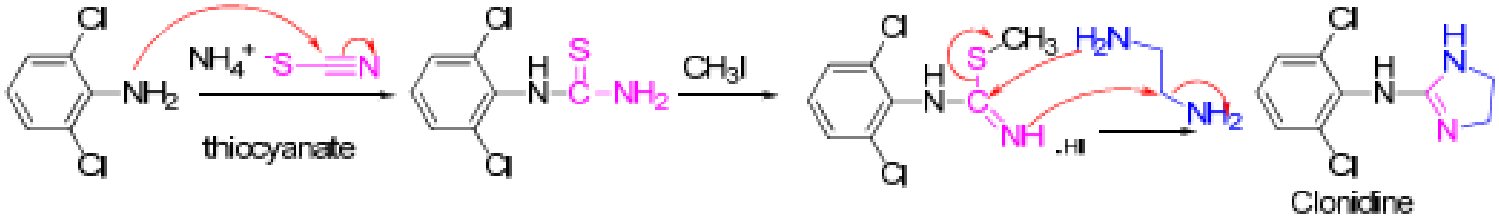
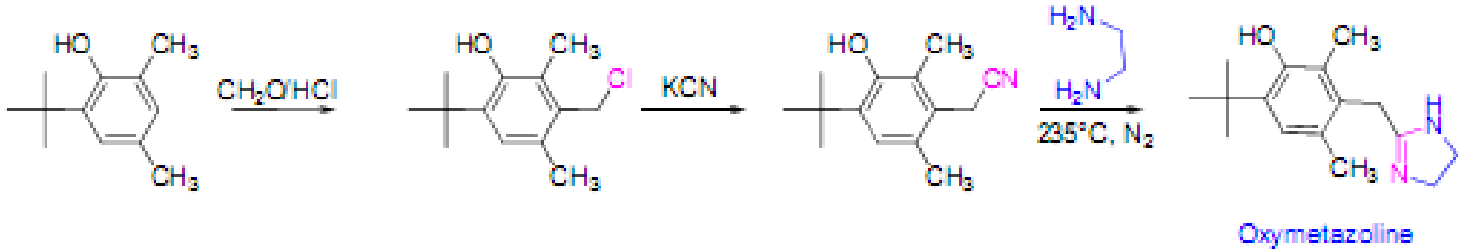
# Dihydroimidazoles

Clonidine (anti-hypertensive agent)

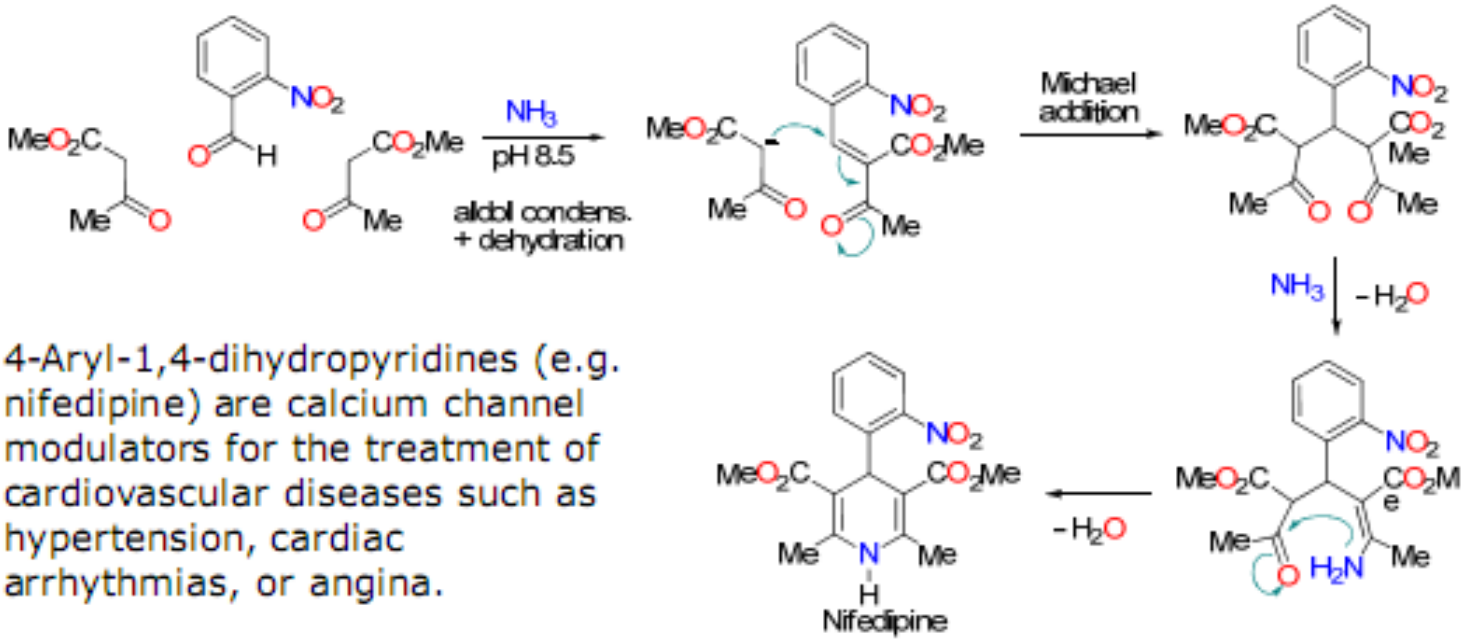



Oxymetazoline (topical decongestant)



# 1,4-Dihydropyridines

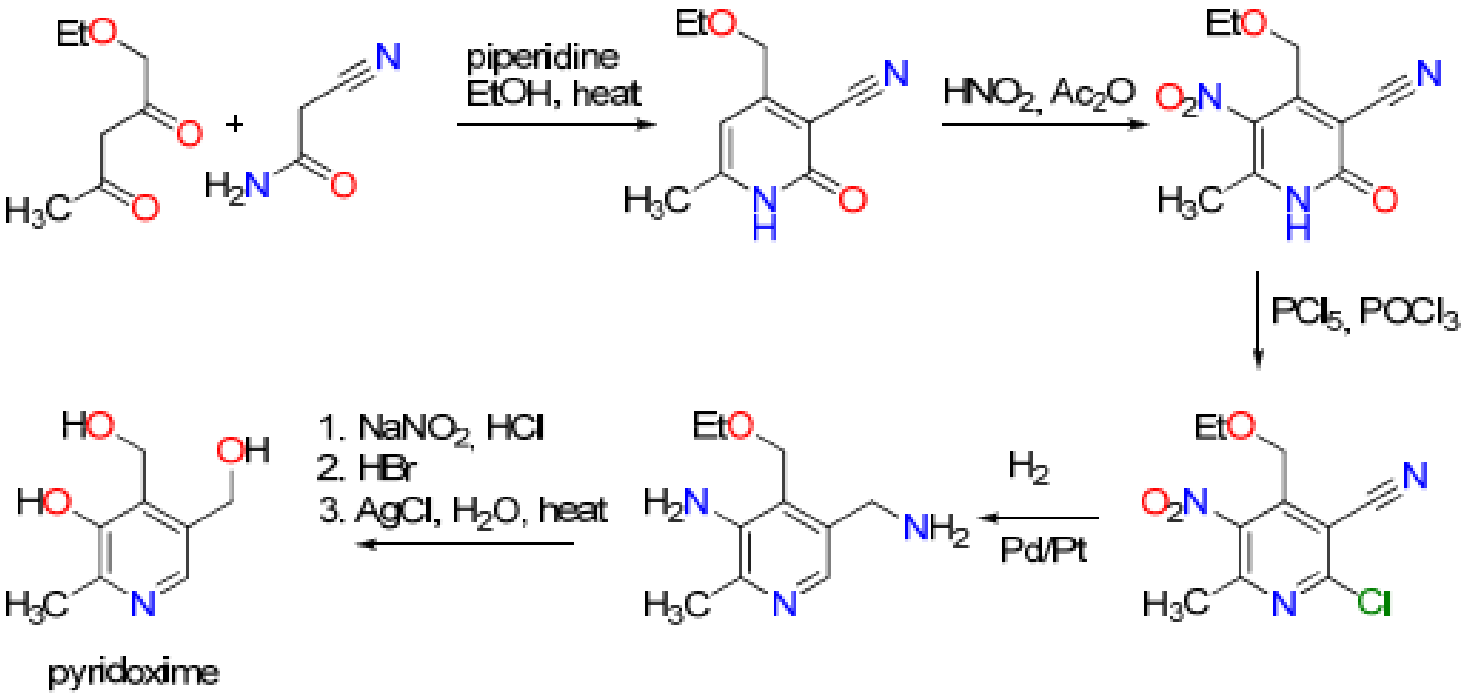
- Hantzsch Dihydropyridine (Pyridine) Synthesis




- 4-Aryl-1,4-dihydropyridines (e.g. nifedipine) are calcium channel modulators for the treatment of cardiovascular diseases such as hypertension, cardiac arrhythmias, or angina.

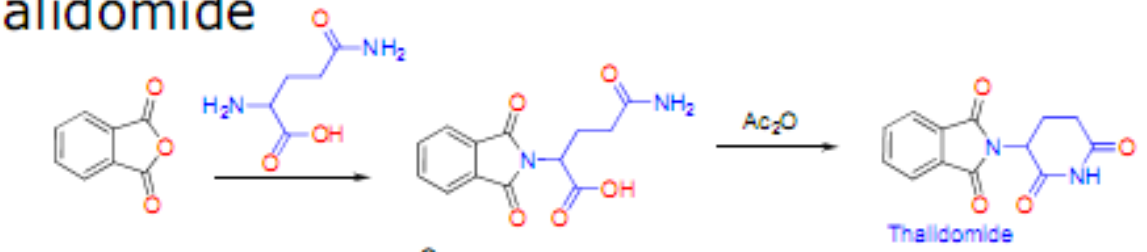
# Pyridines

- Pyridoxine, vitamin B6, has been synthesised by Guareschi ring synthesis

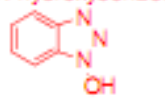


# Glutarimides

- Thalidomide



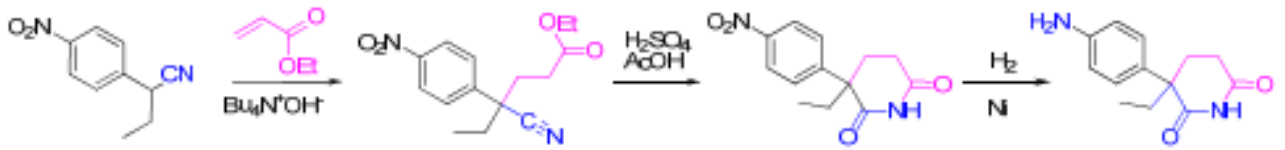

HOBt = N-hydroxybenzotriazole



EDCCl = N-(3-dimethylamino)propyl-N'-ethylcarbodiimide hydrochloride

Tetrahedron Letters (1999), 40(19), 3697-3698.

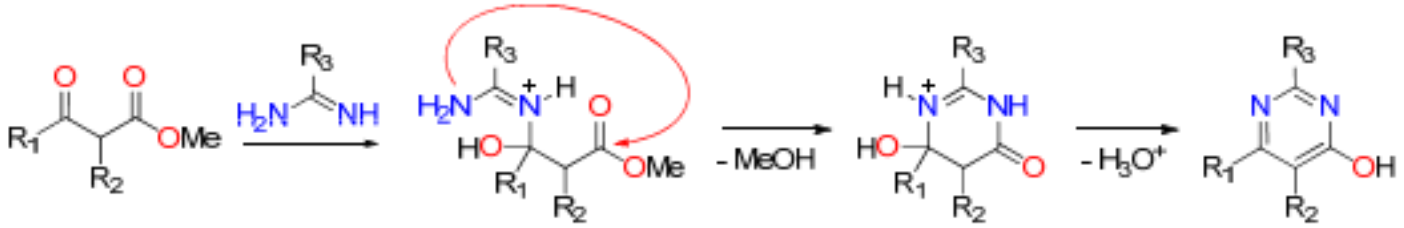
- Aminoglutethimide



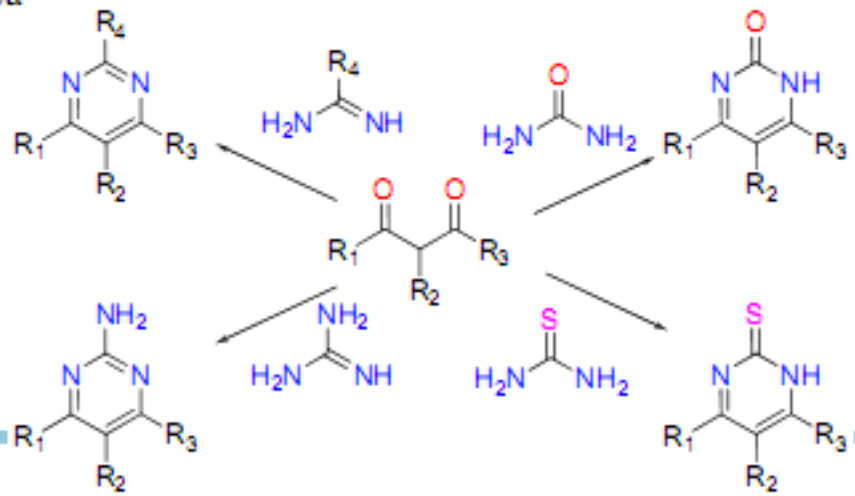

Aminoglutethimide

# Pyrimidines

- Pinner pyrimidine sythesis: from 1,3-dicarbonyl compounds and amidines

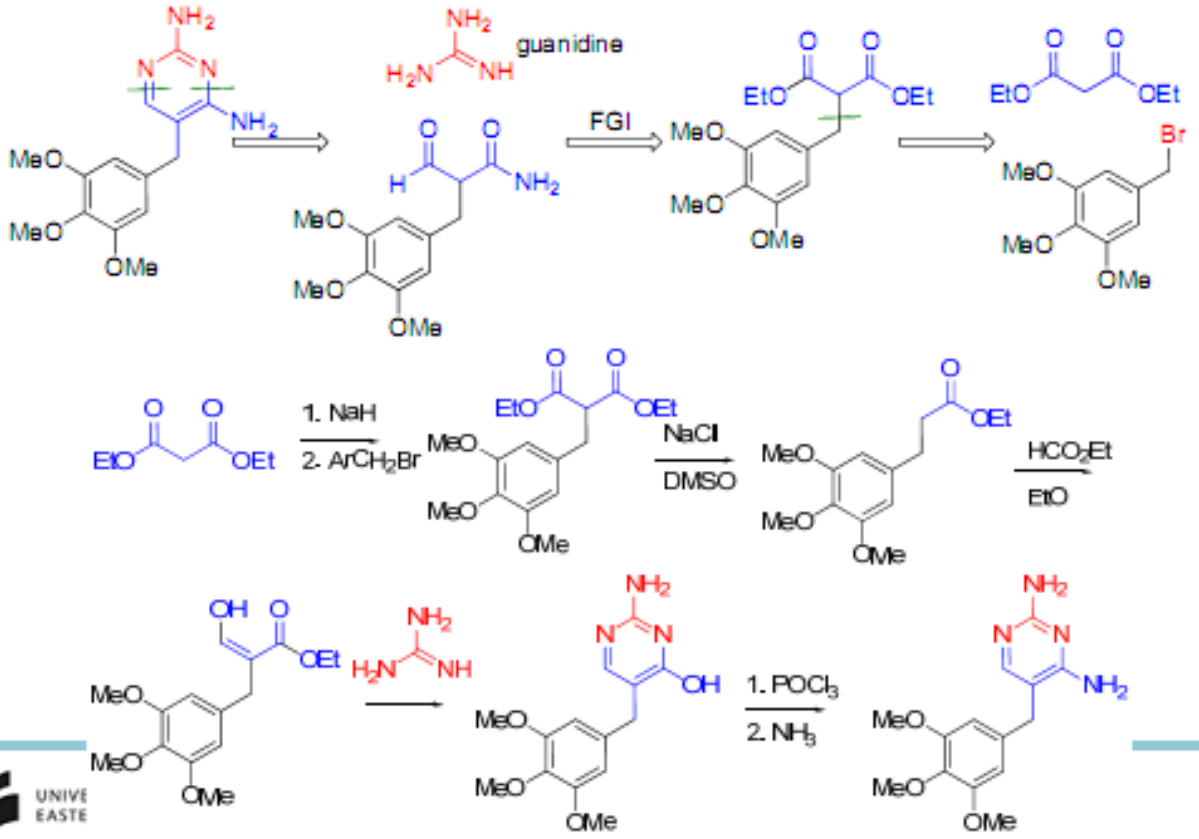



- Instead of amidines, pyrimidines are obtained also by using guanidine, urea and thiourea



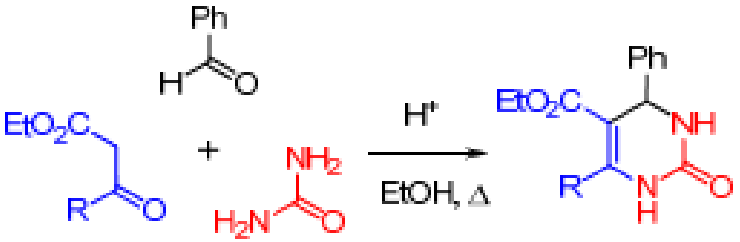
# Pyrimidines

- Example: trimethoprim (bacteriostatic antibiotic)



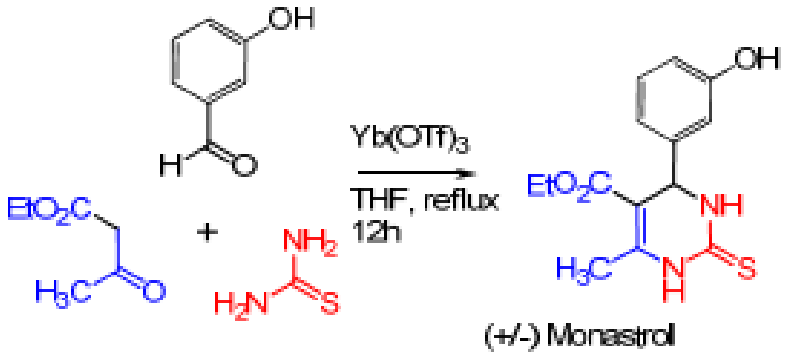
# Pyrimidines

- Biginelli Reaction: acid-catalyzed, reaction between an aldehyde, a,ß-ketoester and urea constitutes a rapid and facile synthesis of tetrahydropyrimidones.




Biginelli, P. Gazz. Chim. Ital. 1893, 23, 360.

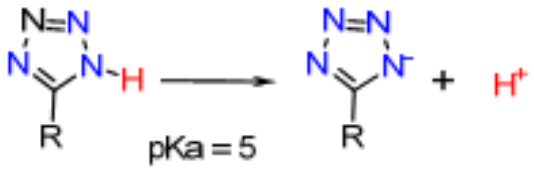
- Synthesis of *rac*-Monastrol (Mitosis blocker by kinase Eg5 inhibition)

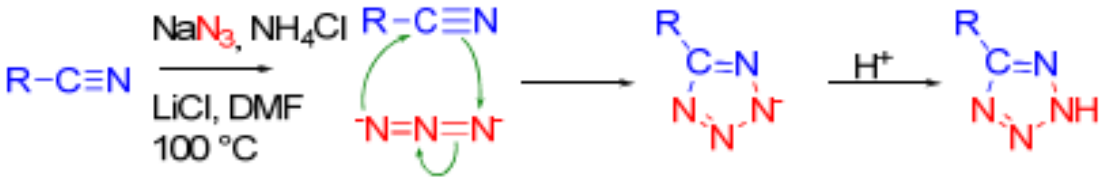



Dondoni, A., et. al. Tet. Lett. 2001, 43, 5913

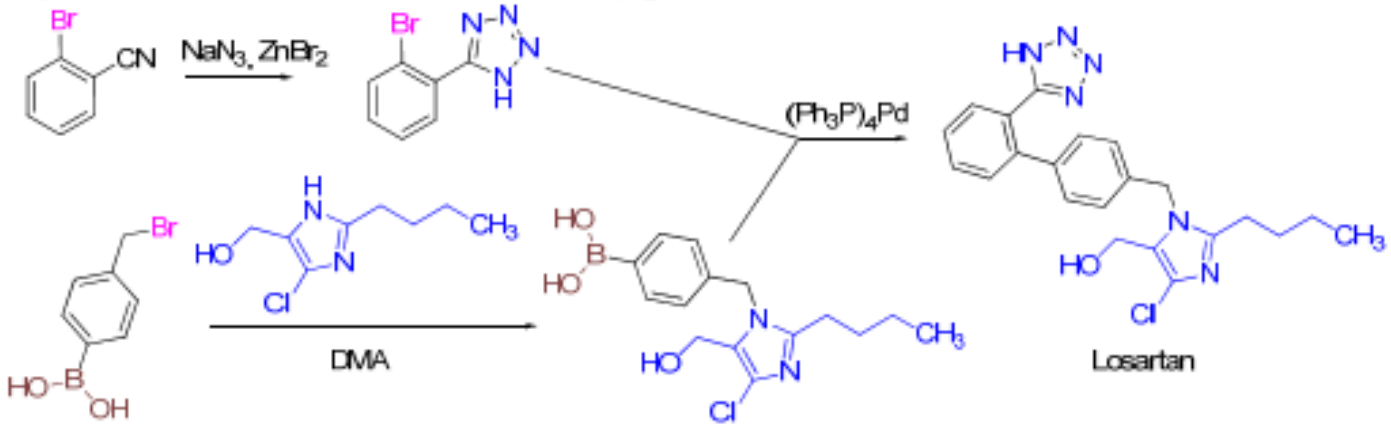
# Tetrazoles

- Carboxylic acid isostere
- Synthesis



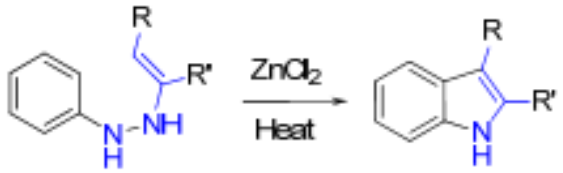




- Synthesis of Losartan (antihypertensive)

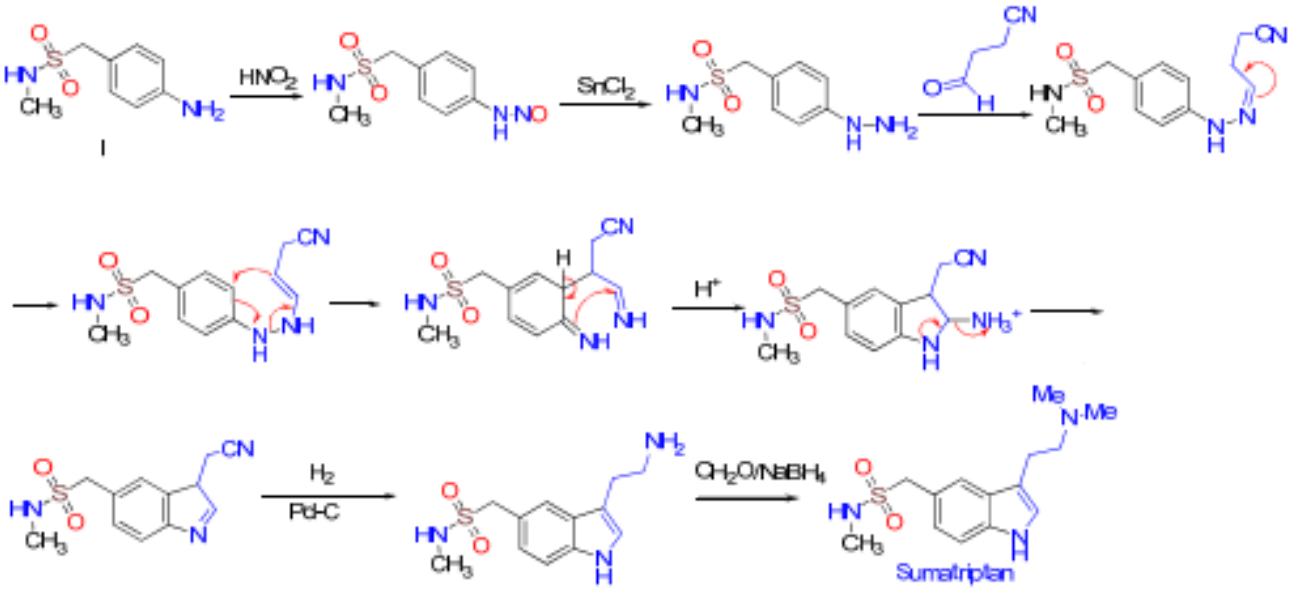


# Indoles

- Fischer Indole Synthesis:
  The conversion of aryl hydrazones to indoles; requires elevated temperatures and the addition of Brønsted or Lewis acids



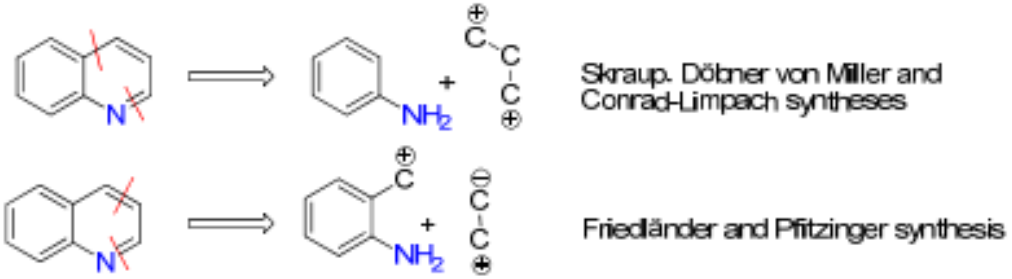

- Synthesis of Sumatriptan



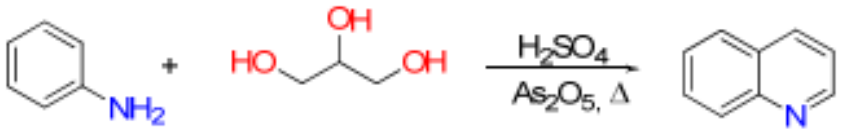

(Daniel Lednicer: Strategies for Organic Drug Synthesis and Design)

# Quinolines

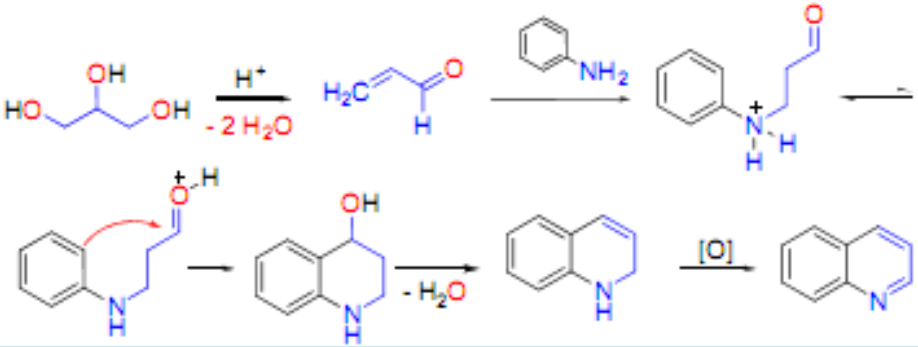
- Quinoline nucleus is usually formed in one of two ways




- Skraup-reaction

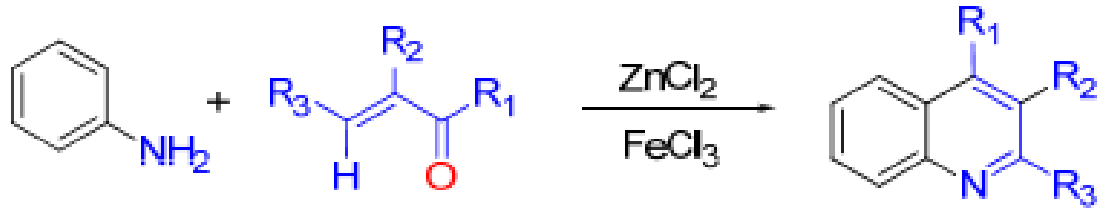



- Mechanism:

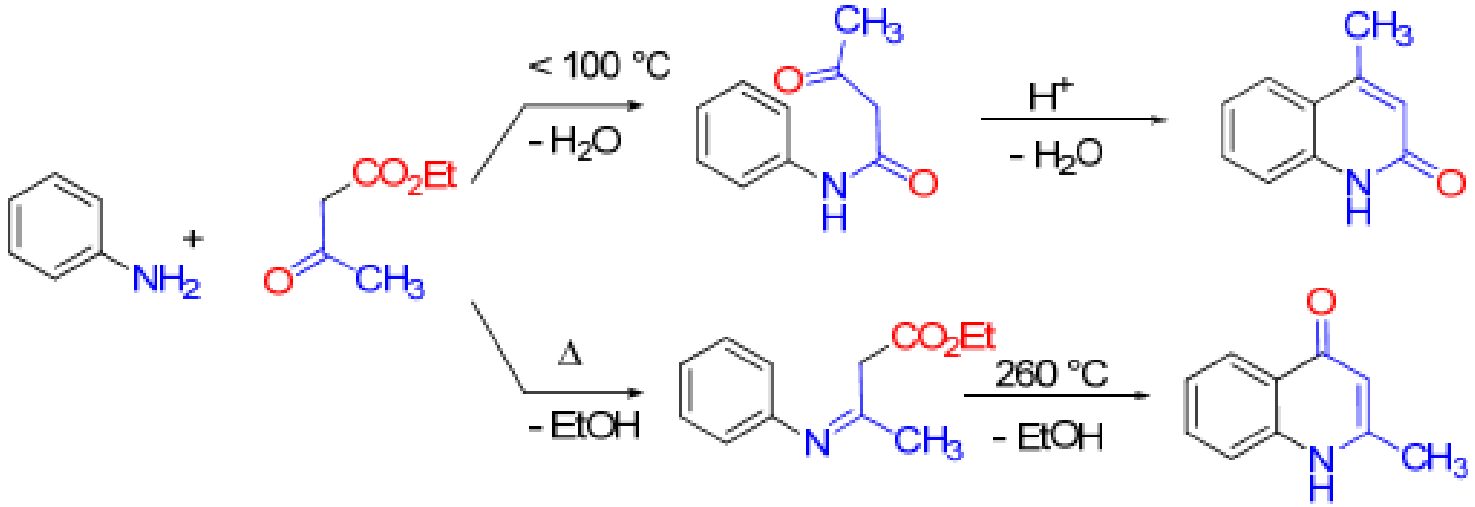


# Quinolines

- **Doebner-Miller –reaction**: α,β-unsaturated ketone or aldehyde can be used instead of glycerol to form a quinoline

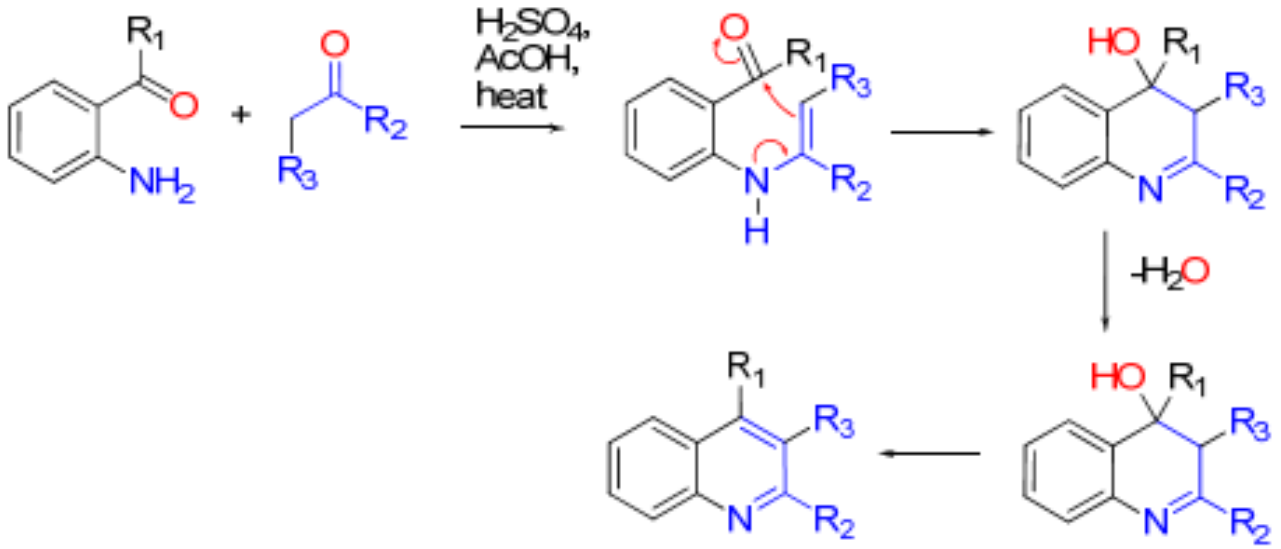



- **Conrad-Limpach reaction**: Synthesis of 4-oxyquinolines by condensation of esters of beta-keto acids with aromatic amines



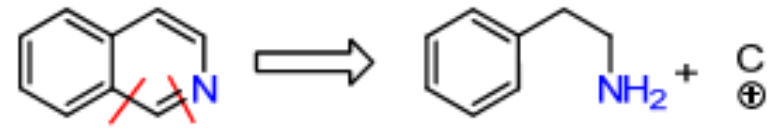
# Quinolines

- Friedländer-quinoline synthesis

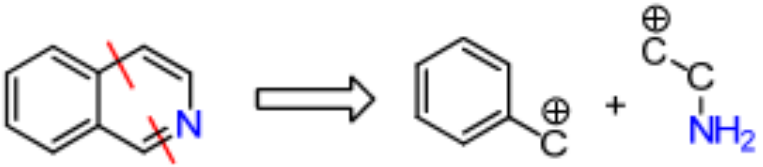


# Isoquinolines

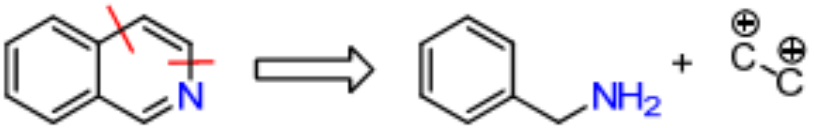
- The general synthetic routes to isoquinolines involve the following skeletal types:




Pictet-Spengler and Bischler-Napieralski syntheses




Pomeranz-Fritsch synthesis

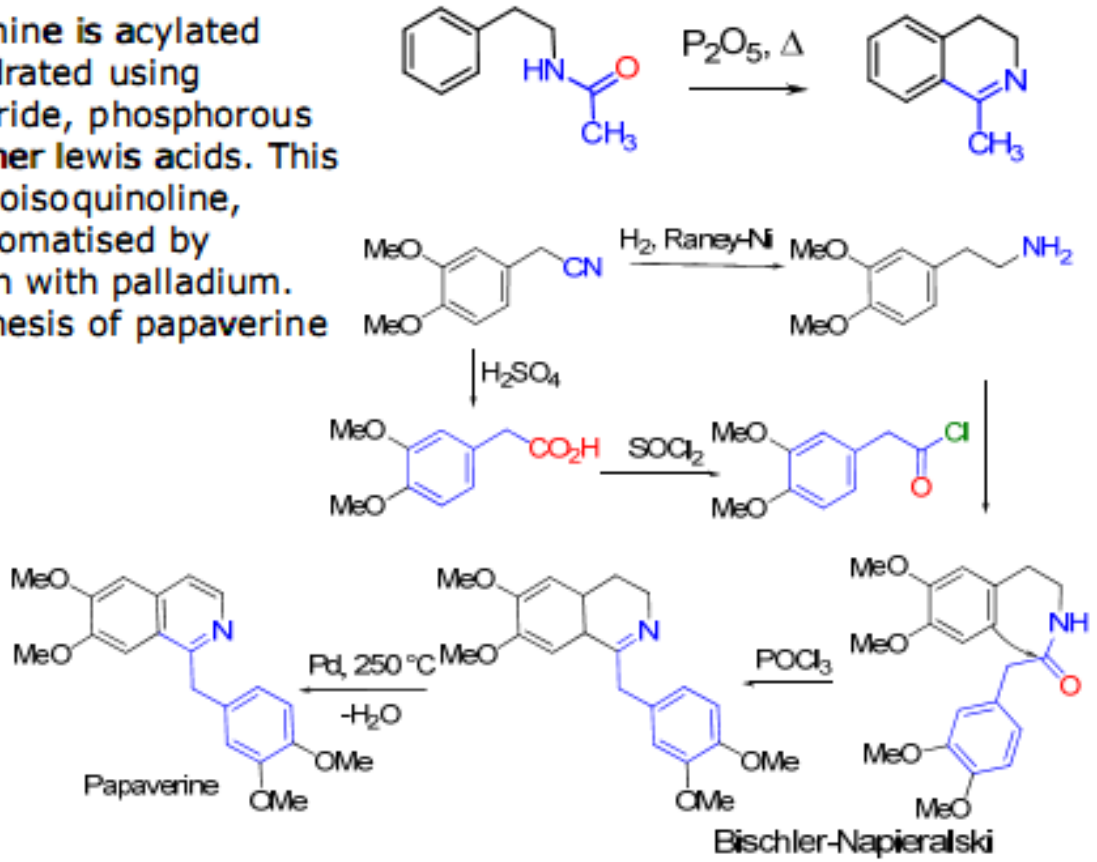



Schlittler-Müller synthesis

# Isoquinolines

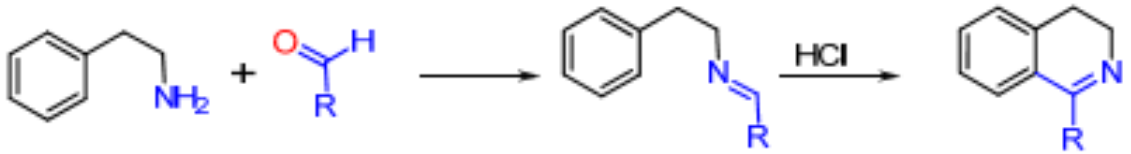
- **Bischler-Napieralski Reaction:**

- β-Phenylethylamine is acylated then cyclodehydrated using phosphoryl chloride, phosphorous pentoxide or other lewis acids. This gives the dihydroisoquinoline, which can be aromatised by dehydrogenation with palladium. E.g. in the synthesis of papaverine



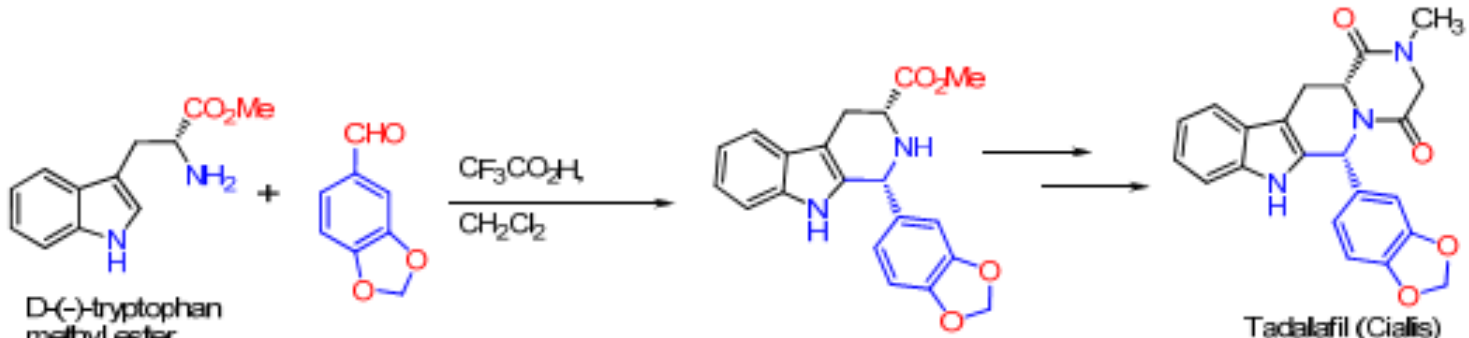
# Isoquinolines

- Pictet-Spengler synthesis: β-Arylethylamine is heated in the presence of an aldehyde and acid.
- A special case of the **Mannich reaction**.




A. Pictet and T. Spengler, Ber. 44, 2030 (1951)

Synthesis of Tadalafil



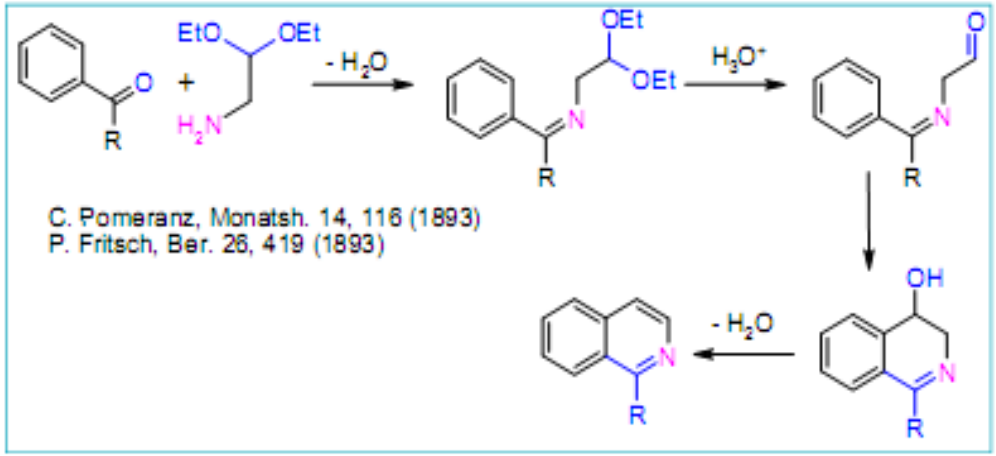

D-(-)-tryptophan methyl ester

Tadalafil (Cialis)

J. Med. Chem. 2003; 46(21); 4525-4532

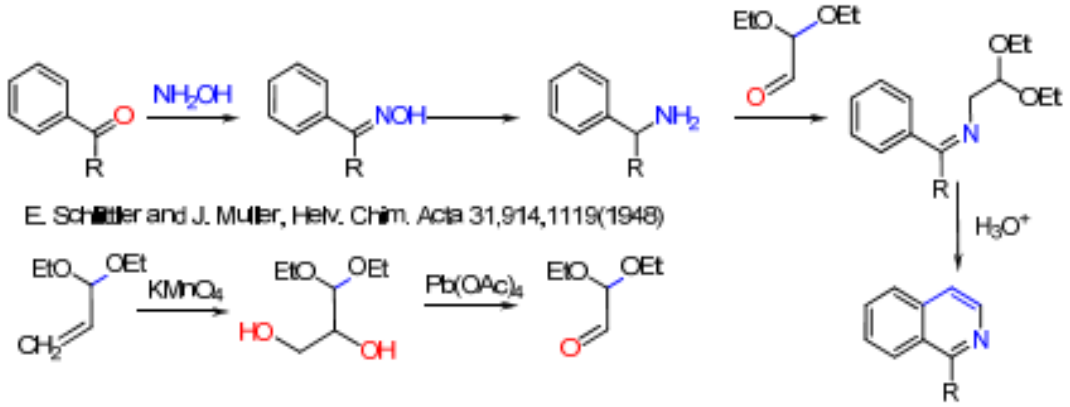
# Isoquinolines

- Pomeranz-Fritsch Reaction




C. Pomeranz, Monatsh. 14, 116 (1893)
P. Fritsch, Ber. 26, 419 (1893)

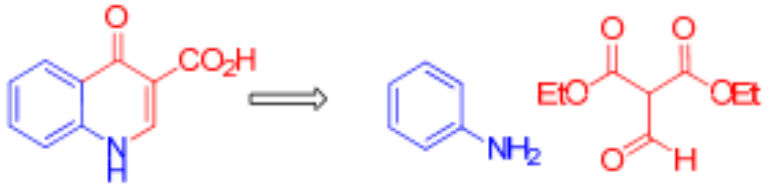
- Schlittler-Müller Reaction

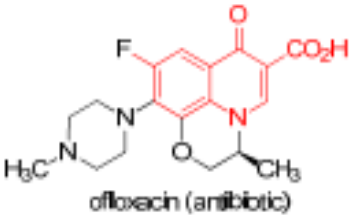



E. Schlittler and J. Müller, Helv. Chim. Acta 31,914,1119(1948)

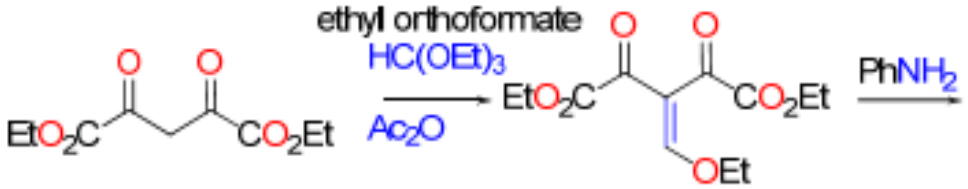
# Quinolones

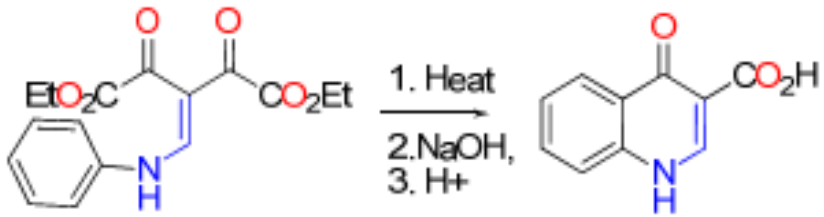
- Retrosynthesis

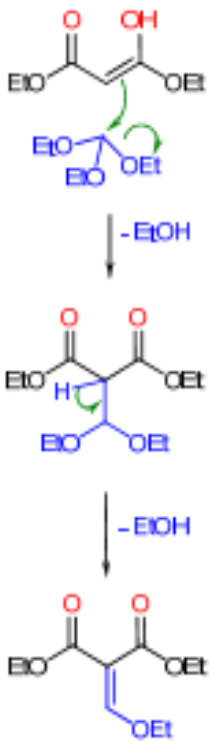





- Synthesis

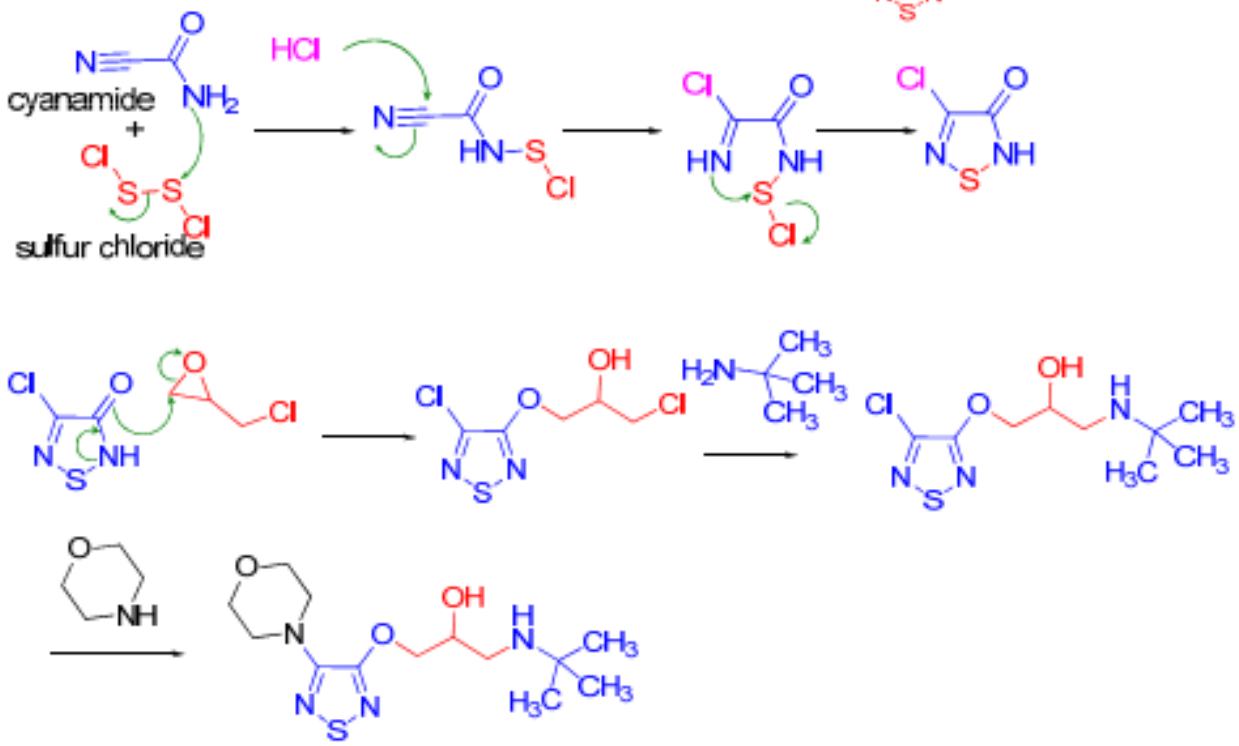


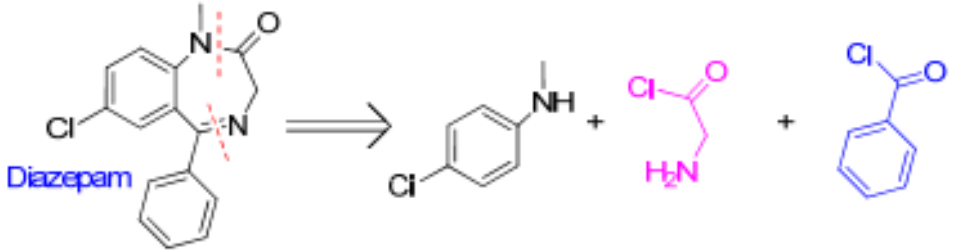
# Thiadiazoles

- Synthesis of Timolol (β-blocker)

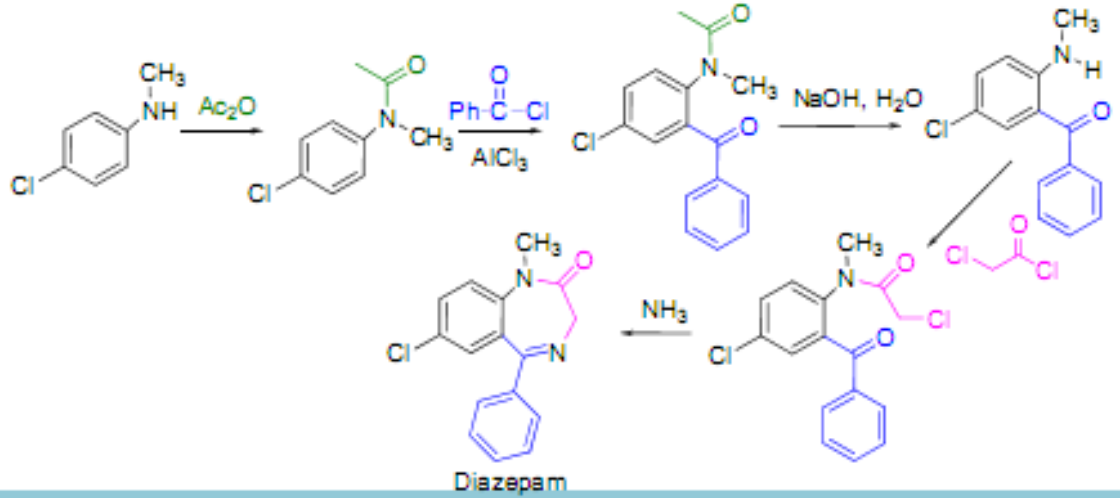



# Benzodiazepines

- The retrosynthesis of diazepam

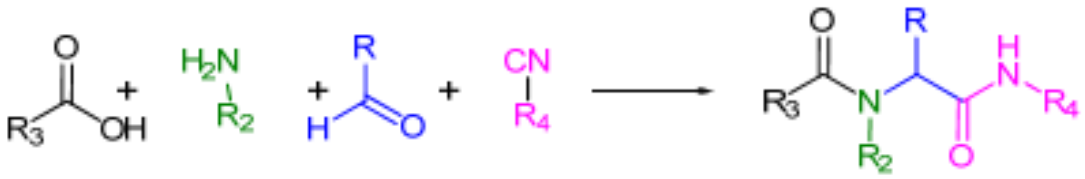



- The synthesis of diazepam (Sternbach et al, 1961).



# Benzodiazepines

- **Ugi Reaction** (Ugi, I., *et. al. Angew. Chem.* **1959**, *71*, 386)



- Concise synthesis of benzodiazepines with Ugi Reaction (Hulme, C., *et. al. J. Org. Chem.* **1998**, *63*, 8021)