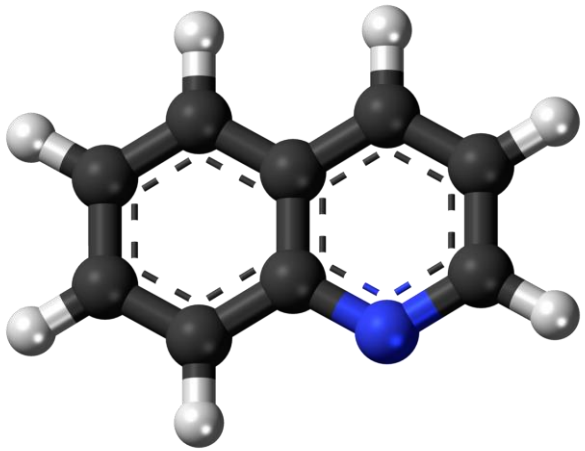
2302687 – Heterocyclic Compounds – Part I

Lecture 4-1

Synthesis of Pyridine Part 1

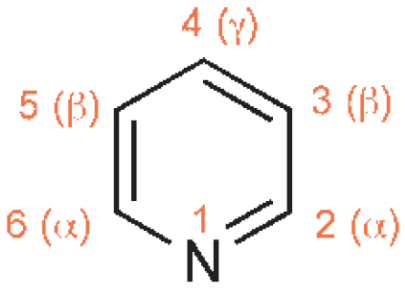


Instructor: Dr. Tanatorn Khotavivattana
E-mail: tanatorn.k@chula.ac.th

Recommended Textbook:

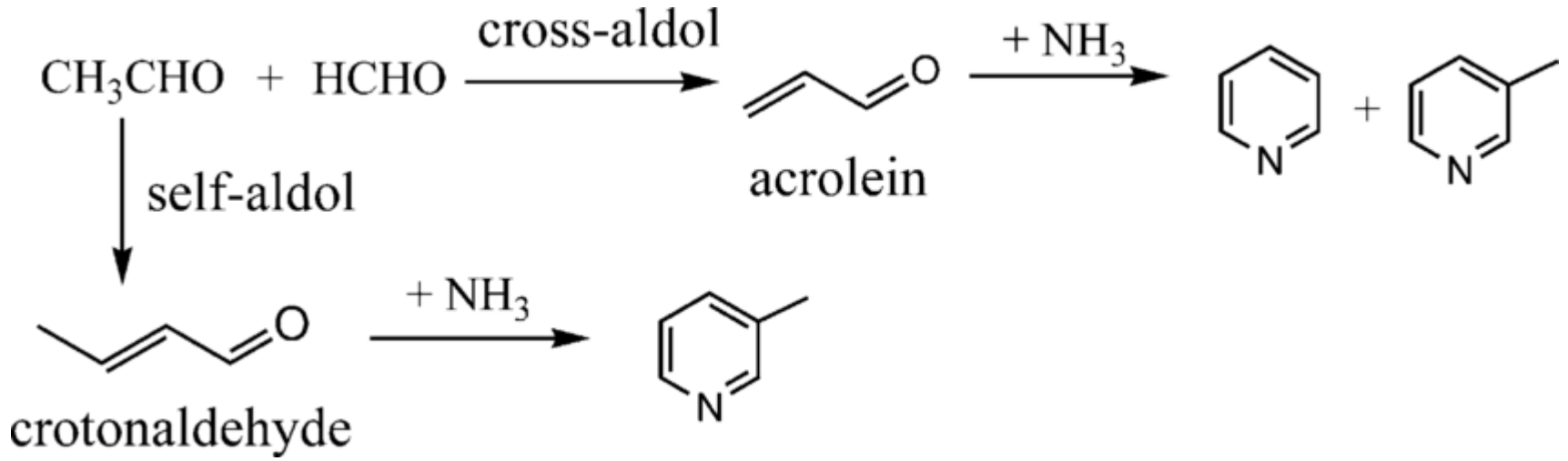
Heterocyclic Chemistry, 5th Edition, J. A. Joule, K. Mills, **2010**, Wiley

Pyridine

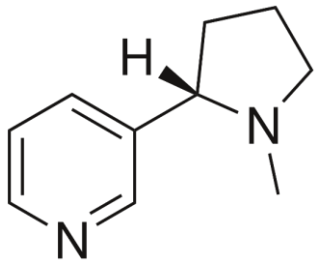


pyridine

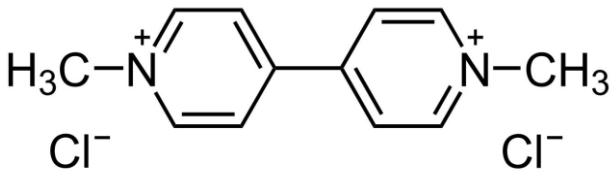
- **Stable** and relatively unreactive liquids, with strong penetrating **odours**
- They are much used as **solvents** and **bases** in many organic reactions
- Completely **miscible** with water
- First isolated from **bone** pyrolysates and **coal tar**
- Produced on a commercial scale in 60 – 70% yields by the gas-phase high-temperature interaction of acetaldehyde, formaldehyde, steam, air and ammonia over a silica–alumina catalyst



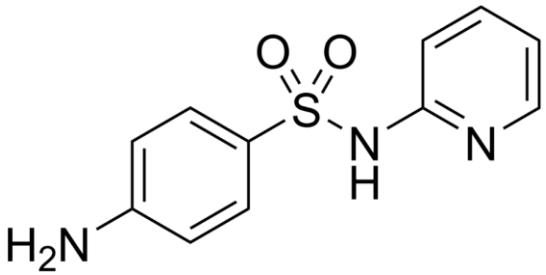
Bioactive Pyridines



Nicotine is a pharmacologically active constituent of tobacco – toxic and addictive

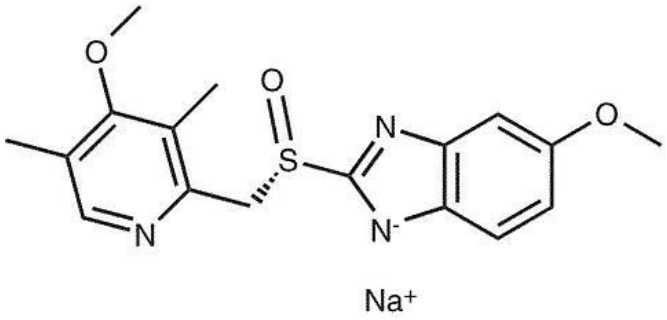


Paraquat is one of the oldest herbicides – toxic and non-selective



Sulphapyridine is a sulphonamide anti-bacterial agent – one of the oldest antibiotics

Drugs Containing Pyridine

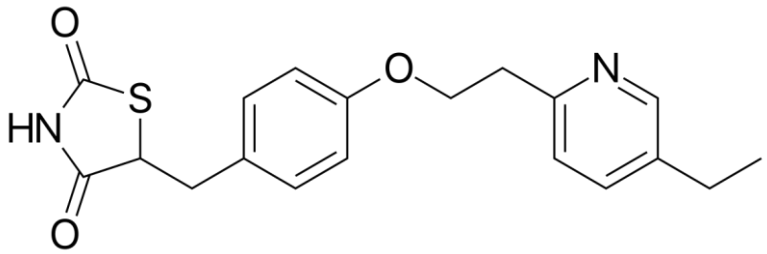


Name: **Nexium**

2008 Sales: $4.79 billion

Company: AstraZeneca

Disease: Acid reflux

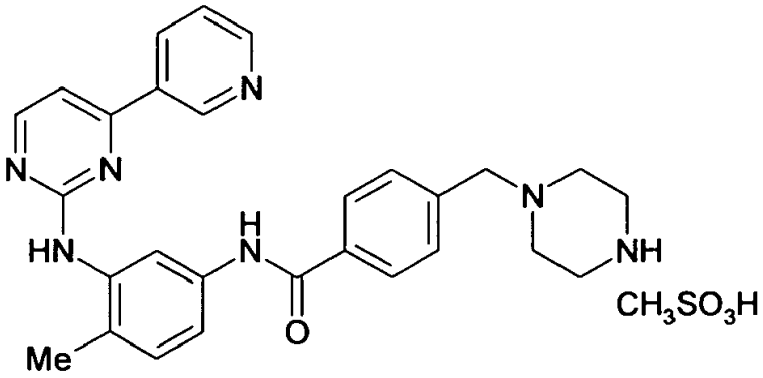


Name: **Actos**

2008 Sales: $2.45 billion

Company: Eli Lilly

Disease: Type 2 diabetes

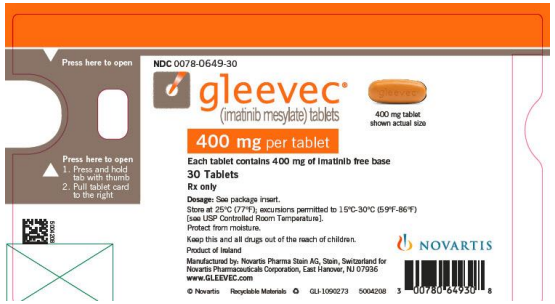


Name: **Gleevec**

2008 Sales: $0.45 billion

Company: Novartis

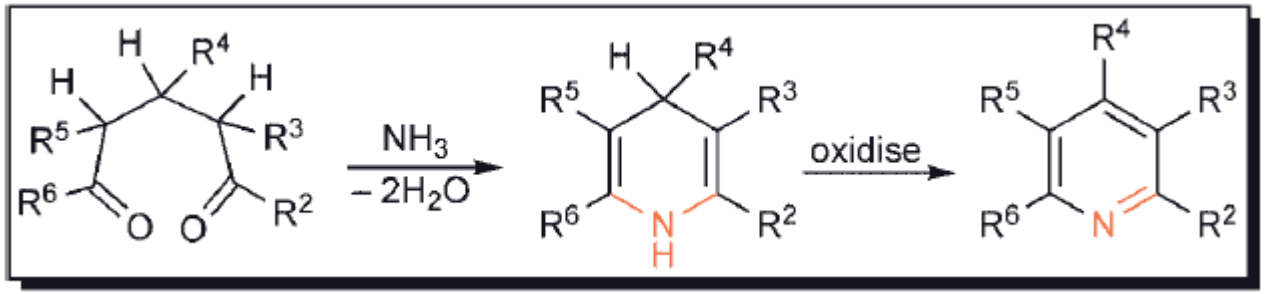
Disease: Leukemia



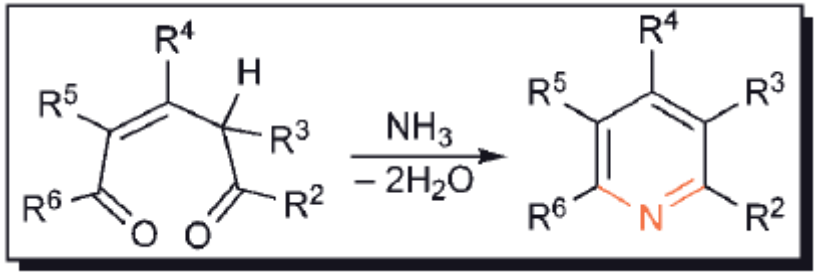
Ring Synthesis of Pyridines

1) From 1,5-Dicarbonyl Compounds and Ammonia

- Ammonia reacts with 1,5-dicarbonyl compounds to give 1,4-dihydropyridines, which are easily dehydrogenated to pyridines



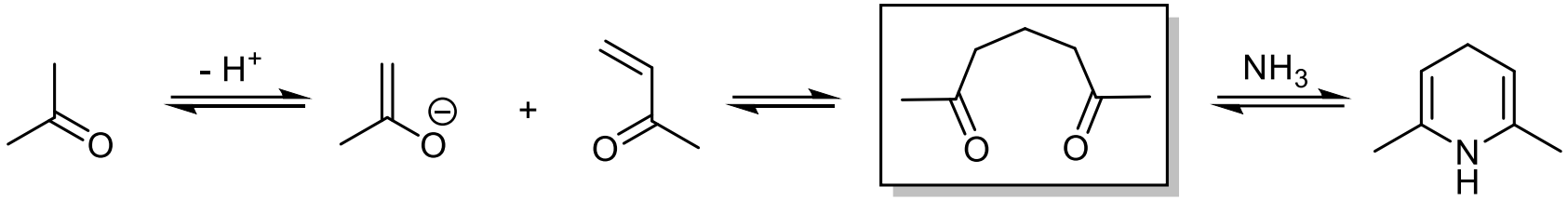
- With unsaturated 1,5-dicarbonyl compounds, or their equivalents (e.g. pyrylium ions), ammonia reacts to give pyridines directly



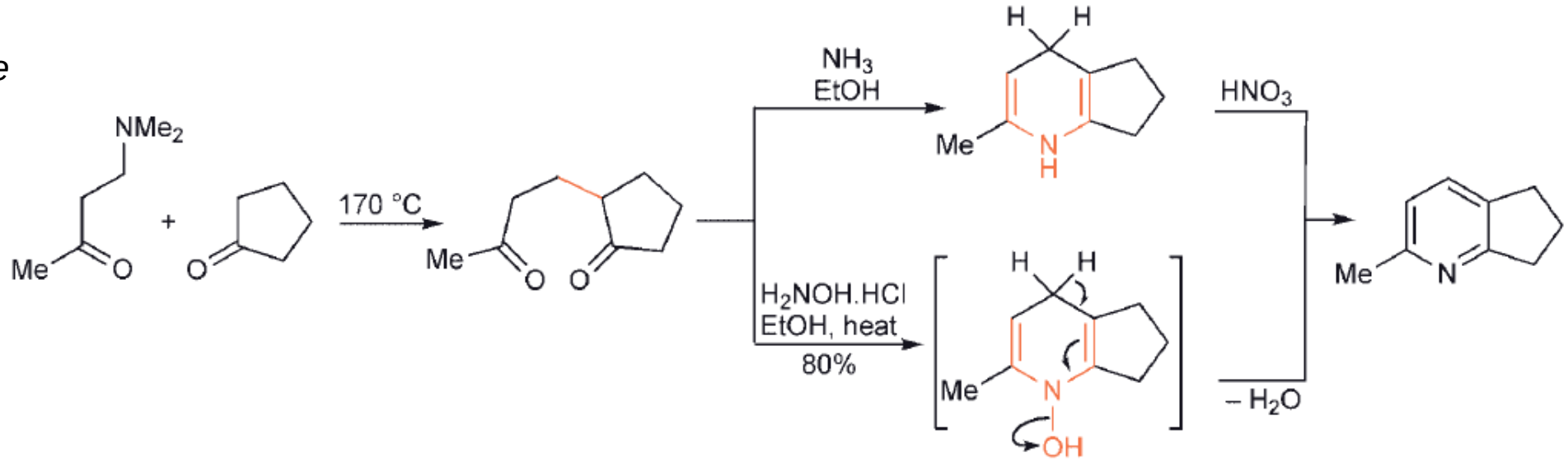
Ring Synthesis of Pyridines

1) From 1,5-Dicarbonyl Compounds and Ammonia

- 1,5-Diketones are accessible via a number routes, for example by **Michael addition of enolate to enone**



Example

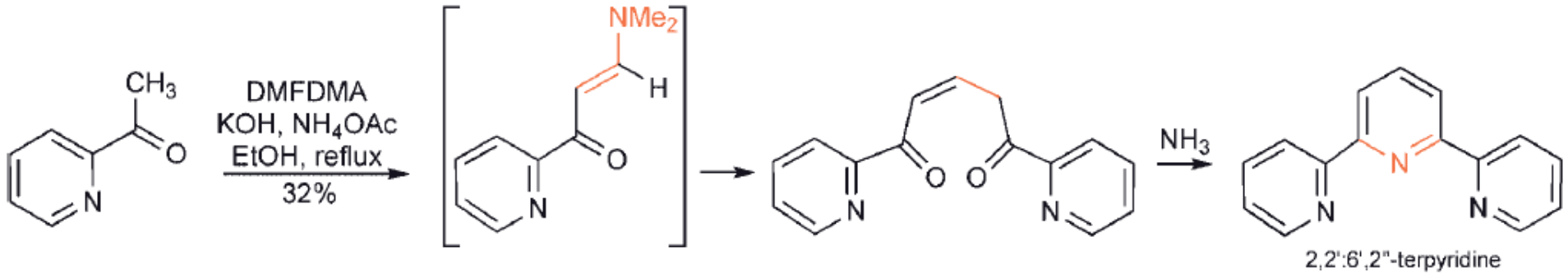


- The oxidative final step can be neatly avoided by the use of hydroxylamine instead of ammonia

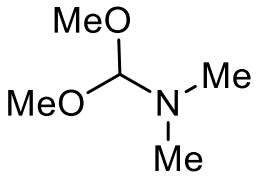
Ring Synthesis of Pyridines

1) From 1,5-Dicarbonyl Compounds and Ammonia

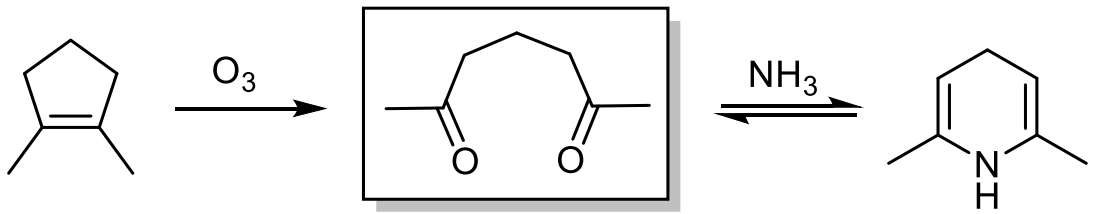
Example



DMFDMA =



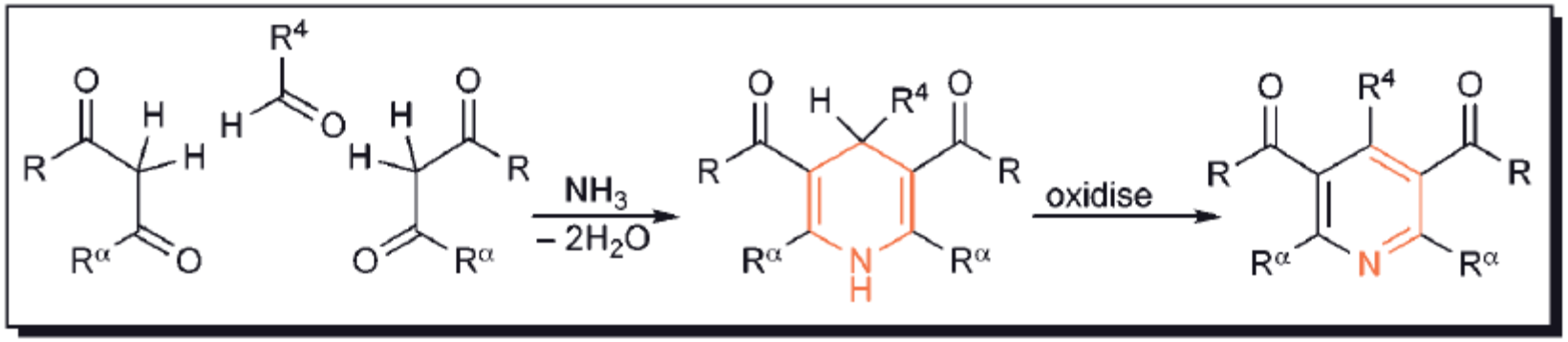
- Ozonolysis of a cyclopentene precursor can also lead to the 1,5-diketone



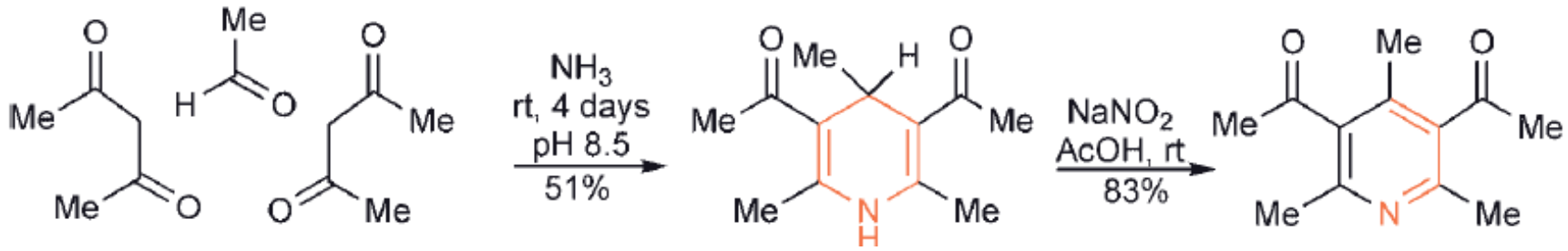
Ring Synthesis of Pyridines

2) From an Aldehyde and Two Equivalents of a 1,3-Dicarbonyl Compound

- Symmetrical 1,4-dihydropyridines, which can be easily dehydrogenated, are produced from the interaction of ammonia, an aldehyde and two equivalents of a 1,3-dicarbonyl compound, which must have a central methylene



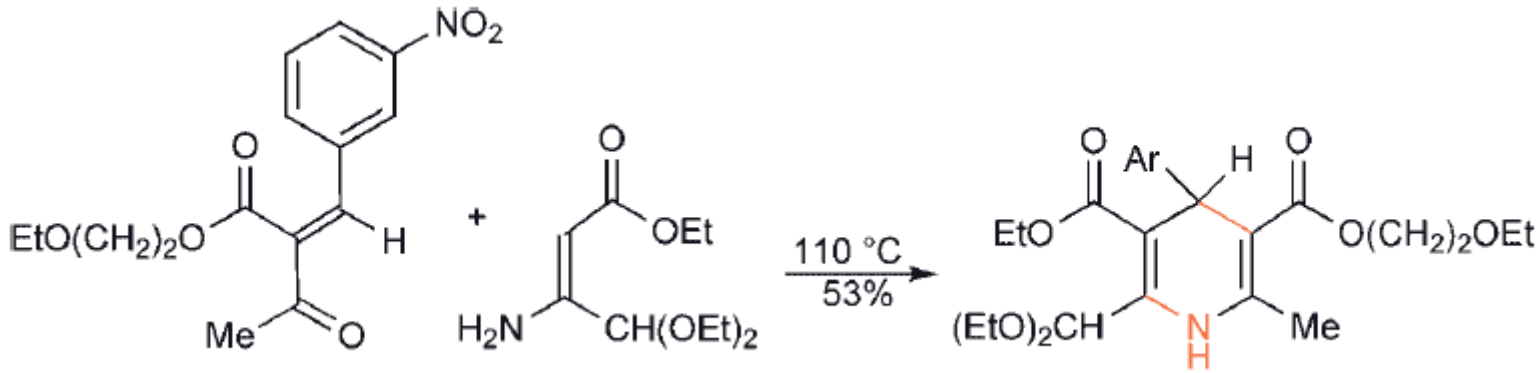
Example: Hantzsch Synthesis



Ring Synthesis of Pyridines

2) From an Aldehyde and Two Equivalents of a 1,3-Dicarbonyl Compound

- Unsymmetrical 1,4 - dihydropyridines are produced by conducting the Hantzsch synthesis in two stages



Ring Synthesis of Pyridines

2) From an Aldehyde and Two Equivalents of a 1,3-Dicarbonyl Compound

- This strategy can also be applied for the synthesis of 2,2′:6′,2″-terpyridines with *in situ* aromatisation there being no *β*-carbonyl groups to stabilise the dihydro-pyridine