Synthetic Routes of some common benzo-fused five-membered π-excessive Htero aromatic compounds

By

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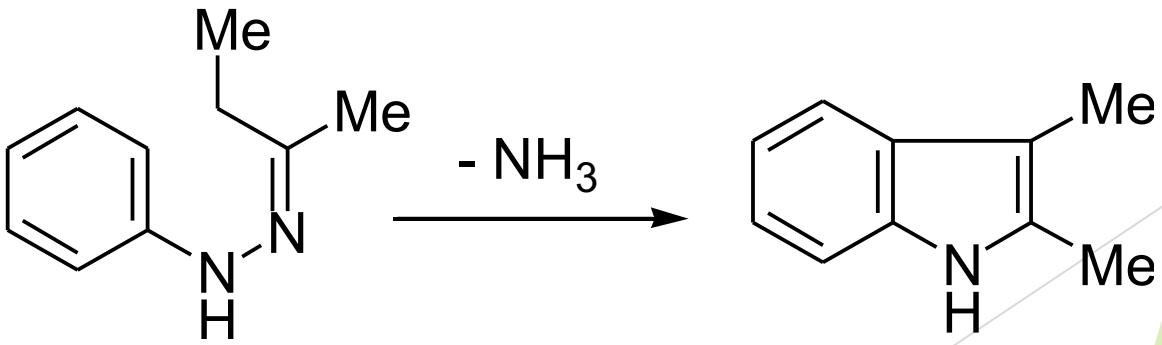
Ph.D. of Organic Chemistry "Synthesis of Hetero Cyclic"

College of Pharmacy-2020

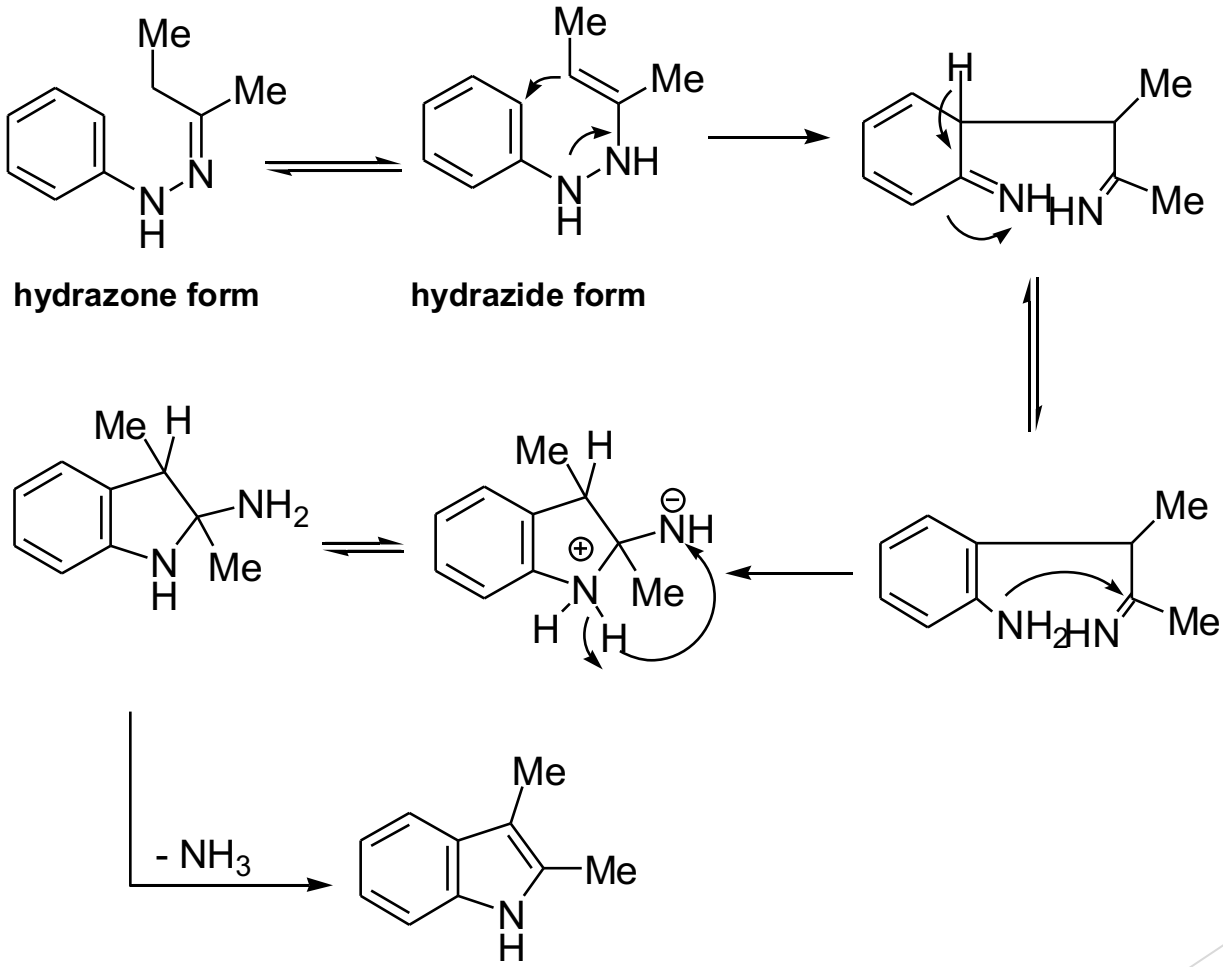
Synthesis of Indole Compounds

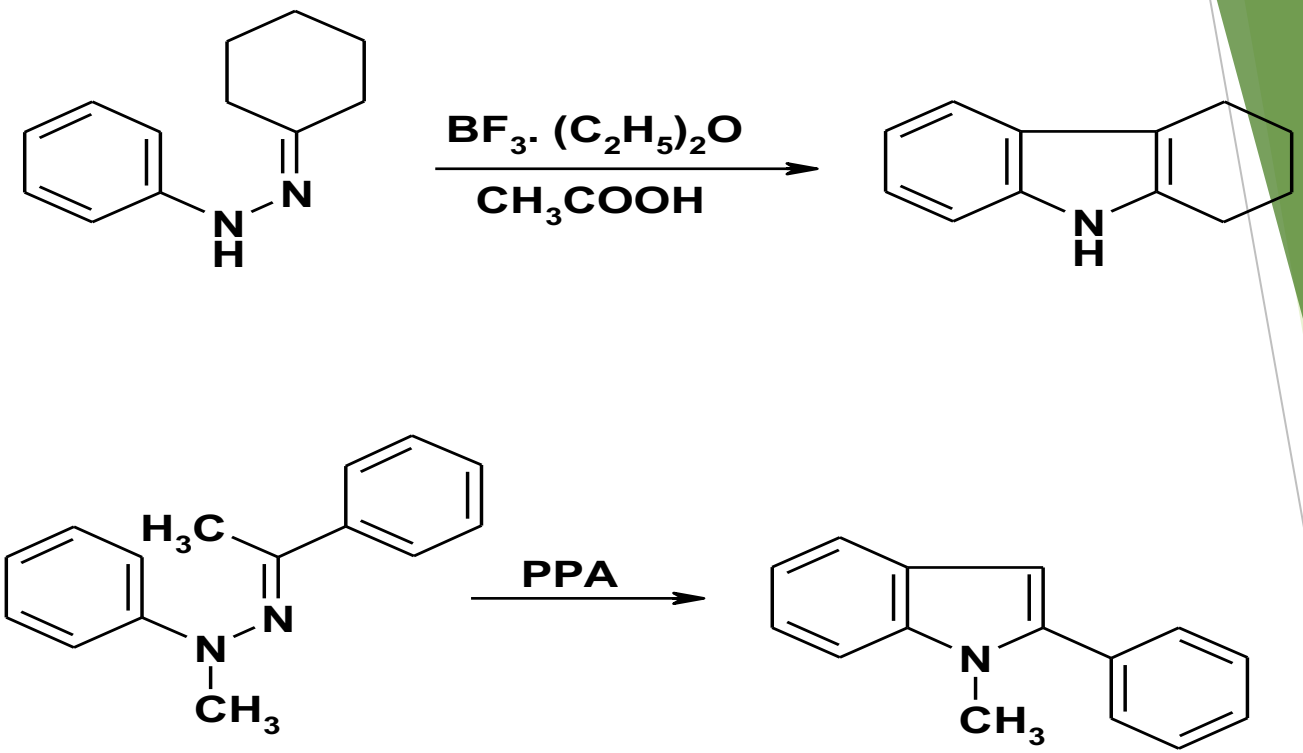
Fischer Indole synthesis

The general procedure by which a phenylhydrazone of an aldehyde or ketone is heated in the presence of a catalyst such as zinc chloride, boron trifluoride, or polphosphoric acid to produce an indole.

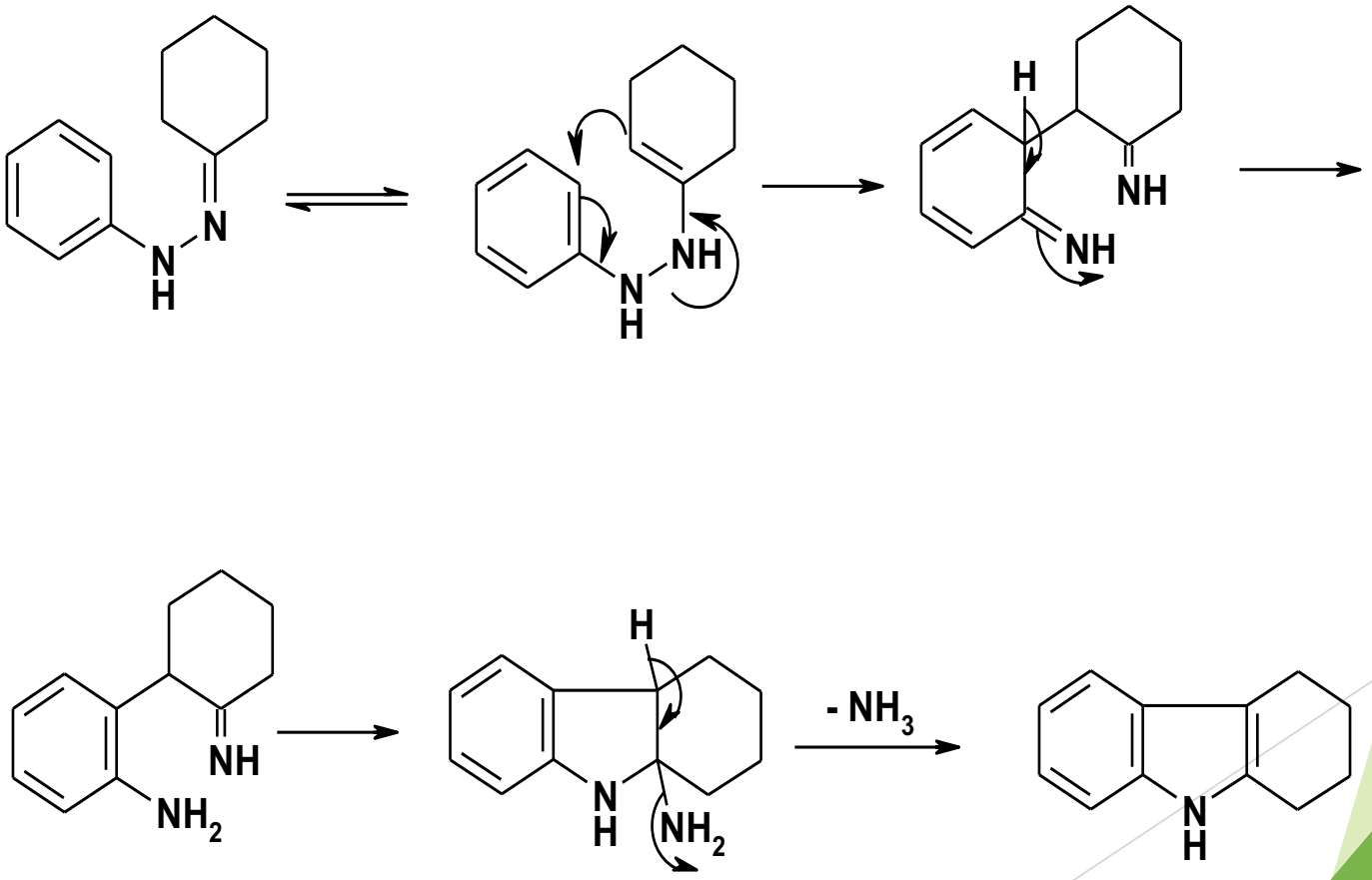


Mechanism


Me
Me
N
N
H
Me
Me
NH
N
H
H
Me
NH
HN
Me
hydrazone form
hydrazide form
Me
H
NH2
N
H
Me
Me
H
NH
N
Me
H
H
Me
NH2
HN
Me
- NH3
Me
Me
N
H


BF3. (C2H5)2O
CH3COOH
PPA
CuCl

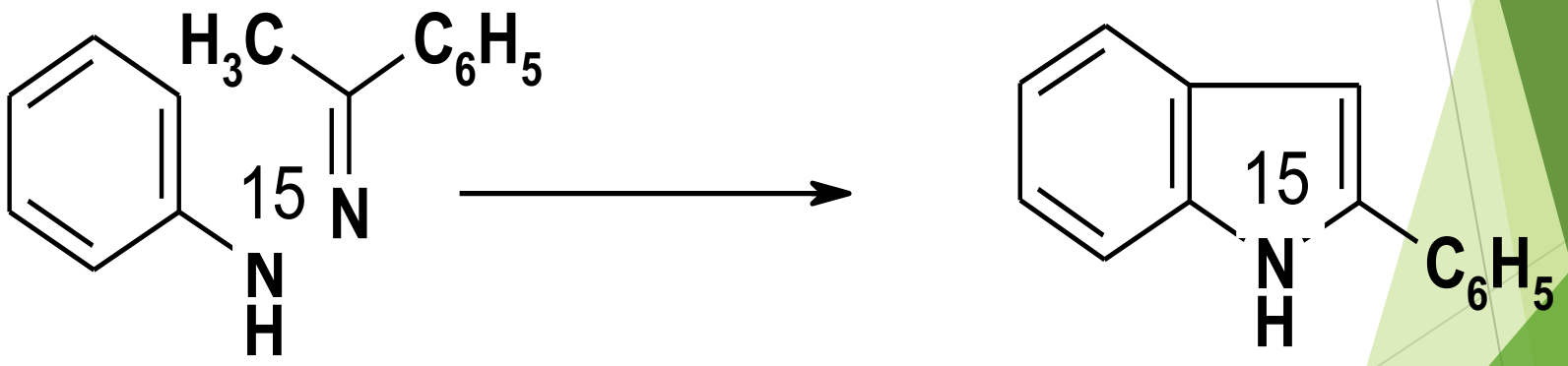
Formally, the Fischer synthesis involves rearrangement with the loss of a molecule of ammonia; the mechanism by which such a molecular manipulation occurs has been the object of much study.



In support of this mechanism may be cited the observations that

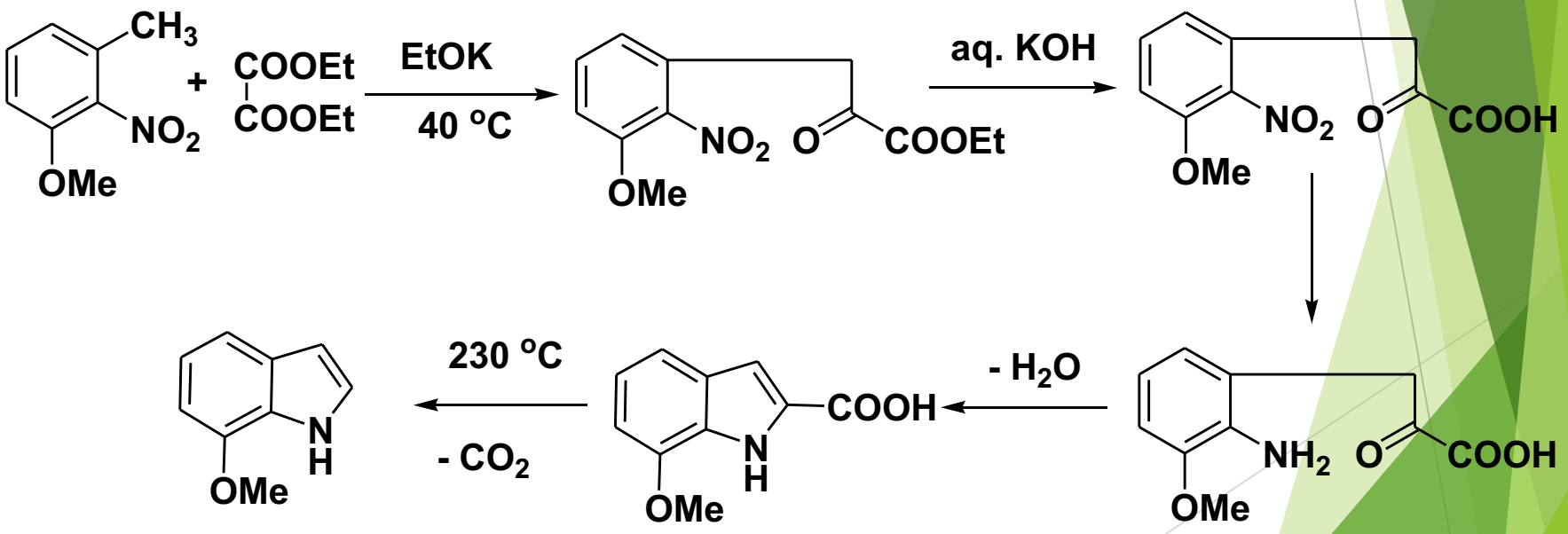
(1) the reaction is acid-catalyzed

(2) the nitrogen atom eliminated as ammonia is the farthest removed from the aromatic ring:



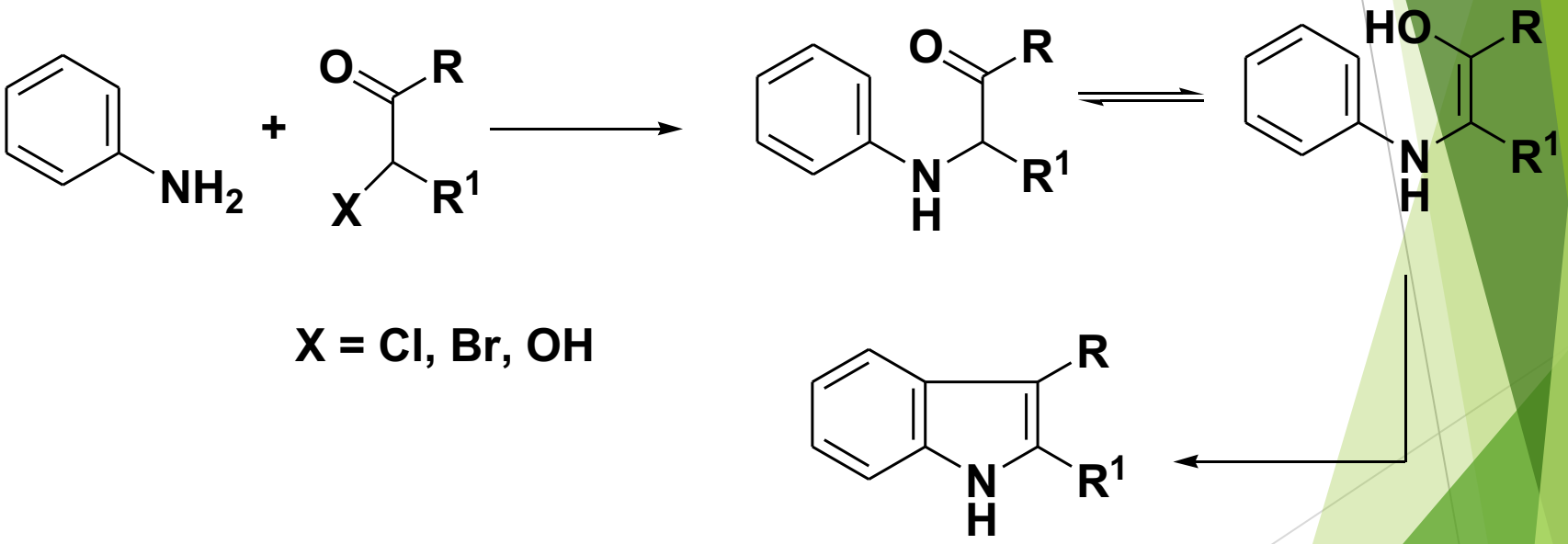
The *Reissert* Indole Synthesis

The best way for synthesis of indole derivatives with substituents on benzene ring. Thus *o*-nitrotoluene can be used as starting material via treatment with diethyl oxalate in basic medium.



The *Bischler* Indole Synthesis

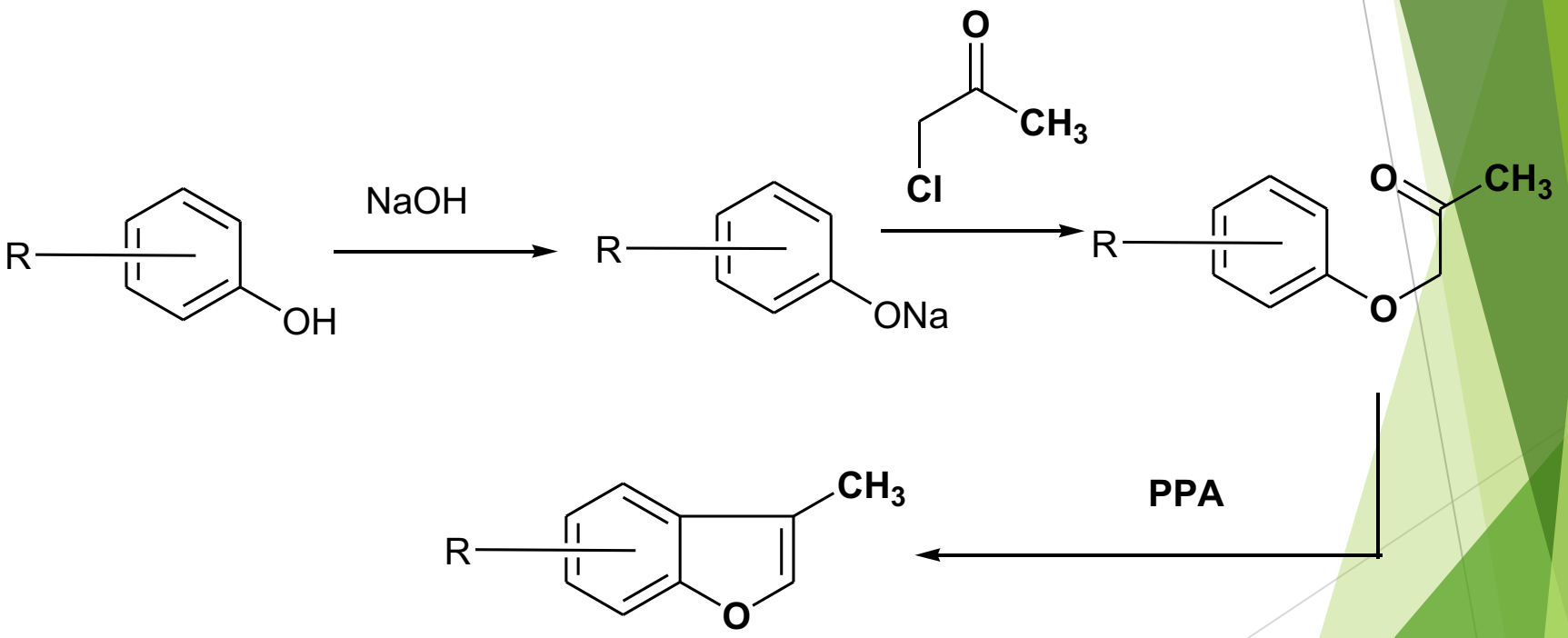
This reaction involves treatment of an arylamine with α-halo-, α-hydroxy-aldehyde or ketones in the presence of an acidic reagent

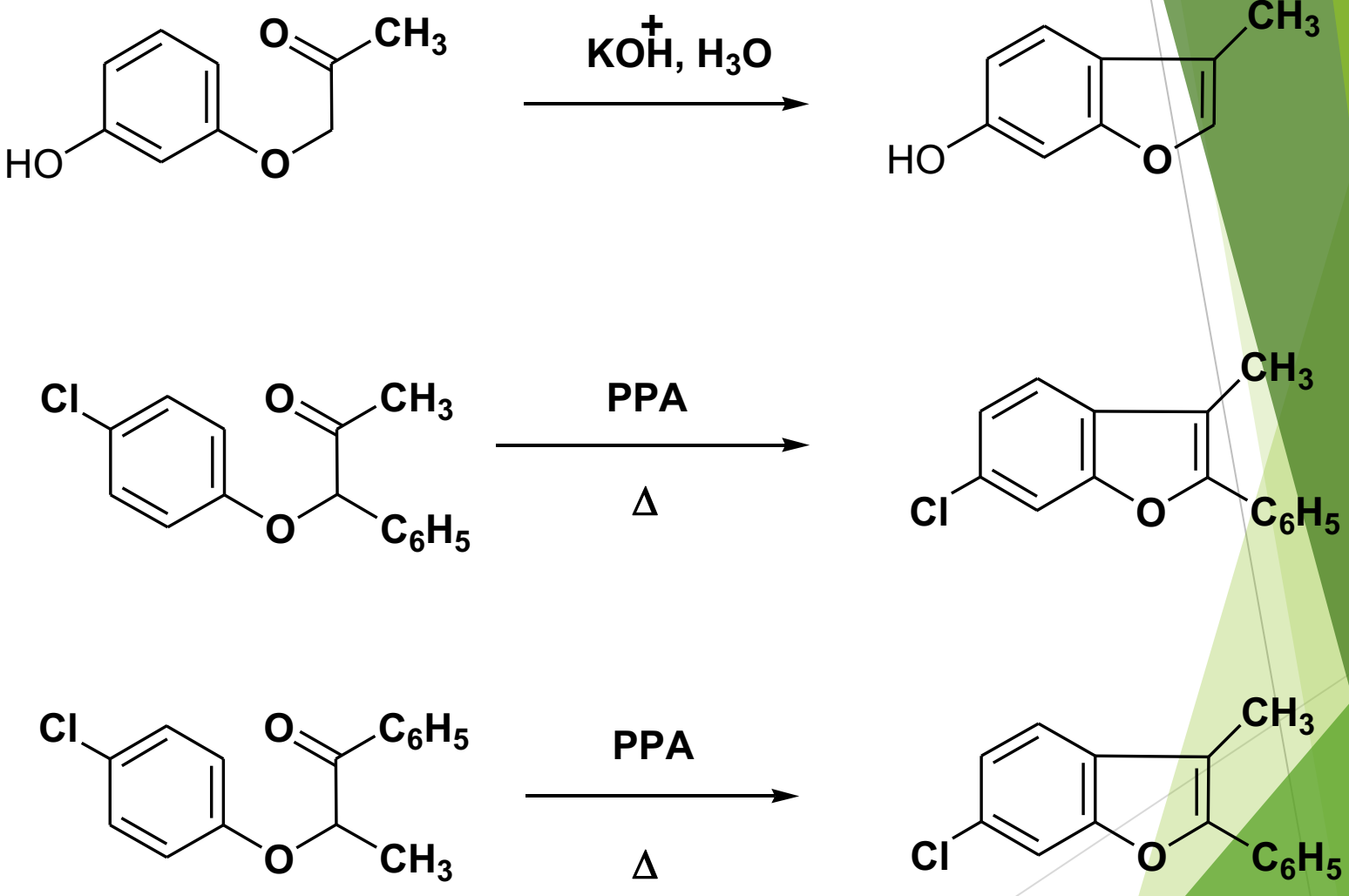


X = Cl, Br, OH

BENZO[*b*]FURANS

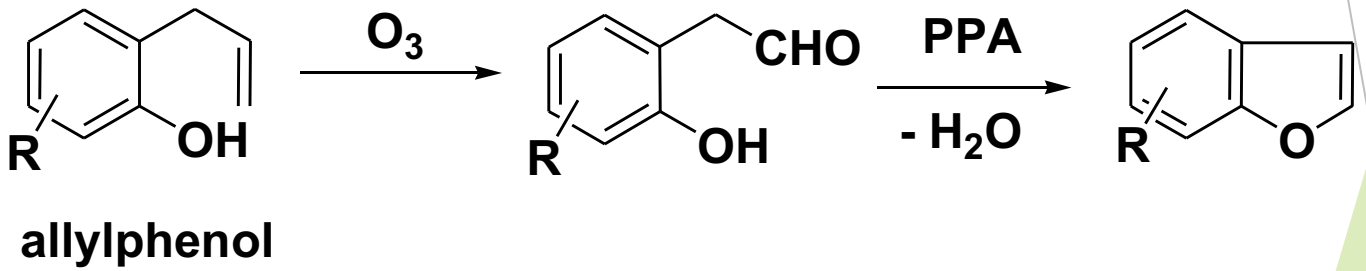
When arloxyacetone is treated with standard regents (H_2SO_4, $ZnCl_2$, $POCl_3$, KOH, or PPA), the corresponding 3-alkylbenzofuran is isolated.



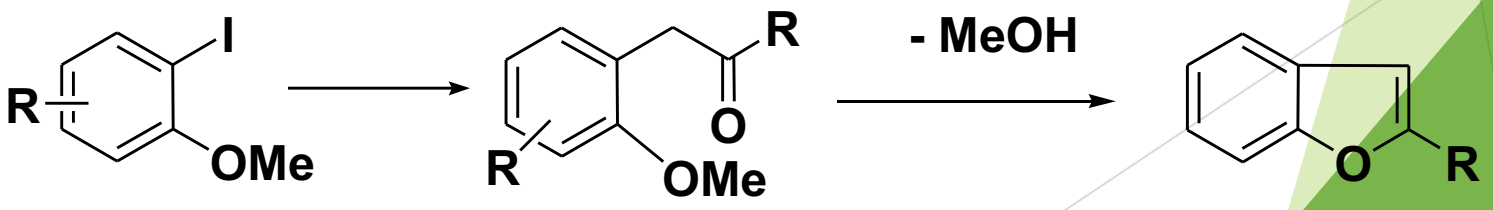

HO
O
CH3
O
KOH, H2O
HO
CH3
O
Cl
O
CH3
O
C6H5
PPA
Δ
Cl
CH3
O
C6H5
Cl
O
C6H5
CH3
O
PPA
Δ
Cl
CH3
O
C6H5

Hansch reaction

Thermal ring closure with subsequent cyclodehydrgenation of ortho-substituted phenols is known as *Hansch* reaction and can best be demonstrated by the acid-catalyzed cyclization of aldehyde. The key aldehyde is conveniently obtained by ozonlysis of allylphenol.

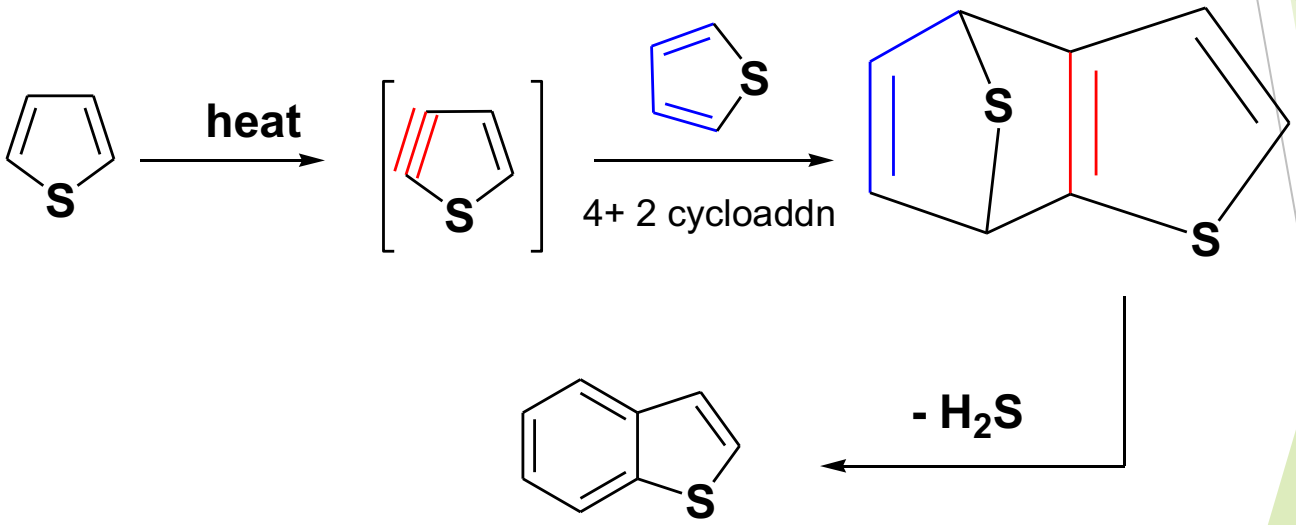


allylphenol

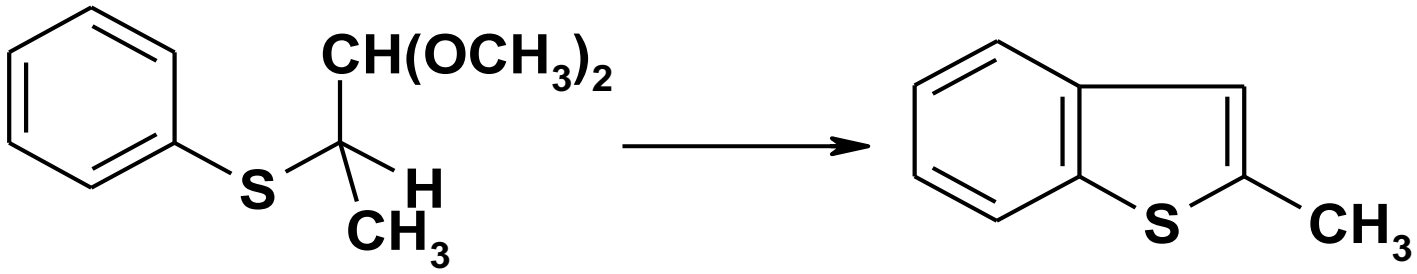


BENZO[b]THIOPHENE

1- Via direct pyrolysis of thiophene

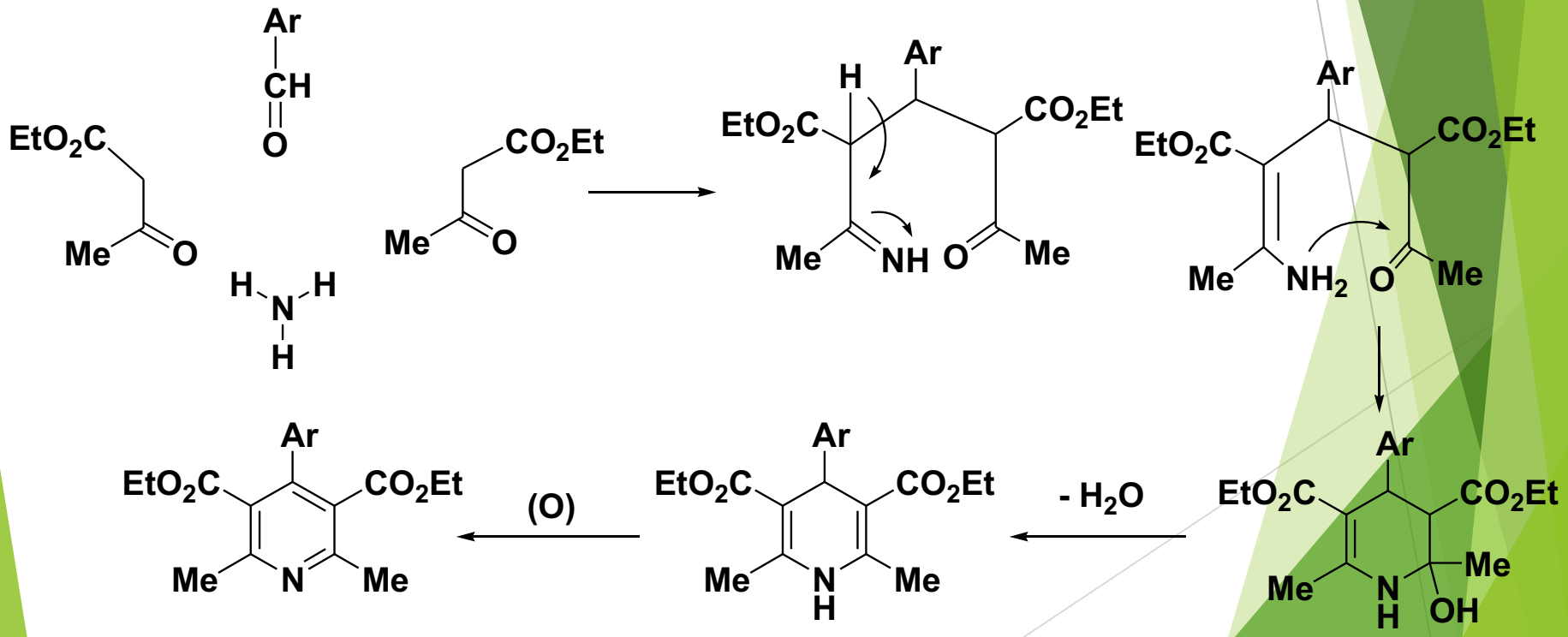


Arylthio dimethoxy propane are readily cyclized in the presence of PPA to give substituted benzo[*b*]thiophene. (Arylthio)acetone, arylphenylsulfides, and S-rylthioglycolic acids react similarly.



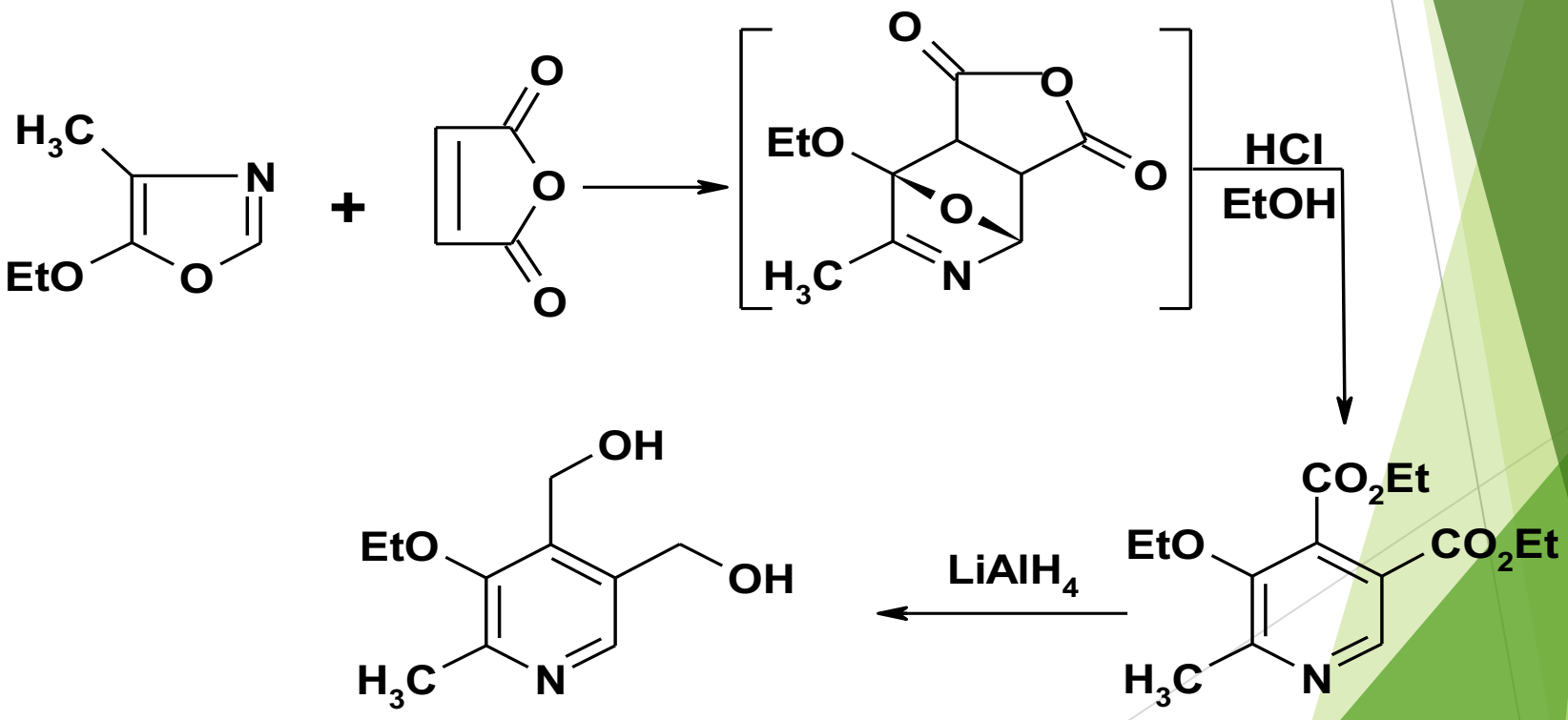
Hantzsch synthesis

Hantzsch synthesis is used to prepare Symmetrical pyridines, which combine two molecule of a β-ketoester like ethyl acetoacetate, an aldehyde, and ammonia source to give the dihydropyridine, which oxidized to pyridines.

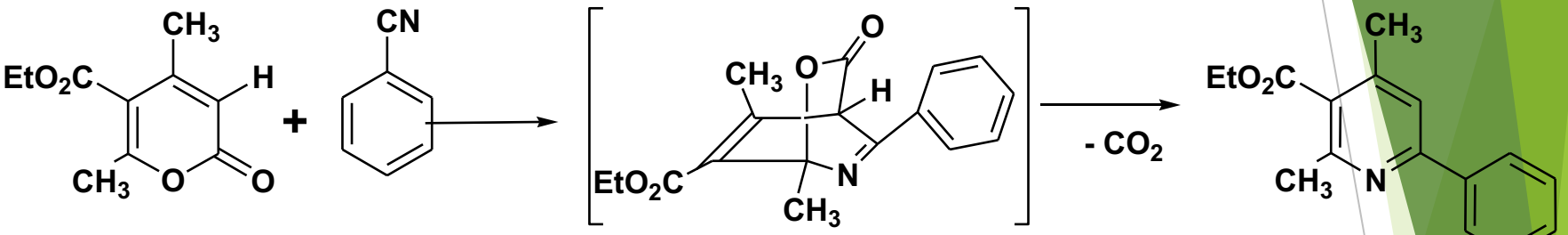


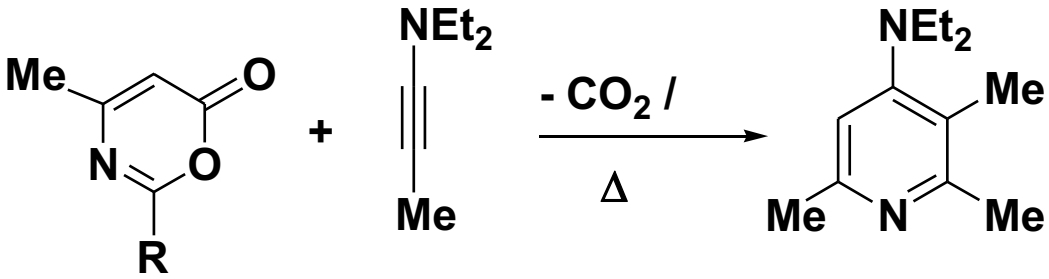
4- Diels-Alder reaction

Diels-Alder reaction of diverse electron-poor heterocycles with electron-rich dienophiles give rise to bicyclic intermediate, which undergo reterocycloaddition to generate the heteroaromatic nucleus. Thus, oxazole has been transformed to pyridoxine.



The α-pyrone react with benzonitrile to give pyridine, and oxazinones react with ynamines to give the corresponding pyridine



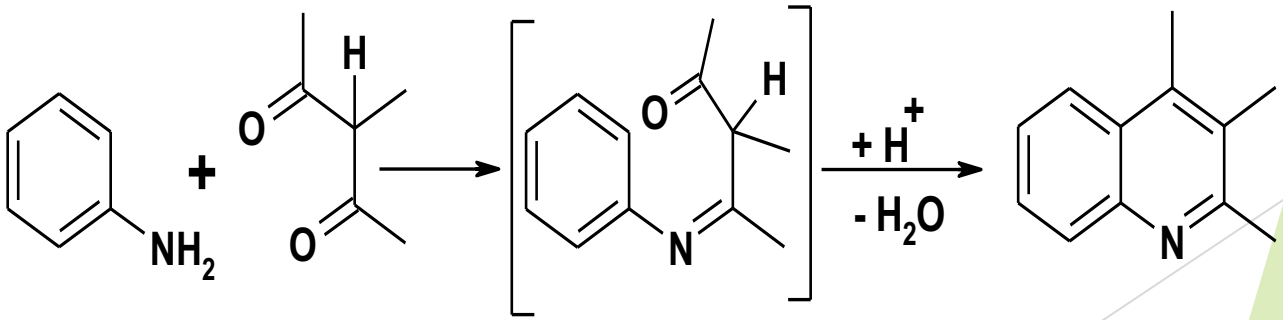


Synthesis of Quinoline compounds

1. Ring Synthesis

There are three important methods for the construction of the quinoline ring system from non-heterocyclic precursors, and all three start with benzene compounds.

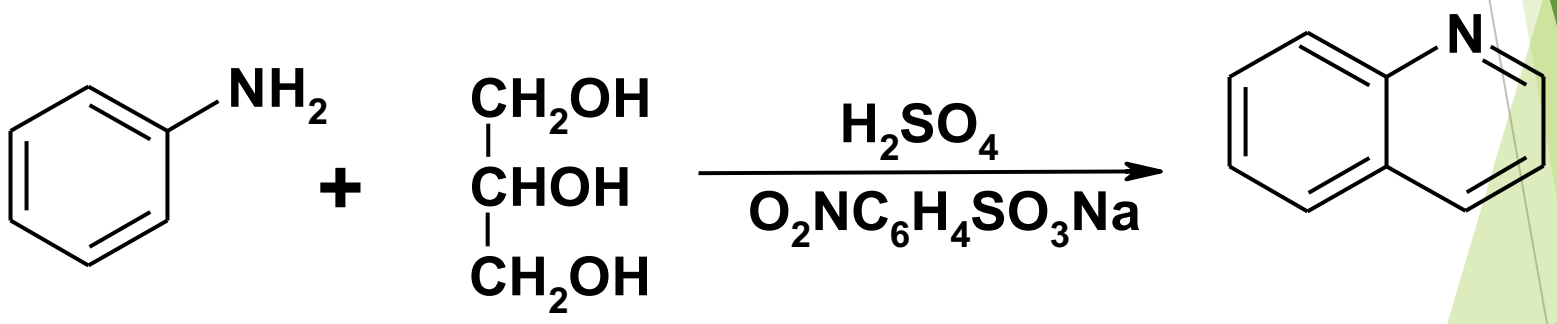
Anilines react with 1,3-dicarbonyl compounds to give intermediates, which can be cyclized with acid.

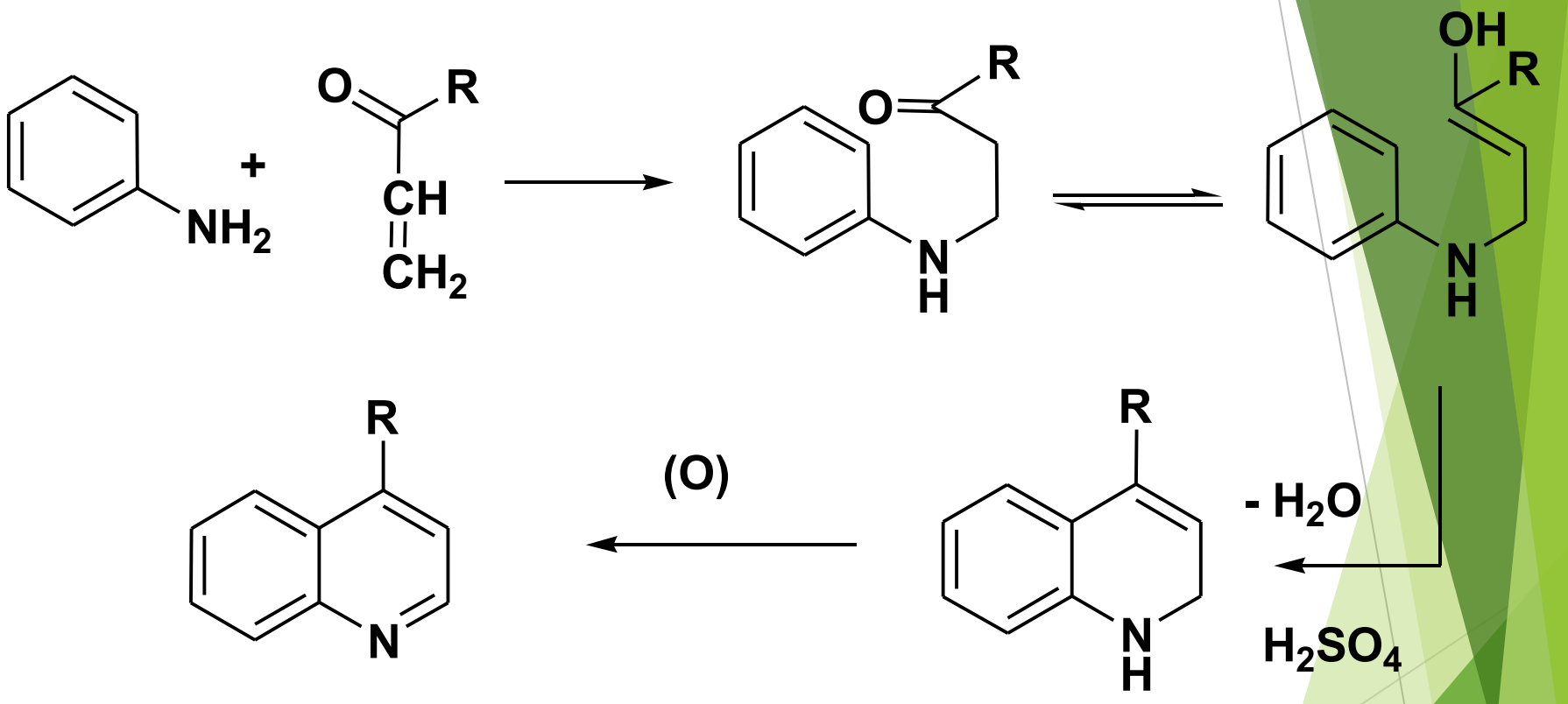


The *Skraup* Synthesis

From arylamines and α,β-unsaturated carbonyl compounds.

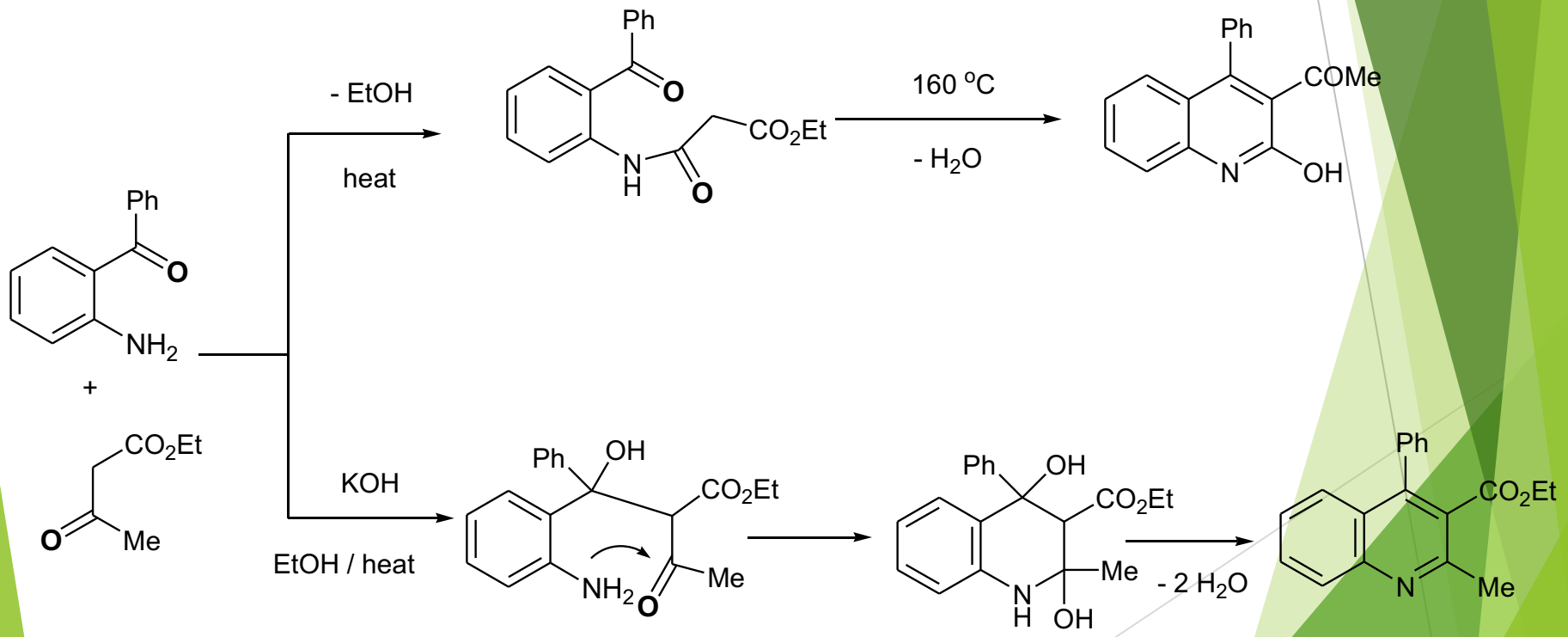
The *Skraup* Synthesis. In this extraordinary reaction, quinoline is produced when aniline, concentrated sulphuric acud, glycerol and a mild oxidizing agent are heated together.

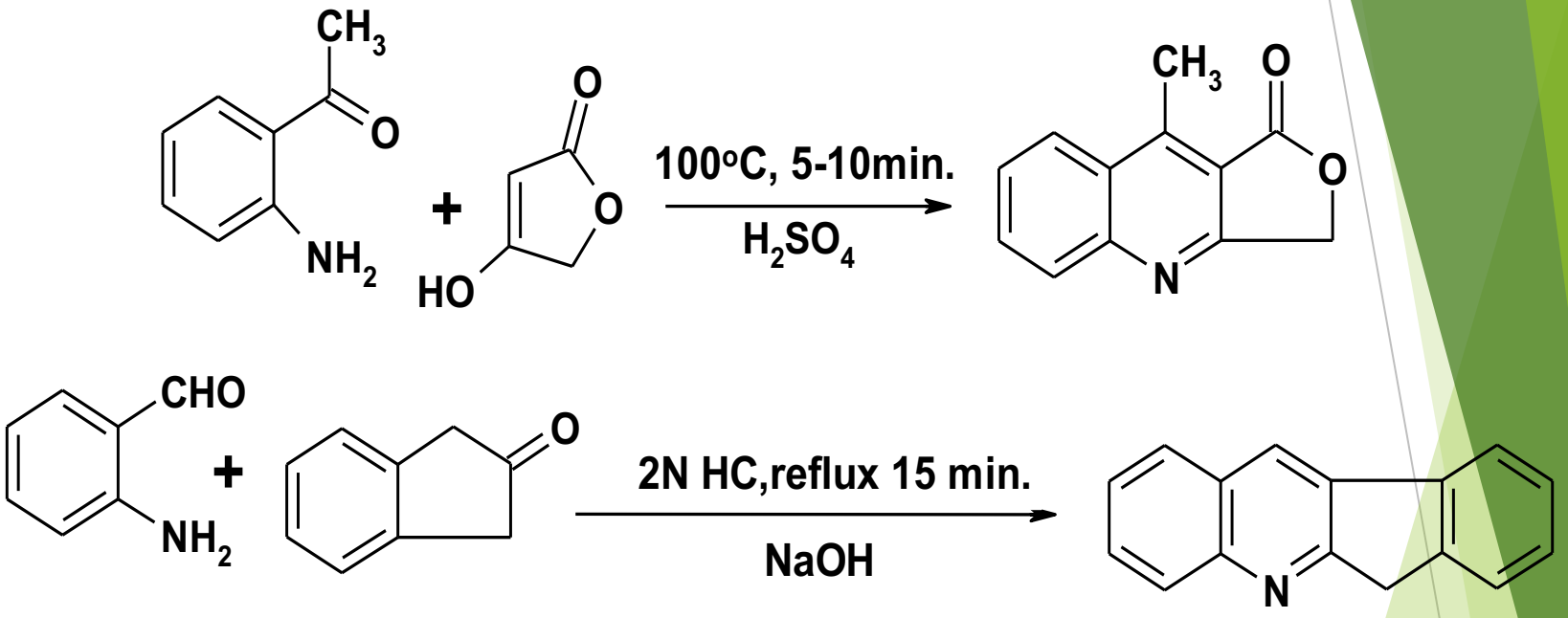



NH2
+
O
R
CH
CH2
R
O
N
H
OH
R
N
H
R
N
H
- H2O
H2SO4
(O)
R
N

The Friedlander and Pftizinger Syntheses

A second generally useful method of preparing substituted quinolines involves the condensation of an *o*-amino aromatic aldehyde or ketone with a carbonyl compound having the grouping $–CH_2CO-$.

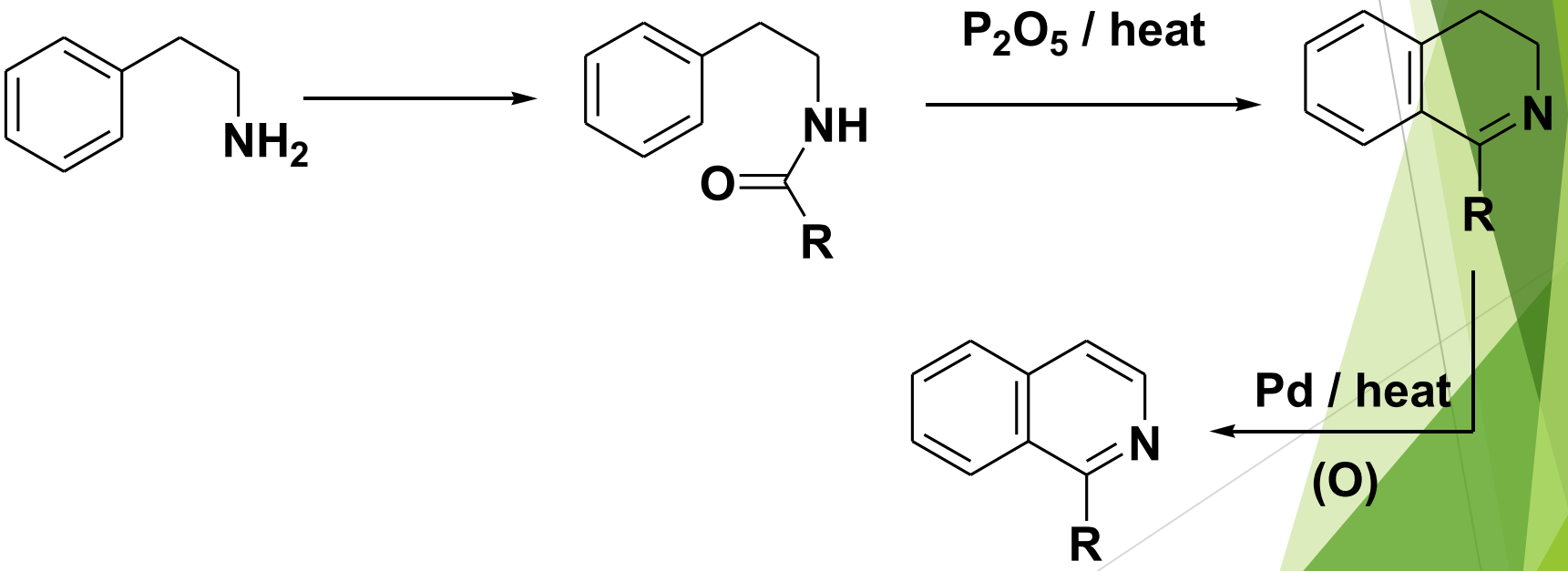



CH3
O
NH2
+
O
O
HO
100°C, 5-10min.
H2SO4
CH3
O
O
N
CHO
NH2
+
O
2N HC,reflux 15 min.
NaOH
N

Isoquinolines

1- Bischler-Napieralski reaction

In the *Bischler-Napieralski* reaction the β-phenylethylamine is acylated and then cyclodehydrated by reaction with phosphoryl chloride, phosphorus pentaoxide, or other Lewis acids.



2- Isoquinoline can be obtained by passing the vapours of benzylidene ethylamine through red hot tube