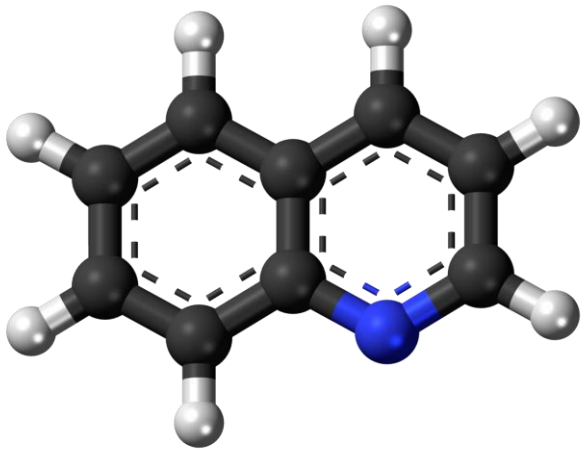
2302687 – Heterocyclic Compounds – Part I

Lecture 4-5

Quinoline and Isoquinoline



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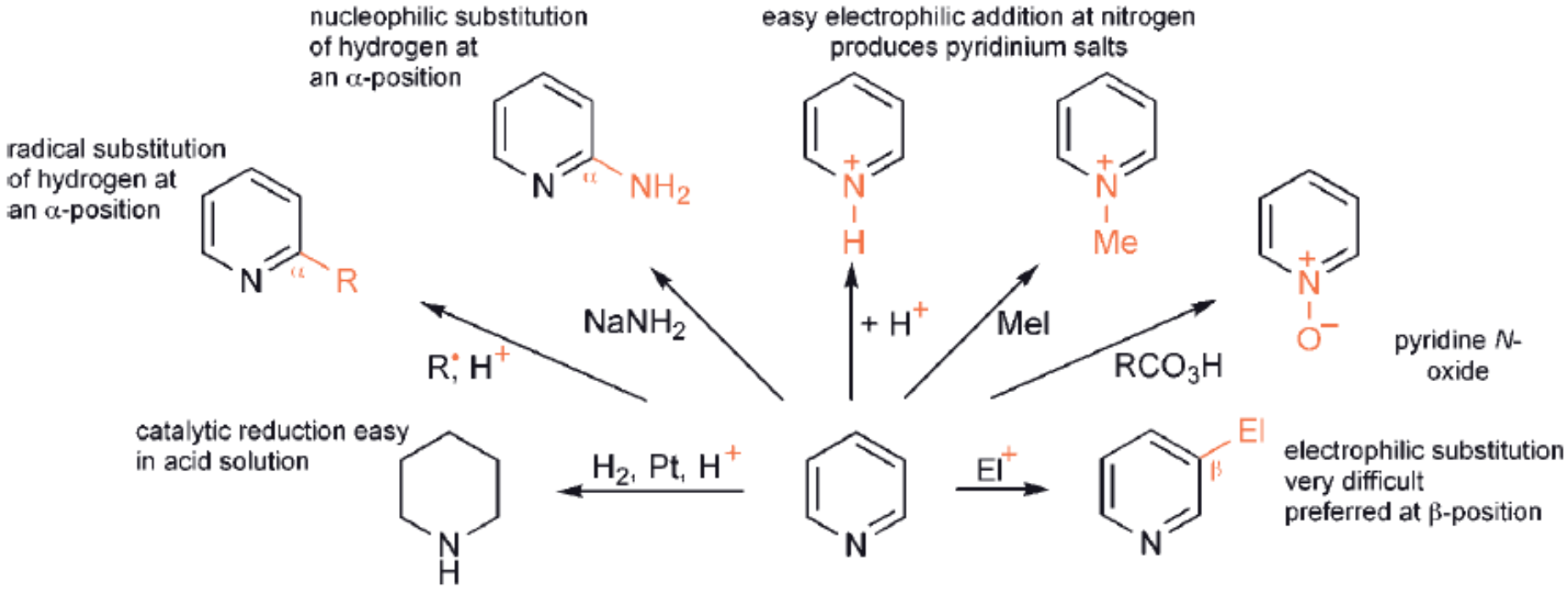
Recommended Textbook:

Heterocyclic Chemistry, 5th Edition, J. A. Joule, K. Mills, **2010**, Wiley

Reactions of Pyridine

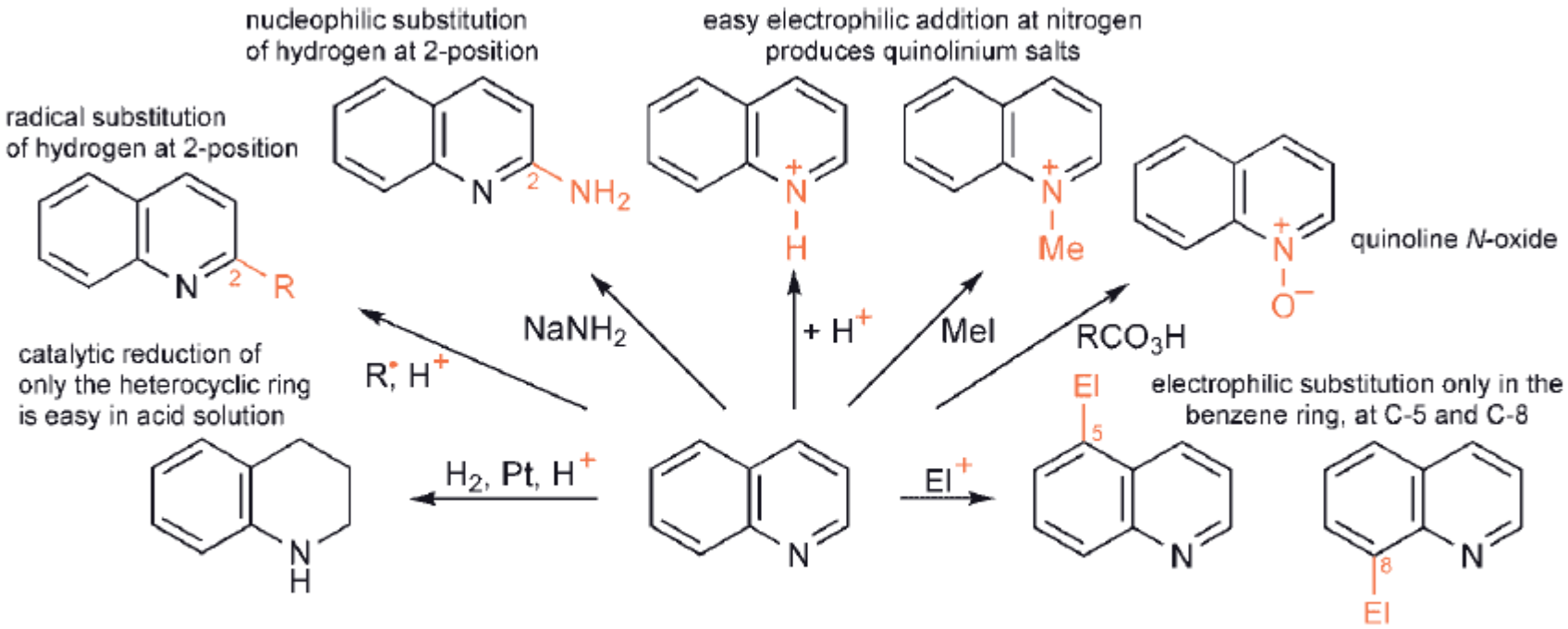
- Pyridines are much **less susceptible to electrophilic substitution** and **more susceptible to nucleophilic attack** than benzene due to their low electron density



Typical reactions of pyridine

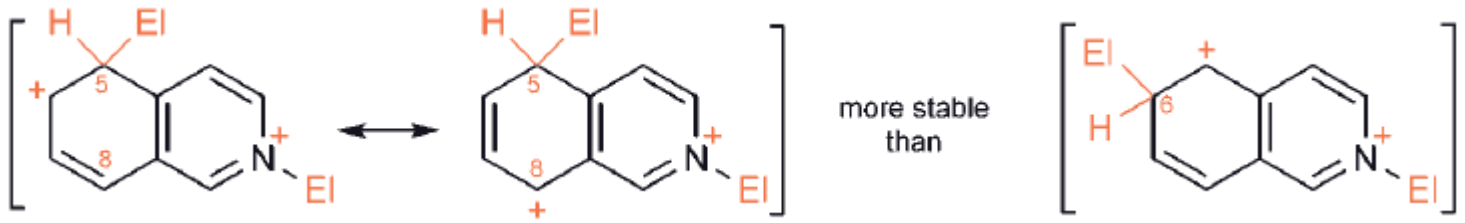
Reactions of Quinoline (and Isoquinoline)

- Electrophilic substitution favours the **benzenoid** ring, rather than the pyridine ring



Typical reactions of quinoline (isoquinoline is very similar)

- preferred substitution at the **5**- and **8**-positions

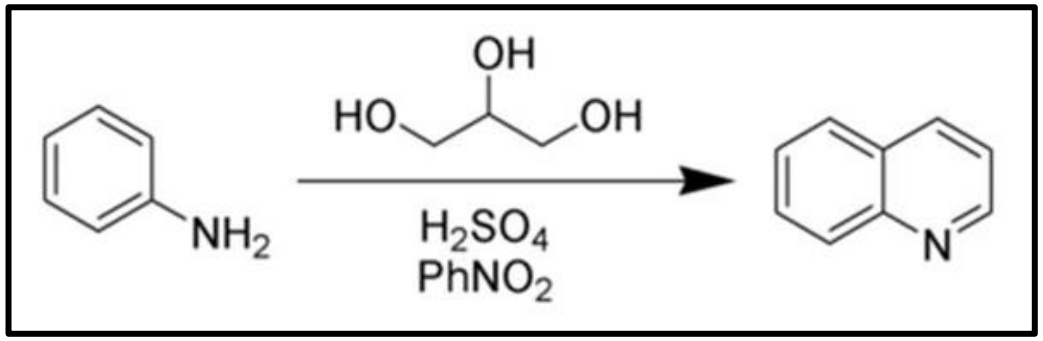


Synthesis of Quinoline – Name Reactions

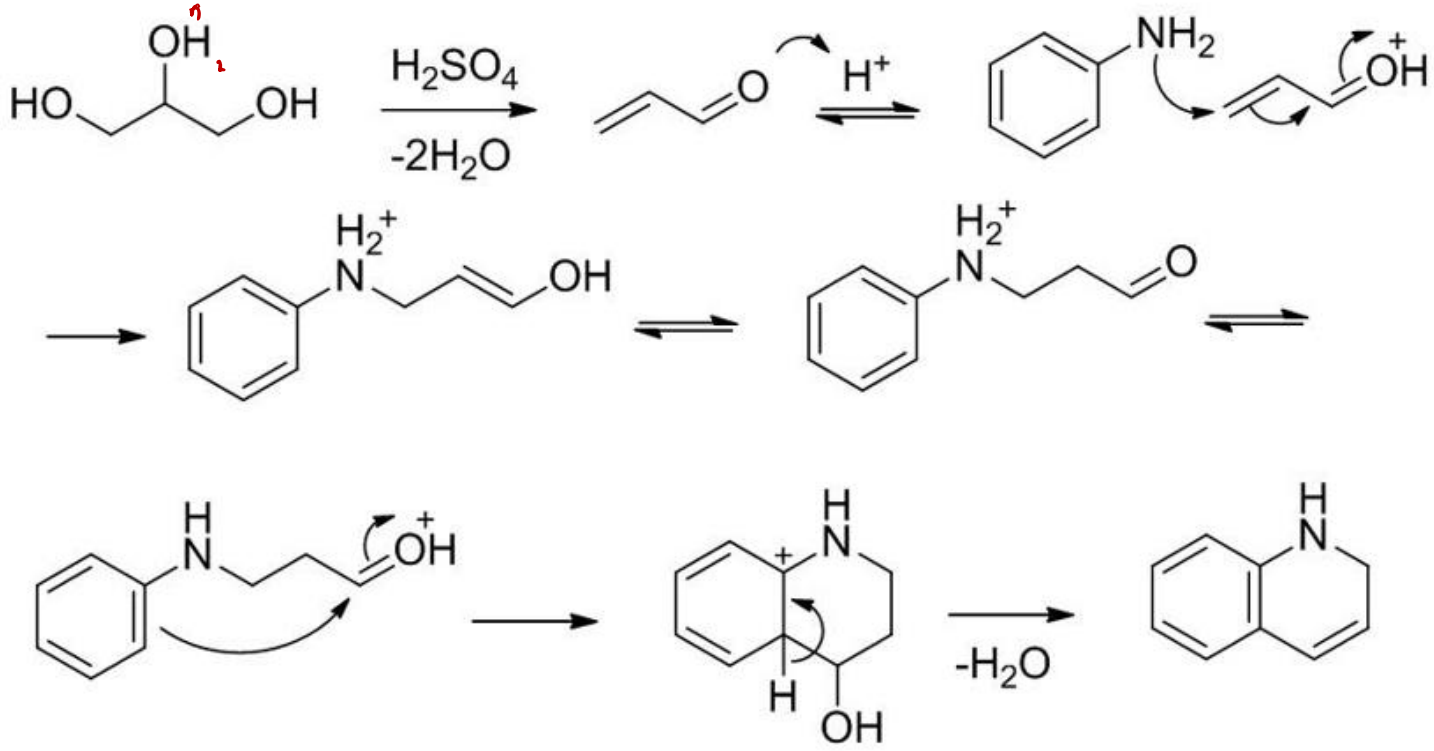
- **Skraup Reaction**

Used to synthesise quinolines. It is named after the Czech chemist Zdenko Hans Skraup (1850-1910)

In this reaction, aniline is heated with H_2SO_4, glycerol and an oxidizing agent such as $PhNO_2$ to yield quinoline



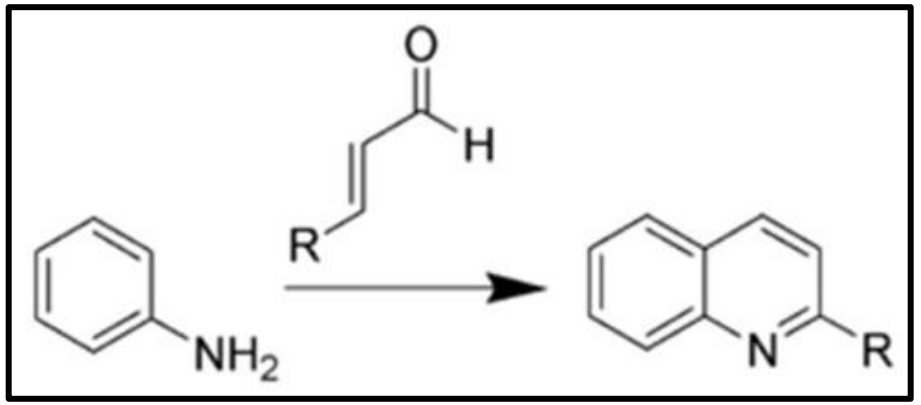
Mechanism



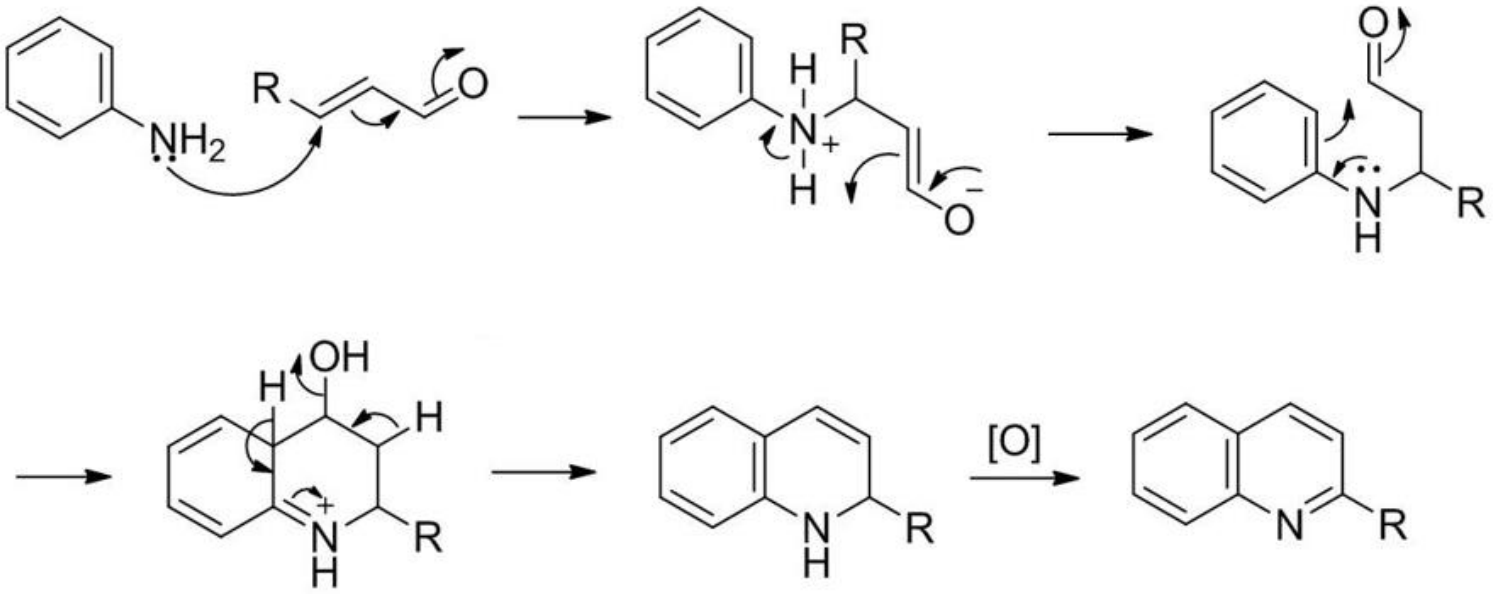
Synthesis of Quinoline – Name Reactions

- **Doebner-Miller Reaction**

Named after the Germans Oscar Döbner and Wilhelm von Miller. The reaction of an aniline with *α*,*β*-unsaturated carbonyl compounds to form quinolines



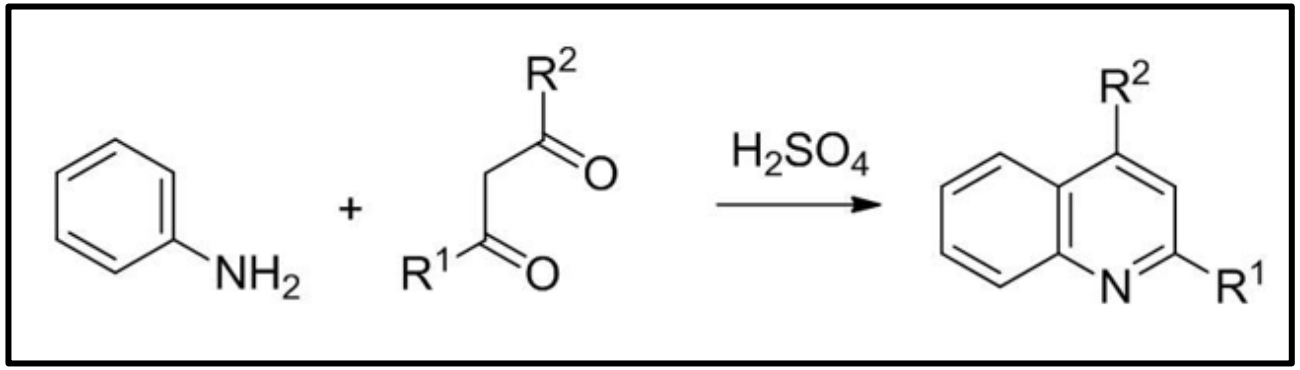
Mechanism



Synthesis of Quinoline – Name Reactions

- **Combes Quinolone Synthesis**

In 1888, Combes has reported the condensation of aniline with *β*-diketones to form disubstituted quinolones by using H_2SO_4 as a catalyst



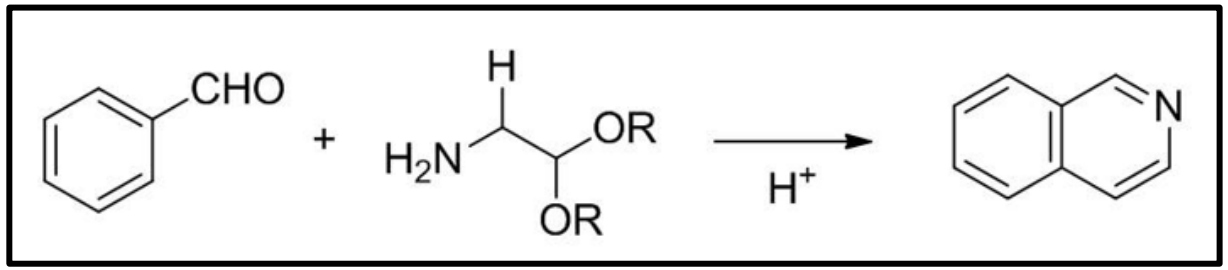
Mechanism

Synthesis of Isoquinoline – Name Reactions

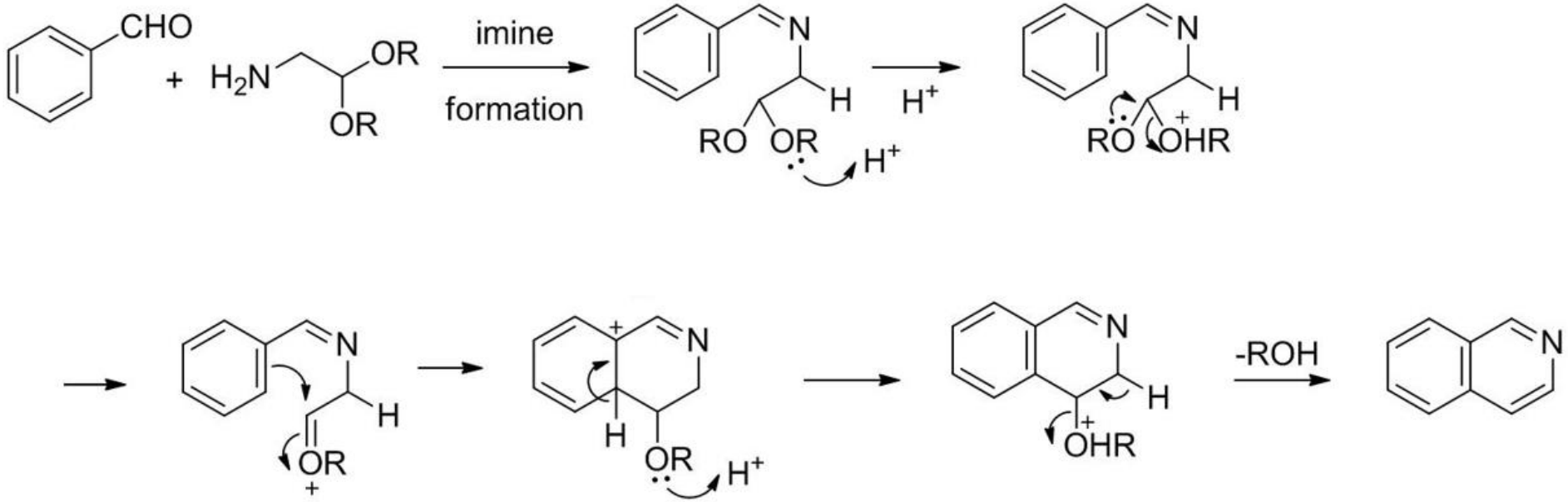
- **Pomeranz-Fritsch Reaction**

Named after Paul Fritsch (1859-1913) and Cäsar Pomeranz (1860-1926)

In general it is a synthesis of Isoquinoline from the acid-promoted condensation and cyclisation of benzaldehyde and 2,2-dialkoxyethylamine



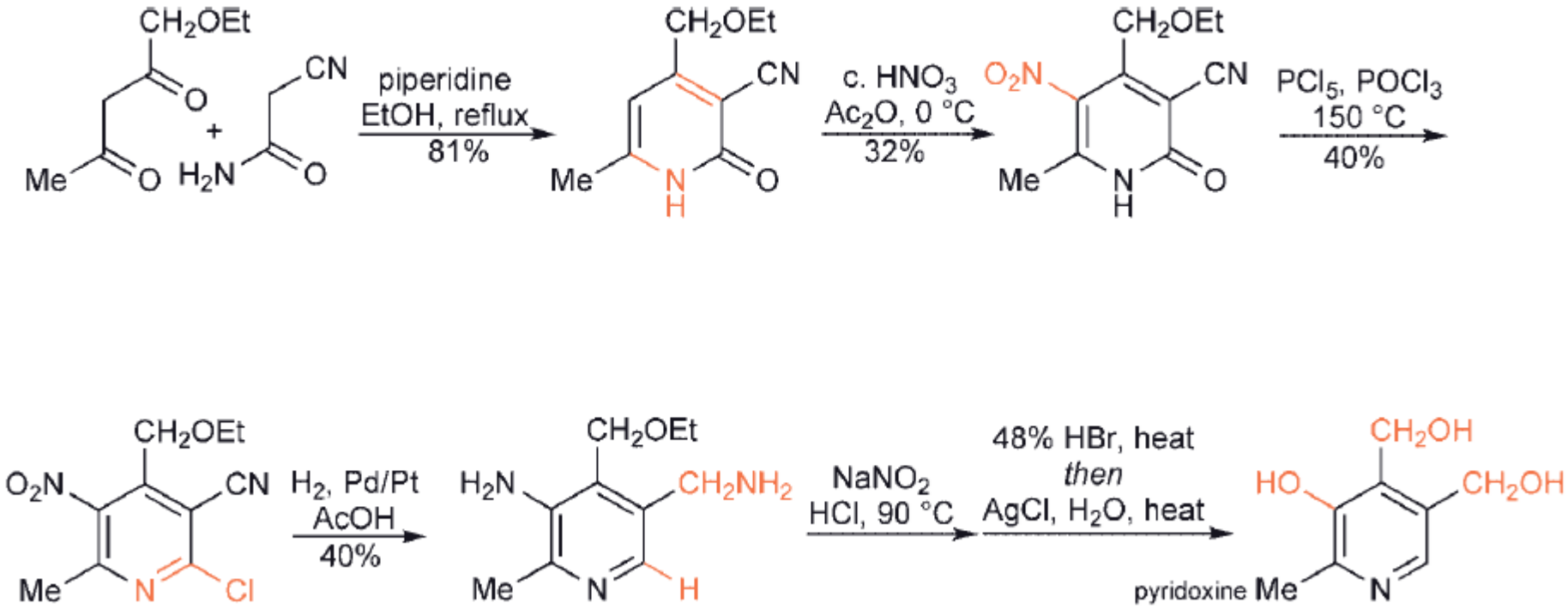
Mechanism



Notable Synthesis of Pyridine

Examples – Pyridoxine

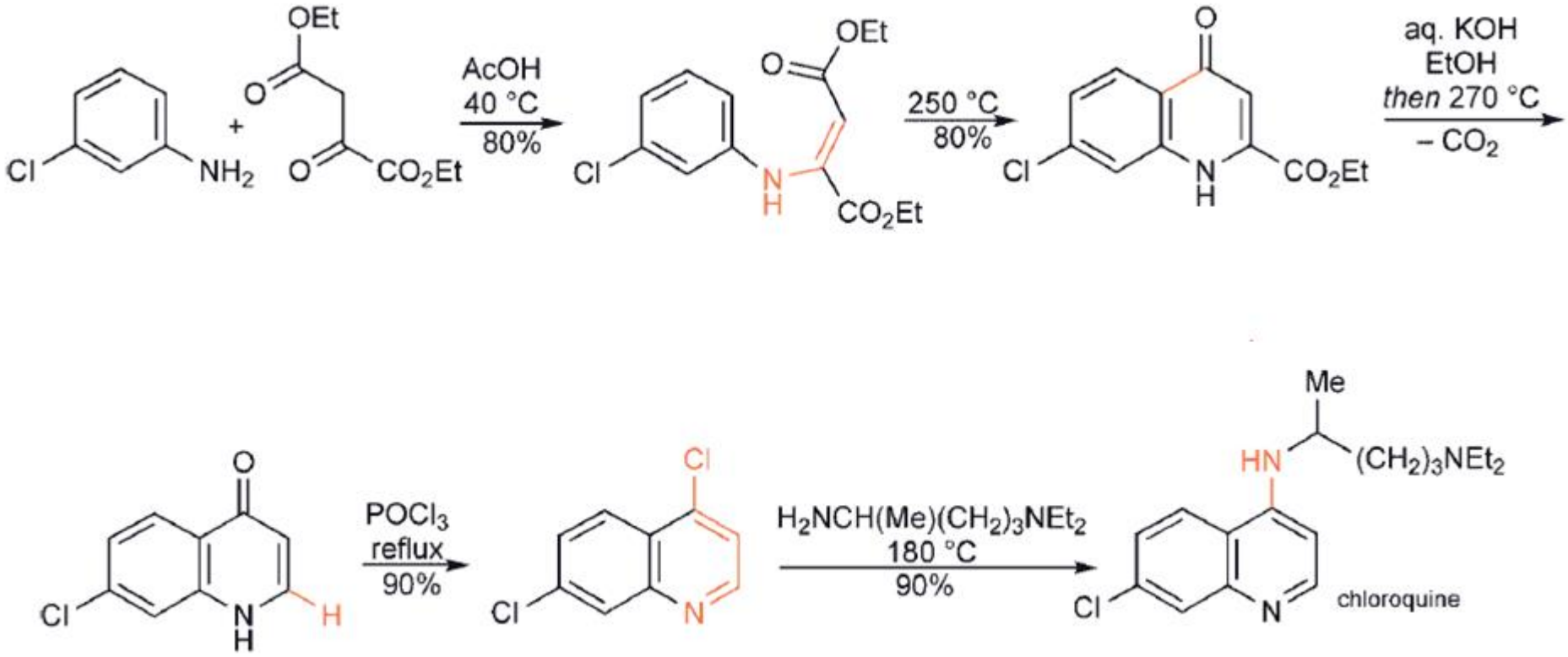
Pyridoxine, vitamin B_6, has been synthesised by several routes, including one that utilises Guareschi ring synthesis



Notable Synthesis of Quinoline

Examples – Chloroquine

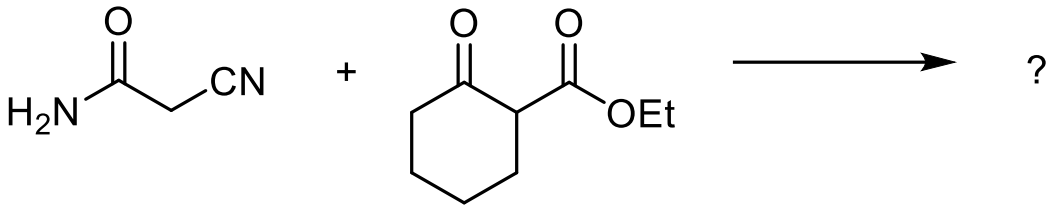
Chloroquine is a synthetic antimalarial drug



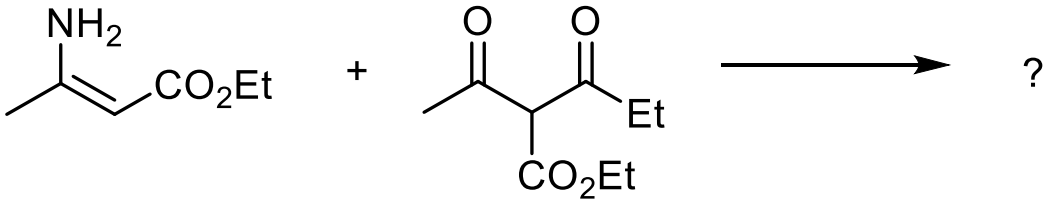
Homework #1

Give the mechanism and the structure of products resulting from the following reagent combinations:

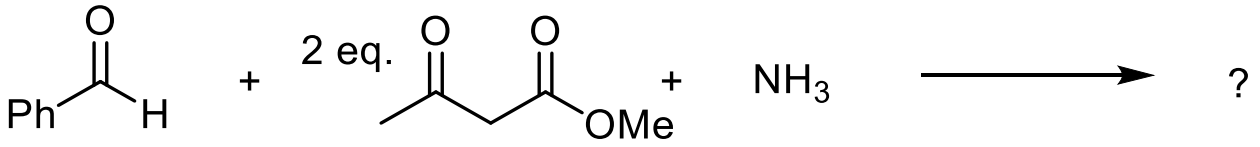
1.1)



1.2)



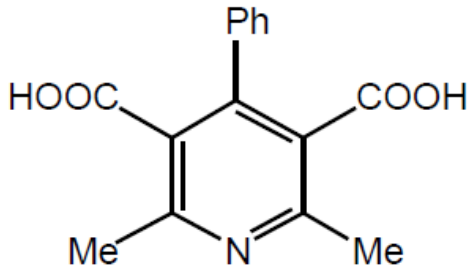
1.3)



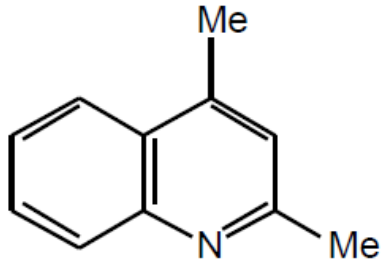
Homework #2

Suggest the synthesis of the following compounds starting from either **A**, **B** or **C**

2.1)



2.2)



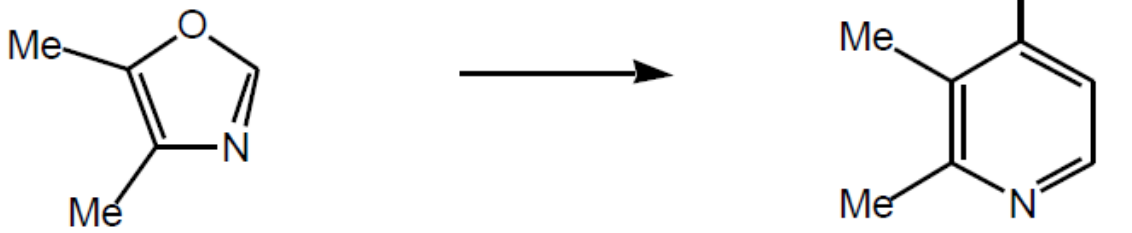
$CH_3COCH_2COCH_3$ **A**

CH_3COCH_2COOEt **B**

$CH_2(COOEt)_2$ **C**

Suggest reagents that would achieve the following transformation

2.3)



Homework #3

3.1) How could one convert 4-pyridone cleanly into 1-ethyl-4-pyridone?

3.2) What would be the result of treating a 1:1 mixture of 2- and 3-methylpyridines with 0.5 equivalents of LDA and then 0.5 equivalents of MeI?

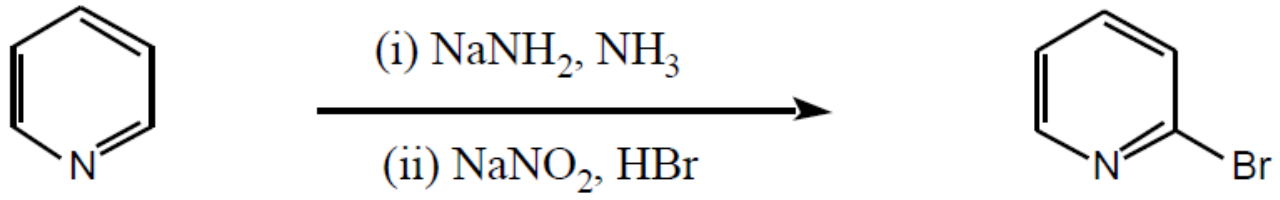
3.3) Suggest a structure for the product $C_7H_8N_2O_3$ produced by treating 3-ethoxypyridine with fuming HNO_3/conc. H_2SO_4 at 100 °C

3.4) Deduce a structure for the product $C_9H_{15}N_3$ produced by reacting pyridine with the potassium salt of $Me_2N(CH_2)_2NH_2$

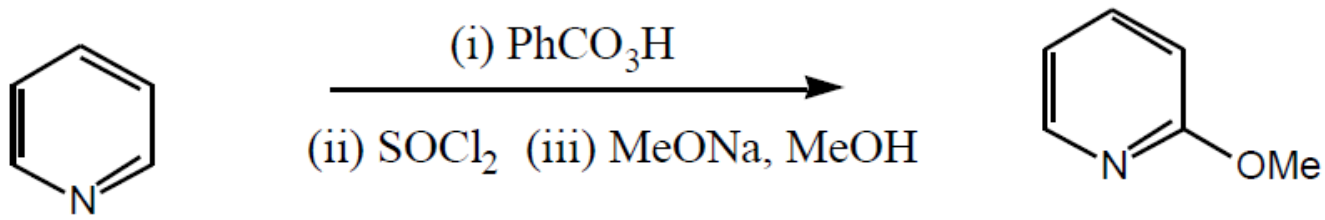
Homework #4

Provide a plausible mechanistic explanation for the chemistry of the following reaction schemes:

4.1)



4.2)



4.3)