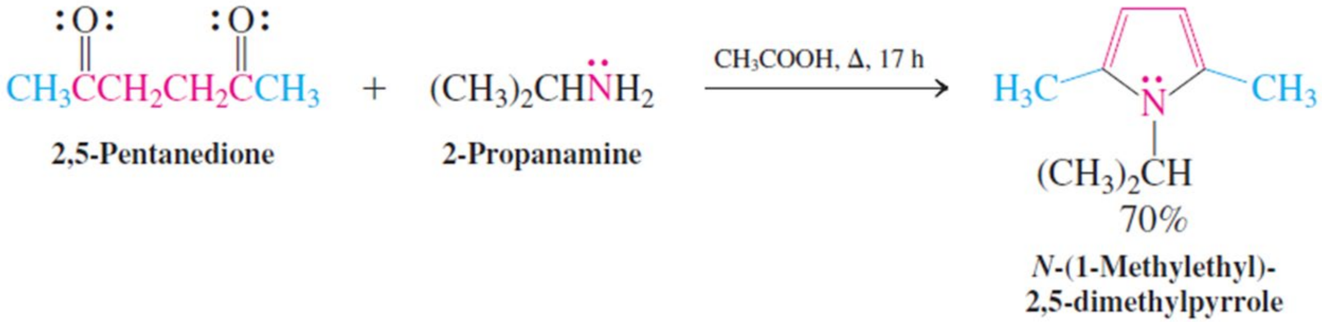


Enolizable Proton sites circled

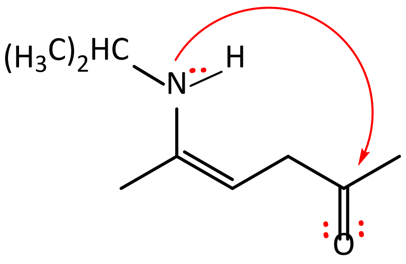


O-rich act as Proton “sponges”
P=O rich: acts as H_2O “sponges”





Mechanism:
Goes via
enamine



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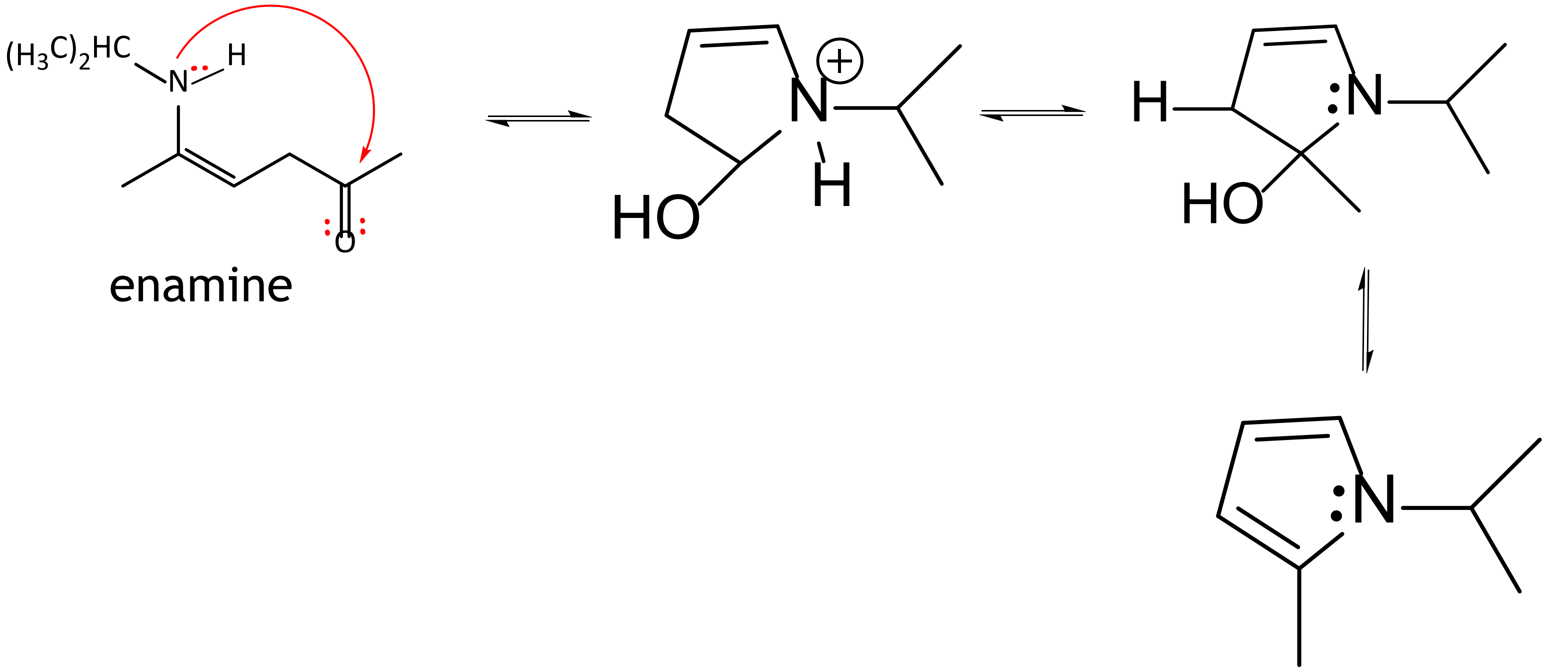
Mechanism of Pyrrole Formation (cont'd)



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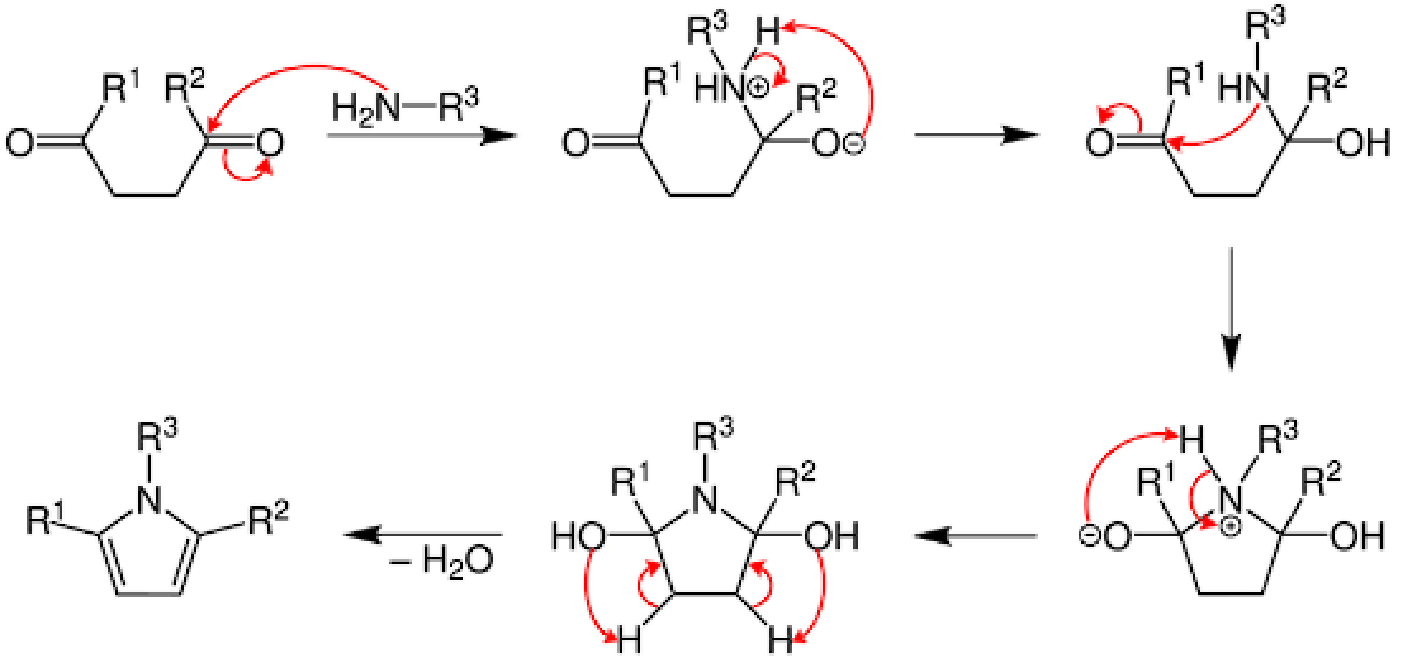
Pyrrole synthesis: Another Mechanism



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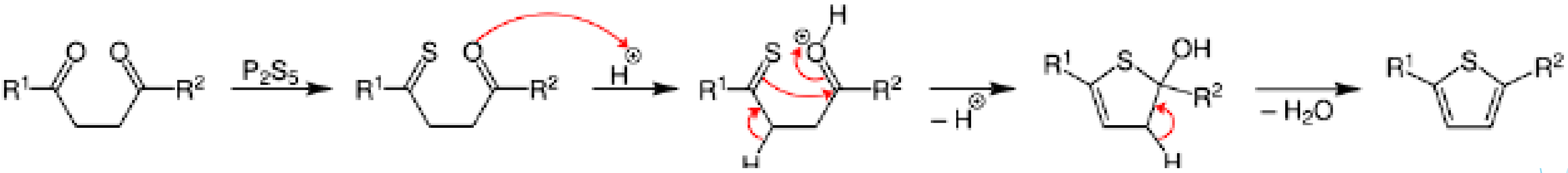
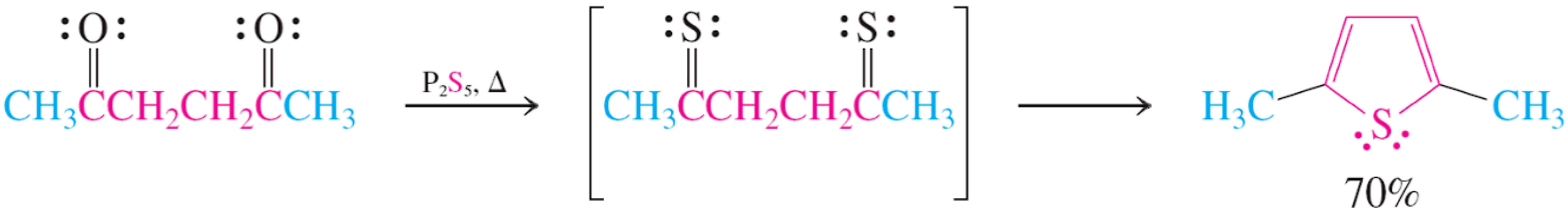
Thiophene synthesis: similar to pyrrole synthesis via thioenol

From Wiki



From Vollhardt



2,5-Dimethylthiophene

Conceptually the same

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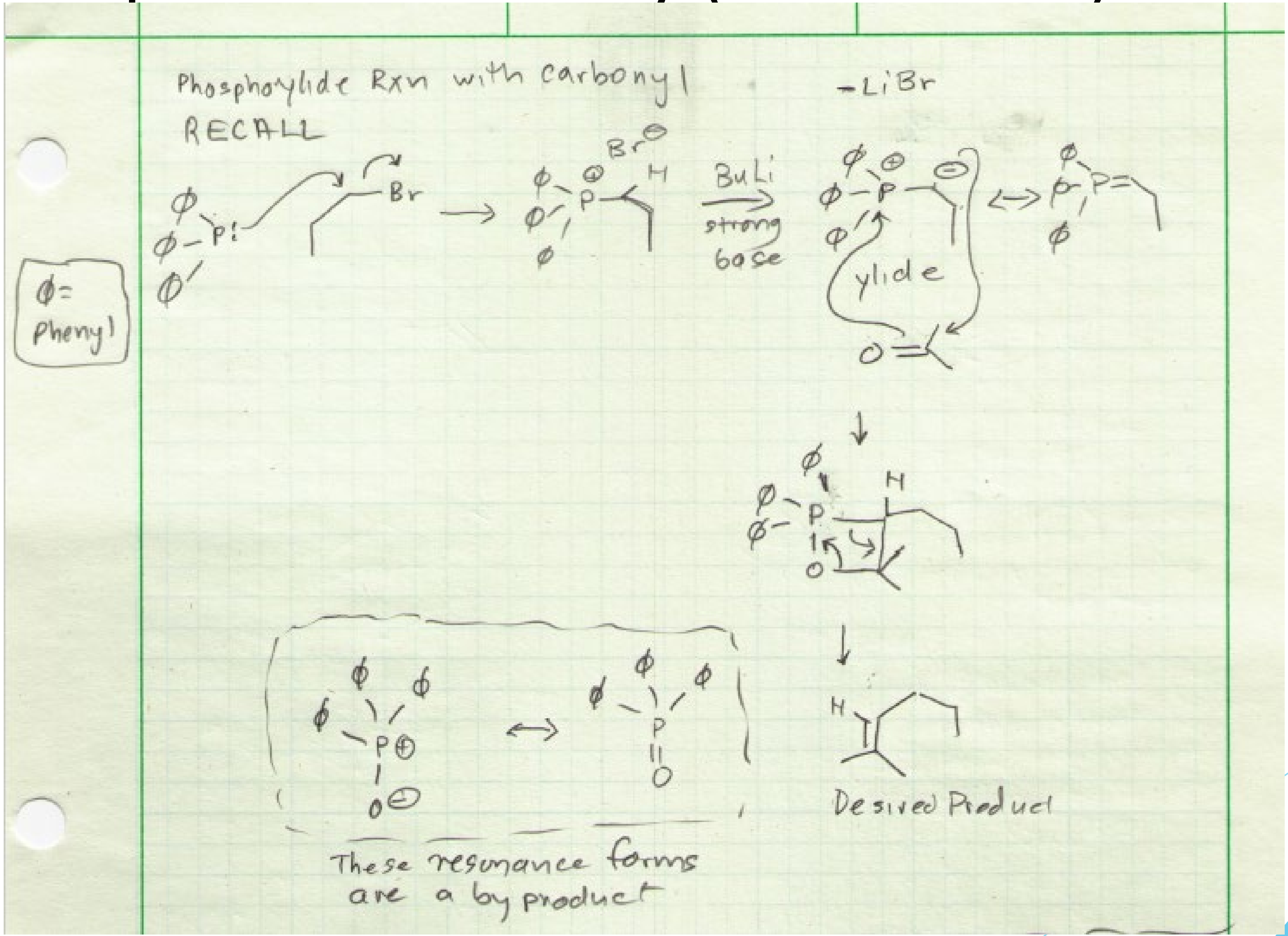
Phosphorus Chemistry (Ylide-based)



Phosphoylide Rxn with carbonyl

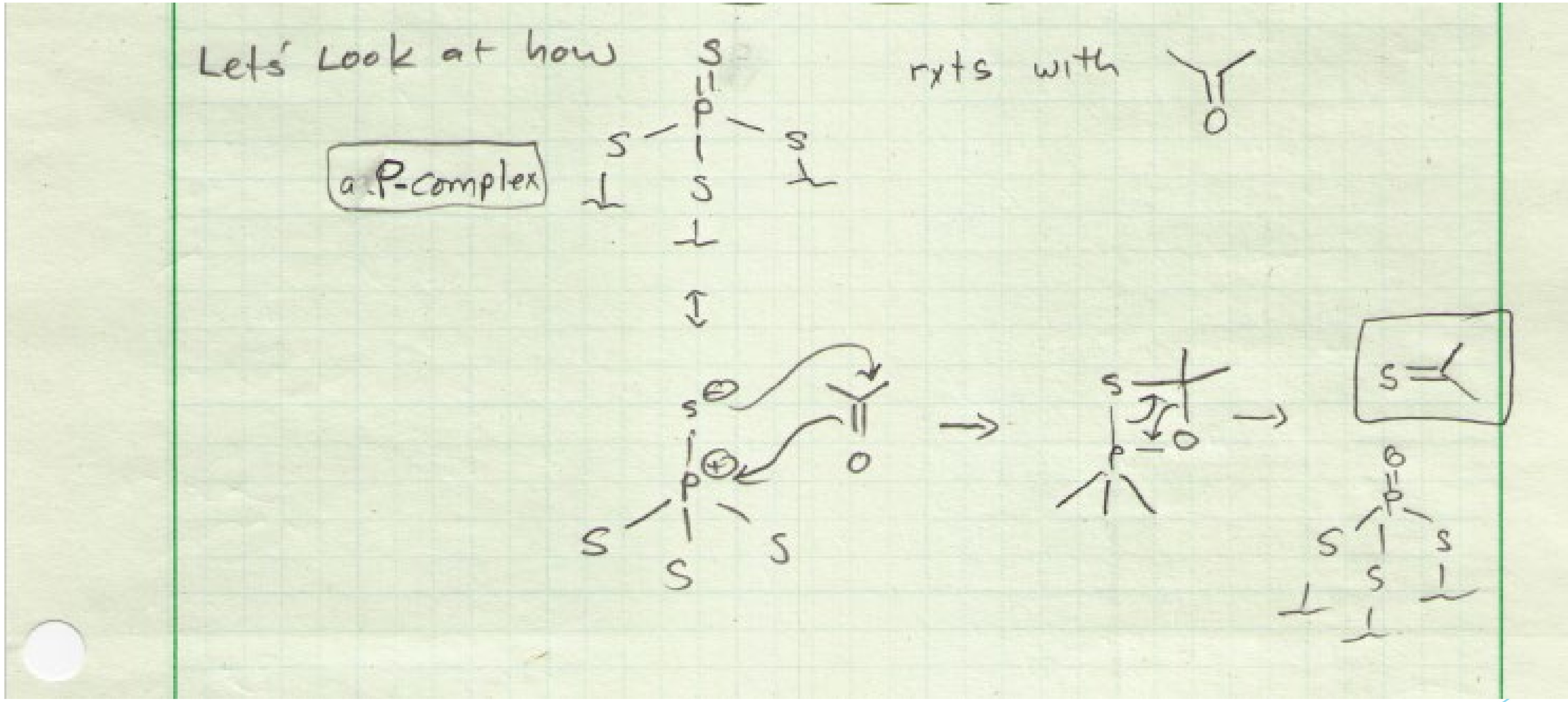
RECALL

ϕ= Phenyl

These resonance forms are a by product

Desired Product

Phosphorus Chemistry (Ylide-based)



Let's Look at how ryts with

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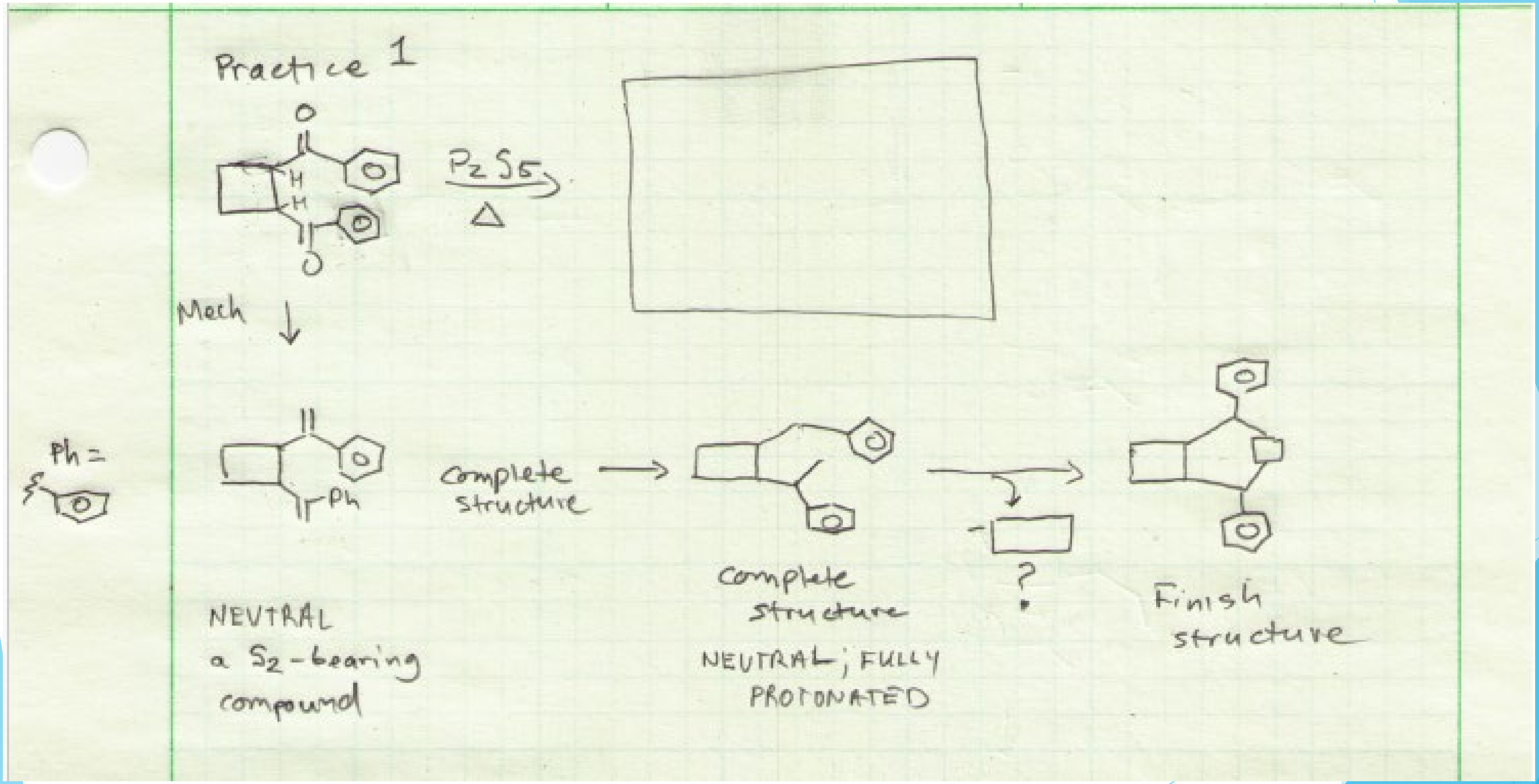
Practice



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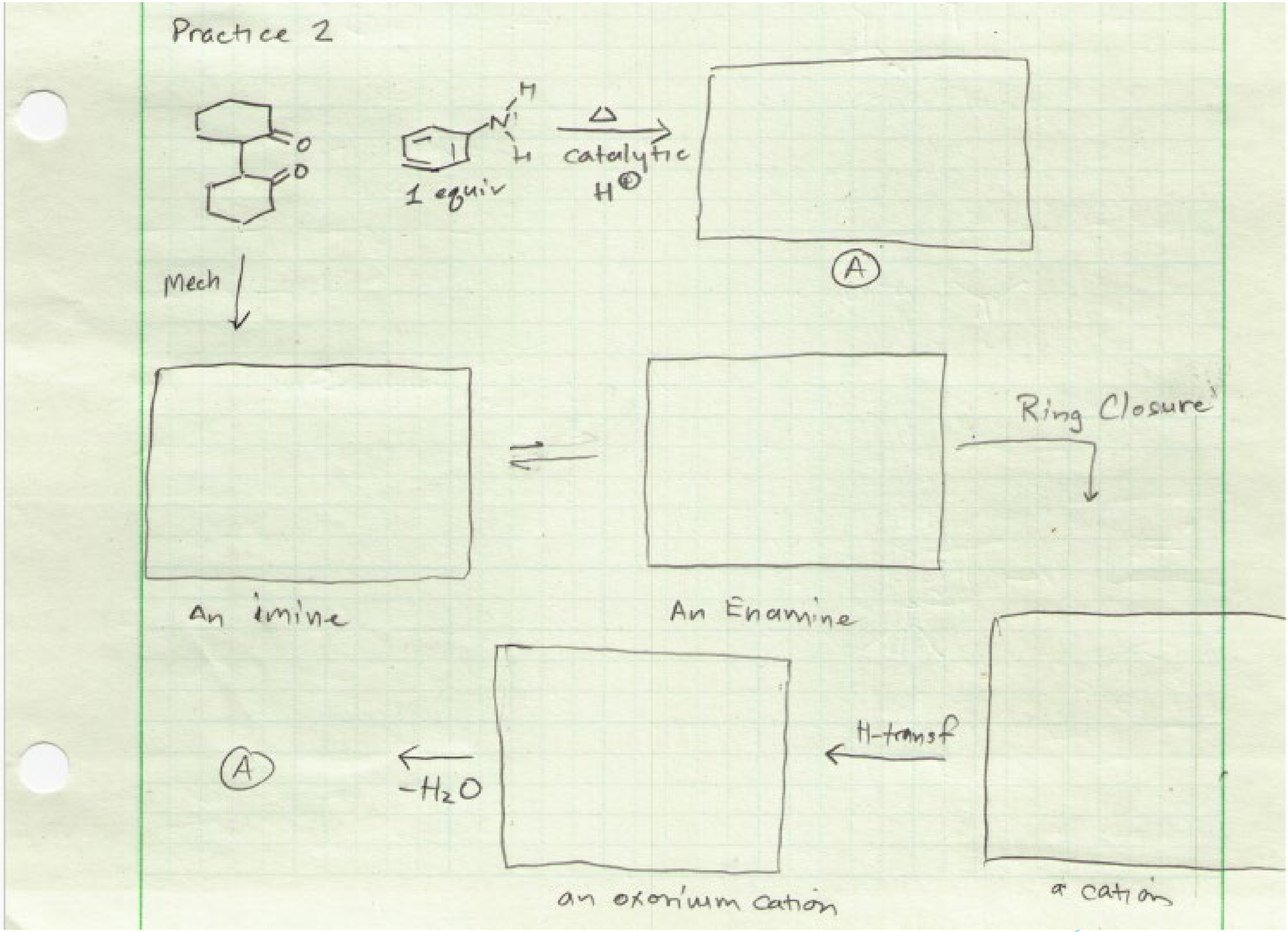
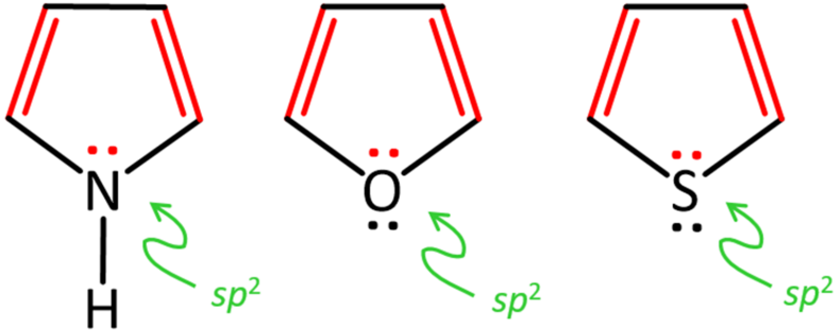
Practice


Practice 2
O
O
H
N
H
1 equiv
Δ
catalytic
H⊕
A
Mech
An imine
An Enamine
Ring Closure
a cation
H-transf
an oxonium cation
A
−H₂O

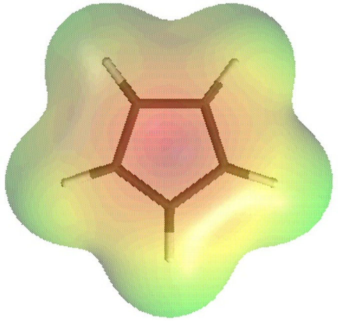
Heterocyclopentadienes: Pyrrole, Furan, and Thiophene

The lone pairs participate in the aromatic cyclic six e system: Like the cyclopentadienyl anion

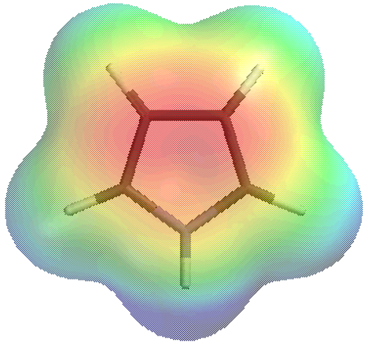


Furan

Thiophene



Cyclopentadienyl anion



Pyrrole

The distribution of 6 π electrons over five atoms makes these systems relatively e-rich, compared to benzene.

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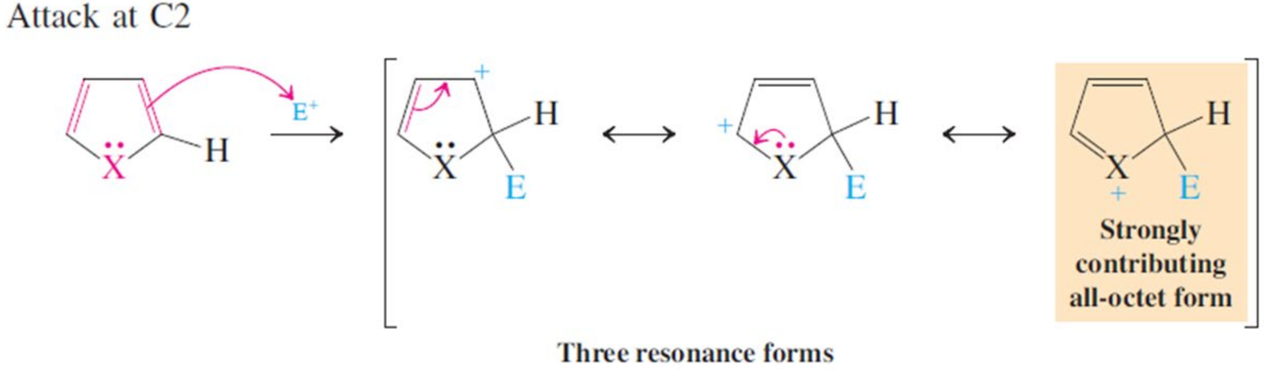
Reactions

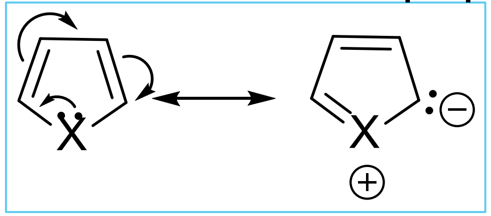
1. Electrophilic Aromatic Substitution: Activated!

Attack at C2 is preferred generally

3 resonance forms stabilize C3 attack



This resonance helps predict this outcome



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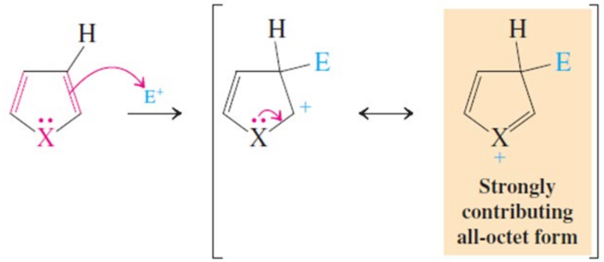
Reactions

1. Electrophilic Aromatic Substitution: Activated!

But often also attack at C3

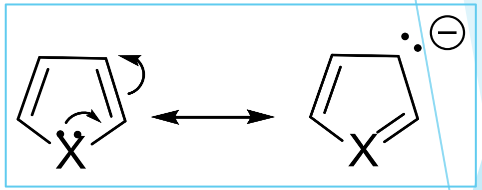
Attack at C3



Strongly contributing all-octet form

Two resonance forms

This resonance helps predict this outcome



Only 2 resonance forms stabilize C3 attack

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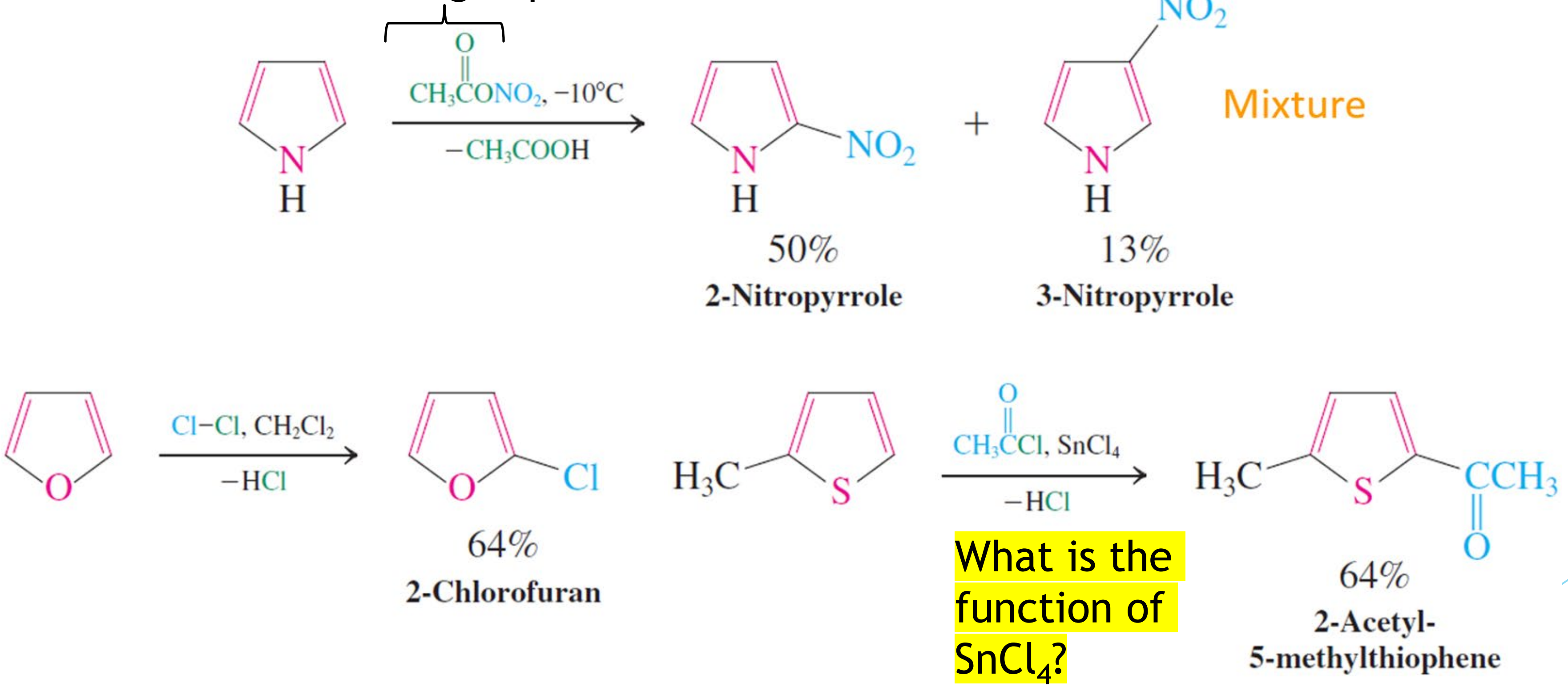
Examples

Relative reactivity: Benzene << thiophene < furan < pyrrole

Electrophilic Aromatic Substitution of Pyrrole, Furan, and Thiophene



What is the function of $SnCl_4$?

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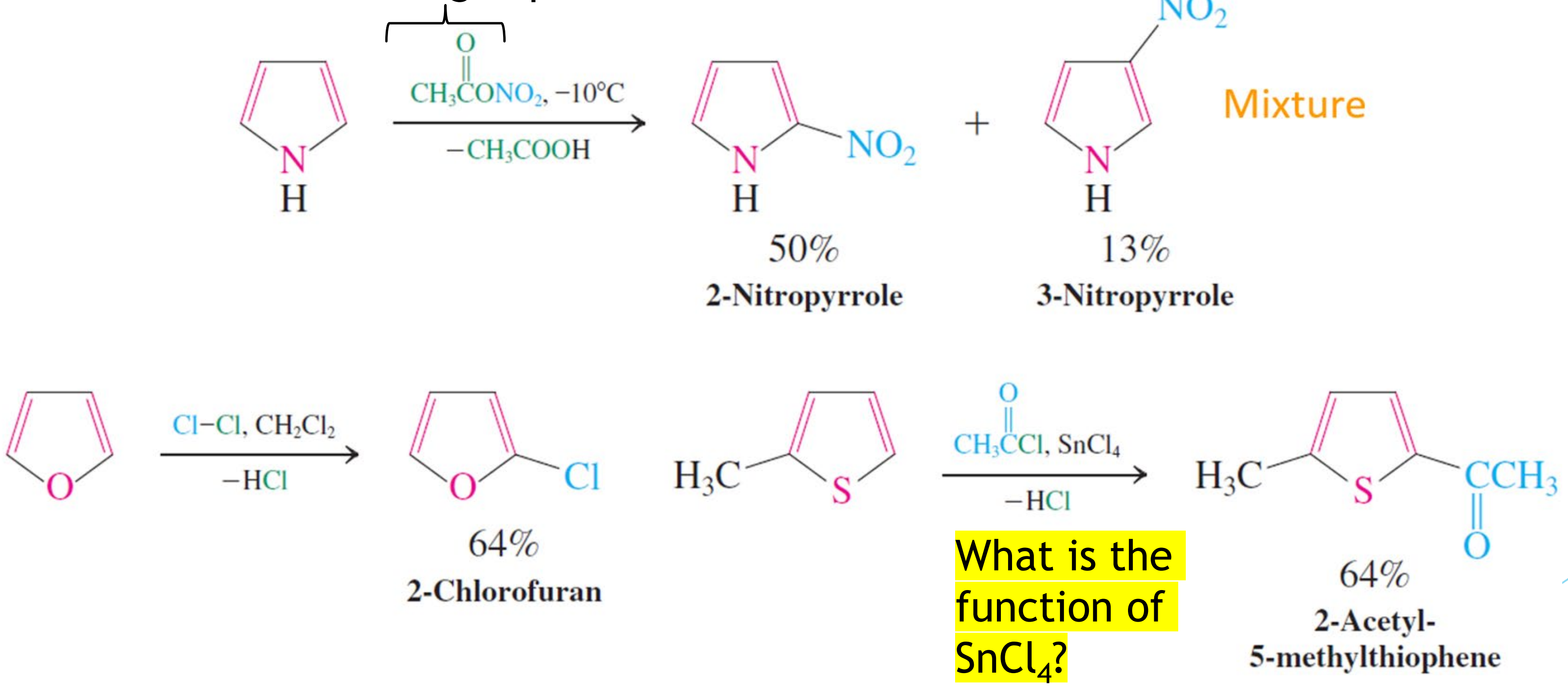
Examples

Relative reactivity: Benzene << thiophene < furan < pyrrole

Electrophilic Aromatic Substitution of Pyrrole, Furan, and Thiophene



Leaving Grp

Mixture

What is the function of $SnCl_4$?

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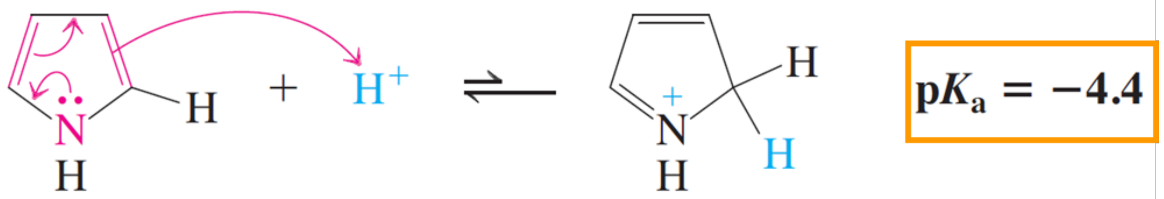
Reactions

2. Basicity of pyrrole (and other heterocyclopentadienes)

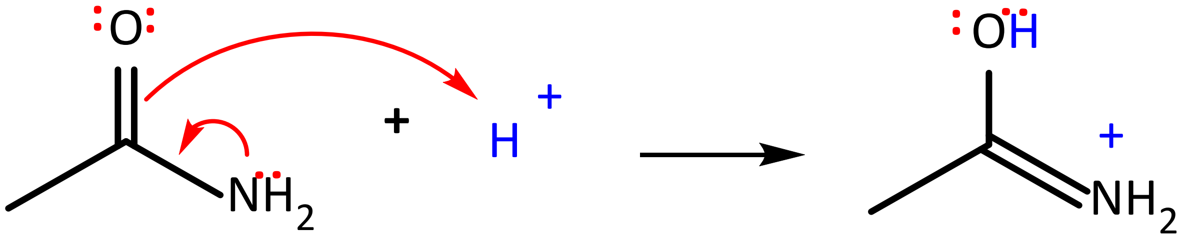
Relatively (cf. normal amines) nonbasic: Lone pair is tied up by resonance. Protonation occurs on carbon!

The Protonation of Pyrrole Occurs on Carbon

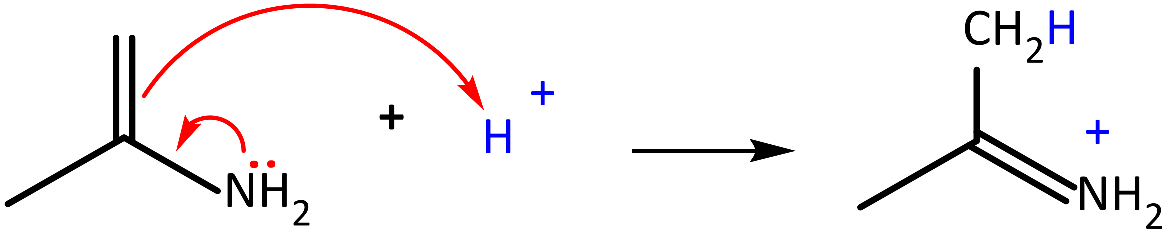


pK_a of ammonium ~ 10; iminium ~8

Recall:



Or:



Lone pair is tied up by resonance

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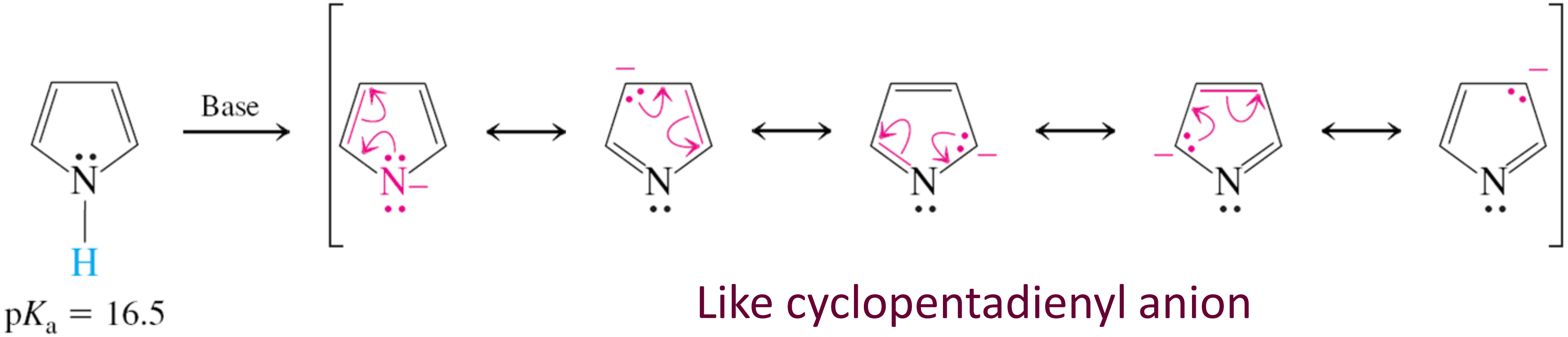
Reactions

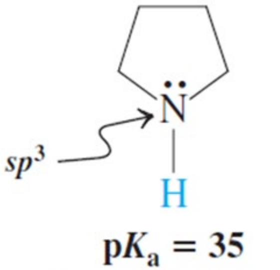
3. Pyrrole is quite acidic



Like cyclopentadienyl anion

Reason is sp^2-hybridization and cyclic delocalization of charge.

Compare:



Azacyclopentane

ARIO: “Atom’s Raisinettes are Induced into Orbit”

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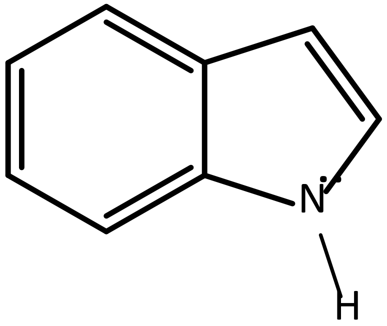
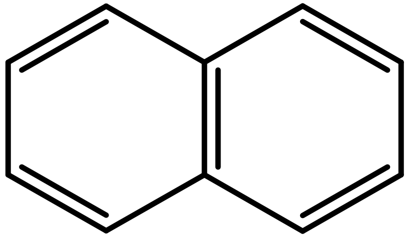
Benzofusion: Indole

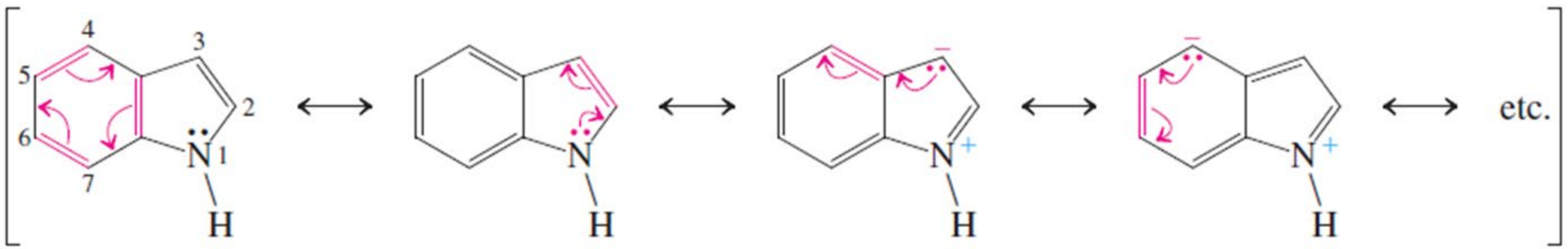


Indole



Compare: naphthalene

Resonance in Indole



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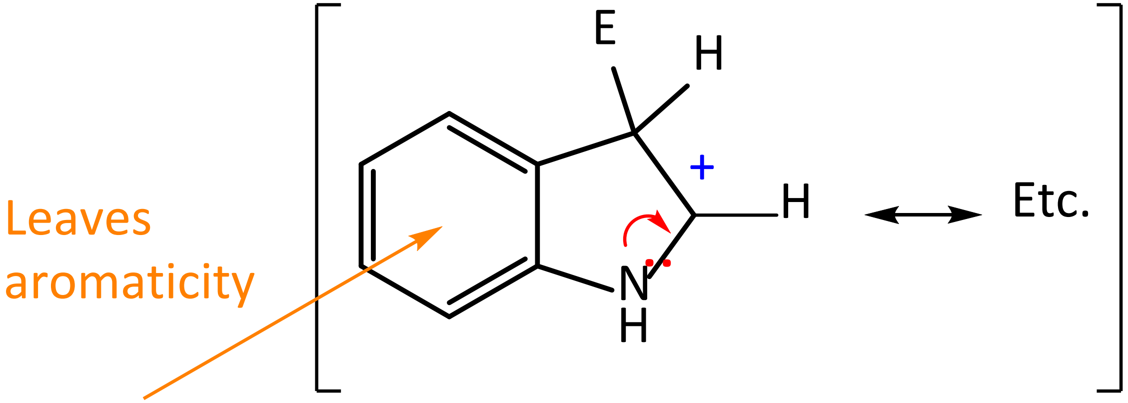
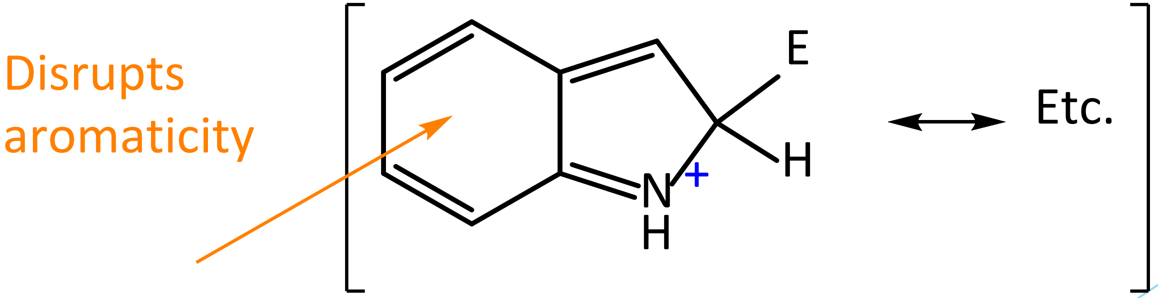
EAS occurs at more e-rich pyrrole ring and at C3

Allows for resonance forms which do not disrupt the benzene ring

Attack at C3:


Leaves aromaticity

Attack at C2:


Disrupts aromaticity

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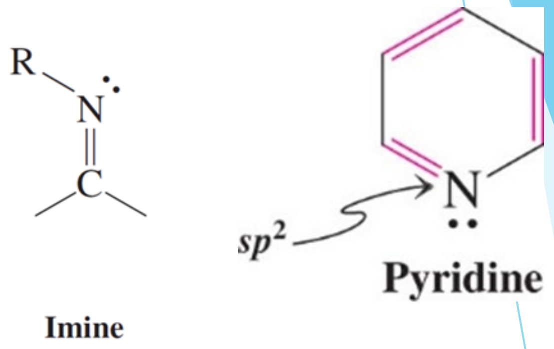
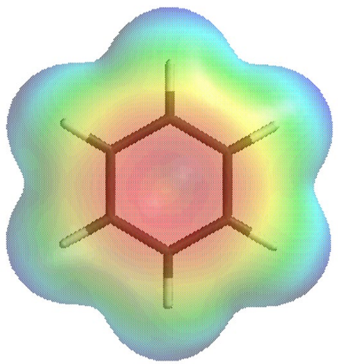
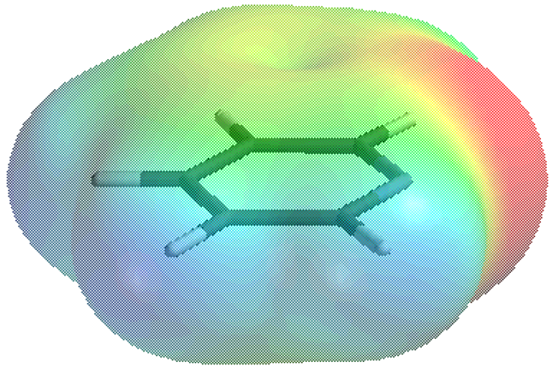
Pyridine: Azabenzene

Can be viewed as a cyclic aromatic imine:

The nitrogen is *sp*^{2}-hybridized, the lone pair is perpendicular to the aromatic π system.



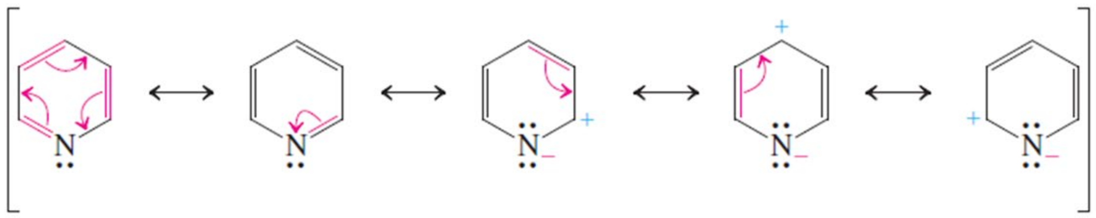




The N does not donate e-density; rather, it withdraws by induction

Cf. benzene

Resonance in Pyridine



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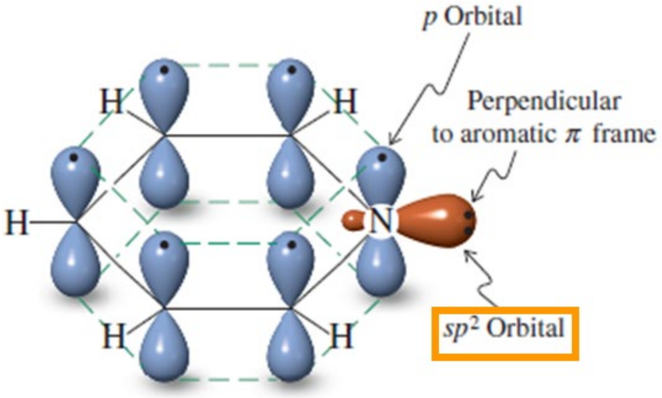
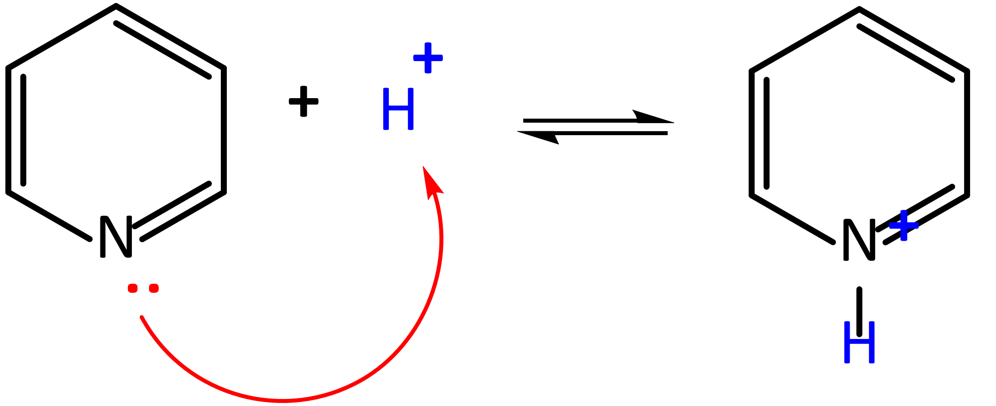
Pyridine is a (weak) base





Pyridine

Pyridinium ion

$pK_a = 5.29$

Compare pK_a of R_3N^+H ~ 9-10

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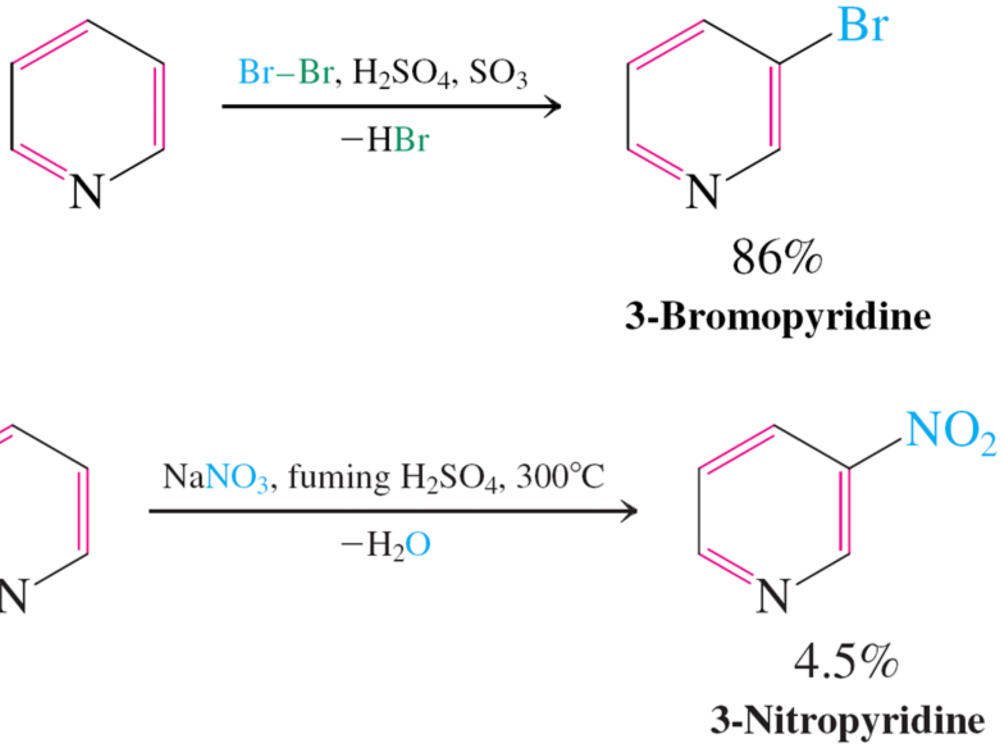
Reactions of Pyridine

Pyridine is relatively (to benzene) electron poor, therefore EAS only under extreme conditions and only at C3



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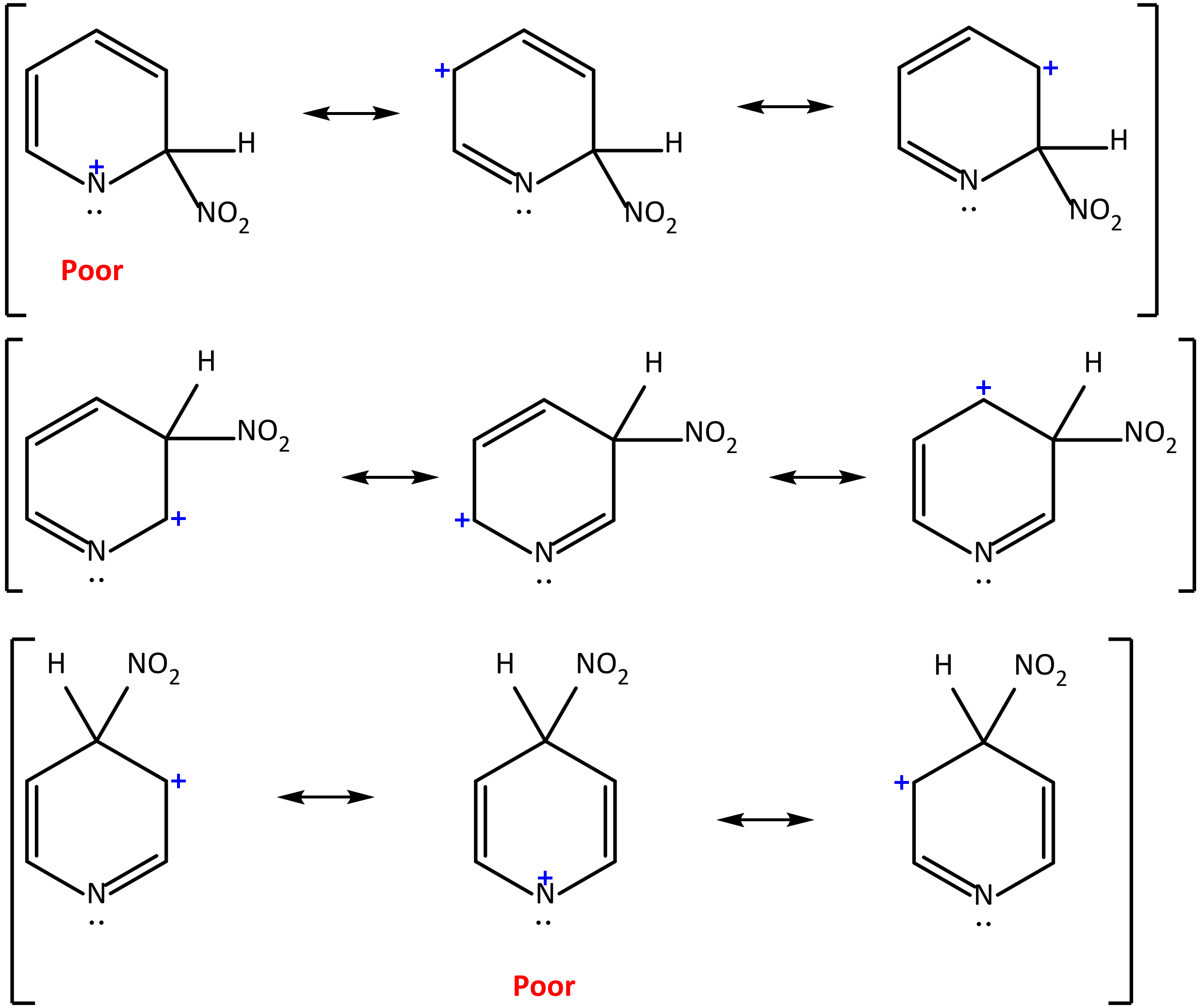
Nitration of Pyridine



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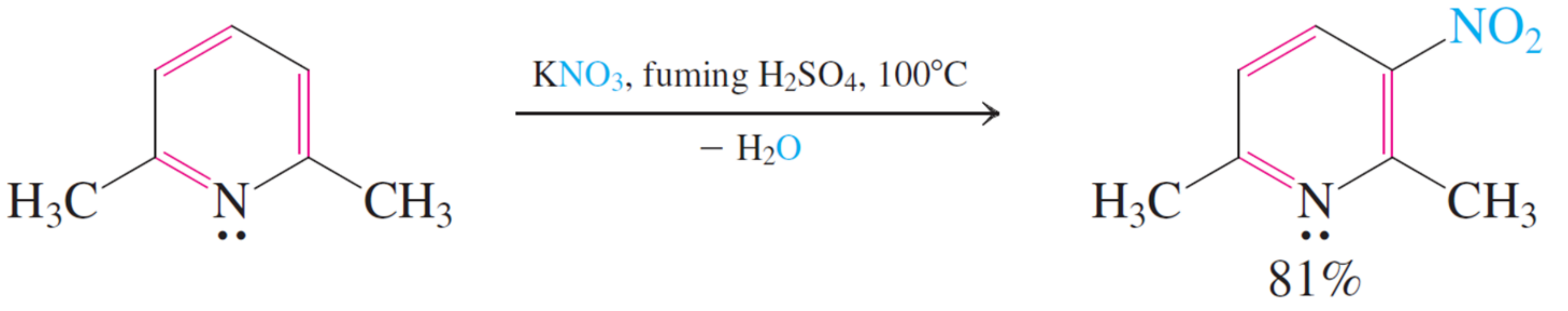
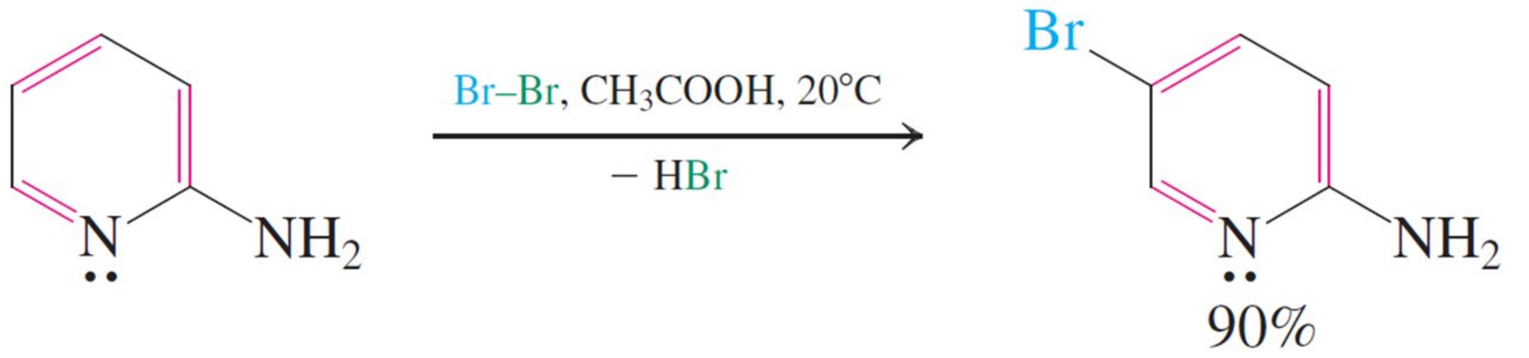
Activating substituents improve yields



2,6-Dimethylpyridine **2,6-Dimethyl-3-nitropyridine**



2-Aminopyridine **2-Amino-5-bromopyridine**

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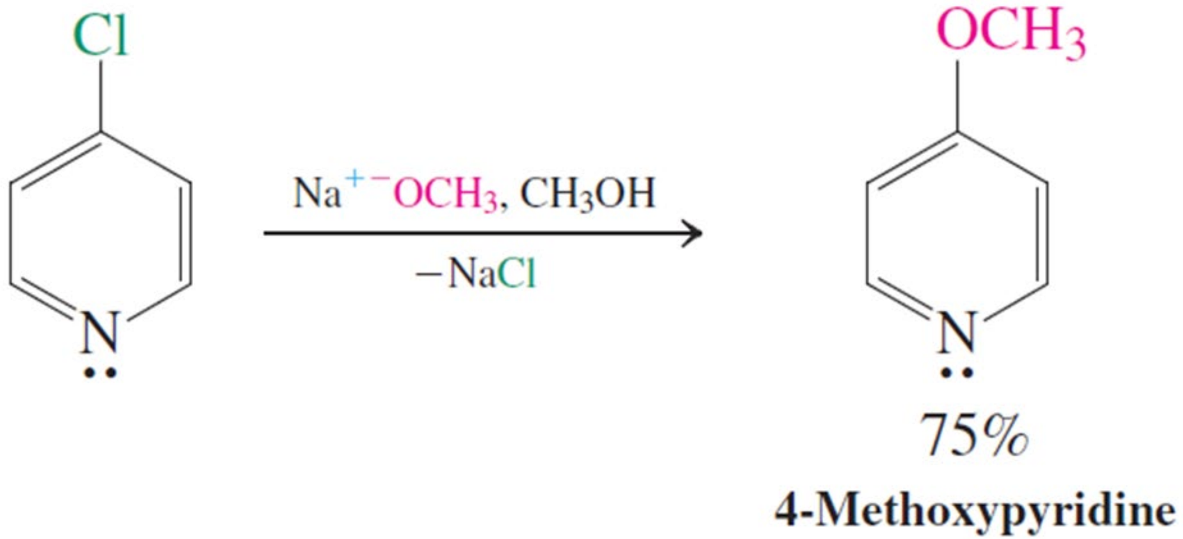
Pyridine undergoes relatively easy nucleophilic aromatic substitution



4-Methoxypyridine

Leaving groups are typically halides; 2- and 4 halopyridines are particularly reactive

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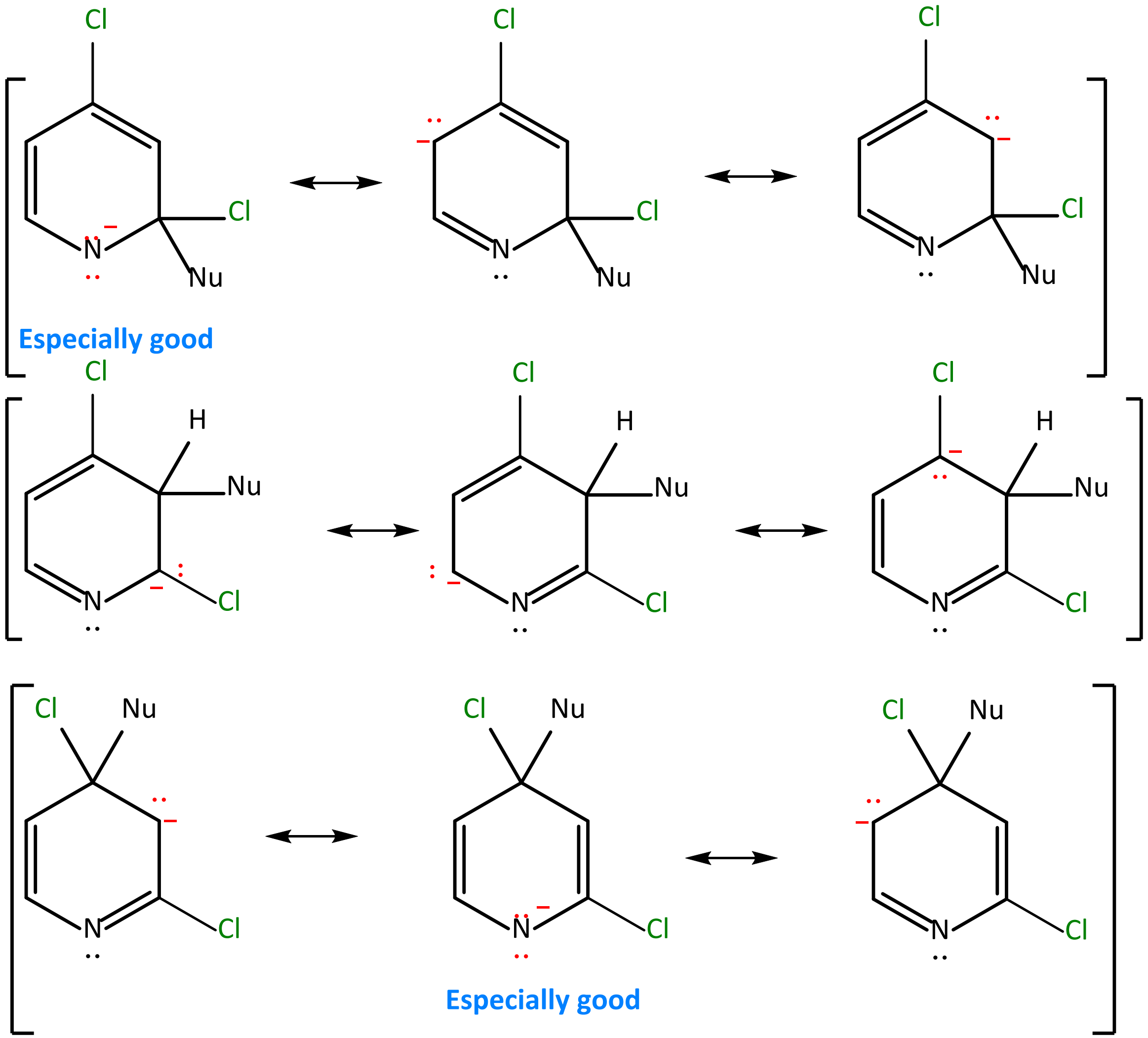
Nucleophilic Attack on Pyridine



Especially good

Especially good

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