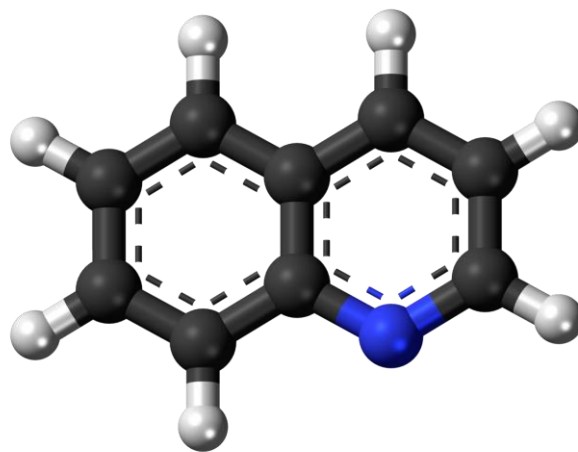


## Synthesis of Pyridine Part 2

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*Instructor: Dr. Tanatorn Khotavivattana*

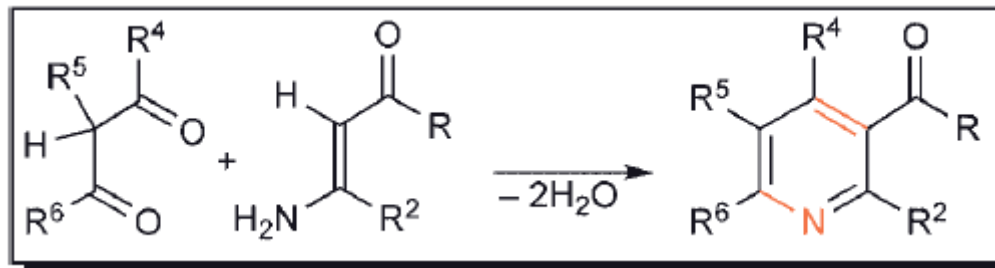
*E-mail: [tanatorn.k@chula.ac.th](mailto:tanatorn.k@chula.ac.th)*

**Recommended Textbook:**

*Heterocyclic Chemistry*, 5<sup>th</sup> Edition, J. A. Joule, K. Mills, **2010**, Wiley

# Ring Synthesis of Pyridines

## 3) From 1,3-Dicarbonyl Compounds and 3-Amino-Enones or -Nitriles

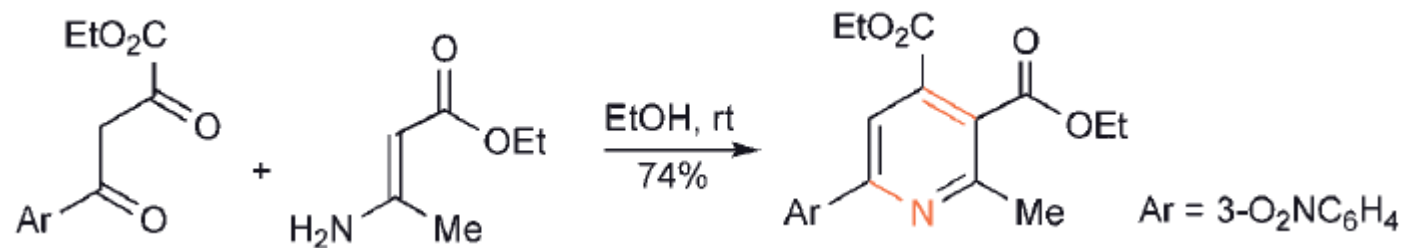


- This approach, in its various forms, is one of the most versatile and useful, since it allows the construction of **unsymmetrically** substituted pyridines from **relatively simple precursors**

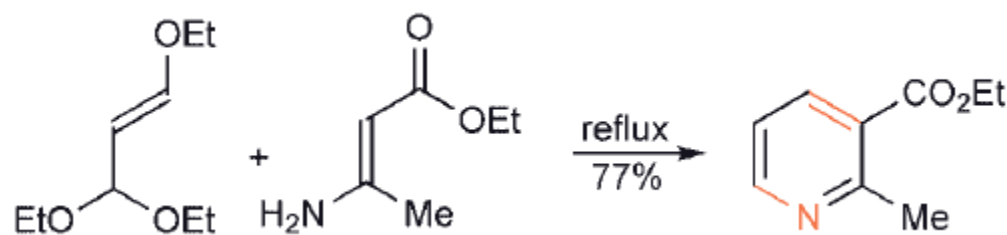
# Ring Synthesis of Pyridines

## 3) From 1,3-Dicarbonyl Compounds and 3-Amino-Enones or -Nitriles

- 3-Amino-enones or 3-amino-acrylates can be prepared by the straightforward reaction of ammonia with a 1,3-diketone or a 1,3-keto-ester.



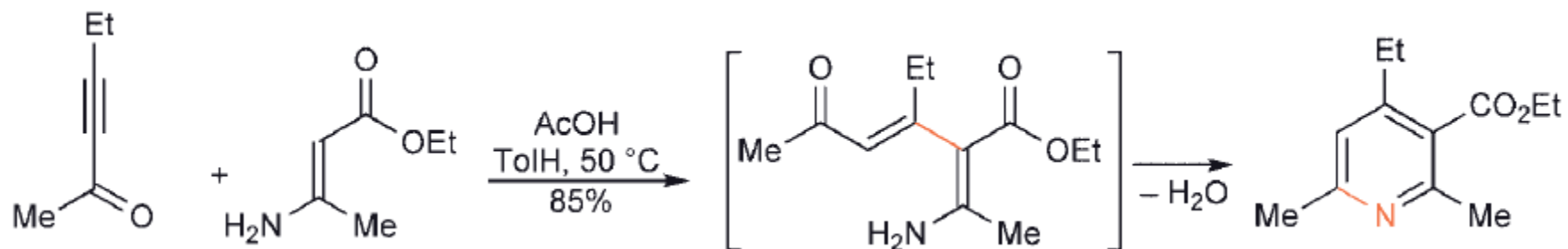
- The simplest 1,3-dicarbonyl compound, malondialdehyde, is too unstable to be useful, but its acetal enol ether can be used instead



# Ring Synthesis of Pyridines

## 3) From 1,3-Dicarbonyl Compounds and 3-Amino-Enones or -Nitriles

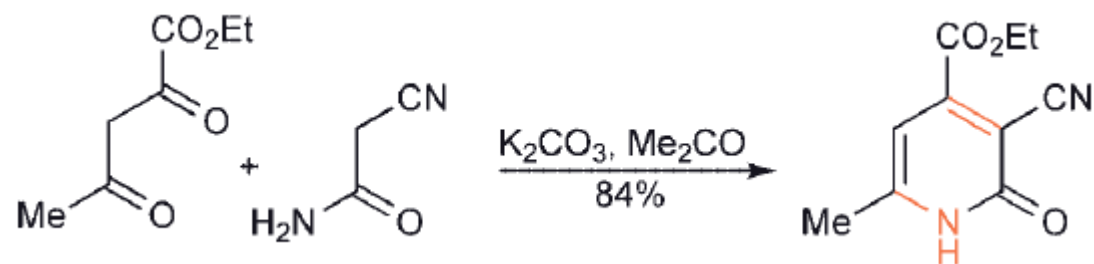
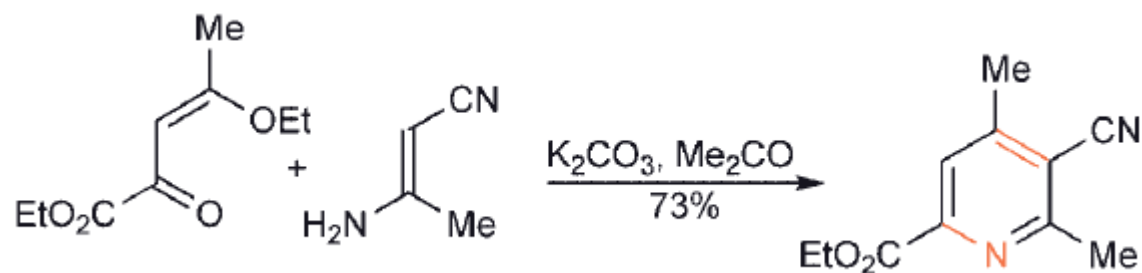
- **Bohlmann–Rahtz reaction:** The reaction of yne-ones (also synthons for 1,3-dicarbonyl compounds) is regioselective; addition of the ketone enamine is the first step



# Ring Synthesis of Pyridines

## 3) From 1,3-Dicarbonyl Compounds and 3-Amino-Enones or -Nitriles

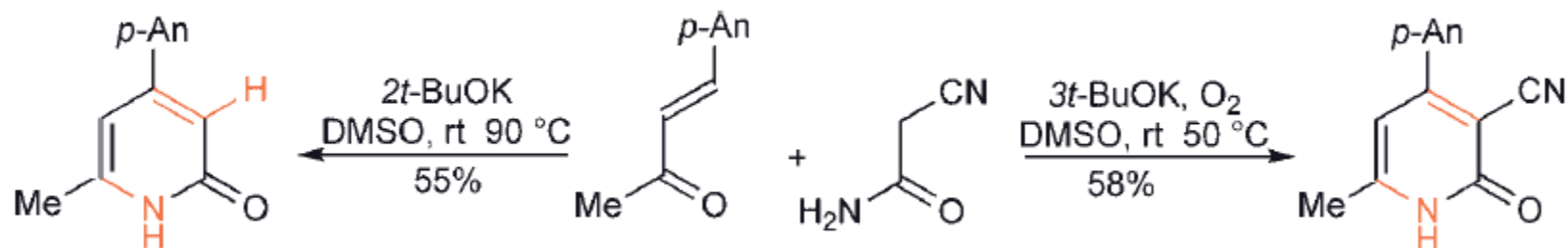
- **The Guareschi Synthesis** : This variation makes use of cyanoacetamide as the nitrogen - containing component and thus leads to 3-cyano-2-pyridones



# Ring Synthesis of Pyridines

## 3) From 1,3-Dicarbonyl Compounds and 3-Amino-Enones or -Nitriles

- Ring closures can also be carried out with starting materials at a lower oxidation level, with *in situ* dehydrogenation by air or added oxygen

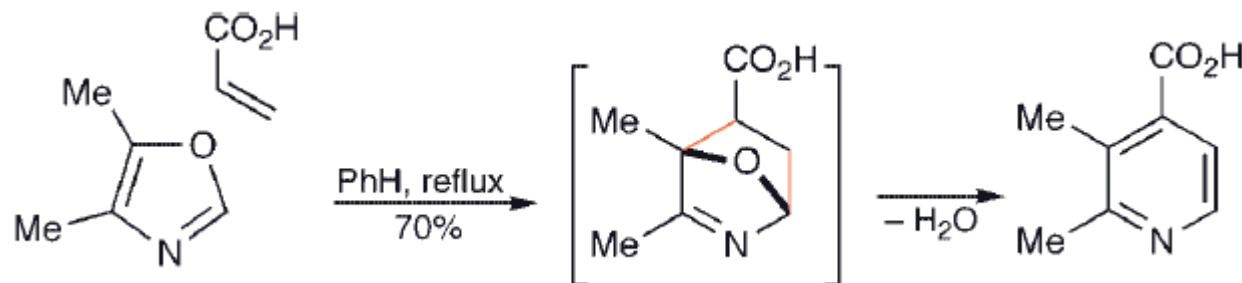
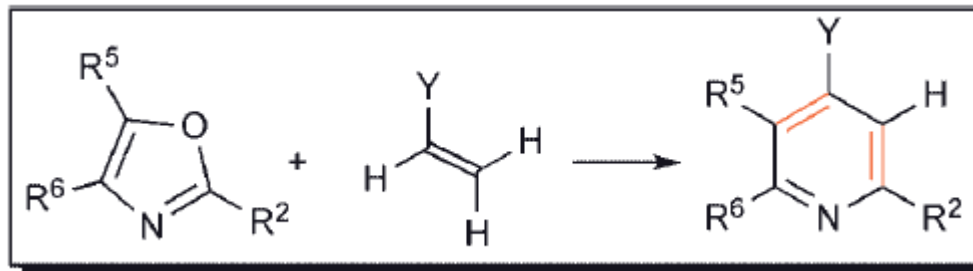


# Ring Synthesis of Pyridines

## 4) Via Cycloaddition

### 4.1) From Oxazoles

- The oxygen is lost as water



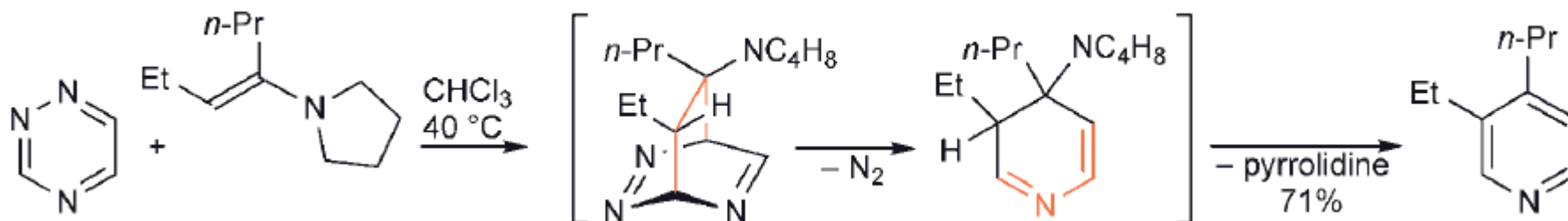
- Historically, the first of these was the addition of a dienophile to an oxazole; using **acrylonitrile**, hydrogen cyanide is lost to aromatise and the oxazole oxygen is retained (giving 3-hydroxypyridines)

# Ring Synthesis of Pyridines

## 4) Via Cycloaddition

### 4.2) From Triazines

- 1,2,3- and 1,2,4-Triazines, acting as inverse electron-demand azadienes, add to enamines; the following extrusion of nitrogen and loss of amine forms a pyridine





# Ring Synthesis of Pyridines

## 4) Via Cycloaddition 4.2) From Triazines

- Norbornadiene can also be used as a dienophile; cyclopentadiene being lost in the final stage

